Tetrahedron Letters 51 (2010) 554–556

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile preparation of alkoxybenzoxazoles via direct S_NAr on the benzoxazole ring

Hervé Germain, Craig S. Harris *, Michel Vautier, Nicolas Warin

AstraZeneca, Centre de Recherches, Z.I. la Pompelle, BP1050, 51689 Reims Cedex 2, France

ARTICLE INFO

Article history:
Received 20 October 2009
Revised 20 November 2009
Accepted 20 November 2009
Available online 26 November 2009

Keywords:
Direct S_NAr
Un-activated fluorides

ABSTRACT

The synthesis of alkoxybenzoxazoles is in general quite challenging. During our investigation, we discovered that C-4 and C-7 fluoro precursors undergo S_NAr with alkoxides affording moderate to excellent yields of substituted product.

During a recent project, we became interested in preparing libraries of benzoxazoles with alkoxy substitution at C-4 and C-7 (Fig. 1). Among the few syntheses described in the literature for the preparation of O-substituted benzoxazoles, most depended on cyclodehydration methodology between the benzoic acid moiety and the appropriate aminophenol precursor (Fig. 1, *approach a*).[1,2] This approach was appealing but has the drawback of preparing the corresponding aminophenols.[3] Surprisingly, there are no methods existing in the literature showing that one can displace halogens by direct S_NAr and just one using assistance from platinum-group metal (PGM) catalysis with oxygen nucleophiles at either C-4 or C-7, which is key for our exploration (Fig. 1, *approach b*).[4]

There are 2 logical possible retrosyntheses of key substructure (Fig. 1): *approach a* requiring the preparation of the benzoxazole directly from the appropriate O-substituted aminophenol, requiring several steps to access, using cyclodehydration protocol;[5] or *approach b* relying on the direct substitution of a suitable leaving group on the phenyl moiety of the benzoxazole ring following cyclodehydration with the appropriate halogen-substituted aminophenol.[4]

Our initial strategy centered around finding an efficient cyclodehydration methodology of the appropriately substituted aminophenol and 2-aminonicotinic acid or 2-aminonicotinic aldehyde with a subsequent oxidation step. After many trials without success employing recently reported mild conditions using 2-aminonicotinic acid (e.g., PS–TPP, Cl_3CCN, microwave;[6] deoxofluor, DIPEA;[7] $POCl_3$;[8] and Mitsunobu conditions[9]) or 2-aminonicotinic aldehyde as the precursor (e.g., DDQ;[10] and MnO_2[11]), we identified that polyphosphoric acid at elevated temperatures was necessary to drive the reaction through to the desired benzoxazole.[5] However, with 2-aminonicotinic acid, we found the reaction to be quite sensitive to electronic and steric effects of the aminophenol precursor resulting in inconsistent yields and in the case of oxygen substitution on the aminophenol, only traces of benzoxazole product were detected (Table 1).

Table 1 shows how substitution on the aminophenol affected the yield of desired benzoxazole in spite of these forcing cyclodehydration conditions. While fluorine substitution was tolerated (entries **2–5**), strong electron-donating (entries **6 and 7**) or electron-withdrawing substitution (e.g., entry **8**) *ortho* to either the amino or phenol group resulted in only traces of cyclised product. In addition, attempts to prepare the desired 7-bromobenzoxazole with a view to process it through to the corresponding phenol via a hydroxydeboronation sequence[12] proved disappointing affording an unseparable mixture of the desired 7-bromobenzoxazole contaminated with the debrominated benzoxazole by-product (entry **9**). As a possible solution and as the cyclisation proceeded efficiently with the appropriate fluoroaminophenols, we proposed the possibility of preparing the 4- and 7-fluorobenzoxazole precursors and attempting direct S_NAr with the appropriate alkoxide. Herein, we communicate to our knowledge the first successful direct S_NAr on 4-F and 7-F benzoxazoles.

