Interaction of diazoimidazoles and their diazonium salts with primary and secondary amines

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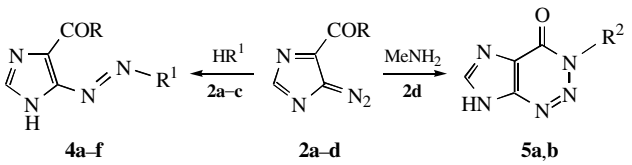
A number of 2- and 5-triazenoimidazoles were prepared by the coupling of diazo compounds with aliphatic amines; however, 4,5-dicyanoimidazole-2-diazonium chloride was transformed into 2-amino-1-methylimidazole-4,5-dicarbonitrile.

It is well known that dacarbazine [5-(3,3-dimethyl-1-triazeno)-imidazole-5-carboxamide, DTIC] is one of the most active anticancer drugs for the treatment of malignant melanomas and Hodgkin tumors.[1] In *in vivo* experiments, dacarbazine generates the corresponding monomethyltriazene derivative, which undergoes proteolytic decomposition into 5-aminoimidazole-4-carboxamide (AIC) and a reactive methanediazonium species. The cytotoxic effect of the latter is due to the methylation of guanine residues in DNA.[2]

Here, we report on the interaction of diazotised 2- and 5-aminoimidazoles[3–5] with primary and secondary amines, which was carried out to prepare more stable structural analogues of dacarbazine and its N-demethylated derivative. 5-(3,3-Dialkyl-1-triazeno)imidazoles bearing nitro, cyano, aminocarbonyl and ethoxy groups at the 4-position were prepared earlier.[4–7] We applied a similar procedure to obtain dialkyltriazenoimidazoles **3a–c** and **4a–d**† on the basis of 4,5-dicyanoimidazole-2-diazonium chloride[3] **1a**, 5-diazoimidazol-4-morpholylcarboxamide **2a**, 5-diazoimidazol-4-*N*-(*p*-tolyl)carboxamide **2b** and its diazonium salt as diazo components.[8]

The reactions of diazo imidazoles with primary amines are of considerable interest. Since it is well known that monoalkyltriazeno derivatives are photosensitive and unstable substances, their reactions were carried out in the dark at low temperature. Monomethyltriazenoimidazoles **4e**,**f**† were obtained by the reactions of 5-diazoimidazol-4-morpholylcarboxamide **2a** and 5-diazoimidazol-4-*N*-methylcarboxamide **2c** with methylamine. Similar conversions of diazo compound **2b** and its diazonium salt allowed us to obtain 3-*p*-tolyl-3,7-dihydroimidazo[4,5-*d*]-[1,2,3]triazine-4-one **5a** in almost quantitative yield as the only product, thus indicating that the intramolecular coupling reaction proceeds faster than the intermolecular one. Ethyl 5-diazoimidazole-4-carboxylate **2d** reacted with methylamine in a similar way to give imidazotriazinone derivative **5b**.

Unexpectedly, the reaction of diazonium salt **1a** with methylamine resulted in the formation of 2-amino-1-methylimidazole-4,5-dicarbonitrile **6** in 78% yield. We believe that unstable triazene **3d** initially formed under the reaction conditions affords diazomethane. It generates a carbene species, which is capable of alkylating at NH of the imidazole ring. The structure of amine **6** was confirmed by ^{1}H NMR spectroscopy, as well as by chemical conversions.‡ Thus, under diazotization conditions ($NaNO_2$/HCl) compound **6** is transformed into 4,5-dicyano-1-methylimidazole-2-diazonium chloride **1b**, which affords



4a R = morpholyl, R^1 = NMe_2
4b R = morpholyl, R^1 = piperidinyl
4c R = NHC_6H_4-Me-*p*, R^1 = piperidinyl
4d R = NHC_6H_4-Me-*p*, R^1 = morpholyl
4e R = R^1 = NHMe
4f R = morpholyl, R^1 = NHMe

2a R = morpholyl
2b R = NHC_6H_4-Me-*p*
2c R = NHMe
2d R = OEt

5a R^2 = C_6H_4-Me-*p*
5b R^2 = Me

Scheme 1

† All melting points are uncorrected. IR spectra were recorded on a Specord M-75 instrument in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker WR-250 instrument (250 MHz) in ([$^2H_6$]DMSO + CCl_4) using TMS as an internal standard.

General procedure for the synthesis of the triazeneimidazoles **3a–c** *and* **4a–f**. To a mixture of 1 mmol of 2- or 5-diazoimidazole (**1a** or **2a–d**) in 3 ml of dry acetonitrile was added 10 mmol of a corresponding amine at –5 to 0 °C. The reaction mixture was kept in the dark at low temperature until the diazo compound disappeared (10–30 min). Crude products were collected by filtration. The precipitates were either crystallised from ethanol–chloroform or washed with diethyl ether.

