Pergamon

Tetrahedron Letters 43 (2002) 7707–7710

TETRAHEDRON LETTERS

Synthesis of *N*-alkoxybenzimidazoles and *N*-alkoxypyrimidazoles

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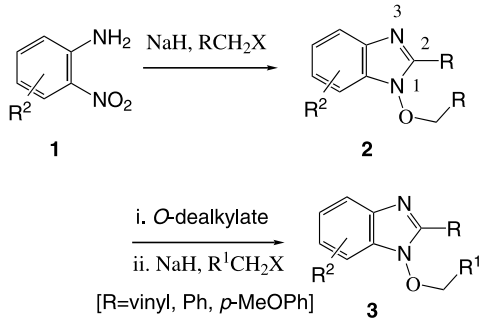
Received 5 June 2002; revised 20 August 2002; accepted 30 August 2002

Abstract—A variety of novel *N*-alkoxy aromatic-fused imidazoles have been prepared in a simple two-step process from 2-fluoro nitroaromatics and 2-chloro-3-nitropyridine. The imidazole forming step involves tandem heterocyclisation and *O*-alkylation with an in situ alkylating agent, and supports prior mechanistic proposals. Additional mechanistic experiments are described. The protocol is versatile with respect to both substrate halo-nitro aromatics and to the nature of the added electrophile (halides) used in the second step, and thereby significantly extends the scope of this reaction and its applicability to diverse synthesis. This methodology can also be used to generate various types of novel *N*-alkoxypyrimidazoles (4-deazapurine analogues), and an X-ray structure of one such pyrimidazole is presented.

The 1-hydroxybenzimidazole ring system was first reported in 1887 (though initially isomerically misassigned as an oxaziridine),[1] and is in tautomeric equilibrium with the alternative benzimidazole-*N*-oxide structure.[2] Syntheses have generally been indirect because benzimidazoles do not undergo direct *N*-oxidation to the benzimidazole-*N*-oxide. Reports of *O*-alkylation generating *N*-alkoxy benzimidazoles have been rare, with only a handful of prior examples, most giving *N*-alkoxy benzimidazoles only as low-yielding side products.[3] We previously described efficient syntheses of a variety of *N*-alkoxy benzimidazoles from 2-nitroanilines in a one-pot tandem process.[4] A number of these compounds showed low or sub-μM anti-HIV or antitumour activity.[5] This process differs substantively from standard condensation and reductive cyclisations used almost universally for benzimidazole construction, and also provides the advantage of concomitant introduction of extra functionality on N1.

This protocol has proven versatile for variations in both nitroaniline substitutions and across a range of alkylating agents constituting various aryls, allylics and simple alkyls (Scheme 1), but the sequential/tandem nature of the process required that substituents at the 2-position and the alkoxy group be derived from the same alkylating agent. We have thus been seeking to modify this general methodology to provide the 2-substituent and *N*-alkoxy group from diverse different sources. This would establish that a matrix of C2 and *O*-alkyl groups could be employed through such a methodology.

We recently demonstrated that certain *N*-alkoxybenzimidazoles **2** can be *O*-dealkylated and then re-alkylated with various types of new electrophiles, providing a method for diversification to C2, *N*-alkoxy differentiated systems **3** (Scheme 1). Although this method involved essentially quantitative *O*-dealkylation and realkylation steps without requiring intermediate purification, it does require introduction of an *N*-alkoxy group and then its removal, and this puts limitations on the nature of R (i.e. substituents suitable for selective



Scheme 1. *O*-Dealkylation–realkylation synthesis of *N*-alkoxybenzimidazoles.[6]

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01841-5

removal are required, e.g. *O*-aryl, allylic), and thus the final C2 substituent. Alternatively, we reasoned that *N*-alkyl nitroanilines are likely intermediates in the single-pot tandem reactions. However, these putative intermediates were only rarely observed, and then only isolable as trace co-products and only in certain cases.[4] We could find no evidence of any build-up of this intermediate in most cases. However, we found that 4-carboxamide substitution of the 2-nitroaniline system does allow interception of the intermediate *N*-alkyl system in good isolable yields, which could then be converted onwards to *N*-alkoxybenzimidazoles by in situ addition of further base and (different) alkylating agents, in what we described as a staged tandem sequence.[6] This was, however, specific to this substrate type.

