Reactions of 4-Cyano- and 4-Methylimidazoles with Isocyanates

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4-Cyano- and 4-methylimidazoles reacted with methyl and aryl isocyanates to give exclusively 1-(substituted carbamoyl)-4-cyano- and 4-methylimidazoles, respectively. Refluxing of 1-carbamoyl-4-methylimidazoles in nitrobenzene yielded 2-carbamoyl-4-methylimidazoles through a known migration, whereas the 4-cyano analogues could not be caused to migrate. On the other hand, the treatment of 4-cyano-1-(methylcarbamoyl)imidazole with methyl isocyanate under the basic conditions resulted in the formation of 2-methyl-1-(methylcarbamoylimino)-2,3-dihydro-1*H*-imidazo[1,5-*c*]imidazol-3-one which must be formed *via* the migration of the carbamoyl group to another nitrogen followed by the intramolecular cyclization of the newly introduced carbamoyl group with its *vic* cyano group.

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It has been thoroughly investigated which nitrogen is the predominant reaction site in electrophilic substitutions such as alkylation and acylation of 4-substituted imidazoles which depends upon the reaction conditions and the electrophiles (1). However, little information has been available concerning such an orientation in carbamoylation reactions (2). The carbamoyl group at the 1-position of unsubstituted imidazole has been also known to migrate to the 2-position by the treatment at higher temperatures (3).

In the present paper, we investigated the reactions of 4-substituted imidazoles such as 4-cyano- and 4-methylimidazoles with isocyantes and the migrations of the carbamoylated imidazoles thus obtained.

4-Cyanoimidazole (**1**) reacted with phenyl isocyanate at room temperature in the presence of a catalytic amount of

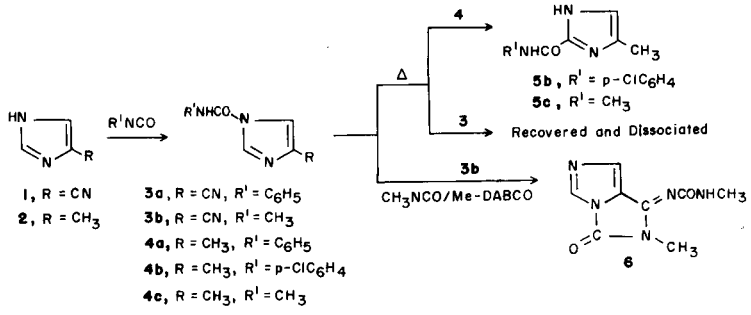

Table I

Preparations of 4-Substituted 1-Carbamoylimidazoles **3** and **4**

Imidazole	Yield, %	Mp, °C	IR (C=O) cm^{-1}	NMR (1) δ	$\Delta\delta$ (2)
3a	60	104-106	1735	7.10-7.58 (m, 5, aromatic), 8.48 (s, 2, imidazole 2H and 5H), 10.33 (br s, 1, NH)	0.80 or 0.75
3b	81	54-57	1730	2.88 (d, 3, CH_3), 8.30 (s, 2, imidazole 2H and 5H), 8.55 (br s, 1, NH)	0.62 or 0.57
4a	95	142-144	1720	2.15 (s, 3, CH_3), 6.98-7.60 (m, 7, aromatic, imidazole 5H, NH), 8.23 (s, 1, imidazole 2H)	———
4b	98	168-170	1720	2.20 (s, 3, CH_3), 7.40 (s, 1, imidazole 5H), 7.43 (A_2X_2, 4, aromatic), 8.20 (s, 1, imidazole 2H), 10.08 (br s, 1, NH)	0.77
4c	99	104-105	1720	2.17 (s, 3, CH_3), 2.86 (d, 3, N-CH_3), 7.33 (s, 1, imidazole 5H), 8.10 (s, 1, imidazole 2H), 8.21 (br s, 1, NH)	0.70

(1) Measured in deuteriochloroform-DMSO-d_6 (2:1). (2) The difference of chemical shift of imidazole 5H between **3** or **4** and their starting materials, being given in ppm downfield.

2-methyl-1,4-diazabicyclo[2.2.2]octane (Me-DABCO) (4) and dibutyltin dilaurate (DBTDL) (5) to give exclusively 4-cyano-1-(phenylcarbamoyl)imidazole (**3a**). The structure of **3a** was determined on the basis of its spectral data; that is, the band due to the carbon-oxygen double bond at 1735 cm^{-1} in the ir spectrum is quite consistent with that of 1-carbamoylimidazole and the strongly deshielded 5H of imidazole compared with that of **1** in the ^1H nmr spectrum supports the carbamoyl group located at the nitrogen atom farther from the cyano group (3). Methyl isocyanate also reacted with **1** to afford 4-cyano-1-(methylcarbamoyl)-imidazole (**3b**). Yields and spectral data of these products are collected in Table 1.

