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Graphical Abstract

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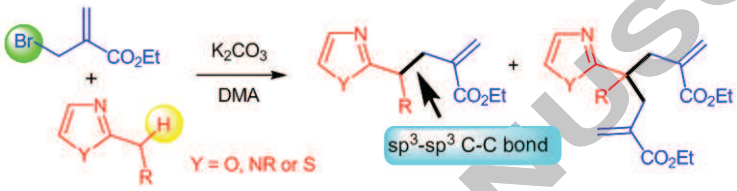
[c] *Département de chimie, UMMTO, BP 17 RP, 15000 Tizi-Ouzou, Algeria.*



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ARTICLE INFO

ABSTRACT

A carbonate base was found to promote the formation of sp^3-sp^3 carbon-carbon bonds of 2-alkylazoles with a bromoacrylate. The reaction tolerates various alkyl substituents and a variety of heteroarenes such as thiazoles, oxazoles or imidazoles.

Keywords:
Thiazoles
Oxazole
Imidazoles
Bromoacrylate
Aza-Cope rearrangement

1. Introduction

Several bioactive compounds contain a 2-alkylheteroaryl motif. For example, Isavuconazole is an antifungal, Oxaprozin is a non-steroidal anti-inflammatory drug, Phenoxan is a HIV-1 inhibitor, Bendamustine is used in the treatment of lymphocytic leukemia, and Mipitroban has antithrombotic properties (Fig. 1). Therefore, the discovery of general simple routes to functionalize 2-alkyl-substituted azoles has potential for medicinal chemistry.

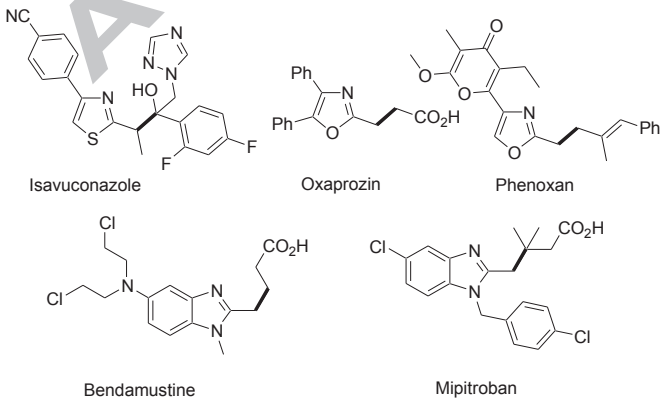
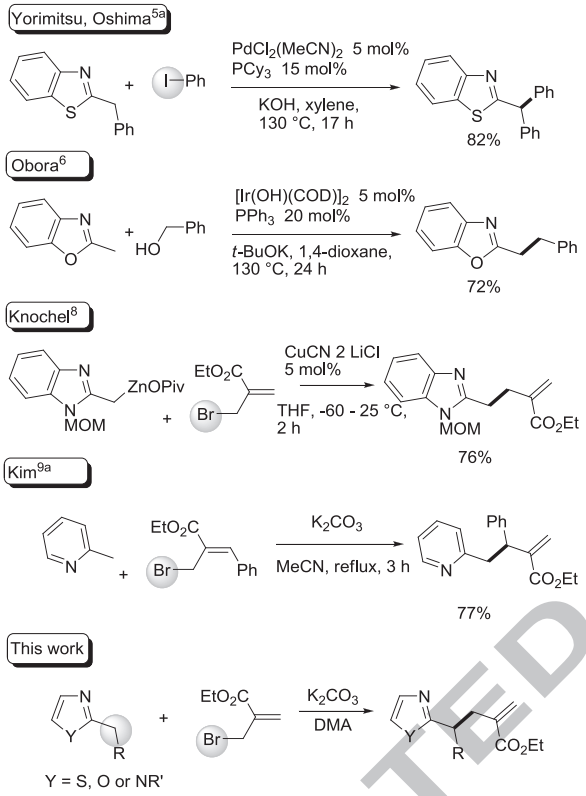


Figure 1 Examples of bioactive 2-Alkylazoles derivatives.

