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A NOVEL CYCLODIMERIZATION OF 3-METHYL-3-BUTENENITRILE. AN EFFICIENT SYNTHESIS OF 4-CYANOISOPHORONE

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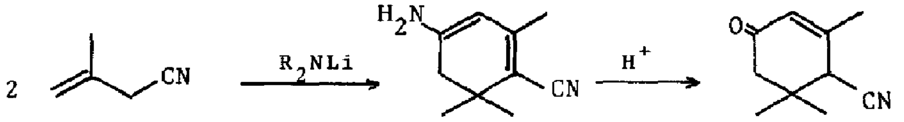
Summary: Dimerization of 3-methyl-3-butenenitrile (1) by lithium dialkylamide gave selectively 3,5,5-trimethyl-1-amino-4-cyanocyclohexa-1,3-diene (2), which was easily hydrolyzed by aqueous acid to afford 4-cyanoisophorone (3,5,5-trimethyl-4-cyano-cyclohex-2-enone) (3) quantitatively.

It is well known that cationic cyclization1) of functionalyzed acyclic isoprenoids provides cyclogeranyl derivatives2) suitably functionalyzed to further elaboration for the synthesis of terpenoids and steroids. Recently several new synthetic methods3) have been also developed for the construction of this skeleton. We now report a novel cyclodimerization of 3-methyl-3-butenenitrile (1) by lithium dialkylamide resulting in an efficient synthesis of 4-cyano-isophorone (3)4).



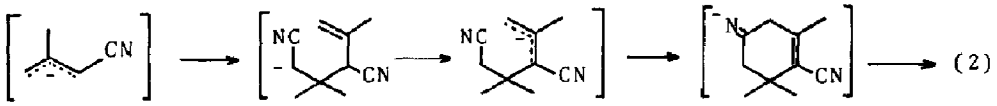
(1) (2) (3)

Dropwise addition of (1) to one equivalent of lithium diethylamide (LDEA) in tetrahydrofuran at -78°C yielded the carbanion (A)5). Then the reaction mixture was allowed to warm to room temperature (25°C), and stirred for 19 hrs. After the usual work-up, the cyclic enaminonitrile (2)6), having functionalyzed cyclogeranyl skeleton, was obtained selectively in 75% isolated yield. [mp: 97-98°C; MS(m/e): 162(M^+); IR(KBr, cm^{-1}): 3440, 3350, 2170 and 1660; NMR(δ, CCl_4): 1.10(6H,s), 1.86(3H,s), 2.04(2H,s), 4.12-4.52(2H,bs) and 5.50-5.66(1H,m).]

Cyclodimerization of (1) was examined with a number of bases, of which LDEA proved most efficient, and lithium diisopropylamide (LDIA) (61% yield)7) and lithium naphthalene-diethylamine (60% yield) were also considerably effective.

Hydrolysis of the enaminonitrile(2) with 3N HCl or aqueous oxalic acid gave 4-cyano-isophorone (3) in a quantitative yield. [mp: 57-58°C; MS(m/e): 163 (M^+); IR(KBr, cm^{-1}): 2250, 1655 and 1630; NMR(δ, CCl_4): 1.12 (3H,s), 1.23(3H,s), 1.97(3H,s), 2.31(2H,s), 3.28(1H,s) and 5.72-5.92(1H,bs).]

The cyclodimerization scheme seems to be as follows, e.g., Michael addition of the carbanion (A) to 3-methyl-2-butenenitrile (4)8) gives acyclic dicyano intermediates (B), which is then cyclized by the modified Thorpe-Ziegler reaction[9] to afford the cyclic enaminonitrile (2).



(A) (B)

Related works are now in progress.

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References and Notes

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4) 4-Functionalyzed isophorones are important key intermediates for the synthesis of a family of terpenoids. For example, J. D. Surmatis, A. Walser, J. Gibas and R. Thommen, J. Org. Chem., 36, 1053 (1970), H. L. Liu, H. K. Hung and G. L. Mhele, Tetrahedron Letters, 4129 (1976), B. R. Davis and S. J. Johnson, J. Chem. Soc. Perkin I, 2840 (1979).

5) Formation of the carbanion of 3-butenenitrile and its α-alkylation were reported by R. H. Schlessinger et al. [G. R. Kieczykowski, R. H. Schlessinger and R. B. Sulsky, Tetrahedron Letters, 4647 (1975).]

6) The similar treatment of 3-butenenitrile gave only an acyclic dimer, 3-methyl-4-cyanohex-4-enenitrile in 67% yield.

7) 3,3,5-Trimethyl-4-cyanohex-4-enenitrile was obtained in 31% yield under the mild condition [LDIA/(1)=1/4, r.t., 2 hrs), together with (2) (8% yield).

8) 3-Methyl-2-butenenitrile (4) seems to be formed in situ because treatment of (1) with NaH in THF gives selectively (4).

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