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TIN (IV) CHLORIDE-PROMOTED REACTIONS OF β-DICARBONYL COMPOUNDS WITH NITRILES. SYNTHESIS OF AMINOPYRIDINES AND AMINOQUINOLINES.

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Summary: *β-Ketoesters and β-diesters react with β-enaminonitriles in the presence of stoichiometric amounts of tin (IV) chloride to give 4-aminopyridines and pyridones while they react with aromatic ortho-aminonitriles to give 4-aminoquinolines and quinolones.*

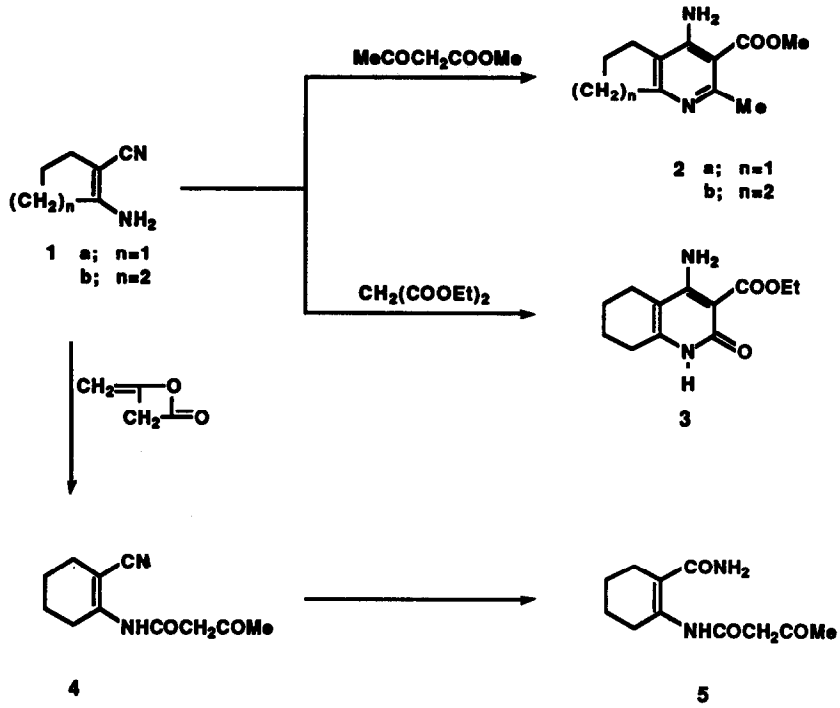
The metal-promoted formation of a carbon-carbon bond between the cyano group of nitriles and the intercarbonylic methylene group of β-dicarbonyls affords β-enaminodione derivatives[1], which, in particular cases, dimerise to pyrimidines[2] or cyclise to pyrrolines[3].

In order to explore further the role of metals in promoting the formation of heterocycles, we undertook the synthesis of 4-aminopyridines and of 4-aminoquinolines, mainly because of the importance of these rings in medicinal chemistry[4].

The synthesis of pyridines was carried out according to scheme 1. Two different approaches were investigated. In the first, we allowed cyclic β-enaminonitriles to react with β-ketoesters and β-diesters in the presence of stoichiometric amounts of tin (IV) chloride. In a typical reaction, β-enaminonitrile, β-dicarbonyl and tin (IV) chloride, in 1:1:2 molar ratio, were heated under reflux in toluene for 3-12 h. After the removal of the solvent, the residue was stirred with an aqueous solution of sodium carbonate. The resulting suspension was extracted with ethyl acetate and the extracts were dried and concentrated to give the desired heterocycles.

The 4-aminopyridine derivatives (**2a-b**)[5a] were obtained in *ca.* 60% yield in the reaction of 1-amino-2-cyano-cyclopentene (**1a**) and of 1-amino-2-cyano-cyclohexene (**1b**) with methyl acetoacetate. Lower yields (32%) of the 4-amino-2-pyridone (**3**)[5a]were obtained in the reaction of nitrile (**1b**) with diethyl malonate.

