ORGANIC LETTERS

2011
Vol. 13, No. 7
1852–1855

# Direct Alkylation of Heteroaryls Using Potassium Alkyl- and Alkoxymethyltrifluoroborates

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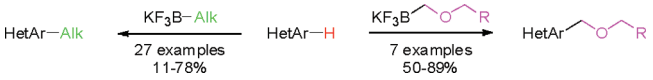
**Received February 7, 2011**

## ABSTRACT




**A direct alkylation of various heteroaryls using stoichiometric potassium alkyl- and alkoxymethyltrifluoroborates has been developed. This method leads to the synthesis of complex substituted heterocycles, which have been obtained with yields up to 89%.**

Heteroaryl moieties are important components in natural products and pharmaceutical drugs.[1] In the past decade, many publications have reported C−H bond activations of heterocycles using base/copper salts with subsequent coupling to aryl halides,[2] and direct C−H activation/arylation of heteroaromatics through palladium activation of aryl and heteroaryl halides has also been observed.[3] Few examples of carbon−carbon bond formation involving organoboron compounds have been reported. In these contributions, C−H bond activation of heteroarenes can be performed with arylboronic acids in the presence of a catalytic amount of palladium acetate and either stoichiometric copper acetate or TEMPO.[4] These transformations were postulated to proceed via organopalladium intermediates generated by transmetalation from the boronic acids.

The Minisci reaction and related processes provide another useful means to alkylate or arylate various heteroarenes via C−H bond substitution[5] in which radical intermediates add to activated aromatic systems (Scheme 1).[6] Within this context, the reactivity of a variety of radical precursors has been studied with quinolines[7] and derivatives such as lepidine,[8] but the conditions often involve the use of the heteroaryl substrate as a solvent.

(1) For bioactive quinoline derivatives, see: (a) Kolasa, T.; Gunn, D. E.; Bhatia, P.; Woolds, K. W.; Gane, T.; Stewart, A. O.; Bouska, J. B.; Harris, R. R.; Hulkower, K. I.; Malo, P. E.; Bell, R. L.; Carter, G. W.; Brooks, C. D. W. *J. Med. Chem.* **2000**, *43*, 690–705. (b) Narayanan, S.; Vangapandu, S.; Jain, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1133–1136. (c) Jain, R.; Vaitilingam, B.; Nayyar, A.; Palde, P. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1051–1054. (d) Payne, J. E.; Bonnefous, C.; Symons, K. T.; Nguyen, P. M.; Sablad, M.; Rozenkrants, N.; Zhang, Y.; Wang, L.; Yazdani, N.; Shiau, A. K.; Noble, S. A.; Rix, P.; Rao, T. S.; Hassig, C. A.; Smith, N. D. *J. Med. Chem.* **2010**, *53*, 7739–7755. For active alkylated benzimidazoles, see: (e) Bali, A.; Bansal, Y.; Sugumaran, M.; Singh Saggu, J.; Balakumar, P.; Kaur, G.; Bansal, G.; Sharma, A.; Singh, M. *Bioorg. Med. Chem.* **2005**, *15*, 3962–3965. (f) Capkauskaite, E.; Baranauskiene, L.; Golovenko, D.; Manakova, E.; Grazulis, S.; Tumkevicius, S.; Matulis, D. *Bioorg. Med. Chem.* **2010**, *18*, 7357–7364. (g) Kumar, S.; Bawa, S.; Gupta, H. *Mini-Rev. Med Chem.* **2009**, *9*, 1648–1654.

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(7) (a) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1986**, *51*, 4411–4416. (b) Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224–5227.

10.1021/ol2003572 
**Published on Web 03/10/2011**

**Scheme 1.** Overview[a]

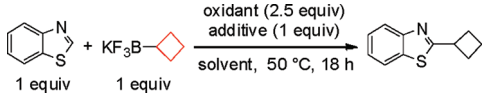

[a] Route A: Minisci reaction using alkyl halides. Route B: direct alkylation with potassium alkyltrifluoroborates.

