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Mild Environment-friendly Oxidative Debenzylation of *N*-Benzylanilines Using DMSO as an Oxidant

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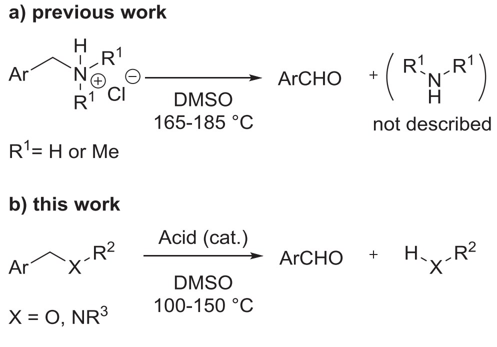
Oxidative debenzylation of *N*-benzyl aromatic amines using DMSO as a non-toxic oxidant and catalyzed by TsOH gave *N*-phenylimines, which were spontaneously hydrolyzed to form anilines and benzaldehydes in good yields. This reaction employs mild, metal-free conditions. The conditions are also suitable for the debenzylation of benzylphenylethers.

Keywords: Debenzylation | DMSO | *N*-benzylanilines

The benzyl group is one of the most frequently used protecting groups for amines and alcohols.[1] Benzylation of these groups is easily performed,[2] and benzyl deprotection can be carried out under various reaction conditions, such as (1) catalytic hydrogenolysis using Pd/C or other heterogeneous metal catalysts,[3] (2) nucleophilic substitution using strong Lewis acid like boron halides,[4] silyl reagents,[5] or other metal salts,[6] (3) oxidation using CAN,[7] DDQ,[8] or Oxone,[9] or (4) reduction using alkali metal naphthalenide.[10] However, these debenzylation reactions sometimes encounter significant problems including difficulty in removing toxic residual metals, the use of hazardous reagents, and the use of harsh reaction conditions that cause undesired side reactions in multi-step syntheses. Therefore, a milder, more environment-friendly, and simple deprotection procedure would be very useful for organic syntheses. Herein, we report a simple oxidative debenzylation of benzylic anilines using DMSO as an oxidant.

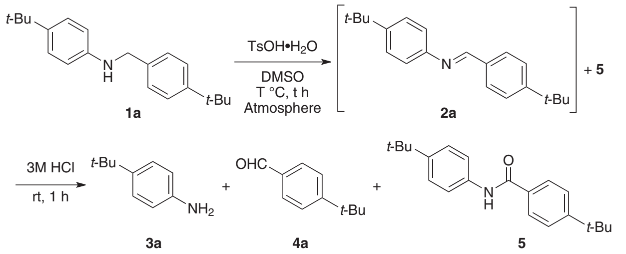
During the course of our research into the synthesis of cyclic amines, we noticed the generation of an imine side product from a benzylic amine under heating in aerobic DMSO (Scheme 1). Since the resulting imines were easily hydrolyzed to give amines and aldehydes, we postulated that this oxidation would be useful for debenzylation of benzylic amines.

In addition, this type of oxidation has not been utilized for debenzylation, although there has been one report of the DMSO oxidation of *N*-benzylammonium salts (Scheme 1).[11] We therefore decided to develop a simple, oxidative debenzylation reaction of benzylic amines.



Scheme 1. Oxidative debenzylation using DMSO.

Table 1. Optimization of reaction conditions using model substrate **1a**.



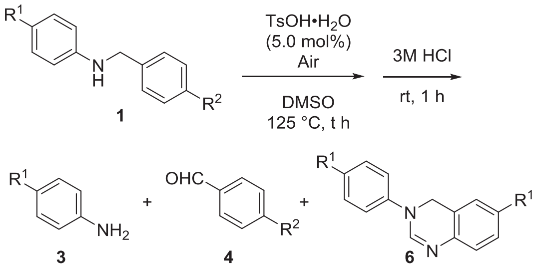
Entry	Atmosphere	$TsOH \cdot H_2O$ (mol %)	DMSO (equiv)	Concentration of **1a** (M)	T (°C)	t (h)	**3a** (%)	**4a** (%)	**5** (%)
1	O_2	0	940	0.015	100	119	94	93	—[c]
2	O_2	5.0	94	0.015	100	9	88	91	—[c]
3	O_2	10	94	0.015	100	8	89	88	—[c]
4	O_2	100	94	0.015	100	4	83	87	—[c]
5	O_2	5.0	94	0.15	100	9	66	67	17
6	air	5.0	94	0.15	100	26	68	70	14
7	air	5.0	94	0.15	125	10	83	84	—[c]
8	air	5.0	47	0.30	125	7	84	81	—[c]
9	air	5.0	24	0.60	125	4	85	85	—[c]
10[a]	air	5.0	12	1.2	125	4	20	24	—[c]
11	air	5.0	2.4[b]	1.0	100	35	81	81	—[c]

