Tetrahedron Letters Vol. 21, pp 1205 - 1208
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0040-4039/80/0322-1205$02.00/0

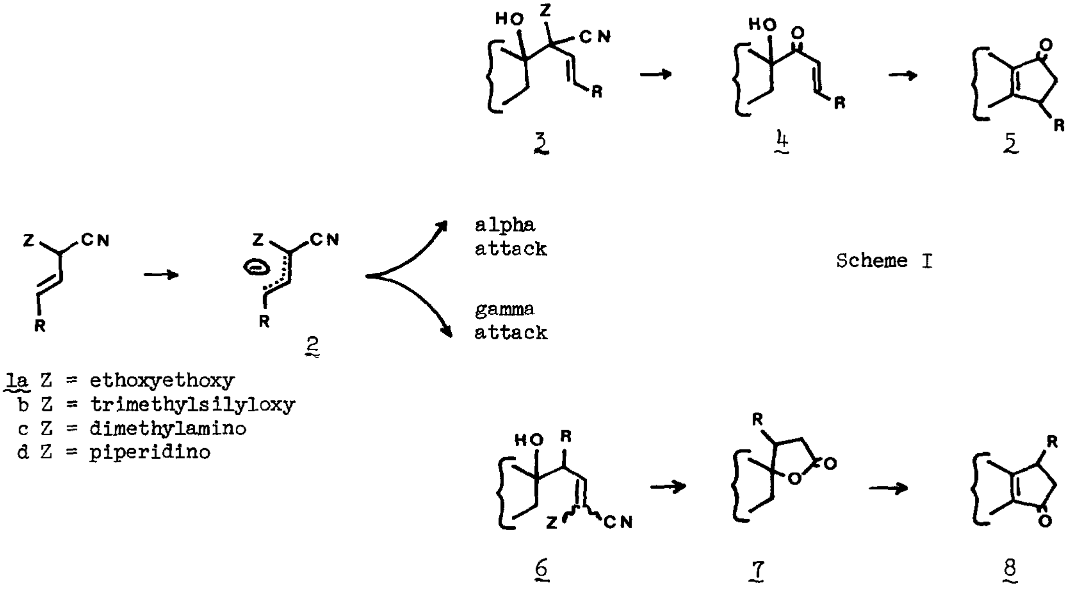
THREE CARBON ANNELATION REAGENTS:
UNSATURATED ALPHA AMINONITRILES AS HOMOENOLATE EQUIVALENTS

Richard M. Jacobson* and John W. Clader
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

α-Aminonitriles 1c and 1d (R = Me) can react as either acyl anion or β-homoenolate equivalents on varying the reaction conditions. Both modes of reaction are potentially useful in three carbon annelations.

In conjunction with our research directed towards the synthesis of a number of biologically active cyclopentenones, we have investigated several derivatives of acrolein and crotonaldehyde as potential ambident "reversed polarity" reagents.[1] Conversion of the aldehyde carbonyl to a suitable anion stabilizing equivalent 1 followed by deprotonation yields an ambident nucleophile 2 which, depending on its mode of reactivity with electrophiles, can act as either an acyl anion equivalent (via alpha attack) or a homoenolate equivalent (via gamma attack). Both modes of reactivity are potentially useful in a three carbon annelation of ketones, Scheme I.

We have previously shown[2] that, upon varying reaction conditions, the ethoxyethyl protected cyanohydrin of acrolein 1a, R = H, can react selectively in either the alpha or gamma modes to give, after further reaction, the appropriate annelated cyclopentenones 5 and 8. The analogous reaction with the crotonaldehyde derivative 1a, R = Me, gave only the products derived from alpha attack.



Scheme I

1a Z = ethoxyethoxy
b Z = trimethylsilyloxy
c Z = dimethylamino
d Z = piperidino

We wish to report that the aminonitriles 1c, R = Me, and 1d, R = Me, can be effectively used as either acyl anion equivalents or homoenolate equivalents in their reactions with ketones by simply varying the reaction conditions. This will allow a general entry to the annelated compounds 8, R = Me. The utility of alpha aminonitriles as acyl anion equivalents has been demonstrated on a number of occasions.[3] Although none of these reports deal with aminonitriles derived from unsaturated aldehydes, Ahlbrecht[4] has recently demonstrated the use of a similar alpha enaminonitrile anion 2 as a homoenolate equivalent but did not observe the corresponding alpha reactivity with ketones.

