Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 511–513

TETRAHEDRON LETTERS

Synthesis of novel 2,2- and 1,1-linked dimeric 'head-to-head' *N*-alkoxybenzimidazoles

John M. Gardiner,[a,*] Andrew D. Goss,[a] Tahir N. Majid[b] and Andrew D. Morley[c,†]

[a]*Department of Chemistry, UMIST, Manchester M60 1QD, UK*
[b]*Aventis Pharma US, Route 202-206, Bridgewater, NJ 08807, USA*
[c]*Aventis Pharma, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

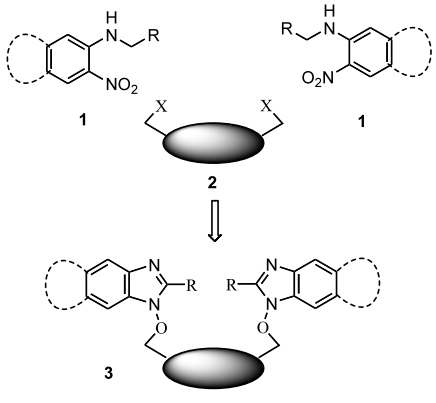
Received 22 August 2002; revised 30 October 2002; accepted 15 November 2002

Abstract—Synthesis of two new types of 'head-to-head' *N*,*N*-alkoxy bisbenzimidazoles is described. The proposed intermediate *N*-oxy benzimidazole from base-induced heterocyclization of *N*-alkylnitroanilines can be trapped with a biselectrophile (to give an *N*,*N*-linked dimer), or double heterocyclization of dimeric nitroanilines can be intercepted by electrophile trapping of both *N*-oxybenzimidazole termini to give C2,C2-linked dimers. These represent two regioisomeric motifs constituting new classes of benzimidazole dimers.

Dimeric benzimidazoles have attracted interest in two primary areas in recent years. A number have been used as ligands for various metals, including lanthanides[1] and a range of transition metals.[2] These have included systems with useful metal-selective binding abilities, and some with intriguing solid state structural features (e.g. triple helical or network assemblies). Some have also been proposed as ligand mimics of Cu(I)/Cu(II) biological redox systems. Certain dimeric systems are effective DNA minor groove binding agents with significant potential for new drug development,[3] and there have also been examples of other bioactivity, for example as dopamine D3 ligands.[4]

We previously reported new methodology for synthesis of *N*-alkoxybenzimidazoles from 2-nitroanilines,[5] and have recently established that this reaction can be intercepted via *N*-alkyl nitroanilines widening its applicability.[6] Critically, we found evidence that the mechanism involves heterocyclization to an *N*-oxybenzimidazole which is *O*-alkylated in the final stage. In this context we saw an opportunity to evaluate whether this methodology could be applied to generating dimeric systems. There are two basic linkage formats we wished to evaluate for generating 'head-to-head' dimeric systems using this methodology.

The ring systems could either be linked between the C2 atoms or via the *N*-alkoxy substitutents. The former approach (to generate **3**) could be achieved using a bifunctional electrophile **2** reacting with a standard *N*-alkylnitro-aniline **1** intermediate, trapping two equivalents of benzimidazole (Scheme 1). The latter approach envisages a dimeric *N*-alkyl nitroaniline (prepared from bisamine **4** and **5**) used as the substrate for a double heterocyclization, both *N*-alkoxy functions might be trapped with electrophiles, which would provide the latter target (**6**) (Scheme 2). The advantages of demonstrating either approach are substantial. The first approach could have applicability to various biselectrophiles with structural variability in the bridging

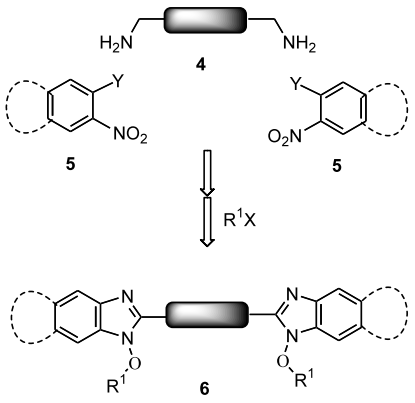


Scheme 1. Biselectrophile trapping to form *N*,*N*-alkoxy-linked dimers.

