The Azetidines. Recent Synthetic Developments

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I. Introduction

Although azetidine was first prepared in 1888,[1] this division of small ring nitrogen heterocycles has been the least studied. The main reason for this sparcity of information is that in many instances the methods used to prepare azetidines give relatively poor yields. In the last decade, however, some important progress has been made toward more productive synthesis of these compounds. This recent activity in the investigation of four-membered cyclic imines has been stimulated considerably by findings in the aziridine series, and by an interest in the relationship between ring size and reactivity. Also the discovery of the naturally occurring azetidine-2-carboxylic acid,[2] which has shown some unique and potentially useful biological activity,[3-5] has caused increased interest in the azetidine field.

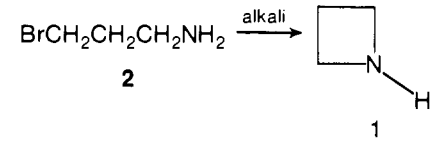
Various methods of synthesizing azetidines have been reviewed up to 1964[6] with a review on the comparative chemistry of azetidines and aziridines being published recently.[7] The present survey covers the literature from approximately 1963 to January 1978 that is available in *Chemical Abstracts* and is limited to the synthesis of azetidine and its derivatives. Reactions of azetidines that destroy the ring system will generally not be included.

II. General Methods of Azetidine Synthesis

The major methods of azetidine preparation can be divided into three groups: (a) cyclization of γ-haloamines or γ-aminoalkyl sulfates, (b) reduction of azetidinones and malonimides, and (c) cyclization of 1,3-dihalides or 1,3-diamines.

A. Cyclization of γ-Haloamines or γ-Aminoalkyl Sulfates

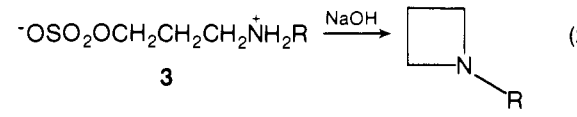
Gabriel and Weiner[1] discovered this method of azetidine formation when they obtained a small amount of the impure parent compound **1** from alkali treatment of γ-bromopropylamine (**2**) (eq **1**). Generally this method of ring closure gives poor



2 **1** (1)

yields when the amine is primary; however, the best results are obtained when the halogen is primary. When the halogen is secondary, competing reactions may dominate, and tertiary halides do not yield azetidines.

Sulfate esters of γ-amino alcohols (**3**) have been used[8] in place of γ-haloamines in the preparation of 1-substituted azetidines (eq 2). Internal nucleophilic substitution reactions of this



3 (2)

type are complicated by competing reactions. Depending upon conditions, dimerization, elimination, fragmentation, and solvolysis may compete with ring closure.

Vaughan and co-workers[8] have suggested that in the 3-aminopropyl system no substituents on any of the carbons and a large substituent on nitrogen is the most favorable case for cyclization. Neither fragmentation nor E2 elimination is expected to interfere if the C_1 leaving group is primary. Only dimerization, which can be controlled by dilution, need be considered. If the leaving group is secondary the S_N1 type process becomes more favorable with respect to the S_N2 process, and ring closure may

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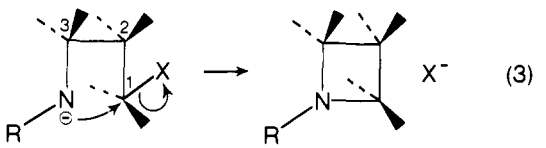
be suppressed by competing reactions of elimination and fragmentation. Vaughan also proposed that if the carbon atoms were substituted, adjacent threo substituents or C_2 geminal substituents would have little effect on the rate of cyclization (eq 3).

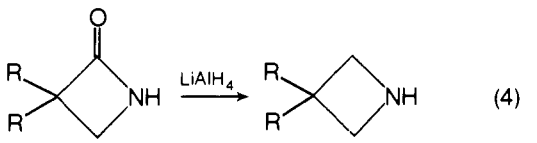


(3)

Erythro substitutes at the C_2 and C_3 positions will retard the rate and decrease the stability of the product because they must become eclipsed in the conformation leading to the transition state, as well as in the transition state and product. In general, the stability of azetidines appears to be enhanced by substitution on the ring carbons. Geminal alkyl or aryl groups especially aid in the stability of the ring as evidenced by the large number of these compounds that have been synthesized.

B. Reduction of Azetidinones and Malonimides

The reduction of 2-azetidinones (**4**) was developed mostly by Testa and co-workers[9,10] and has been widely used for azetidine synthesis (eq 4). It is necessary, however, that there be no



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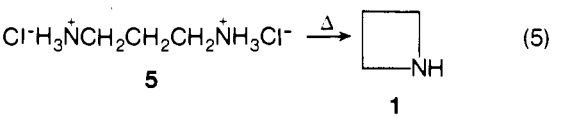
substituent upon the ring nitrogen. Reduction of N-substituted azetidinones with lithium aluminum hydride, Raney nickel, lithium aluminum hydride–aluminum chloride, sodium borohydride–aluminum chloride, and diborane all result in cleavage of the 1–2 bond to give substituted 3-aminopropanols.[11,12] A major limitation to this procedure is that there are only a few ring substituents that can survive the reduction conditions. Alkyl and aryl groups offer no problems, nor do alcohols or amines, but most other groups are attacked by lithium aluminum hydride.

C. Cyclization of 1,3-Diamines and 1,3-Dihalides

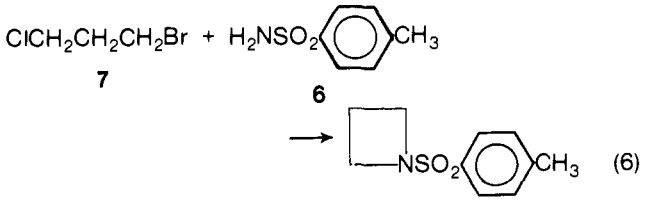
The cyclization of 1,3-diamine **5** to azetidine (**1**) was first reported by Ladenburg and Sieber[13] (eq 5). However, the yields



(5)

5 **1**

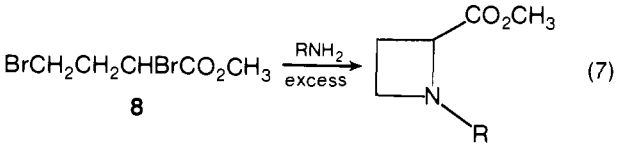
of this reaction are usually very low. An analogous reaction is the cyclization of 1,3-dihalides. Marckwald[14] reported the dialkylation of sulfonamide **6** with 1-bromo-3-chloropropane (**7**) (eq 6). This reaction, however, has not proven to be very useful



(6)

7 **6**

in the synthesis of azetidine derivatives. More recently Cromwell and co-workers have succeeded in cyclizing 1,3-dihalides **8** with amines (eq 7) in the synthesis of *N*-alkylazetidinyl esters,[15] acids,[15] and ketones.[16] The reaction is general when R is any alkyl group other than methyl; however, when R is small a complex mixture of products is obtained.



(7)

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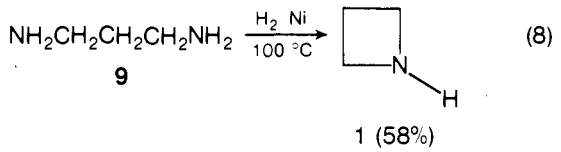
III. Azetidine

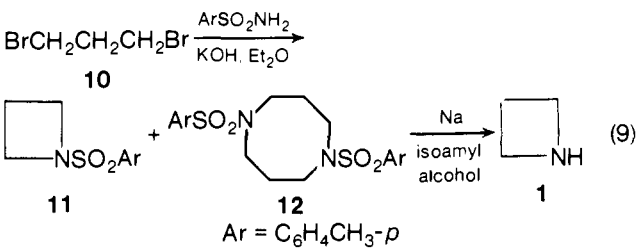
Azetidine was first synthesized in 1888 by the internal cyclization of γ-bromopropylamine[1] (eq 1). Yasamura[17] showed that 1,3-diamine **9** can be cyclized to azetidine (**1**) in approximately 58% yield employing hydrogenation over Raney nickel (eq 8).



(8)

9 1 (58%)

The method involving dialkylation of a sulfonamide, which was originally developed by Marckwald,[14] has also been useful for the preparation of azetidine. The cyclization of 1,3-dibromopropane (**10**) gave, in addition to the sulfonazetidide **11**, a small amount of the eight-membered ring disulfonamide **12** (eq 9).

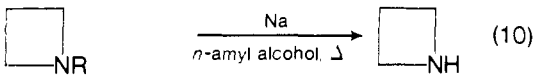


(9)

10 **11** **12** **1**

Ar = $C_6H_4CH_3$-*p*

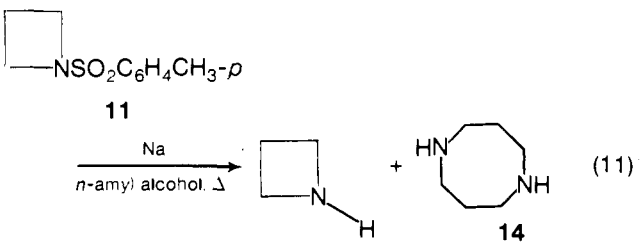
Searles and co-workers[18] have prepared *p*-toluenesulfonazetidide (**11**) from 1-bromo-3-chloropropane in 55% yield, eliminating the formation of the by-product **12**. Owing to the sensitivity of the azetidine ring to hydrolytic conditions, sulfonazetidide **11** must be converted to azetidine by reductive methods. The use of sodium in isoamyl alcohol gave azetidine in yields that varied from 14 to 80%, with most being reported around 30%.[6] Vaughan and co-workers[8] successfully modified the sodium cleavage reaction by trapping the azetidine in the hydrogen gas stream with dilute acid (eq 10). These workers reported that the



(10)

11. R = $-SO_2C_6H_4CH_3$-*p* **1**
13. R = $-SO_2CH_3$

reaction proceeded in 84.7% yield for *p*-toluenesulfonazetidide (**11**) and in 42.5% for methanesulfonazetidide (**13**). Azetidine was also obtained by the hydrogenation of *N*-benzylazetidine, but no yield was reported. Deady[19] repeated these reactions and

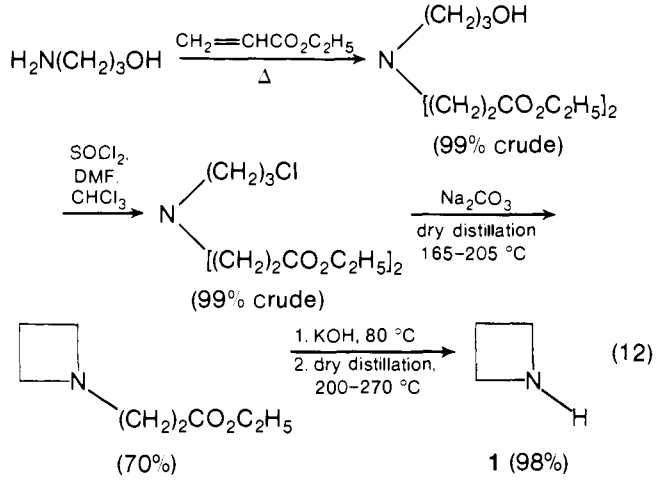


(11)

11 **1** **14**

reported lower yields due to the formation of the dimer, octahydro-1,5-diazocine (**14**) (eq 11). Vaughan also attempted Raney nickel hydrogenation of *p*-toluenesulfonazetidide (**11**), but only recovered starting material.[8] In addition lithium aluminum hydride reduction of methanesulfonazetidide (**13**) gave no azetidine.

By far the most efficient synthesis of azetidine has been reported by Wadsworth.[20] His synthetic route involves only readily available compounds and affords high yields at every step (eq 12). The overall yield from 3-aminopropanol is 69%. For all practical purposes this is the synthetic method of choice for the parent azetidine.

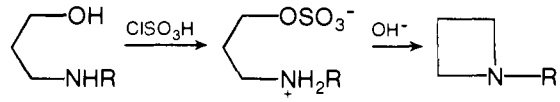


(12)

IV. *N*-Substituted Azetidines

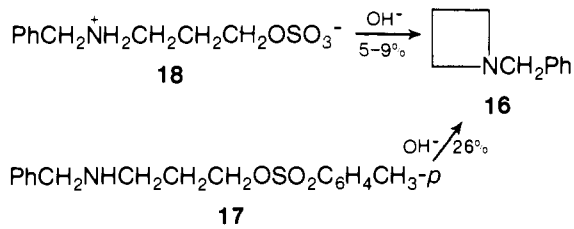
A. *N*-Alkylazetidines

3-(*N*-Alkylamino)propyl sulfates (**3**) or sulfonate esters can be cyclized to yield *N*-alkylazetidines[8] (Table I). The sulfates were readily prepared in situ by the addition of concentrated sulfuric acid or chlorosulfonic acid to the corresponding 3-(*N*-alkylamino)propanol (**15**) (eq 13). The azetidine is formed by



15 **3** (13)

treatment with base and can be distilled from the reaction mixture. Vaughan[8] postulated that cyclization to the azetidine system should be facilitated by large *N*-alkyl substituents. The data in Table I indicate that large *N*-alkyl substituents increase the yields of ring-closed product. Benzylazetidine (**16**) was prepared in 26% yield from 3-(*N*-benzylamino)propyl *p*-toluenesulfonate (**17**), as compared to 5–9% via cyclization of 3-(*N*-benzylamino)propyl sulfate (**18**) (eq 14).[8] The 26% value is more in line



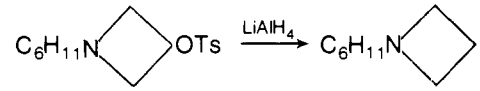
18 **16** **17** (14)

TABLE I. *N*-Alkylazetidines Prepared by Cyclization of 3-(*N*-Alkylamino)propyl Sulfates

R	bp, °C (mm/Hg)	yield, %[a]	ref
CH_3		8	18
C_2H_5		13	21
CH_2Ph	78 (5.5)	5–9	8
n-C_4H_9		30	22
C_6H_{11}	66–73 (22)	26	23
t-C_4H_9		47 (92)	23 (24)

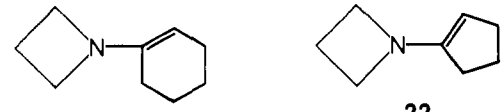
[a] Yield calculated from 3-(*N*-alkylamino)propanol.

with Vaughan's postulation of the effect of *N*-alkyl group size on cyclization. Chen and co-workers[24] prepared 1-cyclohexylazetidine (**19**) in 12% yield by lithium aluminum hydride reduction of crude 1-cyclohexyl-3-tosylazetidine (**20**) (eq 15).



20 **19** (12%) (15)

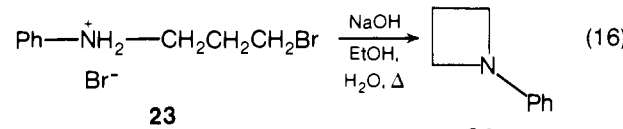
Chen[25] also reported the reaction of azetidine with cyclohexanone and cyclopentanone in benzene in the presence of potassium carbonate to give 1-(1-azetidinyl)cyclohexene (**21**) and 1-(1-azetidinyl)cyclopentene (**22**) in 22 and 15% yield, respectively.



21 **22**

B. *N*-Arylazetidines

Bottini and Nash[26] used ring closure of *N*-phenyl-3-bromopropylamine hydrobromide (**23**) to synthesize *N*-phenylazetidine (**24**) in 8% yield (eq 16). This method also gave an almost



23 **24** (16)

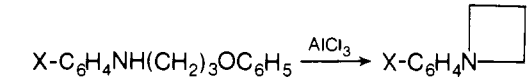
equal amount of *N*-allylaniline as well as 1-ethoxy-3-anilinopropane. Deady and co-workers[27] also prepared *N*-phenylazetidine, as well as *N*-*p*-tolylazetidine, via cyclization of the corresponding *N*-(3-bromopropyl)arylamine. These workers obtained yields in the same range (7–9%) as Bottini and Nash. The major product was formed via substitution ($ArNH(CH_2)_3OEt$), with some elimination product ($ArNHCH_2CH{=}CH_2$) being isolated.

N-Arylazetidines containing *o*- or *p*-nitro groups were prepared by a nucleophilic substitution reaction of azetidine with the corresponding haloaromatic compound (Table II).[19] The general procedure for this reaction involved heating the haloaromatic compound at 50 °C with 10 equiv of azetidine in a sealed tube. Very similar arylazetidines have also been prepared via ring closure (Table III).[27]

TABLE II. *N*-Arylazetidines Prepared by Nucleophilic Displacement

Azetidine	mp, °C
N-(*p*-nitrophenyl)azetidine	119
N-(*o*-nitrophenyl)azetidine	53.5
N-(3-methyl-4-nitrophenyl)azetidine	67–68
1-(*N*-azetidino)2,4-dinitronaphthalene	209–210
2,4-bis(*N*-azetidino)nitrobenzene	123

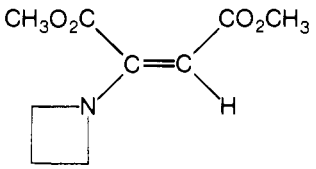
TABLE III. *N*-Arylazetidines Prepared via Ring Closure



X	yield, %	bp, °C (1 mm/Hg)
H	30	70
2-CH_3	22	58
3-CH_3	29	80
4-CH_3	25	85
2-Cl	20	85
3-Cl	20	85
4-Cl	22	80
4-OCH_3	6	80
2,4,6-$(CH_3)_3$	5	78

C. Miscellaneous N-Substituted Azetidines

The reaction of azetidine with activated double and triple bonds and the condensation reaction of azetidine with ketones have been studied by Chen and co-workers.[25,28] The addition of azetidine to dimethyl acetylenedicarboxylate proceeded exothermally to give dimethyl (1-azetidinyl)maleate (**25**) in 57% yield. However, when methyl propiolate was used, only a 5.2% yield of methyl β-(1-azetidinyl)acrylate (**26**) was isolated. The



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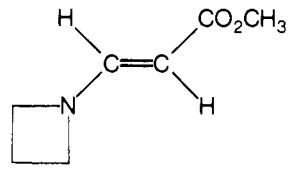

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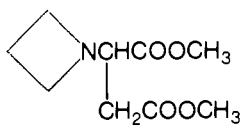
stereochemistry of the addition reaction was followed by NMR. In aprotic solvents only cis addition occurred, irrespective of the polarity of the solvent used. In methanol, however, some trans addition did occur with an approximate ratio of cis-to-trans addition product of 2:1. The reaction of azetidine with dimethyl fumarate or maleate gave dimethyl (1-azetidinyl)succinate (**27**) in 57 and 48% yield, respectively. Similarly β-(1-azetidinyl)-propionitrile (**28**) was formed in 56% yield by the addition of



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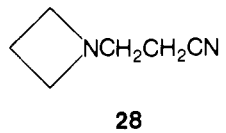
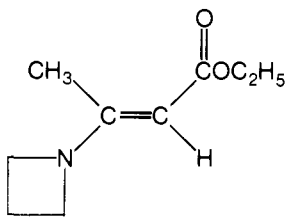


28

azetidine to acrylonitrile. The condensation of ethyl acetoacetate with azetidine in ether, in the presence of sodium sulfate, gave ethyl β-(1-azetidinyl)crotonate (**29**) in 68% yield. The condensation product 2-(1-azetidinyl)pent-2-en-4-one (**30**) was obtained from acetylacetone. This product was originally reported[28] to be a salt of acetylacetone; however, the misassignment was later corrected.[25]



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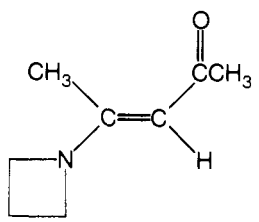
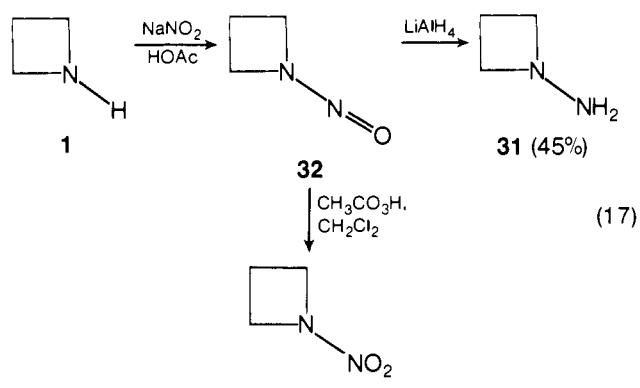


30

Roberts and Horvitz[29] synthesized *N*-aminoazetidine (**31**) in 45% yield by reduction of *N*-nitrosoazetidine (**32**) with lithium aluminum hydride. They prepared *N*-nitrosoazetidine by the method of Howard and Marckward.[30] Baumgardner and co-workers[31] reported the oxidation of *N*-nitrosoazetidine (**32**) to *N*-nitroazetidine (**33**) in 47% yield (eq 17).

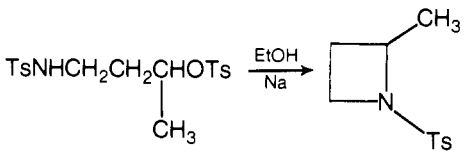


1 **32** **31** (45%) **33** (47%) (17)

V. 1,2-Substituted Azetidines

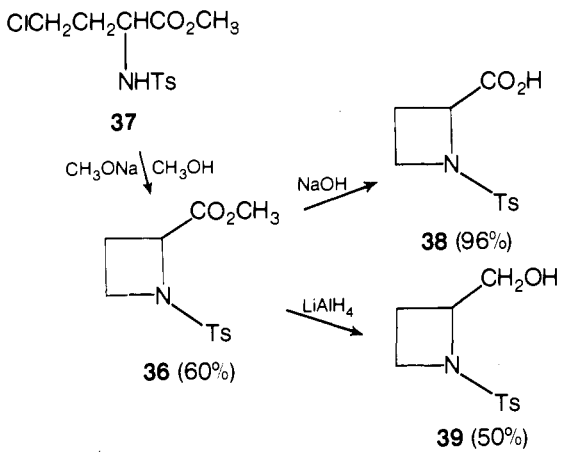
A. N-Tosyl-2-substituted Azetidines

Cyclization of 4-(*p*-toluenesulfonamide)-2-butyl *p*-toluenesulfonate (**34**) using sodium in ethanol gave a 68% yield of *N*-tosyl-2-methylazetidine (**35**) (eq 18).[8] Dimerization was ap-



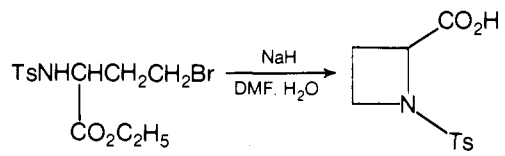
34 **35** (68%) (18)

preciable at lower concentrations, and best results were obtained using high-dilution addition techniques. Chen et al.[32] treated methyl α,γ-dibromobutyrate with tosylamide under a variety of basic conditions but failed to obtain the desired azetidinyl tosylate **36** (eq 19). However, treatment of methyl α-tosylamino-γ-chlorobutyrate (**37**) with sodium methoxide gave a 60% yield of methyl 1-tosylazetidine-2-carboxylate (**36**). The tosylate **36**



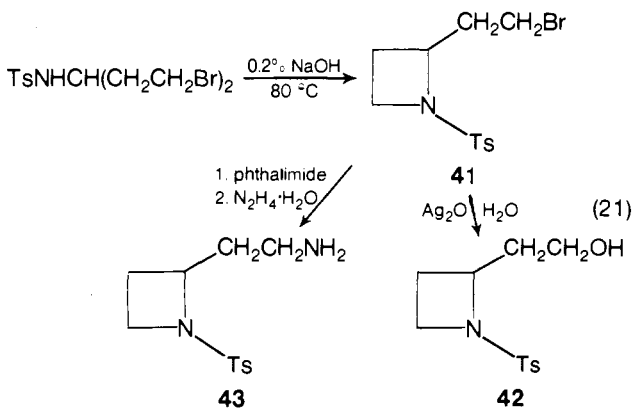
37 **38** (96%) **36** (60%) **39** (50%) (19)

was then converted by sodium hydroxide to the corresponding acid **38,** and by lithium aluminum hydride to the azetidinyl carbinol **39.** More recently Miyoshi and co-workers,[33] while synthesizing azetidine-2-carboxylic acid, were able to convert ethyl α-tosylamino-γ-bromobutyrate (**40**) to the azetidinyl acid (**38**) in 95% yield using sodium hydride in wet dimethylformamide



40 **38** (95%) (20)

(eq 20). Taniyama and Yasui[34,35] have reported the synthesis in good yield of an *N*-tosylazetidinyl bromide **41,** alcohol **42,** and amine **43** (eq 21).



