2-Chloro-4,5-dihydroimidazole, VI[1]

Annulation by Means of 4-(Dimethylamino)pyridine in the Presence of C–H Acids

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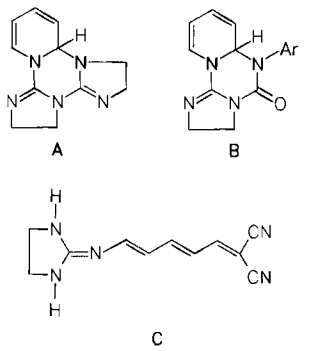
2-Chloro-4,5-dihydroimidazole (**1**) reacts with 4-(dimethylamino)pyridine to yield the stable pyridinium salt **2**, which on treatment with some C–H acids produces 1,2,3,5-tetrahydroimidazo[1,2-*a*]pyrimidines **6**.

Previously, we have demonstrated that 2-chloro-4,5-dihydroimidazole (**1**) reacts with pyridine to give pyrido[1,2-*a*]diimidazo[1,2-*c*:1′,2′-*e*]triazine **A**[2]; the same reaction carried out in the presence of aromatic isocyanates leads to the formation of 5*H*-imidazo[1,2-*a*]pyrido[1,2-*c*]triazin-5-ones **B**[3]. On the other hand, when a C–H acid was present in the reaction mixture, we were able to isolate azaheptamethine neutrocyanines **C** with *all-trans* configuration[3] (Scheme 1). The intermediate pyridinium salt cannot be isolated due to its high instability.

Scheme 1

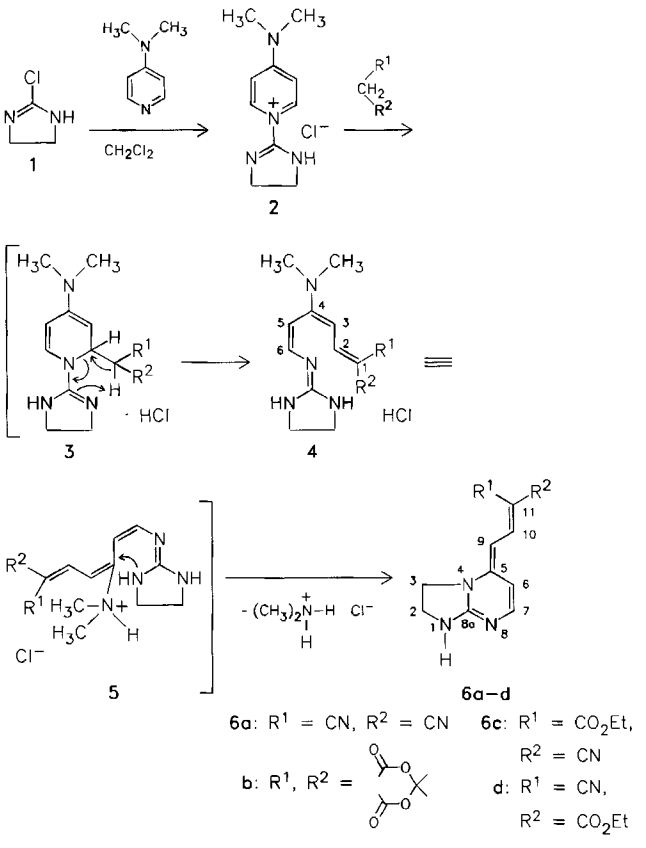


We now found that 4-(dimethylamino)pyridine (DMAP – the widely used hypernucleophilic acylation catalyst[4,5]) subjected to the reaction with **1** produces the pyridinium salt **2**, which proves to be stable enough to survive recrystallization from ethanol. However, when the reaction is carried out in the presence of C–H acids such as malonodinitrile, Meldrum's acid, or ethyl cyanoacetate, an annulation of the imidazoline ring takes place with the formation of imidazo[1,2-*a*]pyrimidine **6**. We propose a reaction sequence for the transformations as shown in Scheme 2.

