DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

Mild Palladium-Catalyzed Regioselective Direct Arylation of Azoles Promoted by Tetrabutylammonium Acetate

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Dedicated to Prof. Renzo Rossi on the occasion of his 76th birthday

Keywords: C–C coupling / Direct Arylation / Azoles / Palladium / Regioselectivity

A mild, general and convenient palladium-catalyzed direct C5 arylation of azoles with aryl bromides, efficiently promoted by tetrabutylammonium acetate, is described. 1-Methylpyrazole, oxazole and thiazole reacted at 70 °C in DMA using $Pd(OAc)_2$ as the catalyst precursor. Electron-poor and electron-rich functional groups, including free hydroxy group, are well tolerated in the electrophilic partner. A variety of 5-aryl-1-methylimidazoles was also very efficiently obtained simply rising the reaction temperature to 110 °C. This phosphine ligand-free protocol has been successfully applied to the one-pot synthesis of two bioactive natural compounds, balsoxin and texaline, starting from oxazole through sequential C5 and C2 direct arylations.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.xxxxxxxxx.

Introduction

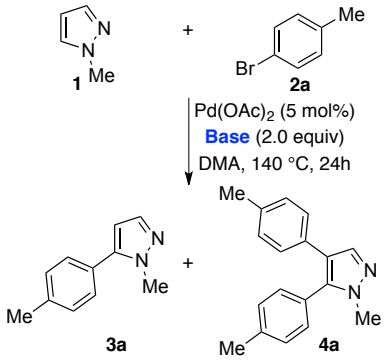
Arylazoles are important structural units frequently found in natural products,[1] pharmaceutics,[2] agrochemicals,[3] and organic functional materials.[4] Due to their widespread applications, the development of straightforward functional group-tolerant synthetic methods that enable direct and selective heterocycle elaboration under mild conditions has aroused considerable attention.[5] Recently, the palladium-catalyzed direct arylation of azoles with aryl halides emerged as an attractive strategy for the effective construction of aromatic Csp2–Csp2 bonds.[6] This synthetic approach, unlike the traditional palladium-catalyzed cross-coupling strategies involving preformed organometallic reagents, enables direct elaboration of heterocyclic cores without the necessity of preactivating both the coupling partners. Moreover, the presence of one or more heteroatoms in such structures contribute to electronic polarization and coordinating ability, which can be exploited to differentiate among different C-H bonds when an appropriate base/catalyst/solvent reaction system has been found. However, despite the growing and widespread interest of organic chemists in these reactions, there are relatively few methods that appears to be generally applicable to the palladium-catalyzed regioselective direct arylation of the broadest range of *simple C-unsubstituted azoles*. In contrast with methods that perform the direct arylation on C-substituted azoles,[6] in which the desired groups have to be introduced at the early stage of the synthesis and are very often necessary to grant the required selectivity, the arylation of unsubstituted azoles allows the introduction of aryl moieties on the parent azole frameworks in a late stage of the synthesis. In their seminal paper on direct arylation of azoles, Miura and co-workers reported that 1-methyl-1*H*-imidazole and thiazole may be regioselectively arylated at their C5 position with aryl bromides or iodides at 140 °C in DMF in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and of 2 equiv of K_2CO_3 (for bromides) or Cs_2CO_3 (for iodides).[7] However, this method suffers from regioselectivity problems and, as we demonstrated later,[8] PPh_3 may be involved in undesired aryl-aryl exchange reactions with the aryl moiety of the halides. In 2009, Fagnou and co-workers demonstrated that thiazole and 1-benzyl-1,2,3-triazole are able to undergo regioselective C5 arylation when treated with aryl bromides and K_2CO_3 in DMA at 100 °C in the presence of 2 mol % of $Pd(OAc)_2$ and of 4 mol% PCy_3HBF_4.[9] The coupling required also 30 mol% of pivalic acid which, according to the authors, granted faster reactions. Unfortunately, very low yields were observed when 1-methyl-1*H*-imidazole was used as the coupling partner, and the protocol proved to be unsuitable for the direct arylation of imidazole, 1-benzyl-1*H*-imidazole and isoxazole. Finally, it is worth mentioning that in a series of papers Doucet and co-workers described a phosphine-free method for the direct C-5 arylation of 1-methyl-1*H*-imidazole,[10] thiazole[11] and 1-methyl-1*H*-pyrazole[12] with aryl bromides, in the presence of 2 equiv of KOAc and with a low loading of $Pd(OAc)_2$ (0.1–1 mol%). This method provides the required 5-arylated azoles in low to satisfactory yields, but it suffers in general from regioselectivity problems when the arylation involves 1-methyl-1*H*-pyrazole despite a 4:1 molar ratio between this expensive azole and aryl bromides was employed.[12] Moreover, this protocol shares with all the others high reaction temperatures (130–150 °C), which constitute a serious issue when thermolabile substrates have to be used,[13] and may cause security problems during scale-up because sealed vessels are generally required.

Recent theoretical investigations revealed that a concerted metalation-deprotonation (CMD) pathway is of relevance for Pd-catalyzed direct arylation of azoles.[14][15] In this mechanistic hypothesis, $Pd(OAc)_2$ is generally the transition metal precatalyst, and a carboxylate (or carbonate) anion plays a fundamental role in the C–H cleavage, which occurs in the rate-determining step of this model simultaneously with carbon–palladium bond formation. In light of these theoretical findings, and due to our knowledge of the

Pd-catalyzed direct arylation of π-electron-rich heteroarenes,[8][16] we reasoned that common reaction conditions should be found for different azoles if they really share the same mechanistic pathway when reacted with aryl halides. In the CMD mechanism the choice of an appropriate base represents an important element of catalyst design; for this reason, we decided to devote a particular attention on the influence of the anionic base and of its countercation[17] on the outcome of the direct arylation of azoles during a re-examination of all the reaction parameters. In this paper we describe the most recent results of these studies, which allowed us to find a common mild protocol for the highly regioselective Pd-catalyzed C5 arylation of 1-methylpyrazole, oxazole and thiazole with aryl bromides. This protocol involves the use of tetrabutylammonium acetate (Bu_4NOAc) as the base under ligandless conditions, and required a reaction temperature of only 70 °C to score good chemical yields. We were also able to perform the selective direct C5 arylation of 1-methyl-1*H*-imidazole with aryl bromides simply rising the reaction temperature to 110 °C. This convenient phosphine ligand-free reaction system, as far as we are aware, has never been used in regioselective direct arylation reactions involving C-unsubstituted heteroarenes.

Results and Discussion

At the onset of our studies, we decided to investigate the Pd-catalyzed direct arylation of 1-methyl-1*H*-pyrazole (**1**) with 4-bromotoluene (**2a**), chosen as a model coupling partner. The regioselective synthesis of C-monoarylated pyrazoles represents a challenging target, and previous studies by Sames on SEM-protected pyrazole,[18] by Mateos and Mendiola[19] and, as mentioned in the Introduction, by Doucet[12] on **1** well evidenced the difficulties in performing a clean monoarylation on simple C-unsubstituted pyrazoles. At first, the impact of the base (2.0 equiv) was evaluated on the outcome of the reaction involving **1** and 1.5 equiv of **2a** in the presence of $Pd(OAc)_2$ (5 mol%) as the catalyst precursor in DMA at 140 °C for 24 h (Scheme 1).



Scheme 1.

As shown in Table 1, where the results of this preliminary screening are reported, a mixture of the C5 arylated pyrazole **3a** and of the corresponding 4,5-diarylated derivative **4a** was invariably observed when the GLC yield of **3a** was higher than 10% (entries 5–9, Table 1), while **4a** was not detected in the crude reaction mixtures when lower GLC yields were recorded (entries 1–4 and 10, Table 1). These results, along with the detection of the other two isomeric C-3 and C-4 monoarylated pyrazoles only in traces (if any), confirmed the higher reactivity of the 5-position relative to the 4-position, while the 3-position resulted substantially unreactive.[18]

Table 1. Direct arylation of **1** with **2a**: preliminary screening of the base.

Entry[a]	Base (2 equiv)	Yield of **3a** (%)[b]	**3a**:**4a** GLC ratio
1	NaOAc	6	100:0
2	KOAc	8	100:0
3	CsOAc	7	100:0
4	AgOAc	1	100:0
5	Bu_4NOAc	54 (49)[c]	86:14
6[d]	KOAc	32	88:12
7	K_2CO_3	19	85:15
8	$KHCO_3$	18	86:14
9	K_3PO_4	24	90:10
10	KF	4	100:0

[a] Unless otherwise stated, the reactions were carried out using **1** (1.0 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (5 mol%) in DMA (5 mL) for 24 h at 140 °C. [b] GLC yield. In parenthesis, isolated yield. [c] 1-Methyl-4,5-di-*p*-tolyl-1*H*-pyrazole (**4a**) was also isolated in 8% yield. [d] This reaction was carried out in the presence of 1.0 equiv of Bu_4NCl.

While the selectivity of the arylation resulted poorly influenced by the base, its chemical nature had a deep impact on the efficiency of the coupling. In particular, the yield of **3a** seems to be related to a specific cation-anion pair and not to a particular anion or cation (compare, as an example, entries 1-5, or entries 2 and 7–10, Table 1). From these first data it clearly emerged that Bu_4NOAc represents the best choice in terms of chemical yield for the regioselective direct C5 arylation of **1** with **2a** in DMA (entry 5, Table 1). Potassium-containing bases K_2CO_3, $KHCO_3$ and K_3PO_4 also showed activities, albeit with a significant lower product yields (entries 7–9, Table 1). All the other bases resulted ineffective at 140 °C in DMA including KOAc, a base frequently used to promote direct arylations of azoles and that, in particular, was previously employed in the direct arylation of **1** with aryl bromides at 150 °C in the same solvent.[12] Interestingly, the low efficiency demonstrated in our hands by KOAc may be improved performing the arylation of **1** in the presence of 1.0 equiv of Bu_4NCl (entry 6, Table 1), but the yield of **3a** remained lower than that obtained using Bu_4NOAc.

Taking into account these results, we then checked the influence of the palladium precatalyst and of the solvent on the efficiency and the selectivity of our model reaction (Table 2). The reaction temperature for this second screening was set to 110 °C to allow a better comparison among solvents with boiling points lower than 140 °C. As regards the catalyst precursor, the best results were obtained using $Pd(OAc)_2$ or $PdCl_2$ (entries 1 and 2, Table 2), while $Pd_2(dba)_3$ and $PdCl_2(PhCN)_2$ gave poorer results in terms of yield (entries 3 and 4, Table 2). The reaction was successful also for reduced palladium loading (entry 5, Table 2), but we proceeded with 5 mol% of $Pd(OAc)_2$ for convenience. Moreover, from the data summarized in Table 2 it clearly emerged that DMA is a better solvent than toluene, dioxane, or NMP (entries 1 and 6–8, Table 2). Interestingly, the observed **3a**:**4a** molar ratio was always higher than 80%, confirming the efficiency of Bu_4NOAc in promoting this particular arylation.

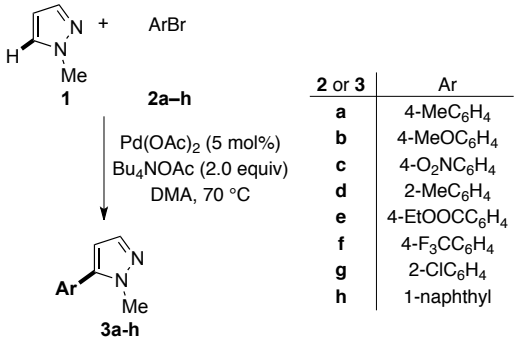
Due to the fact that the yield obtained employing Bu_4NOAc as the base was slightly higher at 110 °C than at 140 °C (compare entry 1 of Table 2, with entry 5 of Table 1), we decided to lower further the reaction temperature and, with our great delight, we found that an even better chemical yield resulted when **1** was reacted with **2a** in the presence of Bu_4NOAc and $Pd(OAc)_2$ in DMA ***at only 70 °C*** (entry 9, Table 2). However, an attempt to carry out the same reaction at 40 °C was unsuccessfully, and the precursors were recovered unchanged after 24 h.

Table 2. Influence of the solvent and of the Pd precatalyst on the direct arylation of **1** with **2a**

Entry[a]	Pd precatalyst (5 mol %)	Solvent (5 mL)	Yield of **3a** (%)[b]	**3a**:**4a** GLC ratio
1	$Pd(OAc)_2$	DMA	58 (52)	82:18
2	$PdCl_2$	DMA	56	84:16
3	$Pd_2(dba)_3$	DMA	38	91:9
4	$PdCl_2(MeCN)_2$	DMA	46	86:14
5[c]	$Pd(OAc)_2$	DMA	40	81:29
6	$Pd(OAc)_2$	Toluene	45	93:7
7	$Pd(OAc)_2$	Dioxane	39	92:8
8	$Pd(OAc)_2$	NMP	50 (47)	83:15
9[d]	$Pd(OAc)_2$	DMA	62 (58)	84:16

[a] Unless otherwise stated, the reactions were carried out using **1** (1.0 mmol), **2a** (1.5 equiv) and Bu_4NOAc (2.0 equiv) in the presence of the selected Pd precatalyst (5 mol% Pd) in a given solvent (5 mL) for 24 h at 110 °C. [b] GLC yield. In parenthesis, isolated yield. [c] This reaction was performed using 1 mol% of $Pd(OAc)_2$. [d] This reaction was performed at 70 °C.

The good result obtained in the preparation of **3a** from **1** and **2a** under the experimental conditions reported in entry 9 of Table 2 prompted us to extend this mild procedure to the selective preparation of 5-aryl-1-methyl-1*H*-pyrazoles **3** starting from **1** and commercially available *para*- and *ortho*-substituted aryl bromides **2a–h** using 5 mol% of $Pd(OAc)_2$ as the catalyst precursor, 2 equiv of Bu_4NOAc as the base, in DMA as the solvent at 70 °C (Scheme 2).



2 or **3**	Ar
a	4-MeC_6H_4
b	4-$MeOC_6H_4$
c	4-$O_2NC_6H_4$
d	2-MeC_6H_4
e	4-$EtOOCC_6H_4$
f	4-$F_3CC_6H_4$
g	2-ClC_6H_4
h	1-naphthyl

Scheme 2. Pd-catalyzed direct arylation of 1-methyl-1*H*-pyrazole (**1**) with aryl bromides **2a–h**

As reported in Table 3, where the results of the arylations involving pyrazole **1** are summarized, good chemical yields and complete C5 regioselectivity were obtained with electron-rich *para*-substituted aryl bromides **2a–b** (entries 1–2), and similar C5 regioselectivities but slightly lower yields were observed when electron-poor *para*-substituted aryl bromides **2c**, **2e** and **2f** were employed as electrophilic partners (entries 3, 5 and 6, Table 3). Similarly to what observed during our preliminary screenings, the crude reaction mixtures were contaminated by the corresponding 4,5-diarylated pyrazoles **4** (detected by GLC and GC-MS analyses), whose amounts resulted lower (16–18 %) for deactivated bromides **2a–b** than for activated bromides **2c**, **2e** and **2f** (20–30 %).

In contrast with the results reported by Doucet,[12] an high C5 regioselectivity was invariably observed whatever the electronic nature of the *para* substituent on aryl bromides **2** was. We argued that the possibility of lowering the reaction temperature from 150 °C to 70 °C due to the successful use of Bu_4NOAc enhanced the kinetic discrimination among C–H bonds with different dissociation energies ($\Delta G^{\neq}$ at 298 K for C–H bond cleavage on **1**: C3, 31.3; C4, 28.5; C5, 27.3)[14]. As a consequence, a strong molar excess of **1** was not necessary to secure an high regioselectivity.

Table 3. Scope of the ligandless Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-pyrazole (**1**) with aryl bromides **2a–h** promoted by Bu_4NOAc

Entry[a]	Ar	Reaction time (h)[b]	Product **3**	Yield (%)[c]	Sel.[d]
1	4-MeC_6H_4	24	**3a**	58	0.84
2	4-$MeOC_6H_4$	23	**3b**	58	0.84
3	4-$O_2NC_6H_4$	46	**3c**	46	0.70
4	2-MeC_6H_4	24	**3d**	47	0.78[e]
5	4-$EtOOCC_6H_4$	48	**3e**	41	0.80
6	4-$F_3CC_6H_4$	48	**3f**	30	0.70
7	2-ClC_6H_4	24	**3g**	42	0.73[f]
8	1-naphthyl	24	**3h**	50	0.76[e]

[a] The reactions were carried out using 1 mmol of pyrazole **1** and 1.5 equiv of a given bromide **2** at 70 °C in the presence of 5 mol% $Pd(OAc)_2$ and 2.0 equiv of Bu_4NOAc in 5 mL of DMA. [b] The reactions were stopped when the conversion was higher than 95%, or when they did not further progress. [c] Isolated yield. [d] C5 arylated pyrazole **3** (% GLC) with respect to all arylated products formed. Unless otherwise stated, the main by-product was the corresponding diarylated pyrazole **4**. [e] The crude reaction mixture was contaminated by ca. 7% of a regioisomeric monoarylated derivative. [f] The crude reaction mixture was contaminated by ca. 14% of a regioisomeric monoarylated derivative.

This simple combination of $Pd(OAc)_2$ and Bu_4NOAc proved to be tolerant also of some typical sterically hindered bromides without the necessity of forcing the reaction conditions. In fact, 2-bromotoluene (**2d**), 2-chlorobromobenzene (**2g**) and 1-naphthyl bromide (**2h**) were smoothly reacted with **1** at 70 °C, giving rise to the corresponding C5 arylated pyrazoles **3d**, **3g** and **3h** in 47, 42 and 50% isolated yields, respectively (entries 4, 7 and 8, table 3). Noteworthy, in these reactions variable amounts (7–14%) of a monoarylated regioisomeric pyrazole (presumably the C-4 isomer)[12] were also detected in the crude reaction mixtures.

Having successfully demonstrated the viability of the $Pd(OAc)_2$-catalyzed regioselective direct C5 arylation of **1** with bromides **2** in the presence of Bu_4NOAc as the base, we then proceeded to broaden the scope of this arylation reaction by applying the optimized reaction conditions of entry 9 of Table 2 to the synthesis of different classes of monoarylated azoles. With our great delight, we found that also 1,3-azoles are able to react at their C5 site with a variety of activated and deactivated aryl bromides **2** (Table 4).

In details, oxazole (**5**) and thiazole (**6**) were efficiently and regioselectively converted into their corresponding C5 arylated derivatives **8a–d** and **9a–d**, respectively, by reaction with 1.5 equiv of aryl bromides **2a–d** (entries 1–4 and 6–8, Table 4). Deactivated bromides **2a–b**, activated 1-bromo-4-nitrobenzene (**2c**) and *ortho*-substituted 2-bromotoluene (**2d**) gave rise to yields ranging from 49 to 72% and high selectivities when reacted with oxazole (**5**) (entries 1–4, Table 4), while the corresponding 5-arylated thiazoles **9a–d** were obtained in 59–70% isolated yields with C5 selectivities up to 100% (entries 6–9, Table 4). For the first time, also unprotected 4-bromophenol (**2i**) took part in a Pd-catalyzed direct arylation; in fact, 4-(oxazol-5-yl)phenol (**8e**) was isolated in 36% yield by reaction of **2i** with oxazole (**5**) after 48 h at 70 °C (entry 6, Table 4). Noteworthy, this convenient synthetic method for the direct C5 arylation of **5** and **6** favorably compete with previously reported protocols. In fact, for their regioselective direct C5 arylation of oxazole (**5**) with (hetero)aryl bromides, Strotman and

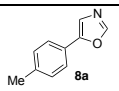
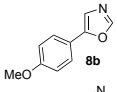
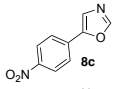
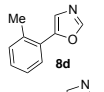
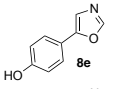
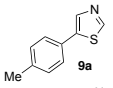
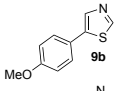
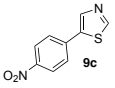
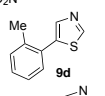
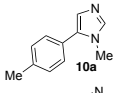
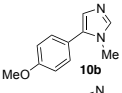
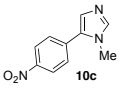
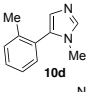
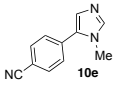
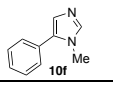
Chobanian worked in DMA for 16 h at 110 °C in a sealed vial in the presence of 5 mol% $Pd(OAc)_2$, 3 equiv of K_2CO_3 and 0.4 equiv of pivalic acid, but a twofold excess of **5** was required to gain high regioselectivities (90–100%) and 10 mol% of the air-sensitive di(1-adamantyl)-*n*-butylphosphine (CataCXium A) was employed as the Pd ligand.[20] As regards thiazole (**6**), Rault and coworkers reported in 2009 that a small library of 5-arylthiazole **9** may be regioselectively obtained in 27–63% yields by reacting **6** with electron-rich, electron poor and heteroaryl bromides.[21] The couplings were carried out in the presence of 5 mol% $Pd(PPh_3)_4$ and 3 equiv of KOAc. However, a strong molar excess (5 equiv) of azole was once again required to attain good regioselectivity, and drastic reaction conditions (150 °C in a sealed tube) were necessary to reduce reaction times. Interestingly, the same authors evidenced in their paper that the ligandless conditions previously reported for the same coupling (2 equiv of **6**, 1 equiv of **2**, 2 equiv of KOAc, 0.4 mol% of $Pd(OAc)_2$, DMA, 130 °C in a sealed tube)[11] gave poorer results in their hands.

Ar–Br **2**

2	Ar
i	4-HOC_6H_4
j	4-NCC_6H_4
k	C_6H_5
l	3,4-$(MeO)_2C_6H_3$
m	3,4-methylenedioxyphenyl
n	3-bromopyridyl

A highly efficient direct C-5 arylation was also obtained when 1-methyl-1*H*-imidazole (**7**) was reacted with a number of aryl bromides, providing a raising of the reaction temperature to 110 °C (entries 10–15, Table 4). Entries 10 and 11 show that yields higher than 80% resulted from the reaction of **7** with electron-rich 4-bromotoluene (**2a**) and 4-bromoanisole (**2b**), and good yields were obtained also when electron-neutral bromobenzene (**2k**), electron-poor 4-bromobenzonitrile (**2j**) and 1-bromo-4-nitrobenzene (**2c**) were used as coupling partners (75, 69 and 45% isolated yields, respectively) (entries 15, 14 and 12). Similarly to what noticed for pyrazole **1**, and also for the parent 1,3-azoles **5** and **6**, the reaction proved to be tolerant also of a typical *ortho*-substituted aryl bromide; in fact, 1-methyl-5-(2-methylphenyl)-1*H*-imidazole (**10d**) was isolated in a satisfactory 68% yield (entry 13). Invariably, the regioselectivity observed was complete, and only less than 10% (GLC) of the corresponding 2,5-diarylated imidazoles were found to contaminate the crude reaction mixtures. It is worth mentioning that this new protocol for the regioselective C5 arylation of **7** gave identical regioselectivities but higher isolated yields than that reported by us in 2008, when we employed 5 mol% of $Pd(OAc)_2$ and 10 mol% of P(2-furyl)$_3$ as the catalyst system, 2 equiv of K_2CO_3 as the base, in DMF at 110 °C.[16e] For comparison, imidazole **10b** was obtained in 49% yield by applying our older method, and *ortho*-substituted aryl bromides did not react at all. The use of Bu_4NOAc at 110 °C in DMA proved to give better results also in comparison with those reported by Doucet and coworkers in 2009.[10] In that case, their harsh low catalyst loading method (0.5–0.01 mol % $Pd(OAc)_2$, 2 equiv of KOAc in DMA at 150 °C) gave rise to significantly lower yields when electron-rich aryl bromides **2a** and **2b** were used (40 and 42% isolated yields, respectively), while results similar to that reported here were described when a typical electron-poor aryl bromide, 4-bromobenzonitrile (**2j**), was used (76% yield).

