1-Alkylation of 4,5-Dicyanoimidazole by Ortho Esters

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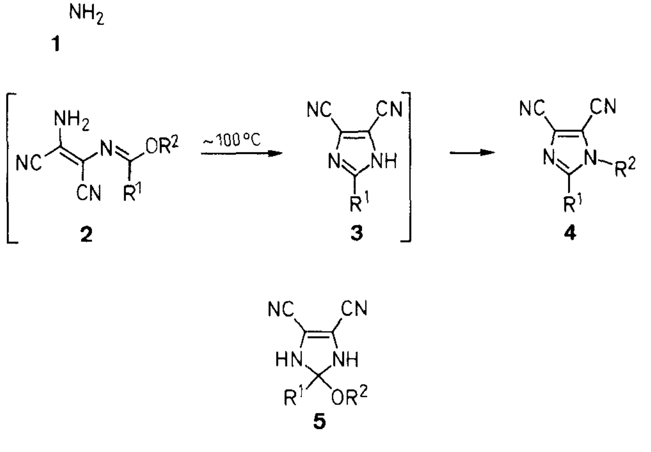
Reexamination of the reaction of ortho esters with diaminomaleonitrile (**1**) or 4,5-dicyanoimidazole (**3a**) revealed that 1-alkyl-4,5-dicyanoimidazoles **4a–f** can be obtained in high yield in a one-pot procedure without any additional reagent. This simple procedure is economically competitive with other known methods. Several products previously reported for similar reactions have been shown to be the imidates of diaminomaleonitrile, **2b** and **7**.

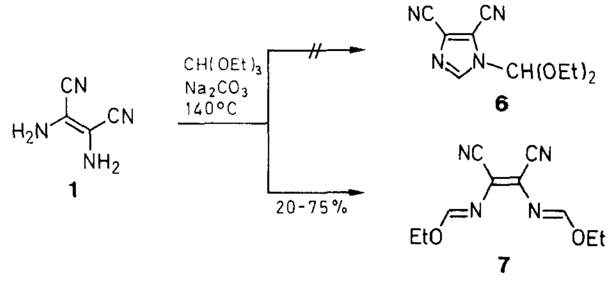
1-Alkyl-4,5-dicyanoimidazoles are useful precursors to a variety of specifically substituted imidazole derivatives.[4] Conventionally, 1-methyl-4,5-dicyanoimidazole (**4a**) is prepared in two steps from diaminomaleonitrile (DAMN) (**1**) which is first reacted with triethyl orthoformate in anisole to afford 4,5-dicyanoimidazole[1,2] (**3a**) which in turn is alkylated with dimethyl sulfate.[3,4]

While experimenting with conditions for the conversion of DAMN (**1**) to 4,5-dicyanoimidazole (**3a**), we ran the reaction at 100 °C using excess triethyl orthoformate without a cosolvent. Initially the reaction occurred as expected but an additional product accumulated as the imidazole formation proceeded. Extended heating of the mixture caused the 4,5-dicyanoimidazole (**3a**) to be consumed and completely converted to the new product, which proved to be 4,5-dicyano-1-ethylimidazole (**4b**). NMR and chromatographic analysis of a commercial sample of 4,5-dicyanoimidazole[10] (**3a**) revealed the presence of the ethyl derivative **4b** in trace amounts (approximately 2%).

This observation appeared to be inconsistent with the outcome of a reportedly similar reaction[1] run in boiling triethyl orthoformate in the presence of sodium carbonate which was claimed to afford 4,5-dicyano-1-(diethoxymethyl)imidazole (**6**). Repetition of the procedure as described in the patent[1] gave a product with the described physical properties and elemental composition,[11] but ^{1}H and ^{13}C-NMR analysis showed the compound to be the symmetrical bisimidate **7** (stereochemistry unproven but assumed to be *E* on steric grounds). It was also found that this product's formation was not dependent on the presence of sodium carbonate, but was due to the higher reaction temperature (140 °C).



2–9[5]	R^1	R^2
a	H	Me
b	H	Et
c	Me	Me

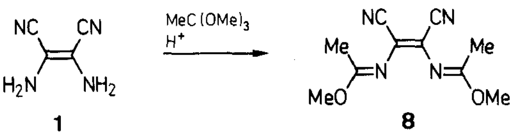


The monoimidate **2b** was prepared according to the patent procedure[1] using equimolar amounts of DAMN (**1**) and triethyl orthoformate in boiling dioxane. The previously proposed[1] alternative structure **5b** was ruled out by spectral correlation with the bisimidate **7** and by the complexity of the NMR spectra which was inconsistent with a symmetrical compound.

