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Zinc-mediated novel and efficient method for N-sulfonylation of amines in the absence of base

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RESEARCH ARTICLE

Zinc-mediated novel and efficient method for N-sulfonylation of amines in the absence of base

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A simple and efficient method of zinc dust-mediated N-sulfonylation of amines to the corresponding sulfonamides is described. The reaction is carried out under neutral and mild conditions. The significant feature of this method is the isolation of the pure product by simple work up in a short time.

Keywords: Sulfonyl chlorides; Zinc dust; Amines

1. Introduction

Sulfonylation is a significant reaction in the synthesis of naturally occurring bioactive molecules [1–3]. The sulfonamides are found in large number of biologically active molecules [4, 5]. This functional group is useful for various chemical transformations in the synthesis of sulfur-nitrogen heterocycles, which are useful as drugs and pharmaceuticals [6, 7]. In particular, the aryl sulfones have received much attention as powerful anti-HIV-1 agents [8]. The sulfonamides are usually prepared by the reaction of an amine with sulfonyl chloride in presence of various bases [9]. The sulfonylation is an important method for the protection of amines [10, 11]. All the reported methods suffer from drawbacks like longer reaction times, tedious work-up, and carrying out the reaction under basic conditions.

The use of zinc dust has gained importance in organic synthesis e.g., in the Barbier reaction [12], Diels-Alder reaction [13], Williamson reaction [14], Friedel-Crafts sulfonylation [15], Fries rearrangement [16] and many important chemical transformations [17, 18]. The synthesis of Z-amino acids was described using activated zinc powder [19].

2. Discussion

In the present work, we describe a green chemical approach for the synthesis of sulfonamides (scheme 1) using zinc dust under mild and neutral conditions. The reaction was carried out on

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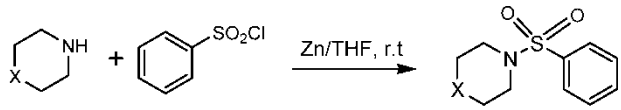
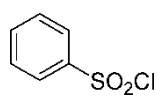
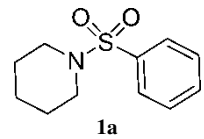
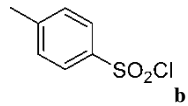
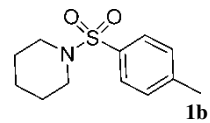
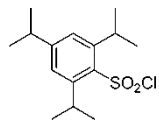
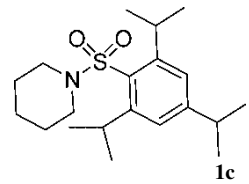
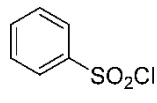
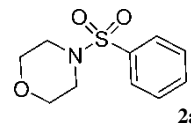
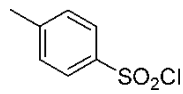
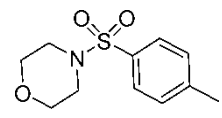
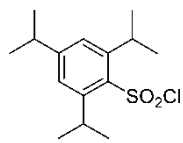
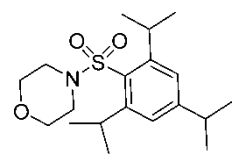


X = CH_2, O or N-Phenyl

SCHEME 1

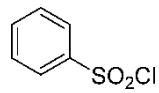
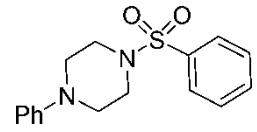
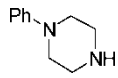
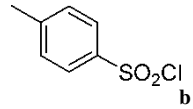
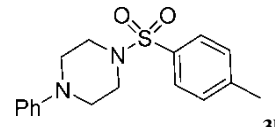
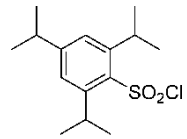
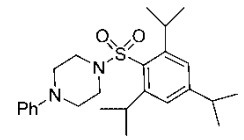
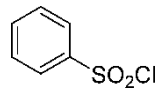
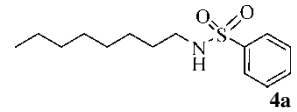
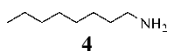
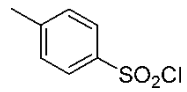
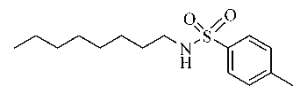
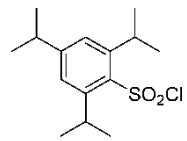
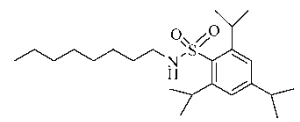
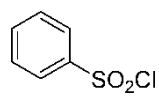
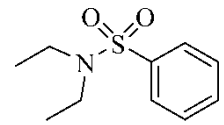
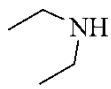
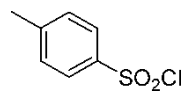
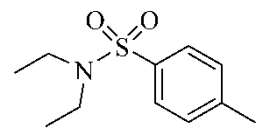
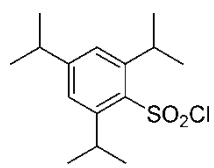
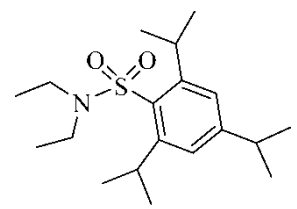
cyclic and acyclic amines (1 equivalent) with various sulfonyl chlorides (1.1 equivalents) in the presence of zinc dust (2 equivalents) in dry THF for a specified reaction time to give the corresponding products in excellent yields with high purity (table 1). In the reaction, the zinc dust is acting as a HCl scavenger and is necessary for the product formation. We observed that the reaction does not work in the absence of zinc dust.

