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p-Toluenesulfonylmethyl Isocyanide: A Versatile Synthon in Organic Chemistry

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p-TOLUENESULFONYLMETHYL ISOCYANIDE: A VERSATILE SYNTHON IN ORGANIC CHEMISTRY

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(In final form 3 February 2003)

TosMIC, a versatile synthon in organic chemistry, has been extensively used for the synthesis of a wide variety of small, medium and large ring heterocycles. It has immense implications in the synthesis of nitriles, aldehydes, ketones, alkanes, cyclophanes and large number of natural products. Several drug intermediates and pharmacologically active compounds have been synthesized from TosMIC. In addition, chiral TosMIC analogs have been synthesized and employed for synthesis of optically active compounds.

Keywords: Synthon; Umpolung; Heterocycles; Cyclophanes; Chiral TosMIC analogs

CONTENTS

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1. INTRODUCTION

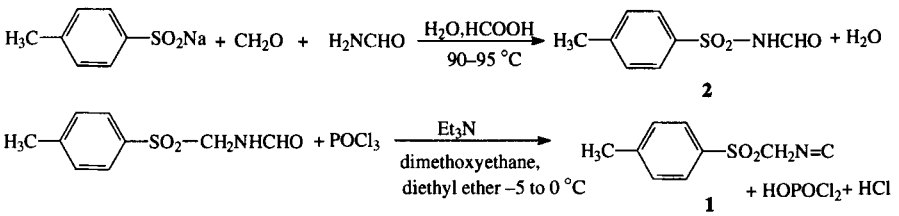
In recent years there have been a multitude of new synthetic methods, catalysts and reagents developed to aid in the construction of an overwhelming variety of heterocycles and chemical structures. In particular the search for new reagents which have the potential to exhibit higher reactivity or greater efficiency has become an extremely active area of chemical research.

p-Toluenesulfonylmethyl isocyanide (TosMIC) is a useful and versatile reagent in organic chemistry [1]. It is a synthon with diverse and rapidly expanding applications. This review begins with synthesis of TosMIC and its derivatives. Application of TosMIC in the synthesis of a large variety of heterocyclic chemical structures is described in detail. Special attention has been paid to the synthesis of intermediates used in pharmacologically active compounds. Following this, the use of TosMIC and chiral TosMIC analogs in asymmetric synthesis is exhaustively reviewed. The review covers the literature up to 2001.

1.1. TosMIC Preparation

p-Tolylsulfonylmethyl isocyanide **1** was originally prepared by irradiation of *p*-tolylsulfonyl diazomethane [2] in liquid HCN [3,4]. It has also been prepared by reaction of *p*-tolylsulfonyl fluoride and isocyanomethyl lithium [3,5].

The most useful and abundantly used procedure is dehydration of *N*-(*p*-tolylsulfonylmethyl) formamide **2** with $POCl_3$ [6] (Scheme 1). This procedure has advantages over the other procedures described earlier since it is a much simpler procedure using readily available and inexpensive starting materials and TosMIC is obtained as a colorless crystalline product.



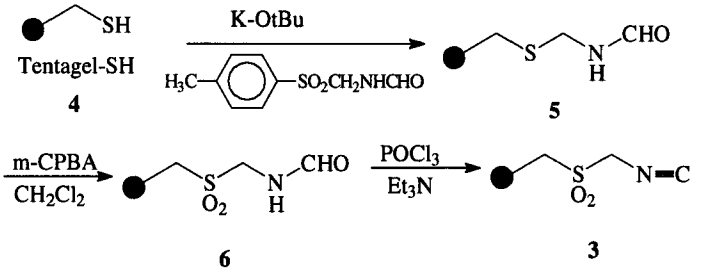
SCHEME 1

1.2. Synthesis of TosMIC Derivatives

Several TosMIC derivatives have been synthesized. The synthesis of the most useful derivatives is described.

1.2.1. Monosubstituted TosMIC Derivatives

A solid phase version of TosMIC **3** has been synthesized by Ganesan *et al.* [7]. Tentagel-SH resin is used as starting material for the synthesis of an immobilized sulfonyl methylisocyanide **3** as shown in Scheme 2.



SCHEME 2

Compound **5** is synthesized from Tentagel-SH resin **4** which is subjected to a sequence of reactions analogous to those for TosMIC. The application of these TosMIC analogs in combinatorial chemistry has been described [8].

1.2.1.1. Aryl-substituted TosMIC Sisko *et al.* [9] have developed an improved procedure for the preparation of aryl-substituted tosylmethyl isocyanides. The TosMIC analogs **7–13** were prepared by Sisko *et al.* (Figure 1).

TosMIC derivatives **7–13** have been used for the synthesis of various heterocycles, described in Section 2. The method of synthesis of **7–13** is outlined in Scheme 3.

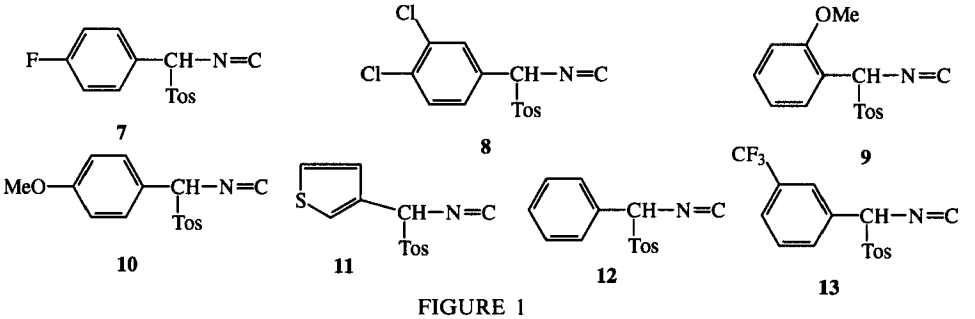
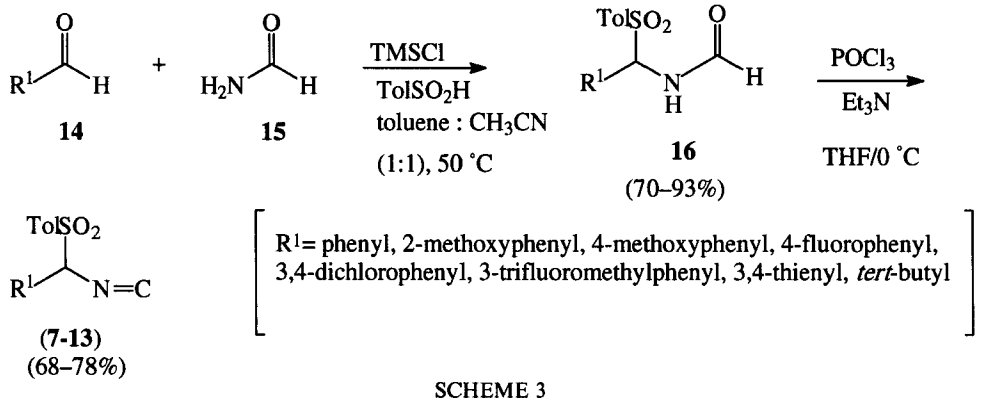


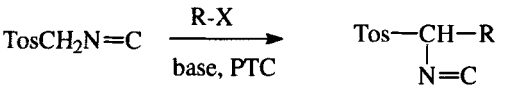
FIGURE 1



SCHEME 3

Tosylformamides **16** were prepared by simply heating the aldehyde, formamide, TMSCl and *p*-toluenesulfinic acid in a 1:1 mixture of toluene and acetonitrite at 50 °C for 5 h in 70–93% yield. Dehydration of formamide **16** with $POCl_3$ in THF gave the isocyanides **7–13** in 68–78% yield [9].

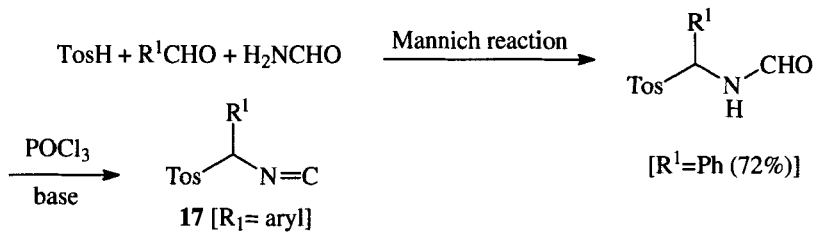
Monoalkylated and arylated TosMIC derivatives, e.g. **17**, are useful in most of the synthetic applications of TosMIC described in Sections 2–4. Several monoalkylated TosMIC derivatives **17** (R = alkyl) have been prepared in good yield by phase transfer catalyzed (PTC) monoalkylation of TosMIC (Scheme 4) [10].



17 (R=Alkyl)

SCHEME 4

Aryl derivatives **17** (R^1 = aryl) have been prepared by Mannich reaction followed by dehydration (Scheme 5) [11,12].

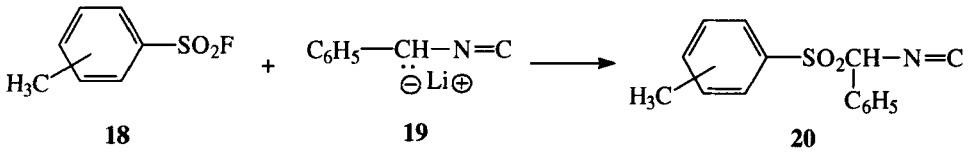


17 [R_1= aryl]

[R^1=Ph (72%)]

SCHEME 5

Alkyl derivatives **17** (R^1 = alkyl) have also been prepared by this method. Sulfonyl aryl derivatives **20** have been prepared by reaction of arylsulfonyl fluorides **18** with lithiobenzyl isocyanides **19** [11] (Scheme 6).



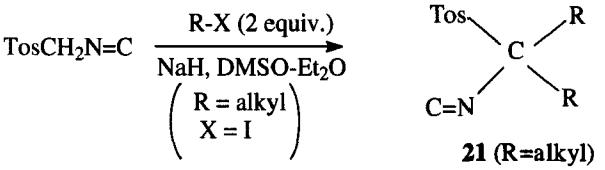
18 **19** **20**

SCHEME 6

A large number of monosubstituted alkenyl and long chain alkyl substituted TosMIC derivatives have been prepared according to Scheme 4 by various groups of workers for the synthesis of intermediates used in natural product synthesis [13–22]. A detailed list of intermediates synthesized has been provided in a recent review [23].

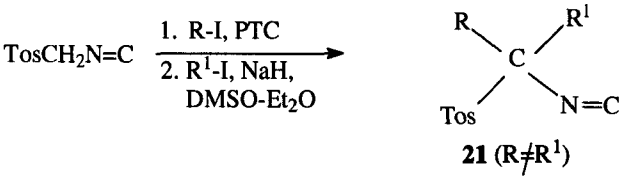
1.2.2. Disubstituted TosMIC Derivatives

Dialkylated TosMIC derivatives **21** can be synthesized by reaction of TosMIC with two equivalents of alkylating agent in the presence of NaH in DMSO and Et_2O as solvents (Scheme 7) [24].



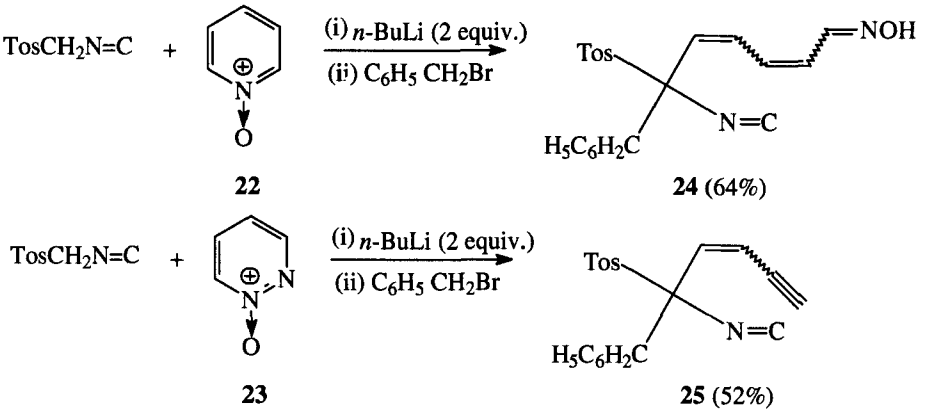
SCHEME 7

The two alkyl groups may be different as shown in Scheme 8 [25].



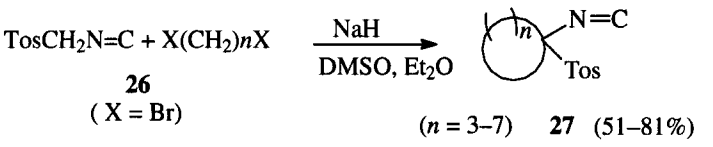
SCHEME 8

The reaction of TosMIC in the presence of *n*-BuLi (2 equiv.) with pyridine *N*-oxide **22** and pyridazine *N*-oxide **23** followed by reaction with $C_6H_5CH_2Br$ leads to ring opening of *N*-oxides, leading to the formation of disubstituted TosMIC derivatives **24** and **25** (Scheme 9) [26].



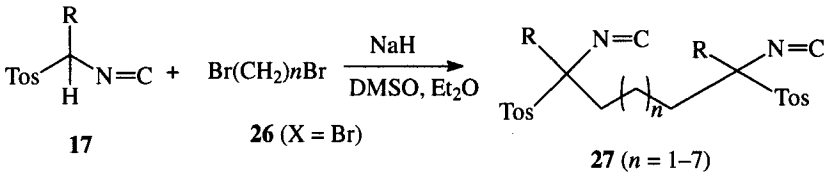
SCHEME 9

Dihalides **26** react with TosMIC to form cycloalkane rings **27** in moderate to good yields (Scheme 10).



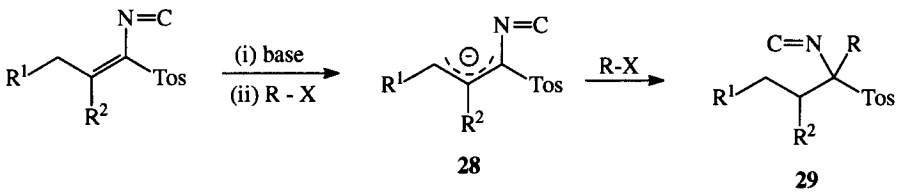
SCHEME 10

Monosubstituted TosMIC derivatives **17** react with **26** to afford dialkylated products **27**, extending the carbon chain to a large number of carbon atoms [27] (Scheme 11).



SCHEME 11

Alkenyl-substituted TosMIC derivatives **29** have been synthesized from anions **28** formed by reaction of Knoevenagel condensation products of TosMIC and ketone with base according to Scheme 12 [28,29].



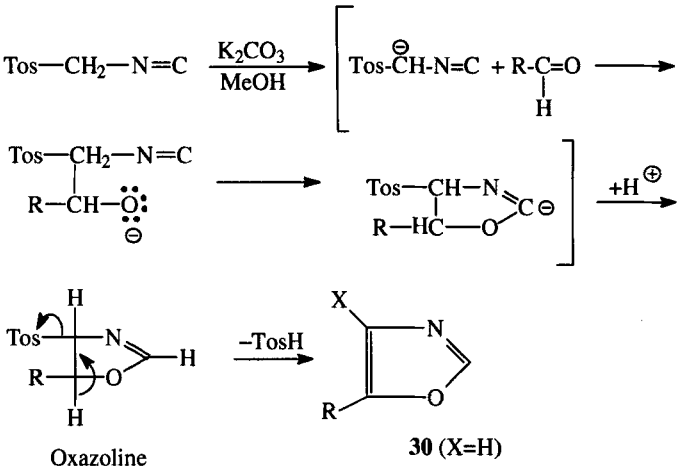
SCHEME 12

2. USE OF TOSMIC IN THE SYNTHESIS OF HETEROCYCLES

TosMIC has been used for the synthesis of several azole ring systems by base-induced addition of its C–N=C moiety to various substrates containing C=O, C=N, C=S, C=C, N≡N, etc. Thus new routes to the synthesis of, for example, oxazoles, imidazoles, pyrroles, thiazoles and 1,2,4-triazoles have been developed.

