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REACTIONS OF ACYL ANION EQUIVALENTS DERIVED FROM CYANOHYDRINS, PROTECTED CYANOHYDRINS AND α-DIALKYLAMINONITRILES

J. DONALD ALBRIGHT
American Cyanamid Company, Medical Research Division, Lederle Laboratories, Pearl River, NY 10965, U.S.A.

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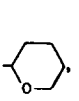
INTRODUCTION

The use of masked functional groups such as masked acyl anion equivalents in the formation of C–C bonds has proved to be a powerful strategy in the development of new synthetic methods.[1-4] The term "umpolung" has been used to describe the inversion of reactivity which occurs when a normally electrophilic CO group is transformed into a nucleophile.[4,5] Metalated S-containing compounds such as S,S-acetals, 1,3-dithianes, and vinyl sulfides are examples of reversal of reactivity of CO compounds through the use of masked reagents. Related masked reagents with CO umpolung are anions of cyanohydrins, protected cyanohydrins **1**, α-dialkylaminonitriles **2**, and α-alkyl-, and α-aryl-N-acylaminoacetonitriles **4**, which are the subject of this review.

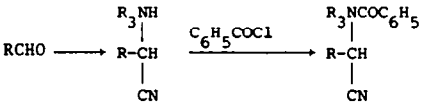
1

R = alkyl, Ar, ArCH=CH, alkyl-CH=CH-

R' = H, $-CH(CH_3)OC_2H_5$, $Si(CH_3)_3$, OCC_6H_5,  , $-CH_2Ar$

2

R=H, alkyl, Ar, ArCH=CH, alkyl-CH=CH-
R' and R" = alkyl, $-(CH_2)_4-$, $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_5-$



3 **4**

R = H, alkyl, Ar

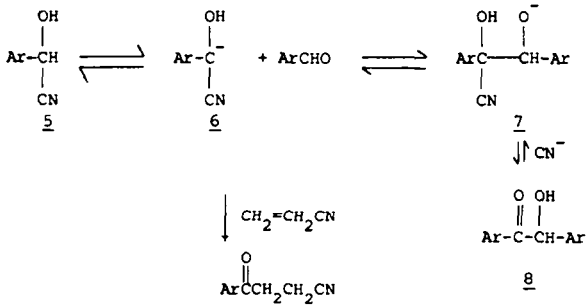
R_3 = Ar, $ArCH_2$

The utility of masked CO equivalents of the structural types **1**, **2** and **4** is derived from their ability to form carbanions and the fact that these carbanions are reactive nucleophiles for forming C–C bonds. In general, protected cyanohydrins from aromatic aldehydes and α-(aryl)-dialkylaminoacetonitriles yield carbanions with hydroxides, alkoxides, and sodium hydride, while stronger bases such as lithium diisopropylamide are required to generate carbanions from masked acyl derivatives of aliphatic aldehydes.

Open chain Reissert compounds in the presence of a suitable base also yield masked acyl anions which react with Michael acceptors, alkylating agents, and undergo 1,2-additions to aldehydes.[6,7]

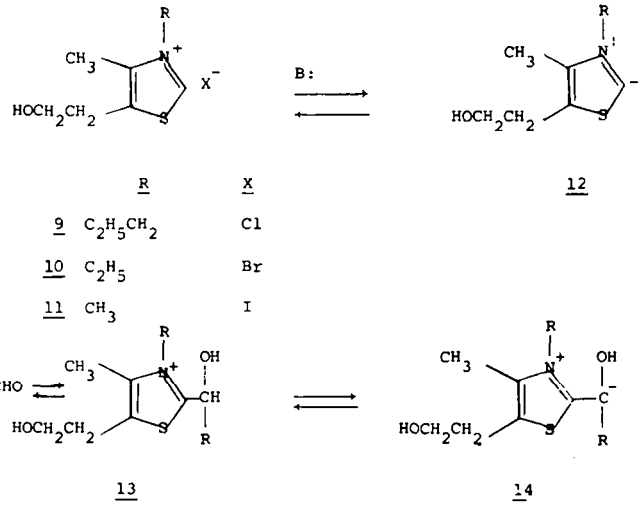
1,4-ADDITIONS OF ALDEHYDES CATALYZED BY CYANIDE ION AND THIAZOLIUM SALTS

In a sequence leading to the 1,4-addition of unprotected aromatic and heterocyclic aldehydes to α,β-unsaturated esters, ketones, and nitriles, catalyzed by cyanide ion, the cyanohydrin carbanion **6** is generated in equilibrium with the benzoin **8**.



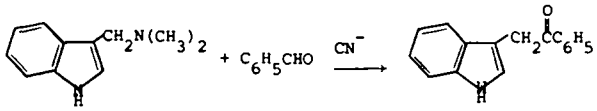
The formation of benzoin is a reversible reaction while the 1,4-addition reaction is irreversible. Thus, the cyanohydrin anion is trapped and the reaction is driven to completion. In fact, the respective benzoin and cyanide ion give the same 1,4-addition products as those obtained from the direct use of cyanide and aromatic aldehydes.[8] Aliphatic aldehydes fail to give 1,4-addition products because of their tendency to undergo aldol condensation. However, under catalysis with thiazolium salts and suitable bases such as triethylamine and sodium acetate, aliphatic aldehydes, as well as aromatic aldehydes, undergo 1,4-addition to α,β-unsaturated esters, ketones, and nitriles.[8]

Studies on the thiamine (vitamin B_1) catalyzed formation of acyloins from aliphatic aldehydes[9,10] and thiamine or thiamine diphosphate catalyzed decarboxylation of pyruvate[11-14] have established the mechanism for the catalytic activity of 1,3-thiazolium salts in carbonyl condensation reactions. Other thiazolium salts such as naphtho[2, 1-d]thiazolium and benzothiazolium salts catalyze the benzoin condensation[15] and quaternary salts of 1-methylbenzimidazole and 4-(4-chlorophenyl)-4H-1,2,4-triazole are reported to have similar catalytic activity.[8,16] Thus the ylid **12** serves as a catalyst in a similar manner to cyanide ion to give a stabilized masked carbonyl anion **14** which undergoes 1,4-addition to α,β-unsaturated esters, ketones, and nitriles.



The benzoin condensation is catalyzed by cyanide ion and involves the formation of an intermediate aryl cyanohydrin anion. The 1,4-addition of aryl cyanohydrin anions to α,β-unsaturated ketones or esters yields 1,4-diketones and γ-ketoesters, respectively.[17-20] Better yields (70–95%) are observed in additions to α,β-unsaturated ketones[19,21] than in additions to α,β-unsaturated esters such as ethyl acrylate, ethyl crotonate, methyl cinnamate, and diethyl fumarate.[17,18,22]

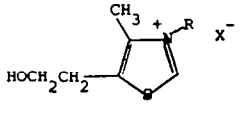
Cyanide catalyzed addition of aryl aldehydes to α,β-unsaturated nitriles such as acrylonitrile, crotononitrile, and cinnamonitrile gives moderate to high yields of γ-ketonitriles.[17,18,23-25] Mannich bases which form α,β-unsaturated ketones *in situ* can be used to synthesize 1,4-diketones.[17,26] 3-(Dimethylaminomethyl) indole (**15**) and benzaldehyde, under cyanide ion catalysis in dimethylformamide, affords α-(3-indolyl)acetophenone (**16**).[26] Cyanide catalyzed addition of 2-thiophenecarboxaldehyde to α,β-unsaturated ketones and nitriles gives γ-diketones and γ-ketonitriles which undergo hydrogenation-desulfurization with Raney–Ni to give chain extended γ-diketones or chain extended γ-ketonitriles.[20]



15 16 (52%)

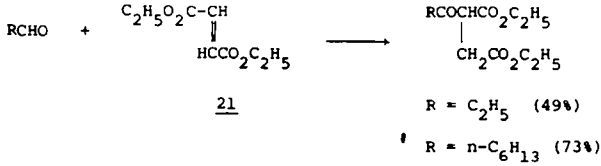
A polar solvent such as dimethylformamide is required and the reactions are carried out with 0.1 to 0.5 mole equivalent of sodium cyanide. The reaction is less versatile than the thiazolium catalyzed addition of aldehydes to activated double bonds. For example, *ortho* substituted benzaldehydes add 1,4 to α,β-unsaturated ketones under thiazolium ion catalysis but fail to react under cyanide ion catalysis.[8] Aliphatic aldehydes are unsatisfactory[27] due to aldol condensations under the alkaline cyanide anion catalysis. Aromatic dialdehydes also fail to react in 1,4-additions under cyanide ion catalysis.[8]

Alkylation of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole with benzyl chloride,[28] methyl iodide,[29,30] ethyl bromide,[16] and 2-ethoxyethyl bromide[31] yields useful salts for catalyzing 1,4-additions of aldehydes to activated double bonds.



	R	X
17	$CH_2C_6H_5$	Cl
18	CH_3	I
19	C_2H_5	Br
20	$CH_2CH_2OC_2H_5$	Br

Differences have been observed in the utility of the ylides of these thiazolium salts to catalyze 1,4-additions.[16,31] 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**17**) is preferred as a catalyst for aliphatic aldehydes,[32] while 3-methyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium iodide (**18**) and 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (**19**) are preferred as catalysts in 1,4-additions of aromatic aldehydes.[16,21,34] In general, yields are lower in aldehyde additions to α,β-unsaturated esters or α,β-unsaturated nitriles than in additions to α,β-unsaturated ketones.[27,35] The 3-benzyl thiazolium salt **17** gives poor yields (*ca* 30%) in 1,4-additions of aliphatic aldehydes to ethyl acrylate or acrylonitrile.[16,36] In contrast, 3-(2-ethoxyethyl)-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (**20**) catalyzes the 1,4-addition of aliphatic aldehydes to ethyl acrylate and acrylonitrile in moderate yields (49–64%).[31] However the use of the 3-(2-ethoxyethyl) bromide salt **20** gave no improvement in yield in the 1,4-addition of aliphatic aldehydes to diethyl fumarate (**21**).[31]



21

R = C_2H_5 (49%)

R = n-C_6H_{13} (73%)

3-(2-Hydroxyethyl)-1,3-thiazolium bromide is an effective catalyst in aldehyde additions to ethyl acrylate while 3-benzyl-1,3-thiazolium chloride, which does not contain the 2-hydroxyethyl group, is ineffective. This result may be due to the insolubility of the latter catalyst in the reaction mixture.[37]

Insoluble polymer-supported thiazolium salts are catalysts for the benzoin condensation and for Michael additions of aldehydes;[38,39] however, yields are approximately 50% of those obtained with 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**17**) as catalyst. In addition, the polymer-supported catalysts lost activity on reuse and, at present, are not synthetically useful.

Decreased yields in some of the thiazolium catalyzed reactions may be the result of reactions of the acyloin anions and the benzoin anions which may be formed *in situ*. Acyloin anions undergo Michael additions[40] and benzoin anions add 1,4 to sodium crotonate or acrylamide.[41] Under thiazolium ion catalysis, benzoin anions give complex mixtures of products.[42] The yields of acyloin by-products increase on short reaction times and at temperatures lower than 100°.[37]

Aldehyde additions to vinyl ketoesters **22** catalyzed by the 3-benzyl or 3-ethyl thiazolium salts (**17** and **19**) proceed in poor to moderate yields but under similar experimental conditions, aliphatic aldehydes (**23**) containing an ester function give high yields of 1,4-addition products **24**.[43]

$$RCHO + CH_2{=}CHCO(CH_2)_2CO_2CH_3 \longrightarrow RCO(CH_2)_2CO(CH_2)CO_2CH_3$$

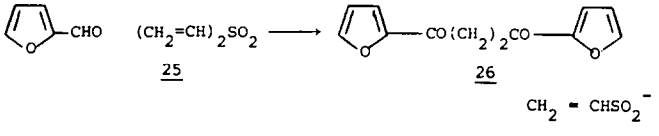
22 $R = C_6H_5$ (33%); $R = n\text{-}C_7H_{15}$ (54%)

$$CH_3O_2(CH_2)_nCHO + CH_2{=}CHCOR \longrightarrow CH_3O_2C(CH_2)_nCO(CH_2)_2COR$$

23 **24**

R	n	
CH_3	2	(70%)
$n\text{-}C_6H_{13}$	3	(69%)
$n\text{-}C_9H_{19}$	7	(86%)

Reaction of divinyl sulfone (**25**) with aldehydes under thiazolium ion catalysis affords symmetrical 1,4-diketones **26** in 35–70% yields.[44,45] The initially formed γ-ketosulfone eliminates vinyl sulfinate and then the newly formed vinyl ketone reacts with another molecule of aldehyde.