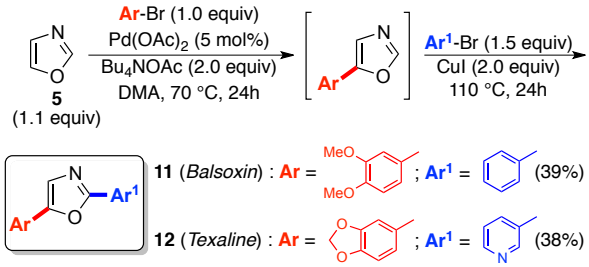
Table 4. Scope of the ligandless Pd-catalyzed direct C-5 arylation of oxazole (**5**), thiazole (**6**) and 1-methyl-1*H*-imidazole (**7**) with aryl bromides **2a–k** promoted by Bu_4NOAc

Entry[a]	Time (h)[b]	Product	Yield (%)[c]	Sel.[d]
1	5	 **8a**	58	0.86
2	24	 **8b**	49	0.88
3	24	 **8c**	57	0.89
4	24	 **8d**	72	0.83
5	48	 **8e**	36	0.95
6	21	 **9a**	65	0.86
7	48	 **9b**	67	1.00
8	48	 **9c**	70	0.94
9	29	 **9d**	59	0.89
10	22	 **10a**	81	0.90
11	24	 **10b**	82	0.97
12	24	 **10c**	45	1.00
13	24	 **10d**	68	0.91
14	24	 **10e**	69	0.92
15	23	 **10f**	75	0.97

[a] The reactions were carried out using 1 mmol of azole **5**, **6** or **7** and 1.5 equiv of a given bromide **2** at 70 °C (entries 1–9) or at 110 °C (entries 10–15) in the presence of 5 mol% $Pd(OAc)_2$ and 2.0 equiv of Bu_4NOAc in 5 mL of DMA. [b] The reactions were stopped when the conversion was higher than 95%, or when they did not further progress. [c] Isolated yield. [d] C5 monoarylated azole (% GLC) with respect to all arylated products formed.

From our data it emerged that the experimental order of reactivity for the three 1,3-azoles, that is oxazole>thiazole>1-methylimidazole, parallels the calculated Gibbs free energy for the cleavage of C5–H bond for a CMD reaction mechanism[14] ($\Delta G^{\neq}$ at 298 K: oxazole, 23.5; thiazole, 23.7; methylimidazole, 25.0). This experimental order of reactivity is distinctly different from that reported for common electrophilic substitution reactions carried out in non-acidic media (1-methylimidazole>oxazole>thiazole),[22] which allows us to reasonably exclude an alternative S_EAr mechanistic pathway, which was also postulated for direct arylations involving these heteroaromatics.[7]

Due to the good results described above, and taking into account our previously reported procedure for the direct ligandless C2 arylation of 1,3-azoles,[16a–c] we argued that it might be also possible to achieve the one-pot sequential C5 and C2 diarylation of 1,3-azoles with different aryl bromides. To probe the feasibility of this approach, we set up the one-pot synthesis of two bioactive natural 2,5-diaryloxazoles, balsoxin (**11**) and texalin (**12**), isolated from *Amyris* species of plant in the Caribbean (Scheme 3).[23] In the first step, 1.1 equiv of oxazole (**5**) were reacted with 1.0 equiv of bromides **2l** and **2m** at 70 °C in DMA. The use of 5 mol% $Pd(OAc)_2$ and 2.0 equiv of Bu_4NOAc as initial quantities proved to be effective for the sequential reactions, and no additional catalyst or base was necessary in the second step. After 24 h, the C2 arylation was achieved simply adding 1.5 equiv of (hetero)aryl bromides **2k** and **2n** to the reaction pot along with 2 equiv of CuI, to give after 24 h at 110 °C the required balsoxin (**11**) and texaline (**12**) in 39 and 38% isolated yield, respectively (Scheme 3).[24]



Scheme 3. One-pot synthesis of balsoxin (**11**) and texaline (**12**)

Undoubtedly, the relevant efficiency and the very high regioselectivity demonstrated by this ligand-free protocol at mild reaction temperatures and without the need of employing a strong molar excess of the heteroaromatic partner has to be attributed to the use, as the base, of Bu_4NOAc. Its efficacy in promoting such ligand-free direct arylations, in our opinion, may be motivated not only by the well known ability of ammonium salts to act as metal-stabilizers in the absence of phosphines or other ancillary ligands (the so-called "Jeffery conditions"), [25][26] but also by the fact that organic ionic bases have good solubility and are fully ionized in organic solvents.[27] In fact, we noticed that arylations involving Bu_4NOAc gave yellow to deep orange solutions, in contrast with reactions carried out in the presence of inorganic bases, which usually gave rise to dark brown heterogeneous reaction mixtures. These last features may lead, as a consequence, to an improved availability in solution of the acetate anion[28] which can then play better its key role in the concerted metalation-deprotonation pathway (CMD) postulated for these Pd-catalyzed reactions (Figure 1), as already mentioned.[14]

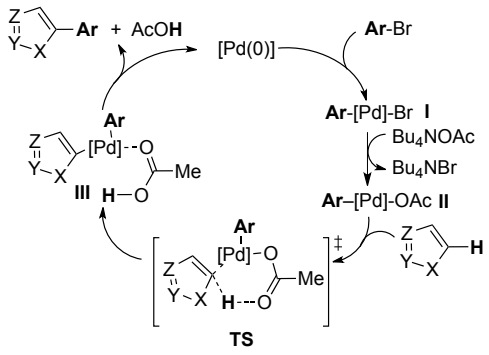
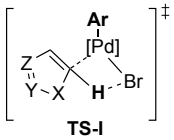


Figure 1. Proposed CMD pathway for the ligandless Pd-catalyzed direct C5 arylation of azoles with aryl bromides **2** mediated by Bu_4NOAc. Coordinating species around Pd (such as solvent molecules or ammonium salts) have been omitted for simplicity.

In particular, the role of Bu_4NOAc may be of relevance in the anionic ligand exchange step that may occur at the aryl palladium intermediate **I**, producing the palladium acetate intermediate **II** which than follows the CMD pathway via a six-membered transition state **TS**. DFT calculations evidenced that this path is energetically more favorable than a pathway involving a σ-bond metathesis, where is the bromine atom that induces deprotonation via **TS-I**.[29]



Hence, if the lower energy pathway involves a bromine/acetate exchange, this may become a limiting step for the entire process when bases which are poorly soluble in reaction media are employed, and may explain the efficiency of Bu_4NOAc in promoting this class of C–C bond-forming reactions.

Conclusions

In this study we developed a simple, mild and effective method for the regioselective Pd-catalyzed direct C5 arylation of several C-unsubstituted azoles with aryl bromides starting from preliminary screenings on the role of bases, catalyst precursors, solvents and reaction temperature on the efficiency and selectivity of the monoarylation of 1-methyl-1*H*-pyrazole (**1**). The observed C5 regioselectivity is in agreement with the calculated Gibbs free energies for the cleavage of C–H bonds of azoles under the hypothesis of a CMD mechanistic pathway.[14] It is noteworthy that under phosphine ligand-free conditions Bu_4NOAc resulted effective at only 70 °C in promoting the direct arylation of azoles for which the regioselectivity of C-H bond metalation is controlled by different contributes to the reactivity.[14] An important consequence of our results is that lipophilic organic acetates may in general secure better performances at lower temperatures when compared with their inorganic counterparts (such as KOAc) in transformations carried out in organic solvents, because they grant better solubility and effective transition metal stabilization. We believe that our findings will be an important clue for the subsequent progresses toward the development of highly efficient and more general direct arylation reactions.

Experimental Section

General information. Fluka precoated 60 F254 aluminium silica gel sheets were used for TLC analyses. GLC analyses were performed using two types of capillary columns: an Alltech AT-35 bonded FSOT column (30 m x 0.25 mm i.d.) and an Alltech AT-1 bonded FSOT column (30 m x 0.25 mm i.d.). Purifications by flash-chromatography were performed using silica gel Merck 60 (particle size 0.040–0.063 mm). EI-MS spectra were measured at 70 eV by GLC/MS. NMR spectra were recorded at room temperature at 200 MHz (^{1}H) and 50.3 MHz (^{13}C) and were referred to TMS or to the residual protons of deuterated solvents. All reactions were performed under argon, by standard syringe and septa technique. The completion of the reactions and the composition of the reaction mixtures

were established on the basis of GLC and GLC-MS analyses of samples of the crude reaction mixtures filtered through a short plug of celite, and eluted with additional EtOAc.

1-Methyl-1*H*-pyrazole (**1**), oxazole (**5**), thiazole (**6**), 1-methyl-1*H*-imidazole (**7**), 4-bromotoluene (**2a**), 4-bromoanisole (**2b**), 4-bromonitrobenzene (**2c**), 2-bromotoluene (**2d**), ethyl 4-bromobenzoate (**2e**), 1-bromo-4-(trifluoromethyl)benzene (**2f**), 1-bromo-2-chlorobenzene (**2g**), 2-bromonaphthalene (**2h**), 4-bromophenol (**2i**), 4-bromobenzonitrile (**2j**), bromobenzene (**2k**), 4-bromo-1,2-dimethoxybenzene (**2l**), 5-bromobenzo[*d*][1,3]dioxole (**2m**), 3-bromopyridine (**2n**), $Pd(OAc)_2$, Bu_4NOAc, CuI, anhydrous DMA were commercially available and were used as received.

Procedure for the screening of the reaction conditions for the Pd-catalyzed C-5 arylation of 1-methyl-1*H*-pyrazole (1) with 4-bromotoluene (2a)

A mixture of 1-methyl-1*H*-pyrazole (**1**) (82 mg, 1.0 mmol), palladium catalyst (0.05 mmol), 4-bromotoluene (**2a**) (0.18 mL, 0.26 g, 1.5 mmol), base (2.0 mmol) in the selected solvent (5 mL) was stirred under argon for 24 h at the temperature reported in Tables 1 and 2. After being cooled to room temperature, the crude reaction mixture was diluted with AcOEt, naphthalene was added as internal standard and the resulting mixture was analyzed by GLC and GC-MS. Tables 1 and 2 summarize the results of this screening.

1-Methyl-5-*p*-tolyl-1*H*-pyrazole (3a) and 1-methyl-4,5-di-*p*-tolyl-1*H*-pyrazole (4a). The crude reaction mixture, which was obtained in entry 6 of Table 1, was concentrated under reduced pressure, and the residue was purified by flash-chromatography on silica gel with a mixture of toluene and AcOEt (70:30 + 0.1% Et_3N) as eluent. Concentration of the first eluted chromatographic fractions allowed isolation of compound **4a** (16 mg, 8% yield) as a pale yellow solid: m.p. 162–164 °C EI-MS *m*/*z* 263 (21), 262 (100), 261 (19), 247 (10), 232 (6), 202 (4), 189 (4), 130 (4). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.20 (m, 4H), 7.04 (m, 4H), 3.79 (s, 3H), 2,41 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 139.7, 138.5, 137.3, 135.4, 130.2, 129.9, 129.4, 129.0, 127.5, 127.1, 120.7, 31.2, 21.4, 21.0. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.84; H, 6.89; N, 10.73.

Concentration of the last eluted chromatographic fractions allowed isolation of compound **3a** (84 mg, 49%) as a light yellow oil. EI-MS *m*/*z* 173 (13), 172 (100), 171 (33), 157 (9), 144 (10), 130 (9), 128 (9), 115 (9). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49 (d, *J* = 1.9 Hz, 1H), 7.27 (m, 4H), 6.26 (d, *J* = 1.9 Hz, 1H), 3.87 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 143.4, 138.3, 138.2, 129.2 (2C), 128.5 (2C), 127.7, 105.7, 37.4, 21.2 ppm. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.76; H, 6.99; N, 16.32. This same compound was also obtained in 52% and 58% isolated yields from the Pd-catalyzed reactions of **1** and **2a** carried out at 110 °C (entry 1, Table 2) or at 70 °C (entry 8, Table 2 and entry 1, Table 3).

General Procedure for the Palladium-Catalyzed Direct C-5 Arylation of 1-Methyl-1*H*-pyrazole (1), Oxazole (5), Thiazole (6) and 1-Methyl-1*H*-imidazole (7) with Aryl Bromides 2a-k. To a flame-dried reaction vessel were added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), Bu_4NOAc (0.60 g, 2.0 mmol), and an aryl bromide **2** (1.5 mmol), if a solid. The reaction vessel was fitted with a silicon septum, was evacuated and back-filled with argon, and this sequence was repeated twice. DMA (5 mL), an aryl bromide **2** (1.5 mmol), if a liquid, and the appropriate azole **1**, **5**, **6** or **7** (1.0 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 70 °C (for azoles **1**, **5** and **6**) or at 110 °C (for azole **7**) under argon for the period of time reported in Tables 3 and 4. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, filtered through a plug of celite, and eluted with additional EtOAc and CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was purified by flash-chromatography on silica gel. This procedure was used to prepare compounds **3b-h**, **8a-e**, **9a-d**, and **10a-f** (Table 3).

5-(4-Methoxyphenyl)-1-methyl-1*H*-pyrazole (3b). The crude reaction product, which was obtained in entry 2 of Table 3 by Pd-catalyzed reaction of **1** with **2b**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60:40 + 0.1% Et_3N) as eluent to give **3b** (0.11 g, 58%) as a yellow oil. EI-MS *m*/*z* 189 (13), 188 (100), 174 (7), 173 (61), 145 (10). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 (d, *J* = 1.9 Hz, 1H), 7.32 (m, 2H), 6.97 (m, 2H), 6.24 (d, *J* = 1.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 159.1, 138.3, 133.0, 129.5 (2C), 127.1, 121.8, 113.9 (2C), 55.1, 32.1 ppm. The spectral properties of this compound were in agreement with those previously reported.[12]

1-Methyl-5-(4-nitrophenyl)-1*H*-pyrazole (3c). The crude reaction product, which was obtained in entry 3 of Table 3 by Pd-catalyzed reaction of **1** with **2c**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and acetone (98:2) as eluent to give **3c** (0.20 g, 46 %) as a yellow solid: m.p. 75–77 °C. EI-MS *m*/*z* 204 (12), 203 (100), 173 (20), 103 (11), 89 (10). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.33 (m, 2H), 7.65 (m, 2H), 7.57 (d, *J* = 1.9 Hz, 1H), 6.47 (d, *J* = 1.9 Hz, 1H), 3.98 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 147.6, 141.4, 139.0, 136.9, 129.4 (2C), 124.0 (2C), 107.4, 38.0 ppm. The physical and spectral properties of this compound were in agreement with those previously reported.[12]

1-Methyl-5-*o*-tolyl-1*H*-pyrazole (3d). The crude reaction product, which was obtained in entry 4 of Table 3 by Pd-catalyzed reaction of **1** with **2d**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70:30 + 0.1% Et_3N) as eluent to give **3d** (80 mg, 47%) as a pale yellow oil. EI-MS *m*/*z* 172 (100), 171 (57), 144 (70), 128 (16), 115 (20). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, *J* = 1.9 Hz, 1H), 7.28 (m, 4H), 6.19 (d, *J* = 1.9 Hz, 1H), 3.65 (s, 3H), 2.16 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 142.3, 138.2, 137.4, 130.4, 130.1 (2C), 128.9, 125.6, 106.2, 36.5, 19.8 ppm. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.65; H, 7.06; N, 16.22.

Ethyl 4-(1-methyl-1*H*-pyrazol-5-yl)benzoate (3e). The crude reaction product, which was obtained in entry 5 of Table 3 by Pd-catalyzed reaction of **1** with **2e**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **3e** (95 mg, 41%) as a yellow oil. EI-MS *m*/*z* 231 (11), 230 (78), 202 (24), 186 (16), 185 (100). ^{1}H NMR(200 MHz, $CDCl_3$): δ 8.13 (m, 2H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.51 (m, 2H), 6.38 (d, *J* = 1.6 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 165.9, 142.4, 138.6, 134.8, 130.2, 129.8 (2C), 128.4 (2C), 106.5, 61.1, 37.7, 14.3 ppm. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.89; H, 6.11; N, 12.21.

5-(4-(Trifluoromethyl)phenyl)-1-methyl-1*H*-pyrazole (3f). The crude reaction product, which was obtained in entry 6 of Table 3 by Pd-catalyzed reaction of **1** with **2f**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (85:15 + 0.1% Et_3N) as eluent to give **3f** (68 mg, 30%) as a pale yellow oil. EI-MS *m*/*z* 227 (13), 226 (100), 225 (47), 207 (9), 198 (9). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.55 (m, 2H), 7.54 (d, *J* = 1.9 Hz, 1H), 6.37 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 142.0, 138.7, 134.3, 130.1, 129.0 (2C), 125.6 (q, *J* = 3.7 Hz, 2C), 123.9 (q, *J* = 272 Hz, CF_3), 106.6, 37.6 ppm. Anal. Calcd for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38. Found: C, 58.35; H, 3.99; N, 12.42.

5-(2-Chlorophenyl)-1-methyl-1H-pyrazole (3g). The crude reaction product, which was obtained in entry 7 of Table 3 by Pd-catalyzed reaction of **1** with **2g**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10 + 0.1% Et_3N) as eluent to give **3g** (82 mg, 42%) as a pale yellow oil. EI-MS *m*/*z* 194 (32), 193 (23), 192 (100), 191 (33), 156 (12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.341 (m, 5H), 6.27 (d, *J* = 1.9 Hz, 1H), 3.72 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.2, 138.2, 134.2, 131.8, 130.3, 129.94, 129.71, 126.7, 106.9, 36.9 ppm. Anal. Calcd for $C_{10}H_9ClN_2$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.40; H, 4.69; N, 14.59.

1-Methyl-5-(naphthalen-1-yl)-1H-pyrazole (3h). The crude reaction product, which was obtained in entry 8 of Table 3 by Pd-catalyzed reaction of **1** with **2h**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20 + 0.1% of Et_3N) as eluent to give **3h** (0.11 g, 50%) as a pale yellow solid: m.p. 87–90 °C. EI-MS *m*/*z* 209 (16), 208 (100), 207 (40), 180 (23), 153 (27). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.47 (m, 5H), 6.34 (d, *J* = 1.8 Hz, 1H), 3.61 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 141.2, 138.4, 133.4, 132.00, 129.2, 128.3, 128.2, 128.1, 126.7, 126.1, 125.2, 124.9, 107.5, ppm 36.9. The spectral properties of this compound were in agreement with those previously reported.[12]

5-*p*-Tolyloxazole (8a). The crude reaction product, which was obtained in entry 1 of Table 4 by Pd-catalyzed reaction of **5** with **2a**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **8a** (92 mg, 58%) as a yellow solid: m.p. 38–41 °C. EI-MS *m*/*z* 159 (100), 131 (26), 130 (38), 104 (34), 103 (21), 91 (21). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.51 (m, 2H), 7.28 (s, 1H), 7.19 (m, 2H), 2.35 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 151.7, 150.2, 138.7, 129.5 (2C), 124.9, 124.3 (2C), 120.6, 21.4 ppm. The spectral properties of this compound were in agreement with those previously reported.[30]

5-(4-Methoxyphenyl)oxazole (8b). The crude reaction product, which was obtained in entry 2 of Table 4 by Pd-catalyzed reaction of **5** with **2b**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **8b** (85 mg, 49%) as a yellow solid: m.p. 45-48 °C. EI-MS *m*/*z* 176 (11), 175 (100), 160 (37), 132 (27), 77 (22). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.57 (m, 2H), 7.23 (s, 1H), 6.94 (m, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 159.7, 151.4, 149.7, 125.8 (2C), 120.5, 119.9, 114.2 (2C), 55.3 ppm. The spectral properties of this compound were in agreement with those previously reported.[20]

5-(4-Nitrophenyl)oxazole (8c). The crude reaction product, which was obtained in entry 3 of Table 4 by Pd-catalyzed reaction of **5** with **2c**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **8c** (0.11 g, 57%) as a yellow solid: m.p. 135-137° C. EI-MS *m*/*z* 190 (100), 160 (43), 132 (25), 89 (91), 63 (21). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.31 (m, 2H), 8.06 (s, 1H), 7.84 (m, 2H), 7.59 (s, 1H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 151.9, 149.5, 147.4, 133.4, 124.9 (2C), 124.7, 124.5 (2C) ppm. The spectral properties of this compound were in agreement with those previously reported.[31]

5-*o*-Tolyloxazole (8d). The crude reaction product, which was obtained in entry 4 of Table 4 by Pd-catalyzed reaction of **5** with **2d**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **8d** (0.11 g, 72%) as a pale yellow oil. EI-MS *m*/*z* 159 (100), 132 (35), 131 (44), 130 (49), 104 (36). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.67 (m, 1H), 7.27 (m, 4H), 2.48 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 150.8, 150.1, 134.9, 131.0, 128.5, 127.0, 126.9, 126.1, 124.1, 21.7 ppm. The spectral properties of this compound were in agreement with those previously reported.[20]

4-(Oxazol-5-yl)phenol (8e). The crude reaction product, which was obtained in entry 5 of Table 4 by Pd-catalyzed reaction of **5** with **2i**, was purified by flash chromatography on silica gel with a mixture of toluene and THF (80:20) as eluent to give **8e** (58 mg, 36%) as a colorless solid: m.p. 229–230 °C. EI-MS *m*/*z* 161 (100), 133 (20), 121 (19), 106 (30), 105 (29). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.85 (s, OH), 8.35 (s, 1H), 7.56 (m, 2H), 7.47 (s, 1H), 6.89 (m, 2H) ppm. ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 157.6, 150.8, 150.6, 125.6 (2C), 119.4, 118.5, 115.6 (2C) ppm. Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.91; H, 4.40; N, 8.62.