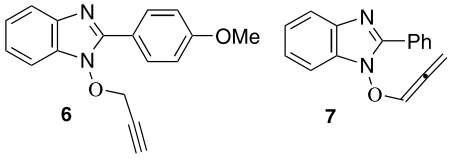
Alternatively, we considered that if *N*-alkyl nitroaniline intermediates were prepared independently by another route, they may then undergo tandem heterocyclisation-*O*-alkylation in a separate second step with potentially wide general applicability.

Such a 2-stage route would greatly extend the scope of the heterocyclisation-*O*-alkylation methodology and make accessible a substantively wider diversity of novel structures with different combinations of the ultimate 2-substituent and the alkoxy group than our previous methodology.

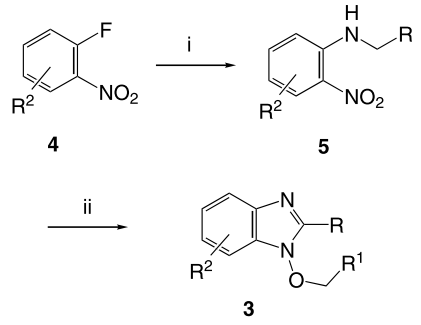
Herein, we report such a protocol, and also on its extension to heterocyclic systems, namely the first examples of *N*-alkoxypyrimidazole systems (*N*-alkoxy-4-deazapurines).

The intermediate alkylated nitroanilines were readily prepared in near-quantitative yields by standard methods (reacting 2-halonitroaromatic substrates with various primary amines). Treatment of the intermediate *N*-alkyl nitroanilines with sodium hydride (2–3 equiv.) in the presence of various alkylating agents (2 equiv.) did lead to formation of the desired *N*-alkoxybenzimidazoles, obtained pure by column chromatography (Scheme 2 and Table 1). This thus supports the proposed intermediacy of **5** in the previously described one-pot process, and achieves the objective of providing a new means to generate diverse novel structures **3** where $R \neq R^1$.

Alternative products competed in two cases. Firstly, when the reaction of **5** (R = PMP; R^2 = H) was carried out using propargyl bromide as the electrophile, the anticipated propargyloxy product **6** was formed. However, similar reaction of **5** (R = Ph; R^2 = H) gave the allenyloxy system **7** as the major product, presumably arising through base catalysed isomerisation.

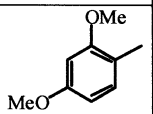
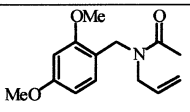
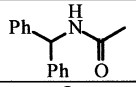
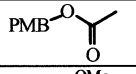
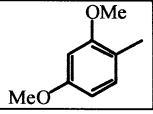
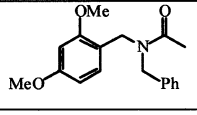


Secondly, in the case of the 4-MeO *N*-alkylated nitroaniline substrates (**8** and **9**), the *N*,*N*-dialkylated material



Scheme 2. *Reagents and conditions*: (i) RCH_2NH_2, K_2CO_3; (ii) NaH, R^1CH_2Br.

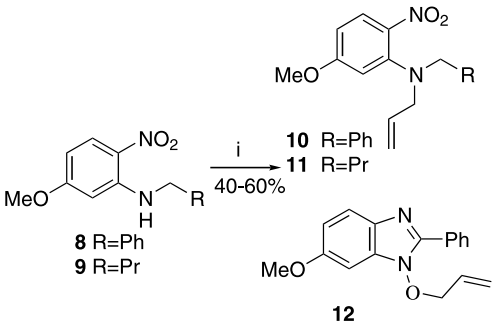
Table 1. Diversity of *N*-alkoxybenzimidazoles[a]

	R	R^1	R^2	Yield %
1	Et	$CH=CH_2$	H	55
2	$CH=CH_2$	Et	H	73
3	Ph	$CH=CH_2$	H	96
4	Ph	Et	H	95
5	Ph	Me	H	97
6	Ph	*p*-$MeOC_6H_4$-	H	75
7	$CH=CH_2$	CH_2OMe	H	54
8	*p*-$MeOC_6H_4$-	$CH=CH_2$	H	100
9	*p*-$MeOC_6H_4$-	Et	H	91
10		$CH=CH_2$		56
11	Ph	$CH=CH_2$		56
12	Ph	*p*-$MeOC_6H_4$-		26
13		Ph		27

[a] R^2 at C6 in entries 10-13.

was obtained as a competing product. Thus, *N*-benzylated substrate **8** was reacted with allyl bromide to afford the corresponding benzimidazole **12** along with *N*,*N*-dialkylated product **10** (2:1 ratio, ~40% purified yield). The analogous *N*-butylated substrate **9** gave dialkylated material **11** in 60% purified yield as the only significant isolated product (Scheme 3). This is of mechanistic relevance as it suggests the electron rich ring methoxy redirects the reaction pathway away from cyclisation.

