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Microwave-assisted N-debenzylation of amides with triflic acid

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ABSTRACT

A new and facile microwave-assisted protocol for the debenzylation of *N*-benzylamides with triflic acid has been developed. Both secondary and tertiary aliphatic or aromatic amides are obtained in moderate to good yields.

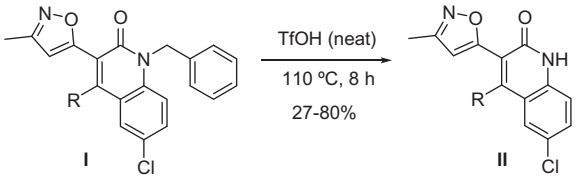
While deprotection of *N*-benzyl-protected amines and ethers is quite a straightforward practice in organic chemistry,[1,2] deprotection of *N*-benzylamides is more challenging, and often the removal conditions may be incompatible with other functional groups present in the molecule. This seriously limits the applicability of the non-expensive and widely accessible benzyl as the protective group for the amide function and several substituted benzyl groups, with increased acid sensitivity, have been used with limited success.[1]

Most typical methods for the cleavage of a simple benzyl group in *N*-benzylamides can be classified into three different types: (i) radical cleavage, which is commonly achieved by the use of NBS,[3] Li or Na in liquid NH_3,[4] Li with catalytic naphthalene,[5] and NHPI/$Co(OAc)_2$/$Mn(OAc)_2$[6], (ii) oxidative deprotection with *t*-BuLi/O_2 (or MoOPH)[7] or *t*-BuOK/O_2[4c,8], and (iii) acidic hydrolysis, for which several conditions have been developed such as aqueous HBr,[9] $MeSO_3H$,[10] HCO_2H,[11] *p*-TsOH[12] or some Lewis acids such as $AlCl_3$.[13] Despite the various acids employed in the deprotection of simple *N*-benzylamides, up to date there is no general method described, which covers a range of structurally diverse *N*-benzylamides.

We have recently reported the use of trifluoromethane sulfonic acid (also referred to as triflic acid or TfOH) for the debenzylation of highly functionalized *N*-benzylquinoline-2-ones (**I**).[14] The N-debenzylation reactions were carried out in neat TfOH under traditional heating (110 °C) to yield the deprotected products (**II**) with variable yields (27–80%), depending on the quinoline-2-one substituents (Scheme 1). Within our company, this method has found a broad use for amide debenzylations where the weaker acids fail to provide satisfactory conversion.

Microwave-Assisted Organic Synthesis (MAOS) has become increasingly popular in recent years to improve the yield and/or to shorten the reaction times in a large variety of synthetic transformations.[15,16] To the best of our knowledge this technology has not yet been applied to the removal of the benzyl moiety of an *N*-benzylcarboxamide.

Encouraged by the initial results shown in Scheme 1, we decided to further explore the potential of TfOH as a new agent for the N-debenzylation of amides. This report describes an efficient and operationally simple method for the selective deprotection of *N*-benzylamides with TfOH upon microwave irradiation. *N*-benzylbenzamide (**1a**) was chosen as a model substrate, as it facilitates the monitoring of the reaction by LCMS and can be easily isolated by column chromatography over silica gel. Scheme 2 shows the preliminary experiment of our study. Treatment of *N*-benzylbenzamide (**1a**) with neat TfOH at 150 °C for 5 min under



Scheme 1. Precedent of N-debenzylation of amides with TfOH.[14]

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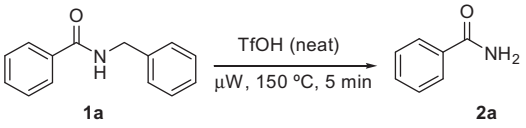


Scheme 2. *N*-Benzylbenzamide as the model reactant for the microwave assisted debenzylation with TfOH.

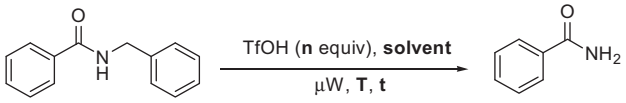
microwave irradiation showed an excellent and clean conversion toward benzamide (**2a**), which was isolated in 45% yield after aqueous work-up followed by column chromatography.

