Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8247-8248, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01880-1

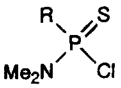
Nucleophilic Substitution in Benzylic Phosphonothioic Dichlorides Formation of a Diamide without Intervention of the Amidic Chloride

Martin J.P. Harger

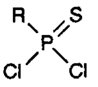
Department of Chemistry, The University, Leicester LE1 7RH, UK.

Abstract: The diamide $RP(S)(NEt_2)_2$ (R = $PhCH_2$ or Ph_2CH) is formed directly from the dichloride $RP(S)Cl_2$ more quickly than it is from the amidic chloride $RP(S)(NEt_2)Cl$
Copyright © 1996 Elsevier Science Ltd

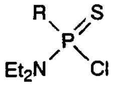
Having had no difficulty preparing the *NN*-dimethyl phosphonamidothioic chloride **1** (R = $PhCH_2$) from the dichloride **2** (R = $PhCH_2$) and Me_2NH (2 equiv.; Me_2NH_2Cl byproduct),[1] we anticipated no problems in obtaining the corresponding *NN*-diethyl compound **3**. In the event, reaction of the dichloride (δ_P 86.6) with two equivalents of Et_2NH (in CH_2Cl_2) gave a mixture of two products, δ_P 93.2 and 82.1, together with unchanged starting material. When a larger quantity of Et_2NH (5 equiv.) was used, the dichloride was completely consumed but the same mixture of products was still obtained. The products were separated by chromatography. One was the expected phosphonamidothioic chloride **3** (R = $PhCH_2$), m.p. 43.5–44 °C, δ_P 93.2, δ_H ($CDCl_3$) 7.42–7.30 (5 H, m), 3.80 (2 H, ABP, δ_A 3.82, δ_B 3.78, J_{AB} 14.5, $J_{AP} = J_{BP}$ = 16.5), 3.34 (4 H, dq, J_{PH} 15.5, J_{HH} 7) and 1.08 (6 H, t, J_{HH} 7), *m/z* 263, 261 (M^+, 20 %) and 91 (100), the other the diamide **4** (R = $PhCH_2$), δ_P 82.1, δ_H ($CDCl_3$) 7.45–7.20 (5 H, m), 3.40 (2 H, d, J_{PH} 15), 3.07 (8 H, m) and 1.01 (12 H, t, J_{HH} 7), *m/z* 298 (M^+, 20 %) and 207 (M^+ –CH_2Ph, 100).[2]



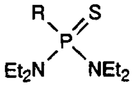
1



2



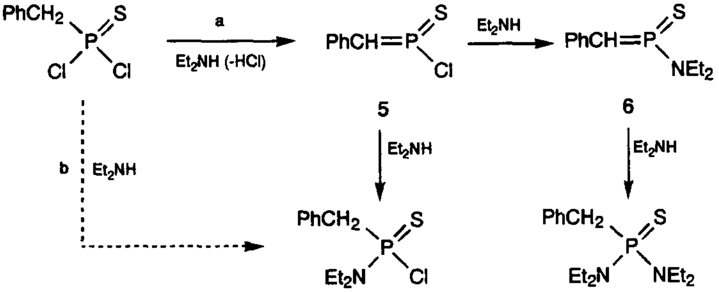
3



4

It is remarkable that formation of the diamide should compete with formation of the amidic chloride; on both electronic[3] and steric[4] grounds, one would expect Et_2NH to react much more quickly with the dichloride **2**, to give **3**, than with the amidic chloride **3**, to give **4**. Indeed, using a large excess of Et_2NH (10 equiv.; 0.8 mol dm^{-3} in CH_2Cl_2; 30 °C), the amidic chloride **3** (R = $PhCH_2$) and the diamide **4** (R = $PhCH_2$) were formed, over 0.8 h, in a 1.3:1 ratio, but that ratio then remained practically unchanged over a further 20 h. Clearly, the amidic chloride does *not* react with Et_2NH under the conditions of our reaction, so the diamide cannot have been formed from the amidic chloride. Rather, it must be a primary product, formed by a faster route directly from the dichloride. As to the nature of the direct route, some further observations are pertinent.