5-*p*-Tolylthiazole (9a). The crude reaction product, which was obtained in entry 6 of Table 4 by Pd-catalyzed reaction of **6** with **2a**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10 + 0.1% Et_3N) as eluent to give **9a** (0.11 g, 65%) as a pale yellow solid: m.p. 82–84 °C. EI-MS *m*/*z* 176 (12), 175 (100), 148 (32), 147 (43), 115 (17). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.02 (s, 1H), 7.44 (m, 2H), 7.18 (m, 2H), 2.35 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 151.4, 139.3, 138.4, 138.3, 129.6 (2C), 128.1, 126.7 (2C), 21.2 ppm. The spectral properties of this compound were in agreement with those previously reported.[32]

5-(4-Methoxyphenyl)thiazole (9b). The crude reaction product, which was obtained in entry 7 of Table 4 by Pd-catalyzed reaction of **6** with **2b**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (92:8) as eluent to give **9b** (0.13 g, 67%) as a bright yellow solid: m.p. 89–92 °C. EI-MS *m*/*z* 191 (100), 176 (58), 149 (20), 148 (27), 121 (20). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.97 (s, 1H), 7.48 (m, 2H), 6.92 (m, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 159.8, 151.2, 139.2, 138.0, 128.2 (2C), 123.6, 114.5 (2C), 55.4 ppm. The spectral properties of this compound were in agreement with those previously reported.[21]

5-(4-Nitrophenyl)thiazole (9c). The crude reaction product, which was obtained in entry 8 of Table 4 by Pd-catalyzed reaction of **6** with **2c**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **9c** (0.14 g, 70%) as a yellow solid: m.p. 139-141° C. EI-MS *m*/*z* 206 (100), 176 (26), 148 (20), 133 (27), 89 (53). ^{1}H NMR: δ 8.93 (s, 1H), 8.29 (m, 2H), 8.26 (s, 1H), 7.76 (m, 2H) ppm. ^{13}C NMR: δ 154.2, 147.4, 141.1, 137.4, 127.4 (2C), 126.2, 124.5 (2C) ppm. Anal. Calcd for $C_9H_6N_2O_2S$: C, 52.42; H, 2.93; N, 13.58. Found: C, 52.35; H, 2.95; N, 13.63.

5-*o*-Tolylthiazole (9d). The crude reaction product, which was obtained in entry 9 of Table 4 by Pd-catalyzed reaction of **6** with **2d**, was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **9d** (0.10 g, 59%) as a pale yellow oil. EI-MS *m*/*z* 176 (12), 175 (95), 148 (49), 147 (100), 115 (52). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.79 (s, 1H), 7.84 (s, 1H), 7.27 (m, 4H), 2.37 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 152.5, 141.5, 137.3, 136.3, 130.7, 130.6, 130.1, 128.5, 126.0, 21.0 ppm. Anal. Calcd for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.59; H, 5.15; N, 8.06.

1-Methyl-5-*p*-tolyl-1*H*-imidazole (10a). The crude reaction product, which was obtained in entry 10 of Table 4 by Pd-catalyzed reaction of **7** with **2a**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **10a** (0.14 g, 81%) as a yellow oil. EI-MS *m*/*z* 173 (13), 172 (100), 171 (17), 144 (14), 130 (16). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.26 (m, 2H), 7.25 (m, 2H), 7.07 (s, 1H), 3.63 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): 138.7, 137.6, 133.3, 129.3 (2C), 128.3 (2C), 127.6, 126.7, 32.4, 21.2 ppm. The spectral properties of this compound were in agreement with those previously reported.[10]

5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (10b). The crude reaction product, which was obtained in entry 11 of Table 4 by Pd-catalyzed reaction of **7** with **2b**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **10b** (0.15 g, 82%) as a light yellow solid: m.p. 73–75 °C. EI-MS *m*/*z* 189 (12), 188 (100), 174 (10), 173 (82), 145 (17). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.30 (m, 2H), 7.02 (s, 1H), 6.96 (m, 2H), 3.83 (s, 3H), 3.61 (s, 3H) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): 159.1, 138.3, 132.3, 129.6 (2C), 127.1, 121.8, 113.9 (2C), 55.1, 32.1 ppm. The spectral properties of this compound were in agreement with those previously reported.[16e]

1-Methyl-5-(4-nitrophenyl)-1*H*-imidazole (10c). The crude reaction product, which was obtained in entry 12 of Table 4 by Pd-catalyzed reaction of **7** with **2c**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **10c** (92 mg, 45%) as a yellow-orange solid: m.p. 169-171 °C. EI-MS *m*/*z* 203 (100), 173 (19), 130 (17), 103 (16), 89 (32). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30 (m, 2H), 7.63 (s, 1H), 7.61 (m, 2H), 7.28 (s, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 146.7, 140.1, 136.2, 131.3, 130.2, 128.1 (2C), 124.1 (2C), 33.1 ppm. The spectral properties of this compound were in agreement with those previously reported.[33]

1-Methyl-5-*o*-tolyl-1*H*-imidazole (10d). The crude reaction product, which was obtained in entry 13 of Table 4 by Pd-catalyzed reaction of **7** with **2d**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (98:2) as eluent to give **10d** (0.12 g, 68%) as a light brown oil. EI-MS *m*/*z* 172 (100), 171 (24), 144 (50), 131 (24) 130 (62). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.27 (m, 4H), 6.97 (s, 1H), 3.42 (s, 3H), 2.19 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 138.0, 137.8, 131.9, 131.0, 130.1, 129.0, 128.7 (2C), 127.9, 125.6 (2C), 31.6, 20.0 ppm. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.77; H, 6.99; N, 16.24.

4-(1-Methyl-1*H*-imidazol-5-yl)benzonitrile (10e). The crude reaction product, which was obtained in entry 14 of Table 4 by Pd-catalyzed reaction of **7** with **2j**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **10e** (0.13 g, 69%) as a light yellow solid: m.p. 148-151 °C. EI-MS *m*/*z* 159 (12), 158 (100), 130 (16), 116 (13), 103 (13), 89 (12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (m, 2H), 7.59 (s, 1H), 7.53 (m, 2H), 7.22 (s, 1H), 3.75 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.5, 134.3, 132.5 (2C), 131.6, 129.8, 128.3 (2C), 118.5, 111.2, 33.0 ppm. The spectral properties of this compound were in agreement with those previously reported.[10]

1-Methyl-5-phenyl-1*H*-imidazole (10f). The crude reaction product, which was obtained in entry 15 of Table 4 by Pd-catalyzed reaction of **7** with **2k**, was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96:4) as eluent to give **10f** (0.12 g, 75%) as a pale yellow oil. EI-MS *m*/*z* 158 (100), 130 (17) 116 (13), 103 (12), 89 (12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.32 (m, 5H), 7.01 (s, 1H), 3.58 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 139.1, 128.8, 128.7 (2C), 128.5 (2C), 128.1, 127.9, 127.0, 32.5 ppm. The spectral properties of this compound were in agreement with those previously reported.[16e]

5-(3,4-Dimethoxyphenyl)-2-phenyloxazole (Balsoxin) (11). To a flame-dried reaction vessel were added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Bu_4NOAc (0.60 g, 2.0 mmol). The reaction vessel was fitted with a silicon septum, was evacuated and back-filled with argon, and this sequence was repeated twice. DMA (5 mL), 4-bromo-1,2-dimethoxybenzene (**2l**) (0.14 mL, 0.22 g, 1.0 mmol), and oxazole (**5**) (72 mL, 76 mg, 1.1 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 70 °C under argon for 24 h. To the resulting deep orange solution were then sequentially added CuI (0.38 g, 2.0 mmol) and bromobenzene (**2k**) (0.16 mL, 0.24 g, 1.5 mmol) under a stream of argon. The reaction mixture was warmed up to 110 °C and stirred at this temperature for 8 h. After being cooled to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was basified with a few drops of aqueous NH_4OH, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70:30) as eluent. The chromatographic fractions containing the required compound were collected and concentrated to give **11** (0.11 g, 39%) as a light yellow solid: m.p. 97–98 °C. EI-MS *m*/*z* 282 (20), 281 (100), 266 (23), 238 (11), 107 (11). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.11 (m, 2H), 7.49 (m, 3H), 7.35 (s, 1H), 7.30 (dd, , *J* = 1.9 and 8.4 Hz, 1H), 7.20 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 160.5, 151.1, 149.3, 149.2, 130.1, 128.7, 127.4, 126.1, 122.1, 121.0, 117.2, 111.4, 107.3, 55.99, 55.95 ppm. The spectral properties of this compound were in agreement with those previously reported.[24c]

5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(pyridin-3-yl)oxazole (Texaline) (12). To a flame-dried reaction vessel were added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Bu_4NOAc (0.60 g, 2.0 mmol). The reaction vessel was fitted with a silicon septum, was evacuated and back-filled with argon, and this sequence was repeated twice. DMA (5 mL), 5-bromobenzo[*d*][1,3]dioxole (**2m**) (0.12 mL, 0.20 g, 1.0 mmol), and oxazole (**5**) (72 mL, 76 mg, 1.1 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 70 °C under argon for 48 h. To the resulting brown solution were then sequentially added CuI (0.38 g, 2.0 mmol) and 3-bromopyridine (**2n**) (0.15 mL, 0.24 g, 1.5 mmol) under a stream of argon. The reaction mixture was warmed up to 110 °C and stirred at this temperature for 24 h. After being cooled to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was basified with a few drops of aqueous NH_4OH, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (50:50) as eluent. The chromatographic fractions containing the required compound were collected and concentrated to give **12** (0.10 g, 38%) as a light yellow solid: m.p. 167–169 °C. EI-MS *m*/*z* 267 (16), 266 (100), 181 (11), 153 (27), 63 (9). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.30 (br s, 1H), 8.67 (d, *J* = 3.7 Hz, 1H), 8.31 (dt, *J* = 8.0 and 1.9 Hz, 1H), 7.40 (dd, *J* = 8.0 and 4.8 Hz 1H), 7.32 (s, 1H), 7.22 (dd, *J* = 8.1 and 1.7 Hz, 1H), 7.14 (d, *J* =1.6 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 158.2, 152.0, 150.9, 148.4, 148.3, 147.5, 133.3, 123.8, 123.7, 122.6, 121.8, 118.7, 109.0, 105.0, 101.6 ppm. The spectral properties of this compound were in agreement with those previously reported.[24c]

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **3a–h**, **4a**, **8a–e**, **9a–d**, **10a–f**, **11** and **12**.

Acknowledgments

We thank the University of Pisa for financial support.

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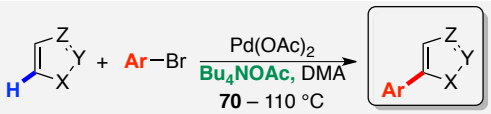
Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

Entry for the Table of Contents

Direct C–H Arylation of Azoles



In the presence of Bu_4NOAc and $Pd(OAc)_2$ 1-methylpyrazole, oxazole and thiazole were regioselectively arylated at their C5 position with aryl bromides at only 70 °C, while the parent 1-methylimidazole required 110 °C to react. This simple ligand-free reaction system was applied to a one-pot sequential C5 and C2 direct arylations of oxazole to give the two natural products balsoxin and texaline.

Fabio Bellina,* Marco Lessi and Chiara Manzini ……..... Page No. – Page No.

Mild Palladium-Catalyzed Regioselective Direct Arylation of Azoles Promoted by Tetrabutylammonium Acetate

Keywords: C–C coupling / Direct Arylation / Azoles / Palladium / Regioselectivity

Mild Palladium-Catalyzed Regioselective Direct Arylation of Azoles Promoted by Tetrabutylammonium Acetate

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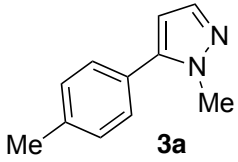
Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, 56125 Pisa, Italy

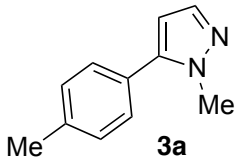
SUPPORTING INFORMATION

^{1}H NMR, 200 MHz
Solv. $CDCl_3$



3a

^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



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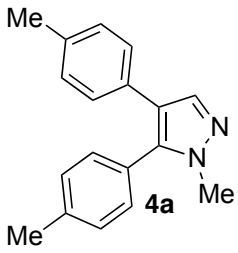
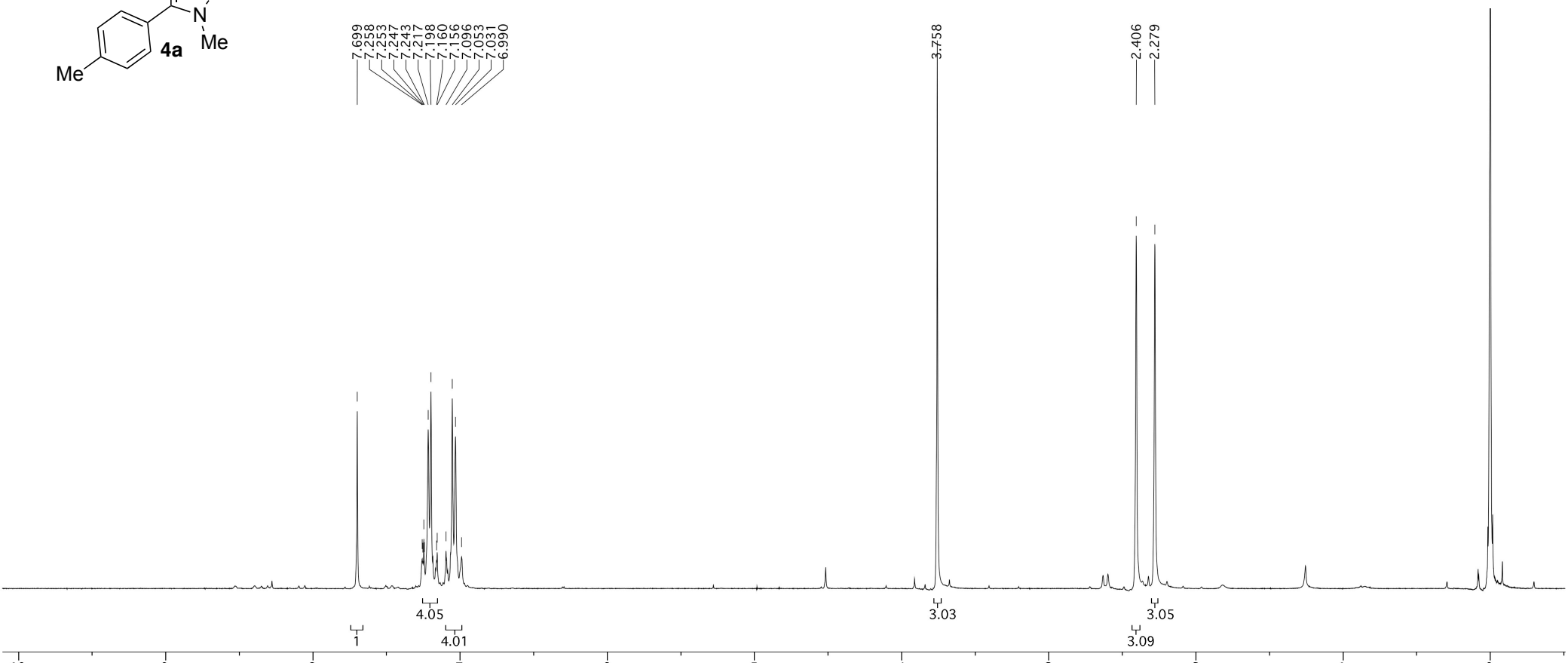
Solv. $CDCl_3$



4a



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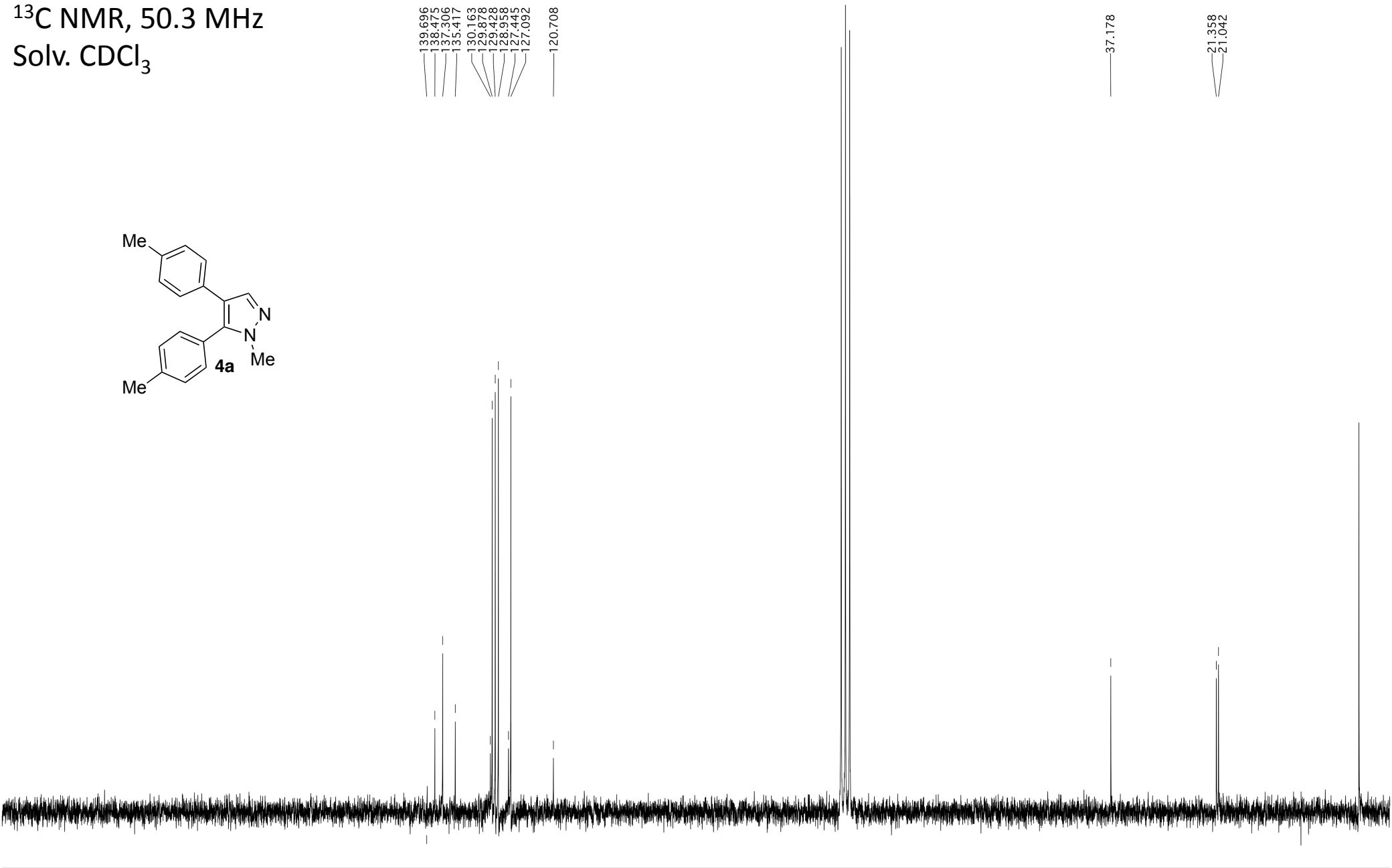
Solv. $CDCl_3$



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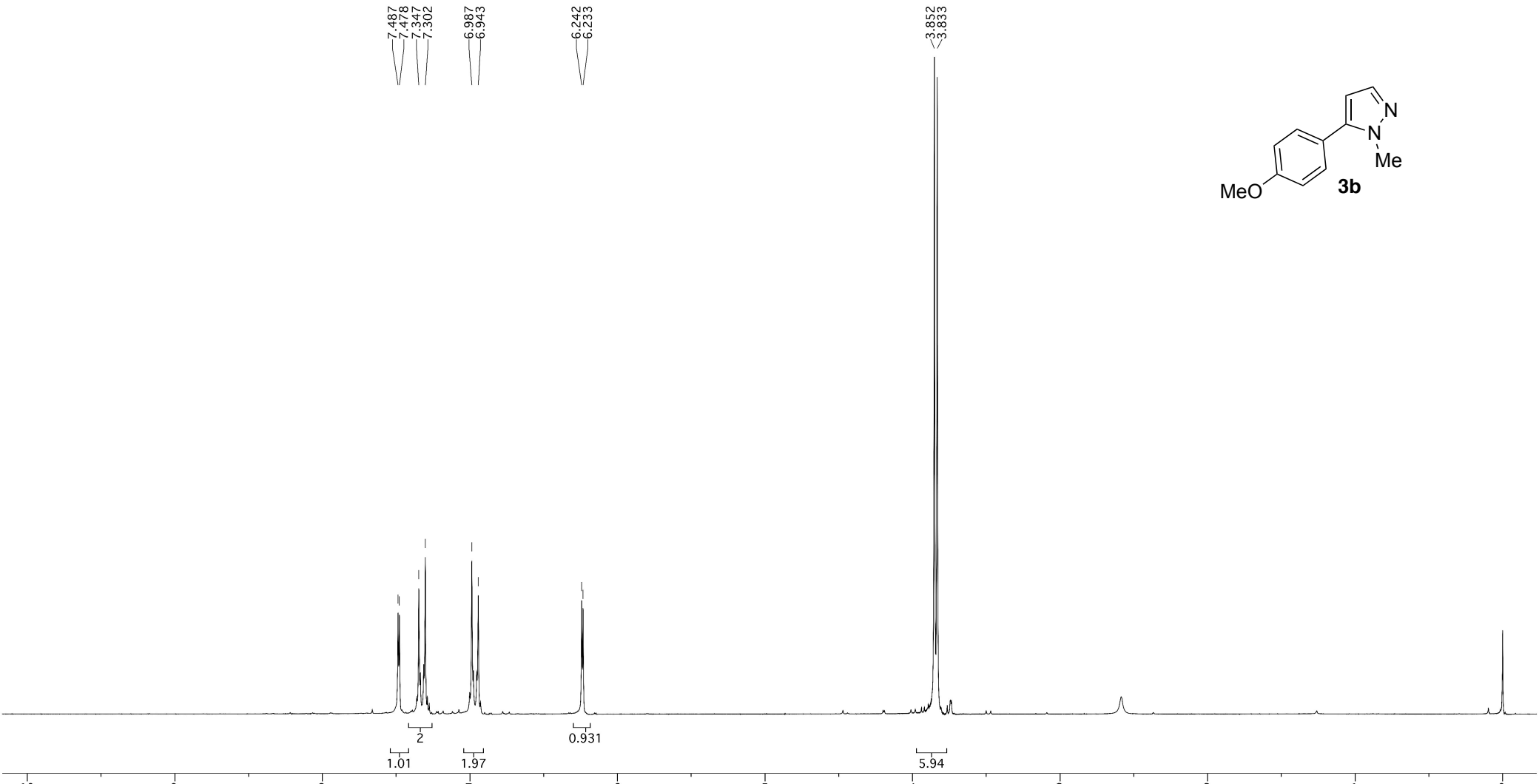

