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Mild N-Dealkylation of Tertiary, Benzylic Amines with Acid Chlorides: Application to Solid-Phase Chemistry

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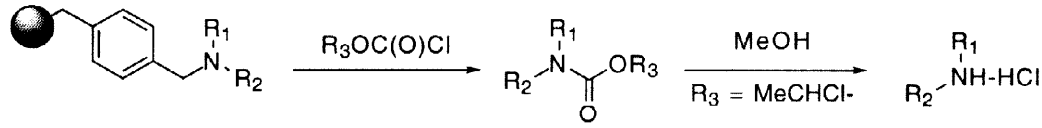
This manuscript is dedicated to the memory of my father, Loren Lee Miller (Oct. 22, 1939 - Feb. 15, 1998)

Abstract: A mild, facile cleavage of appropriately substituted tertiary, benzylic amines with acid chlorides is described for both solution and solid phase.

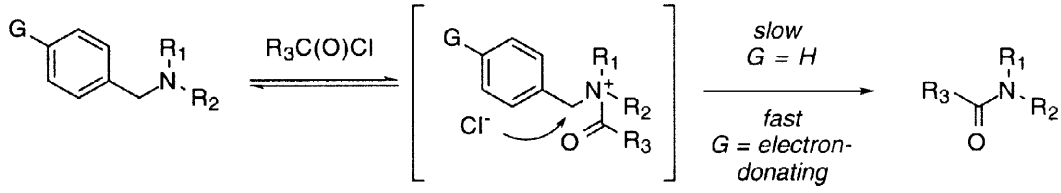
Linker design in solid-phase synthesis remains an area of intense study where attachment and cleavage steps are the cornerstones of the process. A linker that would allow both product diversity and release from the support in one step would be advantageous. For amide products, "traceless" cleavage replacing resin bound C-N with H-N has been demonstrated.[1] However, it is also possible to utilize an amide-forming cleavage step as a diversity element.[2] Here we describe a novel method for the construction of tertiary amides using acylative N-dealkylation as a cleavage step.

Acylative dealkylation of tertiary amines with chloroformates to give carbamates is well established[3] and has recently been extended to the solid phase[4a] (**Scheme 1**). In this study, the α-chloroethyl carbamate was converted into the parent amine (HCl salt) via methanolysis[4b].



Scheme 1

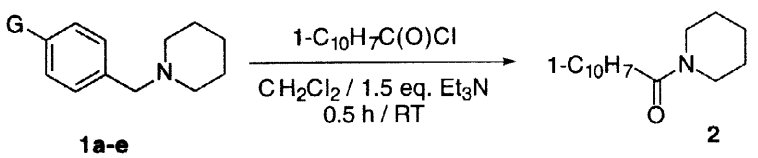
In contrast, acid chlorides are generally less satisfactory partners in this process as observed by the authors in the above study.[5] Seeking to extend the chemistry, we reasoned that appropriate electron donating substituents on an N-benzyl group would facilitate both ease and selectivity of cleavage (**Scheme 2**).



Scheme 2

PII: S0040-4039(98)00584-X

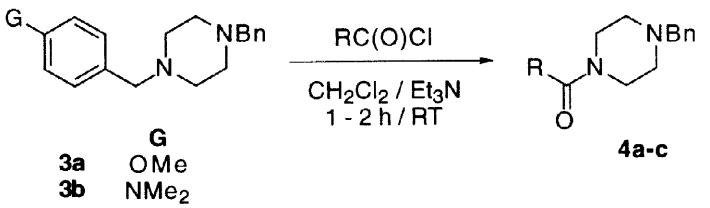
This idea was brought to light by some observations we had made and was corroborated by a recently published route to acylated α–amino ketones.[6] To test the validity of this concept, the reaction of various N-(para-substituted benzyl) piperidines **1a-e** with 1-naphthoyl chloride was investigated (**Scheme 3**).[7] As one can see, the substrates bearing a electron-donating group underwent clean conversion to the naphthamide **2** *at room temperature in less than 1 hour* . N-Benzyl piperidine **1e** (G = H) gave no significant cleavage over 24 h under identical conditions. This illustrates the very large rate acceleration for N-debenzylation when a para-electron donating group is present. Also, N-(4-methoxybenzyl)-pyrrolidine and -diethylamine were cleanly and selectively cleaved under the same conditions to the corresponding napthamides.



