Pergamon

Tetrahedron Letters 42 (2001) 5109–5111

TETRAHEDRON LETTERS

Synthesis of *N*-alkoxybenzimidazoles with differentiated C2 and *O*-substituents

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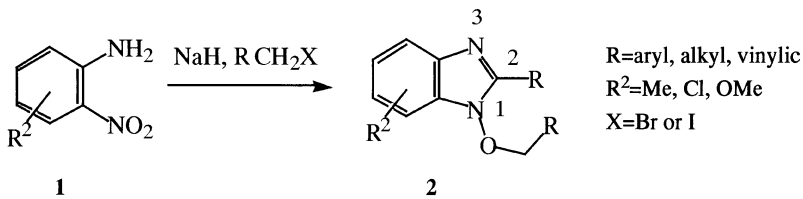
Received 3 April 2001; revised 8 May 2001; accepted 31 May 2001

Abstract—*N*-Alkoxy-, *N*-aryloxy- and *N*-allyloxybenzimidazoles (prepared using tandem *N*-alkylation, heterocyclisation and *O*-alkylation with in situ alkylating agent) can be selectively *O*-deprotected and then independently realkylated to provide a protocol for diversification with differentiated substituents at C2 and on oxygen. In addition, carboxamide functionalised derivatives **8** are amenable to staged interruption of the tandem reaction, allowing sequential additions of two different bases and alkylating agents directly affording **9**. This 'start–stop–start' tandem process also facilitates diversification to analogues bearing different C2 and *N*-alkoxy substituents. © 2001 Elsevier Science Ltd. All rights reserved.

Benzimidazoles are common units in a range of biologically active compounds. However, *N*-alkoxy systems are relatively uncommon. We have previously reported that reaction of a range of 2-nitroanilines (**1**) with strong base and alkylating agents leads directly to 2-substituted-*N*-alkoxy-, -*N*-aryloxy- or -*N*-allyloxybenzimidazoles (**2**) via a novel tandem one-pot *N*-alkylation–heterocyclisation–*O*-alkylation sequence (Scheme 1).[1] Prior to this work, base-induced heterocylisations of this type had been limited to *N*-alkylated nitroanilines with an active methylene[2] (our method extended this to non-activated alkyl functionality) and observation of in situ *O*-alkylation was previously limited to poor yielding side product formation in specific reactions[3] (whereas our method generates *N*-alkoxy products **2** directly in good yield across all general electrophile types).

A number of the new compounds prepared by this method were active against HIV-1,[4] or cancer cell lines (<10 μM to sub-micromolar EC_{50}s).[5] These promising leads (from a modest screen range) encouraged development of methods to prepare diverse further related novel structures. Our previously reported protocol, though versatile for variations in all reagent components, requires that the substituents at the 2-position and on the oxygen are necessarily derived from the same alkylating agent (see Scheme 1). We thus sought to develop modifications of this methodology to provide access to systems with groups on the oxygen and C2 derived from *different* alkylating agents. This would significantly extend the scope of this general methodology to a far wider range of new analogues. We report herein two alternative, complementary, practicable protocols to achieve this objective.

One route to systems bearing different C2 and *N*-alkoxy groups would be to remove the substituent from the oxygen of specific 2-substituted-*N*-alkoxybenzimidazoles, and then independently realkylate the N–OH functionality with a variety of different alkylating agents. This would be applicable to a range of alkylation agents and so provide a versatile route to diversity of novel structures.



1 **2**

Scheme 1.

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PII: S0040-4039(01)00935-2

We evaluated three types of oxygen substituents for removal from the *N*-alkoxy function, specifically *O*-allylic, *O*-benzylic and *O*-*p*-methoxybenzylic groups. To illustrate the viability of this protocol, benzimidazoles **3a**,[1a] **3b**[1b] and **3c** were employed (available in high yields from the precursor 2-methyl-6-nitroaniline). The *O*-benzylic system **3a** was then converted to the desired *N*-hydroxy system (**4a**) in over 90% yield with hydrogen/Pd–C. Notably, this required rigorous control of reaction time, since the reaction was complete in around 15 min (prolonging the reaction any further lead to rapid appearance of the further reduced parent benzimidazole, **6**). The *O*-allyloxy group was also cleanly removed from **3b** by treatment with TMSI (generated in situ), giving **4b** in 92% purified yield, whilst the *O*-*p*-methyoxybenzyloxy group was removed from **3c** by DDQ, affording **4c** in 90% purified yield.

Table 1. *N*-Alkoxybenzimidazoles **5a–c** produced via Scheme 2[a]

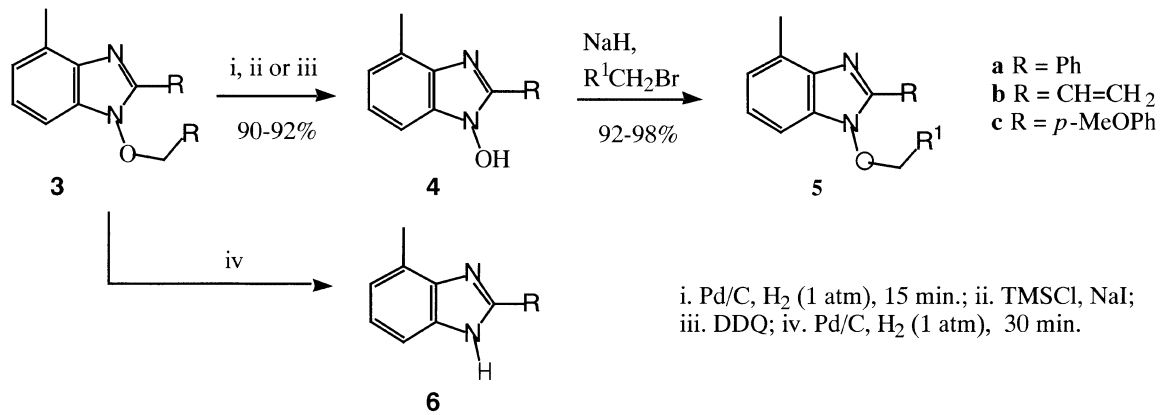
Entry	R	R^1	Yield (%)
1	Ph	Me	97
2	Ph	Et	96
3	Ph	Pr	98
4	$CH{=}CH_2$	Ph	93
5	$CH{=}CH_2$	4-MeO-C_6H_4-	92
6	4-MeO-C_6H_4-	$CH{=}CH_2$	94
7	4-MeO-C_6H_4-	Pr	95
8	4-MeO-C_6H_4-	Ph	96

