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Synthesis of 1-Alkoxy-2-Alkyl-Benzimidazoles from 2-Nitroanilines *via* Tandem N-Alkylation-Cyclization-O-Alkylation[1]

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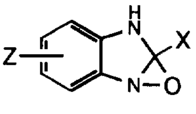
Abstract: Substituted 2-nitroanilines react with benzylic, allyl and alkyl halides to give 2-aryl-1-benzyloxy-, 1-allyloxy-2-vinyl- and 1-alkoxy-2-alkyl-benzimidazoles, in a one-pot cascade process involving 1-alkylation-cyclization-O-alkylation. 2-Aryl-1-benzyloxy- and 1-allyloxy-2-vinyl- derivatives are obtained in high yields (79-98%), while with simple alkyl halides, yields of the benzimidazoles are substrate dependent. An X-ray crystal structure of 2,4-dimethyl-1-ethoxybenzimidazole is presented.

The benzimidazole-N-oxide ring system was first reported in 1887[2a]. Structural assignment was initially incorrectly proposed as the oxaziridine, **1**[2b], but subsequently proven to be a solvent and substituent dependent tautomeric equilibrium between **2a** and **2b**[3]. Benzimidazoles do not undergo direct N-oxidation to afford the benzimidazole-N-oxide system, and reported syntheses have thus been indirect.

Various synthetic methods towards **2** have been reported over the years[4], amongst which base induced cyclization of N-substituted-2-nitroaniline derivatives, **3**, has been most thoroughly investigated[5]. In general, this approach has utilized substrates of type **3**, with N-alkyl groups possessing a relatively acidic proton adjacent to the nitrogen, i.e. X = CO_2R', COR', CN, Ph or other Ar. A variety of R groups have been reported, most typically H, Ts, Ms or CO_2R'. Yields are variable, and are dependent on the nature of R and X, and also, to some degree, on the nature of other substituents on the aromatic ring.



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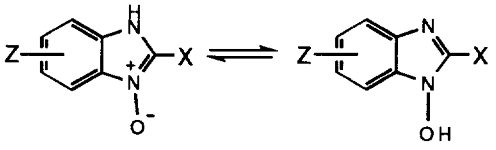
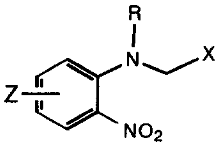


2a **2b**



3

Most notable for the current study is that, although *in situ* O-alkylation of **2** occurs as a by-product of some reactions, this is generally in low yield. For example, using sodium methoxide as base, reaction of **4**[5b-d] proceeds in modest yield to generate **5b** [along with **5a**] *via* generation of TsOMe as a methylation agent *in situ*. O-Alkylation most generally requires subsequent reaction of isolated **2**[5a].

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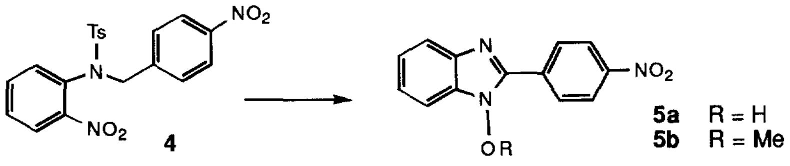
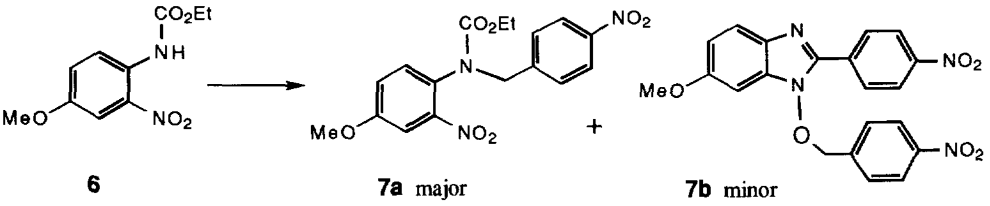
§ Author to whom correspondence regarding X-ray crystal structure data should be directed.

Scheme 1



Reactions where alkylation of a 2-nitroaniline amino group is accompanied by imidazole-N-oxide formation *and* subsequent *in situ* O-alkylation have very limited precedent. The one example of which we are aware is reaction of **6** with 4-nitrobenzyl bromide, in which the O-alkylated benzimidazole-N-oxide, **7b**, is obtained, though in low yield (7%), increased only to 23% by optimization *via* addition of 2 equivalents of both base and alkylating agent (the N-alkylated nitroaniline derivative, **7a**, always being the major product). Thus, even when the apparent requirement for two equivalents of base is met, *in situ* O-alkylation is generally a poor process, and *cyclization of substrates of type 3 (X =alkyl) appears to be unprecedented under basic conditions.*

Scheme 2



We recently reported a new reaction protocol for reaction of benzyl bromide and sodium hydride with 6-methyl-2-nitroaniline in a one-pot alkylation-heterocyclization-O-alkylation sequence, affording 1-benzyloxy-2-phenyl-4-methylbenzimidazole in 98% yield^6. This protocol proved to be similarly efficacious in a one-pot synthesis of 1-allyloxy-4-methyl-2-vinylbenzimidazole in 92% yield using allyl bromide in place of benzyl bromide. Most significantly, this protocol was also successful in effecting a convenient one-pot route to the analogous benzimidazole derivatives using *simple alkyl iodides.* While cyclization of N,N-dialkyl-*o*-nitroanilines related to **3** with X=R=alkyl to give 2-alkyl-benzimidazole-N-oxides does occur on thermolysis or with acid^7, the reactivity during N-alkylation of anilines under basic conditions reported herein was unexpected.

