Direct Decarboxylative C–2 alkylation of azoles through Minisci-type coupling

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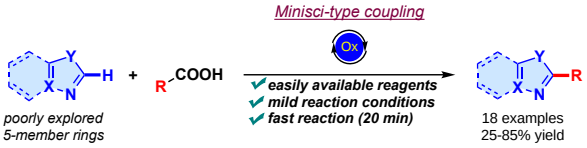


ABSTRACT: This note discusses the application of Minisci-type reaction for the direct alkylation of azoles with carboxylic acids as radical precursors. Different reaction conditions were investigated to achieve high yield of the desired products, focusing on acid strength and solvent screening. Moreover, the reactivity of imidazoles with various carboxylic acids was investigated, showing good yield for most cases. The study reveals the potential of this approach for late-stage functionalization in drug discovery.

INTRODUCTION

The five-member heteroaromatic azole-ring represents a key structural feature in many molecules of significant synthetic interest.[1] Its presence in successful biologically-active molecules makes this class of compounds among the most explored chemical species in medicinal chemistry displaying a broader spectrum of application in clinical medicine. [2-12] In this context, it is interesting to note that the presence of azole nuclei bearing an alkyl-substituent are recurrent in many marketed drugs which show, among the others, antifungal (e.g. Metronidazole, Ketoconazole)[13, 14] antihistaminic (e.g. Bilastine),[15] antibiotic (e.g. Pretomanid),[16] antihypertensive (e.g. Losartan),[17] antiemetic (e.g. Domperidone)[18] and antiretroviral (e.g. Ritonavir)[19] properties. It is therefore not surprising that, in the last decades, many approaches have been developed for the selective synthesis of functionalized azole-derivatives, which traditionally involve cyclization reactions and stepwise syntheses.[20-23] In recent years, many efforts were also oriented on the Late-Stage Functionalization approach (LSF),[24] aiming to introduce a desired moiety on the targeted substrate in a selective fashion and at the end of a synthetic process, in one step.[25-27] In this last context, C–H activation procedures are undoubtedly one of the most striking and exploited approaches for late-stage functionalization in organic and medicinal chemistry.[28, 29] Examples for a direct C–H alkylation of azole derivatives involve, among others, the use of strong bases and alkyl halides,[30, 31] transition-metals catalysis,[32-34] Grignard reagents,[35] alkenes,[36, 37] allenes,[38] sulfinates,[39] boronic esters[40] and potassium alkyltrifluoroborates.[41] (Figure 1a) In the last years, homolytic retrosynthetic disconnections have gained a deeper attention, offering complementary approaches to build complex structures when compared to dipolar strategy.[40] Synthetic pathways based on radical couplings may lead to a rapid and convergent synthesis of very complex molecular structures, thus avoiding functional group over-manipulation which makes more sustainable and efficient the whole synthetic process. A striking example of radical C–H functionalization for the formation of new Csp^2–Csp^3 bonds is undoubtedly the Minisci reaction,[42] whose original protocol was developed for the alkylation of electron-poor six-membered heteroaromatic rings (e.g. pyridine and quinoline moieties) with alkyl-carboxylic acids as radical precursor, in presence of a chemical oxidant and sub-stoichiometric amounts of silver nitrate.[43-45] With the advent of novel synthetic techniques, such as photo- and electrochemistry, the Minisci protocol has been deeply revisited, assessing the development of a great number of parent transformations (Minisci-like reactions).[46-58] (Figure 1b) However, the radical Minisci-like alkylation involving electron-rich azoles with no substrate pre-functionalization and nucleophilic radicals still remains less developed, being limited to few examples and often requiring elevated temperatures, very long reaction time and complementary protocols involving specific devices and/or expensive (photo)catalysts.[47, 59, 60] For this reason, we decided to investigate, as part of our research on the selective functionalization of azoles rings,[61-65] the possible extension of Minisci reaction to the C–2 alkylation of electron-rich azoles. In this communication we report the results and limitations of a protocol for the fast and selective C–2 selective alkylation of electron-rich azoles with nucleophilic radicals. (Figure 1c).