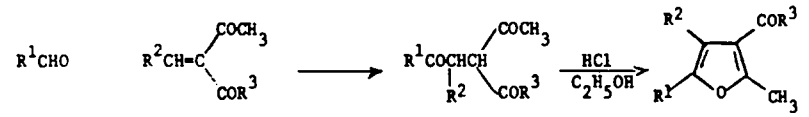


25 **26**

Triketone compounds are prepared (50–80% yield) from divinyl ketone and dibenzylideneacetone by the thiazolium ion catalyzed addition of two aldehyde units.[29] Monoaddition of aldehydes to divinyl ketone gives the mono product in 20–25% yields. Addition of a second aldehyde to the isolated mono product allows the preparation of unsymmetrical 1,4,7-triketones (50–90%).[46] Thiazolium catalyzed additions to vinyl 4,7-dioxoesters[47] and 4,7-dioxonitriles[47] gives 4,7,10-trioxoesters and 4,7,10-trioxonitriles.[48]

Formaldehyde and two moles of methyl vinyl ketone gives 2,5,8-nonanetrione (27%).[21,32] Aldehydes also add 1,4 to monoketals of vinyl diketones under catalysis with thiazolium salts.[48–50] Useful polycarbonyl compounds which can be cyclized to furanes are prepared by the 1,4-addition of aliphatic or aromatic aldehydes to alkylidene-β-dicarbonyl compounds **27** or 3-acylacrylic esters **28**.[34,51] The procedure appears to be a general route to 2,5-disubstituted furanes containing a 3-alkoxycarbonyl group (30–60% overall yields from the Michael acceptor).

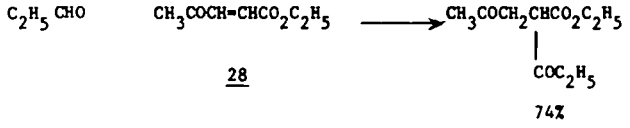
α-Alkoxyaldehydes,[52] pyranecarboxaldehydes,[52] and α-(diethoxy)-acetaldehyde[53] have been used in 1,4-additions to give polycarbonyl derivatives. These diverse polycarbonyl compounds have been shown to be useful intermediates to prepare pyrrols,[34,47] pyridazines[34,50] and 2,3-disubstituted-2-cyclopentenones.[28,50,52–54]



R^1	R_2	R_3
$n\text{-}C_3H_7$	C_6H_5	CH_3
2-furyl	2-furyl	CH_3
$n\text{-}C_3H_7$	CH_3	OCH_3
$n\text{-}C_3H_7$	$CO_2C_2H_5$	OC_2H_5
$n\text{-}C_3H_7$	$CO_2C_2H_5$	CH_3

43-64%

R^1=n-C_3H_7
R_2=$CO_2C_2H_5$
R_3=$CO_2C_2H_5$;CH_3



28

74%

α,β-Unsaturated aldehydes **29** add to vinyl ketones under catalysis with thiazolium salt **17**, but only moderate to poor yields (21–65%) of product are obtained. Only with 3,3-diphenylpropenal (**30**) are high yields observed[55]

$$RCH{=}CHCHO + CH_2{=}CHCOCH_3 \longrightarrow RCH{=}CHCO(CH_2)_2COCH_3$$

29

$R = CH_3$ (28%)

$R = C_4H_5$ (44%)

$$(C_6H_5)_2C{=}CHCHO + CH_2{=}CHCOCH_3 \longrightarrow (C_6H_5)C{=}CHCO(CH_2)_2COCH_3 \ (81\%).$$

30

Since the intermediate cyanohydrin anions from α,β-unsaturated aldehydes are ambident nucleophiles, addition of the electrophile at the γ-carbon could theoretically occur. No such additions (homoenolate) have been reported in thiazolium catalyzed reactions, but α-dialkylaminonitriles and protected cyanohydrins, derived from α,β-unsaturated aldehydes, can function as either acyl anion equivalents or homoenolate equivalents.[56-61]

The absence of observed homoenolate additions in thiazolium ion catalysed reactions may reflect the drastic differences in reaction conditions between unprotected and protected cyanohydrin anion additions. Thiazolium ylid catalyzed reactions are run neat or in solvents such as ethanol, dioxane and dimethylformamide at 65°–100° in the presence of triethylamine or sodium acetate as base, while additions with protected cyanohydrin anions are carried out in nonprotic solvents at low temperatures (0° to −78°). A likely explanation is that products indicative of homoenolate additions were not identified. Polycondensation products are expected if the anions, formed by thiazolium ylid addition to the carbonyl of **29**, react as homoenolates. Addition of the γ-anion to the carbonyl of aldehyde **29** or methyl vinyl ketone would affort intermediates subject to further reactions.

In general, products other than the desired 1,4-additions have not been identified in cyanide ion or thiazolium ylid catalysed reactions. It should be noted that yields are based mainly on the Michael acceptor and in many cases more than one equivalent of aldehyde is used. Thus these additions with unprotected aldehydes have certain limitations, particularly where the aldehyde component is scarce or expensive and cannot be used merely as a reagent.

1,4-ADDITIONS OF ANIONS OF PROTECTED CYANOHYDRINS

The 2-ethoxyethyl[62,63] and the trimethylsilyl[64] groups are the most widely used for protecting cyanohydrins. The tetrahydropyranyl group has been used occasionally.[65,66] Aldehyde cy-

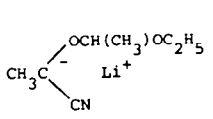
anohydrins react with ethyl vinyl ether under acid catalysis[67] to give O-(2-ethoxyethyl) cyanohydrins and with trimethylsilyl cyanide to give α-silyloxynitriles.[68] Cyanosilylations with trimethylsilyl cyanide are accomplished under thermal conditions or under catalysis with zinc iodide.[68-71]

α-Silyloxynitriles can also be prepared by an exchange process from the O-trimethylsilylated cyanohydrin of acetone. For example, *n*-hexanal is transcyanosilylated in the presence of KCN-18-crown-6 catalyst (0.01–0.02 equiv) in 76% yield.[69] Recently reported is a one pot synthesis of silylated cyanohydrins.[72] Reaction of aldehydes with trimethylsilyl chloride and potassium cyanide in either acetonitrile or dimethylformamide as solvent gives high yields of silylated cyanohydrins. The presence of zinc iodide enhances the rate of cyanosilylation while the presence of 18-crown-6 has very little effect on the yield or the reaction rate. Silyl enol ether formation, a potentially serious side reaction in cyanolsilylations, could be avoided by the use of dimethylformamide as solvent while the presence of zinc iodide failed to eliminate the formation of silyl enol ethers.[72]

A recent paper describes the conversion of aldehyde acetals into α-alkoxyacetonitriles, through exchange of an alkoxy group with a cyano group, on reaction with trimethylsilyl cyanide in the presence of $SnCl_2$ or $BF_3 \cdot OEt_2$ as catalysts.[73] 1-O-Acyl sugars react with trimethylsilyl cyanide in nitromethane in the presence of a Lewis acid ($BF_3 \cdot OEt_2$) as a catalyst to yield glycosyl cyanides.[74]

Anions of suitable protected cyanohydrins of aliphatic, aromatic, and α,β-unsaturated aldehydes undergo 1,4-additions to cyclic and acyclic enones. The synthetic utility of protected cyanohydrins in 1,4-additions depends on regioselectively. A competing reaction is 1,2-addition to the CO group. The regioselectivity (1,4 vs 1,2) is dependent on the structure of the protected cyanohydrin, the enone, and the reaction solvent.[61,63,75-77] Some generalized principles which influence the regioselectivity can be defined.

Conjugate additions predominate with bulky anions or with an enone containing a hindered carbonyl function.[61,63,75] Anions derived from protected cyanohydrins of α,β-unsaturated aldehydes favor 1,4-additions.[63,78,79] Anionic reagents from arylaldehydes, especially if substituted with electron withdrawing substituents, give predominantly conjugate addition.[76,77,80] Increased bulk at the β-position of the enone, such as in β,β-disubstituted enones, leads to increased amounts of 1,2-addition product. The O-(2-ethoxyethyl) cyanohydrin anion **31** of acetaldehyde reacts with 2-cyclohexen-1-one (**32**) in tetrahydrofuran to give 80% conjugate addition and 20% 1,2-addition.[63,77] In tetrahydrofuran-hexamethylphosphoramide, a 9:1 ratio of 1,4 to 1,2 product is observed.[77] With anion **31** and β-substituted cyclic enones **33** and **34** in tetrahydrofuran, equal amounts of 1,2 and 1,4-addition product are formed.[77]



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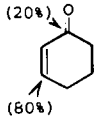

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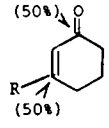

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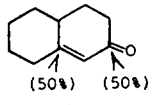
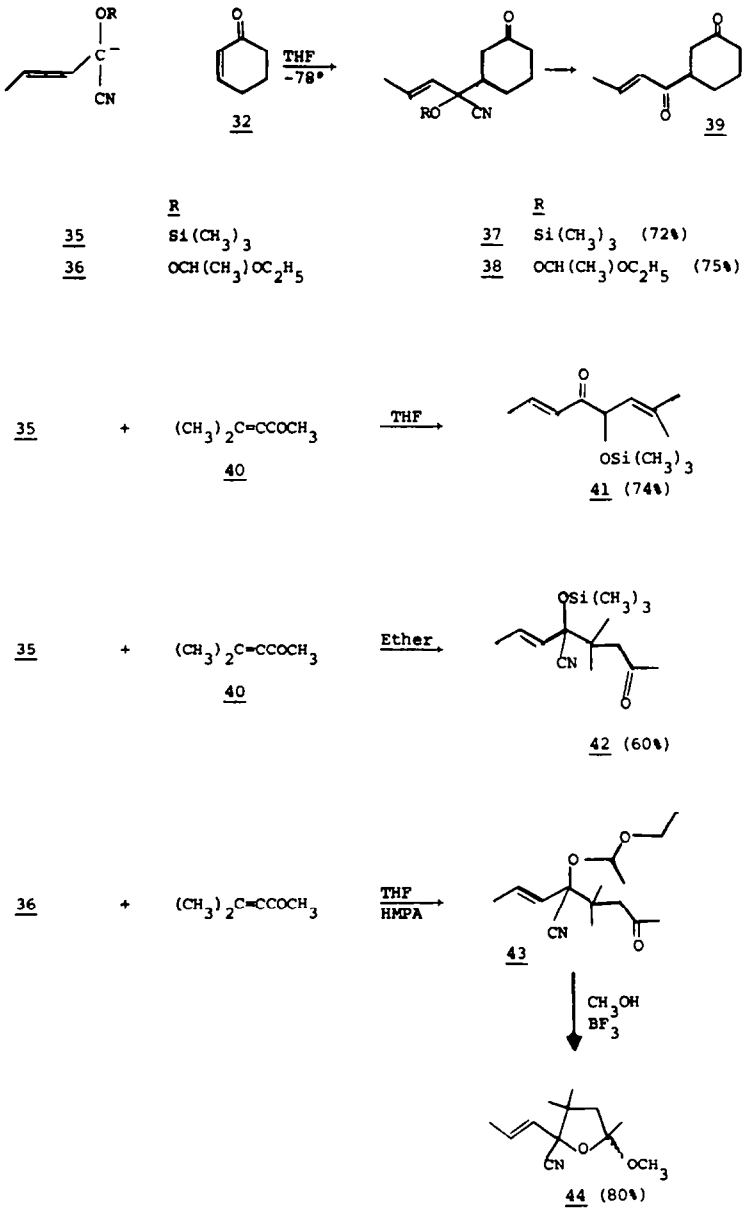


