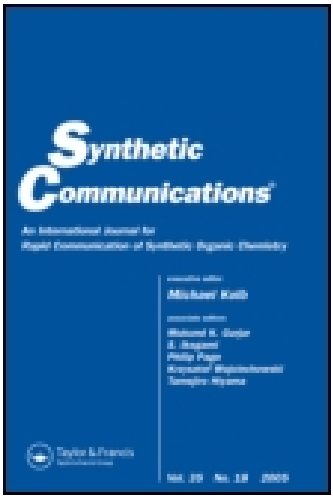

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Synthesis of Ketones with Alkyl Phosphonates and Nitriles as Acyl Cation Equivalent: Application of Dephosphonylation Reaction of β-Functionalized Phosphonate with Hydride

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Synthesis of Ketones with Alkyl Phosphonates and Nitriles as Acyl Cation Equivalent: Application of Dephosphonylation Reaction of β-Functionalized Phosphonate with Hydride

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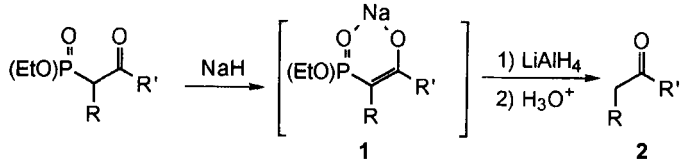
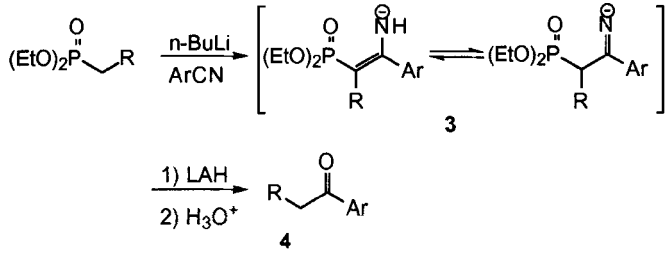
Abstract: The preparation of several α-substituted ketones is performed in a one-pot procedure with alkyl phosphonates and aromatic nitriles by subsequent treatment of $LiAlH_4$. A new method for nitriles used as an acyl cation equivalent is described.

Aromatic nitrile compounds are not readily chosen as a acyl cation equivalent in ketone synthesis, because its reactivity is somewhat lower than other compounds such as acyl chlorides, esters *etc.* Study on the reaction of organolithium compounds and Grignard reagents with nitrile was reported earlier.[1] But the results were of little synthetic value because of low yields and the use of nucleophile in large excess (that may prevent the reversible reaction). We recently reported on the dephosphonylation[2] reaction of β-keto phosphonates with LAH.[3] The main advantage of this reaction is simple and general method which makes the phosphoryl group to act as a temporary α-activating group (Scheme 1).



Scheme 1.

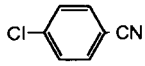
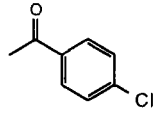
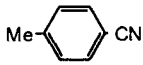
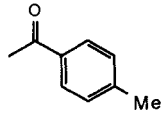
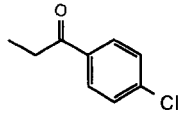
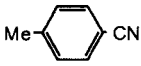
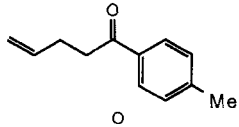
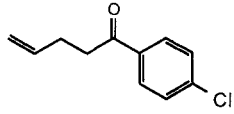
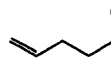
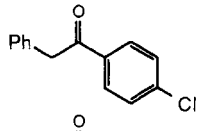
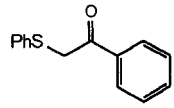
As an extension of this work, we investigated that this reaction could be applied to synthesis of several aromatic ketones using β-enamino phosphonates anion[4] which could be readily produced in the reaction with lithiated diethyl alkyl phosphonate and aromatic nitriles[5] as an acyl cation equivalents shown in Scheme 2. We herein report a new application of dephosphonylation reaction to transformation of aromatic nitriles to ketones.



Scheme 2.

Generally, to a stirred solution of diethyl alkylphosphonate (1 mmol) in dry THF, is added *n*-BuLi (1 mmol) at -78 °C under N_2 atmosphere. After being stirred for 1h at same temperature, Nitrile (1.2 mmol) is added and the mixture is warmed to -5 °C for 30 min. $LiAlH_4$(3 mmole) is added and the mixture is warmed to r.t. for 30 min. After quenched with aq. 5N Sulfuric acid, normal work-up give the desired ketones. These results are summerized in Table 1. As shown in Table 1, the present method successfully gave the desired ketones in good to excellent yields except entry 10. Low yield was shown in case of diethyl phenylthiomethyl phosphonate (Entry 10), because anion generated by base seems too stable to react with nitrile to form the intermediate 3. The ketones produced in

Table 1. Synthesis of α-Substituted-Ketones.

