Tetrahedron Letters No. 38, pp 3383 - 3386, 1974. Pergamon Press. Printed in Great Britain.

N,N-DIHALOPHOSPHORAMIDES. VIII. A NOVEL APPROACH TO PYRROLIDINE DERIVATIVES[1]

A. Zwierzak* and T. Gajda

Institute of Organic Chemistry, Technical University (Politechnika), 90-924 Lodz, Poland

(Received in UK 2 July 1974; accepted for publication 9 August 1974)

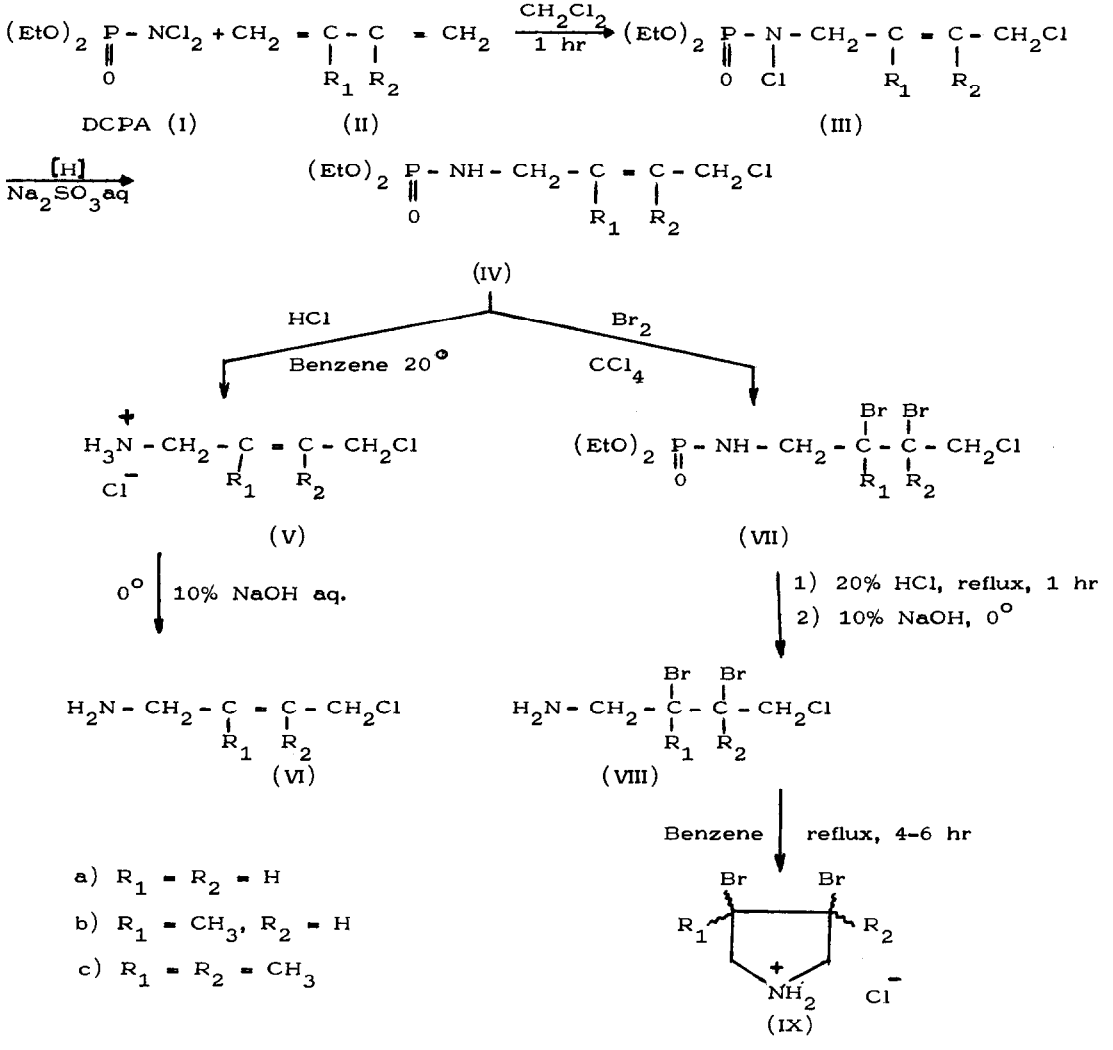
The pyrrolidine ring has been hitherto usually obtained from an existing four-carbon chain by establishing one or both carbon-nitrogen bonds in the most diverse ways[2-8]. With the exception of the Hofmann-Löffler reaction, generally applied for the preparation of N-substituted pyrrolidine derivatives[9-11], all other methods were, however, often limited in their general application by the fortuitous availability of the starting materials.