This positive initial result prompted us to further investigate the conditions suitable for this deprotection reaction under microwave irradiation. The results obtained are summarized in Table 1.

Firstly, in order to avoid the use of neat TfOH, toluene was chosen as a solvent due to its nucleophilic nature, which may add on to the scavenging of the formed benzyl cations. In addition, toluene is immiscible in TfOH at room temperature and forms a top-layer that avoids the evolution of TfOH toxic fumes. Thus, when **1a** was treated with 4 equiv of TfOH in toluene at 150 °C for 5 min, the reaction proceeded with 67% conversion to **2a** (Table 1, entry 2); extension of the irradiation time from 5 to 15 min resulted in the complete conversion and **2a** was isolated in 69% yield (Table 1, entry 3).[17] Attempts to decrease the reaction temperature (Table 1, entry 4) or to reduce the number of equiv of TfOH (Table 1, entries 5 and 6) were unsuccessful. Toluene could be replaced by 1,2-dichloroethane (DCE) with comparable yields (Table 1, entries 7 and 8): the product was however chromatographically more difficult to isolate from the viscous black tar formed using the latter solvent. Protonatable solvents such as 1,4-dioxane and AcOH led to very little conversion and are not suitable for this chemical transformation (Table 1, entries 9 and 10). Finally, bromobenzene gave the fastest and cleanest reaction (Table 1, entry 11), but we decided to keep toluene as the first choice as it facilitates the reaction work-up due to its volatility.

Starting from these data, we chose microwave irradiation of the amide (**1**) with 4 equiv of TfOH in toluene at 150 °C for 15 min as the standard reaction conditions to perform the deprotection reaction of *N*-benzylamides.[18]

Table 1
Debenzylation reaction of *N*-benzylbenzamide (**1a**) with TfOH under microwave irradiation



Entry	TfOH (*n* equiv)	Solvent	*T* (°C)	*t* (min)	Yield[a,b] (%)
1	Neat	—	150[c]	5	45 (100)
2	4	Toluene	150	5	–(67)
3	4	Toluene	150	15	69[d] (96)
4	4	Toluene	100	15	–(4)
5	2	Toluene	150	15	–(0)
6	3	Toluene	150	15	–(53)
7	4	DCE	150	5	–(65)
8	4	DCE	150	15	72 (100)
9	4	AcOH	150	15	–(6)
10	4	Dioxane	150	15	–(8)
11	4	PhBr	150	5	70 (100)

[a] Yield of isolated products.
[b] Figures in brackets refer to conversion of **1a** to **2a** as determined by LCMS analysis of the reaction crude with UV detection.
[c] Traditional heating for 15 min led to 100% conversion by LCMS.
[d] Average of five runs.

Figure 1 displays a set of representative *N*-benzylamides (**1b–k**) and two *N*-benzyltriazolones (**1l**, **1m**) from our internal reagent and building block databases chosen to explore the scope and limitations of this process. The results for each amide are summarized in Table 2.[19]

As shown in Table 2, our microwave-assisted N-debenzylation with TfOH worked well for a variety of alkyl-, aryl-, and heteroaryl-amides (Table 2, entries 1–10). In all the cases the reaction was clean, and the only significant products found by LCMS were the debenzylated amide **2** and a variable amount of the starting

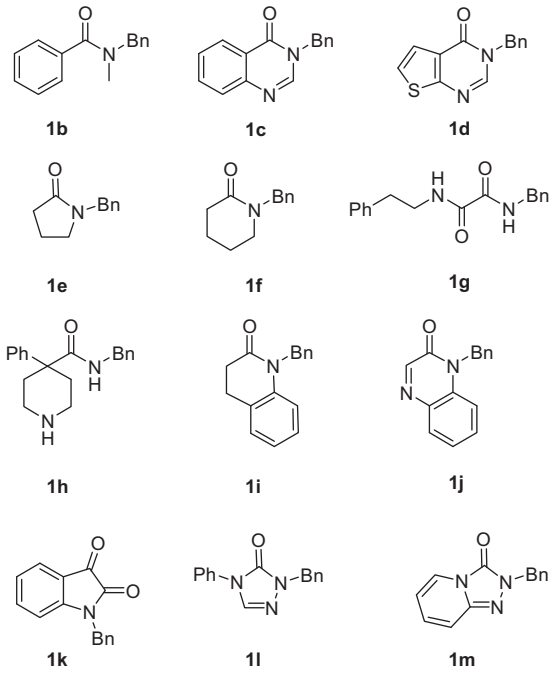
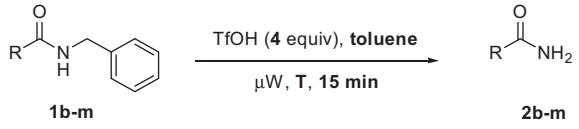


