Tetrahedron Letters 50 (2009) 6106–6109

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Oxidative conversion of amines into benzoxazoles using hydrogen transfer catalysis

A. John Blacker [a], Mohamed M. Farah [a], Stephen P. Marsden [a,*], Ourida Saidi [b], Jonathan M. J. Williams [b]

[a] School of Chemistry and Institute of Process Research and Development, University of Leeds, Leeds LS2 9JT, UK
[b] Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

ARTICLE INFO

Article history:
Received 24 June 2009
Revised 29 July 2009
Accepted 14 August 2009
Available online 20 August 2009

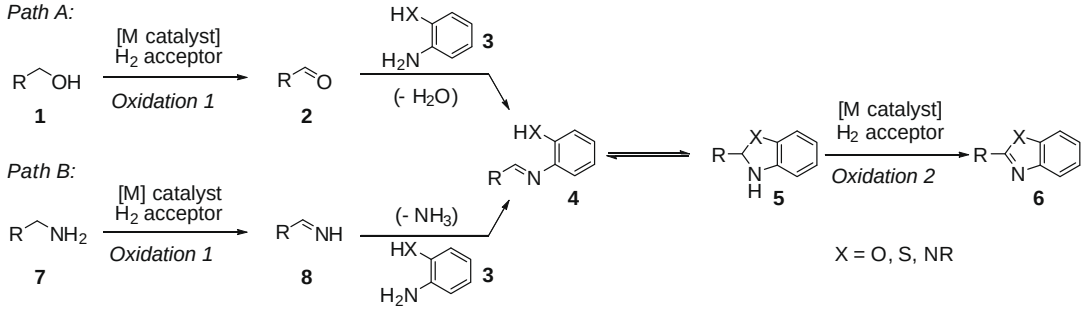
Keywords:
Benzoxazole
Hydrogen transfer
Oxidation
Catalysis

ABSTRACT

Benzoxazoles are synthesised directly by oxidative condensation of primary and secondary amines with *o*-aminophenols under hydrogen transfer catalysis. The optimal system utilises 1 mol % of the Shvo catalyst, with dimethoxybenzoquinone as the hydrogen-accepting terminal oxidant.

Benzoxazoles occur in a diverse range of biologically active natural products[1] and pharmaceutical targets,[2] and as such, new methods for the formation of these heterocycles are in constant demand. Amongst the myriad synthetic approaches to benzoxazoles,[3–5] the use of stoichiometric oxidants to effect the aromatising condensation of alcohols[6] or aldehydes[7] with 2-aminophenols has been widely described. Catalytic oxidative processes have, by contrast, been little studied,[8] although there are reports of aerobic oxidative formation of benzoxazoles using TEMPO derivatives, copper nanoparticles and activated carbon.[9] In this context, we recently reported the use of homogeneous hydrogen transfer catalysis for the oxidative formation of benzazoles from alcohols or aldehydes according to Scheme 1, Path A.[10] Thus, hydrogen abstraction from an alcohol **1** by the catalyst gives an aldehyde **2**, which undergoes condensation with an *ortho*-heterosubstituted aniline **3** to generate Schiff base **4**. Alternatively, **4** may be accessed directly from an aldehyde starting material. Subsequent hydrogen abstraction from the ring-closed dihydrobenzazole **5** generates the desired heterocycle **6**.

In earlier work,[10] we found that the combination of $Ru(PPh_3)_3(CO)H_2$/Xantphos together with crotononitrile as a hydrogen acceptor to mediate catalyst turnover was effective for the conversion of alcohols into benzimidazoles, while the catalyst $[CpIrI_2]_2$ effected conversion of aldehydes into benzoxazoles and benzo-

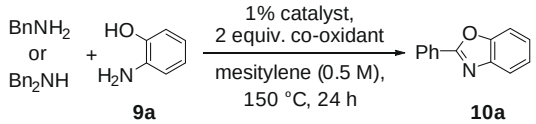


Scheme 1. Oxidative approaches to benzazoles by hydrogen transfer catalysis.