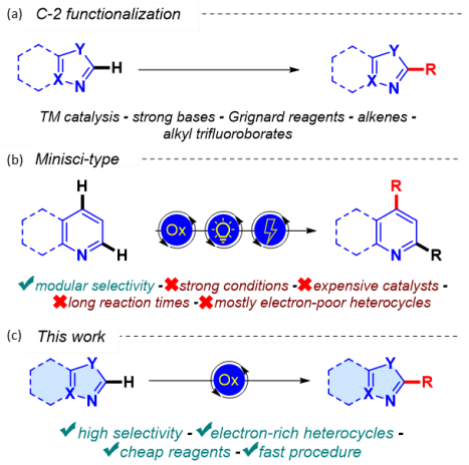


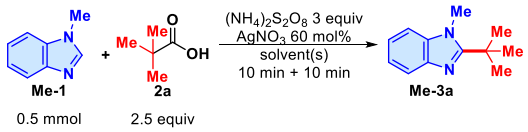
Figure 1. General approaches for the C–2 functionalization of azole-rings

RESULTS AND DISCUSSION

The major concern on the radical alkylation of azole derivatives belongs to their electron-rich character, which makes these species less prone to react with nucleophilic carbon-centered radicals generated under Minisci-like conditions.[66] For these reasons, a good tuning of the conditions is necessary for a satisfactory outcome. To identify the best conditions for a radical alkylation protocol, we conducted a preliminary screening using 1-methylbenzimidazole (**Me-1**) and pivalic acid (**2a**).

We started our investigations inspired by the conditions previously reported for the silver-catalyzed decarboxylative direct C–2 alkylation of benzothiazoles and oxazoles in presence of pivalic acid (**2a**).[67] Hence, 0.5 mmol of N-methylbenzimidazole (**Me-1**) and 2 equiv of **2a** were reacted at room temperature for 8 hours in the presence of $AgNO_3$ (20 mol%), $K_2S_2O_8$ (4 equiv) in a mixture of water and DCM (1:1). However, no coupling product was observed, and **Me-1** was completely recovered. We then decided to perform a re-examination of the reaction conditions, starting from the classical ones reported by Minisci and co-workers.[42, 68, 69] Unfortunately, the procedure for the functionalization of **Me-1** resulted poorly effective on the model substrate and the desired product **Me-3a** was isolated with 12% yield. (Table 1, entry 1).

Table 1. Screening of the Minisci reaction conditions of 1-methylbenzimidazole with pivalic acid

