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Lithium Naphthalenide Induced Reductive Alkylation of α-Cyano Ketones. A General Method for Regiocontrol of α,α-Dialkylation of Ketones

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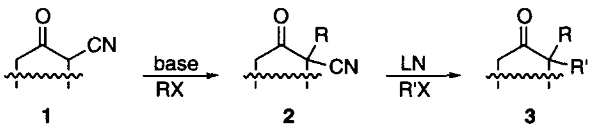
Abstract: An efficient general method for the consecutive introduction of two alkyl groups to the α carbon of a ketone carbonyl has been developed, making use of the lithium naphthalenide induced reductive alkylation of an α-cyano ketone system as a key operation.

Keywords: Carbonyl compounds; Alkylation; Regiocontrol

The consecutive introduction of two alkyl groups to the α-carbon of a ketone carbonyl is an important synthetic process. However, only few general procedures[1-10] are available for this often necessary operation. Among the more direct methods, the use of an α,β-unsaturated ketone to facilitate the geminal dialkylation[9] and the reductive alkylation of a conjugated enone system[5] or its β-alkylthio derivative[6,11] using an alkali metal in liquid ammonia[12] have proven synthetic utility, whereas the use of an α-alkylthio group to control the site of the first alkylation followed by a lithium-ammonia induced reductive alkylation reaction[7,8] and the more recent development involving the formation of a complex of the ketone carbonyl group to effect the selective removal of the proton attached to the more substituted α carbon[10] may also find broad synthetic application. We wish to report herein a convenient general procedure for the α,α-dialkylation of ketones, based on the facile reductive alkylation of α-cyano ketones induced by lithium naphthalenide (LN). This type of reductive alkylation was first demonstrated by Coates *et al.*[13] who reported in 1982 two examples using lithium and liquid ammonia.



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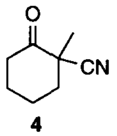

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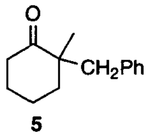

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The facility of the new procedure lies in the ease of α-alkylation of α-cyano ketones (**1**→**2**), which are readily accessible via Thorpe-Ziegler reaction,[14] the base induced rearrangement of isoxazoles[15] and the α-cyanation of ketones,[16] and that of the subsequent reductive alkylation to replace the cyano group (**2**→**3**). Thus, the introduction of various alkyl groups to the α-carbon of a series of selected α-cyano ketones was

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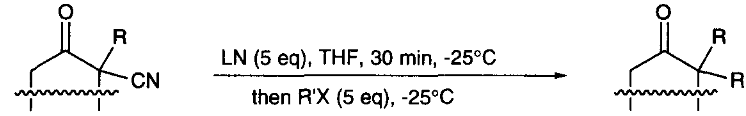
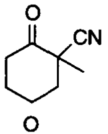
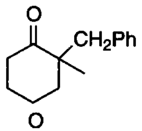
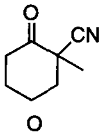
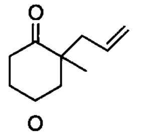
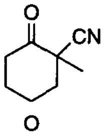
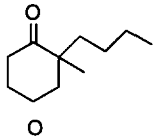
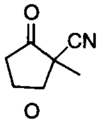
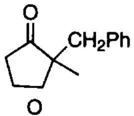
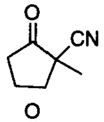
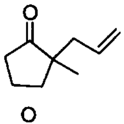
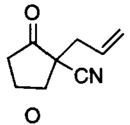
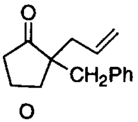
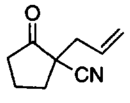
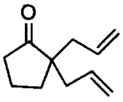
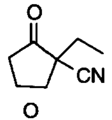
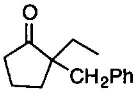
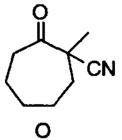
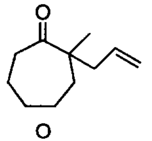
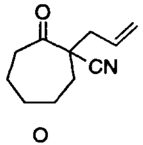
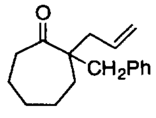
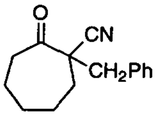
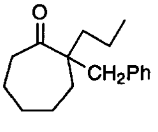
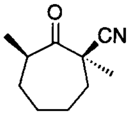
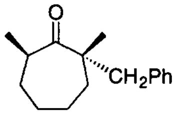
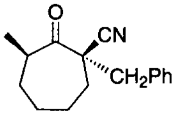
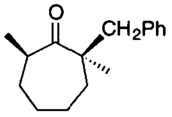
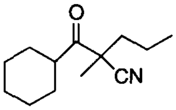
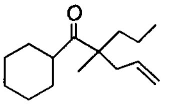
effected simply by treatment of an α-cyano ketone with an appropriate alkylating agent and lithium hydride in tetrahydrofuran at room temperature for 24 h. Yields[17] of the products, which are listed in Table 1