34

Protected cyanohydrins **35** and **36** from crotonaldehyde react with 2-cyclohexen-1-one (**32**) to give exclusively 1,4-addition product **39**.[61,63] Both the solvent and nature of the protecting group affect the regioselectivity in reactions of anions **35** and **36** with 4-methyl-3-penen-2-one (**40**). The O-trimethylsilyl anion **35** and enone **40** in tetrahydrofuran yield 1,2-adduct **41** (74%) while in ether only the 1,4-addition product **42** is isolated.[61] The 2-ethoxyethyl protected anion **36** affords 1,4-adduct as evidenced by cyclization to **44** (81% overall yield).[79]

The regioselectivity of anions of protected cyanohydrins of benzaldehyde in reactions with α-enones has been investigated. Both 1,2 and 1,4-additions of the anion of α-trimethylsilyloxyphenylacetonitrile (**45**) to 4-methyl-3-penten-2-one (**40**) are kinetically controlled.[75] Similar reactions are also reported to be under kinetic control. For example addition of lithiated α-(4-methoxyphenyl) acetonitrile (THF; −78°) to cinnamaldehyde is under kinetic control with the solvent influencing the amount of 1,2 and 1,4-product formed.[81] Factors controlling the regioselectivity in addition to α-enones with anions of phenylacetonitrile,[83,83] and with trimethylstannyllithium, trimethylsilyllithium, and t-butyllithium have been studied.[84]

The effect of solvent on the regioselectivity in additions of anions **45** and **46** to α-enones is

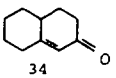


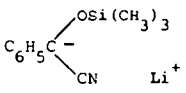
illustrated in Table 1. The 2-ethoxyethyl protected anion **46** reacts with 4-methyl-3-penten-2-one (**40**), 2-cyclohexan-1-one (**32**), and 5,5-dimethyl-2-cyclohexen-1-one (**47**) to give exclusively 1,4-addition. Under similar reaction conditions the O-trimethylsilyl cyanohydrin anion **45** is less regioselective.[75]

The introduction of electron donating or withdrawing substituents in the *para* position of O-trimethylsilyl cyanohydrin anion **45** strongly influences the regioselectivity in additions to 4-methyl-3-penten-2-one (**40**).[76] In dimethoxyethane (DME) as solvent, the amount of 1,4-addition increases from 0% for the *p*-dimethylamino compound to 100% for the *p*-cyano derivative. In ether as solvent only 1,4-product **48** is observed when the *para* substituent is hydrogen, chloro, trifluoromethyl, or cyano. The *p*-OMe derivative in ether gives 70% of 1,4-adduct **48** while the *p*-dimethylamino derivative gives mainly 1,2-product **49** (86%). It is noteworthy that these solvent effects are opposite to those reported for additions of lithiated *p*-methoxyphenylacetonitrile or t-butyllithium to α-enones, where ether and tetrahydrofuran favor 1,2-additions and hexamethylphosphoramide (HMPA) promotes 1,4-additions.[81,84]

Addition of α,β-unsaturated anion **50** to the Michael acceptor **50**, an α,β-unsaturated ester

Table 1.

Anion	Enone	Solvent	Product % 1,2	Product % 1,4	Yield[73,77]
46	$(CH_3)_2C{=}CHCOCH_3$ 40	THF	--	100	95
45	40	THF	78	22	100
45	40	Ether	--	100	84
45	40	DME	80	20	98
45	40	DME+HMPA (11 mmol)	90	10	100
45	40	DME+HMPA (30 mmol)	100	--	98
45	40	DME + 12-crown-4	100	--	88
45	40	Ether + 12-crown-4	76	24	90
45	40	THF + $MgBr_2$	42	58	97
45	 32	THF	25	75	90
45	32	Ether	--	100	96
45	32	DME	25	75	90
46	32	THF	--	100	95
45	 47	Ether	--	100	95
46	47	THF	--	100	95
45	 34	THF	--	100	95
46	34	Ether	--	100	95



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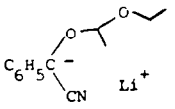

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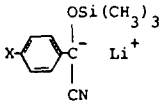
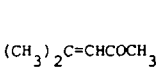


45 X=H



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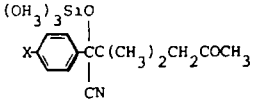
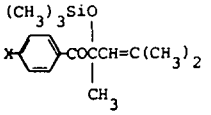


48

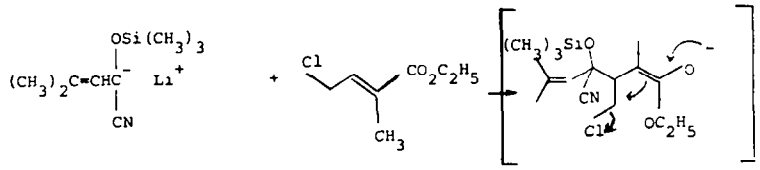
X = $(CH_3)_2N$, CH_3O, H, Cl, CF_3, CN

increasing amount of 1,4-addition →

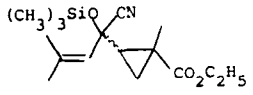


49

in which either alkylation or 1,4-addition is possible, afforts only Michael product. Internal alkylation of the intermediate ester enolate **52** leads to cyclopropyl derivative **53**.[61] Trimethylsilyl protected cyanohydrin anions give only 1,4-additions in reactions with α,β-unsaturated esters.[61,75,85] Except for ethyl acrylate as a Michael acceptor, yields are better than with thiazolium catalyzed additions of aldehydes to α,β-unsaturated esters. The O-ethoxyethyl ether of benzaldehyde cyanohydrin (**54**, R=C_6H_5) fails to react with ethyl 1-cyclohexene-1-carboxylate[86] while the anions from arylacetonitriles give good yields of 1,4-addition products.[86,87]

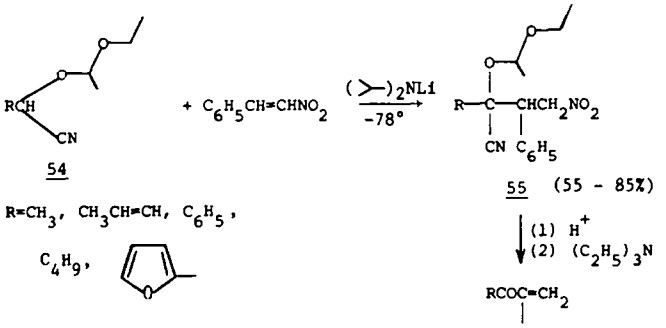


50 **51** **52**



53 (70%)

Addition of the anions of protected cyanohydrins **54** to β-nitrostyrene gives the 1,4-adducts **55**, but only polymeric material is obtained with 2-nitropropene.[88] Deprotection to give the carbonyl function, followed by base elimination of the nitro group gives α-methylene arylketones **56**.



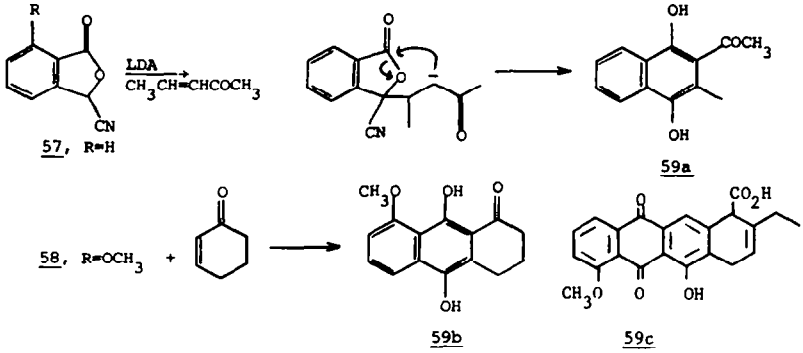
54

R=CH_3, $CH_3CH{=}CH$, C_6H_5, C_4H_9,

55 (55 - 85%)

56 (50 - 82%)

An interesting annelation route to hydroquinones (**59a** and **59b**) from 3-cyanophthalides (**57** and **58**) is reported.[89,90] The cyanophthalide **58** served as a key step in the synthesis of aklavinone, the aglycon of aclacinomycin A (a member of the anthracycline antibiotics).[91] In a connective annelation procedure, 1,4-addition of the anion of cyanophthalide **58** to the appropriate enone gave intermediate **59c** (42%). Anions of phthalides (without the CN group) undergo 1,4-additions to α,β-unsaturated esters, in an annelation reaction which affords substituted naphthols.[92] The procedure appears less useful than annelations based on protected cyanohydrin chemistry.



57, R=H

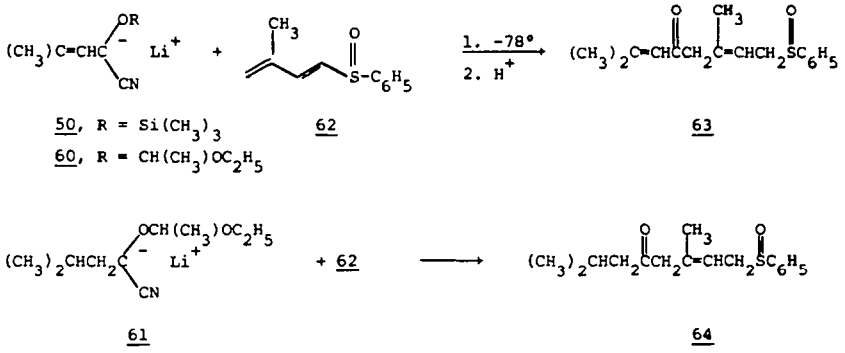
58, R=OCH_3 +

59a

59b

59c

Terpenoid polyenones are prepared through conjugate additions of the lithiated protected cyanohydrins **50**, **60** and **61** to $\alpha,\beta,\gamma,\delta$-diunsaturated sulfoxide **62**. Both *E* and *Z* isomers of the keto sulfoxides **63** and **64** are obtained.[93,94]



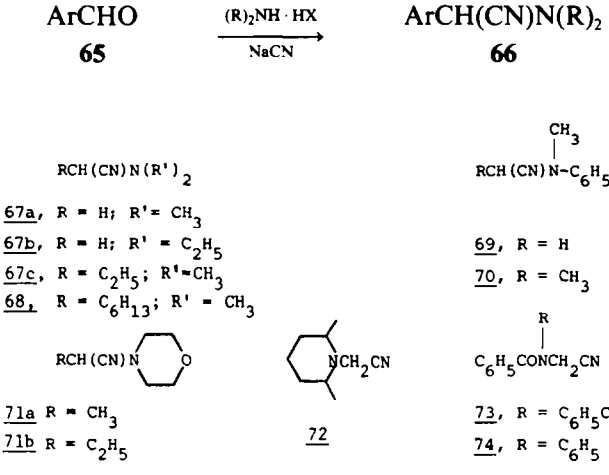
50, R = $Si(CH_3)_3$ **62** **63**

60, R = $CH(CH_3)OC_2H_5$

61 **64**

1,4-ADDITIONS OF ANIONS OF α-DIALKYLAMINONITRILES

Aromatic and aliphatic aldehydes in the presence of dialkylamines and an equivalent of acid, such as hydrochloric, perchloric, or *p*-toluenesulfonic acid, give imminium salts which add cyanide ion to form α-dialkylaminonitriles.[95-99] Alternative preparations involve the reaction of aldehydes with dialkylamines in the presence of acetone cyanohydrin,[99] α-N,N-dialkylaminoisobutyronitriles,[100] or diethyl phosphorocyanidate.[101] With aryl aldehydes, the dimethylamino, diethylamino, and morpholino derivatives are the principal ones studied as aroyl anion equivalents.[102-108] Only limited studies are reported on aliphatic α-dialkylaminonitriles (**67–72**) as acyl anion equivalents.[109-114]