Table 1. Condensation of amines with aryl sulfonyl chlorides in presence of Zinc dust.

Entry	Amine	Sulfonyl chloride	Product[a]	Reaction time (min)	Yield (%)[b]
A		 **a**	 **1a**	20	95
B	 **1**	 **b**	 **1b**	25	92
C		 **c**	 **1c**	25	85
D		 **a**	 **2a**	20	92
E	 **2**	 **b**	 **2b**	20	90
F		 **c**	 **2c**	25	82

(*continued*)

Table 1. Continued.

Entry	Amine	Sulfonyl chloride	Product[a]	Reaction time (min)	Yield (%)[b]
G		 **a**	 **3a**	20	90
H	 **3**	 **b**	 **3b**	25	88
I		 **c**	 **3c**	25	80
J		 **a**	 **4a**	20	95
K	 **4**	 **b**	 **4b**	20	90
L		 **c**	 **4c**	25	90
M		 **a**	 **5a**	20	90
N	 **5**	 **b**	 **5b**	25	90
O		 **c**	 **5c**	25	85

[a]All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b]Isolated and optimized yields.

In conclusion, we have developed a novel methodology of the N-sulfonylation of amines for the preparation of sulfonamides under neutral and mild conditions with short reaction time. The products were obtained with high purity and high yields.

3. Experimental

Infrared spectra were recorded on a FT IR Perkin-Elmer 1310 spectrometer using KBr Pellets. ^{1}H NMR spectra were measured on a Bruker AVANCE 300 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as solvent. The mass spectra were recorded on a VG Auto Spec mass spectrometer. Elemental analyses were performed on Elementar VARIO EL elemental analyzer.

3.1 *General procedure for sulfonylation*

To a solution of piperidine **1** (200 mg, 2.35 mmol) in THF (2 mL) was added benzene sulfonyl chloride a (498 mg, 2.8 mmol) at 10–15 °C and the reaction mixture was stirred for 10 min. Zinc dust (306 mg, 4.7 mmol) was added to the reaction mixture and stirred at room temperature for 20 min. The reaction mixture was filtered and the filtrate was concentrated to give the pure product. The spectral data of previously uncharacterized compounds are described below.

3.2 *Spectroscopic data*

3.2.1 2,4,6-triisopropylphenylsulfonyl-piperidine (1c). IR (KBr, cm^{-1}): 2946, 2868, 1600, 1459, 1309, 1281, 1146, 1096, 911, 717. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 2H), 4.26–4.10 (m, 2H), 3.18–3.07 (m, 4H), 2.97–2.81 (m, 1H), 1.67–1.51 (m, 6H), 1.24 (t, 18H, $J = 7.6$ Hz). MS: m/z = 352. Anal. Calcd for $C_{20}H_{33}NO_2S$ (351.55): C, 68.33; H, 9.46; Found: C, 68.36; H, 9.50.

3.2.2 4-Benzene sulfonylmorpholine (2a). IR (KBr, cm^{-1}) 2899, 2857, 1640, 1579, 1455, 1350, 1295, 1167, 1112, 1093, 934, 743. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.72 (m, 2H), 7.65–7.51 (m, 3H), 3.73 (t, 4H, $J = 4.5$ Hz), 2.98 (t, 4H, $J = 4.5$ Hz). MS: m/z = 227. Anal. Calcd for $C_{10}H_{13}NO_3S$ (227.28): C, 52.85; H, 5.77. Found: C, 52.81; H, 5.79.

