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REACTIONS OF DIAZOACETATES with PHOSPHATE TRIESTERS and THIOPHOSPHATE TRIESTER: $>\overset{+}{P}\text{-O-}\overset{-}{C}<$ and $>\overset{+}{P}\text{-S-}\overset{-}{C}<$ INTERMEDIACY FORMATION

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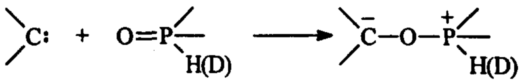
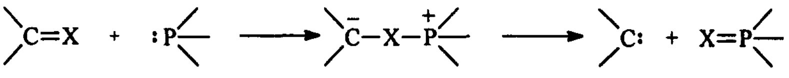
***Abstract*:** Diazoacetates **1a,b** undergo $BF_3 \cdot OEt_2$ catalyzed carbenoid attack on the oxygen of the phosphoryl double bond of phosphate triesters **2a-c** or on the sulfur of thiophosphoryl double bond of thiophosphate **9** to form corresponding O-alkoxycarbonylmethylphosphates **3a-c** or S-alkoxycarbonylmethylphosphate **13**.

The reactions of carbenes or carbenoids with the carbon-oxygen double bond give synthetically valuable intermediate carbonyl ylides.[1,2] Surprisingly, that little is known about analogous reaction of diazo precursors with the phosphoryl-oxygen or phosphoryl-sulfur double bond. Recently, the anomaly low H/D isotope effect was found in the reaction of thermally generated fluorenyl carbene with dimethyl hydrogen phosphite indicating the carbene attack on the oxygen of P=O bond (Scheme 1).[3]



Scheme 1

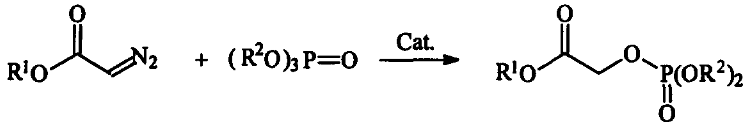
It is interesting that fragmentation of the similar zwitterionic intermediate to carbene is often involved into a possible mechanism of the reactions of ketones or thioketones with tervalent phosphorus compounds (Scheme 2).[4-6]



Scheme 2

Diazo esters **1a,b** and trialkylphosphates **2a-c** were first to be chosen for intermolecular generation of zwitterionic intermediate. On slow (2 h) dropwise addition of a solution of diazo ester **1a,b** (5 mmol) in CH_2Cl_2 (10 ml) to a stirred boiling solution of catalyst (0.5 mmol) and trialkylphosphate **2a-c** (12.5 mmol) in CH_2Cl_2 (10 ml) (Scheme 3) followed by water-Na_2CO_3 work-up and $MgSO_4$ drying O-alkoxycarbonylphosphates **3a-c**[7] have been isolated by distillation.

$BF_3 \cdot OEt_2$ is the catalyst of choice what indicates a Lewis acid promoted process. It is often that $BF_3 \cdot OEt_2$ is a superior catalyst in the typical carbenoid transformations.[8]

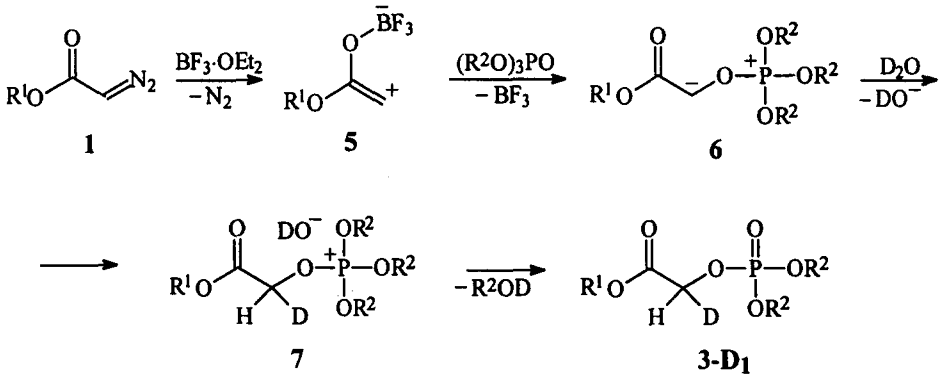


1a, R^1=Me	2a, R^1=Me	3a, R^1=R^2=Me
1b, R^1=Et	2b, R^1=Et	3b, R^1=R^2=Et
	2c, R^1=i-Pr	3c, R^1=Et, R^2=i-Pr

Cat.:	$BF_3 \cdot OEt_2$	$(p\text{-}BrC_6H_4)_3N^{+\cdot} \cdot SbCl_6$	$SnCl_2$	$Rh_2(OAc)_4$	$Cu(OTf)_2$
Yield of 3a:	52%	35%	17%	14%	5%

Scheme 3

We have found that a source of a new hydrogen atom forming the methylene group of the product **3** is water impurity since in the presence of one equivalent of D_2O diazo ester **1a** reacts with phosphate **2a** to give specifically monodeuterated phosphate **3a-D₁**, whereas in the presence of solvent CD_2Cl_2 or substrates $(CD_3O)_3PO$, $N_2CDCOOMe$ does not. Thus, we explain the reaction by a step mechanism *via* zwitterionic intermediate **6** which is protonated at carbon atom by H_2O, followed by dealkylation at phosphorus atom by OH^- anion[8] (Scheme 4).



