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An efficient method for the *N*-debenzylation of aromatic heterocycles

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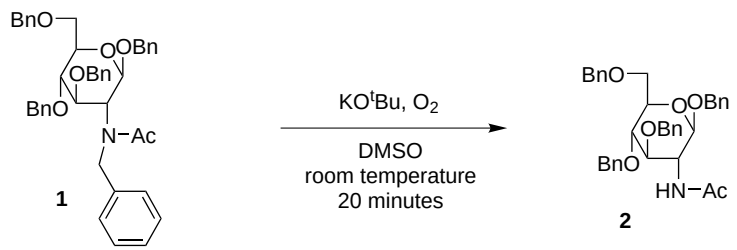
Abstract—The treatment of *N*-benzylated heterocycles with potassium *tert*-butoxide/DMSO and oxygen at room temperature cleanly affords *N*-debenzylated products in high yield. This procedure can be utilized on a variety of functionalized nitrogen-containing heterocycles such as imidazoles, benzimidazoles, pyrazoles, indazoles, carbazoles, and indoles. © 2002 Published by Elsevier Science Ltd.

The protection of heterocycles such as pyrroles, imidazoles, and indoles has been a widely studied topic due to the importance of nitrogen heterocycles in biological systems. Amide, carbamate and sulfonamide groups work very well in protection/deprotection schemes because of the increased acidity of the aromatic amines when compared to simple amines. This allows for easy protection and deprotection of the heterocycle. However, the lability of these protecting groups may lead to problems later in the synthesis. For this reason, there have also been investigations into the use of very stable protecting groups such as *N*-alkyl or *N*-aryl derivatives. With these derivatives, however, deprotection can be difficult and may require forcing conditions for removal.

The *N*-benzyl (Bn) group has been sparingly utilized as a protecting group for nitrogen-containing heterocycles. The small number of procedures available for debenzylation may be the reason for the synthetic chemist's aversion to its use. The most common method of removal is through the use of hydrogenolysis (Pd–C),[1] however, this is not viable if the protected compound also contains reactive olefins, sulfur groups (catalyst poisoning) or alternate aromatic groups that may be reduced as well.[2] Another method for removal utilizes a strong Lewis acid (such as $AlCl_3$),[3] which can also be problematic if reactive functional groups are present in the molecule. Also, side reactions such as Friedel–Crafts alkylation could lead to significant quantities of undesired by-products.[4]

In comparison to work on heterocycles, much more research has been performed to study the *N*-debenzylation of amides. One notable publication by Gigg and Conant outlines the use of potassium *tert*-butoxide/DMSO and O_2 for the rapid *N*-debenzylation of nitrogen-functionalized glucopyranosides (see Scheme 1).[5]



Scheme 1. *N*-Debenzylation of glucopyranosides.

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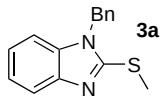
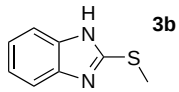
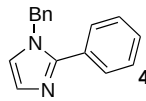
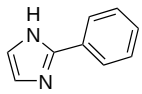
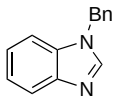
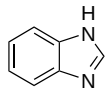
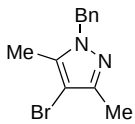
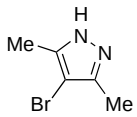
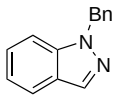
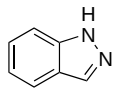
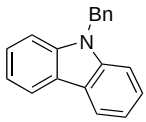
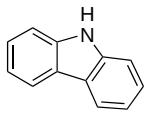
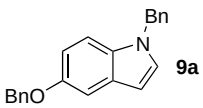
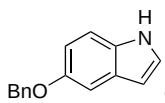
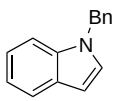
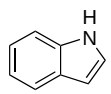
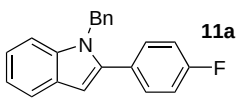
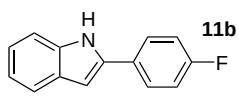
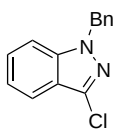
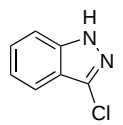
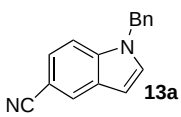
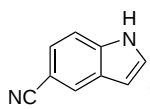
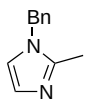
Table 1. *N*-Debenzylation experiments

Entry	Substrate[b]	*T* (°C)	Time	Yield(%)	Product[b]
1	 **3a**	25	5min	94	 **3b**
2	 **4a**	25	15min	94	 **4b**
3	 **5a**	25	10min	92	 **5b**
4	 **6a**	25	10min	82	 **6b**
5	 **7a**	25	5min	100	 **7b**
6	 **8a**	25	10min	93	 **8b**
7	 **9a**	25	20min	82	 **9b**
8	 **10a**	25	15min	87[a]	 **10b**
9	 **11a**	25	1hour	40[a]	 **11b**
10	 **12a**	25	10min	0	 **12b**[8]
11	**12a**	0	10min	60[a]	**12b**
12	 **13a**	25	10min	65	 **13b**
13	**13a**	0	20min	93	**13b**
14	 **14a**	0	15min	85	 **14b**

[a] Yield was based on NMR purity of the starting material

[b] Except in the case of Compound **12b**, the starting materials and products were compared to commercially available standards or literature data via standard analytical techniques.