Herein, we report extension of this methodology to reactions of aryl halides, allyl bromide and simple alkyl iodides with a range of other 2-nitroanilines, present an X-ray structure analysis of a representative benzimidazole of this class, and examine potential influences on the generality of this reaction. The range of 2-nitroanilines, **8**, employed, and the yields of N-alkylated 2-nitroanilines, **9**, and 1-alkoxybenzimidazoles, **10**, as well as any recovered starting material, are given in Table 1.

In this work, we wished to examine the effects of the electronic nature of the aromatic substituent, Z (Scheme 3), and steric influence of positioning this substituent ortho to the amino substituent, on the ratios of conversion to the benzimidazole, **10**, along with intermediate N-alkylated-2-nitroaniline, **9**. Notably, with benzylic and allylic halides, yields of N-alkylated intermediate **9** were always low, generally <5%, with one exception (entry 3, table 1), and yields of benzimidazole **10**, were high, ranging between 79-98% [Entries 3, 6, 10 and 14]. A similar reactivity profile was exhibited by allyl bromide, providing 1-allyloxy-2-vinyl-benzimidazoles in 92% yield from **8b**^{6} (entry 7), and also in 97% yield from 4-methoxy-2-nitroaniline, **8c** (entry 11; Scheme 4).

Scheme 3

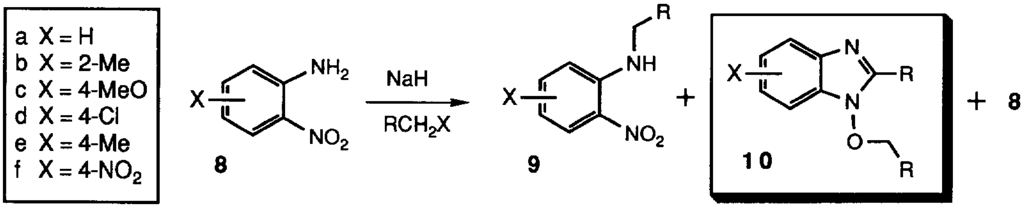
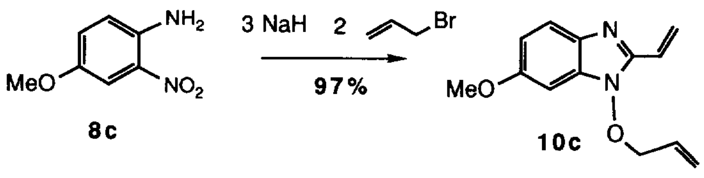


Table 1: Products of reactions of 2-nitroanilines 8a-f

Entry	Nitro-aniline	Base	RCH2X	Method[a]	9	10	Unreacted **8**	Recovery **8+9+10**
1	8a	3 NaH	2 PrI	A	67%	23%	<5%	ca. 95%
2	8a	3 NaH	2 PrI	B	61%	24%	5%	90%
3	8a	3 NaH	2 BnBr	B	14%	**79%**	-	93%
4	8b	3 NaH	2 MeI	B	15%	**63%**	3%	81%
5	*8b	3 NaH	2 PrI	B	<5%	**73%**	21%	ca. 95%
6	*8b	3 NaH	2 BnBr	B	-	**98%**	-	98%
7	*8b	3 NaH	2 allyl Br	B	4%	**92%**	-	96%
8	8c	3 NaH	2 PrI	A	20%	47%	27%	94%
9	8c	3 NaH	2PrI	B	50%	47%	-	97%
10	8c	3 NaH	2 BnBr	B	<5%	**95%**	-	ca. 100%
11	8c	3 NaH	2 allyl Br	B	2%	**97%**	-	99%
12	8d	3 NaH	2PrI	A	48%	37%	9%	94%
13	8d	3 NaH	2PrI	B	35%	33%	-	68%
14	8d	3 NaH	2 BnBr	B	<5%	**81%**	-	ca. 86%
15	8e	3 NaH	2 PrI	B	78%	21%	-	99%
16	8f	3 NaH	2 PrI	B	45%	-	9%	54%

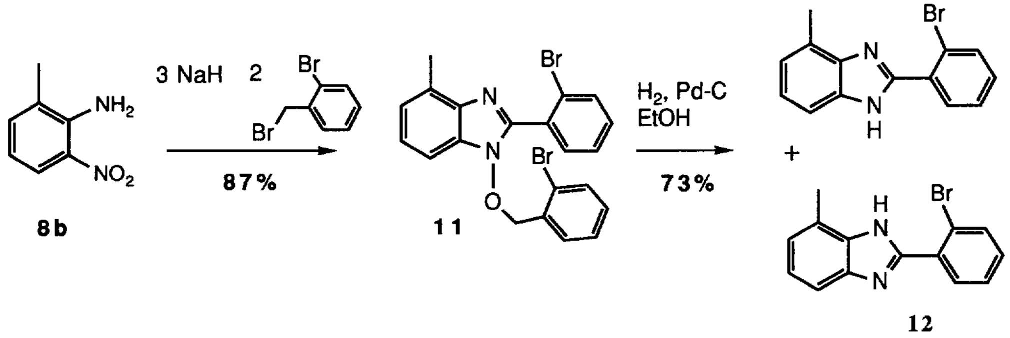
[a] Method A: All reagents added at start of reaction. Method B: Addition of base and alkylating agent staggered over 12 hours. See experimental.
* Reference 6.

