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Amidine Protection For Solution Phase Library Synthesis

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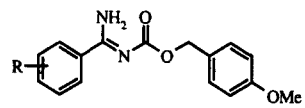
Abstract: The application of 4-methoxybenzyl-4-nitrophenylcarbonate as a reagent for the N-protection of amidinonaphthol has been demonstrated. The facile introduction of the 4-methoxybenzyloxycarbonyl group and the mildness of the deprotection conditions make this reagent well suited for the multiparallel solution phase synthesis of substituted benzamidines.

The amidine group has found frequent application in medicinal chemistry; its highly basic character involves it in strong interactions with protein regions bearing anionic and hydrogen bonding groups and in this context such moieties as benzamidine have frequently been used as substitutes for arginine. Although able to make comparable interactions to guanidines, compounds containing benzamidines tend to have improved pharmacokinetic and toxicity profiles. This has been apparent in the cardiovascular field where factor Xa[1], IIa[2] and fibrinogen receptor antagonists[3] have evolved which bear amidinophenyl moieties as arginine surrogates, and also in other areas, for instance the LTB_4 antagonist CGS 25019c.[4]

It is surprising to note that while there are a number of reagents available for the protection of amines[5] and arginine,[6] which may extend to amidines, little information is available directly concerning the protection of this functionality. There are some instances where it would be desirable to have the amidine already present, but in an inert and easily releasable form. Most published syntheses introduce the amidine as a final step[7] thereby circumventing any need to protect, but often these reactions may not be quantitative and may require product purification, or the method may not be generally applicable to a range of structural types. There are therefore potential benefits in using a pre-formed protected amidine over a final stage amidation strategy, particularly when the requirement is the multi-parallel synthesis of a range of compounds containing a common amidine bearing moiety. Assuming that deprotection is efficient the manipulation and purification of these very polar compounds can be minimised.

In the course of our work with 6-amidinonaphth-2-ol **2** we discovered 4-methoxybenzyloxycarbonyl (Moz) to be a convenient aromatic amidine protecting group (figure 1). The Moz group was easily and selectively introduced, inert to a number of reaction conditions, and cleaved efficiently and rapidly under very mild acidic conditions which were compatible with multiparallel synthesis.

Figure 1



Standard carbamate protecting groups such as *t*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) had proved unsuitable with amidinonaphthol; although the Cbz group could be introduced relatively easily and rendered the amidine stable to alkylation (NaH, BnBr), removal could only be achieved using reagents that were harsh or made product isolation difficult (tetramethyl guanidine or trimethylsilyl iodide).

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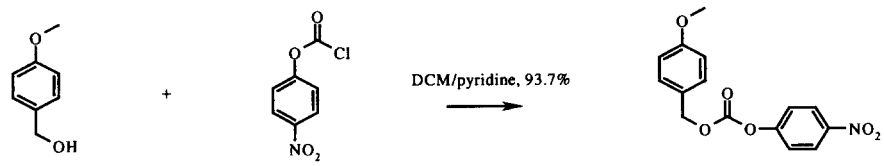
p-Methoxybenzyloxycarbonyl (Moz) has previously been demonstrated as a suitable protecting group for amines,[8] although it has not enjoyed widespread use. To our knowledge it's application to amidine protection has not previously been investigated.

