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A Convenient New Procedure for the Construction of Highly Substituted Acetates. Reductive Alkylation of α-Cyano Esters

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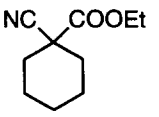
Abstract: A convenient, highly efficient general method for the preparation of highly substituted acetates has been developed, making use of reductive alkylation of α-cyano esters as a key operation.

The most commonly used method for the synthesis of the highly substituted acetates involves sequential alkylation of a suitable ester.[1] Inevitably, it requires a multistep operation along with the application of a strong base which may not be compatible with the existing funtionality. We have developed a new procedure which promises to have broad synthetic utility for the construction of highly substituted acetates, especially the fully substituted ones containing two identical substituents. The newly developed method, which is operationally simple and highly efficient, makes use of the hitherto unknown reductive alkylation of α-cyano esters as a key operation.

It was observed that α-cyano esters could be readily reduced (~40 min)[2] with lithium naphthalenide[3] under mild conditions (-25°C) to give the corresponding ester enolates. When the reduction was followed by the addition of an alkylating agent, α-alkylation was effected resulting in the overall replacement of the cyano group with an alkyl group. As a typical example, treatment of ethyl 1-cyano-1-cyclohexanecarboxylate (**1**) with 3 equivalents of lithium naphthalenide in tetrahydrofuran at -25°C for 40 min followed by addition of 3.5 equivalents of allyl bromide and further reaction at the same temperature for 60 min gave rise to the corresponding trisubstituted acetate **2** in 82% yield after chromatographic purification.[5] This reductive alkylation process proved to be general.[6] An array of disubstituted cyano acetates were subjected to similar treatment using a variety of alkylating agents. In each case, the reaction proceeded smoothly, and the desired product was formed in synthetically useful yield (67-92%).[7] Results are compiled in Table 1.



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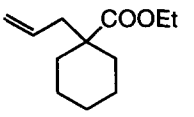

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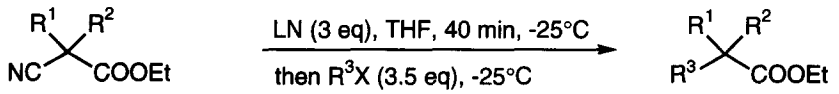
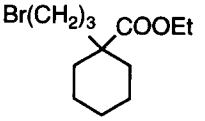
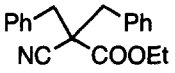
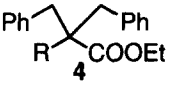
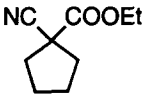
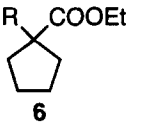
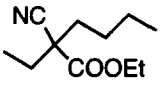
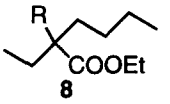
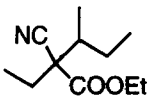
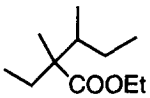
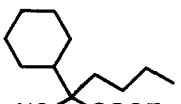
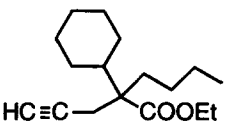
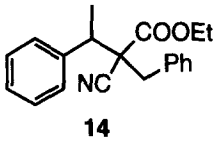
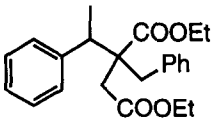
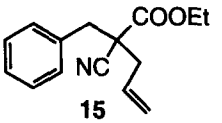
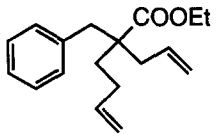
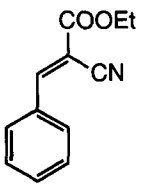
Table 1. Reductive Alkylation of α-Cyano Acetates with Lithium Naphthalenide (LN)

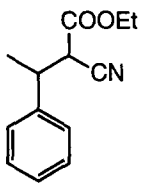


Entry	α-Cyano Acetate	Alkylating agent	Time (min)	Product	% Yield
1	**1**	allyl bromide	60	**2**	82
2	**1**	1,3-dibromo-propane	70		81
3	 **3**	methyl iodide	70	 **4**	
				4 (R = CH_3)	92
4		1,3-dibromo-propane	90	**4** (R = $(CH_2)_3Br$)	78
5	 **5**	benzyl bromide	70	 **6**	
				6 (R = CH_2Ph)	71
6		1,4-dibromo-butane	75	**6** (R = $(CH_2)_4Br$)	67
7	 **7**	allyl bromide	70	 **8**	
				8 (R = $CH_2CH{=}CH_2$)	77
8		ethyl bromo-acetate	75	**8** (R = CH_2COOEt)	67
9	 **9**	methyl iodide	60		80
10	 **10**	3-bromo-1-propyne	85		81

