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HORNER-WADSWORTH-EMMONS REACTION: USE OF LITHIUM CHLORIDE AND AN AMINE FOR BASE-SENSITIVE COMPOUNDS

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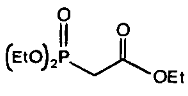
Abstract: A mild olefination procedure, utilizing LiCl and an amine, has been developed for use with base-sensitive aldehydes and phosphonates.

Lithium cations affect the course of the Wittig reaction and its modified version, the Horner-Wadsworth-Emmons (HWE) reaction, in many important ways.[1] For instance, as contrasted with other metal cations, Li$^+$ most likely forms a tight complex with the carbanion derived from phosphonate **1** as shown in **1a**, thereby enhancing the acidity of **1**.[2] The pKa values of **1** in diglyme (Li$^+$) and in dimethylsulfoxide (K$^+$), relative to 9-phenylfluorene,[†] were reported to be 12.2 and 19.2 respectively.[3] These results immediately suggested the possibility that in the presence of a lithium salt, **1** and related phosphonates could be easily deprotonated with an amine, e.g., DBU (pKa 11.6)[4] or diisopropylethylamine (DIPEA, pKa ~10.5)[4] to generate reactive species under simple, mild conditions. In fact, the standard procedure described below has been used for some time in our laboratories in order to achieve successful olefinations by HWE-reactions that involve either a base-sensitive substrate or reagent. Conventional methods, for instance, NaH in THF or K_2CO_3 in toluene,[5] may cause complications in such cases.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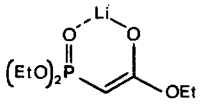
1a

Standard Procedure. To a stirred suspension of LiCl (12 mmol, recrystallized from MeOH and dried at 140°/0.5 torr overnight) in dry acetonitrile (120 ml) under nitrogen at room temperature, was added phosphonate **1** (12 mmol), DBU or DIPEA (10 mmol) and finally an aldehyde (10 mmol). Almost all of the salt soon dissolves and the reaction is normally complete in 1 h with DBU and in 24 h with DIPEA. The progress of the condensation can be followed by tlc or by gas chromatography with an appropriate standard added to the reaction mixture. The usual workup provides an excellent yield of the expected α,β-unsaturated esters in 85-100% yield, E/Z ratio >50:1, with typical saturated aliphatic aldehydes (e.g. isobutyraldehyde, DBU in 5 min, 99%; DIPEA, 7 h, 97%) and 75-95% yield, E/Z ratio >20:1, with unsaturated aldehydes (e.g. crotonal-

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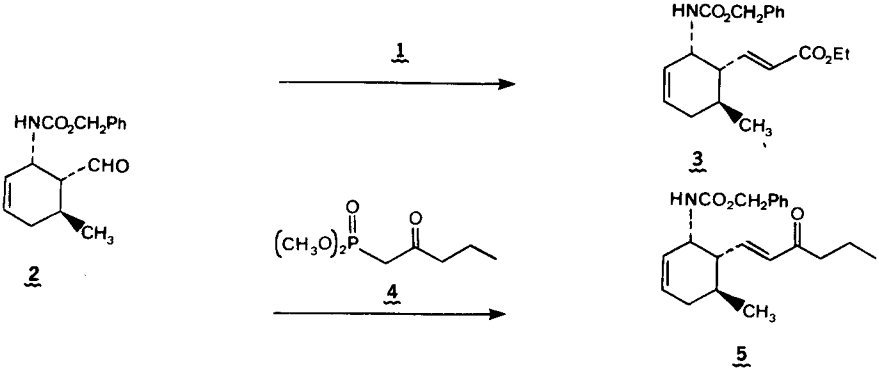
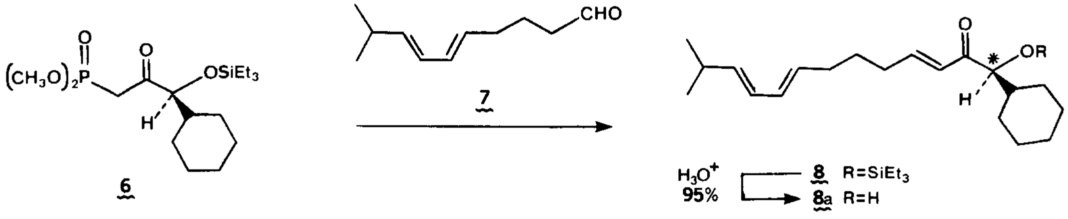
[†] Assumed to be 18.5 in both solvents.

dehyde, DBU, 0.5 h, 83%; DIPEA, 18 h, 85%) and aromatic aldehydes, E/Z >100:1 (e.g. benzaldehyde, DBU, 0.5 h, 81%; DIPEA, 3 d, 87%). The high E/Z ratios deserve attention. Of the many salts and solvents examined, the above combination (LiCl, acetonitrile) appears to bring about the best results.

