Tetrahedron Letters,Vol.27,No.38,pp 4623-4624,1986 0040-4039/86 \$3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

NEW SYNTHETIC 'TRICKS'. ADVANTAGES OF USING TRIETHYLPHOSPHINE IN SOME PHOSPHORUS-BASED REACTIONS

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It is shown that Et_3P can advantageously replace Ph_3P, Bu_3P, and other P(III) reagents in phosphazene reactions (amide and phthalimide formation) and disulphide-cleavage-based reactions (reduction of disulphides, thioester formation, and oxime hydrolysis).

Triphenylphosphine is the characteristic reagent of a series of very popular organic reactions (Staudinger's, Wittig's, Mukaiyama's, Mitsunobu's...). Since, in general, triarylphosphines are less nucleophilic than trialkylphosphines,[1,2] Ph_3P has been replaced by Bu_3P in some of these reactions. Another question associated to the use of many phosphines is the difficulty frequently encountered in the separation of the desired products from the byproducts $R_3P{=}O$ and/or unreacting R_3P; polymer-supported phosphines sometimes solve this problem.[3] We report here that Et_3P overcomes all these phosphorus(III) reagents, and some others, in (at least) the following reactions.

Amide Formation (from RCOOH + N_3R'). The substitution of Et_3P for Ph_3P in the recently reported reaction of carboxylic acids and azides[4] showed two significant advantages: (i) reaction times and/or temperatures could be largely reduced, so that in some cases the reaction worked well at r.t., a fact that may be interesting in peptide chemistry;[4b] (ii) column chromatography could be avoided, since the very good solubility of $Et_3P{=}O$ in water allows one to remove this phosphine oxide by washing the final organic solution.[5] See Table 1 for the conditions and yields, stopping the reactions when indicated.

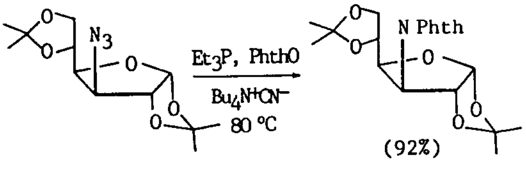
In these connections, Bu_3P turned out to be worse than Et_3P, despite the fact that the tributylphosphazenes were formed almost as quickly as triethylphosphazenes, since in two cases examined (propanoic acid + isopentyl azide + Bu_3P; propanoic acid + benzyl azide + Bu_3P) only traces of the amide were obtained after 24 h at r.t.; furthermore, $Bu_3P{=}O$ could not be extracted with water from the organic layer.

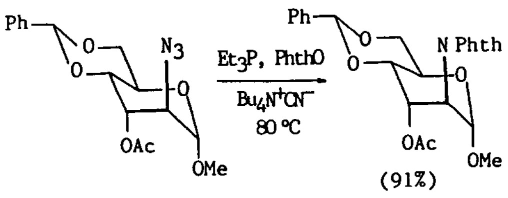
Other P(III) reagents were also inferior to Et_3P.[5b,e]

Table 1. Reaction of Azides (1 mmol), Carboxylic Acids (1.1 mmols), and Et_3P (1.1 mmols) in Anhydrous C_6H_6 (5 ml)

	N_3	N_3CH_2Ph	N_3	N_3Ph
CH_3CH_2COOH	CH_3CH_2CONH 18 °C, 12h, 92% 80 °C, 5h, 99%	$CH_3CH_2CONHCH_2Ph$ 18 °C, 12h, 76% 80 °C, 8h, 93%	CH_3CH_2CONH 18 °C, 24h, 65% 80 °C, 8h, 94%	$CH_3CH_2CONHPh$ 80 °C, 12h, 87%
PhCOOH	PhCONH 80 °C, 8h, 92%	$PhCONHCH_2Ph$ 80 °C, 15h, 89%	PhCONH 80 °C, 12h, 96%	PhCONHPh 80 °C, 12h, 87%

Phthalimides from Phthalic Anhydride and Azides. The following reactions,[6] which with Ph_3P and Bu_3P required one week in refluxing benzene, were accomplished within a day with Et_3P under the same conditions:





Disulphide Reduction. Cleavage of PhS-SPh with Ph_3P in THF-H_2O did not work at r.t. but it required a gentle reflux for 1 h;[7] by contrast, Et_3P gave quantitatively PhSH within 10 min at r.t. With the less reactive $(PhCH_2S)_2$, Et_3P afforded a 96% of cleavage after 1 h at r.t., Bu_3P required 8 h to reach the same yield, $(EtO)_3P$ gave a 14% yield of $PhCH_2SH$ after 24 h, and Ph_3P did not react at all.[8] Thus, the qualitative reaction order appears to be: $Et_3P > Bu_3P > (EtO)_3P > Ph_3P$. (The reaction of $PhCH_2S\text{-}SCH_2Ph$ with $(Me_2N)_3P$ took another course, yielding $PhCH_2SCH_2Ph$ and $(Me_2N)_3P{=}S$.[5c])

