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Graphical Abstract

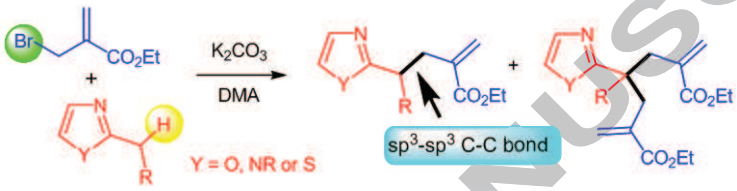
sp^3-sp^3 Carbon-Carbon Bonds Formation using 2-Alkylazoles and a Bromoacrylate as the Reaction Partners

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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.

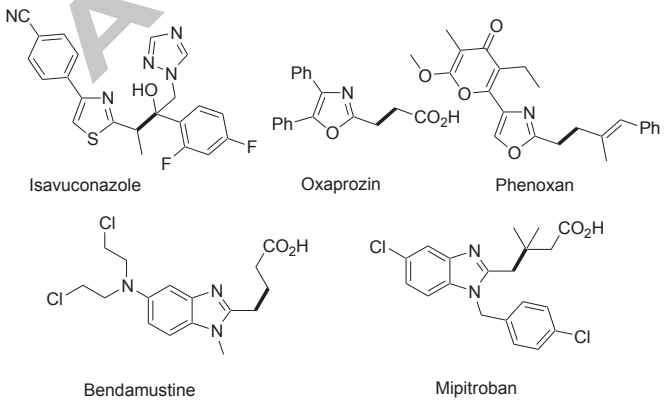


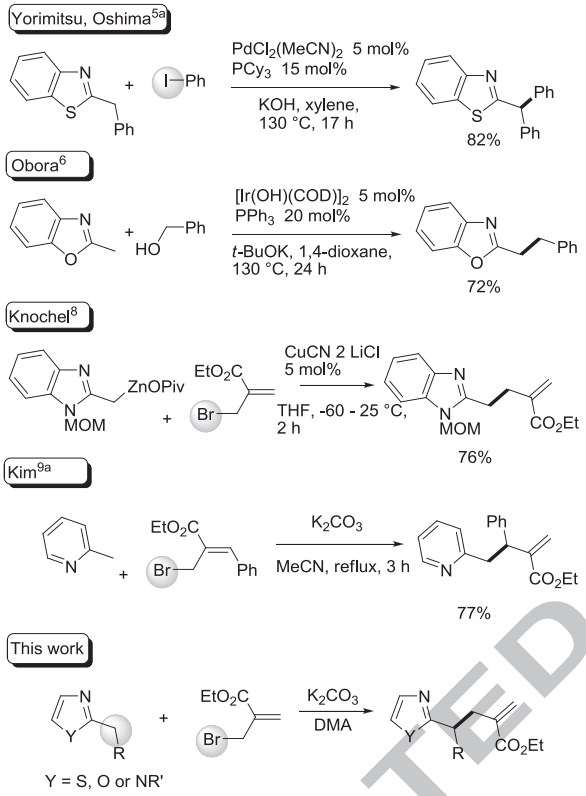
Figure 1 Examples of bioactive 2-Alkylazoles derivatives.

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

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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.

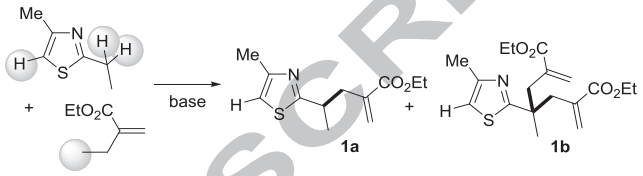


Scheme 1 Reported examples of sp^3 functionalization of 2-alkylazoles or 2-alkylpyridines.

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).

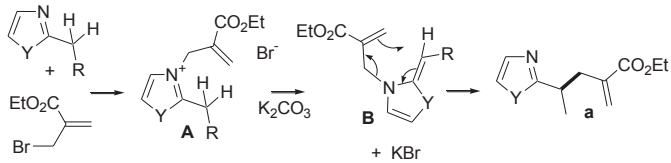
Table 1. Influence of the reaction conditions for the coupling of 2-ethyl-4-methylthiazole with ethyl 2-bromomethylacrylate.



