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A NEW "ONE FLASK" PREPARATION OF 2-ALKYLAMINO-4-CHLOROQUINAZOLINES FROM ORTHO AMINOBENZONITRILES AND PHOSGENIMINIUM SALTS

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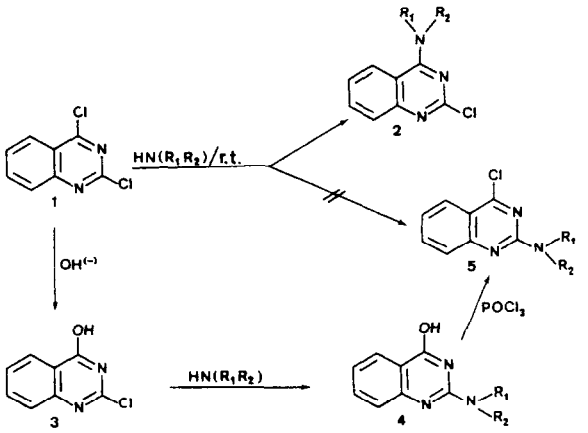
Summary : Phosgeniminium salts 7 react easily with ortho amino-benzonitriles 6 to give, selectively and quantitatively the corresponding 2-dialkylamino-4-chloroquinazolines 5.

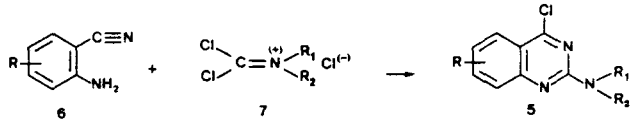
The two chlorine atoms in 2,4-dichloroquinazoline 1 behave differently towards nucleophiles[1],[2] and it is well known that 1 reacts readily at room temperature with primary and secondary amines to give 4-amino-2-chloroquinazolines 2 exclusively. Therefore the isomeric 2-amino-4-chloroquinazolines 5 which cannot be prepared by direct amination of 1 are generally obtained by means of a three steps reaction[3] starting from 1 via the 2,4-disubstituted quinazolines 3 and 4 as it is shown in the following scheme :



Direct "one pot" formation of 2-dialkylamino-4-chloroquinazolines starting from 2,4-dihydroxyquinazoline and using $POCl_3$ and tertiary amines such as triethylamine[4] and N-alkylpyrrolidine[5],[6], has been reported. However, although very interesting, that procedure, which does not seem to work with all kinds of tertiary amines, does not give very good yields of the expected 2-amino-4-chloroquinazolines, the reaction leading also to 2,4-dichloroquinazoline 1 as a by-product[5],[6].

The synthesis of 2,4-disubstituted quinazolines by heterocyclisation of ortho disubstituted benzene derivatives, including ortho aminobenzonitrile is well documented. However, none of the procedures so far described leads, to our knowledge, to a direct preparation of 2-dialkylamino-4-chloroquinazolines 5.

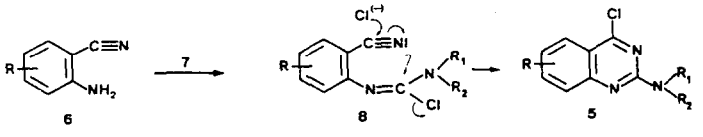
In our attempt to prepare heterocyclic compounds of biological interest, we found that 2-dialkylamino-4-chloroquinazolines 5 can now be prepared selectively under mild "one flask" reaction conditions, starting from ortho aminobenzonitriles 6 and phosgeniminium salts 7 which have already been proved to be very useful in synthetic chemistry, especially in various one-step heterocyclisation reactions by insertion of one carbon atom bearing a dialkylamino group[7],[8].



(R = H,4-CH_3,5-Cl) (R = H,7-CH_3,6-Cl)

Phosgeniminium salts do not react with nitrile groups unless these latter are sufficiently activated or have previously been transformed in their corresponding chloroiminium chloride by means of anhydrous hydrochloric acid.

Since we have been able to isolate quantitatively (for characterisation purpose) the only intermediate adduct 8, we assume that the reaction, which can easily be monitored by infra-red spectroscopy, proceeds as following :



Thus, a mixture of 0.01 mole of ortho aminobenzonitrile 6, 0.012 mole of 7a ($R_1 = R_2 = CH_3$) and 200 ml of dry dichloroethane, kept under stirring and away from atmospheric moisture, was allowed to stand at room temperature for two hours, until phosgeniminium chloride was completely dissolved, then at 45-50°C for 40-50 hours until no characteristic signal of the $-C \equiv N$ group was left on I.R. spectra (Yield : 85 to 95 %).

Spectral data

H^1 - NMR δ (ppm)/TMS (internal reference) ; s = singlet, d = doublet, dd = doublet of doublet, br = broad.
Mass spectrum : electron impact.
IR (cm^{-1}) in KBr.

1) 2-N-dimethylamino-4-chloroquinazolines 5

5a (R = H) : NMR ($CDCl_3$) : 3.25 (s, $N(CH_3)_2$) ; 7.1 to 8.1 (three br, 5,6,7 and 8-H).
M^+ = 207 ($C_{10}H_{10}ClN_3$).
IR : 1550, 1585, 1620 (C = N).

5b (R = 7-CH_3) : NMR ($CDCl_3$) : 2.45 (s, 7-CH_3) ; 3.3 (s, $N(CH_3)_2$) ; 7.05 (dd, 6-H, J_{5-6} = 8.0 Hz) ; 7.4 (br, 8-H) ; 7.85 (d, 5-H, J_{5-6} = 8.0 Hz).
M^+ = 221 ($C_{11}H_{12}ClN_3$).
IR = 1555, 1595, 1620 (C = N).

5c (R = 6-Cl) : NMR ($CDCl_3$) : 3.25 (s, $N(CH_3)_2$) ; 7.5 and 7.95 (two br, 5,7 and 8-H).
M^+ = 241 ($C_{10}H_9Cl_2N_3$).
IR : 1550, 1590, 1620 (C = N).

2) N,N-dimethyl, N'-[(2-cyano)phenyl]-chloroformamidines 8

8a (R = H) : NMR ($CDCl_3$) : 3.2 (s, $N(CH_3)_2$) ; 6.95 to 7.65 (br, 3,4,5 and 6-H).
IR : 2220 ($C \equiv N$).

8b (R = 5-CH_3) : NMR ($CDCl_3$) : 2.35 (s, 5-CH_3) ; 3.05 (s, $N(CH_3)_2$) ; 6.85 (d, 4-H, J_{3-4} = 8.0 Hz) ; 7.35 (d, 3-H, J_{3-4} = 8.0 Hz) ; 8.10 (br, 6-H).
IR = 2220 ($C \equiv N$).

8c (R = 4-Cl) : NMR ($CDCl_3$) : 3.25 (s, $N(CH_3)_2$) ; 6.90 (d, 6-H, J_{5-6} = 8.0 Hz) ; 7.40 (dd, 5-H, J_{5-6} = 8.0 Hz, J_{3-5} = 2.6 Hz) ; 7.50 (br, 3-H).
IR = 2220 ($C \equiv N$).

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