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RADICAL DECARBOXYLATIVE PHOSPHORYLATION OF CARBOXYLIC ACIDS

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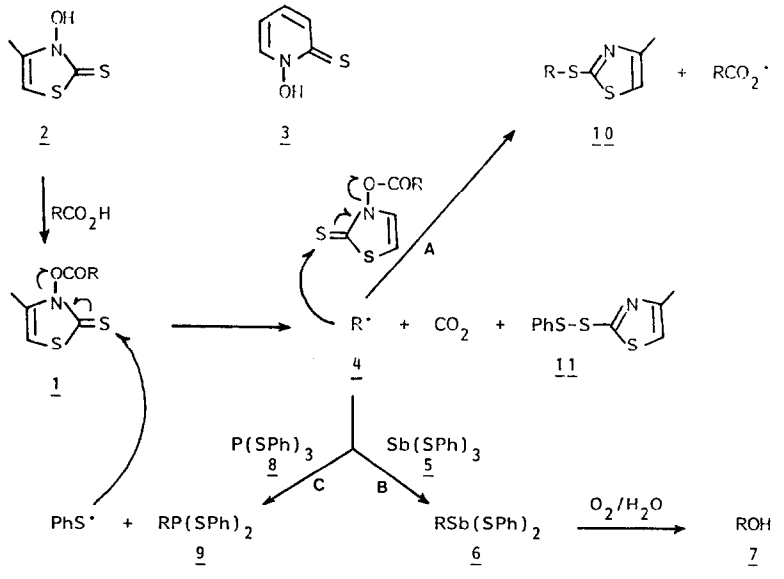
Abstract - Thiohydroxamic carboxylic mixed anhydrides (e.g. 1) react at room temperature with $(PhS)_3P$ to give, through a decarboxylative phosphorylation reaction, the corresponding dithiophosphonates 12 in moderate yields.

The reaction of phosphorus centered radicals with olefins has been extensively employed for making carbon-phosphorus bonds.[1,2] In sharp contrast, the converse process, i.e. the addition of carbon radicals onto phosphorus has seldom found synthetic use, despite substantial mechanistic studies.[2] In view of the importance of organophosphorus compounds and as part of our ongoing work on the radical decarboxylation of carboxylic acids we examined the synthetic potential of the latter approach for the replacement of carboxyl by phosphonate.

Aliphatic and alicyclic (and in some cases, aromatic and α,β unsaturated) carboxylic acids can be made to undergo decarboxylation by heating or irradiating their corresponding mixed anhydrides (esters) 1 derived from appropriate thiohydroxamic acids such as 2 (or 3).[3] As outlined in Scheme 1 (path A), this reaction follows a simple radical chain mechanism and involves the intermediacy of carbon radicals 4.



