

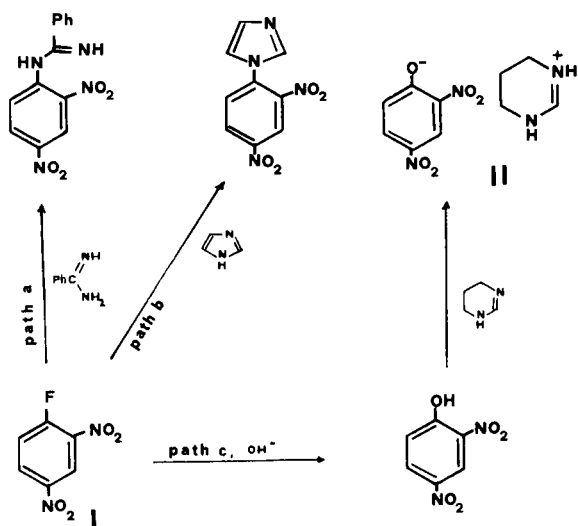
## Failure of Arylation of Reactive Cyclic Amidines Owing to Unusually Facile Ring Opening

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Arylation of amidines (1) with activated aromatic compounds is a well established method of synthesis of arylamidines. Also, arylation of benzamidines with picryl chloride has been long known (2) and, recently, other halonitrobenzenes and halonitronaphthalenes have found similar effective use (Scheme I, path a) (3). Also, a special amidine like imidazole is smoothly arylated in a similar manner (Scheme I, path b) (4).



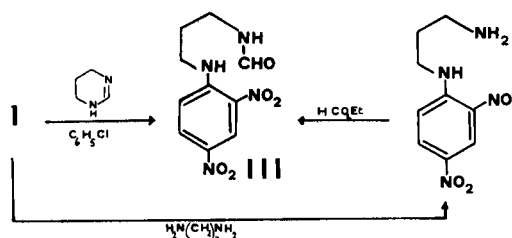
Scheme I

We report here what appears to be a general limitation to the above synthetic method for arylamidines. In fact, arylation of a cyclic amidine like 1,4,5,6-tetrahydropyrimidine along similar lines to those above was unsuccessful, formal ring opening of the arylated product occurring instead. Thus, fluoro-2,4-dinitrobenzene (I), 0.4 M in dried chlorobenzene, reacted vigorously at room temperature with a four molar excess of 1,4,5,6-tetrahydropyrimidine (5). Work-up of the reaction mixture in the usual way led, in our hands, to only one definite compound, m.p. 130-132°, which lacked the characteristics expected for 1-(2,4-dinitrophenyl)-4,5,6-tetrahydropyrimidine, analysing for  $C_{10}H_{12}N_4O_5$ .

The above product cannot be accounted for in terms of hydrolysis of I followed by salt formation between the

phenol and the amidine (Scheme I, path c) as shown by independent preparation of II, m.p. 191°.

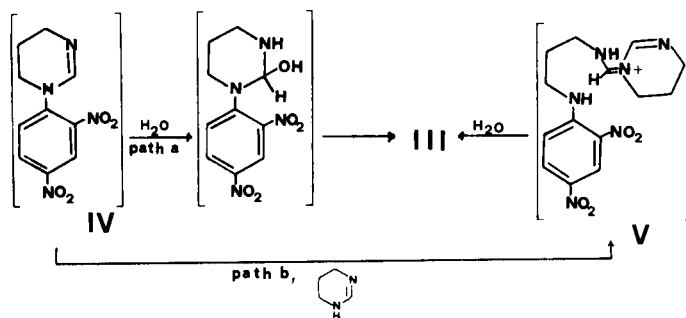
Spectral data suggested, instead, structure III for the above  $C_{10}H_{12}N_4O_5$  compound, which has been confirmed by unequivocal synthesis (Scheme II).



Scheme II

Similar observations were recorded with either fluoro- or chloro-4,7-dinitronaphthalene (6) in the place of I.