Entry	R	Nitriles	Product	Yields (%)[a]
1	H	PhCN		92
2	H			95
3	H			80
4	CH_3	PhCN		92
5	CH_3			99
6	CH_2= $CHCH_2$			79
7	CH_2= $CHCH_2$			99
8	CH_2= $CHCH_2$	PhCN		99
9	Ph			95
10	SPh	PhCN		21

a. Isolated Yield.

this reaction were as pure as no further purification is needed (except Entry 10). Slight excess of nitrile seemed to be reduced to amine by excess of LAH and can be removed in acidic work-up process. It is worthy of note that, in Entry 9, unsymmetrical deoxybenzoins can be easily produced in high yield. Symmetric and unsymmetric deoxybenzoins are well-recognized in organic synthesis as a versatile precursors of a large number of interesting organic compounds.[6] As shown in Scheme 2, Lithiated phosphonate anion can react with nitrile to form a stable intermediate **3** in excellent yields[4], compared to alkyl lithium or Grignard reagent[1]. Since intermediate **3** are analogous to the metal enolate of β-keto phosphonate **1**, dephosphonylation occurred after treatment of LAH with intermediate **3**. Because of its anion, the enamine group in **3** seems to be protected from hydride attack. So hydride may attack the phosphoryl group and after hydrolysis, the corresponding dephosphonylated ketones were obtained in one-pot. Described in earlier report[3], dephosphonylated product might have dianionic character, but cannot be identified.[7]

This simple, convenient synthetic method can provide utility of an aromatic nitrile as a versatile acyl cation equivalent, and shows a new application of phosphonate compound. Further studies using β-keto, and β-enamino phosphonate compounds bearing other functional group are in progress.

Experimental Section

General procedure

To a stirred solution of diethyl methylphosphonate (1 mmol) in dry THF (3 ml), is added BuLi (1 mmol, 1.6 M in hexane) at -78 °C under N_2 atmosphere. After being stirred for 1h at same temperature, Nitrile (1 mmol) is added and the mixture is warmed to -5 °C for 30 min. $LiAlH_4$ (in 2 ml THF) is added and the mixture is warmed to r.t for 30 min. 5N H_2SO_4 is added and stirring continued for 5h. The mixture is extracted with ether (3 x 30 ml). The combined organic extract is washed with sat. $NaHCO_3$ (30 ml) then dried ($MgSO_4$) and evaporated to give desired product.

Acetophenone (1) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.39 - 7.56 (m, 3H), 7.91 - 7.97 (m, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 26.39, 128.13, 128.39, 132.94, 136.93, 197.99.

4'-Chloroacetophenone (2) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.39 - 7.46 (m, 2H), 7.84 - 7.93 (m, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 26.34, 128.71, 129.57, 135.29, 139.37, 196.62.

4'-Methylacetophenone (3) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.56 (s, 3H), 7.24 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 21.57, 26.42, 128.37, 129.17, 134.75, 143.73, 197.56.

Propiophenone (4) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 2.99 (q, J = 7.3 Hz, 2H), 7.38 - 7.59 (m, 3H), 7.92 - 8.00 (m, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 8.01, 31.53, 127.75, 128.33, 132.66, 136.70, 200.60.

4'-Chloropropiophenone (5) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 2.96 (q, J = 7.2 Hz, 2H), 7.37 - 7.45 (m, 2H), 7.85 - 9.98 (m, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 7.98, 31.61, 128.68, 129.24, 135.07, 139.09, 199.34.

1-Phenyl-4-penten-1-one (6) :**^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.41 - 2.55 (m, 2H), 3.05 (t, J = 7.4 Hz, 2H), 4.96 - 5.14 (m, 2H), 5.79 - 6.00 (m, ^{1}H), 7.26 - 7.59 (m, 3H), 7.91 - 7.99 (m, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 27.95, 37.52, 115.08, 127.82, 128.39, 132.81, 136.74, 137.12, 199.14.

1-(4-Chloro)phenyl-4-penten-1-one (7) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.43 - 2.53 (m, 2H), 3.04 (t, J = 7.3 Hz, 2H), 4.98 - 5.13 (m, 2H), 5.81 - 5.97 (m, ^{1}H), 7.42 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H); **^{13}C NMR** : (50 MHz, $CDCl_3$) δ 27.92, 29.58, 37.58, 115.32, 127.90, 128.46, 128.77, 129.32, 135.12, 136.95, 139.29, 198.0.