[a] **1a** was recovered in 51%. [b] DMSO:toluene = 1:5 was used as solvent. [c] Not detected.

The study began with debenzylation of *N*-benzylaniline **1a** as a model substrate (Table 1). Initially, **1a** was heated at 100 °C under oxygen atmosphere in DMSO without any additives (Entry 1). The products were found to be a mixture of imine **2a**, aniline **3a**, and benzaldehyde **4a**. In order to allow easy purification, imine **2a** was completely hydrolyzed to **3a** and **4a** before work-up. Although nothing happened at first, the reaction started after one day, and finally **3a** and **4a** were obtained in excellent yields after five days. We believed this was due to slow thermal decomposition of DMSO to generate the acid necessary to initiate the oxidation.[12] Hence, a catalytic amount of TsOH was added to the reaction, which resulted in dramatic acceleration of the reaction rate, and eliminated any initiation time (Entries 2 and 3). In the presence of a stoichiometric amount of TsOH, the reaction time was further shortened to 4 h (Entry 4).

A higher concentration of **1a** in the presence of 5 mol % TsOH, resulted in a 9-hour reaction and lower yields of **3a** and **4a** due to over-oxidation forming the undesired amide **5** (Entry 5). When the reaction was performed under air atmosphere, more than 1 day at 100 °C was required for it to reach

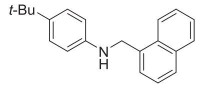
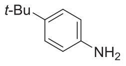
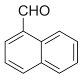
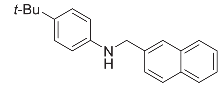
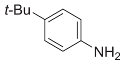
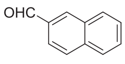
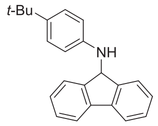
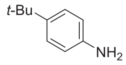
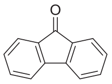
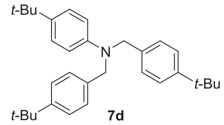
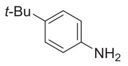
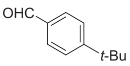
Table 2. Debenzylation of *N*-benzylaniline derivatives.



Entry	R^1	R^2	t (h)	**3** (%)	**4** (%)	**6** (%)
1	*t*-Bu	H	5	71	75	—^{b}
2	*t*-Bu	OMe	7	62	71	—^{b}
3	*t*-Bu	Bn	6	77	75	—^{b}
4	*t*-Bu	Cl	5	71	75	—^{b}
5	*t*-Bu	Br	5	76	70	—^{b}
6	*t*-Bu	CF_3	6	72	21	—^{b}
7	OMe	*t*-Bu	5	73	80	—^{b}
8	Cl	*t*-Bu	45	48	77	29
9^a	Cl	*t*-Bu	14	67	44	—^{b}
10	Br	*t*-Bu	49	31	78	35
11^a	Br	*t*-Bu	19	52	38	8
12	CF_3	*t*-Bu	90	—^{b}	53	—^{b}

^{a}Performed with air bubbling. ^{b}Not detected.

Table 3. Scope of debenzylation of *N*-benzylanilines.

Entry	Reactants	Time (h)	Products	
1	 **7a**	12	 **3a** (69%)^a	 **8a** (61%)^a
2	 **7b**	7	 **3a** (75%)^a	 **8b** (74%)^a
3	 **7c**	46^a 40^b	 **3a** (5%)^{a,c} (16%)^b	 **8c** (91%)^a (89%)^b
4	 **7d**	23^a 20^b	 **3a** (6%)^{a,d} (41%)^b	 **4a** (67%)^a (72%)^b