Attack of the anion of the active methylene compound at the C-2 atom of the pyridinium salt **2** with subsequent shift of the hydrogen atom in an intramolecular retro-ene reaction gives a polymethine derivative **4**. Rotation around the C-4–C-5 and C-6–N bonds in **4** produces intermediate **5**. This process is completed by nucleophilic displacement of the dimethylamino group resulting in the formation of the imidazo[1,2-*a*]pyrimidine ring system **6**.

The conjugated alkenes **6a,b** of *s-trans* configuration are exclusively obtained from malonodinitrile or Meldrum's acid. In the case of ethyl cyanoacetate, two isomeric compounds **6c** and **6d** with *cis,trans* and *trans,trans* configurations are formed in a ratio of 95:5 (Scheme 3).

Scheme 2



Assuming that no *cis*⇌*trans* isomerization of the products takes place, the excess of the *cis,trans* isomer can result from the fact, that during the hydrogen atom migration the ethoxycarbonyl group favors an equatorial position in the transition state, and hence conversion of the chiral center in **3** into the prochiral C-1 centre in olefin **4** proceeds with high stereoselectivity.

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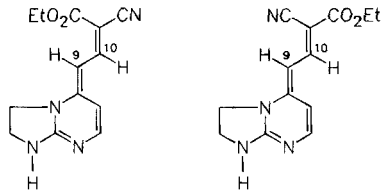
Scheme 3



cis,trans-**6d** (95%) *trans,trans*-**6d** (5%)

An attempted separation of **6c** and **6d** by means of silica-gel chromatography has failed, and the major product **6c** has been obtained in pure state after recrystallization of the mixture from DMF.

The *cis,trans* configuration **6c** has been deduced by means of ^{1}H-NMR spectroscopy: the signal for 10-H of **6c** is shifted downfield as compared with the corresponding signal from **6d**; the isomer **6c** also shows a considerable upfield shift for the 9-H proton relative to isomer **6d**.

Experimental

Melting points (uncorrected): Büchi capillary apparatus. – ^{1}H NMR: Varian VXR 300, 300 MHz, tetramethylsilane as internal standard. – ^{13}C NMR: Varian XL 200, frequency of solvent ([D$_6$]DMSO) for calibration. – MS: LKB 9000 S, 70 eV. – IR: Specord M-80.

1-(4,5-Dihydro-2-imidazolyl)-4-(dimethylamino)pyridinium Chloride (**2**): To a solution of **1** (2.5 g, 25 mmol) in dichlormethane (30 ml) was added 4-(dimethylamino)pyridine (3.7 g, 30 mmol), and the reaction mixture was stirred at room temp. for 4h. After cooling to 5°C, the solid that precipitated was collected by filtration, washed with dichloromethane and recrystallized from ethanol/diethyl ether. Yield 3.1 g of **2** (56%), m.p. 160–163°C (dec.). – IR (KBr): $\tilde{\nu}$ = 3120 cm^{-1}, 1650, 1585, 1430, 1330, 1230, 995. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.5 (s, 6H), 4.0 (s, 4H), 7.4 (d, 2H), 9.0 (d, 2H).

$C_{10}H_{15}ClN_4$ (226.7) Calcd. C 52.97 H 6.67
Found C 52.70 H 6.81

[2-(2,3-Dihydroimidazo[1,2-a]pyrimidin-5(1H)-ylidene)ethylidene]propanedinitrile (**6a**): To a solution of **1** (2.5 g, 25 mmol) and 4-(dimethylamino)pyridine (3.0 g, 25 mmol) in dichloromethane (30 ml) was added with stirring malonodinitrile (2.0 g, 30 mmol). When the exothermic reaction was complete, stirring was continued at 20°C for 1 h. Product **6a** that precipitated was collected by filtration, washed with dichloromethane and recrystallized from DMF. Yield 3.5 g (68%), m.p. > 300°C. – IR (KBr): $\tilde{\nu}$ = 2200 cm^{-1} (C≡N). – ^{1}H NMR ([D$_6$]DMSO): δ = 3.7 (t, 2H), 4.2 (t, 2H), 5.2 (d, 1H, J = 13.7 Hz), 6.85 (d, 1H, J = 6.3 Hz), 7.65 (d, 1H, J = 6.3 Hz), 8.05 (d, 1H, J = 13.7 Hz). – ^{13}C NMR ([D$_6$]DMSO): δ = 39.10, 45.49, 53.68, 92.02, 100.84, 117.18, 119.18, 151.90, 153.29, 154.17, 157.08.

