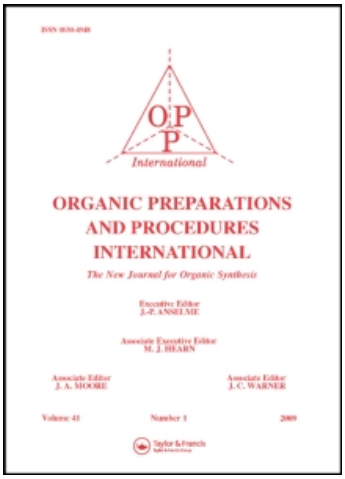

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF α-AMINOALDEHYDES AND α-AMINOKETONES. A REVIEW

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To cite this Article Fisher, Lawrence E. and Muchowski, Joseph M.(1990) 'SYNTHESIS OF α-AMINOALDEHYDES AND α-AMINOKETONES. A REVIEW', Organic Preparations and Procedures International, 22: 4, 399 — 484
To link to this Article: DOI: 10.1080/00304949009356309
URL: http://dx.doi.org/10.1080/00304949009356309

ORGANIC PREPARATIONS AND PROCEDURES INT. 22(4), 399-484 (1990)

SYNTHESIS OF α-AMINOALDEHYDES AND α-AMINOKETONES. A REVIEW†

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SYNTHESIS OF α-AMINOALDEHYDES AND α-AMINOKETONES. A REVIEW†

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INTRODUCTION

α-Aminoaldehydes, α-aminoketones and the masked versions thereof are compounds which have found widespread use as precursors of physiologically important ethanolamine derivatives and as intermediates for the synthesis of a large variety of heterocyclic systems. Numerous syntheses have been developed and new ones continue to be devised to provide access to these important chemical building blocks. It is the purpose of this article to review the methods by which α-aminoaldehydes, α-aminoketones and the functional equivalents thereof have been prepared. Since Mayer[1] has summarized the chemistry of α-aminoketones about ten years ago, as a part of a general review on aminoketones, this article will emphasize information which has been published since that time. On the other hand, the literature surveyed for α-aminoaldehydes will span a much greater time period, even though the synthetic routes to these compounds have recently been reviewed by Cepins et al.,[2] albeit in Russian and in a journal which is not widely available.

I. REACTION OF α-HALOALDEHYDES, α-HALOKETONES OR α-HALOACETALS WITH AMINES, AMINE DERIVATIVES OR AMMONIA

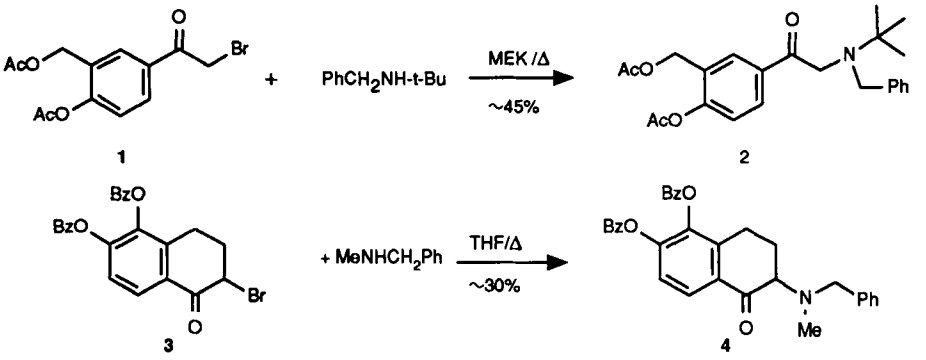
A. α-Aminoketones

The preparation of α-aminoketones from α-haloketones and ammonia or an amine is the most venerable of all the α-aminoketone syntheses. It is also undoubtedly the most widely used, almost certainly the one which first comes to mind when such compounds are

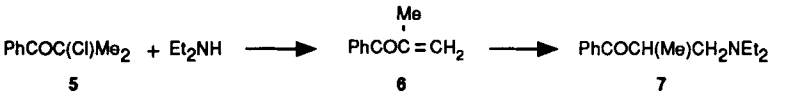
required, and probably the one fraught with the most problems. A detailed account of the applicability of this method and the pitfalls associated therewith is given in Mayer's review.[1] Following below is a summary of the data found therein as well as pertinent information from the recent literature.

1. α-Dialkylaminoketones

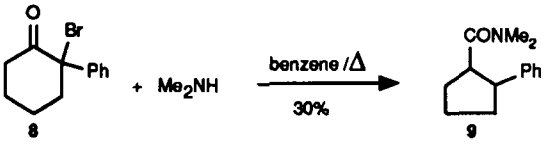
The formation of α-dialkylaminoketones from α-haloketones is broad in scope, especially when the halogen atom (chlorine or bromine) is attached to a primary or a secondary carbon atom (ref. 1, pp. 2258-9). For example, the aminoketones 2 and 4 are produced upon reaction of the phenacyl bromide and tetralone derivatives 1 and 3 with N-t-butylbenzylamine or N-methylbenzylamine.[4,5]



When the halo group is on a quaternary carbon atom, secondary amines can effect dehydrohalogenation and the α,β-unsaturated ketone thus generated may undergo Michael addition of the secondary amine to produce the β-dialkylaminoketone isomeric with the expected product (e.g. 7 from 5, ref. 2, p. 2254).



If the tertiary haloketone is not fully substituted on the α'-carbon atom, as in the bromocyclohexanone derivative 8, a Favorskii[6] type rearrangement product 9 (probably cis isomer) is formed instead of the anticipated aminoketone[7].



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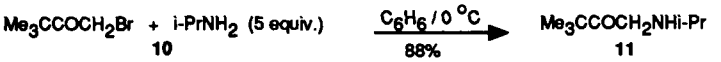
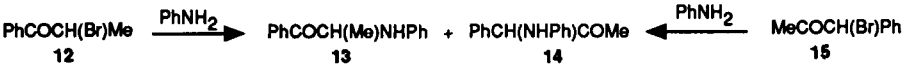
2. α-Alkylaminoketones

Primary amines invariably react with α-haloketones and, in certain cases, the desired α-alkylaminoketones are obtained in very good yields, as in the synthesis of 1-i-propylamino-3,3-dimethyl-2-butanone (11) reported by Corey and Brunelle.[8] Usually, however, the desired products are formed in more modest yields and by-product formation is commonplace.



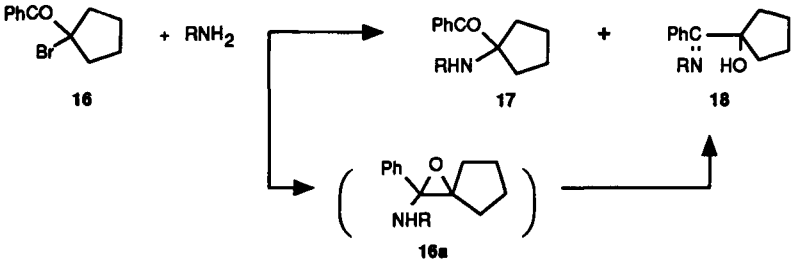
10 11

For example, aniline gives a mixture the of α-anilinoketones 13 and 14, irrespective of whether the bromoketone 12 or 15 is used (ref. 2, p. 2255), perhaps as a consequence of the incursion of Voigt-Amadori rearrangement processes (ref. 2, pp. 2261-66).[9,10]



12 13 14 15

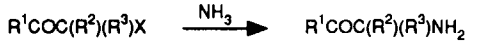
The reaction of tertiary α-haloketones with primary amines is particularly complicated as exemplified by the bromocyclopentane derivative 16. With neat i-propylamine the α-aminoketone 17 (R = i-Pr) is indeed formed but is contaminated with the hydroxyimine 18 (R = i-Pr).[7a] Unbranched primary amines (R = Me, Et), in contrast give 18 as the sole product. The Schiff base 18 may stem from the rearrangement of an intermediate α-aminoepoxide 16a which in turn could arise from primary addition of the amine to the carbonyl group.[7b]



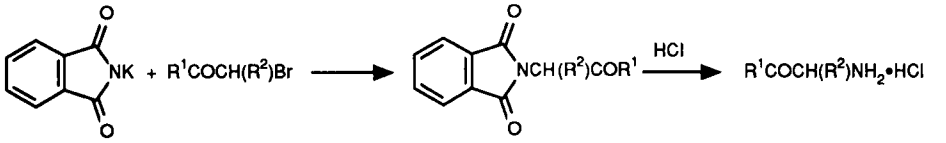
16 17 18 16a

3. α-Aminoketones

The generation of α-aminoketones from ammonia and an α-haloketone is limited to those cases where the halogen atom is bound to a tertiary carbon atom (ref. 2, p. 2256).



When this is not the case, the α-aminoketones dimerize spontaneously, and the dimers are readily oxidized (e.g., by air) to pyrazines. Indeed, this constitutes a generally useful synthesis of pyrazines[11]! As a consequence, primary α-aminoketones are often prepared by means of the Gabriel[12a] or Delépine[12b] synthesis. The Gabriel route to such compounds consists of the reaction of potassium phthalimide with a primary or secondary α-haloketone followed by hydrolysis of the phthalimido ketone under strongly acidic conditions (ref. 2, pp 2257-2263).



A special consequence of the Gabriel synthesis is that the phthalimidoketone derivatives are easily ketalized and the ketals, upon alkaline hydrolysis or hydrazinolysis, are converted into α-aminoketals for which very few syntheses are known (see Table 1).[13a,b]

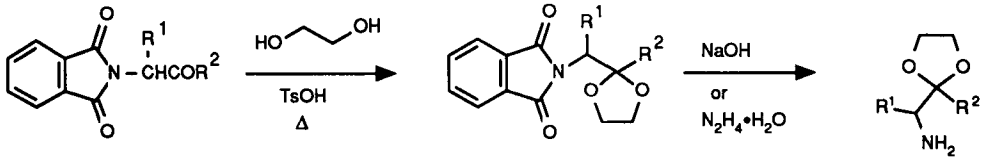
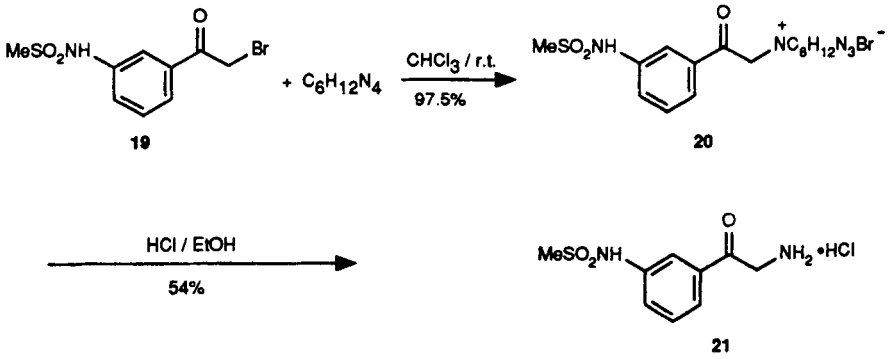


Table 1 . Synthesis of α-aminoketals from α-phthalimidoketone derivative.[a]

		% Yields	
R^1	R^2	Phthalimido ketal	Aminoketal
H	Me	80	88
H	Ph	89	87
Me	Me	95	87
Me	Ph	94	81
Ph	Ph	59	97

[a]Data taken from ref. 13a

The Delépine synthesis, which is frequently used as an alternative to the Gabriel synthesis, involves the reaction of hexamethylenetetramine with a primary α-haloketone (e.g. 19) and hydrolysis of the quaternary ammonium salt thus produced (20) with concentrated hydrochloric acid[14] (see also, ref. 2, pp. 2257-2263).



B. α-Aminoaldehydes

The generation of α-aminoaldehydes from α-haloaldehydes and an amine can only be accomplished when the amine is secondary and even then, careful control of the reaction conditions is necessary. The condensation of ammonia with α-haloaldehydes leads to pyrazines[11]; a study of the reaction of α-haloaldehydes with primary amines does not seem to have been reported.

Secondary amines react with α-bromoaldehydes, at room temperature or above, to produce the α-dialkylaminoketones isomeric with the expected products[15] (also, see below). Duhamel and Cantacuzene[16] demonstrated that the α-dialkylaminoaldehydes were intermediates in this process and that under appropriately modified conditions (low temperature, ether solution) the aldehydes could be isolated in good yields and in high purity (Table 2).[17,18]

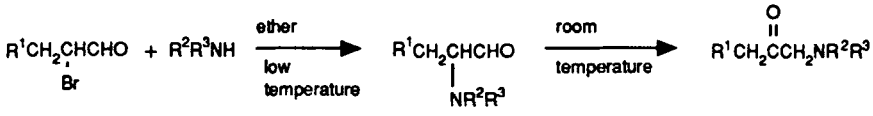


Table 2. Synthesis of α-dialkylaminoaldehydes from α-bromoaldehydes and secondary amines.

R^1	R^2	R^3	% Yield
Me	Et	Et	83
n-Bu	Me	Me	70
n-Bu	--------$(CH_2)_5$--------		52
t-Bu	Me	Me	89
t-Bu	--------$(CH_2)_4$--------		63
t-Bu	--$(CH_2)_2O(CH_2)_2$---		72

Whereas the generation of α-aminoaldehydes directly from the corresponding α-haloaldehydes is beset with considerable difficulty, the amination of α-haloaldehyde acetals is relatively readily accomplished. The displacement reaction has been most extensively studied using ammonia or amines (primary or secondary) on chloro-[19,23], bromo-[22,24-27] or iodoacetaldehyde[22] acetals, but homologous haloacetaldehyde acetals react analogously[24,28-30] (Table 3). In general, the aminolyses are effected by heating the haloacetal with an excess of the amine or ammonia, either neat or in an alcoholic solvent. When the amine component is of low molecular weight, the reaction must be conducted in a pressure vessel. Higher molecular weight amines effect displacement at atmospheric pressure. The fact that this process is

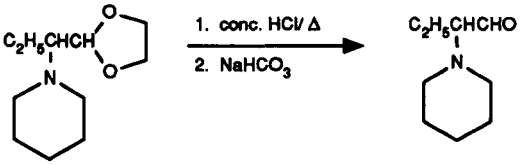
$$R^1R^2NH + R^3CH(X)CH(OR^4)_2 \longrightarrow R^1R^2NCH(R^3)CH(OR^4)_2$$

Table 3. Synthesis of α-haloacetals.

R^1	R^2	R^3	R^4	X	% Yield	Reference
H	H	H	Et	Br	59	26
Me	H	H	Et	Br	65	27
n-Pr	H	H	Me	Cl	63	23
$PhCH_2$	H	H	Et	Br	82	27
t-Bu	H	H	Et	Br	90	27
Ph	H	H	Et	Br	66	27
H	H	Me	Et	Br	46	28
Me	H	Me	Et	Br	50	28
-----$(CH_2)_5$-----		Ph	dioxolane	Cl	56	29a
-----$(CH_2)_5$-----		Et	dioxolane	Br	12	29b
-----$(CH_2)_5$-----		n-C_5H_{11}	dioxolane	Br	20	29b
Me	H	$HO(CH_2)_2$	Et	Br	57	30
H	H	COOH	Me	Cl	37	31

successful with relatively hindered haloacetals (R^3 = i-Pr)[30] augurs well for the extension thereof to the preparation of α-aminoketals from α-haloketals.

The α-aminoacetals derived from secondary amines, in some cases, can be hydrolysed, under acidic conditions to the relatively stable α-aminoaldehydes as exemplified by the generation of α-piperidinobutyraldehyde from the corresponding dioxolane derivative.[29b]



II. FROM α-BROMOKETONES AND METHYL N-ALKYLFORMIMIDATES

The problems associated with the amination of α-haloketones by primary amines can be circumvented by using the much less basic[32,33] methyl N-alkylformimidate as the amine component. Thus, the α-bromoketone (chloroketones react much more slowly) is heated with an excess of the imidate (in a suitable solvent) and the α-formamidoketone so produced is easily cleaved with a methanolic hydrogen halide solution[34,35] (Table 4). It is noteworthy that displacement occurs with secondary alkyl bromides (examples 2,4,8 and 9) and with α-bromoketones containing α′-hydrogen atoms (examples 5 and 6).

The success of the process hinges on the use of the O-methyl imidate and the bromoketone because the intermediate imidate salt, on fragmentation, produces methyl bromide (b.p., ca 4 °C) which escapes from the reaction mixture and thus does not consume the N-alkylformimidate by alkylation. Such a problem has been encountered by Fujii, et.al.[36] Inasmuch as the requisite imidates are easily prepared from the formamide and dimethyl sulfate,[37] this synthesis of α-alkylaminoketones is likely to have wide applicability.

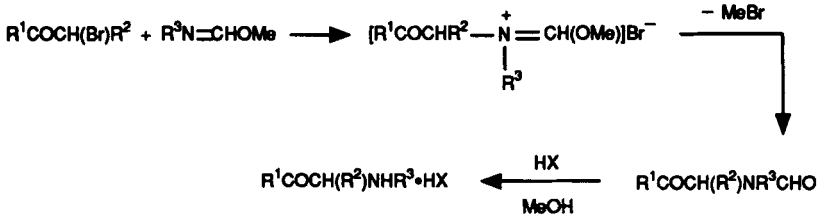


Table 4. Synthesis of N-alkylformidates and α-Alkylaminoketones from α-Bromoketones and Methyl N-alkylformimidates[a]

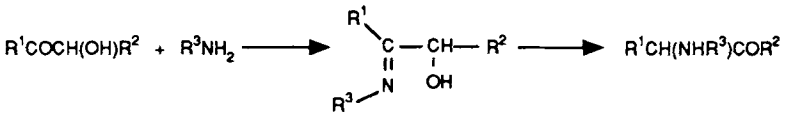
Example	R^1	R^2	R^3	Imidate equiv.	Solvent	% Yield Amide	% Yield Amino ketone:HX
1	Me	H	Me	2.5	DME-toluene	39	
2	Me	Me	Me	2.5	DME-toluene	36	
3	Ph	H	Me	2.5	DME-toluene	67	94 HBr
4	Ph	Me	Me	2.5	DME-toluene	83	
5	$PhCH_2$	H	Me	3.5	DME-toluene	44	85 HBr
6	$PhCH_2CH_2$	H	Me	1.1	Benzene	50[b]	87 HCl
7	Ph	H	$PhCH_2CH_2$	2.5[c]	Toluene	86	98 HBr
8	Ph	Me	$PhCH_2CH_2$	6	Toluene	87	
9	3,4-$(BzO)_2C_6H_3$	Me	$PhCH_2CH_2$	2.5	MeCN	91	

[a] Data from ref. 33 unless indicated otherwise
[b] Data from ref. 34.
[c] With 1.2 equiv. imidate in acetonitrile the formamide yield was 60%.

III. REACTION OF α-HYDROXYKETONES WITH AMINES AND REARRANGEMENT OF α-AMINOALDEHYDES

A. Condensation of α-Hydroxyketones with Amines

α-Hydroxyketones upon reaction with amines are converted into α-aminoketones. When the amine is primary, the reaction proceeds via the initial formation of a Schiff base which is transformed into the α-aminoketone [Voigt-Amadori rearrangement (ref. 2, pp. 2261-6)].

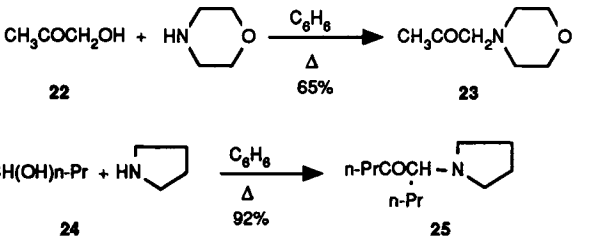


Although the process is acid catalyzed, the reaction can often be driven to completion, in the absence of acid, by the azeotropic removal of water (see below). The precise course of the

rearrangement reaction is very substrate dependent and mixtures of products are frequently obtained. In general, cognizance must be taken of the possibility that a Voigt-Amadori type of rearrangement can occur whenever an α-aminoketone, or salts thereof, are generated and used under more or less vigorous conditions (section 1/Ib). A good case in point is the great ease with which α-amino aldehydes rearrange to α-aminoketones (see below and section1/II).