The palladium-catalysed direct functionalization of several (hetero)aromatics *via* direct sp^2 and sp^3 C–H bond activation using aryl halides has brought a synthesis revolution in recent years (Scheme 1, top).[1-6] Keeping in mind the results previously obtained for the direct arylation of heteroaromatics,[7] we envisioned the assistance of a palladium catalyst for the functionalization of 2-alkylazoles with a 2-bromomethylacrylate as the coupling partner. The arylations of 2-benzylbenzimidazole, 2-benzylbenzothiazole or 2-benzylbenzoxazole using aryl iodides[5a] or aryl chlorides[5b] as the coupling partners, assisted by Pd-catalysts has been reported by Oshima and co-workers (Scheme 1, top). Recently, Obora et al. reported the iridium-catalysed coupling of 2-methylbenzoxazole with benzyl alcohol for formation of sp^3-sp^3 carbon-carbon bonds.[6] The functionalization of a 2-methylbenzimidazole, deprotonated with a zinc-pivalate derivative, with ethyl 2-bromomethylacrylate as the coupling partner, catalysed by CuCN to afford the 2-[2-(benziimidazol-2-yl)-ethyl]-acrylate derivative has also been described by Knochel et al. (Scheme 1, middle).[8] Catalyst-free reactions have attracted less attention for the functionalization of 2-alkylazoles. The reactivity of 2-alkylpyridines with 2-bromomethylacrylate in the presence of K_2CO_3 as base, but without catalyst has also been described by Kim and co-workers (Scheme 1, bottom).[9a] On the other hand, to our knowledge, for 2-alkylazoles, only activated methylene

groups, such as a 2-benzylbenzoxazole, have been functionalised without catalyst.[9b,9c]

As the methods for the construction of sp^3-sp^3 carbon-carbon bonds from unactivated sp^3 C-H bonds of 2-alkylazoles remain scarce, the reactivity of such alkyl groups needed to be investigated. We now report conditions for the functionalization of a 2-ethyl substituent on a thiazole derivative with ethyl 2-bromomethylacrylate as the reaction partner, and show the scope of the sp^3 functionalization of 2-alkyl-substituted thiazoles, imidazoles, oxazoles and pyridines.

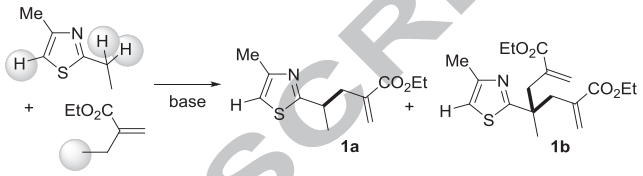


Scheme 1 Reported examples of sp^3 functionalization of 2-alkylazoles or 2-alkylpyridines.

2. Results and discussion

We initially compared the reaction of 2-ethyl-4-methylthiazole and ethyl 2-bromomethylacrylate with and without Pd-catalyst in DMA at 150 °C (Table 1). The presence of $PdCl(C_3H_5)(dppb)$ complex in the reaction mixture had no influence both on yield and selectivity of this reaction (Table 1, entries 1 and 2). The use of such conditions resulted in the formation of mixtures of the target coupling products **1a** and **1b** in a 90:10 and 92:8 ratios, respectively. It should be noted that in both cases, no sp^3 C-H bond functionalization at position C4-Me of the thiazole was observed. Lower selectivities in product **1a** were obtained using NMP and DMF as the solvents, in absence of palladium catalyst (Table 1, entries 3 and 4); whereas CPME, *o*-xylene, ethylbenzene and 1,4-dioxane were completely ineffective for this reaction (Table 1, entries 5-7, 9). No reaction also occurred in ethylbenzene or 1,4-dioxane in the presence of 1 mol% $PdCl(C_3H_5)(dppb)$ (Table 1, entries 8 and 10). The nature of the carbonate cation has an important influence on this reaction, as both Cs_2CO_3 and Na_2CO_3 gave low yields of **1a** (Table 1, entries 11 and 12). The low yield obtained with Na_2CO_3 might be due to its poor solubility in DMA; whereas the higher basicity of Cs_2CO_3 might be harmful for the reaction. Acetates are not suitable bases for this reaction due the side reaction of acetate anion with ethyl 2-bromomethylacrylate which affords ethyl 2-(acetoxymethyl)acrylate (Table 1, entry 13). The relatively strong base NaO*t*Bu in *o*-xylene, with or without palladium catalyst, was also ineffective (Table 1, entries 14 and 15). The use of 2.5 equiv. of 2-bromomethylacrylate allowed to obtained **1b** in 48% selectivity and in 33% yield (Table 1, entry 16). Finally, a lower reaction temperature of 110 °C affords **1a** in high selectivity but in very low yield (Table 1, entry 17).

