Reactions of 4,5-Dicyanoimidazoles with Isocyanates. Novel Formation of the Condensed Tricyclic Imidazoles

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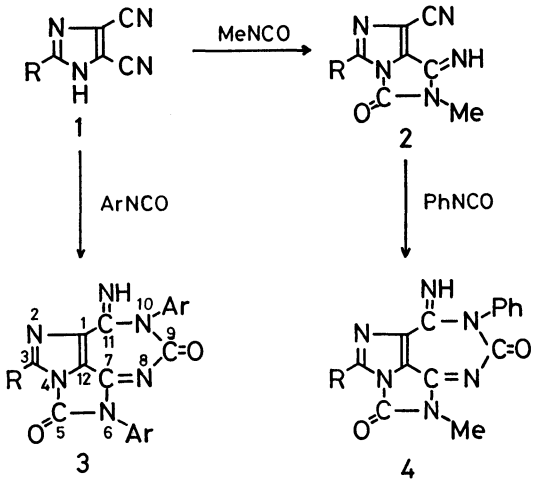
The reactions of 4,5-dicyanoimidazoles with methyl isocyanate gave 7-cyano-1-imino-2-methyl-2,3-dihydro-1*H*-imidazo[3,4-*c*]imidazol-3-ones (**2**), while the similar reactions with phenyl isocyanate resulted in the formation of the tricyclic imidazoles, 11-imino-6,10-diphenyl-2,4,6,8,10-pentaazatricyclo[5.4.1.$0^{4,12}$]dodeca-1(12),2,7-triene-5,9-diones (**3**) and the same type of the tricyclic imidazoles **4** were obtained by carbamoylation of **2** with phenyl isocyanate. The reactions of **2**, **3**, and **4** with amines were further investigated.

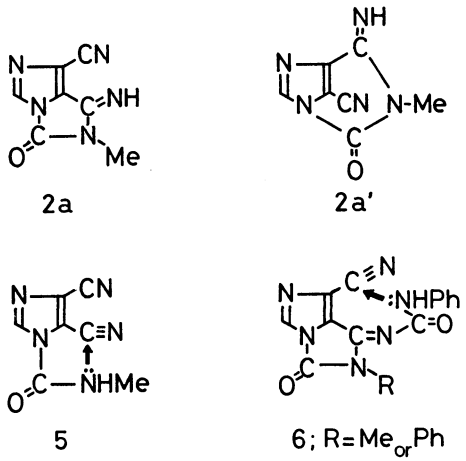
It is well known that imidazole itself reacts with isocyanates under mild conditions to form 1-(substituted carbamoyl)-1*H*-imidazoles,[1-3] which can be rearranged to 2-(substituted carbamoyl)-1*H*-imidazoles at a high temperature and that such 4,5-disubstituted imidazoles as 4,5-diarylimidazoles yield 2-(substituted carbamoyl)-1*H*-imidazoles by the reactions with aryl isocyanates under rather drastic conditions.[4-6] These interesting results of carbamoylation and rearrangement prompted us to apply such reactions to 4,5-dicyanoimidazoles to search some new imidazole derivatives.[7] In the present paper, we wish to report on the reactions of 4,5-dicyanoimidazoles with isocyanates which afford the novel condensed tricyclic imidazoles *via* ready intramolecular cyclization of the assumed intermediates, 4,5-dicyano-1-(substituted carbamoyl)-1*H*-imidazole followed by further cyclization of thus formed bicyclic imidazoles with another isocyanate.



Scheme 1.

Results and Discussion

The reaction of 4,5-dicyanoimidazole (**1a**) with methyl isocyanate was carried out in chloroform at room temperature for 24 h in the presence of 2-methyl-1,4-diazabicyclo[2.2.2]octane (Me-DABCO)[8] and a catalytic amount of dibutyltin dilaurate (DBTDL).[9] Me-DABCO was added not only to dissolve **1a** completely but to accelerate the reaction. The resulting precipitate was collected and recrystallized from chloroform to give the white plates which were assigned to 7-cyano-1-imino-2-methyl-2,3-dihydro-1*H*-imidazo-[3,4-*c*]imidazol-3-one (**2a**) on the basis of its spectral data and elemental analysis. The elemental analysis and the integration in ^{1}H NMR spectrum suggest an 1:1 adduct between **1a** and methyl isocyanate, while the IR spectrum shows bands at 3300(NH), 2220(C≡N), 1780(C=O), and 1670 cm^{-1}(C=N). In particular, band due to carbon-oxygen at 1780 cm^{-1}, which is much higher than that (about 1730 cm^{-1}) in the usual 1-(alkylcarbamoyl)-1*H*-imidazole,[5] strongly supports the five-membered ring structure **2a**.[10] Moreover, the strongly deshielded singlet peak of methyl protons (δ 3.20) in ^{1}H NMR is consistent with this structure.[11] Although the alternative structure **2a'** derived by the participation of 4-cyano group can be anticipated, it is denied from the steric consideration in constructing the model.



