Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A NaH-promoted *N*-detosylation reaction of diverse *p*-toluenesulfonamides

Wanwan Sun [a,1], Xiaobei Chen [b,1], Ying Hu [c,*], Huihui Geng [b], Yuanrui Jiang [a], Yuxin Zhou [a], Wenjing Zhu [a], Min Hu [a], Haohua Hu [a], Xingyi Wang [a], Xinli Wang [a], Shilei Zhang [a,*], Yanwei Hu [a,*]

[a] Jiangsu Key Laboratory of Neuropsychiatric Diseases & College of Pharmaceutical Sciences, Soochow University, 199 Ren'ai Road, Suzhou, Jiangsu 215123, China
[b] State Key Laboratory of Bioreactor Engineering, and Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, China
[c] Department of Pharmacy, Suzhou Vocational Health College, 28 Kehua Road, Suzhou 215009, China

ARTICLE INFO

Article history:
Received 2 July 2020
Revised 29 August 2020
Accepted 1 September 2020
Available online xxxx

Keywords:
Sodium hydride
Detosylation
P-toluenesulfonamides
Indole

ABSTRACT

A NaH-mediated detosylation reaction of various Ts-protected indoles, azaheterocycles, anilines and dibenzylamine was reported. The method features cheap reagent, convenient operations, mild reaction conditions and broad substrate scope. Moreover, this study revealed that the loading of NaH in tosylation reactions of nitrogen-containing compounds with NaH as a base in DMA or DMF should be controlled due to the possibility of adverse detosylation.

© 2020 Elsevier Ltd. All rights reserved.

The protection and deprotection of nitrogen-containing compounds are very important topics in synthetic organic chemistry. Among various protecting groups for amines, sulfonyl plays a vital role due to the advantages of being stable to many reaction conditions as well as easy preparation and isolation. Nevertheless, the desulfonylation procedure is usually distinguished as a troublesome issue. To date, a lot of methods have been developed to remove the sulfonyl groups, and some representative ones are as follows: i) reductive cleavages of N—S bond with alkaline metals [1], Mg [2], Al [3], SmI_2 [4], Red-Al [5], low valent titanium [6], organic electron donors [7], ii) basic conditions such as Grignard reagent [8], MOH [9], M_2CO_3 [10], NaOMe [11], NaO*t*-Bu [12], $KPPh_2$ [13], $LiSiMe_2Ph$ [14], TBAF [15], iii) acidic conditions such as HBr [16], HF [17], H_2SO_4 [18], iv) other approaches including electrochemistry [19], photoinduced electron transfer [20] et al. However, many of these strategies suffer from harsh reaction conditions and low functional group tolerance. Therefore, development of mild and efficient deprotection protocols for sulfonyl groups (especially the most commonly used tosyl group) is urgently required.

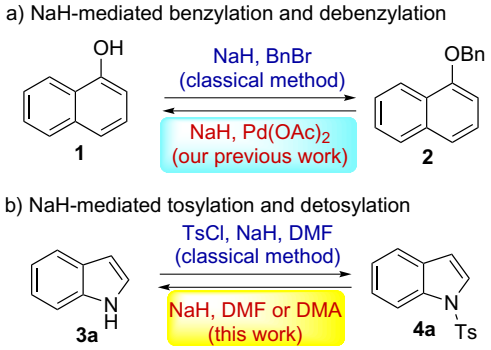
Recently, we disclosed a palladium-catalyzed debenzylation method using sodium hydride (NaH) as a reducing reagent (Scheme 1a, 2 → **1**) [21], which could be considered as a reverse process for the benzylation of phenol (**1** → **2**). In the continuous explorations in the field, we occasionally found that a detosylation reaction took place when treating *N*-tosyl-indole with NaH in DMF (Scheme 1b, 4a1 → **3a**). We were surprised because the tosylation of indole (**3a** → **4a1**) also frequently applied NaH as a base in the same solvent [10a,15]. Our discovery means excessive NaH is actually detrimental to the tosylation reaction. However, to our knowledge, it has never been reported in previous literatures. To confirm this finding and get insight into the novel detosylation reaction, a series of experiments were conducted (Table 1).