The easiest way to conceive formation of III is *via* water attack (possibly base catalyzed by the amidine in excess) on the arylated amidine IV followed by ring opening of the pseudo base (Scheme III, path a).



Scheme III

However, although some analogy may be seen both in the Dimroth rearrangement (7) and in the ring opening of benzimidazole in alkaline benzoyl chloride (8), as well as in some enzymatic processes such as the histidine metab-

olism and urea biosynthesis, the mechanism of Scheme III, path *a*, is unlikely under our dry reaction conditions. Rather, the mechanism of Scheme III, path *b*, reconciles both with lack of water and the excellent yield of arylated imidazole (Scheme I, path *b*) (4,9) imidazole being much less nucleophilic than 1,4,5,6-tetrahydropyrimidine (3,4).

It could be argued that the amidine-catalyzed attack of water on IV could occur during the work up of the reaction mixture. Whilst this possibility is not rigorously excluded by our experiments, uv spectra, in the long wave region, of the reaction mixture before aqueous work up were similar to those obtained after the addition of water, which does not favor path *a*.

Occurrence of amidine degradations of the type described here is an open question. For example, ester amidinolysis by 1,4,5,6-tetrahydropyrimidine has been kinetically investigated without looking for products (10).

#### EXPERIMENTAL

Melting points were taken with a Kofler hot stage apparatus and are uncorrected.  $^1\text{H}$  nmr spectra were obtained with either a Varian A 60 or a JEOL PS 100 spectrometer and are given in  $\delta$  with respect to TMS as an internal standard. Ir spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer. Uv spectra were taken with a SP 800 Unicam spectrophotometer.

1,4,5,6-Tetrahydropyrimidinium 2,4-Dinitrophenolate (II).

A solution of 1,4,5,6-tetrahydropyrimidine (0.089 g., 1.05 mmoles) in 2 ml. of dried benzene was added slowly with stirring to a solution of 2,4-dinitrophenol (0.019 g., 1.06 mmoles) in 3 ml. of the same solvent, whereby a yellow precipitate immediately formed. After 12 hours, the precipitate was filtered and the filtrate was recrystallized from a 95:5 benzene-ethanol mixture to give orange-yellow needles, m.p.  $191^\circ$ ; uv (in ethanol): with maxima at 358 and 396 nm; ir (nujol mull): 3150 (s), 1690 (m), 1600 (m), 1570 (w), 1560 (w), 1520 (m), 1470 (s), 1390 (m), 1320 (m), 1125 (w), and 840 (w).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_5$  (268.23): C, 44.8; H, 4.50; N, 20.9. Found: C, 44.5; H, 4.62; N, 20.6.

*N*-(2,4-Dinitrophenyl)-1,3-diaminopropane.

To a solution of 1,3-diaminopropane (attention: extremely skin irritating) (6 ml.) in 10 ml. of dried benzene was slowly added at room temperature during 0.5 hours with protection from the atmosphere, a solution of 2,4-dinitrofluorobenzene (0.60 g.) in 10 ml. of the same solvent. The mixture was then refluxed for 0.5 hours and the precipitated salt was then filtered under nitrogen. Solvent and excess starting amine were then removed *in vacuo* to leave a dark oil which crystallized on trituration with petroleum ether. Recrystallization from a 40:60 mixture of benzene-cyclohexane gave yellow crystals (0.57 g.) m.p.  $87-88^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.27 (br s, 2H,  $\text{NH}_2$ ), 1.92 (quint,  $J = 4$  Hz, 2H), 2.96 (quart,  $J = 4$  Hz, 2H), 3.59 (quart,  $J = 4$  Hz, 2H), 6.95 (d,  $J = 9$  Hz, 1H), 8.05 (dd,  $J = 9$  Hz, 3 Hz, 1H).

*Anal.* Calcd. for  $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_4$  (240.22): C, 44.6; H, 5.0. Found: C, 44.2; H, 5.4.

Formylation of *N*-(2,4-Dinitrophenyl)-1,3-diaminopropane.

