Nucleophilic Addition to 3-Methyl-1-(4-nitrophenyl)-2-phenyl-4,5-dihydroimidazolium Iodide

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Reactions of the 1,2-diaryl 4,5-dihydroimidazolium, represented by 3-methyl-1-(4-nitrophenyl)-2-phenyl-4,5-dihydroimidazolium iodide **1**, with ethylenediamine afforded a benzylidyne unit transferred product, 2-phenyl-2-imidazoline **2**; a ring-opened adduct **4** was produced when excess ethylenediamine was used. Reactions of **1** with hydroxylamine, malononitrile, and nitromethane anions produced ring-opened products, **5**, **7**, and **8** respectively.

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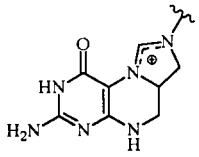
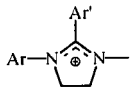
1,2,3-Trisubstituted 4,5-dihydroimidazolium salts possess a unique resonance cation center in the five-member imidazolium ring, therefore, nucleophilic addition reactions related with this structure are expected. Based on the analogy of this structure feature with that of coenzyme N (5), N (10)-methenyl tetrahydrofolic acid, which promotes one-carbon unit transfer at the oxidation level of formate [1], these imidazolium salts have been used to mimic its one-carbon unit transfer function. 3-Methyl-1-



N (5), N (10)-Methenyl tetrahydrofolate

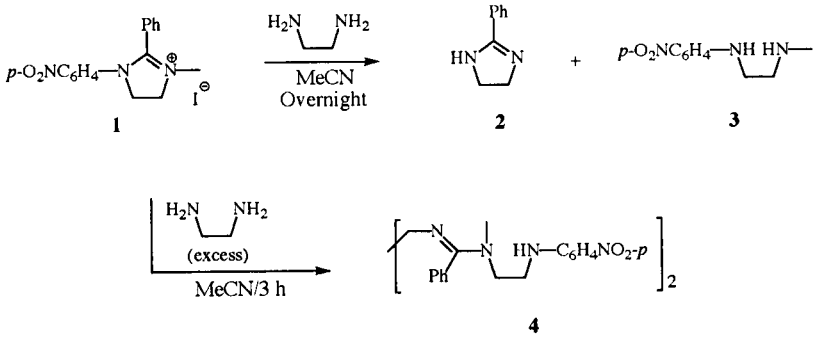


Trisubstituted imidazolium

tolysulfonyl (or acetyl) 4,5-dihydroimidazolium iodides have been employed as vehicles for investigating functionalized one-carbon unit transfer reactions, strategy evolution in alkaloid synthesis, and the mechanistic aspects of thymidylate synthase and methionine synthase enzymatic reactions [2]. Nucleophilic addition of 1-benzyl (or aryl)-3-methyl-4,5-dihydroimidazolium salts with Grignard reagents was proved to be useful in the transfer of C (2) functionalized one-carbon unit to nucleophiles [3]. A series of 1-aryl-3-methyl-2-phenyl-4,5-dihydroimidazolium iodides have been investigated concerning their nucleophilic addition and one-carbon unit transfer reactions [4, 5]. To optimize their potential in one-carbon unit transfer reactions as the coenzyme model, one key approach is to differentiate the basicity of N (1) and N (3) in the imidazolium by using different substitute groups. Compared with other related derivatives with different 1-aryl groups, 3-methyl-1-(4-nitrophenyl)-2-phenyl-4,5-dihydroimidazolium iodide **1** has been found to be more electrophilic in our early research [5]. The electrophilic reactivity of this chosen model compound was examined toward different nucleophilic reagents. Its reactions with one equivalent of ethylenediamine transferred a benzylidyne group to form 2-phenyl-2-imidazoline **2**, as a reaction which mimics the one-carbon transfer function of the N (5), N (10)-methenyl tetrahydrofolate. An adduct **4** was produced when excess ethylenediamine was used. Reactions with other C/N nucleophiles (such as hydroxylamine, nitromethane and malononitrile anions) afforded ring-opened products **5**, **7**, and **8** respectively.