The similar reactions of 2-methyl (**1b**) and 2-ethyl analogues (**1c**) gave the corresponding bicyclic imidazoles **2b** and **2c** (Scheme 1). These results are summerized in Table 1.

On the other hand, the reactions with aryl isocyanates gave the quite different products. The reaction of **1a** with phenyl isocyanate at room temperature in the presence of Me-DABCO and DBTDL gave the tricyclic imidazole, 11-imino-6,10-diphenyl-2,4,6,8,10-pentaazatricyclo[5.4.1.$0^{4,12}$]dodeca-1(12),2,7-triene-5,9-dione (**3a**), in 62% yield. Its structure was determined by an elemental analysis and spectroscopic properties. The elemental analysis, the MS spectrum (*m/e*; 356, M$^+$), and the integration in ^{1}H NMR spectrum indicate an adduct between **1a** and two

Table 1. 7-Cyano-1-imino-2-methyl-2,3-dihydro-1*H*-imidazo[3,4-*c*]imidazol-3-ones (**2**)

Compound	R	Yield[a] %	Mp θ_m/°C	IR $\tilde{\nu}$/cm^{-1} C=O	IR $\tilde{\nu}$/cm^{-1} C=N	Formula	Calcd(Found)(%) C	H	N
2a	H	60	166—169	1780	1670	$C_7H_5N_5O$	48.00 (47.89)	2.88 (2.85)	39.99 (40.15)
2b	Me	64	156—159	1780	1660	$C_8H_7N_5O$	50.79 (50.49)	3.73 (3.47)	37.02 (36.76)
2c	Et	44	119—122	1780	1670	$C_9H_9N_5O$	53.20 (53.29)	4.46 (4.19)	34.46 (34.69)

a) Isolated yields after recrystallization.

Table 2. 11-Imino-2,4,6,8,10-pentaazatricyclo[5.4.1.0^{4,12}]dodeca-1(12),2,7-triene-5,9-diones (**3** and **4**)

Compound	R	Ar	Yield[a] %	Mp θ_m/°C	IR $\tilde{\nu}$/cm^{-1} C=O	C=N	C=O, C=N	Formula	Calcd(Found)(%) C	H	N
3a	H	Ph	62(37)[b]	214—215(decomp)	1780	1685	1640	$C_{19}H_{12}N_6O_2$	64.04 (63.85)	3.39 (3.20)	23.58 (23.51)
3a'	H	1-Naphthyl	23	182—184(decomp)	1795	1690	1650	$C_{27}H_{16}N_6O_2$	71.05 (70.83)	3.53 (3.61)	18.41 (18.56)
3b	Me	Ph	30	203—203.5(decomp)	1780	1690	1645	$C_{20}H_{14}N_6O_2$	64.86 (65.12)	3.81 (3.85)	22.69 (23.09)
3c	Et	Ph	36	183.5—184(decomp)	1780	1680	1640	$C_{21}H_{16}N_6O_2$	65.62 (65.63)	4.20 (4.33)	21.86 (21.81)
4a	H	—	24	199—201(decomp)	1785	1685	1640	$C_{14}H_{10}N_6O_2$	57.14 (57.04)	3.43 (3.15)	28.56 (28.27)
4b	Me	—	33	223—224(decomp)	1785	1695	1640	$C_{15}H_{12}N_6O_2$	58.44 (58.30)	3.92 (3.69)	27.26 (27.56)
4c	Et	—	29	209—210(decomp)	1785	1695	1640	$C_{16}H_{14}N_6O_2$	59.62 (59.32)	4.38 (4.32)	26.07 (26.36)

a) Isolated yields after recrystallization, being based on isocyanates. b) Yield obtained by running the reaction in nitrobenzene without catalyst.

equiv. of phenyl isocyanate. The IR spectrum shows bands at 3270(NH), 1780(C=O), 1685(C=N), and 1640 cm^{-1}(C=O and C=N),[12] no absorption due to the C≡N group being observed. These data support the structure **3a**.