Table 1. Reductive Alkylation of α-Cyano Ketones with Lithium Naphthalenide (LN)



Entry	α-Cyano Ketone	Alkylating agent	Time (min)	Product	%Yield
1		benzyl bromide	45		72
2		allyl bromide	40		70
3		1-bromobutane	a		65
4		benzyl bromide	30		80
5		allyl bromide	30		70
6		benzyl bromide	30		70
7		allyl bromide	30		80
8		benzyl bromide	30		60
9		allyl bromide	20		90
10		benzyl bromide	40		80
11		1-bromopropane	b		65

12	 **8**	benzyl bromide	60	 **6**	70
13	 **9**	methyl iodide	30	 **7**	80
14		allyl bromide	120		90

[a]This reaction was carried out in refluxing tetrahydrofuran for 10 h.
[b]This reaction was carried out at room temperature for 24 h.

under "α-Cyano Ketone", were typically in the range of 70-80%. It is noteworthy that lithium hydride was found to be superior as a base to sodium hydride, potassium hydride, lithium diisopropylamide, potassium carbonate (in acetone) and 1,8-diazabicyclo[5.4.0]undec-7-ene (in *N,N*-dimethyl formamide). By the use of lithium hydride, the competing *O*-alkylation (<10% using LiH) could be suppressed to a large extent.[18] The subsequent reductive alkylation of α-cyano ketones was found to occur readily under mild conditions using LN as a reducing agent. The reaction is completely regioselective as shown by the results obtained for a variety of compounds examined (Table 1) and very easy to be carried out experimentally. In a typical experiment, a 0.365 M solution of LN[19] in tetrahydrofuran (10 mL, pre-cooled at -25°C)[20] was added to 1-cyano-1-methylcyclohexanone (**4**) (100 mg, 0.73 mmol) at -25°C under an argon atmosphere. The resulting solution was stirred at -25°C for 30 min. Benzyl bromide (624 mg, 3.65 mmol) was added. Further reaction at the same temperature for 45 min gave rise to 1-benzyl-1-methylcyclohexanone (**5**) in 72% yield after the usual work-up (addition of saturated aqueous ammonium chloride followed by ether extraction) and chromatographic purification (silica gel, 2.5% ethyl acetate in hexanes).

As illustrated above, the cyano group of the α-cyano ketone system can serve as an effective directing group for the consecutive incorporation of two α substituents with complete regiocontrol. The applicability of the newly developed method for α,α-dialkylation of ketones is further attested by the preparation of the diastereomeric trisubstituted cycloheptanones **6** and **7** from 2-methylcycloheptanone. 2-Methylcycloheptanone was converted to 2-cyano-7-methylcycloheptanone as a mixture of two diastereomers (1:1) via the isoxazole route.[15] Methylation (LiH, MeI) of this mixture gave, interestingly, a single stereoisomer **8** (90% yield) which was then subjected to reductive alkylation (LN then $PhCH_2Br$) to give the trisubstituted ketone **6** (70% yield), again as a single stereoisomer. Conversely, benzylation of 2-cyano-7-methylcycloheptanone followed by reductive alkylation of the resulting cyano ketone **9** (85% yield) using methyl iodide as the alkylating agent furnished the epimeric ketone **7** (80% yield).

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References and Notes

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11. Because of the nature of the reaction, one of the alkyl groups introduced must be methyl group by the use of this procedure.
12. The experimental procedures of these reactions are quite laborious and difficult to handle (especially in small scale preparations) as handling of active metal and low boiling solvent (liquid ammonia) and its subsequent removal prior to the alkylation step are required.
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17. Yields are for isolated yields and unoptimized.
18. Take a more difficult case as an example: treatment of 2-cyanocyclohexanone with lithium hydride (3 eq.) and methyl iodide (4 eq.) in tetrahydrofuran (40 mL/g of the starting ketone) at room temperature for 24 h under an atmosphere of argon gave ketone **4** and the corresponding *O*-methylation product in 70% and 6% yield, respectively after the usual work-up and chromatographic purification (silica gel, 10% ethyl acetate in hexanes). A substantially larger proportion of the *O*-methylation product was formed using the other reagents (*vide supra*).
19. For preparation of LN as a stock solution, see: Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2253-2256.
20. In theory, the reductive decyanation requires only 2 eq. of LN. In practice, however, the use of less than 5 eq. (*e.g.*, 4 eq.) of the reagent often resulted in incompletion of the reaction under the specified conditions which were found to more satisfactory than other conditions attempted (high temperature, longer reaction time, etc.). The amount of the alkylating agent was adjusted accordingly to cover the expected side reactions with cyanide and with the excess LN (reductive dehalogenation, alkylation of the ensuing alkyllithium and of the anionic species derived from naphthalene).