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A Convenient Synthesis of 1-Tosyl-3, 4-Dimethyl Imidazolium Salt and N,N,N′-Trisubstituted Ethylendiamine Derivatives

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ABSTRACT

1-Tosyl-3,4-dimethyl imidazolium iodide **3** was prepared by convenient cyclization, sulfonylation, and methylation from 4-methyl-2-imidazoline, which was obtained by the reaction of ethyl formate with 1,2-diaminopropane. Monofunctional carbon nucleophiles reacted with **3** to yield a series of N,N,N′-trisubstituted ethylendiamine derivatives.

Key Words: Synthesis; THF coenzyme model; N,N,N′-trisubstituted ethylendiamine; 1-tosyl-3,4-diamethyl-imidazolium.

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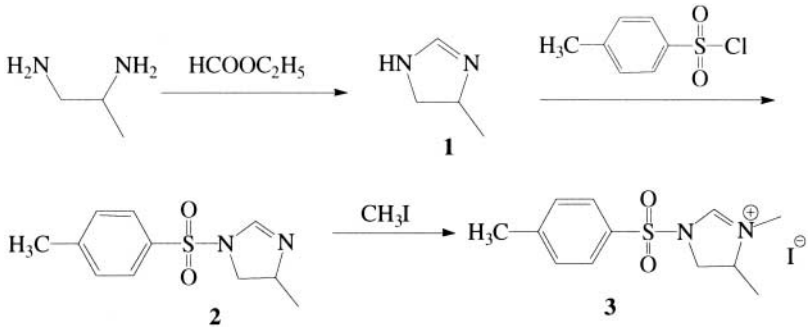
Tetrahydrofolate (THF) was responsible for transfer of one-carbon fragment in biological synthesis and metabolism.[1] Thus, the study on the THF coenzyme model may provide a valuable class of reagents for group transfer reactions for practical utility.[2,3] In order to investigate different types of models that would be capable of transferring substituted one-carbon unit, a series of 1-aryl-2,3-dimethyl-4,5-dihydroimidazolium iodides in our earlier research had been synthesized to improve their potential in one-carbon unit transfer reactions as the THF coenzyme model. One important approach was to adjust the basicity of N(1), C(2), and N(3) in the imidazolium by using different substituted groups.[4] However, the improvement was unobvious by adjusting different substituted groups of N(1) and N(3) in the imidazolium.[5] Consequently, we presumed that the reactions were affected by the steric hindrance and induced effect on C(2). A key approach was to adjust different substituted of N(1), C(2), and C(4) in the imidazolium. In addition, Pandit's group had reported two model compounds: 1-tosyl-3,4,4-trimethyl-imidazolinium iodide and 1-tosyl-3,4,4,5,5-pentamethyl-imidazolinium iodide. From their experiment results, it could be seen that 1-tosyl-3,4,4-trimethyl-imidazolinium iodide was more electrophilic than 1-tosyl-3,4,4,5,5-pentamethyl-imidazolinium iodide.[6] We extrapolated that if some methyls in imidazoline were reduced, the electrophilic ability would be improved. Although the most simple imidazoline (without methyl groups connected to carbons) was described in the literature,[7] it was difficult to prepare and not easy to handle due to its reactivity with carbon dioxide under atmospheric conditions. Hence, we chose 4-methyl imidazoline as a matrix and our new model, 1-tosyl-3, 4-dimethyl-imidazolinium iodide **3**, was synthesized.

Imidazolium iodide **3** was synthesized from 1,2-diaminopropane in three steps: (1) cyclization of 1,2-diaminopropane by ethyl formate in basic conditions produced 4-methyl imidazoline **1**; (2) sulfonylation of **1** by tosyl chloride under basic conditions obtained 1-tosyl-4-methyl imidazoline **2**; (3) further methylation of **2** by reflux with excess iodomethane in benzene synthesized imidazolium salt **3** in the yield of 81%. The synthesis process was shown in Sch. 1.

Furthermore, the structure of 1-tosyl-3, 4-dimethyl imidazolium iodide **3** had been determined by X-ray diffraction, the structure of which was shown in Fig. 1.

It was observed from the X-ray that the length of N2—C11 and N1—C11 were 1.272(8)/%A and 1.325(7)/%A; they were much shorter than standard single C—N bond [Lide (1962) pointed out that the standard single and doubled C—N bond lengths are 1.474 and 1.265/%A]. It suggested that the positive charge delocalized among N1—C11—N2, thus C11 had become the reaction point of nucleophilic reagents in the imidazoline ring.