	G	Yield of 2	
1a	MeO	97	*
1b	EtO(O)CNH	87	* No Et_3N added
1c	PhC(O)NH	91	
1d	Me_2N	97	
1e	H	0	

Scheme 3

N-(4-Methoxybenzyl)piperazine derivative **3a** displayed diminished reactivity towards acid chlorides with respect to the analogous piperidine **1a**.[9,10] However, the dimethylamino derivative **3b** displayed increased reactivity with acid chlorides. Thus, the reaction of **3b** with 1-naphthoyl, 2-methylbenzoyl, and cyclohexyl carbonyl chloride (1-1.5 eq., RT) gave the corresponding amides **4a-c** in good yields (**Scheme 4**). This illustrates the ability to "tune" the efficiency of the N-debenzylation by using various electron donating groups. It should be noted that the other benzylic amine bond remained intact in these reactions. Thus, selectivity of benzylic amine bond cleavage can be controlled by aromatic ring substitution.



	G
3a	OMe
3b	NMe_2

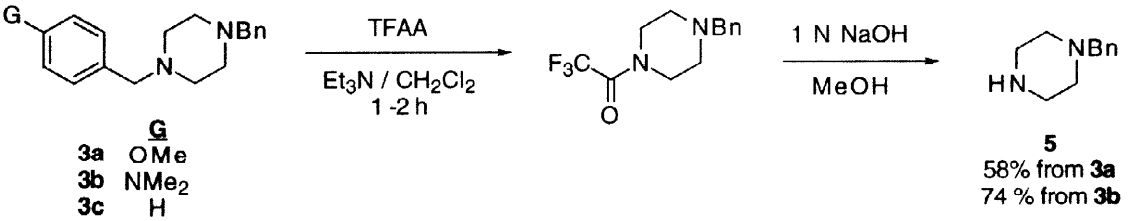
	R	Yield*
4a	1-naphthyl	95
4b	2-methylphenyl	91
4c	cyclohexyl	73

*3b as substrate

Scheme 4

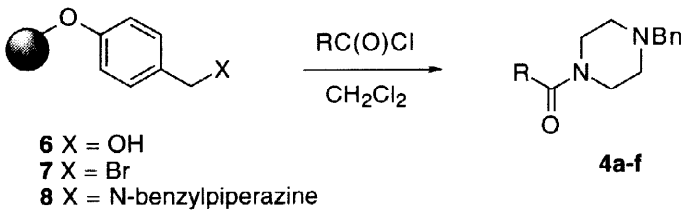
Trifluoroacetic anhydride was found to be one of the most reactive reagents in this process, and rapidly transformed derivatives **3a** and **3b** to the corresponding trifluoroacetamides. The trifluoroacetamides were hydrolyzed (1 N NaOH/MeOH) to the free

NH piperazine **5**. This protocol should find use as an alternative method for deprotection of tertiary, benzylic amines.[11] In contrast, exposure of dibenzyl piperazine **3c** (G = H) to trifluoroacetic anhydride (3 days,CH_2Cl_2, 25° C) gave no detectable reaction.



Scheme 5

We extended this process to the solid phase, creating a small library of amides using Wang resin as the solid phase "p-methoxybenzyl" moiety (**Scheme 6**). Commercial Wang resin **6** (0.87 mmol/g) was converted into the bromo-resin **7**[1b] which was reacted with excess N-benzyl piperazine to give the derivatized resin **8** (0.77 mmol/g. theory from original loading). The piperazine resin **8** was treated with various acid chlorides (7 eq., CH_2Cl_2, 18-24 h) to give the desired piperazine amides **4a-f** in moderate to good yields (42-80 %) after isolation via a resin capture technique.[12] The amides **4a-f** were produced in ≥ 95% purity as judged by ^1H NMR (300 MHz) analysis.



6 X = OH
7 X = Br
8 X = N-benzylpiperazine

4a-f

4	R	Yield
a	1-naphthyl	58
b	2-methylphenyl	71
c	cyclohexyl	42
d	methyl	80
e	phenyl	69
f	4-methoxyphenyl	58

Scheme 6

In conclusion, we have generated a set of reaction parameters that allow for mild, rapid, and clean conversion of tertiary amines to amides. The protocols outlined here are amenable to both solution and solid phase sequences. Further application to both drug discovery and synthesis are under investigation.

References and Footnotes

1. a) Boojamra, C.G.; Burow, K.M.; Ellman, J.A. *J. Org. Chem.* **1995**, *60*, 5742. b) Ngu, K.; Patel, D.V. *Tetrahedron Lett.* **1997**, *38*, 973. c) Raju, B.; Kogan, T.P. *Tetrahedron Lett.* **1997**, *38*, 4965. d) Fivush, A.M.; Willson, T.M. *Tetrahedron Lett.* **1997**, *38*, 7151. d) Swayze, E.E. *Tetrahedron Lett.* **1997**, *38*, 8465.