11	 **14**	ethyl bromo-acetate	60		73
12	 **15**	4-bromo-1-butene	60		71

One of the salient features of the current method lies in the ease of introducing the first two substituents to the acetate unit, especially when these substituents are identical. Thus, by the modification of the procedure developed by Oediger and Moller[8,9] disubstituted cyano acetates **1**, **3** and **5** were easily prepared by treatment of ethyl cyanoacetate with an appropriate alkylating agent [1,5-dibromopentane (1 eq), benzyl bromide (2.2 eq) or 1,4-dibromobutane (1 eq)] in dimethyl formamide at 80°C for ~1 h using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.2 eq) as a base. Yields were typically in the 90% range. For cyano acetates with two different substituents, two procedures were effectively applied. In one procedure, cyano acetate was first subjected to alkylation with *n*-butyl iodide (1 eq) and DBU (1 eq) in benzene[10] at room termperature for 25 h to furnish ethyl 2-cyanohexanoate (71% yield) which was then treated with ethyl iodide (1.2 eq) and DBU (1.3 eq) in dimethyl formamide at room temperature for 17 h to give cyano acetate **7** (93% yield). Compounds **9** and **10** were similarly prepared using 2-iodobutane, iodoethane (for **9**), iodocyclohexane and iodobutane (for **10**). Alternatively, the first alkyl group could be introduced via a Knoevenagel condensation followed by modification of the product. Thus, condensation of benzaldehyde and ethyl cyanoacetate (2 eq) carried out in refluxing benzene (21 h) with water removal in the presence of ammonium acetate (1 eq) and acetic acid (3 eq) gave the expected Knoevenagel product **11**[11] (67% yield) which was converted to compound **12** (72% yield) by 1,4-addition reaction (Me_2CuLi, Et_2O, 0°C, 0.5 h)[12] and to compound **13** (89% yield) by reduction ($NaBH_4$, EtOH, 20°C, 3 h).[13] These products **12** and **13** were alkylated with benzyl bromide and allyl bromide to give the disubstituted compounds **14** and **15**, respectively.


11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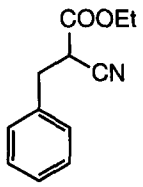
13

As illustrated above, in conjunction with the known methods for alkylation of ethyl cyanoacetate, the reductive alkylation of cyano acetates with lithium naphthalenide provides a useful tool for the synthesis of the highly substituted acetates.[14]

Acknowledgment: We are grateful to the Natural Sciences and Engineering Research Council of Canada, the University of Alberta and National Tsing Hua University for financial support.

References and Notes

1. (a) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318-2320; (b) Cregge, R. J.; Herrmann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425-2428; (c) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433-2436; (d) Schlessinger, R. H.; Herrmann, J. L. *J. Chem. Soc. Chem. Commun.* **1973**, 711-712; (e) Williams, T. R.; Sirvio, L. M. *J. Org. Chem.* **1980**, *45*, 5082-5088.
2. For examples of reductive cleavage of cyano groups with dissolving metals including an isolated case using lithium naphthalenide[2a] see: (a) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199-2202; (b) Guijarro, D.; Yus, M. *Tetrahedron* **1994**, *50*, 3447-3452; (c) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648-7649 and references therein.
3. For preparation of lithium naphthalenide *in situ* or as a stock solution see ref. 4.
4. Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, 2253-2256.
5. Flash chromatography was carried out on silica gel, eluting first with *n*-hexane to remove naphthalene and then a solution of 2-4% ethyl acetate in *n*-hexane to effect isolation of the product.
6. A variety of acid and/or base sensitive functionalities were found to be uneffected under the reductive alkylation conditions. In addition to those listed in Table 1, functional groups shown to be stable towards lithium naphthalenide include ketone enolate, hydroxyl and its tetrahydropyranyl, methoxymethyl and *tert*-butyldiphenylsilyl derivatives.[4]
7. Yields are for isolated products and unoptimized.
8. Oediger, H.; Moller, F. *Liebigs Ann. Chem.* **1976**, 348-351.
9. The work-up procedure was modified as follows. After the reaction, water (same volumn as that of dimethyl formamide used for the reaction) was added and the resulting solution extracted with ether. The combined extracts were washed with 2N hydrochloric acid, water and then dried with magnesium sulfate, filtered and concentrated to give the crude product. This procedure resulted in considerable improvement (> 20%) of yields.
10. Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1979**, 1716-1719.
11. McElvain, S. M.; Clemens, D. H. *Org. Synth.* **1963**, *4*, 463.
12. Dieter, R. K.; Silks, L. A.; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679-4692.
13. Haffer, G.; Eder, V.; Neef, G.; Sauer, G.; Wiechert, R. *Chem. Ber.* **1978**, *111*, 1533-1539.
14. We are currently studying the reductive alkylation of α-cyano ketones. Preliminary results are promising. This investigation will be reported elsewhere in due course.

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