Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3189–3191
Tetrahedron Letters

Microwave promoted amination of 3-bromoisoxazoles

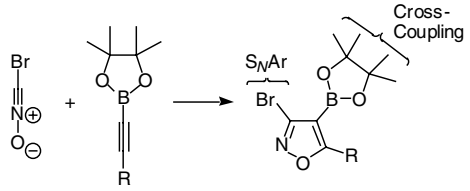
Jane E. Moore,[a] Daniel Spinks[b] and Joseph P. A. Harrity[a,*]

[a]Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK
[b]Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, UK

Received 27 January 2004; accepted 27 February 2004

Abstract—This Letter describes the amination of 3-bromoisoxazoles by a nucleophilic aromatic substitution reaction. We have found 3-bromoisoxazoles to be inert to substitution under thermal conditions, however, the employment of phosphazene bases under microwave irradiation facilitates the amination process and allows the corresponding 3-aminoisoxazoles to be isolated in moderate yield.

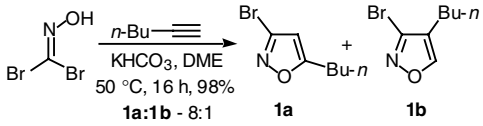
We have recently uncovered a regioselective method for the construction of highly substituted aromatic boronic esters through a series of cycloaddition reactions of alkynylboronates.[1] In particular, we have found that fully substituted isoxazoles can be assembled with the boronate moiety in the 4-position and that these undergo efficient Suzuki coupling reactions. In an effort to broaden the synthetic utility of these intermediates, we opted to investigate some cycloaddition reactions of bromonitrile oxide in the hope that we could elaborate at C-4 through cross-coupling reactions and at C-3 by substitution with an appropriate nucleophile (Scheme 1).[2] In the context of the latter transformation, whilst a small number of alkoxide substitution reactions had been reported, the corresponding amination process appeared to be much less general. Specifically, the direct substitution process was limited to 3-chlorobenzisoxazoles[3] whereas substitution of 3-chloroisoxazoles required a multistep sequence including pre-activation of the isoxazole ring.[4] We decided to examine the feasibility of direct nucleophilic aromatic substitution of 3-bromoisoxazoles and report herein our preliminary findings.



Scheme 1.

We initiated our studies by preparing a relatively simple isoxazole and this was carried out by conducting a [3+2] cycloaddition reaction of in situ generated bromonitrile oxide with 1-hexyne. We were pleased to find that this reaction proceeded efficiently to furnish the 3,5-disubstituted isoxazole **1a** together with a small quantity of its regioisomer **1b** (Scheme 2).

We next turned our attention to the amination reaction and decided to employ piperidine in our optimisation studies, the results are summarised in Table 1. We began by examining thermally promoted amination reactions and were disappointed to find that **1a** was inert to substitution by piperidine under a range of conditions. For example, heating the reaction mixture in a sealed reactivial and in the presence of a nucleophilic catalyst or the employment of inorganic bases failed to furnish any of the desired aminoisoxazole **2** (entries 1–3). The surprisingly sluggish nature of this substitution reaction prompted us to consider alternative means for promoting the amination process.[5] In this context, microwave

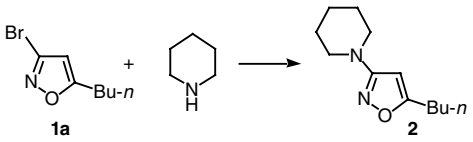


Scheme 2.

Keywords: Isoxazoles; Microwave irradiation; BEMP; Amination.
* Corresponding author. Tel.: +44-0114-222-9496; fax: +44-0114-222-9346; e-mail: j.harrity@shef.ac.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.135

Table 1

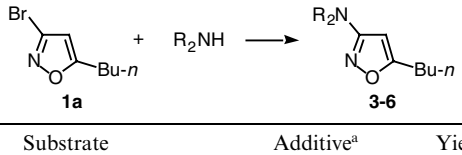


1a **2**

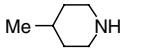
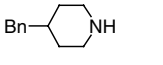
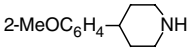
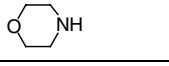
Entry	Conditions	Additive	Yield (%)
1	106 °C, 92 h[a,b]	5% DMAP	0
2	106 °C, 72 h[a]	KOH	0
3	DMF, 153 °C, 120 h	Ag_2CO_3	0
4	MW, MeCN, 200 °C, 15 min	ps-BEMP	57

[a] Piperidine used as solvent.
[b] Reactions heated in a sealed reactivial.