1. α-Dialkylaminoketones

The reaction of α-ketols with secondary amines is preparatively useful when the alcohol is primary or when the α-hydroxyketone is symmetrical. For example, azeotropic removal of water from a 1.4 : 1 solution of acetoin (22) and morpholine in benzene gave morpholinoacetone (23) in 65% yield.[38] The aminooctanone derivative 25 was obtained from 5-hydroxy-4-octanone (24) and pyrrolidine under similar conditions.[39]



Unsymmetrical α-ketols react in an analogous manner to give mixtures of α-aminoketones, the isomeric composition of which corresponds closely to that found in the starting α-hydroxyketones.[39] Although it has not yet been demonstrated, it is likely that isomerically pure unsymmetrical α-ketols will give rise to single α-dialkylaminoketones, of predictable structure, under these conditions. This is because acid catalysis is known to be essential to effect the equilibration of non-symmetrical α-dialkylaminoketones.[40]

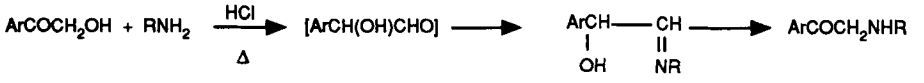
2. α-Alkylaminoketones

The synthesis of α-alkylaminoketones from α-ketols and primary amines has considerable generality and is of preparative significance. This reaction was discovered by Amadori,[41] who used D-glucose and aromatic amines as the reaction components. The true nature of the products was established largely by Kuhn and Weygand[42] who christened the reaction "the Amadori rearrangement". Although a full description of this rearrangement is

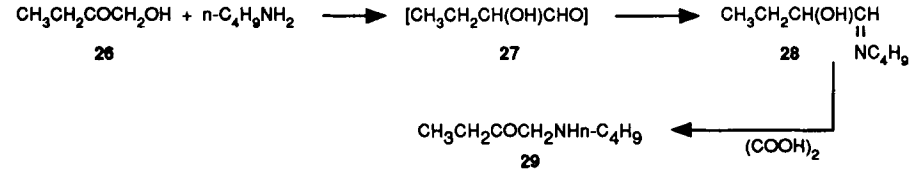
beyond the scope of this review, it is noteworthy that the process is applicable to virtually all types of primary amines and most sugars.[43] In addition, the Amadori rearrangement plays a central role in the Maillard reaction[44] which, in fact, is a complex series of reactions that occurs between an amino acid and a reducing sugar. The Maillard reaction continues to be the object of intensive study.[45]

The course of the reaction between α-ketols and primary amines is strongly dependent on the structure of both reactants. Careful control of the reaction conditions is often necessary to avoid or minimize the formation of mixtures of products.

Terminal α-ketols with an aryl group attached to the ketonic carbon atom react with both aromatic and aliphatic primary amines via the α-hydroxyaldehyde tautomers, and the corresponding imines, to produce the ω-alkylaminoketones directly.[46,47]



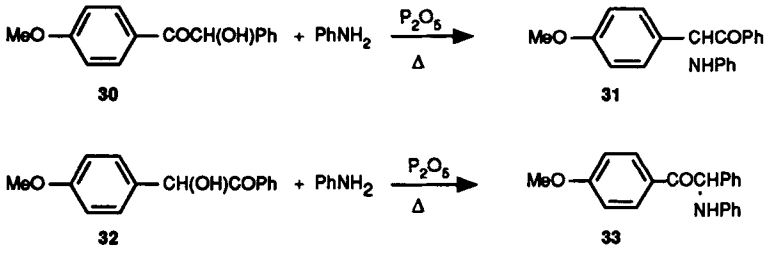
Purely aliphatic terminal α-ketols react in an analogous manner with primary aromatic amines.[46] In contrast, with purely aliphatic primary amines, the aldimine is isolable and acid catalysis is required to effect the Voigt-Amadori rearrangement thereof,[47] as in the case of the synthesis of 1-n-butylamino-2-butanone (29) from 1-hydroxy-2-butanone (26). As expected, identical products are obtained from the α-hydroxyaldehydes isomeric with the above α-ketols.



The reaction of secondary α-hydroxyketones with aliphatic or aromatic primary amines provides the α-aminoketone directly.[46,47] With certain unsymmetrical α-ketols, primary

aromatic amines are reported[48] to give the product in which the amino group is found at the

carbon atom of the original carbonyl group. Thus different α-anilinoketones are obtained from the condensation of aniline with benzanisoin (30) and anisobenzoin (32).[49] Whether this is a phenomenon characteristic of all isomerically pure secondary α-ketols and all primary amines



remains to be determined. In this regard, it is of considerable interest that lithio-aldimine-aldehyde adducts, on protonolysis at room temperature, spontaneously undergo the Voigt-Amadori rearrangement to a single α-aminoketone (Table 5).[50] This process is restricted to isonitriles not possessing α-hydrogen atoms (enolizable ketones are deprotonated).

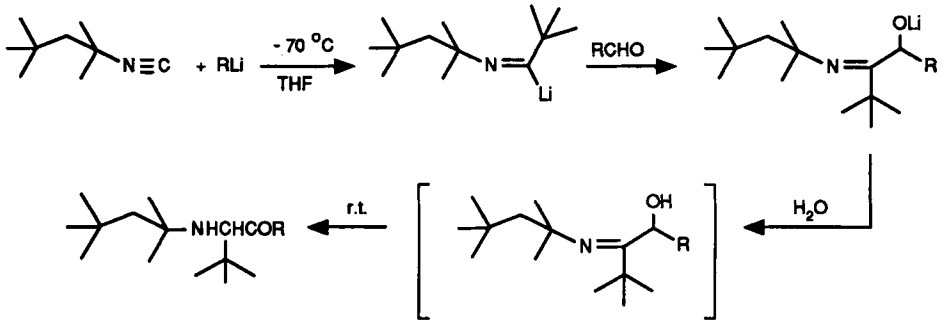
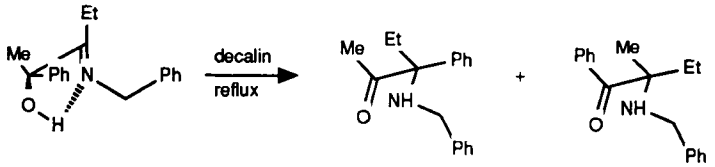


Table 5. Synthesis of α-aminoketones from alkyllithium reagents and 2,4,4-trimethylpentyl isonitrile.

R	% Yield
n-butyl	58
phenyl	54
vinyl	47

The reaction of α-ketols containing tertiary carbon skeletons with primary amines

produces easily isolable Schiff bases which only undergo transposition to α-alkylaminoketones under much more vigorous conditions. Optically active substrates rearrange without racemization. For example, in boiling decalin, the (S)-(+)-α-hydroxyimine 34 undergoes a pinacol-like[51] transposition to an 8-16:1 mixture of the phenyl and methyl migrated α-benzylaminoketones (R)(-) 35 and (R)(+) 36 respectively, in which both products are optically pure.[52]

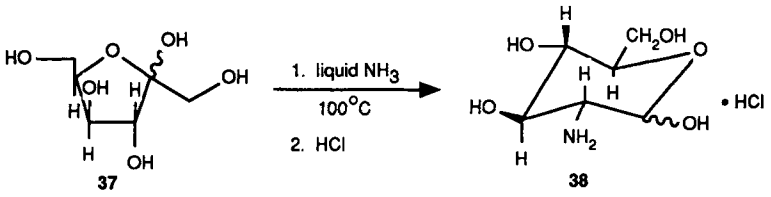


34 (S) (+) **35** (R) (-) **36** (R) (+)

The reaction of methylamine with tertiary α-ketols has found synthetic utility in the synthesis of steroidal D-homo-α-methylaminoketones.[53]

3. α-Aminoketones.

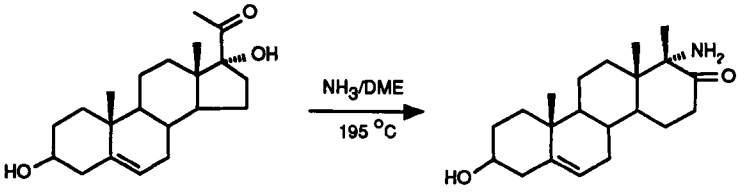
α-Aminoketones are usually not prepared from ammonia and primary or secondary α-ketols because of the proclivity of such aminoketones to undergo self condensation and subsequent oxidation to pyrazines (ref. 11, pp 18-20). Sugars are exceptional in this regard, presumably because the α-amino carbonyl compound, once formed, is protected from dimerization due to the thermodynamically favorable formation of a cyclic hemi-acetal (ketal). For example, d-fructose 37 on heating with liquid ammonia under pressure is converted into d-glucosamine (isolated as hydrochloride salt 38) in ca. 20% yield (~35% based on recovered fructose).[10]



37 **38**

Tertiary α-hydroxyketones, unlike the less substituted congeners, can be converted into

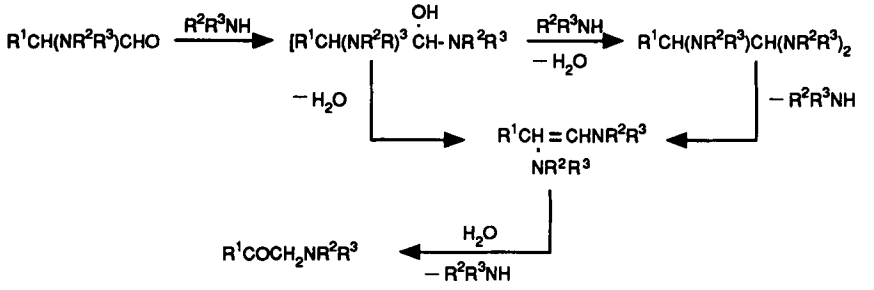
α-aminoketones in the presence of ammonia. Thus the 17α-amino-D-homoandrostenone 40 was formed in 62% yield when the 17α-hydroxypregnenolone derivative 39 was heated with ammonia in dimethoxyethane solution.[52]



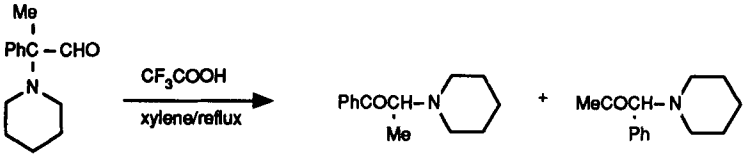
39 40

B. Rearrangement of α-Aminoaldehydes

Unless special precautions are taken, most syntheses of secondary α-dialkylaminoaldehydes lead, at least in part, to the α-dialkylaminoketones isomeric with the expected product (ref. 9, pp 1061,62 and section 1/II above). This rearrangement is catalyzed



by secondary amines and proceeds via 1,1,3-tris-dialkylaminoethane and 1,2-bis-dialkylaminoethene (enediamine) intermediates, which under appropriate conditions, are isoluble.[29a,40] In contrast, α-dialkylaminoaldehydes, such as 41, in which the amine bearing carbon is tertiary, are stable, but rearrangement to the α-dialkylaminoketones (2:1 mixture of 42 and 43 in this case) can be effected under acidic conditions.[40]



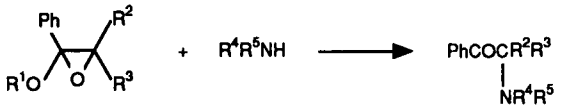
41 42 43

IV. REACTION OF α-SUBSTITUTED EPOXIDES WITH AMINES

A. α-Alkoxyepoxides

1. α-Aminoketones

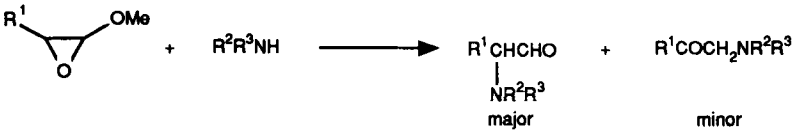
Primary and secondary amines effect the cleavage of α-alkoxyepoxides at the β-carbon to give α-aminoketones (ref. 2, pp. 2266,67). The epoxy compounds are easily prepared from the α-bromoketone and an alkali metal alkoxide. This sequence is a useful alternative route to



α-dialkylaminoketones in which the amine bearing carbon is fully substituted.

2. α-Aminoaldehydes

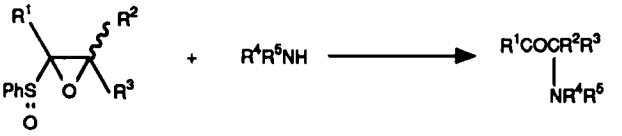
The above cleavage reaction also occurs with 1-alkoxy-2- substituted epoxides and secondary amines. The expected α-dialkylaminoaldehydes are indeed formed, but the process is of little preparative value since the aldehyde is invariably contaminated with the isomeric aminoketone.[54]



B. α-Phenylsulfinylepoxides

1. α-Aminoketones

α-Phenylsulfinylepoxides undergo a cleavage reaction with amines[55] which is entirely analogous to that observed with α-alkoxyepoxides. The ring opening reaction is effected, either with the neat amine or in dipolar aprotic solvents, at room temperature to 100 °C. The epoxide structure can be varied widely and the cleavage reaction is independent of the epoxide stereochemistry. The reaction is successful with secondary amines and aromatic primary amines (Table 6). Primary aliphatic amines, except benzylamine, are reported to give rise to complex mixtures of products. α-Phenylsulfinyl epoxides are easily prepared, in two steps,

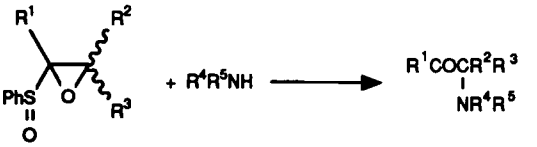


from the α-chlorosulfoxide and the appropriate carbonyl compound.[56]

2. α-Aminoaldehydes

When the above epoxysulfoxide is β,β-disubstituted but α-unsubstituted, the cleavage reaction gives rise to stable α-aminoaldehydes with secondary amines and primary aromatic amines (Table 6).

Table 6. Synthesis of α-aminocarbonyl compounds from α-phenylsulfinylepoxides[a] and amines.

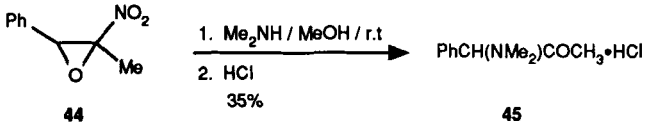


R^1	R^2	R^3	R^4	R^5	Solvent	T °C	% Yield
n-C_6H_{13}	H	Ph	-----$(CH_2)_5$-----		piperidine	r.t	97
n-C_6H_{13}	H	Ph	-----$(CH_2)_5$-----		piperidine	r.t.	100[b]
n-C_6H_{13}	H	Ph	-$(CH_2)_2$ O $(CH_2)_2$-		morpholine	r.t.	100
n-C_6H_{13}	H	Ph	Et	Et	diethylamine	r.t.	96
n-C_6H_{13}	H	Ph	H	$PhCH_2$	DMSO	55	72
n-C_6H_{13}	H	Ph	H	Ph	HMPA	100	97
$PhCH_2$	H	Me	-----$(CH_2)_5$-----		piperidine	r.t.	92
$PhCH_2$	H	Me	H	4-$MeOC_6H_4$	HMPA	100	81
c-C_6H_{11}	H	4-ClC_6H_4	-----$(CH_2)_4$-----		pyrrolidine	80	100
$PhCH_2$	-----$(CH_2)_5$-----		-----$(CH_2)_4$-----		pyrrolidine	80	100
H	-----$(CH_2)_5$-----		-----$(CH_2)_4$-----		pyrrolidine	90	78
H	-----$(CH_2)_5$-----		H	Ph	HMPA	r.t.	84

[a] Less polar isomer used unless indicated otherwise . (The epoxide stereochemistry, i.e., cis or trans, is unknown).
[b] More polar isomer.

C. α-Nitroepoxides

The α-nitroepoxide 44 is converted into 1-dimethylamino-1-phenylacetone (45) with a small excess (1.5 equiv.) of methanolic dimethylamine at room temperture.[57] No other



44 45

examples of this remarkably facile transformation were reported. α-Nitroepoxides are easily prepared from the nitrovinyl compounds and alkaline hydrogen peroxide.[57,58]

D. α-Chloroepoxides

The very reactive monoalkyl α-chloroepoxides are reported[29b] to undergo exceedingly facile cleavage with piperidine to the corresponding α-piperidinoaldehydes (Table 7).

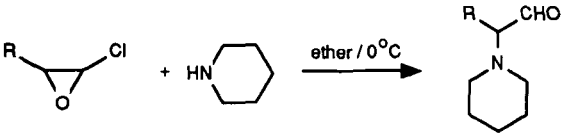


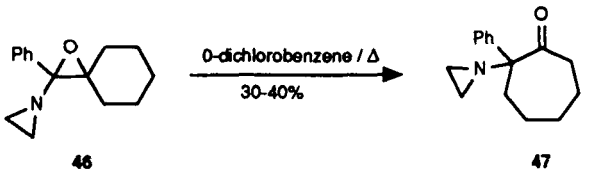
Table 7. Synthesis of α-piperidinoaldehydes from α-chloroepoxides.

R	% Yield
Me	36
Et	50
n-Bu	65

1,2-Disubstituted α-chloroepoxides are said to be converted into α-aminoketones under similar conditions.[29b] These rather unstable epoxy compounds can be prepared by dehydrochlorination of 2,2-dichlorocarbinols with alcoholic potash.[203]

V. REARRANGEMENT OF α-DIALKYLAMINOEPOXIDES

The aziridinyl epoxy compound 46, prepared from N-lithioaziridine and 1-bromo-1-benzoylcyclohexane, undergoes ring expansion to the aziridinylcycloheptanone derivative 47 in boiling o-dichlorobenzene.[59] No other examples of this rearrangement were



46 47

reported but α-aminoepoxides have been proposed as reaction intermediates to rationalize the formation of α-hydroximines from tertiary α-haloketones and primary amines[7b] [see section 1, I(b)]. In addition, an α-aminoepoxide has been invoked as a plausible intermediate in the oxidative conversion of disubstituted enamines to α-dialkylaminoketones by N-sulfonyloxaziridines (Table 8).[202] α-Hydroxyketones are formed from trisubstituted enamines under the same conditions.

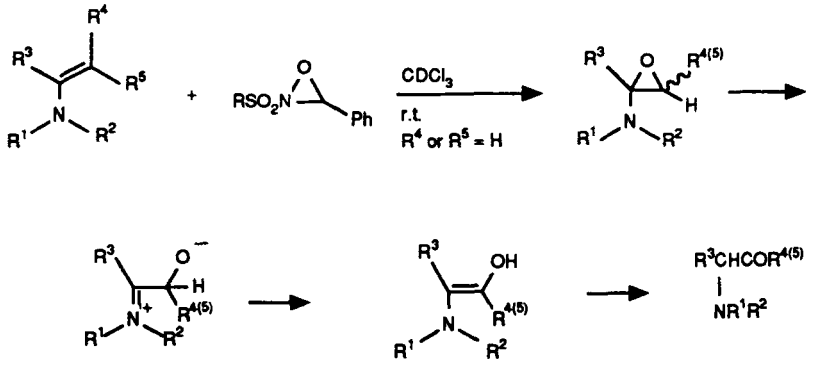
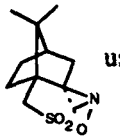


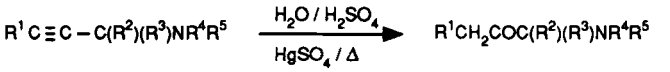
Table 8. Synthesis of α-dialkylaminoketones by oxidation of disubstituted enamines with N-sulfonyloxaziridines.

R^1	R^2	R^3	R^4	R^5	% Yield
----$(CH_2)_4$----		Ph	H	Ph	55
----$(CH_2)_4$----		Ph	H	Me	54
--$(CH_2)_2O(CH_2)_2$--		----$(CH_2)_4$----		H	66[a]

[a]  used in this case

IV. HYDRATION OF 3-AMINOACETYLENES

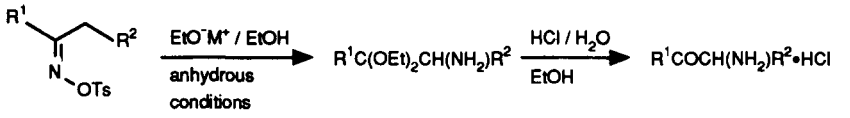
The acid induced, mercuric sulfate catalyzed hydration of 3-aminoacetylenes leads to α-aminoketones (ref. 2, pp 2272,73). The reaction is applicable to primary, secondary, and



tertiary 3-aminoacetylene derivatives but the primary amino compounds must be acylated prior to hydration.[60] The degree of substitution at the amine bearing (C-3) and terminal acetylenic (C-1) carbon atoms can be varied widely, with both fully substituted and completely unsubstituted examples being successful. The starting materials are easily prepared from the corresponding propargyl chlorides and an amine or by Mannich type reactions on terminal acetylenes.

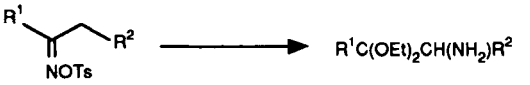
VII. NEBER AND RELATED REARRANGEMENTS

It is generally accepted that the Neber rearrangement involves the reaction of a ketoxime tosylate with an alcoholic solution of sodium or potassium ethoxide followed by acidic hydrolysis (ref. 2, pp. 2272-6; see also ref. 61). The α-aminoketone is usually isolated



as the hydrochloride salt, but if the conditions are appropriately modified the diethyl ketal of the free base can be generated.[62] (see Table 9).