Scheme 4



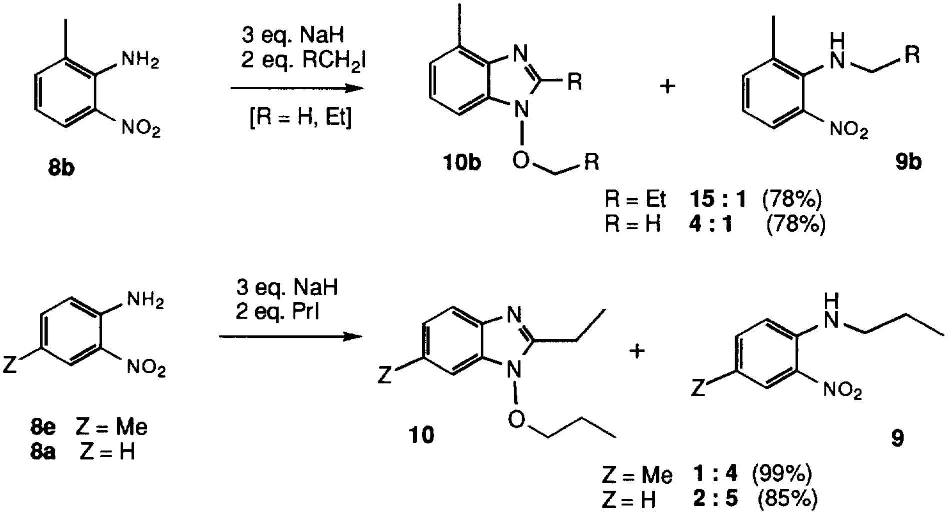
The reaction with benzyl bromide was readily extended to derivatized benzyl bromides, for example reaction of 2-methyl-6-nitroaniline using 2-bromobenzyl bromide, provided the derivative, **11**, in high yield (Scheme 5). The *o*-bromobenzyl group was readily removed by hydrogenolysis, as in the simple benzyl case[6], affording a mixture of imidazole tautomers, **12**. The dibromo compound, **11**, and analogues, could find application to the synthesis of novel biaryl fused eight membered heterocycles *via* intramolecular coupling reactions of the brominated aromatic rings, or could perhaps be employed as a bifunctional monomer in copolymerization with aryl bisboronic acids.

Scheme 5.



While reaction of 2-methyl-6-nitroaniline, **8b**, with propyl iodide gave 73% conversion to the isolated benzimidazole, **10b**[6], when we extended this protocol to the isomeric 4-methyl-2-nitroaniline, **8e**, we were surprised to find that though conversion of starting material was near quantitative (99%), only 21% of the benzimidazole, **10e**, was obtained, with most of the product (78%) being 4-methyl-2-nitro-N-propyl-aniline, **9e**. Thus, we decided to explore the effects of different substituents on the 2-nitroaniline aromatic ring, to elucidate contributions from substituent electronic and/or steric effects. To investigate electronic effects, we examined the parent 2-nitroaniline, and derivatives bearing chloro, methoxy and nitro groups (in positions other than *ortho* to the nitro or amino groups of the nitroaniline), in addition to the previously reported 6-methyl substituent[6]. Steric effects were probed by using parent 2-nitroaniline, **8a**, 6-methyl-2-nitroaniline, **8b**, and the isomeric 4-methyl-2-nitroaniline, **8e**, where the methyl is *para* to the aniline nitrogen.

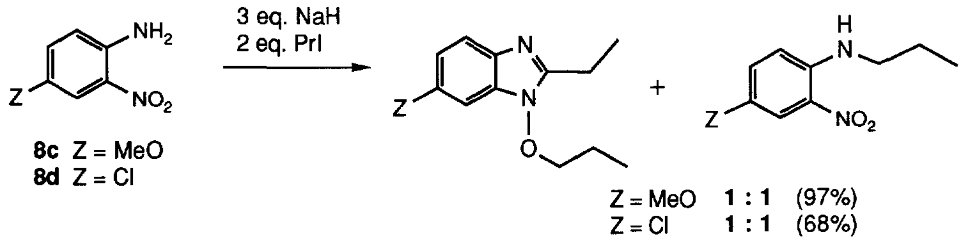
Scheme 6



It can be seen from Table 1 that reactions with simple alkyl iodides do show significant substrate dependence, both in terms of overall conversions of starting material and in the ratio of benzimidazole to N-alkylated 2-nitroaniline obtained. Yields of benzimidazole range from 21% to 73% for **8a-e**, and no benzimidazole could be detected in the case of 2,4-dinitroaniline, **8f**. With 2-methyl-6-nitroaniline the yields of benzimidazole were good at 63% and 73%, in the propyl case giving a >15:1 ratio of benzimidazole, **10b**, to N-alkylated intermediate **9b**[6]. There was also some alkyl halide dependence for reaction of **8b**, methyl iodide giving a reduced 4:1 selectivity for benzimidazole formation. With a 4-methyl group in **8e**, a simple regioisomer of **8b**, conversion was still very high, however, selectivity had dramatically switched to nearly *1:4 in favour of N-alkylation.* The parent 2-nitroaniline gave high conversion, but low yields of 2-alkylbenzimidazoles, with *≥5:2 selectivity in favour of the N-alkylated product, 9.* Thus, with 2-nitroanilines, **8a** and **8e**, electronically similar to **8b** but *lacking a substituent ortho to the aniline nitrogen*, the reaction stops primarily at the N-alkylated-2-nitroaniline stage, with generally less than 25% of benzimidazoles recovered.

