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Efficient One-Pot Conversion of 6-Methyl-2-nitroaniline into 1-Alkyloxy-2-alkyl-4-methyl-, 1-Benzyloxy-2-phenyl-4-Methyl-, and 1-Allyloxy-4-methyl-2-vinyl-benzimidazole

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EFFICIENT ONE-POT CONVERSION OF 6-METHYL-2-NITROANILINE INTO 1-ALKYLOXY-2-ALKYL-4-METHYL-, 1-BENZYLOXY-2-PHENYL-4-METHYL-, AND 1-ALLYLOXY-4-METHYL-2-VINYL-BENZIMIDAZOLE.

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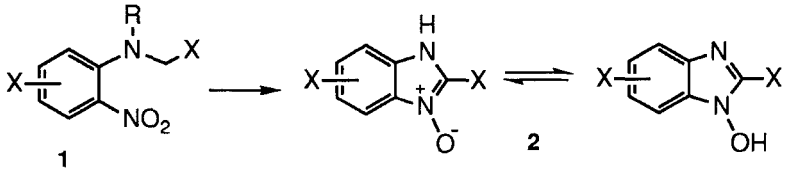
Abstract: 6-Methyl-2-nitroaniline reacts with alkyl, benzyl and allyl halides and NaH as base, to afford 1-alkoxy-2-alkyl-, 1-benzyloxy-2-aryl- and 1-allyloxy-2-vinyl-benzimidazoles in good to excellent yields (73-98%), *via* a novel one-pot N-alkylation-heterocyclization-O-alkylation sequence.

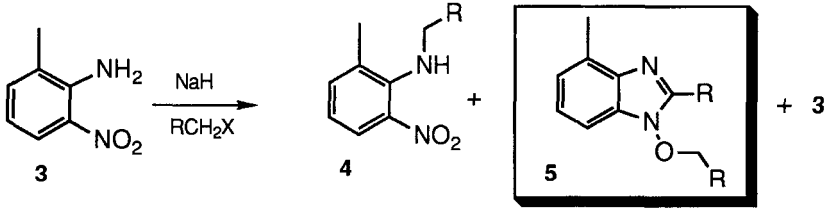
Benzimidazole-N-oxides, tautomeric with 1-hydroxybenzimidazoles, (**2**), cannot be obtained by direct oxidation of benzimidazoles. However, this heterocyclic system has been known for many years[1], a variety of applications have been reported[2], and a number of alternative synthetic methodologies have been developed. Cyclization of o-nitrosoanilines generated *in situ* photolytically[3], quinoline N-oxide rearrangements[4], and reaction of benzofuroxans with active methylene compounds[5] have all had some applications, but the vast majority of methods have utilized N-substituted o-nitroanilines (i.e. **1** → **2**). Reductive protocols[6], condensation of 2-nitroanilines with benzaldehyde[7], and reaction of N-benzylidine-nitroanilines with KCN in methanol[8], have some applications, but base induced cyclization of N-substituted 2-nitroaniline derivatives, constitutes the most explored route[9]. In nearly all reported cases, the N-alkyl group possesses a relatively acidic or benzylic proton adjacent to the nitrogen, with the chemistry of **1** (R = sulfonamide, X = aryl) extensively investigated[9b-d].

Yields are dependant on the nature of R and X, and *there appear to be no reported examples of cyclization when X = alkyl. In situ* O-alkylation occurs as a by-product of reactions with R = Ts, *via* generation of TsOMe, and when R = CO_2Et[9b-d], generally in low yield, but routinely, O-alkylation requires subsequent reaction of isolated **2**[9a].



Herein we report a convenient one-pot protocol for conversion of *N-unsubstituted* o-nitroanilines, specifically 6-methyl-2-nitroaniline, directly to O-alkylated-N-hydroxybenzimidazoles, without isolation of intermediate N-alkylated compounds, or of N-hydroxybenzimidazoles, and the novel observation that this methdology is also successful with simple alkyl halides.

Scheme I



At the outset of this work, we required the N-propyl product, **4** (R=Et). Since this N-propyl compound, **4** (R=Et) does not have the active methylene common to nitroaniline derivatives cyclizing to benzimidazoles under strong base conditions[9], we reasoned it could be prepared by alkylation of 2-methyl-6-nitroaniline, **3**, with propyl iodide using NaH as base, and would not cyclize once generated *in situ*. But when **3** was reacted with one equivalent each of NaH and of propyl iodide, *less than 5%* of the N-propyl compound, **4** (R=Pr), was obtained[10], along with ca. 40% of recovered nitroaniline, **3**, and a similar yield of a second product, readily separated by column chromatography, and identified as 2-ethyl-4-methyl-1-propyloxybenzimidazole, **5** (R=Et)[10]. Thus, N-alkylation, subsequent heterocyclization to the