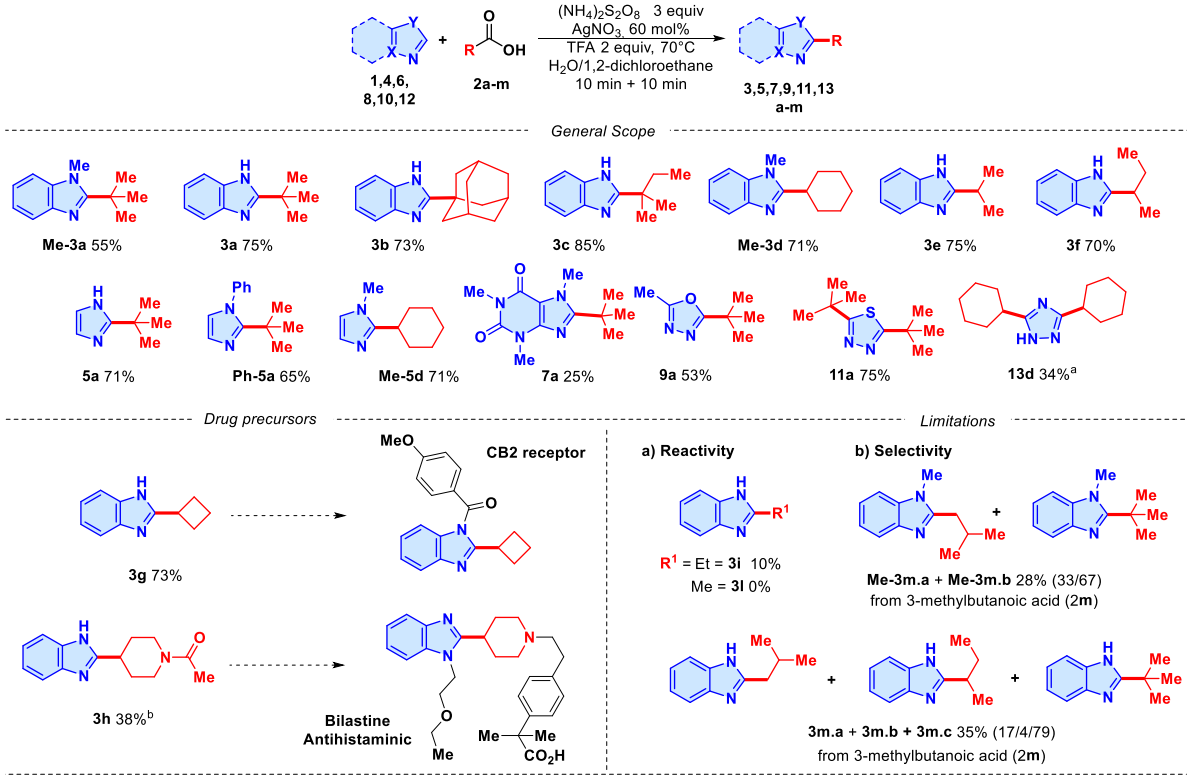


Entry[a]	Solvent(s)	Additive	Me-1 GLC conversion (%) / Me- 3a GLC yield (%) [b]
1[c]	H_2O	H_2SO_4 10% v/v	(12)
2	H_2O	H_2SO_4 10% v/v	(27)
3	H_2O/PhCl	H_2SO_4 10% v/v	No reaction
4	H_2O/PhCl	TFA 10% v/v	70/48
5	H_2O/DCE	TFA 10% v/v	69/57 (55)
6	**H_2O/DCE**	**TFA 2 equiv**	**70/59 (56)**
7	H_2O/DCE	none	46/30
8	H_2O/DCE	pTSA 2 equiv	55/33
9	H_2O/DCE	MeCOOH 2 equiv	69/48
10[d]	H_2O/DCE	TFA 2 equiv	66/53
11[e]	H_2O/DCE	TFA 2 equiv	72/56
12	H_2O/$CHCl_3$	TFA 2 equiv	56/31
13	H_2O/ACN	TFA 2 equiv	16/11
14	H_2O/TFIP	TFA 2 equiv	38/20
15	H_2O/HFIP	TFA 2 equiv	74/54 (49)
16	H_2O/TeCA	TFA 2 equiv	75/58 (54)

(a) Experimental procedure: a mixture of *N*-methylbenzimidazole (**Me-1**) (0.5 mmol), $AgNO_3$ (0.6 equiv), pivalic acid (**2a**) (2.5 equiv), in water (10 mL) or water/organic solvent (1:1, 10 mL) and the select additive was stirred at 70 °C prior addition of an aqueous solution of $(NH_4)_2S_2O_8$ (3 equiv in 5 mL) over 10 minutes. The resulting mixture was stirred for other 10 minutes at 70 °C. (b) GLC conversion of **Me-1** *vs* biphenyl / GLC yield of **Me-3a** *vs* biphenyl. In bracket, isolated yields. (c) $(NH_4)_2S_2O_8$ was added along with all the other reactants. (d) 3.5 equiv. of pivalic acid instead. (e) The aqueous solution of $(NH_4)_2S_2O_8$ was added over 20 minutes instead.

The method proposed by Narayanan and co-workers on the functionalization of histidine, i.e. classical Minisci condition but with the slow addition of the oxidant, led to a slight increase in the reaction outcome, and **3a** was isolated with 27% yield (Table 1, entry 2).[70] The addition of chlorobenzene as organic co-solvent, with the aim of facilitating the dissolution of the precursor, did not lead to any product (Table 1, entry 3), while the replacement of sulfuric acid (pKa = –3) with trifluoroacetic acid (TFA, pKa = –0.25) as an organic acid led to a conversion of 70%, thus providing **Me-3a** in 48% GLC yield (Table 1, entry 4). Replacing chlorobenzene with 1,2-dichloroethane (DCE) raised the isolated yield of **Me3a** up to 55% (Table 1, entry 5), albeit with the same GLC conversion. The attempt to reduce the amount of acid to 2 equiv, seeking for milder conditions, provided good results (Table 1, entry 6), while the acid removal led to a lower yield (30%, Table 1, entry 7), thus proving the need for the protonation of the azole ring to increase its reactivity.[68] The use of *p*-toluenesulfonic (pTSA, pKa = –2.8) instead of TFA resulted in lower GLC conversion and yield (55% and 33%, respectively) (Table 1, entry 8). Using acetic acid (pka = 4.8) instead we obtained a similar conversion but a lower yield (69% and 49%, respectively) (Table 1, entry 9) This two tests, along with the results summarized in entries 3 and 4 of table 1, demonstrate how the nature of the acid may influence the reaction outcome. Increasing the amounts of pivalic acid to 3.5 equivalents, as well as doubling the reaction time, did not lead to any significative improvement in terms of conversion and yield (Table 1, entries 10 and 11). Testing other co-solvents such as chloroform and acetonitrile led to lower yields (table 1, entries 12 and 13). 1,1,1-Trifluoro-2-propanol (TFIP) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[71] (Table 1, entries 14 and 15), provided the desired product with 20% and 54% GLC yield. Finally, 1,1,2,2-tetrachloroethane (TeCA) was tested and **Me-3a** obtained with an isolated yield of 54% (Table 1, entry 16).