41 **43** **42** (21)

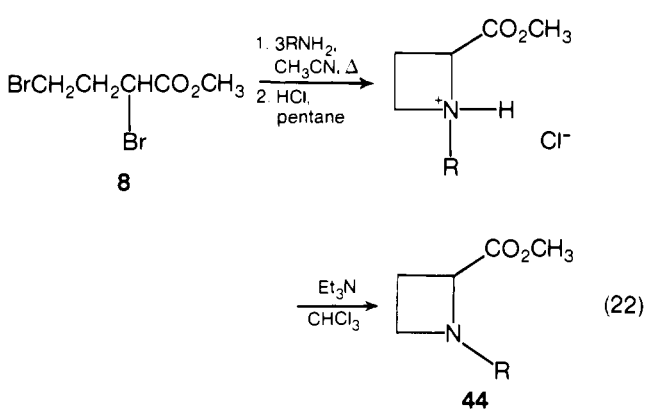
TABLE IV. *N*-Alkylazetidine-2-carboxylates Prepared via Cyclization of 1,3-Dihalides

R	R′	bp, °C (mm/Hg)	yield, %[a]	ref
t-C_4H_9	CH_3	55-56 (2)	35.9	15
C_6H_{11}	CH_3	95-97 (2)	38.0	15
CH_2Ph	CH_3	112-113 (1.5)	34.0	15
$C(CH_3)_2CH_2C(CH_3)_3$	CH_3	83-85 (0.7)	61.8	37
$CHPh_2$	CH_3	142-144 (0.25)	72.2	37
$CH(CH_3)_2$	CH_3	40-42 (0.6)	61.5	37
$CHPh_2$	CH_2Ph	61-63 mp	82.7	16
t-C_4H_9	CH_2Ph	118-119 (0.65)	72.8	37
C_6H_{11}	CH_2Ph	141-142 (0.5)	56.4	37
$CH(CH_3)_2$	CH_2Ph	113-115 (0.9)	54.2	37

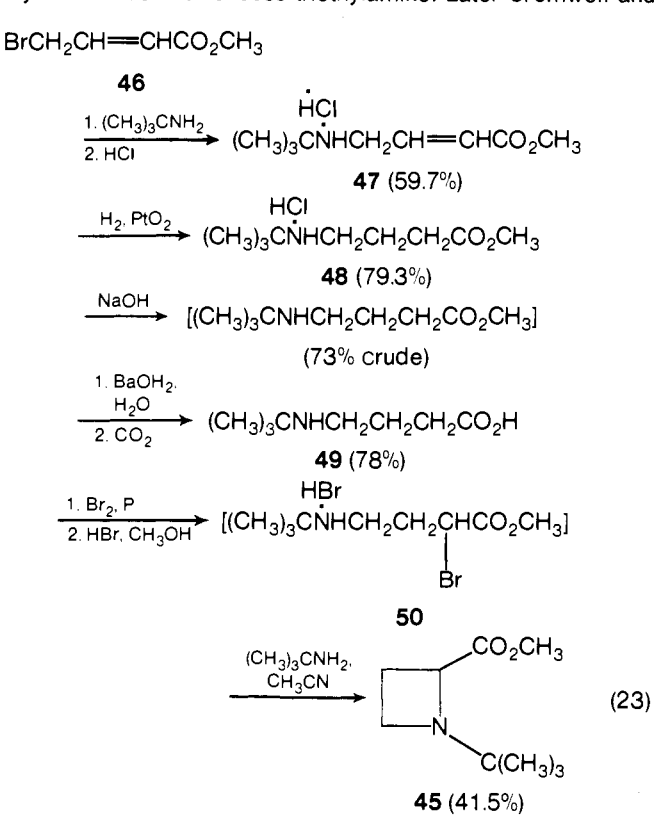
[a] Yields based on conversion from 1,3-dihalide.

B. 1-Alkylazetidine-2-carboxylates

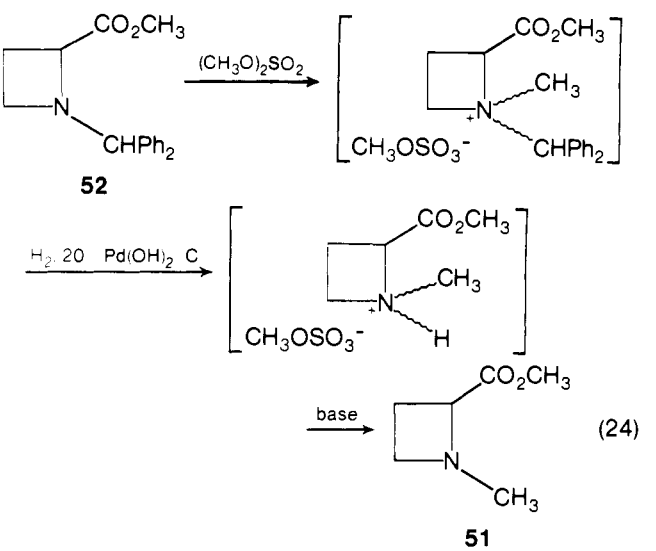
In 1968 Cromwell and Rodebaugh[15] succeeded for the first time in cyclizing 1,3-dibromides with primary amines to form *N*-alkyl-2-carboalkoxyazetidines (eq 22). Methyl α,γ-dibromobutyrate (**8**), which can be obtained in high yield by bromination of γ-butyrolactone,[36] was allowed to react with several primary amines to give the corresponding 1-alkyl-2-carbomethoxyazetidines (**44**) (Table IV). The dibromo ester **8** was refluxed with 3 mol of amine for 24 h, and the azetidine was liberated from its hydrochloride with excess triethylamine. Later Cromwell and Rodebaugh[16,37] extended this procedure to the synthesis of carbobenzyloxyazetidine derivatives.



1-*tert*-Butyl-2-carbomethoxyazetidine (**45**) was prepared[38] from methyl γ-bromocrotonate (**46**) (eq 23). Two molar equivalents of *tert*-butylamine was allowed to react with **46** at room temperature forming the corresponding *tert*-butylaminocrotonic ester, which was isolated as the hydrochloride salt **47.** Catalytic reduction of **47** provided the corresponding saturated amino ester hydrochloride **48** which when neutralized and hydrolyzed under alkaline conditions gave γ-*tert*-butylaminobutyric acid (**49**). Phosphorus-catalyzed bromination of amino acid **49** followed by esterification with acidified methanol gave methyl α-bromo-γ-*tert*-butylaminobutyrate hydrobromide (**50**) as an intermediate. Hydrobromide **50** was not isolated but was treated with *tert*-butylamine in refluxing acetonitrile to give the azetidinyl ester **45.**



The reaction of α,γ-dibromo esters with primary amines appears to be general, except when the primary alkyl group is small. 1-Methyl-2-carbomethoxyazetidine (**51**) has, however, been synthesized in 8% yield by a round-about route starting from 1-benzhydryl-2-carbomethoxyazetidine (**52**) (eq 24).[37]



C. 1-Alkylazetidine-2-carboxylic Acids, Amides, Carbinols, Hydrazides, and Ketones

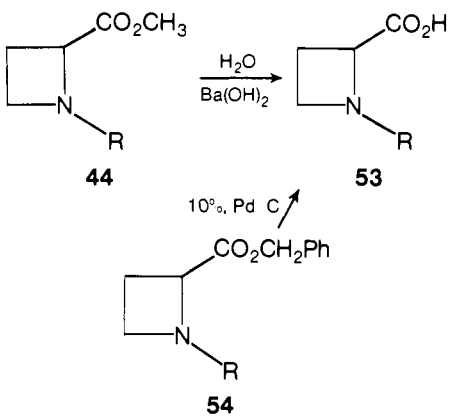
1-Alkyl-2-carbomethoxyazetidines (**44**) have been converted to the corresponding 1-alkylazetidine-2-carboxylic acids[15] (**53**) (Table V) by basic hydrolysis with barium hydroxide octahydrate (eq 25). Acids **53** have also been prepared in good yield by hydrogenolysis of 1-alkyl-2-carbobenzyloxyazetidine (**54**) over 10% palladium on charcoal (eq 25).

1-Alkyl-2-azetidinyl esters and acids have been converted into several 1-alkyl-2-substituted azetidine derivatives. Treatment of 1-*tert*-butylazetidine-2-carboxylic acid (**55**) with triethylamine

TABLE V. 1-Alkylazetidine-2-carboxylic Acids (53)

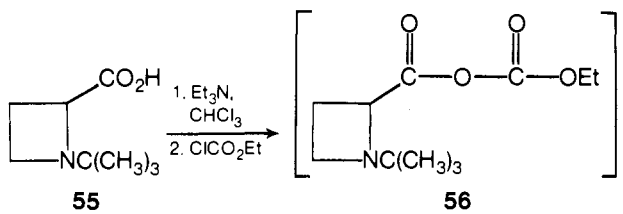
R	method of prepn[a]	yield, %	mp, °C	ref
t-C_4H_9	A	69	173–175	15
t-C_4H_9	B			38
C_6H_{11}	A	71	176–178	15
C_6H_{11}	B			38
CH_2Ph	A	82	159–161	15
$CH(CH_3)_2$	A	81		38
$CH(CH_3)_2$	B	93	177–179	38

[a] A, $Ba(OH)_2$ hydrolysis of ester; B, hydrogenolysis of benzyloxy ester.

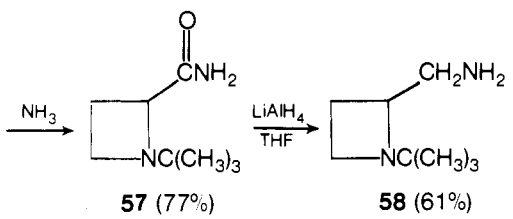


44 53 54 (25)

in chloroform at 0 °C, followed by addition of ethyl chloroformate, gave the corresponding mixed acid anhydride **56,** which, when treated with anhydrous ammonia, afforded azetidinyl amide **57** (eq 26).[38] Other 1-alkylazetidine-2-carboxylic acids, when

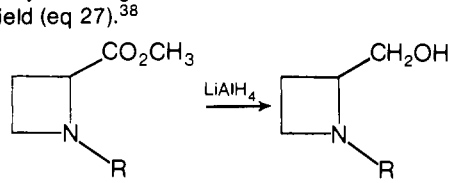


55 56



57 (77%) 58 (61%) (26)

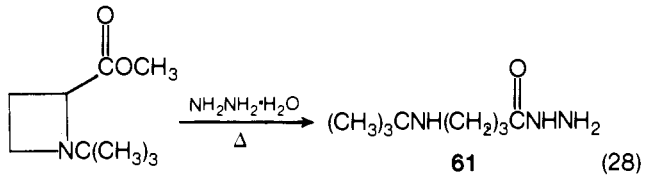
allowed to react under similar conditions, gave oily products which were not further characterized. Reduction of amide **57** with lithium aluminum hydride in refluxing tetrahydrofuran provided 1-*tert*-butyl-2-aminomethylazetidine (**58**) in 61% yield.[38] 1-Alkyl-2-carbomethoxyazetidines were reduced with lithium aluminum hydride to give N-substituted azetidine-2-carbinols **59** in high yield (eq 27).[38]



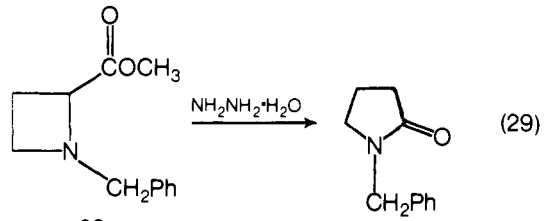
59 (27)

R = t-C_4H_9, C_6H_{11}, $CH(CH_3)_2$, $CH_2C_6H_5$
yield (80–88%)

Cromwell and Rodebaugh[38] reported the reaction of *N*-*tert*-butyl- (**45**), and *N*-benzyl-2-carbomethoxyazetidine (**60**) with excess hydrazine hydrate at reflux temperature. The open-chain

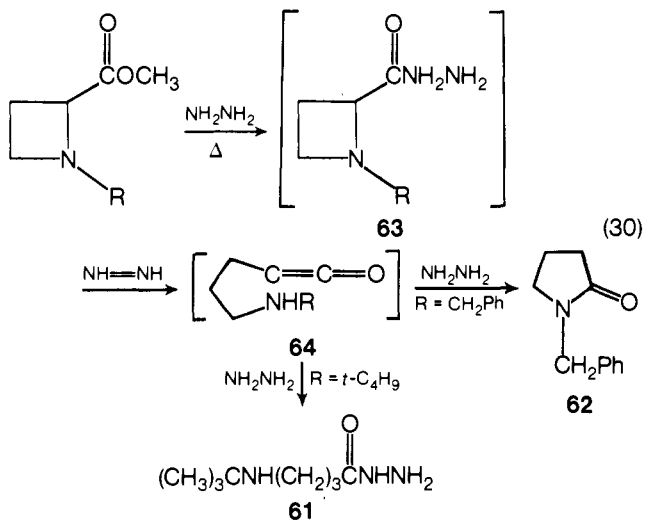


45 61 (28)



60 62 (29)

carbohydrazide **61** (eq 28) and pyrrolidine **62** (eq 29) were isolated, respectively. The authors postulated that the mechanism of these reactions proceeds via initial formation of the azetidinyl hydrazide **63,** followed by ketene **64** formation by loss of diimide (eq 30). In the case of *N*-*tert*-butyl-2-carbomethoxyazetidine,

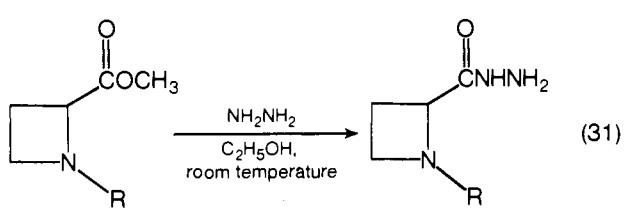


63 (30)

64 62 61

the ketene intermediate is attacked by another mole of hydrazine to give the open-chain carbohydrazide **61,** and in the case of the *N*-benzyl analog, the ketene intermediate reacts intramolecularly to give pyrrolidine **62.** This was explained by the small steric requirement of the benzyl group, allowing intramolecular attack, whereas the sterically large *tert*-butyl group favored an intermolecular reaction.

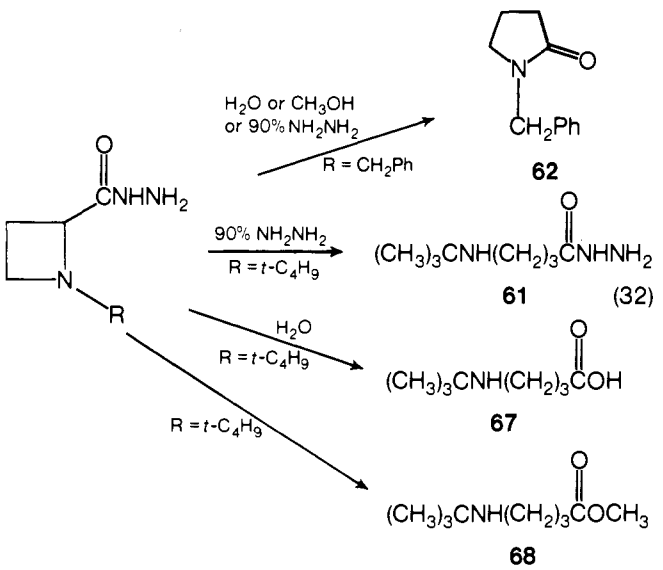
Later Cromwell and co-workers[39] offered evidence to substantiate this proposed mechanism. Reaction of 90% hydrazine hydrate with 1-alkyl-2-carbomethoxyazetidines in ethanol at room temperature gave 1-alkylazetidine-2-carbohydrazides (eq 31). Refluxing **66** respectively in water, methanol, or 90% hydrazine hydrate gave *N*-benzyl-2-pyrrolidone **62** in all cases. Refluxing **65** in 90% hydrazine hydrate yielded γ-*tert*-butylaminobutyrohydrazide **61,** quantitatively. Similar treatment of **65**



(31)

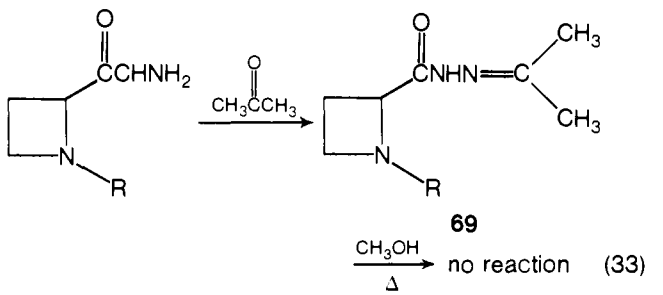
65, R = t-C_4H_9
66, R = CH_2Ph
R = $CH(Ph)_2$
R = C_6H_{11}

in water or methanol gave γ-*tert*-butylaminobutanoic acid (**67**) and γ-*tert*-butylaminobutyrate (**68**), respectively (eq 32). These



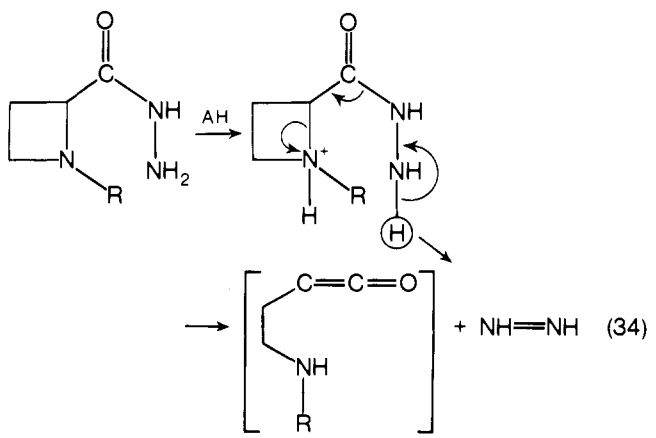
(32)

results indicate that an 1-alkylazetidine-2-carbohydrazide in the first intermediate formed in the reaction between hydrazine and different 1-alkyl-2-carbomethoxyazetidines. Treatment of 1-alkylazetidine-2-carbohydrazides with acetone gave quantitatively the carboxylic hydrazone derivative of acetone (**69**), which was found to be stable in refluxing methanol (eq 33).



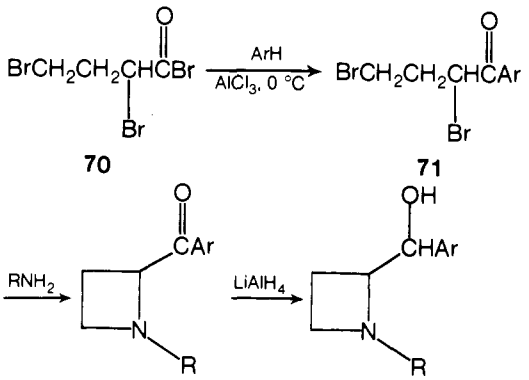
(33)

The intermediacy of diimide in these reactions was also proven by observation of concurrent reduction of azobenzene to hydrazobenzene in the conversion of **65** and **66** to **61** and **62**, respectively. The decomposition of the 1-alkylazetidine-2-carbohydrazide was described as taking place by the mechanism shown in eq 34.



(34)

Cromwell and Rodebaugh used the cyclization of α,γ-dihalides with amines to synthesize the first reported 2-ketoazetidine (eq 35).[16] α,γ-Dibromobutyryl bromide (**70**) was treated with benzene and aluminum chloride to give α,γ-dibromobutyrophenone **71**. The dibromo ketone **71** was condensed with *tert*-butylamine to give 1-(*tert*-butyl)-2-benzoylazetidine (**72**), which



(35)

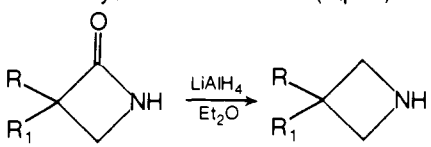
72, R = *t*-C4H9; Ar = Ph
73, R = *t*-C4H9; Ar = Ph
74, R = *t*-CH(CH3)2; Ar = Ph
75, R = *t*-C4H9; Ar = *p*-PhC6H4
76, R = CH3; Ar = *p*-PhC6H4
77, R = CH3; Ar = *p*-PhC6H4

gave 1-(*tert*-butyl)-2-azetidinephenylcarbinol (**73**) upon reduction with lithium aluminum hydride in a diastereomeric ratio of 30:70. This synthesis was later extended to include 1-isopropyl-2-benzoylazetidine (**74**), 1-*tert*-butyl-2-*p*-phenylbenzoylazetidine (**75**) and 1-methyl-2-*p*-phenylbenzoylazetidine (**76**).[37,38] The azetidinyl ketone **76** was also converted by lithium aluminum hydride reduction to 1-methyl-2-azetidinylarylcarbinol (**77**).[37]

VI. 1,3-Substituted Azetidines

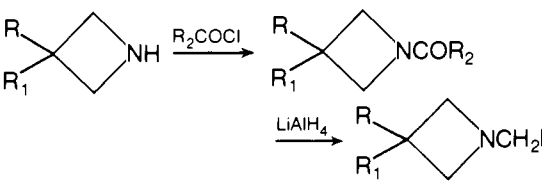
A. Miscellaneous 1,3-Substituted Azetidines

Reduction of lactams to the corresponding cyclic imines with lithium aluminum hydride is an excellent general method with five-, six-, and seven-membered rings,[6] but early attempts[40a,b] to apply the same conversion to tertiary 2-azetidinones with phenyl or benzyl substituents on nitrogen gave almost exclusively ring cleavage and reduction to the corresponding *sec*-aminopropanols. Testa and co-workers[9] found, however, that azetidinones without a nitrogen substituent could be reduced with lithium aluminum hydride to azetidines (eq 36). The reaction



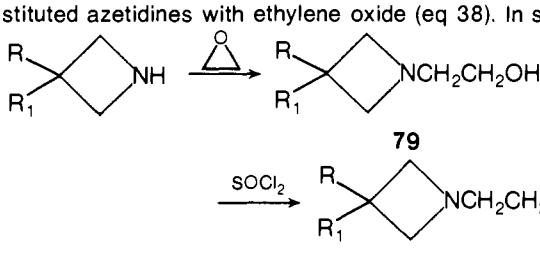
(36)

worked well for 3-monosubstituted or 3,3-disubstituted 2-azetidinones. The reduction of both carbonyl groups of 3,3-disubstituted-1-unsubstituted malonimides to azetidines was also found to be useful.[10] Tertiary azetidines could be prepared, however, by acylating the azetidine and reducing the azetidinyl amide with lithium aluminum hydride (eq 37).[41,42]

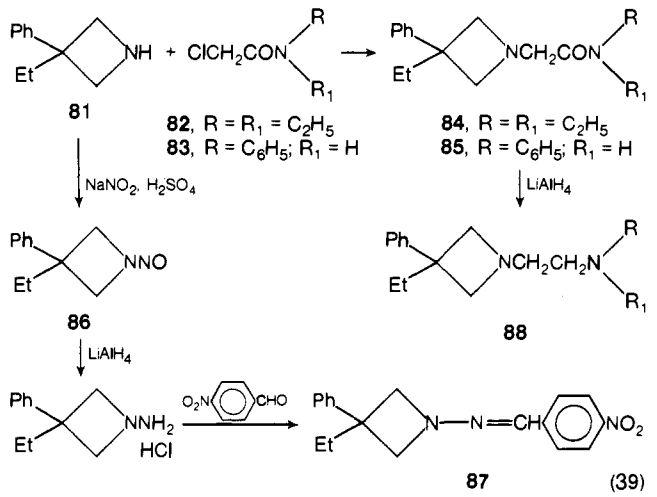


(37)

Testa[43] has also studied the addition reaction of 3,3-disubstituted azetidines with ethylene oxide (eq 38). In several in-



(38)



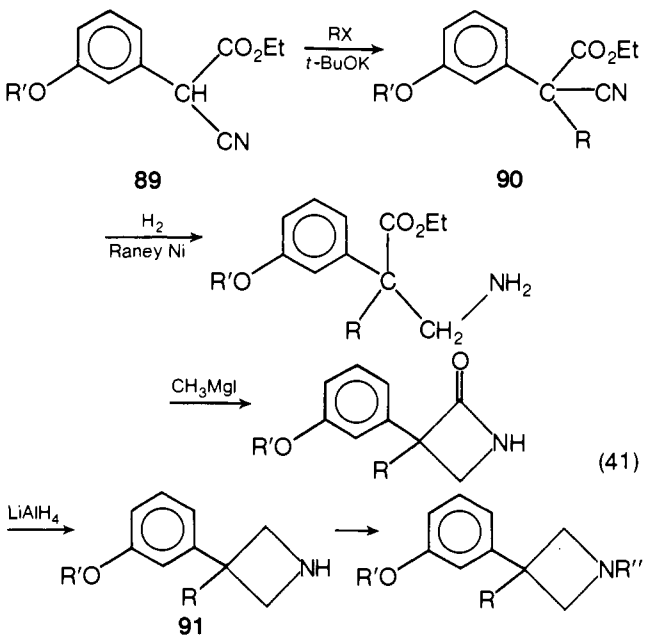
(39)

stances the azetidinyl alcohol **79** was allowed to react with thionyl chloride to form the chloro compound **80.** The reaction of 3-phenyl-3-ethylazetidine (**81**) with the activated chloro compounds **82** and **83** was reported to go in high yield, while the reaction with nitrous acid to form the *N*-nitroso azetidine went in only fair yield (eq 39). The nitrous acid reaction was performed with dilute acid; stronger sulfuric acid would surely have cleaved the ring. The further reduction of **86** and aldehyde condensation to **87** went in good yields. Azetidinyl amides **84** and **85** were also reduced with lithium aluminum hydride to **88;** see eq 39.

