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A HIGHLY EFFICIENT SYNTHESIS OF SULPHONAMIDE DERIVATIVES IN THE PRESENCE OF N-METHYL-2-PYRROLIDONE

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The sulphonamide derivatives are synthesized by two component condensation of alkyl bromide and sodium arylsulphonamide using N-methyl-2-pyrrolidone (NMP) as a reaction medium. This method results in high yields without the formation of unwanted side products, and expanding substrate scopes.

Keywords: Amides; NMP; nucleophiles; solvent effects; synthesis

INTRODUCTION

Multiamines and their derivatives are found to be among the most widely used building block in hyperbranched, linear polymers and supramolecular chemistry.[1–3] For example, in the group of Mcauley, an interesting Ni-N coordinate complex was developed that possessed the pentaerythrityl tetraamine.[4] Moreover, these compounds are intermediates, which could be widely used in drugs and food industries. In addition, these multierythrityltetramines have been suggested as precipitant for nitric acid and synthetic intermediates for many natural products.[5]

Due to the great importance, continuous efforts have been devoted and several synthetic strategies have been reported.[6–8] The methods include the following: (i) treating the readily available 1,3-dichloro-2,2-bis(chloromethyl)propane with excess supercritical ammonia at high temperature; (ii) treatment of 1,3-dibromo-2,2-bis(bromomethyl)propane (TBrMP) with sodium azide in organic solvent; (iii) treatment of TBrMP with sodium *p*-toluenesulphonamide (SPTPA). However, most of these approaches suffer from significant drawbacks and limitations. The first protocol involves the high temperature and pressure and the second includes the easily explosive compound such as sodium azide. In addition, the target products have a number of side unwanted compounds. It should be noted that these methods often result in low to moderate yields. Among them, the third one will lead to more practical applications, which the key step is the synthesis of the sulphonamide-derivatives

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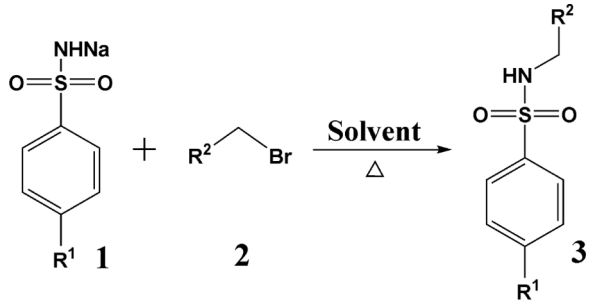

Scheme 1. Synthesis of compound **3**.

in the preparation of organic pentaerythrityltetramine. The low yields of sulphonamide-derivative represent major drawbacks of this approach. Therefore, the development of simple, efficient, and generally synthetic routes using available reagents remains important.

Here we wish to report a novel and highly efficient procedure for the synthesis of sulphonamide derivatives in the presence of NMP solution (Scheme 1).

RESULTS AND DISCUSSION

During the careful investigations, this type of reaction is very sensitive to temperature, the ratio of reactants, reaction time, and solvent. We firstly investigated the temperature effect on the yield of compound **3**. The corresponding tetrasulphonamido-derivative **3a** could not be afforded at 190 °C in NMP solution after 8 h, whereas **3a** was produced in 92% yield at 204 °C in the same time. Moreover, the ratio of reactants plays a very important role in synthesis of the target compounds. Figure 1a shows the yield curves for TBrMP with SPTPA in different ratio. The molar of TBrMP was kept constant and the yield of compound **3a** was followed as a function of increasing molar of SPTPA. When the molar of sodium salt was increased from 50% to 67%, the obtained yields were 30% and 92%, respectively.