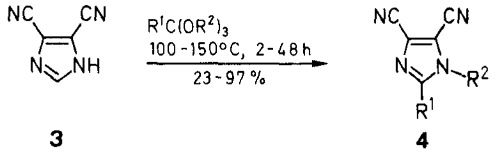
The monoimidate **2b** may be an intermediate in the formation of imidazole **3a** since it is rapidly cyclized in triethyl orthoformate at 100 °C, but the bisimidate **7** is essentially a "dead end" which does not convert to imidazole **3a** under the usual reaction conditions.

Since the original intent had been to prepare 4,5-dicyano-1-methylimidazole (**4a**), the reaction was attempted using trimethyl orthoformate. To achieve the maximum reaction rate at atmospheric pressure, the volatile reaction byproducts (methanol and methyl formate) were fractionally distilled from the reaction mixture. The temperature at the still head dropped from around 65 °C to near 55 °C as the proportion of methyl formate increased, then the head temperature rose as the reaction neared completion. Analysis of the distillate confirmed that four molar equivalents of methanol and one molar equivalent of methyl formate were produced during the reaction. Depending on the efficiency of the fractionation, a certain amount of trimethyl orthoformate codistilled with the more volatile byproducts. Consequently, over two equivalents of this starting material were necessary to achieve complete conversion to the final product. Aqueous workup was unnecessary since Kugelrohr distillation under high vacuum gave essentially pure 4,5-dicyano-1-methylimidazole (**4a**). The yield was close to quantitative.

Several lines of investigation were pursued to demonstrate the scope of this method for preparing 1-alkyl-4,5-dicyanoimidazoles. It should be noted that imidazole itself does not undergo 1-alkylation with ortho esters, but forms *orthoamides* (amide acetals) with both orthoformate[5,6] and orthoacetate[7] which are stable in the presence of excess ortho ester unless Lewis acid is added. What is more, the recently reported *N*-methylation of imidazoles with dimethyl carbonate[8,9] in the presence of sodium carbonate and phase transfer catalyst failed with 4,5-dicyanoimidazole (**3a**).[7]



Reaction of DAMN (**1**) with neat trimethyl orthoacetate (1,1,1-trimethoxyethane) at reflux temperature did not proceed cleanly to 4,5-dicyano-1,2-dimethylimidazole (**4c**),[14] although it was the major product. Analysis of the course of the reaction revealed an intermediate product which was not an imidazole, but proved to be the monoimidate ester **2c** (analogous ethyl derivative **2g** (R^1 = Me, R^2 = Et) reported by Bredereck et al.[2]). Upon extended reaction, the 1,2-dimethylimidazole **4c** and the bisimidate **8** were obtained as a 4 : 1 mixture. The intermediate 4,5-dicyano-2-methylimidazole (**3c**) was not detected and was presumably consumed as quickly as it formed. Formation of bisimidate **8** was strongly catalyzed by acid and it became the only significant product when the reaction was run in the presence of a catalytic amount of *p*-toluenesulfonic acid. On the other hand, complete inhibition of bisimidate **8** formation required addition of almost a full equivalent of triethylamine. The addition of base did not greatly improve the yield of 4,5-dicyano-1,2-dimethylimidazole (**4c**) but did make product isolation and purification easier.



4	R^1	R^2	4	R^1	R^2
a	H	Me	**e**	H	*i*-Pr
b	H	Et	**f**	H	Bu
c	Me	Me	**g**	Me	Et
d	H	Pr			

Additional studies examined the reaction of commercially available 4,5-dicyanoimidazole (**3a**) with a variety of ortho esters. As would be expected from the experiments described above, trimethyl and triethyl orthoformate each gave efficient conversion to the 1-methyl and 1-ethyl derivatives **4a** and **4b** respectively. Tetraethyl orthocarbonate also effected the alkylation to afford **4b**. Both trimethyl and triethyl orthoacetate afforded the 1-alkylated products **4a** and **4b** respectively without any crossover to 2-methylimidazole derivatives **4c** or **4g**. Tripropyl orthoformate and tributyl orthoformate reacted normally, as did triisopropyl orthoformate although the reaction was inefficient and slow. There was no evidence of isomerization of propyl or isopropyl in the spectra of the respective alkylated products.