In an alternative approach, the N-acetoacetylation of enaminonitrile (**1b**) with diketene afforded the N-acetoacetamide (**4**, yield 92%). Attempts to cyclise compound (**4**), heating it under reflux in toluene in the presence of tin (IV) chloride, failed to yield the desired pyridone ring, the only isolated compound being the amido N-acetoacetamide (**5**) (yield: 62%).

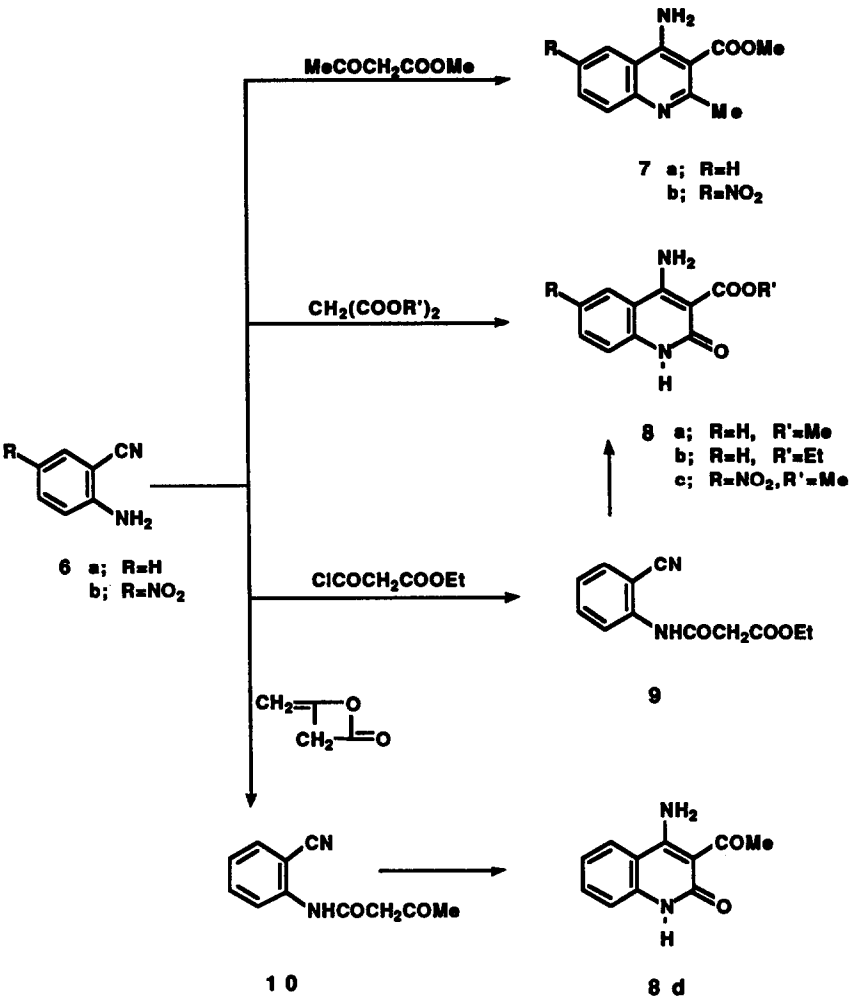


SCHEME 1

The synthesis of 4-aminoquinolines was carried out according to scheme 2. In the first type of approach, 2-aminobenzonitrile (**6a**) and its 5-nitro derivative (**6b**) were allowed to react with methyl acetoacetate to give the 4-aminoquinolines (**7a-b**)[5b] in good yield (60-80%). Lower yields (20-30%) of the 4-amino-2-quinolones (**8a-c**)[5b] were obtained in the reaction of the nitriles (**6a,b**) with dialkyl malonates.

In the alternative approach, treatment of 2-aminobenzonitrile (**6a**) with ethyl malonyl chloride yielded the malonyl ester amide (**9**) while reaction of (**6a**) with diketene afforded the N-acetoacetamide (**10**). Attempts to cyclise compound (**9**), under reflux in toluene in the presence of tin (IV) chloride, gave the quinolone (**8b**) in very low yield (5%), while the N-acetoacetamide (**10**) was cyclised under the same experimental conditions to the quinolone (**8d**) in moderate yield (35%).

