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REACTIONS OF 1,2-DIMETHYL-3-ARYLSULFONYL-4,5-DIHYDRO-3*H*-IMIDAZOL-1-IUM IODIDES WITH BIFUNCTIONAL NUCLEOPHILES

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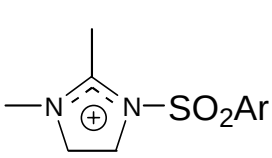
Abstract - The reaction of imidazolium salts, represented by 1,2-dimethyl-3-arylsulfonyl-4,5-dihydro-3*H*-imidazol-1-ium iodides (**1** – **6**), with two types of bifunctional nucleophiles: *ortho*-substituted anilines and ethylenediamine was studied. Their reactions with 1,2-phenylenediamine, 2-aminophenol, and 2-aminothiophenol resulted in exclusively one-carbon unit transfer products: 2-methylbenzoxazole (**7**), 2-methylbenzimidazole (**8**), and 2-methylbenzothiazole (**9**) respectively, which mimics the one-carbon unit transfer reaction of *N* (5), *N* (10)-methenyltetrahydrofolate coenzyme. The reaction of imidazolium (**3**, **4**, and **6)** with ethylenediamine exclusively produced the bis-adducts of two equivalents of imidazolium iodides with one equivalent of ethylenediamine: *N*-methyl-*N*-(2-arylsulfonylamino)ethyl-*N*'-[2-(*N*'-2-arylsulfonylaminoethyl-*N*'-methyl)ethylideneamino]ethylacetamidine bishydroiodides (**10** – **12**) respectively. These different behaviors were explained with addition reaction mechanism.

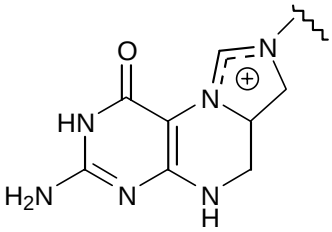
1,2-Dimethyl-3-arylsulfonyl-4,5-dihydroimidazolium salts have a unique resonance C (2) cation center between *N* (1) and *N* (3) in their imidazolium ring (Figure 1). Encouraged by our previous results on this subject with 2,3-diarylimidazolium salts,[1, 2] we reasoned that the resonance C (2) cation in arylsulfonylimidazolum salts (**1** – **6**) has higher susceptibility to nucleophilic attack than 2,3-diaryl-imidazolium salts, and can potentially be used to transfer one-carbon units to nucleophilic acceptors as vehicles to mimic *N* (5), *N* (10)-methenyltetrahydrofolate coenzyme.[3] Tetrahydrofolate coenzymes in biological systems promote biochemical transfer of one carbon unit at the oxidation level of formate and

formaldehyde. By mimicking the natural cofactor, some dihydroimidazolium salts, in which the transferable one carbon unit is linked to *N* (1), *N* (3) with different electronic properties, and related derivatives have been studied.[4] In our continuing investigation of the nucleophilic addition and one-carbon unit transfer reaction of 2,3-diarylimidazolium and 1,2-dimethyl-3-arylsulfonylimidazolium salts, we have found that two types of bifunctional nucleophiles reacted with 1,2-dimethyl-3-arylsulfonylimidazolium salts (**1** – **6**), and formed either the one-carbon unit transferred products or bis-adducts. The first series nucleophiles were *ortho*-substituted anilines: 1,2-phenylenediamine, 2-aminophenol, and 2-aminothiophenol. Both nucleophilic groups in all these reagents have structurally fixed orientations, due to their *ortho* relation on the phenyl ring. The second bifunctional nucleophiles examined were aliphatic ethylenediamine, which has a flexible ethylene group between the nucleophilic amino groups, instead of a phenyl ring.

Figure 1



N (3)-Arylsulfonylimidazolium



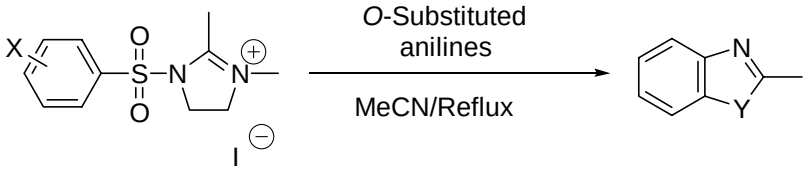
N (5), *N* (10)-Methenyl-tetrahydrofolate

The behavior of the imidazolium salts (**1** – **6**) with *ortho*-substituted anilines could be generalized as an one-carbon unit transfer reaction (Scheme 1), which mimics the one-carbon unit transfer function of *N* (5), *N* (10)-methenyltetrahydrofolate coenzyme.[3, 4] After the imidazolium salts (**1** – **6**) were individually refluxed with one of three *ortho*-substituted anilines in acetonitrile for several hours, yellowish solids crystallized from the reaction medium as the mixture cooled to room temperature. The structure of 2-methylbenzoxazole (**7**), 2-methylbenzimidazole (**8**), or 2-methylbenzothiazole (**9**) was easily assigned by their spectroscopic data and comparison with authentic samples.