Figure 1. Set of amides and triazolones used in the microwave assisted N-debenzylation reaction.

Table 2
Debenzylation reaction of amides (**1b–m**) with TfOH under microwave irradiation



Entry	Amide **1**[a]	*T* (°C)	Conversion (%)[b]	Yield (%)
1	**1b**	150	100	—
2	**1c**	150	100	82[c]
3	**1d**	150	93	78[c]
4	**1e**	210	—	78[d]
5	**1f**	210	—	75[d]
6	**1g**	150	86	67[c]
7	**1h**	150	95	81[c]
8	**1i**	150	94	83[c]
9	**1j**	150	50	38[c]
10	**1k**	150	Decomposed	—
11	**1l**	150	100	92[c]
12	**1m**	150	98	72[c]

[a] The reactions were carried out on 1 mmol scale.
[b] The conversion was determined by LCMS of the reaction crude with UV detection.
[c] Isolated yield.
[d] Yield determined by LCMS of the crude with chemiluminescent nitrogen detection.

material **1**. Primary (**1g**, **1h**) and secondary (**1b**) acyclic amides, and both cyclic aliphatic (**1i**) and aromatic amides (**1c**, **1d**, **1j**) (Table 2, entries 1–3 and 6–9) were easily deprotected under our standard conditions with the only exception of the *N*-benzylisatin (**1k**), which was unstable in the acidic reaction medium and decomposed (Table 2, entry 10). Simple aliphatic *N*-benzylamides such as **1e** and **1f** required higher temperatures and prolonged reaction times to yield the expected compounds: nevertheless the final amides were obtained in good yields (Table 2, entries 4 and 5). Interestingly, compound **1g**, which presents in its structure both an *N*-phenethyl- and *N*-benzylamide, was successfully deprotected under standard conditions without altering the *N*-phenetylcarboxamide moiety (Table 2, entry 6). We were pleased to find that triazolones **1l** and **1m** also underwent the debenzylation process with TfOH without having to modify the reaction conditions, and the corresponding deprotected compounds were obtained in good yield after chromatographic purification.

To further study the scope of this deprotection reaction, a new set of *N*-benzylbenzamides (**1n**–**w**) carrying different functional groups were prepared (Fig. 2) and subjected to the TfOH-mediated debenzylation process in toluene. The results obtained are summarized in Table 3.

As shown in Table 3, both aromatic (**1n**, **1o**) and aliphatic (**1r**) amines were compatible with the microwave-assisted N-debenzylation with TfOH, giving moderate to good yields of the corresponding primary benzamides (Table 3, entries 1, 2 and 5). Furthermore, the debenzylation was found to proceed in moderate to good yield in the presence of non-benzylic amide (**1p**), benzyl chloride (**1q**), sulfone (**1v**), and ketone (**1w**) functional groups (Table 3, entries 3, 4, 9, and 10). Two functional groups, the ester (**1s**), and the aromatic ether (**1t**, **1u**) were found to be unstable under the above-mentioned N-debenzylation conditions. Thus, for the N-debenzylation of **1s** the ester **2s** was isolated in 6% yield, while the major product was the N-debenzylated acid (Table 3, entry 6). The N-debenzylation of amides **1t** and **1u** occurred with the cleavage of the ether function affording moderate yields of the corresponding 3- and 4-hydroxybenzamides (Table 3, entries 7 and 8). These results can be easily explained as both alkyl-aryl ethers and esters are known to cleave under strongly acidic conditions.

