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A practical synthesis of *N*-tosylimines of arylaldehydes

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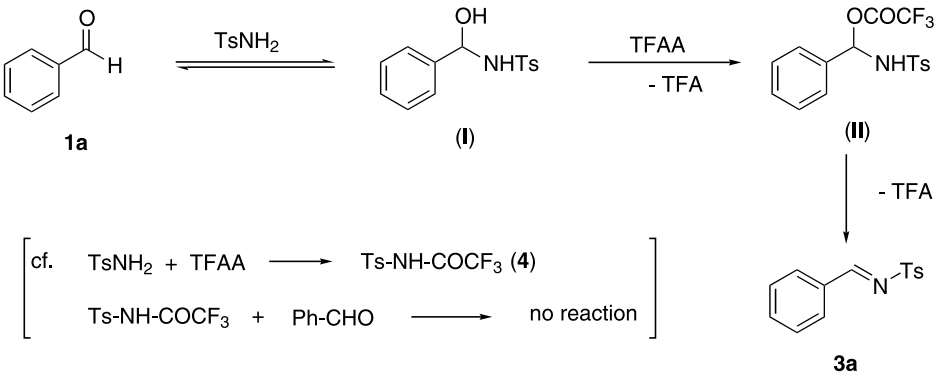
Abstract—Synthesis of *N*-tosylimines of arylaldehydes was carried out by the reaction of arylaldehydes and *p*-toluenesulfonamide in methylene chloride in the presence of trifluoroacetic anhydride as a dehydrating agent.

N-Sulfonylimines are important synthetic intermediates in organic synthesis.[1] Various useful methods of preparing these compounds are known.[2] Chemla and coworkers have reported an easy synthesis of *N*-sulfonylimines by the reaction of aldehyde, sulfonamide and sodium *p*-toluenesulfinate in aqueous formic acid, and subsequent treatment of the generated sulfonamide sulfone intermediate with sodium bicarbonate.[2a] Jennings and Lovely have used titanium tetrachloride and triethylamine for the synthesis of *N*-tosylimines.[2b] The synthesis of *N*-tosylimines from aldehydes and chloramine-T in the presence of tellurium metal was reported by Trost and Marrs.[2c] Synthesis of *N*-sulfonylimines based on the preparation and in situ rearrangement of oxime *O*-sulfinates have been reported.[2d] Sisko and Weinreb have reported the reaction of aldehydes and *N*-sulfinyl *p*-toluenesulfonamide for the in situ generation of *N*-tosylimines.[2e] Georg and co-workers have reported the one-flask conversion of aldehydes and ketones to *N*-sulfonylimines by the reaction of *N*-trimethylsilylaldimine with various sulfonyl chlorides.[2f] Most of all, simple condensation between aldehydes and sulfonamides appeared most frequently.[2b,g] Various reagents and conditions have been used including the use of molecular sieves and Amberlyst under Dean–Stark conditions[2g] or tetraethyl orthosilicate.[2h] Nevertheless, it is important to develop an efficient method of *N*-tosylimines under mild conditions by using readily available reagents.

We were interested in the synthesis of *N*-sulfonylimines during our investigations on the chemical transformations of the Baylis–Hillman adducts of *N*-tosylimines.[3] Basically, major problems for the synthesis of *N*-sulfonylimines might be (1) the cleavage of prepared *N*-sulfonylimines into starting materials, aldehydes and



Scheme 1.

Keywords: *N*-tosylimines; arylaldehydes; trifluoroacetic anhydride; *N*-tosyl enamines.