Given these results, we carried out further investigations to explore the reactivity of benzimidazole core with different carboxylic acids under the reactions conditions of Table 1, entry 6. As summarized in Figure 2, benzimidazoles **3a**, **3b** and **3c** were successfully isolated in 75, 73 and 85% yield, respectively upon reaction of benzimidazole (**1**) with pivalic acid (**2a**), 1-adamantanecarboxylic (**2b**) and 2,2-dimethylbutyrric acid (**2c**), thus showing the applicability of the process in presence of non-protected nitrogen. C–2 functionalization with secondary carboxylic acid was also possible, as proved by the results obtained using cyclohexanecarboxylic acid (**2d**), isobutyric acid (**2e**) and 2-methylbutyric acid (**2f**). The corresponding 2-alkylbenzimidazoles **Me-3d**, **3e** and **3f** were in fact isolated in 71, 75 and 70% yield, respectively (Figure 2). 2-Cyclobutylbenzimidazole **3g**, the key structural motif of CB2-receptor ligands,[15] was obtained in 73% yield from **1** and cyclobutanecarboxylic acid (**2g**) (Figure 2). On the other hand, the precursor of the antihistaminic drug Bilastine[15] **3h** was synthesized in 38% yield from **1** and 1-acetylpiperidine-4-carboxylic acid (**2h**) (Figure 2).Testing the oxidative conditions on imidazoles **4**, **Ph-4** and **Me-4** was proven to be effective. Therefore, compounds **5a**, **Ph-5a** and **Me-5d** were successfully isolated with 71, 65 and 71% yield and complete regioselectivity on C–2 (Figure 2).



Experimental procedure: a mixture of the azole (0.5 mmol), $AgNO_3$ (0.6 equiv), **2a-m** (2.5 equiv), TFA (2 equiv) in a water/1,2-dichloroethane mixture (1:1, 10 mL) was stirred at 70 °C prior addition of an aqueous solution of $(NH_4)_2S_2O_8$ (3 equiv in 5 mL) over 10 minutes. The resulting mixture was stirred for other 10 min at 70 °C. (a) 3.5 equiv of cyclobutanecarboxylic acid (**2g**) (b) The reaction was conducted at 100 °C instead.

Figure 2. General scope and limitations of the direct decarboxylative C–2 alkylation of azole-derivatives through Minisci-type coupling procedure.

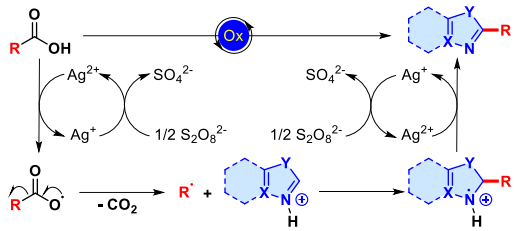
The alkylation of caffeine **6**, on the other hand, gave the expected product **7a** in a low 25% yield (Figure 2), probably due to partial degradation of the precursor under these reaction conditions.

The optimized conditions proved to be effective also for the alkylation of azoles that, to our knowledge, had never previously been subjected to the Minisci reaction conditions. In fact, we were able to react oxadiazole **8** and thiadiazole **10** with pivalic acid (**2a**) (Figure 2). Specifically, 2-tert-butyloxadiazole **9a** was obtained in 53% isolated yield, while the more reactive thiadiazole **10** was di-functionalized with high efficiency (**11a**, 75%). Moreover, the reaction of 1,3,4-triazole (**12**) with cyclohexanecarboxylic acid (**2a**) gave the di-alkylated product **13d** in 34% yield (Figure 2).