We began our studies using Ts-protected indole **4a1** as a model substrate to optimize the reaction conditions. First, several solvents were tested (Table 1, entries 1–7). DMF, DMA and DMSO were identified as effective reaction media to promote the detosylation process [22,23] (Table 1, entries 5–7), whereas other solvents could not give any product (Table 1, entries 1–4). We speculate only polar aprotic solvents have the ability to activate sodium hydride to break the N—S bond. Although the reaction temperature was found to significantly alter the reaction speed, it almost had no effect on the yield (Table 1, entries 6, 8–10). Finally, evaluation of NaH loading revealed 2 equivalents provided the best result (Table 1, entries 6, 11–12). Moreover, several other sulfonyl

* Corresponding authors.
E-mail addresses: yhu@szhct.edu.cn (Y. Hu), zhangshilei@suda.edu.cn (S. Zhang), huyanwei@suda.edu.cn (Y. Hu).
[1] These authors contributed equally to this work.

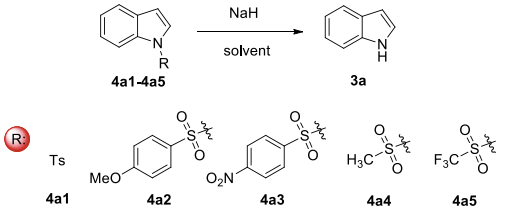
https://doi.org/10.1016/j.tetlet.2020.152442
0040-4039/© 2020 Elsevier Ltd. All rights reserved.

Please cite this article as: W. Sun, X. Chen, Y. Hu et al., A NaH-promoted *N*-detosylation reaction of diverse *p*-toluenesulfonamides, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.152442



Scheme 1. The NaH-mediated 'reversible' reactions.

Table 1
Optimization of the reaction condition.[a]

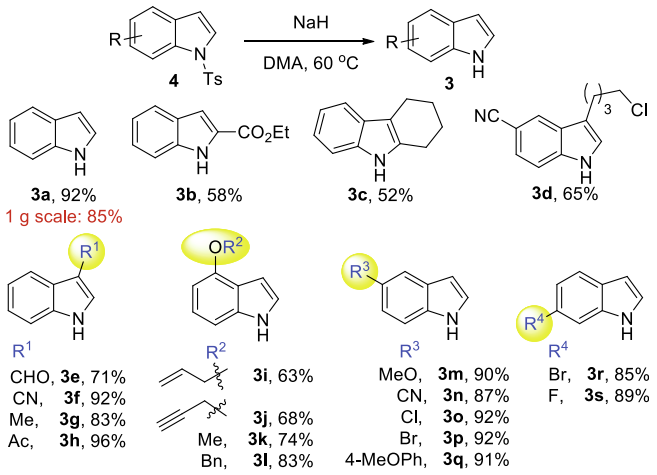


Entry	Substrate	NaH (eq.)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	**4a1**	2	THF	60	12	NR
2	**4a1**	2	toluene	60	12	NR
3	**4a1**	2	1,4-dioxane	60	12	NR
4	**4a1**	2	DME	60	12	NR
5	**4a1**	2	DMF	60	3	90
6	**4a1**	**2**	**DMA**	**60**	**3**	**92**
7	**4a1**	2	DMSO	60	1	88
8	**4a1**	2	DMA	25	8	89
9	**4a1**	2	DMA	40	6	87
10	**4a1**	2	DMA	80	2	89
11	**4a1**	1.4	DMA	60	12	64
12	**4a1**	1.8	DMA	60	4.5	91
13	**4a2**	2	DMA	60	2	72
14	**4a3**	2	DMA	60	3	0[c]
15	**4a4**	2	DMA	60	2	70
16	**4a5**	2	DMA	25	0.5	83