Our interest in developing effective methods for regiospecific functionalization of a double bond[12] has led us to explore the reactions between diethyl N,N-dichlorophosphoramidate (DCPA)(I) and conjugated dienes. This paper describes the 1,4-addition of DCPA (I) to butadiene and some of its analogues (II a-c) which provides the method of direct 1,4-aminochlorination of an olefinic system, thereby opening a new, simple route to pyrrolidine derivatives.

We found that DCPA (I) reacted easily and almost quantitatively with butadiene (IIa) at room temperature in methylene chloride solution (see Scheme) to give diethyl N-(4--chlorobuten-2-yl)-phosphoroamidate (IVa) [pale-yellow oil, 93% yield, n_D^{20} - 1.4678] after reduction of primarily formed adduct (IIIa) with aqueous sodium sulphite. Subsequent P-N bond cleavage in (IVa) with dry hydrogen chloride in benzene yielded 4-chlorobuten-2-yl--amine hydrochloride (Va) [86% yield, m.p. 154-6°]. The reactions of DCPA (I) with isoprene (IIb) and 2,3-dimethylbutadiene (IIc) proceeded analogically affording the corresponding unsaturated δ-chloroamine hydrochlorides (Vb,c) after degradation of (IVb,c) with dry hydrogen chloride. The usual analytical and spectral data (IR, NMR) permitted an unambiguous structural assignment for all the compounds mentioned.

In view of the expected trans-addition of DCPA (I) to conjugated dienes we were not surprised to find that the unsaturated δ-chloroamines (VIa-c) as well as the adducts (IVa-c) were exceptionally resistant to cyclization under conventional reaction conditions.

S C H E M E



a) $R_1 = R_2 = H$

b) $R_1 = CH_3$, $R_2 = H$

c) $R_1 = R_2 = CH_3$

In order to circumvent this difficulty we have modified the synthetic procedure by removal a double bond from the adducts (IVa-c) thus increasing flexibility of these systems and their propensity for cyclization. This could be easily accomplished by bromination of (IVa-c) in carbon tetrachloride prior to degradation and cyclization.

The reaction sequence (II) → (IX) constitute therefore a synthesis of 3,4-dibromopyrrolidine derivatives from the corresponding conjugated dienes. The convenience of the multistep procedure is strongly enhanced by carrying out the preparation without isolation and purification of some intermediate compounds.

