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HIGHLY REGIOSELECTIVE 1,4-ADDITION OF 2-LITHIO-2-(2,6-DIMETHYLPIPERIDINO)ACETONITRILE TO α,β-UNSATURATED KETONES

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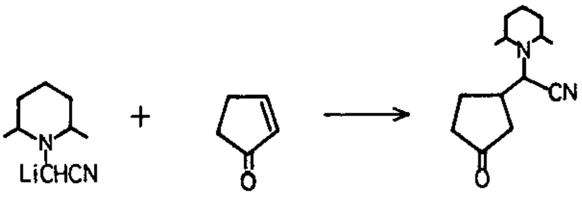
Abstract —— 2-Lithio-2-(2,6-dimethylpiperidino)acetonitrile, a formyl anion equivalent, readily reacts with α,β-unsaturated cyclic ketones to result in a successful conjugate 1,4-addition.

The Michael addition of formyl carbanion equivalents to α,β-unsaturated ketones is a very important reaction which constitutes formation of synthetically useful 1,4-dicarbonyl compounds.[1] Although nitromethane[2] and hydrogen cyanide[3] are most commonly used reagents for formyl carbanion equivalents, conversion of the introduced nitromethyl or cyano group to the formyl group is not an easy process.[4] Thus, there have been continuing interests in investigations on the conjugate 1,4-addition of a formyl anion[5] or an equivalent[6] to α,β-unsaturated ketones. For practical purposes, the latent formyl groups should be easily unmasked after the conjugate addition is effected.[7]

To our knowledge, cyclic 2-enones have not been used for the Michael addition with α-aminoacetonitriles[8] which are widely utilized as acyl carbanion equivalents.[9]

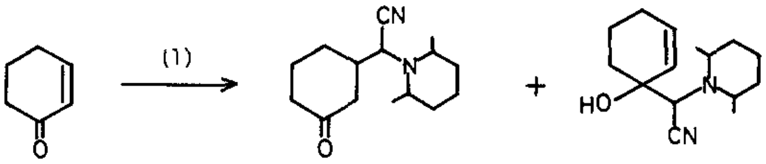
We describe herein the successful utilization of the lithio α-aminoacetonitrile (1) in 1,4-addition to α,β-unsaturated cyclic ketones followed by unmasking to the formyl group and the effects of solvent and temperature on the addition.



(1) (2) (3)

2-(2,6-Dimethylpiperidino)acetonitrile[10] which could be expected to increase the steric hindrance around the carbanion center was selected as a substrate with the reason for preventing the self-condensation reaction of α-aminoacetonitrile during anion formation. It has been found that the lithio derivative (1) derived from 2-(2,6-dimethylpiperidino)acetonitrile undergoes conjugate addition to 2-cyclopentenone (2) giving 1,4-adduct (3) as a sole product. A typical procedure is described in the following. 2-(2,6-Dimethylpiperidino)acetonitrile (6.5mM) in tetrahydrofuran (THF) was added at -78°C to lithium diisopropylamide (6.5mM) in THF (10∿20ml) under argon. Thereto were added hexamethylphosphoramide (HMPA) (16mM) and then 2-cyclopentenone (2) (5.0mM). The whole mixture was allowed to stand at room temperature for 1 hr. After quenching with saturated ammonium chloride (10ml), followed by the usual work-up, the resulting mixture was purified by column chromatography on silica gel to give only 1,4-adduct (3) in 68% yield (mp 75∿76 °C). When this reaction was quenched at -78°C without addition of HMPA, the yield of (3) was found to decrease slightly (53%) but 1,2-adduct could not be detected among the reaction products.

The reaction of the lithio derivative (1) with 2-cyclohexenone (4) smoothly occurred to provide 1,4-adduct (5) and 1,2-adduct (6). The product ratio depends on the reaction conditions. The results are summarized in Table 1.

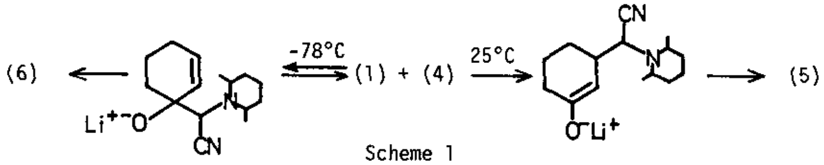


(4) (5) (6)

Table 1. Addition of 2-lithio-2-(2,6-dimethylpiperidino)-acetonitrile to 2-cyclohexenone (4)

Entry	Temp. (°C)	Time (min)	Additive (mol/mol of aminoacetonitrile)	Total yield(%)	1,4-Addition (5) %	1,2-Addition (6) %
1	-78	240	HMPA(2.5)	72	37	63
2	-78	20	None	51	10	90
3	-78∿+25	60	HMPA(2.5)	70	97	3
4	-78∿+25	90	None	47	70	30

The results shown in Table 1 indicate that the production ratio of 1,2- to 1,4-addition is obiously affected by the reaction temperature.[6i,11] Namely, entries 1 and 2 should be compared with entries 3 and 4, where the product ratio of (5) and (6) was reverse in the reactions performed at -78°C and at room temperature. However, the presence of HMPA is effective for increasing the total yield and the ratio of the 1,4- addition product (entries 3 and 4). The solvent effect in this addition reaction is in marked contrast with the recent data[6h] on the reactions of 2-lithio-1,3-dithians with cyclic 2-enones. We suggest that this reaction consists of a rapid reversible 1,2-addition followed by a slow 1,4-addition as illustrated in Scheme 1. In supporting this pathway, when a solution of the lithium salt of 1,2-adduct (6) in THF-HMPA was allowed to stand at room temperature for 1.5 hr, the conjugate addition product (5) (50%) was obtained.

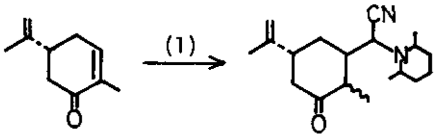


Scheme 1

(7)

(8)

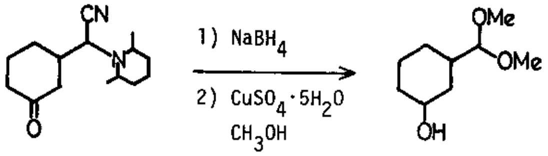
Treatment of (-)-carvone (9) with the lithium salt (1) under the same conditions as shown in Table 1, entry 3 exclusively gave 1,4-adduct (10) in 60% yield.



(9)

(10)

Reduction of 1,4-adduct (5) with $NaBH_4$ in methanol gave the corresponding cyclohexanol derivative, which without further purification was subjected to hydrolysis with $CuSO_4 \cdot 5H_2O$[12] in refluxing methanol for 7 hr to afford hydroxy acetal (11) in 40% isolated yield.[13]



(5)

(11)

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