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Dehydration Induced by Intramolecular Redox Character of a Stable Allylidenetributylphosphorane

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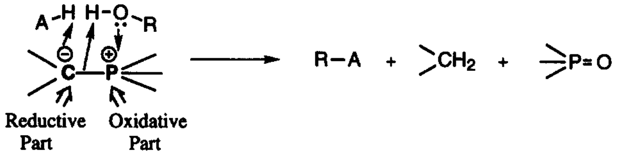
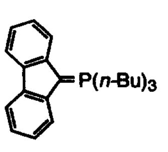
Abstract: An air and moisture stable P-ylide, dimethyl fluorenylidenetributylphosphoranylidenesuccinate acts as a new type of dehydrating agent for synthesizing acid anhydride, ester, and amide. The ylide is most suitable for inducing these reactions in analogous P-ylides. The reaction is considered to be caused by internal reductive and oxidative nature of the P-ylide. © 1997 Elsevier Science Ltd.

In order to exploit new reactions of stable P- and S-ylides insensitive to air and moisture, we expect to induce the characteristic reactions based on a redox property of the ylides which has not hitherto been clearly elucidated. Especially in a P-ylide, there exist reductable carbanion center and oxidizable phosphorus moiety internally. We planned to examine coupling reactions *via* dehydration of various substrates induced by the inherent redox property of the P-ylides (eq. 1). As a result, the reaction induced by the following stable P-ylide gave acid anhydride, ester, and amide in good yields. Thus, the ylide can be regarded as a new type of dehydrating agent.

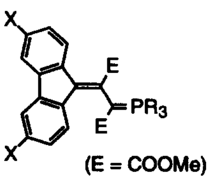


(1)

Similar strategies on the P-ylides have scarcely been studied. Dialkyl ether was formed in the reaction of *p*-nitrobenzylidenetriphenylphosphorane with the corresponding alcohol.[1] Dehydration reactions of carboxylic acids employing tributyl- and triphenylphosphine and *trans*-dibenzoylethylene have been reported previously.[2] Recently, cyanomethylenetributyl- and cyanomethylenetrimethylphosphoranes have been used as unique substitutes for the Mitsunobu reagent.[3] The Mitsunobu reaction has been established as one of the notable synthetic reactions.[4]

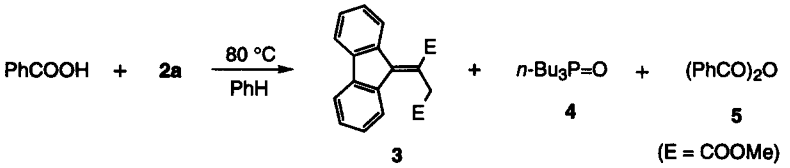


1



2a: X=H, R=*n*-Bu
2b: X=H, R=*p*-MeOC$_6$H$_4$
2c: X=H, R=Ph
2d: X=H, R=*p*-ClC$_6$H$_4$
2e: X=MeO, R=Ph

The objective phosphoranes are fluorenylidenetributylphosphorane (**1**) and fluorenylideneethylidenetributyl- or triarylphosphoranes (**2**).[5] Those were conveniently prepared by the literature procedures.[6] The P-ylides **1** and **2** are very stable to air and moisture and can be stored indefinitely under ordinary laboratory conditions. In the viewpoint of chemical reactivities of those with benzaldehyde, **1** reacted but **2** was recovered completely.[6] Hopefully however, when **2a** was reacted with excess benzaldehyde, it gave a trace amount of dimethyl fluorenylidenesuccinate (**3**). The hydrogen source of **3** was deduced to be benzoic acid contaminated in benzaldehyde employed. This initial conjecture was further supported by the stoichiometric reaction of **2a** with benzoic acid to give **3**, tributylphosphine oxide (**4**), and benzoic anhydride (**5**) in good yields (eq. 2).[7] Some variations of carboxylic acids are examined as shown in Table 1.



(2)

Table 1. Reactions of Carboxylic Acids with P-Ylide **2a**.[a]

Carboxylic Acid	Yield (%) of the Acid Anhydride
i-PrCOOH	87
PhCOOH	61
p-MeC_6H_4COOH	70
o-$C_6H_4(COOH)_2$	90
o-$C_6H_4(OH)(COOH)$	79[b]

a) Reaction time was 7 h, except for PhCOOH (1 h).
b) Salicylsalicylic acid was the product in this reaction.