65 **66**

67a, R = H; R' = CH_3

67b, R = H; R' = C_2H_5

67c, R = C_2H_5; R' = CH_3

68, R = C_6H_{13}; R' = CH_3

69, R = H

70, R = CH_3

71a R = CH_3

71b R = C_2H_5

72

73, R = $C_6H_5CH_2$

74, R = C_6H_5

To our knowledge, reactions of anions of dialkylaminoacetonitriles, (formyl anion equivalents)[109,115,116] **67a**, **67b** and **69** or the formyl equivalents[6] **73** and **74** with α,β-unsaturated esters have not been reported. A recent communication describes the reactions of 2-(2,6-dimethylpiperidino) acetonitrile (**72**) as a formyl anion equivalent in 1,4-additions to α,β-unsaturated cyclic ketones.[117] The lithio derivative of **72** undergoes conjugate addition with 2-cyclopentenone regioselectively while with 2-cyclohexenone both 1,4- and 1,2-adducts are obtained. The product ratio depends on the reaction conditions (time, temperature, solvent) with the presence of hexamethylphosphoramide (HMPA) promoting 1,4-addition. Further studies of such formyl anion equivalents in 1,4-additions are warranted as the method is potentially useful for introduction of a latent formyl group. The utility of dialkylaminoacetonitriles may be dependent on the choice of the dialkylamine component; e.g. dimethylaminoacetonitrile **67a** undergoes self-condensation on deprotonation.[111] The anion of diethylaminoacetonitrile (**67b**) exhibits increased stability and the anion of α-dimethylaminobutyronitrile (**67c**) is reported to be stable.[118]

Alkylation of diethylaminoacetonitrile (**67b**) with *cis*-hexenyl iodide (**75**), followed by 1,4-addition of the anion of intermediate **76** to 3-buten-2-one, gives *cis*-undec-8-ene-2,5-dione (**77**) (70%).[111] In essence, the conversion of **67b** to **77** demonstrates that **67b** can serve as the equivalent of a carbonyl dianion. The anion of α-(dimethylamino) cyclohexylacetonitrile (**68**) adds to ethyl acrylate, ethyl crotonate, methyl methacrylate, and methyl cinnamate to give 30–50% yields of 1,4-addition products.[114]

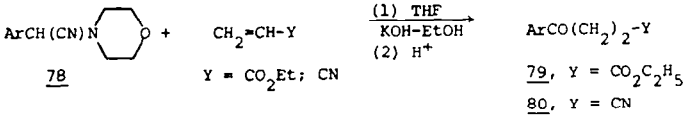
$$(R)_2NCH_2CN + C_2H_5CH{=}CH(CH_2)_2I \xrightarrow[THF]{LDA} [C_2H_5CH{=}CH(CH_2)_2CH(CN)N(C_2H_5)_2]$$

67b, R = C_2H_5 **75** **76**

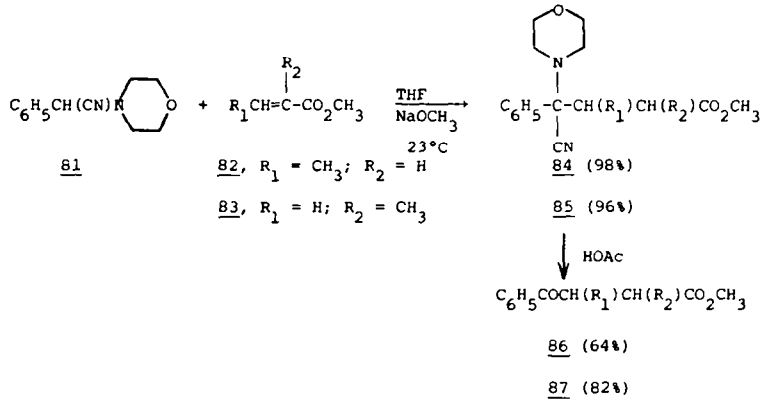
(1) LDA
$CH_2{=}CHCOCH_3$
(2) H^+

$C_2H_5CH{=}CH(CH_2)_2CO(CH_2)_2COCH_3$
77 (70%)

α-(Dialkylamino) arylacetonitriles **66** exhibit several properties which make them attractive in synthetic applications. They are readily prepared and their anions are formed with a variety of bases such as sodium methoxide,[108] potassium hydroxide in alcohols[102,104–106] or sodium hydride.[98,107] High yields are observed in 1,4-addition to ethyl acrylate or acrylonitrile.[103–108,119,120] The 1,4-addition to ethyl acrylate or acrylonitrile followed by hydrolysis of the masked acyl function is a convenient route to ethyl 3-aroylpropionates[106,107] **79** and 3-aroylpropionitriles[106–108] **80**. Yields are superior to those obtained under cyanide ion or thiazolium ylid catalysed 1,4-additions of arylaldehydes and, further, 4-morpholineacetonitrile derivatives of *ortho* substituted benzaldehyde add to ethyl acrylate. However, 2,6-disubstituted phenyl derivatives, such as α-(2,6-dichlorophenyl)-4-morpholineacetonitrile, fail to undergo conjugate additions with ethyl acrylate or acrylonitrile,[106] due to steric hindrance. Additions of α-(dialkylamino) arylacetonitriles to α,β-unsaturated ketones affords 1,4-diketones.[121]

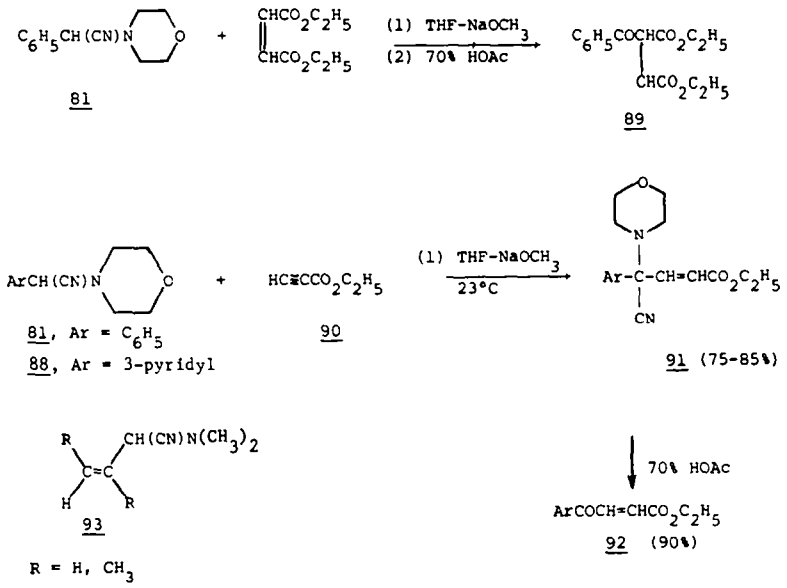


A systematic study on the effect on yields of the conditions used to form the anions of α-dialkylaminonitriles has not been reported. Poor yields are reported for conjugate additions to ethyl crotonate and methyl methacrylate in tetrahydrofuran as solvent and potassium hydroxide in ethanol as catalyst.[106] However, in recent work we have found that α-phenyl-4-morpholineacetonitrile (**81**) gives good yields of 1,4-adducts **84** and **85** with methyl crotonate (**82**) or methyl methacrylate (**83**) under catalysis with sodium methoxide (0.2 mole equiv) in tetrahydrofuran.[122] Early work with α-(dimethylamino) phenylacetonitrile and potassium amide catalysis in liquid ammonia demonstrated 1,4-additions to benzalacetophenone (84%) and ethyl cinnamate (52%), but mainly tarry materials were observed with ethyl acrylate or ethyl crotonate.[102] A low yield (38%) is reported for the sodium ethoxide catalyzed 1,4-addition of α-(dimethylamino)phenylacetonitrile to benzalacetophenone in ethanol.[102]



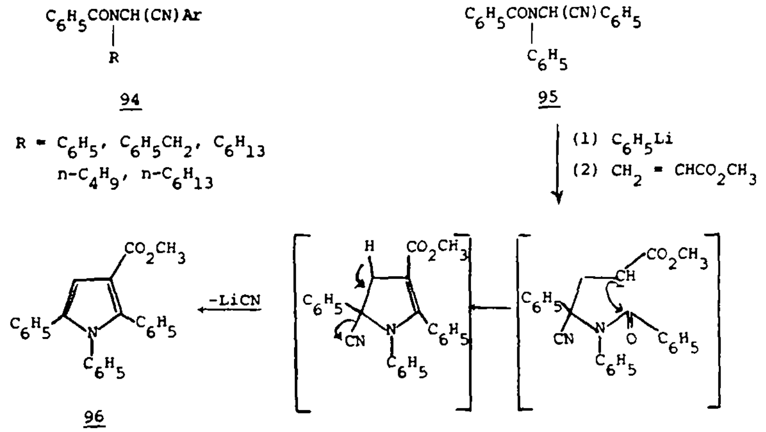
Michael additions of α-aryl or α-alkyl dialkylaminoacetonitriles to cyclic α,β-unsaturated enones or esters are unreported. The closest related reaction is the reported failure of α-(diethylamino)-3,4,5-trimethoxybenzeneacetonitrile to give clean 1,4-addition with 2-(5H) furanone;[123] however, the failure of the corresponding O-ethoxyethyl cyanohydrin to give clean 1,4-addition product with 2-(5H)-furanone is also reported[123] with no details given on either reaction. Whether α-(dialkylamino) benzeneacetonitriles will parallel the failure of benzaldehyde cyanohydrin and benzaldehyde cyanohydrin O-ethoxyethyl ether in conjugate additions to ethyl 1-cyclohexene-1-carboxylate[86] is unknown. Similar reactivities are anticipated, although studies comparing anions of protected cyanohydrins and anions of α-dialkylaminonitriles under similar reaction conditions have not been reported. One apparent difference is the failure[122] of α-phenyl-4-morpholineacetonitrile (**81**) to react with 4-methyl-3-penten-2-one (**40**), in contrast to the reactivity of protected cyanohydrin anions **45**, **46** (Table 1) and the 2-ethoxyethyl protected cyanohydrin anion of *p*-tolualdehyde.[80]

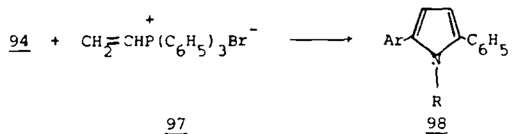
Reaction of **81** (or **88**) with diethyl maleate or ethyl propiolate (**90**) in tetrahydrofuran ($NaOCH_3$ catalysis) gives 1,4-addition products **91**.[122] Hydrolysis of the masked carbonyl function of **91** affords a convenient high yield route to ethyl 3-aroylacrylates **92**. As an alternative to acid hydrolysis for regeneration of carbonyl groups, copper sulfate,[108,117,124,125] ferrous sulfate[108] or cupric acetate[126] have been employed as mild hydrolytic agents. Hydrolysis on a silica gel column is also reported.[126]



The anions of α-aminoacetonitriles **93**, derived from α,β-unsaturated aldehydes, can function as acyl anion equivalents or as homoenolate equivalents in 1,2-additions to aldehydes and ketones,[56-58] but their reactions with α,β-unsaturated ketones or esters remain unreported.