2.1. Oxazoles

Aldehydes are efficiently converted in a one-pot reaction into 5-substituted oxazoles [30] **30**. Equimolecular quantities of TosMIC and an aldehyde are reacted together in the presence of K_2CO_3 in refluxing methanol. The TosMIC undergoes nucleophilic α-addition at the terminal carbon and the reaction pathway shown in Scheme 13 has been suggested for the synthesis of oxazoles [30]. Oxazoles are also obtained by reaction of TosMIC with acid chlorides or anhydrides. In these cases a tosyl substituent is present at position 4 in the ring. Various 5-substituted oxazoles synthesized are listed in Table I.

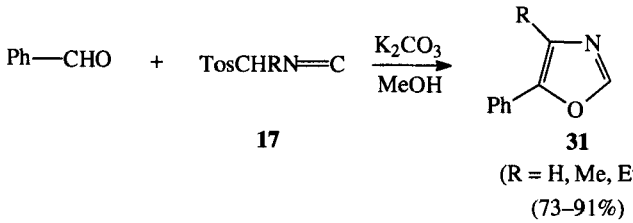


SCHEME 13

TABLE I Synthesis of oxazoles **30** from TosMIC and aldehydes

RCHO (*R*)	*Yield of* **30** (%)
Ph	91
4-NO_2–C_6H_4	91
4-Cl–C_6H_4	57

Alkyl-substituted TosMIC homologs **17** on reaction with benzaldehyde in the presence of K_2CO_3 and MeOH yield 4-alkyl-5-aryl substituted oxazoles (**31**) [31,32] (Scheme 14).

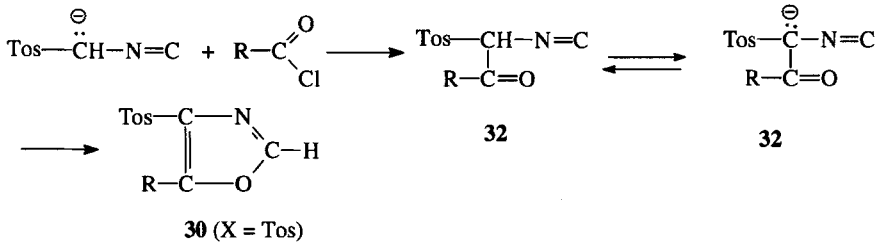


17

31
(R = H, Me, Et)
(73–91%)

SCHEME 14

Reaction of TosMIC with acid chlorides presumably occurs via the acyl derivative **32** which has not been isolated [30], giving oxazoles **30** (X = Tos) in yields of 57–65%:

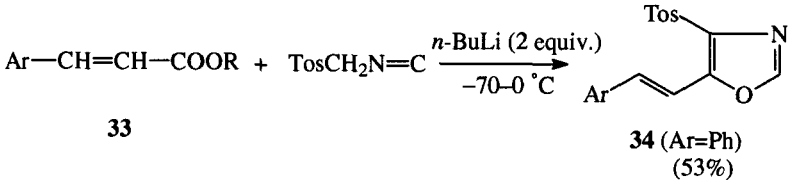


32

32

30 (X = Tos)

Esters **33** also react with TosMIC in the presence of 2 equivalents of *n*-BuLi at −70 to 0 °C to form 4-tosyloxazoles (**34**). The dianion of TosMIC is essential to act as a nucleophile during the course of its reaction with the ester carbonyl function [26] (Scheme 15).



33

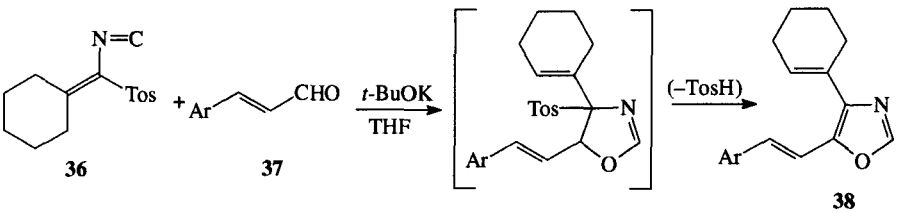
34 (Ar=Ph)
(53%)

SCHEME 15

5-Heteroaromatic substituted oxazoles **35** were prepared using a similar method by condensation of heteroaromatic aldehydes with tosylmethyl isocyanide [32]:

35

Various oxazoles prepared are listed in Table II. The only exception is the reaction with pyrrole-2-carbaldehyde, leading to formation of 3-tosylpyrolo[1,2-*c*]pyrimidine [32]. TosMIC and monosubstituted TosMIC homologs (**36**) react with α,β-unsaturated aldehydes (**37**) to form oxazoles **38** [33] (Scheme 16).

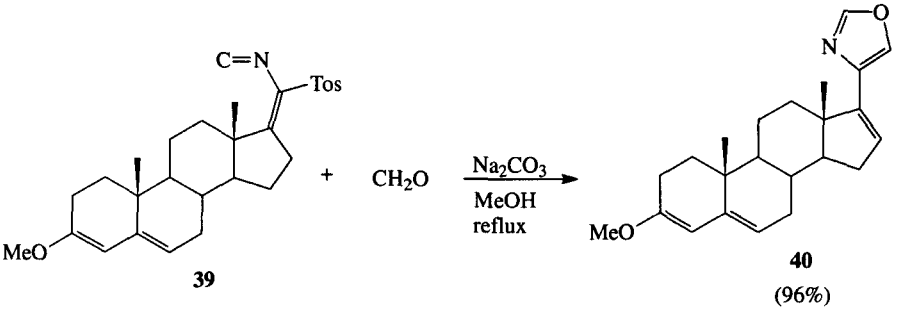


36 **37**

38
(90%)

SCHEME 16

Similarly, the monosubstituted derivative of TosMIC (**39**) on reaction with formaldehyde forms oxazole **40** [34] (Scheme 17).

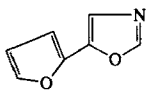
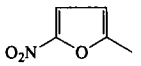
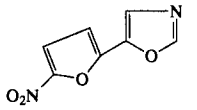
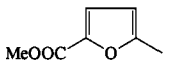
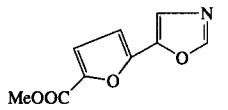
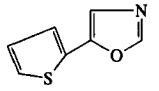
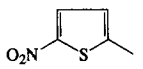
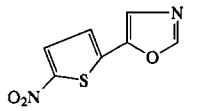
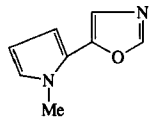
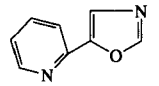
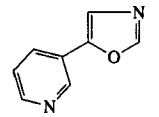
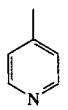
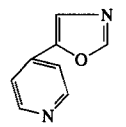


39

40
(96%)

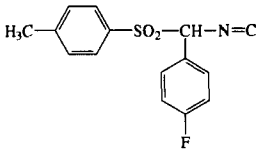
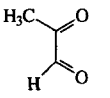
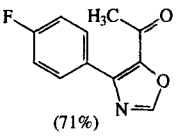
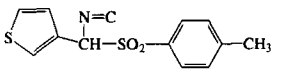
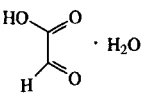
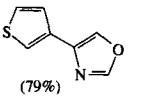
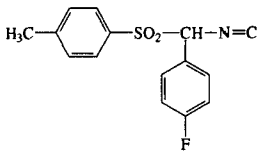
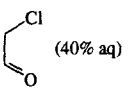
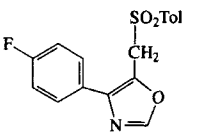
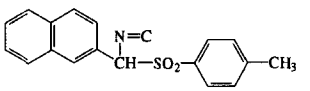
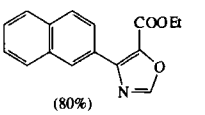
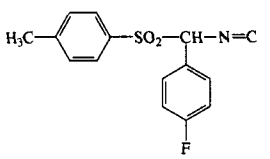
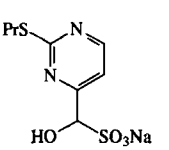
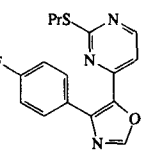
SCHEME 17

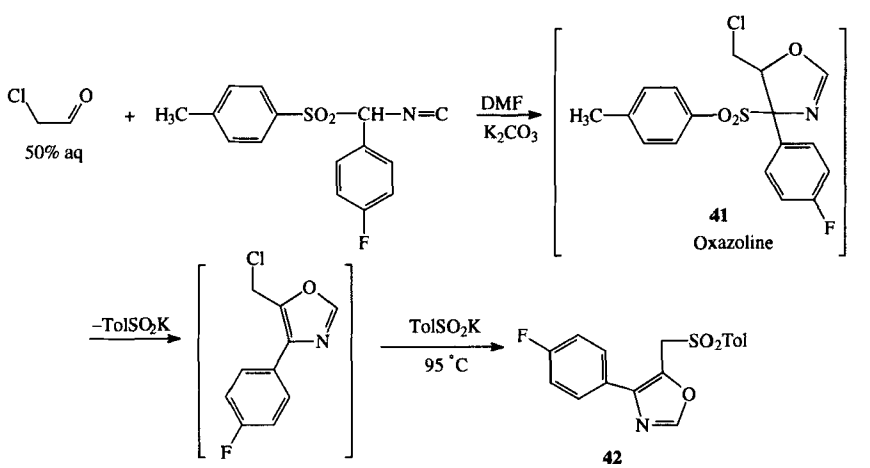
TABLE II 5-Substituted oxazoles **35** formed from the reaction of heteromaromatic aldehydes and TosMIC [32]

R of RCHO	*Oxazole* **35**	*Yield* (%)
		82
		83
		88
		80
		68
		47
		82
		80
		67

4-Substituted and 4,5-disubstituted oxazoles have recently been synthesized from the reaction of aryl-substituted TosMIC reagents with simple and multifunctional aldehydes [35]. These results are summarized in Table III. As expected, glyoxalic acid undergoes cycloaddition with TosMIC reagents to produce the monosubstituted oxazole in good yield (entry 2, Table III). Reaction of TosMIC derivative **7** with chloroacetaldehyde gives an unexpected product (entry 3, Table III). The reaction in DMF and K_2CO_3 at room temperature for 18 h leads to formation of oxazoline **41** (Scheme 18) as the major poduct (mixture of *cis* and *trans* isomers).

TABLE III Synthesis of 4- and 4,5-disubstituted oxazoles from substituted TosMIC derivative and multifunctional aldehydes

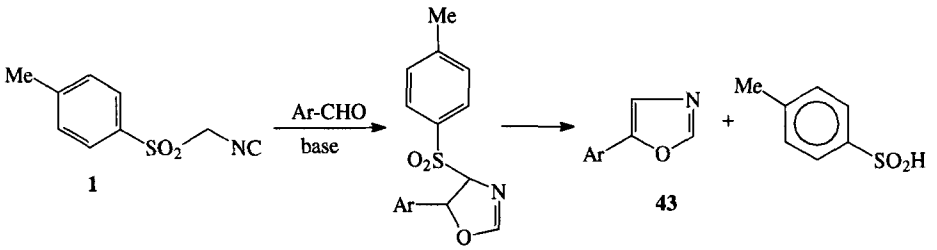
Entry	*Substituted TosMIC derivative*	*Aldehyde*	*Product (yield)*
1		 (40% aq)	 (71%)
2			 (79%)
3		 (40% aq)	 (63%)
4			 (80%)
5			 (62%)



SCHEME 18

The solution on heating at 95 °C leads to elimination of $TolSO_2H$, resulting in the formation of tosylmethyloxazole **42**. The bisulfite adduct (entry 5) is also capable of smooth cycloaddition with TosMIC derivative to give oxazole via the intermediacy of the corresponding aldehyde.

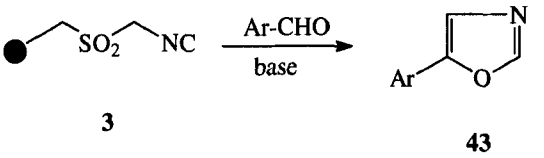
A quaternary ammonium hydroxide ion exchange resin has been used by Ganesan *et al.* [8] to catalyze the reaction of TosMIC with aromatic aldehydes to give 5-aryloxazoles **43** (Scheme 19). The heterogeneous base is removed by simple filtration while the sulfinic acid would exchange with the resin and be tightly bound by ionic interactions.



SCHEME 19

In a typical procedure used by Ganesan *et al.* [8] a solution of the aldehyde (0.135 mol) and TosMIC (1.1 mol equiv.) and Ambersep 900 $OH^{(-)}$ resin (250 mg) in DME–MeOH (4 mL) was heated at reflux for 8 h. The filtrate after filtration from the resin was concentrated and the crude product was purified by preparative thin layer chromatography. The broad range of aryl oxazoles prepared is listed in Table IV. The commendable features of the resin catalyzed procedure make it the method of choice for solution-phase oxazole synthesis with TosMIC.

The solid phase version of TosMIC **3** synthesized from Tentagel-SH resin or PS-TosMIC synthesized from polystyrene-SH was used by Ganesan *et al.* [7] to synthesize 5-aryloxazoles **43** according to Scheme 20.



SCHEME 20

TABLE IV Synthesis of 5-aryloxazoles using an ion exchange resin as base

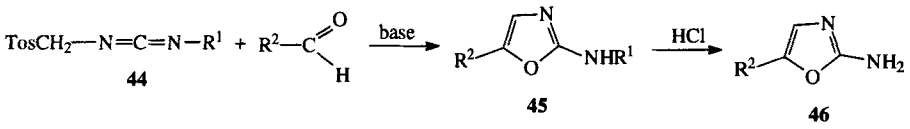
Aldehyde, Ar–CHO (Ar)	*Crude purity* (%)	*Yield of* **43** (%)
Ph	87	85
2-MeC_6H_4	85	64
2,4-$Me_2C_6H_3$	69	54
2-isoquinolinyl	70	69
4-MeO–C_6H_4	82	62
4-PhO–C_6H_5	90	67
2-Furyl	73	59
3-Cl–C_6H_4	87	72
4-Cl–C_6H_4	57	57
4-Cl-3-$NO_2C_6H_3$	88	83
4-NO_2–C_6H_4	94	84
4-CF_3–C_6H_4	71	70
2-Naphthyl	82	72

TABLE V Synthesis of 5-aryloxazoles from PS-TosMIC and aldehydes, ArCHO

Aldehyde ArCHO (Ar)	*Yield of 5-aryloxazole* **43** (%)
Ph	50
4-*tert*-BuC_6H_4	33
2-Me–C_6H_4	43
2,4-Me_2–C_6H_3	42
4-Ph–C_6H_4	45
4-CN–C_6H_4	40
4-NO_2–C_6H_4	44
2-NO_2–C_6H_4	42
3-Br–C_6H_4	25
3-F–C_6H_4	32

Tentagel resin is unstable to basic conditions and hence polystyrene-SH was prepared from Merrifield resin according to the method of Kobayashi by Ganesan *et al.* [7]. This resin **3** known as PS-TosMIC was found to be stable and worked efficiently for the synthesis of 5-aryloxazoles (**43**). The yields of **43** obtained are reported in Table V.