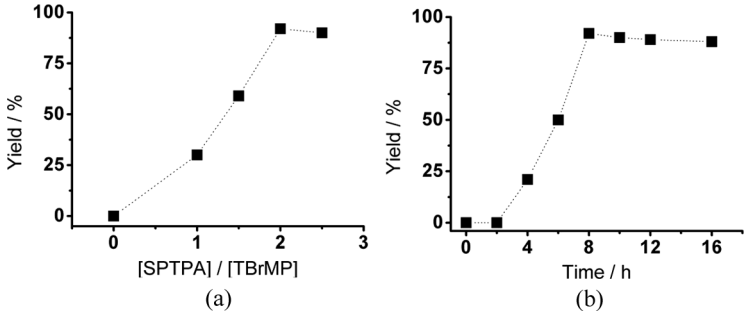

Figure 1. (a) The yield curves for TBrMP with SPTPA in different ratio. (b) Time dependent yield measurement for TBrMP with SPTPA.

Table 1. Synthesis of compound **3**

Entry	Compound **1** (R=)	Compound **2**	Solvent	Temp. (°C)	T.M.	Yield[a] (%)
1	4-CH_3-	TBrMP	NMP	204	**3a**	92
2	4-CH_3-	TBrMP	DMF	152		trace
3	4-CH_3-	TBrMP	DMAc	165		trace
4	4-CH_3-	TBrMP	DMSO	189		0
5	4-CH_3-	TBrMP	DEG	210		0
6	4-CH_3-	TBrMP	NMP/DEG	210		0
7	4-CH_3-	1-bromodecane	NMP	140	**3b**	85
8	4-CH_3-	1,3-dibromopropane	NMP	20	**3c**	95
9	4-CH_3-	1,4-dibromomethyl benzene	NMP	20	**3d**	95
10	4-CH_3-	1-bromo-2,2-dibromo Methyl-butane	NMP	204	**3e**	85
11	4-H-	TBrMP	NMP	204	**3f**	67
12	4-CH_3O-	TBrMP	NMP	204	**3g**	93
13	4-Cl-	TBrMP	NMP	204	**3h**	0

[a]Yields refer to pure isolated products.

With further addition of sodium salt to the reaction mixture, the yield (90%) was slightly decreased. The observation might result from the carbonized sodium *p*-toluenesulphonamide and the interaction of solvent and SPTPA as a strong base at high temperature. These results also indicated the optimal ratio was 1:2 ([TBrMP]:[SPTPA]). The time dependence of yields was investigated as shown in Figure 1b. The yield increased gradually with increasing reaction time and reached a constant value at 8 h. Shorter or longer reaction time gave the lower yields of **3a**.

Various solvents were tested for the reaction of TBrMP and sodium salt at high temperature, and selected examples were summarized in Table 1 (entries 1–6). The reaction in the presence of NMP solution afforded the desired product **3a** in high yield (entry 1). However, when performing in *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMAc) solution at refluxed temperature, the trace yields were observed as determined by TLC analysis (entries 2 and 3). The above results suggested that the low activity energy deactivated the reaction in DMF or DMAc solution. As a comparison, compound **3a** could not be obtained in diethylene glycol (DEG) or NMP/DEG solution, which might result from the nucleophilic competition of hydroxy and amino groups. Among the conditions tested, the reaction in NMP solution gave the best yield and this was selected as the optimal condition in the following experiments.

In NMP solution, the desired products (**3b, 3c, 3d, 3e, 3f, 3g**) were afforded in excellent yields and high purities (entries 7, 8, 9, 10, 11, and 12). This reaction condition was also applicable to other aromatic salts even in the presence of other functionalities such as hydrogen, methoxyl groups (Table 1, entries 11 and 12). It should be noted that condensation of the aromatic salt with electron-withdrawing units (entry 13, -Cl) with TBrMP could not afford the target compound (**3h**). All the products were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analysis, which were shown to be in full agreement with the structures presented.

In summary, this article describes a facile synthesis of sulphonamide derivatives in the presence of NMP. The method offers several advantages including very

high yields, cleaner reactions, inexpensive solvent, and ease of isolation of the products which makes the process convenient.