Scheme 1.

In our current research, through a series of attempts towards different nucleophilic reagents,[8] model compound **3** was found to be more electrophilic. When 1-tosyl-3,4-dimethyl imidazolium iodide **3** was treated with a malononitrile, ethyl malonate, and nitromethane, the corresponding N,N,N′-trisubstituted 2-methyl-ethylenediamines **4**, **5**, and **6** were produced in the yield of 79–95%. These experiments were carried out by stirring in tetrahydrofuran and the reaction time depended on the nucleophilicity of carbon anion, generally from 1 to 5 h. When the mixture was cooled to 0°C, the products **4** and **5** were crystallized as white crystals and the product **6** was purified by column chromatography as an oil. Compared with our earlier results,[9,10] the model compound **3** proved to be more electrophilic under the same conditions. Some data was shown in Table 1.

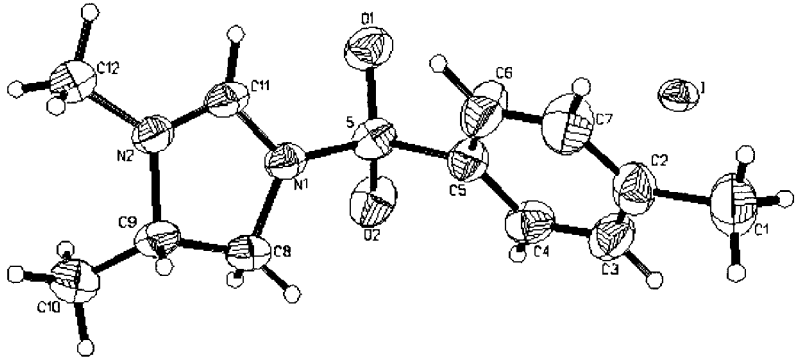
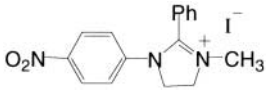
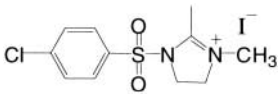
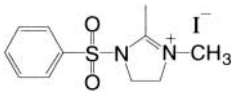
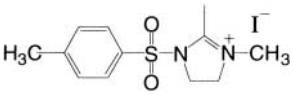
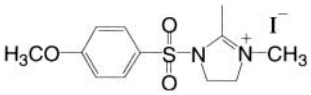
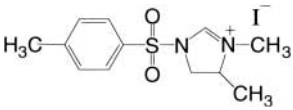


Figure 1. X-ray structure of 1-tosyl-3,4-dimethyl imidazolium iodide **3**.

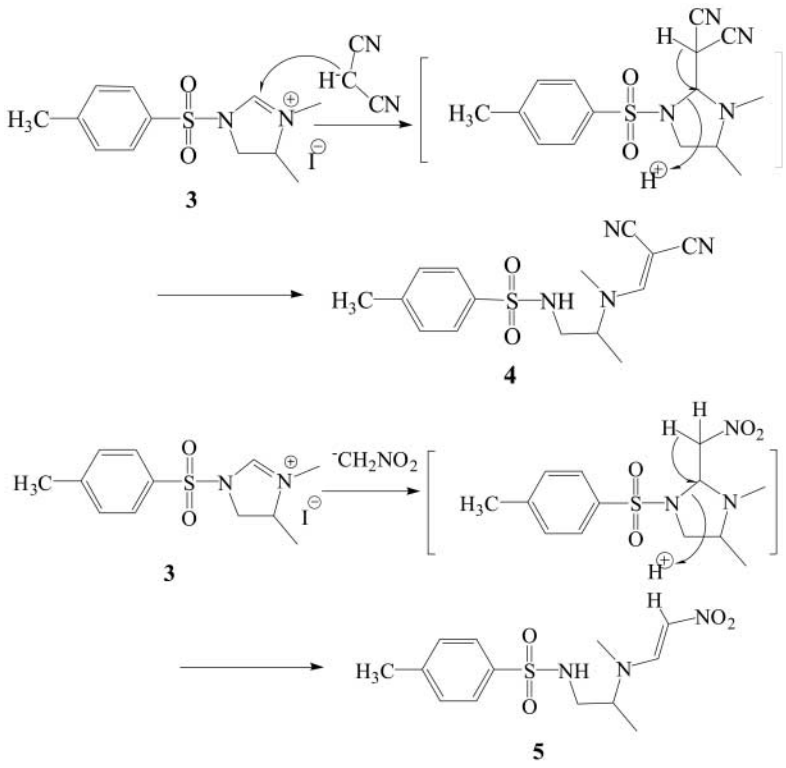
Table 1. Comparison of model compound **3** with the other models reported before.