Direct S_NAr on un-activated aryl fluorides can be viewed as an acceptable strategy affording moderate to excellent yields of substituted product.[13] However, there are no records of direct S_NAr on benzoxazoles with any substitution at any position of the benzene ring, probably because benzoxazoles can readily undergo ring-opening under basic conditions to afford the corresponding amidophenol precursors.[14] Therefore, we were surprised to observe that the first trials (4 equiv of 2,4-dimethoxybenzylalcohol

* Corresponding author. Tel.: +33 (0)3 26 61 5912; fax: +33 (0)3 26 61 6842.
E-mail address: craig.harris2@astrazeneca.com (C.S. Harris).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.095

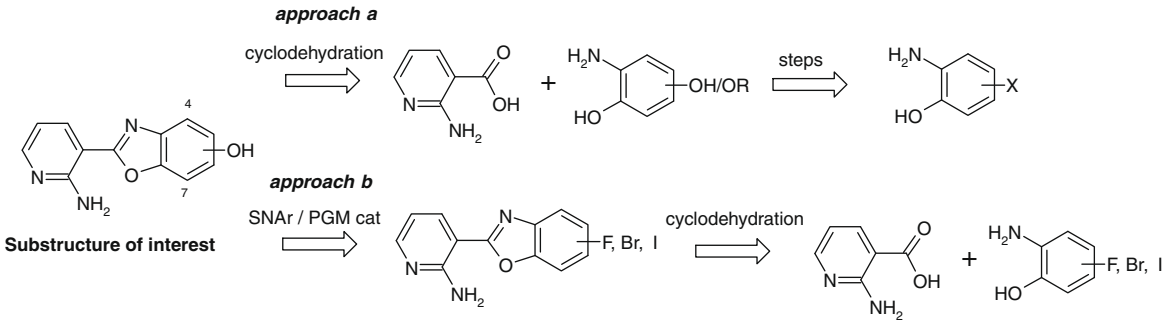
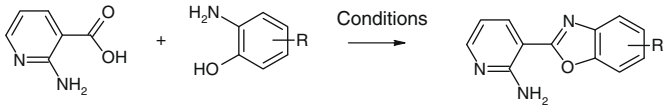


Figure 1. Synthons which could give the desired substructure.

in the presence of NaH, THF and 80 °C) proceeded surprisingly well at C-4 (**2**), affording the C-4-(2,4-dimethoxybenzyloxy)benzoxazole (**10**) in quantitative yield. The resulting C-4–OH (**11**) was revealed under hydrolytic conditions (TFA and DCM). However, attempts to apply the same chemistry failed for the C-7–F precursor (**5**). Ring-opening dominated affording the 'amidophenol' intermediate. After investing some time in process development, we managed to isolate the C-7-methoxybenzoxazole (**12**) in a respectable 45% yield, using similar conditions but changing the solvent from THF to dry NMP. Subsequent revelation of the C-7–OH (**13**) was achieved in quantitative yield using HBr in acetic acid (Scheme 1).

Table 1
Selected results from cyclisation in PPA at 200 °C for 16 h with a variety of aminophenols with 2-aminonicotinic acid