EXPERIMENTAL

Melting points were taken on a TX-4 hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 400 spectrometers using $CDCl_3$ as a solvent with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were measured on a Nicolet 380 instrument. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Preparation of Compound 3

Compound 3a. A mixture of sodium *p*-toluenesulphonamide (35.82 g, 185.6 mmol) and 1,3-dibromo-2,2-bis(bromomethyl)propane (9.0 g, 23.2 mmol) in NMP (30 mL) was stirred for 8 h at refluxed temperature. After cooling down to room temperature, ice-water (1 L) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (3:2, v/v). The product was obtained as white solid (92%). Mp: 255–256 °C; FT-IR (KBr): 3309, 3062, 2922, 1597, 1451, 1329, 1281, 1159, 660, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.69$ (d, $J = 8.0$ Hz, 8H), 7.31 (d, $J = 8.0$ Hz, 8H), 5.79 (t, 4H), 2.70 (s, 8H), 2.43 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.2$, 136.7, 129.0, 127.2, 40.2, 32.9, 24.3; Anal. Calcd. for $C_{33}H_{40}N_4O_8S_4$: C, 52.92; H, 5.38; N, 7.48; O, 17.09; S, 17.13. Found: C, 52.93; H, 5.39; N, 7.49; O, 17.05; S, 17.14. Compound **3a** was prepared in other solvents (DMF, DMAc, DMSO, DEG, NMP/DEG) according to this typical method.

Compound 3b. A mixture of sodium *p*-toluenesulphonamide (1.73 g, 9.0 mmol) and 1-bromodecane (1.0 g, 4.5 mmol) in NMP (20 mL) was stirred for 8 h at 140 °C. After cooling down to room temperature, ice-water (200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (2:1, v/v). The product was obtained as white solid (85%). Mp: 120–121 °C; FT-IR (KBr): 3486, 3284, 2922, 2852, 1458, 1323, 1158, 1094, 813, 663, 550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.74$ (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 4.23 (s, 1H), 2.93 (q, 2H), 2.43 (s, 3H), 1.44 (m, 2H), 1.23 (m, 14H), 0.88 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.2$, 136.7, 129.2, 127.2, 40.3, 32.0, 29.7, 29.5, 29.3, 26.9, 24.4, 23.2, 14.1; Anal. Calcd. for $C_{17}H_{29}NO_2S$: C, 65.55; H, 9.38; N, 4.50; O, 10.27; S, 10.29. Found: C, 65.53; H, 9.38; N, 4.53; O, 10.27; S, 10.29.

Compound 3c. A mixture of sodium *p*-toluenesulphonamide (3.83 g, 19.8 mmol) and 1,3-dibromopropane (1.0 g, 4.95 mmol) in NMP (20 mL) was stirred for 8 h at 20 °C. After cooling down to room temperature, ice-water (200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (2:1, v/v). The product was obtained as white solid (95%). Mp: 188–189 °C; FT-IR (KBr): 3485, 2995, 2915, 2872, 1594, 1445, 1344, 1162, 1131, 953, 819, 669, 609, 548 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.73$ (d, $J = 8.0$ Hz, 4 H), 7.37 (d, $J = 8.0$ Hz, 4H), 3.77 (t, 4H), 2.46 (s, 6H), 2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.1$, 136.7, 129.2, 127.2, 33.9, 26.9, 23.9; Anal. Calcd. for $C_{17}H_{22}N_2O_4S_2$: C, 53.38; H, 5.80; N, 7.32; O, 16.73; S, 16.77. Found: C, 53.36; H, 5.81; N, 7.30; O, 16.75; S, 16.78.

Compound 3d. A mixture of sodium *p*-toluenesulphonamide (4.52 g, 23.4 mmol) and 1,4-dibromomethyl benzene (1.54 g, 5.8 mmol) in NMP (20 mL) was stirred for 8 h at 20 °C. Ice-water (200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (4:1, v/v). The product was obtained as white solid (95%). Mp: 134–135 °C; FT-IR (KBr): 3425, 3242, 2919, 2865, 1652, 1592, 1455, 1439, 1239, 1148, 1068, 970, 827, 649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.70$ (d, $J = 8.4$ Hz, 4H), 7.32 (d, $J = 8.4$ Hz, 4H), 7.06 (s, 4H), 5.79 (t, $J = 8.0$ Hz, 2H), 4.44 (s, 4H), 2.42 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.1$, 139.7, 136.8, 129.5, 128.1, 126.9, 46.2, 24.3; Anal. Calcd. for $C_{22}H_{24}N_2O_4S_2$: C, 59.44; H, 5.44; N, 6.30; O, 14.40; S, 14.43. Found: C, 59.46; H, 5.44; N, 6.28; O, 14.39; S, 14.43.