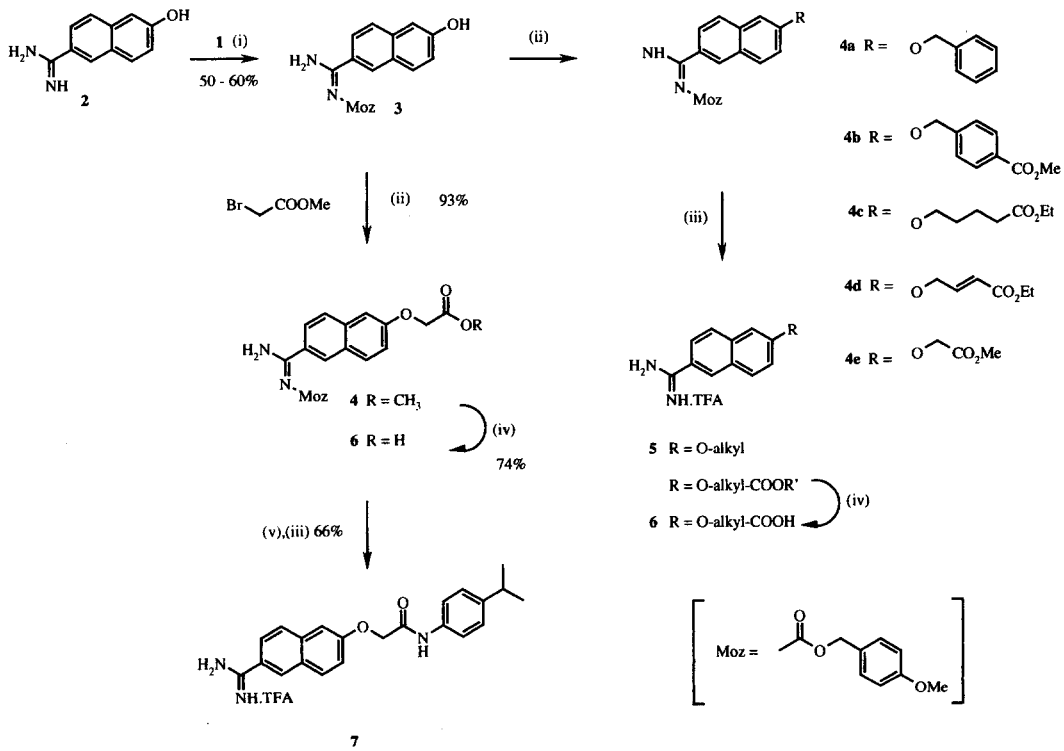
Scheme 1: Preparation of 4-methoxybenzyl-4-nitrophenylcarbonate **1**[10]



1

Treatment of amidinonaphthol with a small excess of **1** (scheme 2) cleanly gave the Moz protected amidine **3** typically in 50-60% yields. In our hands this reagent was superior to the commercially available Moz-ON.[9]

Scheme 2:



2 **3** **7**

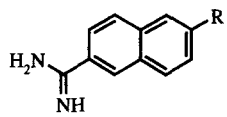
(i) Et_3N, DMF, 50°C; (ii) alkyl bromide, K_2CO_3, acetone, RT; (iii) TFA, DCM;
(iv) (a) 1N NaOH. MeOH, (b) 1N HCl; (v) 4-isopropylaniline, DIPEA, TBTU, DCM, RT

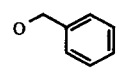
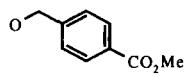
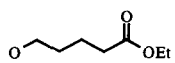
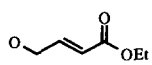
The utility of the protection strategy for rapid parallel synthesis was demonstrated by carrying out a number of alkylations with various alkyl bromides (Table 1).[11] Deprotection under mild conditions (0.5% TFA in DCM)

led to the respective amidines **5** which could in turn be followed by a basic hydrolysis for R groups which contained carboxylic acid esters. The Moz group is however stable to both basic hydrolysis and standard peptide coupling conditions, as shown by the synthesis of the amidinonaphthyl ether anilide **7**.

This two-step (or three when including ester hydrolysis) alkylation/deprotection process could be adapted for multiparallel synthesis.

Table 1



Compound	R	yield*
5a		78%
5b		74%
5c		56%
5d		87%
5e		93%

* Overall yield for two stages (alkylation and deprotection)

References

(1) Katakura, S.; Nagahara, T.; Hara, T.; Iwamoto, M. *Biochem. Biophys. Res. Comm.* **1993**, 197 (2), 965-972.

(2) (a) Brundish, D. E.; *Current Drugs*, **1992**, pp1457-1466. (b) Ripka, William C.; *Curr. Opin. Chem. Biol.* **1997**, 1(2), 242-253. (c) Weitz, J.; *Drugs* **1994**, 48(4), 485-97.

(3) Weller, T.; Alig, L.; Beresini, M; Blackburn, B.; Hadváry, P.; Hürzeler, M.; Knopp, D; Levet-Trafit, B.; Lipari, M.T.; Modi, N.B.; Müller, M.; Refino, C.J.; Schmitt, M.; Schünholzer, P.; Weiss, S.; Steiner, B.; *J. Med. Chem.* **1996**, 39, 3139-3147.

(4) Brooks, C.D.W.; Summers, J.B.; *J. Med. Chem.* **1996**, 39, 2629-2654.

(5) Jarowicki, K.; Kocienski, P.; *Contemp. Org. Synth.* **1996**, 3(5), 397-431.

(6) Rzeszotarska, B.; Masiukiewicz, E.; *Org. Prep. Proced. Int.* **1988**, 20(5), 427-64.