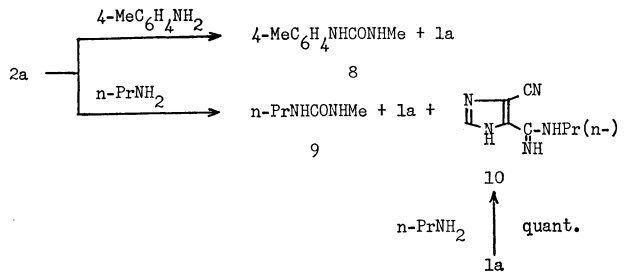
Reaction of **1a** with 1-naphthyl isocyanate and of **1b** and **1c** with phenyl isocyanate gave also the corresponding tricyclic imidazoles **3a'**, **3b**, and **3c** (Scheme 1, Table 2).

Under more drastic conditions of refluxing in nitrobenzene for 2.5 h, the reaction of **1a** with phenyl isocyanate was carried out and only the tricyclic imidazole **3a** was obtained. The formation of 4,5-dicyano-2-(phenylcarbamoyl)-1*H*-imidazole expected through rearrangement[4] couldn't be observed at all.

Though the bicyclic imidazole **2a** didn't undergo the further reaction with another molecule of methyl isocyanate, it reacted with phenyl isocyanate to give the similar tricyclic imidazole, 11-imino-6-methyl-10-phenyl-2,4,6,8,10-pentaazatricyclo[5.4.1.0^{4,12}]dodeca-1(12),2,7-triene-5,9-dione (**4a**), of which structure was also identified on the basis of its elemental analysis and spectral data. The bicyclic imidazoles **2b** and **2c** gave the similar results which were summerized in Table 2.

The formation of **2**, **3**, and **4** can be explained in terms of the intramolecular cyclization of the presumed intermediates **5** and **6**. The bicyclic imidazole **2** may be led *via* the attack of the carbamoyl nitrogen of **5** at the carbon of 5-cyano group causing proton transfer. In the case of methyl isocyanate the reaction terminates at this step, whereas in the case of more reactive phenyl isocyanate, it may further proceed *via* addition of another molecule of isocyanate followed by the cyclization with 4-cyano group to give **3** and **4**.

Next the reactivity of **2**, **3**, and **4** toward amines was investigated. 4-Methylaniline reacted with **3a** giving *N*-(4-methylphenyl)-*N'*-phenylurea (**7**) and with **4a** to yield urea **7** along with a small amount of *N*-(4-methylphenyl)-*N'*-methylurea (**8**). These results seem to suggest that amine initially attacks the carbonyl group of the diazepine ring and then that of imidazolidine ring. The reaction of **2a** with 4-methylaniline was then carried out, affording urea **8** and **1a** in 42 and 35% yields, respectively, whereas the



Scheme 2.

similar reaction with a more nucleophilic amine, propylamine, gave not only *N*-methyl-*N'*-propylurea (**9**) (41%) and a trace amount of **1a** but also 4-cyano-5-(*N*^{1}-propylamidino)-1*H*-imidazole (**10**) in 26% yield (Scheme 2). From the fact that **1a** reacted with propylamine to give the imidazole **10** quantitatively, it is supposed that **10** was obtained by the reaction of propylamine with the initially formed **1a**.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-PMX 60 spectrometer using tetramethylsilane (TMS) as an internal standard, the chemical shifts being given in δ ppm downfield from TMS. MS spectra were recorded on a Finnigan 3300E GC-MS spectrometer operating at 120 eV.

Dicyanoimidazoles **1a**—**c** were prepared by routes reported in the previous paper.[13] Elemental analyses and $\nu_{C=O \text{ and } C=N}$ in IR (KBr) for **2**, **3**, and **4** are summerized in Tables 1 and 2.

*Reaction of **1a** with Methyl Isocyanate.* A solution of 4.8 g (40 mmol) of **1a**, 5 drops of DBTDL, 4 ml of Me-DABCO, and 2.3 g (40 mmol) of methyl isocyanate in 60 ml of anhydrous chloroform was stirred at room temperature for 24 h. The precipitated white solid was collected and recrystallized from chloroform to give the white plates **2a** (4.2 g, 60%), mp, 166—169 °C. ^{1}H NMR (DMSO-d_6–$CDCl_3$) δ 3.20 (s, 3, N–CH_3), 8.35 (s, 1, imidazole 2H), and 9.90 (s, 1, NH). IR (KBr) 2220 (C≡N) and 3300 cm^{-1} (NH).

Similarly **2b** was obtained in 64% yield, mp, 156—159 °C (recrystallized from chloroform–carbon tetrachloride). ^{1}H NMR (DMSO-d_6–$CDCl_3$) δ 2.70 (s, 3, CH_3), 3.20 (s, 3, N–CH_3), and 9.40 (s, 1, NH). IR (KBr) 2220 (C≡N) and 3295 cm^{-1} (NH).