1-(4-Methyl)phenyl-4-penten-1-one (8) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.38 - 2.54 (m, 2H), 3.02 (t, J = 7.4 Hz, 2H), 4.95 - 5.13 (m, 2H), 5.78 - 6.00 (m, ^{1}H), 7.20 - 7.28 (m, 2H), 7.81 - 7.88 (m, 2H).

1-(4-Chlorophenyl)-2-Phenyl Ethanone (9) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 4.22 (s, 2H), 7.24 - 7.41 (m,7H), 7.89 - 7.93 (d, 2H); **Mass** m/z

(relative intensity %) 232(M^{+2}, 2.1), 230(5.8), 165(3.0), 141(32.9), 139(100), 113(13.0), 111(37.7), 91(18.4), 75(22.9).

1-(4-Chlorophenyl)-2-Thiophenyl Ethanone (10) : **^{1}H NMR** : (200 MHz, $CDCl_3$) δ 4.19 (s, 2H), 7.24 - 7.43 (m, 7H), 7.82 - 7.87 (d, 2H).

Acknowledgement : This paper was supported by NON DIRECT RESEARCH FUND, Korea Research Foundation

References and Notes

1. (a) Carmeron, G. G; Milton, A. J. S. *J. Chem. Soc. Perkin Trans. II*, **1976**, 378. (b) Kharasch, M. S. And Reinmuth, O. *Grignard reagents of Non-metallic Substances* ; Constable; London, **1954.** (c) Hauser C. R. ; Humphlett, W. J. *J. Org. Chem.*, **1950**, *13*, 359. (d) Sumrell, G. *J. Org. Chem.*, **1954**, *19*, 817.

2. To tell between "dephosphorylation" and "dephosphonylation", we use the term "dephosphonylation" as a limited meaning of P-C bond cleavage in compound including phosphonate group.

3. Hong, J. E; Shin, W. S.; Jang W. B.; Oh, D. Y. *J. Org. Chem.*,**1996**, *61*, 2199.

4. (a) Lee, K.; Oh, D. Y. *Bull. Korean Chem. Soc.*, **1989**, *10*, 613. (b) Lee, K.; Oh, D. Y. *Synthesis*, **1991**, 213. (c) Lee, K.; Shin,W. S.; Oh, D. Y. *Synthetic Commun.*, **1991**, *21*, 1657. (d) Lee, K. ; Oh, D. Y. *Bull. Kor. Chem. Soc.*, **1991**, *12*, 254. (e) Shin, W. S.; Lee, K.; Oh, D. Y. *Tetrahedron Lett.*, **1995**, *36*, 281.

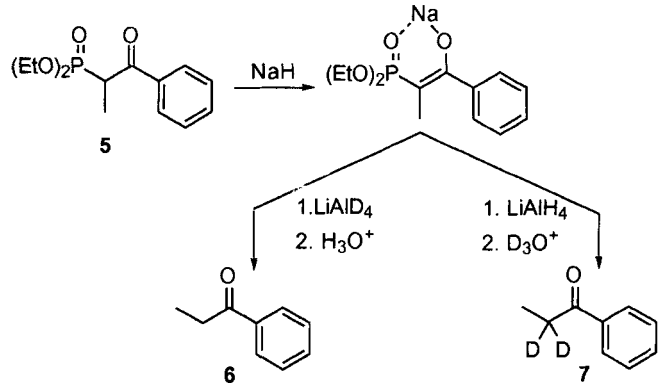
5. In general, the addition of organolithium compounds to aliphatic nitriles are subjected to various side reactions, notably α-deprotonation (ref. 1(d)). We investigated the result on that, and described that in previous report (ref. 4(b)).

6. Robinson G. E.; Vernon, J. M. *J. Chem. Soc. Perkin Trans . I*, **1972**, 1277.

7. In earlier report (ref 3), several experiments with β-keto phosphonate were carried out to investigate the detailed mechanism. When reduction of β-keto phosphonate **5** with $LiAlD_4$ was followed by quenching with dilute H_2SO_4, the reaction afforded the ketone **6** containing no deuterium. In case of using $LiAlH_4$ and deuterized acid, the reaction gave the ketone **7** involving two deuteriums.

Because ketones do not exchange its α-proton rapidly, this two result can be the evidence that hydride attacked the phosphorus atom directly. However in the case

of enamine, proton exchange is occured rapidly in hydrolysis step, so above experiment cannot be adapted in this paper. But mechanisms of these two reactions are presumed to be identical.



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