Compared with their reactions with *ortho*-substituted anilines, reactions of the imidazolium salts with ethylenediamine produced some interesting results (Scheme 2). When the imidazolium salts (**3**), (**4**), or (**6**) were treated with ethylenediamine in acetonitrile, yellowish solids precipitated immediately at room temperature and the reactions were finished in less than 2 hours. The solubility of these products in organic solvents was generally very poor, due to their polar structure and bishydroiodide salt nature. This

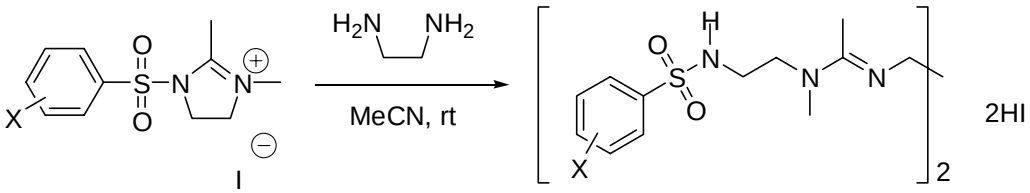
was in accordance with our previous results of the reaction of 4,5-dihydro-1-methyl-3-(4-nitrophenyl)-2-phenyl-1*H*-imidazolium iodide with ethylenediamine. Their structures were assigned based on their elemental analysis and spectroscopic data.

Scheme 1



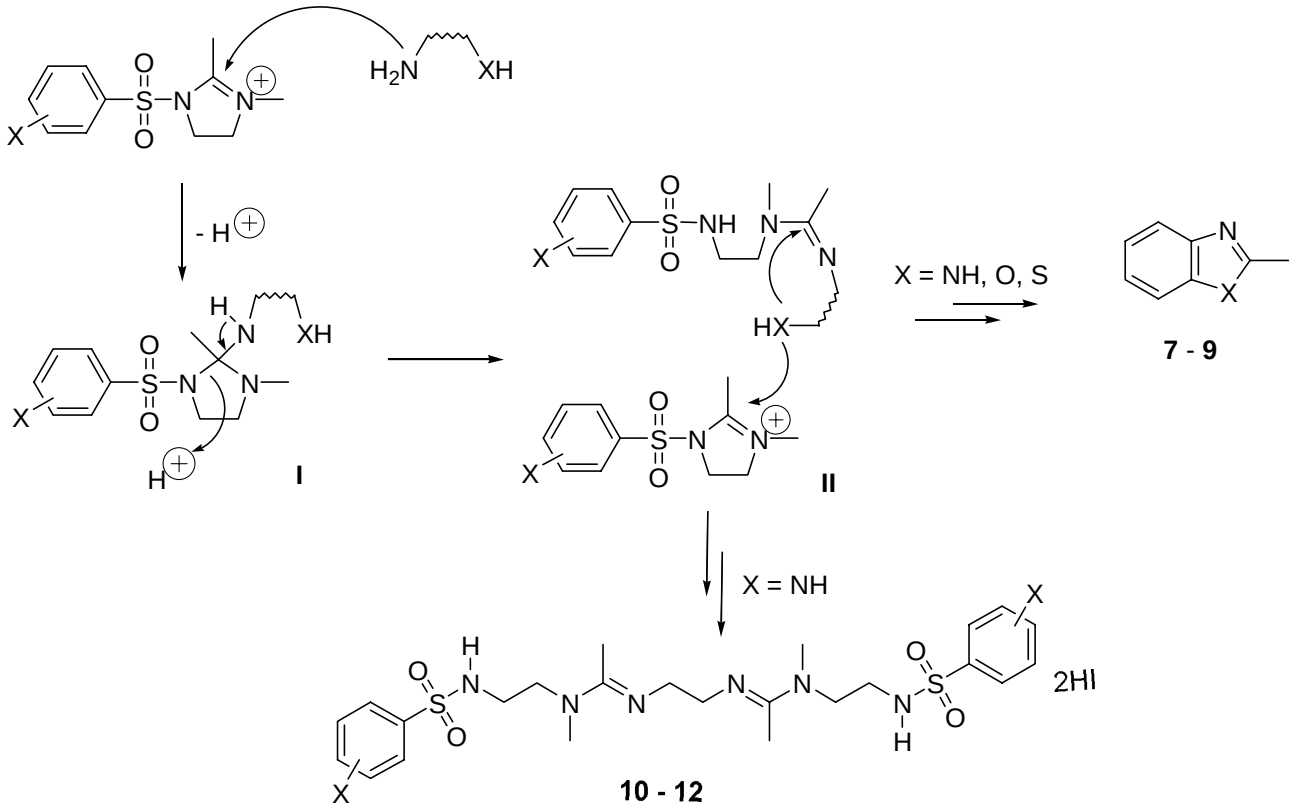
X	Substrate	Reagent	Product, Y	Yield (%)
H	**1**	1,2-phenylenediamine	**7**, N	60
		2-aminophenol	**8**, O	75
4-Me	**2**	1,2-phenylenediamine	**7**, N	63
		2-aminophenol	**8**, O	75
4-Cl	**3**	1,2-phenylenediamine	**7**, N	82
		2-aminophenol	**8**, O	64
4-OMe	**4**	1,2-phenylenediamine	**7**, N	73
		2-aminophenol	**8**, O	90
		2-aminothiophenol	**9**, S	88
4-NO_2	**5**	1,2-phenylenediamine	**7**, N	80
		2-aminophenol	**8**, O	72
3-NO_2	**6**	1,2-phenylenediamine	**7**, N	75
		2-aminophenol	**8**, O	60