Compound 3e. A mixture of sodium *p*-toluenesulphonamide (3.60 g, 18.6 mmol) and 1-bromo-2,2-di(bromomethyl)-butane (1.0 g, 3.1 mmol) in NMP (20 mL) was stirred for 8 h at refluxed temperature. After cooling down to room temperature, ice-water (200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (3:2, v/v). The product was obtained as white solid (85%). Mp: 250–252 °C; FT-IR (KBr): 3524, 3354, 2928, 1654, 1620, 1415, 1239, 1148, 970, 927, 847, 805, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.75$ (d, $J = 8.0$ Hz, 6H), 7.31 (d, $J = 8.0$ Hz, 6H), 5.79 (t, $J = 7.2$ Hz, 3H), 2.70, (s, 6H), 2.43 (s, 9H), 1.25 (q, 2H), 0.88 (t, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.1$, 136.7, 129.2, 127.2, 42.3, 32.8, 24.3, 23.5, 8.8; Anal. Calcd. for $C_{27}H_{35}N_3O_6S_3$: C, 54.61; H, 5.94; N, 7.08; O, 16.17; S, 16.20. Found: C, 54.61; H, 5.95; N, 7.09; O, 16.16; S, 16.29.

Compound 3f. A mixture of sodium phenylsulphonamide (4.3 g, 24.0 mmol) and TBrMP (1.15 g, 2.96 mmol) in NMP (30 mL) was stirred for 8 h at refluxed temperature. After cooling down to room temperature, ice-water (200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (4:1, v/v). The product was obtained as white solid (67%). Mp: 237–238 °C; FT-IR (KBr): 3442, 2955, 2932, 2853, 1641, 1558, 1457, 1399, 1377, 1334, 1156, 1091, 812, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.83$ (d, $J = 7.2$ Hz, 8H), 7.54–7.63 (m, 12H), 5.88 (t, $J = 7.2$ Hz, 4H), 2.72 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 139.7$, 132.1, 129.1, 127.3, 40.2, 32.8; Anal. Calcd. for $C_{29}H_{32}N_4O_8S_4$: C, 50.27; H, 4.66; N, 8.09; O, 18.47; S, 18.51. Found: C, 50.26; H, 4.64; N, 8.09; O, 19.49; S, 18.51.

Compound 3g. A mixture of sodium (4-methoxyphenylsulfonyl)amide (5.05 g, 24.2 mmol) and TBrMP (1.16 g, 3.0 mmol) in NMP (30 mL) was stirred for 6 h at refluxed temperature. After cooling down to room temperature, ice-water

(200 mL) was added and the precipitate was filtered off and carefully dried. The crude solid was purified on silica gel column using petroleum ether/ethyl acetate (5:1, v/v). The product was obtained as white solid (93%). Mp: 235–238 °C; FT-IR (KBr): 3441, 3262, 2919, 1853, 1652, 1455, 1401, 1321, 1154, 1086, 811, 659, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.83$ (d, $J = 7.2$ Hz, 8 H), 7.59 (d, $J = 7.2$ Hz, 8H), 5.80 (t, $J = 7.6$ Hz, 4H), 3.74 (s, 12H), 2.70 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 161.9$, 132.0, 128.1, 114.4, 55.9, 40.5, 33.1; Anal. Calcd. for $C_{33}H_{40}N_4O_{12}S_4$: C, 48.75; H, 4.96; N, 6.89; O, 23.62; S, 15.78. Found: C, 48.75; H, 4.96; N, 6.89; O, 23.63; S, 15.78.

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