* Corresponding author. Tel.: +44 113 343 6425; fax: +44 113 343 6565.
E-mail address: s.p.marsden@leeds.ac.uk (S.P. Marsden).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.042

Table 1
Optimisation of oxidative benzoxazole formation from amines



9a **10a**

Entry	Amine	Catalyst	Co-oxidant	Yield (%)
1[a,b]	$BnNH_2$	$[CpIrI_2]_2$	None	0
2[a,b]	$BnNH_2$	Shvo	None	0
3[b]	$BnNH_2$	Shvo	None	0
4[a,b]	$BnNH_2$	Shvo	Styrene	0
5	$BnNH_2$	Shvo	DMBQ	43
6[c]	$BnNH_2$	Shvo	DMBQ	31
7	Bn_2NH	$[CpIrI_2]_2$	None	0
8	Bn_2NH	$[CpIrI_2]_2$	DMBQ	43
9	Bn_2NH	Shvo	None	0
10	Bn_2NH	Shvo	Crotononitrile	0
11	Bn_2NH	Shvo	$^tBuCH{=}CH_2$	5
12	Bn_2NH	Shvo	DMBQ	66
13[d]	Bn_2NH	Shvo	DMBQ	46
14[c]	Bn_2NH	none	DMBQ	20
15	Bn_2NH	Shvo	Air	27

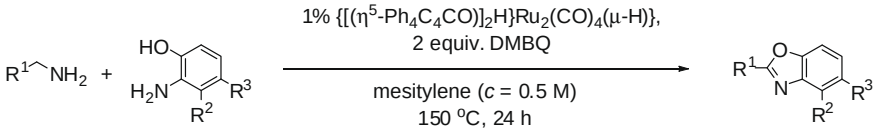
[a] Solvent = toluene, sealed tube.
[b] Concentration = 4 M.
[c] Reaction in toluene at reflux.
[d] 1 equiv of co-oxidant used.

thiazoles without the need for an external hydrogen acceptor. However, all of our attempts to form benzoxazoles by direct oxidative condensation of alcohols with 2-aminophenols met with failure. This was particularly disappointing given the reports of Watanabe[8a] and Huh[8b] that $RuCl_2(PPh_3)_3$ catalysed the oxidative condensation of 2-aminophenols and primary alcohols in moderate yields, albeit at relatively high temperatures (180–215 °C). However, given that the final hydrogen abstraction step in all the above-mentioned reactions is effectively an amine dehydrogenation, we wondered whether alkyl amines might themselves serve as substrates for the direct oxidative formation of benzoxazoles. Thus, hydrogen abstraction (e.g., from a primary amine **7**) would lead to the formation of a Schiff base **8** which upon transimination with the *ortho*-heteroaniline **3** would generate the same intermediate Schiff base **4** for oxidative benzazole formation (Scheme 1, Path B). Such use of an amine as the oxidation substrate for heterocyclisation is, to our knowledge, unprecedented, and we report herein the successful demonstration of this strategy for the conversion of primary and secondary amines into benzoxazoles.

In our initial experiments, we examined the oxidative coupling of benzylamine with *ortho*-aminophenol using two catalysts, namely $[CpIrI_2]_2$[11] and the Shvo catalyst $\{[(\eta^5\text{-}Ph_4C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)\}$.[12] In the event, neither catalyst gave any benzoxazole when heated with the two reactants alone (Table 1, entries 1–3).

Given the known ability of each of these catalysts to promote hydrogen borrowing from amines,[11,13] we reasoned that one possible explanation for the lack of reactivity might be an unfavourable equilibrium between the amine and imine, leading to a low concentration of the latter for participation in the transimination. We therefore investigated additives which might accept hydrogen from the catalyst, and hence shift the equilibrium towards the

Table 2
Scope of the oxidative conversion of amines into benzoxazoles[14]

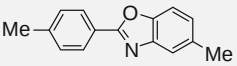
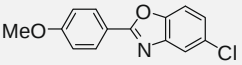
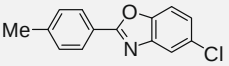
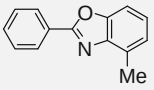
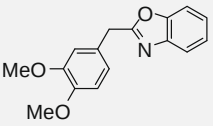
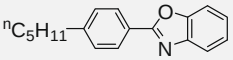


7 **9** **10**

Entry	Amine	R^1	Aminophenol	R^2	R^3	Product	Yield (%)
1	**7a**	Ph	**9a**	H	H	**10a**	43
2	Bn_2NH	Ph	**9a**	H	H	**10a**	66
3	**7b**	4-$MeOC_6H_4$	**9a**	H	H	**10b**	70
4	**7c**	4-MeC_6H_4	**9a**	H	H	**10c**	62
5	**7d**	4-ClC_6H_4	**9a**	H	H	**10d**	36
6	**7e**	2-thienyl	**9a**	H	H	**10e**	30
7	**7a**	Ph	**9b**	H	Me	**10f**	64
8	**7b**	4-$MeOC_6H_4$	**9b**	H	Me	**10g**	68