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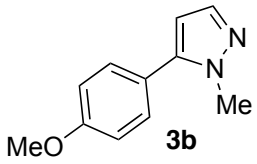

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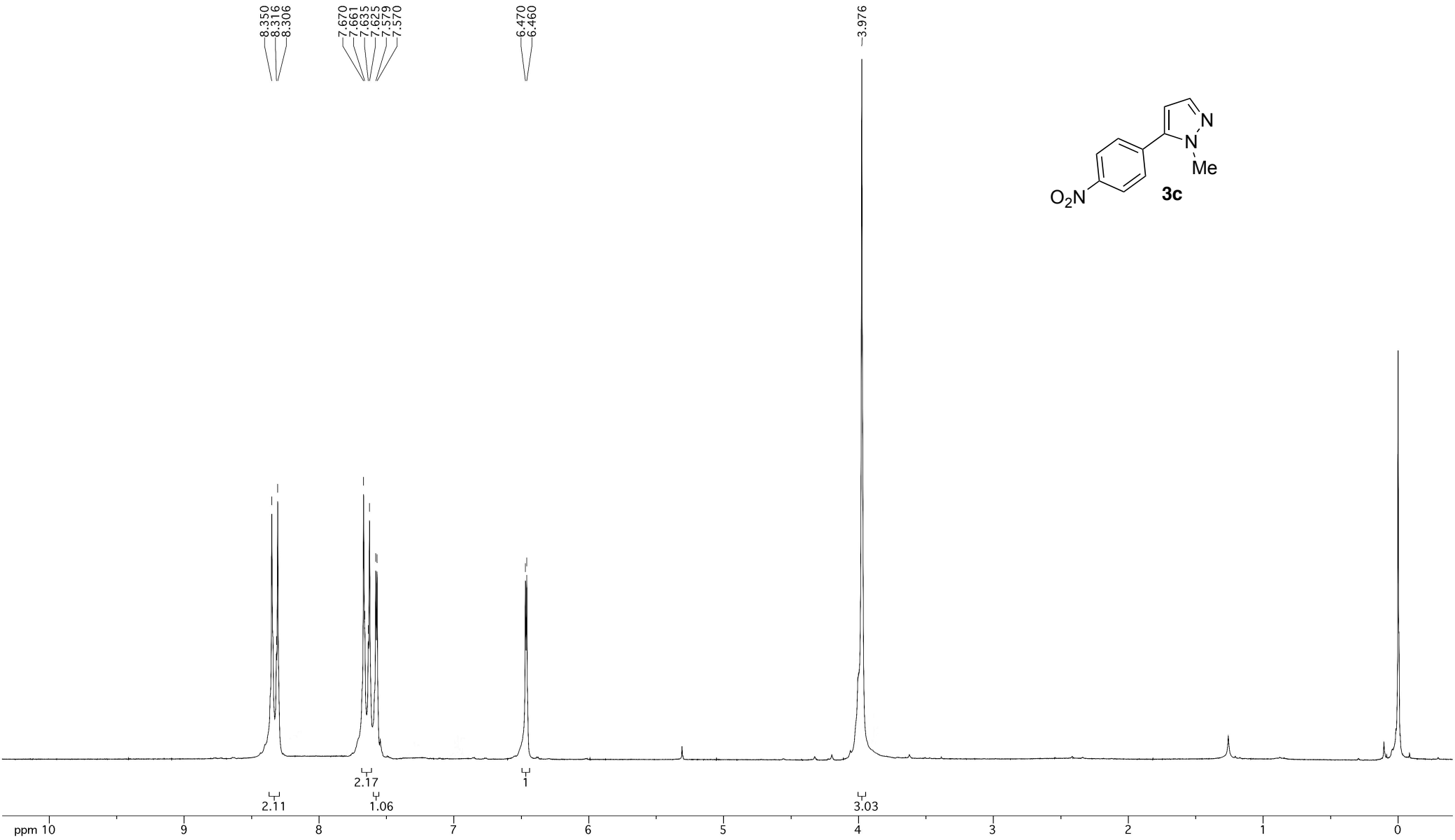

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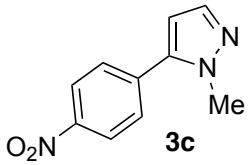
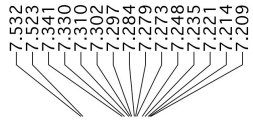
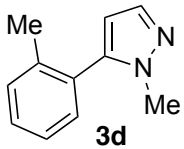


3c

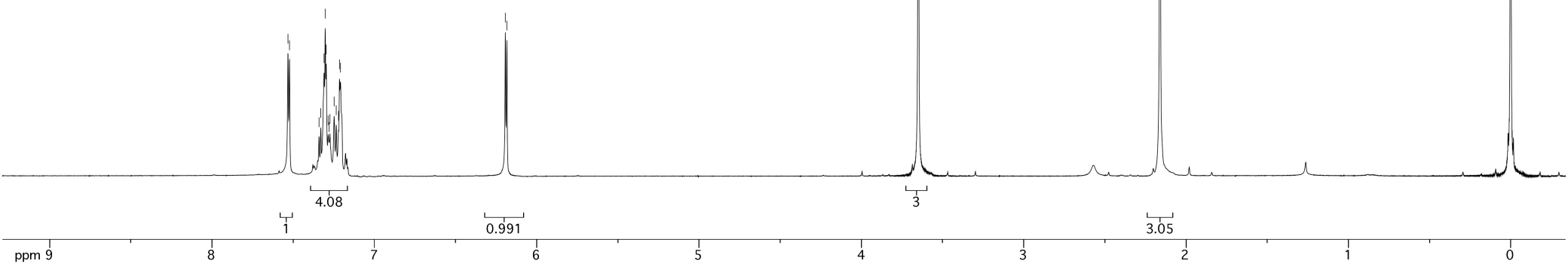
^{1}H NMR, 200 MHz

Solv. $CDCl_3$





3d



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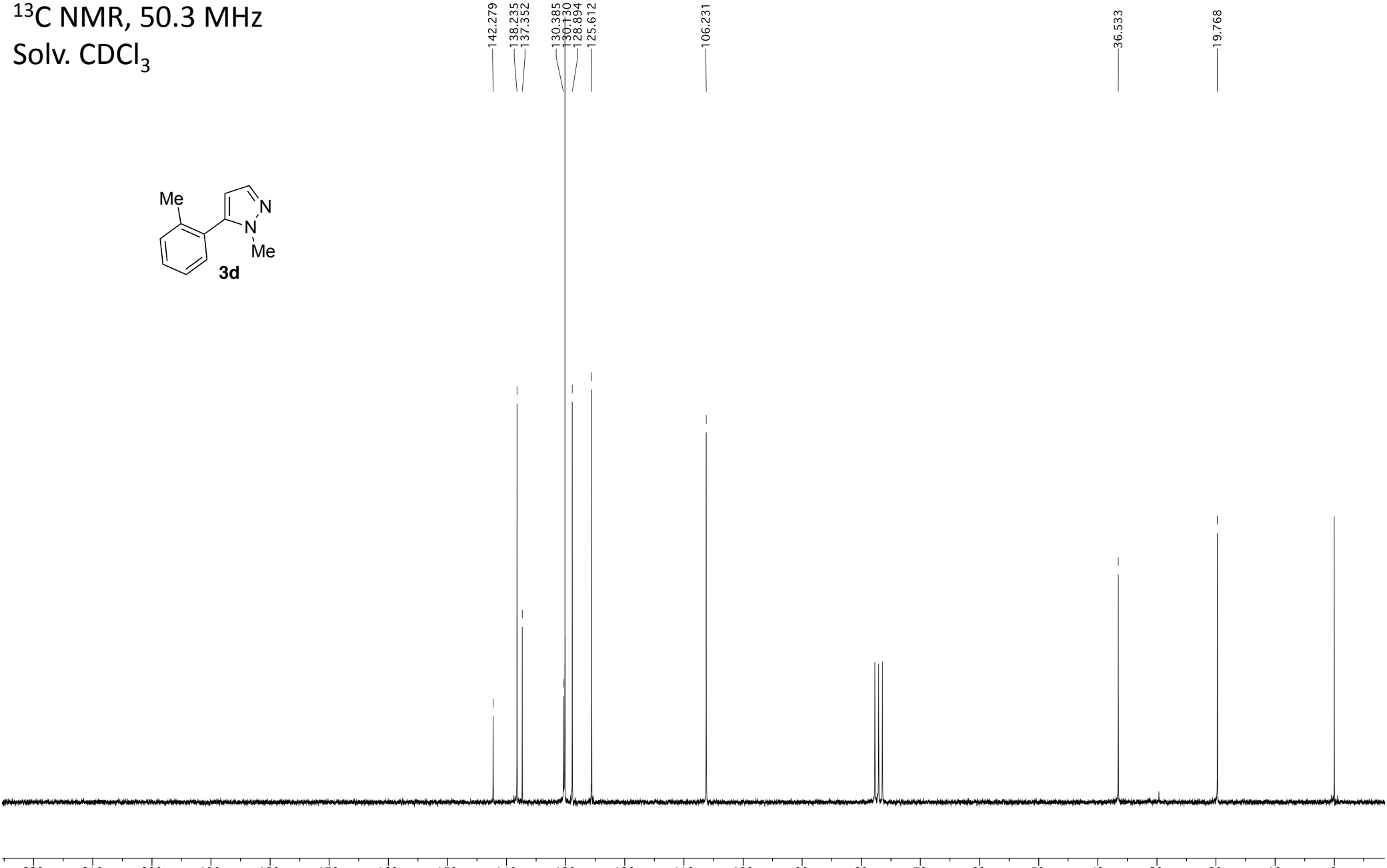

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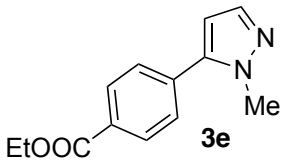

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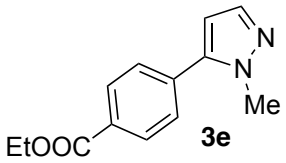

3e

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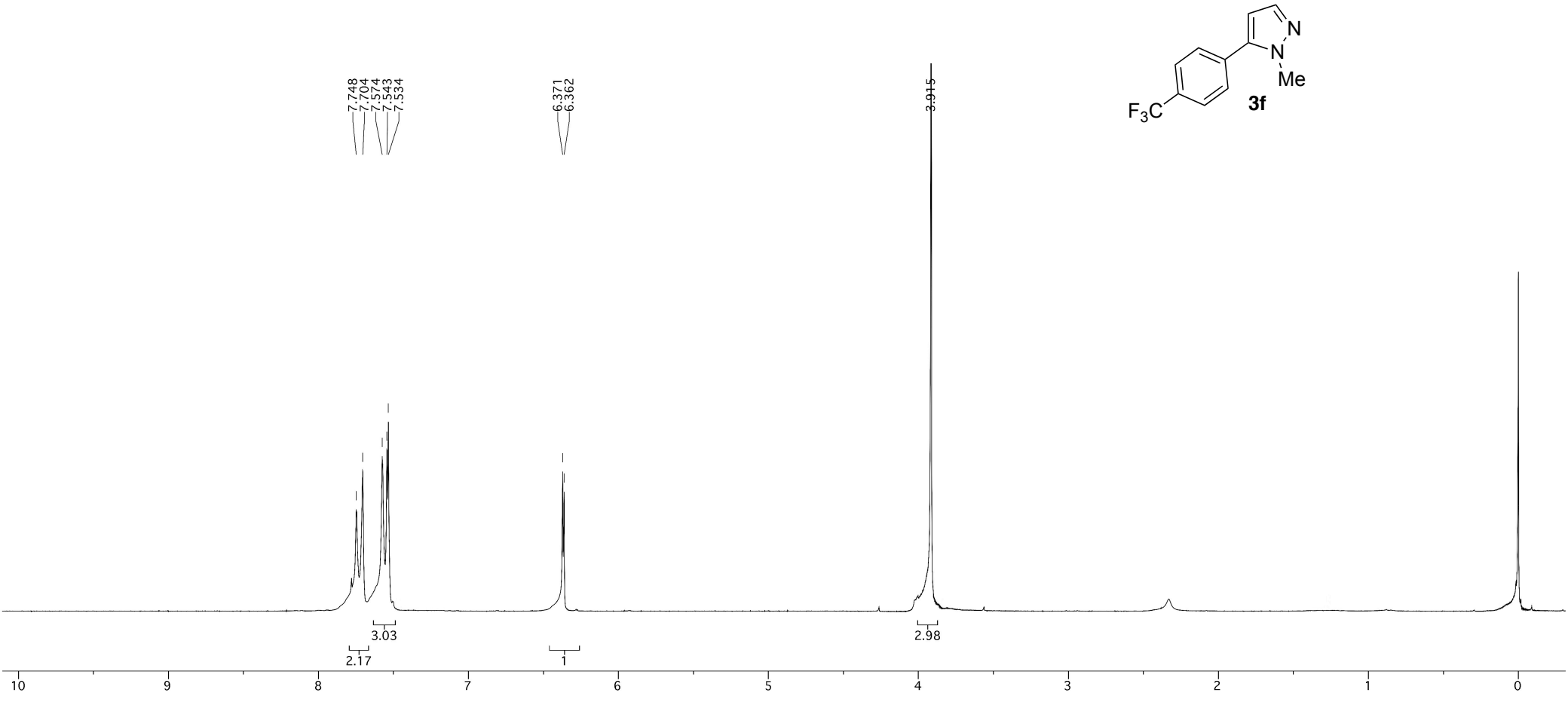

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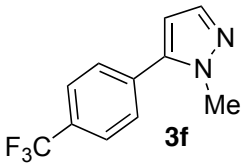

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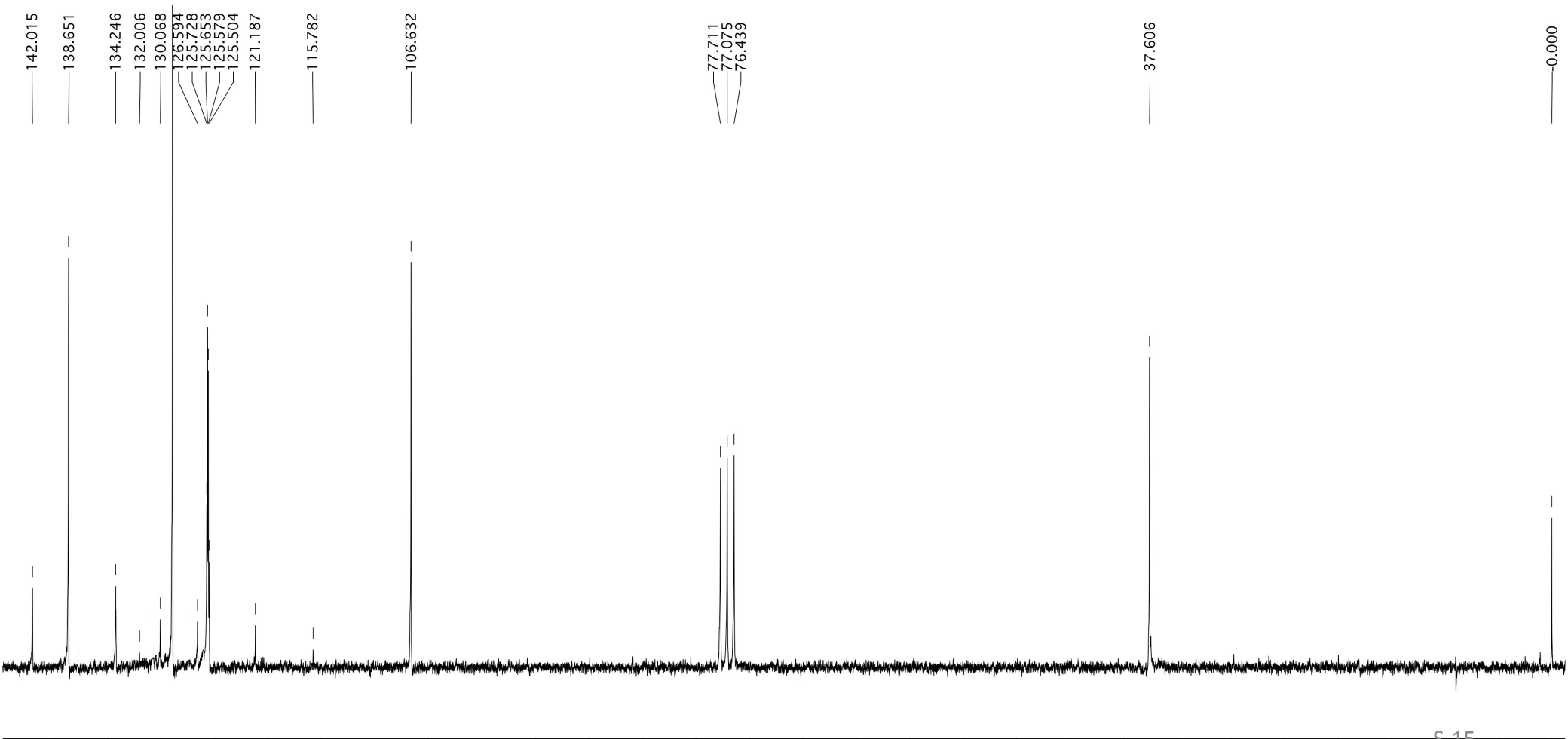

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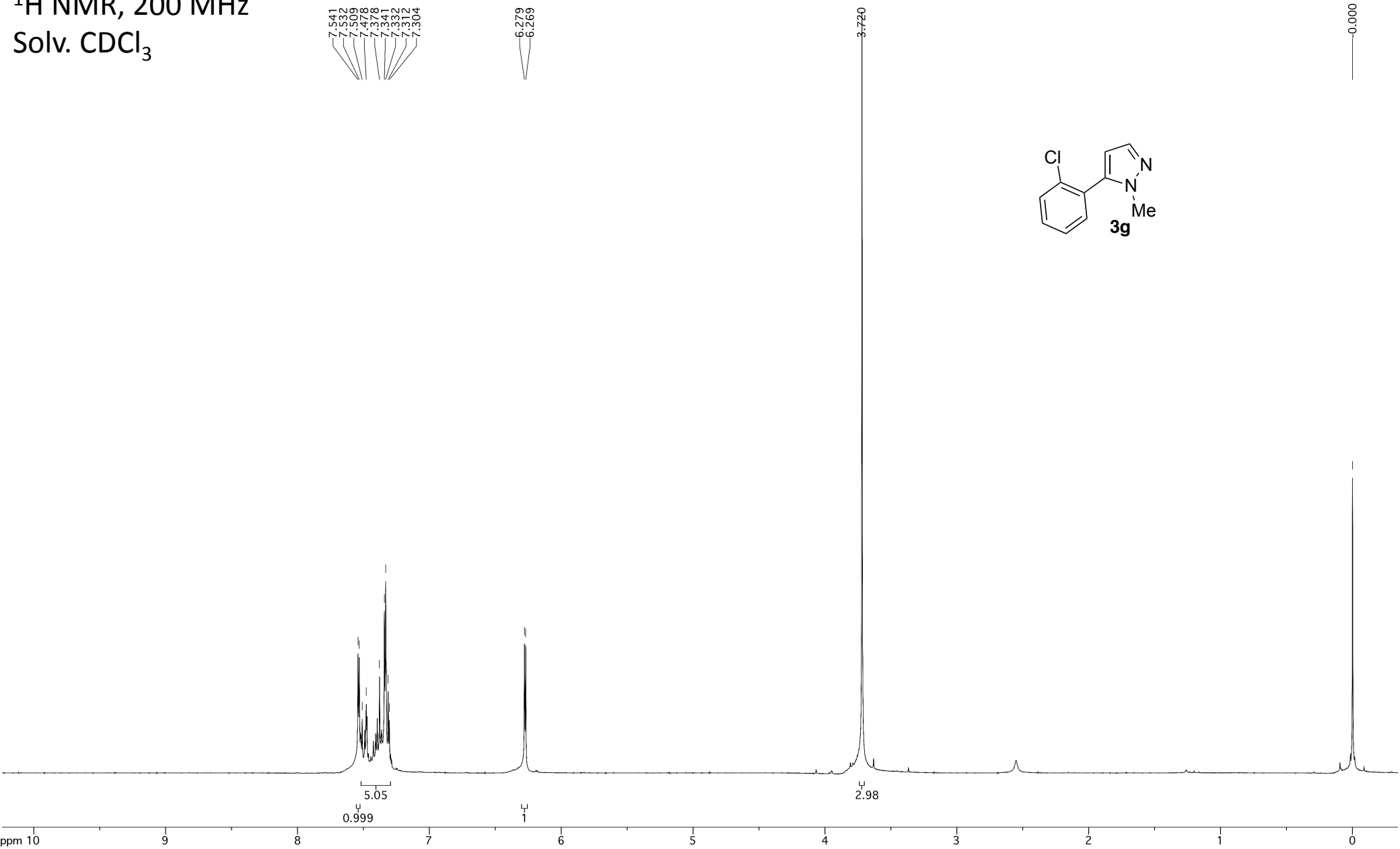