First, unlike the benzylic dichloride (R = $PhCH_2$), the phenyl and methyl compounds **2** (R = Ph or Me) behave in the expected way with Et_2NH, *i.e.* they form the amidic chlorides **3** quantitatively. The diamides **4** can be obtained, but only by much slower subsequent reaction of the amidic chlorides. Second, when the benzylic dichloride **2** (R = $PhCH_2$) was treated with Et_2ND (90 atom % D; 0.8 mol dm^{-3}; 30 °C) and the reaction quenched at 25 % completion (t = 3 min), the recovered dichloride contained deuterium [^1H NMR: benzylic methylene *ca.* 1.2 H/ 0.8 D (average) by integration]. Since H/D exchange occurs as readily as substitution, deprotonation of the α-carbon atom may be involved in substitution. Third, the benzhydryl substrate **2** (R = Ph_2CH)[5] (δ_P 89.7) also exhibits the direct route to diamide; with 0.8 mol dm^{-3} Et_2NH, the amidic chloride **3** (R = Ph_2CH), δ_P 97.3, and the diamide **4** (R = Ph_2CH), δ_P 81.2, are formed in a 1:4 ratio, *i.e.* the diamide is the major product. Now the direct route is seen even with Me_2NH, to the extent that the yield of the diamide (δ_P 85.8) is ten times that of the amidic chloride (δ_P 99.6), and its formation direct from the dichloride is $\geqslant 10^3$ times faster than its formation *via* the amidic chloride. Clearly, a single hydrogen on the α-carbon of the substrate is sufficient for direct disubstitution to proceed.



Scheme 1

Scheme 1 shows (for R = $PhCH_2$) what may be happening in these reactions. The normal $S_N2(P)$ pathway **b** is retarded by steric factors, in the substrate[4] (when R = Ph_2CH) and/or the nucleophile (when the amine is Et_2NH).[6] This, and the acidity of the benzylic hydrogen atoms, allows pathway **a** to compete. Here the amine acts initially as a base (ElcB-like elimination of HCl), not as a nucleophile. The resulting three-coordinate P^V species **5** is reactive and sterically accessible. The amine does now act as a nucleophile, forming the amidic chloride by addition or the new three-coordinate P^V species **6** by substitution (displacement of Cl). The latter, on addition of amine, gives the diamide.

There are many precedents for transient three-coordinate P^V species reacting by addition, but not by substitution.[7] Indeed, it is precisely because they add so readily, forming stable four-coordinate products, that their existence is so fleeting.[7] Nonetheless, in our reactions it seems that substitution (**5** → **6**) competes with addition, even though it serves only to convert one transient three-coordinate P^V species into another.

REFERENCES AND NOTES

1. Coogan, M.P.; Harger, M.J.P. *J. Chem. Soc., Perkin Trans. 2*, 1994, 2101.
2. All new compounds were fully characterised (NMR, MS, elemental analysis or accurate M^+).
3. Crunden, E.W.; Hudson, R.F. *J. Chem. Soc.*, 1962, 3591.
4. Razvodovskaya, L.V.; Grapov, A.F.; Mel'nikov, N.N. *J. Gen. Chem. USSR*, 1969, **39**, 1230.
5. New substrate **2** (R = Ph_2CH) prepared from $Ph_2CHP(O)Cl_2$ by O/S exchange ($PSCl_3$-P_2S_5, DMF cat., 140 °C); m.p. 84.5–85 °C; *m/z* (CI; NH_3) 318, 320, 322 [$(M+NH_4)^+$, 100 %].
6. Kanavarioti, A.; Stronach, M.W.; Ketner, R.J.; Hurley, T.B. *J. Org. Chem.*, 1995, **60**, 632.
7. Westheimer, F.H. *Chem. Rev.*, 1981, **81**, 313; Regitz, M; Mass, G. *Top. Curr. Chem.*, 1981, **97**, 71.

(*Received in UK* 4 *September* 1996; *accepted* 20 *September* 1996)