Table 1: Products of reactions of 6-methyl-2-nitroaniline

Nitro-aniline	Base	RCH_2X	Method	**4**	**5**	Unreacted S.M.
3	2 NaH	1 PrI	A	-	44%	48%
3	2 NaH	2 EtI	A	2.5%	48%	38%
3	3 NaH	2 PrI	A	11%	45%	41%
3	**3 NaH**	**2 PrI**	**B**	**<5%**	**73%**	**21%**
3	**3 NaH**	**2 BnBr**	**B**	**-**	**98%**	**-**

Method A: One portion of base followed by one portion addition of alkyl halide
Method B: 3 portions of base and 2 portions of RX added over reaction period.
See discussion and experimental section.

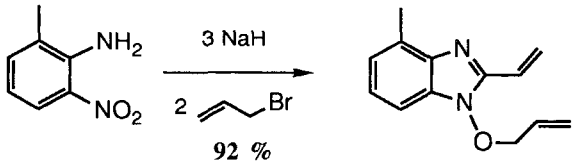
intermediate N-oxide, and finally O-alkylation had occurred *as the major reaction pathway*, equating to ca. 70% conversion based on recovered nitroaniline.

Since formation of the 2-ethyl-4-methyl-1-propyloxy-benzimidazole clearly requires two equivalents of alkylating agent, the predominance of **5**, with little of **4** and *none* of the 1-hydroxy-2-ethylbenzimidazole, on reaction with *one* equivalent of alkyl halide, indicates that O-alkylation of the intermediate 1-hydroxybenzimidazole competes with the initial N-alkylation. Very similar results were obtained for other simple alkyl iodides. When, the reaction was repeated with *two* equivalents of both base and, for example, ethyl iodide the yield of benzimidazole increased only marginally to 48%, with 38% of starting material recovered, along with traces of N-alkylated nitroaniline (table, entry 2). Reaction with *three* equivalents of base and two equivalents of alkyl halide afforded *almost no change* in yields of benzimidazole, and recovered starting material, with a small increase in the yield of N-alkylated products, **4**, [to 11% in the case of propyl iodide with **3**]. Benzyl bromide reacted in similar manner to afford varying yields of benzimidazoles. None of the intermediate 1-hydroxybenzimidazole was ever isolated, and, under the typical method A protocol, the N-alkoxybenzimidazole, **5**, could never be obtained in >50% yield, even with excess base and alkylating agent.

Since unreacted nitroaniline was recovered in all cases, we reasoned that N-anion decomposition might be compromising the reaction sequence. Consequently, we developed a procedure of initially adding only 1 equivalent of alkylating agent and 1 equivalent of base, then further similar portions of alkylating agent and base after 4 hours reaction, and then a further equivalent of base 4 hours later, followed by heating a further 4 hours. For alkylation employing benzyl bromide this lead to a remarkable improvement in yield of the benzimidazole product, **5**, with purified yield of 98%, with only traces of either starting material or N-alkylated product observed! With simple alkyl halides, for example propyl iodide, this new protocol also lead to significant improvement in yield of benzimidazole, with **3** affording 73% isolated yield (after chromatography) of 2-ethyl-4-methyl-1-propyloxybenzimidazole, **5** (R=Et). As far as we are aware this is a novel reaction of 2-nitroanilines, and this reactivity of the intermediate N-alkyl nitroaniline does not appear to have been reported.

This procedure therefore offers a novel, one-pot process to N-alkoxy-2-alkylbenzimidazoles, including to those bearing simple alkyl groups, unavailable by previously reported methodologies. Since, this synthesis with simple alkyl halides appears to be unprecedented, structural assignment was confirmed by single crystal X-ray analysis of an analogue prepared by the same methodology using ethyl iodide, 2,4-dimethyl-1-ethoxy-benzimidazole, **5** (R=Me)[11].

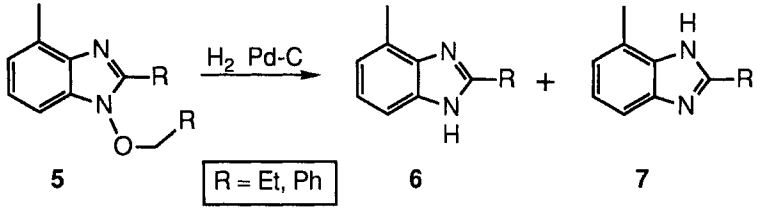
Scheme 2



Reaction with allyl bromide was similarly successful in providing the 1-allyloxy-2-vinyl-benzimidazole in 92% yield from **3** (Scheme 2), providing a convenient single step entry to 2-vinylbenzimidazole functionality.