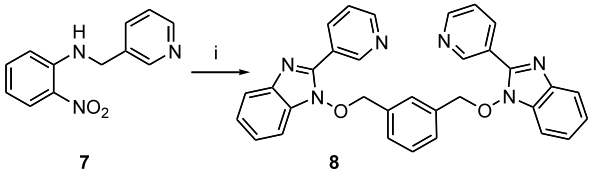
* Corresponding author. Tel.: +44 (0)161 200 4530; e-mail: john.gardiner@umist.ac.uk

† Present address: AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG; tel.: +44 (0)1625 512782.

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02590-X



Scheme 2. Bisamine strategy towards 2,2-linked dimers.



Scheme 3. *Reagents and conditions*: (i) NaH, Δ, 12 h then 1,3-bis(bromomethyl)benzene.

linker envisaged. The second approach offers the potential of extension to various diamine-derived bridges, but also trapping with diverse electrophiles, R^1.

Our recent work on monomeric systems indicates that many different electrophiles can be used for a final *O*-alkylation, and such chemistry ought thus to be extendable to dimers, opening the way to diverse analogue availability.

As an illustration of the potential for synthesis of 1,1-linked dimers of type **3**, the 2-pyridylmethyl system **7**, (prepared by reaction of 2-nitrofluorobenzene with 3-aminomethyl pyridine), was treated with base, and then with 1,3-bis(bromomethyl)benzene to afford the target dimer **8** in ca. 30% purified yield over the two steps (Scheme 3).[7]

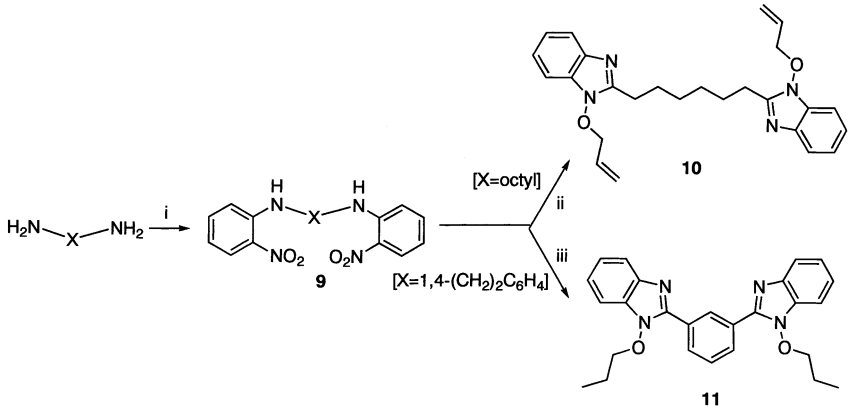
We then turned to assessing whether the diamine-based approach could be used for forming a double *N*-oxybenzimidazole with concomitant trapping of the intermediate *N*-oxy functions of targets of type **6**. In this case, we used examples of both an alkyl diamine and an aryl containing diamine. Thus, reaction of 1,8-octyldiamine with 2-nitrofluorobenzene afforded the bisaniline **9** [X = $(CH_2)_8$)] and treatment of this under our *N*-alkoxybenzimidazole forming conditions in the presence of excess allyl bromide led to isolation of the target bis-*N*,*N*-allyloxybenzimidazole **10**. To illustrate that aryl linkers could be employed and also to vary the nature of the trapping electrophile, an analogous reaction using 1,3-bisaminomethylbenzene, with propyl iodide as the trapping electrophile, afforded the dimeric target **11** (Scheme 4).[7] In these examples, the overall two-step yields were usually slightly lower than for dimer system **8**.

Although the yields are not optimized,[8] the two-step synthesis offers access to complex, otherwise unavailable, dimers in two novel families by elaboration of simple diamines and 2-nitrofluorobenzene, in adequate overall yields in short sequences.

This work demonstrates that our general methodology for *N*-alkoxybenzimidazoles is applicable to generation of both possible modes of dimeric 'head-to-head' *N*-alkoxybenzimidazoles, and this work coupled with the versatility demonstrated in the monomeric systems indicates this has potential for wide applicability to generation of further novel types of 2,2- or *N*,*N*-linked dimeric *N*-alkoxybenzimidazoles.[9] The biological activities of novel dimeric *N*-alkoxybenzimidazoles will be evaluated and reported in due course.