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]

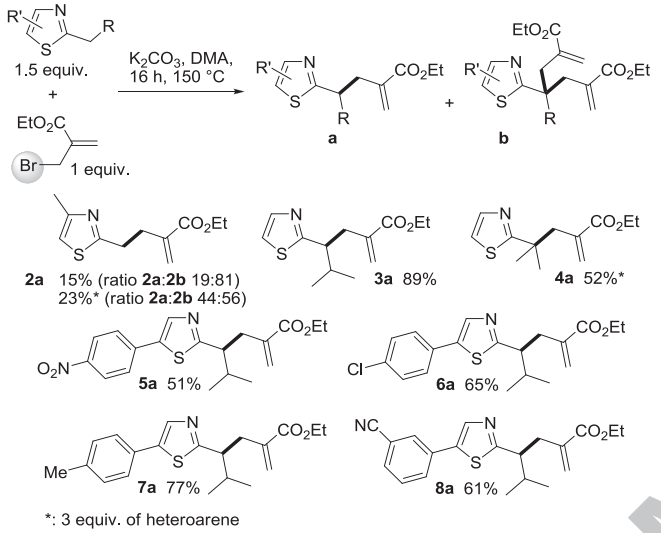


Scheme 2 Proposed mechanism

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

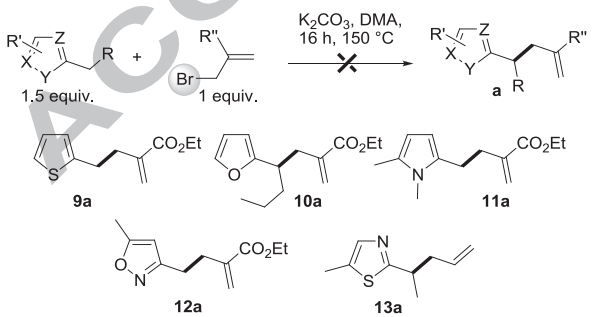
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larger excess of 2,4-dimethylthiazole (3 equiv.) did not allowed to obtain **2a** in good selectivity. Again, no sp^3 C-H bond functionalization at position C4-Me thiazole was observed. On the other hand, the reaction of 2-*i*butylthiazole or 2-*i*propylthiazole (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.



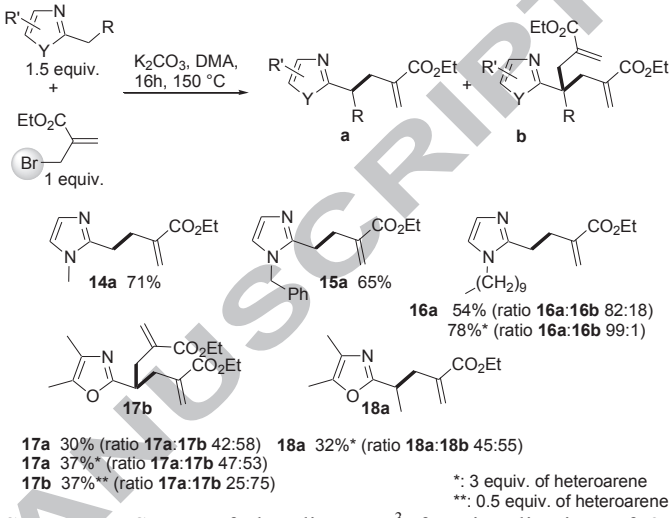
Scheme 3 Scope of the sp^3 functionalization of 2-alkylthiazoles.[13,14]

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).



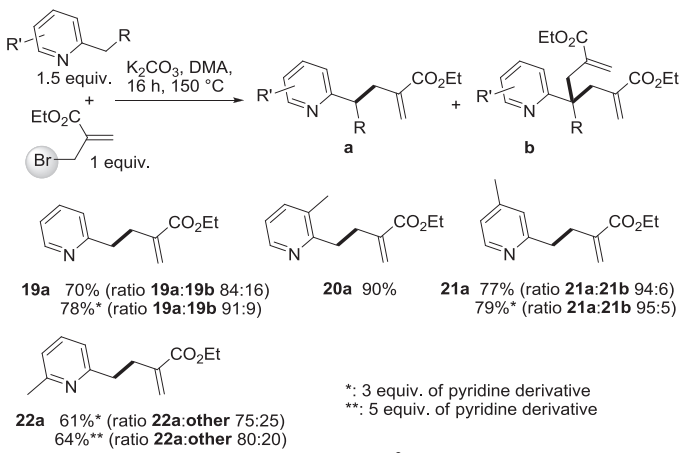
Scheme 4 Limitations of the sp^3 functionalization of 2-alkylheteroarenes.[13,14]

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.

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Acknowledgments

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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.