Some of the chemistry of 1,3-disubstituted azetidines that have other functional groups on their substituents has also been reported by Testa and co-workers (eq 40).[44]

Bishop and co-workers[45] used the procedure developed by Testa[41,43] to synthesize a series of 1,3-disubstituted azetidines (eq 41) and examined them for analgesic activity.

It was found that using sodium ethoxide, as Testa did, as the basic reagent in the C-alkylation of cyanoacetate **89** gave lower yields of **90** than did sodium or potassium *tert*-butoxide. The azetidines **91** were converted to N-substituted derivatives via

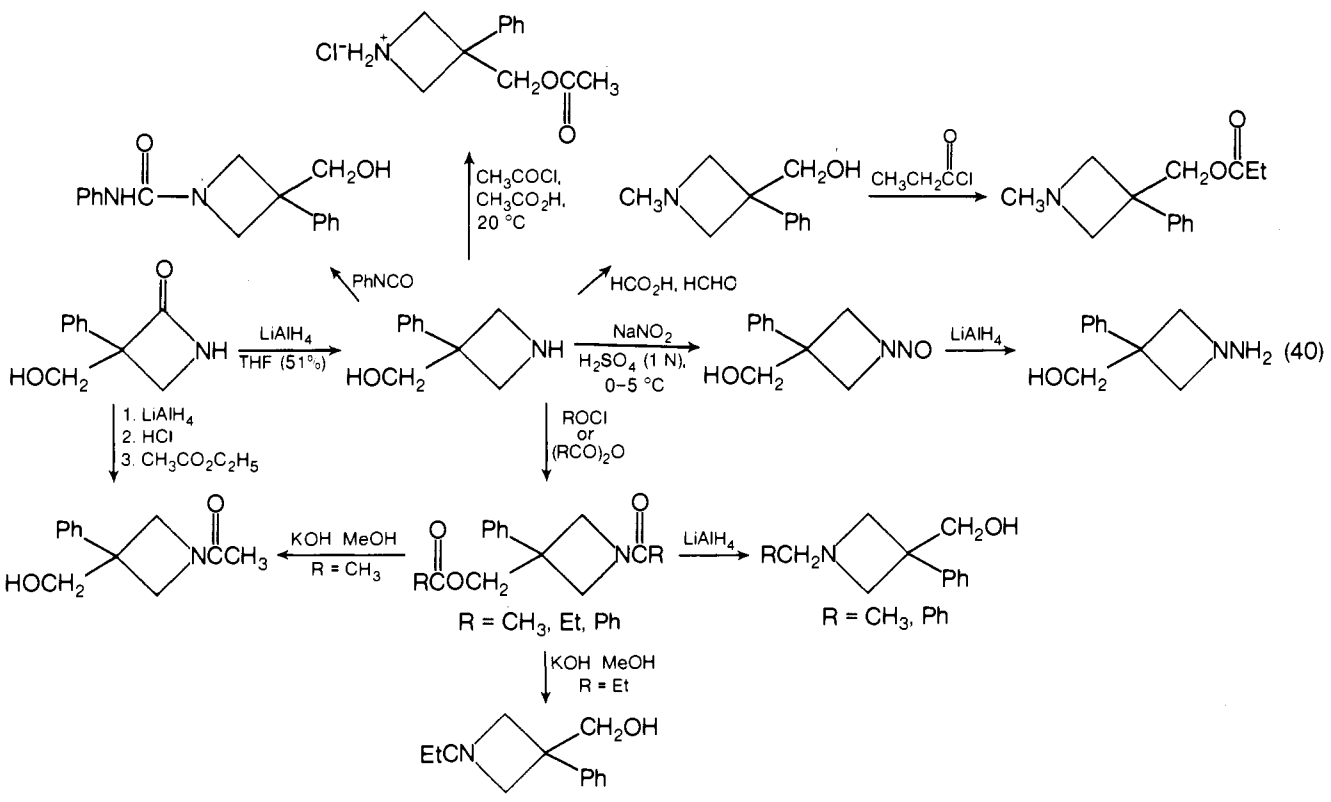


(41)

a variety of methods (Table VI).

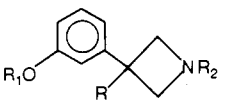
Bellasio and Cristiani[46] reported the synthesis of a series of 3,3-disubstituted *N*-(β-guanidinoethyl)azetidines **92** and 3,3-disubstituted *N*-guanylazetidines **93** (Table VII) in search of compounds that possessed hypotensive activity (eq 42). None of these compounds showed a significant activity.

Anderson and Wills[47] used the ring closure of α-aminoalkyl sulfates or sulfonate esters to prepare some N-substituted 3,3-dimethylazetidines (eq 43). The hydroxyaldehyde **94** was readily available from the base-catalyzed condensation of formaldehyde with isobutyraldehyde. Reductive alkylation of **94** gave the 2,2-dimethyl-3-hydroxypropanols **95–97.** The creation of a suitable leaving group was achieved by conversion of the hydroxyl function to a sulfate group. The transformation of **97** to **100** was affected with concentrated H_2SO_4. Treatment of the inner salts **98–100** with aqueous alkali gave the corresponding



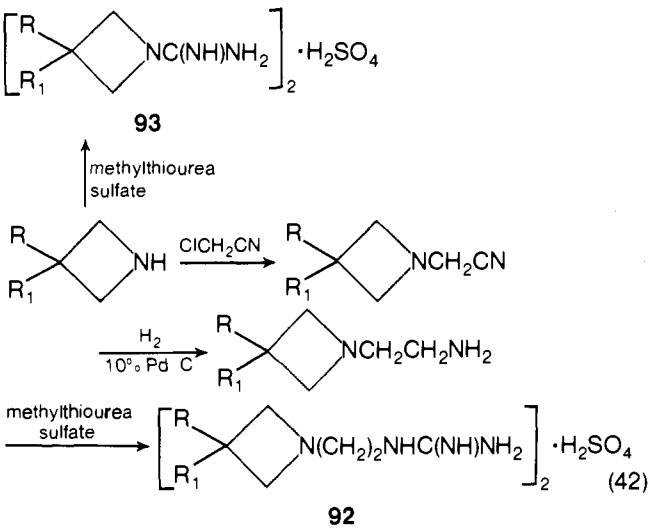
(40)

TABLE VI. 1-Substituted-3-arylazetines



R	R′	R″	mp bp (mm/Hg), °C	pK	yield, %
Me	Me	H	152–153[a]	9.45	74
Me	Me	Me	78–80 (0.2)	8.39	55
Me	H	Me	154–155	8.60	37
Me	Me	$(CH_2)_2Ph$	140–142 (0.09)	8.34	50
Et	Me	H	114 (1.0)		84
Et	Me	Me	88 (0.5)		74
n-Pr	Me	H	115 (0.9)	9.44	60
n-Pr	Me	Me	117–118[a]	8.28	85
n-Pr	H	Me	147–149	8.53	85
n-Pr	COMe	Me	123 (0.8)	8.20	95
n-Pr	CH_2Ph	Me	52–53		53
n-Pr	H	Et	121–123		72
n-Pr	Me	$(CH_2)_2Ph$	174–178 (0.5)	7.6	50
n-Pr	H	$(CH_2)_2Ph$	70–73[a]	11	50
n-Pr	CH_2Ph	$(CH_2)_2C_6H_4$-*p*-NO_2	114–115		91
n-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NO_2	53–56	7.4	85
n-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NH_2	245–246[b]		89
n-Pr	Me	COMe	162–163 (0.5)		65
n-Pr	H	COMe	98–100		96
n-Pr	CH_2Ph	COMe	99–101		92
n-Pr	Me	COEt	160–163 (0.5)		42
n-Pr	Me	CO_2Et	128–130 (0.1)		84
n-Pr	Me	$CONH_2$	159–160		80
n-Bu	Me	H	134 (1.5)		69
n-Bu	Me	Me	113–114 (0.8)		82
n-Bu	H	Me	132–133		53
n-Am	Me	H	104–105[a]	9.48	55
n-Am	Me	Me	109–111 (0.45)	9.28	55
n-Am	H	Me	153–155	8.0	40
n-Am	Me	$(CH_2)_2Ph$	75–82		47

[a] Hydrochloride. [b] Dihydrochloride.



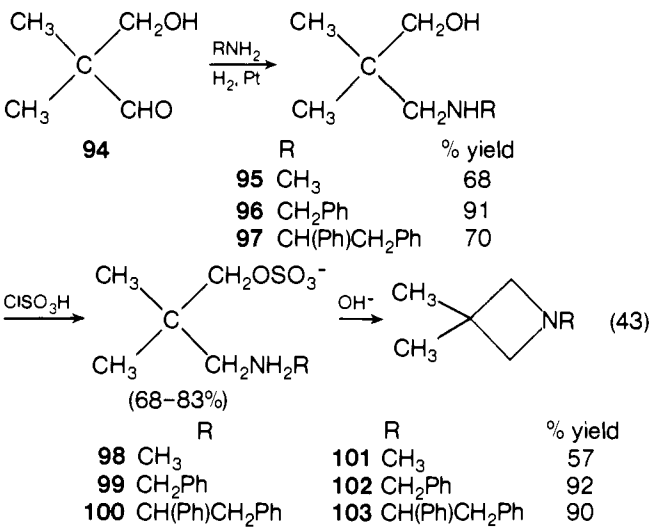
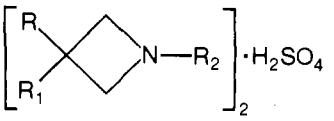


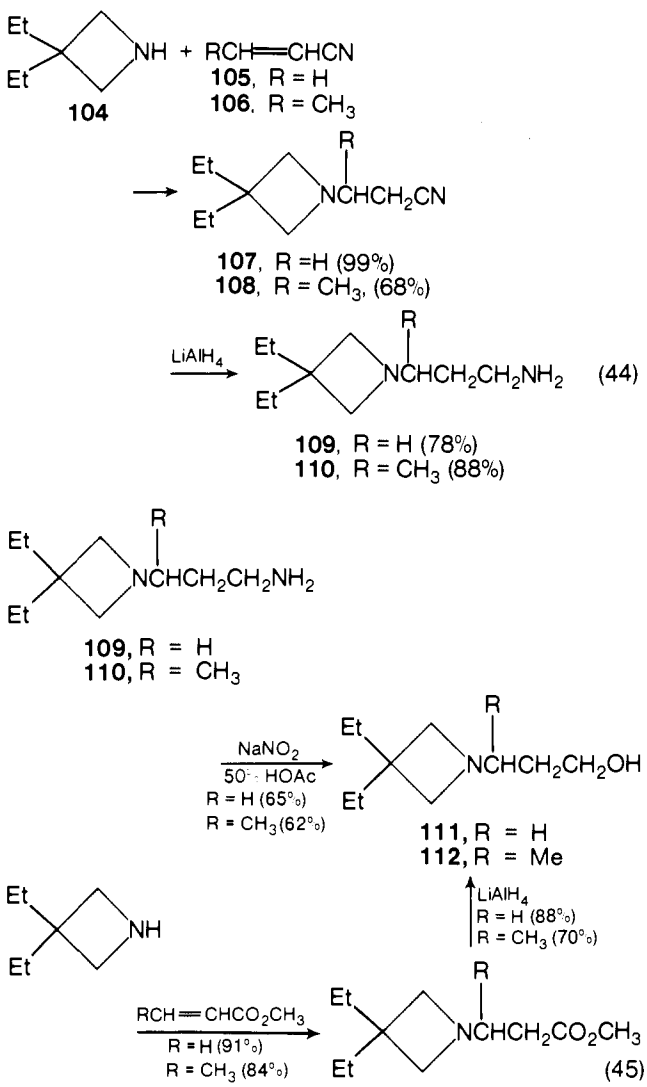
TABLE VII. *N*-(β-Guanidinoethyl)- and *N*-Guanylazelidines



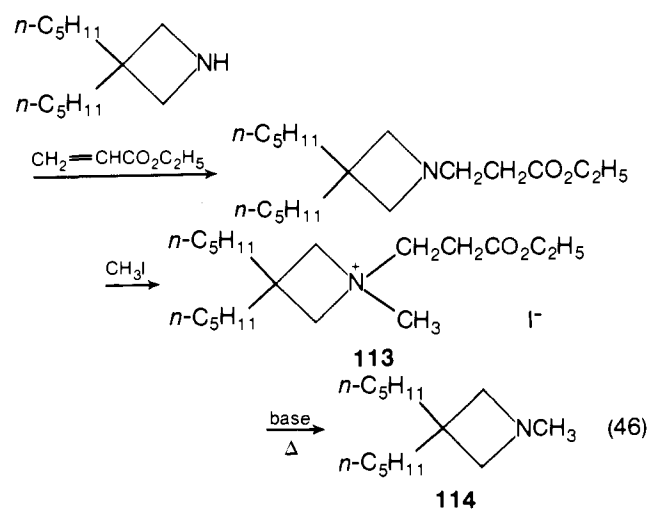
R	R_1	R_2	mp, °C	yield, %
n-C_3H_7	*n*-C_3H_7	$(CH_2)_2NHC(NH)NH_2$	187–189	91
CH_3	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	239–240	56
C_2H_5	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	214–215	87
n-C_4H_9	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	151–154	73
C_2H_5	C_6H_5	$C(NH)NH_2$	278–281	79
n-C_4H_9	C_6H_5	$C(NH)NH_2$	240–241	68

azetidines **101–103.**

Chen[48] reported the addition of 3,3-diethylazetidine (**104**) to acrylonitrile (**105**) and crotononitrile (**106**) to give β-(3,3-diethylazetidenyl)-1-propionitrile (**107**) and 3-(3,3-diethylazetidinyl)-1-butylamine (**108**), respectively (eq 44). The azetidinyl nitriles were reduced to the corresponding azetidinylpropylamines **109** and **110.** The deamination products of amines **109** and **110** were identical with alcohols **111** and **112** prepared by the addition of diethylazetidine to methyl acrylate and crotonate, followed by reduction with lithium aluminum hydride (eq 45). It is worth noting that deaminations with nitrous acid gave yields in the 60's. It is surprising that the azetidine ring could withstand those conditions.



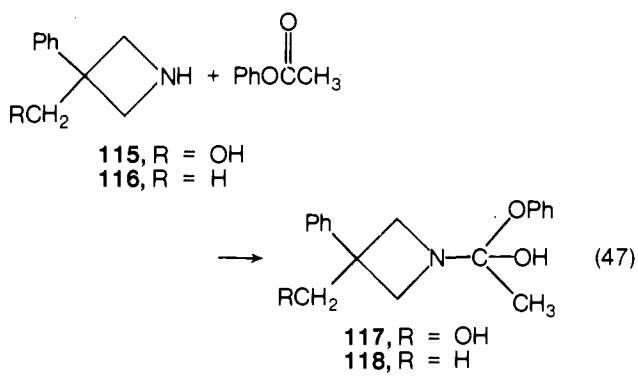
Wadsworth and Schupp[49] used the Hoffman decomposition of 1-(2-carboethoxyethyl)-1-methyl-3,3-di(*n*-pentyl)azetidinium iodide (**113**) to synthesize 1-methyl-3,3-di(n-pentyl)azetidine (**114**) (eq 46). The azetidine **114** was prepared quantitatively by heating a mixture of **113** with an equal weight of sodium bicarbonate or sodium carbonate. This procedure offers an advantage when *N*-methylazetidine derivatives are desired.



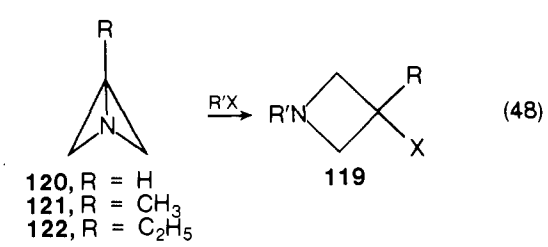
Bruce and co-workers[50,51] studied the nucleophilicity of two azetidines **115** and **116** in their reaction with phenyl acetate to form the azetidine derivatives **117** and **118.** The authors felt initially that the enhanced nucleophilicity of these azetidines, with respect to other organic bases, was due to less crowding in the transition state. However, after completing their Hammett plots they found that they could not directly relate the ρ value to steric factor or the pK_a of the base.

TABLE VIII. 1,3-Substituted Azetidines Prepared from 1-Azabicyclo[1.1.0]butanes

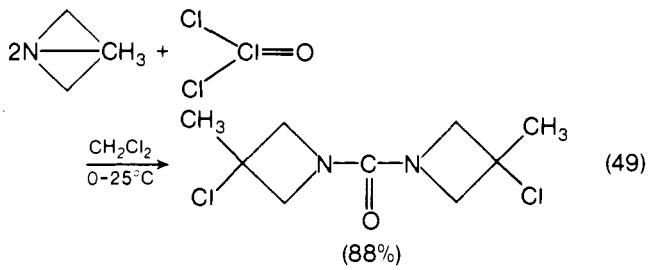
azabicyclobutane	R'X	azetidine	yield, %
120	*p*-$CH_3C_6H_4SO_2Cl$	*p*-$CH_3C_6H_4SO_2N$ Cl	72
121	*p*-$CH_3C_6H_4SO_2Cl$	*p*-$CH_3C_6H_4SO_2N$ CH_3 Cl	62
122	*p*-$CH_3C_6H_4SO_2Cl$	*p*-$CH_3C_6H_4SO_2N$ C_2H_5 Cl	85
121	PhCOCl	PhCON CH_3 Cl	48
121	PhCOCl	CH_3CON CH_3 Cl	70
121	CH_3CO CH_3CO O	CH_3CON CH_3 $OCOCH_3$	56
120	PhSH	HN H SPh	64
121	PhSH	HN CH_3 SPh	79
121	NH	HN CH_3 N	36
121	NH	HN CH_3 N	50
121	HCl	H_2N^+ CH_3 Cl Cl^-	85

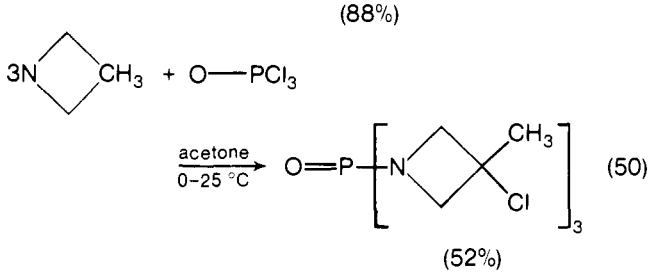


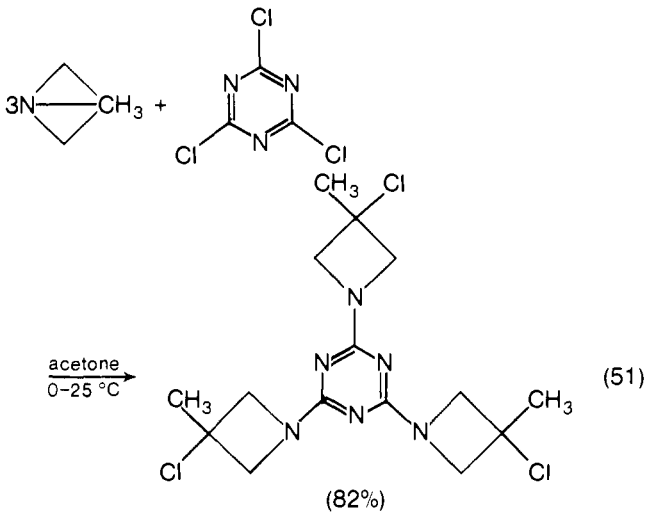
Funke[52,53] has reported the synthesis of azetidines **119** (Table VIII) via the reaction of acid halides, acid anhydrides, thiophenols, and amines with 1-azabicyclo[1.1.0]butanes **120–122** (eq 48).

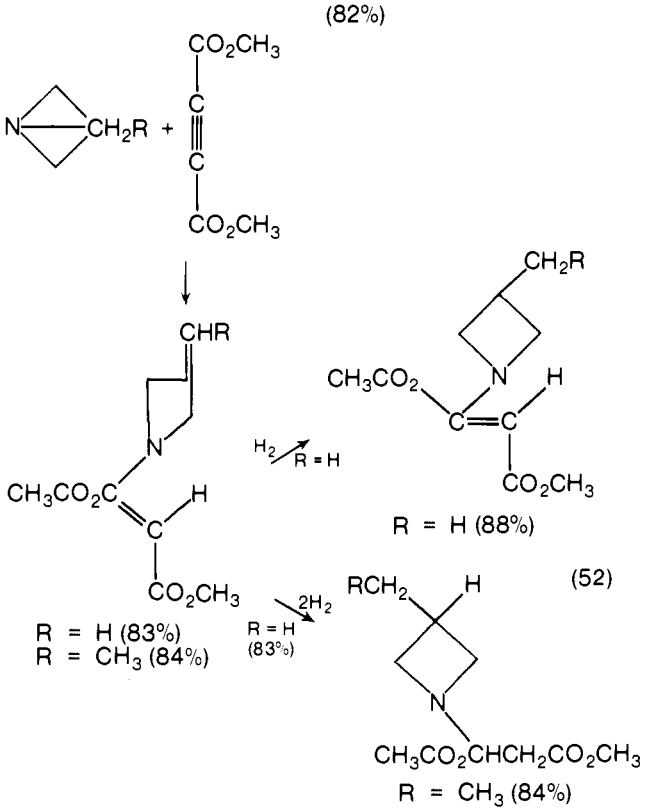


Several other reactions of 1-azabicyclo[1.1.0]butanes were also reported (eq 49–52).