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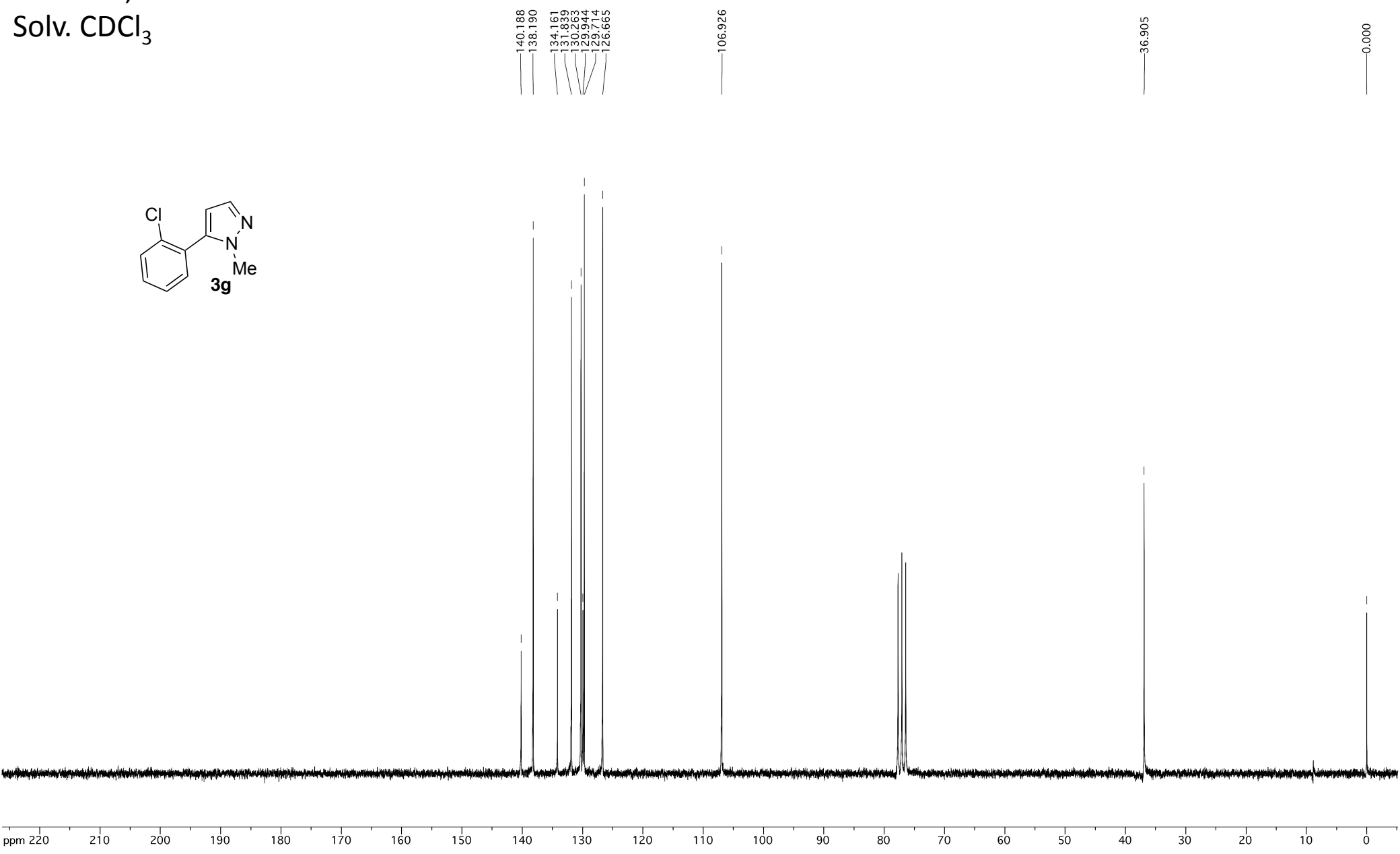
Solv. $CDCl_3$



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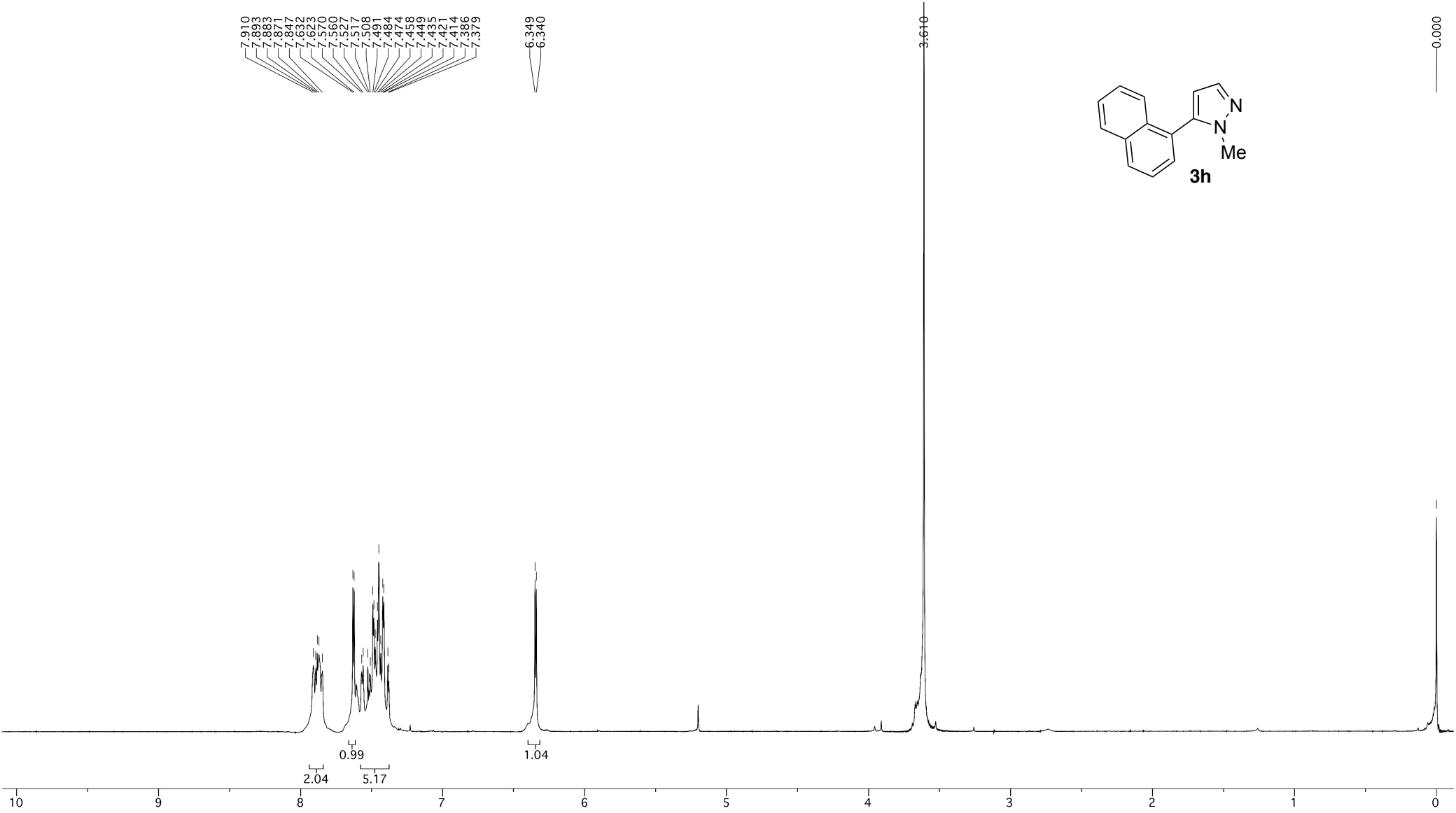

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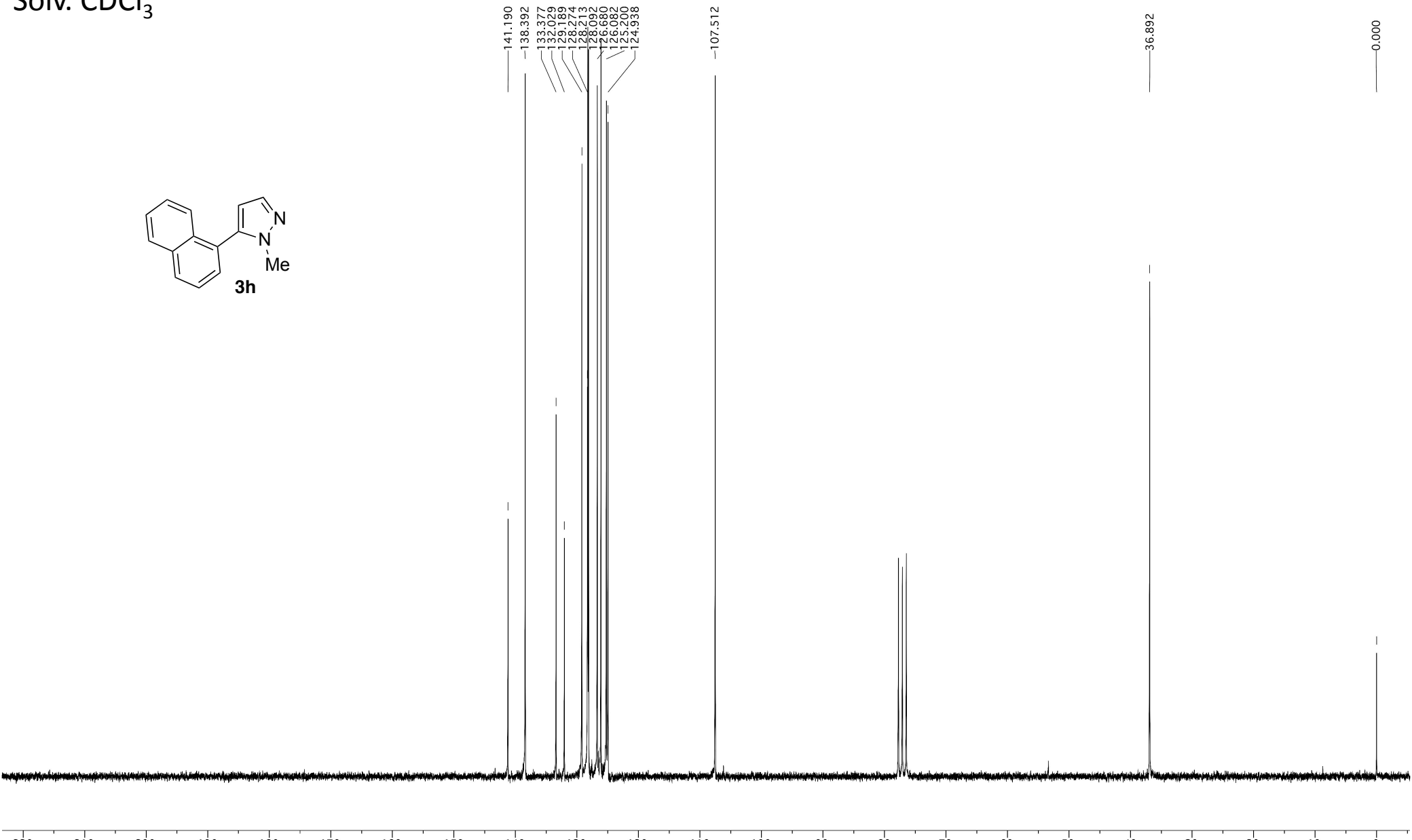

3h

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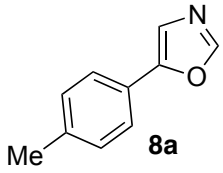
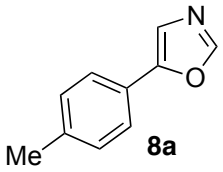


8a

^{1}H NMR, 200 MHz
Solv. $CDCl_3$



8a

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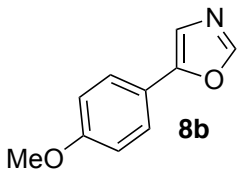
Solv. $CDCl_3$



8b

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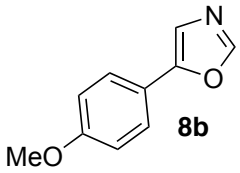
Solv. $CDCl_3$



8b

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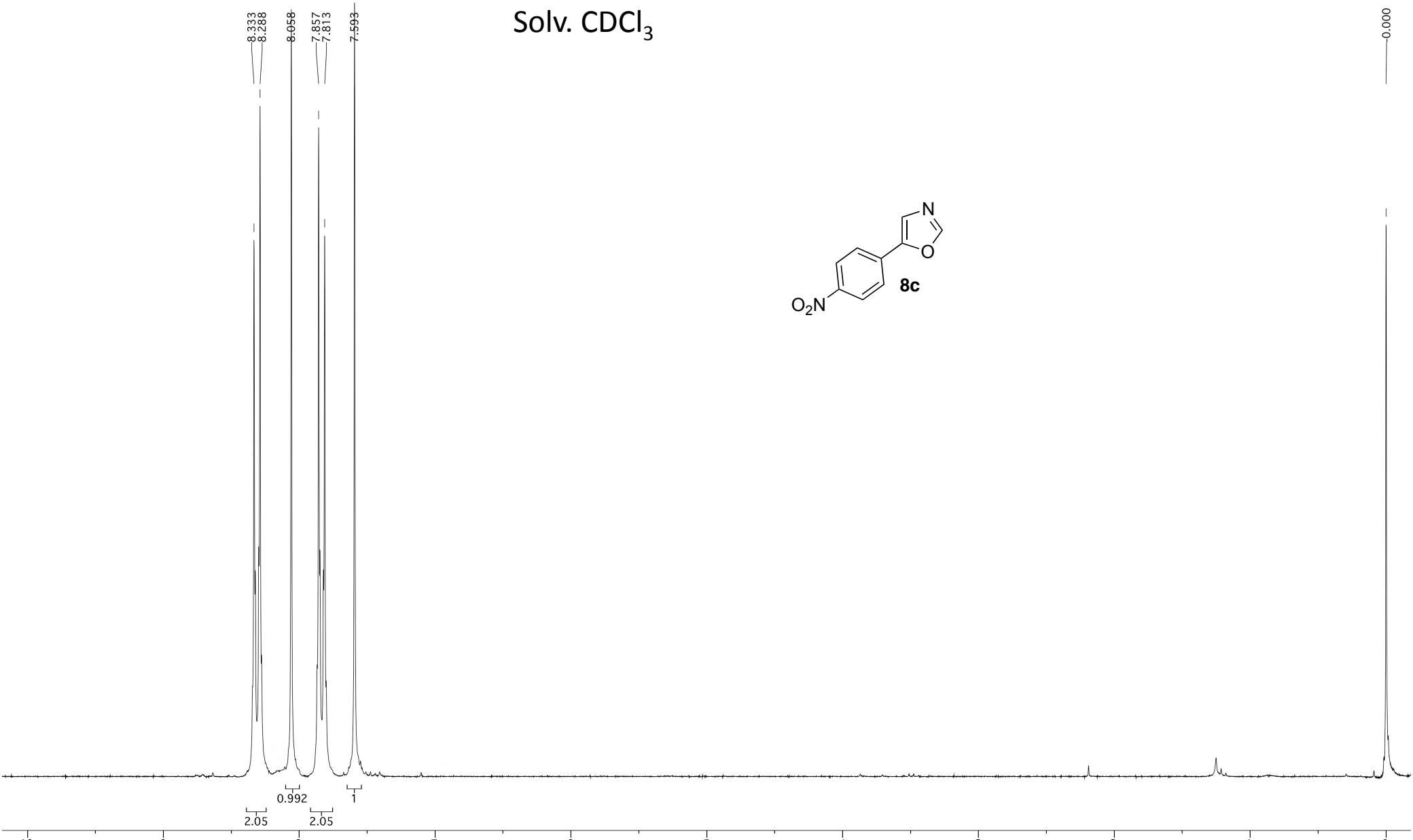

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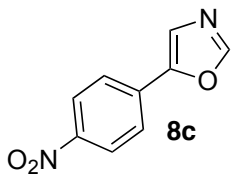

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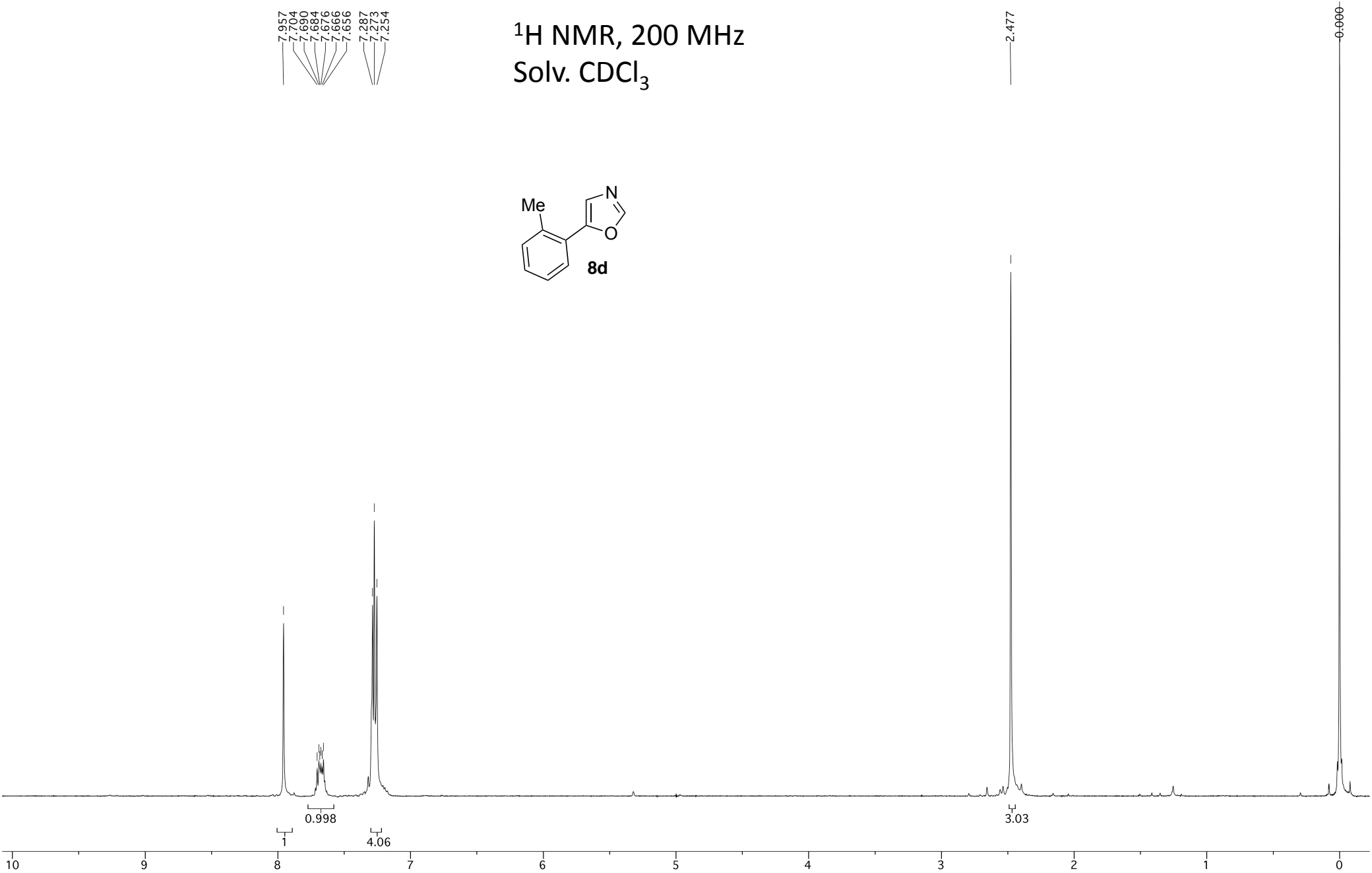

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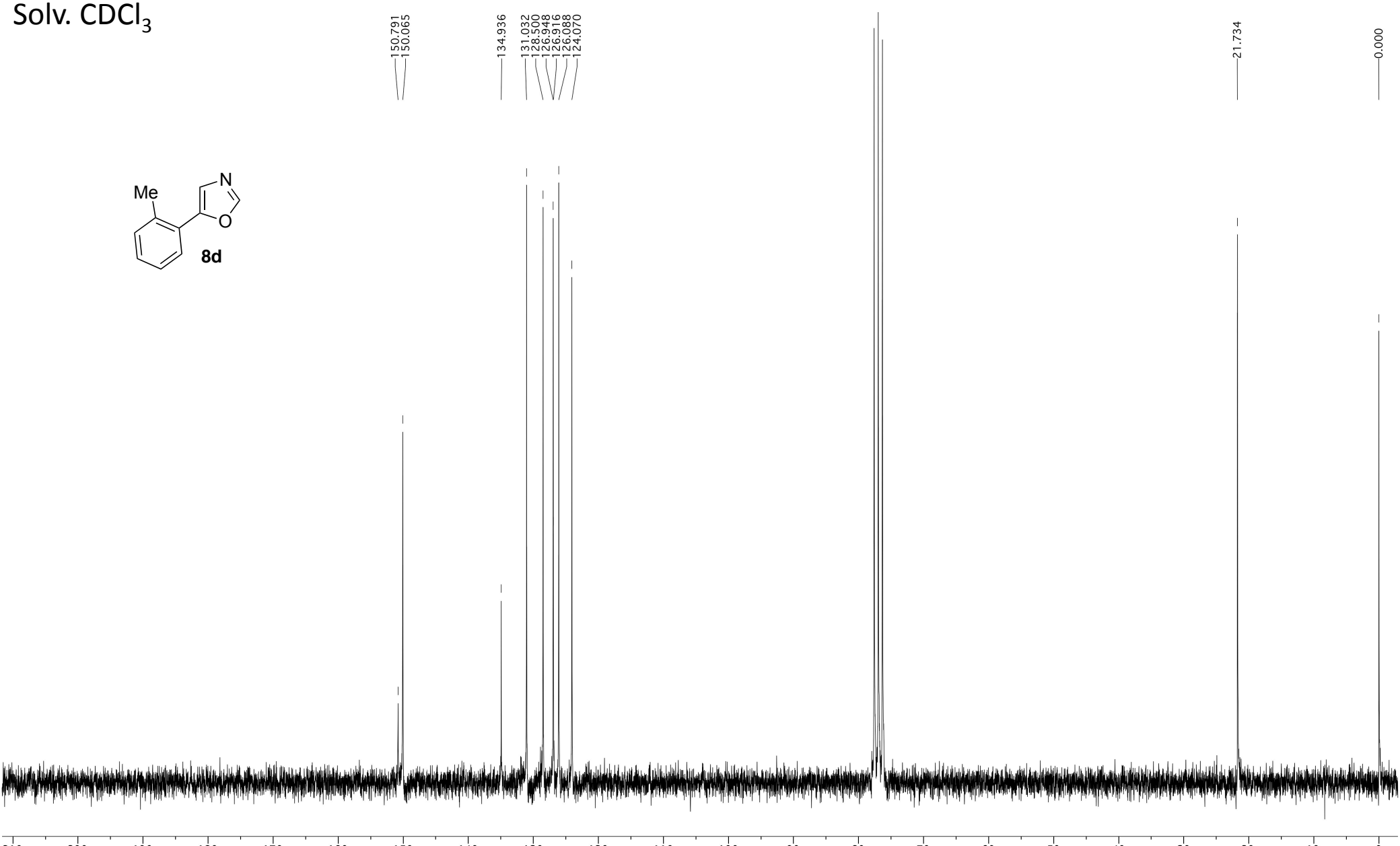
Solv. $CDCl_3$