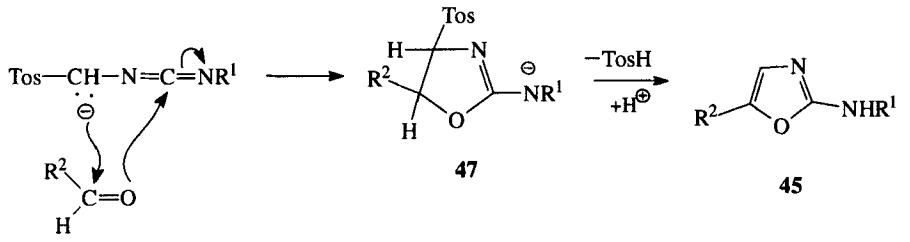
TosMIC derivatives *N*-(tosylmethyl)carbodiimides **44** have been used to synthesize 2-*tert*-butylamino and (triphenylmethyl)amino **45** and 2-amino-1,3-oxazoles **46** according to Scheme 21 [36].



44 **45** **46**

SCHEME 21

The central carbodiimidocarbon of *N*-(tosylmethyl)carbodiimides **44** plays a role similar to the isocyano carbon of TosMIC. Attack of the anion of **44** at the electrophilic end of the carbon–oxygen double bond of the aldehyde and ring closure through the isocyano carbon to **47**, followed by *in situ* elimination of TosH, gives **45** as shown in Scheme 22.



47 **45**

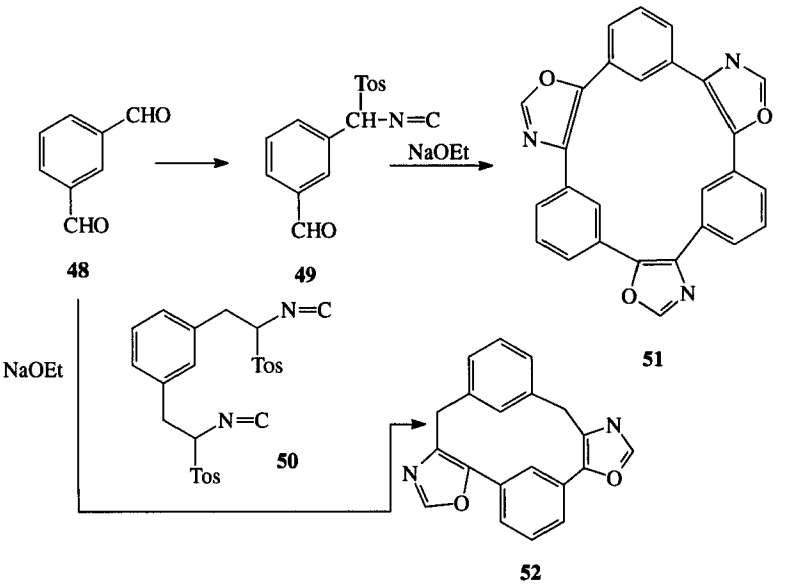
SCHEME 22

The compounds **45** and **46** synthesized are listed in Table VI.

Unusual macrocycles containing oxazole rings **51** and **52** have been synthesized from TosMIC derivatives **49** and **50** by reaction with *m*-phenylene dialdehyde **48** (Scheme 23) [12,37].

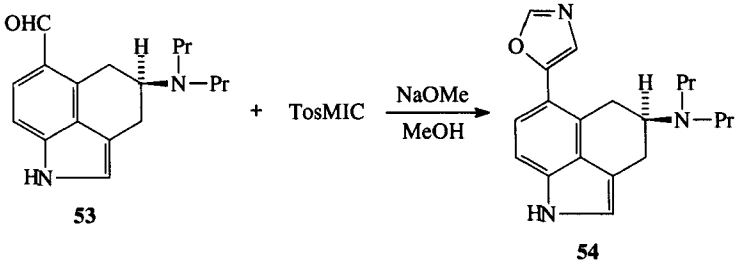
TABLE VI Synthesis of 2-*tert*-butylamino-1,3-oxazoles (**45**, $R^1 = t$-Bu), 2-[(triphenylmethyl)amino]-1,3-oxazoles (**45**, $R^1 = Ph_3C$) and 2-amino-1,3-oxazoles (**46**)

Compound	R^1	R^2	*Yield* (%)	*Reaction conditions*
45a	Ph_3C	Ph	78	PTC
45a	Ph_3C	Ph	73	NaH–DME
45b	$(CH_3)_3C$	Ph	80	PTC
45c	Ph_3C	4-$NO_2C_6H_4$	71	PTC
45d	$(CH_3)_3C$	4-$NO_2C_6H_4$	73	PTC
45e	$(C_6H_5)_3C$	4-$OCH_3C_6H_4$	60	PTC
45f	$(CH_3)_3C$	4-$OCH_3C_6H_4$	63	PTC
45g	$(C_6H_5)_3C$	4-ClC_6H_4	76	PTC
45h	$(CH_3)_3C$	4-ClC_6H_4	70	NaH–DME
46a	–	C_6H_5	84	HCl–MeOH
46b	–	4-$NO_2C_6H_4$	79	HCl–MeOH
46c	–	4-$H_3COC_6H_6$	66	HCl–MeOH
46d	–	4-ClC_6H_4	66	HCl–MeOH



SCHEME 23

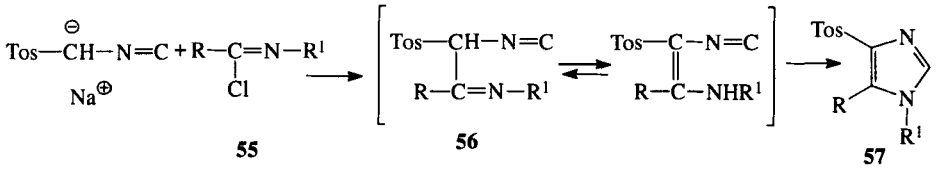
The 5-oxazole derivative **54**, a potent 5-HT_1A agonist, has been synthesized by reaction of carboxaldehyde **53** with TosMIC in the presence of NaOMe and MeOH (Scheme 24) [38].



SCHEME 24

2.2. Imidazoles

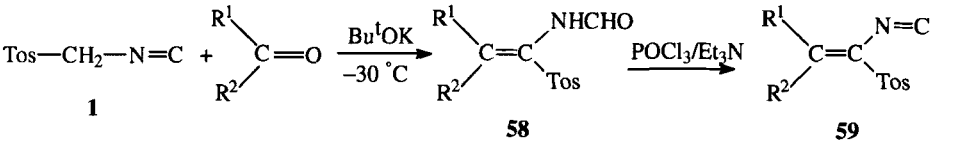
TosMIC reacts with imidoyl chlorides **55** in the presence of NaH in DMSO to form tosyl-substituted imidazoles **56** in good yields [39]. The sodium salt of TosMIC anion reacts with imidoyl chloride **55** to form the adduct **56** by attack of the nucleophilic carbon of the TosMIC anion at the electrophilic carbon of the imidoyl chloride. The adduct undergoes cycloaddition to form tosyl-substituted imidazole **57** as shown in Scheme 25. The tosyl imidazoles **57** synthesized using this method are listed in Table VII [39].



SCHEME 25

No reaction was observed when R was the *tert*-butyl group in the imidoyl chlorides [40] since the product hydrolyzes into the corresponding amide before reaction takes place.

Tosylmethyl isocyanide **1** reacts with aldehydes and ketones to form *N*-(1-tosyl-1-alkenyl) formamides **58**. Compounds **58** on dehydration with $POCl_3$ form 1-isocyano-1-tosyl-1-alkenes **59** which are useful synthons for the preparation of imidazoles [41] (Scheme 26).

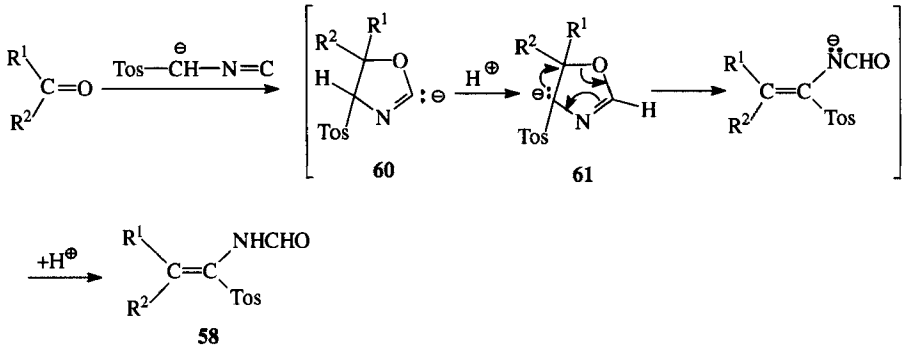


SCHEME 26

The formation of **58** is known to proceed through cycloaddition of TosMIC anion to give the conjugate bases **60** and **61** of 4-tosyl-2-oxazolines followed by cycloreversion as shown in Scheme 27.

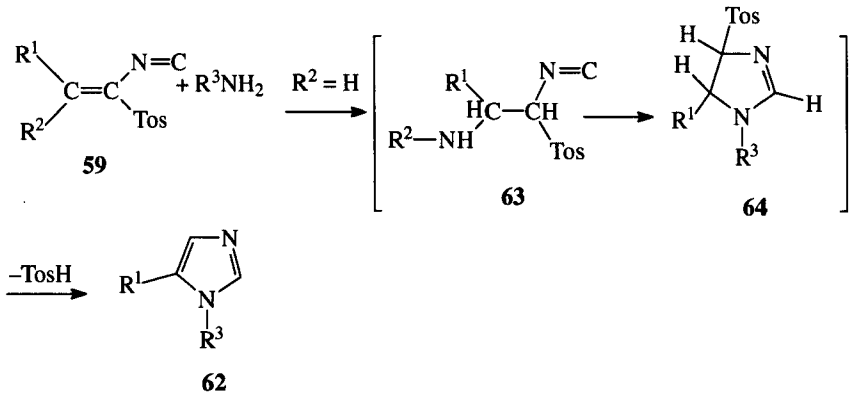
TABLE VII Synthesis of tosyl imidazoles **57** according to Scheme 25

Imidoyl chloride	*R*	*R*^{1}	*Yield of* **14** (%)
52a	C_6H_5	C_6H_5	60
52b	C_6H_5	4-$NO_2C_6H_4$	85
52c	4-$NO_2C_6H_4$	C_6H_5	88
52d	C_6H_5	C_6H_{11}	80
52e	4-$NO_2C_6H_4$	C_6H_{11}	75
52f	*tert*-C_4H_9	C_6H_{11}	–



SCHEME 27

Imidazoles **62** were obtained from **59** by reaction with primary aliphatic amines as depicted in Scheme 28. Compound **59** exists as a mixture of *E* and *Z* isomers as evidenced by ^1H nuclear magnetic resonance (NMR) spectroscopy.



SCHEME 28

A Michael-type addition of R^3NH_2 on **59** to yield **63** followed by ring closure to **64** and subsequent β-elimination of TosH leads to formation of **62** [41]. **59** and **62** synthesized according to Schemes 26 and 28 respectively are listed in Tables VIII and IX.

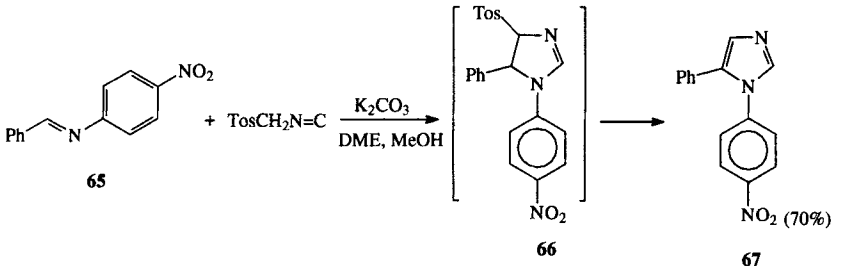
1,5-Disubstituted imidazoles **67** have been synthesized in variable yields by reaction of aldimines **65** with TosMIC and base [11] (Scheme 29).

TABLE VIII Synthesis of 1-isocyano-1-tosyl-1-alkenes **59** according to Scheme 26

Compound	R^1	R^2	*Yield of* **59** *from* **58** (%)
59a	C_6H_5	H	54
59b	4-$NO_2C_6H_4$	H	55
59c	$(CH_3)_3C$	H	77
59d	H	H	Unstable
59e	CH_3	CH_3	68
59f	C_6H_5	C_6H_5	68

TABLE IX Synthesis of **62** from **59** and R^3NH_2

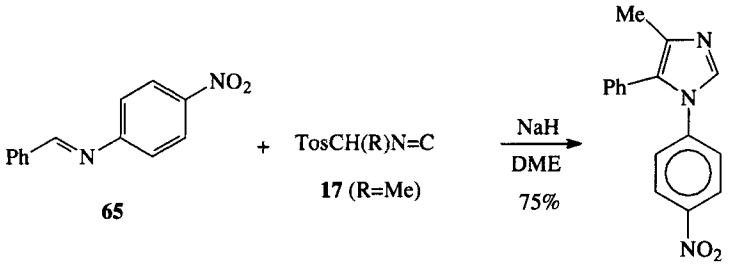
Compound	R^1	R^3	*Yield of* **62** (%)
19a	C_6H_5	H	65
19b	C_6H_5	CH_3	87
19c	C_6H_5	$(CH_3)_3C$	82
19d	C_6H_5	⬡	97
19e	4-$NO_2C_6H_4$	CH_3	88
19f	$(CH_3)_3C$	CH_3	46 (picrate)
19g	H	CH_3	5



65 **66** **67**

SCHEME 29

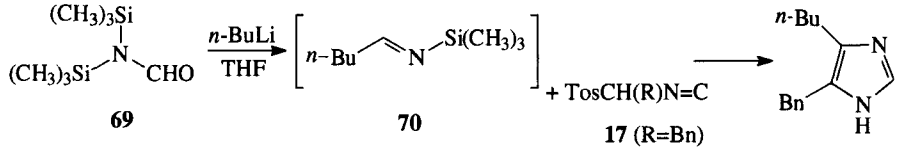
Imidazoline **66** can be obtained by carrying out the reaction at −20 °C in the absence of MeOH [11]. A similar procedure has been used for the synthesis of the 1,4,5-trisubstituted imidazole **68** by using monoalkylated TosMIC **17** (R=Me) instead of TosMIC (Scheme 30) [31].



65 **68**

SCHEME 30

N-(trimethylsilyl)aldimines **70** react with the TosMIC derivative **17** (R=Bn) to produce *N*-unsubstituted-4,5-disubstituted imidazoles **71** (Scheme 31) [42].

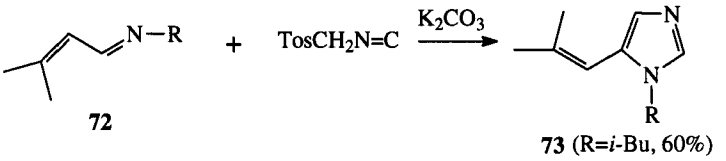


69 **70** **71**

(66%)

SCHEME 31

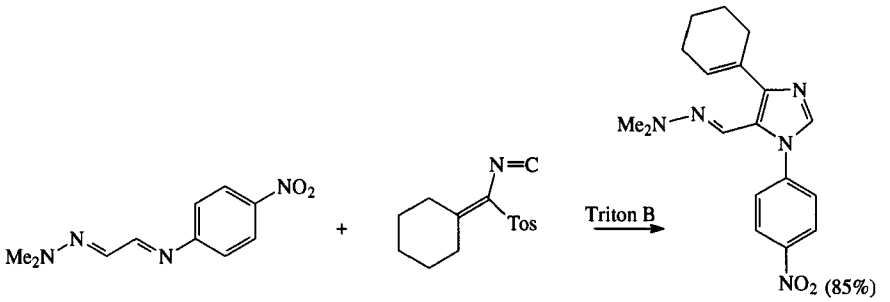
The α,β-unsaturated aldimine **72** reacted with TosMIC to form the imidazole **73** (Scheme 32) [43,44].