The mild conditions used in the present procedure become critically important in certain cases. Thus olefination of the base labile 2[6] with the phosphonates 1 or 4 using the standard procedure with DIPEA as base proceeded smoothly (Table 1, Entries 1 & 2). In contrast, Overman and coworkers had noted that the conventional means of deprotonating 1 and 4 with NaH apparently resulted in varying degrees of epimerization of the aldehyde prior to olefination.[7]



Phosphonate 6[8] has one epimerizable center and aldehyde 7[9] is readily subject to base-catalyzed aldol-type reactions. Use of NaH (Entry 4) or t-BuOK (Entry 5) thus led largely to the self-condensation of 7. Therefore, the successful olefination under the standard procedure (Entry 3) is particularly gratifying. No epimerization took place at the asterisked center α to the carbonyl of 8.[10]



Phosphonate 9 is prone to undergo elimination of a molecule of ROH under basic conditions. As expected, this elimination reaction occurred quite readily when NaH (1.1 equiv) (Entry 7) or K_2CO_3 (6 equiv) (Entry 8) was added to a mixture of 9 and 10.[11] This undesired side reaction was again avoided by use of the standard procedure with DBU as base (Entry 6).

Finally, we should add some information concerning the effects of reagents on 1 in $MeCN\text{-}d_3$ as revealed by ^1H-decoupled ^{31}P NMR spectroscopy (Table 2). The chemical shift (δ 20.8) of the phosphorus nucleus of 1 remained virtually unchanged upon addition of either DBU or LiCl alone. However, mixing both reagents with 1 brought about a rather remarkable change, the spectrum now consisting of one sharp singlet (δ 29.5) and a temperature-dependent, broad singlet centered around δ 34. This latter spectrum can be reproduced almost exactly by adding DBU·HCl (1 equiv) to 1a (δ 40.7)[2b] prepared from 1 with n-BuLi in hexane followed by replacement of the solvent by

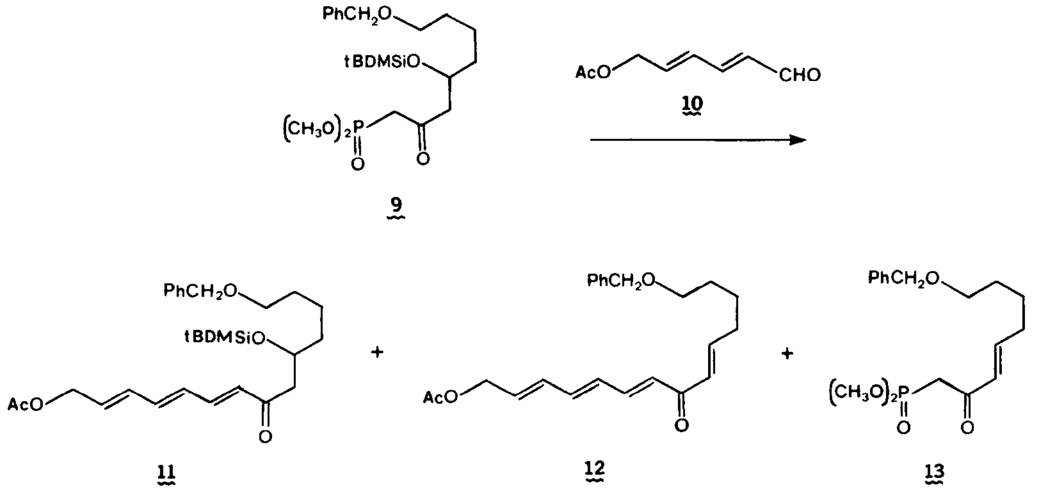


Table 1. Horner-Wadsworth-Emmons reactions with base-sensitive compounds

Entry	Aldehyde	Phosphonate	Reaction Conditions	Product and Yield (%)
1	2	1	LiCl, DIPEA, CH_3CN, 24 h, r.t.	3 (85%) + recovered 2 (10%)
2	2	4	LiCl, DIPEA, CH_3CN, 17 h, r.t.	5 (90%)
3	7	6	LiCl, DIPEA, CH_3CN, 24 h, r.t.	8 (63-70%)
4	7	6	NaH (1.3 equiv), DME, 0°→r.t.	8 (0%)
5	7	6	t-BuOK (1.3 equiv), DME, 0°→50°C	8 (34%)
6	10	9	LiCl, DBU, CH_3CN, 2 h, r.t.	11 (70%) + recovered 9 (23%)
7	10	9	NaH (1.1 equiv), tol, 9 h, r.t.	11 (0%) + 12 (6%) + 13 (54%)
8	10	9	K_2CO_3 (6 equiv), 18-crown-6 (12 equiv), toluene, 2.5 h,r.t.	11 (44%) + 12 (50%)