[a] Yields are for **4** to **5**. All products **5** are fully characterised and are analytically pure.

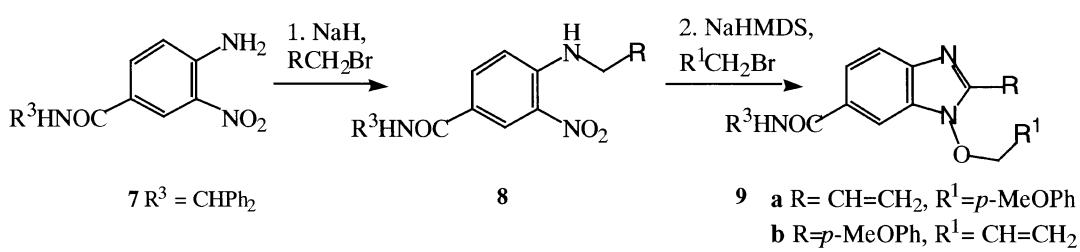
The three *N*-hydroxy products **4a–c** were then realkylated in parallel with various types of alkylating agents to give the new *N*-alkoxybenzimidazoles **5** in 92–98% isolated yields (Table 1), demonstrating that alkyl halides, benzylic halides and allylic halides are all suitable electrophiles. These reactions were simply quenched, extracted and the organic solution dried, filtered and solvent removed to provide high yields of analytically pure material in all cases, without the need for any chromatography.

These experiments establish that for three different C2 substituents, the group on the oxygen can be readily removed and replaced by a range of different electrophile types. This sequence should be generally extendable to a wide range of further electrophiles, to provide a wide diversity of *N*-alkoxy groups (as well as being applicable to variations in the nature and position of the substituent in the benzene ring of the benzimidazole skeleton (see R^2 in Scheme 1).

We believe that these benzimidazole *N*-alkoxide forming reactions (Scheme 1) proceed via the intermediacy of *N*-alkylated nitroanilines (e.g. **8**); however, although we have previously isolated traces of this type of intermediate in certain reactions, benzimidazole formation always commences well before all nitroaniline starting material has been *N*-alkylated (even using 1 equiv. of alkylating agents), and so a step-wise process has not previously been possible. However, we sought a protocol for selective *N*-alkylation of 2-nitroanilines using 1 equiv. of an electrophile, but not converting this on to benzimidazole. Ideally, we then hoped to be able to add further (new) base and a second, different, electrophile, *into the same reaction vessel*, restarting the tandem



Scheme 2. *Reagents and conditions*: (i) Pd/C, H_2 (1 atm), 15 min; (ii) TMSCl, NaI; (iii) DDQ; (iv) Pd/C, H_2 (1 atm), 30 min.



Scheme 3.

process and converting *N*-alkylnitroanilines **8** into *N*-alkoxybenzimidazoles **9** in a 'one-pot' 'start–stop–start' sequence in which the intermediate is 'parked' before heterocyclisation. Such a protocol would provide access to a substantially wider range of new analogues akin to **5** above.

We report here such a modified protocol from carboxamide-bearing substrate nitroanline **7** (Scheme 3). This protocol relies on discovering that with carboxamide-bearing nitroaniline **6**, use of limited NaH and alkylating agent (e.g. allyl and *p*-methoxybenzyl) leads to clean conversion to the *N*-alkyl intermediate **8** without any concurrent benzimidazole formation.[6] On addition of an equivalent of NaHMDS to the reaction mixture containing **8**, followed by an equivalent of a *different* alkylating agent, the reaction recommences, converting **8** into **9**[7] in at least 90% *overall* yield. The carboxamide functionality should facilitate application of this protocol to substrates immobilised through a ring carboxyl, as well as to solution phase synthesis of ranges of targets of type **9**.

In summary, C2-vinyl-, -*p*-methoxyphenyl and -phenyl-bearing *N*-alkoxybenzimidazoles (prepared in one-pot reactions from precursor 2-nitroaniline) can be diversified to new analogues with various oxygen substituents by a simple highly efficient two-step alkoxy removal–realkylation. In addition, a carboxamide-bearing nitroaniline provides a step-wise 'one-pot' protocol of sequential addition of NaH/alkylating agent (for C2), then NaHMDS/second alkylating agent (for *N*-alkoxy group). *These methodologies significantly expand the scope of this chemistry and the diversity of targets available using parallel synthesis.*

Acknowledgements

NMR and IR characterisations were carried out using instrumentation funded with support from EPSRC grants GR/L52246 (NMR) and GR/M30135 (IR).

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6. This selectivity was not seen with any other nitroanilines, where reaction under these conditions leads to unreacted starting material, *N*-alkylated intermediate (usually very small amounts) and benzimidazole product (as observed previously).[1b]
7. Use of NaHMDS as the base in the initial stage, with 1 equiv. alkylating agent, leads directly to a mixture of starting material (ca. 40%), *N*-alkylated intermediate (trace) and benzimidazole (ca. 50%).