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine	R^1	Aminophenol	R^2	R^3	Product		Yield (%)
9	**7c**	4-MeC_6H_4	**9b**	H	Me	**10h**		68
10	**7b**	4-$MeOC_6H_4$	**9c**	H	Cl	**10i**		50
11	**7c**	4-MeC_6H_4	**9c**	H	Cl	**10j**		42
12	**7a**	Ph	**9d**	Me	H	**10k**		52
13	**7f**	$ArCH_2$[a]	**9a**	H	H	**10l**		48
14	**7g**	C_5H_{11}	**9a**	H	H	**10m**		55

[a] Ar = 3,4-$(MeO)_2C_6H_3$–.

imine. Styrene was found to be ineffective (entry 4), but 2,6-dimethoxybenzoquinone (DMBQ)[13b–d] delivered moderate yields of the desired benzoxazole in both mesitylene and toluene as solvents (entries 5 and 6). We also considered the possibility that the primary amine (benzylamine) might be more difficult to oxidise than a more electron-rich secondary amine. The resulting *N*-alkylbenzaldimine ought still to be able to participate in transimination and hence in benzoxazole formation. We therefore examined the reactions using dibenzylamine as the substrate. In the absence of a hydrogen accepting co-oxidant, no reaction was observed (entries 7 and 9), but the addition of co-oxidants again proved effective, with DMBQ proving most efficient. The Shvo catalyst appears more effective than $[CpIrI_2]_2$ in this transformation (entries 8 and 12).

We next attempted to determine the role of the DMBQ. Use of a single stoichiometric equivalent of DMBQ gave a much-reduced yield of benzoxazole (entry 13), suggesting its involvement in both oxidation steps. A control reaction in the absence of a catalyst showed that DMBQ alone can mediate benzoxazole formation, but this reaction returned only a low yield of product (entry 14), demonstrating a significant role for the catalyst. Finally, we examined whether the formal dehydrogenation of the catalyst might be mediated aerobically, to circumvent the need for the organic co-oxidant. Again, this was successful but low yielding (entry 15). Although we cannot comment further on the exact mode of action of DMBQ, it is clear from these results that both catalyst and co-oxidant are required for the most efficient transformation, and that the latter has a role in both putative oxidation steps.

With an optimised protocol in hand, we next examined the scope and limitations of the method with respect to both amine and aminophenol reactants. The results are outlined in Table 2.

The reaction is effective for a range of primary benzylic and heterobenzylic amines. Higher yields are obtained for substrates bearing electron-donating substituents (*p*-MeO–, *p*-Me) and lower yields are obtained for the electron-poor *p*-chloro derivative (entries 3 and 4 cf. entry 5). This is consistent with a mechanism involving hydride abstraction with a resulting build-up of partial positive charge at the benzylic carbon. Similarly, the presence of an electronegative chlorine atom in the aminophenol gives lower yields (entries 10 and 11) than the corresponding electronically neutral (entries 3 and 4) or electron-rich (entries 8 and 9) variants. Notably, the steric impediment presented by a methyl substituent *ortho* to the amino function does not impact significantly upon the efficiency of the process (entry 12). Finally, the reaction was found to be general for simple (non-benzylic) substrates (entries 13 and 14). This is in contrast to our previously reported approach to benzoxazoles commencing from aliphatic aldehydes, in which enamine-based pathways caused the formation of undesired 8-hydroxyquinolines as the only observable products of the reactions.[10]

In summary, we have developed a new oxidative approach to benzoxazoles starting from primary amines as the source of the C2-carbon,[14] further broadening the scope of chemistry that can be accomplished by hydrogen transfer from amines. The results of further studies from our laboratories in the latter area will be disclosed in due course.

Acknowledgement

We thank the EPSRC for funding through Grants EP/F038321/1 and EP/F0376431/1. SPM is a Royal Society Industry Fellow (2008-10).