Reactions of compound **1** with ethylenediamine are shown in Scheme I. 2-Phenyl-2-imidazoline hydroiodide was collected which was neutralized to obtain 2-phenyl-2-imidazoline **2**, when **1** reacted with one equivalent of ethylenediamine at room temperature. *N*-Methyl-*N'*-(4-

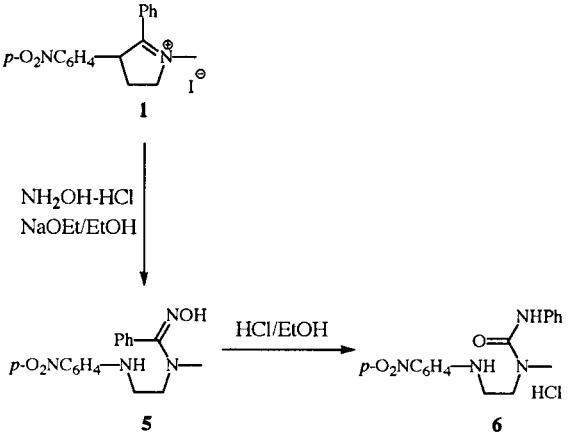
Scheme 1



nitrophenyl)ethylenediamine **3** was also separated and identified as the leftover part of the one-carbon unit transfer reaction. The formation of **2** and **3** may be explained by an intramolecular addition-elimination mechanism through a corresponding aminolyzed intermediate of the imidazolium **1**. Interestingly, when excess ethylenediamine was used, adduct **4** was a main product. The formation of **4** was through the aminolysis of two equivalents of imidazolium **1** with one equivalent of ethylenediamine. Aminolysis of related imidazolium salts with primary monoamines, which led to ring-opened aminolyzed products, was reported by Perillo [4]. Reactions of **1** with aliphatic diamines that have a longer methylene chain between two amino groups, such as 1,3-diaminopropane, hexamethylenediamine, were also attempted, but were not successful in our hands.

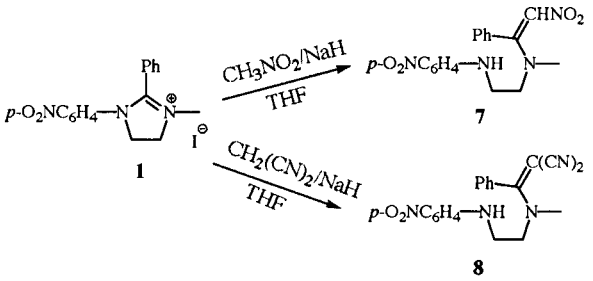
The imidazolium **1** also reacted with hydroxylamine (Scheme II) and a ring-opened product **5** was separated and identified. The amidoximic acid **5** is an acyclic aminolyzed product. This ring-opening process may be explained again by an addition and subsequent elimination mechanism, which is similar to the addition-elimination mechanism of nucleophiles to normal acyclic carbon-hetero multiple bonds. The amidoximic acid **5** was easily transformed to an urea derivative, *N'*-phenyl-*N*-methyl-*N*-[2-(4-nitrophenylamino)ethyl] urea hydrochloride **6** through a Backmann rearrangement, when dry HCl was bubbled into its ethanol solution.This ring-opened reaction

Scheme 2



pattern was also found in the reactions of **1** with carbanion nucleophiles, such as anions formed from the reaction of sodium hydride with nitromethane and malononitrile respectively (Scheme III). No tetrahydroimidazole isomers were found in our hand, as both **7** and **8** were ring-opened products. This process may be rationalized by the stability of a conjugated system in ring-opened products **7** and **8**; on the other hand, the steric hindrance of the phenyl ring prevents the formation of the tetrahydroimidazole intermediate at the end of the process. These factors favor the formation of a ring-opened product rather than the corresponding tetrahydroimidazole intermediate in the reaction. In other related research, a mixture of tetrahydroimidazole intermediates and ring-opened isomers were often found when reacted with similar nucleophilies [6].

Scheme 3



In summary, the nucleophilic addition to 3-methyl-1-(4-nitrophenyl)-2-phenyl-4,5-dihydroimidazolium iodide **1**, yielded two types of products: either ring-opened products, **4**, **5**, **7**, and **8**, or one-carbon unit transferred products, **2**. We continue to explore the chemistry of 1,2,3-trisubstituted 4,5-dihydroimidazolium salts and will report on our progress in due course.

EXPERIMENTAL

Mass spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^1H and ^{13}C nmr were obtained on a JOEL FX-60Q, Varian FT-80A or Bruker AC-P 300 MHz, with TMS as an internal standard. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. Infrared spectra were obtained on a Shimadzu IR-1700 spectrometer. Melting points were uncorrected. All reactions were performed under an inert atmosphere of nitrogen, all reagents and solvents were purified and dried as required. The imidazolium **1** was prepared as previously reported [5].

2-Phenyl-2-imidazoline (**2**) and *N*-Methyl-*N'*-(4-nitrophenyl)-ethylenediamine (**3**).