Interestingly, there is a relatively recent recognition that arylborons can serve as radical precursors in C−C bond-forming reactions via oxidative carbon−boron bond cleavage.[9] Among the different metal oxidants that can be employed for this reaction, manganese(III) acetate has proven to be efficient for the C−H arylation of olefins,[10] arenes, and heteroarenes using arylboronic acids.[11] However, in the latter cases either the substrate was used as a solvent or the reaction was performed with a 10-fold excess of the arene/heteroarene at 170 °C under microwave conditions. During the course of our investigations, Baran and co-workers reported a method for direct arylation of heterocycles using a 50% excess of arylboronic acids, employing potassium persulfate and catalytic silver nitrate as oxidants.[12]

Because of their lack of an empty *p*-orbital, potassium organotrifluoroborates are more stable toward numerous reagents than their corresponding boronic acids. This important characteristic facilitates their ease of handling, storability, and robustness under harsh reaction conditions. Over the past decade, these compounds have proven to be excellent partners in Suzuki−Miyaura cross-coupling and other transition metal catalyzed reactions.[13] As is the case with boronic acids, there has been a recognition that trifluoroborates can also serve as radical precursors. Indeed, Fensterbank et al. recently reported that potassium alkyltrifluoroborates serve as precursors to radicals in a variety of reactions under oxidative conditions employing copper acetate or copper chloride and TEMPO.[14]

Herein, we reveal our initial investigations on the use of stoichiometric organotrifluoroborates as radical precursors in the first direct C−H alkylation of heteroaryls with potassium alkyl- and alkoxymethyltrifluoroborates. We chose to optimize this reaction by testing the direct alkylation of benzothiazole with potassium cyclobutyltrifluoroborate. First, different metal and nonmetal oxidants were tried (Table 1, entries 1−8). Next, different additives (entries 9−13) and various solvents (entries 14−19) were tested, and from these studies it appeared that the highest conversion was obtained with manganese(III) acetate in the presence of trifluoroacetic acid in a 1:1 mixture of acetic acid/water (entry 10).

**Table 1.** Optimization of C−H Alkylation




| entry | oxidant | additive | solvent | GCMS conversion |
|---|---|---|---|---|
| 1 | $Mn(OAc)_3$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 71% |
| 2 | $Cu(OAc)_2$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 1% |
| 3 | $KMnO_4$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 20% |
| 4 | $Ce(SO_4)_2$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 54% |
| 5 | $K_2Cr_2O_7$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 26% |
| 6 | $Fe(SO_4)_2$•$7H_2O$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 6% |
| 7 | $(NH_4)_2S_2O_7$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 12% |
| 8 | benzoquinone | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 3% |
| 9 | $Mn(OAc)_3$ | $H_2SO_4$ | AcOH:$H_2O$ 1:1 | 6% |
| 10 | $Mn(OAc)_3$ | TFA | AcOH:$H_2O$ 1:1 | 78% (60%)[a] |
| 11 | $Mn(OAc)_3$ | TFA[b] | AcOH:$H_2O$ 1:1 | 71% |
| 12 | $Mn(OAc)_3$ | $KHF_2$ | AcOH:$H_2O$ 1:1 | 71% |
| 13 | $Mn(OAc)_3$ | – | AcOH:$H_2O$ 1:1 | 65% |
| 14 | $Mn(OAc)_3$ | TFA | AcOH | 48% |
| 15 | $Mn(OAc)_3$ | TFA | DMSO | 4% |
| 16 | $Mn(OAc)_3$ | TFA | $CH_3CN$ | 41% |
| 17 | $Mn(OAc)_3$ | TFA | MeOH | 54% |
| 18 | $Mn(OAc)_3$ | TFA | $ClCH_2CH_2Cl$ | 51% |
| 19 | $Mn(OAc)_3$ | TFA | acetone | 31% |

[a] Reaction performed at room temperature. [b] Reaction performed with only 0.2 equiv of trifluoroacetic acid.