Both the O-benzyl and O-alkyl groups from benzimidazoles **5** are readily removed by hydrogenolysis to give good yields of the corresponding 2-substituted NH benzimidazoles, as a mixture of regioisomers, **6** and **7** (Scheme 3). In the allyl case, rhodium catalysed allyl to vinyl isomerization then deprotection should offer a route to 2-vinyl-NH benzimidazoles.

Scheme 3



5 6 7

In summary, a protocol has been developed for convenient, high yielding, one pot direct conversion of 6-methyl-2-nitroaniline, into C-2 substituted N-alkoxy-, N-allyloxy- or N-benzyloxy-benzimidazoles. This reaction provides very competitive access to 2-phenylbenzimidazoles over previous two or three step approaches, and appears unprecedented for the alkyl halide cases. This methodology is practically straightforward and isolation of benzimidazole products is readily achieved up to gram scales. This protocol should be routinely applicable to synthesis of a wide range of 1-functionalized-2-substituted benzimidazoles in good yields, from readily available 2-nitroanilines. We have now shown that similar reactions proceed with several other 2-nitroaniline substrates, and a fuller discussion on these further applications will be reported in due course[11].

A number of the benzimidazoles, **5**, along with some other analogues[13] and related 2-alkylthiobenzimidazoles, have been evaluated for HIV-I Reverse Transcriptase inhibition, several proving to be modest inhibitors, with a novel propyl iodide derived N-propyloxy-benzimidazole, prepared by the methodology described here[11], being amongst the best with an EC_{50} of 0.6μM. In the cases evaluated so far, the benzimidazoles were generally one or two orders of magnitude better RT inhibitors than precursor N-alkylated 2-nitroanilines. Full details of testing data for these compounds, and synthesis, and testing of other related systems we have prepared, will be presented later[13].

Experimental section.

Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded using Bruker 200-AC (UMIST), Bruker 250-AC (Aston University) and Bruker 300-AC (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 a VG 70/70 Hybrid Mass spectrometer [low resolution], a Kratos Concept 1H [high resolution], or Kratos MS-50 [FAB] spectrometer (UMIST Centre for Mass Spectrometry). 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 5 and 6. (Method B table 1): Nitroaniline (1.45mmol) was dissolved in THF (10 mL), and NaH (80% in oil, 1.45mmol) 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 emperature, 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 futher 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 (5ml), and extracted with CH_2Cl_2 (3x40mls). The organic extracts were combined, washed with brine (25mls), 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 **5** as impurities. Silica gel flash column chromatography eluting with hexanes/ethyl acetate afforded the pure benzimidazole N-alkoxide, as a thick oil or a coloured solid, in 63-98%. 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.

5b [R=H] 1-methoxy-4-methylbenzimidazole:
^{1}H NMR (250MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.24 (m, 2H), 7.06 (d, *J*=6.9Hz, 1H), 4.11 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 138.6, 136.6, 130.7, 128.8, 123.5, 12.8, 105.9, 67.1, 16.0. IR ν_{max} cm^{-1} 3400 (broad), 3060, 2980, 2940, 1200, 1590, 1480, 1460, 1380, 1320, 1235, 1155, 1010, 970, 855, 750. *m/z* 163 (M^+ + H)

5b [R=Me] 2-methyl-1-ethoxy-4-methylbenzimidazole:
^{1}H NMR (250MHz, $CDCl_3$) δ 7.14-7.02 (m, 2H), 6.94 (d, *J*=7.0Hz, 1H), 4.17 (q, *J*=7.1Hz, 2H), 2.56 (s, 3H), 2.54 (s, 3H), 1.33 (t, *J*=7.1Hz, 3H). ^{13}C NMR

(62.5MHz, $CDCl_3$) δ 146.7, 137.2, 130.1, 129.1, 122.4, 122.3, 105.6, 73.8, 16.0, 13.6, 12.3. IR ν_{max} cm^{-1} 3054, 2971, 2881, 1598, 1523, 1457, 1402, 1322, 939, 752. Elemental analysis for $C_{11}H_{14}N_2O$ calculated C 69.5%, H 7.4%, N 14.7%, found C 68.4%, H7.4%, N 14.3%. HRMS requires 190.1106 found 190.1106.