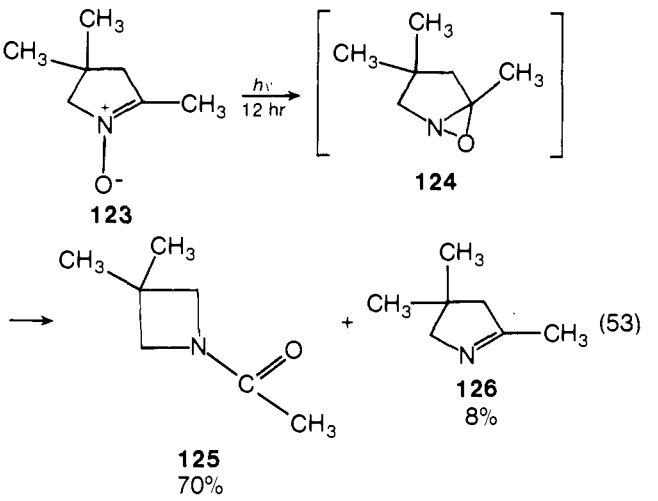






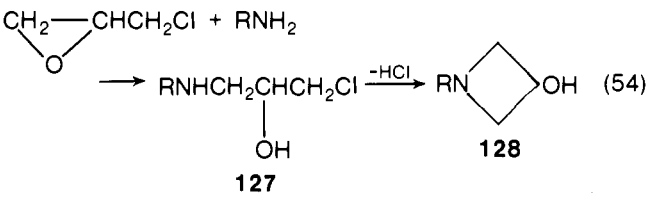


In a very specific reaction prolonged irradiation of 2,4,4-trimethyl-1-pyrroline 1-oxide (**123**) gave 3,3-dimethyl-*N*-acetylazetidine and a pyrroline derivative (eq 53).[19] The reaction was shown to proceed via the intermediate oxaziridine **124.**

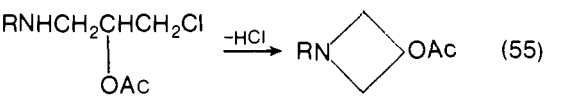


B. N-Substituted Azetidin-3-ols

The chemistry of azetidin-3-ols blossomed after Gaertner reported a simple two-step method for their preparation.[55,56] He found that 1-alkylamino-3-chloro-2-alkanols carrying tertiary, secondary, or hindered primary *N*-alkyl groups cyclized spontaneously, optimally at 50 °C (eq 54). Moderate steric hindrance



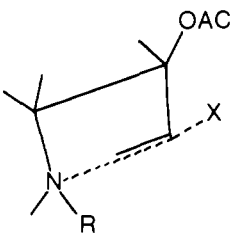
in the alkyl group is apparently necessary to suppress intermolecular reactions. *n*-Alkyl or aryl groups did not provide sufficient hindrance or nucleophilicity. The 1-alkylamino-3-chloro-2-propanols **127,** which were obtained from primary amines and epichlorohydrin,[57,58] could be cyclized in situ to the azetidinyl alcohol **128.** Better yields were obtained (Table IV) when the 1-alkylamino-3-chloro-2-propanols were isolated and purified before cyclization. The cyclizations were carried out either neat or in Me_2SO or methanol. Epibromohydrin was also used in the synthesis without particular advantage. Cyclization of the acetate esters **129** proceeded slower and in lower yields than the free alcohol (eq 55). The author attributed these results



129

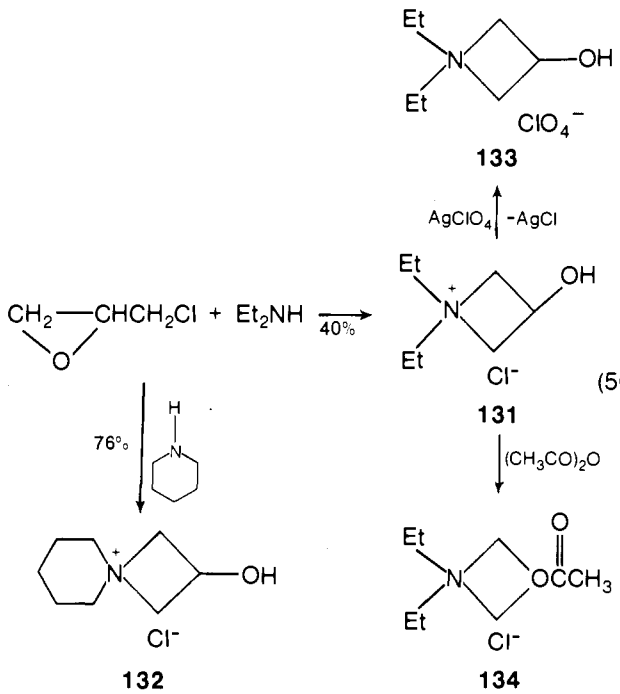
P = *t*-butyl (30%)
R = *t*-octyl (14%)

to the steric interaction of the *N*-alkyl and acetoxy groups in the transition state **130.**

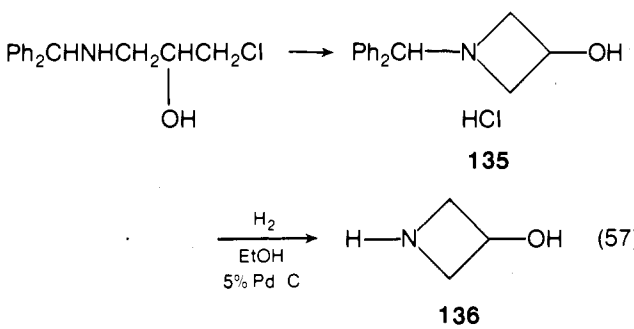


130

This method was also used to prepare *N,N*-dialkyl-3-hydroxyazetidinium salts **131** and **132** (eq 56).[58-60] The 3-hydroxyazetidinium chloride **131** was converted to the perchlorate salt **133** and azetidinium ester **134.**

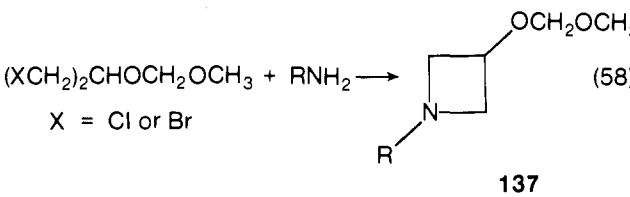


Chatterjee and Triggle[61] used Gaertner's method to synthesize *N*-benzhydrylazetidin-3-ol (**135**) which they further converted by hydrogenolysis to the parent azetidin-3-ol (**136**) (eq 57). An-



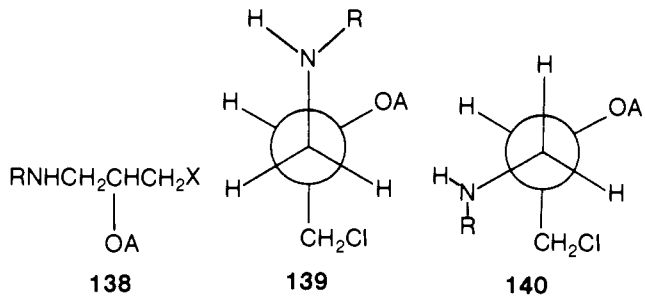
dersen and Lok[62] prepared *N*-benzhydrylazetidin-3-ol (**135**) directly from epichlorohydrin and benzhydrylamine in 61% yield. Chatterjee[61] also attempted to prepare *N*-benzylazetidin-3-ol, but failed because the 3-chloro-1-benzylamino-3-hydroxypropane intermediate could not be cyclized.

Gaj and Moore[63] extended Gaertner's synthesis to include 3-substituted ethers **137** (eq 58). These authors used excess of



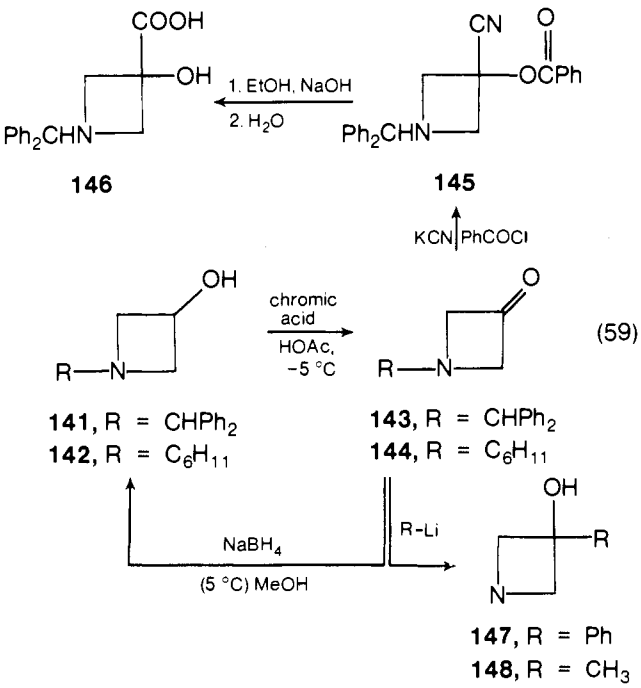
R	% yield
CH_3	40–50
n-Bu	23
$PhCH_2$	13–15
$PhCH_2CH_2$	4

the amine to take up the 2 molar equiv of acid being liberated. Gaertner generally isolated the salt of the azetidine and then carefully released it with basic workup. Gaj and Moore were restricted to distillation; thus their yields probably suffered. Under these conditions the authors reported that excess methylamine reacts with epichlorohydrin or 1,3-dichloro-2-propanol to give 1,3-bis(methylamino)-2-propanol in 37 and 53% yield, respectively. No 1-methyl-3-azetidinol could be detected in the reaction mixtures by distillation and gas–liquid chromatography examination. These results, when considered with those of Gaertner, are consistent with azetidine formation occurring through intermediate **138** and being controlled by the steric bulk of the RNH and OA groups. When the sum of the steric bulk of



the two groups is low (CH_3NH and OH), the preferred staggered conformation **139** favors intermolecular reactions. When the sum of the steric bulk is increased somewhat [$(CH_3)_2CHNH$, OH, or CH_3NH, (CH_2OCH_3)], the preferred staggered conformation becomes **140** to minimize the RNH–OA interaction. Conformation **140** approaches the eclipsed transition state **130** required for cyclization, and thus promotes azetidine formation. When the sum of the steric bulk is increased even further, a reduction in the yield of azetidines is observed, indicating that an optimum steric bulk exists favoring cyclization.

Chatterjee and Shoeb[64] reported a general method for the preparation of substituted *N*-alkylazetidin-3-ols (eq 59). 1-Al-

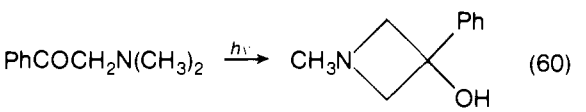


kylazetidin-3-ols **141** and **142**, which were prepared via Gaertner's method, were oxidized with chromic acid in acetic acid to the *N*-alkylazetidin-3-ones **143** and **144**, respectively. Ketone **143** could be stored at 0–5 °C for several weeks; however, **144** could not be stored for more than 12 h without less than 60% decomposition. Azetidinones **143** and **144** were reduced with sodium borohydride in cold methanol to give the parent azetidin-3-ols. Ketone **143** gave cyanohydrin benzoate **145** on treatment with potassium cyanide and benzoyl chloride. The nitrile **145** could be converted to the corresponding hydroxyl acid **146** by controlled hydrolysis. Treatment of **143** with phenyllithium or methyllithium gave *N*-benzhydryl-3-phenylazetidin-3-ol (**147**) and *N*-benzhydryl-3-methylazetidin-3-ol (**148**).

TABLE IX. N-Substituted Azetidine-3-ols

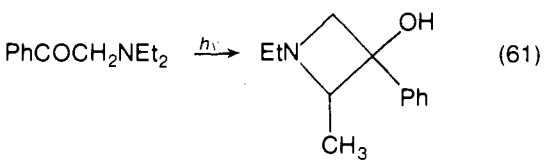
R	R_1	mp bp (mm/Hg), °C	yield, %	ref
C_6H_{11}	H	79–80	55	56
t-C_4H_9	H	45–46	78	56
$CH_3(CH_3)_2CCH_2C(CH_3)_2$	H	52–53	68	56
$CH(CH_3)_2$	H	57–58	20–35	55, 56
$(CH_3)_3CCH_2$	H	55–56 (0.3)	20–35	55, 56
$CHPh_2$	H	107–110 (115)	61	61, 62
CH_3	Ph			65
$CHPh_2$	COOH	178 (dec)	40	64
$CHPh_2$	Ph	195	71	64
$CHPh_2$	CH_3	80 (dec)	64	64
t-C_4H_9	CH_3	63–64 (2)	32 (28)	56, 66
C_6H_{11}	CH_3	75–76 (0.01)	28	66

A unique synthesis of the azetidine ring that employed photolysis to close phenacylamines to azetidin-3-ols was reported by Claisen and Searles[65a] (eq 60–62). Naturally this method is



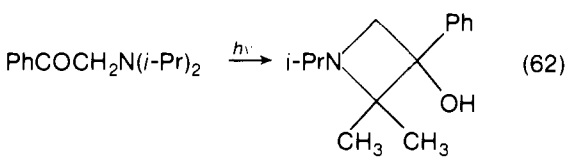
(60)

(9%)



(61)

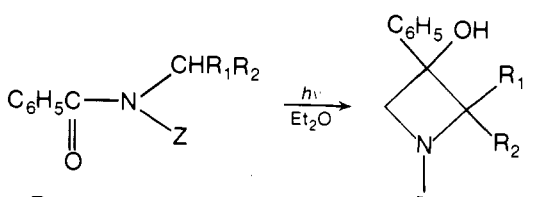
(26%)



(62)

(22%)

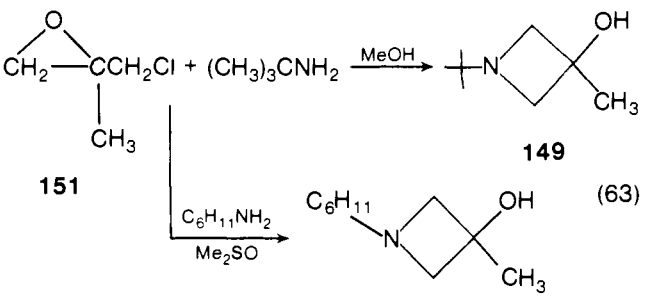
only suitable when the alkyl groups on the nitrogen have an α hydrogen. Also, the major products in reactions 60–62 were the cleavage products from the phenacylamines. Gold[65b] was unable to repeat this general procedure with phenacylamines obtaining a 95% yield of acetophenone. However, he reported that the photolysis of α-*N*-alkylamidoacetophenones, when Z = tosyl, gave high yields (74–95%) of the N-substituted 3-azetidinols which were then converted to the corresponding amines.



$R_1 = R_2 = H$
$R_1 = R_2 = CH_3$
$R_1 = H; R_2 = CH_3$

amines (Z = H)

Cromwell and co-workers[66] reported the synthesis of 1-*tert*-butyl-3-methylazetidin-3-ol (**149**) and 1-cyclohexyl-3-methylazetidin-3-ol (**150**) using Gaertner's method (eq 63). *tert*-Butylamine was added to 3-chloro-2-methyl-1,2-epoxypropane (**151**) in methanol and the solution was stirred at room temperature for 3 days and then refluxed for 3 days to give the azetidinol **149.** Azetidinol **150** was prepared by allowing cyclohexylamine and epoxide **151** to reflux for 4 days in Me_2SO (Table IX).



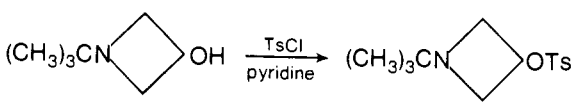
151 **149**

(63)

150

C. N-Substituted 3-Azetidinyl Sulfonates

Chen et al.[67] reported that 1-(*tert*-butyl)-3-azetidinol (**152**), when allowed to react with tosyl chloride in pyridine, gave a 73% yield of 1-(*tert*-butyl)azetidinyl-3 tosylate (**153**) plus a small amount (1.6%) of 1-tosylazetidinyl-3 tosylate (**154**) (eq 64). The

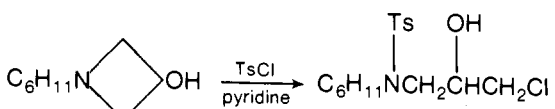


152 **153** (7.3%)

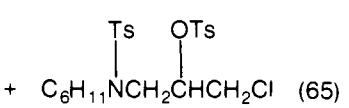
(64)

154 (1.6%)

N-tosylazetidine **154** may have been formed by the reaction of tosyl chloride with 3-azetidinol, a possible impurity in 1-(*tert*-butyl)-3-azetidinol. 1-Cyclohexyl-3-azetidinol (**155**) did not give the expected tosylate derivative, but the ring opened to give *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol (**156**) and *N*-tosyl-1-cyclohexylamino-3-chloropropyl-2 tosylate (**157**) (eq 65).



155 **156** (66%)

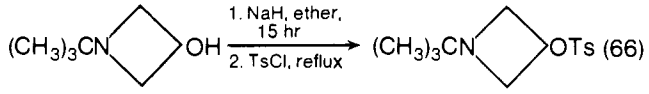


(65)

157 (3%)

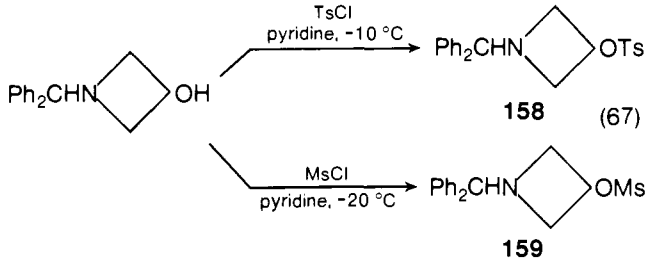
Cromwell and co-workers[68] modified this procedure by using sodium hydride in ether, followed by addition of tosyl chloride to provide the tosylated product **153** in 78% yield (eq 66).

Andersen and Lok[62] used Chen's method to synthesize *N*-benzhydrylazetidinyl-3 tosylate (**158**) in 39% yield (eq 67). The



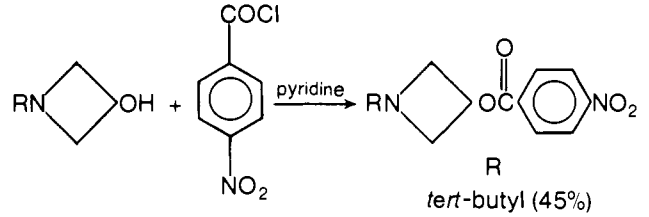
152 153

mesylate **159** was also prepared in high yield using the same procedure.

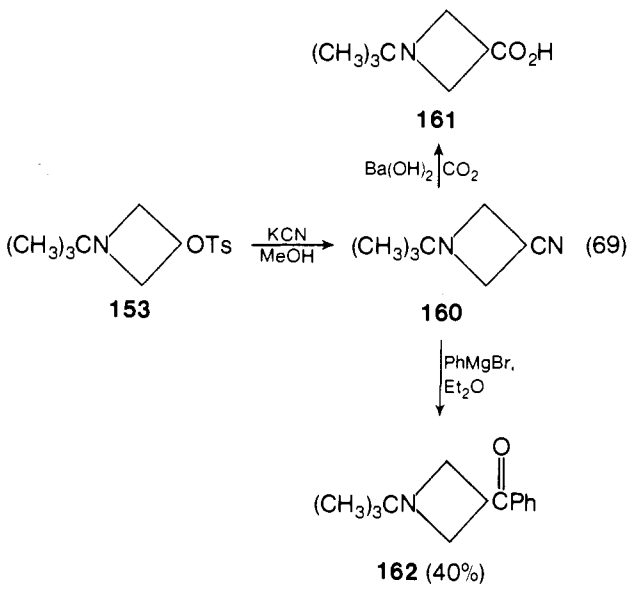


D. Reactions of N-Substituted Azetidin-3-ols, 3-Tosylates, and Related Compounds

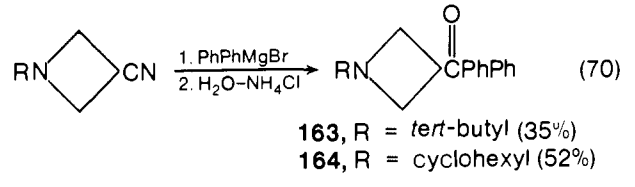
The availability of azetidin-3-ols and tosylates opened the door to the synthesis of many 3-functionally substituted azetidines. Chen and co-workers[67] reported that both *N*-(*tert*-butyl)azetidin-3-ol and *N*-cyclohexylazetidin-3-ol gave the corresponding benzoates when allowed to react with *p*-nitrobenzoyl chloride in pyridine (eq 68). *N*-(*tert*-Butyl)azetidinyl-3 tosylate (**153**) was



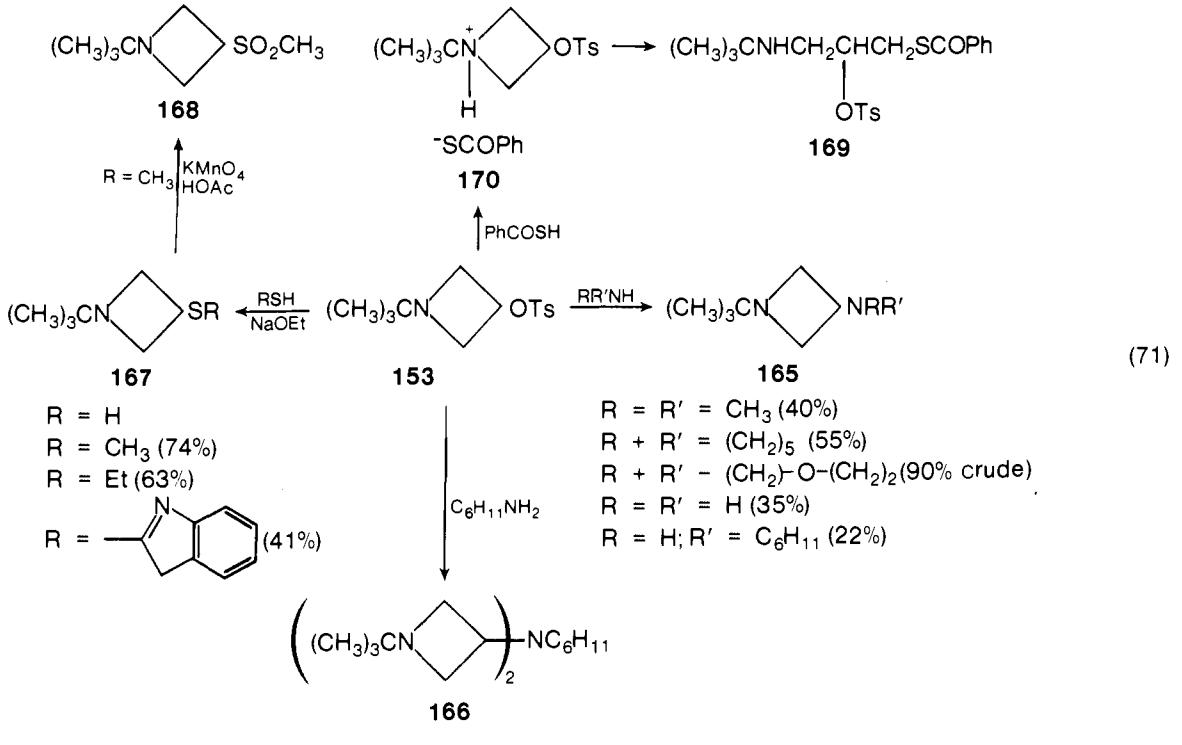
converted in 52% yield to *N*-(*tert*-butyl)-3-cyanoazetidine (**160**) when allowed to react with potassium cyanide in methanol (eq 69). The nitrile **160** was hydrolyzed with barium hydroxide to produce 1-(*tert*-butyl)azetidine-3-carboxylic acid (**161**) in 73% yield. The azetidine **160** could also be converted to 1-(*tert*-butyl)-3-benzoylazetidine (**162**) via a Grignard reaction.[69]

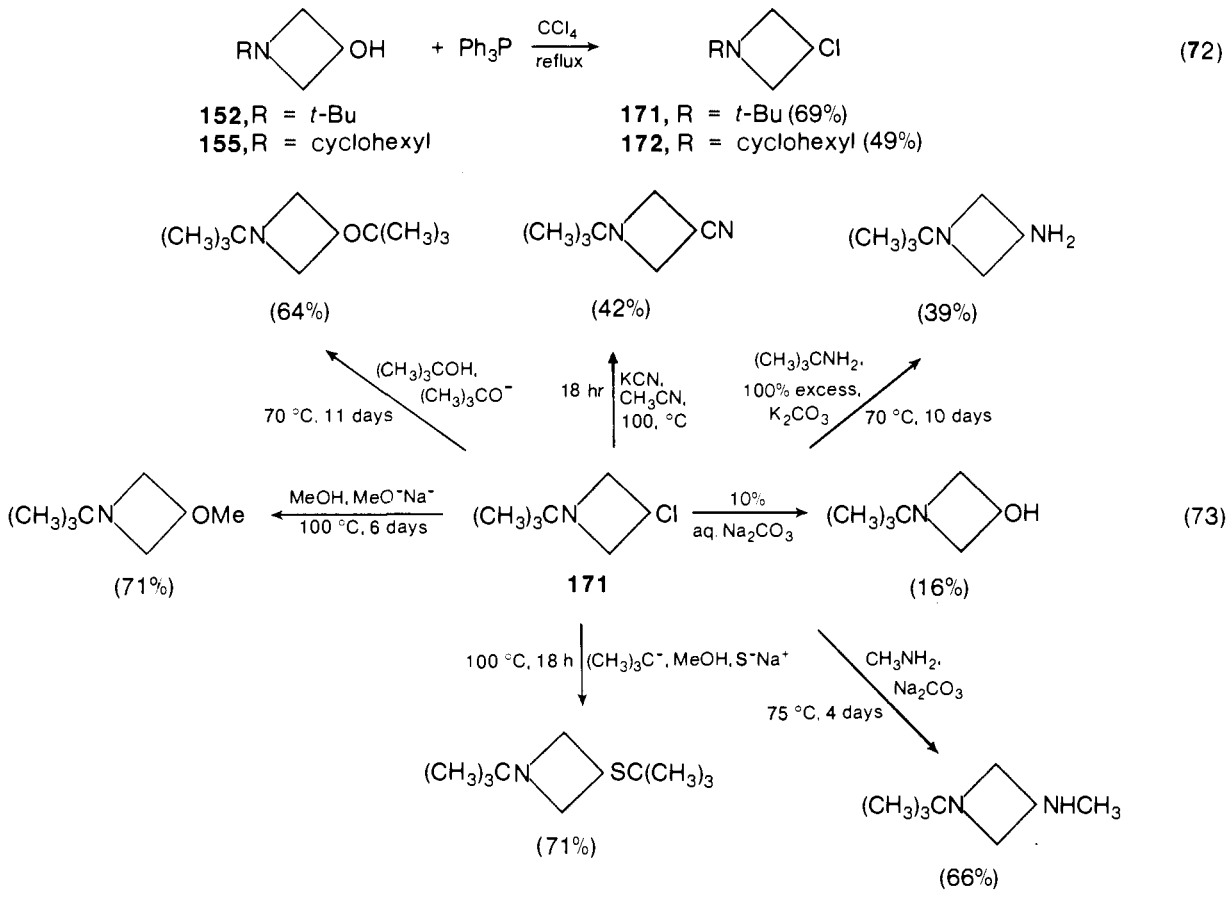


Cromwell and co-workers[68] reported the preparation of *N*-alkyl-2-aroylazetidine derivatives **163** and **164** from the corresponding 3-cyanoazetidine (eq 70).