This exclusive orientation is also observed in the case of 4-methylimidazole (**2**), having an electron-releasing methyl group contrary to a cyano group. The reaction of **2** with phenyl isocyanate at room temperature without a catalyst proceeded readily to give 4-methyl-1-(phenylcarbamoyl)imidazole (**4a**) quantitatively. The position of the carbamoyl group was also determined by the chemical shift of highly deshielded 5H of imidazole compared with that of **2**. Similarly *p*-chlorophenyl and methyl isocyanates with **2** yielded the corresponding 1-carbamoyl-4-methylimidazoles **4b** and **4c** as summarized in Table 1.

The migrations of the carbamoyl group of **3** and **4** were next investigated under rather drastic conditions such as refluxing in nitrobenzene. The expected migration occured in the case of **4b**, giving 52% yield of 2-(*p*-chlorophenylcarbamoyl)-4-methylimidazole (**5b**). The structure of **5b** was determined by its spectral data and elemental analysis; appearance of the carbonyl band at 1660 cm^{-1} in the ir spectrum indicates the carbonyl group attached to ring carbon and disappearance of the peak due to 2H of imidazole in the ^1H nmr spectrum supports the carbamoyl group situated at the 2-position. Similarly **4c** gave the corresponding 4-methyl-2-(methylcarbamoyl)imidazole (**5c**), though the yield was as low as 7%. In contrast, 4-cyano analogues **3a-b** did not undergo the migration, only recovering **3a-b** along with the dissociated product **1**.

2-Carbamoylimidazoles **5** may be formed *via* the dissociation of isocyanates from **4** and the subsequent recombination of isocyanates at the 2-position, as described in the previous paper (3). A difference in reactivity of the migrations between **3** and **4** may be attributed to the electronic effect of 4-substituent on the electron density at the 2-position.

It should be noted that the treatment of **3b** with an excess of methyl isocyanate and Me-DABCO at room temperature gave 18% yield of 2-methyl-1-(methylcarbamoylimino)-2,3-dihydro-1*H*-imidazo[1,5-*c*]imidazol-3-one (**6**) and 63% of the unchanged **3b** (6). The structure of **6** was established by its elemental analysis and spectral data. The elemental analysis, the mass spectrum and the integration in the ^1H nmr spectrum support an 1:2 adduct between **1** and methyl isocyanate. The higher shifted band (1783 cm^{-1}) due to the carbonyl group and disappearance of the cyano group in the ir spectrum, as well as the strongly deshielded singlet peak of methyl protons (δ 3.10) in the ^1H nmr spectrum, indicate the five membered ring of imidazolone (7). For the formation of **6**, an excess of both Me-DABCO and methyl isocyanate were found to play an important role, since lack of either of these did not promote the cyclization. The imidazoimidazolone **6** was also directly obtained from **1** with an excess of methyl isocyanate in the presence of Me-DABCO in 31% yield along with 35% of **3b**. The similar reaction of **3a** or **1** with an excess of phenyl isocyanate did not produce the corresponding imidazoimidazolone, giving only **3a**. In the case of 4-methyl analogue **4c**, such a migration to another nitrogen did not take place and only **4c** was recovered.

The formation of **6** could be interpreted by elimination of the carbamoyl group and the simultaneous attack of methyl isocyanate upon the 3-nitrogen atom, followed by an intramolecular cyclization of the newly introduced carbamoyl group with its *vic* cyano group. Failure in the similar cyclization with phenyl isocyanate might be due to the lower nucleophilic reactivity of the carbamoyl nitrogen than that of methylcarbamoyl analogue.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrometer and the ms spectra measured with a Finnigan 3300E GC-MS spectrometer operating at 120 eV. The ^1H nmr spectra were observed with a JEOL JNM-PMX60 spectrometer using tetramethylsilane (TMS) as an internal standard in deuteriochloroform-DMSO-d_6 (2:1), the chemical shift (δ) being given in ppm downfield from TMS.

4-Methylimidazole (**2**) was commercially obtained and its ^1H nmr shows δ 2.18 (s, 3, CH_3), 6.63 (s, 1, imidazole 5H), 7.40 (s, 1, imidazole 2H), and 10.3 (br s, 1, NH).

Preparation of 4-Cyanoimidazole (**1**).

A solution of 0.69 g (5 mmoles) of 4-cyano-5-imidazolecarboxylic acid in 20 ml of nitrobenzene was refluxed for 20 hours. After the solution was cooled, the precipitated yellow solid was collected, washed with hexane, and recrystallized from chloroform-acetonitrile to give 0.37 g of yellow plates of **1**, yield 80%, mp 143.5-144.5°; ^1H nmr: δ 7.68 (s, 1, imidazole H), 7.73 (s, 1, imidazole H), and 12.7 (br s, 1, NH); ir (potassium bromide): 2225 cm^{-1} (C≡N). These spectral data are consistent with those reported (8).