^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



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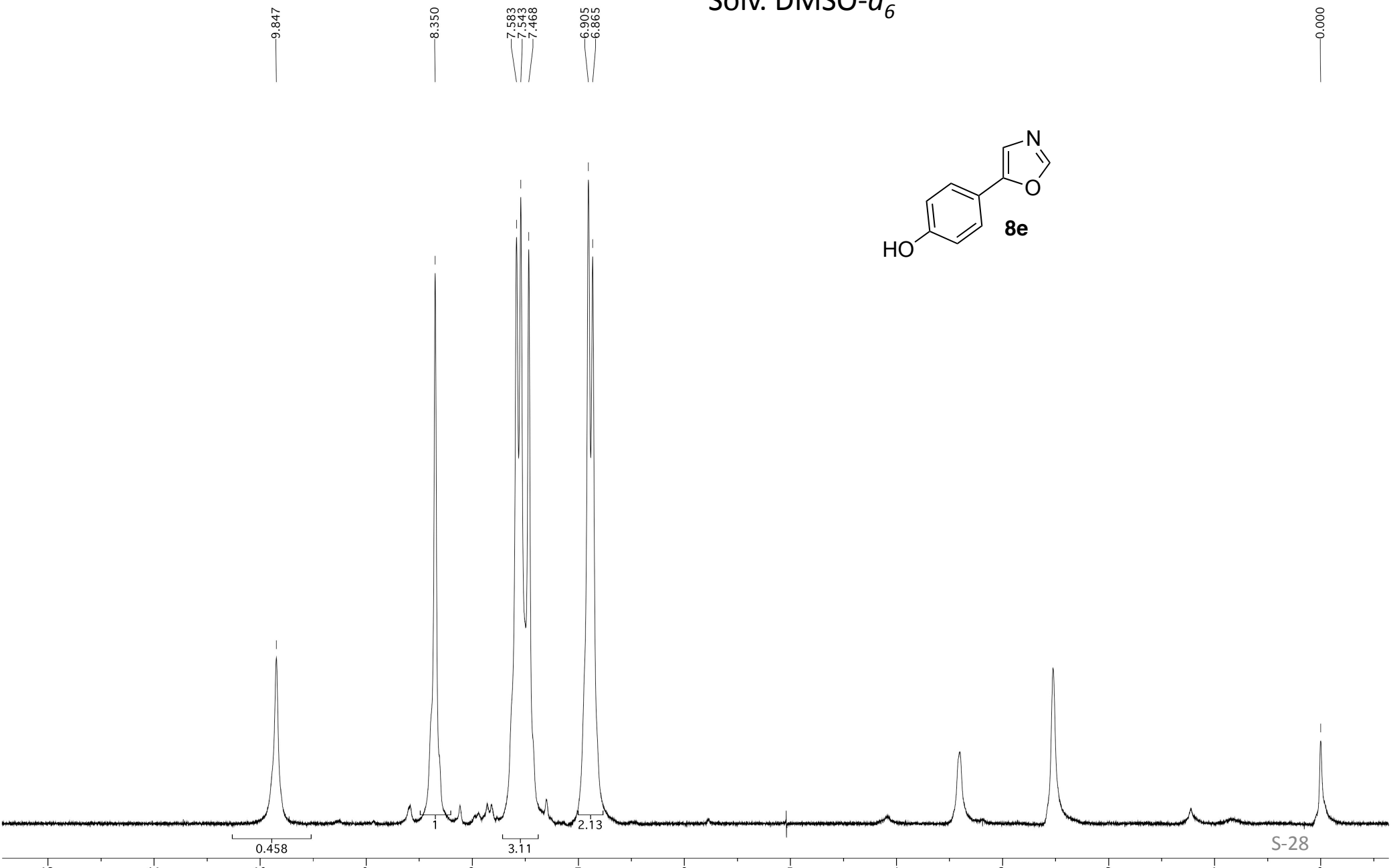

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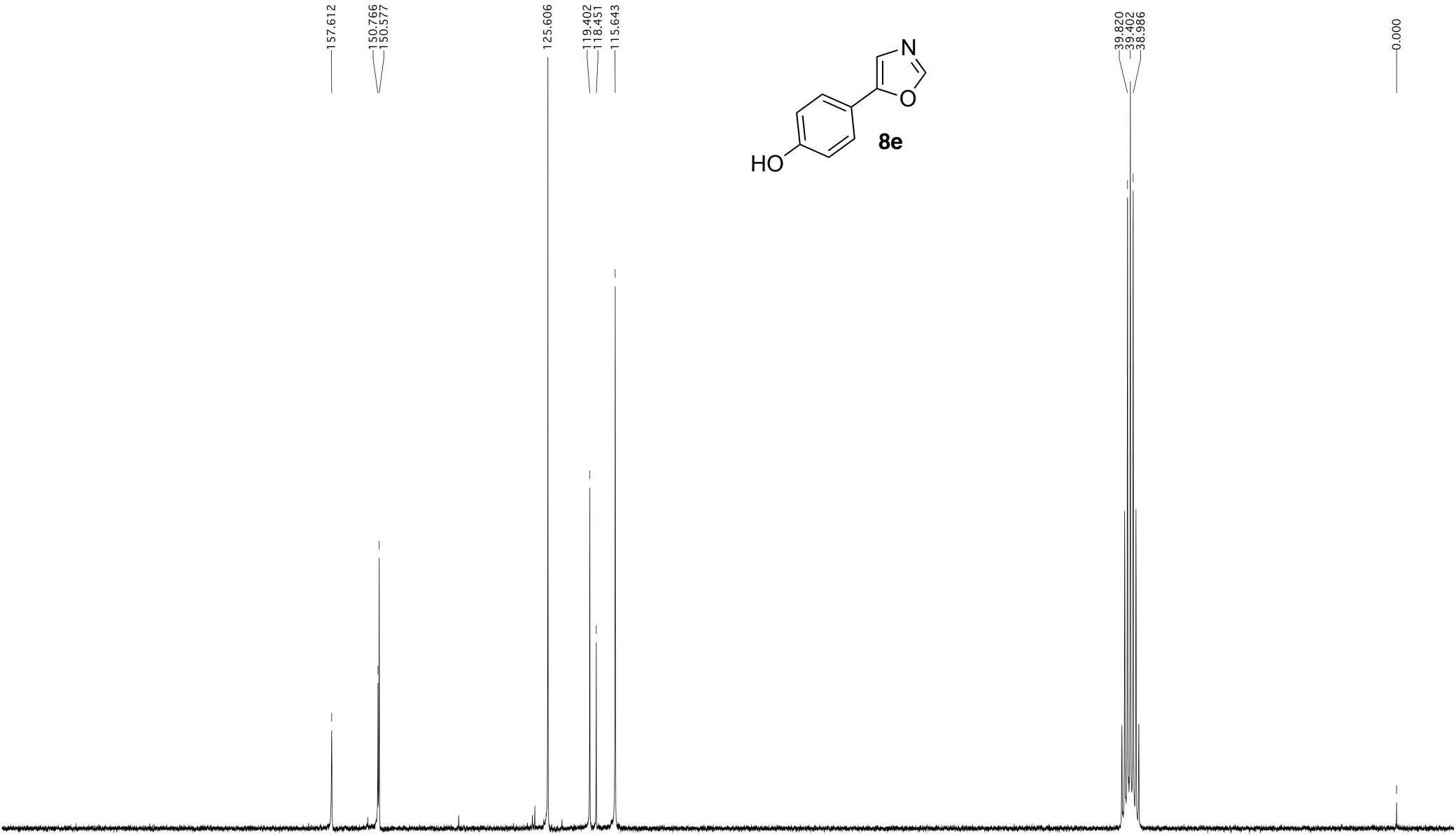
Solv. DMSO-d_6



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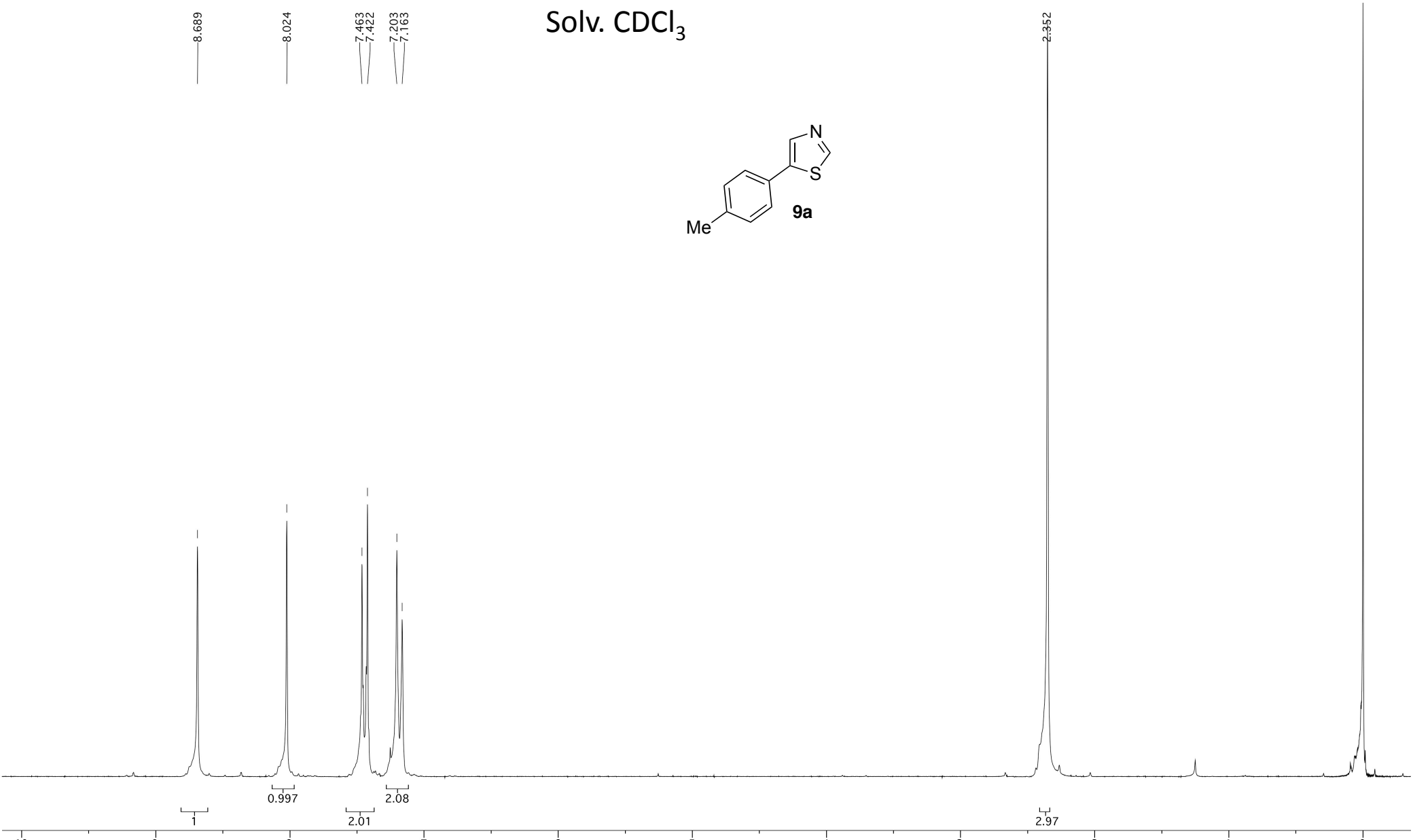

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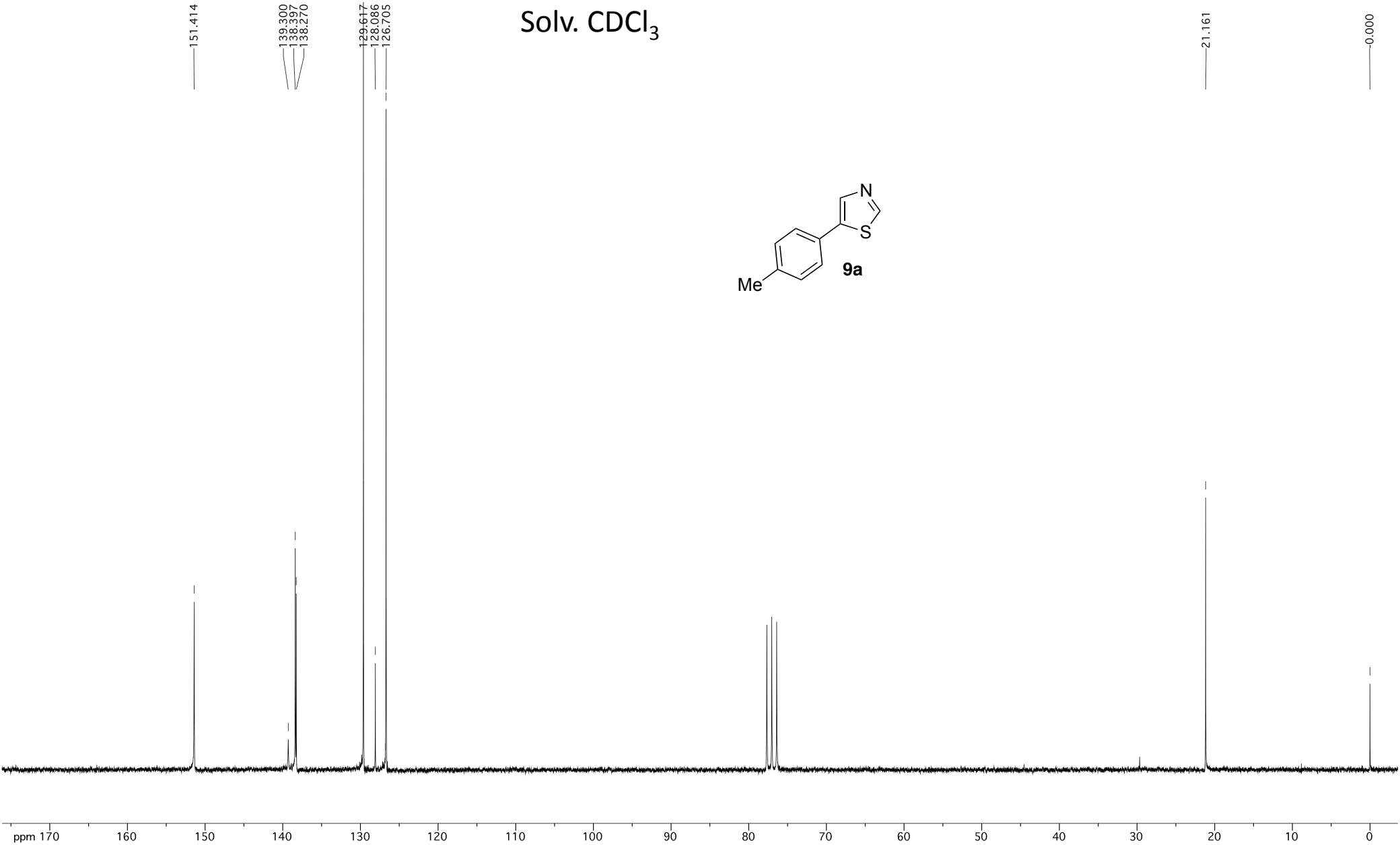

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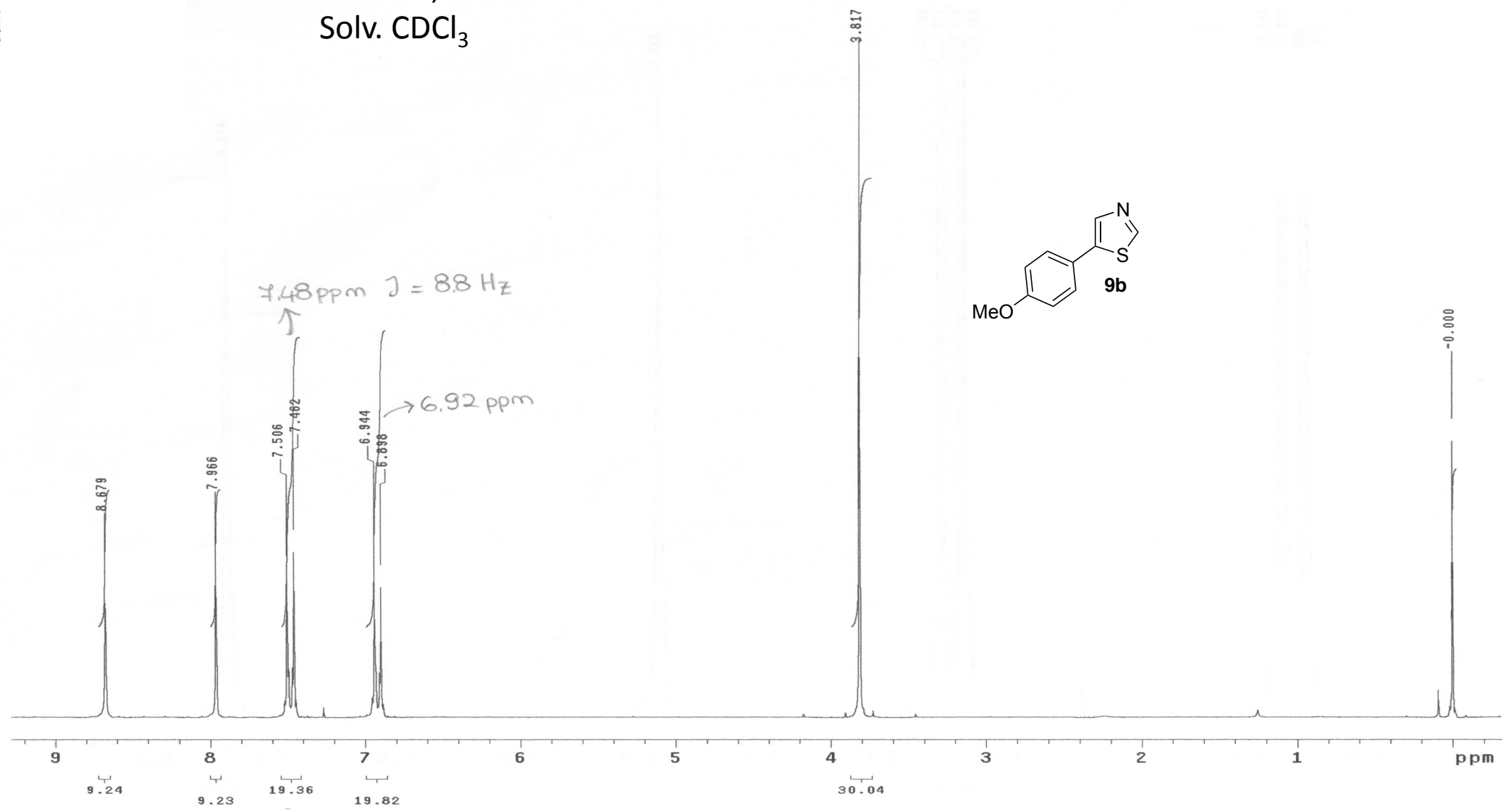

9b

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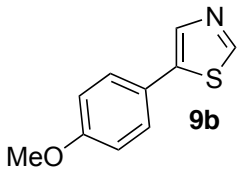

9b

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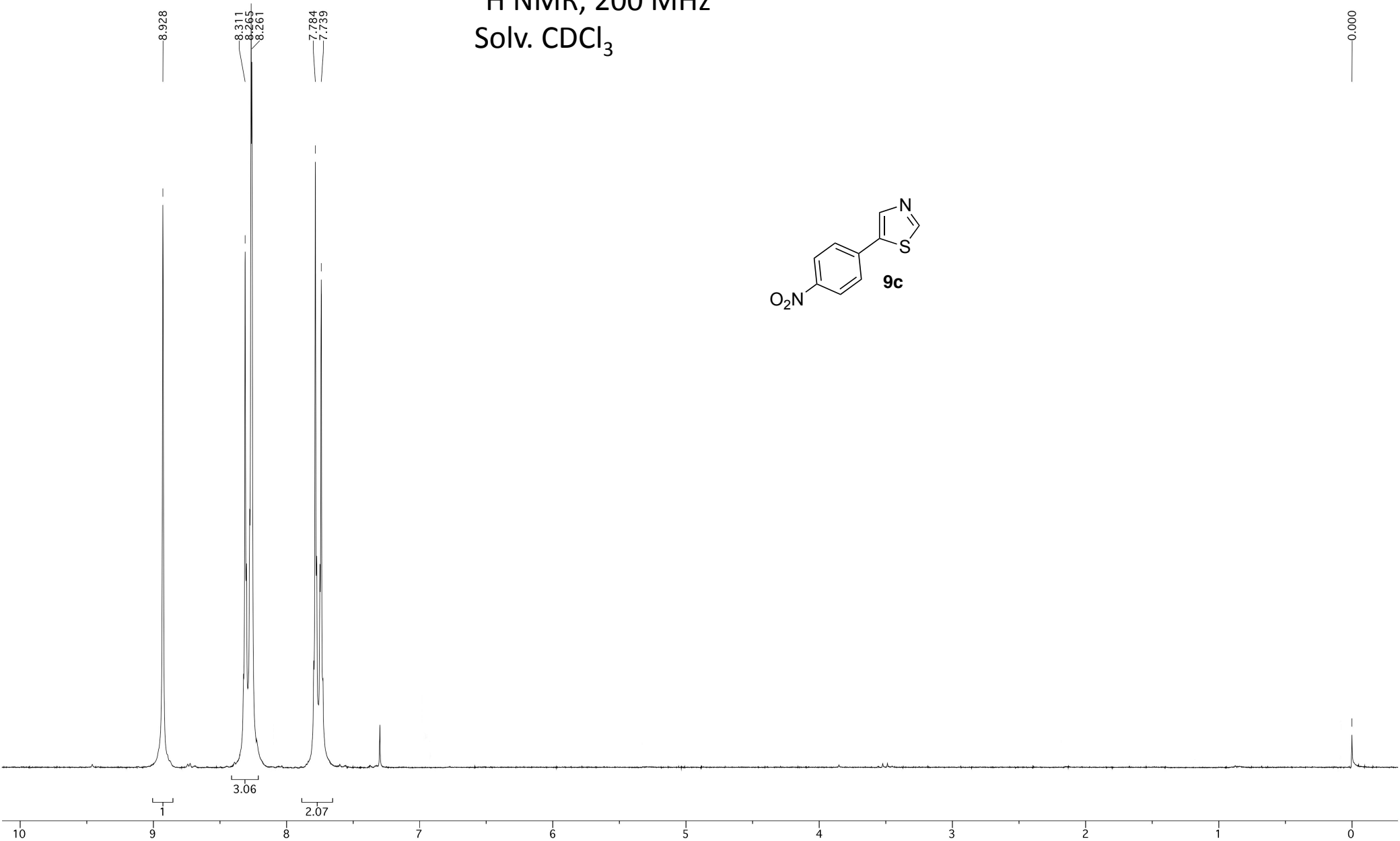
Solv. $CDCl_3$