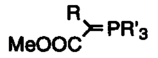
Table 2. Reactions of *p*-Toluic Acid with P-Ylides **2**.[a]

Ylide	p*K*a[b]	Yield (%) of *p*-Toluic Anhydride
2a	5.9	70
2b	5.1	11
2c	4.9	10
2d	---[c]	5
2e	5.2	3

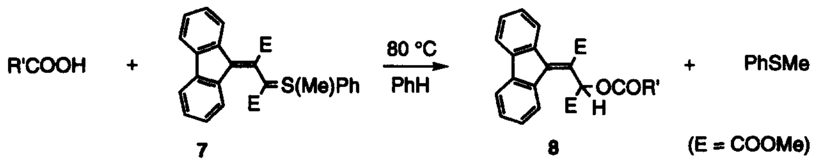
a) Reaction time was 10 h, except for **2a** (7 h).
b) The value is for the corresponding phosphonium salt.
c) Not measured.

The results show that aliphatic, aromatic, and dicarboxylic acid reacted readily. Although the isolated yields of products after column chromatography depend on the stabilities or adsorption nature on a column packing material, time dependent NMR spectra of the reaction mixture suggest that the reaction proceeds quantitatively (isobutyric and *p*-toluic acids). The reaction with salicylic acid did not give salicylic anhydride but gave salicylsalicylic acid (yield, 79%). It shows that **2a** may be possible to act as dehydrating agent to produce esters and amides. Actually, the reactions of *p*-toluic acid with *p*-methylphenol and *p*-toluidine gave the corresponding ester (yield, 77%) and the amide (yield, 89%). In both cases, the yields of *p*-toluic anhydride were less than 5%.

Concerning the reaction mechanism and whether this dehydrating ability is for **2a** solely or not, an efficacy of other P-ylides having analogous structures (**1**, **6a-c**[8]) were examined. These congeners did not show dehydrating ability at all. Moreover, substituent effect of the phosphorus and fluorene moieties of **2** on the dehydrating ability were tested by employing some derivatives (**2b-e**) (Table 2 together with p*K*a values of the corresponding phosphonium salts of **2**[9]). The reactivity of **2** decreased with an electron-withdrawing substituent on phosphorus and an electron-donating substituent on the fluorene. An apparent parallel relationship was observed between the ylide reactivities and p*K*a values of their phosphonium salts. In contrast to the P-ylide, when an analogous S-ylide (**7**)[5,10] was employed in this reaction, none of the acid in Table 1 gave acid anhydrides. Instead, dimethyl acyloxyfluorenylidenesuccinate (**8**) was afforded quantitatively (eq. 3).

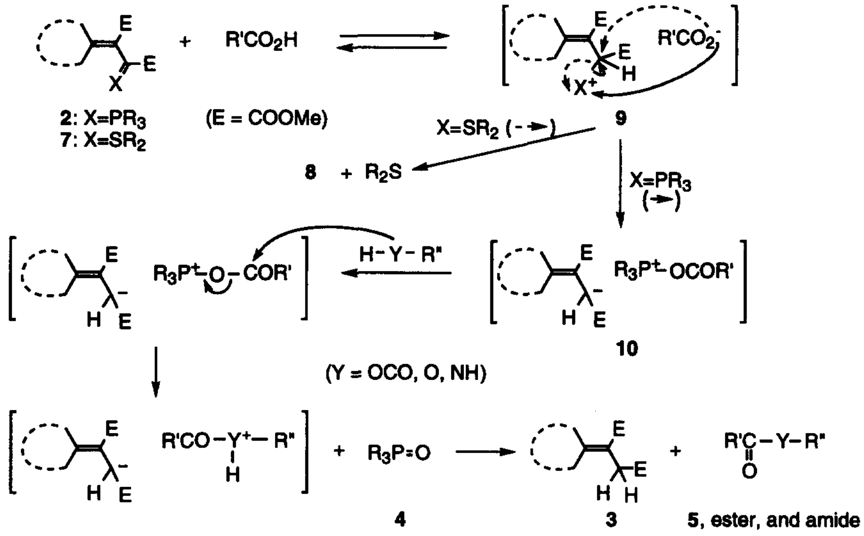


6a: R=Me, R'=Ph
6b: R=Me, R'=*n*-Bu
6c: R=H, R'=*n*-Bu



(3)