$C_{11}H_9N_5$ (211.2) Calcd. C 62.55 H 4.29
Found C 62.78 H 4.11

5-[2-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)ethylidene]-1,2,3,5-tetrahydroimidazo[1,2-a]pyrimidine (**6b**): To a solution of **1** (2.5 g, 25 mmol) and 4-(dimethylamino)pyridine (3.0 g, 25 mmol) in dichloromethane (30 ml) was added with stirring Medrum's acid (3.4 g, 25 mmol). When the exothermic reaction was complete, the reaction mixture was kept at 20°C for 24 h. The solution was then washed with water (3 × 50 ml), the organic layer was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was treated with water (30 ml) and the crude products **6b** that precipitated collected by filtration. Yield 1.8 g (25%), m.p. 260–263°C (dec.) (DMF/H_2O). – IR (KBr): $\tilde{\nu}$ = 1665 cm^{-1} (C=O). – MS: m/z (%) = 289 (52.1) [M$^+$], 232 (13.6), 203 (13.5), 188 (16.5), 187 (35.9), 186 (100.0), 159 (41.1), 158 (67.6), 157 (14.7). – ^{1}H NMR ([D$_6$]DMSO): δ = 1.6 (s, 6H), 3.75 (t, 2H), 4.2 (t, 2H), 6.7 (d, 1H, J = 14.6 Hz), 6.85 (d, 1H, J = 6.1 Hz), 7.8 (d, 1H, J = 6.1 Hz), 8.1 (d, 1H, J = 14.6 Hz). – ^{13}C NMR ([D$_6$]DMSO): δ = 26.45, 39.22, 46.07, 88.97, 97.93, 100.68, 101.70, 146.22, 156.58, 156.63, 157.48, 162.73, 164.48.

$C_{14}H_{15}N_3O_4$ (289.3) Calcd. C 58.12 H 5.23
Found C 57.81 H 5.15

Ethyl Cyano[2-(2,3-Dihydroimidazo[1,2-a]pyrimidine-5(1H)-ylidene)ethylidene]acetate (**6c**): To a solution of **1** (2.5 g, 25 mmol) and 4-(dimethylamino)pyridine (3.0 g, 25 mmol) in dichlormethane (30 ml) was added with stirring ethyl cyanoacetate (3.4 g, 30 mmol). When the exothermic reaction was complete, the reaction mixture was kept at 20°C for 8 h. The product that precipitated (mixture of **6c** and **6d**; first fraction) was collected by filtration. The filtrate was washed with water (3 × 50 ml), dried with $MgSO_4$, and evaporated to dryness under reduced pressure. The residue was treated with water (20 ml), and a second fraction of product was collected by filtration. The combined fractions of product were recrystallized from DMF to give pure isomer **6c**. Yield 3.2 g (50%), m.p. 267–269°C. – IR (KBr): $\tilde{\nu}$ = 2190 cm^{-1} (C≡N), 1695 (C=O). – MS: m/z (%) = 258 (100.0) [M$^+$], 229 (16.9), 213 (48.1), 190 (12.3), 186 (27.8), 185 (72.8), 184 (16.7), 158 (12.7), 146 (10.5). – ^{1}H NMR ([D$_6$]DMSO): δ = 1.2 (t, 3H), 3.7 (t, 2H), 4.1 (q, 2H), 4.2 (t, 2H), 5.2 (d, 1H, J = 13.5 Hz), 6.65 (d, 1H, J = 6.3 Hz), 7.55 (d, 1H, J = 6.3 Hz), 8.1 (d, 1H, J = 13.5 Hz). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.46, 39.36, 45.31, 59.56, 79.94, 90.95, 100.42, 118.75, 148.80, 153.40, 157.15, 165.09.

$C_{13}H_{14}N_4O_2$ (258.3) Calcd. C 60.45 H 5.46
Found C 60.11 H 5.37

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