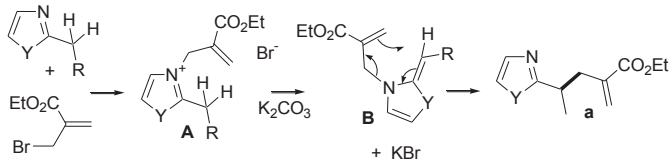
Table 1. Influence of the reaction conditions for the coupling of 2-ethyl-4-methylthiazole with ethyl 2-bromomethylacrylate.



Entry	Base (equiv.)	Solvent	Ratio **1a**:**1b**	Yield in **1a** (%)
1	K_2CO_3 (1.5)	DMA	92:8	80
2	K_2CO_3 (1.5)	DMA	90:10	79[a]
3	K_2CO_3 (1.5)	DMF	76:24	nd
4	K_2CO_3 (1.5)	NMP	87:13	61
5	K_2CO_3 (1.5)	CPME[b]	-	0[c]
6	K_2CO_3 (1.5)	*o*-xylene	-	0[d]
7	K_2CO_3 (1.5)	ethylbenzene	-	0[d]
8	K_2CO_3 (1.5)	ethylbenzene	-	0[a,d]
9	K_2CO_3 (1.5)	1,4-dioxane	-	0[c]
10	K_2CO_3 (1.5)	1,4-dioxane	-	0[a,c]
11	Cs_2CO_3 (1.5)	DMA	100:0	trace
12	Na_2CO_3 (1.5)	DMA	100:0	12
13	KOAc (1.5)	DMA	-	0
14	NaO*t*Bu (1.5)	*o*-xylene	-	0[d]
15	NaO*t*Bu (1.5)	*o*-xylene	-	0[a,d]
16	K_2CO_3 (3)	DMA	52:48	33 of **1b**[e]
17	K_2CO_3 (1.5)	DMA	97:3	<10[c]

Conditions: 2-ethyl-4-methylthiazole (1.5 mmol), ethyl 2-bromomethylacrylate (1 mmol), under argon, 16 h, 150 °C, isolated yields. [a] 1 mol% $PdCl(C_3H_5)(dppb)$. [b] CPME: cyclopentyl methyl ether. [c] 110 °C. [d] 130 °C. [e] 2-ethyl-4-methylthiazole (1 mmol), ethyl 2-bromomethylacrylate (2.5 mmol), K_2CO_3 (3 mmol).

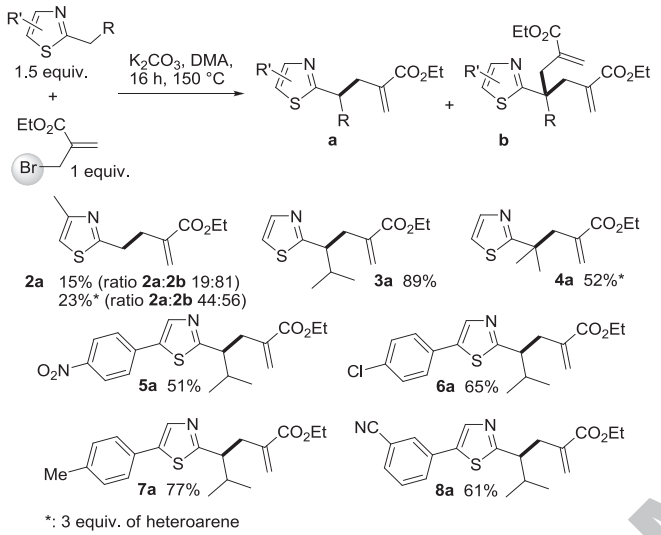
The first step of the reaction is certainly the addition of the bromomethylacrylate to the nitrogen atom of the azole derivative to form the *N*-alkylated species **A** (Scheme 2). Deprotonation of **A** in the presence of K_2CO_3 affords intermediate **B**. Then, an aza-Cope rearrangement leads to the final product **a**.[10-12]