5b [R=Et] 2-ethyl-4-methyl-1-propyloxybenzimidazole:

^1H NMR (250MHz, $CDCl_3$) δ 7.18-7.06 (m, 2H), 6.97 (d, *J*= 7.0Hz, 1H), 4.12 (t, *J*=6.5Hz, 2H), 2.93 (q, *J*=7.6Hz, 2H), 2.61 (s, 3H), 1.81 ([apparent sextet] *J*=6.8Hz, 2H), 1.40 (t, *J*=7.6Hz, 2H), 1.07 (t, *J*=7.4Hz). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 151.3, 137.4, 130.1, 129.4, 122.4, 122.3, 105.6, 79.9, 21.5, 19.8, 16.1, 12.1, 10.3. IR ν_{max} cm^{-1} 3054, 2971, 2881, 1598, 1523, 1457, 1402, 1322, 939. Elemental analysis for $C_{13}H_{18}N_2O$ calculated C 71.6%, H 8.3%, N 12.8%, found C 71.1%, H 8.7%, N 11.7%. HRMS requires 218.1419 found 218.1413.

5b [R=Ph] 1-benzyloxy-4-methyl-2-phenylbenzimidazole:

^1H NMR (200MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.50 (m, 3H), 7.34 (m, 7H), 7.16 (m, 1H), 5.01 (s, 2H), 2.79 (s, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$) δ 147.0, 137.4, 133.1, 131.2, 130.6, 130.5, 130.2, 130.0, 129.3, 129.0, 128.7, 128.6, 123.4, 123.2, 106.5, 80.1, 16.4. IR ν_{max} cm^{-1} 3413, 3060, 3031, 2921, 1604, 1473, 1446, 1375, 1319, 1243, 906, 752. Elemental analysis for $C_{20}H_{16}N_2O$ calculated C 80.3%, H 5.7%, N 8.9%, found C 80.0%, H 5.7%, N 8.8%. HRMS requires 314.1419 found 314.1423. M. pt. 41-42°C.

5b [R= $CH=CH_2$] 1-allyloxy-4-methyl-2-vinylbenzimidazole:

^1H NMR (200MHz, $CDCl_3$) δ 7.26-6.80 (m, 4H), 6.55 (dd, *J*=1.5, 17.1Hz, 1H), 6.11 (m, 1H), 5.72 (dd, *J*=1.5, 11.2Hz, 1H), 5.36 (m, 2H), 4.67 (d, *J*=6.6Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 145.6, 138.0, 130.6, 130.5, 123.5, 123.4, 123.3, 123.2, 122.8, 122.7, 106.3, 79.3, 16.4. IR ν_{max} cm^{-1} 3060, 3020, 2920, 1600, 1510, 1420, 1320, 1260, 1240, 1170, 1080, 980, 940, 750. Elemental analysis for $C_{13}H_{14}N_2O$ calculated C 72.9%, H 6.5%, N 13.1%, found C 72.6%, H 6.8%, N 12.9%.

6 and 7 [R=Ph] 4-methyl-2-phenyl-benzimidazole; 7-methyl-2-phenyl-benzimidazole:

^1H NMR (200MHz, DMSO) δ 12.83 and 12.57 (br s, [total 1H]), 8.21 (m, 2H), 7.58-7.32 (m, 2H), 7.05 (m, 2H), 2.57 (s, 3H). ^{13}C NMR (75MHz, DMSO) δ 137.3, 134.3, 133.7, 133.5, 132.9, 132.6, 132.5, 132.2, 130.6, 166.4, 126.1, 110.8, 20.9. [most peaks doubled for two regioisomers] IR ν_{max} cm^{-1} 3400,

2971, 1651, 1537, 1456, 1417, 1371, 1309, 1280, 1115, 1075, 746, 703. Elemental analysis for $C_{14}H_{12}N_2$ calculated C 80.8%, H 5.8%, N 13.5%, found C 80.5%, H 5.8%, N 13.2%.

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References and notes

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D. J.; Smith, D. M. *ibid.*, **1988**, 1939. (j) Harvey, H. W.; McFarlane, M. D.; Moody, D. J.; Smith, D. M. *ibid.*, **1988**, 681. (k) Livingstone, D. B.; Tennant, G. *J. Chem. Soc. Chem. Commun.*, **1973**, 96.

10. ^{1}H NMR, ^{13}C NMR, DEPT, IR, mass spectral data and microanalysis were consistent only with this structure. All compounds **4**, **5** and **6/7** were fully characterized by NMR, and gave satisfactory elemental analysis and/or high resolution mass spectral data.

11. Details of X-ray crystal structure analysis of benzimidazole **5** (R=Me) will be reported: Gardiner, J. M.; Loyns, C. R.; Schwalbe, C. H.; Barrett, G. C.; Lowe, P. R. *manuscript in preparation* July **1994**

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13. Testing was against HIV-1_{IIIB} in C8166 cells, carried out at the MRC Collaborative Centre by Dr. Naheed Mahmood.

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