Pergamon

Tetrahedron Letters 39 (1998) 359–362

TETRAHEDRON LETTERS

o-Nitrobenzyl as a Photocleavable Nitrogen Protecting Group for Indoles, Benzimidazole, and 6-Chlorouracil.

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Received 24 September 1997; revised 30 October 1997; accepted 3 November 1997

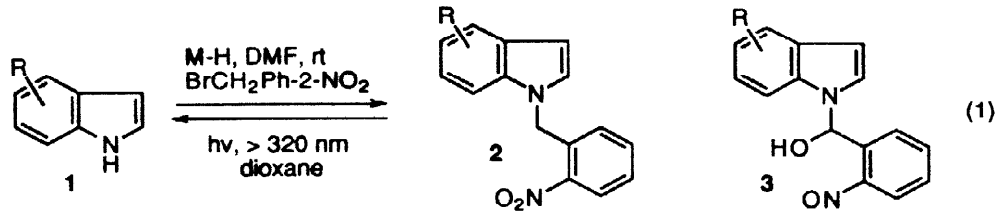
Abstract: The potential for the o-nitrobenzyl group as an alternative nitrogen protecting group for various indoles, benzimidazole, and 6-chlorouracil was determined. Treatment of the appropriate N-H containing substrate with LiH or NaH in DMF followed by o-nitrobenzyl bromide afforded reasonable yields of *N*-alkylated products. To effect removal of this group, simple photolysis with 300 nm light afforded good yields of starting substrate.

The selection of a suitable protecting group for heterocyclic N-H functions, in which the nitrogen lone pair is resident in an aromatic network, has special requirements in contrast to the protection strategies for basic nitrogen groups. Carbamates and sulfonyl derivatives are the most common electron-withdrawing groups serving in this capacity.[1] However, in many cases alkyl based protection strategies are desirable where the electronic effect of the nitrogen atom needs to be preserved. In this regard limited options are available, namely mixed acetals [2-(trimethylsilyl)ethoxymethyl (SEM),[2a] benzyloxymethyl (BOM)[2b]] and β-ethyl substituted derivatives (2-pyridylethyl,[2c] 2-chloroethyl[2d]). Although *N*-benzyl groups have been used in the past, demanding reaction conditions required for their removal forebodes more widespread applications.[3] As a consequence the 2,4-dimethoxybenzyl group[4] was implemented for protection of a pyrrole nitrogen which can be removed under mild acidic conditions (TMSI or TFA).[5a] However, in the context of a project aimed at the synthesis of pyrrolo[2,3-*d*]pyrimidine based nucleotide analogues, this group proved troublesome.[5b] In response the *p*-nitrophenethyl (PNPE) group was applied as an alternative protecting group for a pyrrole nitrogen, cleavable under mild basic conditions. Recently we desired an alkyl based protecting group for pyrroles and indoles which can be removed under neutral reaction conditions.[6] In surveying the literature the photocleavable o-nitrobenzyl (ONB) group[7] was identified as a likely prospect and serves as the basis for the current study. There are two prior reports using

0040-4039/98/$19.00
PII: S0040-4039(97)10600-1

ONB to protect the imidazole ring in histidine[8a] and N^3 of benzo- and imidazotriazinones.[8b]

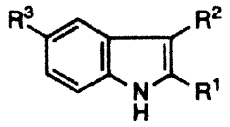
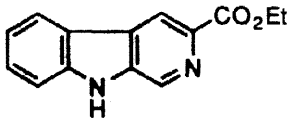
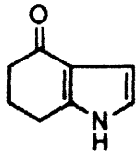
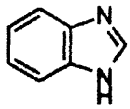
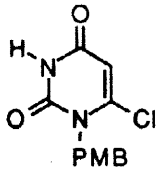
The typical reaction scheme is illustrated below (eq 1). Thus, treatment of the appropriate indole **1** with either LiH (10 eq) or NaH (1.2 eq)[9] in DMF at room temperature for 30 min followed by the addition of *o*-nitrobenzyl bromide and stirring for several hours afforded the 1-*o*-nitrobenzyl protected indoles **2**. Photolysis of the ONB-protected products **2** in dioxane (0.01-0.04 M) using 300 nm lamps in a Rayonet photoreactor typically afforded an initial reaction mixture comprised of the free indole and varied amounts of the intermediate nitrosohemiaminal **3**.[10] After consumption of the starting material, the solvent was evaporated and then replaced with MeOH and 2-3 drops of 40% NaOH solution. Upon stirring for 2-3 h the breakdown of any remaining **3** into free indole was completed, as determined by TLC analysis.



(1)

The feasibility for the ONB group for the protection of nitrogen atoms in substituted indoles and other representative N-H heterocyclic systems is summarized in Table 1. The results demonstrate the viability of the ONB group for protection of indoles bearing an electron withdrawing group at either the 2, 3, or 5 position. On the other hand, indole itself and two other systems[11] afforded modest yields of deprotection. TLC analysis of the crude reaction mixture from **4a** showed the presence of the free indole, intermediate **3** (R = H), and other by-products. One possible source for these by-products would be from attack of the liberated *o*-nitrosobenzaldehyde upon the free indole.[12] A more likely explanation for the lower yields in these cases would be competing single-electron-transfer (SET) from the indole to the photo-excited nitroarene group.[13] This secondary reaction process would logically be diminished with attendant electron-withdrawing groups on the indole ring. In three alternative systems; tetrahydroindol-4-one **7**, benzimidazole **8**, and 6-chlorouracil **9** deprotection proceeded in reasonable yields, although longer photolysis reaction times were required. Overall the mildness of the photo-deprotection procedure shows compatibility with other functional groups including aldehyde, ester, activated chloride, and nitrile.