72 **73** (R=*i*-Bu, 60%)

SCHEME 32

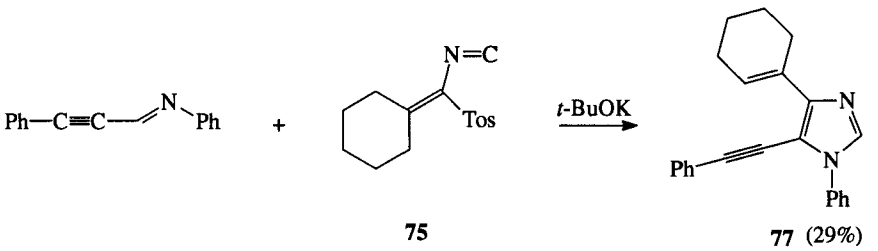
The 4-nitrophenylimine of cinnamaldehyde **74** reacted similarly with a TosMIC homolog derived from cyclohexanone (**75**) to form the imidazole derivative **76** (Scheme 33) [33].



74 **75** **76**

SCHEME 33

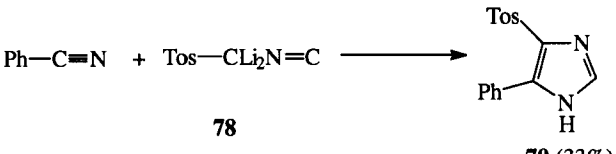
In order to avoid formation of pyrroles, the C=C was replaced by C≡C (Scheme 34) [33], leading to formation of the imidazole derivative **77**.



75 **77** (29%)

SCHEME 34

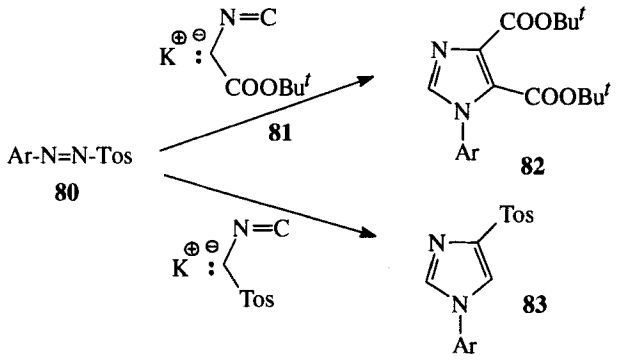
5-Phenyl-4-tosylimidazole **79** has also been synthesized from dilithio-TosMIC **78** by reaction with benzonitrile (Scheme 35) [26].



78 **79** (33%)

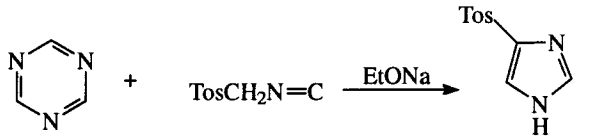
SCHEME 35

The reactions of arylazasulfones **80** with the potassium salts of (*tert*-butoxycarbonyl)methyl isocyanide **81** and TosMIC in DMSO yield 4,5-bis(*tert*-butoxycarbonyl) **82** and 4-tosyl-1-arylimidazoles **83,** respectively, in moderate to excellent yields (Scheme 36) [26].



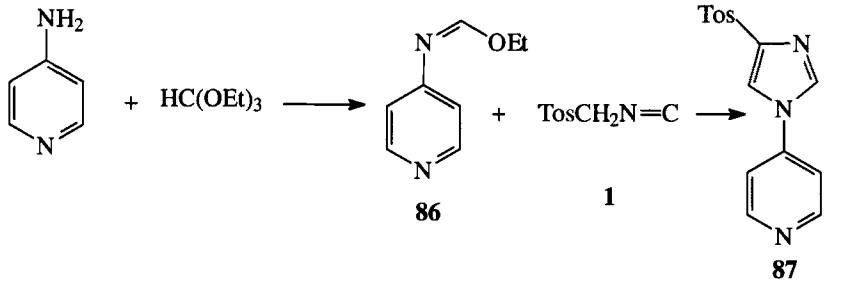
SCHEME 36

4-Tosyl-imidazole **85** can also be prepared by reaction of *sym*-triazine **84** with TosMIC in the presence of EtONa (Scheme 37) [45].



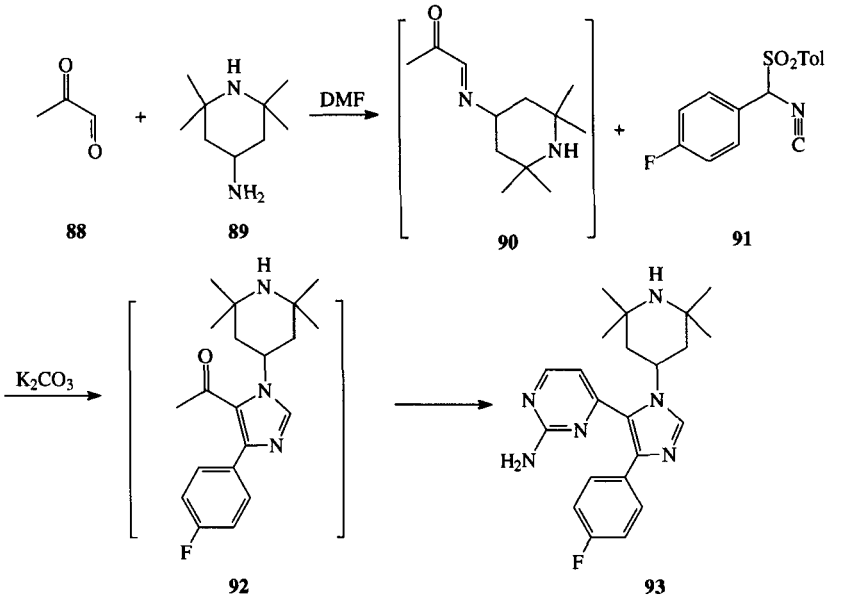
SCHEME 37

N-substituted-4-tosylimidazoles **87** have been synthesized from formimidates (**86**) by reaction with TosMIC [46] (Scheme 38).



SCHEME 38

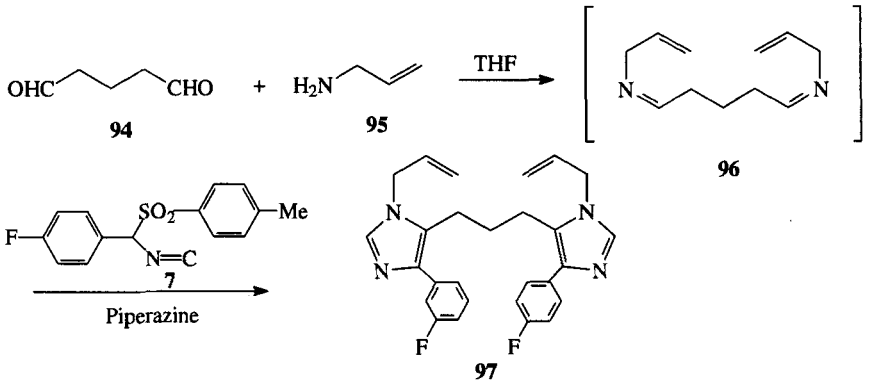
A one-pot synthesis of imidazoles has been described by Sisko *et al.* [47] employing the route shown in Scheme 39 from (4-fluorophenyl)tosylmethyl isonitrile **91**.



SCHEME 39

Conversion of pyruvaldehyde **88** to imidazole **92** by the reaction of tosylisonitrile **91** with imine **90** is a significant part of the synthesis of imidazole as the reaction can be carried out in the presence of water. **93**, a potent inhibitor of p38MAP kinase, has been synthesized using this procedure. Several 1,4,5-trisubstituted imidazoles described in Table X have been synthesized from tosylisonitriles and imines generated *in situ* [35].

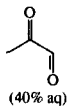
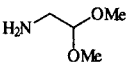
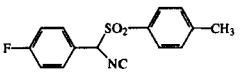
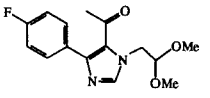
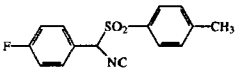
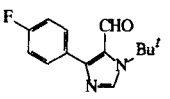
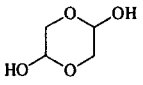
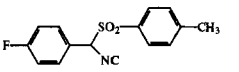
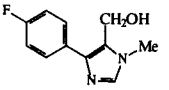
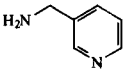
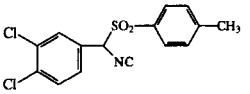
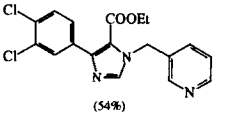
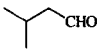
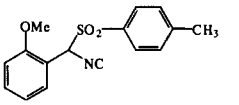
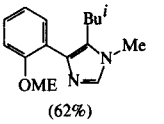
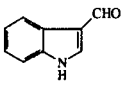
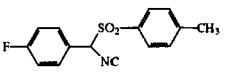
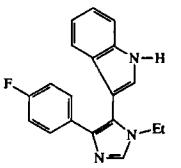
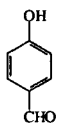
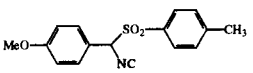
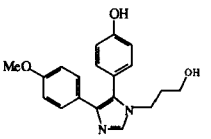
Dialdehydes have also been used to synthesize successfully bis-imidazoles **97**. Glutaric aldehyde **94** (50% aqueous solution) reacts readily with 2 equivalents of allylamine **95** to form the diimine **96** which undergoes cycloaddition with 4-(fluorophenyl)tosyl methyl isonitrile **7** to form bisimidazole **97** in 50% yield (Scheme 40).

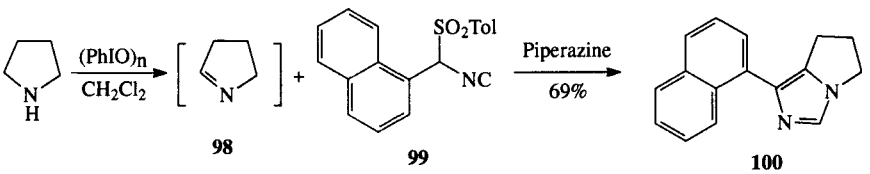


SCHEME 40

The bicyclic imidazole nucleus is present in a number of antiviral and antibiotic agents. Previous syntheses of bicyclic imidazoles are lengthy and products are obtained in low yield. Using the cyclic imine **98** and TosMIC reagent **99**, the bicyclic imidazole **100** was obtained in a single operation (Scheme 41) [35].

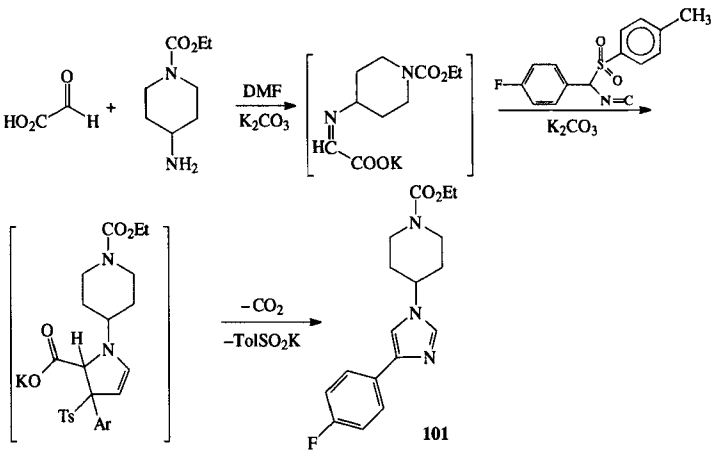
TABLE X Synthesis of 1,4,5-trisubstituted imidazoles according to Scheme 37

Entry	*Aldehyde*	*Amine*	*Tosylisonitrile*	*Product (yield)*
1	 (40% aq)			 (71%)
2	 (40% aq)	t-BuNH$_2$		 (63%)
3		MeNH$_2$ (40% aq)		 (83%)
4				 (54%)
5		MeNH$_2$ (40% aq.)		 (62%)
6		EtNH$_2$ (70% aq)		 (49%)
7				 (67%)



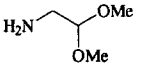
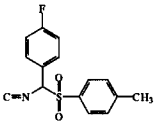
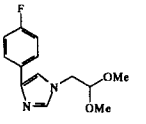
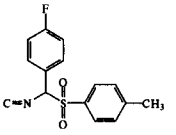
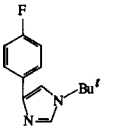
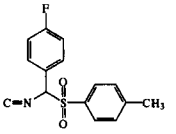
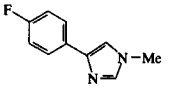
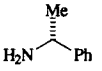
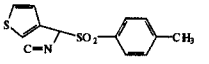
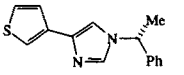
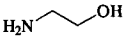
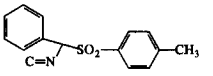
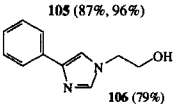
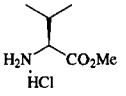
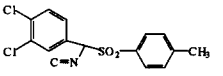
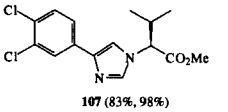
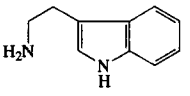
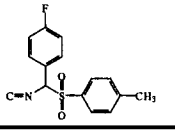
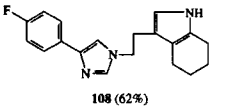
SCHEME 41

1,4-Disubstituted imidazoles (e.g. **101**) are prepared in high yields [48] by reaction of glyoxalic acid, amines and tosylisonitriles in K_2CO_3 and DMF as shown in Scheme 42 [35] and Table XI.