The mechanism of the sequential heterocyclisation-*O*-alkylation may involve base-induced cyclisation to the *N*-oxy intermediate which is then alkylated in situ. However, alternatively, there could be alkylation of a nitro-derived oxygen during the process, which then



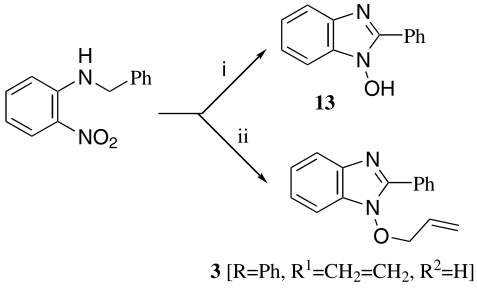
Scheme 3. *Reagents and conditions*: (i) NaH, allyl bromide.

allows for the loss of an alkoxy from nitrogen to facilitate the final functionalisation (via a second oxygen alkylation).

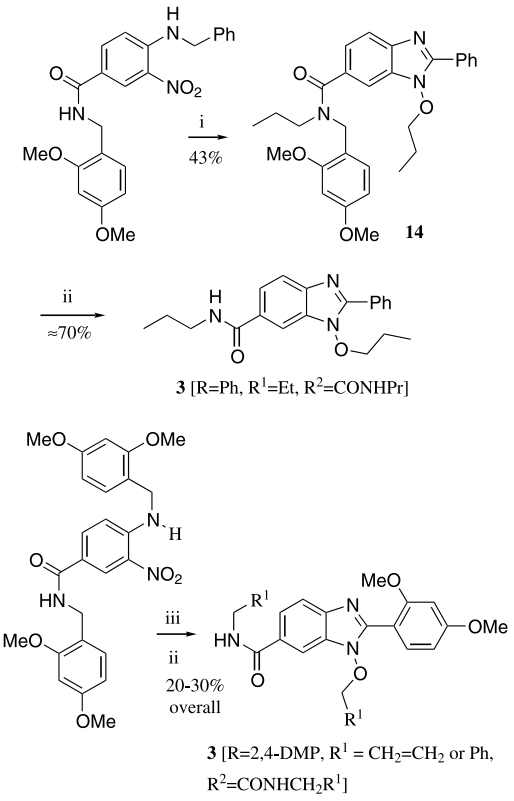
We carried out additional experiments to illuminate the mechanism using *N*-benzylnitroaniline **5** [R = Ph, R^2 = H] with allyl bromide as the electrophile. Thus, reactions were carried out using 0, 1 and 2 equiv. of alkyating agent. In the absence of alkylating agent, the heterocyclisation proceeded yielding the *N*-hydroxybenzimidazole **13** (Scheme 4). Reaction using allyl bromide as alkylating agent returned similarly good yields (76–82%) of *N*-alkoxybenzimidazole **3** [R = Ph, $R^1 = CH_2 = CH_2$, R^2 = H], irrespective of whether 1 or 2 equiv. of alkylating agent were added. Together these results provide compelling evidence that the mechanism does *not* require alkylation of either oxygen prior to, or during, heterocyclisation, and that the *O*-alkylation is likely to be the final step.

In some cases using carboxamide-bearing precursors, the heterocyclisation-*O*-alkylation was accompanied by concomitant amide *N*-alkylation (see Table 1; entries 10 and 13), providing more elaborate benzimidazoles.

For example, reaction of **5** [R = Ph, R^2 = $CONHCH_2(2,4\text{-}(OMe)_2C_6H_3]$ with propyl iodide gave **14**. Removal of the dimethoxybenzyl group then gave **3** [R = Ph, R^1 = Et, R^2 = CONHPr]. Similar chemistry could be applied in other cases with both the 2-substituent on the imidazole and the alkylating agent being varied, for example, to targets such as **3** [R = 2,4-DMP, $R^1 = CH_2{=}CH_2$ or Ph, $R^2 = CONHCH_2R^1$] (Scheme 5).



Scheme 4. *Reagents and conditions*: (i) NaH; (ii) NaH, allyl bromide (1 or 2 equiv.).