Scheme 2



X	Substrate	Product	Yield (%)
4-Cl	**3**	**10**	76
4-OMe	**4**	**11**	70
3-NO_2	**6**	**12**	74

Figure 2



Reactions of the imidazolium salts with aliphatic ethylenediamine were conducted at room temperature and took shorter times to finish, which is easier than their reactions with aromatic amines. No meaningful effect of the different substituents on the phenylsulfonyl group was observed regarding the reactivity of the imidazolium salts to both kind of amino-nucleophiles. Through nucleophilic addition to the C=N double bond in the imidazolium ring by an amine group, a tetrahydroimidazolidine intermediate (**I**) was formed, which subsequently offered a thermodynamically favored intermediate (**II**). This ring-opening process 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, which would be a kinetically controlled process governed by protonation of the more basic nitrogen.[5, 6] Reactions of the imidazolium salts with monofunctionallized nucleophiles stopped at this stage, as previously demonstrated by their reaction with aromatic amines.[7] With bifunctional nucleophiles such as 1,2-phenylenediamine, 2-aminophenol, and 2-aminothiophenol, however, the reaction led to one-carbon unit transferred products (**7** – **9**).[5] The second nucleophilic group (amino, hydroxy, or mercapto) attacked the C=N double bond through an intramolecular nucleophilic addition, and followed by an elimination to kick off the leaving group. The orientation of the second nucleophilic groups on the phenyl ring favored this ring closure step. These

reactions exclusively produced one-carbon unit transferred products (**7** – **9**). For ethylenediamine, the orientation of the second amino group was not fixed as in the phenyl ring, and it also has stronger nucleophilicity, an intermolecular nucleophilic addition occurred to the intermediate (**II**). The initial nucleophilic addition and ring-opening reaction was repeated, which resulted in a reaction between two equivalents of imidazolium salts and one equivalent of ethylenediamine.

In summary, 3-arylsulfonyl-4,5-dihydro-1,2-dimethyl-1*H*-imidazolium iodides (**1** – **6**) reacted with *ortho*-substituted anilines such as 1,2-phenylenediamine, 2-aminophenol, and 2-aminothiophenol resulted in exclusively one-carbon unit transferred products: 2-methylbenzoxazole (**7**), 2-methylbenzimidazole (**8**), or 2-methylbenzothiazole (**9**), respectively. These reactions mimic the one-carbon unit transfer function of tetrahydrofolate coenzymes. The reactions of the imidazolium salts (**3**, **4**, and **6**) with ethylenediamine exclusively produced the bis-adducts of two equivalents imidazolium salts with one equivalent of ethylenediamine: *N*-methyl-*N*-(2-arylsulfonylamino)ethyl-*N*'-[2-(*N*'-2-arylsulfonylaminoethyl-*N*'-methyl)ethylideneamino]ethylacetamidine bishydroiodides (**10** – **12**), respectively. These different behaviors could be explained with an addition reaction mechanism.