Using these conditions a variety of heteroaryl substrates have been engaged in reactions with potassium cyclobutyltrifluoroborate (Table 2). Reactions with quinoline and derivatives **1a**−**k** afford yields up to 65% (entries 1−8).

As reported in the literature,[15] quinoline **1a** presents two electron-deficient positions, so both regioisomers were isolated in a 44% combined yield, and $^1$H NMR analysis of the crude mixture indicated the presence of a 70:30 ratio of **2aa**/**2ab**. Isoquinoline **1d** gives not only the expected heteroaryl **2d** but also the corresponding dimer. This side product is obtained by reaction between two radical intermediate species.[16]

Azole compounds **1l**−**r** also gave good conversions (entries 9−12), but the yields are low because of the difficulty in separating compounds **2o**−**r** from the corresponding starting material (entries 11−12).

(8) (a) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146–7150. (b) Minisci, F.; Fontana, F.; Pianese, G.; Ming Yan, Y. *J. Org. Chem.* **1993**, *58*, 4207–4211.

(9) (a) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434. (b) Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71–106. (c) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129–131. (d) Pouliot, M.; Renaud, P.; Schenk, K.; Studer, A.; Vogler, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6037–6040.

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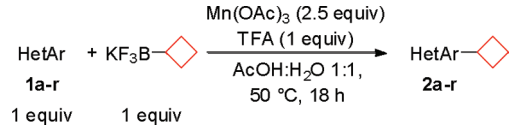
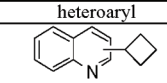
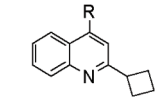
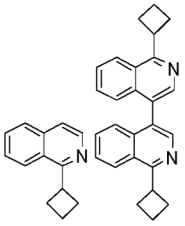
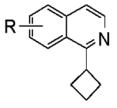
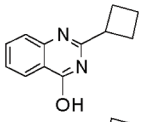
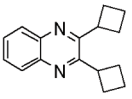
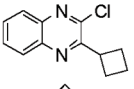
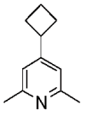
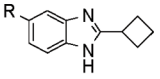
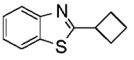
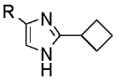
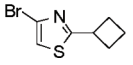
(15) Gebauer, M.; Heinisch, G.; Lötsch, G. *Tetrahedron* **1988**, *44*, 2449–2455.

(16) Minisci, F.; Galli, R.; Malatesta, V.; Caronna, T. *Tetrahedron* **1970**, *26*, 4083–4091.

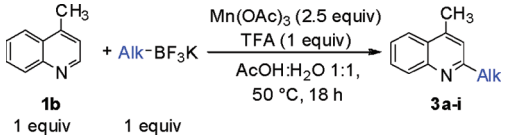
**Table 2.** Scope of Coupling with Diverse Heteroaryls[a]

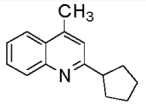
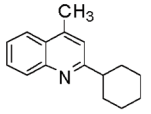
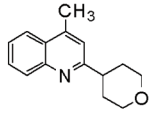
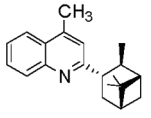
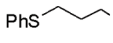
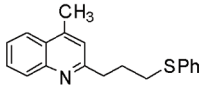
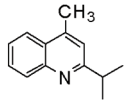
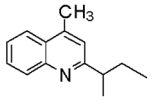
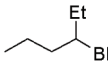
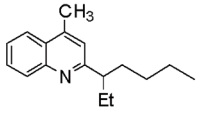
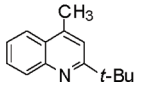