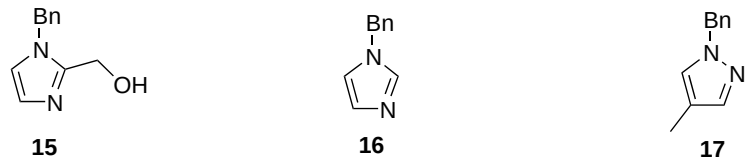
We became aware of this work when we were having difficulty carrying out an *N*-debenzylation of a functionalized imidazole. Both hydrogenolysis and $AlCl_3$-catalyzed deprotection had been attempted and were unsuccessful. We decided to investigate whether the KO^{t}Bu/DMSO conditions were viable for our desired purpose. With very little optimization, the reaction was found to be successful and high-yielding. This result led us to investigate the general utility of this procedure for the *N*-debenzylation of heterocycles.

In order to determine the scope and limitations of this procedure, we needed a variety of *N*-benzylated heterocycles. Although most of these types of compounds are commercially available, many of the compounds were synthesized for our purposes.[6] With the benzylated heterocycles in hand, experiments to determine the scope and utility of this *N*-debenzylation protocol were carried out (Table 1).[7]

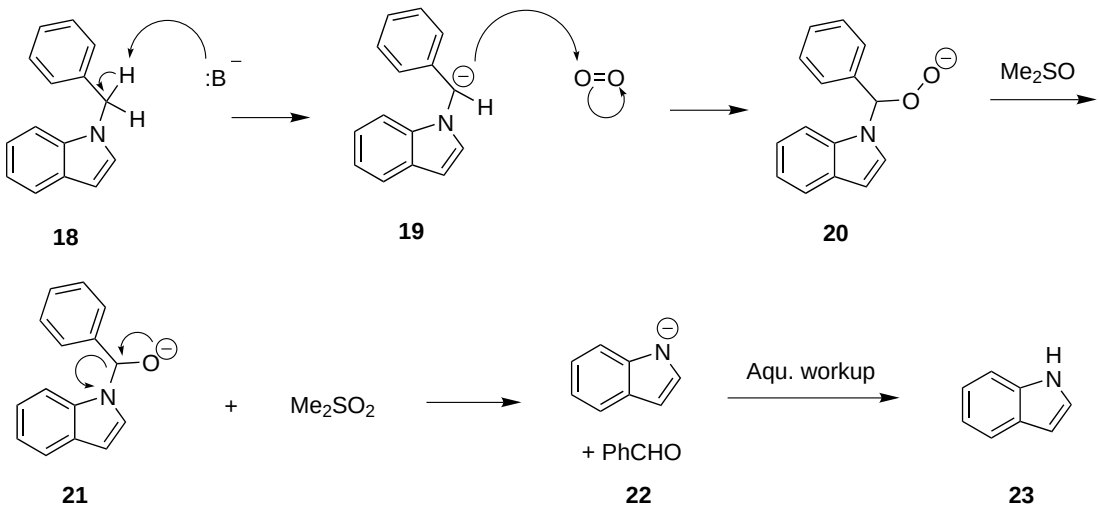
As shown in entries 1–14, the debenzylation reactions were rapid and high-yielding. A variety of heterocycles, including functionalized imidazoles, pyrazoles, indazoles, carbazoles, benzimidazoles, and indoles, were tolerant of the reaction conditions. The reaction conditions appear to be amenable to thioethers (entry 1) as there was no sulfoxide or sulfone formation seen. Also, under no circumstances were *N*-oxides of any of the heterocycles observed. Halogens and nitriles are stable to the oxidative conditions, as shown in entries 4, 9, 11 and 13. It was also determined that the reaction is selective for *N*-benzyl groups and does not lead to the concomitant oxidation of benzyl ethers (entry 7). Entries 10–14 illustrate that in problematic cases it was beneficial to run the reaction at lower temperatures. Entries 10 and 11 are noteworthy examples, wherein the 0°C reaction temperature was the difference between no product recovery and a yield of 60%. The debenzylation of 1-benzyl-2-(4-fluorophenyl)indole (entry 13) was also low yielding.