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, with TMS as an internal standard. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 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. The imidazolium (**1** – **6**) were prepared according to our published procedures.[8]

General procedure for the reaction of 1,2-dimethyl-3-arylsulfonyl-4,5-dihydro-3*H*-imidazol-1-ium iodides (1 – 6) with 1,2-phenylenediamine (2-aminophenol, and 2-aminothiophenol) The formation of 2-methylbenzimidazole (**7**) by the reaction of the imidazolium (**6**) with 1,2-phenyldiamine as an example: To a solution of the imidazolium (**6)** (1.0 g, 2.5 mmol) in 5 mL of dry acetonitrile was added 1,2-phenylenediamine (295.0 mg, 2.75 mmol). The reaction mixture was heated to reflux for 4 h. After cooled to rt, a solid was crystallized out. It was collected by vacuum filtration, dried, and recrystallized from water to yield 270 mg (82%) of **7** as a white solid, mp 176 –178 °C, (lit., [9] mp 176 – 177 °C). Its ^{1}H NMR and IR spectra were identical with an authentic sample. 2-Methylbenzoxazole (**8**) and 2-

methylbenzothiazole (**9**) were also separated from the corresponding reactions and they were identical with authentic samples.[9]

General procedure for the reaction of 1,2-dimethyl-3-arylsulfonyl-4,5-dihydro-3*H*-imidazol-1-ium iodides (3, 4, and 6) with ethylenediamine: *N*-Methyl-*N*-[2-(4-methoxyphenylsulfonylamino)ethyl]-*N*'-{2-[*N*'-2-(4-methoxyphenylsulfonylaminoethyl)-*N*'-methyl]ethylideneamino}ethylacetamidine bishydroiodide (11) as an example To a solution of the imidazolium (**4)** (800.0 mg, 2.02 mmol) in 10 mL acetonitrile was added ethylenediamine (0.10 mL, 1.50 mmol). The reaction mixture was stirred for 2 h at rt and a precipitate was observed. The precipitate was collected by vacuum filtration, washed with 5 mL of acetonitrile, dried, and recrystallized from acetonitrile to offer 600 mg (70%) of **11** as a white powder, mp 179 – 181 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 2.37 (s, 6H, 2CH_3), 3.05 (s, 6H, 2NCH_3), 2.71 – 3.80 (m, 12H, 3CH_2CH_2), 3.33 (br, 2H, 2NH) 3.84 (s, 6H, 2OCH_3), 7.00 - 8.01 (q, *J* = 8.6 Hz, 8H, aromatic), 8.06 (br, 2H, 2SO_2NH); IR (KBr): ν 3433, 3219 (NH), 3010 (aromatic CH), 1642 (CN), 1598 (aromatic C=C), 1323, 1152 (SO_2), 1269 (C-O), 834 (aromatic CH) cm^{-1}; MS: *m*/*z* 428, 415, 371, 310, 171. *Anal*. Calcd for $C_{26}H_{42}N_6O_6I_2S_2$: C, 36.63; H, 4.97; N, 9.86. Found: C, 36.60; H, 4.93; N, 9.88.

***N*-Methyl-*N*-[2-(4-chlorophenylsulfonylamino)ethyl]-*N*'-{2-[*N*'-2-(4-chlorophenylsulfonylaminoethyl)-*N*'-methyl]ethylideneamino}ethylacetamidine bishydroiodide (10)** This compound was obtained as a white powder, yield 76%, and mp 215 – 216 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 2.39 (s, 6H, 2CH_3), 3.07 (m, 10H, NCH_2CH_2N, NCH_3), 3.64 (s, 8H, 2NCH_2CH_2N), 7.78 - 8.30 (m, 8H, aromatic), 8.47 (br, 4H, NH); IR (KBr): ν 3203 (NH), 3115 (aromatic CH), 1634 (C=N), 1535, 1346 (NO2), 1160 (SO_2) cm^{-1}. *Anal*. Calcd for $C_{24}H_{36}N_6O_4Cl_2I_2S_2$: C, 33.46; H, 4.21; N, 9.76. Found: 33.27; H, 4.30; N, 9.68.

***N*-Methyl-*N*-[2-(3-nitrophenylsulfonylamino)ethyl]-*N*'-{2-[*N*'-2-(3-nitrophenylsulfonylaminoethyl)-*N*'-methyl]ethylideneamino}ethylacetamidine bishydroiodide (12)** This compound was obtained as a white powder, yield 74%, and mp 227 – 228 °C (benzene). ^{1}H NMR (DMSO-d_6): 2.40 (s, 6H, 2CH_3), 3.06 (m, 10H, NCH_2CH_2N, NCH_3), 3.61 (s, 8H, NCH_2CH_2N), 7.78 – 8.50 (m, 12H and 4H exchangeable with D_2O, aromatic and NH); IR (KBr): ν 3199, 3232 (NH), 3115 (aromatic CH), 1633 (C=N), 1538, 1356 (NO2), 1165 (SO_2) cm^{-1}. *Anal*. Calcd for $C_{24}H_{36}N_8O_8I_2S_2$ C, 32.66; H, 4.11; N, 12.70. Found: 32.81; H, 4.38; N, 12.70.

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