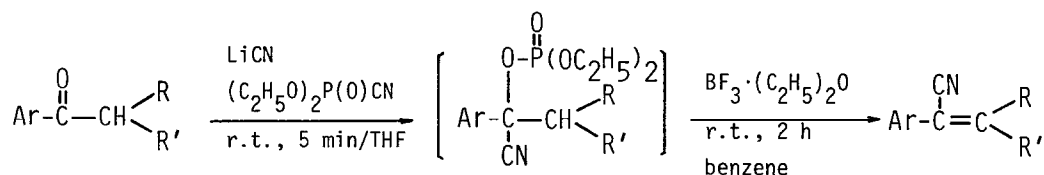


A NOVEL SYNTHESIS OF α,β -UNSATURATED NITRILES FROM AROMATIC KETONES
 VIA CYANOPHOSPHATES¹⁾

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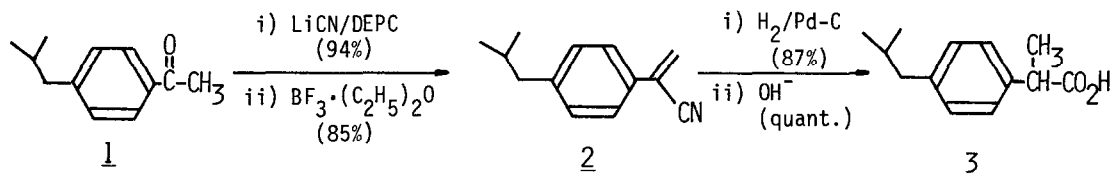
Summary : Reaction of aromatic ketones with diethyl phosphorocyanidate in the presence of lithium cyanide gave cyanophosphates, which were converted into α,β -unsaturated nitriles by treatment with boron trifluoride etherate in high yields.

Formation of cyanohydrins followed by dehydration is a practical way for the transformation of ketones to α,β -unsaturated nitriles²⁾ which are important versatile synthetic intermediates. Likewise, it has been shown³⁾ that trimethylsilyloxy nitriles, prepared from ketones and trimethylsilyl cyanide, give α,β -unsaturated nitriles with pyridine and phosphoryl chloride under refluxing conditions. As our continued interest on the use of diethyl phosphorocyanidate [DEPC, $(C_2H_5O)_2P(O)CN$] as a cyanation reagent,⁴⁾ we reported a novel and high-yield cyanophosphorylation of ketones and aldehydes by the reaction with DEPC in the presence of a catalytic amount of lithium diisopropylamide.⁵⁾ We have now found that DEPC rapidly reacts with aromatic ketones in the presence of lithium cyanide⁶⁾ in tetrahydrofuran (THF) to give cyanophosphates, which are readily converted into α,β -unsaturated nitriles by treatment with boron trifluoride etherate in benzene at room temperature in high yields.



A representative experimental procedure is as follows : A mixture of ketone (1 mmol), DEPC (489 mg, 3 mmol), and lithium cyanide (100 mg, 3 mmol) in THF (10 ml) was stirred at room temperature for 5 min. After removal of the THF by evaporation, the residue was dissolved in water (10 ml) and benzene-ethyl acetate (1 : 1, 50 ml). The organic layer was separated, and washed with water (10 ml \times 2) and saturated aqueous sodium chloride (10 ml \times 1). Drying over sodium sulfate followed by concentration gave a brown oil, which was stirred with boron trifluoride etherate (426 mg, 3 mmol) in benzene (3 ml) at room temperature for 2 h under argon. After the addition of benzene (50 ml) and water (10 ml), the organic layer was separated, and washed with water (10 ml \times 2) and saturated aqueous sodium chloride (10 ml \times 1). Drying over sodium sulfate followed by concentration gave the crude α,β -unsaturated nitrile, which was purified by silica gel column chromatography. The results are summarized in Table.

Various aromatic ketones have been effectively converted to α,β -unsaturated nitriles. Interestingly, however, the cyanophosphate function derived from an aliphatic ketone remains intact under dephosphorylation conditions (run 6). When the reaction was applied to 4-isobutylacetophenone (**1**), ibuprofen (**3**), which is known as an *anti*-inflammatory agent, was effectively obtained via the α -cyanostyrene (**2**), followed by hydrogenation and hydrolysis, in 70% overall yield from **1**.



The procedure described here as α,β -unsaturated nitrile synthesis offers a convenient, high-yield, and mild method. Application of the cyanophosphates to the other synthetic utility is now actively under way.

Table. A Novel Transformation of Ketones to α,β -Unsaturated Nitriles

run	Ketones	Products	Yield (%)	run	Ketones	Products	Yield (%)
1			80	4			94
2			74	5			78
3			61	6			92

a) The (Z)-stereochemistry was confirmed by ^{13}C NMR [$^3\text{J}(\text{CN-H})=14.6$ Hz] and ^1H NMR spectral analysis.

References and Notes

- 1) This paper constitutes Part 39 of a series of papers entitled "New Methods and Reagents in Organic Synthesis". For Part 38, see N. Kato, Y. Hamada, and T. Shioiri, *Chem. Pharm. Bull.*, submitted.
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