A typical experiment can be illustrated by the preparation of 3,4-dibromopyrrolidine hydrochloride (IXa). Gaseous butadiene was introduced to a solution of DCPA (11.1 g, 0,05 mole) in methylene chloride (20 ml) with stirring and efficient external cooling (5-10°). When the evolution of heat ceased stirring was continued for additional 30 min. at room temperature. The solution was then diluted with methylene chloride (80 ml) and reduced with aqueous sodium sulphite (18.9 g of Na_2SO_3 in 75 ml of water) at room temperature until it gave negative test for "positive" chlorine. The organic phase was washed with water (3 x 50 ml), dried and evaporated. Oily residue was dissolved in carbon tetrachloride (60 ml), cooled to 5° and a solution of bromine (4.4 g, 0,055 mole) in carbon tetrachloride (20 ml) was added dropwise at this temperature. Stirring was continued for 1 hr at room temperature. The solution was then washed with 1% Na_2SO_3 aq. and water, dried and evaporated. 20% Hydrochloric acid (32 ml, ca. 0,5 mole) was added to the residue and the mixture was refluxed until it became homogenous (30-40 min.). The solution was then filtered, cooled to 0° and treated with an excess of ice-cold 10% sodium hydroxide solution. The organic phase was extracted with benzene (3 x 150 ml), the extract was dried over anh. $MgSO_4$, filtered and refluxed gently for 6 hr to give 3,4-dibromopyrrolidine hydrochloride (IXa), which separated from the solution. Yield - 41% (based on DCPA). (IXa) had m.p. 185-186°; [IR : 1560 cm^{-1} (NH_2^+); NMR(D_2O): δ 4.00-4.20 (6 lines, 2H, AB part of ABX system, $C\underline{H}_2$), 5.05 - 5.15 (m, 1 H, X part, $C\underline{H}$), 5.07 (s, 2 H, NH_2^+)]. Similar results, were obtained for other pyrrolidine derivatives [(IXb): yield - 30%; m.p. 166 - 7°; IR: 1580 cm^{-1} (NH_2^+); NMR (D_2O) : δ 2.21 (s, 3 H, $C\underline{H}_3$), ABX system (δ_A = 4.35, δ_B = 4.02, δ_X = 4.69, J_{AX} = -7.6 Hz, J_{BX} = -11.4 Hz, J_{AB} = = +11.8 Hz), A'B'system ($\delta_{A'}$ = 4.46, $\delta_{B'}$ = 4.02, $J_{A'B'}$ = 13.5 Hz), 5.04 (s, 2 H, NH_2^+); (IXc): yield - 19%; m.p. 195 - 7°; IR: 1575 cm^{-1} (NH_2^+); NMR (D_2O) : δ 2.37 (s, 6 H, $C\underline{H}_3$), AB system (4 H, δ_A = 4.44, δ_B = 4.18, J_{AB} = 13.4 Hz), 5.07 (s, 2H, NH_2^+)].

Our new entry to 3,4-dibromopyrrolidine derivatives offers some further possibilities to functionalization of the pyrrolidine ring. This can be exemplified by effective debromina-

tion of (IXa) to Δ^3-pyrroline hydrochloride [m.p. 169.5-171.5°; picrate - m.p. 155.5-156.5° (lit.[13] - m.p. 155.6-157°); NMR (D_2O) δ 6.25 (s, 2H, vinyl protons), 5.00 (s, 2H, NH_2^+), 4.42 (s, 4H, CH_2); 71% yield] on refluxing it with zinc dust in anh. ethanol for 30 min.

It seems that the reported application of DCPA addition to conjugated dienes is capable of producing a variety of five-membered ring nitrogen heterocycles. We are continuing our effort to examine these and other aspects of the conceptually general dihalophosphoramide-diene addition-cyclization sequence.

REFERENCES

1. Part VII of this series, A. Zwierzak and S. Zawadzki, Tetrahedron, 29, 3899 (1973).
2. S. Gabriel, Ber. 24, 3231 (1891).
3. W. Jacobi and G. Merling, Ann. 278, 1 (1894).
4. J. von Braun and E. Beschke, Ber. 39, 4120 (1906).
5. H. Freundlich and G. Salomon, Ber. 66, 355 (1933).
6. W. Keil, Ber. 63B, 1614 (1930).
7. R. Appel and O. Büchner, Angew. Chem. 74, 430 (1962).
8. D. B. Denney, R. L. Powell, A. Taft and D. Twitchell, Phosphorus 1, 151 (1971).
9. M. E. Wolff, Chem. Rev. 63, 55 (1963).
10. E. J. Corey and W. R. Hertler, J. Amer. Chem. Soc. 82, 1657 (1960).
11. E. Schmitz and D. Murawski, Chem. Ber. 99, 1493 (1966).
12. A. Zwierzak and A. Koziara, Tetrahedron 26, 3521, 3527 (1970); S. Zawadzki and A. Zwierzak, Tetrahedron 29, 315 (1973).
13. J. M. Bobbitt, L. H. Amundsen and R. I. Steiner, J. Org. Chem. 25, 2230 (1960).