Reaction conditions: TsOH•H_2O (5 mol %), DMSO, 125 °C. ^{a}Performed under air atmosphere. ^{b}Performed with air bubbling. ^{c}Corresponding dihydroquinazoline derivative was obtained in 6%. ^{d}Corresponding dihydroquinazoline derivative was obtained in 17%.

completion (Entry 6). Significant improvement was observed when the reaction was conducted at 125 °C, with high yields of **3a** and **4a** and no formation of **5** (Entry 7). Further increasing the concentration of **1a** resulted in reduced reaction time, without significant decrease in yields until 0.6 M (Entries 8 and 9), while **1a** was not fully consumed when a 1.2 M solution was used (Entry 10). Based on these results, Entry 9 was selected as optimized conditions. Furthermore, when toluene was used as a co-solvent, the amount of DMSO could be decreased to 2.4 equivalents although longer reaction time was necessary (Entry 11, for details, see SI).

Next, the scope of the debenzylation reaction was examined using benzylaniline derivatives having various substituted groups on the aromatic rings (Table 2). Starting with aromatic substitution of benzyl group, H, MeO, Bn, Cl, and Br moieties were all well tolerated, giving *tert*-butylaniline (**3a**) and the corresponding benzaldehydes **4** in satisfactory yields (Entries 1–5). Introduction of an electron-deficient CF_3 group caused partial degradation of the aldehyde **4** (Entry 6). Next, the substitution of electron-donating group (MeO) on aniline afforded both **3** and **4** in good yields (Entry 7), while introduction of electron-withdrawing groups (Cl, Br, and CF_3) resulted in lower reaction rates and decreased yields (Entries 8, 10, and 12). These prolonged reaction times caused side reactions with formaldehyde derived from DMSO[12] to produce dihydroquinazoline **6**. To remove formaldehyde from the reaction mixture, air was bubbled through the solution (Entries 9 and 11), which successfully improved the yield of anilines **3**.

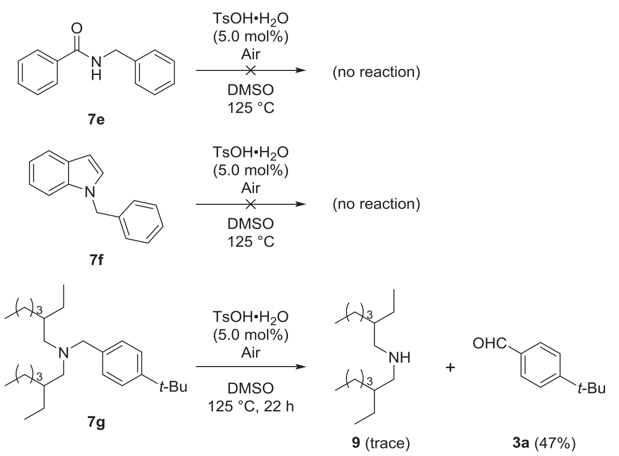
The oxidative debenzylation reaction was also conducted using other *N*-benzyl substrates (Table 3). Naphthylmethylamines **7a**, **b** were efficiently converted into the corresponding aniline **3a** and aldehydes **8a**, **b** (Entries 1 and 2). When 9-aminofluorene **7c** and dibenzylamines **7d** were tested, the corresponding ketone **8c** and aldehyde **4a** were obtained in good yields; however, the yields of aniline **3a** were diminished due to the formation of dihydroquinazoline **6** (Entries 3 and 4). The air bubbling conditions utilized above were also effective in improving yields of these entries to some degree. These substrates also required prolonged reaction time, most likely due to the higher steric hindrance (Entry 3) and the introduction of a second benzyl group (Entry 4), which led to the inevitable side reactions.

The debenzylation of non-aromatic amine substrates was also investigated. When the optimized conditions were applied in the oxidative debenzylation of *N*-benzylamide **7e** and *N*-benzylindole **7f**, the reaction did not proceed (Scheme 2). In contrast, for *N*-benzyl aliphatic amine **7g**, the oxidation occurred at both benzyl and non-activated positions, which provided the desired amine **9** in low yield, along with many unidentified products. These results show that application of this mild debenzylation method into these substrates requires further study.