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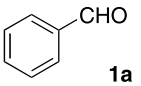
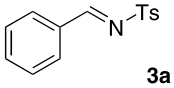
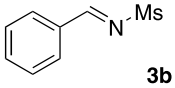
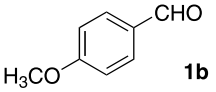
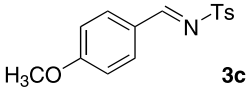
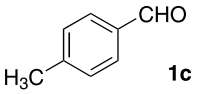
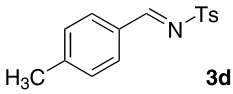
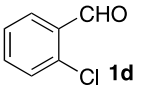
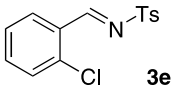
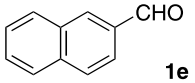
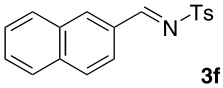
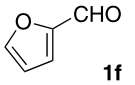
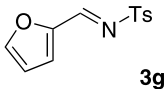
sulfonamide, especially in hydrolytic conditions, (2) limited nucleophilicity of sulfonamide toward aldehydes, which makes the equilibrium for the formation of aminal stage backwards, as a result, requiring strong acidic conditions in order to eliminate water, (3) side reactions of aldehydes having acidic α-hydrogen atoms. In these respects, we focused initially our attention to find a condition for shifting the equilibrium for the formation of aminal forwards easily by simply quenching it with acetic anhydride (see, Scheme 1). The use of acetic anhydride meets our rational approach very well. The reaction of benzaldehyde (**1a**) and tosylamide (**2a**) in methylene chloride in the presence of acetic anhydride gave the desired benzaldehyde *N*-tosylimine (**3a**) in 81% yield. It is very interesting to note that the use of acetic anhydride for the synthesis of *N*-sulfonylimines has not been reported.

The same reaction with trifluoroacetic anhydride showed improved results (88%, entry 1 in Table 1) both in yield and purity. In Scheme 1, the reaction pathway is shown with the reaction of benzaldehyde and *p*-toluenesulfonamide as an example. The equilibrium for the formation of *N*-tosyl hemiaminal[4] derivative **I** can be shifted forward by the following trifluoroacetylation into **II**. Next step, elimination of trifluoroacetic acid from **II**, can occur more easily than the corresponding dehydration from **I**. In the reaction mixture, *N*-trifluoroacetyl tosylamide (**4**)[5] was found in trace amounts on TLC. In order to examine the involvement of **4**, we prepared **4** from tosylamide and trifluoroacetic anhydride quantitatively (99%).[5] However, the reaction of benzaldehyde and **4** did not give **3a** at all in refluxing CH_2Cl_2. From the results the mechanism involving **4** was not seemed plausible. The use of methanesulfonyl chloride (62%) or *p*-tosyl chloride (52%) instead of acetic anhydride or trifluoroacetic anhydride did not show good results. Thus, we prepared some *N*-tosylimines from arylaldehydes by using trifluoroacetic anhydride and the results are summarized in Table 1. As shown, various kinds of arylaldehydes showed similar results (83–89% isolated yields).[6] However, the reaction of aliphatic aldehydes with acidic α-hydrogen atom showed different results. The results are shown in Table 2. As shown in entries 1–3, the corresponding *N*-tosyl enamines **5a–c** were obtained.[6–9] For *n*-hexanal (**1j**), major product was obtained via successive aldol condensation followed by formation of *N*-tosylimine.[6]

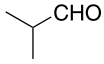
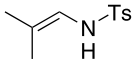
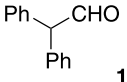
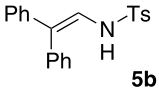
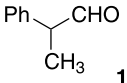
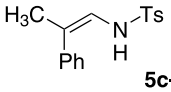
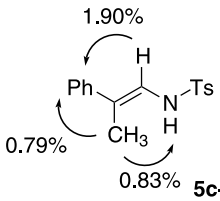
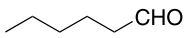
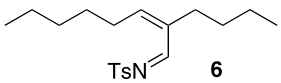
Table 1. Synthesis of *N*-tosylimines of arylaldehydes

entry	aldehyde	conditions	products	yields (%)[a,b]
1	 **1a**	$TsNH_2$ (**2a**, 1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 12 h	 **3a**	88 (112-113)[2j]
2	**1a**	$CH_3SO_2NH_2$ (**2b**, 1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 12 h	 **3b**	83 (91-92)[2j]
3	 **1b**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 7 h	 **3c**	89 (127-128)[2c]
4	 **1c**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 14 h	 **3d**	86 (111-112)[1a]
5	 **1d**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 8 h	 **3e**	88 (129-130)[2c]
6	 **1e**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 12 h	 **3f**	88 (115-116)[2j]
7	 **1f**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 12 h	 **3g**	89 (100-101)[2c]

[a]Isolated yields of purified *N*-tosylimines (estimated to be >95% pure by ^1H NMR).

