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ACTION OF PHENYL ISOCYANIDE DICHLORIDE ON CYCLIC TERTIARY AMINES A NEW AND CONVENIENT DEALKYLATION REACTION

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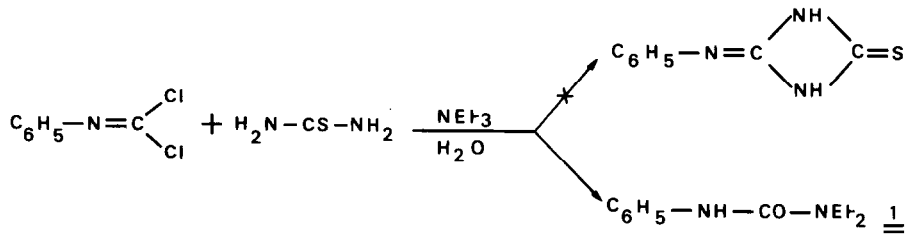
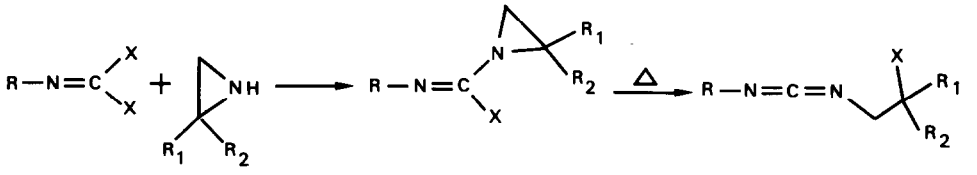
During studies related to the synthesis of derivatives of clonidine [1] phenyl isocyanide dichloride (PID) was treated with thiourea in the presence of triethylamine as acid acceptor. Instead of the expected heterocycle, the phenylurea derivative 1 was obtained.



The formation of hygroscopic salts by the action of PID on tertiary amines has been observed previously apparently without further investigation[2]. The recent disclosure [3] of the action of PID on N-unsubstituted aziridines leading to carbodiimides in accordance with the equation :

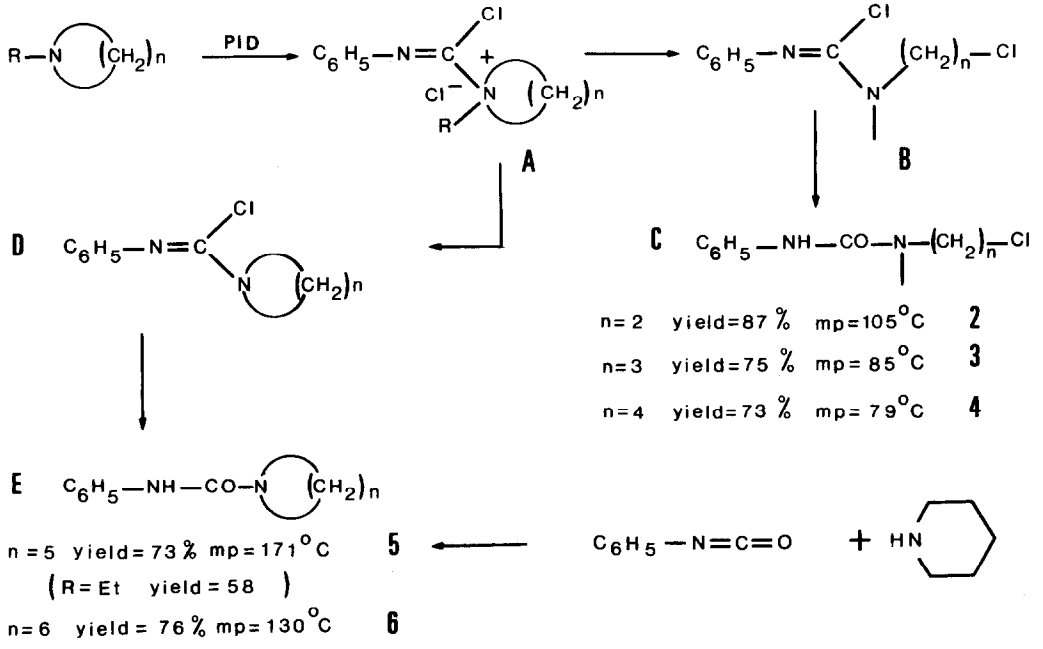


R_1, R_2 = H, or alkyl

prompted us to publish our own work, related to the action of PID with cyclic tertiary amines.

Thus PID reacted (AcOEt, - 75° C, under N_2) with N-methyl pyrrolidine to give a hygroscopic salt A (n=4) (NMR [4] : ($CDCl_3$) δ = 2.4 (m, 4H), 4.0 (s, 3H), 4.6 (m, 4H) which decomposed (24 - 26° C) to give the ring-opened chloroformamidine B (n = 4) (NMR : δ = 3.15 (s, 3H), 3.58 (m, 4H), 1.82 (q. 4H), and urea 4 after hydrolysis.