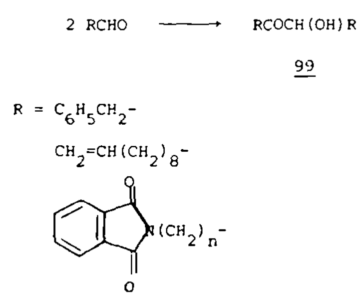
Anions of open chain Reissert compounds **94** can be generated conveniently with sodium hydride in dimethylformamide.[6,7] Generation of the lithium salt of **95** with phenyllithium and reaction with methyl acrylate is reported to give pyrrol derivative **96** (48%).[6] Presumably, the mechanism involves 1,4-addition, followed by an intramolecular ring closure through nucleophilic addition of the resultant carbanion to the amide CO. In a similar manner, the sodium anions of open chain Reissert compounds of structural type **94** undergo conjugate addition with vinyl triphenylphosphonium bromide (**97**) in refluxing dimethylformamide to give 2,5-disubstituted pyrrols **98**.[7] The lithium salt of O-(trimethylsilyl)benzaldehyde cyanohydrin failed to react with vinyl triphenylphosphonium bromide in dimethoxyethane at 0°;[127] however, because of the much milder reaction conditions, this failure to react does not necessarily indicate differences in reactivity between the protected cyanohydrin anion and the anion of **94**.





1,2-ADDITIONS OF ALDEHYDES CATALYZED BY THIAZOLIUM SALTS

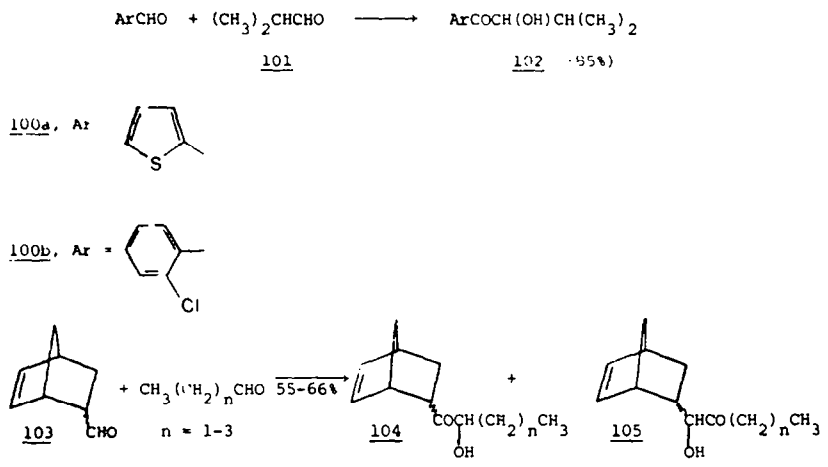
The thiazolium salts, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**17**), 3,4-dimethyl-5-(2-hydroxyethyl)-1,3-thiazolium iodide (**18**), and 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (**19**) catalyze the formation of acyloins. Symmetrical acyloins **99** are obtained from aliphatic aldehydes in 60–90% yields.[128-130] With aromatic aldehydes, there may be some advantage over cyanide ion catalysis (benzoin condensation) in terms of yield and purity of product.[128] The reaction of aliphatic aldehydes with aromatic



aldehydes under thiazolium ion catalysis generally gives a mixture of the two isomeric unsymmetrical acyloins along with the symmetrical acyloins. The utility of the reaction depends on the regioselectivity and the ease in separation of the unsymmetrical acyloins (e.g. **104** and **105**) from the symmetrical acyloins. As a method for preparing 1-aryl-2-alkyl-1,2-diketones, the reaction offers some synthetic utility since the mixture of the isomeric unsymmetrical acyloins can be oxidized to a single unsymmetrical 1,2-diketone.[129,131] In certain cases such as the reaction of 2-chlorobenzaldehyde (**100a**) or 2-thiophenecarboxaldehyde (**100b**) with 2-methylpropanal (**101**) only the regioisomer **102**, derived from 1,2-addition of the arylcyanohydrin anion to 2-methylpropanal, is obtained.[129]

Acyloins are formed in significant amounts in 1,4-additions of aliphatic aldehydes to methyl acrylate under catalysis with thiazolium salt **17**.[36,37] 3-Butyl-1,3-thiazolium bromide fails to catalyze the 1,2-addition of aldehydes to form acyloins while 3-dodecyl-1,3-thiazolium bromide in aqueous phosphate buffer (pH 8) catalyzes acyloin formation with aliphatic or aromatic aldehydes.[10] With benzaldehyde or 2-furanecarboxaldehyde, benzoin (80%) or furoin (95%) are obtained.[10]

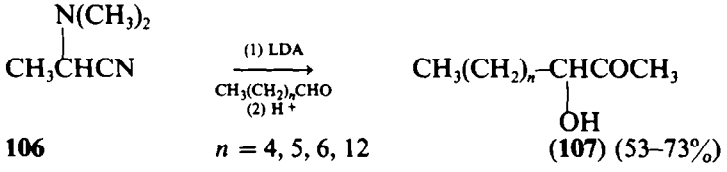
Polymer supported thiazolium salts such as 5-(2-hydroxyethyl)-4-methyl-3-(polystyrylmethyl) thiazolium chloride catalyze the benzoin condensation but give low yields of acyloins with aliphatic

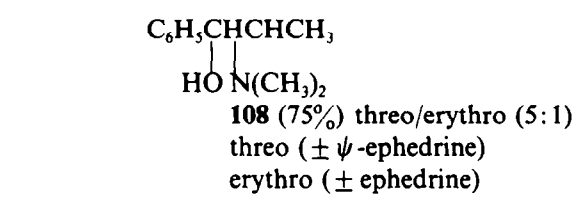


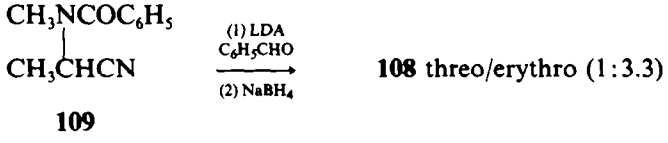
aldehydes.[38] Optically active thiazolium salts lead to asymmetric induction (35–51% optical purity) in a low yield (6–20%) conversion of benzaldehyde to benzoin.[132,133]

1,2-ADDITIONS OF PROTECTED CYANOHYDRINS AND α-DIALKYLAMINONITRILES

α-Hydroxyketones are prepared in high yield from 1,2-addition of the lithium salt of α-(trimethylsiloxy)phenylacetonitrile to aliphatic aldehydes, cyclic ketones, or acyclic ketones.[134] This method gives excellent yields (80–90%) of acyloins and should allow the selective synthesis of unsymmetrical benzoins.[64] O-Benzyl aromatic aldehyde cyanohydrins react with aliphatic aldehydes to give O-benzoyl acyloins.[135] α-Dialkylaminonitriles undergo 1,2-addition with cyclic ketones, arylaldehydes, and aliphatic aldehydes.[113,118]





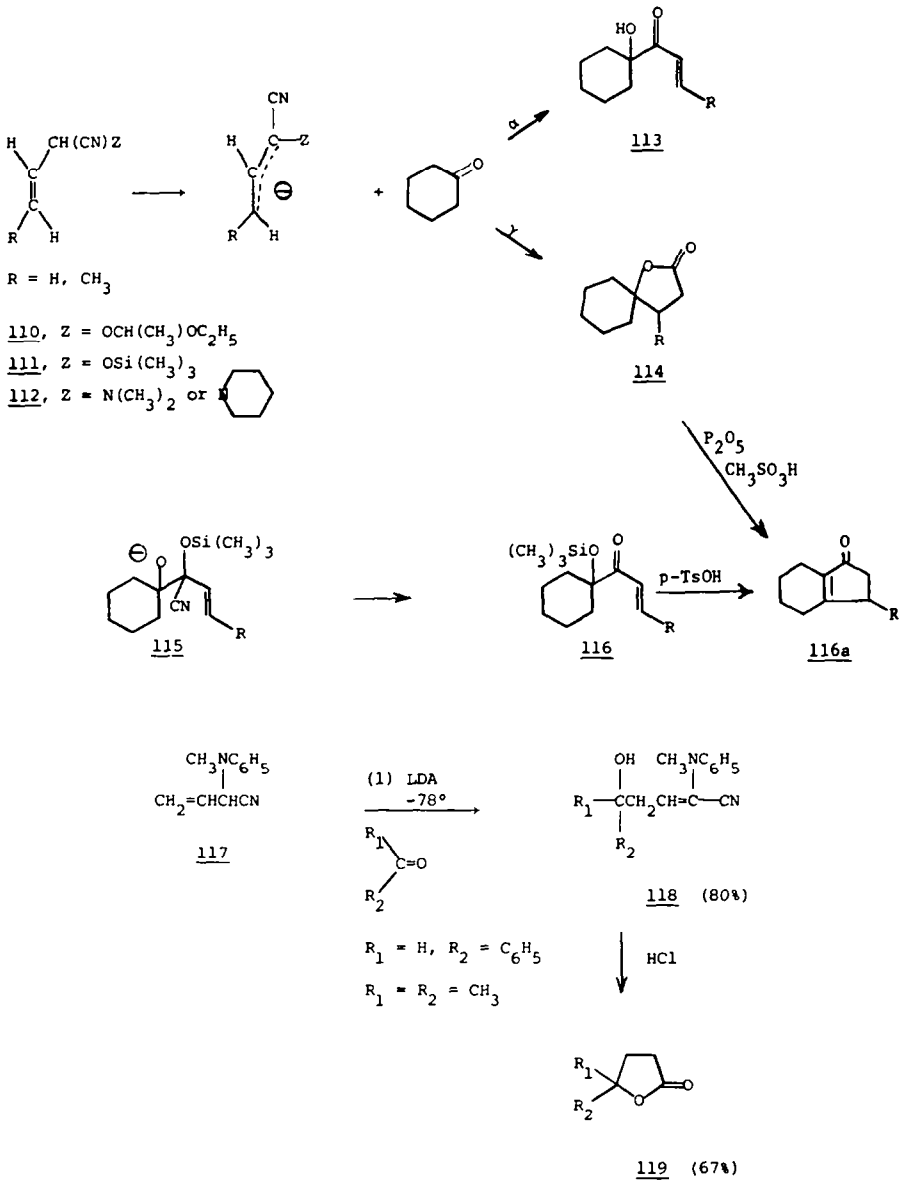


Either α-hydroxyketones[118] **107** or ethanolamines[113] **108** can be obtained. Stereoselectivity in favor of the erythro isomer occurs with α-dimethylaminopropionitrile (**106**) while reversed stereoselectivity is observed with the open chain Reissert compound **109**. A high degree of stereoselectivity is also observed in the condensation of N-benzoyl-2-cyanopiperidine with benzaldehyde in a key step for the synthesis of ± conhydrine (erythro α-ethyl-2-piperidinemethanol).[113]

2-Ethoxyethylcyanohyrdins **110**, trimethylsilyloxy cyanohydrins **111** and α-dialkylaminonitriles **112**, derived from α,β-unsaturated aldehydes, on deprotonation, form ambident anions which can react with electrophiles at the α-position (acyl anion equivalent) or at the γ-position (homoenolate equivalent).[56–59,136–138] At low temperatures (−78°), the Li salts of **110** and **112** react with aldehydes and ketones at the α-position (kinetic product—**113**) while warming to 0° produces the thermodynamic γ-product **114**.[57,58] O-Trimethylsilyl cyanohydrins **111** react exclusively at the α-position

with aldehydes and ketones.[58,61,136] The initial kinetic product **115** formed at $-78°$ undergoes an intramolecular 1,4-O-silyl rearrangement at higher temperatures to give **116**. Thus, the initial kinetic adduct is trapped and only products resulting from α-attack are observed.[58,61] The α'-hydroxy enones **113**, γ-lactones **114** and the α'-trimethylsilyloxy enones **116** are useful precursors to cyclopentenones **116a** and the over-all reaction sequence constitutes a three-carbon annelation procedure.