Model compound	Reagent	Reaction time (h)	Yield (%)
	$CH_2(CN)_2$	overnight	85
	CH_3NO_2	2	59
	$CH_2(CN)_2$	4.5	82
	$CH_2(CN)_2$	—	77
	$CH_2(CN)_2$	—	78
	$CH_2(CN)_2$	—	60
	CH_3NO_2	overnight	92
	$CH_2(CN)_2$	2	89
	CH_3NO_2	1	95

[a]All reactions were performed in tetrahydrofuran.

We considered that a possible mechanism is that nucleophilic addition to the C═N double bond in the imidazolium forms an imidazolidine intermediate, which subsequently leads to ring-opened products **4** and **5**. The thermodynamically favored products were obtained from the imidazolidine intermediate through a ring-opening process (Sch. 2). But compound **6** was special, and we obtained a ring-locking process (Sch. 3).

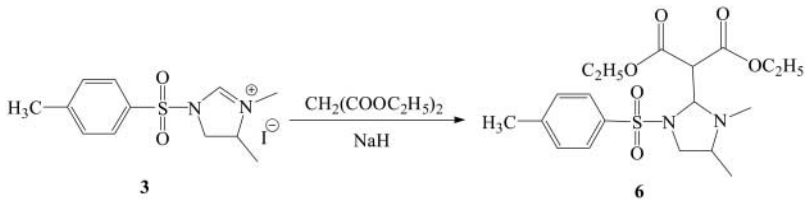
In summary, N,N,N′-trisubstituted 2-methyl-ethylenediamine derivatives **4**, **5**, and **6** were prepared by using a commercially available heterocyclic compound, 4-methyl-2-imidazoline. The approach should be wildly applicable for the preparation of other relevant N,N,N′-trisubstituted 2-methyl-ethylenediamine derivatives. Model compound **3** was treated with a series of aromatic amines and research is being continued in our group.



Scheme 2.

EXPERIMENTAL

Mass spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^{1}H and ^{13}C nmr were obtained on a JOELFX-60Q, Varian FT-80A or Bruker AC-P 300 MHz, with TMS as an internal standard. Combustion



Scheme 3.

analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. Infrared spectra were obtained on a Shimadzu IR-1700 spectrometer. The TLC were carried out on silica gel GF-254 $20 \times 20\,cm^2$ plate. Melting points were uncorrected. All reactions were performed under an inert atmosphere of nitrogen; all reagents and solvents were purified and dried as required.

4-Methyl imidazoline (1): Ethyl formate (14.8 g, 0.2 mmol) was added dropwise to 17.6 g (0.2 mmol) of 1,2-diaminopropane, the latter being cooled in ice about 2 h. After having stirred for 1 h at room temperature, the reaction mixture was heated and ethanol was distilled off. The resulting mixture was heated at 150°C–160°C for 2 h. Then cooling, the mixture was distilled under reduced pressure. Yield: 11.2 g (67%); boiling point (bp) 100–110°/15 mm; ^{1}H NMR ($CDCl_3$): 1.12 (d, 3 H), 3.08 (m, 1 H), 3.65 (m, 1 H), 3.84 (m, 1 H), 4.17 (s, 1 H), 6.96 (s, 1 H).

1-Tosyl-4-methyl imidazoline (2): 4-Methyl imidazoline 1 (8.4 g, 0.1 mol) was dissolved in 20 mL dry dichloromethane at 0°C, followed by the addition of triethyl amine (10.1 g, 0.1 mol). To this solution was added dropwise a solution of tosyl chloride (19.05 g, 0.1 mol) in 10 mL dichloromethane. The reaction mixture was stirred and warmed to room temperature in an additional 1.5 h. The resulted solution was washed with 5% sodium hydroxide solution (20 mL) and water (50 mL), and dried over anhydrous sodium sulfate. Evaporation of dichloromethane in vacuo gave a crude solid, while was recrystallized from anhydrous ethyl alcohol to yield 12.36 g (52%) of 2 as a white crystal, mp 53–55°C. ^{1}H NMR ($CDCl_3$): 1.15 (d, 3 H), 2.44 (s, 3 H), 2.97 (t, 1 H), 3.53 (t, 1 H), 4.22 (m, 1 H), 7.34 (t, 3 H), 7.71 (d, 2 H) IR (KBr) cm^{-1}: 3284, 1652 (υC=N), 1598, 1494, 1436, 1359, 1163 (υC=N). MS m/e: 237.2($[M\text{-}1]^+$), 207, 149, 91. Anal. calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found C, 55.27; H, 5.88; N, 11.69.

