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CYANOPHOSPHATE: AN EFFICIENT INTERMEDIATE FOR CONVERSION OF CARBONYL COMPOUNDS TO NITRILES

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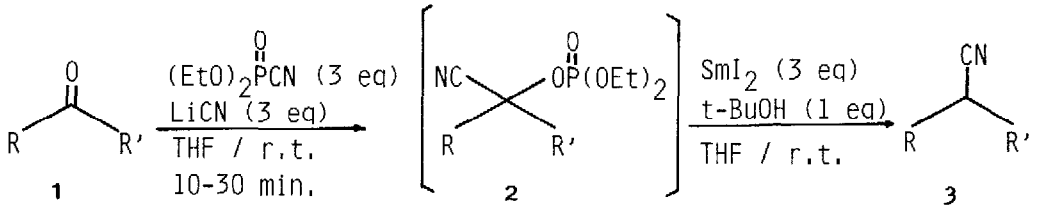
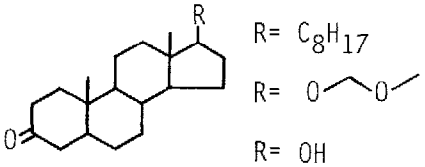
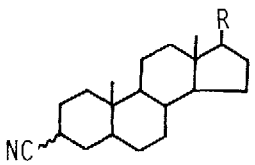
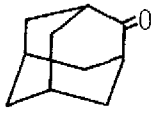
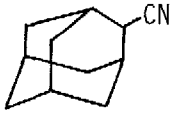
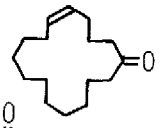
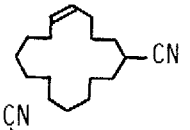
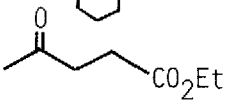
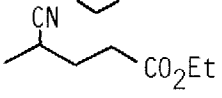
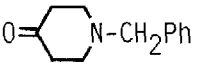
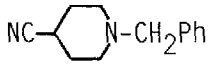
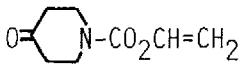
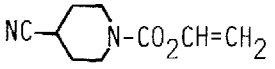
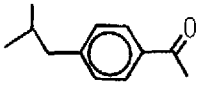
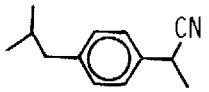
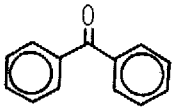
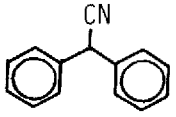
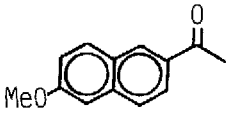
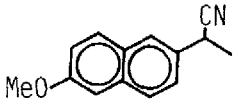
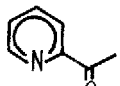
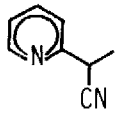
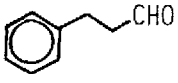
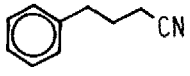
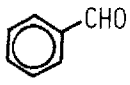
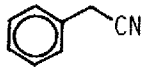
Abstract: A novel and high yield conversion of saturated or unsaturated carbonyl compounds to nitriles *via* cyanophosphates by samarium diiodide in the presence of *tert*-butanol is described.

The conversion of a carbonyl group into a nitrile is an important technique for one-carbon homologation in organic synthesis and has so far been extensively investigated.[1] The tosylmethyl isocyanide (TosMIC) method by van Leusen[2] is efficient for synthesis of nitriles from ketones. However, it involves the use of a strong base such as *tert*-BuOK and generally gives low yields in the cases of aliphatic and α,β-unsaturated aldehydes.[3] We report here a simple and high yield conversion of a variety of carbonyl compounds into nitriles *via* cyanohydrin O,O'-diethyl phosphates (cyanophosphates) using samarium diiodide (SmI_2). Previously, we reported the synthesis of arylacetonitriles from aromatic ketones *via* cyanophosphates as a continuation of our research on its application to organic synthesis.[4]



Recently, SmI_2, prepared readily from Sm and diiodoethane (ICH_2CH_2I) in tetrahydrofuran (THF), has been widely noted not only for its moderate reducing power for organic compounds, but also ease of handling in THF.[5] Thus, we examined the reactivity of cyanophosphates with SmI_2. The cyanophosphorylation of carbonyl compounds (**1**) has been successfully carried out by treatment with diethyl phosphorocyanidate (DEPC) and lithium cyanide (LiCN) in THF in almost quantitative yield.[6] The crude cyanophosphate (**2**) reacted with