With 2-nitroanilines bearing chloro or methoxy substitution *para* to the amino group, conversion of starting material was high (68-97%), but the ratio of benzimidazoles to N-alkylated-nitroaniline derivatives **9** was close to 1:1. With 2,4-dinitroaniline, total recovery was modest and only the N-alkylated product was obtained (45%) - no benzimidazole was formed. Unsurprisingly, no reaction at all was observed for 2,6-dinitroaniline. Thus, reactivity is attenuated by introduction of a second nitro group, and benzimidazole formation is shut down entirely.

Scheme 7



8c Z = MeO
8d Z = Cl

Z = MeO 1 : 1 (97%)
Z = Cl 1 : 1 (68%)

Thus, it can be concluded that while the benzyl halide reactions proceed efficiently through to the benzimidazole product with all substrates, and are relatively indifferent to steric or electronic effects of other ring substituents, the reactions with alkyl halides appear to be very dependent on both the *electronic nature* and *position* of other ring substituents.

Substituent effects on reactions employing simple alkyl iodides is clearly evident. For the parent 2-nitroaniline, **8a**, reaction with propyl iodide, leads to a 23:67 ratio, *disfavouring* benzimidazole formation. For reaction of the chloro and methoxy substituted nitroanilines using propyl iodide, selectivity is essentially 1:1. In the case of methyl substituents, the 2-methyl starting material affords ca. 73:5 in favour of benzimidazole, a ratio switched to 21:78 by location of the methyl group *para* to the aniline nitrogen. From this data, it can be suggested that the reaction to afford the benzimidazole is more finely balanced using simple alkyl halides, electronic effects from (non-*ortho*) chloro or methoxy groups push the reaction a little further than in the parent system, but having a substituent *ortho* to the aniline nitrogen has the greatest effect, appearing to sterically drive benzimidazole formation (the N-alkyl-2-methyl-6-nitroaniline intermediate, **9b**, is sterically cluttered).

Mechanistic considerations need to account for the facts that no N-dialkylation products are observed in any case, and no unalkylated 1-hydroxy-benzimidazoles are obtained under any conditions. Following N-alkylation, these reactions formally appear to involve addition of an α-amino anion to the nitro group, followed by dehydration, O-alkylation and subsequent tautomerism. [Alternative mechanisms involving either a redox process from the N-alkylated nitroaniline to generate a hydroxylamine-imine species, or base-mediated iminium formation[7] would then require a 5-endo-trig process to effect cyclization.] While anion generation has been previously reported in benzimidazole-N-oxide cyclizations from *isolated N-alkylated nitroanilines*, these have invariably possessed groups acidifying the α-position, and possessing no free NH. The simple N-alkyl intermediate systems herein are surprising in this context, since they possess an aniline NH, which must be more acidic than the α-amino carbon. Since *no aniline N-dialkylation is observed in any of these cases*, the anticipated intermediate N-alkyl 2-nitroaniline sodium amide salt must either (i) effectively undergo a further carbon deprotonation α to the nitrogen, (ii) tautomerize to an amino α-anion, and then the carbanion rapidly cascades through to the benzimidazole-N-oxide, then rapidly alkylated under the reaction conditions, or (iii) undergo intramolecular deprotonation by the nitro oxygen *via* mesomeric form of the amino anion, followed by cyclization onto the resulting imine, regenerating a cyclic nitrogen anion, with dehydration then tautomerism leading to the immediate N-alkoxide precursor to N-alkoxybenzimidazoles, **10**. The apparent necessity for *three* equivalents (not just two) of base in this context to obtain good conversions, may be pertinent to an understanding of the process. The relative rates of these processes are intriguing, since *no unalkylated benzimidazole N-oxide is ever isolated*, and following the reaction by tlc shows only starting material and final product at any time. *The reaction appears to be an interesting cascade process involving N-alkylation, carbanion or N-anion generation, cyclization, finally followed by O-alkylation.*

Since N-alkoxybenzimidazole synthesis with simple alkyl iodides appears to be unprecedented, we sought to confirm our structural assignment by single crystal X-ray analysis of 2,4-dimethyl-1-ethoxy-benzimidazole, **10b** (R=Me)[8]. An ORTEP plot is given in Figure 1.

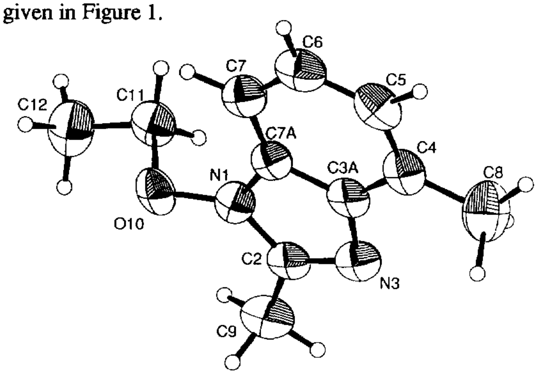


Figure 1: ORTEP[11] drawing of **10b** (R = Me) with 50 % probability thermal ellipsoids, with atom labelling system used in the crystallographic analysis.