*Reaction of **1c** with Methyl Isocyanate.* Methyl isocyanate (1.1 g, 20 mmol) was added to a solution of 2.9 g (20 mmol) of **1c**, 5 drops of DBTDL, and 2 drops of Me-DABCO in 30 ml of anhydrous chloroform. After the reaction mixture was stirred at room temperature for 24 h, the solvent was distilled out under reduced pressure to give the residual oil. The oil was placed on the column (silica gel) and eluted with chloroform to give the crude white solid **2c**. The solid was recrystallized from carbon tetrachloride to afford the white plates **2c** (1.8 g, 44%), mp, 119—122 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3, CH_3), 3.05 (q, 2, CH_2), 3.30 (s, 3, N–CH_3), and 8.75 (s, 1, NH). IR (KBr) 2220 (C≡N) and 3295 cm^{-1} (NH).

*Reaction of **1a** with Phenyl Isocyanate.* *(A)*: Five drops of DBTDL and 4 ml of Me-DABCO was added to a suspension of 4.8 g (40 mmol) of **1a** in 60 ml of anhydrous chloroform under stirring. Me-DABCO (4 ml) thoroughly dissolved **1a**. Phenyl isocyanate (4.8 g, 40 mmol) was then added to the solution. After the mixture was stirred at room temperature for 24 h, a precipitate formed was filtered out and the filterate was evaporated under reduced pressure. The residual yellow solid and a precipitate were combined, washed with ethyl acetate to remove the excess **1a**, and recrystallized from acetonitrile to yield the yellow needles **3a** (4.4 g, 62% based on phenyl isocyanate), mp, 214—215 °C (decomp). MS (*m/e*) 356 (M$^+$). ^{1}H NMR (DMSO-d_6) δ 6.95—7.75 (m, 10, aromatic-H), 8.85 (s, 1, imidazole 2H), and 10.05 (s, 1, NH). IR (KBr) 3270 cm^{-1} (NH).

(B): Phenyl isocyanate (3.6 g, 30 mmol) was added to a suspension of 2.4 g (20 mmol) of **1a** in 30 ml of nitrobenzene. The mixture was refluxed for 2.5 h, cooled, and a precipitate formed was collected. The precipitate was washed with carbon tetrachloride and a small amount of ethanol to remove the excess **1a** and recrystallized from acetonitrile to give the yellow needles **3a** (2.0 g, 37% based on phenyl isocyanate), mp, 214—215 °C (decomp).

Similarly **3a'** and **3b** were obtained in 23 and 30% yields, respectively, by following method *(A)*. **3a'**: mp, 182—184 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 7.35—8.25 (m, 14, aromatic-H), 8.90 (s, 1, imidazole 2H), and 9.95 (s, 1, NH). IR (KBr) 3200 cm^{-1} (NH). **3b**: mp, 203—203.5 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 2.65 (s, 3, CH_3), 6.85—7.65 (m, 10, aromatic-H), and 9.90 (s, 1, NH). IR (KBr) 3360 cm^{-1} (NH).

*Reaction of **1c** with Phenyl Isocyanate.* A solution of 2.9 g (20 mmol) of **1c**, 6 drops of DBTDL, 2 ml of Me-DABCO, and 2.4 g (20 mmol) of phenyl isocyanate in 40 ml of anhydrous chloroform was stirred at room temperature for 17 h. The solvent was evaporated under reduced pressure and the residual oil was washed with hexane and benzene to give the crude yellow solid. The solid was recrystallized from acetonitrile to afford the yellow needles **3c** (1.4 g, 36% based on phenyl isocyanate), mp, 183.5—184 °C (decomp). ^{1}H NMR (DMSO-d_6–$CDCl_3$) δ 1.30 (t, 3, CH_3), 2.90 (q, 2, CH_2), 6.90—7.60 (m, 10, aromatic-H), and 8.85 (s, 1, NH). IR (KBr) 3220 cm^{-1} (NH).

*Reaction of **2a** with Phenyl Isocyanate.* Phenyl isocyanate (1.2 g, 10 mmol) was added to a suspension of 1.8 g (10 mmol) of **2a**, 5 drops of DBTDL, and 2 ml of Me-DABCO in 30 ml of anhydrous chloroform. The reaction mixture was stirred at room temperature and **2a** completely dissolved after 1 h. After the solution was stirred for 23 h, the yellow solid precipitated. The solid was collected, washed with chloroform, and recrystallized from acetonitrile to give the yellow needles **4a** (0.7 g, 24%), mp, 199—201 °C. MS (*m/e*) 294 (M$^+$) and 175 (M$^+$—PhNCO). ^{1}H NMR (DMSO-d_6) δ 3.20 (s, 3, N–CH_3), 6.95—7.70 (m, 5, aromatic-H), 8.65 (s, 1, imidazole 2H), and 10.10 (s, 1, NH). IR (KBr) 3280 cm^{-1} (NH).

