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Preparation of Ketones from Nitriles and Phosphoranes

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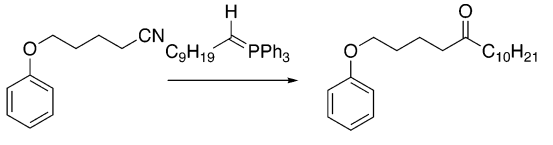

The preparation of a ketone from a phosphorane and a nitrile is described. The workup conditions are mild, and the yields are high. The unreacted starting materials can easily be recovered.

The ketone is the central functional group in organic synthesis. One route to a ketone is the addition of an organometallic reagent to the nitrile. The disadvantage of this approach is that any unreacted organometallic reagent is protonated on workup and so lost. We describe an improved procedure for the addition of a phosphorane to the nitrile. The advantage of this approach is that any unreacted phosphonium salt can easily be recovered and reused.

In 1967, McEwen reported[1] that the ylide produced by deprotonating a triphenylphosphonium iodide with BuLi can react with a nitrile to give the corresponding ketone. The procedure included vigorous hydrolysis with methanol and HCl. Perhaps because of the harsh workup conditions, the procedure has been little used.[2,3] We have found that the hydrolysis procedure specified by McEwen is not required. Mild workup of the reaction with aqueous ammonium chloride gives the ketone directly.

Our procedure begins by suspending the phosphonium salt in anhydrous THF. As specified by McEwen, 0.5 equiv of LiI is added if the phosphonium salt is not the iodide. At ice−water temperature, BuLi in hexane is added to produce the red solution of the phosphorane. The nitrile is added, and the reaction mixture is maintained at 50 °C for 8 h. The reaction is then quenched with aqueous NH_4Cl. Any unreacted phosphonium salt and nitrile can easily be recovered by crystallization or column chromatography.

Our results are summarized in Table 1. Ketones **2c**,[4] **3c**,[5] **5c**,[6] **6c**,[7] and **7c**[8] have previously been described. The preparation of the phosphonium iodide **1a** has also been described before.[9]

This procedure for preparing ketones appears to be general (Table 1). Each of the condensations proceeded effectively with only a small excess of the less expensive component. We expect that this approach will be particularly useful when it is necessary to prepare a ketone by coupling two advanced intermediates in a synthesis.[10,11]

Experimental Section

Procedure from Phosphonium Iodide, Ketone 1c. [2-(2,2-Dimethyl-[1,3]dioxolan-4-yl-ethyl]-triphenyl-λ^5-phosphonium iodide (**1a**, 9.79 g, 18.90 mmol, 1.0 equiv) was suspended in 140 mL of anhydrous THF. The reaction flask was wrapped with aluminum foil. At ice−water temperature, 10.0 mL of 2.5 M BuLi in hexane (25.00 mmol, 1.3 equiv) was added, producing the orange-red solution of the phosphorane. After 20 min, 5 mL of THF containing 3.42 g of isovaleronitrile (**1b**, 28.7 mmol, 1.5 equiv) was added. The reaction mixture was then maintained at 50 °C for 8 h.

After cooling to room temperature, the reaction mixture was partitioned between saturated aqueous NH_4Cl (80 mL) and, sequentially, CH_2Cl_2 (15 mL) and 25% MTBE/PE (25 mL × 3). The organic extracts were washed with saturated aqueous NaCl (45 mL), dried (Na_2SO_4), and concentrated. Anhydrous Et_2O was added. The resulting suspension was filtered to recover a small amount of the starting phosphonium iodide salt (3.80 g, 61% conversion rate). The solution residue was absorbed by silica gel and chromatographed to yield ketone **1c** (1.11 g, 6.99 mmol, 61% yield from **1a**) as a colorless oil (TLC R_f (20% MTBE/PE) = 0.52). IR (cm^{-1}) 1713, 1369, 1064; ^1H NMR δ 4.10−3.95 (m, 2H), 3.5 (m, 1H), 2.58−2.40 (m, 2H), 2.25 (d, $J = 7.1$ Hz, 2H), 2.18−2.10 (m, 1H), 1.90−1.80 (m, 1H), 1.79−1.70 (m, 2H), 1.39 (s, 3H), 1.30 (s, 3H), 0.93 (d, 3H), 0.92 (d, 3H); ^{13}C NMR δ u 210.2, 108.9, 69.2, 51.9, 39.1, 27.2, d 75.1, 26.9, 25.6, 24.6, 22.6, 22.5; MS *m/z* 199(100), 157 (17), 156 (18), 113 (24); HRMS calcd for $C_{11}H_{19}O_3$ 199.1334, obsd 199.1343.