Scheme 1

1, 9, 10, 12

a, R = n-$C_{15}H_{31}$-

b, R = Ph_2CHCH_2-

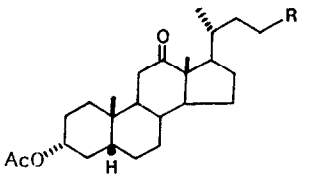
c, R = cyclohexyl-

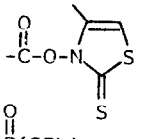
e, R = Ph_2CH-

f, R = 1-adamantyl

g, R = $(PhCH_2)_2CH$-

h, R = 1-methylcyclohexyl



1d, R = 

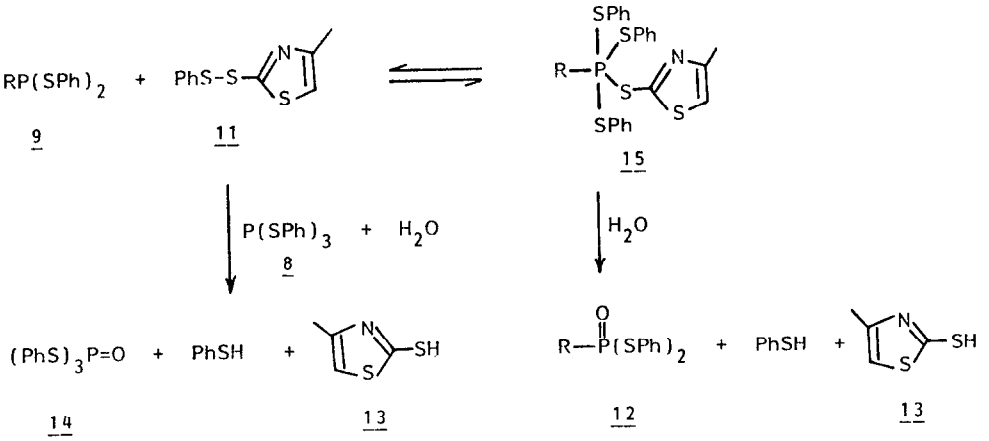
12d, R = $P(SPh)_2$

Furthermore, we have shown, among other modifications, that in the presence of trisphenylthioantimony 5, these transient carbon radicals participate in an S_H2 type reaction to give the oxygen sensitive organoantimony derivative 6 (Scheme 1, path B). Aerial oxidation and hydrolysis furnishes the nor-alcohol 7 in excellent yield.[4] A similar substitution can be envisaged in the case of the phosphorus analogue 8 (path C). In this case, oxidation of the corresponding organophosphorus product 9 should provide the phosphonate without fear of rupture of the C-P bond.

On stirring the palmitic acid derivative 1a with two equivalents of the easily available triphenyltrithiophosphite 8[5] a very rapid reaction took place to give the dithiophosphonate 12a directly in 58% yield. Pentadecane was also observed (~20%). The heterocyclic part of 1a was recovered as 4-methyl-2-mercaptothiazole 13 (90%). Other products included thiophenol, diphenyl disulphide and the trithiophosphate 14, all derived from the reagent 8.

This preliminary experiment was carried out without rigourous exclusion of oxygen and required no heating or irradiation. Clearly autoxidation of the reagent was sufficient to trigger the radical chain process. In fact the yield of the desired dithiophosphonate 12a could be slightly raised (to 67%) by operating under nitrogen containing small amounts of oxygen. As for the pentadecane, its formation was due to hydrogen abstraction by the pentadecyl radical from the thiophenol contaminant present before the reaction (thiophenol is also produced on work-up, *vide infra*). This side reaction could not be easily suppressed in small scale work. Furthermore, increasing the quantity of the trithiophosphite 8 to 10 equivalents resulted in a lowering of the yield of the desired adduct 12a.

Although, according to Scheme 1 (path C), the reaction should produce the tervalent phosphorus species 9 and the mixed disulphide 11, neither of the two is in fact observed. Phosphines and phosphites are known to react rapidly and irreversibly with water in the presence of a disulphide[6] via an ionic pathway, involving pentavalent phosphorus species which, in this case, would be 15 (Scheme 2). Irreversible hydrolysis of this reactive intermediate would give the observed products namely the dithiophosphonate 12, thiophenol and the thiazole 13. In principle, a mixture of 12 and 16, where one of the phenylthio groups has been replaced by a 2-mercaptothiazole unit, would have been expected. However the better leaving ability of the heterocyclic thiol ensures the absence of 16. We have verified this point by subjecting the mixed disulphide 11 (prepared separately) to the action of the reagent 8 and water. This gave immediately the trithiophosphate 14, thiazole 13 and thiophenol and none of the mixed trithiophosphate 17.



Scheme 2

This direct conversion of a carboxylic acid into a phosphonate was extended to other examples (Table). Best yields were obtained with primary acids. Mixed anhydrides (e.g. 18, 19) derived from N-hydroxy-2-pyridinethione 3 could also be employed (entries 7,8).

Table[a]

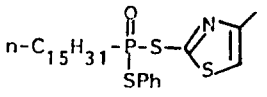
Entry	Ester	Reagent (2 eq.)	Major Product (Yield %)
1	1a	8	12a (67)
2	1b	8	12b (64)
3	1c	8	12c (50)
4	1d	8	12d (60)
5	1e	8	10e (50)
6	1f	8	20 (70)
7	18	8	12g (35)
8	19	8	12h (26)
9	1b	21	22 (40)
10	1b	$P(NMe_2)_3$	23
11	1b	24	25 (60)

a) Reactions were run at room temperature in chlorobenzene except for entries 7 and 8 where dichloromethane was used.