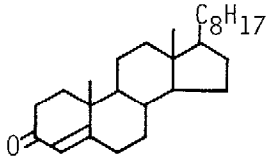
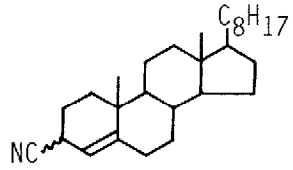
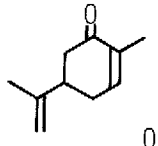
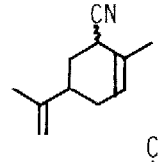
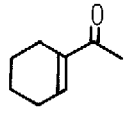
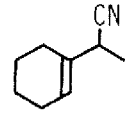
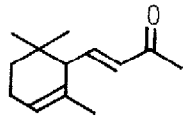
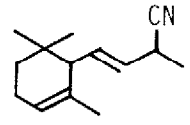
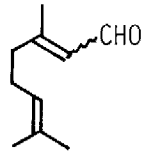
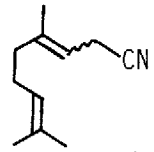
Table I. Reductive Cyanation of Ketones and Aldehydes *via* Cyanophosphates with SmI_2

Run	Starting Material	Product	Reaction time	Yield(%)[a]
1	 R= C_8H_{17}		3 h	83[b]
2	R=		3 h	84[c]
3	R= OH		4 h	92[d]
4			4 h	100
5			3 h	97
6			2 h	80
7			2 h	79
8			1 h	92
9			10 min	94
10			10 min	90
11			10 min	96
12			10 min	69
13			3 h	82
14			2 h	85

a. Yield of pure, isolated product from starting material
b. 3α/3β=6/4 c. 3α/3β=6/4 d. 3α/3β=8/2

SmI_2 in the presence of an equivalent amount of tert-butanol (t-BuOH) in THF at room temperature to give the corresponding nitriles (**3**), the results of which are summarized in Tables I and II. The following is a representative procedure: A carbonyl compound (**1**) (0.5 mM) was stirred with DEPC (1.5 mM) and LiCN (1.5 mM) in THF (10 ml) at room temperature for 10-30 min. Water (10 ml) was added, and the mixture was then extracted with EtOAc-hexane (1 : 1) (50 ml). The organic layer was washed with brine (2 x 20 ml) and dried over anhyd. Na_2SO_4 and evaporated at reduced pressure. A solution of the crude cyanophosphate (**2**) thus obtained and t-BuOH (0.5 mM) in THF (5 ml) was added to a solution of SmI_2, prepared from Sm (2.3 mM) and ICH_2CH_2I (1.5 mM) in THF (10 ml) at room temperature. This mixture was stirred for an appropriate time (Table). HCl (10%, 10 ml) was added and the mixture was extracted with Et_2O (2 x 50 ml). The extract was washed with 5% $Na_2S_2O_3$ (10 ml), brine (2 x 10 ml), dried over $MgSO_4$ and evaporated at reduced pressure. The residue was purified by flash chromatography (SiO_2) to afford nitrile (**3**) as a colorless oil.

Table II. Reductive Cyanation of α,β-Unsaturated Ketones via Cyanophosphates with SmI_2

Run	Starting Material	Product	Reaction time	Yield(%)[a]
1			10 min	76
2			30 min	86
3			15 min	86
4			10 min	97
5			2 h	89 (58)[b]

a. Yield of pure, isolated product from starting material
b. Reported yield by TosMIC method (ref. 3)

As shown in Table I, even bi-functional ketones (run 2, 3, 5-8) having hydroxyl, ether, double bond, ester, amino, and carbamate groups smoothly afforded nitriles in good yields. Interestingly, aromatic and heteroaromatic ketone cyanophosphates reacted much faster with SmI_2 in excellent yields (run 9-11) than did aliphatic ketone cyanophosphates. Furthermore, the method was also applicable to aliphatic and aromatic aldehydes (run 13, 14).

It is well known that the TosMIC method has not been used in the reductive cyanation procedure to α,β-unsaturated ketones since it gives 3-acylpyrroles under basic conditions.[7] The reductive cyanations of a variety of enones (run 1-4) including enal (run 5) were successively achieved by our current procedure to give only β,γ-unsaturated nitriles without any migration of the double bond in excellent yields, as shown in Table II. In order to make a comparative study, an attempt was made to react cholest-4-en-3-one and α-ionone with TosMIC in the presence of t-BuOK.[8] However, only a complex mixture was obtained.[9]

In conclusion, our method using cyanophosphates as intermediates offers a convenient, high yield and mild method for the preparation of nitriles and should find application to a wide scope of structural types.

Acknowledgment This work was supported in part by a Grant-in Aid for the Encouragement of Young Scientists, Japan (to R. Y.).

References and Notes

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8. O.H. Oldenziel, J. Wildeman, and A.M. van Leusen, Org. Synth., **57**, 8 (1977).
9. Trace amounts of β,γ-unsaturated nitriles were detected on TLC.

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