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A ONE-POT AND SELECTIVE PREPARATION OF ALKYLATED 3-CYCLOHEXEN-1-ONE

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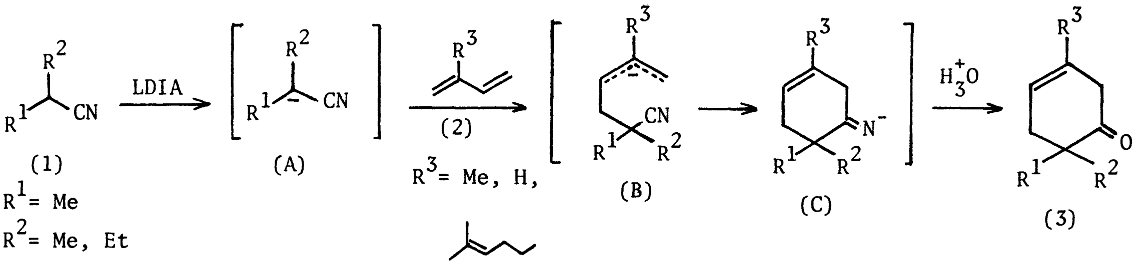
Treatment of lithiated nitrile with conjugated 1,3-dienes, such as isoprene, myrcene, and butadiene, followed by hydrolysis with 3N-HCl gave selectively alkylated 3-cyclohexen-1-ones.

Alkylated cyclohexenones are well-known to be key intermediates in the synthesis of natural products. However, it is difficult to synthesize alkylated 3-cyclohexen-1-one selectively. Corey et al.1) reported that Diels-Alder addition of 2-chloroacryloyl chloride to 1,3-dienes gave 1-chloro-3-cyclohexenecarbonyl chlorides which were transformed into 3-cyclohexen-1-ones.

Recently the reactions of lithiated nitrile with electrophiles have been widely used for the purpose of the synthesis of a variety of organic compounds.2) In this communication we wish to report a simple and selective preparation of alkylated 3-cyclohexen-1-one via the cycloalkenylation3) of lithiated nitrile (A) using 1,3-dienes (2), such as isoprene, myrcene, and butadiene.



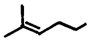
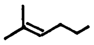
For example, treatment of 2-methylpropanenitrile [(1): R^1=R^2=Me, 14 mmol] in anhydrous ether (15 ml) with an equivalent of lithium diisopropylamide (LDIA), prepared from 15% butyllithium in hexane and diisopropylamine in ether (10 ml) in situ, at -78°C for 30 min gave a solution of the carbanion (A). To this solution was added dropwise a solution of isoprene (42 mmol) in hexane (40 ml) at -78°C, followed by gradual warming up to room temperature with stirring for 18 hr. The reaction mixture was then cooled to 0-5°C, treated with cold 3N-HCl, and stirred for 4 hr at room temperature. The products were extracted with ether, and the etheral extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. Evaporation of unreacted substrates and the solvents under reduced pressure gave the crude 3,6,6-trimethyl-3-cyclohexen-1-one [(3): R^1=R^2=R^3=Me], which was found to be 97% pure by GLC analysis. The distillation (bp 39-42°C/1.7 mmHg) gave pure (3) (0.89 g) in 46% isolated yield.4)

Table 1 summarized the yields of the typical examples.5, 6) This reaction was examined with a variety of bases and solvents systems, of which LDIA in ether-hexane was proved most efficient, but LDIA in tetrahydrofuran (THF)7) and lithium-naphthalene in THF7) were not so effective for the selective preparation of (3).8)

The reaction scheme seems to be as follows: the addition of a lithiated nitrile (A) to 1,3-diene (2) gives an acyclic intermediates (B), which is then cyclized intramolecularly to afford an alkylated 3-cyclohexen-1-one (3) via (C).

Extention of this reaction to the synthesis of natural products is now under investigations. The authors wish to express thanks to Messrs. T. Takagi, T. Sato, and G. H. Tang for preliminary experiments, and Mr. T. Yamada for NMR measurements.

Table 1. Selective preparation of alkylated 3-cyclohexen-1-one (3)a)

(1) R^1	 R^2	(2) R^3	(2)/(1)b)	Solvent	Time (hr)	Yields of (3) (%)c)
Me	Me	Me	3	ether-hexane	18	46
Me	Me	Me	1	ether-hexane	18	37
Me	Et	Me	1	ether-hexane	18	40
Me	Me	H	1	ether-hexane	12	31
Me	Me		1	ether-benzene	18	29
Me	Et		1	ether-benzene	45	23

a) LDIA. b) Molar ratio. (c) Isolated yields.

References and Notes

1) E. J. Corey, T. Ravindranathan, and S. Terashima, J. Am. Chem. Soc., 93, 4326 (1971).

2) J. C. Stowell, "Carbanions in Organic Synthesis", John Wiley & Sons, Inc., New York, N.Y. (1979) p.164; G. Stork, A. A. Ozorio, and A. Y. W. Leong, Tetrahedron Lett., 1978, 5175; idem, ibid., 1979, 771; K. Takaki, K. Neguro, and T. Agawa, J. Chem. Soc. Perkin I, 1979, 1490, and references cited therein.

3) K. Takabe, H. Fujiwara, T. Katagiri, and J. Tanaka, Tetrahedron Lett., 1975, 1239.

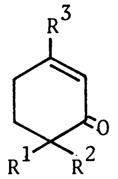
4) Viscous liquid (0.03 g) was obtained as the residue.

5) When the reaction was quenched with ethanol and then hydrolyzed with 3N-HCl, a small amount of the corresponding 2-cyclohexen-1-one (4) was isolated, together with (3) [$R^1=R^2=R^3=$Me, (2)/(1)=1, LDIA in ether-hexane, 18 hr: yields of (3) and (4) were 33 and 3%, respectively].

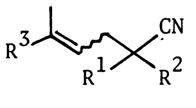
6) The structures of all compounds were verified by compatible spectral data.

7) A mixture of (3), (4),6) and alkenylated nitrile (5)6) was obtained, together with a considerable amount of high boiling point products, and the ratio of the products was extremely dependent on the reaction conditions.

8) The reaction of the nitrile (1) with 1,3-diene (2) using Na or NaH gave only alkenylated nitrile (5)6) as a 1:1 adduct.



(4)



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