Chen[70] also studied the reaction of 1-(*tert*-butyl)azetidinyl-3 tosylate (**153**) with amines and mercaptans (eq 71). The amine reaction gave *N*-(*tert*-butyl)-3-aminoazetidine derivatives **165** in yields ranging from 22 to 90%. The reaction of cyclohexylamine gave, in addition to *N*-(*tert*-butyl)-3-cyclohexylaminoazetidine, a 60% yield of *N*,*N*-bis[1-(*tert*-butyl)azetidinyl]-3-cy-





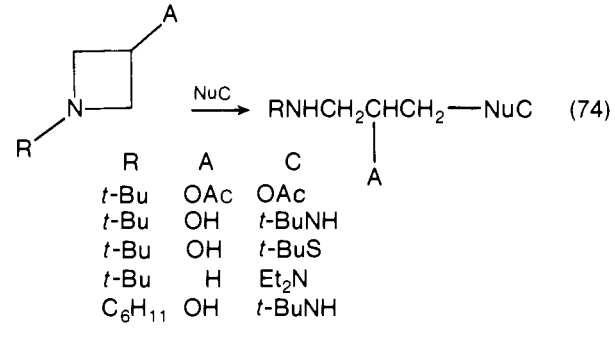
clohexylamine (**166**) as an oil, which was purified by conversion to its trihydrochloride monohydrate. The reaction of tosylate **153** with mercaptans in the presence of sodium ethoxide proceeded smoothly to give the corresponding sulfides **167.** The authors attempted the reaction of potassium hydrogen sulfide with tosylate **153;** however, no products could be identified. 1-(*tert*-Butyl)-3-methylthioazetidine was oxidized by potassium permanganate to methyl 1-(*tert*-butyl)azetidinyl-3 sulfone (**168**) in 29% yield. The reaction of excess thiobenzoic acid with **153** provided a ring cleavage product **169.** The authors postulated that the cleavage reaction proceeds via formation of the azetidinium salt **170** followed by attack of the thiobenzoate anion.

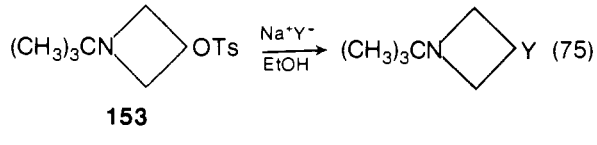
Gaertner[56,71,72] converted 1-(*tert*-butyl)azetidin-3-ol (**152**) and 1-cyclohexylazetidin-3-ol (**155**) to the corresponding 3-chloroazetidines **171** and **172** by refluxing for 3 days in carbon tetrachloride with triphenylphosphine[72] (eq 72). *N*-(*tert*-Butyl)-3-chloroazetidine (**171**) was used to prepare a wide variety of 3-substituted azetidines via nucleophilic substitution (eq 73).

Gaertner[74] also reported a series of nucleophilic ring opening reactions on tertiary azetidines (eq 74). The reactions proceeded in generally good yields (57–91%) depending upon the nucleophile and catalyst. Cromwell and Higgins[75] studied the C-3 nucleophilic substitution of *N*-(*tert*-butyl)azetidinyl-3 tosylate **153** involving the formation of C–C bonds. The reaction was found to proceed best in ethanol solvent (eq 75).

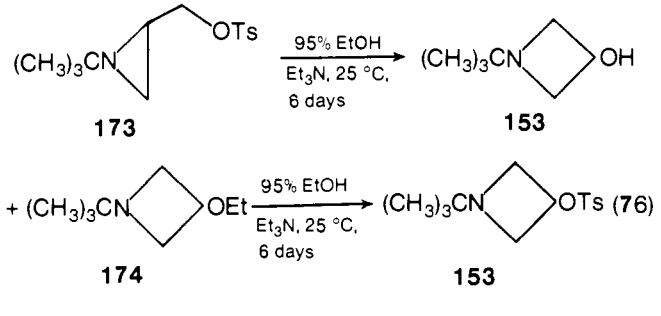
The rearrangement of aziridine tosylate **173** to give a 38% yield of azetidinyl alcohol **152,** 4% of the ether **174,** and 5% of corresponding aziridinyl alcohol was reported by Deyrup and Moyer[76,77] (eq 76). The conversion from tosylate **153** gave a 16% yield of alcohol **152** and a 20% yield of ether **174.**

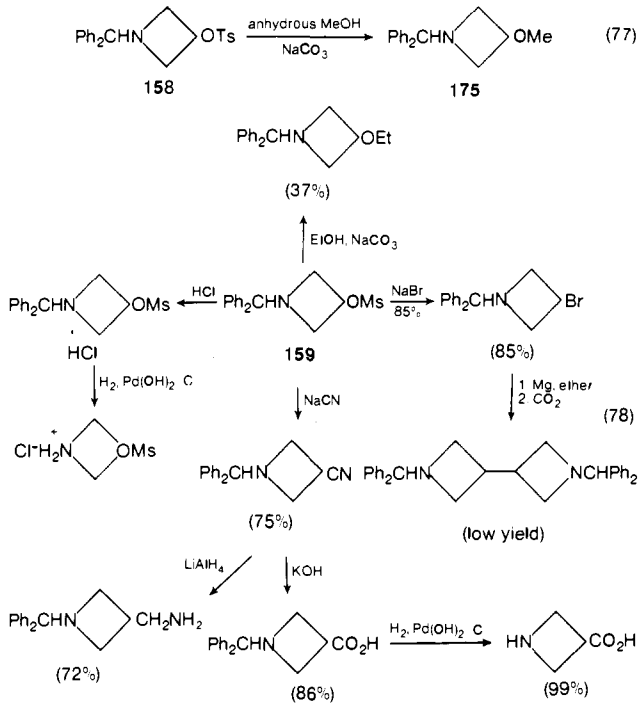
Andersen and Lok[62] prepared *N*-benzhydrylazetidinyl-3 tosylate (**158**) and converted it to *N*-benzhydryl-3-methoxyazetidine (**175**) in 51% yield (eq 77). These authors also prepared a variety of azetidines using *N*-benzhydrylazetidinyl-3 mesylate (**159**) as the starting material (eq 78).





Y	yield, %
$CN(CO_2Et)CH$	11
$(CO_2Et)_2CH$	39
$Ac(CO_2Et)CH$	67

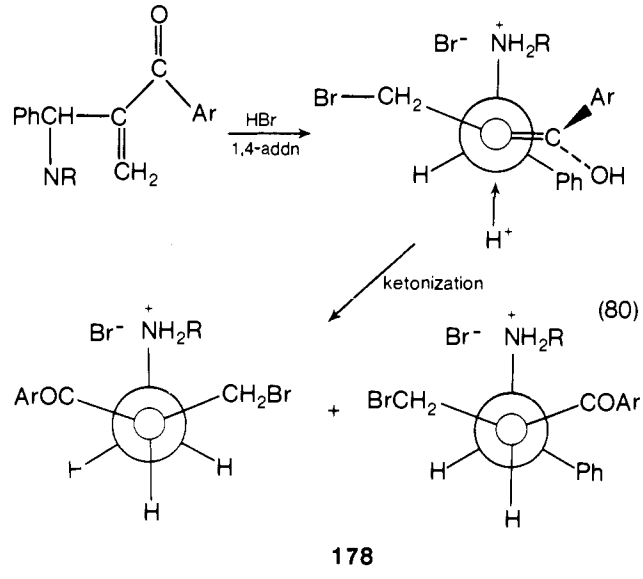




VII. 1,2,3-Substituted Azetidines

A. 1-Alkyl-2-aryl-3-aroyl (or -acetyl, -carbomethoxy, -cyano) Azetidines

Cromwell and co-workers[78-80] reported the first synthesis of azetidinyl ketones (eq 79). The 2-(α-substituted aminobenzyl)acrylophenones **177,** which are readily available from the reaction of *trans*-2-bromomethylchalcones (**176**) with amines, were treated with hydrogen bromide in chloroform to give, in a highly stereoselective fashion, the pure erythro racemates **178,** apparently from the operation of asymmetric induction (eq 80).



Neutralization of the γ-bromoamine hydrobromides **178** with base resulted in the high yield, stereospecific formation of *cis*-1-alkyl-2-aryl-3-aroylazetidines **179.** The azetidinyl ketones **179** were readily epimerized to the thermodynamically more stable trans isomers **182.** Epimerization with deuterated methanol in the presence of sodium methoxide gave the deuterated trans azetidines **183** (eq 79).

A similar series of reactions carried out with the amino ketone **180** (formed quantitatively by rearrangement of **177**) produced a 50% yield of a mixture of the erythro and threo racemate **181** in the ratio of 2:1, respectively. Treatment of this mixture with amines produced the cis azetidines **179** and the trans azetidines **182** in a 2:1 ratio.

The azetidines prepared are summarized in Table X. The stereochemistry of the epimers **179** and **182** was assigned by analysis of the vicinal proton spin–spin coupling constants in these ring systems[78-80] as well as from infrared, ultraviolet, and mass spectral[81] data. Information obtained from the coupling constants suggested[80] that the four-membered imine ring is slightly puckered and that the degree of puckering is dependent upon the steric requirement of the N substituent. The yields of the cyclization were higher with bulky R groups (Table X). This was consistent with Vaughan's suggestions[8] that a larger N substituent favors cyclization and increases the stability of the azetidine ring. However, contrary to Vaughan's other conformational suggestions, Cromwell's results imply that eclipsing in the transition state leading to the highly substituted cis azetidines does not seriously hinder cyclization.

Since 1-alkyl-2-phenyl-3-aroylazetidines readily exchange the proton at the C_3 for a deuteron and epimerize in the presence of sodium methoxide, it was not surprising to find that alkylation (methylation) at this position was facile. Doomes and Cromwell[82] reported that C_3-methylation of the potassium salt of 1-(*tert*-butyl)-2-phenyl-3-aroylazetidines with methyl iodide gave a mixture of the cis and trans products in a ratio that was independent of the stereochemistry of the starting material, but dependent upon the nature of the solvent (eq 81). In contrast to the results obtained upon proton exchange, where the thermodynamically more stable product was obtained in near-quantitative yield, C-methylation gave mixtures of products. The cis isomers, which predominate in ether and THF, are apparently the kinetically favored products resulting from the least crowded transition state involving either the carbanion C or the enolate anion B.

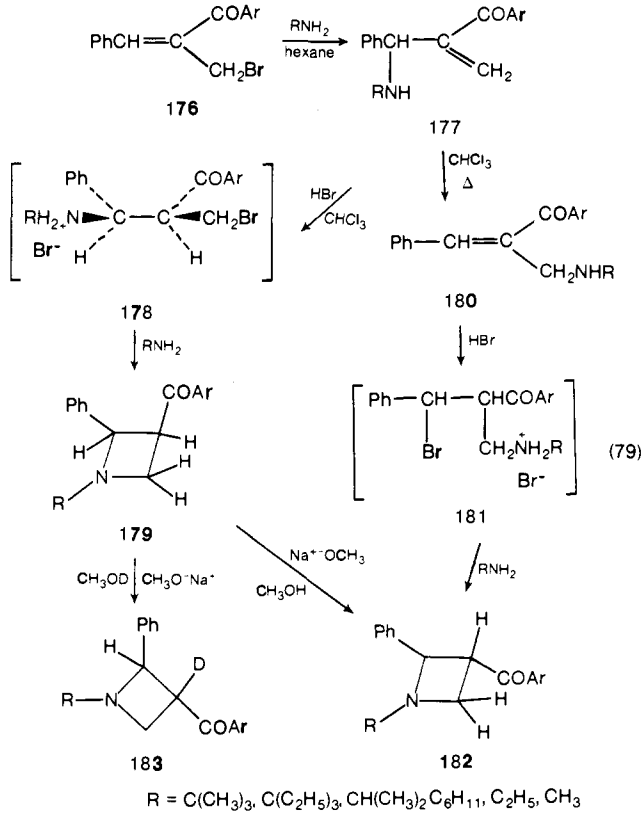
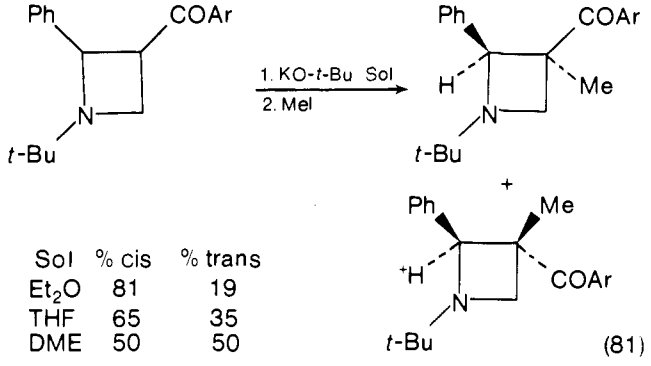


TABLE X. 1-Alkyl-2-phenyl-3-aroylazetidines

R	Ar	stereochemistry	mp, °C	yield, %[a]	ref
$C(CH_3)_3$	p-$C_6H_4C_6H_5$	cis	165	78 (92)	78 (80)
$C(CH_3)_3$	C_6H_5	cis	116-118	80	81
$C(CH_3)_3$	p-$C_6H_4C_6H_5$	trans	127-128	75 (91)	78 (80)
$C(CH_3)_3$	C_6H_5	trans	61-63	75	81
$C(C_2H_5)_3$	p-$C_6H_4C_6H_5$	cis	109-110	74	80
$C(C_2H_5)_3$	p-$C_6H_4C_6H_5$	trans	75-76	80	80
$CH(CH_3)_2$	p-$C_6H_4C_6H_5$	cis	141-142	79	80
$CH(CH_3)_2$	C_6H_5	cis	84-85	76	80
$CH(CH_3)_2$	p-$C_6H_4C_6H_5$	trans	109-110	92	80
$CH(CH_3)_2$	C_6H_5	trans	42-43	80	80
C_6H_{11}	p-$C_6H_4C_6H_5$	cis	172-173	74	80
C_6H_{11}	C_6H_5	cis	102-103	61	80
C_6H_{11}	p-$C_6H_4C_6H_5$	trans	142-143	87	80
C_6H_{11}	C_6H_5	trans	96-97	80	80
C_2H_5	p-$C_6H_4C_6H_5$	cis	137-138	58	80
C_2H_5	p-$C_6H_4C_6H_5$	trans	70-71	65	80
CH_3	p-$C_6H_4C_6H_5$	cis	142-143	32	80
CH_3	p-$C_6H_4C_6H_5$	trans	63-64	40	80

[a] Yield for the cis isomer is from amino ketone **2** (eq 1), and yield for trans isomers is from epimerization of the cis isomer.



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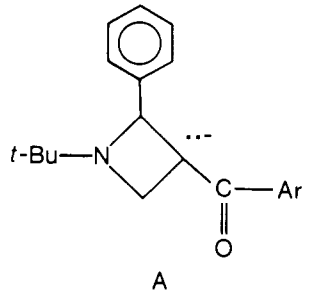
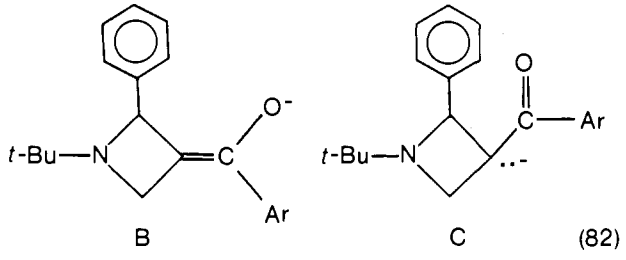


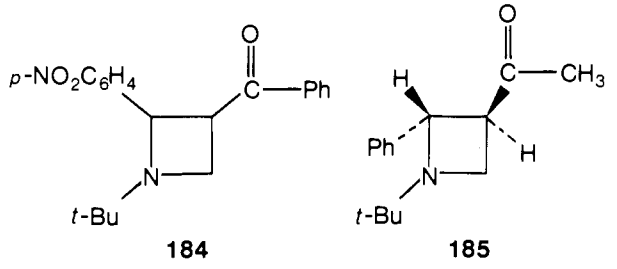


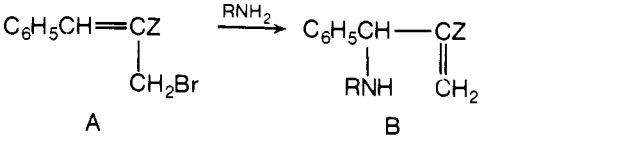
(82)

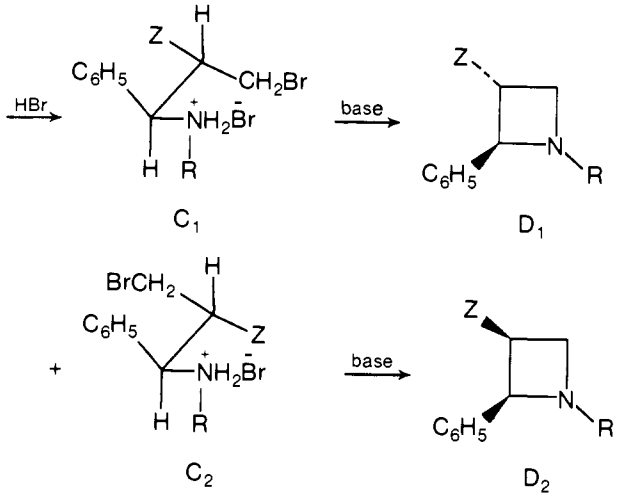
Carbanion A should be the least stable of the three anions (eq 82).

Cromwell and co-workers extended this procedure to the synthesis of *cis*- and *trans*-1-*tert*-butyl-2-(*p*-nitrophenyl)-3-benzoylazetidine (**184**)[83] and *trans*-1-*tert*-butyl-2-phenyl-3-acetylazetidine (**185**).[84a]

The steric controls[79] operating during the addition of hydrogen bromide to the allylamines B to form the threo (C_1) and erythro (C_2) γ-bromoamines when the activating group Z in A was varied from benzoyl to acetyl to carbomethoxy to cyano have been fully explored by Cromwell and co-workers.[84b] The stereochemistry and mechanism for the subsequent reactions involved in the synthesis of the stereoisomeric substituted azetidines (D_1 and D_2) were also discussed in the same publication.[84b]





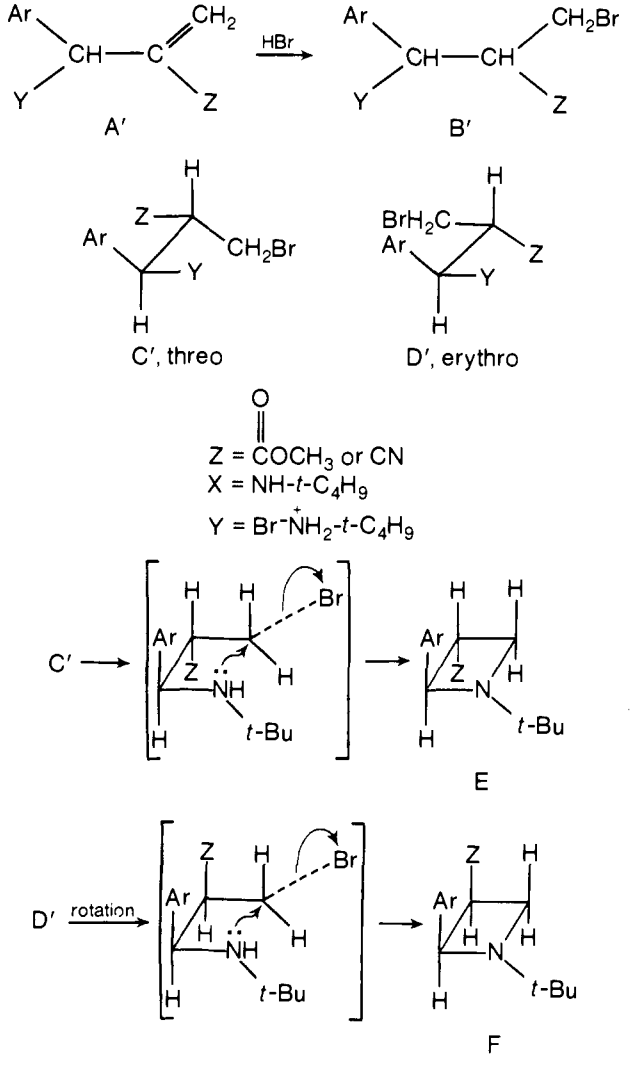


The addition of hydrogen bromide to A′ gives B′ which can exist in two diastereomeric forms, C′ for the threo, and D′ for the erythro.

As pointed out by Vaughan,[8] and later by Cromwell,[79] the cyclization of these γ-haloamines should be treated as a conformational problem. Therefore, C′ would give *trans*-azetidine E, and D′ would give *cis*-azetidine F. A′ → C′ → E. For the case when Z is cyano, A′ goes to C′ and D′, giving E and F rather nonselectively.

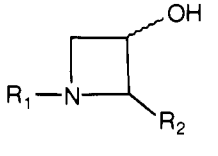
Epimerization of the *cis*-2-carbomethoxyazetidine to its trans isomer is unlikely in an acidic medium. In one experiment, the reaction of B (R, t-C_4H_9; Z, CO_2CH_3) with HBr/$CHCl_3$ was inter-

rupted purposely before it went to completion, and was then treated with triethylamine. However, no signal corresponding to the *cis*-arylcarbomethoxyazetidine could be observed in the ^1H NMR spectrum of the reaction mixture; thus it seems improbable that B produced any of the cis product in this reaction sequence.



B. 1,2-Substituted 3-Azetidinols

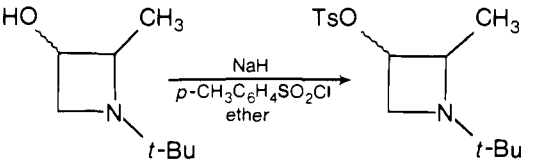
Gaertner[56] obtained a mixture of diastereomeric 1-(*tert*-butyl)-2-methylazetidin-3-ols **186** and **187** by allowing *tert*-butylamine to react with 3-bromo-1,2-epoxybutane in Me_2SO, and was successful in obtaining one isomer in pure form (eq 83). Cromwell and Higgins[85] repeated this reaction and were able to separate both of these isomers by fractional distillation followed by fractional crystallizations. When cyclohexylamine was allowed to condense with 3-bromo-1,2-epoxybutane, only the trans isomer **190** was isolated. Okutani and co-workers[86] reported the synthesis and separation of *cis*- and *trans*-1-cyclohexyl-2-phenylazetidin-3-ol (**188** and **189**). The configuration of these isomers was determined by NMR using tris(dipivalomethanato)europium(III) as a shift reagent.



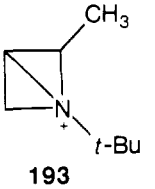
	trans	cis
R_1 = *t*-Bu; R_2 = CH_3	**186**	**187**
R_1 = C_6H_{11}; R_2 = C_6H_5	**188**	**189**
R_1 = C_6H_{11}; R_2 = CH_3		**190**

(83)

cis- and *trans*-1-(*tert*-butyl)-2-methyl-3-azetidinyl tosylates **191** and **192** were synthesized by Cromwell and Higgins[87] in order to study the mechanism of hydrolysis (eq 84). The hydrolysis of tosylates **191** and **192** in 60% aqueous acetone proceeded with stereospecific retention of configuration. Anchimeric assistance leading to intermediate 1-azabicyclo[1.1.0]butonium ions (**193**) was postulated as the exclusive mechanism by which **186** undergoes hydrolysis and is at least an important mechanism by which **187** undergoes hydrolysis.



cis **186** cis **191**
trans **187** trans **192** (84)



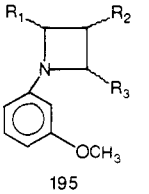
193

C. Miscellaneous 1,2,3-Substituted Azetidines

Tilak and co-workers[88] reported the synthesis of 1-aryl-2,3-, 2-, and 2,4-substituted azetidines from 1-arylamino-3-alkanols (**194**) by treatment with triphenylphosphine dibromide in acetonitrile solution followed by treatment with triethylamine (eq 85). In addition to the azetidines **195,** which were formed via intermediate **196,** the corresponding mixed tetrahydroquinolines **197** and **198** were obtained. Table XI summarizes the results. When R_1 and R_3 or R_1 and R_2 were phenyl substituents the reaction failed. Tilak[89] also prepared 1-(3'-methoxyphenyl)-2-phenylazetidine **199** by treatment of 1-(3'-methoxyphenylamino)-3-phenylpropan-3-ol (**200**) with 70% sulfuric acid (eq 86). However, this method failed to give *N*-arylazetidines in many cases, and only the rearranged tetrahydroquinolines **198** were obtained as end products.