1-Tosyl-3,4-dimethyl imidazolium iodide (3): 1-Tosyl-4-methyl imidazoline 2 (2.38 g, 10 mmol) and iodomethane (1.9 mL, 30 mmol) were refluxed in 20 mL dry benzene for 2 h. A lot of solid was separated out. Then cooled to room temperature, a precipitate was collected by filtration and crystallized from ethyl alcohol to give 3.04 g (80%) of 3 as a white crystal. mp 175.2–176.7°C ^{1}H NMR ($CDCl_3$): 1.51 (d, 3 H), 2.46 (s, 3 H), 3.63 (s, 4 H), 4.33 (t, 1 H), 4.80 (s, 1 H), 7.45 (d, 2 H), 8.15 (d, 2 H) 9.72 (s, 1 H). IR (KBr) cm^{-1}: 3430, 1661 (υC=N), 1594, 1451, 1422, 1374, 1166 (υC=N). MS m/e: 253 ($[M\text{-}HI]^+$), 238, 155, 91. Anal. calcd. for $C_{12}H_{17}N_2O_2SI$: C, 37.90; H, 4.51; N, 7.37. Found C, 38.04; H, 4.59; N, 7.30.

N-Methyl-N-(2-dicyanovinyl)-N′-(*p*-toluenesulphonyl)-ethylenediamine (4): Sodium hydride (43 mg, 1.8 mmol) was added into a solution of

malononitrile (78 mg, 1.5 mmol) in 10 mL of dry tetrahydrofuran, which was cooled in an ice-water bath. The reaction mixture was stirred for 30 minutes, then the imidazolium 3 (380 mg, 1 mmol) was added and the mixture was allowed to warm to room temperature for 2 h. Then the solution was extracted with dichloromethane (3 × 30 mL), the combined organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of dichloromethane in vacuo gave a crude solid, which was recrystallized from anhydrous ethyl alcohol to yield 2.8 g (88%) of 4 as a white crystal, mp 179.1°C–180.4°C. ^{1}H NMR (CD_3COCD_3): 1.26 (d, 3 H), 2.42 (s, 3 H), 2.89 (s, 1 H), 3.12 (s, 4 H), 3.83 (s, 1 H), 7.25 (s, 1 H), 7.42 (d, 2 H), 7.74 (d, 2 H). IR (KBr) cm^{-1}: 3429 (m, NH), 2211 (s, CN), 1631, 1448, 1417, 1358, 1163 (υC=N). MS m/e: 318 ([M]$^+$), 238, 155, 91. Anal. calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found C, 56.39; H, 5.70; N, 17.59.

N-Methyl-N-(2-dicyanovinyl)-N′-(*p*-toluenesulphonyl)-ethylenediamine (5): Sodium hydride (43 mg, 1.8 mmol) was added into a solution of nitromethane (91.5 mg, 1.5 mmol) in 10 mL of dry tetrahydrofuran, which was cooled with an ice-water bath. The reaction mixture was stirred for 30 minutes, then the imidazolium 3 (380 mg, 1 mmol) was added and the mixture was allowed to warm to room temperature for 1 h, then the solution was extracted with dichloromethane (3 × 30 mL), the combined organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of dichloromethane, a crude solid was yielded by column chromatography, yield: 0.302 g (96%) of 5 as a white crystal, mp 136–138°C; ^{1}H NMR ($CDCl_3$): 1.22 (d, 3 H), 2.43 (s, 3 H), 2.74 (s, 3 H), 3.01 (m, 2 H), 3.68 (m, 1 H), 6.17 (s, 1 H), 6.68 (d, 1 H), 7.33 (d, 2 H), 7.56 (d, 2 H), 8.17 (d, 2 H). IR (KBr) cm^{-1}: 3430, 1661 (υC=N), 1594, 1451, 1422, 1374, 1166 (υC=N). MS m/e: 253 ([M-HI]$^+$), 238, 155, 91. Anal. calcd. for $C_{13}H_{19}N_3O_4S$: C, 49.84; H, 6.11; N, 13.41. Found C, 50.29; H, 6.29; N, 13.78.