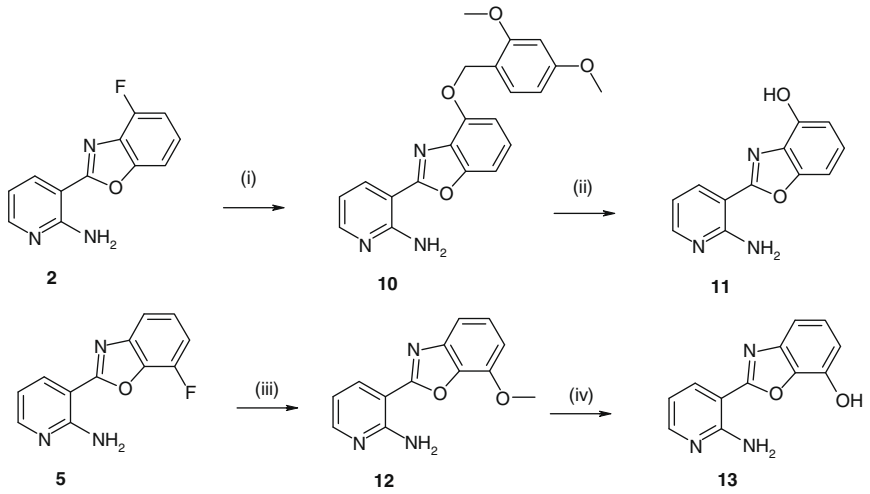


Entry	R	Yield of benzoxazole (%)
1	H	84
2	4-F	62
3	5-F	60
4	6-F	75
5	7-F	53
6	7-OMe	Traces
7	4-OH	Traces
8	4-CO2H	Traces
9	7-Br	23[a]

[a] Product contaminated with debrominated side product.

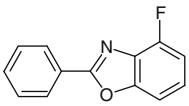
With this knowledge in hand, we turned our attention to investigating the wider application of S_NAr on simple fluoro-substituted benzoxazole substrates. The corresponding C-4, C-5 and C-7–F precursors (**14**, **15** and **16**) were prepared using similar cyclodehydration chemistry to that described above. We decided to carry out a solvent screen on **14** using freshly-prepared MeONa as the nucleophile. 1,2-Dimethoxyethane (DME) and *N*-methylpyrrolidinone (NMP) were identified as the best solvents whereas in MeCN, toluene and methanol only traces of product were observed and in dry DMSO, ring-opening dominated affording the amidophenol and only traces substituted product.

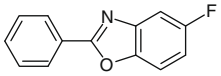
From Table 2, one can potentially deduce that the ease of fluorine atom displacement is determined by the inductive effect, that is, **14** > **16** ≫ **15**, which is what we expected. Displacement at C-4, however, is notably much easier than at C-7, also benefiting from a similar inductive effect. We postulate that the reason for this difference is the fact that the charge can be delocalised throughout the benzoxazole and neighbouring C-2-phenyl ring whereas the charge resulting from an attack at C-7 can only be stabilised by the inductive effect of the benzoxazole. In both cases, yields remained very much superior to those obtained via C-6–F displacement as this position experiences the weakest inductive effect and ring-opening dominated. Attempts to effect the displacement with amines, even at C-4 using piperidine (entry **25**) as the solvent, failed affording only traces of product.

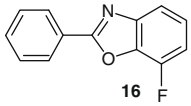


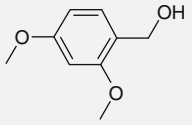
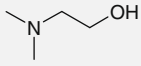
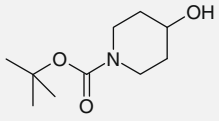
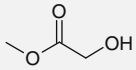
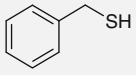
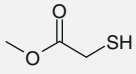
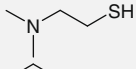
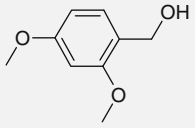
Scheme 1. Synthesis of key precursors **11** and **13**. Reagents and conditions: (i) 2,4-Dimethoxybenzylalcohol, NaH, THF, 75 °C, quant.; (ii) TFA, DCM, 91%; (iii) MeOH, NaH, NMP, 16 h, 45%; and (iv) HBr in AcOH, 120 °C, 100%.

Table 2
Results of S_NAr with various nucleophiles on **14**, **15** and **16**


14


15


16

Entry	Benzoxazole	Nucleophile	Yield of substituted product (%)
17	**14**		81[a]
18	**14**		72[a]
19	**14**		60[a]
20	**14**		49[a]
21	**14**		10[a]
22	**14**		50[b]
23	**14**		11[b]
24	**14**		49[b]
25	**14**		Traces[c]
26	**15**		0[a]
27	**16**		43[b]
28	**16**		32[b]

3–4 equiv of alcohol or thiol, 3–4 equiv of NaH were used in [a]1,2-dimethoxyethane, 70 °C, 16 h; [b]NMP used as the solvent, 85 °C, 5–16 h; [c]piperidine used as the solvent at 180 °C.