Table 2



1a **3-6**

Entry	Substrate	Additive[a]	Yield
1		BEMP ps-BEMP	**3**; 40% **3**; 55%
2		BEMP ps-BEMP	**4**; 42% **4**; 59%
3		BEMP ps-BEMP	**5**; 30% **5**; 38%
4		BEMP ps-BEMP	**6**; 20% **6**; 37%

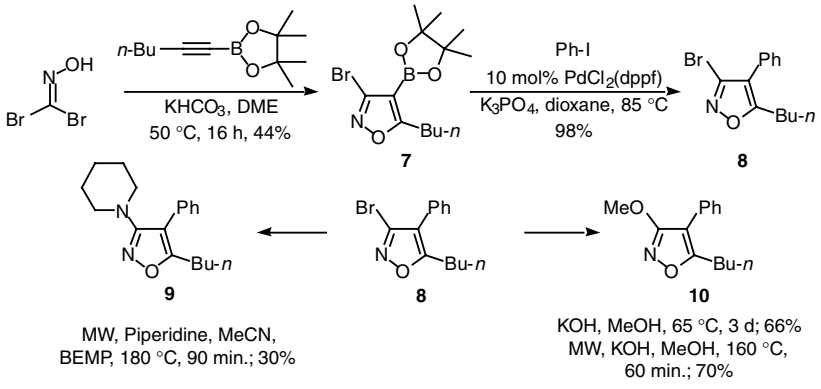
[a] BEMP mediated reactions were run at 180 °C, MW, for 30 min and ps-BEMP mediated reactions were run at 200 °C, MW, for 15 min.

(MW) reactors have recently been reported to facilitate nucleophilic aromatic substitution reactions.[6] Additionally, N-alkylation processes of weakly acidic amines have been shown to proceed efficiently in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP).[7] We therefore speculated that the conversion of **1a** to **2** would be feasible if the process were run under microwave conditions[8] in the presence of phosphazene base. Accordingly, we subjected a mixture of **1a**, piperidine and 1.1 equiv of polymer supported BEMP (ps-BEMP) to microwave irradiation at 200 °C in acetonitrile and were pleased to find that 3-aminoisoxazole **2** was produced in 57% yield after only 15 min.

This encouraging result prompted us to investigate the microwave promoted reaction further. We briefly examined the substitution reaction of a series of cyclic amines in the presence of BEMP and ps-BEMP and found that these conditions furnished the appropriate 2-aminoisoxazoles, albeit in moderate yields. Notably however, the mass balance of isoxazole material consisted of starting bromide **1a** that was readily recovered after column chromatography. Therefore the moderate yields reported in Table 2 are a consequence of low reaction conversion and not compound decomposition. We have found that ps-BEMP provides optimum yields of amination product over solution phase BEMP. This is likely due to the fact that the former reagent can be heated at 200 °C whereas the latter base is restricted to reaction temperatures of 180 °C.[9]

Having successfully uncovered conditions to carry out the amination of 3-bromoisoxazoles our final goal was to incorporate this technique in sequence with our alkynylboronate cycloaddition process. As outlined in Scheme 3, [3+2] cycloaddition of bromonitrile oxide with the alkynylboronate proceeded smoothly to furnish the desired boronic ester as a single regioisomer that underwent efficient cross-coupling to provide isoxazole **8**. Unfortunately, employment of the microwave promoted amination conditions provided 3-aminoisoxazole **9** in a disappointing 30% yield (70% recovery of **8**), likely because of the increased steric demands at C-4.[10] More pleasingly however, we had previously shown that 3-bromoisoxazoles could be substituted by methoxide under thermal conditions albeit over extensive reaction times.[2] However, the use of microwave irradiation produced 3-methoxyisoxazole **10** in high yield but in a significantly reduced reaction time.

