REACTION OF N-(1-OXIDO-4-PYRIDYLMETHYL)-3,5-DIMETHYLBENZAMIDE WITH MALONONITRILE IN ACETIC ANHYDRIDE

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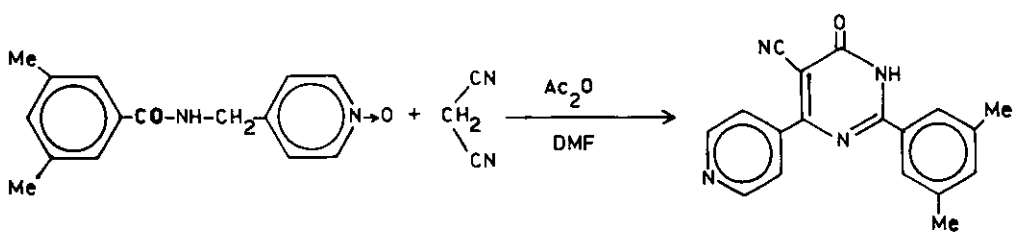
Abstract — Reaction of N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide with malononitrile in acetic anhydride gives 5-cyano-2-(3,5-dimethylphenyl)-6-(4-pyridyl)-4-(3H)-pyrimidinone.

As part of the research now underway in this laboratory on the chemical behaviour of N-(1-oxido-4-pyridylmethyl)benzamides towards compounds containing active methylene group in acetic anhydride[1], the reaction of N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide with malononitrile has been studied.

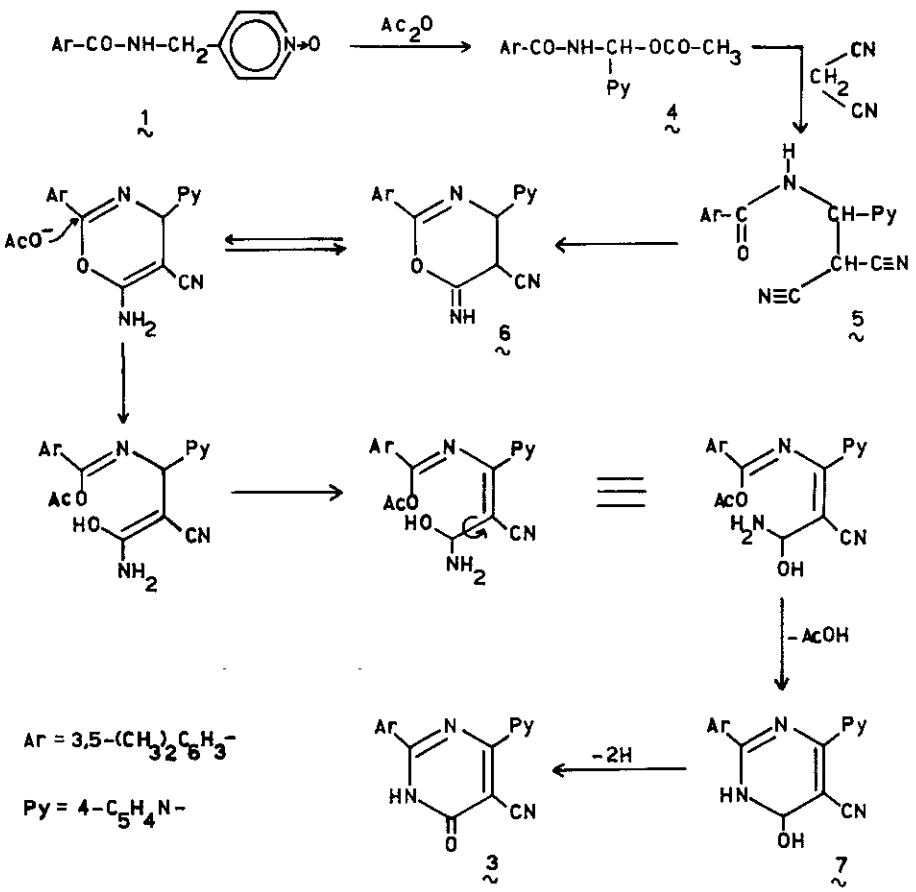
N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide 1 (0.01 mole) and malononitrile 2 (0.01 mole) were heated at 80°C for 4 h with dimethylformamide (10 ml, DMF) and acetic anhydride (1 ml); the solvent was removed in vacuo, and the residual oil treated with ethyl acetate; a white crystalline solid (16.5%) was obtained. This compound was recrystallized from DMF to give crystals, mp >350°C, which was identified as 5-cyano-2-(3,5-dimethylphenyl)-6-(4-pyridyl)-4-(3H)-pyrimidinone 3, by analysis of spectral data as shown in experimental.

Fig. 1



As reported for other reactions carried out in the same medium[2], the first step of the reaction must be the formation of the acetate 4, followed by that of the α-dicyanomethyl derivative 5. The intermediate thus formed undergoes an internal cyclization by nucleophilic attack of oxygen to one of the cyano groups to give the intermediate oxazine 6 wich gives 7 by ring opening followed by a new cyclization, via nucleophilic addition of an acetate ion. Spontaneous aromatization of 7 in the reaction medium leads to pyrimidinone 3, according to a mechanism similar to the one proposed by Soto et al.[3] for the formation of 4H-pyrans from α-benzoylcinnamonitriles, of Dimroth rearrangement type[4]. (Scheme 1).

Scheme 1



The presence of a variety of dehydrogenating agents seems to have no effect on the reaction yield.

In order to ensure its role as an intermediate, independently prepared 4[5] (0.01 mole) was refluxed with malononitrile (0.01 mole) in chloroform (20 ml); 3 was actually obtained in higher yield (42%).

EXPERIMENTAL

All melting points were determined in open capillary on a Büchi SMP-20 and are uncorrected. IR spectra were performed on a Perkin-Elmer 257. Reported values are the more intense or characteristic peaks. ^{1}H-NMR spectra were registred on a Varian MAT 711.

Reaction of N-oxide 1. 1.6 g (0.01 mole) of N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide, 0.7 g (0.01 mole) of malononitrile, 10 ml of dimethylformamide and 1 ml of acetic anhydride are placed in a round bottomed flask and refluxed at 80°C during 4 h. After standing overnight at room temperature, the solvent is removed in vacuo and the residual oil is treated with ethyl acetate, obtaining 0.5 g (16.5%) of 2-(3,5-dimethylphenyl)-5-cyano-6-(4-pyridyl)-4(3H)-pyrimidinone, mp >350°C (DMF). IR (potassium bromide): 3220 (NH), 2230 (CN) and 1665 (CO) cm^{-1}; ^{1}H-NMR (trifluoracetic acid): δ = 2.502 (s, 6H, $2CH_3$), 7.529 (s, 1H, H_4-phenyl), 7.987 (s, 2H, H_2 and H_6-phenyl), 8.897 (d, 2H, H_3 and H_5-pyridine), 9.200 (d, 2H, H_2 and H_6-pyridine) ppm; MS: m/e = 302 (100 M^+), 274 (80), 259 (15), 171 (75), 143 (20), 132 (25), 116 (20), 105 (15), 77 (10).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.22; H, 4.82; N, 18.56.

Reaction of Acetate 4. 3 g (0.01 mole) of N-(α-acetoxy-4-pyridylmethyl)-3,5-dimethylbenzamide, 0.66 g (0.01 mole) of malononitrile and 20ml of chloroform were refluxed during 8 h. After elimination of the solvent in vacuo, the residual oil is triturated with benzene, giving 1.3 g (42%) of 3.

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