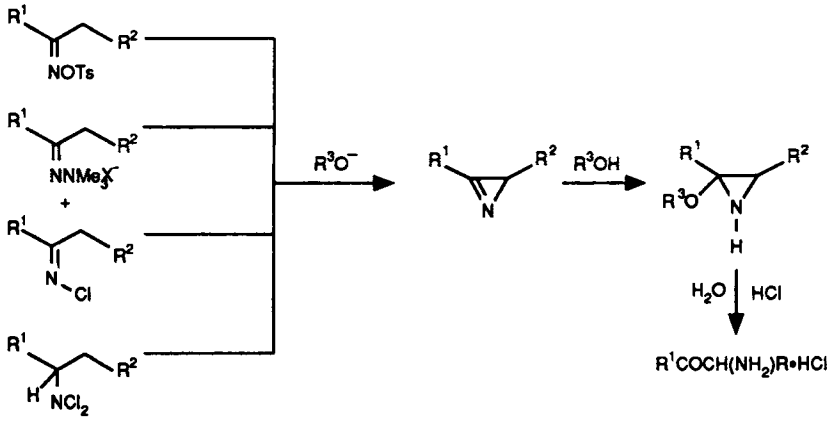
Table 9. Synthesis of α-aminoketone diethyl ketals by the Neber rearrangement.



R^1	R^2	% Yield
2-pyridyl	H	58
3-pyridyl	H	53
4-pyridyl	H	76
4-pyridyl	Me	40
$4\text{-}NO_2C_6H_4$	H	79
$4\text{-}BrC_6H_4$	H	92

The Neber rearrangement is broad in scope, and if the oxime tosylate can be prepared, it is one of the preferred routes to α-aminoketones. There is some question regarding the applicability of the process to α-methinylketoxime tosylates (ref. 61, pp 84,5) but this purported limitation does not apply to some of the "Neber type" rearrangement reactions (see below). The rearrangement is independent of the oxime stereochemistry and if two different methylene groups are present, the α-aminoketone formed stems from deprotonation at the carbon atom bearing the thermodynamically more acidic hydrogens. The reaction fails for the tosylates of aldoximes which are transformed into nitriles or isonitriles (ref 61, p. 84).

There are three reactions which are mechanistically closely related to the Neber rearrangement and which also produce α-aminoketones. The trimethylimidrazonium salts, N-chloroimines and N,N-dichloroimines related to the oxime tosylate all give the α-aminoketone hydrochlorides on treatment with base and subsequent acidic hydrolysis. The

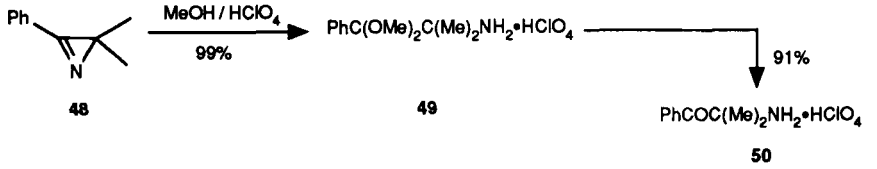


N,N-dichloroimine is first converted into the N-chloroimine on treatment with alkoxide anion (ref. 62 pp. 661,62). Obviously, any ketimino compound which bears a good leaving group on the nitrogen atom is likely to be an appropriate substrate for a "Neber-like" rearrangement.

There is considerable evidence in support of the mechanistic pathway, depicted above, for Neber type transpositions. Both the azirine and the alkoxyaziridine can be isolated upon treatment of the oxime tosylate or the imidrazonium salt with alkoxide anion under appropriate conditions and there is convincing evidence for these intermediates when the N-chloroimine is

the starting material (ref. 62, p. 662). Furthermore, the azirine can be converted into the alkoxyaziridine and either intermediate can be transformed into the α-aminoketone hydrochloride.

It is noteworthy that azirines can be generated in a variety of ways with few restrictions on the degree of substitution.[63] This is of great importance because hydrolysis of such azirines does provide the corresponding aminoketones, thus circumventing the limitation of the classical Neber rearrangement, referred to above. For example, the trisubstituted azirine 48 can be converted into either the α-aminoketal 49 or the α-aminoketone 50 with remarkable efficiency.[64]



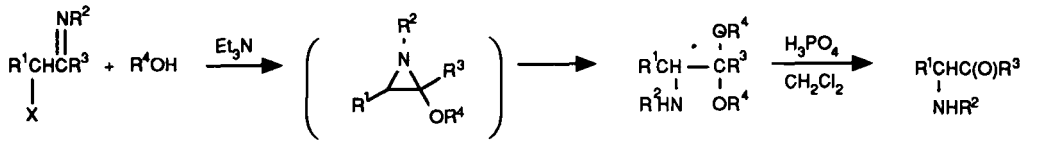
48 49 50

VIII. α-AMINOCARBONYL COMPOUNDS FROM α-HALOIMINES, α,α-DIHALOIMINES, α-HALOIMINIUM SALTS OR β-HALOENAMINES UNDER BASIC CONDITIONS, OR FROM ENAMINES OR ENOL ETHERS AND N-CHLOROAMIDES

A. α-Haloimines

1. α-Alkylaminoketones

The reaction of α-haloketimines with alcohols, in the presence of a tertiary base, gives rise to α-aminoketals which can be hydrolysed to α-alkylaminoketones under acidic conditions.[64] (see Table 10). The α-haloketimines are easily prepared by the titanium tetrachloride mediated condensation of α-haloketones with primary amines.[65]



The α-alkylaminoketal probably arises via an intermediate α-alkoxyaziridine, as in the Neber rearrangement. The formation of the α-aminoketals 53 and 56 upon methoxide[66] or phenol[67] induced cleavage of the chloroaziridine 51 or the allenimine 54 respectively, also clearly belong to the same family of reactions.

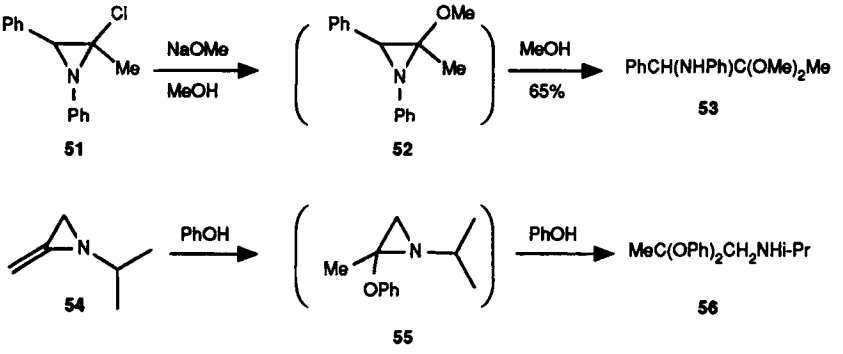
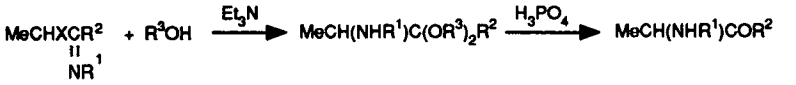


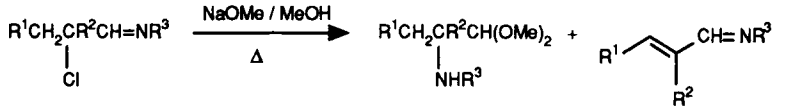
Table 10. Synthesis of α-alkylaminoketals and α-alkylaminoketones from α-haloketimines.



				Yield (%)	
R^1	R^2	R^3	X	aminoketal	aminoketone
i-Pr	Me	Me	Cl	84	65
t-Bu	Me	Me	Cl	81	64
t-Bu	Me	Et	Cl	33	
allyl	Me	Me	?	85	84
i-Pr	Et	Me	Br	53	

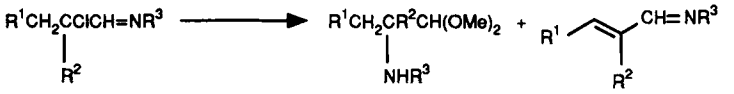
2. α-Alkylaminoaldehydes

α-Chloroisobutyraldimines are converted, by boiling methanolic sodium methoxide (2 equiv.), into nearly equal amounts of an α-alkylaminoisobutyraldehyde dimethyl acetal and an α,β-unsaturated aldimine (Table 11)[68] which are separable by distillation. The formation of



the α-alkylamino acetal is limited to isobutyraldehyde aldimines since the α-chloroimines of 2-methylbutanal and cyclohexane carboxaldehyde give the products of dehydrohalogenation exclusively under these conditions (Table 11). The α-alkylamino acetals of isobutyraldehyde are obtained exclusively (as their hydrochloride salts) when the α-chloroaldimine is heated in methanol, at reflux temperature, for five days (Table 11), but this reaction also is apparently restricted to isobutyraldehyde derivatives.[68]

Table 11. Reaction of α-Chloroaldimines with Methanol.



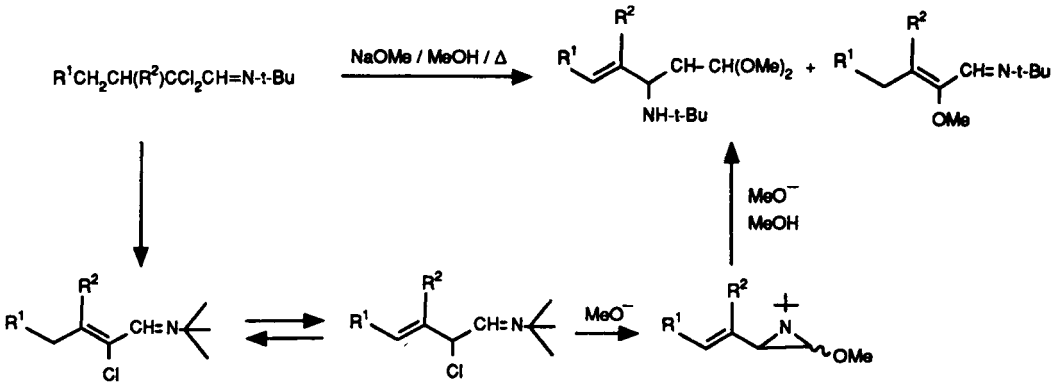
				% Yield	
R^1	R^2	R^3	Conditions	Aminoacetal	Unsat. aldimine
H	Me	t-Bu	MeOH/MeONa	33	40
H	Me	t-Bu	MeOH	70[a]	--
H	Me	c-C_6H_{11}	MeOH/MeONa	51	38
H	Me	c-C_6H_{11}	MeOH	93[a]	--
H	Me	$PhCH_2$	MeOH/MeONa	40	37
Me	Me	t-Bu	MeOH/MeONa	--	87
----$(CH_2)_4$----		t-Bu	MeOH/MeONa	--	98

[a] Isolated as the hydrochloride salt

B. α,α-Dihaloimines

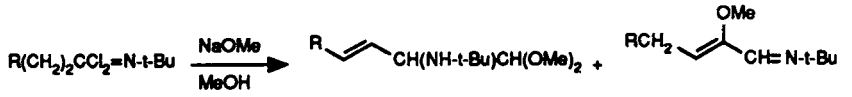
Treatment of α,α-dichloro-N-t-butylaldimines with excess methanolic sodium methoxide, at reflux temperature, leads to mixtures which consist mainly of β,γ-unsaturated α-t-butylaminoaldehyde dimethyl acetals and α,β-unsaturated α-methoxy-t-butylaldimines

(Table 12).[69] This process is of little synthetic use because the products can be difficult to separate and because other α,α-dichloroaldimines, e.g., where R^1,R^2 = H or where $R^2 \neq H$, give rise to much more complex mixtures which may or may not contain the desired α-aminoacetal. The genesis of the α-t-butylamino acetal is also likely to involve the methoxide induced cleavage of an intermediate α-methoxyaziridine which may possibly arise as shown below.



α,α-Dichloroketimines are not converted into α-aminoketals on reaction with alcoholic alkali metal alkoxide solutions.[70]

Table 12. Synthesis of β,γ-unsaturated-α-t-butylaminoaldehyde dimethyl acetals from α,α-dichloro-t-butylaldimines.



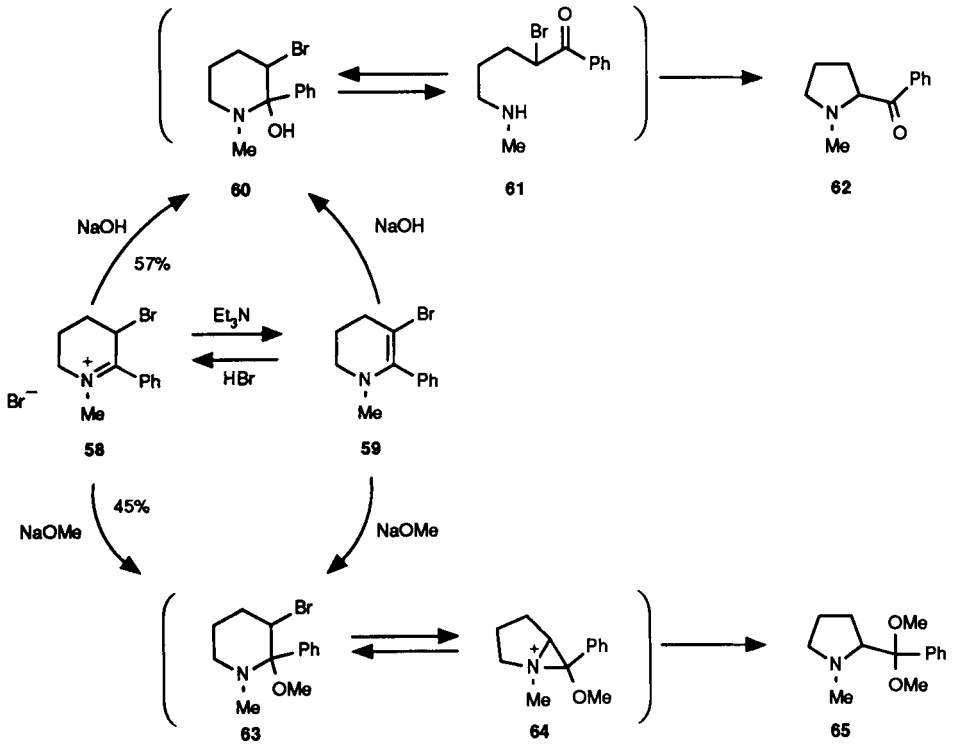
R	% Yields Aminoacetal	Unsat. aldimine
Me	38	58
Et	22	57
n-Pr	48	48

C. α-Haloiminium Salts or β-Haloenamines

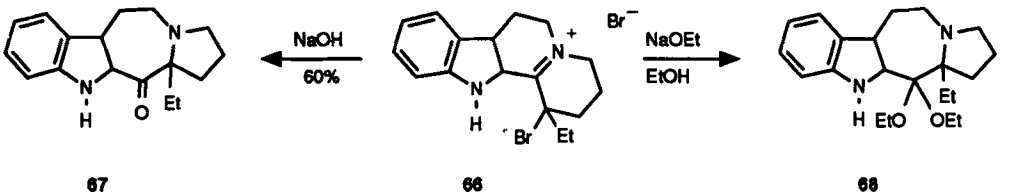
1. α-Aminoketones

Depending on the structure, cyclic α-bromoketiminium salts, or the β-bromoenamines

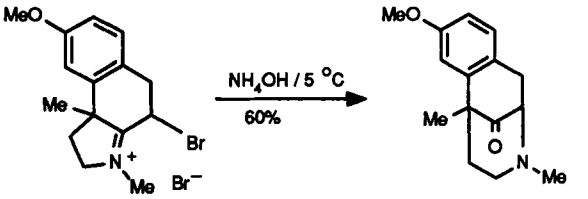
easily obtained therefrom (e.g., deprotonation with triethylamine), are transformed into ring expanded or ring contracted α-aminoketones, or the corresponding α-aminoketals, on reaction with aqueous hydroxide or alcoholic sodium alkoxide solutions.[71-3] Thus, either the 3-bromopiperidinium bromide 58, or the corresponding enamine 59, can be converted into the α-aminoketone 62, or the α-aminoketal 65, upon reaction with aqueous sodium hydroxide or methanolic sodium methoxide respectively.[72] The formation of 62 perhaps proceeds by the intramolecular amination of an intermediate acyclic α-bromoketone 61, whereas the α-aminoketal 65 may stem from the solvolytic ring opening of an α-alkoxyaziridinium species



64. In a similar way, bromoiminium bromide 66 can be converted into the tetracyclic aminoketone 67 or the diethylacetal 68[73], and 69 undergoes a fragmentation-recyclization process[72] to the 6,7-benzomorphan derivative 70.



67 66 68

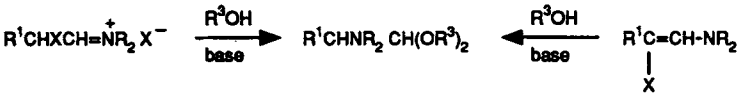


69 70

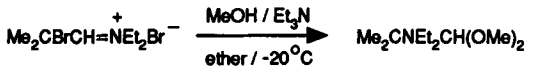
The α-bromoiminium bromides are easily prepared by reaction of the enamine with bromine. It is important to note that α-haloketiminium salts derived from enamines not formed in the intramolecular sense (e.g., enamines of cyclohexanone) do not undergo reactions analogous to those described above on treatment with alcoholic bases.[74]

2. α-Aminoaldehydes

In a manner quite analogous to that described above, the α-haloiminium salts or β-haloenamines derived from aldehydes, are transformed into α-dialkylaminoaldehyde dialkyl acetals in alcoholic solutions containing bases (Table 13).[75,76] The formation of the



α-aminoacetal from the iminium salt does not require the intermediacy of the β-haloenamine since the α-bromoiminium bromide 71, where deprotonation to the enamine is impossible, nevertheless easily gives α-diethylaminoisobutyraldehyde dimethyl acetal (72) on reaction with ethereal methanol containing triethylamine.[76]



71 72

Table 13. Synthesis of α-dialkylaminoaldehyde acetals from β-haloenamines.

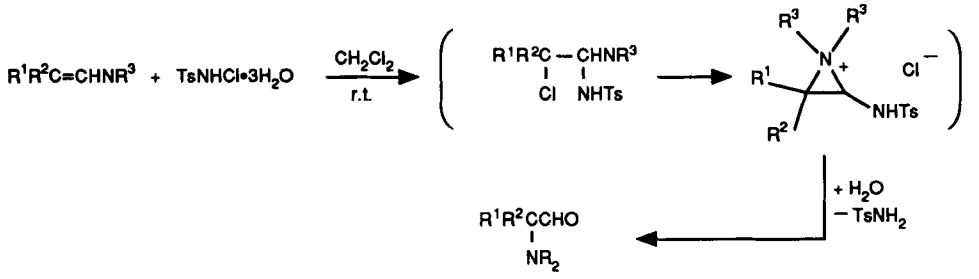
$R^1CX{=}CH\text{-}NR^2R^3 \longrightarrow R^1CHNR^2R^3CH(OR)_2$

R^1	R^2	R^3	X	Alcohol	Base	Yield %	Ref.
Et	Et	Et	Cl	MeOH	MeONa	49	76
Et	Et	Et	Cl	MeOH	Et_3N	60	76
Et	Et	Et	Cl	$HO(CH_2)_2OH$	Et_3N	46	76
t-Bu	----$(CH_2)_5$----		Br	MeOH	MeONa	83	75
t-Bu	----$(CH_2)_5$----		Cl	EtOH	EtONa	50	75
t-Bu	----$(CH_2)_5$-----		Cl	MeOH	Et_3N	55	76

D. From Enamines or Enol Ethers and N-Chloroamides

1. Enamines and Chloramine-T Trihydrate

Enamines derived from α-α-disubstituted aldehydes react with the trihydrate of chloramine-T, at room temperature, to give the corresponding stable α-dialkylaminoaldehyde derivatives (Table 14).[77]



This reaction, which belongs to the same mechanistic family as those discussed above in this section, probably proceeds by aqueous hydrolysis of an intermediate α-tosylaminoaziridinium salt.

Table 14. Synthesis of α-dialkylaminoaldehydes from aldehyde enamines and hydrated chloramine-T.