Based on the previous work[2] and on these data, a plausible mechanism for dehydration was considered as in Scheme 1. Formations of ester and amide can be considered similarly. That is, an extremely stable P-ylide **2** can be protonated to give a phosphonium salt **9**. The data of p*K*a values suggest that **2a** displaces most highly an equilibrium of a P-ylide—phosphonium salt (**9**) in favor of **9**. Then a carboxylate attacks a phosphonium moiety to afford an ensuing phosphonium salt (**10**) whose anionic moiety is stabilized by efficient delocalization of anion throughout an ethylidenefluorene moiety. A P-cation is also stabilized by an electron-donating *n*-butyl group on phosphorus like **2a**. In the case of **2e** having a 3,6-dimethoxy group on the fluorene moiety (Table 2), an internal salt transformation (**9** to **10**) is disfavored due to an electronic destabilization of a resulting anion. The salt **10** further reacts with another mole of nucleophile. The large counteranion in **10** acts subsequently as a proton scavenger of the coupling product. Eventually **3**, **4**, and **5** were formed. By contrast, **8** seemed to be formed by a nucleophilic substitution in **9** due to a higher eliminating nature of the sulfonium moiety similar to oxirane and cyclopropane formations of S-ylides.[11]



Scheme 1. Reaction mechanism of dehydration (P-ylide) or substitution (S-ylide).

Thus, the present method carries some advantages that not only is the reaction performed under neutral conditions, but also all substrates can be mixed without any activations or modifications of them. The color change of the ylide clearly shows the reaction progress. Furthermore, the P-ylide does not show usual Wittig reactivity and the reaction proceeds well without any precautions such as dryness of solvent and/or anaerobic circumstance. The dehydration reaction induced by **2a** occurred by a strong basicity of it[12] and by activation of an acid as an acyloxyphosphonium ion. A large counteranion in **10** shows lower nucleophilicity, yet sufficient basicity and it contributes to simplifying the reaction. A further study is now underway based on the conception of stable ylides mentioned at the beginning.