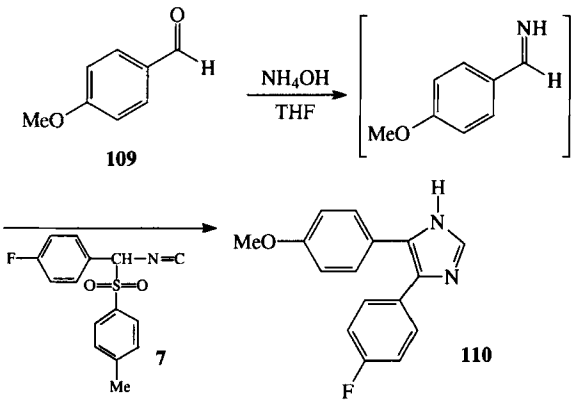


SCHEME 42

TABLE XI Synthesis of 1,4-disubstituted imidazoles 102–108 from tosylisonitriles and amines

Entry	*Amine*	*Tosylisonitrile*	*Product (yield)*
1			 **102** (81%)
2	$t\text{-BuNH}_2$		 **103** (86%)
3	$MeNH_2$ (40% aq)		 **104** (53%)
4			 **105** (87%, 96%)
5			 **106** (79%)
6			 **107** (83%, 98%)
7			 **108** (62%)

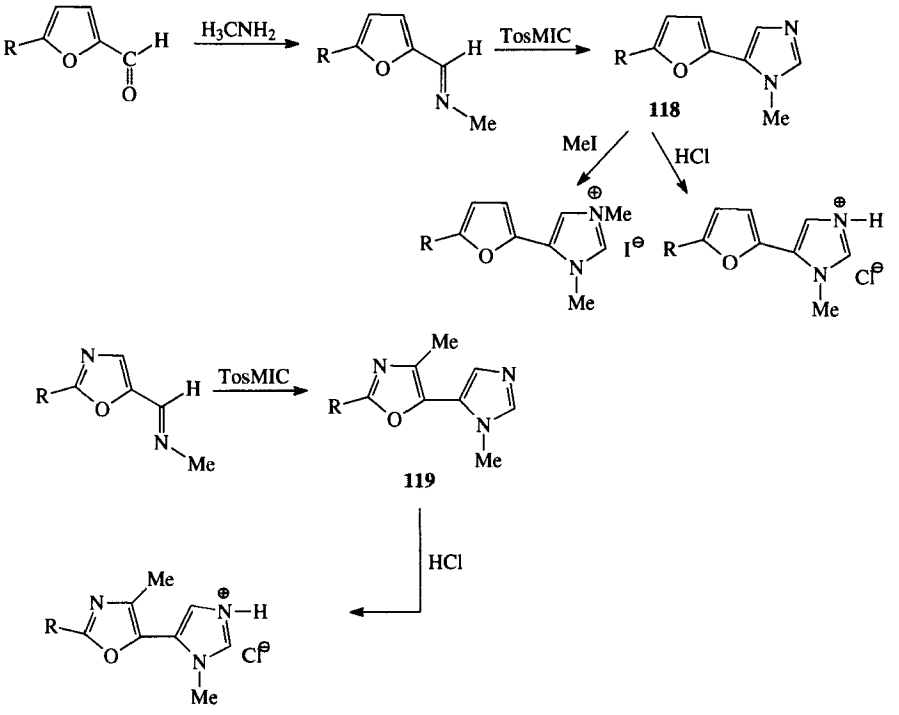
The 4,5-disubstituted imidazole **110** has been synthesized from the aldehyde **109** and NH_4OH (30% aqueous) in THF followed by addition of isonitrile **7** as shown in Scheme 43 [35].



SCHEME 43

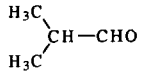
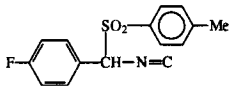
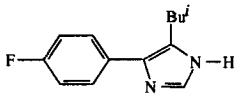
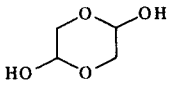
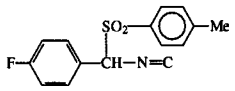
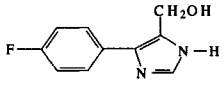
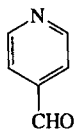
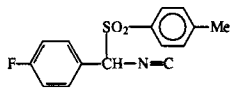
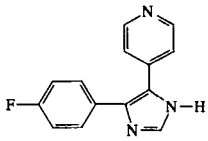
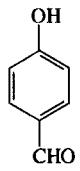
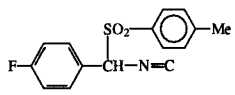
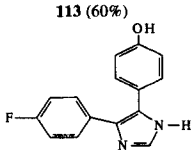
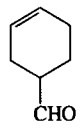
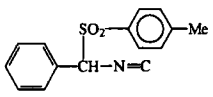
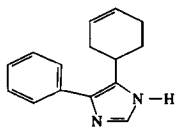
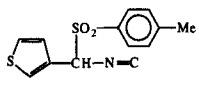
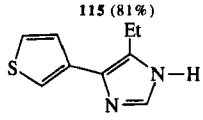
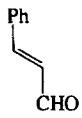
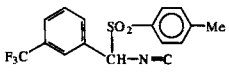
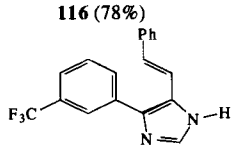
Other imidazoles (**111–17**) have been prepared by a similar procedure as outlined in Table XII.

Oxalyl-5- (**119**) and furanyl-2-substituted imidazoles (**118**) have been synthesized by coupling the two ring systems by dipolar cycloaddition of TosMIC to the corresponding oxazolyl and furanyl aldimines in basic media (Scheme 44) [35].



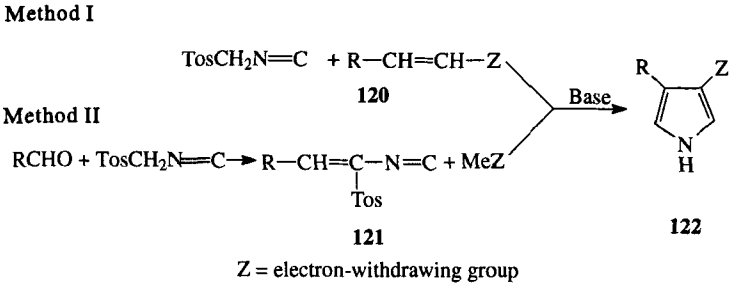
SCHEME 44

TABLE XII 4,5-Disubstituted imidazoles synthesized from tosylisonitriles and imines generated from aldehydes and NH_4OH

Entry	*Aldehyde*	*Tosylisonitrile*	*Product (yield)*
1			 **111** (66%)
2			 **112** (23%)
3			 **113** (60%)
4			 **114** (73%)
5			 **115** (81%)
6	EtCHO		 **116** (78%)
7			 **117** (41%)

2.3. Pyrroles

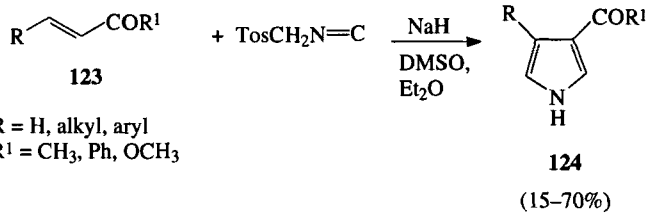
TosMIC is an attractive reagent largely employed in the synthesis of pyrroles with a variety of substituents at 2, 3 and 4 positions. Two significant methods of synthesis of pyrroles **122** are outlined in Scheme 45. Method I consists of reaction of TosMIC under basic conditions with Michael acceptors **120** such as α,β-unsaturated ketones, ester, nitriles, etc. [49]. The second method consists of base-induced reaction of 1-isocyano-1-tosyl-1-alkenes **121** (generated by reaction of TosMIC with aldehydes) with activated methyl compound which acts as the Michael acceptor in the second method of synthesis (Scheme 45).



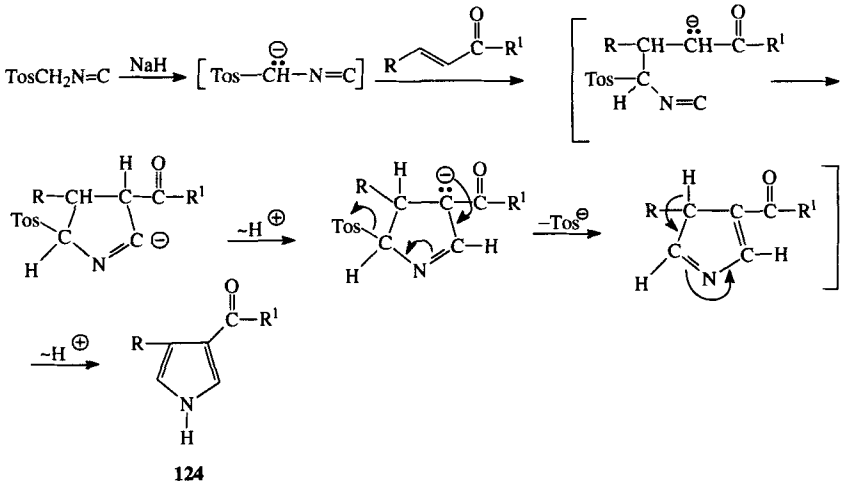
SCHEME 45

2.3.1. Synthesis of Pyrroles by Method I Using α,β-Unsaturated Compounds as Michael Acceptors

TosMIC reacts under basic conditions (NaH, DMSO, Et_2O) with α,β-unsaturated ketones or esters **123** or nitriles to form 3,4-disubstituted pyrroles **124** (Scheme 46) [49]. Prototropic shifts followed by aromatization leads to formation of pyrrole (Scheme 47).

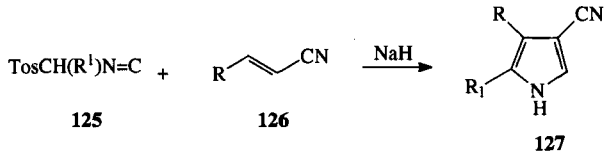


SCHEME 46



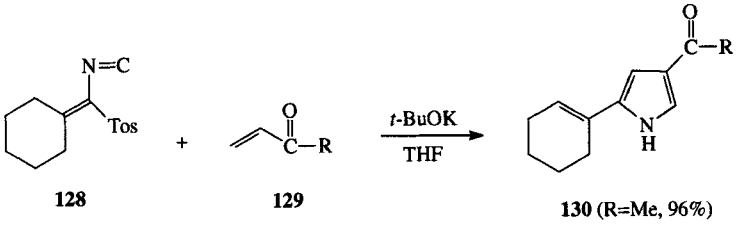
SCHEME 47

The reaction of the monosubstituted TosMIC analog **125** with the α,β-unsaturated nitrile **126** leads to formation of the 2,3,4-trisubstitued pyrrole **127** [31] (Scheme 48).



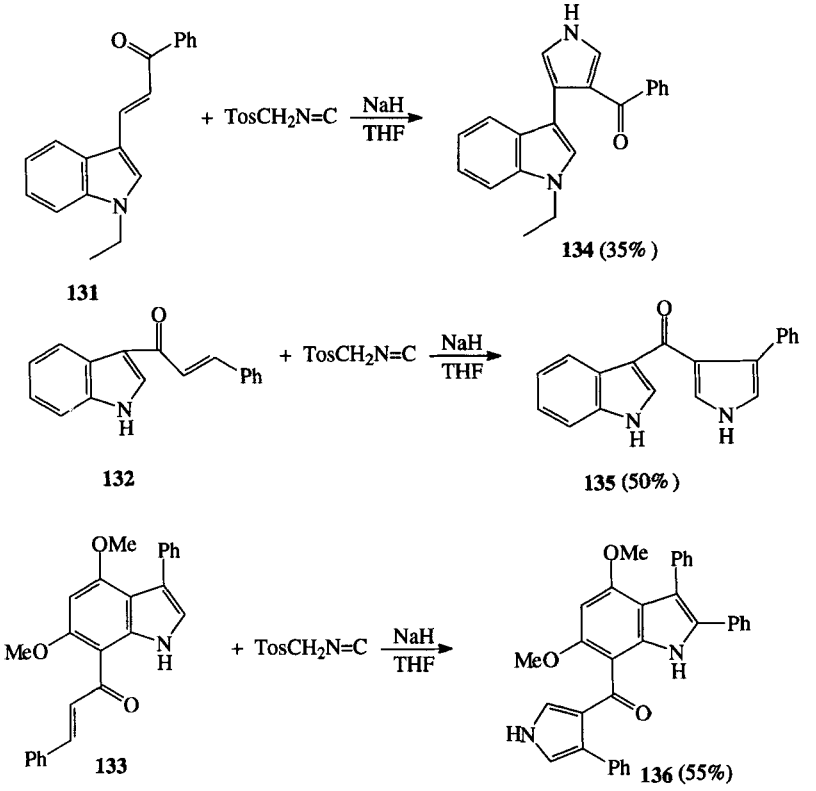
SCHEME 48

2,4-Disubstituted pyrrole **130** has been synthesized by condensation of the TosMIC derivative **128** with the α,β-unsaturated ketone **129** [50] (Scheme 49).



SCHEME 49

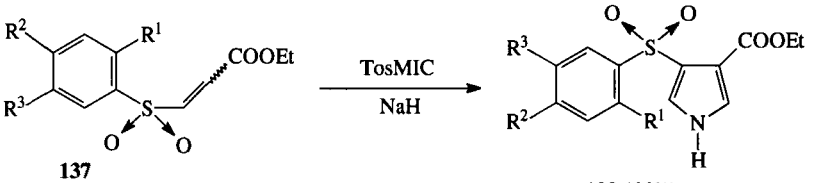
Reaction of TosMIC with α,β-unsaturated ketones **131–133** yields the indolyl pyrrole **134** and the indolylpyrrolyl ketones **135** and **136** (Scheme 50) [50].



SCHEME 50

3,4-Disubstituted and 2,3,4-trisubstituted pyrroles have also been synthesized by reactions of α-alkali metalated TosMIC with vinyl nitro compounds [51,52]. Pyrroles

containing the NO_2 group have thus been synthesized. *E*- and *Z*-3-phenylsulfonylacrylates **137** readily react with TosMIC in the presence of base leading to the formation of ethyl-4-phenylsulfonyl pyrrole-3-carboxylate **138** (Scheme 51) [53].

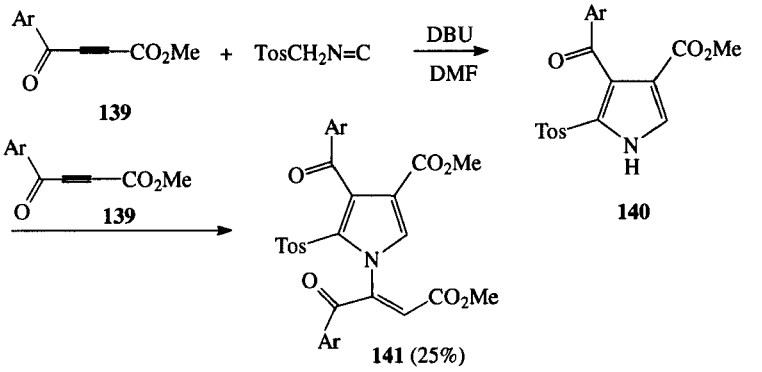


137
(R^1 = H, NO_2, NH_2
R^2 = H, Me, NO_2
R^3 = H, Cl)

138 (66%)

SCHEME 51

3-Aroyl propiolates **139** have been used as acetylenic Michael acceptors in reactions with TosMIC. The reaction leads to the formation of tri- (**140**) or tetra- (**141**) substituted pyrroles having a tosyl group at the 2 position of the pyrrole ring (Scheme 52) [54].



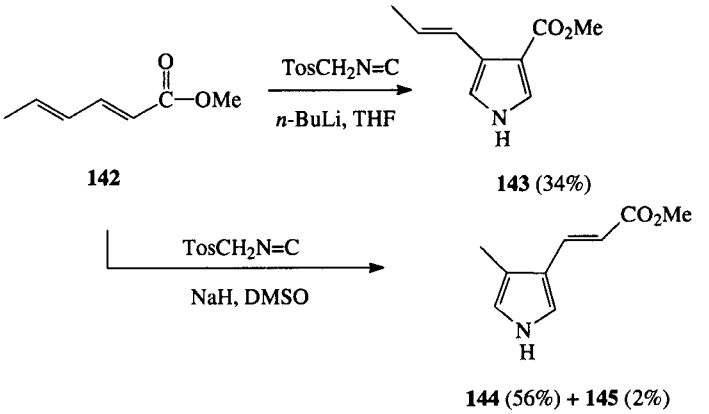
139

140

141 (25%)

SCHEME 52

TosMIC reacts with extended Michael acceptors **142**; addition can take place at either the α,β or γ,δ double bond depending on the reaction conditions employed, leading to the formation of 3,4-disubstituted pyrroles **143**–**145** [55] (Scheme 53).