[a]Reaction conditions: **4a** (0.2 mmol, 1 equiv) and NaH (1.4–2.0 equiv) in dry solvent (1.5 mL) was stirred under N_2 for specified time. [b]Isolated yield. [c]No desired **3a** was detected, and **4a3** was recovered in 78% yield.

groups were evaluated under the optimial deprotection conditions (Table 1, entries 13–16). Although 4-methoxybenzenesulfonyl protected indole **4a2** gave **3a** in good yield (Entry 13), no desired deprotective product was detected in the case of 4-nitrobenzenesulfonyl substrate **4a3** (Entry 14). Methanesulfonyl (Entry 15) and trifluoromethanesulfonyl (Entry 16) also proved to be good leaving groups under NaH/DMA conditions.

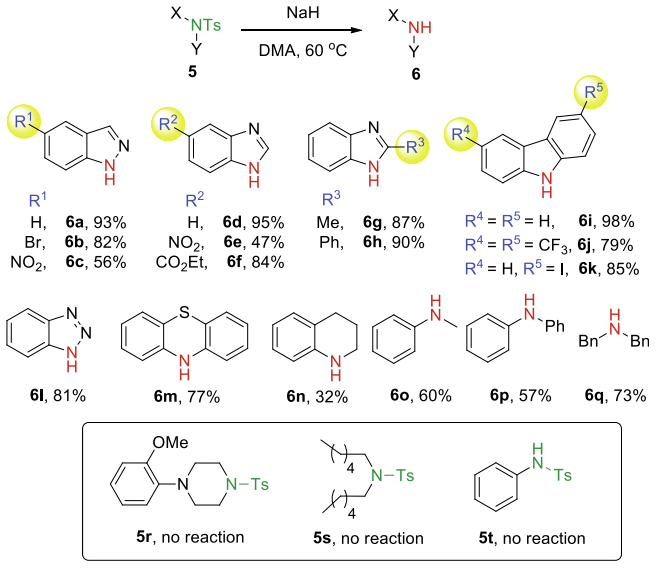
With the optimized conditions in hand, we then investigated the substrate scope of the detosylation reaction. As shown in Scheme 2, a number of Ts-protected indoles bearing electron-donating and electron-withdrawing substituents were successfully detosylated by NaH in DMA at 60 °C. The corresponding Ts-free products **3a-s** were isolated in moderate to excellent yields (52–96%). It is worthy noting that substrate **4b** containing an ester moiety also generated desired product **3b** by selectively deprotecting the tosyl group, which was difficult to achieve for other basic



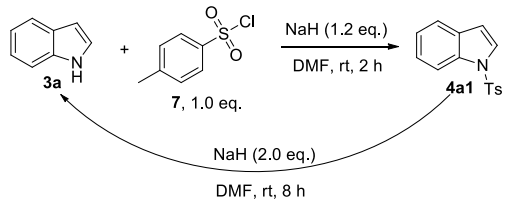
Scheme 2. Substrate scope for the detosylation of indole-based sulfonamides.

detosylation reagents.[9a] In addition, the potentially reactive alkyl chloride of **4d** and acidic acetyl group of **4h** did not affect the detosylation reaction, smoothly delivering the indole products **3d** and **3h**. Gratifyingly, scale-up of **4a1** to 1g level gave target product **3a** in good yield (85%).

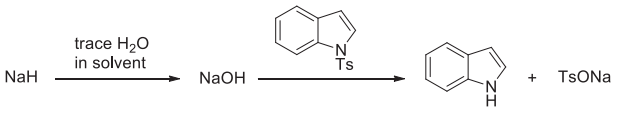
Encouraged by the success of indoles, we next tried to expand the substrate scope to other heterocycles and secondary amines (Scheme 3). To our delight, many types of biologically important azaheterocycles, such as 1*H*-indazole (**6a-c**), benzimidazole (**6d-h**), benzotriazole (**6l**), dibenzopyrrole (**6i-k**) and phenothiazine (**6m**), could be produced from their Ts-protected precursors under the NaH/DMA conditions. It seems that the nitro group has some adverse impact on the reaction by generating messy byproducts, but still could afford deprotection products in moderate yields (**6c** and **6e**). The competitive ester group in benzimidazole **5f** survived the detosylation conditions to give **6f** in 84% yield. Moreover, it was demonstrated the methodology was also suitable for various Ts-protected common secondary amines, represented by the generation of tetrahydroquinoline **6n**, *N*-methylaniline **6o**, diphenylamine **6p**, and dibenzylamine **6q**.