General Preparations of **3** and **4**.

(i) Compounds **3a-b**.

A solution of 10 mmoles of **1**, 10 mmoles of isocyanate and a catalytic amount of Me-DABCO and DBTDL in 40 ml of dichloromethane was stirred at room temperature for 16 hours and the solvent was then evaporated under reduced pressure to leave a residual solid. The solid was washed with hexane three times and with carbon tetrachloride three times to give a white solid.

(ii) Compounds **4a-c**.

Isocyanate (10 mmoles) was added to a solution of 10 mmoles of **2** in 30 ml of dichloromethane and the mixture was stirred at room temperature for 2 hours. The solvent was then evaporated under reduced pressure to

leave a residual solid which was thoroughly washed with hexane to give a white solid.

Thus obtained carbamoylimidazoles **3** and **4** tend to dissociate so readily into the corresponding imidazole and isocyanate upon recrystallization that the reliable elemental analyses could not be performed but their tolerable purity was confirmed by their ir and ^{1}H nmr data.

Migration of **4b** to **5b**.

A solution of 1.37 g (5.8 mmoles) of **4b** in 35 ml of nitrobenzene was heated under reflux for 2 hours and afterwards cooled, and then a large amount of hexane was added. The precipitated solid was collected, washed with hexane, and recrystallized from chloroform-acetone to give 0.71 g of white powder of **5b**, yield 52%, mp 226.5-227°. ^{1}H nmr: δ 2.27 (s, 3, CH_3), 6.73-6.93 (m, 1, imidazole H), 7.17-7.93 (A_2X_2, 4, aromatic), 9.93 (br s, 1, CONH), 12.8 (br s, 1, NH); ir (potassium bromide): 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.90; H, 4.18; N, 17.77.

Migration of **4c** to **5c**.

A sealed tube containing a solution of 0.28 g (2.0 mmoles) of **4c** in 6 ml of nitrobenzene was immersed into an oil bath and kept at 220° for 3 hours. The reaction mixture was extracted with hexane several times and extracts were evaporated under reduced pressure to leave a solution of nitrobenzene. After the solution was cooled, the precipitated solid was collected, washed with hexane and carbon tetrachloride, and recrystallized from hexane-chloroform to give 0.02 g of white powder of **5c**, yield 7%, mp 206.5-207°; ^{1}H nmr: δ 2.22 (s, 3, CH_3), 2.86 (d, 3, N−CH_3), 6.75 (br s, 1, imidazole H), 7.90 (m, 1, CONH), and 12.5 (br s, 1, NH); ir (potassium bromide): 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.84; H, 6.47; N, 29.96.

Reaction of **3b** with Methyl Isocyanate.

Methyl isocyanate, 1.03 g (18 mmoles), was added to a solution of 0.75 g (5 mmoles) of **3b**, 1.5 ml of Me-DABCO, and a catalytic amount of DBTDL in 15 ml of chloroform and the mixture was stirred at room temperature for 9 days. The resulting solid was collected on a filter, washed with hexane, and recrystallized from acetonitrile to afford 0.19 g of white needles of **6**, yield 18%, mp 216-217.5° dec; ^{1}H nmr (DMSO-d_6): δ 2.73 (d, 3, NH−CH_3), 3.10 (s, 3, N−CH_3), 7.56 (s, 1, imidazole 4H), 7.73 (br s, 1, NH), and 8.40 (s, 1, imidazole 2H); ir (potassium bromide): 3220 (NH), 1783 (C=O), 1680 (C=N), 1640 cm^{-1} (C=O); ms: m/e 207 (M^+) and 150 ($M^+ - CH_3NCO$).

Anal. Calcd. for $C_8H_9N_5O_2$: C, 46.38; H, 4.38; N, 33.80. Found: C, 46.48; H, 4.27; N, 33.65.

On the other hand, the filtrate was evaporated under reduced pressure to leave an oily product which was washed with hexane. Its ^{1}H nmr analysis using 1,1,2,2-tetrachloroethane as an internal standard indicated 63% of **3b** recovered.

Reaction of **1** with Methyl Isocyanate.

A solution of 0.47 g (5 mmoles) of **1**, 1.43 g (25 mmoles) of methyl isocyanate, 1.5 ml of Me-DABCO and a catalytic amount of DBTDL in 15 ml of chloroform was stirred at room temperature for 9 days. The precipitated solid was collected, washed with hexane, and recrystallized from acetonitrile to give 0.32 g of **6**, yield 31%, mp 216-217.5° dec. Again from the ^{1}H nmr analysis of the filtrate, 35% of **3b** was detected.

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