Scheme 2 Proposed mechanism

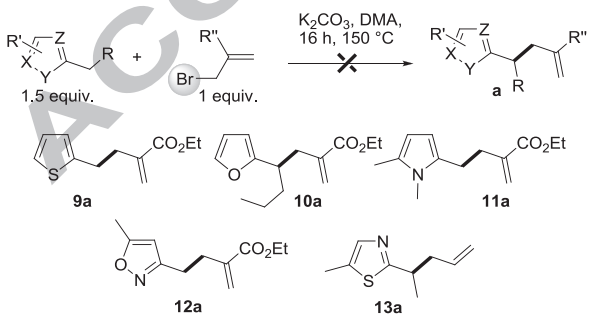
Using K_2CO_3 as base in DMA, (Table 1, entry 1), the scope of the sp^3 C-H bond functionalization using various 2-alkylthiazole derivatives was examined (Scheme 3). From 1.5 equiv. of 2,4-dimethylthiazole and 1 equiv. of ethyl 2-bromomethylacrylate, a mixture of **2a** and **2b** was obtained in a 19:81 ratio. The use of a

larger excess of 2,4-dimethylthiazole (3 equiv.) did not allowed to obtain **2a** in good selectivity. Again, no sp^3 C-H bond functionalization at position C4-Me thiazole was observed. On the other hand, the reaction of 2-*i*butylthiazole or 2-*i*propylthiazole (1.5 equiv.) with ethyl 2-bromomethylacrylate (1 equiv.) led exclusively to mono-coupling products **3a** and **4a** in moderate to high yields. Then, we studied the influence of benzene substituents of 2-*i*butyl-5-arylthiazoles for such couplings (Scheme 3). Nitro-, chloro- or cyano- substituents are tolerated to afford **5a**, **6a** and **8a** in 51-66% yields. The highest yield was obtained from 2-*i*butyl-5-*p*-tolylthiazole to give **7a** in 77% yield.



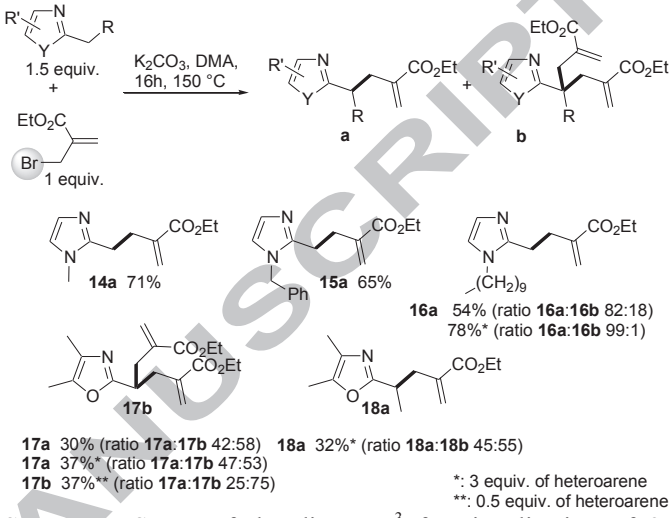
Scheme 3 Scope of the sp^3 functionalization of 2-alkylthiazoles.[13,14]

We then studied the reactivity of a set of 2-alkylheteroarenes which do not contain a nitrogen atom at 3-position with and without $PdCl(C_3H_5)$(dppb) catalyst (Scheme 4). As expected, both 2-methylthiophene and 2-*n*-butylfuran gave no trace of coupling products **9a** and **10a**. The reactions in the presence of 1,2,5-trimethylpyrrole and 2,4-dimethylisoxazole were also unsuccessful as **11a** and **12a** were not detected by GC/MS analysis of the crude mixtures. The reaction of 2-ethyl-4-methylthiazole with allyl bromide or allyl acetate in order to produce **13a** was also unsuccessful (Scheme 4, bottom).



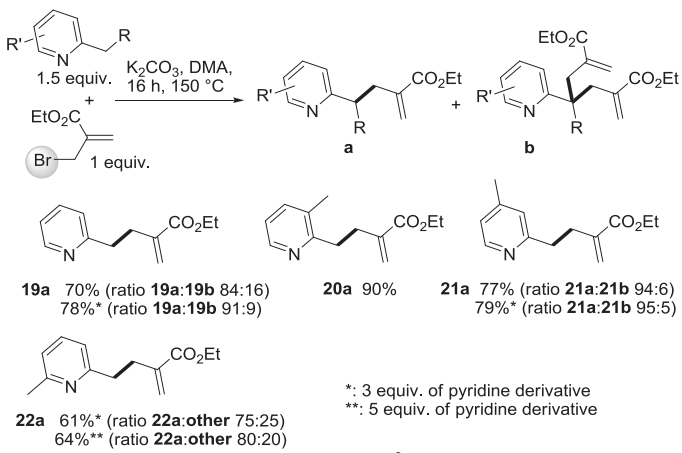
Scheme 4 Limitations of the sp^3 functionalization of 2-alkylheteroarenes.[13,14]