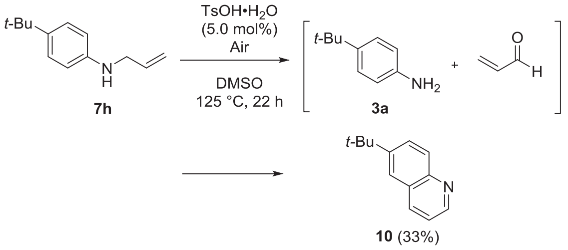
Oxidative cleavage of other active functional groups investigated next. *N*-Allylaniline **7h** reacted under the optimized conditions to produce quinoline derivative **10**, which was likely formed via Doebner-von Miller reaction between the resulting aniline **3a** and acrolein (Scheme 3).[13] Pleasingly, substituted *O*-benzyl phenyl ether **7i** also afforded phenol **11** in 39% yield (Scheme 4). However, *N*-Cbz-aniline **7j** did not react under the optimized conditions.

This oxidative debenzylation could be applied in gram-scale synthesis (Scheme 5). Starting with 1.1 g of *N*-benzylaniline **2a**, 0.36 g (67%) of aniline **3a** was obtained utilizing the air-bubbling conditions.

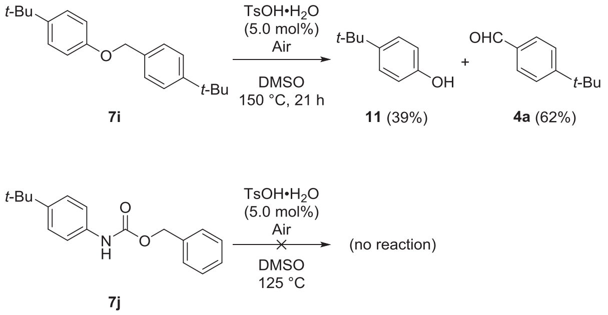
A plausible reaction mechanism is shown in Scheme 6, which is analogous to the Kornblum reaction.[14] The reaction



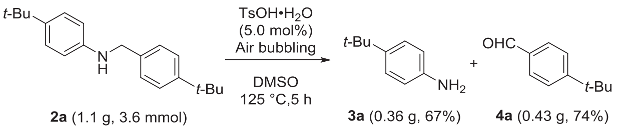
Scheme 2. Debenzylation of other benzyl substrates.



Scheme 3. Deallylation of *N*-allylaniline.

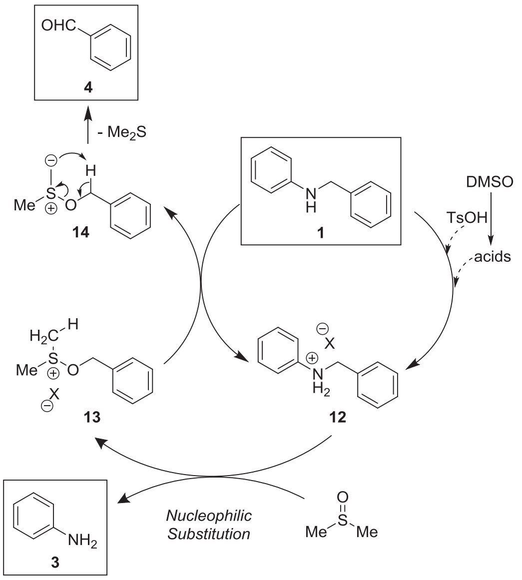


Scheme 4. Debenzylation of *O*-benzyl phenyl ether and *N*-Cbz-aniline.



Scheme 5. Gram-scale experiment.

begins with the formation of ammonium salts **12** from benzylamines **1**. This process is equally viable using TsOH or other acids such as methanesulfonic acid generated from DMSO. The nucleophilic substitution between **12** and DMSO provides the sulfonium ion **13** in addition to the aniline **3**. Compound **13** is deprotonated to form sulfonium ylide **14**, which would lead to benzaldehyde **4** with emission of dimethylsulfide.



Scheme 6. Plausible reaction mechanism.

In conclusion, we have developed a mild and environment-friendly benzyl deprotection of amines and ethers in DMSO. This procedure utilizes readily-available, non-toxic and inexpensive DMSO and requires no transition metals, Lewis acids, or other hazardous reagents. The benzyl deprotection proceeds smoothly under air atmosphere and tolerates moisture. This procedure provides an alternate, greener benzyl deprotection procedure that will be helpful for organic synthesis.

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Supporting Information is available on https://doi.org/10.1246/cl.190854.

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