Table 2. Selected Bond Lengths

N1 C2	1.353(5)
N1 O10	1.375(5)
N1 C7A	1.373(5)
C2 N3	1.309(5)
C2 C9	1.491(6)
N3 C3A	1.397(5)
C3A C4	1.381(6)
C3A C7A	1.388(6)
C4 C5	1.393(7)
C4 C8	1.484(7)
C5 C6	1.388(7)
C6 C7	1.377(7)
C7 C7A	1.386(6)
O10 C11	1.463(6)
C11 C12	1.470(7)

Table 3. Selected Bond Angles

C2 N1 O10	124.5(4)	C3A C4 C8	121.7(4)
C2 N1 C7A	108.5(3)	C5 C4 C8	123.0(5)
O10 N1 C7A	126.8(4)	C6 C5 C4	122.3(5)
N3 C2 N1	112.0(4)	C7 C6 C5	122.5(5)
N3 C2 C9	126.2(4)	C6 C7 C7A	115.1(5)
N1 C2 C9	121.8(4)	N1 C7A C3A	104.5(4)
C2 N3 C3A	105.1(4)	N1 C7A C7	132.6(4)
C4 C3A C7A	121.9(4)	C3A C7A C7	122.9(4)
C4 C3A N3	128.1(4)	N1 O10 C11	111.2(3)
C7A C3A N3	110.0(4)	O10 C11 C12	106.3(4)
C3A C4 C5	115.3(4)		

The C2-N3 bond length (1.309Å) is shorter than the C2-N1 bond (1.353Å), indicating the degree of double bond localization, though C2-N1 is considerably shorter than C3A-N3 (1.397Å), evidencing resonance contribution from C2-N1 π character. As anticipated, N1 is essentially planar, with N1 not deviating at all and O10 deviating by -0.08Å from a plane containing C2, N3, C3A and C7A. Torsion angles C2-N1-O10-C11 and N1-O10-C11-C12 of -99.2(5)° and 169.8(4)° respectively, show that the side chain avoids interference with the heterocycle. The structure bears good analogy to 5,6-dimethylbenzimidazole[12], though the structure of **10b** (R=Me) shows a larger bond angle at N1. Selected bond lengths are presented in Table 2, and selected bond angles in Table 3.

N-Alkoxyheteroaromatic ring systems are structural units found in a number of biologically active compounds[13], for example some acyclic antiviral nucleosides, and the methodology reported here should prove valuable for synthesis of a range of novel 1-alkoxy-2-functionalized benzimidazoles for biological evaluation. All the 2-alkyl-1-alkoxy benzimidazoles reported here show inhibition of HIV-1 infectivity with selectivity indices between 6 and 167, with EC_{50} values down to 0.6μM[14].

In summary, we have developed conditions for reaction of variously substituted 2-nitroanilines with allyl, benzyl and alkyl halides to provide a general synthesis of 1-alkoxy-2-alkyl-benzimidazoles. This work has shown that while alkyl iodides provide good yields of benzimidazole with 2-methyl-6-nitroaniline, yields are more modest with other 2-nitroanilines, for which, however, the only other competing product is the N-alkylated-2-nitroaniline intermediate. In this latter case of reactions with simple alkyl halides, the ratio of 1-alkoxybenzimidazole to N-alkylated nitroaniline is shown to be a function of both the electronic nature, and the position of, the third substituent on the starting 2-nitroaniline. The product functionalized heterocyclic framework has previously only been accessible in several steps, and this protocol has applications to the synthesis of compounds with useful therapeutic activities.

Acknowledgement. We would like to thank the Medical Research Council (MRC) for supporting this work through an AIDS Directed Programme Studentship (to C.R.L.), and UMIST for generous start-up support (JMG).

Experimental section.

Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded using Bruker AC-200 (UMIST), Bruker AC-250 (Aston University) and Bruker AC-300 (UMIST) instruments. Resonances are reported in ppm (δ) downfield of tetramethylsilane. Infrared spectra were obtained using Perkin Elmer 1605 FTIR and 783 instruments. Mass spectra were obtained on VG 70/70 Hybrid [low resolution], or Kratos MS-50 [FAB] spectrometers (Michael Barber Centre for Mass Spectrometry, UMIST) or a Kratos Concept 1H spectrometer [high resolution] (University of Manchester). Melting points were recorded on a Gallenkamp melting point apparatus. THF was distilled from sodium benzophenone ketyl. Column chromatography employed Prolabo Silica Gel 60 (70-230 Mesh), and thin-layer chromatography used Merck 60 F_{254} aluminium backed plates.

General procedure for synthesis of benzimidazoles 10a-e, 11, and N-alkylated 2-nitroanilines, 9a-e. (Method A Table 1): Nitroaniline (1.45mmol) was dissolved in THF (10 mL), and NaH (80% in oil, 4.35mmol, 3 equivalents) added at ambient temperature. The reaction was warmed to gentle reflux with efficient magnetic stirring, alkyl halide (2.9 mmol, 2 equivalents) added, and the reaction refluxed for 4 hours. The reaction was cooled to ambient temperature, and quenched by addition of brine (5 mL), and extracted with CH_2Cl_2 (3x40 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to afford the crude mixture of benzimidazole, **10**, starting 2-nitroaniline and **9**. Silica gel flash column chromatography eluting with hexanes/ethyl acetate afforded pure samples of benzimidazole N-alkoxide, starting nitroaniline and **9** in various ratios (Table 1). The order of elution was N-alkylated nitroaniline first (when present), followed by benzimidazole and starting material (when remaining). In the majority of cases, the benzimidazole was the last compound to elute.