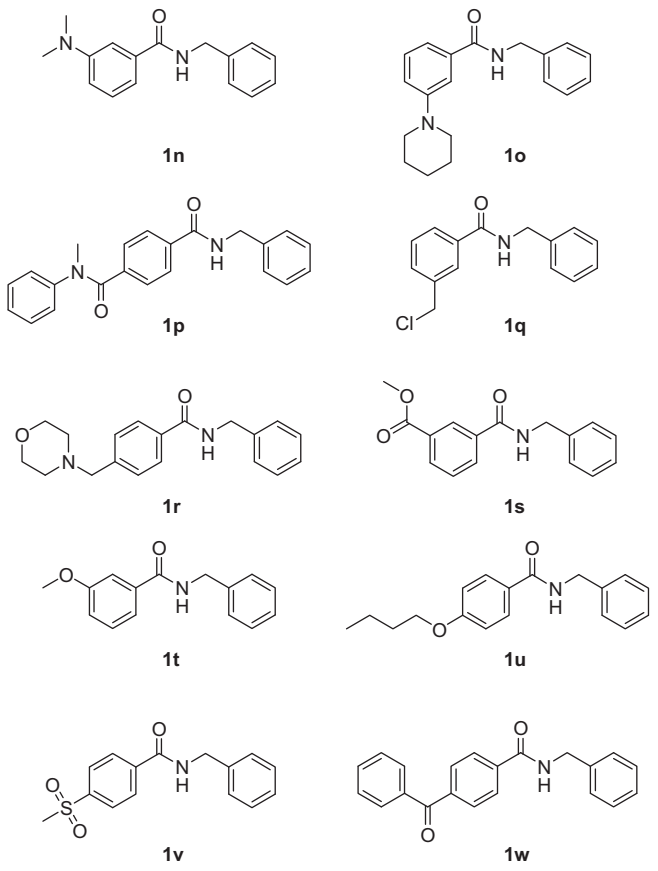
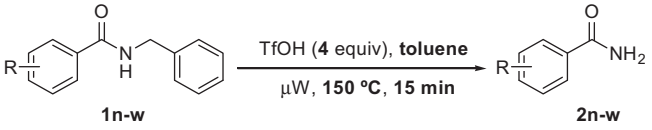


Figure 2. Set of differently substituted *N*-benzylbenzamides used in the microwave assisted N-debenzylation reaction.

Table 3
Debenzylation reaction of benzamides (**1n**–**w**) with TfOH under microwave irradiation



Entry	Amide **1**[a]	Yield[b] (%)
1	**1n**	86
2	**1o**	55
3	**1p**	71
4	**1q**	57
5	**1r**	78
6	**1s**	6 (45)[c]
7	**1t**	0 (55)[d]
8	**1u**	0 (62)[d]
9	**1v**	88
10	**1w**	63

[a] The reactions were carried out on 1 mmol scale.
[b] Isolated yield.
[c] Yield in brackets refers to the isolated 3-carbamoylbenzoic acid, which was obtained instead of the ester.
[d] Yield in brackets refers to the isolated hydroxybenzamide, which was obtained instead of the ether.

In summary, we have developed a new method for the debenzylation of *N*-benzylamides with TfOH under microwave irradiation. Initial results point to the use of TfOH as a good alternative to the known Brönsted acids for this synthetic transformation. The N-debenzylation method has shown quite a general application and secondary/tertiary, aliphatic/aromatic, and acyclic/cyclic amides are suitable substrates for this process. In addition, good functional group tolerability has been found. Further studies on the scope and limitations of this methodology are ongoing and will be reported in due course.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 2003; (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: New York, 2005.
2. For 4-methoxybenzyl (PMB) see: Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538–549; For 2,4,6-trimethoxybenzyl see: Weygand, F.; Steglich, W.; Bajrnason, J. *Chem. Ber.* **1968**, *101*, 3642–3648; For 1-phenylethyl see: Paik, S.; Lee, J. *Tetrahedron Lett.* **2006**, *47*, 1813–1815.
3. (a) Baker, S. R.; Parson, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331–332; (b) Kuang, L.; Jing, Z.; Chen, S.; Ding, K. *Synthesis* **2007**, 3129–3133.
4. For recent examples see: (a) Ghosh, S.; Shashidhar, J. *Tetrahedron Lett.* **2009**, *50*, 1177–1179; (b) Kündig, E. P.; Seidel, T. M.; Jia, Y.; Bernadinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484–8487; (c) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159; (d) Almiento, G. M.; Balducci, D.; Bottoni, A.; Calvaresi, M.; Porzi, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2695–2711; (e) Lerchner, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *12*, 8208–8219.
5. (a) Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355–14368; (b) Huang, P. Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309–3317.
6. Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. *Adv. Synth. Catal.* **2005**, *347*, 1632–1642.