3a: yield 62%, mp 136 °C. ^{1}H NMR, δ: 13.26 (br. s, 1H, NH), 3.64 (s, 3H, Me), 3.28 (s, 3H, Me). IR, ν/cm^{-1}: 3400, 2970, 2925, 2245, 1570. Found (%): C, 44.15; H, 3.77; N, 51.91. Calc. for $C_7H_7N_7$ (%): C, 44.44; H, 3.73; N, 51.83.

3b: yield 98%, mp 143 °C. ^{1}H NMR, δ: 13.44 (br. s, 1H, NH), 3.67 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 1.70 (m, 6H, $3CH_2$). IR, ν/cm^{-1}: 3450, 2970, 2945, 2860, 2210, 1610. Found (%): C, 52.28; H, 4.79; N, 42.83. Calc. for $C_{10}H_{11}N_7$ (%): C, 52.39; H, 4.84; N, 42.77.

3c: yield 96%, mp 157 °C. ^{1}H NMR, δ: 13.28 (br. s, 1H, NH), 3.73 (m, 6H, $2CH + 2CH_2$), 3.11 (m, 2H, 2CH). IR, ν/cm^{-1}: 3470, 2990, 2915, 2870, 2210, 1625. Found (%): C, 46.66; H, 3.88; N, 42.47. Calc. for $C_9H_9N_7O$ (%): C, 46.75; H, 3.92; N, 42.40.

4a: yield 74%, mp 152 °C. ^{1}H NMR, δ: 12.32 (br. s, 1H, NH), 7.45 (s, 1H, 2-H), 3.57 (s, 3H, Me), 3.53 (s, 3H, Me), 3.43 (m, 6H, $2CH + 2CH_2$), 3.16 (m, 2H, 2CH). IR, ν/cm^{-1}: 3415, 2955, 2900, 2860, 1610. Found (%): C, 47.64; H, 6.41; N, 33.21. Calc. for $C_{10}H_{16}N_6O_2$ (%): C, 47.61; H, 6.39; N, 33.31.

4b: yield 89%, mp 114 °C. ^{1}H NMR, δ: 12.17 (br. s, 1H, NH), 7.38 (s, 1H, 2-H), 3.73 (m, 4H, $2CH_2$), 3.57 (m, 8H, $4CH_2$), 1.69 (m, 6H, $3CH_2$). IR, ν/cm^{-1}: 3390, 2965, 2935, 2910, 2850, 1590. Found (%): C, 53.35; H, 6.93; N, 28.67. Calc. for $C_{13}H_{20}N_6O_2$ (%): C, 53.41; H, 6.90; N, 28.75.

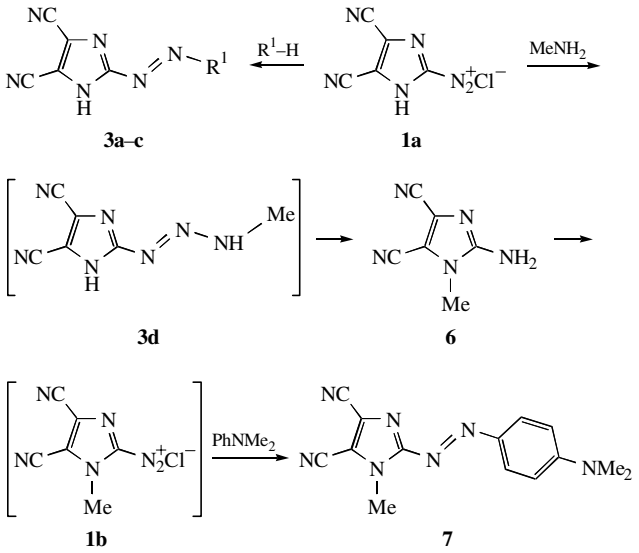
4c: yield 85%, mp 216 °C. ^{1}H NMR, δ: 12.29 (br. s, 1H, NH), 7.84 (s, 1H, 2-H), 7.38 (d, 2H, 2′,6′-H, *J* 8.24 Hz), 7.31 (d, 2H, 3′,5′-H, *J* 8.24 Hz), 3.01 (m, 4H, $2CH_2$), 2.39 (s, 3H, Me), 1.63 (m, 6H, $3CH_2$). IR, ν/cm^{-1}: 3435, 3350, 2985, 2940, 2925, 2860, 1690, 1620. Found (%): C, 61.44; H, 6.45; N, 26.93. Calc. for $C_{16}H_{20}N_6O$ (%): C, 61.52; H, 6.45; N, 26.90.