References and notes

1. See, for example, UK-1 (Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089), the boxazomycins (Kusumi, T.; Ooi, T.; Wälchli, M. R.; Kakisawa, H. *J. Am. Chem. Soc.* **1998**, *110*, 2954) and calcimycin (Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932).
2. For recent examples, see: (a) Yoshida, S.; Watanabe, T.; Sato, Y. *Bioorg. Med. Chem.* **2007**, *15*, 3515; (b) Wang, B.; Vernier, J.-M.; Rao, S.; Chung, J.; Anderson, J. J.; Brodkin, J. D.; Jiang, X.; Gardner, M. F.; Yang, X.; Munoz, B. *Bioorg. Med. Chem.* **2004**, *12*, 17; (c) Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455.
3. For discussion of general synthetic approaches to benzoxazoles, see: (a) Boyd, G. V.. In *Science of Synthesis*; Schaumann, E., Ed.; Thieme: Stuttgart, 2002; Vol. 11, pp 481–492; (b) Döpp, H.; Döpp, D.. In *Houben-Weyl: Methoden der Organischen Chemie*; Schaumann, E., Ed.; Thieme: Stuttgart, 1993; Vol. E8a, pp 1020–1193.
4. For recent transition metal catalysed approaches to benzoxazoles from *ortho*-haloanilines, see: (a) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452; (b) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665; (c) Barbero, N.; Carril, M.; San Martin, R.; Dominguez, E. *Tetrahedron* **2007**, *63*, 10425; (d)

Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802; (e) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.
5. For recent approaches to benzoxazoles by copper-catalysed oxidative cyclisation of anilides, see: (a) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411; (b) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.
6. MnO_2: Wilfred, C. D.; Taylor, R. J. K. *Synlett* **2004**, 1628.
7. $Pb(OAc)_4$: (a) Costa, S. P. G.; Batista, R. M. F.; Raposo, M. M. M. *Tetrahedron* **2008**, *64*, 9733; $Mn(OAc)_3$: (b) Ozokan, K. G.; Gumus, M. K.; Kaban, S. *J. Heterocycl. Chem.* **2008**, *45*, 1831; I_2: (c) Sahu, D. P. *Synth. Commun.* **2006**, *36*, 2189; DDQ: (d) Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951; $PhI(OAc)_2$: (e) Jung, M. H.; Choi, S.-W.; Cho, K.-W. *J. Heterocycl. Chem.* **2000**, *37*, 969; MnO_2: (f) Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055; Ag_2O: (g) Yoshifuji, M.; Nagase, R.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 873.
8. (a) Kondo, T.; Yang, S.; Huh, K.-T.; Kobayashi, M.; Kotachi, S.; Watanabe, Y. *Chem. Lett.* **1991**, 1275; (b) Huh, K.-T.; Shim, S. C. *Bull. Korean Chem. Soc.* **1993**, *14*, 449.
9. TEMPO: (a) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330; Cu-nanoparticles: (b) Kidwai, M.; Bansal, V.; Saxena, A.; Aerry, S.; Mozumdar, S. *Tetrahedron Lett.* **2006**, *47*, 8049; Activated carbon: (c) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713.
10. Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039.
11. (a) Blacker, A. J.; Stirling, M. J. WO2006046059, Avecia Pharmaceuticals Ltd., 2006; *Chem. Abstr.* **2006**, *144*, 450503.; (b) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642; (c) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247.
12. Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1985**, *282*, C7.
13. (a) Pàmies, O.; Ëll, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 4699; (b) Samec, J. S. M.; Ëll, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327; (c) Ëll, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. *Chem. Commun.* **2002**, 1144; (d) Ëll, A. H.; Johnson, J. B.; Bäckvall, J.-E. *Chem. Commun.* **2003**, 1652.
14. *General method for the synthesis of benzoxazoles*. A mixture of the appropriate amine (1.0 mmol, 1.0 equiv), 2-aminophenol (1.0 mmol, 1.0 equiv), 2,6-dimethoxy-1,4-benzoquinone (2.0 mmol, 2.0 equiv) and Shvo catalyst (0.01 mmol) in mesitylene (2.0 mL) was charged to a 100 mL Radley's carousel tube under a nitrogen atmosphere, and the reaction mixture was heated at 150 °C for 24 h. After cooling, the crude reaction mixture was loaded directly onto a silica gel column and eluted with petroleum ether followed by the appropriate mixture of ethyl acetate/petroleum ether to afford the appropriate benzoxazole.