Some special acids did not undergo the desired reaction. Thus, the diphenylacetic acid derivative 1e gave only a very low yield (<7%)of 12e. The major product was the sulphide 10e (45-50%) along with small amounts of diphenylmethane (16%) and tetraphenylethane (10%), the latter arising by dimerisation of the diphenylmethyl radicals. In retrospect this poor behaviour is not wholly unexpected in view of an earlier report[7] on the unreactivity of benzylic radicals towards tervalent phosphorus species. In contradistinction, adamantyl radicals attacked the sulphur atom of the ligands leading to 1-adamantyl phenyl sulphide 20 in 70% yield.

The presence of a sulphur ligand (in this case a phenylthiyl group) capable of acting as a chain propagator appears necessary for the success of the reaction. Thus, the mixed phosphite 21 lead to a moderate yield (40%) of the expected phosphonate 22 (entry 9). Trimethyl or triphenyl phosphite neither triggered the radical chain reaction nor underwent carbon radical addition when the decarboxylation was initiated thermally. Only decarboxylative rearrangement to sulphides 10 prevailed under these conditions. In the presence of hexamethyl phosphorus triamide, an ionic reaction occured to give amide 23 (entry 10). Perhaps not unexpectedly, the selenium analogue 24[8] of the original reagent 8 afforded the corresponding selenide 25 (entry 11). We[9] and others[10] had noted earlier the marked reactivity of diselenides towards carbon radicals as compared to disulphides. Finally, a preliminary examination of the trisulphenamide $N(SPh)_3$[11] for the

introduction of C-N bonds (i.e. a radical counterpart of the Hoffman degradation) gave only negative results.



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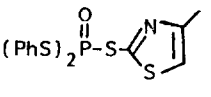

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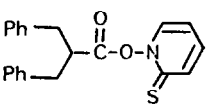

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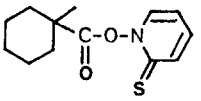

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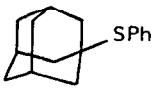

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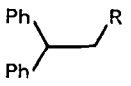
$(EtO)_2P\text{-}SPh$

21



22, R = $-P(OEt)_2$

23, R = $-C\text{-}NMe_2$

25, R = -SePh

$(PhSe)_3P$

24

In spite of the various shortcomings and overall moderate yields, this decarboxylative phosphorylation provides for an expedient access to phosphonates. This method should be particularly useful in cases where the phosphorus conterparts of a biologically active carboxylic acids need to be assessed as in the field of leucotrienes.

References

1. *"Comprehensive Organic Chemistry"*, D.H.R. Barton W.D. Ollis and I.O. Sutherland Eds., Pergamon Press, 1979, vol. 2; see also S. Trippet and D.W. Allen in *"Specialist Periodical Reports: Organophosphosphorus Chemistry"* for a comprehensive coverage of the literature.
2. For a review, see W.G. Bentrude in *"Free Radicals"* Ed. J.K. Kochi, Wiley Interscience, 1973, vol. II, p. 595.
3. D.H.R. Barton, D. Crich and W.B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 939 (1983); for an account of this work see: D.H.R. Barton and S.Z. Zard, *Pure & Appl. Chem.*, **58**, 675 (1986).
4. D.H.R. Barton, D. Bridon and S.Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1066 (1985).
5. C. Wu, *J. Am. Chem. Soc.*, **87**, 2522 (1965).
6. L.E. Overman, D. Matzinger, E.M. O'Connor and J.D. Overman, *J. Am. Chem. Soc.*, **96**, 6081 (1974), and references there cited.
7. R.S. Davidson, *Tetrahedron*, **25**, 3383 (1969).
8. L. Maier, *Helv. Chim. Acta*, **59**, 252 (1976).
9. D.H.R. Barton, D. Bridon and S.Z. Zard, *Tetrahedron Letts.*, 5777 (1984); idem, *Heterocycles*, in press.
10. G.A. Russell and H. Tashtoush, *J. Am. Chem. Soc.*, **105**, 1398 (1983).
11. D.H.R. Barton, I.A. Blair, P.D. Magnus and R.K. Norris, *J. Chem. Soc., Perkin Trans. 1*, 1031 (1973).

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