(Method B Table 1)[6]: Nitroaniline (1.45mmol) was dissolved in THF (10 mL), and NaH (80% in oil, 1.45 mmol) added at ambient temperature. The reaction was warmed to gentle reflux with efficient magnetic stirring, alkyl halide (1.45 mmol) added, and the reaction refluxed for 4 hours. The reaction was cooled to ambient temperature, and a further 1.45 mmol of NaH were then added, the reaction heated a further 4 hours, and the second portion (1.45 mmol) of alkyl halide was added. After a further 4 hours, the reaction was again cooled to ambient temperature, a third portion of NaH (1.45 mmol) was added and the reaction heated for a further 4 hours, then cooled and quenched by addition of brine (5 mL), and extracted with CH_2Cl_2 (3x40 mL). The organic extracts were combined, washed (brine, 25 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to afford the crude mixture of benzimidazole and either or both of starting nitroaniline and **9** as impurities. Silica gel flash column chromatography eluting with hexanes/ethyl acetate afforded the pure benzimidazole N-alkoxide, as thick oils or coloured solids (mp indicated for solids), in 63-98%. The order of elution was as described under method A above.

9a [R=Et] N-Propyl-2-nitroaniline: Obtained as an orange oil.
^{1}H NMR (200MHz, $CDCl_3$) δ 8.10 (dd, *J*=1.6, 8.6Hz, 1H), 8.05 (br s, 1H), 7.38 (m, 1H), 6.77 (d, *J*=7.8Hz), 6.57 (m, 1H), 3.23 (q, *J*=5.2Hz, 2H), 1.69 ([apparent sextet], *J*=7.5Hz, 2H), 1.01 (t, *J*=7.3Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 145.6, 136.2, 127.1, 115.0, 113.8 (2C), 45.1, 22.5, 11.6. IR ν_{max} cm^{-1} 3380, 2960, 2940, 1620, 1570, 1510, 1420, 1350, 1260, 1160, 740. Elemental analysis for $C_9H_{12}N_2O_2$ calculated C 60.0%, H 6.7%, N 15.6%, found C 59.7%, H 6.9%, N 15.3%.

9c [R=Et] 4-Methoxy-2-nitro-N-propylaniline: Obtained as a red oil.
^{1}H NMR (250MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.59 (d, *J*=3.0Hz, 1H), 7.14 (dd, *J*=3.1, 9.4Hz, 1H), 6.81 (d, *J*=9.4Hz, 1H), 3.78 (s, 3H), 3.26 (q, *J*=5.4Hz, 2H), 1.76 ([apparent sextet], *J*=7.2Hz, 2H), 1.04 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 149.5, 141.9, 130.7, 127.6, 115.4, 106.9, 55.9, 45.1, 21.2, 11.7. IR ν_{max} cm^{-1} 3380, 2960, 1520, 1410, 1350, 1225, 1150, 1040, 820. Elemental analysis for $C_{10}H_{14}N_2O_3$ calculated C 57.1%, H 6.7%, N 13.3%, found C 57.4%, 7.0%, 13.4%. HRMS *m/z* requires 210.1005, found 210.1002.

9d [R=Et] 4-Chloro-2-nitro-N-propylaniline: Obtained as an orange oil.
^{1}H NMR (250MHz, $CDCl_3$) δ 8.11 (t, *J*=2.1Hz, 1H), 8.02 (br s, 1H), 7.33 (dd, *J*=2.4, 9.2Hz, 1H), 6.78 (d, *J*=11.5Hz, 1H), 3.24 (q, *J*=7.0Hz, 1H), 1.73 ([apparent sextet], *J*=7.3Hz, 2H), 1.03 (t, *J*=7.3Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 144.3, 136.6, 136.4, 125.9, 119.8, 115.4, 45.0, 22.3, 11.6. IR ν_{max} cm^{-1} 3380, 3100, 2960, 1625, 1570, 1510, 1350, 1260, 1160, 980. HRMS (MH$^+$) for $C_9H_{12}N_2O_2{}^{35}Cl$ requires 215.0588, found 215.0584.

9e [R=Et] 4-Methyl-2-nitro-N-propylaniline: Obtained as a red oil.
^{1}H NMR (250MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.21 (dd, *J*=2.1, 8.7Hz, 1H), 6.73 (d, *J*=8.8Hz, 1H), 3.20 (q, *J*=7.0Hz, 2H), 2.22 (s, 3H), 1.69 ([apparent sextet], *J*=7.2Hz, 2H), 1.01 (t, *J*=7.3Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 143.9, 137.7, 131.2, 125.9, 124.5, 113.8, 44.7, 22.2, 20.2, 11.5. IR ν_{max} cm^{-1} 3280, 2960, 2930, 1635, 1570, 1525, 1410, 1350, 1270, 1230, 1160, 920, 805, 770. Elemental analysis for $C_{10}H_{14}N_2O_2$ calculated C 61.9.0%, H 7.2%, N 14.4%, found C 62.0%, H 7.5%, N 14.5%. MS (FAB, MH$^+$) *m/z* 195.