Scheme 3. Substrate scope for the detosylation of Ts-protected azaheterocycles and secondary amines.



Scheme 4. Tosylation and detosylation of indole under the same conditions.



Scheme 5. The proposed mechanism.

The limitations of the method were also realized. Ts-protected secondary amines with two aliphatic groups, such as **5r** and **5s**, could not be transformed into free amines by NaH/DMA. Primary amines with Ts protection (such as **5t**) also failed to afford detosylation products due to the easy ionization of this type of substrates, which prevented the further attack by NaH.

One important application of our discovery, as mentioned above (Scheme 1b), is to guide the tosylation of secondary amine substrates. In order to get optimal reaction yield, the loading of NaH must be carefully regulated because extra NaH may destroy the tosylation product. We designed an experiment to support this point of view (Scheme 4). To a suspension of NaH (0.24 mmol) in DMF (1.5 mL) was sequentially added indole **3a** (0.2 mmol) and TsCl (0.2 mmol), and the mixture was stirred at rt for 2 h, with TLC indicating **3a** was completely transformed into **4a1**. Then additional NaH (0.4 mmol, 2.0 eq.) was put into the reaction system and continued to stir for 8 h. It was observed **4a1** was throughly restored to the starting material **3a** in 89% isolated yield, and the structure of **3a** was identified by ^{1}H NMR.

To verify the reaction mechanism, a series of experiments were conducted. Please see the Supporting Information for the experiment details. The proposed mechanism for the NaH-mediated detosylation reaction is depicted in Scheme 5.

In summary, we have developed a simple and efficient protocol for the *N*-detosylation of tosylated indoles, several azaheterocycles, some anilines and dibenzylamine using cheap and convenient NaH/DMA conditions. Our studies revealed that the NaH-mediated tosylation of nitrogen-containing compounds should control the loading of NaH due to the risk of detosylation by excessive NaH.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by National Natural Science Foundation of China (21202112 and 21702058), PAPD (A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions) and East China University of Science and Technology, the '111' Project. We are also grateful to the financial supports from Suzhou Vocational Health College, Qing Lan Project of Jiangsu Province.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152442.