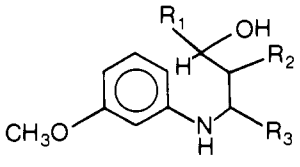
Nerdel et al.[90] reported the preparation of 2-methoxy-3,3-dimethyl-1-phenylazetidine (**201**) in low yield (eq 87). Treatment of **201** with methanol gave the anilino acetal **202** in 45% yield and the *N*-phenyl-3,3-dimethylazetidine (**203**) in 1% yield.

TABLE XI. *N*-(*m*-Methoxyphenyl)azetidines



195

R_1	R_2	R_3	Mp or bp (mm/Hg), °C	yield, %
Ph	H	H	140–5 (9×10^{-4})	
Ph	H	CH_3	89	
CH_3	H	Ph		
Ph	CH_3	H	94	
CH_3	H	CH_3	100 (2.13×10^{-2})	



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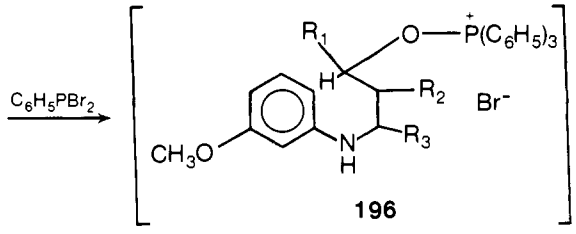

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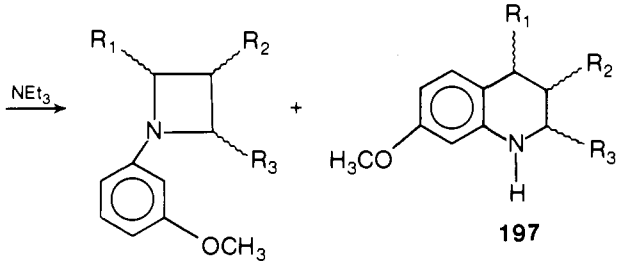
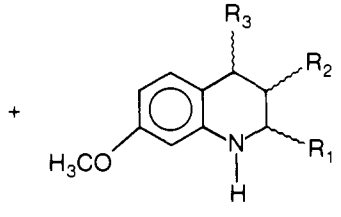
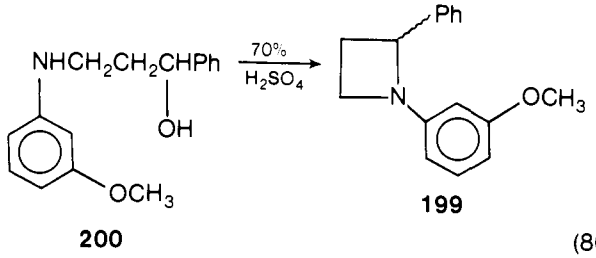


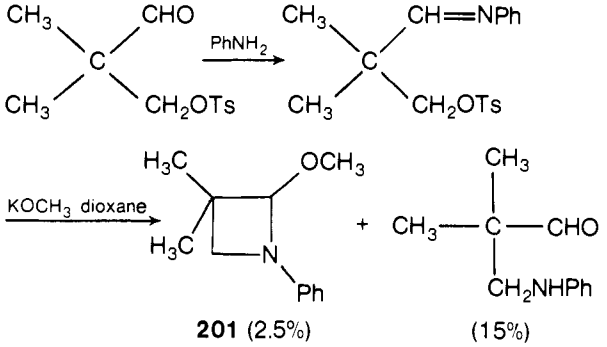
195 197



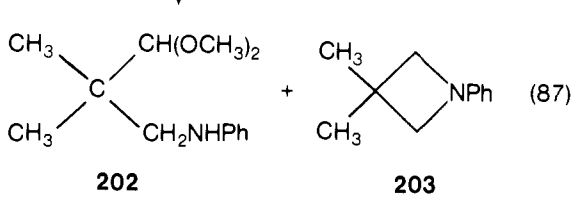
198 (85)



200 199 (86)

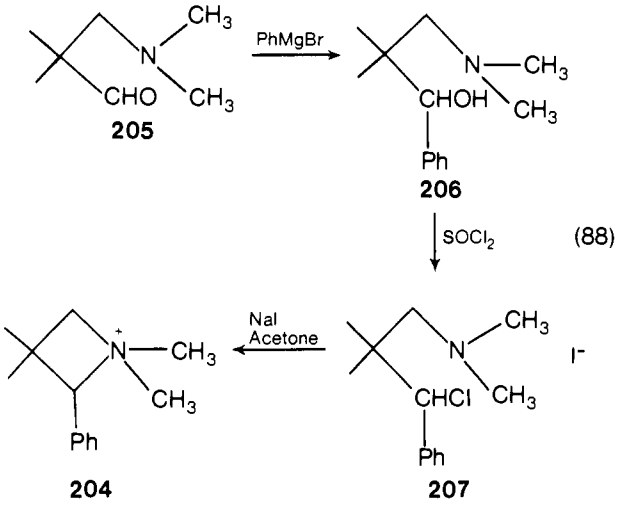


201 (2.5%) (15%)



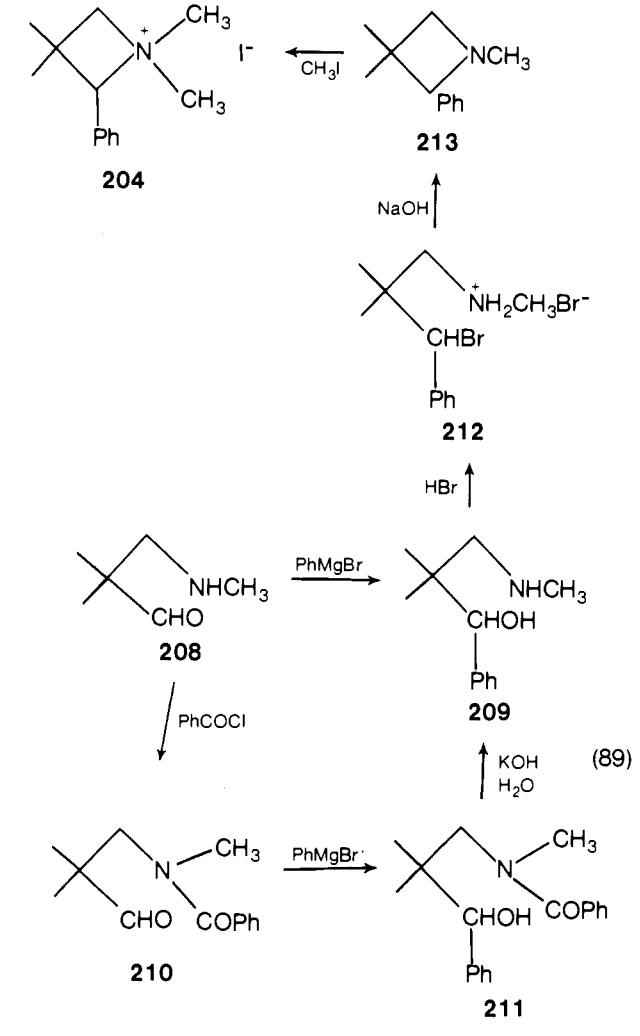
202 203 (87)

Anderson and Wills[91] synthesized 2-phenyl-1,1,3,3-tetramethylazetidinium iodide (**204**) by two routes. One route to **204** consisted of the addition of phenylmagnesium bromide to 2,2-dimethyl-3-dimethylaminopropanal (**205**) to give 2,2-dimethyl-3-dimethylamino-1-phenyl-1-propanol (**206**), conversion of **206** with thionyl chloride into 1-chloro-2,2-dimethyl-3-dimethylamino-1-phenylpropane (**207**), and ring closure of **207** with sodium iodide in acetone (eq 88). This procedure was satisfactory except for the cyclization which gave at best 11% of **204** along with a considerable amount of tarry material.



205 206 204 207 (88)

In the second route (eq 89) direct conversion of 2,2-dimethyl-3-methylaminopropanal (**208**) into **209** was found to give



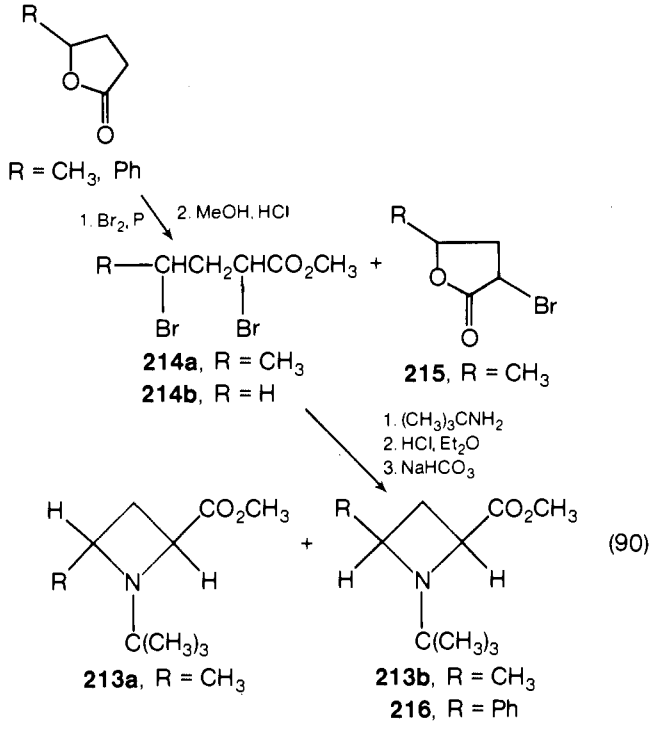
204 213 212 208 209 210 211 (89)

low (4%) yields despite the use of a molar excess of the Grignard reagent. This difficulty was partially overcome (31% overall yield) by carrying out the Grignard reaction on the more stable benzamide derivative **210**, with subsequent hydrolysis of the product **211** to **209.** Treatment of **209** with hydrobromic acid gave **212** (68%), and reaction of the latter with sodium hydroxide afforded **213** in 65% yield. The azetidinium salt **204** was obtained in 80% yield from **213** by reaction with methyl iodide in acetonitrile.

VIII. 1,2,4-Substituted Azetidines

A. 1-(*tert*-Butyl)-2-carbomethoxy-4-substituted Azetidines

Cromwell and Rodebaugh[38] prepared a mixture of *cis*- and *trans*-1-(*tert*-butyl)-2-carbomethoxy-4-methylazetidine (**213a** and **213b**) by condensation of the α,γ-dibromocarbonyl ester **214a** with *tert*-butylamine (eq 90). The dibromo ester **214a** was



contaminated with the bromolactone **215** formed by bromination of the starting lactone. The cis and trans isomers were separated by preparative VPC.

The originally assigned configuration[38] of **213a, b** was later reversed.[92] The NMR spectrum of one isomer showed the C_4-methine proton at a multiplet at 252 Hz while the C_4-methine proton of the other isomer appeared at 190–213 Hz as a multiplet, and it is known that protons lying in conical regions, extending above and below the plane of the trigonal atom of the carbonyl group, will be shielded by this function while those lying elsewhere, and particularly those in the plane of the trigonal atom, will be deshielded. The authors reported that careful examination of molecular models revealed that the C_4-methine proton comes in the carbonyl deshielding zone and, therefore, appeared at a comparatively lower field. The isomer that showed the C_4-methine absorption at a lower field (252 Hz) was assigned the trans structure (**213a**) and the compound with the C_4-methine at 190–213 Hz was assigned the cis (**213b**).

The NMR spectrum of the product **213** indicated the mixture to consist of approximately 57% of the cis isomer and 43% of the trans isomer. Refluxing this mixed product with sodium methoxide in methanol for 48 h increased the cis/trans percentage ratio to 74%/26% with no destruction of product. This indicated that the cis isomer is thermodynamically more stable than the trans isomer. When the mixed product was stirred for 72 h with sodium methoxide in deuterated methanol, 60% deuterium incorporation was observed and the cis/trans percentage ratio increased to 74%/26%.[92]

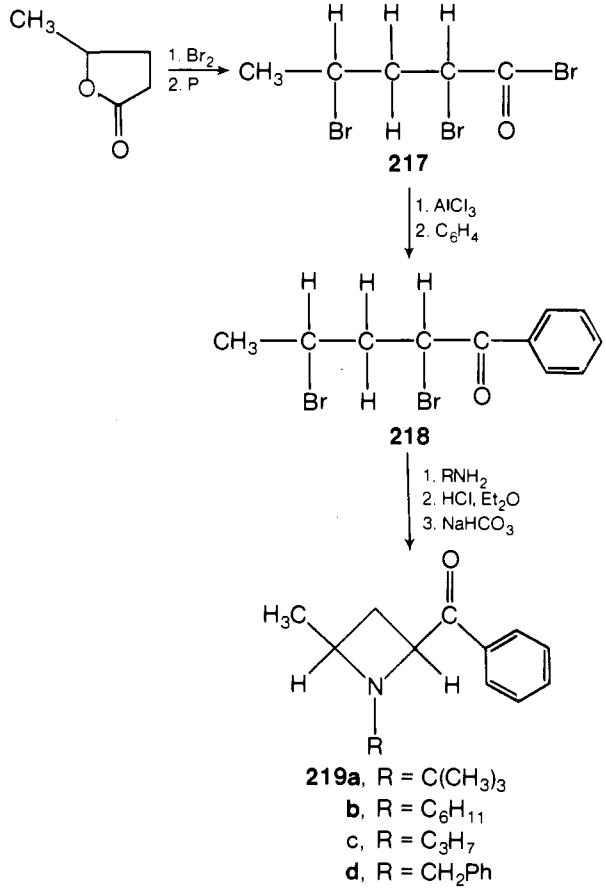
1-Methyl-2-carbomethoxy-4-phenylazetidine (**216**) was prepared[92] from methyl 2,4-dibromo-4-phenylbutyrate (**214a**) by condensation with *tert*-butylamine (eq 90). The NMR spectrum of **216** indicated the product to be only one isomer. Refluxing this product with sodium methoxide in methanol did not effect epimerization to another isomer. When **216** was stirred for 72 h with potassium *tert*-butoxide in deuterated methanol 50% deuterium incorporation was observed; however, no epimerization was detected. Since the cis azetidinyl ester skeleton is of greater thermodynamic stability than the trans, the cis configuration was assigned to **216.** Similar results have been obtained by Carrie and co-workers[93] in the case of 1,4-diphenyl-2-carbomethoxyazetidine.

B. 1-Alkyl-2-benzoyl-4-methylazetidines

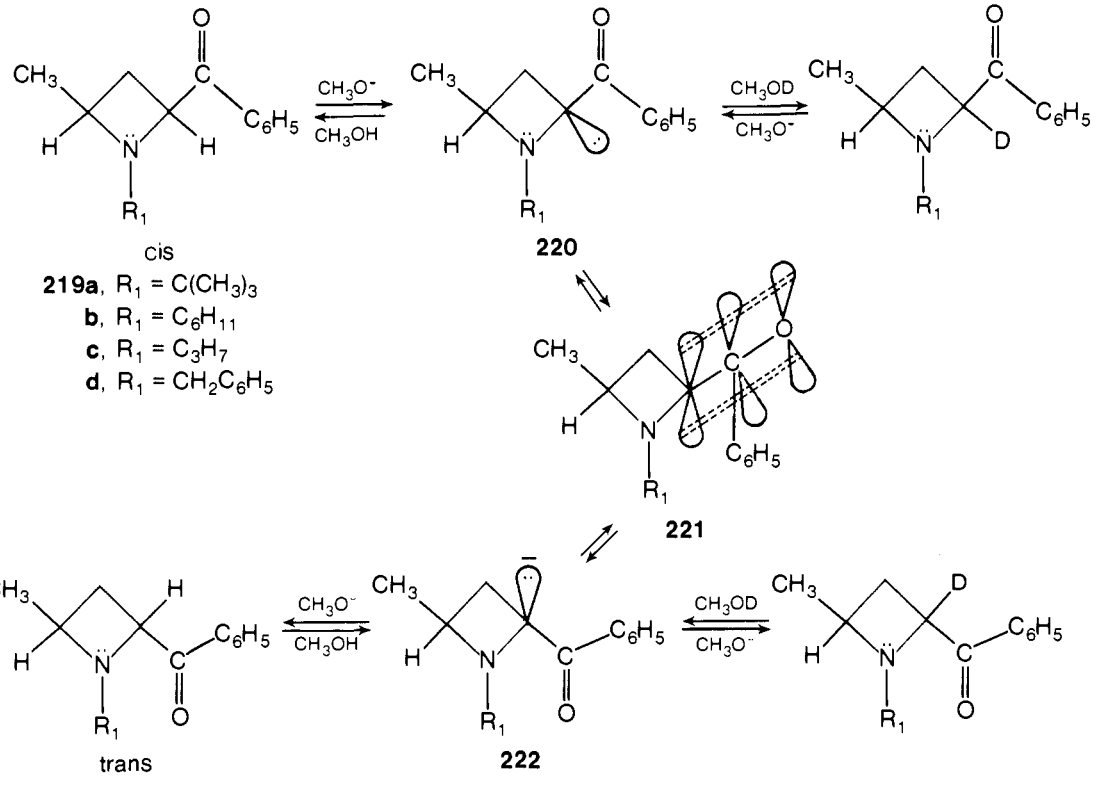
In a subsequent investigation,[92b] γ-valerolactone was converted to α,γ-dibromovaleryl bromide (**217**) by treatment of the former with bromine and phosphorus. Tribromo compound **217** was treated with aluminum chloride and benzene to give α,γ-dibromovalerophenone (**218**). 1-Alkyl-2-benzoyl-4-methylazetidines (**219a–d**) were obtained (62–77% yield) by the reaction of **218** with primary amines (see Scheme I).

The NMR spectrum of azetidines **219** showed that each product consisted of only one isomer. When azetidines **219** were refluxed with sodium methoxide and methanol for 48 h, the NMR spectrum of the resulting products did not show any epimerization to another isomer. But when azetidines **219** were stirred with potassium *tert*-butoxide in deuterated methanol for 72 h, 65% deuterium incorporation was observed; however, no epimerization was detected.

SCHEME I



SCHEME II



cis

219a, $R_1 = C(CH_3)_3$
b, $R_1 = C_6H_{11}$
c, $R_1 = C_3H_7$
d, $R_1 = CH_2C_6H_5$

220

221

trans

222

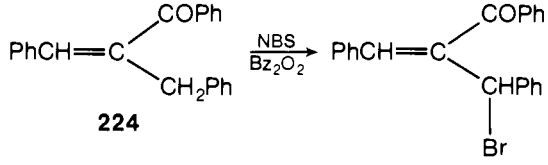
Molecular models for these cis and trans pairs of azetidines **219a–d** were examined. The molecular models clearly reveal that 1,2 nonbonded interactions will be minimal in case of the cis isomer, because in its preferred conformation the *N*-alkyl group will be anti to the groups at C_2 and C_4 (see Scheme II). Also, there will be less lone pair–lone pair interactions in the carbanion of the cis isomer **220** than in that of the trans carbanion **222.** Therefore, the carbanion of the cis isomer will immediately take up the hydrogen or deuterium and retain its configuration. On the other hand, the trans carbanion is expected to stereomutate[92a] via the intermediate enolate **221** to the more stable cis carbanion which then again acquires a hydrogen or deuterium to form the cis isomer. In the preferred conformation of the trans isomer, the group on nitrogen is expected to be oriented mainly syn to the carbonyl group, which further destabilizes the trans isomer and aids the formation of the cis carbanion **220.**

When these systems tend toward equilibrium the cis isomer seems to be more stable than the *trans* isomer. Hence the cis skeleton is assigned to the 1-alkyl-2-benzoyl-4-methylazetidines (**219a–d**). This result is in agreement with the behavior of the related 1-(*tert*-butyl)-2-carbomethoxy-4-methyl(phenyl)azetidines for which the cis isomer was shown to be thermodynamically more stable.[92a]

IX. 1,2,3,4-Substituted Azetidines

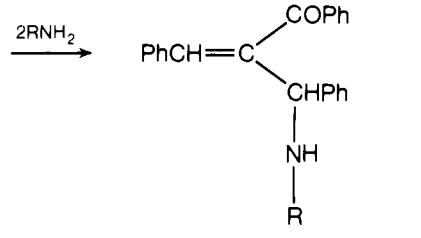
A. 1-Alkyl-2,4-diphenyl-3-benzoylazetidines

Cromwell and Stevens[94] prepared several 1-alkyl-2,4-diphenyl-3-benzoylazetidines by the cyclization of α-(α'-alkylaminobenzyl)chalcones (eq 91). The major starting material **223** was prepared by allowing α-benzylchalcone (**224**) to react with *N*-bromosuccinimide in the presence of benzoyl peroxide. Treating **223** with 2 equiv of various amines led to the α-(α'-alkylaminobenzyl)chalcones **225, 226,** and **227.** The azetidines **228, 229,** and **230** were prepared by treating **225** and **227** first with hydrogen bromide in chloroform and then with a suitable amine base. Cyclization of **227** gave an approximate 50:50 mixture of **229** and **230.** The yields in general were low

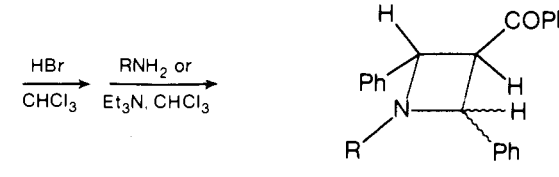


224

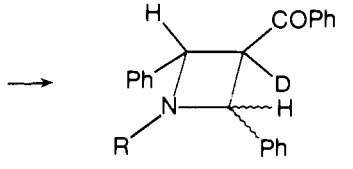
223 (64.5%)



225, R = t-C_4H_9 (27%)
226, R = $CH(CH_3)_2$ (65.6%)
227, R = C_6H_{11} (43.7%)



228, R = t-C_4H_9, trans, trans (22.9%)
229, R = C_6H_{11}, trans, trans (26.8%)
230, R = C_6H_{11}, cis, trans (26.8%)



(91)

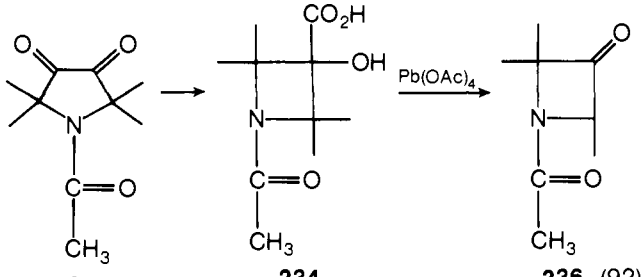
231, R = t-C_4H_9, trans, trans
232, R = C_6H_{11}, trans, trans
233, R = C_6H_{11}, cis, trans

and small amounts of regenerated α-(α′-alkylaminobenzyl)chalcone were found.

The configurations were assigned primarily by ^{1}H NMR spectra and mass spectra data. The azetidinyl ketones **228, 229,** and **230** could not be isomerized with base, but they did undergo deuterium exchange at the C_3 position to form the 1-alkyl-2,4-diphenyl-3-deuterio-3-benzoylazetidine derivatives **230, 232,** and **233** when treated with sodium methoxide in deuteriomethanol.

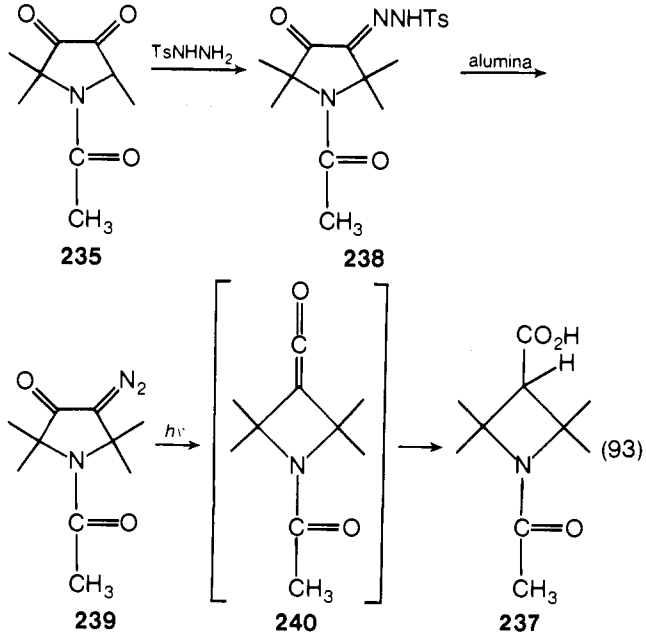
B. Miscellaneous 1,2,3,4-Substituted Azetidines

Sandris and Ourisson[95] reported the synthesis of 1-acetyl-3-hydroxy-2,2,4,4-tetramethyl-3-azetidinecarboxylic acid (**234**) via the benzilic rearrangement of pyrrolidinedione **235** (eq 92).