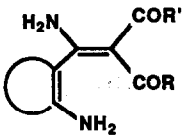
The obtained results show that tin (IV) chloride is efficient in promoting the cyclisation reactions of β-enaminonitriles and aromatic *ortho*-aminonitriles with β-dicarbonyls. The desired heterocycles were recovered in good yield in the reactions of nitriles with β-ketoesters, whilst lower yields were obtained in the reactions with β-diesters.



SCHEME 2

According to our previous results[1] the heterocycles obtained in the reactions between aminonitriles and β-dicarbonyls are formed *via* the intermediate β-enaminodiones (**11**). These intermediates have never been isolated possibly due to their fast intramolecular cyclisation to heterocyclic rings.

The promotion of these syntheses by tin (IV) chloride may be related to its well known ability to coordinate both the β-dicarbonyls[6] and the nitriles[7], enhancing their nucleophilic and electrophilic character respectively.



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The failure to cyclise of the N-acetoacetamide (**4**) and the low yields obtained in the cyclisation of the malonyl ester amide (**9**) and acetoacetamide (**10**) could be explained by a difficulty in coordinating both the β-dicarbonyl moiety and the cyano group of the same molecule, possibly due to steric and geometric reasons.

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5. Spectral data for key compounds are given below. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively:
   a) pyridine derivatives: (**2a**), IR (Nujol): ν 3425, 3340-3260, 3220-3160, 1690, 1610, 1250 cm^{-1}; δ_H ($CDCl_3$): 2.2 (m, 2H, CH_2), 2.65 (s, 3H, Me), 2.70 (t, J=6.1 Hz, 2H, CH_2), 2.95 (t, J=6.1 Hz, 2H, CH_2), 3.89 (s, 3H, Me), 5.7 (bs, 1H, NH), 7.3 (bs, 1H, NH);
   (**3**), IR (KBr): ν 3410, 3290, 1660, 1620, 1530, 1270, 1190, 1090 cm^{-1}; δ_H ($CDCl_3$): 1.40 (t, J=7.1 Hz, 3H, Me), 1.79 (m, 4H, 2 CH_2), 2.30 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 4.34 (q, J=7.1 Hz, OCH_2), 5-10 (vb, 2H, NH_2), 11.7 (bs, 1H, NH); δ_C ($CDCl_3$): 14.38 (q, J=125 Hz, Me), 20.77 (t, J=123 Hz, CH_2), 21.19 (t, J=123 Hz, CH_2), 21.54 (t, J=129 Hz, CH_2), 26.37 (t, J=126 Hz, CH_2), 58.82 (t, J=146 Hz, OCH_2), 91.61 (s, C-5), 101.66 (s, C-3), 145.58 (s, C-6), 160.24 (s, C-4 and C-2), 169.38 (s, COO).
   b) quinoline derivatives: (**7a**), IR (KBr): ν 3360, 3160, 1670, 1615, 1550, 1260 cm^{-1}; δ_H ($CDCl_3$): 2.80 (s, 3H, Me), 3.90 (s, 3H, Me), 7.08 (bs, 2H, NH_2), 7.4 - 7.9 (m, 4H, Ph); δ_C ($CDCl_3$): 27.9 (q, J=128 Hz, Me), 51.6 (q, J=148 Hz, OMe), 102.1 (s, C-3), 116.9 (s, Ar), 120.6 (d, J=158 Hz, Ar), 124.9 (d, J=161 Hz, Ar), 129.0 (d, J=163 Hz, Ar), 131.3 (d, J=162 Hz, Ar), 147.5 (s, Ar), 153.7 (s, C-4), 159.5 (s, C-2), 169.9 (s, COO);
   (**8a**), IR (KBr): ν 3380-3200, 1670, 1640, 1620, 1280, 740 cm^{-1}; δ_H (DMSO-d_6): two tautomers are present, the main one (80%) corresponding to structure (**8a**): 3.74 (s, 3H, Me), 7.09-7.21 (m, 2H, Ar), 7.49-7.57 (m, 1H, Ar), 8.11 (d, J=9 Hz, 1H, Ar), 8.43 (bs, 2H, NH_2), 10.92 (bs, 1H, NH).
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