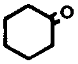
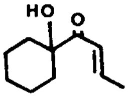
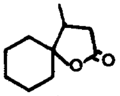
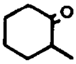
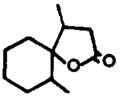
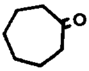
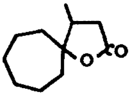
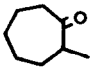
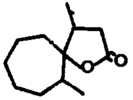
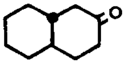
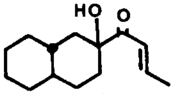
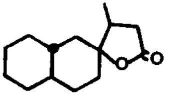
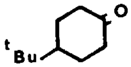
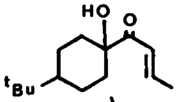
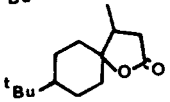
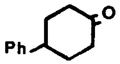
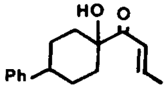
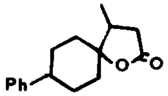
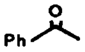
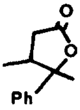
Aminonitrile 1c, R = Me, is conveniently prepared by the reaction of crotonaldehyde with stoichiometric quantities of dimethylamine and hydrogen cyanide in methylene chloride at 0°C. Alternatively, one can react crotonaldehyde with 2-methyl-2-(dimethylamino)-propionitrile at 90°C.[5] The piperidine derived 1d, R = Me, is similarly prepared.

Dropwise addition of 1c, R = Me, or 1d, R = Me, to one equivalent of lithium diisopropylamide (LDA) in THF at -78° C yields anion 2. Reaction with 0.9 equivalents of ketone for 90 seconds yields, after quenching with water and aqueous workup, the expected alpha condensation product 3. When the same sequence is carried out at 0° C, only the gamma product 6 is observed. Furthermore, if 3 is treated with LDA at -78° C and then warmed to 0° C, 6 is the observed product. A significant competing reaction under the 0° C conditions is enolization of the ketone and subsequent aldol condensation. These competing reactions can be significantly reduced by the addition of an equivalent of anhydrous zinc chloride[6] to the ketone prior to its addition to 2. This procedure completely eliminates self-condensation and significantly increases the overall yield of gamma addition products, although slightly longer reaction times, on the order of 5 minutes, are required.

Both alpha products 3 and gamma products 6 can be isolated and purified by silica gel chromatography. We have found it more convenient, however, to hydrolyze the crude reaction products by refluxing with 0.5 M HCl or oxalic acid in 50% aqueous THF. Upon further workup and chromatography, the pure alpha-hydroxyenones 4 or spirolactones 7 are obtained. Table I shows the reactions that have been performed.

Spirolactones, such as those produced by this method, have been converted into cyclopentenones by reaction with reagents such as polyphosphoric acid[7] or phosphorous pentoxide/methanesulfonic acid (1:10).[8] We have found the latter reagent to be exceptionally useful in this regard. One millimole of spirolactone 7 is dissolved in 5 milliliters of a 10% solution of P_2O_5 in methanesulfonic acid and heated at 60° C for 1-2 hours. The reaction mixture is then added to 25 milliliters of 50% aqueous K_2CO_3. After stirring for 5 minutes the product is extracted into ether and purified. Our results are summarized in Table Two.

Table One -- REACTIONS OF α-AMINONITRILES WITH KETONES

Ketone	Temperature	Product[c]	Yield[a](method)[b]
	-78°		43(C) 45(D)
	0°		45(C) 78(D)
	0°		41(C) 63(D)
	0°		53(C)
	0°		16(C) 50(D)
	-78°		26(D)
	0°		44(C) 71(D)
	0°		61(D)
	0°		43(C)
	-78°		46(D)
	0°		51(D)
	0°		77(D)

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a) Yield after chromatography and bulb-to-bulb distillation

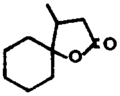
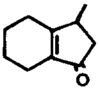
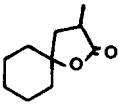
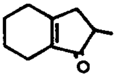
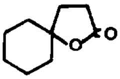
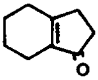
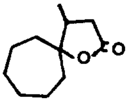
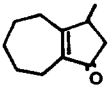
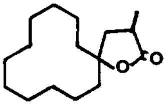
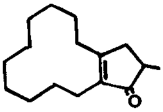
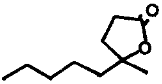
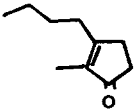
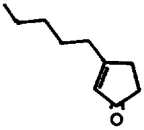
b) Method C: (α-aminonitrile + LDA) + ketone

Method D: (α-aminonitrile + LDA) + (ketone + $ZnCl_2$)

c) All new compounds showed satisfactory analytical data

Products are mixtures of diastereomers.

Table Two -- CYCLOPENTENONES DERIVED FROM SPIROLACTONES

Spirolactone	Cyclopentenone	% Yield[a]
		94
		76
		89
		99
		85
	 	89(93:7)[b]

a) Yield after bulb-to-bulb distillation, product > 95% pure by glc

b) Isolated as a mixture, ratio by NMR and glc

References

1. For recent reviews on reactivity umpolung, see (a) O. W. Lever, Tetrahedron, 19, 1943 (1976); (b) D. Seebach, Angew Chem. I. E. E., 18, 239 (1979).
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(Received in USA 10 December 1980)