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BASE-CATALYSED ALKYLATIONS AND CONJUGATED ADDITIONS OF α-CYANOENAMINES : A METHOD FOR CHAIN EXTENSION AT THE β-CARBON OF TERTIARY AMIDES

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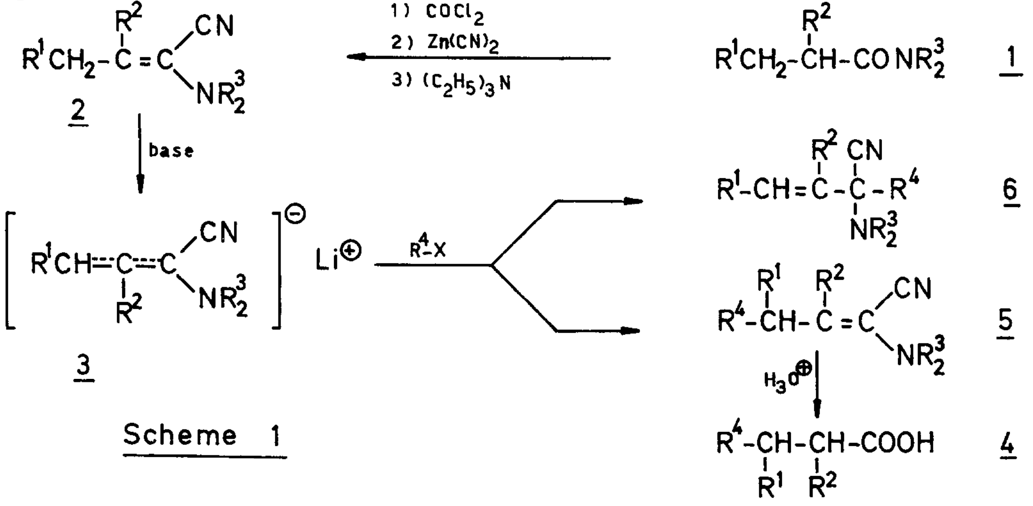
Summary : Anions derived from α-cyanoenamines which are readily available from tertiary amides, react at the γ-carbon atom with alkylating agents and α-enones.

In 1975, two of us described(1) a practical one-pot procedure for the conversion of tertiary amides 1 into α-cyanoenamines 2. It was pointed out that 2a reacted with non-nucleophilic strong bases to give a delocalised anion 3a allowing thus, in principle, for chain extension at the γ-carbon atom. This preliminary observation coupled with the possibility of regenerating readily carboxylic acids 4 from the modified α-cyanoenamines 5 provided the incentive for further studies of 3 as synthetic equivalents(2) of homoenolate anions $>\overset{\ominus}{C}-\underset{|}{\overset{|}{C}}-CONR_2$. The reaction of 3 with electrophilic reagents has been independently studied(3) by Albrecht and Vonderheid.

We describe here : (a) a summary of our findings on the formation and alkylation of 3, (b) some preliminary results on the reaction of 3 with Michael acceptors.



Scheme 1

Table 1 Formation and Alkylation of 3

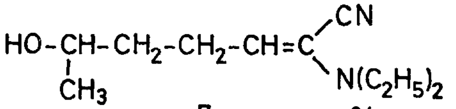
	R^1	R^2	R^3	Experimental Conditions	R^4-X	5(%)	6(%
2a	H	CH_3	CH_3	n-C_4H_9Li + 1 eq. HMPT in THF, 8 hrs. at -60°C	CH_3I	54	36
2a	H	CH_3	CH_3	LDA in THF, 3 hrs. at -40°C to -30°C	CH_3I	60	28
2b	H	CH_3	C_2H_5	n-C_4H_9Li + 1 eq. HMPT in THF at -60°C	CH_3I	70	0
2c	H	H	C_2H_5	LDA in THF, 2 hrs. at -40°C to -30°C	CH_3I	75	0
2c	H	H	C_2H_5	LDA in THF, 2 - 3 hrs. at -40°C to -30°C	CH_2=CH-CH_2Br	75	0
2c	H	H	C_2H_5	LDA in THF, 2 - 3 hrs. at -40°C to -30°C	$C_6H_5CH_2Br$	65	0
2d	CH_3	H	C_2H_5	LDA in THF, 2 - 3 hrs. at -40°C to -30°C	CH_3I	55	0

The results of the formation and alkylation of 3 (Scheme 1 and Table 1) can be summarized as follows :

(1) α-Cyanoenamines 2 underwent metalation with LDA in THF at -40°C or with n-C_4H_5Li in HMPT-THF at -60°C. This was also the case when the site of metalation was secondary as in 2d. Under these conditions, 1,2 addition of n-C_4H_5Li to the nitrile group is completely suppressed.

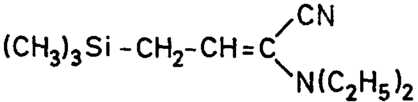
(2) Mixtures of α- and γ-alkylated products(4) were obtained from 3a and CH_3I. Replacement of two methyl groups on nitrogen by the slightly bulkier ethyl groups was already sufficient to force alkylation to occur exclusively at the γ-position, even when it was secondary.