3.2.3 1-Phenyl-4-[(2,4,6-triisopropyl phenyl) sulfonyl] piperazine (3c). IR (KBr, cm^{-1}) 2958, 2865, 1601, 1500, 1451, 1362, 1268, 1149, 1110, 940, 760. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.20–7.16 (m, 2H), 7.10 (s, 1H), 6.87–6.81 (m, 3H), 4.25–4.15 (m, 2H), 3.35–3.29 (m, 4H), 3.23–3.16 (m, 4H), 2.95–2.84 (m, 1H), 1.28 (d, 6H, $J = 6.8$ Hz), 1.26 (d, 12H, $J = 6.3$ Hz). MS: m/z = 429. Anal. Calcd for $C_{25}H_{36}N_2O_2S$ (428.56): C, 70.05, H, 8.47; Found: C, 70.09, H, 8.44.

3.2.4 N-Ethyl-N-tosyl ethylamine (5b). IR (KBr, cm^{-1}) 2973, 2930, 1920, 1596, 1462, 1332, 1156, 927. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.64 (d, 2H, $J = 8.3$), 7.28–7.23 (d, 2H, $J = 8.3$), 3.24–3.15 (q, 6H, $J = 7.5$), 2.44 (s, 3H), 1.17–1.09 (t, 4H, $J = 6.8$). MS: m/z = 227. Anal. Calcd for $C_{11}H_{17}NO_2S$ (227.32): C, 58.12, H, 7.54; Found: C, 58.10, H, 7.56.

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References

[1] Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, Y. Tanabe. *Tetrahedron*, **55**, 2183 (1999).
[2] Y. Tanabe, H. Yamamoto, Y. Yoshida, T. Miyawaki, N. Utsumi. *Bull. Chem. Soc. Jpn.*, **68**, 297 (1995).
[3] Y. Yoshida, K. Shimonishi, Y. Sakakura, S. Okada, N. Aso, Y. Tanabe. *Synthesis*, 1633 (1999).
[4] J. Schroder, A. Henke, H. Wenzel, H. Brandstetter, H.G. Stammler, A. Stammler, W.D. Pfeiffer, H. Tschesche. *J. Med. Chem.*, **44**, 3231 (2001).
[5] Y. Tamaru, F. Watanabe, T. Nakatani, K. Yasui, M. Fuji, T. Komurasaki, H. Tsuzuki, R. Maekawa, T. Yoshioka, K. Kawada, K. Sugita, M. Ohtani. *J. Med. Chem.*, **41**, 640 (1998).
[6] H.L. Holland. *Chem. Rev.*, **88**, 473 (1988).
[7] E. Block. *Angew. Chem., Int. Ed. Engl.*, **31**, 1135 (1992).
[8] J.B. McMohan, R.J. Gulakowsky, O.S. Weislow, R.J. Schultz, V.L. Narayanan, D.J. Clanton, R. Pedemonte, F.W. Wassmundt, R.W. Buckheit Jr, W.D. Decker, E.L. White, J.P. Bader, M.R. Boyd. *Antimicrob. Agents. Chemother.*, **37**, 754 (1993).
[9] L.F. Fieser, M. Fieser. *Reagents for Organic Synthesis*, vol. 1, p. 1179, Wiley, New York (1967).
[10] D.A. Alonso, P.G. Andersson. *J. Org. Chem.*, **63**, 9455 (1998).
[11] C.S. Pak, D.S. Lim. *Synth. Commun.*, **31**, 2209 (2001).
[12] A. Jogi, U. Maeorg. *Molecules*, **6,** 964 (2001).
[13] F. Bertozzi, R. Olsson, T. Frejd. *Org. Lett.*, **2**, 1283 (2000).
[14] S. Paul, M. Gupta. *Tetrahedron Lett.*, **45**, 8825 (2004).
[15] B.P. Bandgar, S.P. Kasture. *Synth. Commun.*, **31**, 1065 (2001).
[16] S. Paul, M. Gupta. *Synthesis*, 1789 (2004).
[17] M.S.R. Murty, B. Jyothirmai, P.R. Krishna, J.S. Yadav. *Synth. Commun.*, **33,** 2483 (2003).
[18] Y. Ogawa, A. Saiga, M. Mori, T. Shibata, K. Takagi. *J. Org. Chem.*, **65**, 1031 (2000).
[19] H.N. Gopi, K. Ananda, B.V. Suresh Babu. *Prot. Pept. Lett.*, **6**, 233 (1999).