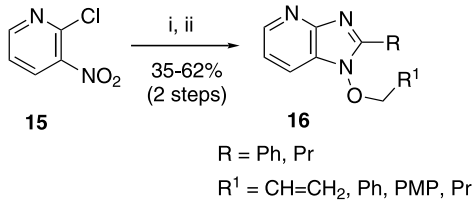


Scheme 5. *Reagents and conditions*: (i) NaH, PrI; (ii) TFA/CH_2Cl_2, 2–3 h, rt; (iii) NaH, allylbromide or benzyl bromide.

We have also extended the protocol to 2-chloro-3-nitropyridine (**15**) as starting material to provide a number of new *N*-alkoxypyrimidazoles **16** (Scheme 6). The structure of **16** [R = Ph; R^1 = PMP] was confirmed by X-ray analysis. The versatility of this chemistry with this example set of reagents indicates that this should now be applicable to generate a wide diversity of new *N*-alkoxypyridimidazoles (*N*-alkoxy-4-deazapurines) for biological evaluation.

In the X-ray structure of **16** [R = Ph, R^1 = PMP] (Fig. 1) the 2-phenyl is twisted out of planarity with the bicyclic heteroaromatic system, tipping C14 and C15 away from the large *N*-(*p*-methoxybenzyloxy) group.

The development of this efficient 2-step protocol significantly expands the range of compounds of this type now accessible by this tandem heterocyclisation-*O*-alkylation protocol. It appears to be applicable to a range of aromatic ring systems, and a wide range of substituent types can be included at the ultimate 2-posi-



Scheme 6. *Reagents and conditions*: (i) RCH_2NH_2, K_2CO_3; (ii) NaH, R^1CH_2Br.

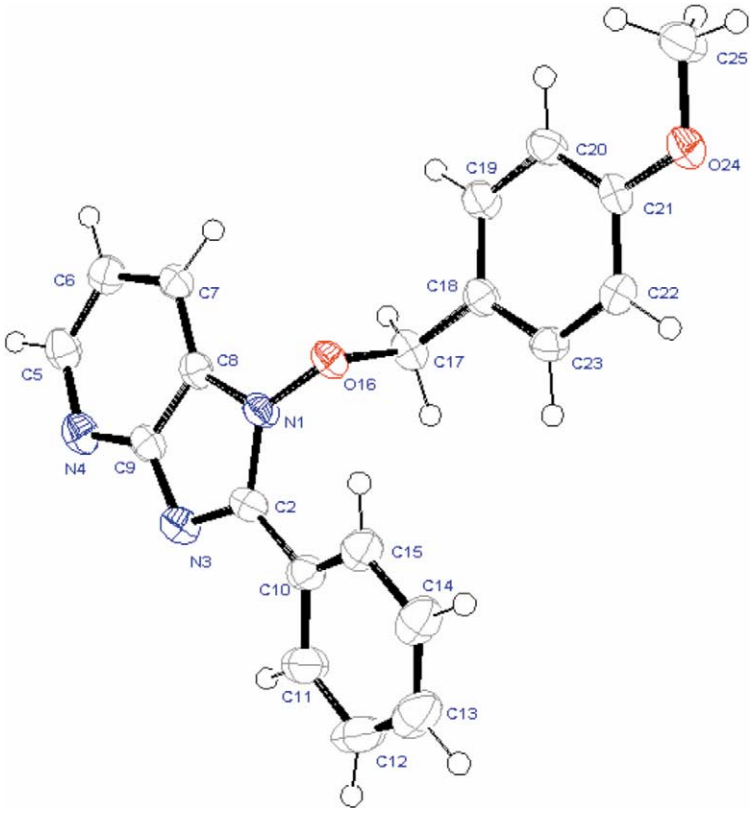


Figure 1. X-Ray structure of pyrdimidazole **16** [R = Ph, R^1 = PMP].

tion and in the alkoxy group. This versatility lends itself to the development of parallel/combinatorial syntheses of libraries of novel *N*-alkoxy benzimidazoles. We have also adapted this approach to facilitate solid-supported synthesis of libraries of benzimidazole *N*-alkoxides.[7]

Acknowledgements

We thank Aventis Pharma for supporting this work through a CASE award (to A.D.G.). NMR, HPLC and IR characterisation was carried out on instrumentation funded with support from EPSRC grants GR/L52246 (NMR), GR/M30135 (IR) and GR/L84391 (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.

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