Acknowledgements

Aventis are thanked for support through a CASE collaboration. NMR, HPLC and IR characterization used instrumentation funded through EPSRC grants GR/L52246 (NMR), GR/M30135 (IR) and GR/L84391

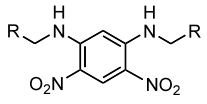


Scheme 4. *Reagents and conditions*: (i). K_2CO_3, DMF, 2-nitrofluorobenzene (2 equiv.), Δ; (ii) NaH, 18 h then allyl bromide (2 equiv.), 30 min; (iii), NaH, 2 h, then PrI, 2 h.

(HPLC). The EPSRC Mass Spectrometry Service at Swansea is thanked for carrying out low and high resolution analyses on a number of the new compounds described.

References

1. Muller, G.; Bünzli, J.-C. G.; Schenk, K. J.; Piguet, C.; Hopfgartner, G. *Inorg. Chem.* **2001**, *40*, 2642–2651.
2. (a) Su, C.-Y.; Cai, Y.-P.; Chen, C.-L.; Kang, B.-S. *Inorg. Chem.* **2001**, *40*, 2210–2211; (b) Gupta, M.; Mathur, P.; Butcher, R. J. *Inorg. Chem.* **2001**, *40*, 878–885; (c) Matthews, C. J.; Clegg, W.; Heath, S. L.; Martin, N. C.; Hill, M. N. S.; Lockhart, J. C. *Inorg. Chem.* **1998**, *37*, 199–207; (d) Matthews, C. J.; Leese, T. A.; Clegg, W.; Elsegood, M. R. J.; Horsburgh, L.; Lockhart, J. C. *Inorg. Chem.* **1996**, *35*, 7563–7571; (e) Matthews, C. J.; Leese, T. A.; Thorp, D.; Lockhart, J. C. *J. Chem. Soc., Dalton Trans.* **1998**, 79–88 and references cited therein.
3. (a) Neidle, S.; Mann, J.; Rayner, E. L.; Baron, A.; Opoku-Boahen, Y.; Ian, J.; Simpson, I. J.; Smith, N. J.; Fox, K. R.; Hartley, J. A.; Kelland, L. R. *Chem. Commun.* **1999**, 929–930; (b) Neidle, S. *FEBS Lett.* **1992**, *298*, 97–99; (c) Czarny, A.; Boykin, D. W.; Wood, A. A.; Nunn, C. M.; Neidle, S.; Zhao, M.; Wilson, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 4716–4717; (d) Bose, D. S.; Thompson, A. S.; Smellie, M.; Berardini, M. D.; Hartley, J. A.; Jenkins, T. C.; Neidle, S.; Thurston, D. E. *J. Chem. Soc., Chem. Commun.* **1992**, 1518–1520.
4. Wright, J.; Downing, D.; Heffner, T.; Pugsley, T.; MacKenzie, R.; Wise, L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2451–2456.
5. (a) Gardiner, J. M.; Loyns, C. R.; Schwalbe, C. H.; Barrett, G. C.; Lowe, P. R. *Tetrahedron* **1995**, *51*, 4101–4110; (b) Gardiner, J. M.; Loyns, C. R. *Synth. Commun.* **1995**, *25*, 819–827; (c) Evans, T. M.; Gardiner, J. M.; Mahmood, N.; Smis, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 409–412; (d) Gardiner, J. M.; Procter, J. *Tetrahedron Lett.* **2001**, *42*, 5109–5111.
6. Gardiner, J. M.; Goss, A. D.; Majid, T.; Morley, A. D.; Pritchard, R. G.; Warren, J. E. *Tetrahedron Lett.* **2002**, *43*, 7707–7710.
7. All the dimeric systems were fully characterized after purification by column chromatography. In the case of **8**, dimerization is evident in ^{1}H NMR, where a 4H benzylic singlet is observed, and integration is conclusive.
8. A number of parameters could be systematically evaluated for changing conditions from those successful for monomers, including timing and rate of electrophile additions and concentrations, all of which may effect the efficiency of the reactions.
9. We have also prepared the dimeric nitroanilines **9** [X = $(CH_2)_4$)], **9** [X = 1,4-$(CH_2)_2C_6H_4$], which are precursors to linker structural analogues of **10** and **11**. A precursor to 'tail-to-tail' analogues **12**, has also been prepared, but pure bis-benzimidazoles have not yet been isolated from reactions of this intermediate.



12