The influence of the nature of the heteroatom at position 1 of the heteroarene was also examined (Scheme 5). The reaction of 1.5 equiv. of 1,2-dimethylimidazole with 1 equiv. of ethyl 2-bromomethylacrylate only gave mono-coupling product **14a** in 71% yield. Similarly, 1-benzyl-2-methylimidazole only afforded the mono-coupling product **15a** in 65% yield. On the other hand, a mixture was obtained from 1-decyl-2-methylimidazole with the formation of **16a** and **16b** in a 82:18 ratio. However, the use of a larger excess of 1-decyl-2-methylimidazole gave **16a** in 99% selectivity and 78% yield. From both 2,4,5-trimethyloxazole and 2-ethyl-4,5-dimethyloxazole (3 equiv.), again the formation of mixtures of mono- and di-alkylation products **17a**:**17b** and **18a**:**18b** in 47:53 and 45:55 ratios was observed.



Scheme 5 Scope of the direct sp^3 functionalization of 2-methylimidazoles, 2-methyloxazoles or 2-alkylpyridines.[13,14]

The reactivity of a few 2-alkylpyridine derivatives using K_2CO_3/DMA as reaction conditions was also studied (Scheme 6). A mixture of 1 equiv. of ethyl 2-bromomethylacrylate and 1.5 equiv. of 2-methylpyridine gave the products **19a** and **19b** in a 84:16 ratio. Under similar conditions, the coupling with 2,3-dimethylpyridine only gave **20a** in a very high yield. A high selectivity in favour of the formation on mono-coupling product **21a** was also observed with 2,4-dimethylpyridine.



Scheme 6 Scope of the direct sp^3 functionalization of 2-methylpyridines.[13,14]

In summary, we have demonstrated that the sp^3 functionalisation of 2-alkyl substituents of azoles with a 2-bromomethylacrylate to form sp^3-sp^3 carbon-carbon bonds proceeds using only K_2CO_3 as base without catalyst. The reaction selectively promotes the functionalization at C2-alkyl of thiazoles, oxazoles or imidazoles even in the presence of other alkyl substituents. These conditions offer routes for fast access to functionalised alkyl chains at C2 of these heteroarenes.

Acknowledgments

We are grateful to the "Chinese Scholarship Council" for a grant to Z. L.

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13. **General procedure for the synthesis of 1a-22a**: As a typical experiment, reaction of the heteroarene (1.5 mmol), ethyl 2-bromomethylacrylate (0.193 g, 1 mmol), K_2CO_3 (0.207 g, 1.5 mmol) at 150 °C during 16 h in DMA (4 mL) under argon afforded the corresponding products after extraction with dichloromethane, evaporation and filtration on silica gel. All compounds gave satisfactory ^1H, ^{13}C and elementary analysis.
14. **Ethyl 2-[2-(4-methylthiazol-2-yl)-propyl]-acrylate (1a)** ^1H NMR (400 MHz, $CDCl_3$): □ 6.64 (s, 1H), 6.10 (s, 1H), 5.43 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.45-3.30 (m, 1H), 2.77 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.56 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.35 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 166.9, 152.0, 138.1, 127.1, 112.0, 60.7, 39.8, 37.4, 20.9, 17.0, 14.2. **Ethyl 4-methyl-2,6-dimethylene-4-(4-methylthiazol-2-yl)-heptanedioate (1b)** was also isolated: ^1H NMR (400 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.04 (s, 2H), 5.19 (s, 2H), 4.10-4.00 (m, 4H), 2.91 (d, *J* = 13.2 Hz, 2H), 2.78 (d, *J* = 13.2 Hz, 2H), 2.37 (s, 3H), 1.23 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 167.6, 151.9, 137.0, 128.5, 112.5, 60.7, 45.1, 42.7, 22.7, 17.1, 14.1.