The alkylation of 4,5-dicyanoimidazole by ortho esters appears to be analogous to the esterification of carboxylic acids by ortho esters which is assumed to involve alkylation of the carboxylate ion by the dialkoxycarbocation

Table 1. Experimental Data for Preparations of **4a**–**f**

Product	Reactants (mol)	Method	Temperature (°C) (Time, h)	Yield (%)	mp (°C)	Molecular Formula
4a	**1** (0.925), $HC(OMe)_3$ (3.2)	A	70–100(3)	96	87–89[a]	$C_6H_4N_4$
	3a (0.38), $HC(OMe)_3$ (3.2)	B	100(36)	97	87–89	(132.1)
	3a (0.1), $MeC(OMe)_3$ (0.2)	B	100(2)	97	87–89	
4b	**1** (0.02), $HC(OEt)_3$ (0.24)	A	100(1)–150(3)	97	65–67[b]	$C_7H_6N_4$
	3a (0.023), $HC(OEt)_3$ (0.034)	B	100(0.3)–150(1)	94	65–67	(146.1)
	3a (0.1), $MeC(OEt)_3$ (0.15)	B	100(2)	97	66–67.5	
	3a (0.1), $C(OEt)_4$ (0.13)	B	100(0.5)–150(2)	96	65–67.5	
	2b (0.003), $HC(OEt)_3$ (0.05)	B	100(16)–140(8)	90	65–67.5	
4c	**1** (0.023), $MeC(OMe)_3$ (0.19)	A	95–85(72)	59[c]	101–103[d]	$C_7H_6N_4$
	1 (0.0925), $MeC(OMe)_3$ (0.139), Et_3N (0.08)	A	100–75(18)	76	97–101	(146.1)
4d	**3a** (0.1), $HC(PrO)_3$ (0.115)	B	105(1)–135(3)	86	oil	$C_8H_8N_4$ (160.15)
4e	**3a** (0.025), $HC(i\text{-}PrO)_3$ (0.035)	B	100(2)–140(48)	23[e]	41–43.5	$C_8H_8N_4$ (160.15)
4f	**3a** (0.025), $HC(BuO)_3$ (0.028)	B	135(48)	78	oil	$C_9H_{10}N_4$
	3a (0.05), $HC(BuO)_3$ (0.075)	B	130(2)–150(6)	91	oil	(174.2)

[a] Lit. [3] mp 89–89.5°C.

[b] Recrystallized mp 67–68°C.

[c] Isolated by chromatography. Compound **8** (an oil) was also isolated in 15% yield.

[d] Recrystallized mp 101–103.5°C. See Ref. 14.

[e] Chromatographed then distilled.

Table 2. Spectral Data for Compounds **2**, **4**, **7** and **8** Prepared

Compound	IR (KBr) (cm^{-1}) ν_{CN}	^1H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (70 eV) m/z (%)
2b	2207, 2246	1.35 (t, 3H, $J = 7.1$), 4.26 (q, 2H, $J = 7.1$), 5.9 (br s, 2H), 7.93 (s, 1H)	13.9, 63.6, 101.0, 113.9, 114.1, 122.6, 156.6	164 (M^+, 30), 119 (23), 108 (14), 81 (100), 54 (35)
2c	2199, 2250	2.20 (s, 3H), 3.76 (s, 3H), 4.5 (br s, 2H)	18.0, 54.2, 103.7, 114.0, 115.2	164 (M^+, 20), 149 (10), 134 (10), 133 (100), 53 (17), 43 (93)
4a	2240	3.83 (s, 3H), 7.64 (s, 1H)	34.0, 107.6, 111.4, 116.5, 122.4, 141.7	132 (M^+, 100), 91 (27), 80 (22), 77 (18), 76 (15), 67 (31), 49 (13), 44 (14)
4b	2239	1.58 (t, 3H, $J = 7.4$, 4.22 (q, 2H, $J = 7.4$), 7.75 (s, 1H)	15.6, 43.2, 107.7, 111.6, 111.8, 122.9, 140.6	147 (94), 146 (M^+, 100), 118 (77)
4c	2241	2.48 (s), 3.75 (s)	13.4, 32.7, 108.3, 111.9, 112.9, 121.1, 151.0	146 (M^+, 100), 131 (12), 105 (28)
4d	2239	1.03 (t, 3H, $J = 7.4$), 1.98 (sextet, 2H, $J = 7.3$), 4.19 (t, 2H, $J = 7.2$), 7.81 (s, 1H)	10.8, 23.8, 49.7, 108.1, 111.9, 112.2, 122.7, 141.6	161 (100), 160 (M^+, 72), 43 (87)
4e	2239	1.67 (d, 6H, $J = 6.8$), 4.64 (septet, 1H, $J = 6.8$), 7.81 (s, 1H)	23.0, 52.2, 108.2, 111.2, 111.8, 123.3, 139.0	160 (M^+, 17), 119 (10), 43 (100)
4f	2240	1.00 (t, 3H, $J = 7$), 1.40 (sextet, 2H, $J = 7$), 1.90 (quintet, 2H, $J = 7$), 4.19 (t, 2H, $J = 7$), 7.76 (s, 1H)	13.3, 19.5, 32.3, 48.0, 108.0, 111.8, 112.2, 122.8, 141.3	175 (100), 174 (M^+, 49), 132 (60)
7	2218	1.36 (t, 6H, $J = 7$), 4.34 (q, 4H, $J = 7$), 8.10 (s, 2H)	13.9, 64.6, 113.4, 120.6, 161.5	221 (79), 220 (M^+, 71), 163 (20), 147 (35), 119 (58), 81 (100)
8	2216	2.05 (s, 6H), 3.73 (s, 6H)	18.2, 54.5, 114.4, 118.7, 167.1	221 (19), 220 (M^+, 35), 189 (14), 147 (12), 43 (100)