(7) (a) Kusumoto, T.; Ogino, K.; Sato, K.; Hiyama, T.; Takehara, S.; Nakamura, K.; *Chem. Lett.* **1993**, 7, 1243-1246. (b) Iwanowicz, E. J.; Lau, W. F.; Lin, J.; Roberts, D. G. M.; Seiler, S. M.; *Bioorg. Med. Chem. Lett.* **1996**, 6 (12), 1339-1344. (c) Garigipati, R. S.; *Tetrahedron Lett.*, **1990**, 31, 1969.
(8) (a) Vandesande, F.; *Bull. Soc. Chim. Bel.*, **1970**, 79, 397. (b) Yajima, H.; *Chem. Pharm. Bull.*, **1978**, 26, 2752. (c) Yajima, H.; Fujii, N.; Akaji, K.; Sakurai, M.; Nomizu, M.; Mizuta, K.; Aono, M.; Moriga, M.; Inoue, K.; Hosotani, R.; Tobe, T.; *Chem. Pharm. Bull.* **1985**, 33(8), 3578-3581.
(9) Chen, S.T., Wang, K.T.; *Synthesis*, **1989**, (1), 36-37.
(10) Preparation of **1**: To a stirring solution of p-anisyl alcohol (5.0g, 36.2mmol) in dichloromethane (DCM) (100ml) and pyridine (4.4ml, 54.4mmol) at 0°C (ice-salt bath), was added dropwise over 30 mins a solution of *p*-nitrophenylchloroformate (7.3g, 36.2mmol) in DCM (100ml). After 2 hours the reaction mixture was washed with water (3 x 50ml), the combined aqueous layers back extracted with DCM (50ml) and the combined organics washed with saturated brine, dried ($MgSO_4$), evaporated to dryness and pumped under high vacuum for 4 hrs to afford 4-methoxybenzyl-4-nitrophenylcarbonate **7** (10.29g, 93.7%), one spot on tlc (EtOAc/hexane 1:1)
(11) Preparation of **5d**: To a stirring solution of 6-Amidinonaphth-2-ol hydrochloride (1) (4.16g, 18.7mmol) and triethylamine (7.06ml, 3eq) in DMF (80ml) was added a solution of 4-methoxybenzyl-4-nitrophenylcarbonate **1** (5.20g, 17.16mmol) in DMF (80ml) dropwise over 30 minutes. When addition was complete the reaction mixture was stirred at 50°C for 3hrs, and at room temperature for 15hrs, poured into water (200ml), acidified with cold 10% citric acid and extracted with dichloromethane (3 x 50ml). The combined organic solution was washed with 10% sodium bicarbonate solution, saturated brine, dried ($MgSO_4$), concentrated and purified by flash chromatography [EtOAc/hexane 1:3 (250ml) changing to EtOAc/hexane 1:1] to give N-(4-methoxybenzyloxycarbonyl)-6-amidinonaphth-2-ol (3.18g, 9.08mM, 53%).
A solution of N-(4-methoxybenzyloxycarbonyl)-6-amidino-2-naphthol (150mg, 0.43mM) in acetone (10ml) was treated with potassium carbonate (200mg, 1.37mM), ethyl bromocrotonate (120mg, 0.59mM) and stirred at room temperature for 48hrs. The reaction mixture was concentrated, extracted with ethyl acetate and washed with water and brine. The organics were dried, evaporated and purified by flash chromatography (EtOAc/hexane 1:1) to give the required ethyl 4-[N-(4-methoxybenzyloxycarbonyl)-6-amidinonaphth-2-yloxy]but-2-enoate **4d** in quantitative yield
The Moz protected amidine **4d** (0.148g, 0.32mM) was dissolved in DCM (20ml), TFA (0.1ml, 4eq) added and the reaction mixture stirred at room temperature for 10mins. The solvent was evaporated, ether added and the resultant solid filtered, washed with ether and dried in vacuo to give **5d** (0.144g, 0.277mM, 87%) as the TFA salt: $M^+ = 289.9$; NMR ^1H (400MHz) (MeOD)δ 1.3 (t, J = 7Hz, 3H), 4.2 (q, J = 7Hz, 2H), 4.92 (m, 2H), 6.22 (dt, J=15.8 & 2Hz, 1H) 7.16 (dt, J=15.8 & 4.1Hz, 1H) 7.38 (dd, J=9.15Hz & 2.5Hz, 1H) 7.41 (d, J=2Hz, 1H) 7.77 (dd, J=8.7Hz & 2Hz, 1H) 7.99 (dd, J=8.7 & 2Hz, 1H) 8.01 (dd, J=8.7 & 5.85Hz 1H) 8.37 (d, J=2Hz, 1H)