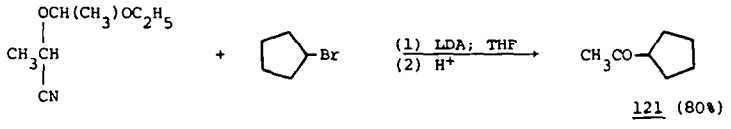
The Li salt of unsaturated α-aminonitrile **117** reacts as a homoenolate (γ-attack) with aldehydes or ketones to give 1,2-addition products **118**. Deprotection of the masked CO affords substituted lactones **119**.[56]



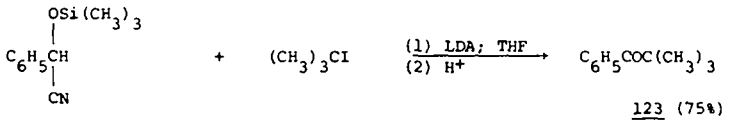
ALKYLATIONS OF PROTECTED CYANOHYDRINS

The anions of protected cyanohydrins are excellent nucleophiles in reactions with both primary and secondary alkyl halides or tosylates.[59,62,127,137,139 142] Stork and Maldonado first demonstrated the utility of 2-ethoxyethyl protected cyanohydrins in the synthesis of ketones.[62] The protected cyanohydrin of acetaldehyde **120** reacts with both primary and secondary bromides or iodides and, for example, gives product **121** on reaction with cyclopentylbromide.[62] Anions from O-trimethylsilyl cyanohydrins of aryl and heteroaryl aldehydes are alkylated with primary and

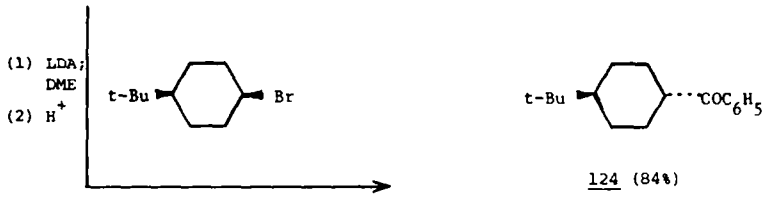
secondary bromides or tosylates in high yield.[127,139] Alkylations with t-butylchloride, t-butylbromide, 1-iodoadamantane, neopentyl iodide or tosylate failed; however, reaction of protected cyanohydrin **122** with t-butyliodide proceeds readily.[127] 1-bromo-4-t-butylcyclohexane with the lithium salt of **122** gives *trans* product **124** (inversion of configuration in SN2 displacement). Protected cyanohydrin anions of arylaldehydes and reactive aryl halides, such as 2-nitro-4-trifluoromethylchlorobenzene, affort substituted benzophenones.[66] A key intermediate in the synthesis of the macrolide, zearalenone, was synthesized through alkylation of the bis 2-ethoxyethyl protected cyanohydrin of 5-hydroxypentanal with 5-iodo-1-pentene.[143] Alkylation of the methoxymethyl ether of acrolein cyanohydrin with 1,3-dibromopropane afforded a key system in a reaction sequence leading to the construction of A-ring aromatic steroids.[144]



120 121 (80%)



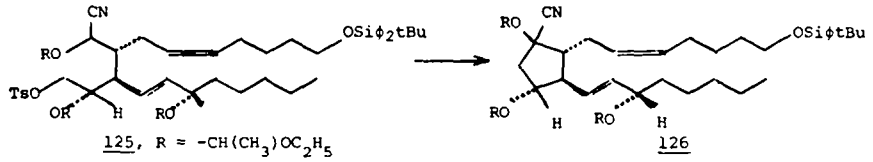
122 123 (75%)



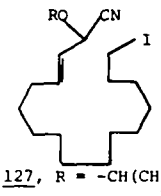
124 (84%)

Of special interest is the use of protected cyanohydrins in the formation of carbocyclic rings.[145-149] Ring closure of acyclic intermediates to form 5-membered rings (72–85% yields) in the synthesis of prostaglandins has been described.[145,146] Protected intermediate **125** was cyclized with potassium hexamethyldisilazane in benzene to give **126** (72%). The method is applicalbe to the formation of cyclopropyl,[150] cyclobutyl,[150] and cyclohexyl[147] rings (60–70% yields). Intramolecular cyclization by reaction of a protected cyanohydrin anion via ring opening of an internal epoxide gave the 5-membered ring product and none of the 4-membered cyclized product.[151]

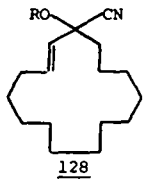
Macrocyclic ketones are prepared by intramolecular alkylation without the use of high dilution conditions.[148] For example, ring closure by internal alkylation of the protected cyanohydrin function in **127** gave *trans*-2-cyclopentadecenone (**128**) (75%) which is a precursor of the natural products ± muscone and exaltone. Only 50% yields are observed via intramolecular ketophosphonate reactions (internal Wittig) in the construction of carbocylic intermediates in the synthesis of ± muscone under high dilution conditions.[152]



125, R = -CH(CH3)OC2H5 126

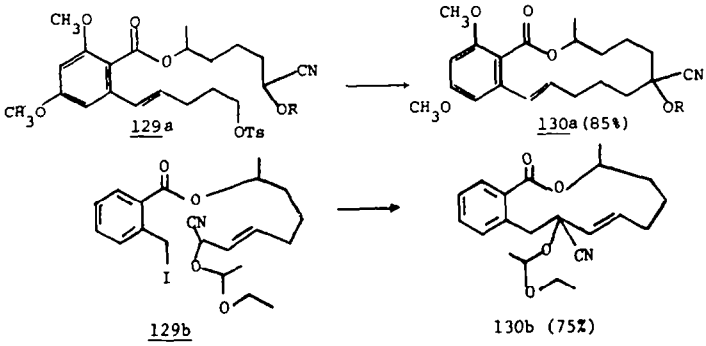


127, R = $-CH(CH_3)OC_2H_5$



128

The formation of macrocyclic lactones by alkylation of protected cyanohydrins has been investigated as an alternative to the efficient macrolide synthesis based on intramolecular alkylations of ω-haloalkyl-2-phenylthiomethylbenzoates,[143,153,154] N-haloalkyl phenylthioacetates,[155] or internal ketophosphonate cyclizations.[156] Intramolecular alkylations of protected cyanohydrin anions gave good yields of 12-membered and 14-membered lactones.[149,157] For example, the protected cyanohydrins **129a** and **129b** were cyclized to macrocyclic lactones **130a** and **130b** without the use of high dilution conditions.



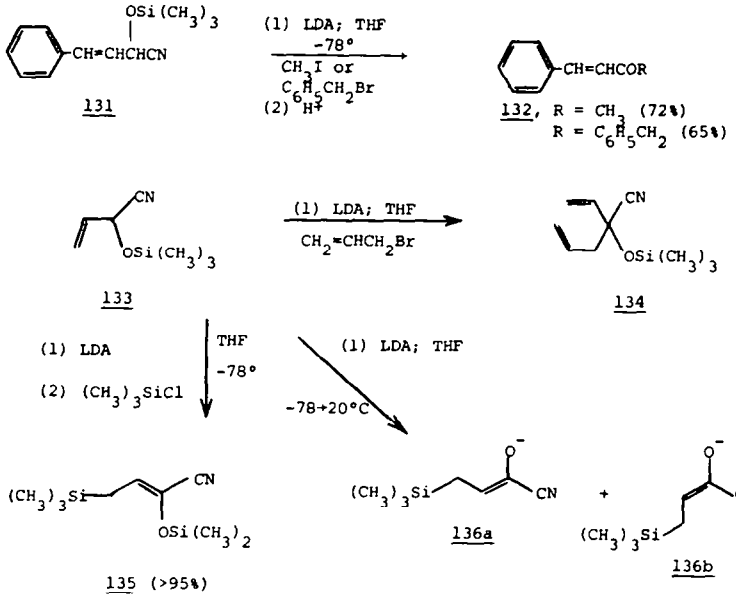
129a

130a (85%)

129b

130b (75%)

In general, protected cyanohydrins from α,β-unsaturated aldehydes (**131**, **133**) undergo alkylation at the α-position of the ambident anion.[137-139,158,159] However, upon silylation of O-trimethylsilyl cyanohydrin anions from acryloin or α-methylacryloin with trimethylsilyl chloride,[60] γ-silylation to give product **135** is the principal reaction. The O-trimethylsilyl acyl anion equivalent from propenal is silylated with trimethylsilyl chloride to give a mixture of α (42%) and γ (58%) silylated product. Increases in the bulk of the substituents at the α- or β-positions of the double bond leads to exclusive α-silylation.[60] At room temperature, anions of structural type **133** undergo a smooth 1,4-O→C silyl group rearrangement to give a mixture of *E* and *Z* isomers **136**.[60] Alkylation of the anion derived from γ-silyl compound **135** with methyl iodide gives a mixture (40/60) of α- and γ-alkylated product.[138]



131

(1) LDA; THF, -78°
CH_3I or $C_6H_5CH_2Br$
(2) H^+

132, R = CH_3 (72%)
R = $C_6H_5CH_2$ (65%)

133

(1) LDA; THF
$CH_2{=}CHCH_2Br$

134

(1) LDA
(2) $(CH_3)_3SiCl$
THF, -78°

(1) LDA; THF
-78→20°C

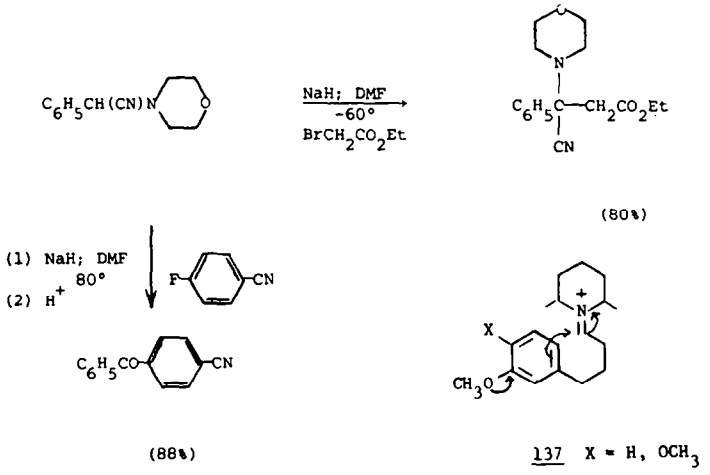
135 (>95%)

136a

136b

ALKYLATIONS OF α-DIALKYLAMINONITRILES

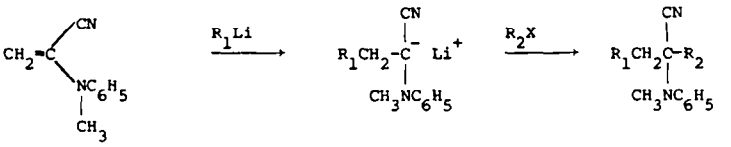
The generation of α-(dimethylamino) phenylacetonitrile anion with sodium amide followed by alkylation to synthesize ketones[160] or desoxybenzoins[161] was the first utilization of α-dialkylaminoacetonitriles as acyl anion equivalents. Anion generation with sodium hydride in dimethylformamide and alkylation with benzyl halides gives good yields of desoxybenzoins.[98,162,163] The lithium salt of α-(dimethylamino) phenylacetonitrile reacts readily with alkyl halides such as isopropyl bromide, 1,3-dibromopropane and cyclohexyl bromide.[112] Anions of α-dialkylamino aryl- and heteroarylacetonitriles are alkylated with alkyl halides,[112,160,163,164] epichlorohydrin,[107,165] allyl chloride,[107,166] and ethyl bromoacetate.[107] Deuterium-labeled aryl aldehydes are prepared through anion formation and exchange with deuterium oxide.[96,97]