Scheme 4

The resulting R^2OH can also donate the proton to form R^2O^- followed by dealkylation to afford R^2OR^2. This was shown in the reaction of **1a** with **2a** (in a 1:1.5 molar ratio) in the presence of $PhCH_2OH$ (1 equivalent to **1a**) resulted in isolation of $PhCH_2OMe$ (35%) along with **3a** (45%).

Experiment with BzOH suggests that alternative mechanisms including as a key step hydrolysis of phosphate **2** by water or O-H insertion of diazoacetate **1** to water could be excluded (Scheme 5).

$$2 \xrightarrow{H_2O} (R^2O)_3P(O)OH \xrightarrow{1} 3$$

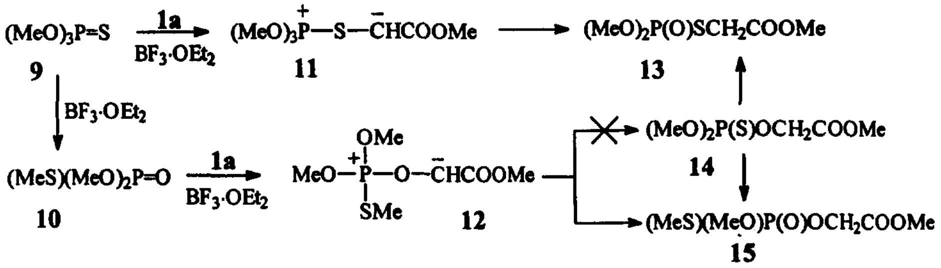
$$1 \xrightarrow{H_2O} ROOCCH_2OH \xrightarrow[\text{-MeOH}]{2} 3$$

Scheme 5

In order to demonstrate the formation of the intermediate phosphonium salt **7**, we examined the reaction of diazo ester **1b** with hexamethyltriamidophosphate. Under the same conditions (in refluxing CH_2Cl_2) reaction was extremely slow presumably due to deactivation of $BF_3 \cdot OEt_2$ by basic P=O group. Only by refluxing of a toluene solution of **1b**, hexamethyltriamidophosphate and $BF_3 \cdot OEt_2$ (at molar ratios of 1:2:1) a salt $[(Me_2N)_3POCH_2COOEt]^+[OH]^-$ **8** obtained.[9]

In a special experiment including manipulations in Ar atmosphere with very dry reagents the yield of **3a** was simply dropped to 17%. The well known decomposition of zwitterionic intermediate $>P^+\text{-O-C}^-<$ to carbene and P=O group[5] can lower the yield of **3** (Scheme 2). The participation of water in such low concentration is likely associated with involving of very active intermediate.

Our next attention was given to the possibility of carbenoid attack on the P=S double bond. The $BF_3 \cdot OEt_2$ -catalyzed interaction of diazo ester **1a** with trimethylthiophosphate **9** at the similar to phosphate protocol conditions competes with Pistchemuki rearrangement[10] of substrate thiophosphate **9** into S-methylphosphate **10**, what is greatly facilitated by strong Lewis acid.[11] Upon slow addition of diazo ester **1a** to a solution of thiophosphate **9** and $BF_3 \cdot OEt_2$ (at molar ratios 1:2.5:0.4) in CH_2Cl_2 three product phosphates **10**, **13** and **15** were produced[12] (Scheme 6).



Scheme 6

A 2:7 molar ratio of **13**/**15** was found after distillation. Neither starting thiophosphate **9**, nor the product thiophosphate **14** was found. Reaction of authentic **10** with diazoester **1a** gave only **15**, proving the origin of **13** from only **9**. Indeed, in contrast to the original procedure, upon back addition of $BF_3 \cdot OEt_2$ for only 10 min. into a solution of substrates **1a** and **9** the rearrangement of **9** was not completed, diazo ester being quickly decomposed (CAUTION, do not add $BF_3 \cdot OEt_2$ at once, diazoacetate is potentially explosive while decomposes too fast). A 2:1 molar ratio of **9**/**10** in the fraction one and a 1:1 molar ratio of **13**/**15** in the fraction two were found after distillation.