R^1	R^2	NR^3	% Yield
Me	Me	piperidino	77
Et	Et	pyrrolidino	72
Ph	Me	dimethylamino	83
—— $(CH_2)_5$ ——		piperidino	70

2. Enol Ethers and α-Chloroamides

a. α-Aminoketones

N-Chlorocarbamates and N-chlorocarboxamides undergo a chromous chloride promoted addition to 1-methoxycyclohexene at -78 °C. The adducts which are generated can be converted into α-acylaminocyclohexanone derivatives by hydrolysis with aqueous sulfuric acid or into the corresponding dimethyl ketals by reaction with methanolic sodium methoxide (Table 15).[78] The addition reaction is a radical chain process, catalysed by chromous ion, in which the N-haloamide acts as the transfer agent.[79]

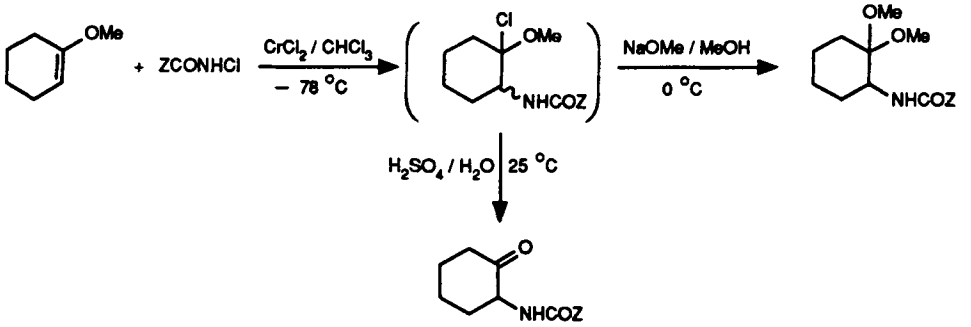
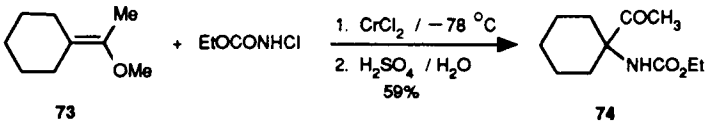


Table 15. Chromous Chloride promoted addition of N-chloroamines to 1-methoxycyclohexene.

Z	Ketal	Ketone
Me		82
EtO		85
$PhCH_2O$	60	
$ClCH_2CH_2O$	74	80
CCl_3CH_2O	75	86

The process is also applicable to acyclic systems as exemplified by the conversion of enol ether 73 to the α-ethoxycarbonylaminoketone 74 in good yield.[78]

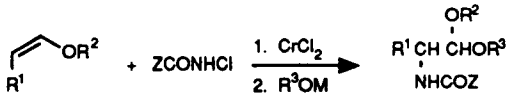


73 74

b. α-Aminoaldehydes

In the presence of chromous chloride, N-haloamides give adducts with cyclic and acyclic enol ethers of aldehydes and the adducts are converted into the corresponding α-acylamino acetals on reaction with alcohols or metal alkoxides (Table 16).[78] The process is not applicable to the enol ethers of β,β-disubstituted aldehydes because the amido radical adds preferentially to the less substituted carbon atom. Application of this methodology to glycals gave adducts which could be converted into acylamino derivatives of various 2-amino sugars.[78]

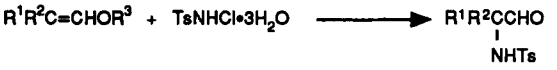
Table 16. Synthesis of α-Acylaminoacetals from Aldehyde Enol Ethers and N-Haloamides.



R^1	R^2	R^3	Z	M	% Yield
---$(CH_2)_3$---		Me	MeO	H	66[a]
---$(CH_2)_3$---		Me	EtO	H	72[a,b]
---$(CH_2)_3$---		Me	$PhCH_2O$	H[c]	77[a,b]
H	Et	Et	$ClCH_2$	Na	78
H	Et	Me	$ClCH_2CH_2O$	Na	74
H	Et	Me	$PhCH_2O$	Na	81

[a] Trans isomer.
[b] Cis isomer, also produced (4%).
[c] Silver carbonate added as base.

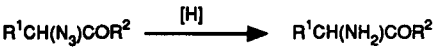
β,β-disubstituted vinyl ethers are reported to react with chloramine-T trihydrate prviding α-tosylaminoaldehydes but no details concerning the scope of this process have been dislcosed.[77] It has been suggested that this reaction is ionic in nature and proceeds in a manner



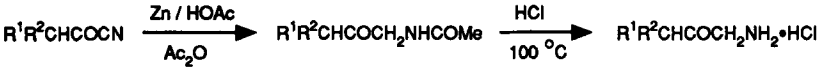
analogous to the corresponding reaction of chloroamine-T with aldehyde enamines [see D. i, this section].

IX. REDUCTION OF KETONES BEARING A NITROGEN CONTAINING α-SUBSTITUENT

The chemoselective reduction of α-azido, α-cyano, α-oximino and α-nitroketones has been reviewed by Meyer (ref. 2, pp 2276-8), but useful modifications of some of these reductive processes have recently been published.



α-Azidoketones are usually converted into α-aminoketones by catalytic reduction[2,80], but stannous chloride has also been used on occasion.[81]



Acyl cyanides are readily reduced with zinc in acetic acid solution provided that a large excess of acetic anhydride is present (Table 17).[82] Aroyl cyanides and α-β-unsaturated acylcyanides give overreduction products under these conditions. Hydrolysis of the acetamido moiety can be accomplished with hot aqueous hydrochloric acid.

Table 17. Reduction of acylcyanides to α-acetamidoketones.

R^1	R^2	% Yield
Me	Me	75
$PhCH_2$	H	71
$CH_2CH{=}CH$	H	74
MeO_2CCH_2	H	83
$MeCO(CH_2)_3$	H	70

$$R^1CCOR^2 \xrightarrow{[H]} R^1CH(NH_2)COR^2$$
$$\underset{NOH}{\overset{\|}{}}$$

α-Oximinoketones are easily accessible and can be reduced under a variety of conditions which include, catalytic hydrogenation in acidic solution or chemical reduction under acidic or basic conditions (ref 2, pp 2276-8).

$$R^1COCH(NO_2)R^2 \xrightarrow[EtOH\text{-}HCl,\ 50\ ^\circ C]{H_2 / Pt\text{-}C\text{-}S} R^1COCH(NH_2)R^2 \cdot HCl$$

The catalytic reduction of α-nitroketones, over a 5% platinum on carbon catalyst poisoned with sulfur, at atmospheric pressure in alcoholic hydrochloric acid, is a particularly efficacious route to α-aminoketones (Table 18).[83] Such reductions can also be achieved with zinc chloride in acidic solution (ref 2, p 2277).

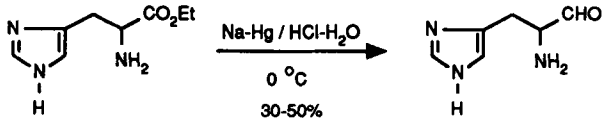
Table 18. Synthesis of α-aminoketone hydrochlorides by catalytic reduction of α-nitroketones.

R^1	R^2	%Yield
Et	H	84
Me_2CHCH_2	H	66
Ph	H	98
4-ClC_6H_4	H	85
2-naphthyl	H	85
Me	Me	85
— $(CH_2)_4$ —		61

X. SYNTHESIS OF α-AMINOALDEHYDES BY SELECTIVE REDUCTION OF α-AMINO ACID DERIVATIVES

The chemoselective reduction of α-amino acid derivatives to the corresponding aminoaldehydes was first reported by Neuberg[84] and Fischer[85] in 1908 who demonstrated that

α-amino acid ethyl esters, as the hydrochloride salts, were reduced by sodium amalgam in aqueous hydrochloric acid medium, to give solutions from which derivatives of α-aminoaldehydes could be obtained in low yields. Although α-aminoaldehydes have been isolated, on occasion, from such reaction mixtures, e.g., histidinal (76) from histidine ethyl



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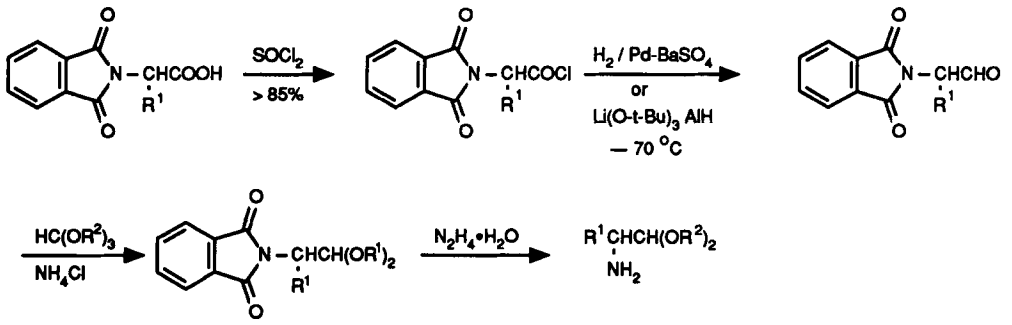
ester (75),[86] this process is no longer used,[87] at least in part because of the difficulty associated with the isolation of a highly reactive, water soluble entity from aqueous medium. These problems are now largely obviated by reduction of various N-protected amino acid derivatives in non-aqueous media.

A. Reduction of N-Phthaloyl Acid Chlorides



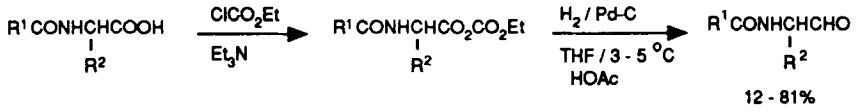
The reduction of N-phthaloyl protected α-amino acid chlorides under Rosenmund condtions,[88] first described by Radde[89] and since used by various investigators[90-93] is ample in scope and proceeds without racemization (Table 19). The aldehydes thus produced can be successively converted into the corresponding acetals with trialkyl orthoformates and thence into the free α-aminoaldehyde acetals with hydrazine hydrate, both transformations occurring without loss of optical purity. The phthaloyl aminoaldehydes can also be generated, with comparable efficiency, by reduction of the acid chlorides with lithium tri-t-butoxyaluminum hydride at – 70 °C (Table 19).[91]

Table 19. Synthesis of N-phthaloyl α-aminoaldehydes, N-phthaloyl α-aminoaldehyde acetals and α-aminoaldehyde acetals from N-phthaloyl amino acid chlorides.[a]

R^1	R^2	Redn. method[b]	%Yields Aldehyde	N-Phth. acetal	Amino acetal	Ref.
Me	Me,Et	A, B	65-67	76	58[c]	90, 91
Me	----	A	60[d]			93
Me_2CH	Me	B	60	46	48	91
Me_2CHCH_2	----	A	85			92
$PhCH_2$	Me	B	50	65	61	91
$PhCH_2SCH_2$	Et	A	67	97		91
4-$MeOC_6H_4CH_2$	Et	A	100	81		91

[a] Derived from the natural (S) amino acids unless indicated otherwise.
[b] A = H_2/Pd-$BaSO_4$; B = $Li(O\text{-}t\text{-}Bu)_3AlH$.
[c] Yield of dimethyl acetal.
[d] Derived from (R)-alanine.

B. Catalytic Reduction of Mixed Carbonic-Carboxylic Acid Anhydrides of N-Acylated α-Amino Acids



The mixed anhydrides prepared from ethyl chloroformate and N-acylated α-amino acids are catalytically reduced, over palladium on charcoal, to the corresponding aldehydes.[94] In several instances the process is of low efficiency (e.g., R^1 = Me, R^2 = Ph; 12%), it fails for the sulfur containing α-amino acid derivative N-acetyl-L-valine, and in all cases substantial racemization of the products is observed.

C. Hydride Reduction of α-Amino Acid Esters

Both lithium aluminum hydride and diisobutylaluminum hydride in ether solution, effect the reduction of α-dialkylamino acid esters to the corresponding aldehydes at low temperature (– 72 °C).[95,96] The latter reagent is, however, preferred because it provides products of superior purity in higher yields (Table 20).

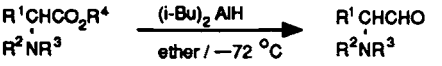
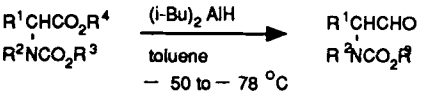


Table 20. Synthesis of α-dialkylamino aldehydes by hydride reduction of α-dialkylamino acid esters.

R^1	R^2	R^3	R^4	Hydride[a] reagent	% Yield	Ref.
Ph	----$(CH_2)_5$----		Me	LAH	35	95
Ph	Me	Me	Me	DIBAL	75	95
Et	----$(CH_2)_5$----		Me	DIBAL	64	95
H	----$(CH_2)_5$----		Et	LAH	40	95
H	----$(CH_2)_5$----		Et	DIBAL	63	95
------CH_2------		t-Bu	Me	DIBAL	73	95
----$(CH_2)_2$-----		t-Bu	Me	DIBAL	89	95
----$(CH_2)_3$-----		Me	Me	DIBAL	47	95
-----(CH_2)-----		Me	Me	DIBAL	64	95
-$CH_2NMe(CH_2)_2$-		Me	Me	DIBAL	65	96
--$CH_2NEt(CH_2)_2$--		Et	Me	DIBAL	88	96

[a]LAH = $LiAlH_4$; DIBAL = $(i\text{-}Bu)_2AlH$

N-Alkoxycarbonylated α-amino acid esters also undergo chemoselective low temperature reduction to the N-protected α-aminoaldehyde derivatives with diisobutylaluminum hydride.[97-100,106] This process has considerable generality (Table 21) and



proceeds without loss of optical purity if column chromatographic purification of the products on silica gel is avoided.

Table 21. Synthesis of N-Protected α-Aminoaldehydes by DIBAL Reduction of N-Protected α-Amino Acid Esters.[a]

R^1	R^2	R^3	R^4	% Yield	ref.
Me	H	$PhCH_2$	Me	50	97
Me_2CHCH_2	H	$PhCH_2$	Et	48	97
Me_2CHCH_2	H	t-Bu	Me	85	99a
EtCHMe	H	$PhCH_2$	Me	59	97
$PhCH_2$	H	$PhCH_2$	Et	55	97
$PhCH_2$	H	t-Bu	Me	97	99b
$MeSCH_2$	H	$PhCH_2$	Me	61	97
$PhCH_2SCH_2$	H	$PhCH_2$	Et	68	97
$PhOCO(CH_2)_4$	H	$PhCH_2$	Me	53	97
--------$(CH_2)_3$--------		$PhCH_2$	Me	64	97

[a] Derived from natural amino acids.

D. Hydride Reduction of N-Protected α-Amino Acid Amides

Over 25 years ago, Ried and Pfaender[101] demonstrated that the 3,5-dimethylpyrazolides of N-tosyl α-amino acids were reduced by ethereal lithium aluminum hydride, at room temperature, to give mixtures from which the aldehydes could be isolated as the Wanzlick[102] derivatives, upon reaction with 1,2-dianilinoethane (see Table 22). Recovery of the aldehyde from the aminal could be achieved in some cases by hydrolysis with dilute aqueous acid but in others the hydrolysis failed completely (Table 22). The amino aminals were readily generated by reduction of the N-tosyl compounds with sodium in liquid ammonia (Table 22).

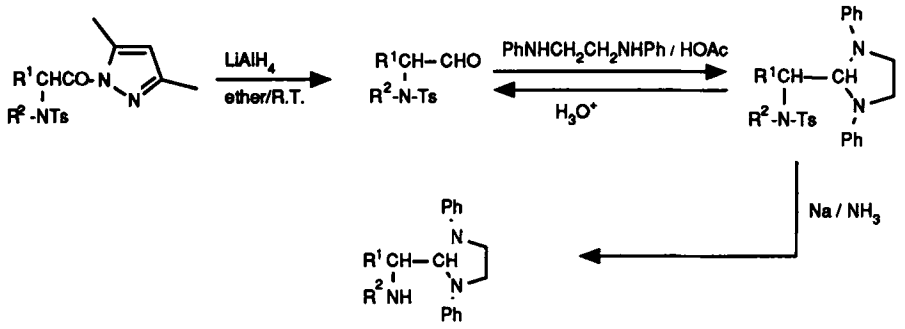
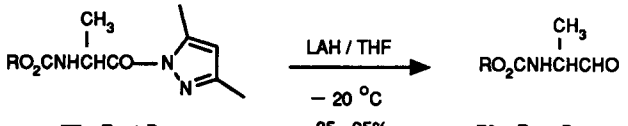


Table 22. Synthesis of α-Aminoaldehyde Derivatives from 3,5-Dimethylpyrazolides of N-Tosyl α-Amino Acids.[a]

R^1	R^2	% Yields Aldehyde	Tosylaminal	Aminoaminal
Me	H	80	29	50
i-Pr	H		39	
$PhCH_2$		10	93	
-----$(CH_2)_3$-----		0	73	69

[a] Derived from natural (L) - amino acids except for R^1 = Me, R^2 = H (±).

The lithium aluminum hydride reduction of the 2,5-dimethylpyrazolides of N-alkoxycarbonyl α-amino acids would appear to be of greater synthetic significance than the reduction of the N-tosyl congeners. Thus the BOC and Z derivatives of D-alanine (77a and 77b) were reduced to the corresponding aldehydes 78a and 78b in excellent yields.[93] These compounds were utilized for the synthesis of (2S, 3S, 4R)-4-amino-3-hydroxy-2--methylp anoic acid, an amino acid constituent of the antitumor antibiotic bleomycin.



77a, R = t-Bu
77b, R - $PhCH_2$

78a, R = t-Bu
78b, R = $PhCH_2$

N-Alkoxycarbony α-amino acid imidazolides are also chemoselectively reduced to the corresponding aldehydes with either lithium aluminum hydride[103,104] or diisobutylaluminum hydride[105] (Table 23). The aldehydes thus produced had undergone partial racemization, presumably upon column chromatographic purification (silica gel).[105]

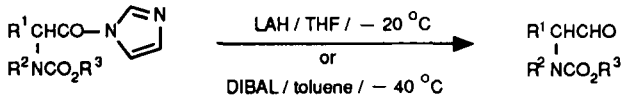
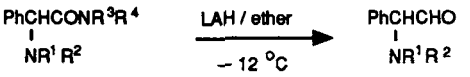


Table 23. Synthesis of α-Aminoaldehyde Derivatives by Reduction of N-Alkoxycarbonyl α-Amino Acid Imidazolides.

R^1	R^2	R^3	Reagent	% Yield	Ref.
$HN{=}C(NHNO_2)NH(CH_2)_3$	H	$PhCH_2$	LAH	70	103
$HN{=}C(NHNO_2)NH(CH_2)_3$	H	$PhCH_2$	DIBAL	63	105
$HN{=}C(NHNO_2)NH(CH_2)_3$	H	t-Bu	LAH	51	103
$HN{=}C(NHNO_2)NH(CH_2)_3$	H	t-Bu	DIBAL	57	105
$PhCH_2$	H	$PhCH_2$	LAH	50	104
$PhCH_2$	H	$PhCH_2$	DIBAL	70	105
i-Bu	H	$PhCH_2$	DIBAL	63	105
----------$(CH_2)_3$----------		$PhCH_2$	DIBAL	52	105

The N,N-dialkylamides of various dialkylamino derivatives of phenyl glycine are reduced to the corresponding aldehydes with ethereal lithium aluminum hydride at – 12 °C.[95] This process does not, however, have any advantage over the use of diisobutylaluminum hydride on the α-dialkylamino acid esters (sec. 10, iii).



E. Lithium Aluminum Hydride Reduction of O,N-Dialkylhydroxamates of N-Protected α-Amino Acids

The reaction of O,N-dialkylhydroxamates with lithium aluminum hydride constitutes a particularly efficacious synthesis of aldehydes which owes its success to the formation of a highly favored chelated intermediate, further reduction of which does not take place.[107] Extension of this process to the analogous hydroxamate derivatives of N-protected α-amino acids gave the expected N-protected α-aminoaldehydes in excellent yields (Table 24).[108,112] The chemical and optical purity of the products was such that chromatographic purification thereof was unnecessary.

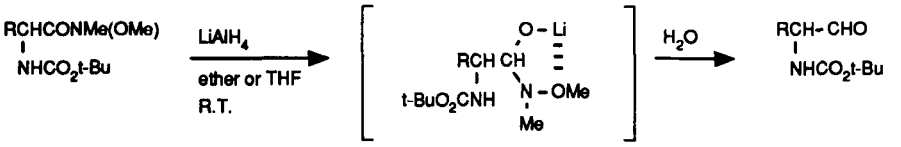


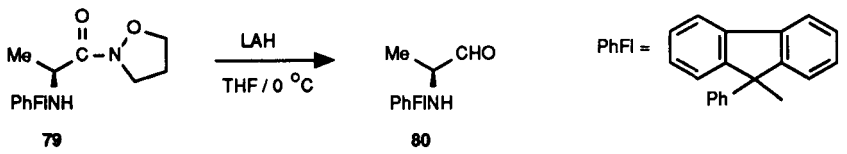
Table 24. Synthesis of N-t-BOC-α-Aminoaldehydes from N-t-BOC-α-Amino O,N-Dimethylhydroxamates.[a]

R	% Yield
Me	88
Me_2CHCH_2	96
EtCHMe	90
i-Pr	93
$PhCH_2$	86
$PhCH_2OCHMe$	95

[a] Derived from amino acids of the natural (L) series. All data taken from ref. 108.

Lubell and Rapoport[109] have recently applied an analogous process to the synthesis of N-[9-phenylfluorenyl)]-L-alaninal (80), an α-aminoaldehyde which is extraordinarily resistant

to racemization by silica gel or non-nucleophilic bases. This resistance to α-deprotonation stems from the steric screening properties of the 9-phenylfluorenyl moiety, cleavage of which can be effected by acid or by hydrogenolysis.