To a stirred solution of the imidazolium **1** (820.0 mg, 2.0 mmol) in 20 ml of dry acetonitrile, ethylenediamine (130 µl, 2.0 mmol) was added. The reaction mixture was maintained at room temperature overnight. A white precipitate was observed and collected by vacuum filtration, and recrystallized from acetonitrile to yield 300 mg 2-phenyl-2-imidazole hydroiodide. ^1H nmr (perdeuteriodimethyl sulfoxide): δ 3.79 (s, 4H, CH_2CH_2), 5.96 (br, 2H, NH, exchangeable), 7.59-7.79 (m, 5H, Ph). This salt was dissolved in 2 ml acetonitrile, and 10 ml of 2 *M* sodium hydroxide solution was added. The mixture was stirred for 3 hours at room temperature. The emulsion was extracted by chloroform (3 × 10 ml), the combined organic layers were washed with water (15 ml), and dried over anhydrous sodium sulfate. 2-Phenylimidazoline (150 mg, 52%) was obtained as white needles after evaporation, mp 101-102 °C (acetonitrile), lit [7] mp 100-101 °C. ^1H nmr (deuteriochloroform): δ 3.89

(s, 4H, CH_2CH_2), 5.19 (b, 1H, NH), 7.46-7.78 (m, 5H, Ph). The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, gradient benzene and ethanol) to provide 241 mg (62%) of **3** as yellow crystals, mp 83-84 °C, lit [8] mp 84 °C. ^{1}H nmr (deuteriochloroform): δ 1.37 (1H, b, NH, exchangeable), 2.43 (s, 3H, CH_3), 2.92-3.23 (m, 4H, CH_2CH_2), 5.23 (b, 1H, NH, exchangeable), 6.51 (d, 2H, J = 8.6 Hz) 8.07 (d, 2H, J = 8.6 Hz).

N-Methyl-*N*-[2-(4-nitrophenylamino)ethyl]-*N'*-{2-[*N'*-2-(4-nitrophenylamino)ethyl-*N'*-methyl]benzamidoylaminoethyl}-benzamidine (**4**).

To a stirred solution of **1** (820.0 mg, 2.0 mmol) in 5 ml acetonitrile at room temperature was added 1.5 ml ethylenediamine. A yellow precipitate was observed after several minutes, the suspension was stirred for an additional 3 hours. The yellow solid was collected by vacuum filtration, washed by ethanol, and dried to yield 283 mg of **4** (46%) as a yellowish powder, mp 256 °C dec; ^{1}H nmr (trifloroacetic acid-*d*): δ 3.05 (b, 2H, NH, exchangeable), 3.35 (s, 6H, NCH_3), 3.43 (s, 4H, CH_2CH_2), 3.75 (s, 8H, CH_2CH_2), 6.95 (d, 4H, J = 8.6 Hz), 7.20–7.60 (m, 10H, Ph), 8.25 (d, 2H, J = 8.6 Hz); ir (potassium bromide): 3346 (s, NH), 1612 (s, C=N) cm^{-1}.

Anal. Calcd. for $C_{34}H_{38}N_8O_4$: C, 65.57; H, 6.15; N, 18.00. Found: C, 65.27; H, 6.38; N, 18.38.

N'-Hydroxyl-*N*-methyl-*N*-[2-(4-nitrophenylamino)ethyl]-benzamidine (**5**).

A sodium ethoxide solution (5.0 ml, 0.26 *M*) in ethanol was added dropwise into a suspension of hydroxylamine hydrochloride (410.0 mg, 6.0 mmol) in absolute ethanol (10 ml) at 0 °C, and stirred for 0.5 hour. The imidazolium **1** (820.0 mg, 2.0 mmol) was added into this solution in several portions. The reaction mixture was heated to reflux for 2 hours then the solvent was removed by evaporation. The residue was purified by column chromatography (silica gel, gradient benzene and ethanol) to obtain 360 mg (61%) of **5** as yellow needles, mp 180-182 °C; ^{1}H nmr (perdeuteriodimethyl sulfoxide): δ 2.73 (s, 3H, NCH_3), 3.15 (s, 4H, CH_2CH_2), 3.34 (b, 1H, NH), 6.47 (d, 2H, J = 8.6 Hz), 7.33 (s, 5H, Ph), 7.89 (d, 2H, J = 8.6 Hz), 9.08 (b, 1H, OH); ir (potassium bromide): 3345 (s, NH), 3126 (s, OH), 1537, 1631 (C=N) cm^{-1}; EIMS: m/z 314 (M^+), 296 ($C_{16}H_{16}N_4O_2$), 236, 157, 77.

Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82. Found: C, 60.85; H, 5.72; N, 18.13.

N'-Phenyl-*N*-methyl-*N*-[2-(4-nitrophenylamino)ethyl]urea Hydrochloride (**6**).

