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A Radical Approach to Debenzylation of Amides

S. Richard Baker[b], Andrew F. Parsons[a]* and Michelle Wilson[a]

[a]Department of Chemistry, University of York, Heslington, York, YO1 5DD, U.K.

[b]Eli Lilly and Company Ltd, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, U.K.

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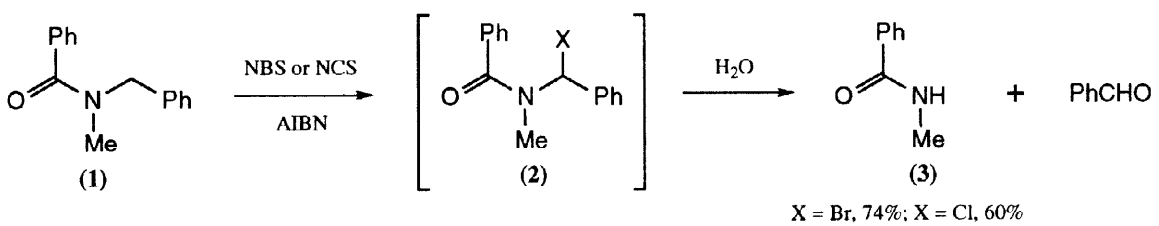
Abstract: The deprotection of *N*-benzylamides can be achieved under neutral conditions by reaction with *N*-bromosuccinimide in boiling chlorobenzene or ethyl acetate. Good to excellent yields are obtained using either acyclic or cyclic amides. © 1997 Elsevier Science Ltd. All rights reserved.

The benzyl group is a well used protecting group in organic synthesis and the preparation of *N*-benzylamines represents a common method for the protection of amines.[1] Deprotection is typically achieved by catalytic hydrogenolysis which, although slow using H_2/Pd-C, is often very efficient. The deprotection of *N*-benzylamides, however, is much less straightforward and these can be extremely difficult to cleave by hydrogenolysis.[1] This has led to the development of alternative but harsher deprotection methods including Na in liquid ammonia,[2] t-BuLi/O_2 (or MoOPH),[3] t-BuOK/O_2,[4] HCO_2H[5] or aqueous HBr.[6] Nevertheless a number of functional groups are vulnerable to the strong basic or acidic reaction conditions required for these methods. Alternative, more expensive, substituted benzylic groups (such as *p*-methoxybenzyl) which can be cleaved under milder conditions are often employed. We now wish to report that *N*-bromosuccinimide (NBS) can be used to deprotect *N*-benzylamides (as well as benzyl ethers/esters[7]) under neutral reaction conditions.

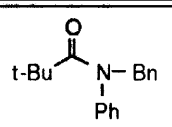
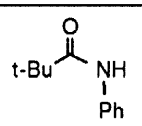
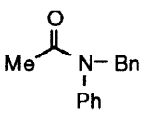
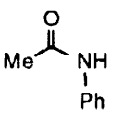
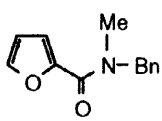
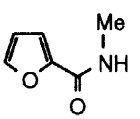
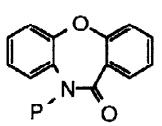
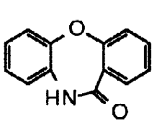
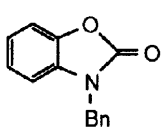
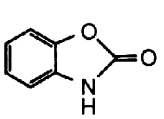
Initial studies centred on the deprotection of the benzamide **(1)** using NBS (1.2 equiv.) and AIBN (0.2 equiv.) in boiling chlorobenzene (Scheme). This afforded the desired product **(3)** in 74% yield together with unreacted starting material **(1)** (in 11% yield) after work-up and column chromatography.[8] Increasing the number of equivalents of NBS did not improve the yield of **(3)** while the same reaction using *N*-chlorosuccinimide (1.5 equiv.) afforded deprotection in 60% yield (or 63% based on recovered starting material). These reactions were thought to proceed *via* benzylic halogenation to produce intermediate **(2)** which on aqueous work-up is expected to afford **(3)** and benzaldehyde (the presence of which was evident from both TLC analysis and the crude ^{1}H NMR spectrum).



Scheme

PII: S0040-4039(97)10480-4

The NBS reaction could be extended to other precursors (Table) and deprotection was also effective at lower temperature in boiling EtOAc (entry 2). An alternative method of deprotection using nickel peroxide[9] [to effect benzylic hydroxylation to give an intermediate of type (2) X=OH] was found to be slow and less efficient than NBS (entry 1). In summary, the use of NBS has been shown to provide a mild, neutral procedure for deprotection of amides and related compounds (such as an oxazolidone, entry 5) in 63-96% yield.

Entry	Precursor	Product	Yield (%)
1			96 (52‡)
2			63#
3			69
4			72 (P=Bn) 67 (P=PMB)
5			77

‡Using nickel peroxide (20 equiv.) and heating for 6 days. #Ethyl acetate was used as solvent.

Table. Debenzylations mediated by NBS.

Typical Procedure

Deprotection of (**1**): A solution of (**1**) (261 mg, 1.16 mmol) in chlorobenzene (15 ml) containing NBS (206 mg, 1.16 mmol) and AIBN (38 mg, 0.23 mmol) was heated to reflux under a nitrogen atmosphere. After 4h further AIBN (0.1 equiv.) and NBS (0.2 equiv.) were added. The solution was heated overnight then cooled, filtered and concentrated. Diethyl ether (10 ml) and water (20 ml) were added to the residue which was stirred for 4 h, the organic layer separated, dried ($MgSO_4$), evaporated and the crude product purified by column chromatography (silica) to afford (**3**) (116 mg, 74%) as a white solid.[10]

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