A mixture of *N*-(2,4-dinitrophenyl)-1,3-diaminopropane (0.313 g.) and ethyl formate (18 ml.) was refluxed for 14 hours. The mixture was then evaporated *in vacuo* and the solid residue was recrystallized from benzene to give yellow crystals, m.p.  $121-122^\circ$  in a 95% yield which could not be raised on further recrystallizations.  $^1\text{H}$  nmr, ir, and uv spectra were identical to those recorded for the product of m.p.  $130-132^\circ$  (III) as described below. Clearly, there are at least two different crystalline modifications for III. In fact, recrystallization with seeding by crystals of the last type led to yellow crystals of m.p.  $130-132^\circ$ .

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_5$  (268.23): C, 44.8; H, 4.50; N, 20.9. Found: C, 44.7; H, 4.63; N, 20.4.

Reaction of Fluoro-2,4-dinitrobenzene with 1,4,5,6-Tetrahydropyrimidine.

To a solution of 1,4,5,6-tetrahydropyrimidine (0.2 ml., 2 mmoles) in 1.5 ml. of dried benzene was added a solution of fluoro-2,4-dinitrobenzene (0.146 g., 0.78 mmole) in 2 ml. of the same solvent. The mixture became immediately dark-red with formation of a precipitate. After 2 hours water was added to the mixture. Because neither ether nor dichloromethane were efficient in extracting from this mixture, a gummy material was separated from the water layer and extracted with dichloromethane. All extracts were combined, evaporated and the residue was chromatographed on silica gel, eluent 2:1 ethanol-benzene. The main band,  $R_F = 0.7$ , was extracted with ethanol which, on evaporation, led to a solid material which was recrystallized from benzene to give orange-yellow crystals (0.07 g.) m.p.  $130-132^\circ$ . The mass spectrum showed peaks at  $m/e$  269 ( $M+1$ )<sup>+</sup>; 268  $M$ <sup>+</sup>; 252 ( $M-O$ )<sup>+</sup>; 230 ( $M-NO$ )<sup>+</sup>; 222 ( $M-NO_2$ )<sup>+</sup>, and 167 (probably the 2,4-dinitrophenyl moiety); ir (nujol mull): 3330 (s), 1675 (s), 1620 (s), 1580 (m), 1530 (w), 1500 (w), 1340 (w), 1315 (m), 1300 (m), 1273 (w), 1240 (w), 1153 (w), 1131 (m), 1102 (w), 924 (w), 721 (m).  $^1\text{H}$  nmr (deuterioacetonitrile):  $\delta$  9.10 (d,  $J = 3$  Hz, 1H), 8.87 (br, s, 1H, NH), 8.39 (dd,  $J = 9$  Hz, 3 Hz, 1H), 8.27 (s, 1H, CHO), 7.22 (d,  $J = 9$  Hz, 1H), 6.70 (br s, 1H, NH), 3.50 (m, 4H) (one methylene group is overshadowed by the residual absorption of the solvent; such a methylene group was detectable in hexadeuterio dimethyl sulfoxide as solvent, were, however, the other two methylene groups were overshadowed by the residual solvent absorption); uv (ethanol): with maxima at 346 and 400 nm.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_5$  (268.23): C, 44.8; H, 4.50; N, 20.9. Found: C, 44.6; H, 4.78; N, 20.6.

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2H).

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(9) Reaction of fluoro-2,4-dinitrobenzene with 1,4,5,6-tetrahydropyrimidine was carried out by very slow addition of one molar equivalent of the amidine to the fluoro compound in dry benzene so that the amidine was never present in excess with respect to the fluoro compound. Also this method failed to lead

to the isolation of IV. Chromatography on silica gel with a 1:9 mixture of ethanol-chloroform gave a main yellow band at  $R_f = 0.55$  which afforded a crystalline material, m.p. 148-150°, which analyzed: C, 44.0; H, 3.15; N, 18.6; and O, 33.5. This material failed to give any signal in mass spectrometry under ordinary conditions, strong heating leading to decomposition. Our expectation was that IV, if present in a mixture, should be volatile enough to give signals in mass spectrometry under ordinary conditions.

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