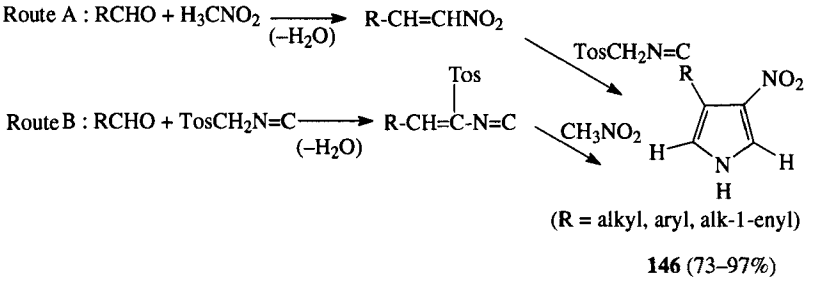
142

143 (34%)

144 (56%) + **145** (2%)

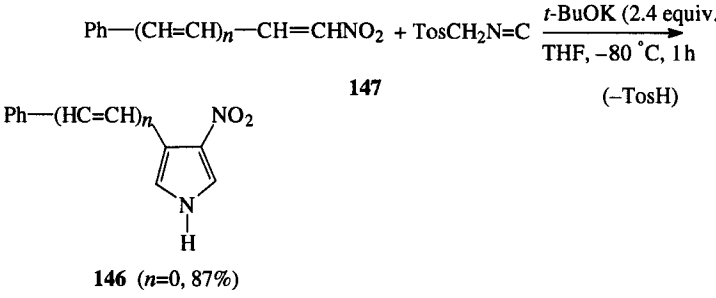
SCHEME 53

An efficient synthesis of 4-substituted and 4,5-disubstituted-3-nitropyrroles was developed by Van Leusen and co-workers [56]. Two routes A and B described in Scheme 54 lead to the synthesis of substituted-3-nitropyrroles (**146**).



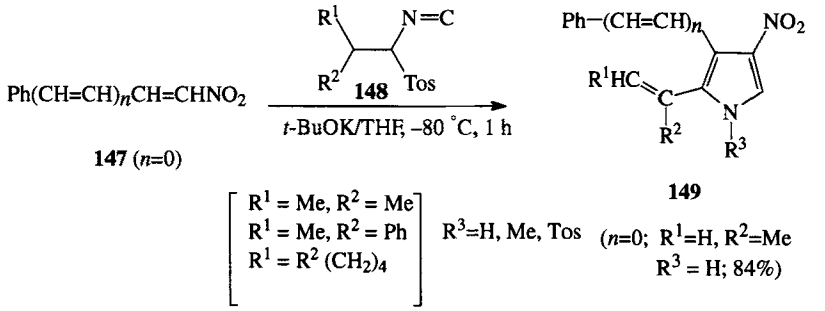
SCHEME 54

Route A involves condensation of the aldehyde with nitromethane followed by reaction with $TosCH_2N{=}C$ (TosMIC). In route B, the aldehyde is first condensed with $TosCH_2N{=}C$ (TosMIC) followed by reaction with nitromethane. Both of these methods lead to low yields of substituted pyrroles (27–55%) **146**. The yield was improved to 87% by using 2.4 equivalents of *t*-BuOK at −80 °C in THF in the reaction between TosMIC and the extended Michael acceptor **147** as outlined in Scheme 55.



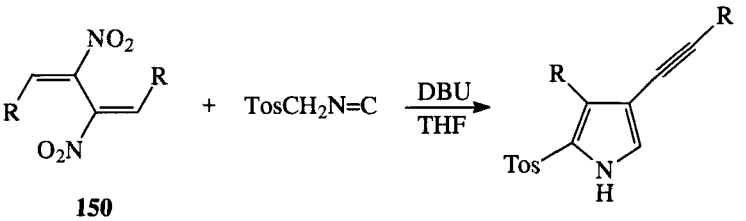
SCHEME 55

2,3-Di(alk-1-enyl)-4-nitro pyrroles [56] **148** were synthesized according to Scheme 56 by reaction of the extended Michael acceptors **147** and alk-1-enyl substituted TosMIC **148**. Excellent yields of **149** were obtained by the procedure outlined in Scheme 56.



SCHEME 56

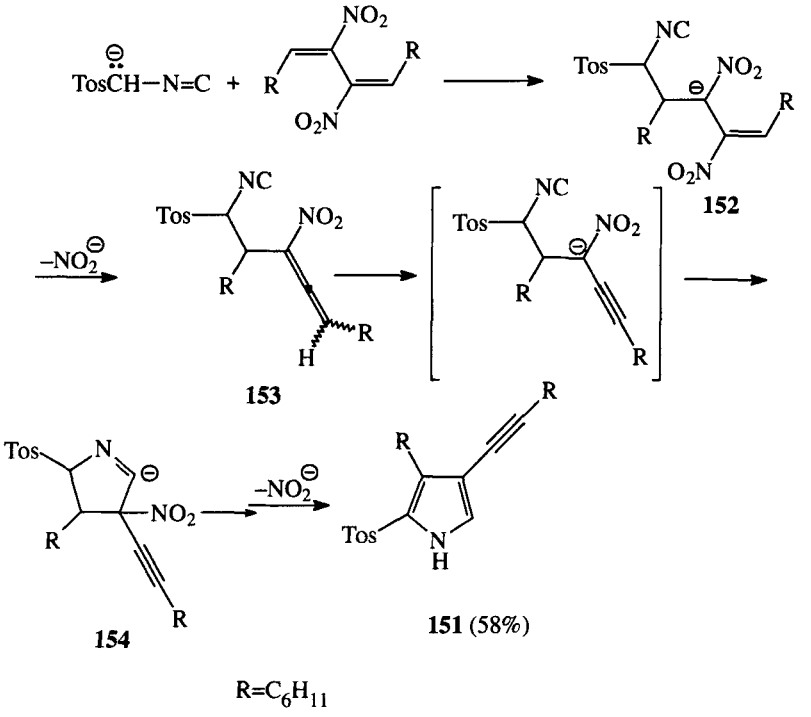
1,4-Disubstituted-2,3-dinitro-1,3-butadienes **150** react with TosMIC in the presence of DBU to form 2,3,4-trisubstituted pyrroles **151** [57] (Scheme 57).



150 **151** (R=Et,11%)

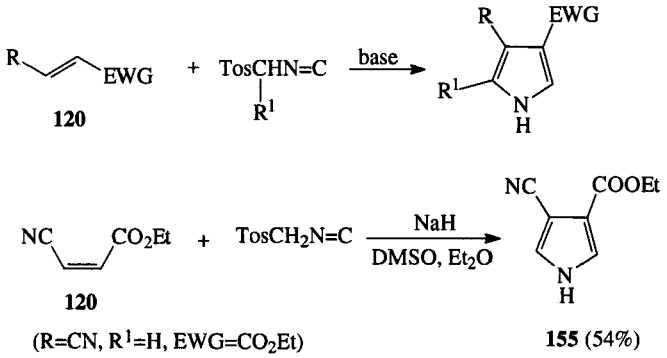
SCHEME 57

The first step of the overall process should involve formation of nitronate anion **152** by attack of isocyanide conjugate base at C-1 of the 2,3-dinitro-1,3-butadiene system. An intramolecular cyclization leading to formation of **154** would be expected via a nitroallene intermediate **153** (Scheme 58).



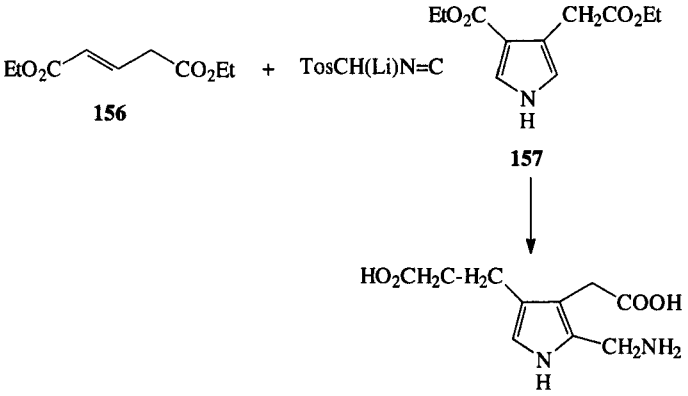
SCHEME 58

The variation in Michael acceptor **120** where R represents a second electron-withdrawing group is feasible with two different electron-withdrawing groups in **120**; the reaction with TosMIC affords a single pyrrole **155** [58] (Scheme 59).



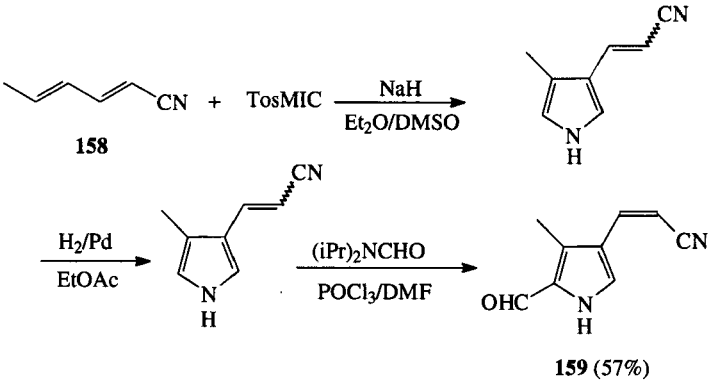
SCHEME 59

Diethyl glutaconate **156** reacts with the monolithium salt of TosMIC to form the 3,4-disubstituted derivative of pyrrole **157** (Scheme 60). The pyrrole diester **157** has further been used towards synthesis of porphobilinogen, a natural product [59].



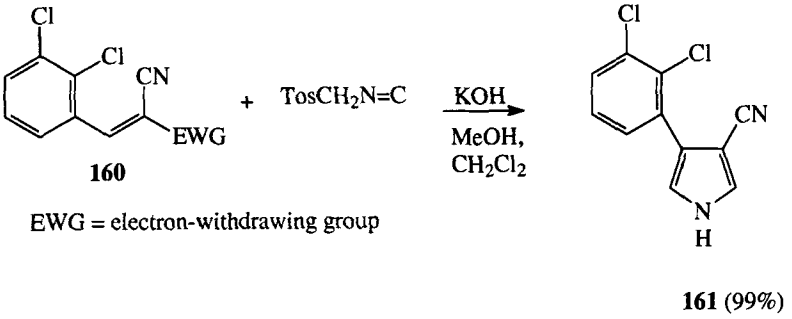
SCHEME 60

3,4-Disubstituted pyrrole 2-carboldehydes **159** were prepared by reaction of hexa-2,4-dienenitrile **158** and TosMIC (Scheme 61) [60].



SCHEME 61

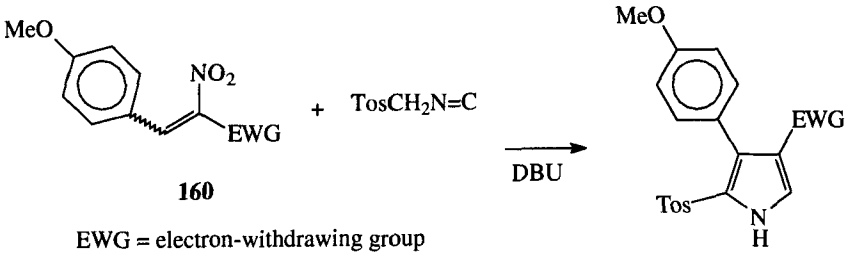
The Michael acceptor activity can be further increased by using two electron-withdrawing groups at the same carbon atom (**160**) to form a pyrrole **161**; one of these groups has to be removed during the course of reaction with TosMIC (Scheme 62) [61].



EWG = electron-withdrawing group

SCHEME 62

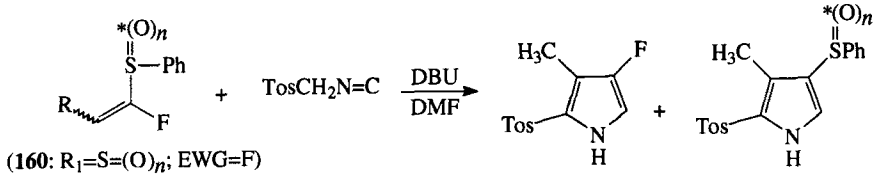
Using R as 4-$MeOC_6H_5$ and R^1 as NO_2 in **160**, the reaction with TosMIC in the presence of DBU leads to formation of the pyrrole **162**, the NO_2 group being the leaving group (Scheme 63) [62].



EWG = electron-withdrawing group

SCHEME 63

Two different electron-withdrawing groups at the same carbon atom in **130** may compete, leading to the formation of a mixture of pyrroles **163** and **164** [63] (Scheme 64).

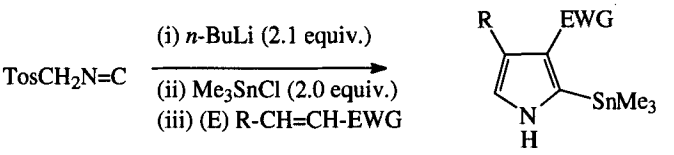


(**160**: R_1=S=(O)$_n$; EWG=F)
n = 1,2 R = Me

163 (n =1, 24%) (n = 2, 8%) **164** (n = 1, 24%) (n = 2, 23%)

SCHEME 64

2-(Trimethylstannyl)pyrroles **165** with substituents at the 3- and 4-positions were synthesized by the base-induced reaction [64] of stannylated TosMIC with Michael acceptors (Scheme 65).

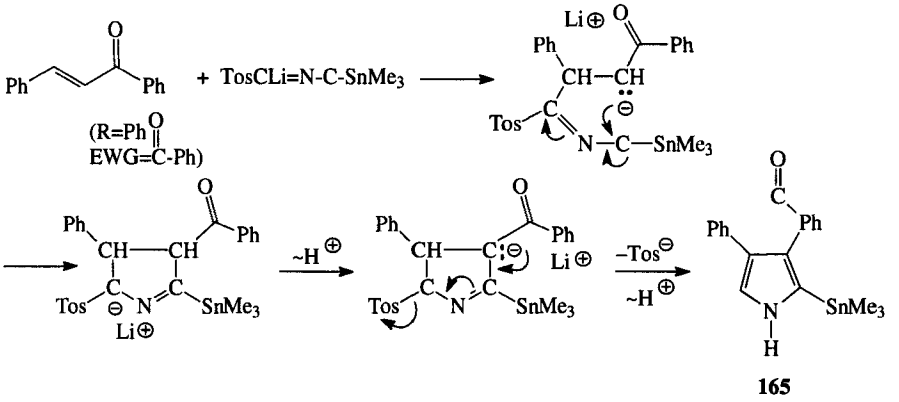


165 (61–90%)

(R = Ph, CO_2Me, Ph-CH=CH
EWG = COPh, COMe, CO_2Me,
CO_2Et, CO_2Ph, CN, NO_2)

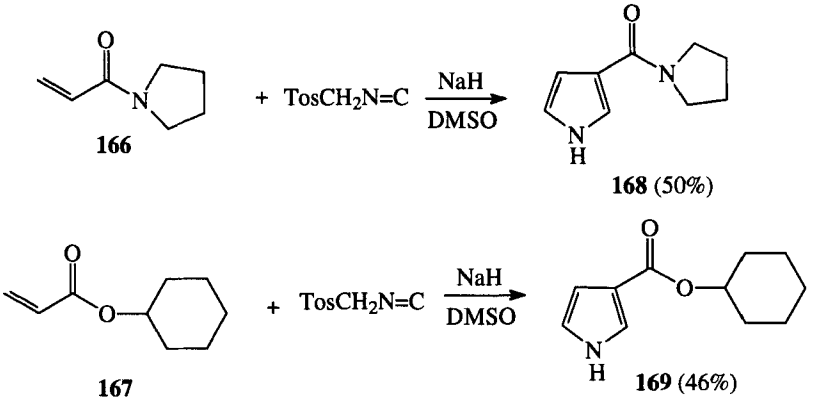
SCHEME 65

The proposed mechanism for the formation of **165** is outlined in Scheme 66 [64].