Other electrophilic reagents such as propylene oxide and trimethylchlorosilane also reacted at the γ-position of 3b to give 7 and 8.



$$HO-\underset{CH_3}{CH}-CH_2-CH_2-CH=C\begin{matrix}CN\\N(C_2H_5)_2\end{matrix}$$

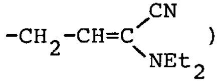
7 55%



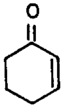
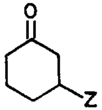
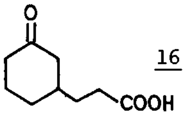
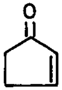
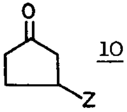
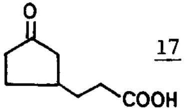
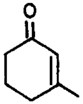
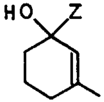
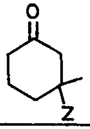
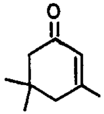
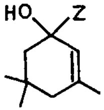
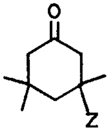
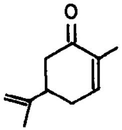
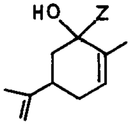
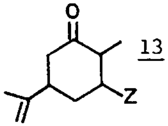
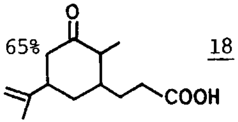
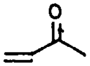
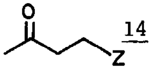
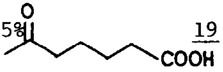
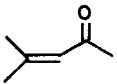
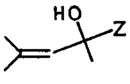
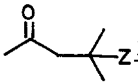
$$(CH_3)_3Si-CH_2-CH=C\begin{matrix}CN\\N(C_2H_5)_2\end{matrix}$$

8 80%

The reactions of 3c with a serie of α-enones were examined (Table 2). The anion 3c was formed from 2c and lithium diisopropylamide (LDA) (10% in THF) at -40°C to -30°C. The α-enone (10% in THF) was added to the solution of 3c at -65°C. Then the experimental conditions described in Table 2 were applied. The crude reaction mixtures were carefully analysed by nmr and ir spectroscopy, glc and tlc. Reported yields are for isolated products(4). It can be seen that the observed products resulted from the attack of the γ-carbon atom of 3c on the α-enone. Cyclohexenone, cyclopentenone and methylvinylketone yielded only 1,4 addition products. Steric factors are most probably responsible for the formation of mixture of 1,2 and 1,4 adducts with the more substitued α-enones.

Table 2 Base-catalysed Addition of 2b to α-enones (Z = )

$Z = -CH_2-CH=C(CN)(NEt_2)$

α-enone	Experimental Conditions	1,2 Addition Product	1,4 Addition Product	Starting Material	Hydrolysis of the 1,4 Adduct
	60' at -50°C	-	65%  9	-	60%  16
	60' at -50°C	-	65%  10	-	55%  17
	60' at -60°C to -20°C	32% 	36%  11	16% α-enone	-
	60' at -60°C to -20°C 30' at -60°C then 60' at RT 30' at -60°C then 7h. at RT	40% 22% 10% 	16% 30% 38%  12	30% α-enone 30% α-enone 30% α-enone 25% 2c	-
	45' at -60°C 2h. at -60°C to +5°C 50' at -60°C then 1h. at RT	30% 20% 	45% 65%  13	15% α-enone 10% α-enone	65%  18
	60' at -60°C	-	60%  14	-	55%  19
	45' at -60°C	38% 	33%  15	10% 2c	-

However yields of 1,4 adducts could be increased by allowing the kinetic products to equilibrate(5), as shown in the case of carvone or isophorone. The sequence has been completed on the 1,4 adducts 9, 10 and 14. Treatment of a 20% ether solution of these adducts with 6N hydrochloric acid at 20° smoothly yielded the corresponding acids(6) 16, 17 and 19. The acid 18 was obtained from the hydrolysis of the crude mixture of 1,2 and 1,4 adducts to carvone.

The overall procedure provides a convenient method for a three-carbon chain extension at the conjugated position·of an α-enone.

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(1) J. Toye, L. Ghosez, J. Am. Chem. Soc., 97, 2276 (1975).

(2) For other homoenolate equivalents at the same oxidation level, see for example :
E.J. Corey, R.B. Mitra, and H. Uda, J. Am. Chem. Soc., 86, 485 (1964); E.J. Corey, D.E. Cane, J. Org. Chem., 10, 3405 (1970); P. Picard and J. Moulines, Bull. Soc. Chim. Fr., 2256 (1974); G. Sturtz, B. Corbel, and J.P. Paugam, Tetrahedron Lett., 47 (1976); E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., 99, 7360 (1977); D. Caine and A.S. Frobese, Tetrahedron Lett., 883 (1978).

(3) H. Albrecht, C. Vonderheid, Synthesis, 512 (1975).

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(5) For a recent discussion on kinetic vs thermodynamic control of additions to α-enones, see, for example : R. Sauvetre, J. Seyden-Penne, Tetrahedron Lett., 3349 (1976).

(6) Hydrolysis of α-cyanoenamines in HCl-methanol yielded the corresponding amides : B. Lesur and L. Ghosez, unpublished results; N. De Kimpe, R. Verhé, L. De Buyck, J. Chys and N. Schamp, Org. Prep. Proced. Int., 10, 149 (1978).

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