2. For use of amines and polymer bound acyl equivalents to produce amides see: Kenner, G.W.; McDermott, J.R.; Sheppard, R.C. *J. Chem. Soc. Chem. Commun.* **1971**, 636. DeGrado, W.F.; Kaiser, E.T. *J. Org. Chem.* **1980**, *45*, 1295. Degrado, W.F.; Kaiser, E.T. *J. Org. Chem.* **1982**, *47*, 3258. Backes, B.J.; Ellman, J.A. *J. Am. Chem. Soc.* **1994**, *116*, 11171. Ley, S.V.; Mynett, D.M.; Koot, W.-J. *Synlett* **1995**, 1017. Backes, B.J.; Virgilio, A.A.; Ellman, J.A. *J. Am. Chem. Soc.* **1996**, *118*, 3055. Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041. Barn, D.R.; Morphy, J.R.; Rees, D.C. *Tetrahedron Lett.* **1996**, *37*, 3213. Vlattas, I.; Dellureficio, J.; Dunn, R.; Sytwu, I.I.; Stanton, J. *Tetrahedron Lett.* **1997**, *38*, 7321.

3. For a review see: Cooley, J.H.; Evain, E.J. *Synthesis* **1989**, 1.

4. a) Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H.C.J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915. For the solution phase procedure see: b) Yang, B.V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195. c) Olofson, R.A.; Martz, J.T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

5. Leysen *et al* (ref. 4) stated that cleavage of the resin bound amines with chloroformates gave the corresponding cabamates (i.e. methyl and vinyl chloroformate. However, they stated that no cleavage was observed with acetyl or benzoyl chloride.

6. Coskun, N.; Tirli, F. *Synthetic Comm.* **1997**, *27*, 1.

7. Piperidines **1a-e** were prepared by reductive amination of piperidine with the corresponding benzaldehyde derivative ($Na(AcO)_3BH$, CH_2Cl_2; see ref. 8). Representative example of acylative dealkylation in solution: To a stirred solution of piperidine **1a** (100 mg, 0.49 mmol) in CH_2Cl_2 (3 mL) at r.t. was added naphthoyl chloride (81 µL). After stirring at r.t. for 0.5 h, the solution was diluted with CH_2Cl_2. The solution was washed with 1 N $NaOH_{(aq.)}$, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over Na_2SO_4. Filtration and concentration afforded a yellow oil. Purification via flash chromatography (1/1 hexanes/EtOAc, SiO_2) gave 113 mg (97 %) of **2** as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2 H), 1.72 (m, 4 H), 3.14 (t, 2 H, J = 5.7 Hz), 3.88 (q, 2 H, J = 5.0 Hz), 7.38-7.54 (m, 4 H), 7.86 (m, 3 H). HRMS (FAB) calc'd for $C_{16}H_{18}NO$ (MH^+): 240.1388. Measured: 240.1386. Triethylamine (1.5 eq.) was used in reactions with **1b-d** to quench the reactive benzylic chlorides formed in these reactions.

8. Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shar, R.D. *J. Org. Chem.* **1996**, *61*, 3849.

9. Piperazines **3a-c** were prepared by reductive amination of N-benzyl piperazine with the corresponding benzaldehyde derivative ($Na(AcO)_3BH$, CH_2Cl_2; see ref. 8).

10. For example, the reaction of piperidine **1a** with 1-naphthoyl chloride (1.2 - 1.5 eq.) is complete in 0.5 h. The analogous reaction with piperazine **3a** is only ~ 50 % complete after 2 hours (~98 % complete after 8 hours).

11. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* John Wiley and Sons, New York. Kocienski, P.J. *Protective Groups* Thieme, New York, 1994.

12. Representative example of acylative dealkylation using resin bound amines: The piperazine resin **8** (150 mg, 0.115 mmol) was suspended in CH_2Cl_2 (2 mL). The mixture was agitated at r.t. for 2.5 h. Acetyl chloride (60 µL, 0.81 mmol) was added to the mixture, and the mixture was agitated at r.t. for 25.5 h. The mixture was filtered, and the filtrate was concentrated. The residue was taken up in MeOH (10-15 mL), and Dowex H^+ resin (1.0g, 50 x 2 - 100) was added. After stirring at r.t. for 10-15 minutes, the resin was filtered (glass frit). The resin was rinsed with MeOH (4 x 15 mL). The resin was rinsed with 7 N NH_3/MeOH (2 x 15 mL). The NH_3/MeOH solution was concentrated to furnish 20 mg (80 %) of **4d** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3 H), 2.49 (m, 4 H), 3.47 (t, 2 H, J = 4.9 Hz), 3.54 (s, 2 H), 3.63 (t, 2 H, J = 4.9 Hz), 7.32 (m, 5 H). HRMS (FAB) calc'd for $C_{13}H_{19}N_2O$ (MH^+): 219.1497. Measured: 219.1490.