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A CONVENIENT SYNTHESIS OF N, N, N'-TRISUBSTITUTED ETHYLENEDIAMINE DERIVATIVES FROM 2-METHYL-2-IMIDAZOLINE

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Abstract: A series of N, N, N'-trisubstituted ethylenediamine derivatives has been prepared from 2-methyl-2-imidazoline by a convenient three-step process in high yields: sulfonylation, methylation, and reactions with nucleophiles.

N, N, N'-trisubstituted ethylenediamine derivatives are important in organic synthesis and pharmaceutical research.[1-4] In connection with an ongoing project in our laboratory, to develop imidazolium chemistry which mimics the one-carbon unit transfer function of tetrahydrofolate coenzymes,[5-7] we have found that unique derivatives of ethylenediamine could be easily synthesized in

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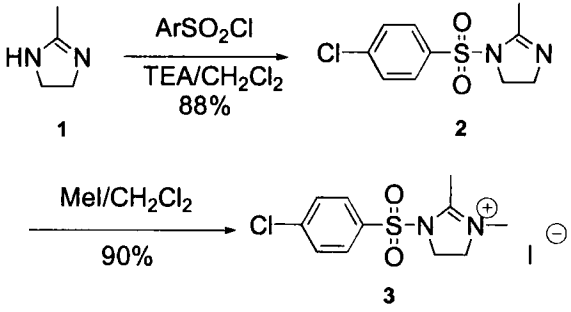
high yields, through reactions of the imidazolium iodides with nucleophiles. This method could be demonstrated by the preparation of 3-chlorophenylsulfonyl-4,5-dihydro-1,2-dimethyl imidazolium iodide **3** and its reactions with nucleophiles.

Preparation of imidazolium iodide **3** was accomplished in two steps from commercially available 2-methyl-2-imidazoline **1**: sulfonylation of 2-methyl-2-imidazoline by 4-chlorobenzenesulfyl chloride in dichloromethane under basic conditions produced 1-(4-chlorophenylsylfonyl)-2-methyl imidazoline **2** in 88% yield. Further methylation of **2** by reflux with excess iodomethane in dichloromethane produced **3** in 90% yield (Scheme I). The imidazolium salt **3** became highly susceptible to nucleophilic attack after simply sulfonylation and methylation of imidazoline **1**.

Scheme I



When 4,5-dihydro-1*H*-imidazolium salt **3** was treated with an aromatic amine such as *p*-toluidine, *p*-anisidine, aniline, or *p*-chloroaniline, and

benzylamine, the corresponding N, N, N'-trisubstituted ethylenediamines **4** – **8** were produced in 65 -98% yields (Table 1). These reactions were conducted by reflux in acetonitrile, and the reflux times were dependent on the nucleophility of amines, generally from two to nine hours. The products **4** – **8** crystallized from the reaction medium as the mixture was allowed to cool to room temperature. The imidazolium **3** remained unchanged even with longer reflux time when aromatic amines have a strong electron withdrawing group, *p*-nitroaniline and 2-aminopyridine were attempted in this category.

Nucleophilic addition to the C=N double bond in the imidazolium formed an imidazolidine intermediate, which subsequently produced a ring-opened product. The thermodynamically favored product was obtained from the imidazolidine intermediate through a ring-opening process (Scheme II). This occurred as a result of an unfavorable proton transfer to the less basic sulfonamide nitrogen, instead of the more basic amine nitrogen in the imidazolidine system, which would be a kinetically controlled process governed by protonation of the more basic nitrogen, followed by rearrangement. Pandit and Perillo have demonstrated this kind of mechanism by similar substrates independently. [8, 9]

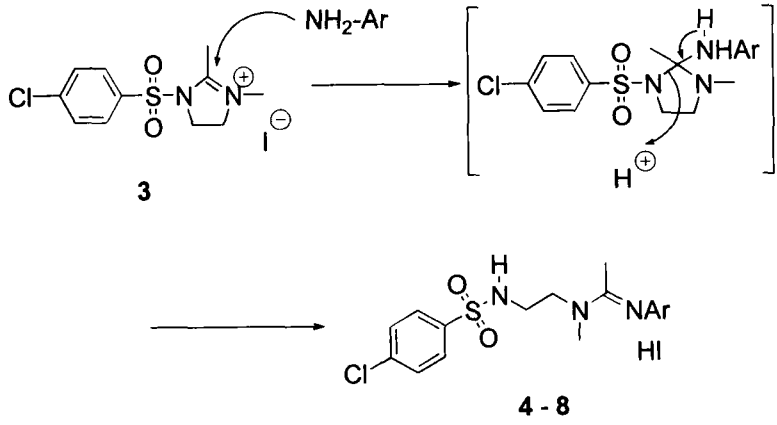
The imidazolium **3** also reacted with sodium hydroxide or sodium borohydride to produce another two N, N, N'-trisubstituted ethylenediamines **9** and **10**, both with high yields (Scheme III).