9f [R=Et] 2,4-Dinitro-N-propylaniline: Obtained as a tan solid.
^{1}H NMR (250MHz, $CDCl_3$) δ 9.05 (d, *J*=2.7Hz, 1H), 8.56 (br s, 1H), 8.22 (dd, *J*=2.7, 9.5Hz, 1H), 6.91 (d, *J*=9.6HZ, 1H), 3.38 (q, *J*=7.1Hz, 2H), 1.82 ([apparent sextet], *J*=7.3Hz, 2H), 1.06 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 148.3, 135.6, 130.1, 129.9, 124.1, 113.9, 45.1, 21.9, 11.3. IR ν_{max} cm^{-1} 3380, 3100, 2980, 2960, 1630, 1590, 1520, 1420, 1350, 1300, 1200, 1130, 1050, 930, 830, 740. Elemental analysis for $C_9H_{11}N_3O_4$ calculated C 48.0%, H 4.9%, N 18.7%, found C 48.3%, H 4.9%, N 18.5%. MS (FAB, MH$^+$) *m/z* 226. mp 90-91°C.

10a [R=Et] 2-Ethyl-1-propyloxybenzimidazole: Obtained as a brown oil.
^{1}H NMR (200MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.35 (m, 1H), 7.22 (m, 1H), 4.16 (t, *J*=6.6Hz, 2H), 2.92 (q, *J*=7.6Hz, 2H), 1.85 ([apparent sextet], *J*=6.7Hz, 2H), 1.43 (t, *J*= 7.4Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ

152.0, 138.5, 130.6, 12.7, 122.2, 119.8, 108.2, 80.2, 21.6, 19.6, 11.5, 10.6. IR ν_{max} cm^{-1} 2920, 2830, 2780, 1520, 1430, 1360, 1340, 1230, 1190, 1140, 1030, 1000. Elemental analysis for $C_{12}H_{16}N_2O$ calculated C 70.6%, H 7.8%, N 13.7%, found C 70.0%, H 7.2%, N 14.7%. HRMS requires 204.1263, found 204.1260.

10c [R=Et] 2-Ethyl-6-methoxy-1-propyloxybenzimidazole: Obtained as a brown oil.
^{1}H NMR (250MHz, $CDCl_3$) δ 7.50 (d, *J*=9.5Hz, 1H), 6.80 (m, 2H), 4.12 (t, *J*=6.6Hz, 2H), 3.81 (s, 3H), 2.85 (q, *J*=7.6Hz, 2H) 1.82 ([apparent sextet], *J*=6.9Hz, 2H), 1.40, (t, *J*=7.6Hz, 3H), 1.08 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 156.4, 151.4, 132.6, 131.1, 120.2, 110.7, 91.7, 79.8, 55.7, 21.6, 19.3, 11.3, 10.3. IR ν_{max} cm^{-1} 2970, 1630, 1490, 1455, 1400, 1230, 1030, 940. Elemental analysis for $C_{13}H_{18}N_2O_2$ calculated C 66.7%, H 7.7%, N 12.0%, found C 66.4%, H 8.0%, N 12.2%. HRMS (MH$^+$) requires 235.1447, found 235.1443.

10d [R=Et] 6-Chloro-2-ethyl-1-propyloxybenzimidazole: Obtained as a tan solid.
^{1}H NMR (200MHz, $CDCl_3$) δ 7.52 (d, *J*=8.6Hz, 1H), 7.29 (d, *J*=1.9Hz, 1H), 7.10 (dd, *J*=2.0, 8.6Hz, 1H), 4.11 (t, *J*=6.6Hz, 2H), 2.85 (q, *J*=7.6Hz, 2H), 1.82 (apparent sextet, *J*=6.8Hz, 2H), 1.39 (t, *J*=7.5Hz, 3H), 1.06 (t, *J*=7.4Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 153.0, 136.7, 131.0, 128.2, 122.5, 120.4, 108.0, 80.1, 21.5, 19.5, 11.2, 10.2. IR ν_{max} cm^{-1} 3050, 2960, 1520, 1460, 1400, 1270, 1050, 930, 820. Elemental analysis for $C_{12}H_{14}N_2OCl$ calculated C 60.4%, H 6.3%, N 11.6%, Cl 14.9%, found C 60.7%, H 6.6%, N 11.5%, 14.4%. HRMS requires 238.0873, found 238.0872. mp 54-56°C.

10e [R=Et] 2-Ethyl-6-methyl-1-propyloxybenzimidazole: Obtained as a yellow oil.
^{1}H NMR (250MHz, $CDCl_3$) δ 7.54 (d, *J*=8.2Hz, 1H), 7.14 (br s, 1H), 7.02 (dd, *J*=1.2, 8.2Hz, 1H), 4.17 (t, *J*=6.6Hz, 2H), 2.90 (q, *J*=7.6Hz, 2H), 2.47 (s, 3H), 1.84 ([apparent sextet], *J*=6.8Hz, 2H), 1.43 (t, *J*=7.5Hz, 3H), 1.11 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 151.6, 136.3, 132.4, 130.7, 123.3, 119.2, 107.8, 79.7, 21.4, 19.5, 11.2, 10.4. IR ν_{max} cm^{-1} 3020, 2980, 2960, 2880, 1630, 1530, 1490, 1460, 110, 1320, 1270, 1220, 1070, 940, 810. Elemental analysis for $C_{13}H_{18}N_2O$ calculated C 71.6%, H 8.3%, N 12.8%, found C 71.9%, H 8.0%, N 12.5%. MS (FAB, MH$^+$) *m/z* 219.