of an intermediate ion pair.[13] The reaction is not general for imidazoles since imidazole itself reacts with ortho esters by alkoxyl displacement to give orthoamides (amide acetals).[6,7] The 1-proton in 4,5-dicyanoimidazole is fairly acidic[3] (pKa 5.2 at 18 °C) and it is likely that the reacting nucleophile is the 4,5-dicyanoimidazolyl anion possibly formed by heterolytic scission of a reactive intermediate such as orthoamide **6**. The simultaneously produced dialkoxycarbocation would also be a reactive alkylating agent.

In conclusion, the described methods constitute convenient, simple and economically competitive alternatives to current procedures for preparing 1-alkyl-4,5-dicyanoimidazoles. Potently mutagenic alkylating agents such as dimethyl sulfate and methyl iodide are avoided. A clear limitation is that of the three alkyl groups on the ortho ester only one is transferred to the imidazole. Presumably, this will limit the utility of the method to the introduction of simple, inexpensive substituents.

Melting points (uncorrected) were determined on a Thomas Hoover capillary tube melting point apparatus. IR spectra were recorded on a Nicolet MX-1 FT Spectrophotometer. ^1H-NMR and ^{13}C-NMR spectra were recorded on a Varian XL200, a Bruker AM250 or a Varian XL300 NMR spectrometer using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on a Finnegan 4500 or a VG Analytical 7070E/HF mass spectrometer. Ortho esters were obtained from commercial sources (Aldrich or Lancaster Synthesis) except for triisopropyl orthoformate which was prepared from trimethyl orthoformate by transesterification.[12] Diaminomaleonitrile (98 %) was purchased from the Aldrich Chemical Co. and was used without further purification despite its dark color. 4,5-Dicyanoimidazole (95 %) was purchased from Aldrich and was usually further purified by trituration from THF with hexane.

4,5-Dicyano-1-methylimidazole (4a): Typical Procedures:

Method A: A mixture of diaminomaleonitrile (**1**; 100 g, 0.925 mol) and trimethyl orthoformate (350 mL, 339.5 g, 3.20 mol) is stirred and heated under partial reflux through a 25 centimeter vigreux distillation column. Distillate (approximately 200 mL) with bp 55–70 °C is collected over 140 min. Then the distillation temperature is allowed to rise to 102 °C and distillate is slowly collected for 2 h (pot temperature 115 °C). The fractionating column is then removed, and the bulk of the remaining trimethyl orthoformate is distilled off. The residue is kugelrohr distilled under vacuum (1.5 mbar, oven temperature 130–140 °C) to afford **4a** as a colorless solid; yield: 117.3 g (96 %); mp 87–89 °C (Lit.[3] mp 89–89.5 °C).

Method B: A mixture of 4,5-dicyanoimidazole (**3a**; 11.8 g, 0.10 mol) and trimethyl orthoacetate (25.5 mL, 24 g, 0.2 mol) in a flask equipped for short path distillation is heated on an oil bath at 100 °C. Liquid begins to distill almost immediately at 65 °C and the distillation temperature drops to 57 °C as MeOH (1 equiv), MeOAc (1 equiv) and trimethyl orthoacetate (approximately 0.4 equiv) codistill over a 2 h period. The remaining trimethyl orthoacetate is then evaporated under vacuum and the residue is Kugelrohr distilled to afford **4a**; yield: 12.9 g (97 %); mp 87–89 °C.

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(11) As previously reported,[1] the N analysis is slightly high for this compound **7b**. NMR analysis revealed the presence of compound **5b** (approximately 7%) which accounts for the discrepancy.

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