N-methylaziridine reacted instantaneously (Et_2O,- 75° C) with PID to give, after hydrolysis, the chlorourea derivative 2 (NMR : ($CDCl_3$) δ = 3.09 (s, 3H), 3.69 (s, 4H), as did azetidine to give the chlorourea derivative 3 (NMR : ($CDCl_3$) δ = 2.08 (quintuplet, J = 5.5 Hz, 2H), 3.01 (s, 3H), 3.60 (q, 4H). By irradiation at the quintuplet frequency the quartet gave 2 singlets (δ = 3.62 (s, 2H), 3.72 (s, 2H) showing the presence of 3 linear methylene groups.



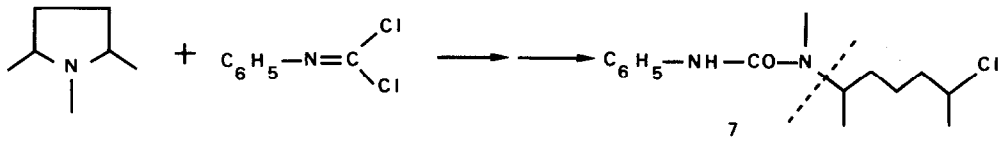
When N-methylpiperidine or N-ethylpiperidine was reacted with PID, they gave after hydrolysis of the iminochlorocompound D (n = 5) (isolated and characterized by IR and NMR) exclusively the urea derivative 5, also obtained by the addition of phenylisocyanate to piperidine.

N-methylazepine behaved similarly, leading by a clean reaction to

the demethylated derivative 6.

It is noteworthy that in these cases the reaction proceeds by dealkylation without any significant formation of ring-opened compounds (NMR and TLC). It clearly appears that PID reacts with small cyclic amines ($n \leqslant 4$) to give ring-opened compounds of type B, whereas it reacts with larger ones ($n \gg 5$) to give compounds of type D.

It was expected that by using hindered amine, increase of the bulk of the methyl groups would result in a decrease of reactivity. Thus, when submitted to PID, 1,2,6-trimethylpiperidine failed to react, probably due to steric hindrance excluding the approach of PID. However 1,2,5-trimethylpyrrolidine reacted readily to give the corresponding ring-opened compound 7 (mp = 112° C, NMR : ($CDCl_3$) δ = 1.15 (d, J = 5 Hz, 3H), 1.5 (d, J = 5 Hz, 3H), 2.82 (s, 3H), 4.1 (m, 1H), 4.6 (m, 1H) : MS [5], M^+ = 268, $\frac{m}{e}$ = 177 α fragmentation).



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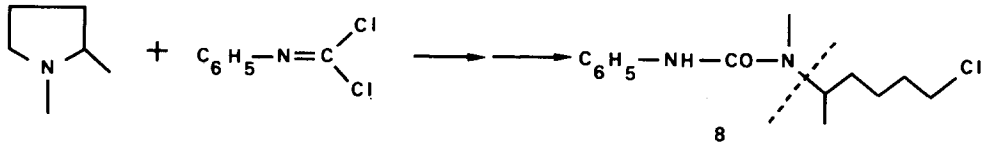
To get a further insight into the mechanism of this reaction PID was mixed with an unsymmetrical amine eg 1,2-dimethylpyrrolidine, compound 8 (mp = 94° C) being obtained.



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The structure 8 was assigned after careful examination of its NMR spectrum ($CDCl_3$) δ = 1.13 (d, J = 5 Hz, 3H), 2.8 (s, 3H), 3.54 (t, J = 5 Hz, 2H), 4.5 (m, 1H) and especially by its MS (M^+ = 254, $\frac{m}{e}$ = 177, α fragmentation) compared with that of 7.

It would seem that the mechanism of the cleavage involves nucleophilic attack by the chlorine ion on the less hindered side of the molecule, rather than an SN_1 type of reaction. Elderfield and Hageman [6] in a study of the action of cyanogen bromide on unsymmetrical pyrrolidines and aziridines had shown the same direction of opening.

The action of PID on tertiary amines thus presents an attractive method, not previously reported, for dealkylation or for ring-opening under mild conditions, in very good yields. This reaction is akin to the Von Braun degradation of tertiary amines. Nevertheless it presents the advantages of utilizing a non-toxic reagent (without loss of yield) and of allowing the isolation of the chloroformamidine intermediates which can be precursors for the synthesis of amino tetrazolyl and of asymmetric cyclic urea derivatives. Work continues on the utility, application and extension of this reaction.

REFERENCES AND FOOTNOTES

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2) Von E. Kühle, B. Anders, E. Klauke, H. Tarnow and G. Zumach, Angew. Chem. internat. Edit., 8, 20 (1969)
3) D.A. Tomalia, T.J. Giacobbe and J. Midland, Dow Chemical, U.S. Pat. 3 754 032 (C.A., 80, 14722 a, 1974)
4) NMR spectra were recorded on a Perkin Elmer R 12 A or R 12 B in $CDCl_3$ solution with TMS as internal reference. Chemical Shifts in δ
5) MS were carried out on a LKB 9000
6) R.C. Elderfield and H.A. Hageman, J. Org. Chem., 14, 105 (1949)

All the new compounds gave proper analysis and appropriate IR, UV and NMR absorption and MS.