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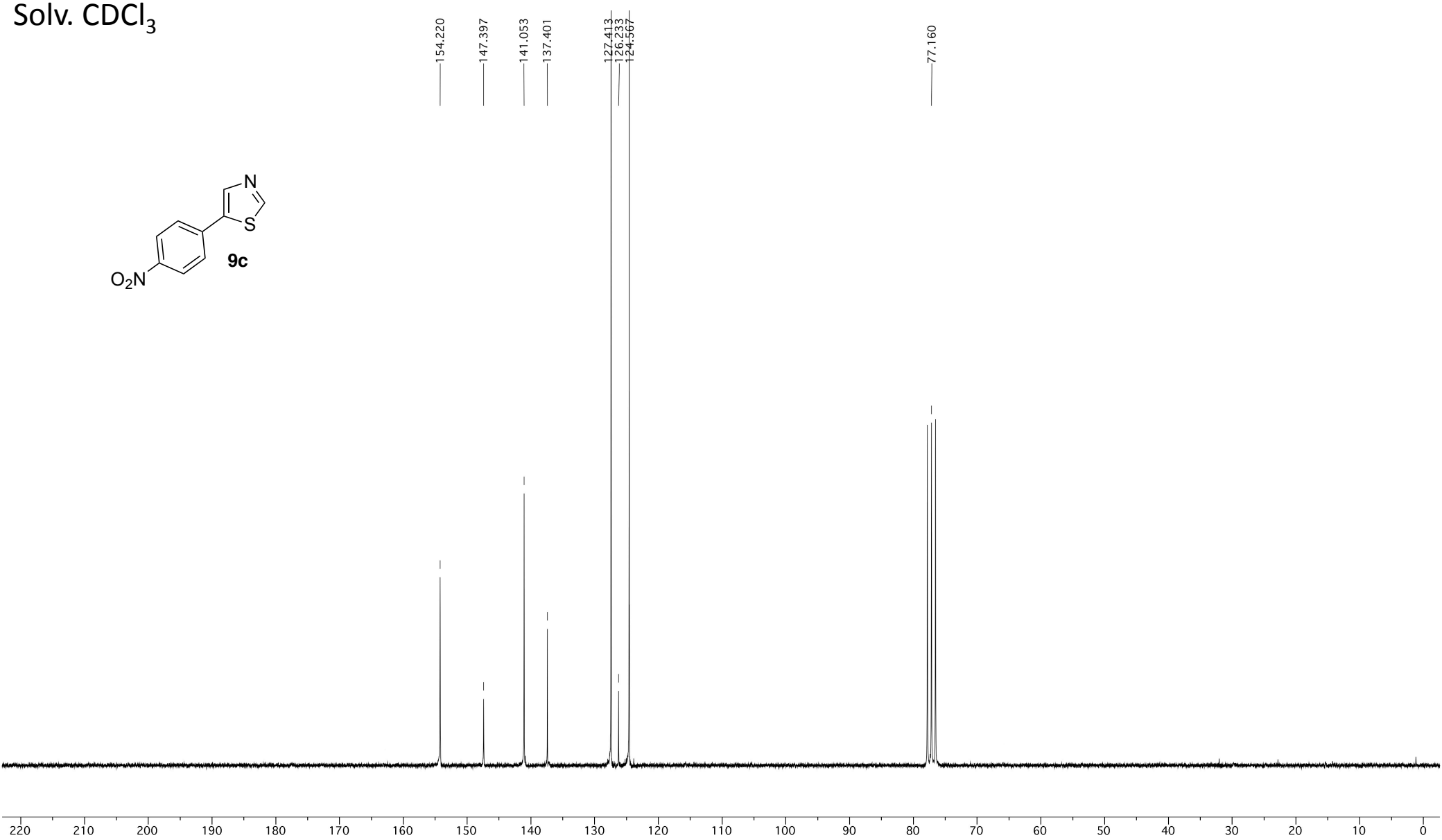

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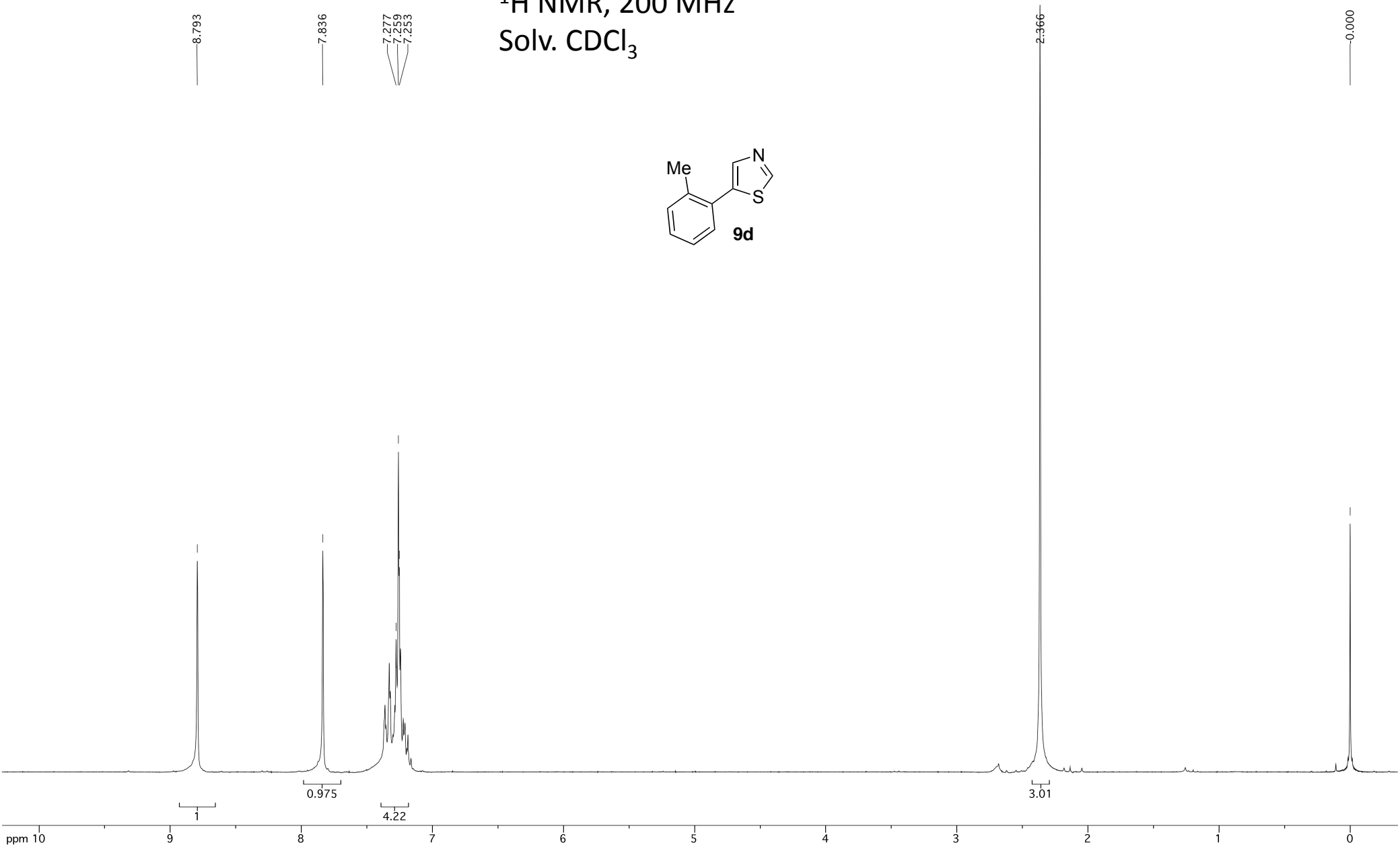

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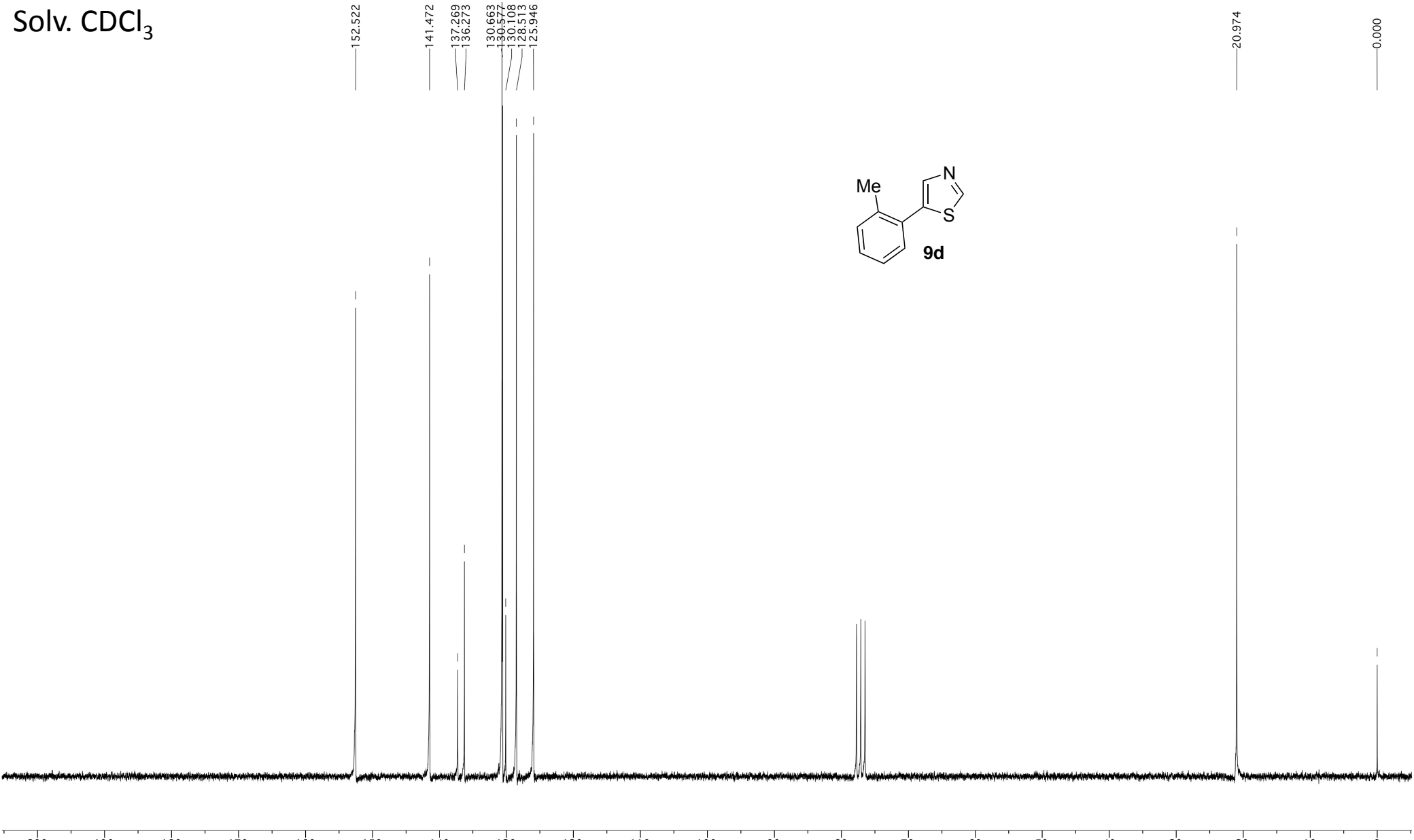

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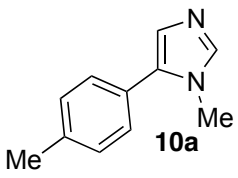

10a

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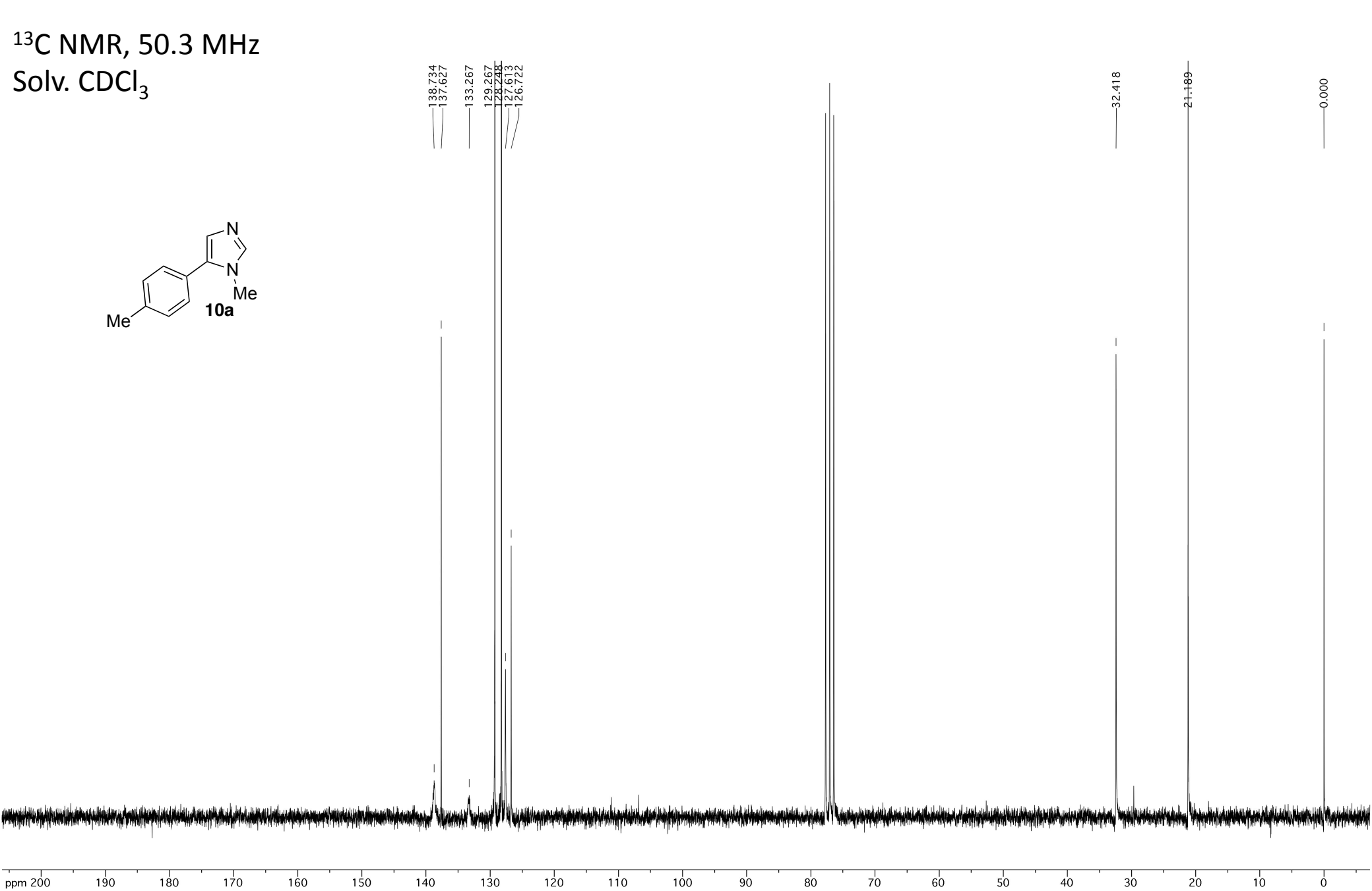

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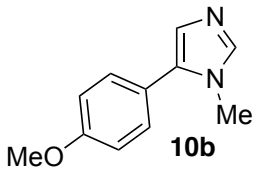

10b

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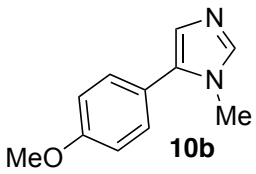

10b

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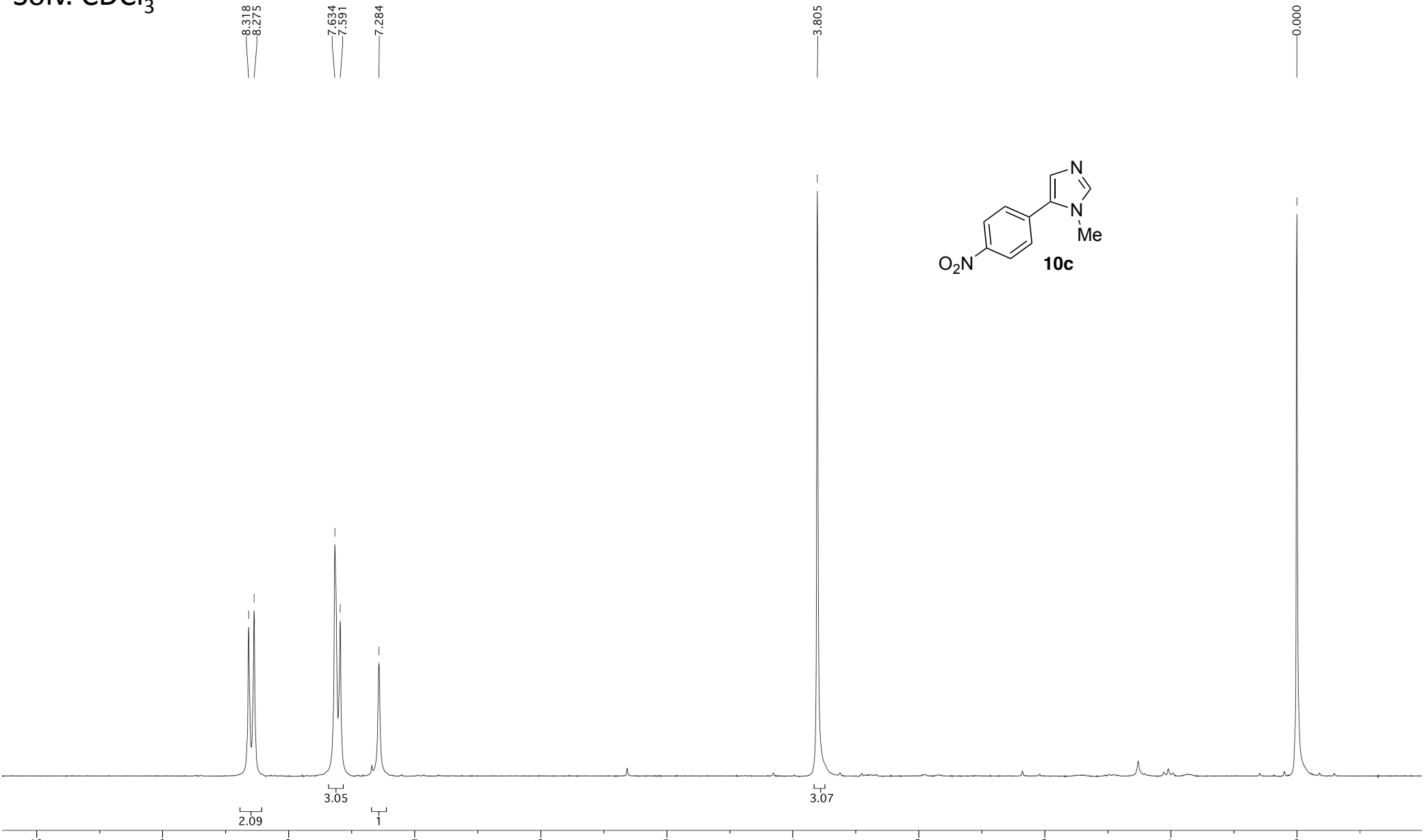
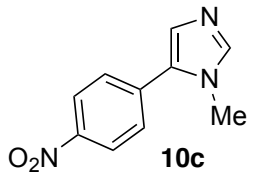
Solv. $CDCl_3$