1-Carbethoxy-2-[2′(4-methylbenzenesulphonyl)amine-1′-methyl]amino acrylic acid ethyl ester (6): Sodium hydride (43 mg, 1.8 mmol) was added into a solution of ethyl malonate (240 mg, 1.5 mmol) in 10 mL of dry tetrahydrofuran, which was cooled with an ice-water bath. The reaction mixture was stirred for 30 minutes, then the imidazolium 3 (380 mg, 1 mmol) was added and the mixture was allowed to warm to room temperature for 5 h. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, gradient chloroform, and methanol) of 6 as an oil, yield: 0.325 g (79%). ^{1}H NMR ($CDCl_3$): 1.14 (m, 9 H), 2.36 (s, 3 H), 2.61 (s, 3 H), 2.92 (d, 2 H), 3.50 (m, 1 H), 4.11 (m, 5 H), 7.23 (d, 2 H), 7.68 (d, 2 H); IR (KBr) cm^{-1}: 3205(m), 1680(m), 1650, 1417, 1375, 1150 (υC=N); MS m/e: 355, 281, 267, 253, 225, 207, 155, 91, 73.

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Supporting information available: X-ray data for model compound **3** (CIF).

REFERENCES

1. Blakley, R.L., Benkovic, S.J, Eds. *Folates and Pteridines*, Vol. 1, Wiley: New York, 1984; Vol. 2, John Wiley and Sons, New York, 1985.
2. Anderson, M.W.; Jones, R.C. Nucleophilic addition to 4,5-dihydroimidazoles: a ketone synthesis via tetrahydrofolate coenzyme models. J. Chem. Soc. Perkin. Trans. I. **1986**, 1995.
3. Pandit, U.K. Models of biological systems and biological processes. Pure Appl. Chem. **1994**, *66*, 759.
4. Xia, C.Z.; Wang, H.X.; Zhao, B.J.; Chen, J.X.; Kang, C.M.; Ni, Y.P.; Zhou, P.W. A convenient synthesis of imidazolium salts and trisubstituted ethylenediamine derivatives. Synth. Commun. **2002**, *32* (9), 1447–1455.
5. Xia, C.Z.; Zhou, P.W.; Ding, J.F. Tetrahydrofolate coenzyme models I. Synthesis of 1-methyl-2-phenyl-3-aryl imidazolinium iodide and benzylidyne (phenyl-substituted one carbon unit) transfer reactions. Chin. J. Chem. (Eng. Ed.). **1990**, *8* (4), 333.
6. Bieraugel, H.; Plemp, R.; Hiemstra, H.C.; Pandit, U.K. Synthesis and carbon transfer reactions of N^5,N^{10}-methenyl and N^5,N^{10}-methylenetetrahydrofolate models. Tetrahedron **1983**, *39* (23), 3971–3979.
7. Suzuki, H.; Ohashi, M.; Itoh, K.; Matsuda, I.; Ushi, Y. Reaction of group IV organometallic compounds. XXXII Modified synthesis of imidazolidines with *N*,*N*′-bis(trimethylsilyl)-1,2-diamines. Bull. Chem. Soc. Jpn. **1975**, *48*, 1922.
8. Xia, C.Z.; Wang, H.X.; Zhou, P.W.; Ding, J.F. Synthesis and carbon transfer reactions of 1,2-dimethyl-3-arylsulfonyl (aryl = p-tolyl, phenyl)-Δ^2-imidazolinium iodide. Chin. Chem. Lett. (Eng. Ed.). **1992**, *3*, 407.
9. Xia, C.Z.; Tang, Y.Q.; Zhou, P.W. Nucleophilic addition to 3-methyl-1-(4-nitrophenyl)-2-phenyl-4,5-dihydroimidazolium iodide. J. Heterocyclic. Chem. **2000**, *37*, 1329–1331.

10. Xia, C.Z.; Chen, J.X.; Wang, H.X.; Kang, C.M.; Zhao, B.J.; Ni, Y.P.; Zhou, P.W. Nucleophilic addition to 1,2-dimethyl-3-arylsulfonyl-4,5-dihydroimidazolium iodides. Synth. Commun. **2002**, *32* (19), 2979–2984.

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