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CARBANION-MEDIATED OXIDATIVE DEPROTECTION OF NON-ENOLIZABLE BENZYLATED AMIDES

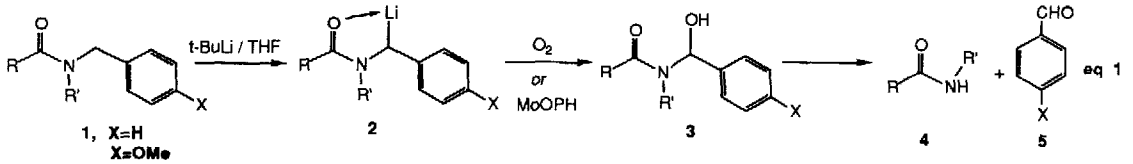
Robert M. Williams* and Ewa Kwast

Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523

Summary: Treatment of non-enolizable N-benzyl or N-*para*-methoxybenzyl amides with butyllithium generates the corresponding benzylic carbanions that can be oxidized with either molecular oxygen or MoOPH; the resulting hemi-aminals suffer loss of the corresponding aldehyde generating the products of amide dealkylation.

Protection of the amide functionality has become an increasingly important and as yet, poorly solved problem in organic synthesis. An increasing number of natural products containing amide moieties have posed substantial synthetic challenges,[1] particularly where protection of the N-H residue of primary and secondary amides is required by non-compatible synthetic operations. Largely due to the tremendous chemical stability of the amide linkage to many chemical reagents and conditions, relatively few protecting groups have been devised for the selective and mild protection/deprotection of this functional group. Amongst the protecting groups most widely employed for amides,[2] the N-benzyl and N-*para*-methoxybenzyl amides have enjoyed particularly widespread use.[3] Amides efficiently react under basic conditions with the corresponding benzyl halides to give good yields of N-alkylation. A variety of experimental protocol have been devised for debenzylating these systems. Unlike N-benzyl amines, N-benzylated amides and urethanes are quite resistant to deprotection by catalytic hydrogenolysis.[4] Dissolving metal reduction[5], acidic solvolysis[6] under forcing conditions and oxidative methods (ceric ammonium nitrate,[3,7] photooxidation[8]) have proven to be the most widely used. During the course of our work on the synthesis of the mycotoxin brevianamide B,[9] we were completely unable to remove the N-*para*-methoxybenzyl group under any of the prescribed reductive, oxidative or solvolytic methods. This was primarily due to the sensitivity of the indoxyl moiety to reduction and oxidation; only

decomposition attended solvolytic attempts. In an effort to devise a new method for removing the *para*-methoxybenzyl group in the presence of oxidation-sensitive indole and indoxyl moieties, we have found that formation of the dipole-stabilized[10] benzylic carbanion (**2**) followed by oxidation, effects dealkylation via the incipient hemi-aminal (**3**, eq 1), furnishing the debenzylated amide **4**.



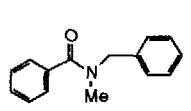
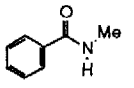
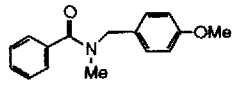
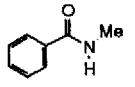
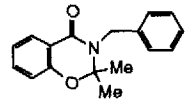
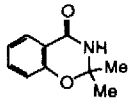
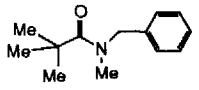
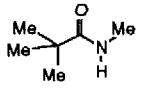
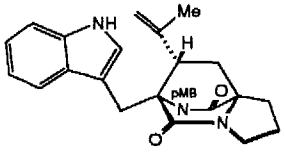
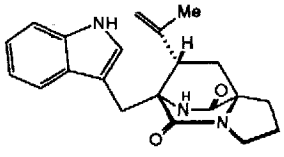
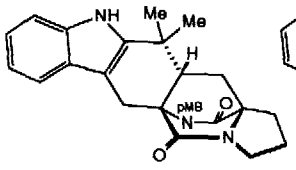
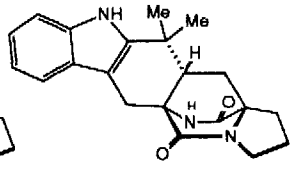
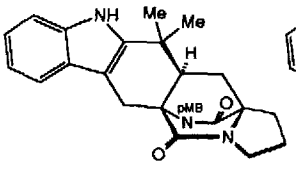
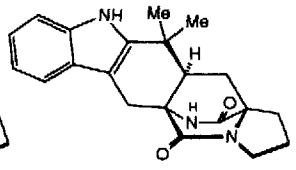
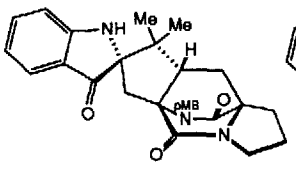
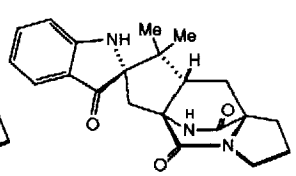
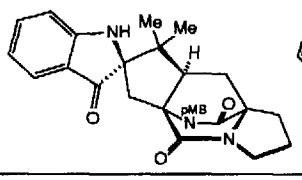
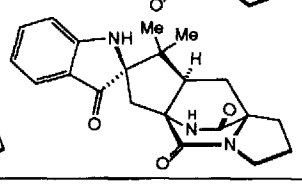
The yields[11] for this reaction range from modest to good as can be seen from inspection of the examples collected in the Table.[12] It is noteworthy that in cases where there are two potential sites for deprotonation, such as the N-methyl-N-benzyl benzamide, we observe only products resulting from benzylic deprotonation. Furthermore, it is interesting that such systems have two possible rotamers around the amide moiety, but only the *cis*-rotamer (see **1**, eq. 1) can give the dipole-stabilized[10] carbanion (**2**), presumed to be an intermediate in this process. This ambiguity does not of course, pertain to the cyclic amides which are rigidly locked in the correct orientation; ^{1}H NMR spectra of the benzamides show a single rotamer at ambient temperature; these have been assigned the conformations shown based on their chemical behavior. We have not detected phenolic or benzoylated products from these reactions; the latter being expected side-products from the O_2 oxidations wherein the incipient peroxy aminal might be expected to fragment to the corresponding benzoyl derivative.