Table 1. Alkylation and Photoinduced Deprotection of Indoles, Benzimidazole, and 6-chlorouracil.

Substrate	Alkylation Yield, %[a]	Photolysis time, h	Deprotection yield, %[d]
			
4a, R^1, R^2, R^3 = H	59[b], 67[c]	5	45[e]
b, R^1, R^3 = H, R^2 = CHO	81[b], 73[c]	5	95
c, R^2, R^3 = H, R^1 = CO_2Et	85[b], 84[c]	7	72
d, R^1, R^2 = H, R^3 = CN	96[b]	7	70 + 9 (s.m.)[f]
 **5**	64[b] + 23 (s.m.)[f]	3	91
 **6**	87[b]	14	79 + 9 (s.m.)[f]
 **7**	79[b]	12	77
 **8**	99[b]	40	76 + 22 (s.m.)[f]

[a]isolated yield following recrystallization from ethyl acetate hexanes, except for compounds 5 and 7 which were purified by column chromatography over silica gel. [b]Reaction conducted with LiH (10 eq) for 12-24 h at room temperature. [c]Reaction conducted with NaH (1.2-1.4 eq) for 2 h at r.t. [d]isolated yield following column chromatography over silica gel. [e]see text. [f]recovered starting material.

In summary, the 2-nitrobenzyl protecting group's range of utility has been extended to nitrogen containing heterocyclic systems typified by substituted indoles, 6-chlorouracil, and benzimidazole. It accordance with these results, it is likely that this group can be used with other heteroaromatic systems which are less electron rich than indole.

Acknowledgements: This research was supported, in part, by the donors of the Petroleum Research Fund, administered by the American Chemical Society and by funds provided from the Research Office, University of Montana.

References and Notes

[†]Summer undergraduate research participants.

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3. Removal of *N*-benzyl groups from indoles and imidazoles typically requires strong basic, acidic, or reducing reaction conditions. a) (MeLi, rt, >12 h) Suzuki, H.; Tsukuda, A.; Kondo, M.; Aizawa, M.; Senon, Y.; Nakajima, M.; Watanabe, T.; Yokoyama, Y.; Murakami, Y. *Tetrahedron Lett.* **1995**, *31*, 1671. b) ($AlCl_3$, PhH) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738. c) (H_2, 50 psi, Pd black, AcOH/H_2O, 3 d) Evans, D. A.; Lundy, K. M. *J. Am. Chem. Soc.* **1992**, *114*, 1495.
4. A 2,4-dimethoxybenzyl group was first used to protect the amide side-chain of glutamine and asparagine residues and can be readily cleaved using TFA or aqueous HF. Pietta, P. G.; Cavallo, P.; Marshall. G. R. *J. Org. Chem.* **1971**, *36*, 3966.
5. a) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403. b) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1994**, *59*, 6902.
6. Specifically, the need arose for an alkyl-based pyrrole protecting group which is stable to acid and basic reaction conditions and can be removed selectively in the presence of acid or base cleavable protecting groups elsewhere in the molecule.
7. For previous use of the ONB group of amino and carboxyl function of amino acids, see: a) Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333. b) Barltrop, J. A.; Plant, P. J.; Schofield, P. *Tetrahedron Lett.* **1966**, 822. For a review on photoremovable protecting groups, see: c) Pilla Rajasekharen, V. N. *Synthesis* **1980**, 1.
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9. The use of NaH was less desirable due to competing deprotonation of the ONB-Br which lead to dark colored by-products. This problem was avoided by the use of less basic LiH. Excess (10 eq) of this hydride was used in order to shorten the reaction times which were monitored by TLC.
10. For substrates **4b-d**, **5**, **6**, and **7** the nitrosoaminal was either faintly evident or nonexistent by TLC analysis. Only in the case of indole and two other sluggish cases (ref 11) did significant accumulations of this intermediate arise. Evidence for compound **3** (R = H) was suggested by the following spectral characteristics; ^1H NMR (270 MHz, $CDCl_3$) δ, 8.76 (d, J = 4.6 Hz, 1H, CHOH), 7.94 (br d, J = 7.3 Hz, 1H), 7.75 (br t, 1H), 7.58 (br d, 2H), 7.36 (br t, J = 7.3 Hz, 1H), 7.20-7.08 (m, 3H), 6.51 (d, J = 3.3 Hz, 1H), 6.26 (dd, J = 1.3, 7.9 Hz, 1H), 4.23 (br d, J = 4.6 Hz, 1H, CHOH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 161.9, 140.9, 136.7, 135.4, 129.1, 128.8, 128.1, 124.9, 122.2, 121.1, 120.4, 110.3, 106.2, 103.4, 78.0 (CHOH),
11. For example, ONB protected 3-indolylacetonitrile and 2-pyridinone afforded less than satisfactory deprotection yields (<50%).
12. For a related problem involving the secondary reaction of the liberated amino group from ONB protected amino acid derivatives with the aldehyde group of this by-product, see: ref 7a.
13. We give thanks to a referee for suggesting this explanation.