There were several cases where the reaction conditions were problematic or failed. Compounds **15**–**17** were not cleanly *N*-debenzylated (Scheme 2). The reaction of 1-benzyl-2-(hydroxymethyl)imidazole, **15**, led to a complex mixture of products and the desired compound could not be isolated. In the case of 1-benzylimidazole **16**, the product, imidazole, is water-soluble and could not be retrieved in the workup. However, the reaction of this material was closely followed and the starting material was consumed in less than 15 min. In the case of 1-benzyl-4-methylpyrazole, **17**, the reaction proceeded very quickly but appeared to form a very polar by-product with no desired product present.

During our efforts to study this reaction, it was also found that, in general, heterocycles which incorporate either nitro groups or ester groups in the molecule were not tolerant of the reaction conditions. In these cases, the starting materials appear to decompose to a complex mixture of products as soon as they come in contact with the KO^{t}Bu/DMSO mixture, prior to the addition of oxygen. It is believed that the nitro-functionalized heterocycles are most likely undergoing an undesired formylation and/or acetylation.[9]



Scheme 2. Problematic *N*-debenzylations.



Scheme 3. Proposed mechanism of *N*-debenzylation.

The proposed mechanism for this *N*-debenzylation reaction is shown in Scheme 3. This mechanism is very similar to the one that has previously been proposed by Gigg and Conant for the *N*-debenzylation of amides. The base in this reaction may be either potassium *tert*-butoxide itself or the methylsulfinylmethyl anion, which could be formed in small amounts under the reaction conditions.[10] The newly formed benzylic anion, **19**, reacts with oxygen as it is being bubbled into the reaction mixture.[11] The intermediate peroxy anion, **20**, is easily reduced in the presence of DMSO to afford the sulfone and an anion, **21**, which breaks down to afford benzaldehyde and the deprotected heterocycle.

In conclusion, the *N*-debenzylation of heterocycles can be carried out rapidly and efficiently via the use of KO^{t}Bu/DMSO and O_2. This procedure works well on a wide variety of nitrogen-containing heterocycles and is also well tolerated by a variety of functional groups. Being a base-promoted process, it is a complementary addition to the methods for *N*-debenzylation.

Supplementary material. All compounds (other than Compound **12b**[8]) that are described in this article are either commercially available materials or they have been previously cited in the scientific literature. The reaction products were compared via standard analytical techniques (NMR, HPLC, MS) to the analytical data that is available for these materials.

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5. Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465–466.
6. *Typical procedure for N-benzylation:* NaH (2.4 mmol) was dissolved in anhydrous THF and added to a flame-dried flask. While stirring the solution at room temperature, benzimidazole (2 mmol) was added dropwise. The reaction was allowed to stir for 30 min. Benzyl bromide (2.2 mmol) was then added. Upon completion, the reaction was quenched with satd NH_4Cl and extracted with EtOAc. The organics were combined and dried over $MgSO_4$ and concentrated. Column chromatography afforded pure product in 87% yield.
7. *A typical procedure for N-debenzylation*: 1-Benzyl-benzimidazole (2.4 mmol) was dissolved in DMSO (24 mmol) and added to a flame-dried flask. While stirring the solution at room temperature, KO^{t}Bu (16.8 mmol, 1 M soln in THF) was added (total reaction volume of $\sim$19 ml). Oxygen was then bubbled into the solution, via a gas dispersion tube, for 10 min. Upon completion (determined by TLC) the reaction was quenched with saturated ammonium chloride. The product was extracted three times with EtOAc. The organics were combined, dried over Na_2SO_4 and concentrated. Column chromatography using 8% MeOH/CH_2Cl_2 gave benzimidazole in 92% yield (entry 3, Table 1).
8. Physical data on compound **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dt, $J_1=8.2$ Hz, $J_2=1.0$ Hz, 1H), 7.47–7.21 (m, 8H), 5.61 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 53.8, 110.1, 120.3, 121.7, 121.9, 127.7, 128.0, 128.4, 129.2, 133.6, 136.7, 141.3. IR ν (cm^{-1}) 702, 753, 1177, 1339, 2900–3100. HRMS: calcd for $C_{14}H_{12}ClN_2$ [(M+1)$^+$]: 243.0689. Found: 243.0701.
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10. The pK_a of potassium *tert*-butoxide in DMSO is 32.2. The pK_a of the methylsulfinylmethyl anion in DMSO is 35.1. pK_a values obtained from: Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Druker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
11. This reaction is successful if just left open to the air, however, it is much more rapid if the oxygen is added to the system intentionally. Also, because the reaction is slower in that case, decomposition of the starting materials can be a major side reaction. If the reaction is run under an inert atmosphere, no *N*-debenzylation occurs and, after an extended period of time, decomposition products are predominant.