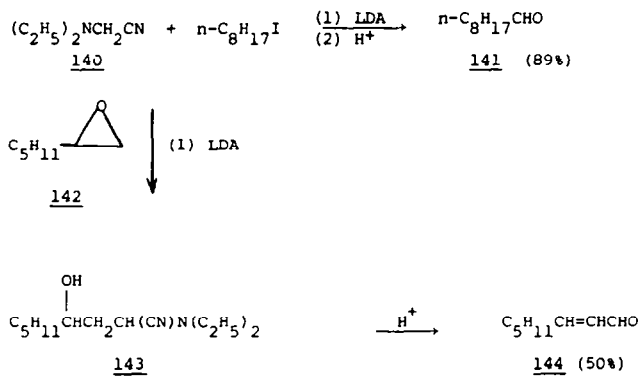
Alkylation of lithio 2-(2,6-dimethylpiperidino)acetonitrile, a formyl anion equivalent, affords only monoalkylation products due to steric hindrance.[125] Hydrolysis gives aldehydes in moderate yields (45–48%). Methoxy substituted phenylpropyl halides give monoalkyl products and on hydrolysis give iminium intermediates **137** which cyclized to 1,2-dihydronaphthalenes.[125] 2,6-Dialkylpiperidine alkaloids have been synthesized by alkylation of the cyclic α-aminonitriles, such as N-benzyl-2-cyano-6-methylpiperidine.[167-169] Reductive decyanation and debenzylation affords 2,6-dialkylpiperidines.[167]

Alkylation of α-dialkylaminonitriles from aliphatic aldehydes yields ketones after deprotection of the masked carbonyl function.[110,112] Generation of intermediate anions through Michael addition of alkyllithium or aryllithium anions to 2-(N-methylanilino)acrylonitrile (**138**) is reported.[170] Reaction of these anions with methyl iodide, ethyl iodide, or benzyl bromide affords masked ketone derivatives **139** which are hydrolyzed to ketones.[110,170] Alkylation of the anion of α-diethylaminoacetonitrile (**140**), a formyl anion equivalent, affords aldehyde **141** while reaction with epoxide **142** gives trans α,β-unsaturated aldehyde[111] **144** via intermediate **143**. The scope and limitations of reactions with epoxides have not been fully defined. The lithium salt of α-(trimethylsilyloxy) phenylacetonitrile is reported to give unidentified products on reaction with epoxides.[127]

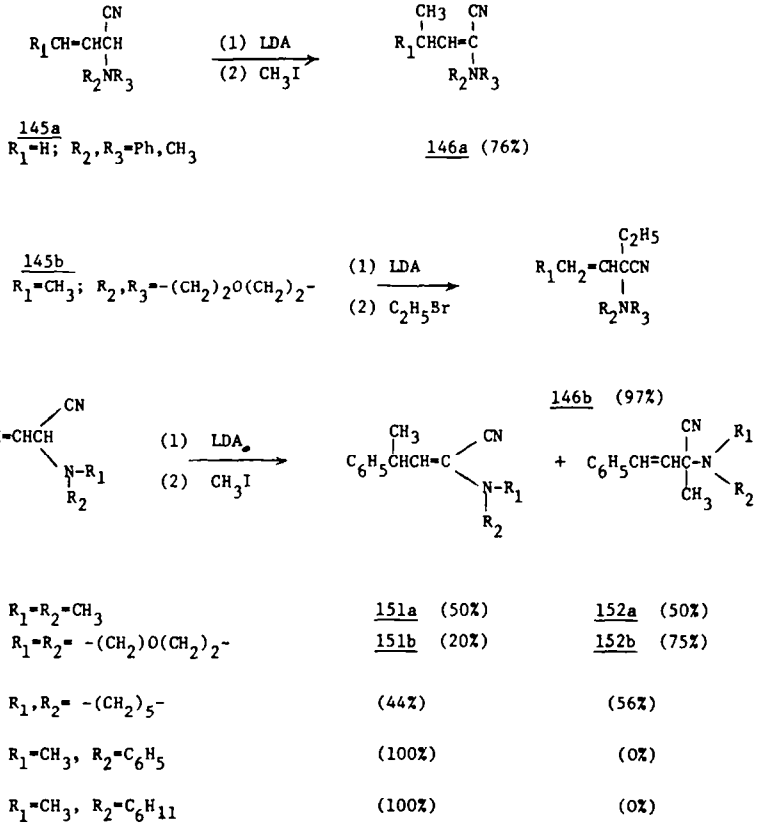
Unsaturated α-dialkylaminoacetonitriles **145a**, **147a** and **148–150** form ambident anions which are alkylated at either the α- or γ-position.[56] Alkylation of **145a** (R_1=H) with methyl iodide is



138 139

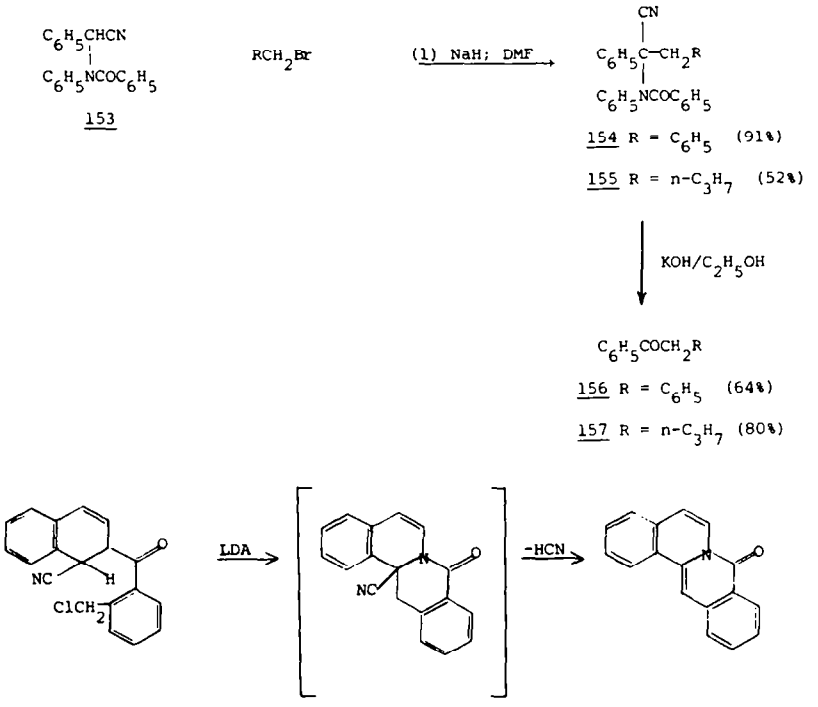


completely selective to give only γ-alkylated regioisomer **146a**,[56] while alkylation of **145b** (R_1=CH_3) with ethyl bromide gave exclusively α-alkylated product **146b**.[126] The structure of the secondary α-amino group as well as the steric bulk of the alkylating reagent influences the regioselectivity. With dimethylamine or piperidine as the amine component (**147a** and **148**), the alkylation with methyl iodide gives approximately equal amounts of α- and γ-alkylation product,[56] while with the morpholine derivative **147b**, α-alkylation is the major product.[126] Increased amounts of γ-alkylation are observed with isopropyl bromide. N-Methylaniline or N-methyl-N-cyclohexylamine derivatives (**149–150**) which exhibit greater steric bulk give exclusively γ-alkylation product **151** on alkylation with methyl iodide.[56]



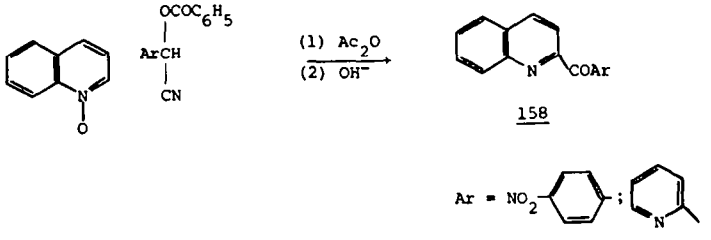
147a	R_1=R_2=CH_3	**151a** (50%)	**152a** (50%)
147b	R_1=R_2= $-(CH_2)O(CH_2)_2-$	**151b** (20%)	**152b** (75%)
148	R_1,R_2= $-(CH_2)_5-$	(44%)	(56%)
149	R_1=CH_3, R_2=C_6H_5	(100%)	(0%)
150	R_1=CH_3, R_2=C_6H_{11}	(100%)	(0%)

Open chain Reissert compounds of structural type **153** are alkylated and ketones **156** and **157** are obtained on hydrolysis of the intermediates **154** and **155** with potassium hydroxide in ethanol.[6] Ring closures through intramolecular alkylations of Reissert compounds have been described.[171,172]

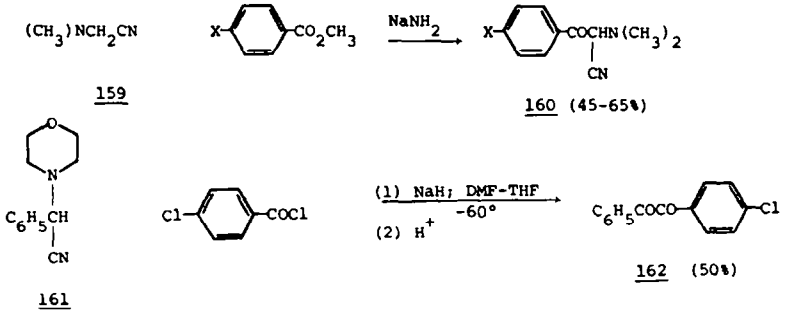


MISCELLANEOUS REACTIONS

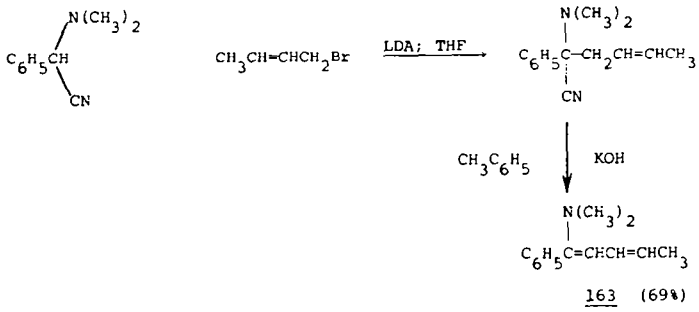
O-Benzoyl cyanohydrins of aromatic aldehydes react with N-oxides of pyridine, quinoline, and isoquinoline in the presence of acetic anhydride to give α-aroyl products[173] **158**. In a similar manner, cyanohydrin carbonates of aromatic aldehydes react with the N-oxides of quinoline and isoquinoline.[174] The reaction is dependent on the acidity of the protected cyanohydrin, for O-benzoyl cyanohydrins of benzaldehyde, 4-chlorobenzaldehyde, and aliphatic aldehydes fail to react.



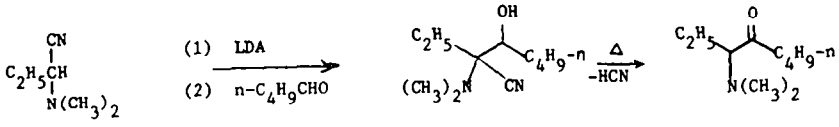
Aroylations of α-dialkylaminonitriles have been reported. Reaction of α-dimethylaminoacetonitrile (**159**) with substituted methyl benzoates in liquid ammonia in the presence of sodium amide affords products **160**[109] while α-(phenyl)-4-morpholinoacetonitrile (**161**) reacts with 4-chlorobenzoyl chloride to give diketone **162**.[107]



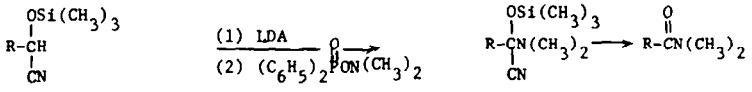
α-Dialkylaminonitriles undergo dehydrocyanation with powdered potassium hydroxide, potassium t-butoxide,[112] or potassium amide in liquid ammonia[160] to give enamines. The method provides a simple synthesis of dieneamines **163**.[112]



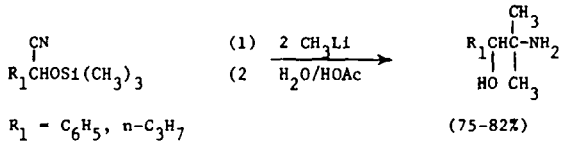
α-Dialkylaminoketones are prepared by reaction of α-dialkylaminonitriles with aldehydes (1,2-addition) followed by the thermal elimination of hydrogen cyanide from the initial adducts.[175] In this manner unsymmetrical α-aminoketones are obtained in a simple three-step synthesis from aldehydes and secondary amines.