4d: yield 83%, mp 237 °C. ^{1}H NMR, δ: 12.42 (br. s, 1H, NH), 8.03 (s, 1H, 2-H), 7.41 (d, 2H, 2′,6′-H, *J* 8.24 Hz), 7.33 (d, 2H, 3′,5′-H, *J* 8.24 Hz), 3.65 (m, 4H, $2CH_2$), 2.93 (m, 4H, $2CH_2$), 2.40 (s, 3H, Me). IR, ν/cm^{-1}: 3430, 3350, 3075, 2980, 2930, 2875, 1680, 1615. Found (%): C, 57.22; H, 5.74; N, 26.46. Calc. for $C_{15}H_{18}N_6O_2$ (%): C, 57.31; H, 5.77; N, 26.73.

4e: yield 55%, mp 168 °C. ^{1}H NMR, δ: 12.65 (br. s, 1H, NH), 10.70 (q, 1H, N*H*Me, *J* 3.66 Hz), 7.78 (q, 1H, CON*H*Me, *J* 4.58 Hz), 7.52 (s, 1H, 2-H), 3.03 (d, 3H, NH*Me*, *J* 3.66 Hz), 2.85 (d, 1H, CONH*Me*, *J* 4.58 Hz). IR, ν/cm^{-1}: 3290, 3090, 1640, 1570. Found (%): C, 39.67; H, 5.42; N, 46.22. Calc. for $C_6H_{10}N_6O$ (%): C, 39.56; H, 5.53; N, 46.13.

4f: yield 61%, mp 139 °C. ^{1}H NMR, δ: 12.24 (br. s, 1H, NH), 10.45 (m, 1H, N*H*Me), 7.34 (s, 1H, 2-H), 3.59 (m, 8H, $4CH_2$), 3.01 (d, 3H, *J* 3.60 Hz, NH*Me*). IR, ν/cm^{-1}: 3320, 3070, 2955, 2900, 2860, 1585. Found (%): C, 45.34; H, 5.84; N, 35.23. Calc. for $C_9H_{14}N_6O_2$ (%): C, 45.37; H, 5.92; N, 35.27.

‡ *2-Amino-1-methylimidazole-4,5-dicarbonitrile* **6**. To a solution of 0.2 g (1.11 mmol) of diazonium salt **1a** in 5 ml of acetonitrile a solution of 0.05 ml (1.11 mmol) of methylamine in 5 ml of acetonitrile was added at 0 °C. The mixture was kept in the dark for 5 min. The removal of the solvent under a reduced pressure gave amine **6**, which was crystallised from ethanol (0.12 g, 75%). Mp 165 °C. ^{1}H NMR, δ: 6.83 (br. s, 2H, NH_2), 3.46 (s, 3H, Me). IR (KBr, ν_{max}/cm^{-1}): 3250, 3170, 2910, 2240, 2220, 1630, 1580. Found (%): C, 49.04; H, 3.42; N, 47.69. Calc. for $C_6H_5N_5$ (%): C, 48.98; H, 3.43; N, 47.60.



3a–c **1a**

3d **6**

1b **7**

3a $R^1 = NMe_2$
3b R^1 = piperidinyl
3c R^1 = morpholyl

Scheme 2

2-(4-dimethylaminophenylazo)-1-methylimidazole-4,5-dicarbonitrile **7**§ upon coupling with *N*,*N*-dimethylaniline.

§ *2-(4-Dimethylaminophenylazo)-1-methylimidazole-4,5-dicarbonitrile* **7**. A suspension of 0.1 g (0.68 mmol) of amine **6** in 5 ml of 2 N HCl was cooled to –5 °C with stirring. Then, 0.06 g (0.82 mmol) of sodium nitrite in 1 ml of water was added dropwise to the reaction mixture. The resulting mixture was stirred for 15 min. After diazotization, 0.1 ml (0.82 mmol) of *N*,*N*-dimethylaniline was added. The resulting suspension was filtered, and the product was recrystallised from ethanol (0.15 g, 79%). Mp 202 °C. ^{1}H NMR, δ: 7.82 (d, 2H, 2′,6′-H, *J* 9.16 Hz), 6.83 (d, 2H, 3′,5′-H, *J* 9.16 Hz), 3.42 (s, 3H, Me), 3.17 (s, 6H, 2Me). IR (KBr, ν_{max}/cm^{-1}): 3160, 3050, 2910, 2230, 2220, 1595. Found (%): C, 60.13; H, 4.61; N, 35.19. Calc. for $C_{14}H_{13}N_7$ (%): C, 60.20; H, 4.69; N, 35.10.

Thus, we found that the reactions of diazoimidazoles with aliphatic amines result in a variety of compounds, one of which is N-methylated imidazole derivative **6**.

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