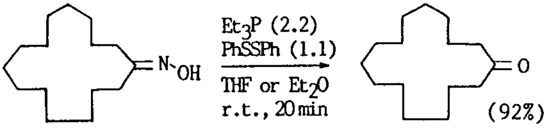
Thioester Formation.[9] Table 2 shows thioesterifications performed with Et_3P (1.2-1.3 equiv.) plus PhS-SPh (1.1-1.2 equiv.) in anh. C_6H_6 or Et_2O, at r.t. under N_2 for 1 h, the reactions being quenched with water. After washing the organic phase with a pH 8.5 buffer (to eliminate $Et_3P{=}O$ and PhSH) and solvent evaporation, pure thioesters were obtd.

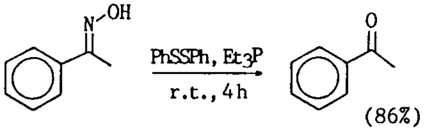
Table 2. Reaction of Carboxylic Acids with Et_3P + PhS-SPh

	product	yield		product	yield
$AcN(CH_3)CH_2COOH$	$AcN(CH_3)CH_2COSPh$	80%	$CH_2{=}CH(CH_2)_8COOH$	$CH_2{=}CH(CH_2)_8COSPh$	95%
Z-Try-OH	Z-Try-SPh	80%	$PhCH_2COOH$	$PhCH_2COSPh$	99%

The following results are also illustrative of the performance of Et_3P: whereas Et_3P furnished already a 70% yield of $PhCH_2COSCH_2Ph$ after 2 h and a 95% yield after 4 h, Bu_3P gave only a 38% yield after 2 h and a 56% yield after 6 h. Ph_3P gave no thioester at all.

Oxime Hydrolysis. Barton, Zard, and coworkers[10] reported very recently the use of Bu_3P + PhS-SPh to reduce ketoximes to ketimines, which then can be either hydrolised to ketones, reduced *in situ*, *etc*. A modification of the BMSZ reaction,[10] using 2 equiv. of Et_3P instead of 1 equiv. of Bu_3P, allowed us to recover readily pure ketones from oximes:





Workup was limited to partitioning between ether and water (pH 8.5), drying, and evaporating. PhS-SPh + Bu_3P gave only a 65% yield of cyclopentadecanone after 7 h under identical conditions and only a 10% yield of acetophenone after 24 h in refluxing THF.

Some other applications of Et_3P are in progress.

References and Footnotes

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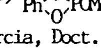
5. (a) Me_3P could work like (or even better than) Et_3P in all connections (nucleophilic power, lack of steric hinderance in the reaction intermediates, and easy elimination of its oxide), but its low boiling point, bad odour, and flammability are disappointing; (b) although $(Me_2N)_3P{=}O$ and $(EtO)_3P{=}O$ are also very soluble in water, $(Me_2N)_3P$ and $(EtO)_3P$ cannot be recommended here since they are not so good nucleophiles as Et_3P (the qualitative react. order that we have found is $Et_3P > Bu_3P > (Me_2N)_3P > (EtO)_3P > Ph_3P$), since in the case of $(Me_2N)_3P$ heating is necessary to produce the nitrogen elimination, and chiefly since they give side reactions (desulphurisation of disulphides[5c] and obtention of $RCONMe_2$ together with the desired $RCONHR'$ in the case of phosphorus triamide; the Michaelis-Arbuzov and related rearrangements[5d] in the case of triethyl phosphite); (c) D. N. Harpp and J. Gleason, J. Am. Chem. Soc., 93, 2437 (1971); (d) A. K. Bhattacharya and G. Thyagarajan, Chem. Rev., 81, 415 (1981); (e)  $Ph\langle^{O}_{O}\rangle POMe$, Ph_2POMe, and Ph_2PX worked worse than Ph_3P (V. Bou, Graduation Thesis, Univ. Barcelona, 1986).
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7. See also L. E. Overman, J. Smoot, and J. D. Overman, Synthesis, 59 (1974).
8. According to ref. 3b, polymer-supported Bu_3P needed 19 h at r.t. to reach a 92% yield. See also ref. 3a.
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Acknowledgments. Thanks are due to Dr. G. Muller for ^{31}P NMR spectra and to Mr. A. Vergara, Firmenich, for a generous gift of cyclopentadecanone. A fellowship to F. U. from the Ministerio de Educación y Ciencias is acknowledged.

(Received in UK 7 July 1986)