While there remains a great need for additional development of amide and urethane protecting groups, the present method offers an alternative for specific cases where competing enolization and sensitivity to strong base are not a problem.

Typical Experimental Procedure for Oxidative Deprotection of a Benzylated Amide.

To a solution of N-methyl-N-benzylbenzamide (25 mg, 0.11 mmol, 1 eq) in THF (1 mL), cooled to -78°C, *t*-BuLi (0.125 mL, 0.22 mmol, 2 eq. of 1.78 M solution in pentane) was added dropwise upon stirring. After 5 min. stirring at -78°C a stream of dry oxygen gas was passed

Table. Carbanion-mediated oxidative deprotection of benzylated amides.

SUBSTRATE	*PRODUCT*	*BASE*	*OXIDANT*	*YIELD* [a]
		t-BuLi	MoOPH[13]	39.5%
		t-BuLi	O_2	67.8% (79.4%)
		t-BuLi	O_2	45.5% (56.6%)
		t-BuLi	O_2	59%
		n-BuLi	MoOPH	20.8%
		n-BuLi	MoOPH	34.7%
				
		n-BuLi	MoOPH	30.1%
		t-BuLi	O_2	40%

pMB = *para*-methoxybenzyl a. Yield in parenthesis is based on recovered starting material.

through the solution for 10 min. (The dark yellow color of the anion faded away during the first 50 sec. of the oxidation). A few drops of Me_2S were added followed by 25 mg of solid NH_4Cl and a drop of water. The cooling bath was removed, and the mixture was allowed to warm to room temperature. After filtering, the mixture was concentrated under reduced pressure and the resulting oil was subjected to PTLC separation on slica gel (eluted with EtOAc/hexanes 2:1) to furnish 8 mg of N-methylbenzamide (68%) 4 mg of the starting material was recovered.

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References and Footnotes

1. For some selected examples, see: (a) Williams, R.M.; Armstrong, R.W.; Dung Y.S. *J. Am. Chem. Soc.* **1985**, *107*, 3253, and refs. cited therein; (b) Williams, R.M.; Armstrong, R.W.; Dung Y.S. *J. Med. Chem.* **1985**, *28*, 733; (c) Zibuck, R.; Liverton, N.J.; Smith, A.B., *J. Am. Chem. Soc.* **1986**, *108*, 2451; (d) Kishi, Y.; Fukuyama, T.; Nakatsuka, S., *J. Am. Chem. Soc.* **1973**, *95*, 6491; (e) Kishi, Y.; Nakatsuka, S.; Fukuyama, T., *J. Am. Chem. Soc.* **1973**, *95*, 6493.
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11. Yields (unoptimized) refer to isolated, purified products.
12. All new compounds gave satisfactory ^1H NMR, IR, mass spectra and combustion analytical data. Details of the indole and indoxyl substrates to be reported elsewhere.
13. MoOPH = Oxodiperoxymolybdenum (hexamethylphosphorictriamide) (pyridine); Vedejs, E,; Telschow, E., *J. Org. Chem.* **1976** *41*, 740.

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