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ALKYLATION OF QUINOLINES WITH TRIALKYL PHOSPHATES

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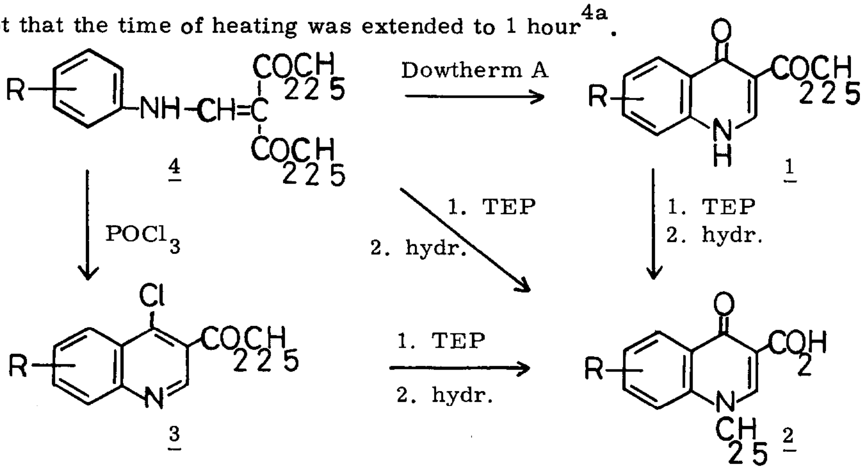
Recently Yamauchi and coworkers reported the use of trialkylphosphates for the alkylation of N-heterocycles[1-3], apparently unaware of our own extensive work with trimethyl and triethyl phosphates as alkylating agents reported in the patent literature some years ago[4-6]. As our procedures offer some advantages, and our investigations have in some directions been more extensive, we now produce a brief report of both alkylation and cyclisations followed by N-alkylation of 4-quinolones and related compounds. Our procedures involving the use of the readily available, non toxic and inexpensive phosphates as solvents, give high yields in short reaction times.

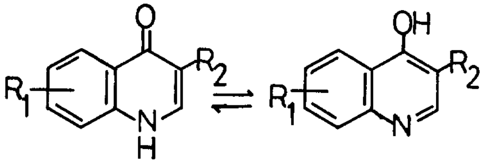
Ethyl 4-quinolone-3-carboxylates (1A-D) were heated in 3-5 mol equiv. of triethylphosphate (TEP) at 220 °C (reflux) for 20-30 minutes in the presence of a base (K_2CO_3), followed by alkaline hydrolysis at 90 °C for 1 hour, yielding the N-alkylated acids (2A-D) in 90-95%[4b]. The same type of product 2 can alternatively be prepared from the 4-chloroderivatives 3 under identical conditions in yields of 90-93%[4d]. 3 is formed by cyclisation of 4 in $POCl_3$[4c]. Furthermore we found that starting from 4 the formation of the quinoline ring and N-ethylation could be accomplished simultaneously: again the same procedure was used except that the time of heating was extended to 1 hour[4a].



A, R = H; B, R = 6,7-CH_2O_2; C, R = 6-$C_{10}H_{21}O$, 7-C_2H_5O; D, R = 6,7-C_2H_5O

Conversions analogous to 1 → 2 and 3 → 2 were accomplished with trimethylphosphate (TMP) to give the N-methyl derivatives in excellent yields.

The generality of the reaction is shown by application to the conversion of 4-quinolones (5-6) and 3-cyano-4-quinolones (7-8) into the corresponding N-alkyl derivatives[5]. An example with a related ring system is the preparation of the N-ethyl-1,8-naphthyridine 9[6].

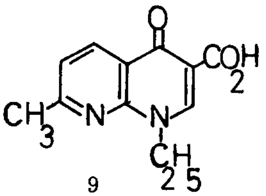


5 R_1 = H, R_2 = H

6 R_1 = 6,7-CH_2O_2; R_2 = H

7 R_1 = H, R_2 = CN

8 R_1 = 6,7-CH_2O_2; R_2 = CN



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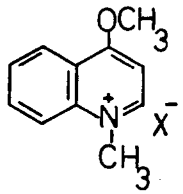

11 X = $(CH_3O)_2PO_2$

12 X = ClO_4^-

13 X = BF_4^-

In a detailed study of the alkylation of 4-quinolone with trimethylphosphate, 4-methoxyquinoline (10) was detected in the early stages but later the reaction mixture contained only the quaternary salt 11 and 1-methyl-4-quinolone (14). The ratio of 11 to 14 depends on the reaction temperature; at high temperatures the salt 11 is predominant. The quaternary perchlorate 12[7] and fluoroborate 13 were precipitated from the reaction mixture by the addition of perchloric or fluoroboric acid.

In independent experiments, it was found (i) that TMP converted 1-methyl-4-quinolone (14) partially into the quaternary salt (11), (ii) that TMP converted 4-methoxyquinoline (10) into a mixture of 11 and 14 in the same ratio as found above, and (iii) 4-methoxyquinoline (itself stable at 150° in inert solvents) was converted to 1-methyl-4-quinolone at 130° in propylene carbonate by the quaternary salt 12.

Experiments (i) and (iii) above indicate that the quaternary salt transfers the O-methyl to the nitrogen of a 4-methoxyquinoline[8], thus effecting the O → N intermolecular rearrangement and simultaneously regenerating the quaternary salt.

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(7) 4-Methoxy-N-methylquinolinium perchlorate (12) m.p. 251-253 °C, lit. m.p. 250-252 °C, P. Schroeder and M. Kuckner, Arch. Pharm. 301, 39 (1968).

(8) cf. P. Beak, J. Bonham, J.T. Lee, Jr., J. Am. Chem. Soc. 90, 1569 (1968).