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2. Kuwajima, I.; Mukaiyama, T. *J. Org. Chem.* **1964**, *29*, 1385-1386.
3. (a) Tsunoda, T.; Ozaki, F.; Itô, S. *Tetrahedron Lett.* **1994**, *35*, 5081-5082. (b) Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2531-2534. (c) Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2457-2458. (d) Tsunoda, T.; Nagino, C.; Oguri, M.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2459-2462. (e) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2463-2466. The P-ylides utilized in these papers are reported as sensitive to air and moisture.
4. Formations of anhydrides in the Mitsunobu reaction: Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933-3942, and references cited therein. The Mitsunobu reaction, general: (a) Mitsunobu, O. *Synthesis*, **1981**, 1-28. (b) Hughes, D. L. The Mitsunobu Reaction. In *Organic Reactions*; Beak, P. *et al.* Eds.; John Wiley & Sons, Inc.: New York, Vol. 42, 1992; pp. 335-656.
5. Single-crystal X-ray crystallographic studies revealed that the structure of **2a** is s-*cis* and that of **2c** is s-*trans* by our laboratory and the data correspond well with the energy-optimized structures estimated by molecular orbital calculations (MOPAC PM3-SCF[13]). *A priori*, the stereochemistry of **7** is deduced to be s-*trans* based on a result of the same calculation. Details will be published elsewhere in due course.
6. Compound **1**: Johnson, A. W.; LaCount, R. B. *Tetrahedron* **1960**, *9*, 130-138. Compound **2c**: (a) Brown, G. W.; Cookson, R. C.; Stevens, I. D. R. *Tetrahedron Lett.* **1964**, 1263-1266. (b) Brown, G. W. *J. Chem. Soc. (C)* **1967**, 2018-2021. Other ylides; **2a**: Red needles, mp 142-143 °C (recrystallized from ether-hexane); IR (KBr) ν cm^{-1} 1722s, 1630s; Anal. Calcd for $C_{31}H_{41}O_4P$: C, 73.19; H, 8.14%, Found: C, 73.08; H, 7.88%. **2b**: Vermilion needles, mp 220-221 °C (recrystallized from MeOH-$CHCl_3$); IR (KBr) ν cm^{-1} 1702s, 1599s; Anal. Calcd for $C_{40}H_{35}O_4P$: C, 72.94; H, 5.37%, Found: C, 72.69; H, 5.54%. **2d**: Orange needles, mp 214-215 °C (recrystallized from MeOH-$CHCl_3$); IR (KBr) ν cm^{-1} 1703s, 1608s; Anal. Calcd for $C_{37}H_{26}O_4Cl_3P$: C, 66.13; H, 3.91%, Found: C, 66.16; H, 4.00%. **2e**: Orange needles, mp 244-245 °C (recrystallized from MeOH-$CHCl_3$); IR (KBr) ν cm^{-1} 1713s, 1612s; Anal. Calcd for $C_{39}H_{33}O_6P$: C, 74.45; H, 5.29%, Found: C, 74.16; H, 5.39%. Ylide **2** showed temperature dependent NMR spectra and the analyses are elaborated. Manuscript is now in preparation.
7. Representative procedure: A phosphorane **2a** (374 mg, 0.735 mmol) and *p*-toluic acid (200 mg, 1.47 mmol) were dissolved in dry benzene (30 ml) and the mixture was refluxed for 5 h. The color of the mixture turned from dark red to light yellow. The residue obtained by evaporation of the solvent *in vacuo* was subjected to column chromatography (silica gel, 10% Ethyl acetate in hexane as an eluent) to give *p*-toluic anhydride (132 mg, 0.516 mmol, 70%) and a succinate **3** (226 mg, 0.733 mmol, 100%). The formation of tributylphosphine oxide **4** was confirmed by ^1H NMR and gas chromatography.
8. Compound **6a**: Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta*, **1957**, *40*, 1242-1249. **6b**: Prepared by applying the synthetic method of **6a**. Due to the low stability, **6b** was prepared *in situ* and used without isolation. **6c**: It was obtained by the Michael reaction of **1** and dimethyl fumarate, in which methyl fluorenylideneacetate and **6c** were formed quantitatively.[14]
9. Measurement of p*K*a values: Flexser, L. A.; Hammett, L. P.; Dingwall, A. *J. Am. Chem. Soc.* **1935**, *57*, 2103-2115. It is known that the stable P-ylides, acylmethylenetriphenylphosphoranes, react with acid anhydrides to give more acylated ones, which undergo further transformations upon treatment with alcoholic mineral acid or pyrolysis: Chopard, P. A.; Searle, R. J. G.; Devitt, F. H. *J. Org. Chem.* **1965**, *30*, 1015-1019. In the reactions of **2b-e**, however, unreacted starting materials were recovered.
10. Prepared by applying the following literature method: Burgert, W.; Rewicki, D. *Chem. Ber.* **1984**, *117*, 2409-2421. Yellow needles, mp 173-175 °C (recrystallized from ether-acetone); ^1H NMR (400 MHz, C_6D_6) δ 7.46-8.01 (4H, m), 7.54 (2H, d, J=7.8 Hz), 7.08-7.20 (3H, m), 6.85-7.92 (4H, m), 3.60 (3H, s), 3.51 (3H, s), 2.63-2.73 (3H, br); IR (KBr) ν cm^{-1} 1725s, 1640s; MS (20 eV) m/z (%) 430 (M, 20), 306 (M-SMePh, 11), 274 (69), 124 (SMePh, 100); Anal. Calcd for $C_{26}H_{22}O_4S$: C, 72.54; H, 5.15%, Found: C, 72.31; H, 5.34%. This ylide showed a temperature dependent NMR spectra similar to those of **2**. The analyses will be presented elsewhere.
11. (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364. (b) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972-3975. (c) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351-3355.
12. The p*K*a of the phosphonium salt of **1** was measured to be 8.0.
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14. McClure reported an analogous ylide transformation to prepare cyanomethylenetriphenylphosphorane from the reaction of ethoxycarbonylmethylenetriphenylphosphorane with acrylonitrile: McClure, J. D.; *Tetrahedron Lett.* **1967**, 2407-2410.

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