| entry | heteroaryl | | yield (%)[b] |
|---|---|---|---|
| 1 |  | **2aa**, **2ab** ($C_2$:$C_4$ (70:30)) | 44 (58) |
| 2 |  | **2b** R= Me<br>**2c** R= Cl | 65 (83)<br>56 (81) |
| 3 |  | **2da**<br>**2db** | 54% +<br>17% (92) |
| 4 |  | **2e** R= 3-$CO_2$Me<br>**2f** R= 4-Br<br>**2g** R= 5-Br | 59 (75)<br>61 (80)<br>64 (82) |
| 5 |  | **2h** | 59 (72) |
| 6 |  | **2i** | 59 (81)[c] |
| 7 |  | **2j** | 61 (70) |
| 8 |  | **2k** | 34 (77) |
| 9 |  | **2l** R: H<br>**2m** R: Me | 60 (63)<br>60 (70) |
| 10 |  | **2n** | 54 (76) |
| 11 |  | **2o** R= H<br>**2p** R= Br<br>**2q** R= Ph | 31 (93)<br>42 (54)<br>34 (66) |
| 12 |  | **2r** | 11 (74) |

[a] Heterocycle (1.0 mmol), potassium cyclobutyltrifluoroborate (1.0 mmol), $Mn(OAc)_3$ (2.5 mmol), TFA (1.0 mmol), AcOH/$H_2O$ 1:1 (0.08 M), 50 °C, 18 h. [b] Isolated yields and conversions (indicated in parentheses) determined by $^1$H NMR spectroscopic analysis of the crude mixture. [c] Heterocycle (1.0 mmol), potassium cyclobutyltrifluoroborate (3.5 mmol), $Mn(OAc)_3$ (5.0 mmol), TFA (1.0 mmol), AcOH/$H_2O$ 1:1 (0.08 M), 50 °C, 18 h.

**Table 3.** Scope of the Alkyltrifluoroborates[a]




| entry | potassium alkyl trifluoroborate | product | | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **3a** | 75 (83) |
| 2 |  |  | **3b** | 75 (79) |
| 3 |  |  | **3c** | 40 (57) |
| 4 |  |  | **3d** | 48 (52) |
| 5 |  |  | **3e** | 25 (45) |
| 6 |  |  | **3f** | 69 (85) |
| 7 |  |  | **3g** | 78 (83) |
| 8 |  |  | **3h** | 68 (70) |
| 9 | *t*-Bu−$BF_3K$ |  | **3i** | 50 (58) |

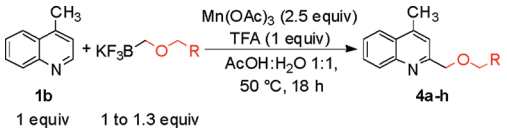
[a] Lepidine (1.0 mmol), potassium alkoxymethyltrifluoroborate (1.0 mmol), $Mn(OAc)_3$ (2.5 mmol), TFA (1.0 mmol), AcOH/$H_2O$ 1:1 (0.08 M), 50 °C, 18 h. [b] Isolated yields and conversions (indicated in parentheses) determined by $^1$H NMR spectroscopic analysis of the crude mixture.

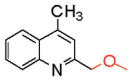
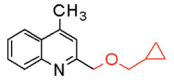
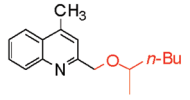
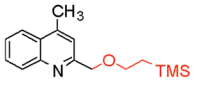
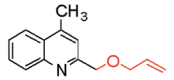
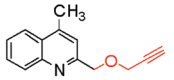
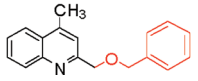
We next evaluated the reactivity of lepidine toward different primary, secondary, and tertiary potassium alkyltrifluoroborates (Table 3). The alkylated heteroaryls **3a**−**i** were obtained with yields between 25 and 78%.

Cyclopentyl and cyclohexyl substituents were successfully added from the corresponding potassium cyclo-

alkyltrifluoroborates with 75% yields for both (entries 1, 2), but the tetrahydropyranyl derivative gave a lower yield (entry 3). The hindered potassium isopinocampheyltrifluoroborate was also coupled to give substituted lepidine **3d** with complete stereoselectivity (entry 4). The ease of alkyltrifluoroborate oxidation and the nucleophilic character of the *in situ* formed alkyl radicals could combine to provide the driving force for the reaction, as the reactivity appears to increase on going from primary to secondary and tertiary radicals.[17] This could explain the low yield obtained for compound **3e**. Good yields are observed for heteroaryls **3f**−**i**, which are substituted by