In conclusion, we have developed surprisingly efficient and mild conditions for the introduction of nucelophiles, notably oxygen-based, at C-4 and to some extent at C-7 of the benzoxazole ring in poor to excellent yields.

Acknowledgements

The authors would like to acknowledge Dr. Gilles Ouvry, Dr. Bernard Barlaam, Dr. Bénédicte Délouvrie, Mr. Fabrice Renaud and Mr. Christian Delvare for their interest and analytical support for this sub-series.

Supplementary data

Supplementary data (full experimental procedures and supporting LC–MS and ^1H and ^{13}C NMR characterisation data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.095.

References and notes

1. For recent methods for C-4-oxy substituted benzoxazoles via cyclisation see: (a) Brehu, L.; Fernandes, A.-C.; Lavergne, O. *Tetrahedron Lett.* **2005**, *46*, 1437–1440; (b) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411–6413; (c) Barlaam, B. C.; Bower, J. F.; Delouvrie, B.; Fairley, G.; Harris, C. S.; Lambert, C.; Ouvry, G.; Winter, J. J. G. PCT Int. Appl. WO 2009053737, 2009 (includes also C-7-oxy substituted benzoxazoles).
2. For recent methods for C-7-oxy substituted benzoxazoles via cyclisation see: (a) Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. *Org. Lett.* **2008**, *10*, 2589–2591; (b) Corfield, J. A.; Grimes, R. M.; Harrison, D.; Hartley, C. D.; Howes, P.D.; Le, J.; Meeson, M. L.; Mordaunt, J.E.; Shah, P.; Slater, M. J.; White, G. V. PCT Int. Appl. WO 2007071434, 2007.
3. For C-4-hydroxysubstituted benzoxazoles, the most direct method depended on the reduction of 2-nitroresorcinol: Ausin, C.; Ortega, J.-A.; Robles, J.; Grandas, A.; Pedroso, E. *Org. Lett.* **2002**, *4*, 4073–4075; for the preparation of 7-oxy substituted benzoxazoles, the most direct method depended on the nitration and subsequent reduction of Guaiacol (2-methoxyphenol), Kanoo, F.; Yamane, T.; Kondo, H.; Hashizume, T.; Yamashita, K.; Hosoe, K.; Kuze, F.; Watanabe, K. Eur. Pat. Appl. EP 333176, 1989.
4. Malamas, M. S.; Manas, E. S.; McDevitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021–5040.
5. (a) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427–429; for a nice library procedure using polymer bound esters see: (b) Lim, H.-J.; Myung, D.; Lee, I. Y. C.; Jung, M. H. *J. Comb. Chem.* **2008**, *10*, 501–503.
6. Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823–4826.
7. Kangani, C. O.; Kelley, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6497–6499.
8. Rose, U. *J. Heterocycl. Chem.* **1992**, *29*, 551–557.
9. Wang, F.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 6529–6532.
10. Chang, J.; Kang, Z.; Shifeng, P. *Tetrahedron Lett.* **2002**, *43*, 951–954.
11. Bougrin, K.; Loupy, A.; Souflaoui, M. *Tetrahedron* **1998**, *54*, 8055–8064.
12. For a recent large-scale hydroxydeboronation protocol see: Germain, H.; Harris, C. S.; Renaud, F.; Warin, N. *Synth. Commun.* **2009**, *39*, 523–530.
13. (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119–2183. and references cited therein; (b) Ouellet, S. G.; Bernardi, A.; Angelaud, R.; O'Shea, P. *Tetrahedron Lett.* **2009**, *50*, 3776–3779; (c) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399–11428; (d) Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron Lett.* **1999**, *40*, 1219–1222; (e) Belfield, A. J.; Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron* **1999**, *55*, 13285–13300. and corrigendum 2000, 56, 4107.
14. Brunner, H.; Olschewski, G.; Nuber, B. *Synthesis* **1999**, *3*, 429–434.