7. (a) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451–454; (b) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905–6919.
8. (a) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399–402; (b) Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465–466.
9. (a) Ban, H.; Muraoka, M.; Ohashi, N. *Tetrahedron Lett.* **2003**, *44*, 6021–6023; (b) Moudam, O.; Ajamaa, F.; Ekouaga, A.; Mamlouk, H.; Hahn, U.; Holler, M.; Welter, R.; Nierengarten, J.-F. *Eur. J. Org. Chem.* **2007**, 417–419.
10. (a) Yamaguchi, S.; Oh-hira, Y.; Yamada, M.; Michitani, H.; Kawase, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 952–954; (b) Ranganathan, D.; Farooqui, F.; Bhattacharyya, D.; Mehrotra, S.; Kesavian, K. *Tetrahedron* **1986**, *42*, 4481–4492; (c) Hoffmann-Emery, F.; Hilpert, H.; Scalone, M.; Waldmeier, P. *J. Org. Chem.* **2006**, *71*, 2000–2008.
11. Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510.
12. Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039–1041.
13. Jayachandran, T.; Paramasivam, R.; Ramakrishnan, V. T. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1986**, *25B*, 89–91.
14. (a) Wall, M. J.; Chen, J.; Meegalla, S.; Ballentine, S. K.; Wilson, K. J.; DesJarlais, R. L.; Schubert, C.; Chaikin, M. A.; Crysler, C.; Petrounia, I. P.; Donatelli, R. R.; Yurkow, E. J.; Bozcon, L.; Mazzulla, M.; Player, M. R.; Patch, R. J.; Manthley, C. L.; Molloy, C.; Tomczuk, B.; Illig, C. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2097–2102; (b) Wall, M. J.; Player, M. R.; Patch, R. J.; Meegalla, S.; Liu, J.; Illig, C. R.; Cheung, W.; Chen, J.; Asgari, D. WO 2005/009967, 2005.
15. For reviews in Microwave-Assisted Chemistry see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432; (b) Lidström, P.; Tierney, J.; Wathney, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (c) Wathey, B.; Tierney, J.; Lidstrom, P.; Westman, J. *Drug Discovery Today* **2002**, *7*, 373–380; (d) Alcázar, J.; Diels, G.; Schoentjes, B. *Comb. Chem. High Throughput Screening* **2007**, *10*, 918–932; (e) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355.
16. De la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178.
17. This yield is in accordance with reported yields for this transformation: see Ref. 3b (NBS: 80%) and also see: Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *5*, 1152–1156. $AlCl_3$: 74%.
18. *Representative experimental procedure*: Triflic acid (4 mmol) was added to a mixture of the *N*-benzylamide (1 mmol) and toluene (1 mL). The resulting mixture was stirred for 15 min at 150 °C under microwave irradiation. After cooling to rt, 1.5 equiv of Dowex OH^- resin or (polystyrylmethyl)ammonium bicarbonate was added, (heat develops) followed by 4 mL MeOH. The mixture was shaken for 4 h at rt before the resin was filtered off and washed with DCM (20 mL), MeOH (20 mL), DCM (20 mL), and finally again MeOH (20 mL). The filtrate was evaporated to dryness and co-evaporated with toluene. The residue thus obtained was purified by flash column chromatography over silica gel using a gradient (DCM to 10% MeOH in DCM).
19. Analytical data of all isolated products corresponded to those reported in the literature and can be obtained upon request.