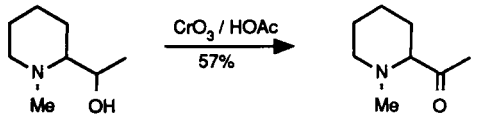


79 80

XI. OXIDATION OF β-AMINO ALCOHOLS

I. α-Aminoketones

The oxidation of β-amino substituted secondary alcohols is for practical purposes, limited to those compounds in which the amino moiety is tertiary. Primary and secondary β-amino congeners of secondary alcohols usually require N-protection (most frequently acylation) for the oxidation to be successful. The most often used oxidizing agent is some form of Cr^{VI} [e.g., the oxidation of 81 to 1-methyl-2-acetylpiperidine (82)], although on occasion, potassium permanganate, palladium catalysed aereal oxidation, catalytic dehydration and Oppenauer type oxidations have all been employed (ref. 2, pp 2278,81).



81 82

Rapoport and Lubell[148] have demonstrated that various L-alanine derived β-amino alcohols, in which the amino moiety bears the sterically demanding 9-phenyl-fluorenyl group, are oxidized by the N-chlorosuccinimide-dimethyl sulfide reagent,[149] without racemization and without the need for any other form of N-protection (Table 25). The N-phenylfluorenyl group, in addition to being easily removable[109], imparts high stability (no dimerization) to the α-aminoketones.

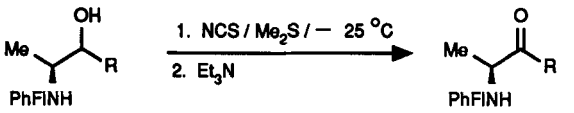
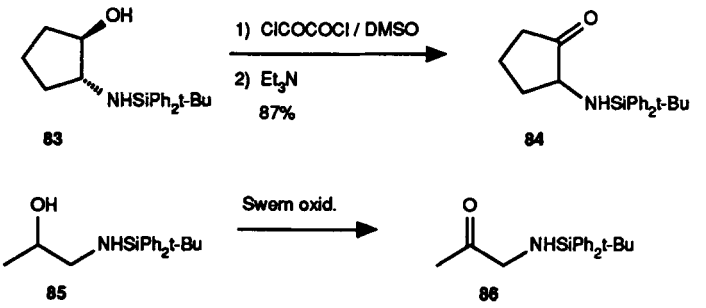


Table 25. Synthesis of α-(9-phenylfluorenyl)aminoketones by Oxidation of the Alcohols with the Corey-Kim Reagent.[149]

R	% Yield
n-Bu	80
$PhCH_2$	67
(R)-$PhCHCH_3$	80
CH_2=C-Ph	84

Overman, et.al.[110] have recently reported that the N-t-butyldiphenylsilylated β-amino secondary alcohol 83 is readily oxidized to the N-silylated α-aminoketone 84 under Swern conditions.[111] This aminoketone is remarkably stable at ambient temperature showing no tendency to dimerize. The aminoacetone derivative 86 is prepared in a similar fashion. The marked stability of these compounds undoubtedly stems from the steric and electronic (electron withdrawing) properties of the t-butyldiphenylsilyl substituent. These interesting α-aminoketone derivatives merit further study.



B. α-Aminoaldehydes

A much utilized route to α-aminoaldehyde derivatives consists of a two step process involving selective reduction of an α-amino acid ester (usually N-protected) followed by

oxidation of the primary alcohol thus produced. The reduction has been effected with lithium aluminum hydride[113-6], sodium borohydride,[114,117,118,135] lithium borohydride[119], borane-dimethyl sulfide[120,121], or borane-THF,[115,120,122,123] while the oxidation has been conducted using Collins[125] reagent,[112,124] pyridinium dichromate[126] in dichloromethane,[116,122] Pfitzner-Moffat conditions[127] (RC=N=CR/DMSO/H^+),[119,128,129] the Parikh-Doering reagent[130] (Py:SO_3/DMSO/Et_3N)[118,131] and Swern[111] oxidation (DMSO/$COCl_2$/R_3N).[124,132] In general the reduction step proceeds without racemization[121] and the oxidation processes are chemically efficient (Table 26) and give α-aminoaldehydes of high optical purity under appropriate workup conditions (avoidance of column chromatographic purification).

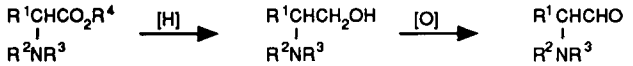
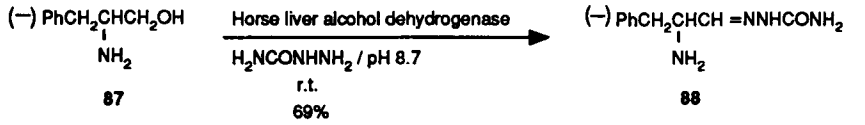


Table 26. Synthesis of N-Protected α-Aminoaldehydes by Oxidation of the Corresponding Primary Alcohols.[a]

R^1	R^2	R^3	Oxid. method	% Yield	Ref.
Me	H	BOC[b]	Parikh-Doering	66	118a
Me	H	BOC	pyridinium dichromate	75	122
$PhCH_2$	H	$COCF_3$	Pfitzner-Moffat	69	128a
$PhCH_2$	H	Bz	Parikh-Doering	85	118a
$PhCH_2$	H	BOC	pyridinium dichromate	80	122
$PhCH_2$	H	trityl	Swern	>67	124
$MeSCH_2CH_2$	H	BOC	Parikh-Doering	90	118a
i-$PrCH_2$	H	BOC	Parikh-Doering	86	118a
i-$PrCH_2$	H	BOC	Collins	67	123
i-Pr	H	BOC	Parikh-Doering	86	118a
i-Pr	H	BOC	pyridinium dichromate	95	122
------$(CH_2)_3$------		Bz	Parikh-Doering	96	118a
-----CH_2CO------		t-BDMS	Swern	100	132

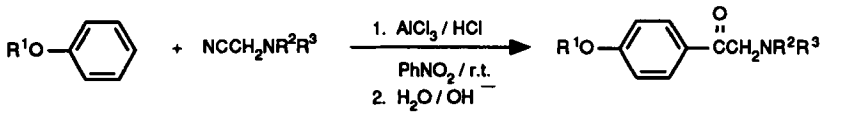
[a] Derived from the natural amino acids.
[b] BOC = t-butoxycarbonyl, Bz = benzyloxycarbonyl, trityl = triphenyl methyl; t-BDMS = t-butyldimethylsilyl

α-Aminoalcohols with nonpolar side chains serve as substrates for horse liver alcohol dehydrogenase and are converted into α-aminoaldehydes.[133] The oxidation proceeds under very mild conditions, does not require amino group protection, but the aldehyde must be trapped as the semicarbazone. L-Phenylalaninal semicarbazone (88) was prepared on close to a gram scale by this method.



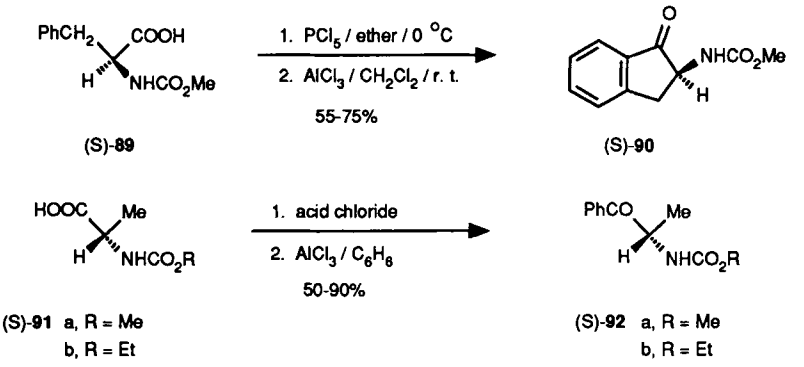
XII. ACYLATION OF AROMATIC HYDROCARBONS WITH α-AMINO ACID DERIVATIVES

The generation of α-aminoketone derivatives from aromatic hydrocarbons has been accomplished by acylation with α-amino acid chlorides as the hydrochloride salts, N-carboxy anhydrides of α-amino acids, and α-phthalimido acid chlorides under Friedel-Crafts conditions. In addition, α-aminoacetonitriles condense with phenol or anisole, in the presence of aluminum chloride and hydrogen chloride, to give p-substituted α-aminoketone derivatives (ref. 2, pp. 2281,82). This reaction (Houben-Hoesch reaction) is successful with primary, secondary, and tertiary amino acetonitriles but homologous acetonitriles failed to give the desired products.[134]



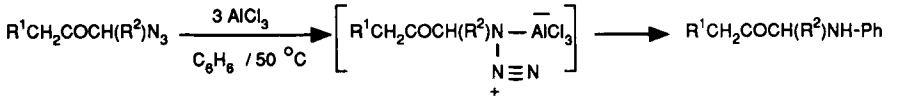
The acid chloride of N-methoxycarbonyl (S)-phenylalanine underwent an intramolecular Friedel-Crafts acylation, at room temperature, to give the indanone derivative 90 without appreciable racemization (98% ee).[135] Similary, the acylation of benzene with the acid chlorides of (S)-alkoxycarbonylalanines 91 gave the acyclic α-aminoketone derivatives with excellent retention of optical activity (92-94% ee for 92a[135], >99% ee for 92b[150]). Thus, both the intra- and intermolecular versions of this acylation provide α-amino arylketones with

high optical purity and in synthetically useful yields. Aryl methyl ethers are not, however, acylated under these conditions because of catalyst complexation with the ethereal oxygen atom.[150]



XIII. ALUMINUM CHLORIDE INDUCED AMINATION OF BENZENE WITH α-AZIDOKETONES

Cyclic and acyclic α-azidoketones react with benzene, in the presence of aluminum chloride, to give α-anilinoketones in modest yields.[136] The reaction presumably proceeds via the aluminum chloride-azidoketone complex, which functions as a preformed nitrenium ion, and which reacts with benzene in the electrophilic sense with loss of nitrogen.



XIV. REACTION OF ETHOXYCARBONYLNITRENE WITH KETONES OR KETONE DERIVATIVES

Thermolysis of ethyl azidoformate, in dichloromethane solution containing excess acetone, gave the aminoacetone derivative 93, a triplet ethoxycarbonylnitrene derived product.[136] The analogous reaction with cyclohexanone produced the anticipated

α-insertion product in only 18% yield, but if ethyl azidoformate was heated (110 °C) in a tenfold excess of the trimethylsilyl enol ether of cyclohexanone, this compound was formed much more efficiently (Table 27). This reaction of enol trimethylsilyl ethers appears to be general and may proceed by rearrangement of an intermediate silyloxyaziridine.[137]

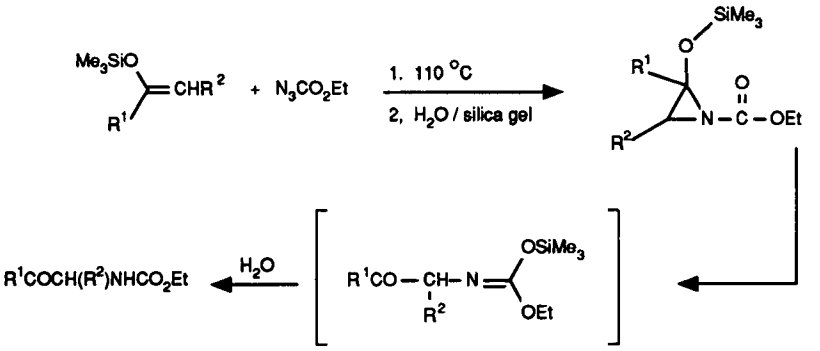
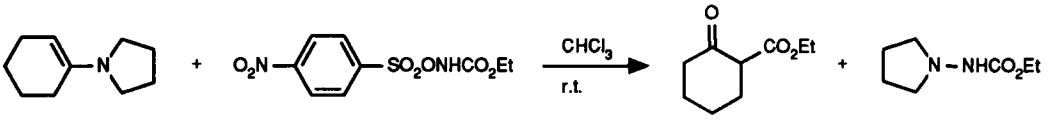


Table 27. Synthesis of α-Ethoxycarbonylaminoketones from Ethyl Azidoformate and Trimethylsilylenol Ethers.

R^1	R^2	% Yield
Me_3C	H	65
Ph	H	35
n-Pr	Et	56
----------$(CH_2)_3$----------		40
----------$(CH_2)_4$----------		49

A reaction related to those described above takes place between the pyrrolidine examine of cyclohexanone and the ethoxycarbonylnitrene precursor 94. The α-amino-cyclohexanone derivative 95 and the hydrazino compound 96 were formed in equal amounts.[138]

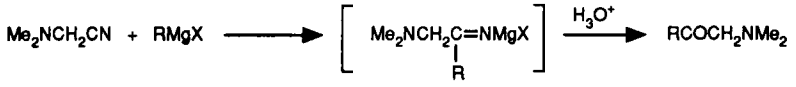


94 95 96

XV. REACTION OF α-AMINONITRILES, N-PROTECTED AMINO ACIDS, AND N-PROTECTED AMINO ACID DERIVATIVES WITH ORGANOMETALLIC REAGENTS

A. α-Aminonitriles

The addition of Grignard reagents to α-aminonitriles is limited to the tertiary amino compounds (ref. 2, pp 2283-5).[139] The addition product is hydrolysed to the α-aminoketone under mildly acidic conditions.



With homologous dialkylaminoacetonitriles, Grignard reagents give a mixture of the desired compound and the tertiary amine formally derived from the displacement of cyanide. This undesired product can be largely eliminated by the use of the much more nucleophilic alkyllithium reagents.

B. N-protected α-amino acids

Rapoport, et.al.[148,150-152] have established that the known conversion of carboxylic acids into ketones with alkyllithium[153] or alkyl Grignard[154] reagents, when appropriately modified, is an excellent source of a wide variety of optically pure α-aminoketone derivatives. Thus, reaction of an N-protected (acetyl, benzoyl, ethoxycarbonyl, benzenesulfonyl) α-amino acid with three equivalents of an alkyllithium reagent produces the α-aminoketone, usually in very good yield (Table 28). The presence of an acidic hydrogen on the amino group is essential and its removal in the second step of the reaction probably is associated with the preservation of the optical integrity of both the starting material and the product since racemization would entail the generation of a dianion on contiguous atoms. The analogous reaction with Grignard reagents generates the expected α-aminoketone contaminated with substantial amounts of the tertiary alcohol.[151] This problem is easily avoided by first forming

the lithium carboxylate and then reacting this species with two equivalents of the Grignard reagent. This process is of broad scope (Table 28), indeed, it is even successful for the synthesis of vinylketones, whereas the reaction with vinyllithium fails.

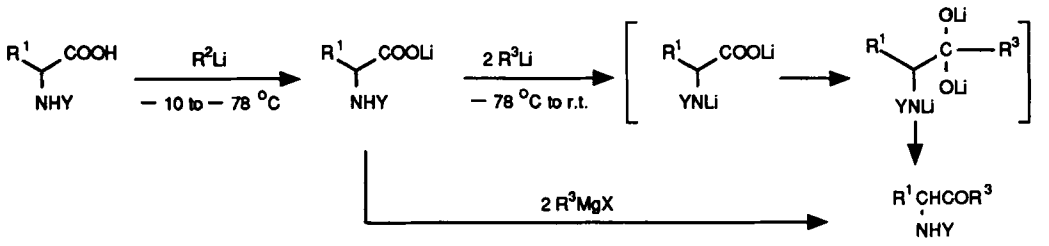


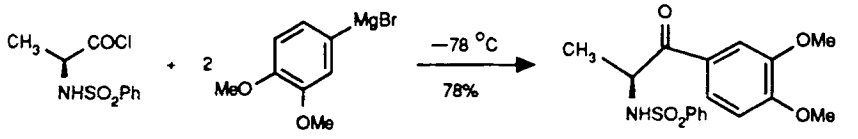
Table 28. Synthesis of α-Aminoketone Derivatives from N-Protected α-Amino Acids[a] and Alkyllithium or Alkyl Grignard Reagents.

R^1	Y	R^2Li	R^3M	% Yield	Ref.
Me	CO_2Et	Ph	PhLi	85-90	150
Me	SO_2Ph	Ph	PhLi	94	150
Me	SO_2Ph	n-Bu	n-BuLi	54	148
Me	CO_2Et	n-Bu	CH_2=$CHCH_2MgBr$	74	151
Me	COMe	n-Bu	CH_2=$CHCH_2MgBr$	40	151
Me	COPh	n-Bu	CH_2=$CHCH_2MgBr$	87	151
i-Pr	SO_2Ph	n-Bu	CH_2=$CHCH_2MgBr$	62	151
$MeSCH_2CH_2$	SO_2Ph	n-Bu	n-BuLi	54	151
$MeSCH_2CH_2$	SO_2Ph	n-Bu	CH_2=CHMgBr	35	151
$HOCH_2$[b]	SO_2Ph	n-Bu	CH_2=CHMgBr	48	151
$HOCH_2$[b]	SO_2Ph	n-Bu	n-PrMgBr	78	152
$HOCH_2$[b]	SO_2Ph	Me	MeLi	60	152
$HOCH_2$[b]	SO_2Ph	3,4-$(MeO)_2C_6H_3$	3,4$(OMe)_2C_6H_3$	83	152
$PhCH_{20}C_6H_4CH_2$	CO_2Et	n-Bu	CH_2=$CHCH_2MgBr$	71	151

[a] Derived from natural amino acids.
[b] Inital addition of 2 R^2Li.

C. N-Protected α-amino acid chlorides

The acid chlorides of N-protected (ethoxycarbonyl, benzenesulfonyl) alanine derivatives (e.g., 97) reacted, at low temperature, with two equivalents of an aryl Grignard reagent to give the optically pure ketone (e.g., 98).[150] The presence of an acidic NH is required for the success of this reaction since, in the absence thereof, the tertiary carbinol is obtained.



D. N-Protected α-amino acid thiopyridyl esters

The N-phthaloyl or N-trityl derivatives of α-amino acid 2-thiopyridyl esters react with Grignard reagents to give the corresponding protected α-aminoketones in good yields [140-143] (Table 29). Diaddition of the Grignard reagent does not occur because the mono-adduct is stabilized by chelation with the pyridine nitrogen atom.

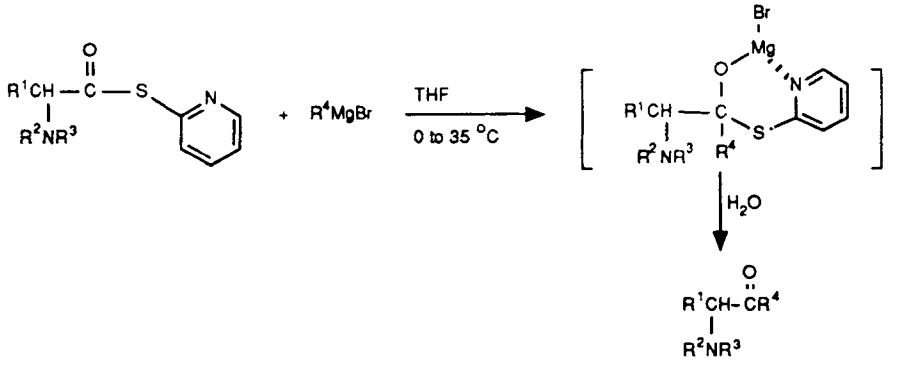
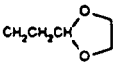
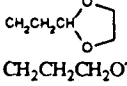
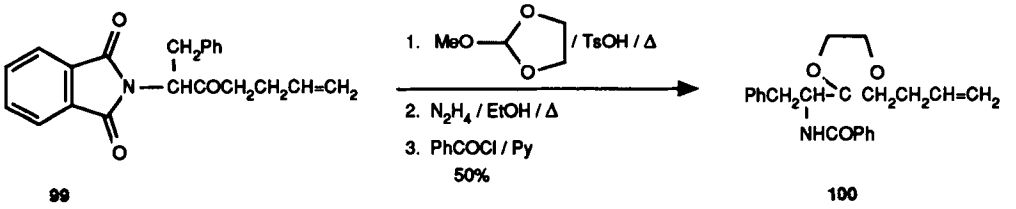


Table 29. Synthesis of N-Protected α-Aminoketones from N-Protected α-Aminoacid 2-Thiopyridyl Esters[a] and Grignard Reagents.

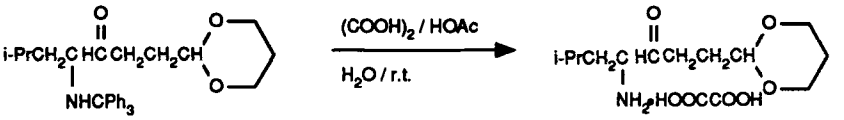
R^1	R^2	R^3	R^4	% Yield	Ref.
$PhCH_2$	-----Phthaloyl-----			35	140
$PhCH_2$	-----Phthaloyl-----		CH_2=$CHCH_2CH_2$	53	141
$PhCH_2$	-----Phthaloyl-----		CH_2=$CHCH(Me)CH_2$	49	141
i-$PrCH_2$	H	trityl	Me	78	142
i-$PrCH_2$	H	trityl		95	142
i-$PrCH_2$	H	trityl	$CH_2CH_2CH_2OTHP$	63	142
-----$(CH_2)_3$-----		trityl	Me	82	142

[a] Derived from natural amino acids.