References

[1] (a) K.M. Harmon, A.B. Harmon, B.C. Thompson, J. Am. Chem. Soc. 89 (1967) 5311–5312;
(b) D.A. Alonso, P.G. Andersson, J. Org. Chem. 63 (1998) 9455–9461;
(c) P. Nandi, M.Y. Redko, K. Petersen, J.L. Dye, M. Lefenfeld, P.F. Vogt, J.E. Jackson, Org. Lett. 10 (2008) 5441–5444;
(d) M. Carraro, L. Pisano, U. Azzena, Synthesis (2017) 1931–1937.
[2] (a) S.-Z. Zhao, G. Sirasani, S. Vaddypally, M.J. Zdilla, R.B. Andrade, Angew. Chem. Int. Ed. 52 (2013) 8309–8311;
(b) H. Miura, S. Terajima, K. Tsutsui, T. Shishido, J. Org. Chem. 82 (2017) 1231–1239;
(c) B. Nyasse, L. Grehnb, U. Ragnarsson, Chem. Commun. (1997) 1017–1018;
(d) B. Nyasse, L. Grehn, H.L.S. Maia, L.S. Monteiro, U. Ragnarsson, J. Org. Chem. 64 (1999) 7135–7139.
[3] P. Carter, S. Fitzjohn, P. Magnus, J. Chem Soc, Chem. Commun. (1986) 1162–1164.
[4] (a) T. Ankner, G. Hilmersson, Org. Lett. 11 (2009) 503–506;
(b) H. Knowles, A.F. Parsons, R.M. Pettifer, Synlett (1997) 271–272.
[5] K. Nagata, H. Ishikawa, A. Tanaka, M. Miyazaki, T. Kanemitsu, T. Itoh, Heterocycles 81 (2010) 1791–1798.
[6] (a) N. Shohji, T. Kawaji, S. Okamoto, Org. Lett. 13 (2011) 2626–2629;
(b) E. Vellemae, O. Lebedev, U. Maeorg, Tetrahedron Lett. 49 (2008) 1373–1375.
[7] (a) S. O'Sullivan, E. Doni, T. Tuttle, J.A. Murphy, Angew. Chem. Int. Ed. 53 (2014) 474–478;
(b) S.S. Hanson, E. Doni, K.T. Traboulsee, G. Coulthurd, J.A. Murphy, C.A. Dyker, Angew. Chem. Int. Ed. 54 (2015) 11236–11239;
(c) F. Schoenebeck, J.A. Murphy, S. Zhou, Y. Uenoyama, Y. Miclo, T. Tuttle, J. Am. Chem. Soc. 129 (2007) 13368–13369.
[8] R.R. Milburn, V. Snieckus, Angew. Chem. Int. Ed. 43 (2004) 892–894.
[9] (b) B.M. Baron, R.J. Cregge, R.A. Farr, D. Friedrich, R.S. Gross, B.L. Harrison, D.A. Janowick, D. Matthews, T.C. McCloskey, S. Meikrantz, P.L. Nyce, R. Vaz, W.A. Metz, J. Med. Chem. 48 (2005) 995–1018;
(b) Y.-G. Liu, L.-C. Shen, M. Prashad, J. Tibbatts, O. Repic, T.J. Blacklock, Org. Process Res. Dev. 12 (2008) 778–780;
(c) Q.A. Huchet, B. Kuhn, B. Wagner, N.A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E.M. Carreira, K. Müller, J. Med. Chem. 58 (2015) 9041–9060;
(d) Z. Chen, H. Duan, X. Tong, P. Hsu, L. Han, S.L. Morris-Natschke, S. Yang, W. Liu, K.-H. Lee, J. Nat. Prod. 81 (2018) 465–474;
(e) M. Arisawa, Y. Kasaya, T. Obata, T. Sasaki, T. Nakamura, T. Araki, K. Yamamoto, A. Sasaki, A. Yamano, M. Ito, H. Abe, Y. Ito, S. Shuto, J. Med. Chem. 55 (2012) 8152–8163.
[10] (a) K.N. More, V.S. Hong, A. Lee, J. Park, S. Kim, J. Lee, Bioorg. Med. Chem. Lett. 28 (2018) 2513–2517;
(b) D.J. St, Jean Jr., S.F. Poon, J.L. Schwarzbach, Org. Lett. 9 (2007) 4893–4896.
[11] R. Akue-Gedua, D. Couturier, J.-P. Henicharta, B. Rigo, G. Sanz, L.V. Hijfte, A. Bourry, Tetrahedron 68 (2012) 1117–1127.
[12] C. Chaulet, C. Croix, J. Basset, M.-D. Pujol, M.-C. Viaud-Massuard, Synlett (2010) 1481–1484.
[13] S. Yoshida, K. Igawa, K. Tomooka, J. Am. Chem. Soc. 134 (2012) 19358–19361.
[14] I. Fleming, J. Frackenpohl, H. Ila, J. Chem. Soc., Perkin Trans. 1 (1998) 1229–1235.
[15] (a) A.C. Smith, D.W. Kung, A. Shavnya, T.A. Brandt, P.D. Dent, N.E. Genung, S. Cabral, J. Panteleev, M. Herr, K.N. Yip, G.E. Aspnes, E.L. Conn, M.S. Dowling, D.J. Edmonds, I.D. Edmonds, D.P. Fernando, P.M. Herrinton, N.F. Keene, S.Y. Lavergne, Q. Li, J. Polivkova, C.R. Rose, B.A. Thuma, M.G. Vetelino, G.-Q. Wang, J.D. Weaver, D.W. Widlicka, K.E.P. Wiglesworth, J. Xiao, T. Zahn, Y.-X. Zhang, Org. Process Res. Dev. 22 (2018) 681–696;
(b) J. McNulty, K. Keskar, H.A. Jenkins, N.H. Werstiuk, C. Bordón, R. Yolken, L. Jones-Brando, Org. Biomol. Chem. 13 (2015) 10015–10024;
(c) T. Wang, T.R. Hoye, J. Am. Chem. Soc. 138 (2016) 13870–13873.
[16] (a) D.I. Weisblat, B.J. Magerlein, D.K. Myers, J. Am. Chem. Soc. 75 (1953) 3630–3632;
(b) H.R. Snyder, R.E. Hekert, J. Am. Chem. Soc. 74 (1952) 2006–2009.
[17] W. Oppolzer, H. Bienayme, A. Genevois-Borella, J. Am. Chem. Soc. 113 (1991) 9660–9661.
[18] (a) C. Nolan, T. Gunnlaugsson, Tetrahedron Lett. 49 (2008) 1993–1996;
(b) T. Tsunoda, A. Tanaka, T. Mase, S. Sakamoto, Heterocycles 63 (2004) 1113–1122.
[19] (a) V. Coeffard, C. Thobie-Gautier, I. Beaudet, E. Le Grognec, J.-P. Quintard, Eur. J. Org. Chem. (2008) 383–391;
(b) P. Viaud, V. Coeffard, C. Thobie-Gautier, I. Beaudet, N. Galland, J.-P. Quintard, E. Le Grognec, Org. Lett. 14 (2012) 942–945;
(c) H. Senboku, K. Nakahara, T. Fukuhara, S. Hara, Tetrahedron Lett. 51 (2010) 435–438.
[20] (a) J. Xuan, B.-J. Li, Z.-J. Feng, G.-D. Sun, H.-H. Ma, Z.-W. Yuan, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, Chem. Asian J. 8 (2013) 1090–1094;