SCHEME 66

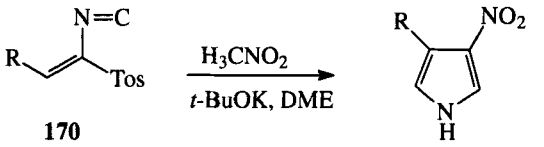
Acrylamides **166** and esters **167** have been reacted with TosMIC under basic conditions to form pyrroles **168** and **169** respectively (Scheme 67). Compounds **168** and **169** on Birch reduction and removal of the activating group give the corresponding *N*-protected *β*-proline derivatives [65].



SCHEME 67

2.3.2. *Synthesis of Pyrroles by Method II Using 1-Isocyano-1-tosyl-1-alkenes as Michael Acceptors*

1-Isocyano-1-tosyl-1-alkenes **170** have been used as Michael acceptors to synthesize pyrroles **171** [66]. Nucleophilic attack takes place at the β-carbon while the isocyano carbon acts as an electrophilic carbon atom (Scheme 68).

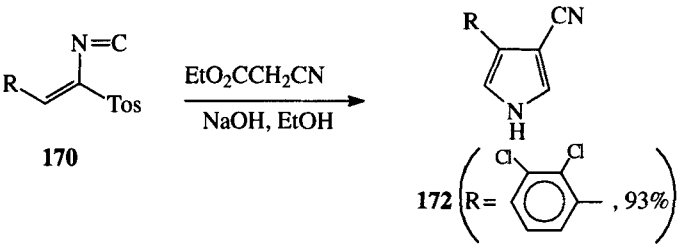


170 (R=CN, COOEt, $COCH_3$, COC_6H_5, *t*-Bu, Me, Ph etc.)

171 (R=*t*-Bu, 90%)

SCHEME 68

Replacement of NO_2 by CN in **171** can be accomplished by reaction of **170** with ethyl cyanoacetate (Scheme 69) [66].

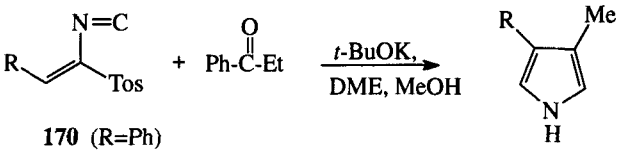


170

172

SCHEME 69

Electron-withdrawing substituents at position 3 in **171** and **172** can be replaced by electron-donating substituents. The 3-methyl pyrrole derivative **173** can be synthesized from **170** by reaction with phenylethylketone in the presence of base (Scheme 70) [66].

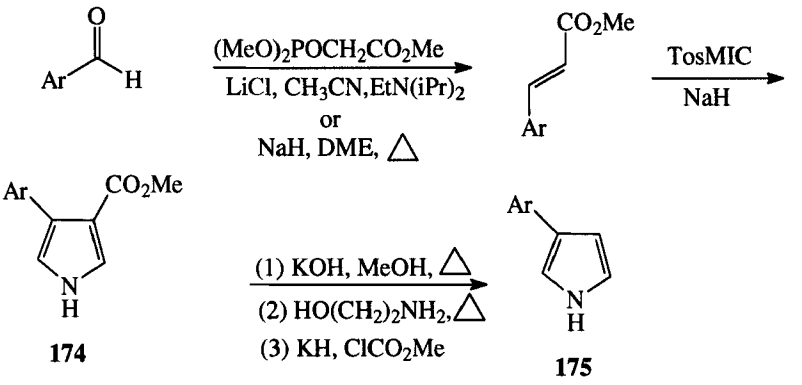


170 (R=Ph)

173 (R=Ph, 73%)

SCHEME 70

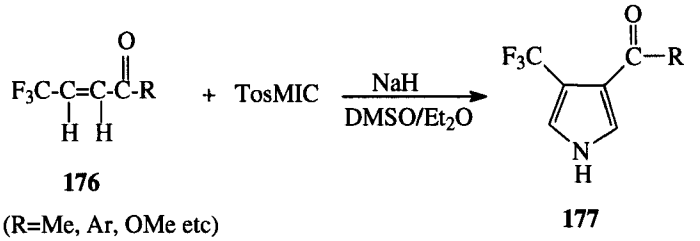
The introduction of a substituent at the 3-position of pyrrole is significant as these intermediates are used for the synthesis of natural products and conducting polymers. 3-Arylpyrrole **175** was synthesized from an aromatic aldehyde by conversion into the corresponding methyl-3-arylacrylate using a Masamune–Rousch or a Wadsworth Emmons reaction. Further treatment with TosMIC afforded the pyrrole derivative **174** which on hydrolysis and decarboxylation yielded 3-aryl pyrroles **175** [67] (Scheme 71).



174 175

SCHEME 71

Pyrroles containing fluorine as a substituent at the 3-position were prepared by the method of Aoyagi *et al.* [68]. A variety of 3-perfluoroalkylpyrroles **177** were prepared by reaction of β-perfluoroalkyl-α,β-unsaturated carbonyl compounds **176** with TosMIC (Scheme 72).



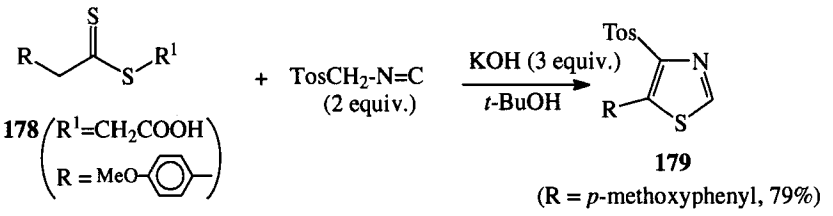
176 (R=Me, Ar, OMe etc)

177

SCHEME 72

2.4. Thiazoles

Base-induced cycloadditions of TosMIC to the C=S of thiocarbonyl compounds lead to the formation of thiazoles having a tosyl group at 4-position. Thiocarbonyl compound **178** on reaction with TosMIC in the presence of KOH formed the thiazole derivative **179** (Scheme 73) [69] with SR_1 acting as a leaving group.

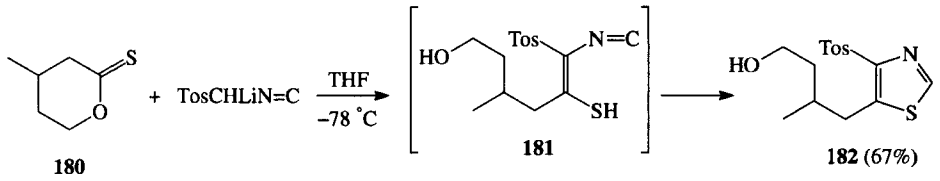


178

179 (R = *p*-methoxyphenyl, 79%)

SCHEME 73

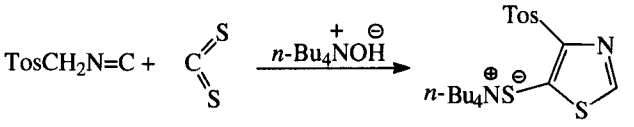
Thionolactone **180** on reaction with the monolithium derivative of TosMIC leads to ring opening of the lactone and formation of the intermediate thiol **181** which cyclizes to form the thiazole derivative **182** (Scheme 74) [70].



180 **181** **182** (67%)

SCHEME 74

The reaction of TosMIC with CS_2 leads to formation of 5-thio-4-tosylthiazoles **183** (Scheme 75) [71]. Alkylation or acetylation leads to isolation of stable thiazole derivatives.

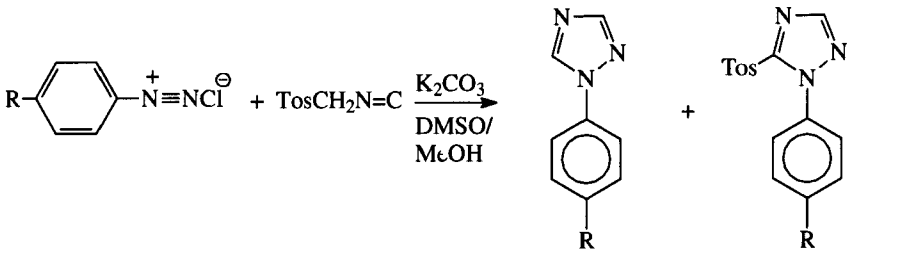


183

SCHEME 75

2.5. 1,2,4-Triazoles

1,2,4-Triazoles **184** and **185** are formed by base-induced cycloaddition of TosMIC with diazonium salts [72] (Scheme 76).

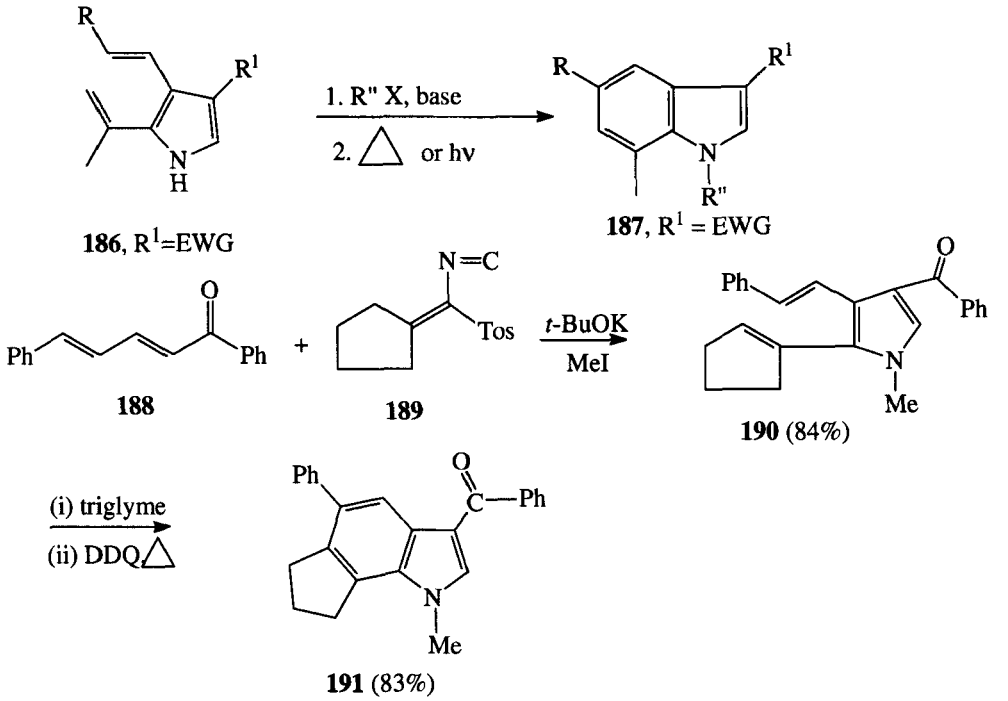


184 (80%, R=OMe) **185** (12%, R=OMe)

SCHEME 76

2.6. Indoles

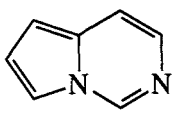
2,3-Dialkenyl-substituted pyrroles **186** are precursors to the synthesis of indoles. The six π-electron system of **186** undergoes electrocyclic ring closure followed by dehydrogenation resulting in the synthesis of indole **187** (Scheme 77). 2,3-Dialkenyl-substituted pyrrole **190** was synthesized from the dienic Michael acceptors **188** and TosMIC derivative **189** in the presence of *t*-BuOK. Compound **190** undergoes electrocyclic ring closure followed by dehydrogenation with DDQ to form indole derivatives **191** (Scheme 77) [50].



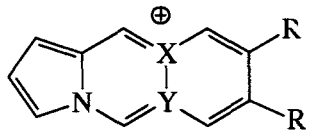
SCHEME 77

2.7. Pyrrolodiazines

Pyrrolodiazines **192** can be used in the synthesis of heteroaromatic polycyclic cations **193**. These have been studied as antitumor agents for their ability to interacalate with DNA [73].



192

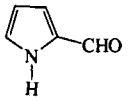
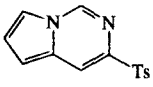
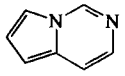
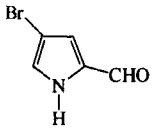
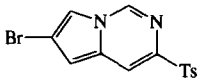
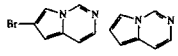
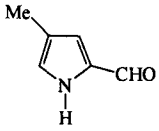
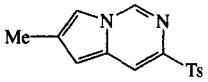
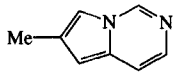
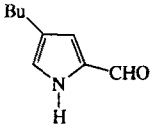
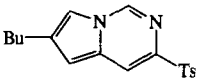
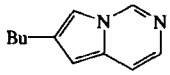
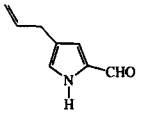
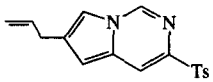
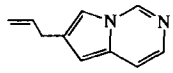
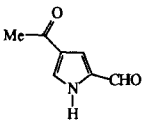
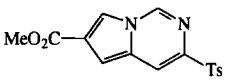
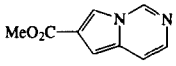
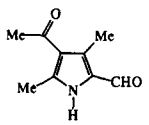
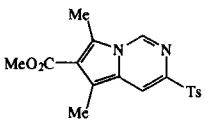
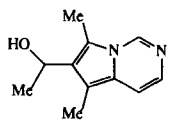
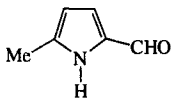
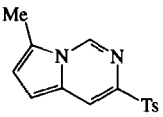
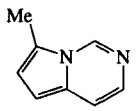
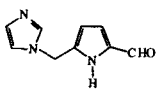
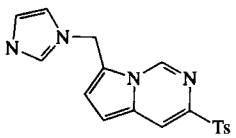
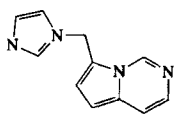
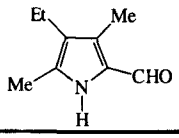
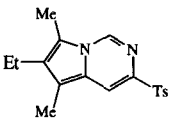
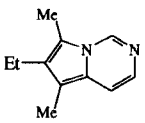


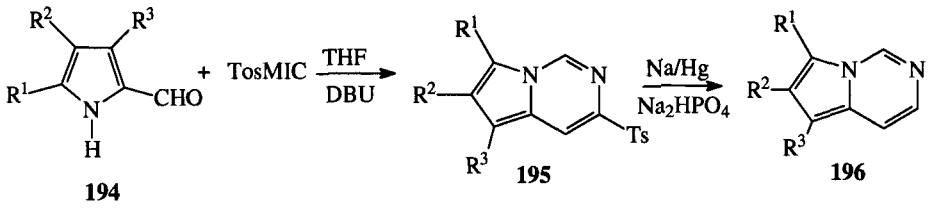
193

2.7.1. Pyrrolo[1,2-c]pyrimidines

Pyrrolo[1,2-*c*]pyrimidines (**196**) have been synthesized [44] by sequential condensation of substituted pyrrole 2-carboxaldehydes **194** with TosMIC, followed by desulfonylation of the formed tosylpyrrolo[1,2-*c*]pyrimidines **195** (Scheme 78) [73]. Desulphonylation of **195** was carried out with Na–Hg and Na_2HPO_4 in THF–MeOH. The yields of **196** obtained are shown in Table XIII.