Dry hydrochloride gas was slowly bubbled into a solution of **5** (200.0 mg, 0.60 mmol) in absolute ethanol (10 ml) for 10 minutes. A precipitate was observed and the suspension was stirred for an additional 2 hours. The precipitate was collected by vacuum filtration and recrystallized with ethanol to yield 590 mg (90%) of **6** as white crystals, mp 160–162 °C; ^{1}H nmr (perdeuteriodimethyl sulfoxide): δ 3.16 (s, 3H, NCH_3), 3.39 (b, 2H, exchangeable), 3.39–3.53 (m, 4H, CH_2CH_2), 6.56 (d, 2H, J = 8.6 Hz), 7.39 (s, 5H, Ph), 7.92 (d, 2H, J = 8.6 Hz); ir (potassium bromide): 3315 (s, NH), 1601 (C=O) cm^{-1}; EIMS: m/z, 314 (M^+), 296 ($C_{16}H_{16}N_4O_2$), 236, 157, 77.

Anal. Calcd. for $C_{16}H_{19}N_4O_3Cl$: C, 54.80; H, 5.50; N, 16.00. Found: C, 54.70; H, 5.60; N, 16.20.

N-Methyl-*N*-(1-phenyl-2-nitrovinyl)-*N'*-(4-nitrophenyl)ethylenediamine (**7**).

Sodium hydride (120.0 mg, 5.0 mmol) was added into a solution of nitromethane (0.270 ml, 5.0 mmol) in 10 ml of dry tetrahydrofuran, which was cooled to 0 °C, and the reaction mixture was stirred for 20 minutes. A solution of the imidazolium **1** (1.640 g, 4.0 mmol) in 10 ml dry tetrahydrofuran was added dropwise, then the mixture was stirred at 0 °C for 30 minutes, and allowed to warm to room temperature in 2 hours. The solvent was removed by evaporation. Flash chromatography (silica gel, gradient benzene and acetone) of the residue oil and further recrystallization with acetone yielded 800 mg (59%) of **7** as yellow crystals, mp 163-165 °C; ^{1}H nmr (perdeuteriodimethyl sulfoxide): δ 3.06 (s, 3H, NCH_3), 3.31 (s, 5H, N*H*, CH_2CH_2), 6.39 (d, 2H, J = 8.6 Hz), 6.87 (s, 1H, $CHNO_2$), 7.39 (m, 5H, Ph), 7.90 (d, 2H, J = 8.6 Hz); ir (potassium bromide): 3305 (s, NH), 1537, 1351 (NO_2) cm^{-1}; EIMS: m/z, 342 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.50; H, 5.46; N, 15.99.

N-Methyl-*N*-(1-phenyl-2-dicyanovinyl)-*N'*-(4-nitrophenyl)-ethylenediamine (**8**).

Sodium hydride (60.0 mg, 2.5 mmol) was added into a solution of malononitrile (166.2 mg, 2.5 mmol) in 15 ml of dry tetrahydrofuran, which was cooled with an ice-water bath. The reaction mixture was stirred for 20 minutes, then the imidazolium **1** (820.0 mg, 2.0 mmol) was added in one portion and the mixture was allowed to warm to room temperature overnight. The solvent was removed by evaporation. Flash chromatography (silica gel, gradient benzene and acetone) of the residue oil and further recrystallization with acetone yielded 590 mg (85%) of **8** as yellow crystals, mp. 205-207 °C; ^{1}H nmr (perdeuteriodimethyl sulfoxide): δ 3.18 (br, 1H, NH), 3.32 (s, 3H, CH_3), 3.54 (m, 4H, CH_2CH_2), 6.40 (d, 2H, J = 8.6 Hz), 7.30 (m, 5H, Ph), 7.90 (d, 2H, J = 8.6 Hz); ir (potassium bromide): 3339 (s, NH), 2206 (s, CN), 1512, 1347 (NO_2) cm^{-1}; EIMS: m/z, 347 (M^+).

Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.43; H, 4.54; N, 20.18.

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REFERENCES AND NOTES

[1] R. G. Matthews and J. T. Drummond, *Chem. Rev.*, **90**, 1275 (1990).

[2] U. K. Pandit, *Pure & Appl. Chem.*, **66**, 759 (1994).

[3] M. W. Anderson and R. C. Jones, *J. Chem. Soc., Perkin. Trans. I*, 1995 (1986).

[4] A. Salerno, V. Ceriani and I. A. Perillo, *J. Heterocyclic Chem.*, **34**, 709 (1997).

[5] C. Z. Xia, P. W. Zhou and J. F. Ding, *Chin. J. Chem. (Eng. Ed.)*, 333 (1990).

[6] C. Z. Xia, H. X. Wang, P. W. Zhou and J. F. Ding, *Chin. Chem. Lett. (Eng. Ed)*, **3**, 407 (1992).

[7] S. A. Okecha and F. Stansfield, *J. Chem. Soc., Perkin Trans.1*, 1811 (1977).

[8] I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans.1*, 894 (1975)