(b) E. Hasegawa, Y. Nagakura, N. Izumiya, K. Matsumoto, T. Tanaka, T. Miura, T. Ikoma, H. Iwamoto, K. Wakamatsu, J. Org. Chem. 83 (2018) 10813–10825;
(c) P.-P. Yeh, J.E. Taylor, D.G. Stark, D.S.B. Daniels, C. Fallan, J.C. Walton, A.D. Smith, Org. Biomol. Chem. 15 (2017) 8914–8922.

[21] (a) Y.-J. Mao, Y. Liu, Y.-W. Hu, L. Wang, S.-L. Zhang, W. Wang, ACS Catal. 8 (2018) 3016–3020;
(b) Y. Liu, Y.-J. Mao, Y.-W. Hu, J.-J. Gui, L. Wang, W. Wang, S.-L. Zhang, Adv. Synth. Catal. 361 (2019) 1554–1558.

[22] Recently, it was reported that the reaction of NaH in DMSO, DMF and DMA has explosion hazards (see reference 23). Noncondensable gaseous products from the thermal decomposition of a mixture of NaH/solvent is responsible for the explosion. In our experiments, non-sealed system, low content of NaH and low reaction temperature greatly reduced the potential hazards. In fact, no real explosion event was mentioned in reference 23 when DMF and DMA was used.

[23] Q. Yang, M. Sheng, J.J. Henkelis, S. Tu, E. Wiensch, H. Zhang, Y. Zhang, C. Tucker, D.E. Ejeh, Org. Process Res. Dev. 23 (2019) 2210–2217.