In conclusion, we have demonstrated that the amination reaction of 3-bromoisoxazoles is promoted by microwave irradiation in the presence of phosphazene bases. Notably, the reactions do not take place under thermal conditions and whilst the corresponding 3-aminoisoxazoles are generated in only moderate yield, the reactions are clean and starting isoxazole can be efficiently recovered.



Scheme 3.

Acknowledgements

We gratefully acknowledge funding from the EPSRC and Organon and Dr. Mark York for helpful discussions.

References and notes

1. (a) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *Chem. Commun.* **1999**, 2107; (b) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525; (c) Davies, M. W.; Wybrow, R. A. J.; Johnson, C. N.; Harrity, J. P. A. *Chem. Commun.* **2001**, 1558.
2. Moore, J. E.; Goodenough, K. M.; Spinks, D.; Harrity, J. P. A. *Synlett* **2002**, 2071.
3. Amination reactions of 3-chlorobenzisoxazole derivatives have been reported: (a) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L. *J. Med. Chem.* **1986**, *29*, 359; (b) Boeshagen, H. *Chem. Ber.* **1967**, *100*, 3326; (c) Wagner, E.; Becan, L. *Pol. J. Chem.* **1995**, *69*, 70; (d) Villalobos, A.; Blake, J. F.; Biggers, C. K.; Butler, T. W.; Chapin, D. S.; Chen, Y. L.; Ives, J. L.; Jones, S. B.; Liston, D. R.; Nagel, A. A.; Nason, D. M.; Nielsen, J. A.; Shalaby, I. A.; White, W. F. *J. Med. Chem.* **1994**, *37*, 2721; (e) Urban, F. J.; Breitenbach, R.; Murtiashaw, C. W.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1995**, *6*, 321.
4. Sugai, S.; Sato, K.; Kataoka, K.; Iwasaki, Y.; Tomita, K. *Chem. Pharm. Bull.* **1984**, *32*, 530.
5. Attempts at transition metal catalysed amination reactions failed and starting material was recovered in all cases. For a review of Pd-catalysed amination reactions see: Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
6. Li, W.; Yun, L.; Wang, H. *Synth. Commun.* **2002**, *32*, 2657; For an excellent review see: Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
7. (a) Schwesinger, R.; Wiharedt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435; (b) Xu, W.; Mohan, R.; Morrissey, M. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1089; (c) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253.
8. Microwave promoted reactions were carried out using an Emrys™ Optimiser EXP instrument with 'Fixed Hold Time' set to 'Off' and 'Absorption Level' set to 'High'. Representative experimental procedure: The starting bromoisoxazole **1a** (0.20 g, 0.98 mmol) was weighed into a microwave process vial. ps-BEMP (0.45 g, 1.0 mmol), acetonitrile (0.5 mL) and piperidine (0.97 mL, 9.8 mmol) were added sequentially. The vial was sealed and irradiated in the microwave (200 °C, 900 s, 9 bar). The vial was cooled to room temperature and the ps-BEMP filtered off. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (eluting solvent 4:1:0.1 heptane:ethyl acetate:triethylamine) to give aminoisoxazole **2** as a yellow oil wt. 0.120 g, 57% yield. 1H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, $J = 7.28$ Hz), δ 1.33–1.48 (2H, m), δ 1.56–1.68 (8H, m), δ 2.61 (2H, t, $J = 7.53$ Hz), δ 3.22–3.31 (4H, m), δ 5.6 (1H, s). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 13.7, 22.2, 24.2, 25.1, 26.8, 29.49, 29.7, 48.3, 91.8, 167.5, 173.3 ppm. FT-IR: (ν_{max}/$CHCl_3$) 1448 (s), 1505 (m), 1613 (s), 1698 (m), 2858 (s), 2931 (s) cm^{-1}. HRMS (EI+): calcd for $C_{12}H_{20}N_2O$ 208.1576, found: 208.1572.
9. The microwave reactor would not tolerate heating reaction mixtures containing solution phase BEMP to temperatures >180 °C because of the high pressures generated inside the reaction vessel.
10. ps-BEMP was found to decompose over the extended reaction times required for conversion of **8** into **9**.