The above α-aminoketone derivatives can be transformed into various synthetically useful entities. For example the phthalimido compounds 99, upon sequential ketalization, dephthaloylation and benzoylation, gave the α-aminoketal derivative 100 in acceptable overall yield.[141] Also detritylation of 101 was readily accomplished with oxalic acid in aqueous acetic acid at room temperature, without removal of the acetal moiety.[142]



99 100



101 102

E. Reaction of organometallic reagents with N-protected O,N-dialkyl α-amino acid hydroxamates

Grignard and alkyllithium reagents, like lithium aluminum hydride (section 10,v), undergo monoaddition to the carbonyl group of O,N-dimethyl hydroxamates.[107] Application of this process to N-protected O,N-dimethyl α-amino acid hydroxamates of (S)-leucine gave various multifunctionalized ketones in good yields, with no loss in optical purity (Table 30).[143] The successful utilization of this process for the synthesis of acetylenic α-aminoketone derivatives from lithium acetylides is an impressive demonstration of its generality (Table 30).[155]

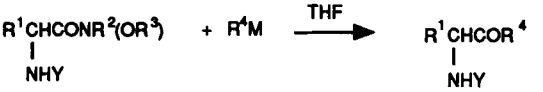


Table 30. Synthesis of α-Aminoketone Derivatives by Addition of Organometallic Reagents to N-Protected O,N-Dialkyl α-Amino Acid Hydroxamates.[a]

R^1	Y	R^2	R^3	R^4M	% Yield	Ref.
Me	CO_2Et	Me	Me	n-BuC≡C-Li	84	155
Me	CO_2Et	-----$(CH_2)_3$-----		n-BuC≡C-Li	88	155
Me	CO_2Et	-----$(CH_2)_4$-----		n-BuC≡C-Li	74	155
Me	CO_2Et	-----$(CH_2)_3$-----		HC≡C-Li	80	155
CH_3	CO_2t-Bu	-----$(CH_2)_3$-----		HC≡C-Li	84	155
CH_3	SO_2Ph	-----$(CH_2)_3$-----		HC≡C-Li	73	155
CH_3	SO_2Ph	-----$(CH_2)_3$-----		n-BuC≡C-Li	80	155
i-Pr	CO_2t-Bu	Me	Me	i-$PrCH_2CH_2MgBr$	95	143
i-Pr	CO_2t-Bu	Me	Me	i-$PrOCH_2MgCl$	90	143
i-Pr	CO_2CH_2Ph	Me	Me	t-$BuOCOCH_2MgCl$	60	143
i-Pr	CO_2t-Bu	Me	Me	$(MeO)_2POCH_2Li$	97	143
Ph	CO_2Et	-----$(CH_2)_3$-----		HC≡C-Li	88	155
$MeSCH_2$	CO_2Et	-----$(CH_2)_3$-----		HC≡C-Li	87	155

[a] Derived from natural amino acids.

XVI. REACTION OF α-AMINONITRILE ANIONS WITH ALDEHYDES

Metalated α-aminonitriles condense, at low temperature, with aldehydes to give thermolabile adducts which, upon distillation, lose hydrogen cyanide with the formation of α-dialkylaminoketones (Table 31).[144]

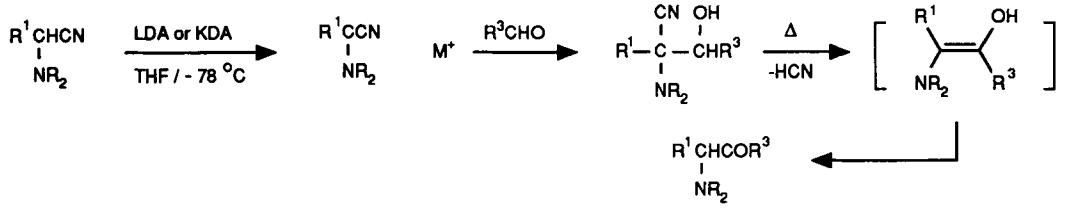
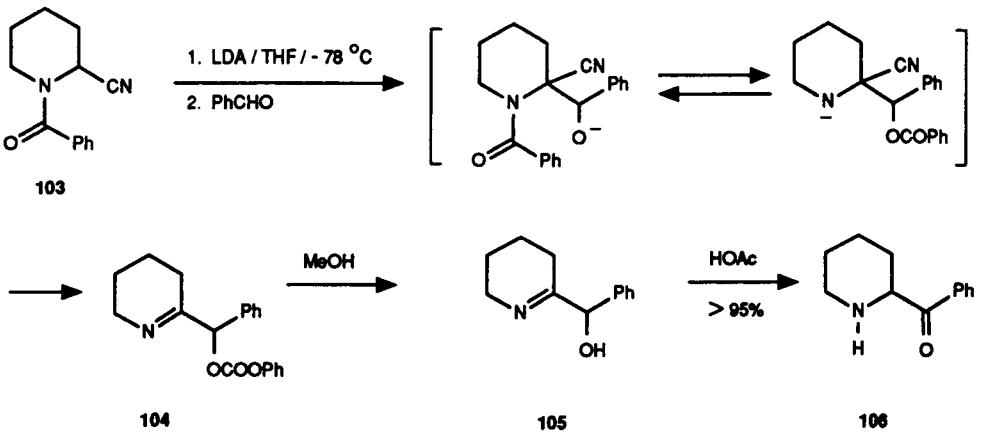


Table 31. Synthesis of α-Dialkylaminoketones from α-Aminonitrile Anions and Aldehydes.

R^1	R^2	R^3	% Yield
H	i-Pr	n-Bu	44
Me	Me	c-Hexyl	72
Me	Et	t-PhCH=CH	79
Et	Et	Et	55
Et	Me	n-Bu	67
n-Pr	Me	n-Pr	60

In a related reaction sequence, sequential lithiation, condensation with benzaldehyde and protonolysis with methanol, of 1-benzoyl-2-cyanopiperidine (103), generated the α-hydroxyimine 105 which, in the presence of acetic acid, gave the Voigt-Amadori rearrangement product 106 in high yield.[145]



Inasmuch as the above condensation can also be effected with acyclic α-benzamidonitriles, this promises to be a route of considerable utility to α-alkylaminoketones.

XVII. FROM NITROSOAMINE ANIONS AND ACYL CYANIDES

The dipole stabilized anions generated by low temperature lithiation of nitrosamines, react with esters[146] or acyl cyanides[147] to provide α-nitrosaminoketones (Table 32), which should, in principle, be denitrosated with ease[146] to the corresponding α-alkylaminoketones.

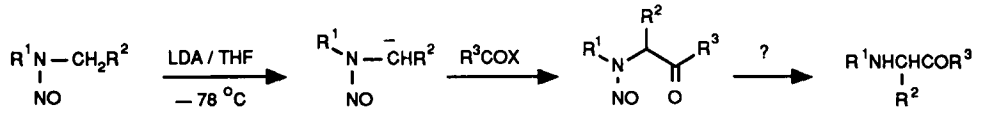


Table 32. Synthesis of α-Nitrosaminoketones by Acylation of α-Nitrosamino Anions.

R^1	R^2	R^3	X	% Yield	Ref.
Me	H	Me	OMe[a]	50	146
Me	H	Me	CN	22	147
Me	H	Ph	OMe	28	146
Me	H	Ph	CN	54	147
t-Bu	H	Me	CN	28	147
t-Bu	H	Ph	CN	69	147
t-Bu	H	Ph	OMe	40	146
-----$(CH_2)_3$-----		Ph	CN	67	147

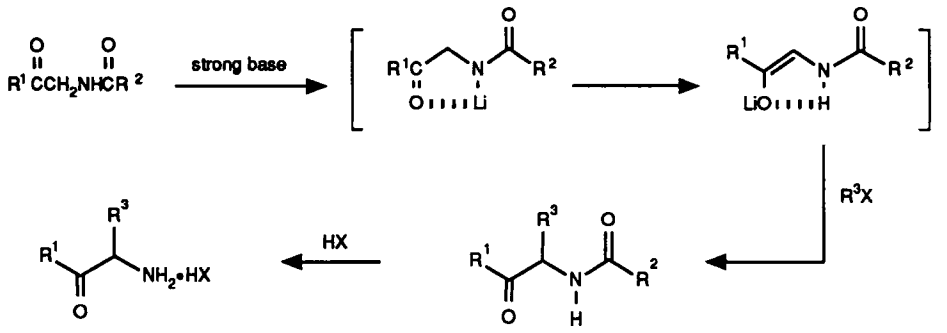
[a] Acylation with methyl esters gave rise to substantial amounts of the symmetrical tertiary alcohol (bis-adduct).

XVIII. ALKYLATION OF N-PROTECTED α-AMINOKETONE ANIONS

Garst and coworkers[156] examined the direction of enolization of tertiary α-aminoketones under strongly basic conditions. When the N-substituent was an alkyl group, deprotonation under kinetic (LDA / THF / – 78 °C) and thermodynamic control (lithium hexamethyldisilazide / THF / O °C) caused predominant enolization away from and towards the amino group, respectively. All other N-substituents (alkoxycarbonyl, trifluoromethane-

sulfonyl, phthalimido) favored deprotonation towards the amino group under either kinetic or thermodynamic conditions. N-Substituted 3-pyrrolidinones were exceptional in that deprotonation away from the amino substituent was favored under both kinetic and thermodynamic control. The alkylation of these latter anionic species with methyl iodide gave regioisomeric mixtures of mono- and dimethylated products. The alkylation of the other tertiary α-aminoketone anions was not reported.

In contrast to the tertiary α-aminoketones described above, reaction of an N-acylated α-aminoketone, in which an NH group is present, with one equivalent of a strong base, gives an anion which is regioselectively alkylated with alkyl bromides or iodides, on the carbon atom flanked by the acylamido and ketone moieties.[157-161] Presumably the amide anion is formed under kinetic control and this species, upon proton transfer, generates the thermodynamically favored dipole stabilized[162] ketone enolate anion.

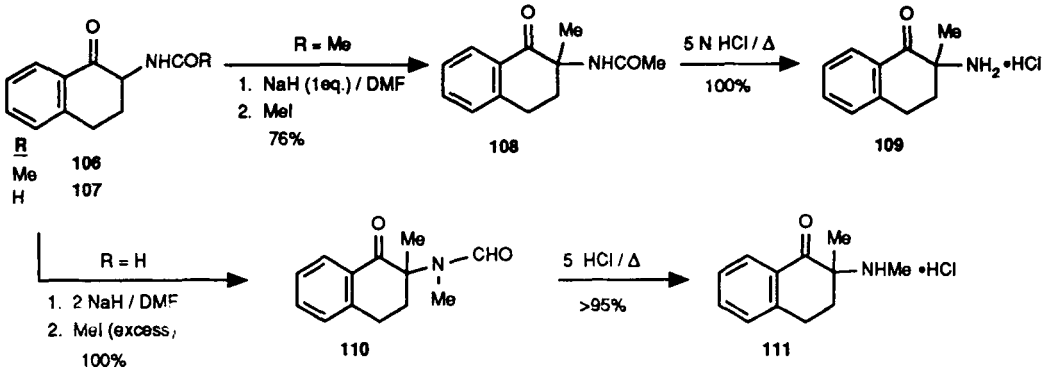


A variety of strong bases (NaH, LDA, LiHMDS, KH), in diverse solvents, has been used to effect deprotonation, but sodium hydride in DMF (O °C) is operationally the most convenient. The acyl moiety can be varied considerably, but formyl or acetyl groups are preferable if the aminoketone itself is the synthetic objective. This process has quite broad generality (Table 33). If the aminoketone is required, hydrolysis of the formamides is easily effected with aqueous hydrochloric acid or methanolic hydrobromic acid.

Table 33. Synthesis of α-Alkyl-α-Aminoketones by Alkylation of N-Acyl-α-Aminoketones.

R^1	R^2	R^3	Base	Solvent	% Yield: Amido ketone	% Yield: Amino ketone.HX	Ref.
Me	Ph	MeI	LDA	THF	60		159
Me	Ph	$PhCH_2Br$	LDA	THF	42		159
Me	Ph	n-BuI	LDA	THF	35		159
Ph	H	MeI	NaH	DMF	57		160
Ph	H	EtI	NaH	DMF	67		160
Ph	H	$PhCH_2Br$	NaH	DMF	90	94.HBr	160
3,4-$OCH_2OC_6H_3$	H	n-BuI	NaH	DMF	83		160
3,4-$OCH_2OC_6H_3$	H	$PhCH_2Br$	NaH	DMF	66	95.HBr	160
$PhCH_2CH_2$	H	n-BuI	NaH	DMF	43		160
$PhCH_2CH_2$	H	$PhCH_2Br$	NaH	DMF	59	77.HBr	160

A second α-alkyl group can be introduced into α-acylamidoketones which are already α-alkylated.[157-160] For example, the α-tetralone derivative 106 can be methylated on carbon[159] via the monoanion. N,C-Dimethylation can also be accomplished on the formamido compound 107 using two equivalents of base. In each case, the products, 108 and 110 can be hydrolysed to the corresponding α-aminoketone derivatives 109 and 111 with hot 5 N hydrochloric acid.



The preferential alkylation of α-acylamidoketones on the α-carbon atom is in marked contrast to the alkylation of α-aminoketones, the nitrogen atom of which is protected with the 9-phenylfluorenyl moiety.[148] This bulky N-substituent shields the α-carbon from deprotonation; indeed potassium hexamethyldisilazide effects enolization at the carbon atom away from the amino group and this enolate can be C-alkylated with alkyl halides (Table 34). In all cases, the alkylation occurs with modest "re" face selectivity and each product is obtained optically pure.

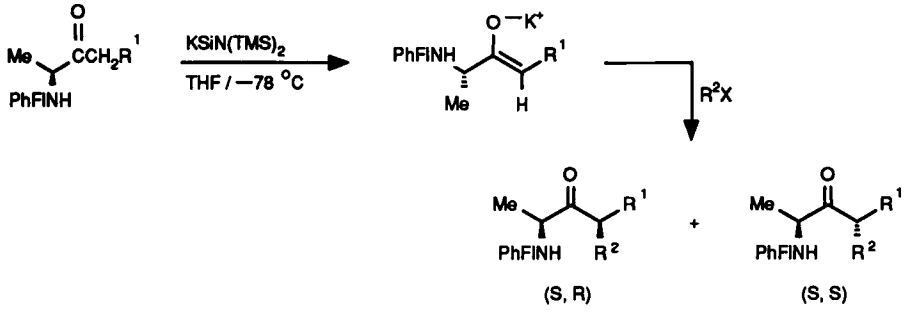


Table 34. Alkylation of N-(9-Phenylfluoren-9-yl)α-Aminoketones.

R^1	R^2	(S, R) / (S, S)	% Yield
n-Pr	MeI	2.2	94
n-Pr	$PhCH_2Br$	5	80
n-Pr	$CH_2=CHCH_2Br$	5	77
n-Pr	$CH_3CHBrCO_2Me$	2.2	38
Ph	MeI	4	79

XIX. C-ACYLATION OF N-ACYLATED α-AMINO ACID ESTERS FOLLOWED BY HYDROLYTIC DECARBOXYLATION

The dianion of ethyl hippurate, generated at low temperature with 2 equivalents of LDA, was acylated on carbon with acid anhydrides or mixed carbonic-carboxylic anhydrides. Hydrolysis and decarboxylation of the β-keto ester thus produced with 6 N hydrochloric acid,

gave the α-aminoketone, isolated as the hydrochloride salt (Table 35).[163]

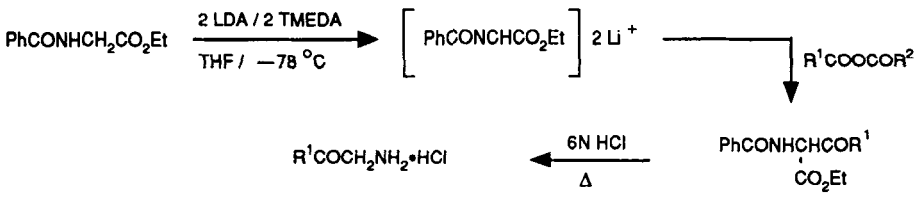
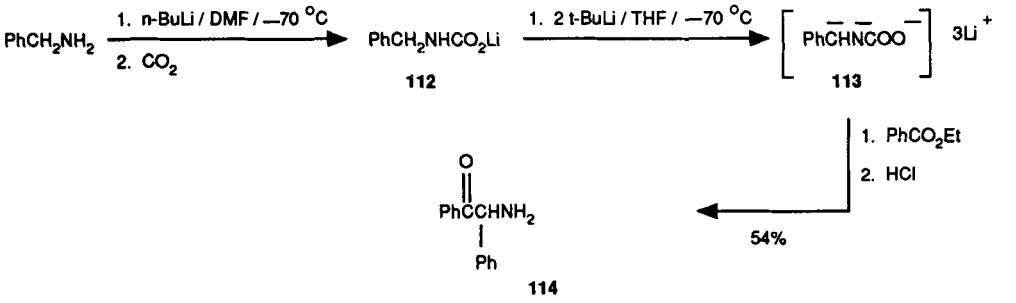


Table 35. Synthesis of α-Aminoketones from Ethyl Hippurate.

		% Yields	
R^1	R^2	β-Keto ester	α-Aminoketone
Me	Me	40	
-----$(CH_2)_2$-----		59	68
-----$(CH_2)_3$-----		47	71

XX. ACYLATION OF TRIPLY LITHIATED N-BENZYL CARBAMIC ACID

The lithium salt of benzylcarbamic acid (112) is converted into a trianionic species 113 which on sequential acylation and acidification provides the aminoketone 114. This is the only reported instance of the use of this metalation strategy for the synthesis of α-aminoketones.[164]



XXI. OXIDATIVE CLEAVAGE OF N-ACYLAZIRIDINES WITH DIMETHYLSULFOXIDE

N-Acylaziridines undergo oxidative cleavage to α-acylaminoketones in hot dimethylsulfoxide solution.[165-167] This reaction is thought to proceed by an SN_2 like attack of

DMSO at the most electropositive carbon atom, to give a betaine, which is converted into the product by a proton shift and loss of dimethyl sulfide. Mixtures of α-acylaminoketones are predicted when R^1 and R^2 are similar or when steric factors interfere with the cleavage process (see footnote in Table 36). Apart from this limitation, the process would appear to have considerable synthetic potential (Table 36).

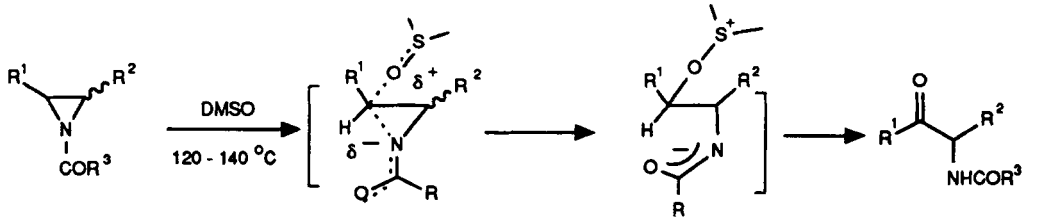


Table 36. Synthesis of α-Acylaminoketones by Oxidative Cleavage of N-Acylaziridines with DMSO.

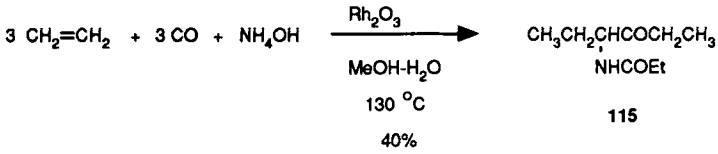
R^1	R^2	R^3	Isomer	Temp. (°C)	Yield %	Ref.
Ph	H	OMe		120	66	167
Ph	H	4-$NO_2C_6H_4$		117	83	165
Ph	Me	OEt	cis[a]	120	95	167
Ph	Me	OEt	trans[a]	120	96	167
Ph	Ph	4-$NO_2C_6H_4$	cis	117	80	165
Ph	Ph	4-$NO_2C_6H_4$	trans	117	52	165
----$(CH_2)_4$----		OEt	cis	120	65	166
----$(CH_2)_6$----		OEt	cis	120	48	167

[a] Rearrangement in acid washed glassware. In the absence of acid, varying amounts of the isomeric α-acylaminoketone (R^1=Me, R^2=Ph) were also obtained.

XXII. RHODIUM CATALYSED CARBONYLATION AND HYDROFORMYLATION OF OLEFINIC COMPOUNDS

A. α-Aminoketones

The rhodium oxide catalysed carbonylation of ethylene, in the presence of aqueous ammonia, gave 3-propionamido-4-hexanone (115) in modest yield.[168] When a more concentrated ammonia solution was used, 2,4,5-triethylimidazole (116) was produced instead. Thus, 115 is undoubtedly an intermediate in the formation of the imidazole. This is the only reported example of the synthesis of α-acylamidoketones by this method, but since this is a practical means of preparing symmetrical trialkylimidazoles, it would seem that under the modified conditions cited above, symmetrically substituted α-acylamidoketones should also be readily available from terminal olefins. Cyclohexene is not converted into either type of product under conditions analogous to those described above.