Despite the elevated tolerance toward highly reactive azoles, some limitations emerged when primary carboxylic acids were used as alkyl radical precursors. As summarized in Figure 2, the reaction between benzimidazole (**1**) and propionic acid (**2i**) provided **3i** in a low 10% yield, while the use of acetic acid (**2l**) led to complete recovery of **1**. A related limitation was observed using isovaleric acid (**2m**) as coupling partner. In presence of **Me-1**, the *tert*-butyl-substituted benzimidazole **Me-3a** was detected alongside the expected *iso*-butyl derivative **Me-3m**. The reaction yielded less efficiently (28% isolated), and a ratio of 33:67 of **Me-3m** *vs* **Me-3a** was observed. An even more complex result was detected when **1** was reacted with **2i**. In this case, three distinct isomers were detected, with a ratio of 17:4:79 and an overall 35% yield. The isomers were subsequently identified by NMR spectroscopy to be 2-isobutyl-, 2-*sec*-butyl-, and 2-*tert*-butylbenzimidazole **3m**, **3f** and **3a**, respectively (see the supporting information for details). These results could be potentially attributed to the concomitant

formation of all three radicals, whose reaction rate varies according to the nature of the azole nucleus.

Similarly to the classical mechanism reported by Minisci,[68] the formation of alkyl radical occurs presumably after the pattern of silver-mediated decarboxylation. The protonated heterocycle is prone to radical addition which is followed by oxidation and re-aromatization steps to deliver the desired alkylated heterocycle (Scheme 1). Further studies are however required to better understand the formation of isomers when linear carboxylic acids, such as propionic acid, are used to generate the alkyl radicals.



Scheme 1. Proposed mechanism

In conclusion, we disclosed a simple Minisci-type approach for the rapid and straightforward alkylation of electron-rich azoles. The robustness of this method was proven by the successful and selective functionalization of differently reactive heteroarenes, thus opening the way to a fast and functional-group tolerant approach to alkyl-substituted azoles. The application of our procedure to LSF methodologies for azole alkylation is ongoing.

EXPERIMENTAL SECTION

General Procedure for the scope of the decarboxylative radical alkylation of azole-based heterocycles. A mixture of azole-heterocycle (**1**) (0.5 mmol), $AgNO_3$ (51 mg, 0.30 mmol), carboxylic acid (1.25 or 1.75 mmol), in water/organic solvent (1:1, 10 mL) and TFA (2.5 equiv, 77 µL) was stirred at 70 °C prior addition of an aqueous solution of $(NH_4)_2S_2O_8$ (342 mg, 1.5 mmol, in 5 mL) over 10 minutes. The resulted mixture was vigorously stirred for other 10 minutes then cooled down to room temperature prior addition of aqueous ammonia solution until alkaline pH. The basified solution, diluted with other 30 mL of water, was extracted with DCM (40 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered and concentred under *vacuum*. When indicated, the desired product was recovered upon flash chromatography on silica gel. This protocol was applied to obtain compounds **3a-m**, **Me-3a**, **Me-3d**, **5a**, **Ph-5a**, **Me-5d**, **7a**, **9a**, **11a**, **13d** (Figure 2)

2-(t-butyl)benzimidazole (3a) The product was obtained by the decarboxylative coupling reaction of benzimidazole (**3**) with pivalic acid (**2**). Compound **3a** did not required any further purification and appears as a white solid (65 mg, 75%) with a melting point of 303-305°C (lit. 310 °C).[74] ESI-MS m/z 175 $[M+H]^+$. EI-MS, m/z (%): 159 (100), 174 (35), 173 (23), 119 (12), 160 (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 2H), 7.17 – 7.01 (m, 2H), 1.38 (s, 9H). The spectral properties of this compound are in agreement with those previously reported.[74]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Full experimental details, complete characterization data and NMR spectra of **3a-m**, **Me-3a**, **Me-3d**, **5a**, **Ph-5a**, **Me-5d**, **7a**, **9a**, **11a**, **13d**.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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