Table 1. Analytical Data for the N-(N'-arylacetimidoyl)-N-methyl-N'-(4-chlorobenzenesulfonyl)-ethylenediamine monohydroiodides **4 - 8**

Comp.	Yield % [a]	Mp °C	IR (KBr) ν (cm^{-1})	^{1}H-NMR δ ppm [b]	MS m/z	Found/Calcd. (%) C	H	N
4	98	123 - 125	3438, 3050, 1635, 1332, 1164, 825, 758	2.20 (s, 3H), 2.38 (s, 3H), 3.28 (m, 5H), 3.75 (m, 2H), 7.23 (q, 4H), 7.76 (m, 4H and 2H [c])	380	42.27	4.54	8.15
					(M - I)	42.57	4.57	8.28
5	78	134 - 136	3439, 3043, 1634, 1331,1164, 829, 758	2.21 (s, 3H), 3.28 (m, 5H), 3.86 (m, 5H), 7.18 (q, 4H), 7.80 (m, 4H and 2H [c])	396	41.30	4.37	7.91
					(M - HI)	41.27	4.34	8.02
6	65	140 - 142	3430, 1637, 1338, 1163, 833, 744	2.25 (s, 3H), 3.15 (m, 5H), 3.65 (t, 2H), 4.65 (s, 2H), 7.30 (s, 5H), 7.53 - 7.69 (q, 4H), 8.15 (br, 2H [c])	380	42.41	4.57	8.30
					(M - I)	42.57	4.57	8.28
7	95	114 - 115	3069, 1635, 1332,	2.22 (s, 3H), 3.25 (m, 5H), 3.72 (t, 2H), 7.40 (m, 4H and 2H [c]), 7.58 (d, 2H), 7.82 (d, 2H)	369	41.17	4.88	8.39
					(M - HI)	41.10	4.97	8.46
8	90	178 -179	3149, 1634, 1334	2.28 (s, 3H), 3.35 (m, 5H), 3.78 (t, 2H), 7.40 (m, 2H and 1H [c]), 7.56 (d, 2H), 7.74 (d, 2H), 7.90 (d, 2H), 10.48 (br, 1H [c])	400	38.36	3.78	7.80
					(M - I)	38.65	3.82	7.95

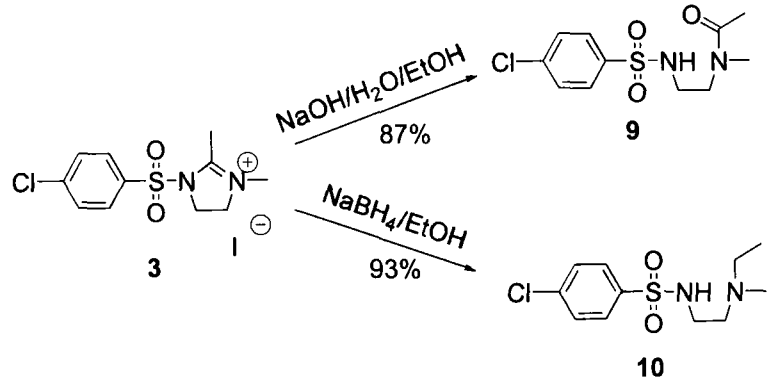
[a] Not optimized yields. [b] In DMSO-d_6. [c] Deuterium oxide exchangeable.

Scheme II



Ar: 4-$CH_3C_6H_4$, (**4**); 4-$CH_3OC_6H_4$, (**5**); Bn, (**6**); Ph, (**7**); 4-ClC_6H_4, (**8**)

Scheme III



In conclusion, we have developed a straightforward, simple and high yielding route to the N, N, N'-trisubstituted ethylenediamine derivatives using a commercially available heterocyclic compound, 2-methyl-2-imidazoline. This

methodology should be widely applicable to the preparation of other relevant N, N, N'-trisubstituted ethylenediamine derivatives.

EXPERIMENTAL

MS spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^{1}H and ^{13}C-NMR were obtained on a JOEL FX-60Q, Varian FT-80A or Bruker AC-P 300 MHz spectrometer, with TMS as an internal standard. Combustion analyses were performed on a Perkin-Elmer 240C instrument. IR spectra were obtained on a Shimadzu IR-1700 spectrophotometer. Melting points were uncorrected. All reactions were performed under an inert atmosphere of nitrogen, all reagents and solvents were purified and dried as required.