[b]Melting points (°C) and references are cited in parenthesis.

Table 2. The reaction of aliphatic aldehydes and tosylamide

entry	aldehyde	conditions	products	yields (%)[a]
1	 **1g**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, rt, 12 h	 **5a**	53 (114-115)[7]
2	 **1h**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 15 h	 **5b**	63 (170-171)[8]
3	 **1i**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, reflux, 15 h	 **5c-*Z***	30[b] (151-153)[6,9]
			 **5c-*E***	42[b] (oil)[6,9]
4	 **1j**	$TsNH_2$ (1.1 equiv.) TFAA (1.1 equiv.) CH_2Cl_2, rt, 12 h	 **6**	41 (oil)[6]

[a]Melting points (°C) and references are cited in parenthesis.

[b]The structure of *Z* and *E* was confirmed by NOE experiment as shown for **5c-*E***.

As a summary we disclosed a facile synthetic method of *N*-tosylimines of arylaldehydes by using the simple concept: elimination of trifluoroacetic acid is easier than dehydration.

Acknowledgements

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2. Synthesis of *N*-tosylimines, see: (a) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75 and further references cited therein. (b) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561; (c) Trost, B. M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468; (d) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777; (e) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393; (f) Georg, G. I.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366; (g) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth. Coll. Vol. VIII* **1993**, 546; (h) Love, B. E.; Raje, P. S.; Williams, T. C., II. *Synlett* **1994**, 493; (i) Suzuki, H.; Takeda, S.; Hanazaki, Y. *Chem. Lett.* **1985**, 679; (j) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725.
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6. Typical experimental procedure for the synthesis of **3a**: To a stirred mixture of benzaldehyde (106 mg, 1 mmol) and *p*-tosylamide (188 mg, 1.1 mmol) in methylene chloride (5 mL) was added trifluoroacetic anhydride (231 mg, 1.1

mmol) and heated to reflux for 12 h. The reaction mixture was poured into cold water and extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and evaporated to afford crude product. Flash column chromatography (hexane/ether = 8:1) gave pure **3a** as a white solid, 228 mg (88%). ^{1}H NMR spectroscopy and its melting points were identical with reported. The purity of **3a** was >95%. Selected spectroscopic data of *N*-tosyl enamines, **5c**-*Z* and **5c**-*E*, and tosylimine **6** are as follows. **5c**-*Z*: white solid, mp 151–153°C; ^{1}H NMR ($CDCl_3$) δ 1.92 (d, J = 1.2 Hz, 3H), 2.45 (s, 3H), 6.10 (d, J = 10.9 Hz, 1H), 6.17 (dq, J = 10.9 and 1.2 Hz, 1H), 6.91–7.70 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.59, 21.89, 118.39, 121.19, 126.85, 127.43, 127.64, 129.16, 129.80, 136.85, 138.37, 143.75. **5c**-*E*: oil; ^{1}H NMR ($CDCl_3$) δ 1.87 (d, J = 1.5 Hz, 3H), 2.41 (s, 3H), 6.48 (dq, J = 10.8 and 1.5 Hz, 1H), 6.66 (d, J = 10.8 Hz, 1H), 7.18–7.82 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.24, 21.52, 119.89, 119.96, 125.37, 126.73, 126.78, 128.39, 129.86, 137.14, 140.59, 143.84. **6**: oil; ^{1}H NMR ($CDCl_3$) δ 0.81–0.93 (m, 6H), 1.25–1.34 (m, 8H), 1.39–1.51 (m, 2H), 2.30–2.39 (m, 4H), 2.43 (s, 3H), 6.48 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.22, 14.31, 22.00, 22.80, 22.98, 25.40, 28.97, 29.97, 31.00, 31.89, 128.11, 129.99, 136.27, 140.11, 144.42, 157.93, 174.31.

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