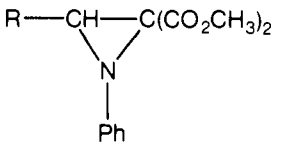
235 **234** **236** (92)

Lead tetraacetate oxidation of α-hydroxy acid **234** yielded 1-acetyl-2,2,4,4-tetramethyl-3-azetidinone (**236**). Chen and co-workers[32] repeated these experiments and obtained comparable results. Using the same starting material these authors also prepared 1-acetyl-2,2,4,4-tetramethyl-3-azetidinecarboxylic acid (**237**) (eq 93). The diketone **235** was treated with *p*-toluenesulfonhydrazide to give the corresponding monotosyl hydrazone **238,** which was converted to the stable diazo ketone **239** by elution through an alumina column. Photolysis of **239** in aqueous tetrahydrofuran caused a contraction of the pyrrolidine ring (via formation of ketene **240**), giving the carboxylic acid **237** in good yield.

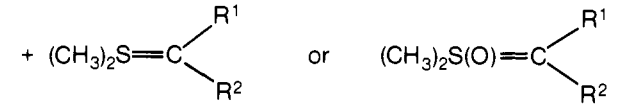


235 **238** **239** **240** **237** (93)

Carrie and co-workers[93,96] have reported a novel synthesis of azetidines by the reaction of aziridines with sulfur ylides (eq 94). The sulfur ylide **244b** did not react with aziridine **241** and the dimethylsulfonium methylide **243a** did not lead to azetidines **245a** and **246a.** These azetidines were prepared with dimethylsulfonium methylide **244a,** and the authors showed that azetidines **245a** and **246a** are unstable in the presence of **243a.**

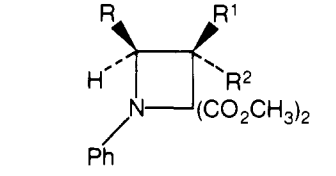


241, R = Ph
242, R = CO_2CH_3

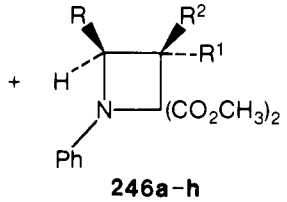


243a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CO_2CH_3$
c, $R^1 = H$; $R^2 = CO_2C_2H_5$
d, $R^1 = H$; $R^2 = COPh$
e, R^1, $R^2 = C_{13}H_{18}$[a]
f, $R^1 = Cl$; $R^2 = CO_2C_2H_5$
g, $R^1 = Br$; $R^2 = CO_2C_2H_5$

244a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = COPh$



245a, R = Ph; $R^1 = R^2 = H$
b, R = Ph; $R^1 = H$; $R^2 = CO_2CH_3$
c, R = Ph; $R^1 = H$; $R^2 = CO_2C_2H$
d, R = Ph; $R^1 = H$; $R^2 = COPh$
e, R = Ph; R^1, $R^2 = C_{13}H_{18}$[a]
f, R = Ph; $R^1 = Cl$; $R^2 = CO_2C_2$
g, R = Ph; $R^1 = Br$; $R^2 = CO_2C_2$
h, R = CO_2CH_3; $R^1 = H$; $R^2 = CO$



(94)

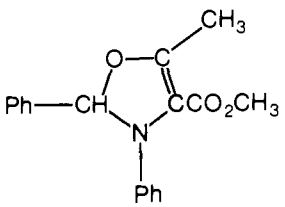
246a-h

[a]Fluorenylidene

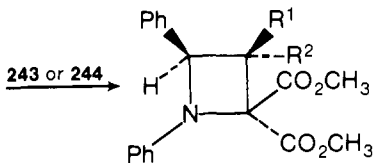
Azetidines were also produced when the sulfur ylides **243** or **244** were allowed to react with the 4-oxazoline **247** (eq 95). The products were formed in the following relative percentages: **248a,** 90%; **249a,** 10%; **239b, c,** and **d,** ≥90%; **249b, c,** and **d,** none detected; **248e,** 91%; **249e,** 9%.

In the reactions of ethyl chloro- (or bromo-) (dimethylsulfuranylidene)acetate (**243f** or **243g**) with aziridine **241** and 4-oxazoline **247** no chloride or bromide elimination was observed. The authors attempted to prepare C_2-monosubstituted azetidines by heating aziridine **250** with the sulfonium ylides in benzene. No reaction was observed except the isomerization of **250** and the partial decomposition of the sulfur ylide. The C_2-monosubstituted azetidines were, however, prepared in good yield by dimethoxycarbonylation of **245** with piperidine in boiling toluene or xylene (eq 96).

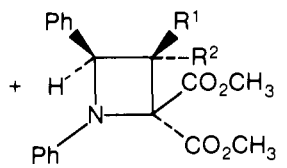
In the resulting mixtures, compound **251** was always the major product (≥90%). Azetidines **251a-c** and **251e** were recovered unchanged after refluxing with piperidine in toluene. When **251b** or **251c** was treated with *N*-deuteriopiperidine there was no isomerization or deuterium exchange with H_2 or H_3. *N*-Deuteriopiperidine converted **245b** to **251b** with a deuterium on C_2 only, providing a simple method to deuterate the azetidines on C_2. These results indicate that the dimethoxycarbonylation of



247

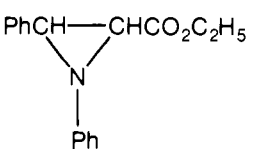


248a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CO_2CH_3$
c, $R^1 = H$; $R^2 = CO_2C_2H_5$
d, $R^1 = H$; $R^2 = COPh$
e, R^1; $R^2 = C_{13}H_{18}$[a]

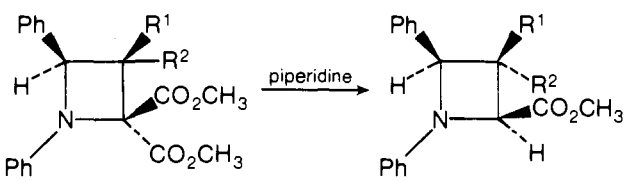


(95)

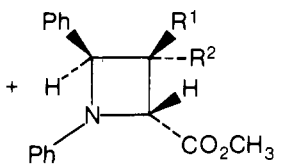
249a-e



250



245a-e **251a-e**



(96)

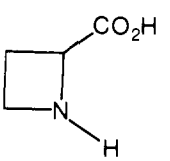
252a-e

245a-c and **245e** is under kinetic control and takes place without changing the configuration at C_3. Azetidine **245d** is a special case since H_3 is acidic enough to be replaced by deuterium, owing to the presence of a benzoyl group.

X. 2-Substituted Azetidines

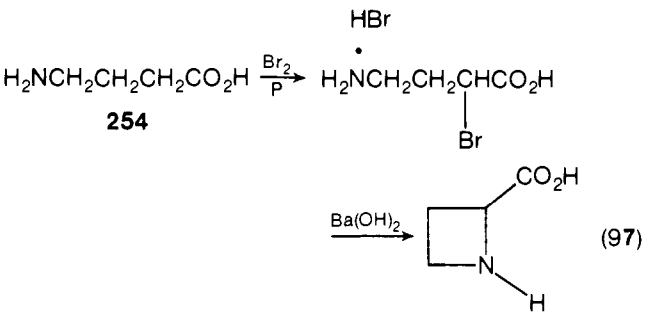
A. Azetidine-2-carboxylic Acid

The azetidine derivative with potentially the most important biological properties is L-azetidine-2-carboxylic acid (**253**). This



253

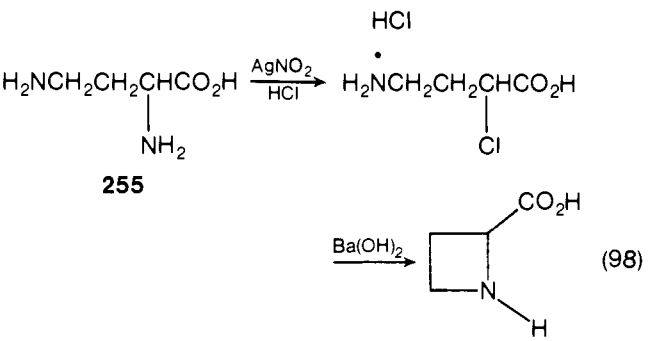
uniquely simple azetidine was isolated by Fowden[2,97] from 70% aqueous ethanol extracts of fresh leaves of *Canvallaria majalis* (lily-of-the-valley) and is the only known naturally occurring azetidine. Virtanen and Linko[98] are credited with independent discovery of the compound; however, they proposed an incorrect structural formula and later[99] acknowledged Fowden's formulation as correct. The structure of the compound was verified[2,97] by its identity with racemic and optically active forms synthesized from γ-aminobutyric acid (**254**) (eq 97) and L-α,γ-diaminobutyric acid (**255**) (eq 98), respectively. On treatment of **253** with boiling



254

(97)

253
DL-form

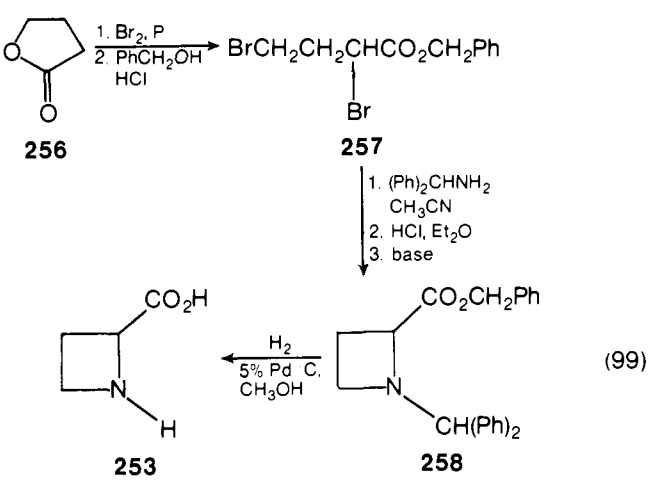


(98)

253
D-form

6 N hydrochloric acid the products were homoserine, α-hydroxy-γ-aminobutyric acid, α-chloro-γ-aminobutyric acid, and α-amino-γ-chlorobutyric acid.[2]

Several workers have since reported improved methods of preparation for azetidine-2-carboxylic acid (**253**). Cromwell and Rodebaugh[100] synthesized **253** from γ-butyrolactone (**256**) in 53.5% yield (eq 99). Benzyl α,γ-dibromobutyrate (**257**) was

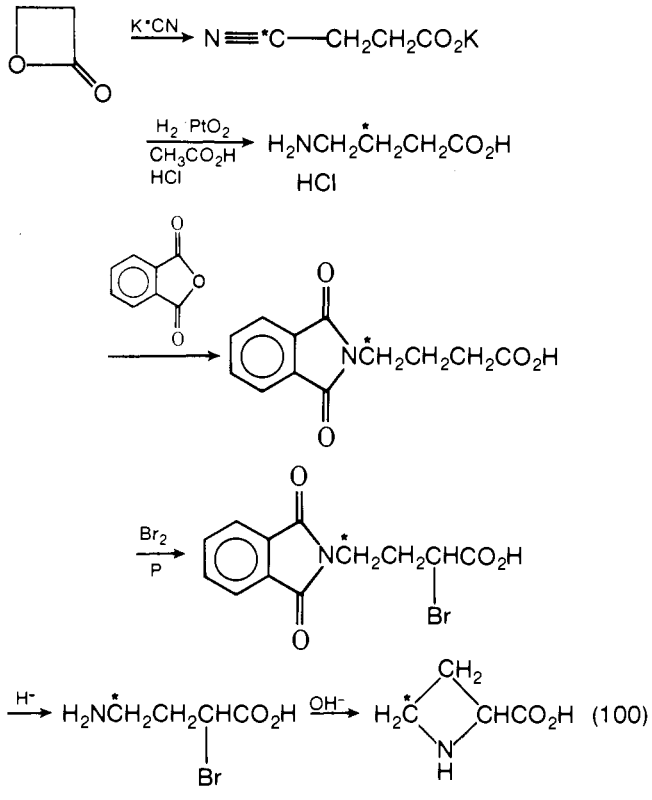


(99)

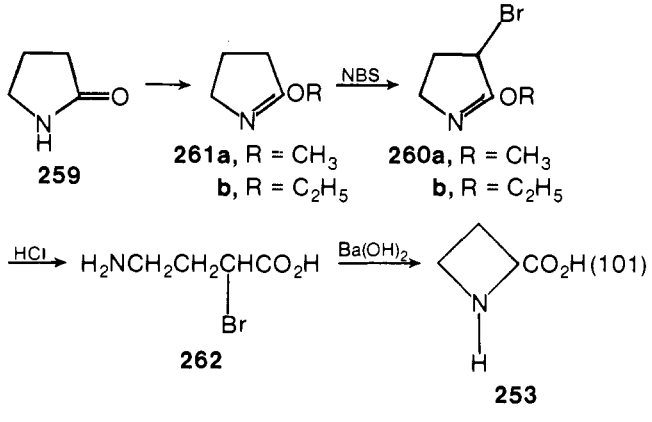
253 **258**

prepared from **256** by a modification of the method used by Wladislaw for methyl α,γ-dibromobutyrate.[36] The reaction of **257** with benzhydrylamine to give 1-benzhydryl-2-carbobenzyloxyazetidine (**258**) was found to proceed best when the

reactants were allowed to reflux in acetonitrile for 24 h. The crude azetidinyl ester **258** could be purified by column chromatography. However, this lengthy purification step is not necessary for the preparation of **253.** Crude **258** can be directly hydrogenated over Pearlman catalyst.[100,101] Pichat and coworkers[102] prepared azetidine-2-carboxylic acid (^{14}C-4) as

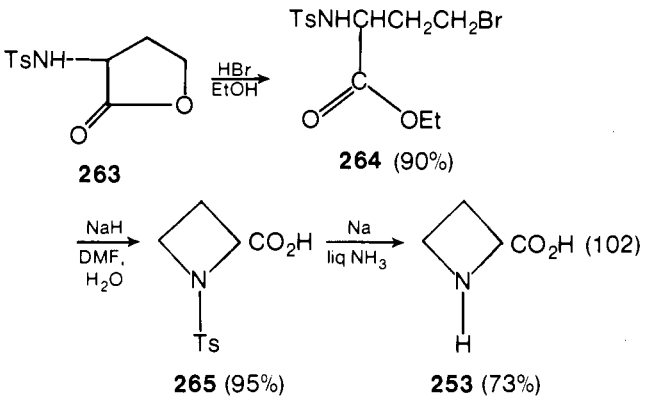


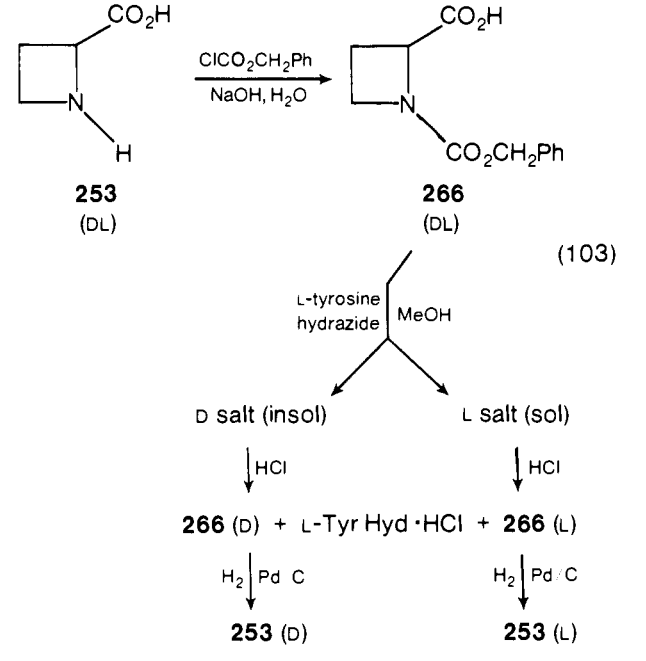
shown in eq 100. The synthesis of azetidine-2-carboxylic acid from 2-pyrrolidinone (**259**) via 3-bromo-2-methoxy-1-pyrroline (**260a**) was reported by Okada[103] (eq 101). 2-Methoxy- (**261a**) and 2-ethoxy-1-pyrroline (**261b**) were prepared from **259** by treatment with dimethyl sulfate[104] or triethyloxonium fluoroborate. These 2-alkoxy-1-pyrrolines were converted to 3-bromo-2-alkoxy-1-pyrrolines (**260**) in 45–50% yield by refluxing with NBS. Hydrolysis of **260a** gave the α-bromo acid **262,** which was cyclized to **253** in 50–58% yield with barium hydroxide. Optically



active L-azetidine-2-carboxylic acid has been synthesized by Miyoshi and co-workers[105] (eq 102). Treatment of tosyl-L-homoserine lactone (**263**) with hydrogen bromide, followed by recyclization of **264** with sodium hydride below 20 °C, gave tosyl-L-azetidine-2-carboxylic acid (**265**). After detosylation with sodium in liquid ammonia, the optically active L-azetidine-2-carboxylic acid (**253**) was obtained in a 62.5% overall yield.

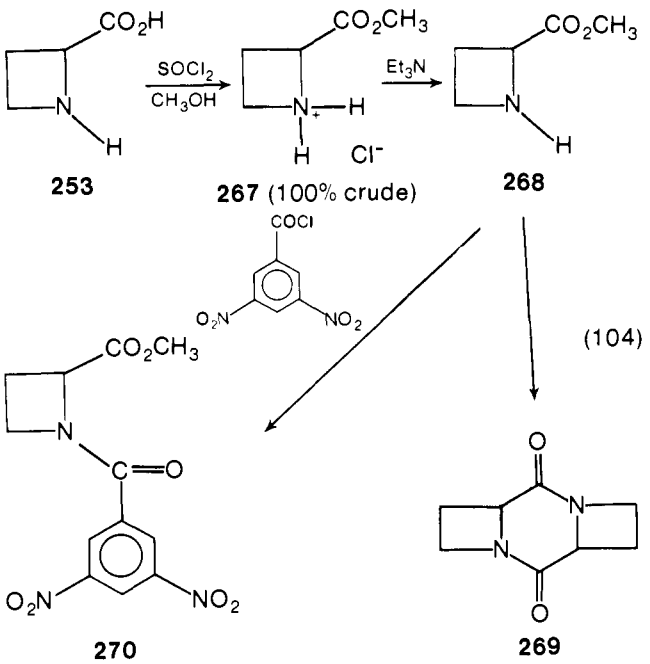
The DL form of **253** was resolved by Cromwell and Rodebaugh[106] using the L-tyrosine hydroazide salt of the *N*-carbobenzoxy derivative **266.**



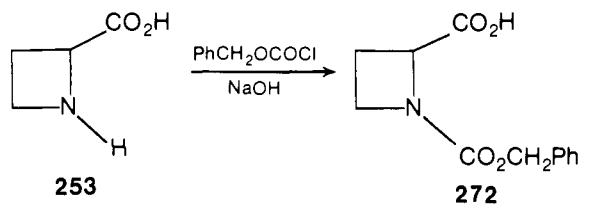


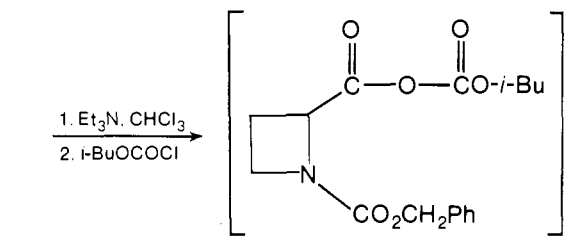
B. Azetidine-2-carboxylic Acid Derivatives

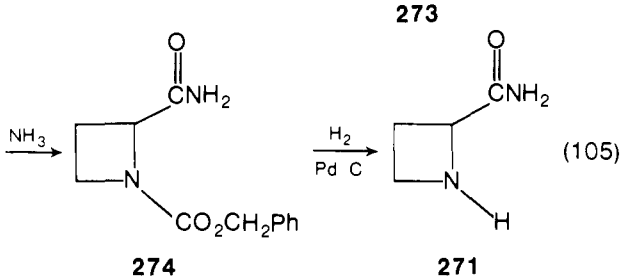
Cromwell and Phillips[101] reported the synthesis of the first N–H derivatives of azetidine-2-carboxylic acid. The acid **253** was found to react with thionyl chloride in methanol to give 2-carbomethoxyazetidine hydrochloride (**267**) as a noncrystalline oil (eq 104). Treatment of **267** with triethylamine led to the isolation of 2-carbomethoxyazetidine (**268**) in 76% yield. The azetidinyl ester **268** proved, however, to be unstable. Attempted distillation at reduced pressure led to formation of azetidine-2-carboxylic acid anhydride as well as straight-chain condensation polymerization products. Also, upon standing at room temperature **268** loses two molecules of methanol and cyclizes to form **269.** The cyclization can be readily followed by NMR and IR and is approximately 70% complete after 1 day. 2-Carbomethoxyazetidine can be conveniently stored as the hydrochloride **267** and used immediately upon liberation. The reaction of 3,5-dinitrobenzoyl chloride with freshly liberated **268** gave the dinitrobenzoyl derivative **270**; however, formation of **269** is a competitive reaction. Attempted preparation of azetidinyl amide **271** directly from 2-carbomethoxyazetidine hydrochloride (**267**) or the free base **268** was not successful. Upon treatment of **267** or **268** with excess amine the only isolable product is diketopiperazine **269.** The amino function of azetidine-2-carboxylic acid was protected with the carbobenzoxy group to prevent the formation of **269** (eq 105). Treatment of the *N*-carbobenzoxyazetidinyl acid **272** with triethylamine in chloroform at 0 °C followed



by the addition of isobutyl chloroformate gave the corresponding mixed ester anhydride intermediate **273.** When treated with



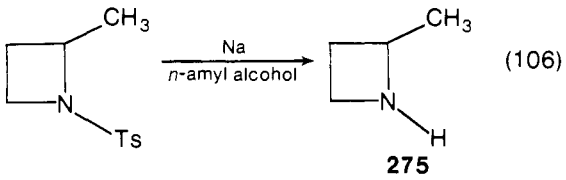




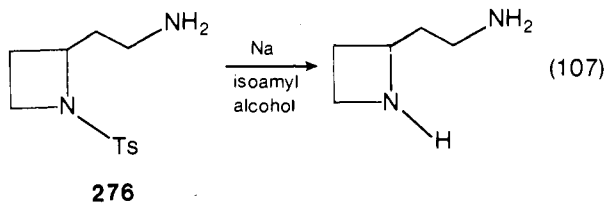
excess anhydrous ammonia, **273** afforded the primary amide **274** in good yield. Hydrogenolysis of **274** over 5% palladium on carbon gave azetidine-2-carboxamide (**271**) in 71.5% overall yield.

C. 2-Methyl- and 2-Phenylazetidine

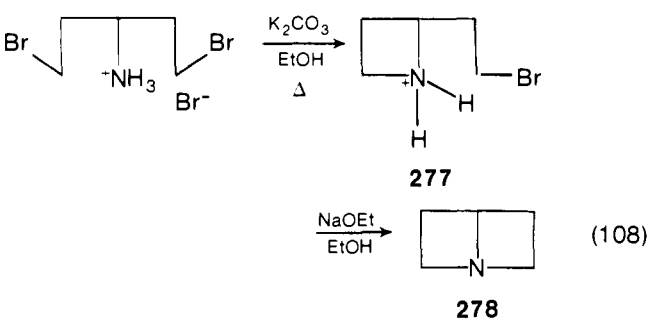
Vaughan and co-workers[8] reported the synthesis of 2-methylazetidine (**275**) by modification of the previously reported[14] sodium *n*-amyl alcohol cleavage of N-tosylated azetidines (see section III). Although later attempts to duplicate the original work had failed,[107] the authors were able to prepare 2-methylazetidine (**275**) in 78.2% yield by passing the reaction exit gases through a dilute solution of sulfuric acid (eq 106). Treatment of a pyridine solution of **275** with *p*-toluenesulfonyl chloride followed by dilution with water gave 2-methyl-*N*-tosylazetidine. Taniyama and Yasui[34,35] used sodium and isoamyl



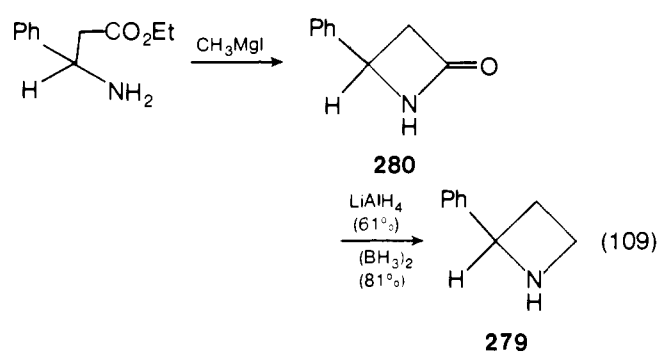
alcohol to remove the tosyl group of 2-alkylamino azetidine **276** (eq 107). The yield of their reaction, however, was very poor.