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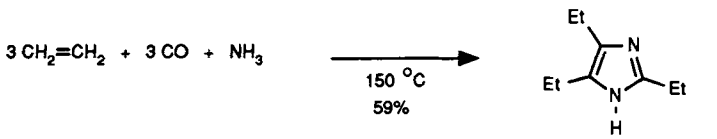


116

B. α-Aminoaldehydes

Rhodium tricarbonyl[169] or carbonyltris(triphenylphosphine)hydridorhodium[170] catalysed the hydroformylation of N-vinylimides and N-vinylamides, under moderate synthesis gas (1:1 H_2:CO) pressure, to α-imido- or α-amidoaldehydes which, in some cases, were contaminated by the β-aminoaldehyde derivative (Table 37). If the hydroformylation of N-vinylimides was conducted in the presence of an optically active phosphine, such as DIPHOL[2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(5H-dibenzophospholyl)butane], the α-imidoaldehydes were obtained with a modest degree of asymmetric induction (20-40% ee).[170]

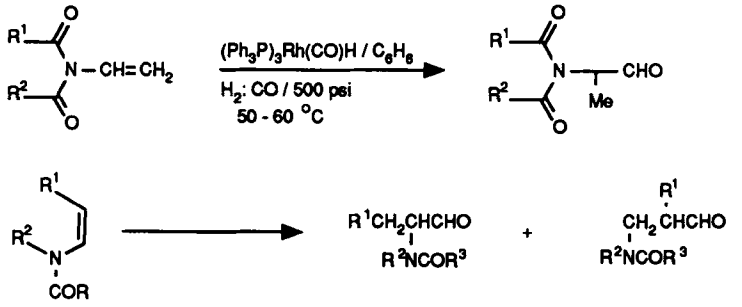


Table 37. Synthesis of α-Aminoaldehyde Derivatives by Hydroformylation N-Acylated Vinylamine Derivatives.[a]

R^1	R^2	R^3	% Yields α-Imidoketone	% Yields α-Amidoketone
-----$(CH_2)_2$-----			61	
=C-$(CH{=}CH)_2$-C=			41	
H	H	Me		39[b]
-----$(CH_2)_3$-----		Me		33
-----$(CH_2)_3$-----		O-t-Bu		56

[a] Data taken from ref. 170.
[b] Also contained 32% of β-acetamidopropionaldehyde.

XXIII. ACID INDUCED AMIDOALKYLATION OF AROMATIC HYDROCARBONS WITH METHYLGLYOXAL-BISMETHYLCARBAMATE

The reaction of methylglyoxal-bismethylcarbamate with aromatic hydrocarbons, under strongly acidic conditions, gives rise to 1-methoxcarbonylamino-1-arylacetone derivatives.[171] This reaction has considerable breadth (Table 38) and is likely to occur by attack of the highly electrophilic acyliminium species on the aromatic substrate. The formation of mixtures of ortho- and para- products from monosubstituted benzene derivatives is consistent with this assumption.

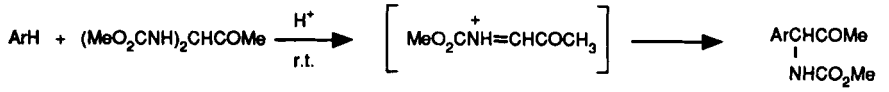


Table 38. Synthesis of α-Aryl-α-Methoxycarbonylaminoacetone Derivatives from Aromatic Hydrocarbons and Methylglyoxal-Bismethylcarbamate.

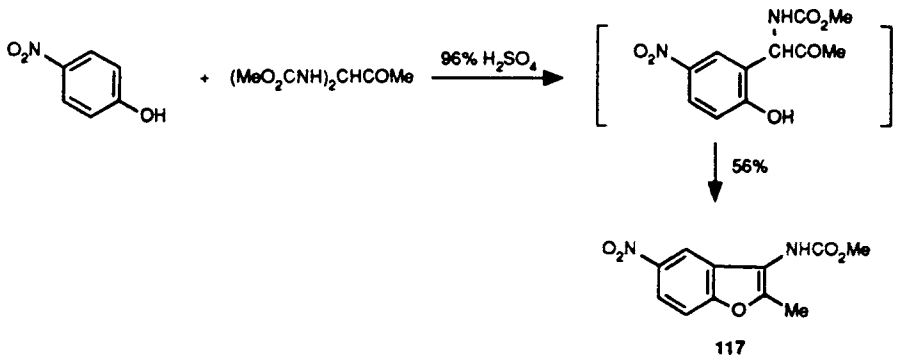
Aryl compound	Reaction medium	% Yield
benzene	96% H_2SO_4	75
toluene	96% H_2SO_4	50[a]
chlorobenzene	96% H_2SO_4	56[a]
phenol	10% H_2SO_4 in HOAc	70[a]
anisole	$MeSO_3H$-CH_2Cl_2 (1:1)	64[a]
p-xylene	96% H_2SO_4	52
guaiacol	$MeSO_3H$-CH_2Cl_2 (1:1)	67[a]
furan	5% $MeSO_3H$ in CH_2Cl_2	34
thiophene	10% H_2SO_4 in CH_2Cl_2	47

[a] Mixtures of o- and p-isomers with para predominating.

[b] Side chain para to hydroxyl group.

Methylglyoxal-bismethylcarbamate is readily prepared (77% yield) from methylglyoxal dimethyl acetal and methyl carbamate under acidic conditions.

There are two important limitations of this synthesis. Firstly, homologous α-oxo-biscarbamates are, as yet, not readily available. Secondly, the primary products from p-substituted phenols, e.g., 4-nitrophenol, spontaneously cyclize to benzofuran derivatives, e.g., 117, in the highly acidic reaction medium.



XXIV. PYROLYSIS OF WITTIG-HORNER PRODUCTS FROM α-AMINOPHOSPHINOXY CARBANIONS AND ALDEHYDES

The condensation products of N,N-dialkylaminophosphinoxy carbanions and aldehydes undergo pyrolytic fragmentation, in ethylene glycol or toluene (H^+ catalysis), to phosphine oxides and α-dialkylaminoketones.[172] Although both the nature of the aldehyde and the amine substituents can be varied widely, the process is limited to the synthesis of α-t-aminoketones (Table 39). It is not known whether α-substituted dialkylaminophosphinoxy compounds participate in the above reaction sequence.

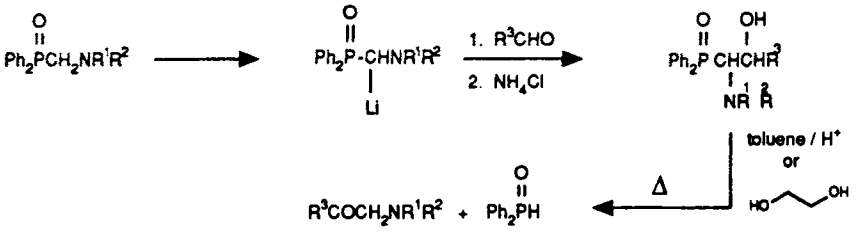


Table 39. Conversion of Aldehydes into α-Dialkylaminoketones

R^1	R^2	R^3	Conditions	% Yield
Ph	Me	Ph	A[a]	82
--$(CH_2)_2$-O-$(CH_2)_2$--		Ph	B[b]	79
--------$(CH_2)_5$--------		Ph	B	77
Ph	Me	$PhCH_2$	A	75
Ph	Me	n-Heptyl	A	82
--$(CH_2)_2$-O-$(CH_2)_2$--		Et_2CHCH_2	A	81
Ph	Me	Cyclohexyl	B	79
Ph	Me	t-PrCH=CH	B	58

[a] Ethylene glycol / 140 - 150 °C.
[b] Toluene / reflux / catalytic TsOH·H_2O.

XXV. FROM ACYL CHLORIDES AND N,N-DIALKYLAMINOMETHYL-TRI-N-BUTYLSTANNANES

Carboxylic acid chlorides react with N,N-dialkylaminomethyl-tri-n-butylstannanes, under very mild conditions, to form α-dialkylaminoketones.[173] Wide variation in both the nature of the acid chloride and the dialkylamino moiety is tolerated (Table 40) but the reaction is restricted to the synthesis of α-dialkylaminoketones and acetyl chloride does not give the expected products. The dialkylaminomethylstannanes are easily prepared from tri-n-butylstannyl magnesium chloride and aminoacetals or immonium salts.

$$R^1COCl + Bu_3SnCH_2NR^2R^3 \longrightarrow R^1COCH_2NR^2R^3$$

Table 40. Synthesis of α-Dialkylaminoketones from N,N-Dialkylamino-Methyltri-n-Butylstannanes and Acyl Chlorides.

R^1	R^2	R^3	Conditions	% Yield
Et	Et	Et	A[a]	65
i-Pr	Et	Et	A	64
Ph	Me	$PhCH_2$	B[b]	84
3-BrC_6H_4	Et	Et	B	82
4-$MeOC_6H_4$	------$(CH_2)_5$------		C[c]	77
4-HOC_6H_4	Et	Et	C	81
4-NCC_6H_4	Et	Et	C	78

[a] Neat, O to 20 °C.
[b] Neat, 20 °C.
[c] THF, 60 °C.

XXVI. THIAZOLIUM SALT CATALYSED DIALKYLAMINOMETHYLATION OF ALDEHYDES

Dialkylaminomethylation of an aldehyde, at the carbonyl carbon atom, which is known in the formal sense (see section 24, for example), can be accomplished in fact, by

dialkylaminomethylation of an aldehyde with an imminium salt in the presence of a thiazolium ylid source.[174] This process, which has mechanistic kinship to the Mannich reaction and the benzoin condensation, generates α-dialkylaminomethylketones in moderate yields from both aromatic and aliphatic aldehydes (Table 41).

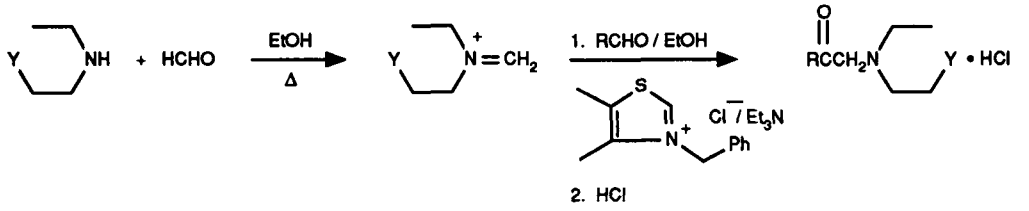


Table 41. Synthesis of α-Dialkylaminoketones from Aldehydes and Iminium Salts.

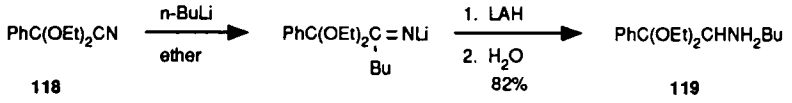
R^1	Y	% Yield[a]
i-Pr	O	47
n-Heptyl	O	20
Ph	O	33
4-$MeOC_6H_4$	O	30
4-$MeOC_6H_4$	CH_2	38
3,4-$(MeO)_2C_6H_3$	O	33
3,4,5-$(MeO)_3C_6H_2$	O	25

[a] Yield of hydrochloride salt.

XXVII. REACTION OF PROTECTED α-ACYL CYANIDES WITH ORGANOMETALLIC REAGENTS

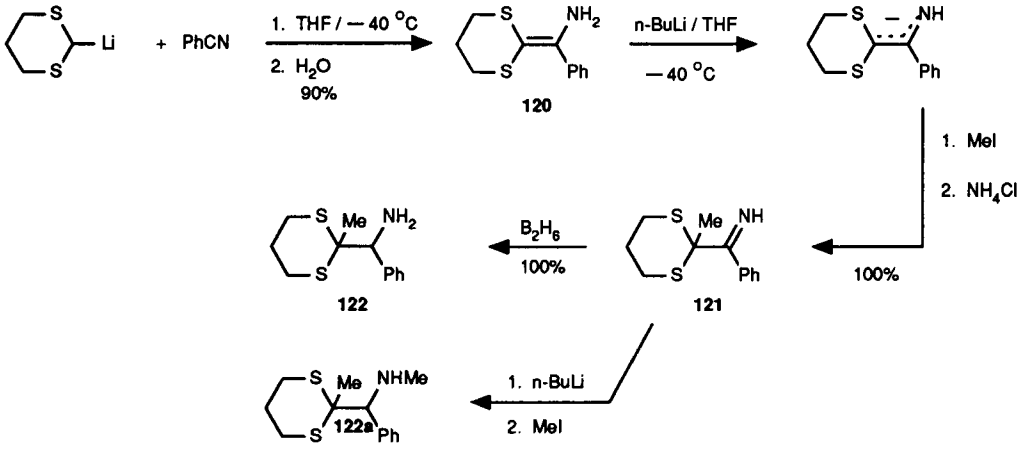
A. α-Aminoketones

The diethylketal of benzoyl cyanide 118, upon consecutive reaction with n-butyllithium and lithium aluminum hydride, in the same pot, gave the α-aminoketal 119.[175]



118 119

In a related process, 2-lithio-1,3-dithiane added to benzonitrile to give the stable aminoketone dithioacetal 120. Deprotonation of 120 and alkylation of the ambident anion thus generated, with methyl iodide, gave the α-iminothioketal 121. This compound could be converted into the primary or secondary α-aminothioketals 122 or 123 by diborane reduction or by N-methylation and reduction, respectively.[176]



These reaction sequences are likely to have some breadth since 2-lithiodithiane adds to a variety of nitriles which do not have α-hydrogen atoms.[177]

B. α-Aminoaldehydes

Grignard or organolithium reagents add to the cyano function of diethoxyacetonitrile and the metalated ketimines obtained thereby, upon addition of another organolithium reagent, give α-aminoacetals on protonolysis (Table 42).[175]

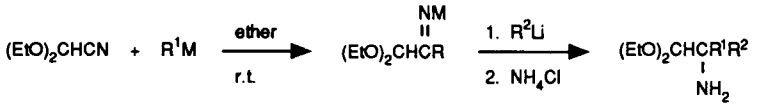


Table 42. Synthesis of α-Aminoacetals by Diaddition of Organometallic Reagents to Diethoxyacetonitrile.

R^1M	R^2	% Yield
n-BuMgBr	n-Bu	89
n-BuLi	n-Bu	95
PhMgBr	n-Bu	90
n-BuMgBr	Ph	60
PhMgBr	Ph	80

XXVIII. ADDITION OF SULFUR STABILIZED ANIONS TO IMINIUM SALTS

2-Lithio-1,3-dithiane and lithio methylsulfinyl methylthio methane undergo nucleophilic addition to iminium salts which lack an α-hydrogen atom.[178] Hydrolysis of the dithiane derivatives to the α-dialkylaminoaldehydes could only be accomplished with chloramine-T but even this reagent failed in several cases (Table 43). The hydrolysis of the sulfoxide derivatives in contrast, occurred easily at room temperature in the presence of concentrated hydrochloric acid.

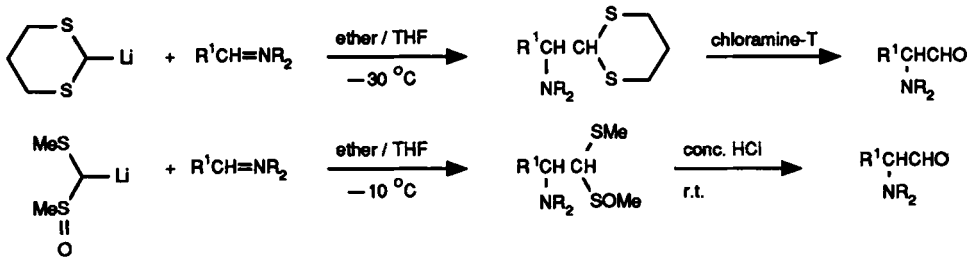


Table 43. α-Dialkylaminoaldehyde Derivatives from Sulfur Stabilized Anions and Iminium Salts.

R^1	NR^2	Dithiane	Sulfoxide	α-Aminoaldehyde
Ph	Morpholino	53		30 - 40
i-Pr	Dimethylamino		29	50
Mesityl	Morpholino	38		0
Mesityl	Morpholino		55	92
2-Thienyl	Piperidino	70		0
2-Thienyl	Piperidino		60	

XXIX. CLEAVAGE OF AZIRIDINONES WITH ORGANOMETALLIC REAGENTS

Aziridinones undergo selective cleavage of the carbonyl-nitrogen bond, with organolithium reagents at low temperature, to give α-substituted-α-alkylaminoketones.[179-181] While the reaction is quite general (Table 44) with respect to the organolithium reagent, it is limited by the unavailability of unhindered 1,2-disubstituted aziridinones.[182] It is not known if trisubstituted aziridinones undergo an analogous reaction.

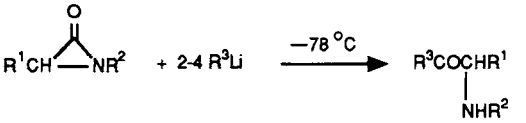
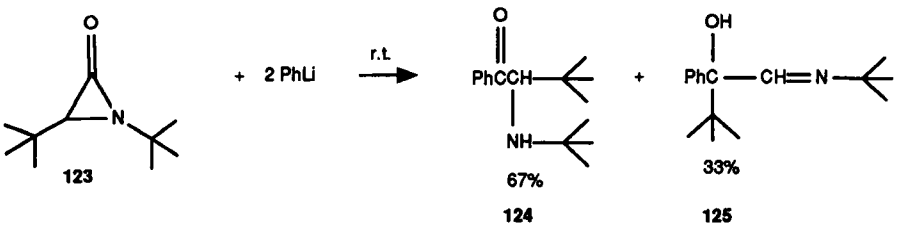


Table 44. Synthesis of α-Alkylaminoketones and Alkyllithium Reagents.