Similarly **4b** and **4c** were obtained in 33 and 29% yields, respectively. **4b**: mp, 223—224 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3, CH_3), 3.20 (s, 3, N–CH_3), 7.00—7.80 (m, 5, aromatic-H), and 10.20 (s, 1, NH). IR (KBr) 3360 cm^{-1} (NH). **4c**: mp 209—210 °C (decomp). ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3, CH_3), 2.95 (q, 2, CH_2), 3.20 (s, 3, N–CH_3), 7.00—7.80 (m, 5, aromatic-H), and 10.25 (s, 1, NH). IR (KBr) 3380 cm^{-1} (NH).

*Reaction of **3a** with 4-Methylaniline.* A suspension of 0.7 g (2 mmol) of **3a** and 0.6 g (6 mmol) of 4-methylaniline in 30 ml of anhydrous chloroform was refluxed for 65 h and after cooled, the formed solid was collected (0.4 g), mp, 219—220 °C (lit,[14] 218 °C). This was identified to be urea **7** by its IR spectrum. The filtrate was evaporated under reduced pressure to leave the residual solid. Its IR and ^{1}H NMR spectra showed it to be the mixture of urea **7** and the starting material.

*Reaction of **4a** with 4-Methylaniline.* A suspension of 0.8 g (3 mmol) of **4a** and 0.6 g (6 mmol) of 4-methylaniline in 80 ml of anhydrous chloroform was refluxed for 96 h until **4a** thoroughly disappeared. After cooled, the formed solid was separated, 0.3 g, mp, 219—220 °C. This was identified to be urea **7** by its IR spectrum. The filtrate was evaporated under reduced pressure to give the residual solid. The solid was placed on the column (silica gel) and eluted with chloroform to give 0.38 g of urea **7** and 0.08 g of urea **8**, mp, 175—177 °C (lit,[15] 178 °C).

Reaction of ***2a*** *with 4-Methylaniline.* A solution of 0.97 g (5.5 mmol) of **2a** and 1.18 g (10 mmol) of 4-methylaniline in 50 ml of anhydrous chloroform was refluxed for 24 h. The solvent was evaporated under reduced pressure to leave the residual solid. The solid was placed on the column (silica gel) and eluted with chloroform to give the mixture of 4-methylaniline and urea **8**. The mixture was washed with hexane and toluene to yield 0.76 g (42%) of urea **8**, mp, 175—177 °C. In addition, the residual solid was eluted with ethanol to give the crude **1a**. This crude **1a** was recrystallized from water to afford the pure **1a** (0.46 g, 35%).

Reaction of ***2a*** *with Propylamine.* A solution of 1.75 g (10 mmol) of **2a** and 1.18 g (20 mmol) of propylamine in 30 ml of anhydrous chloroform was refluxed for 24 h. After cooled, the formed solid was collected and recrystallized from chloroform–acetonitrile to give 0.92 g of the pure amidine **10** (26%), white needles, mp, 142—144 °C. IR (KBr) 3220 (NH), 2220 (C≡N), and 1610 cm^{-1} (C=N). ^1H NMR ($CDCl_3$–DMSO-d_6) δ 1.00 (t, 3, CH_3), 1.60 (q of t, 2, CH_2), 2.85 (t, 2, N–CH_2), 7.25 (br.s, 3, 3NH), and 7.40 (s, 1, imidazole 2H). Found: C, 53.82; H, 5.87%. Calcd: C, 54.22; H, 6.26%.

The filtrate was evaporated under reduced pressure to leave the residual solid. By column chromatography (silica gel, chloroform) of the residue, 0.96 g of urea **9** was isolated (41%), mp 63.5—64.5 °C (lit,[15] 67—68 °C). The structure was identified by its IR spectrum.

Reaction of ***1a*** *with propylamine.* A solution of 1.18 g (10 mmol) of **1a** and 0.59 g (10 mmol) of propylamine in 40 ml of anhydrous chloroform was refluxed for 1 h and then stirred at room temperature for 24 h. The formed solid was collected and recrystallized from chloroform–acetonitrile to give 1.7 g of the pure amidine **10** (96%), mp 142—144 °C.

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