**Table 4.** Scope of Alkoxymethyltrifluoroborates



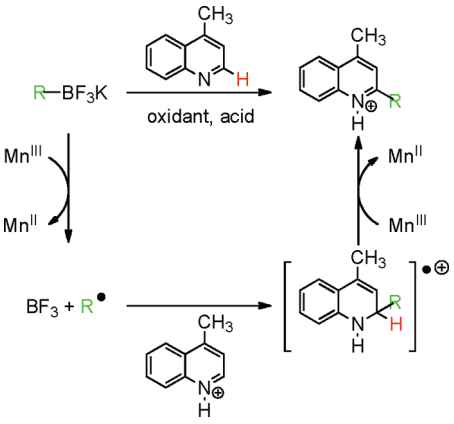

| entry | product | | yield (%)[a] |
|---|---|---|---|
| 1 |  | **4a** | 50 (70)[b] |
| 2 |  | **4b** | 68 (72)[b] |
| 3 |  | **4c** | 58 (76)[b] |
| 4 |  | **4d** | 89 (100)[c] |
| 5 |  | **4e** | 65 (76)[b] |
| 6 |  | **4f** | 65 (74)[c] |
| 7 |  | **4g** | 67 (83)[b] |

[a] Isolated yields and conversions (indicated in parentheses) determined by $^1$H NMR spectroscopic analysis of the crude mixture. [b] Lepidine (1.0 mmol), potassium alkoxymethyltrifluoroborate (1.0 mmol), $Mn(OAc)_3$ (2.5 mmol), TFA (1.0 mmol), $AcOH/H_2O$ 1:1 (0.08 M), 50 °C, 18 h. [c] 1.3 mmol of potassium alkoxymethyltrifluoroborate.

linear secondary and tertiary alkyls, respectively (entries 6−9).

For the third part of our investigation, it was of interest to test the reactivity of various potassium alkoxymethyltrifluoroborates toward lepidine, because ethers induces a change in solubility that is important in drug administration.[18] Diverse potassium alkoxymethyltrifluoroborates were successfully coupled to lepidine (Table 4) with yields between 58 and 89%. Some of these organoborons were made by a process that started with bromomethyltrifluoroborate and may have contained some bromide salts.[19] To counter that possibility, in these cases the trifluoroborates were used in excess (entries 4, 6). The alkoxymethylation reaction

**Scheme 2.** Proposed Mechanism with Lepidine




is tolerant of a range of functional groups present on the boron reagent, including alkene, alkyne, and benzyl groups (entries 5, 6, and 7).

In accord with precedents established in previous studies,[7b,8b,12,14] a possible mechanism can be proposed (Scheme 2). The first step involves a homolytic cleavage of the C−B bond using 1 equiv of manganese(III) acetate. Subsequently, the alkyl radical adds to the protonated heteroaryl to form the corresponding radical cation intermediate, which leads to the protonated heteroaromatic after a second oxidation. Basic workup leads to the final observed product.

In summary, we have reported the first direct alkylation of various heterocyles using potassium alkyl- and alkoxymethyltrifluoroborates as nucleophilic radical precursors. Moderate to good yields are achieved, in most cases, using a stoichiometric amount of both reacting partners. This method fills an important void in that Friedel−Crafts alkylations fail for nearly all heterocyclic systems, and it also represents an efficient way to decorate heteroaryl subunits with unique alkyl substituents (e.g., cyclobutyl and alkoxymethyl groups). Current research efforts seek to expand the process to other distinctive substrates and substituents.

**Acknowledgment.** We thank Frontier Scientific and Aldrich for a donation of boronic acids. Financial support has been provided by the NIH General Medical Sciences (R01 GM035249). Dr. Floriane Beaumard and Luciana Felix (University of Pennsylvania) are acknowledged for making potassium alkoxymethyltrifluoroborates and cyclobutyltrifluoroborate, respectively. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data.

**Supporting Information Available.** Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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