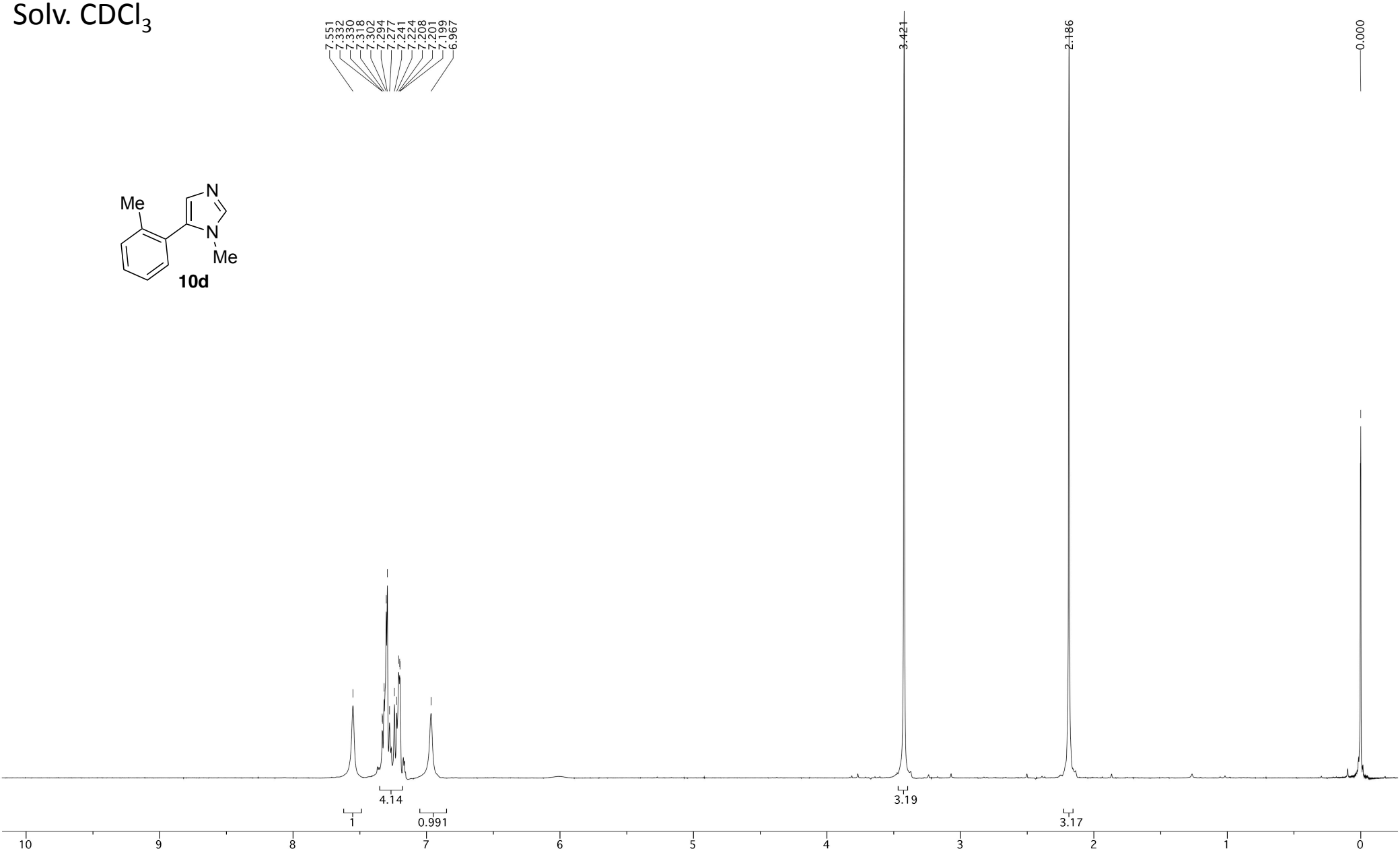


^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$

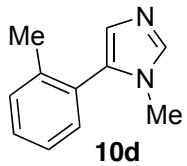


10c

^{1}H NMR, 200 MHz
Solv. $CDCl_3$

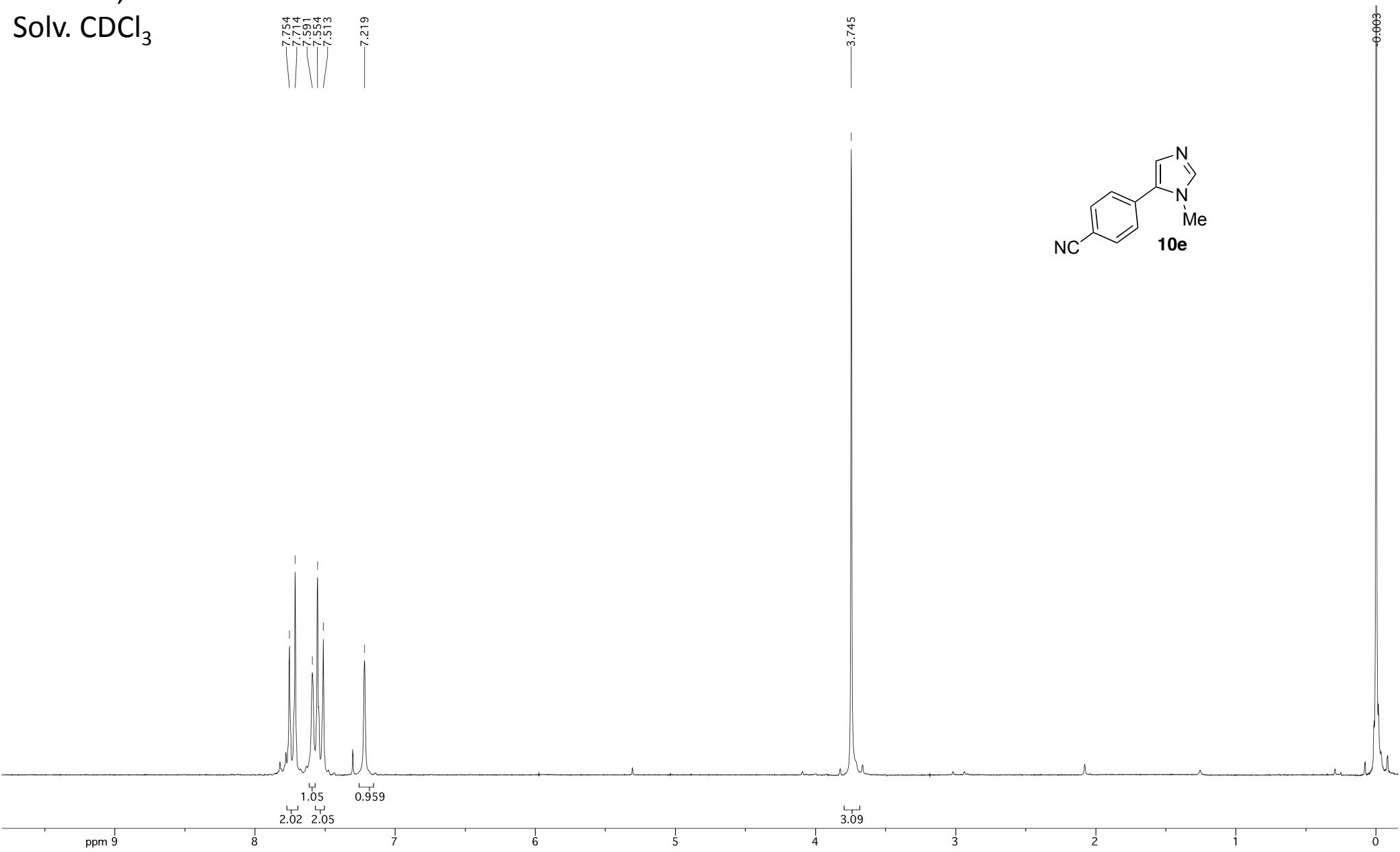


^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$

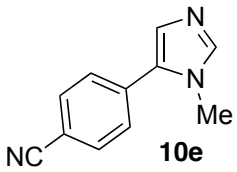


10d

^{1}H NMR, 200 MHz
Solv. $CDCl_3$

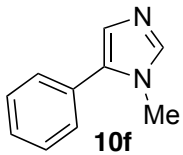


^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



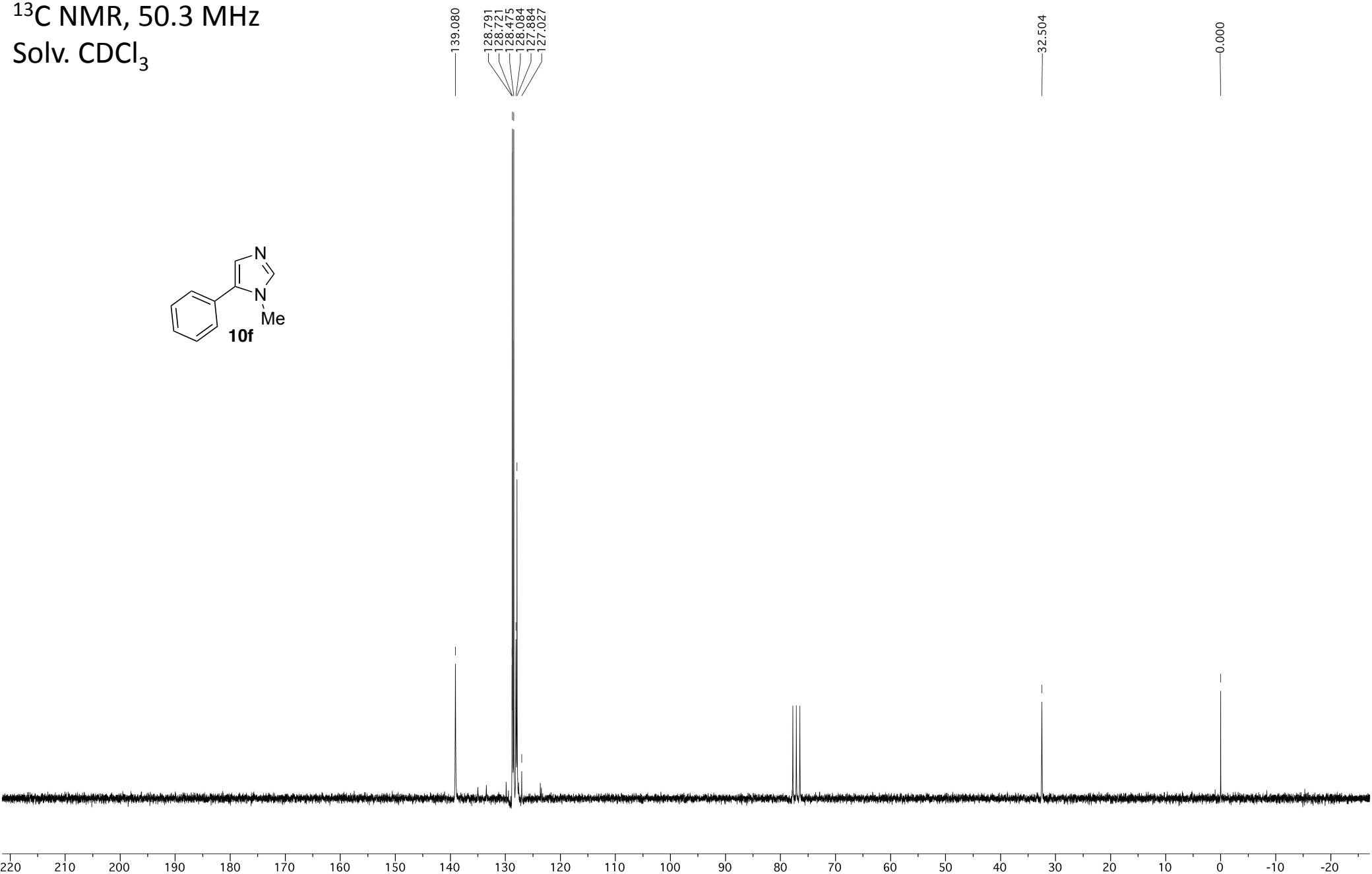
10e

^{1}H NMR, 200 MHz
Solv. $CDCl_3$

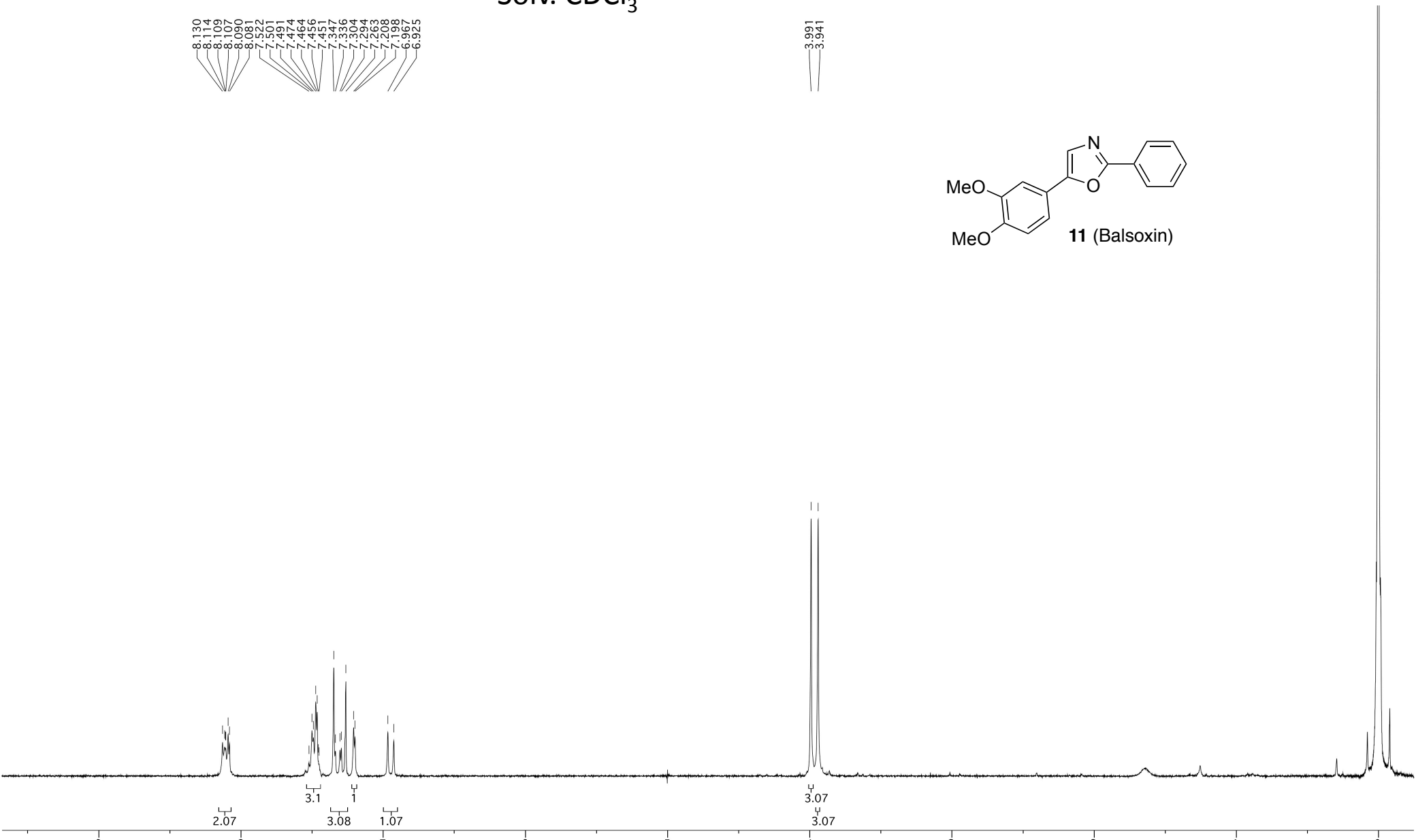


10f

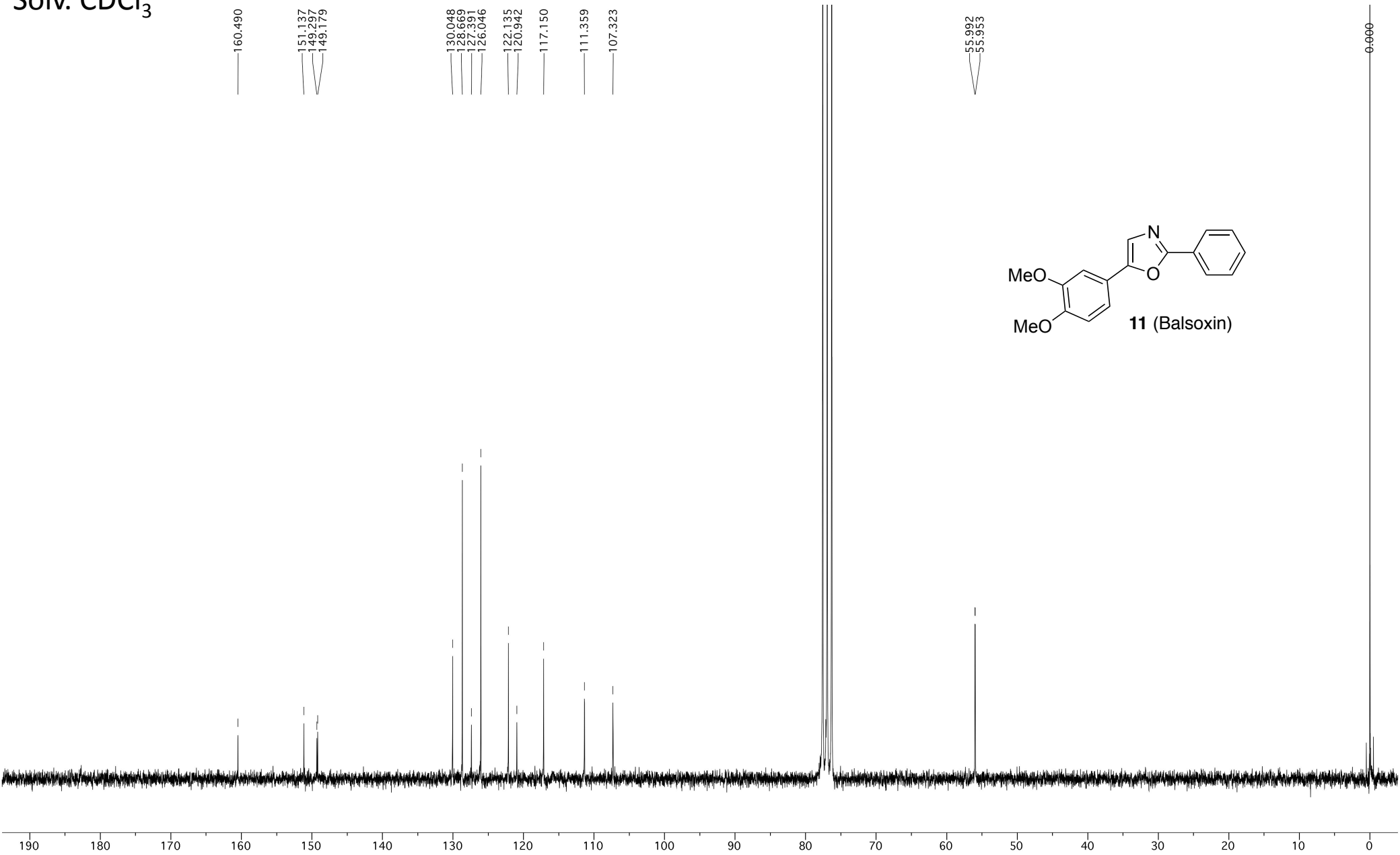
^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



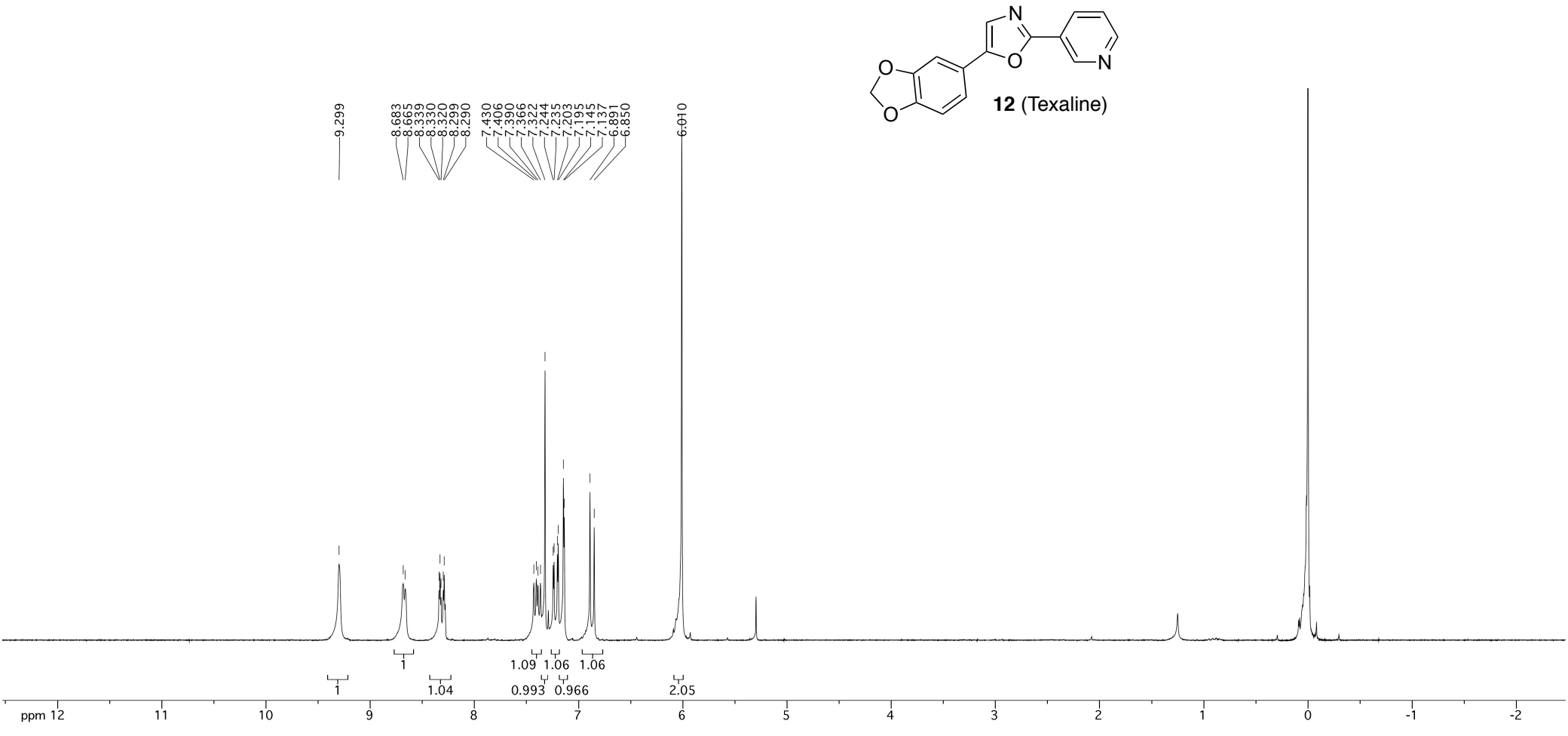
^{1}H NMR, 200 MHz
Solv. $CDCl_3$



^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



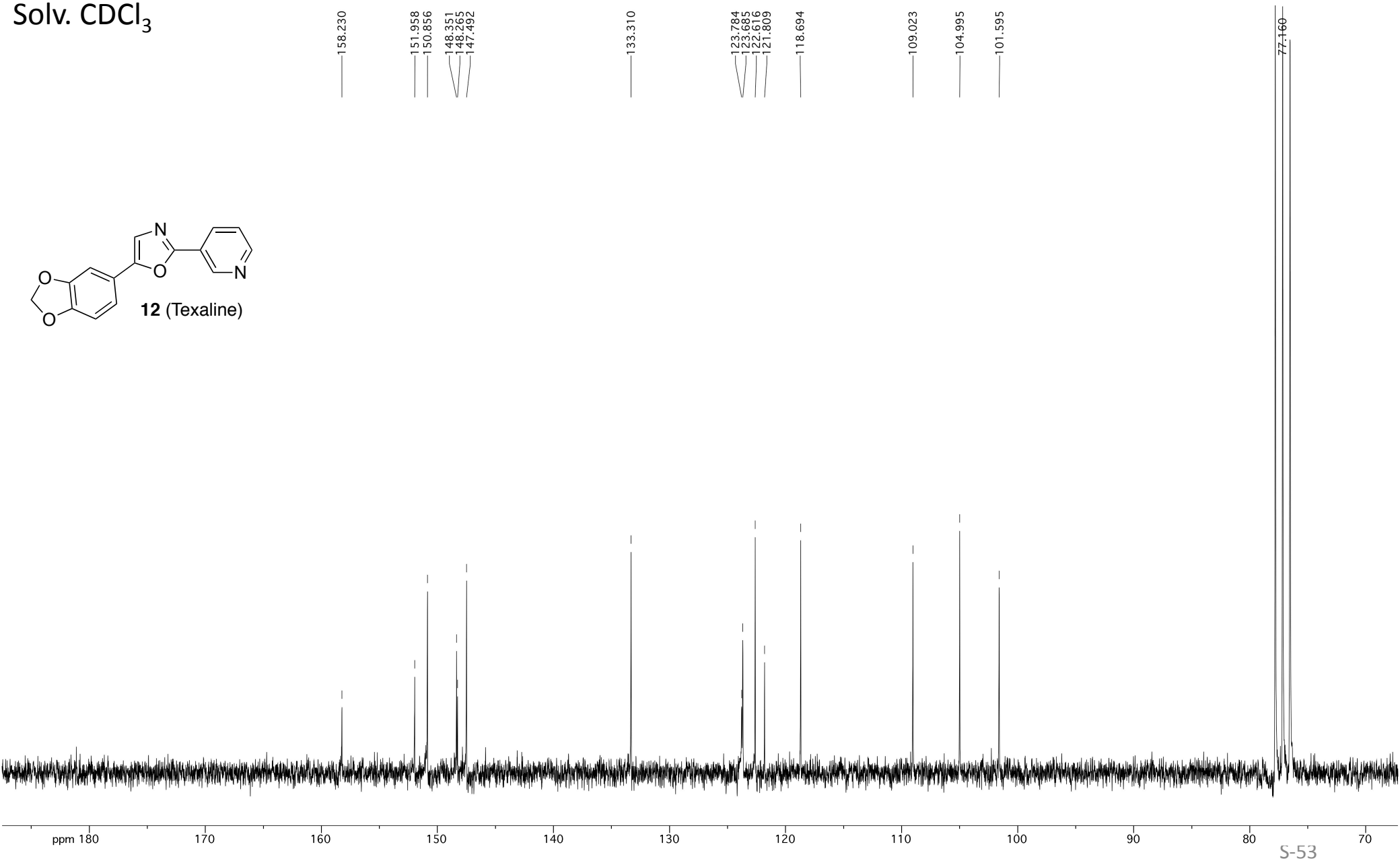
^{1}H NMR, 200 MHz
Solv. $CDCl_3$



12 (Texaline)

^{1}H NMR, 200 MHz
Solv. $CDCl_3$

^{13}C NMR, 50.3 MHz
Solv. $CDCl_3$



12 (Texaline)