3-(4-Chlorobenzenesulfonyl)-2-methyl imidazoline (2): 2-methyl-2-imidazoline **1** (4.0 g, 48.0 mmol) was dissolved in 20 mL dry dichloromethane at 0 °C, followed by the addition of triethyl amine (7.0 mL, 50.2 mmol). To this solution was added dropwise a solution of 4-chlorobenzenesulfonyl chloride (10.1 g, 48.0 mmol) in 10 mL dichloromethane. The reaction mixture was stirred and warmed to room temperature in an additional 2 hours. The resulted solution was washed by saturated sodium bicarbonate (30 mL) and water (30 mL), dried over anhydrous sodium sulfate. Evaporation of dichloromethane *in vacuo* gave a crude solid, which was recrystallized from anhydrous ethyl alcohol to yield 10.9 g (88%) of **2** as white crystals, mp. 114 – 116 °C. ^{1}H-NMR ($CDCl_3$): 2.20 (s, 3H), 3.64 (m, 4H), 7.43 - 7.86 (m. 4H). IR (KBr) cm^{-1}: 1657 (ν C=N), 1361, 1173 (ν

S=O). MS m/e: 258 (M^+), 175, 111, 83, 55 (base peak). *Anal.* Calcd for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.29; N, 10.83. Found C, 46.58; H, 4.30; N, 10.72.

3-(4-Chlorobenzenesulfonyl)-4,5-dihydro-1,2-dimethyl 1*H*-imidazolium iodide (3): 3-(4-Chlorobenzenesulfonyl)-2-methyl imidazoline **2** (8.0 g, 30.9 mmol) and iodomethane (5.8 mL, 92.8 mmol) were refluxed in 20 mL dry dichloromethane for 3 hours. After cooled to room temperature a precipitate was collected by filtration and crystallized from anhydrous ethyl alcohol to give 11.2 g (90%) of **3** as a white powder, mp. 178 – 180 °C. ^{1}H-NMR ($CDCl_3$): 2.61 (s, 3H), 3.30 (s, 3H), 4.18 (m, 4H), 7.65 - 8.21 (m, 4H). ^{13}C-NMR ($CDCl_3$): 166.6, 165.1, 130.7, 126.1, 115.6, 56.2, 52.1, 47.3, 36.9, 14.8. IR (KBr) cm^{-1}: 1657 (ν C=N), 1373, 1169 (ν S=O). *Anal.* Calcd for $C_{11}H_{14}ClIN_2O_2S$: C, 32.97; H, 3.52; N, 6.99. Found C, 32.84; H, 3.49; N, 6.67.

General procedure for the reaction of imidazolium 3 with aromatic amines, N-(N-tolylacetimidoyl)-N-methyl-N'-(4-chlorobenzenesulfonyl)-ethylenediamine monohydroiodide as an example: a solution of imidazolium **3** (1.0 g, 2.5 mmol) and *p*-toluidine (0.28 g, 2.6 mmol) in 7 mL anhydrous acetonitrile was refluxed for 4 hour. After cooled to room temperature a yellow precipitate was observed. The yellowish solid was collected by vacuum filtration and recrystallized from anhydrous ethyl alcohol to yield 1.25 g (98%) of **4** as white crystals.

N-2-(N'-Acetyl-N'-methyl)ethyl 4-chlorobenzenesulfonamide 9: To a solution of imidazolium **3** (1.0 g, 2.5 mmol) in 10 mL ethyl alcohol was added 10 mL 5% sodium hydroxide solution. The reaction mixture was stirred for 2 hours at room temperature. The resulted solution was extracted with chloroform (3 × 30 mL), the combined organic layers were washed with water and dried over anhydrous sodium sulfate. After concentration the crude product was recrystallized from acetone to yield 0.68 g (87%) of **9** as a white solid, mp. 128 – 130 °C. ^{1}H-NMR ($CDCl_3$): 2.12 (s, 3H), 2.96 (s, 3H), 3.17 (t, 2H), 3.36 (t, 2H), 5.87 (b, 1H), 7,60 (q, 4H). IR (KBr) cm^{-1}: 3429, 1618, 1322, 757. MS m/e: 291 ([M+1]$^+$), 204, 115, 86. *Anal.* Calcd for $C_{11}H_{15}ClIN_2O_3S$: C, 45.44; H, 5.20; N, 9.83. Found C, 45.04; H, 5.20; N, 9.63.

N-2-(N'-ethyl-N'-methyl)ethyl 4-chlorobenzenesulfonamide 10: To a solution of imidazolium **3** (1.0 g, 2.5 mmol) in 20 mL dry ethyl alcohol was added 450 mg sodium borohydride. The reaction mixture was stirred for 3 hours at room temperature. water (30 ml) was added dropwise (caution: forming!) and continuously stirred until bubbling subsided, then the solution was extracted with chloroform (3 × 25 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and concentrated to yield 0.64 g (93%) of **10** as a white solid, mp. 43 – 44 °C. ^{1}H-NMR ($CDCl_3$): 0.98 (t, 3H), 2.06 (s, 3H), 2.38 (m, 4H), 2.99 (t, 2H), 5.21 (b, 1H), 7,54 (q, 4H). IR (KBr) cm^{-1}: 3432, 1631, 1322, 831, 753. MS m/e: 277 ([M+1]$^+$), 111, 72. *Anal.* Calcd for $C_{11}H_{17}ClIN_2O_2S$: C, 47.73; H, 6.19; N, 10.12. Found C, 47.56; H, 6.25; N, 10.35.

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