R^1	R^2	R^3	% Yield	Ref.
t-Bu	t-Bu	Me	95	180
t-Bu	1-Adamantyl	Me	65	179
t-Bu	1-Adamantyl	i-Pr	92	179
t-Bu	1-adamantyl	t-Bu	69	179
1-adamantyl	1-adamantyl	Me	67	179
1-adamantyl	1-adamantyl	i-Pr	72	179
1-adamantyl	1-adamantyl	Ph	64	179

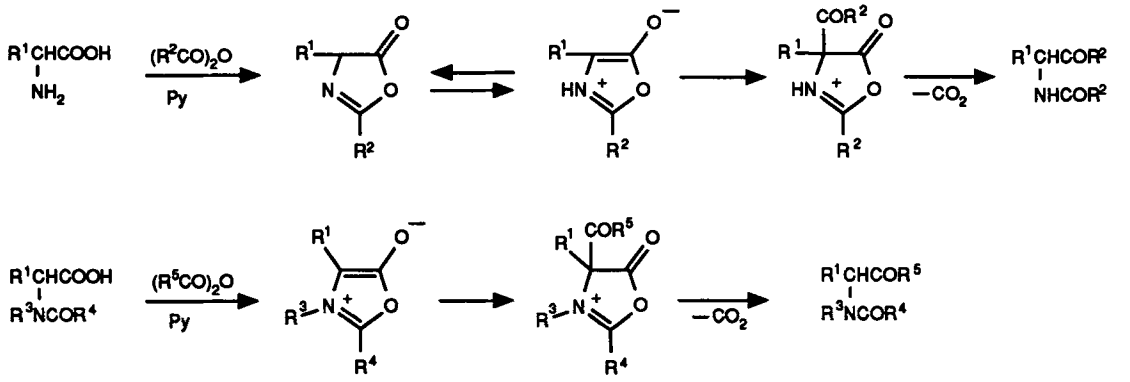
When the reaction is effected at room temperature the product is exclusively the α-hydroxyimine (the reverse Voigt-Amadori product) or a mixture of the α-hydroxyimine and the α-alkylaminoketone.[180,183] An example of the latter case is the reaction of phenyllithium with 1,3-di-t-butylaziridinone (123).[180]



The reaction of Grignard reagents with aziridinones is much more complex. Although the α-aminoketone can be the major product,[180,184] it is frequently accompanied by the α-hydroxyimine, as well as other products.[180]

XXX. DAKIN-WEST SYNTHESIS

The reaction of an α-amino acid, or an N-acyl derivative thereof, with a carboxylic acid anhydride, in the presence of a base such as pyridine, to effect decarboxylation and introduction of an acyl moiety at the α-carbon atom, is known as the Dakin-West reaction (ref. 2, pp 2286-8). The process is one of considerable scope. Both primary and secondary

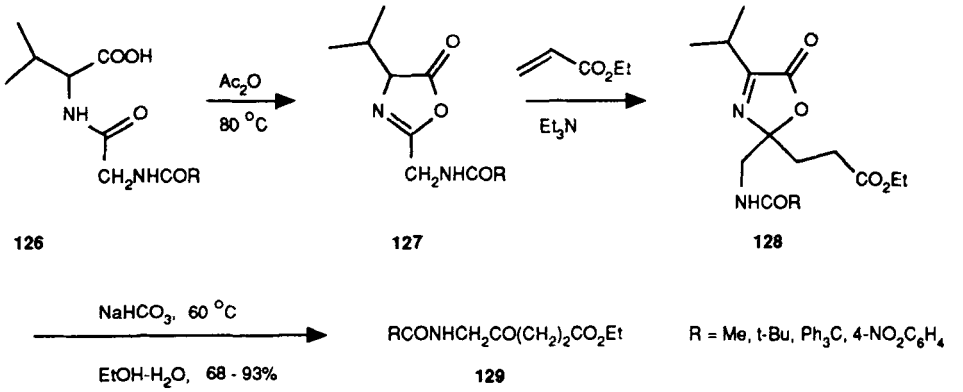


α-amino acids give the expected products and the α-substituent (R^1) and the N-acyl moiety (R^4) can be varied widely. The N-acyl moiety can be derived from the carboxylic acid anhydride or a different N-acyl group can be introduced prior to the Dakin-West reaction and this group is then found in the product. Although other carboxylic acid anhydrides do participate in the reaction, acetic anhydride is preferred and usually gives the best results. It is now generally accepted that the azlactones and the mesoionic counterparts thereof, are

necessary intermediates. These intermediates can be trapped with numerous dipolarophiles and are widely used for the synthesis of 5-membered heterocyclic systems.[185-187]

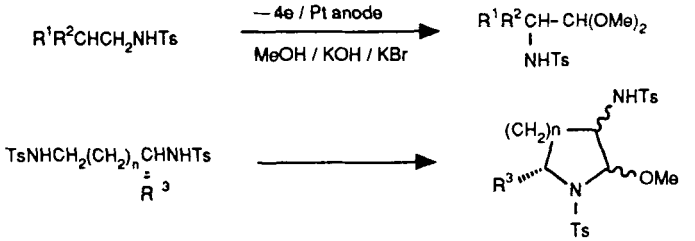
XXXI. FRAGMENTATION OF 2,2-DISUBSTITUTED 3-OXAZOLIN-5-ONES

Cyclization of the N-acylated glycylvaline derivatives 126 with acetic anhydride, gives the Dakin-West azlactones 127, which undergo base catalysed addition to ethyl acrylate. The 3-oxazolin-5-ones 128 thus generated are easily hydrolysed to the ω-acylaminolevulinic acid derivatives 129. No other examples of this potentially useful reaction sequence have been reported.[188]



XXXII. ANODIC OXIDATION OF p-TOLUENESULFONAMIDES OF PRIMARY AMINES

Oxidation of the N-tosyl derivatives of primary amines, at a platinum anode, in methanol containing potassium hydroxide and potassium bromide, gives α-tosylaminoaldehyde dimethyl acetals in synthetically useful yields (Table 45).[189] Electrolysis of the bistosylamides of α,ω-diamines, of a 4-or 5-carbon chain length, generates

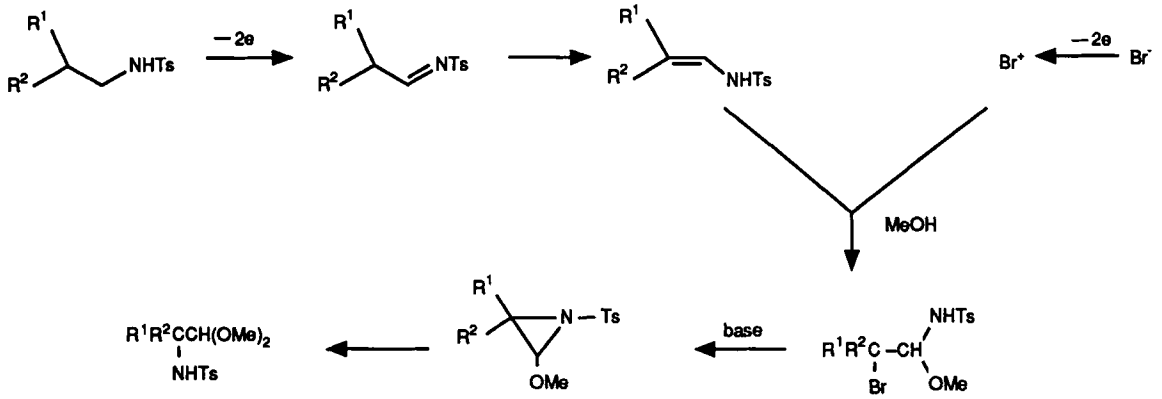


cyclic hemiamidals. The ornithine derivative ($R^3 = CO_2Me$, n = 2) and the next higher homolog, also undergo electrooxidative cyclization to give cyclic α-amino acid derivatives in which the absolute stereochemistry of the carboxyl group is retained (Table 45).

Table 45. Anodic Oxidation of Primary Tosylamides.

R^1	R^2	R^3	n	% Yield
H	H			59
H	Me			61
H	Et			61
H	i-Pr			50
Me	Et			52
		H	2	91
		CO_2Me	2	78
		H	3	79
		CO_2Me	3	46

This process is considered to proceed by methanolysis of an intermediate α-alkoxyaziridine and thus is closely related to the Neber and related rearrangements discussed above.



XXIII. OXIDATIVE CLEAVAGE OF N-PROTECTED β,γ-DIHYDROXYAMINES

N-Protected α-amino-β,γ-diols are oxidatively cleaved, by sodium metaperiodate or lead tetraacetate, to N-protected α-aminoaldehydes, without racemization (Table 46).[190,191] Analogous synthetic procedures have been used routinely in the amino glycoside antibiotic area.[192,193]

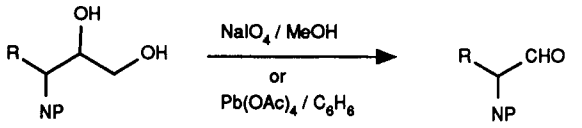
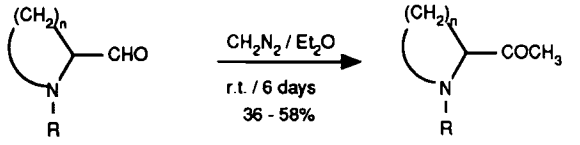


Table 46. Synthesis of α-Aminoaldehyde Derivatives by Oxidative Cleavage of N-Protected α-Amino-β,γ-Diols.

R	P	Stereochem.	Reagent	% Yield	Ref.
Me	Phthalimido	R	$Pb(OAc)_4$	70	191
Et	Phthalimido	R	$Pb(OAc)_4$	77	191
n-Pr	Phthalimido	R	$Pb(OAc)_4$	89	191
$PhCH_2$	$PhCH_2OCO$	S	$NaIO_4$	85	190
CH_2=$CHCH_2$	Phthalimido	R	$Pb(OAc)_4$	76	191
CH_2=CH	Phthalimido	R	$Pb(OAc)_4$	75	191

XXXIV. REACTION OF α-DIALKYLAMINOALDEHYDES WITH DIAZOMETHANE

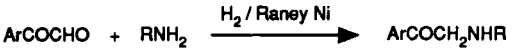
Duhamel, et.al.[96] have shown that certain cyclic α-aminoaldehydes react very slowly, at room temperature, with ethereal diazomethane, to provide the corresponding methyl ketones in modest yields.



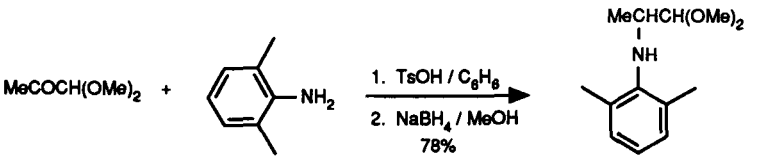
R = Me, t-Bu; n = 2 - 4

XXXV. REDUCTIVE AMINATION OF α-KETOALDEHYDES AND DERIVATIVES THEREOF

Reductive amination of aryl glyoxals over Raney-Nickel catalyst occurs selectively at the aldehydic carbon to give α-alkylaminoacetophenone derivatives (ref. 2, p 2293).



α-Aminoaldehyde derivatives can be prepared in an analogous manner if the reductive amination is effected on an α-ketoaldehyde dimethyl acetal,[194] as exemplified by the synthesis of the propionaldehyde derivative 130.



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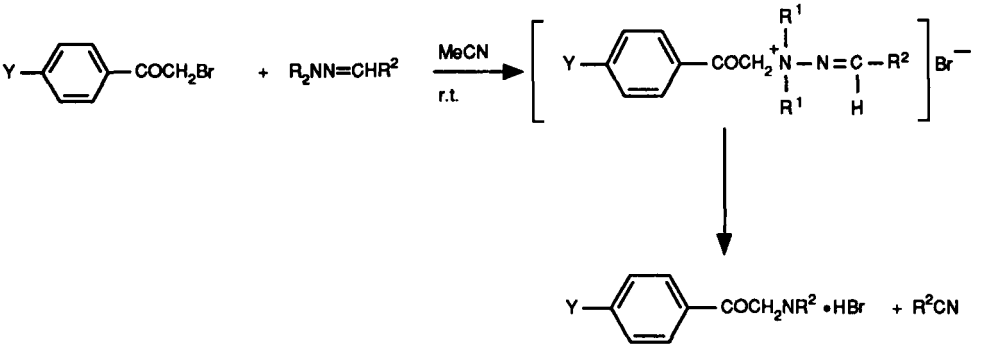
XXXVI. REACTION OF ALDEHYDE DIALKYLHYDRAZONES WITH PHENACYL BROMIDES

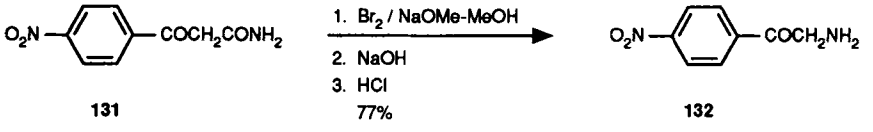
Aldehyde dialkylhydrazones react with phenacyl bromides, at room temperature, to produce α-dialkylaminoacetophenones.[195] This reaction presumably occurs by the fragmentation of an initially formed quaternary hydrazonium salt.



As expected, a nitrile is formed concomitantly and the N,N-dialkylhydrazones of ketones do not undergo this fragmentation. 2-Bromopropiophenone failed to participate in this reaction.

XXXVII. α-AMINOKETONES BY THE HOFFMANN OR CURTIUS REACTIONS

The Hoffmann and Curtius degradations have occasionaly been used to prepare primary α-aminoketones as shown in the examples below (Ref. 2, p 2294).



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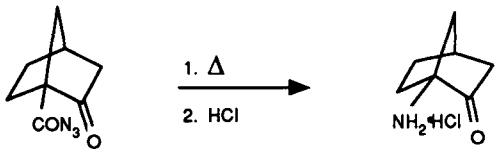
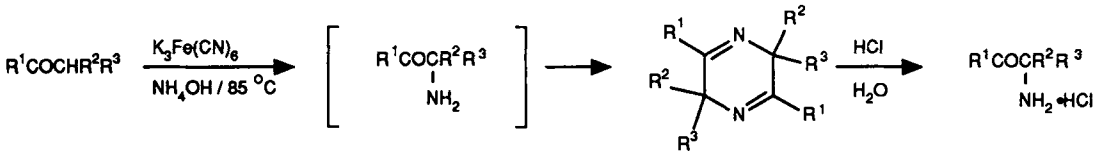


133 134

XXXVIII. OXIDATION OF KETONES WITH ALKALINE FERRICYANIDE

Trialkyl ketones react with warm ammoniacal potassium ferricyanide to give hexaalkyl 2,5-dihydropyrazines which, upon hydrolysis with dilute hydrochloric acid, are converted into α,α-dialkyl-α-aminoketone hydrochlorides (ref. 2, p 2294).

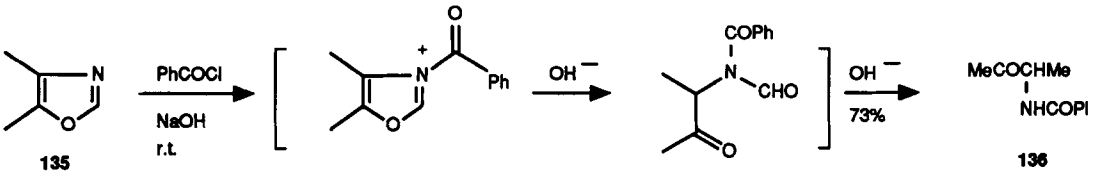


The source of the amine nitrogen in this curious reaction, discovered more than 60 years ago by Conant[196], is unknown, but exogenous ammonia is unnecessary, since the reaction still proceeds, although less efficiently, in the absence thereof.

XXXIX. α-AMINOKETONE DERIVATIVES FROM OXAZOLE DERIVATIVES

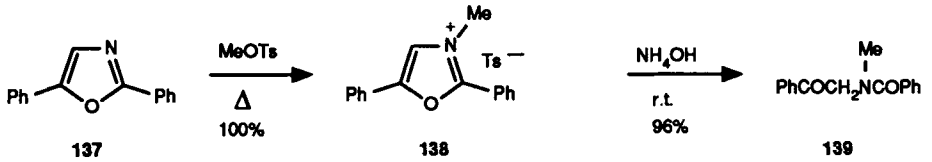
Oxazoles, oxazolin-2-ones and oxazolin-2-thiones are formal masked α-aminoketones and the unmasking thereof can be effected under appropriate conditions. Indeed, the conversion of oxazoles and oxazolium salts to imidazoles and other heterocyclic compounds is, in large part, based on this concept.[197]

4,5-Dimethyloxazole (135) is hydrolytically cleaved to 3-benzamido-2-butanone (136) under Schotten-Baumann conditions.[198]



135 136

Oxazolium salts are even more prone to cleavage. For example, the N-methyloxazolium tosylate 138 is rapidly and quantitatively converted into the α-acylaminoketone 139 with dilute aqueous ammonia at room temperature.[199] In addition, the isoxazole 140 is hydrolysed to the α,α'-diaminoketone derivative 142, an intermediate in the synthesis of the phytosiderophore mugineic acid, with aqueous benzyl alcohol (1:10) containing excess (10 equiv.) methane sulfonic acid at ambient temperature.[205] The intermediate formamido compound 141 does not survive these mild hydrolysis conditions.



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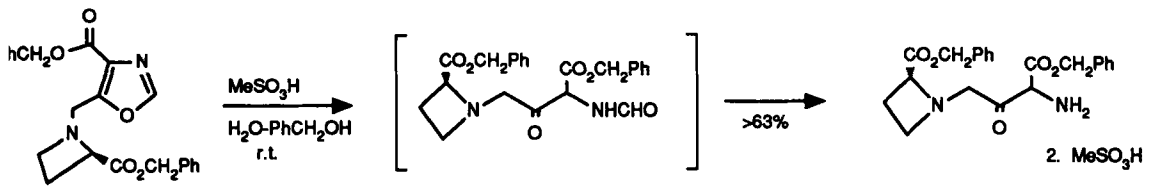

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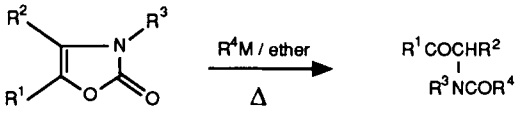
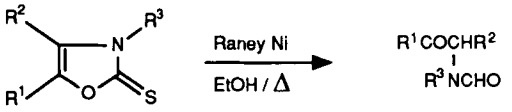
Oxazolin-2-ones react with Grignard or alkyllithium reagents to generate α-acylaminoketones, a process which even occurs when the nitrogen atom is unsubstituted.[200]

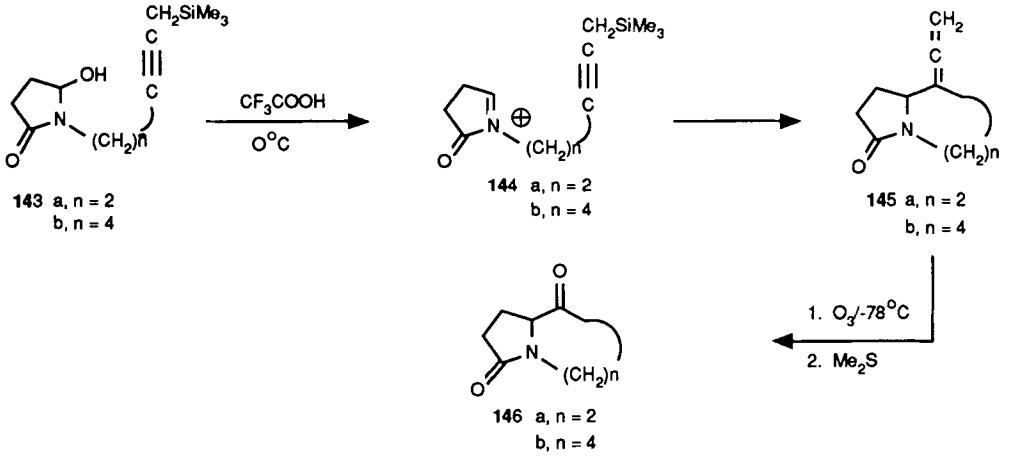


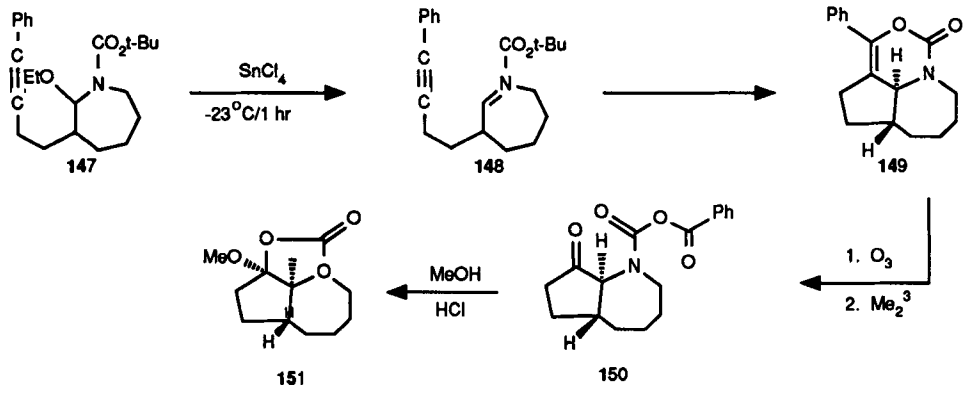
A related reaction takes place when oxazolin-2-thiones, easily prepared from the oxo compound and phosphorous pentasulfide, are heated with a large excess of Raney-Nickel in ethanol solution.[201] α-Formamidoketones are obtained in quite acceptable yields.



XL. OXIDATIVE DEGRADATION OF N-PROTECTED β,γ-UNSATURATED AMINES

N-acylated β,γ-unsaturated amines contain latent α-amino ketone functionality which can be revealed by ozonolysis. This principle is exemplified by the generation of the cyclic α-amino ketones 146a, 146b and 150 (characterized as the mixed acetal 151) from the bicyclic allenes[206] 145a, 145b, and the tricyclic oxazinone[207] 149, respectively. Inasmuch as 145 and 149 are conveniently produced by the cyclization of the acyliminium species 144 and 148, which in turn are derived from the readily available acetylenic precursors 143 and 147. This route to α-amino ketones is likely to find considerable use.





SUMMARY

In addition to the more traditional uses of α-aminoaldehydes and α-aminoketones as precursors of heterocyclic systems and ethanolamine derivatives of biological interest, they have recently served as embarkation points for the synthesis of a wide variety of peptidic natural products and congeners thereof (see refs. 97-100, 105, 116, 118, 123,124, 140-143). This latter application has required α-aminoaldehydes and ketones of high optical purity and a considerable number of useful synthetic routes to such compounds have been devised (see refs 90-93, 95-100, 108-133, 140-143, 148, 150-152, 155). Nevertheless, there is still a need for new, efficient syntheses which provide these compounds in optically pure form and with predictable absolute configuration. In addition to the design of new α-aminoaldehyde and ketone syntheses, certain aspects of some long known syntheses should be reexamined in the light of today's knowledge and with modern analytical techniques (e.g., the Voigt-Amadori rearrangement). Other existing syntheses merit further study to determine the degree of applicability (e.g., the α-aminoketone syntheses of Overman[110], Stork[142] and Katritzky[164]) or to establish the mechanistic course of the process (e.g., Conant[196] α-aminoketone synthesis). In closing, it would appear that interest in this area is likely to remain high for some time to come.

Acknowledgement--The authors are most grateful to Annie Green, Nicole Grinder, Lani Russell and Jeanne Sheldon for their help in the preparation of this manuscript.

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† Contribution No. 785 from the Syntex Institute of Organic Chemistry.

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(Received July 21, 1989; in revised form February 23, 1990)