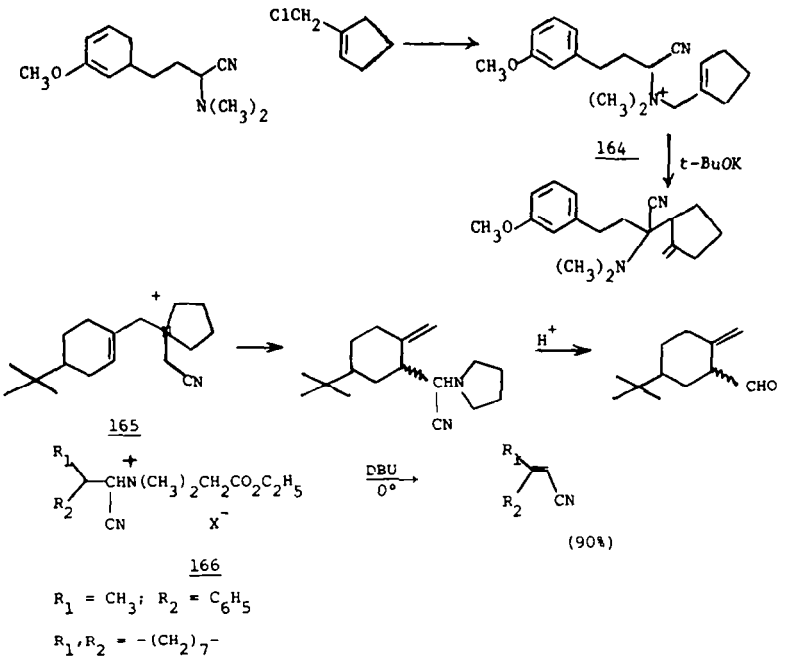
Electrophilic amination of O-trimethylsilyl cyanohydrin anions constitutes a mild oxidative method for conversion of aldehydes to carboxamides.[176]



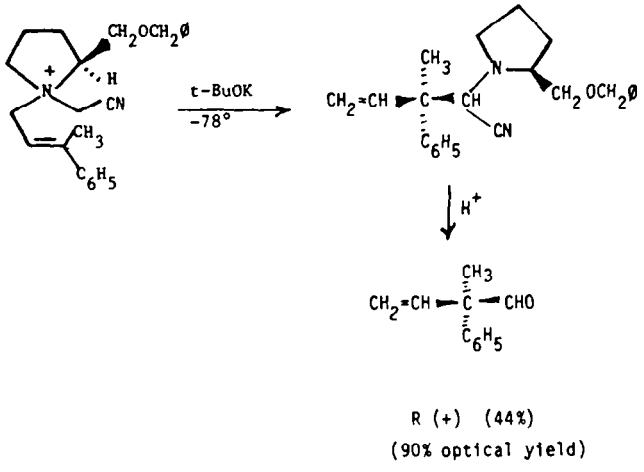
Double addition of an organometallic reagent to O-silylated cyanohydrins leads to β-aminoalcohols in good yields.[177]



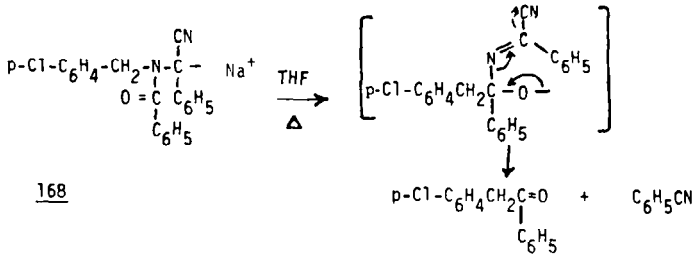
Allylic halides alkylate α-dialkylaminonitriles to form tetraalkylammonium salts **164** and **165** which on conversion to ylides undergo a [2,3]-sigmatropic rearrangement.[163,164,178-180] The method provides a convenient route to 2-methyl-3-formylpyridines or 2-methyl-3-acylpyridines.[163,164] Rearrangement of 1-(cyanomethyl)-1-(2-pyridinylmethyl)-pyrrolidinium salts followed by hydrolysis gives the 3-formyl derivatives while reaction of the α-aminonitrile, obtained after rearrangement, with alkyl halides affords 2-methyl-3-acylpyridines. Benzylic salts of 1-cyanomethylpyrrolidine afford *ortho* methylbenzaldehydes.[178] Ester stabilized ammonium ylids of α-dialkylaminonitriles, formed by treatment of ammonium salts **166** with DBU (1,5-diazabicyclo[5·4·0]undec-5-ene), undergo spontaneous fragmentation to give α,β-unsaturated nitriles.[181]

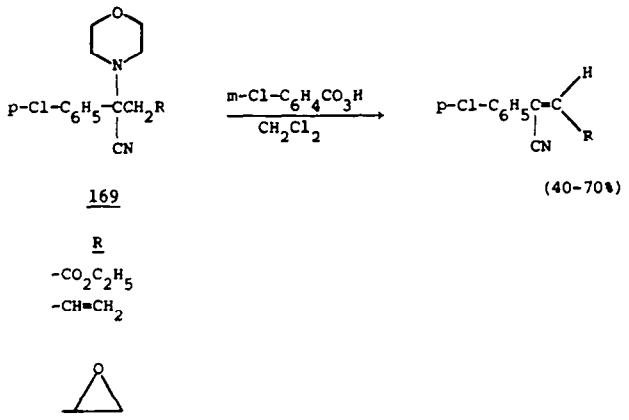


Asymmetric induction is observed in [2,3]-sigmatropic rearrangements via chiral ammonium chlorides, such as **167** which was obtained from (*S*)-proline ethyl ester.[182] Ylid formation with potassium *t*-butoxide, rearrangement and acid hydrolysis of the aminonitrile afforded (*R*)-(+)-2-methyl-2-phenyl-3-butenal (90% optical purity).



The thermal rearrangements (Stevens-type) of conjugate bases of N-benzyl open-chain analogues of Reissert compounds leads to deoxybenzoins (50–96% yields). The reaction may involve initial homolyis followed by radical recombination.[183] Oxidation of α-morpholinonitriles **169** with *m*-chloroperbenzoic acid leads to unsaturated nitriles.[107]





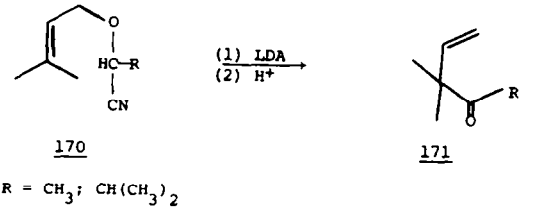
169

R

$-CO_2C_2H_5$

$-CH=CH_2$

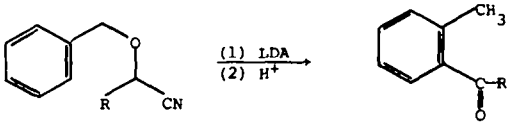
α-Substituted α-allyloxyacetonitriles **170** are prepared by phase transfer catalyzed alkylation of aliphatic cyanohydrins with allylic bromides.[184,185] These β,γ-unsaturated ethers of cyanohydrins, on formation of the lithio-derivatives, undergo a [2,3]-sigmatropic rearrangement[184,186,187] to form β,γ-unsaturated ketones **171**. Benzylic ethers **172** of aliphatic cyanohydrins on treatment with lithium diisopropylamide (LDA) give *o*-methylaryl ketones **173**.[188] The method has been used to prepare 3-methyl-1-(3-methyl-2-furyl)-1-butanone, a naturally occurring C_{10}-terpene.[189] Rearrangement of propargylic ethers **174** of aliphatic cyanohydrins provides a route to α-allenic ketones **175**.[190] Mixed acetals of acryloin and aliphatic cyanohydrins give enolic monoethers of γ-ketoaldehydes via [2,3]-sigmatropic rearrangement of their respective carbanions.[187]



170

$R = CH_3;\ CH(CH_3)_2$

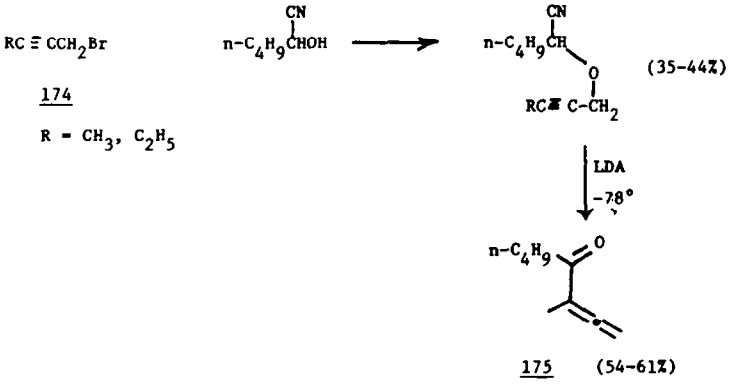
171



172

$R = CH_3;\ CH(CH_3)_2$

173

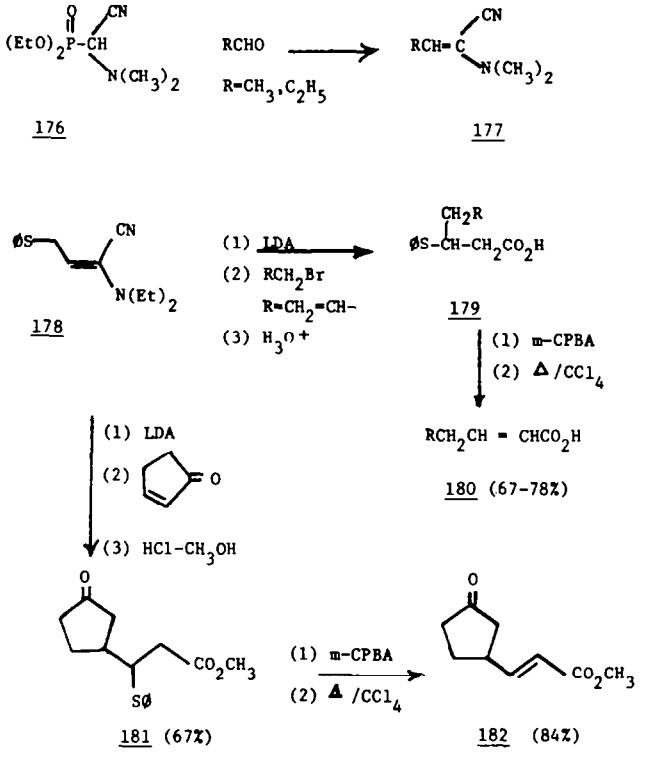


174

R = CH_3, C_2H_5

175 (54-61%)

A number of diverse substituted α-cyanoenamines which yield homoenolate anions have been reported. The cyanophosphonate **176** on deprotonation reacts with aliphatic aldehydes to give α-cyanoenamines **177** which are useful synthons for further reactions.[191,192] The anion of α-cyanoenamine **178** is an interesting β-carbonyl vinyl anion equivalent which reacts with electrophiles exclusively at the γ position.[193] The anion of the related ether (2-trimethylsilyloxy-4-methylthio-2-butenonitrile) is reported to undergo exclusive α-alkylation.[138] Alkylations, followed by oxidation of the thio function to a sulfoxide, affords α,β-unsaturated acids or esters. In addition, exclusive 1,4-addition to enones cyclopentenone and cyclohenenone was observed.[193]



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