Presuming that **9** and **14** rearrange at the similar rates, an attempt for identification of **14** was done. Upon fast addition of $BF_3 \cdot OEt_2$ for 10 min. to a solution of **1a** and **10** in CH_2Cl_2 no **14** was found by the NMR spectra in the crude mixture proving that the demethylation by OH^- from S atom in the intermediate **12** was not occurred.

By analogy to **6**, phosphonium intermediates **11** and **12** were suggested.

Zwitterionic intermediates $>P^+\text{-O-C}^-<$ and $>P^+\text{-S-C}^-<$ chemoselectively generated from diazoacetates and phosphates (thiophosphates) show a new reactivity which is under further investigation.

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7. Dimethyl(methoxycarbonylmethyl)phosphate (**3a**): Yield 52%.-Bp (°C)/mm. Hg. 63/0.05.-n_D^{20} 1.4198.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ 1.6 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$): δ 3.74(s, 3H), 3.75 (d, 6H, 11 Hz), 4.43 (d, 2H, 11 Hz).-^{13}C-NMR (50.3 MHz, CDCl$_3$): δ 52.64 (s), 54.98 (d, 5.9 Hz), 64.02 (d, 5.9 Hz), 168.73 (d, 5.9 Hz).

   Diethyl(ethoxycarbonylmethyl)phosphate (**3b**): Yield 58 %.-Bp (°C)/mm. Hg. 96/0.05.-n_D^{20} 1.4060.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ -3.6 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.26 (t, 3H, 7 Hz,), 1.30 (t, 7 Hz, 6H), 4.05 (m, 6H), 4.25 (d, 2H, 11 Hz).-^{13}C-NMR (50.3 MHz, CDCl$_3$): δ 14.82 (s), 16.63 (d, 5.9 Hz), 62.13 (s), 64.73 (d, 5.8 Hz), 66.42 (d, 5.9 Hz), 167.54 (d, 5.9 Hz).

   Diisopropyl(ethoxycarbonylmethyl)phosphate (**3c**): Yield 42 %.-Bp (°C)/mm. Hg. 82/0.01.-n_D^{20} 1.3952.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ -4.0 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.26 (t, 3H, 7Hz), 1.27 (d, 12H, 7 Hz), 3.79-4.66 (m, 6H).-^{13}C-NMR (50.3 MHz, CDCl$_3$): δ 15.21 (s), 24.63 (d, 5.9 Hz), 61.12 (d, 7.4 Hz), 68.30 (s), 71.88 (d, 5.9), 168.22 (d, 5.9 Hz).

   Compounds **3a-c** have good elemental analysis (C ± 0.33, H ± 0.22, P ± 0.42).
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9. Trisdimethylamino(ethoxycarbonylmethyl)phosphonium hydroxide (**7**): White crystalls. Yield 76 %.-Mp (°C) 104.5-105.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ 37.6 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.25 (t, 3H, 7.2 Hz), 2.77 (d, 6H, 10.2 Hz), 4.21 (q, 2H, 7.2 Hz), 4.70 (d, 2H, 12.6 Hz).-^{13}C-NMR (50.3 MHz, CDCl$_3$): δ 12.2 (s), 35.03 (d, 4.3 Hz), 60.37 (s), 62.09 (d, 6.1 Hz), 165.29 (d, 4.9 Hz). MS, m/z (EI): 283 (M^+).
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11. Hilgetag, G.; Teichmann, H. *Angew. Chem.* 1965, *77*, 1001.
12. O,O-Dimethyl-S-methoxycarbonylmethylphosphate (**13**): Bp (°C)/mm. Hg. 97/0.5.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ 28.7 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$):, δ 3.49 (d, 2H, 16.2 Hz), 3.69 (d, 6H, 12.4 Hz), 3.71 (s, 3H), .-^{13}C-NMR (50.3 Hz, CDCl$_3$): δ 31.93 (d, 3.7 Hz), 52.19 (s), 53.60 (d, 5.4 Hz), 167.81 (d, 6.5 Hz).

    O-methyl-S-methyl-O-methoxycarbonylmethylphosphate (**15**): Yield 40 %.-Bp (°C)/mm. Hg. 97/0.5.-^{31}P-NMR (121.42 MHz, CDCl$_3$): δ 31.9 ppm.-^{1}H-NMR (200 MHz, CDCl$_3$): δ 2.22 (d, 3H, 15.6 Hz), 3.68 (s, 3H), d 3.69 (d, 3H, 12.6 Hz), 4.52 (d, 2H, 13.6 Hz).-^{13}C-NMR (50.3 MHz, CDCl$_3$): δ 12.12 (d, 4.7 Hz), 52.68 (s), 54.03 (d, 5.9 Hz), 62.48 (d, 4.9 Hz), 167.91 (d, 6.5 Hz).

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