10a [R=Ph] 1-Benzyloxy-2-phenylbenzimidazole: Obtained as a tan solid.
^{1}H NMR (200MHz, $CDCl_3$) δ 8.19 (m, 2H), 7.84 (m, 1H), 7.49 (4H), 7.30 (m, 7H), 5.02 (s, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 147.3, 138.6, 132.9, 131.4, 130.2, 129.9, 129.6, 128.7, 128.6 (2C), 128.5, 123.4, 122.9, 120.4, 108.9, 80.2. IR ν_{max} cm^{-1} 3050, 3020, 2960, 1500, 1470, 1440, 1385, 1360, 1320, 1270, 1240, 1060, 950, 900, 730, 690. Elemental analysis for $C_{20}H_{16}N_2O$ calculated C 80.0%, H 5.3%, N 9.3%, found C 79.7%, H 5.4%, N 9.2%. MS (FAB, MH$^+$) *m/z* 301. mp 102-104°C.

10c [R=Ph] 1-Benzyloxy-6-methoxy-2-phenylbenzimidazole: Obtained as a tan solid.
^{1}H NMR (200MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.64 (d, *J*=8.8hz, 1H), 7.48 (m, 3H), 7.34-7.20 (m, 5H), 6.90 (dd, *J*=2.4, 8.8Hz), 6.78 (d, *J*=2.4,Hz, 1H), 5.01 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 157.0, 146.6, 132.9, 132.8, 132.1, 129.8, 129.4, 129.2, 128.8, 128.7, 128.6, 128.0, 120.8, 112.4, 91.9, 79.9, 55.6. IR ν_{max} cm^{-1} 3020, 2950, 1620, 1520, 1490, 1440, 1370, 1250, 1210, 1020, 890, 810. Elemental analysis for $C_{21}H_{18}N_2O$ calculated C 76.4%, H 5.5%, N 8.5%, found C 76.4%, H 5.5%, N 8.5%. MS (FAB, MH$^+$) *m/z* 331. mp 75-77°C.

10d [R=Ph] 6-Chloro-1-benzyloxy-2-phenylbenzimidazole: Obtained as a tan solid.
^{1}H NMR (200MHz, $CDCl_3$) δ 8.14 (m, 2H), 7.68 (d, *J*=8.6Hz, 1H), 7.49 (t, *J*=3.3Hz, 3H), 7.37-7.16 (m, 7H), 5.00 (s, 2H). ^{13}C NMR (75MHz, $CDCl_3$) δ 148.5, 137.2, 132.6, 132.2, 130.5, 130.1, 129.7, 129.3, 129.1, 128.6, 128.5, 127.5, 123.7, 121.3, 109.1, 80.5. IR ν_{max} cm^{-1} 3040, 3020, 1615, 1460, 1440, 1380, 1330, 1290, 1270, 1230, 1080, 900, 810, 760, 740. Elemental analysis for $C_{20}H_{15}N_2OCl$ calculated C 71.7%, H 4.5%, N 8.0%, Cl 10.6%, found C 71.5%, H 4.6%, N 8.4% Cl 10.6%. MS (FAB, MH$^+$) *m/z* 335. mp 122-124°C.

10c [R= CH=CH$_2$] 1-Allyloxy-6-methoxy-2-vinylbenzimidazole:
^{1}H NMR (200MHz, CDCl$_3$) δ 7.51 (d, *J*=8.6Hz, 1H), 6.90-6.75 (m, 3H), 6.42 (dd, *J*=1.5, 17.6Hz, 1H), 6.06 (m, 1H), 5.59 (dd, *J*=1.5, 11.2Hz, 1H), 5.36-5.26 (m, 2H), 4.63 (d, *J*=6.6Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (75MHz, CDCl$_3$) δ 157.2, 145.6, 133.1, 131.3, 130.3, 122.7, 122.6, 121.5, 120.9, 112.5, 91.7, 79.2, 55.8. IR ν_{max} cm^{-1} 3080, 3000, 2940, 2840, 1630, 1590, 1490, 1420, 1340, 1240, 1210, 1180, 1100, 1020, 940, 820.
HRMS (MH$^+$) for $C_{13}H_{14}N_2O_2$ requires 230.1055, found 230.1052.

11 1-(o-Bromobenzyloxy)-2-(o-bromophenyl)-4-methylbenzimidazole: Obtained as a light brown oil. ^{1}H NMR (200MHz, CDCl$_3$) δ 7.68 (m, 1H), 7.44-7.20 (m, 6H), 7.15-7.10 (m, 3H), 6.95 (m, 1H), 5.14 (s, 2H), 2,72 (s, 3H). ^{13}C NMR (75MHz, CDCl$_3$) δ 146.8, 137.7, 133.0, 132.9, 132.8, 132.2, 132.0, 131.4, 131.2, 130.6, 130.0, 129.1, 127.6, 127.1, 125.2, 124.0, 123.6, 123.1, 106.3, 79.3, 16.2. IR ν_{max} cm^{-1} 3060, 2920, 1590, 1560, 1450, 1370, 1190, 1030, 870, 750. HRMS for $C_{21}H_{16}N_2O^{79}Br_2$ requires 269.9629, found 269.9625.

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