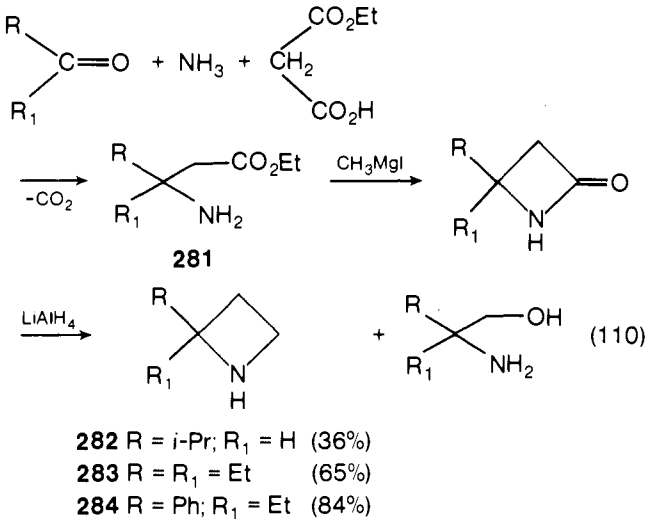
Grob and Kransnobajew[108] prepared the 2-alkylbromoazetidine (**277**) in their synthesis of 1-azabicyclo[2.2.0]hexane (**278**) (eq 108). The ring closure to **277** went in high yield (90–95%), isolated as the picrate, but the second ring closure could not be estimated. The 1-azabicyclo[2.2.0]hexane (**278**) was so thermally unstable and highly reactive that it could not be isolated.



The reduction of 2-azetidinones has been used successfully in the preparation of 2-substituted azetidines. Testa and coworkers[109] described the synthesis of 2-phenylazetidine (**279**) using lithium aluminum hydride to reduce the azetidin-2-one **280** (eq 109). Wells and Tarwater[110] used diborane to reduce **280**

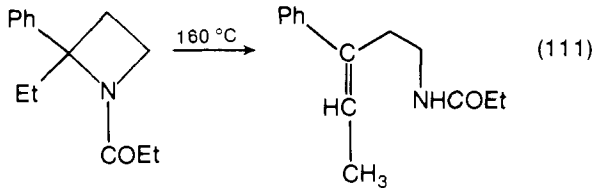


and obtained 2-phenylazetidine (**279**) in 81% yield. The synthesis of some 2,2-disubstituted azetidines has also been reported by Testa[111] (eq 110). The amino ester **281** was also made with R = R_1 = Ph; however, the ring-closure step failed with this compound. The yields for the isopropyl (**282**) and the diethyl (**283**) substituted compounds in both the ring closure (22 and 32%, respectively) and reduction (36 and 65%, respectively) were rather poor. However the phenylethyl-substituted derivative (**284**) gave high yields in both steps. It appears that an aromatic ring at the 2 position along with an alkyl substituent aids in ring formation, but geminal diaryl substituents prevent ring formation.



282 R = *i*-Pr; R_1 = H (36%)
283 R = R_1 = Et (65%)
284 R = Ph; R_1 = Et (84%)

Also, in the case of the *n*-propyl and the phenylethyl substituted azetidinones, small amounts of ring-opened amino alcohols **285** were isolated along with the azetidine. The *N*-propionyl derivative of the phenylethyl azetidine **284** was prepared and during distillation underwent thermal cleavage (eq 111). These results



reflect the general fact that these systems are finely balanced and that it is very difficult to determine any general rules of behavior.

XI. 2,3-Substituted Azetidines

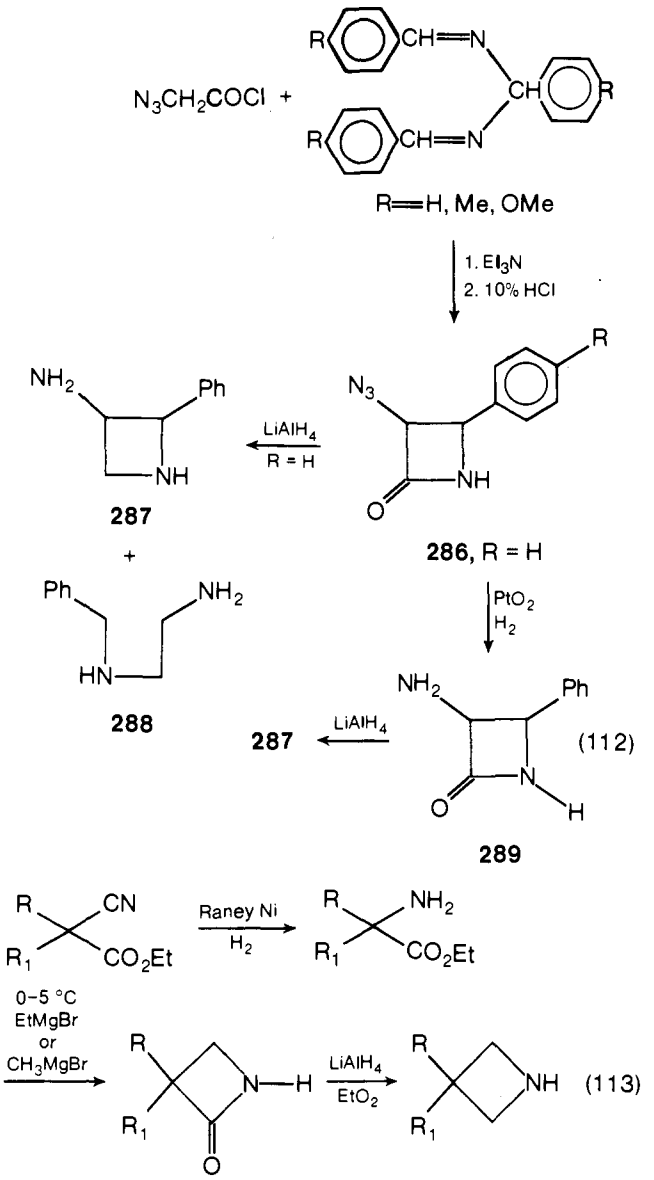
A. 3-Amino-2-arylazetidines

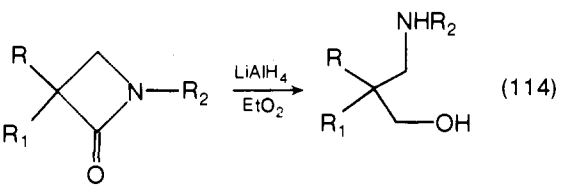
Very few 2,3-substituted azetidines have been reported in the literature. Wells and Lee[112] reported the synthesis of N-unsubstituted azetidinones and a conversion of one of them, *cis*-3-azido-4-phenyl-2-azetidinone (**286**), to an azetidine (eq 112). When treated with lithium aluminum hydride **286** gave a mixture of 3-amino-2-phenylazetidine (**287**) and *N*-benzylethylenediamine (**288**).[110] Catalytic reduction of **286** gave 3-amino-4-phenyl-2-azetidinone (**289**) in 80% yield. Reaction of **289** with lithium aluminum hydride gave **287** in 84% yield with no formation of **288.** Diborane was also used to reduce both **286** and **289.** When **289** was allowed to react with diborane in THF, followed by hydrolysis with dilute hydrochloric acid, *a* 66.5% yield of **287** was obtained. Treatment of **286** with diborane afforded **287** in 65% yield, both the azido and the carbonyl function being reduced in one step. This reduction procedure was also used to prepare 3-amino-2-(*p*-chlorophenyl)azetidine.

XII. 3-Substituted Azetidines

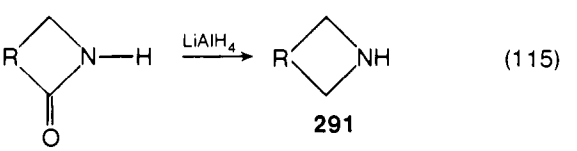
A. 3-Alkyl and 3-Aryl Substituted Azetidines

Any discussion of 3-substituted azetidines should start with the work of one of the foremost researchers in the area, Emilio Testa, who has made a large contribution to the field of azetidine synthesis in general, and 3,3-disubstituted azetidines in particular. Testa and co-workers[113] developed a reasonable synthetic route to 3,3-disubstituted azetidin-2-ones, and reduced them to azetidines with lithium aluminum hydride[9,113-115] (eq 113, Table I). It is necessary that the ring nitrogen be unsubstituted; otherwise ring opening to a 3-aminopropanol results (eq 114). However, N-substituted azetidines were prepared by N-acylation with acetyl chloride[42] followed by reduction with lithium aluminum hydride.[41,42]





Testa and co-workers[41] also synthesized a series of 3-monosubstituted azetidin-2-ones **290** and reduced them to azetidines **291** with lithium aluminum hydride (eq 115). It is interesting to note that the yields obtained for the 3-monosubstituted de-



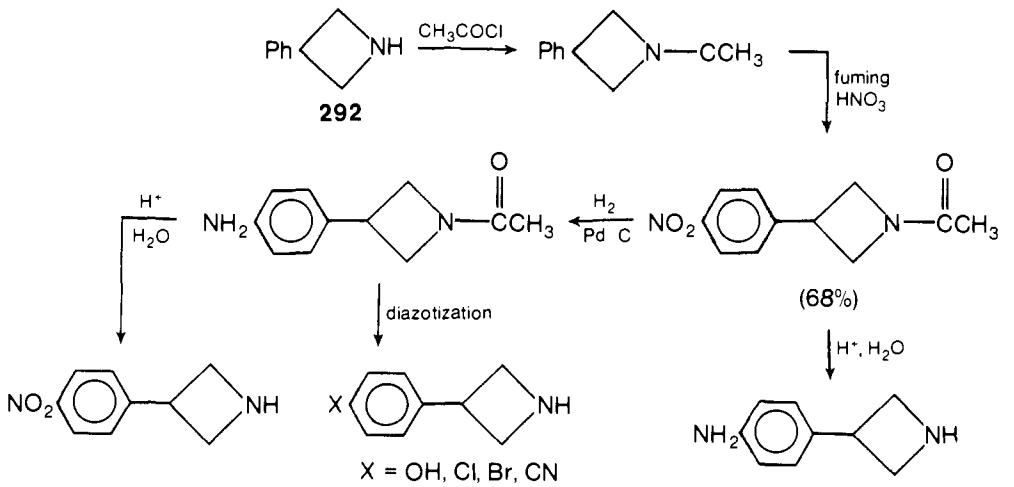
290

R = *i*-Bu (68%)
R = cyclohexyl (50%)
R = benzyl (49%)
R = α-naphthyl (45%)

TABLE XII. 3,3-Disubstituted Azetidines

R	R_1	mp or bp (mm/Hg), °C	yield, % [a]	ref
Ph	CH_3	73 (0.9)	65	113, 114
Ph	C_2H_5	85–87 (1)	70.5	114, 115
Ph	n-C_3H_7	88–90 (0.4)	73.5	9, 113
Ph	i-C_3H_7	36–38	75.3	113, 115
Ph	n-C_4H_9	85–90 (0.2–0.4)	73.5	114, 115
Ph	CH_2Ph	62–64	85.5	114, 115
Ph	C_6H_{11}	85–87	74.5	114, 115
Ph	Ph	95–96	43	114
Ph	CH_2OH	135–137	51	44, 116
Ph	OH		31	117
C_2H_5	CH_2Ph	120–130 (0.4)	24	113
CH_3	CH_3	90–92 (760)	44.5	115
C_2H_5	C_2H_5	50 (20)	71	115
n-C_3H_7	n-C_3H_7	87 (20)	72.4	115
n-C_4H_9	n-C_4H_9	110 (15)	87	115

[a] Yield refers to reduction from azetidinone.



(116)

rivatives were significantly lower than for the 3,3-disubstituted ones. As previously mentioned Bishop[45] used Testa's method to prepare a series of 3- and 1,3-substituted azetidines (see Table XII). Using the procedure shown in eq 116 Testa[118] prepared several para-substituted 3-phenylazetidines and reported a series of transformations for 3-phenylazetidine **292** (eq 116). The yields of these reactions were generally high (70–80%); however, more impressive are the conditions that the azetidine ring can withstand. The acetyl group on the nitrogen must give great stability to the ring to allow it to survive the fuming nitric acid even at temperatures below 0 °C.

XIII. References

(1) S. Gabriel and J. Weiner, *Ber.*, **21**, 2669 (1888).
(2) L. Fowden, *Biochem. J.*, **64**, 323 (1956).
(3) P. J. Peterson and L. Fowden, *Nature (London)*, **200**, 148 (1964).
(4) T. Takeuchi and D. J. Prokop, *Biochem. Biophys. Acta*, **175**, 142 (1969).
(5) D. J. Prokop, *Biochem. Biophys. Acta*, **175**, 156 (1969).
(6) J. A. Moore in "Heterocyclic Compounds with Three and Four-Membered Rings", Part II, A. Weissberger, Ed., Interscience Publishers, New York, 1964, pp 885–977.
(7) N. H. Cromwell, *J. Heterocycl. Chem.*, **13**, S-1 (1976).
(8) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).
(9) E. Testa, L. Fontanella, and G. F. Cristiani, *Justus Liebigs Ann. Chem.*, **626**, 14 (1959).
(10) E. Testa, L. Fontanella, G. F. Cristiani, and T. Mariani, *Helv. Chim. Acta*, **42**, 2370 (1959).
(11) E. Testa, A. Wittgens, G. Maffi, and G. Bianchi in "Research in Organic Biological and Predicinal Chemistry", Vol. I, U. Gallo and L. Santamaria, Eds., Scuole Grafiche Pavoniane Artigianelli, Milan, Italy, 1964, p 482.
(12) J. N. Wells and O. R. Tarwater, *J. Pharm. Sci.*, **60**, 156 (1971).
(13) A. Ladenberg and J. Sieber, *Ber.*, **23**, 2727 (1890).
(14) W. Marckwald and A. F. van Droste-Huelschoff, *Ber.*, **31**, 3264 (1898).
(15) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 309 (1968).
(16) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 439 (1969).
(17) J. Yasumura, *Nippon Kagaku Zasshi*, **82**, 1700 (1961); *Chem. Abstr.*, **59**, 2313d (1963).
(18) S. Searles, Jr., M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, **78**, 4917 (1956).
(19) L. W. Deady, G. J. Leary, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **28**, 511 (1963).
(20) D. H. Wadsworth, *J. Org. Chem.*, **32**, 1184 (1967).
(21) A. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).
(22) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 622 (1949).
(23) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 1063 (1971).
(24) T. Chen, T. Sanjik, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2401 (1967).
(25) T. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 1964 (1967).
(26) A. T. Bottini and C. P. Nash, *J. Am. Chem. Soc.*, **84**, 734 (1962).
(27) L. W. Deady, R. D. Topsom, R. E. J. Hutchinson, J. Vaughan, and G. J. Wright, *Tetrahedron Lett.*, 1773 (1968).
(28) T. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **39**, 1618 (1966).
(29) I. M. Roberts and D. Horvitz, U.S. Patent 3,069,412 (Dec. 18, 1962); *Chem. Abstr.*, **58**, 1017e (1963).
(30) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2031 (1899).
(31) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 4417 (1961).
(32) T. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2398 (1967).
(33) M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chem. Lett.*, 5 (1973).
(34) H. Taniyama and B. Yasui, *Yakugaku Zasshi*, **81**, 1493 (1961); *Chem. Abstr.*, **56**, 10069j (1962).
(35) H. Taniyama and B. Yasui, *Yakugaku Zasshi*, **81**, 1497 (1961).
(36) B. Wladislaw, *J. Org. Chem.*, **26**, 711 (1961).
(37) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 421 (1971).
(38) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 19 (1971).
(39) H. K. Leung, B. A. Phillips, and N. H. Cromwell, *J. Heterocycl. Chem.*, (1976).
(40) (a) F. F. Blicke and W. A. Gould, *J. Org. Chem.*, **23**, 1102 (1958); (b) M. E. Speeter and W. H. Maroney, *J. Am. Chem. Soc.*, **76**, 5810 (1954).
(41) E. Testa, A. Bonati, G. Pagani, and E. Gatti, *Justus Liebigs Ann. Chem.*,

647, 92 (1961).
(42) E. Testa, L. Fontanella, L. Mariani, and G. F. Cristiani, *Justus Liebigs Ann. Chem.*, **633**, 56 (1960).
(43) E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Justus Liebigs Ann. Chem.*, **635**, 119 (1960).
(44) E. Testa, L. Fontanella, and M. Vobara, *Justus Liebigs Ann. Chem.*, **671**, 97 (1964).
(45) D. C. Bishop, J. F. Cavalla, I. M. Lockhart, and M. Wright, *J. Med. Chem.*, **11**, 466 (1968).
(46) E. Bellasio and G. Cristiani, *J. Med. Chem.*, **12**, 196 (1969).
(47) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 2123 (1968).
(48) T-Y. Chen, *Bull. Chem. Soc. Jpn.*, **41**, 2486 (1968).
(49) D. H. Wadsworth and O. E. Schupp, III, *J. Heterocycl. Chem.*, **3**, 230 (1966).
(50) L. R. Fedor, T. C. Bruce, K. L. Kirk, and J. Meinwald, *J. Am. Chem. Soc.*, **88**, 108 (1966).
(51) T. C. Bruce, A. Donzel, R. W. Huffman, and A. R. Bulter, *J. Am. Chem. Soc.*, **89**, 2106 (1967).
(52) W. Funke, *Angew. Chem., Int. Ed. Engl.*, **80**, 70 (1969).
(53) W. Funke, *Chem. Ber.*, **102**, 3148 (1969).
(54) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc. C*, 2295 (1966).
(55) V. R. Gaertner, *Tertrahedron Lett.*, 4691 (1966).
(56) V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967).
(57) V. R. Gaertner, *Tetrahedron Lett.*, 141 (1964).
(58) J. H. Ross, D. Baker, and A. T. Coscia, *J. Org. Chem.*, **29**, 824 (1964).
(59) V. R. Gaertner, *Tetrahedron Lett.*, 343 (1967).
(60) V. R. Gaertner, *J. Org. Chem.*, **33**, 523 (1968).
(61) S. S. Chatterjee and D. J. Triggle, *Chem. Commun.*, 93 (1968).
(62) A. G. Anderson and R. Lok, *J. Org. Chem.*, in press.
(63) B. J. Gaj and D. R. Moore, *Tetrahedron Lett.*, 2155 (1967).
(64) S. S. Chatterjee and A. Shoeb, *Synthesis*, **No. 3**, 153 (1973).
(65) (a) R. A. Claisen and S. Searles, Jr., *Chem. Commun.*, 289 (1966); (b) E. H. Gold, *J. Am. Chem. Soc.*, **93**, 2793 (1971).
(66) R. H. Higgins, N. H. Cromwell, and W. W. Paudler, *J. Heterocycl. Chem.*, **8**, 961 (1971).
(67) T.-Y. Chen, T. Sankiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2401 (1967).
(68) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 1063 (1971).
(69) T.-Y. Chen, *Bull. Chem. Soc. Jpn.*, **41**, 2540 (1968).
(70) T.-Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **41**, 712 (1968).
(71) V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968).
(72) V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).
(73) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).
(74) V. R. Gaertner, *J. Heterocycl. Chem.*, **6**, 273 (1969).
(75) R. H. Higgins and N. H. Cromwell, *J. Org. Chem.*, **37**, 2918 (1972).
(76) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).
(77) C. L. Moyer, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1968.
(78) N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, 4037 (1966).
(79) J. L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).
(80) E. Doomes and N. H. Cromwell, *J. Org. Chem.*, **34**, 310 (1969).
(81) J. L. Imbach, E. Doomes, N. H. Cromwell, H. E. Baumgarten, and R. G. Parker, *J. Org. Chem.*, **32**, 3123 (1967).
(82) E. Doomes and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 153 (1969).
(83) M. C. Eagen, R. H. Higgins, and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 851 (1971).
(84) (a) M. C. Eagen and N. H. Cromwell, *J. Org. Chem.*, **39**, 911 (1974); (b) H.-K. Leung, S. B. Kulkarni, M. C. Eagan, and N. H. Cromwell, *ibid.*, **42**, 2094 (1977).
(85) R. H. Higgins and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 1059 (1971).
(86) T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Lett.*, 1115 (1971).
(87) R. H. Higgins and N. H. Cromwell, *J. Am. Chem. Soc.*, **95**, 120 (1973).
(88) V. N. Gogte, S. B. Kulkarni, and B. D. Tilak, *Tetrahedron Lett.*, 1867 (1973).
(89) V. N. Gogte, H. M. El-Namaky, M. A. Salama, and B. D. Tilak, *Tetrahedron Lett.*, 3319 (1969).
(90) F. Nerdel, P. Weyerstahl, and K. Zabel, *Chem. Ber.*, **102**, 1606 (1969).
(91) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 536 (1968).
(92) (a) S. B. Kulkarni, R. M. Rodebaugh, and N. H. Cromwell, *J. Hetercycl. Chem.*, **13**, 329 (1976); (b) S. B. Kulkarni and N. H. Cromwell, *ibid.*, **14**, 981 (1977).
(93) M. Vaultier, R. Bougot, D. Danian, J. Hamelin, and R. Carrie, *J. Org. Chem.*, **40**, 2990 (1975).
(94) M. F. Stevens and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 253 (1971).
(95) C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.*, 345 (1958).
(96) M. Vaultier, R. Bougot, D. Danion, J. Hamelin, and R. Carrie, *Tetrahedron Lett.*, 1923 (1973).
(97) L. Fowden, *Nature (London)*, **176**, 347 (1955).
(98) A. I. Virtanen and P. Linko, *Acta Chem. Scand.*, **9**, 551 (1955).
(99) A. I. Virtanen, *Nature (London)*, **176**, 984 (1955).
(100) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 435 (1969).
(101) (a) B. A. Phillips and N. H. Cromwell, *J. Heterocycl. Chem.*, **10**, 795 (1973); (b) H.-K. Leung, B. A. Phillips, and N. H. Cromwell, *ibid.*, **13**, 247 (1976).
(102) L. Pichat, P. N. Liem, and J. P. Guermont, *Bull. Chim. Soc. Fr.*, 4079 (1968).
(103) Y. Yamada, T. Emori, S. Kinoshita, and H. Okada, *Agr. Biol. Chem.*, **37**, 649 (1973).
(104) A. E. Wick, P. A. Bartlett, and D. Dolphin, *Helv. Chim. Acta*, **54**, 513 (1971).
(105) M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chem. Lett.*, 5 (1973).
(106) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 993 (1969).
(107) (a) F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5928 (1955); (b) H. C. Brown and M. Gerstein, *ibid.*, **72**, 2926 (1950); (c) G. P. Jones, *J. Org. Chem.*, **9**, 484 (1944).
(108) C. A. Grob and V. Krasnobajew, *Helv. Chim. Acta*, **47**, 2145 (1964).
(109) E. Testa, L. Fontanella, and V. Aresi, *Justus Liebigs Ann. Chem.*, **656**, 114 (1962).
(110) J. N. Wells and O. R. Tarwater, *J. Pharm. Sci.*, **60**, 156 (1971).
(111) E. Testa, L. Fontanella and V. Aresi, *Justus Liebigs Ann. Chem.*, **673**, 60 (1964).
(112) J. N. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).
(113) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Justus Liebigs Ann. Chem.*, ***64***, 158 (1958).
(114) E. Testa, L. Fontanella, and F. Fava, *Farmaco (Pavia), Ed. Sci.*, **13**, 152 (1958).
(115) E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **625**, 95 (1959).
(116) E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **661**, 187 (1963).
(117) E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **671**, 106 (1964).
(118) A. Bonati, G. F. Cristiani, and E. Testa, *Justus Liebigs Ann. Chem.*, **647**, 83 (1961).