Procedure from Phosphonium Bromide, Ketone 4c. *n*-Decyl triphenylphosphonium bromide (**2a**, 1.57 g, 3.25 mmol, 1.8 equiv) and LiI (0.13 g, 0.97 mmol, 0.5 equiv) were suspended in 40 mL of anhydrous THF. The reaction flask was wrapped with aluminum foil. At ice−water temperature, 1.6 mL of 1.8 M BuLi in hexane was added, producing the red solution of the phosphorane. After 20 min, 5 mL of THF containing 0.318 g of 4-phenoxybutanenitrile (**4b**, 1.82 mmol, 1.0 equiv) was added. The reaction mixture was then maintained at 50 °C for 8 h.

After cooling to room temperature, the reaction mixture was partitioned between saturated aqueous NH_4Cl and, sequentially, CH_2Cl_2 (10 mL) and 25% MTBE/PE (25 mL × 3). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated. The residue was chromato-

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[2] Trabelsi, H.; Cambon, A. *Synthesis* **1992**, 315.

[3] Hamzaoui, M.; Provot, O.; Gregoire, F.; Riche, C.; Chiaroni, A.; Gay, F.; Moskowitz, H.; Mayrargue, J. *Tetrahedron: Asymmetry 1997*, *8*, 2085.

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[7] Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982.

[8] Veenstra, G. E.; Zwanenburg, B. *Tetrahedron* **1978**, *34*, 1585.

[9] Taber, D. F.; Xu, M. *J. Am. Chem. Soc.* **2002**, *124*, 13121.

[10] For such a construction, see Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374.

[11] For a recent report of ketone construction by the condensation of Weinreb amides with phosphoranes, see: Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427.

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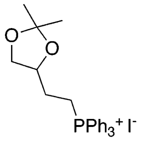
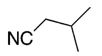
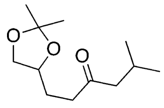
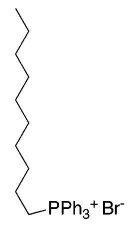
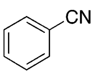
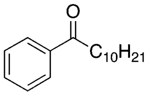
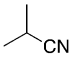
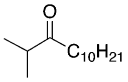
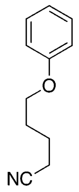
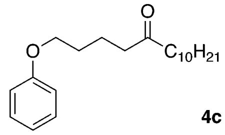
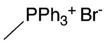
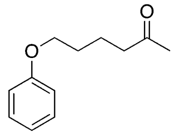
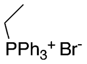
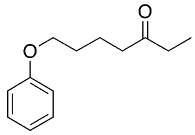
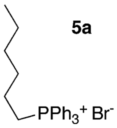
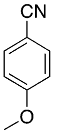
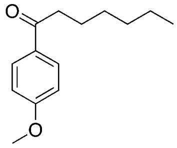
TABLE 1. Condensation of Phosphoranes and Nitriles To Produce Ketones

Triphenyl phosphonium halide salt	eq.	Nitrile	eq.	Product	equivalent of LiI used	Yield
 **1a**	1.0	 **1b**	1.5	 **1c**	none	61%
 **2a**	1.0	 **2b**	1.3	 **2c**	0.5	95%
	1.0	 **3b**	1.5	 **3c**	0.5	76%
	1.5	 **4b**	1.0	 **4c**	0.5	76%
 **3a**	1.3		1.0	 **5c**	0.5	92%
 **4a**	1.2		1.0	 **6c**	0.5	81%
 **5a**	1.0	 **5b**	1.3	 **7c**	0.5	95%

graphed to yield 7-phenoxy-3-heptanone (**4c**, 0.347 g, 1.09 mmol, 76% yield from **4b**) as a colorless oil (TLC R_f (20% MTBE/PE) = 0.79). A small amount of the starting nitrile (0.067 g, 79% conversion, R_f (20% MTBE/PE) = 0.43) was also recovered.

Ketone 4c: IR (cm^{-1}) 1710, 1499, 1258; ^{1}H NMR δ 6.81−7.28 (m, 5H), 3.92 (m, 2H), 2.50 (m, 2H), 2.38 (m, 2H), 1.78 (m, 4H), 1.6 (m, 2H)1.32−1.20 (m, 14H), 0.89 (3H, t); ^{13}C NMR δ u 211.6, 159.3, 67.8, 43.3, 42.7, 32.3, 30.0, 29.9, 29.8, 29.7, 29.6, 29.2, 24.3, 23.1, 20.8 d 129.9, 121.0, 114.8, 14; MS *m/z* 225(100), 111 (16), 98 (31); HRMS calcd for $C_{21}H_{34}O_2$ 318.2559, obsd 318.2544.

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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