MeCN-d_3. Thus, we reason that the reaction medium used in the present procedure contains at least two LiCl•DBU•1 complexes, one of which may be interconverting to 1a with a rate comparable to the NMR time scale. The lithium enolate 1a has been assumed to be the reactive species for olefination. While the structural formulation of these complexes, as noted above, obviously requires further elaborate work, the spectral data evidently shows that the lithium salt plays a unique role in this modified Horner-Wadsworth-Emmons reaction.[12]

Table 2. ^{1}H-decoupled ^{31}P NMR (109.4 MHz) spectra of 1 in various conditions

System[a]	1	1 + DBU	1 + LiCl[c]	1 + LiCl + DBU	1a[d]
$\delta^{31}P$[b]	20.8	20.8	21.9	29.5 and broad signal at ~34	40.7

[a] Solvent, MeCN-d_3; concentration of each reagent, ca 0.2M; temperature, ambient.
[b] Using 85% H_3PO_4 as external standard. [c] LiCl did not completely dissolve.
[d] See text.

References and Footnotes

1. Several representative articles pertaining to this subject are: (a) Gosney, I.; Rowley, A.G. In "Organophosphorus Reagents in Organic Synthesis." Cadogan, J.I.G., Ed.; Academic Press; New York, 1979; Chap. 2. (b) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (c) Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (d) Bottin-Strzalko, T.; Etemad-Moghadam, G.; Seyden-Penne, J. *Nouv. J. Chim.* **1983**, *7*, 155 and references quoted in (a)-(d).
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3. Petrov, E.S.; Tsvetkov, E.N.; Terekhova, M.I.; Malevannaya, R.A.; Shatenshtein, A.I.; Kabachnik, M.I. Izv. Akad. Nauk. SSSR, Ser. Khim. 1976, (3), 534. These values should not be directly compared with those of DBU and DIPEA which were measured in water.
4. For DBU, see Nakatani, K.; Hashimoto, S. *Soc. of Synthetic Organic Chem., Japan (Yuki-Gosei-Kagaku-Kyokaishi)* **1975**, *33*, 925. For DIPEA, see Kricheldorf, H.R. *Makromol. Chem.* **1974**, *175*, 3325.
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6. Masamune, S.; Reed, III, L.A.; Davis, J.T.; Choy. W. *J. Org. Chem.* **1983**, *48*, 4441.
7. (a) Overman, L.E.; Jessup, P.J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. (b) Overman, L.E.; Lesuisse, D.; Hashimoto, M. *Ibid.* **1983**, *105*, 5373. The HWE reaction of an aldehyde similar to **5** was effected with $LiN[Si(TMS)_2]_2$ as base at -78°C.
8. Prepared from methyl (*S*)-O-triethylsilylhexahydromandelate in 75-80% yield with the lithium anion derived from dimethyl methylphosphonate (THF, -78°C→-20°C). $[\alpha]_D$ -11.9° (c 2.13, $CHCl_3$), >98% e.e. as determined by chiral shift experiments $[Eu(tfc)_3]$.
9. Roush, W.R.; Gillis, H.R.; Ko, A.I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.
10. Optical purity of **8a** (>97% e.e.) obtained from **8** was determined by the Mosher ester technique $[\alpha]_D^{25}$ +65.1° (c 0.85, $CHCl_3$). 250 MHz ^1H NMR ($CDCl_3$) of **8**: δ 6.94 (dt, J=15.6, 6.9 Hz, 1H), 6.51 (d, J=15.6 Hz, 1H), 5.94 (m, 2H), 5.54 (m, 2H), 3.77 (d, J=6.2 Hz, 1H), 2.33-2.16 (m, 3H), 2.07 (m, 2H), 1.75-1.04 (m, 13H), 0.97 (d, J=6.7 Hz, 6H), 0.91 (t, J=7.9 Hz, 9H), 0.55 (q, J=7.9 Hz, 6H).
11. This reaction was carried out in connection with the synthesis of amphotericin B. ^1H NMR of **11**: δ 0.0 (s, 3H), 0.03 (s, 3H), 0.83, (s, 9H), 1.36-1.61 (m, 6H) 2.07 (s, 3H), 2.70 (m, 2H), 3.44 (t, J=6.50, 2H), 4.14 (m, 1H), 4.47 (s, 2H), 4.66 (d, J=6.0, 2H), 5.89 (dt, J=6.0, 15.2, 1H), 6.12 (d, J=15.5, 1H), 6.26 (dd, J=10.0, 15.2, 1H), 6.29 (dd, J=10.5, 15.0, 1H), 6.49 (dd, J=10.0, 15.0, 1H), 7.07 (dd, J=10.5, 15.5, 1H), 7.30 (s, 5H).
12. We thank the National Institutes of Health (AI15403 and GM31124) and the National Science Foundation (CHE-8106987) for financial support.

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