TABLE XIII Synthesis of 3-tosylpyrrolo[1,2-*c*]pyrimidines **195** and pyrrolo[1,2-*c*]pyrimidines **196**

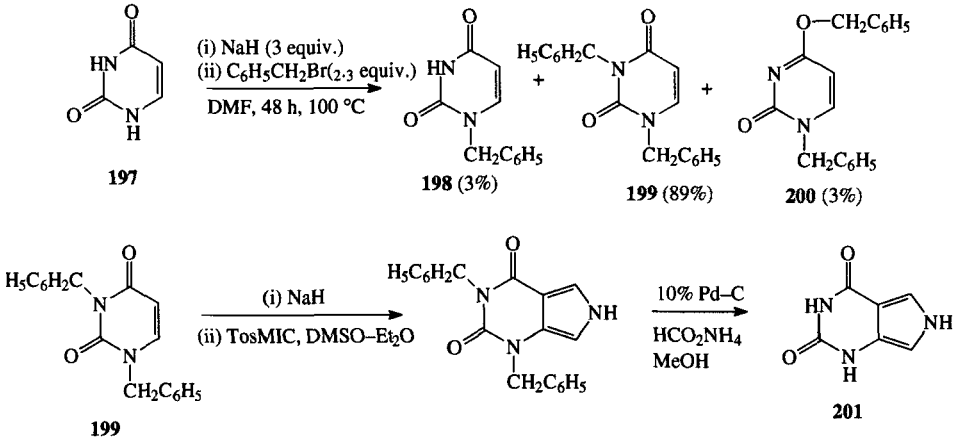
Entry	*Aldehyde*	*Cyclocondensation product* **195** *with TosMIC*	*Yield of* **196** (%)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			



SCHEME 78

2.7.2. *Pyrrolo[3,4-d]pyrimidine-2,4-dione*

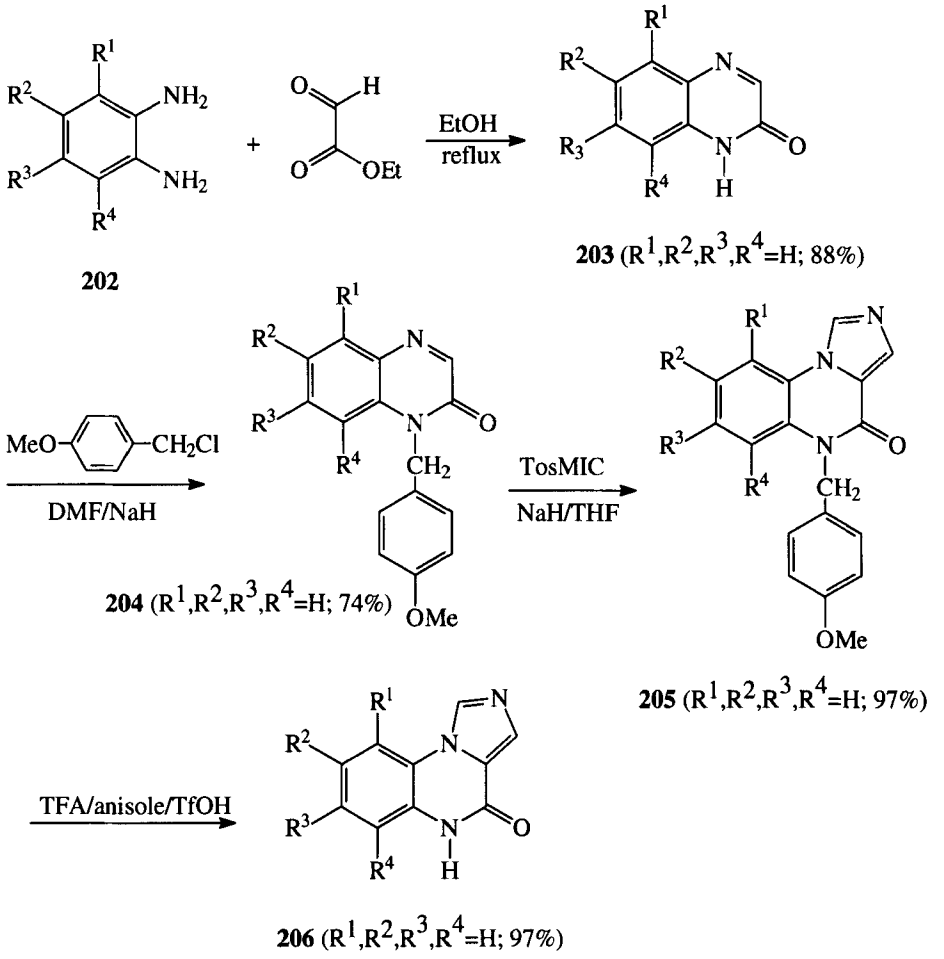
Pyrrolo[3,4-*d*]pyrimidine-2,4-dione **201** has been synthesized from uracil **197** by benzylation with $C_6H_5CH_2Br$ in the presence of NaH and DMF to form a mixture of mono- and dibenzylated products **198**, **199** and **200**. The major product **199** on reaction with TosMIC under base-catalyzed conditions with NaH and DMSO underwent cycloaddition to form the dibenzyl derivative of **201**. Debenzylation with 10% Pd–C in MeOH and HCO_2NH_4 leads to formation of **201** (Scheme 79) [74].



SCHEME 79

2.8. Imidazo[1,5-*a*]quinoxalin-4-ones

Imidazo[1,5-*a*]quinoxalin-4-ones **206** are important intermediates for synthesis as this structural unit is common in a variety of medicinally useful agents. Compounds **206** were prepared in four steps starting from 1,2-phenylene-diamines **202** as shown in Scheme 80. Diamines **202** on condensation with ethylglyoxalate gave quinoxalin-2(1*H*)-ones **203**. *N*-(*p*-methoxybenzyl)-quinoxalin-2-one **204** on reaction with TosMIC in the presence of base (NaH) provided 5-(*p*-methoxybenzyl)-imidazo[1,5-*a*]quinoxalin-4-ones **205**, in excellent yield. Compound **205** afforded **206** on deprotection of the *N*-(*p*-methoxybenzyl) group with TFA–anisole–triflic acid [75].



202

203 (R^1,R^2,R^3,R^4=H; 88%)

204 (R^1,R^2,R^3,R^4=H; 74%)

205 (R^1,R^2,R^3,R^4=H; 97%)

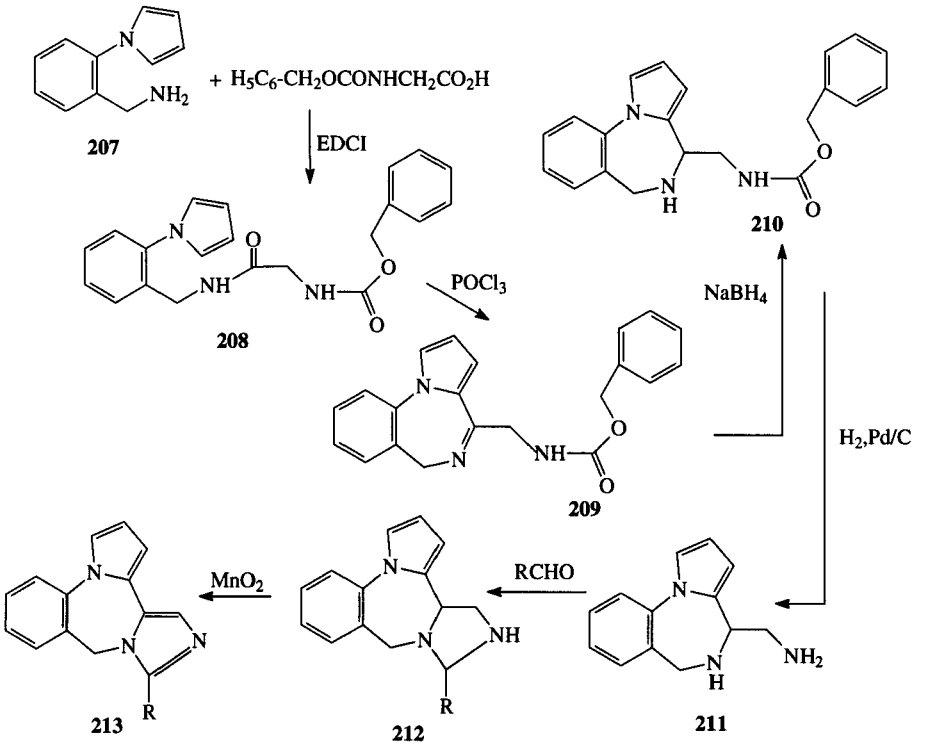
206 (R^1,R^2,R^3,R^4=H; 97%)

SCHEME 80

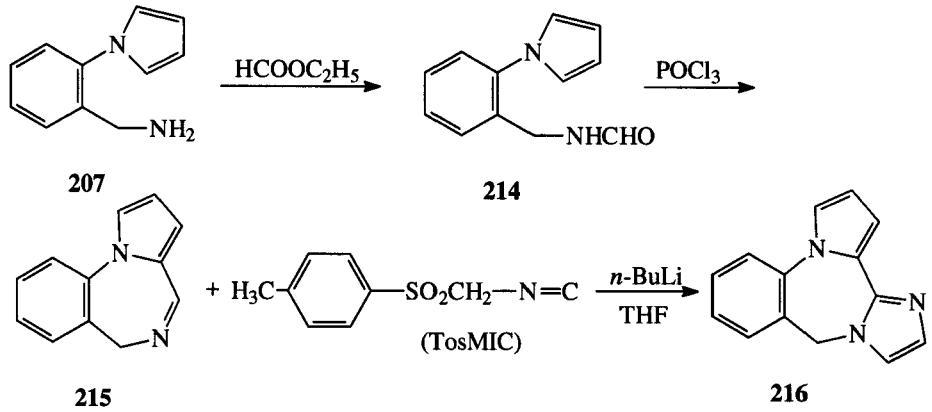
2.9. Imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine Derivatives

1,4-Benzodiazepines annulated with two azole rings have been widely studied by medicinal chemists as antianxiety, neuroleptic and antidepressant agents. 8H-Imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine **213** and its six derivatives have been synthesized from 1*H*-1-(2-aminomethylphenyl)pyrrole **207** which was reacted with *N*-benzyloxycarbonyl-glycine in the presence of *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimidie (EDCI) and Et_3N to give 1*H*-1-(2-benzyloxycarbonylaminoacetylaminomethylphenyl)pyrrole (**208**). Intramolecular cyclization of **208** by $POCl_3$ furnished tricyclic pyrrolobenzodiazepine **209**. Compound **209** on reduction with $NaBH_4$ gave the aminoamide **210**. Removal of the benzyloxycarbonyl group yielded 5,6-dihydro-4-aminomethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine **211**. Compound **211** on treatment with RCHO (R=H, CH_3, C_6H_5) under Pictet–Spengler reaction conditions gave 3b,4,5,6-tetrahydro-8*H*-imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine **212**.

Aromatization of the imidazolidine ring in **212** was accomplished by heating with MnO_2 to yield **213** (Scheme 81) [76]. The six-step sequence described above for the synthesis of **213** can be accomplished in one step by 1,3-dipolar cycloaddition of TosMIC anion with the azomethine bond of 6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine **215**. Compound **215** in turn was synthesized from **207** according to Scheme 82.



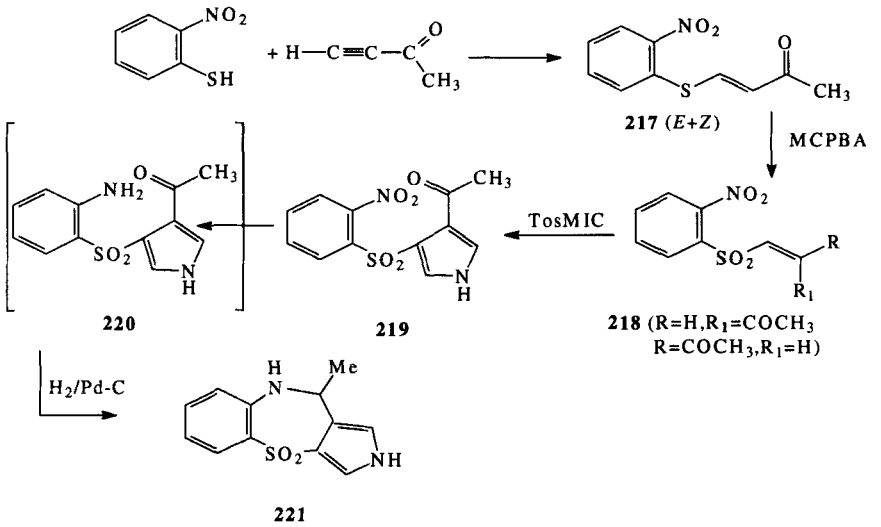
SCHEME 81



SCHEME 82

2.10. Pyrrolo[3,4-*b*][1,5]benzothiazepine Derivatives

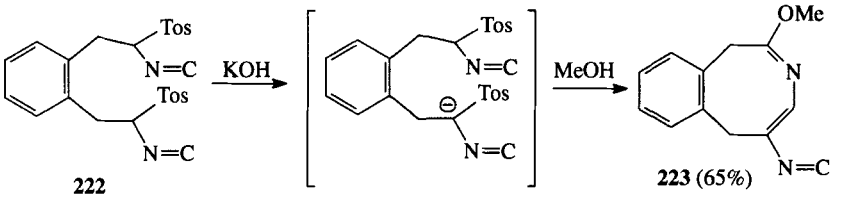
Pyrrolobenzothiazepines have recently been studied as non-nucleoside inhibitors of HIV-1 reverse transcriptase. The isomeric 2*H*-pyrrolo[3,4-*b*][1,5]benzothiazepine derivative **221** has been synthesized from 2-nitrothiophenol according to Scheme 83 [77]. 2-Nitrothiophenol on reaction with 3-butyn-2-one afforded a mixture of isomeric *E*/*Z* 4-(2-nitrophenylthio)-3-buten-2-one **217**, which on oxidation with MCPBA gave the corresponding mixture of sulfone **218**. Reaction of **218** with TosMIC gave 3-acetyl-4-(2-nitrophenylsulphonyl)-1*H*-pyrrole **219**. Compound **219** on catalytic reduction led to the formation of **221** via the intermediate **220**.



SCHEME 83

2.11. Benzazocines

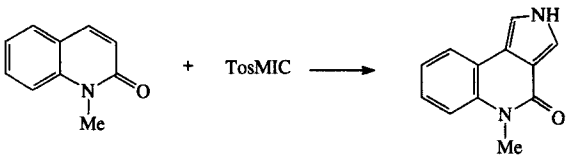
1,2-Dibromomethyl benzene and TosMIC (two molecules) react together in the presence of base to form the product **222** which undergoes a base-induced intramolecular cyclization to form the benzazocine derivative **223** (Scheme 84) [12].



SCHEME 84

2.12. Pyrrolo[3,2-*c*]quinoline

The synthesis of the tricyclic pyrrolo[3,2,-*c*]quinoline ring system **224**, present in the natural product martinelline, was carried out by reaction of *N*-methylquinolone with TosMIC using NaH as a base (Scheme 85) [78].



224

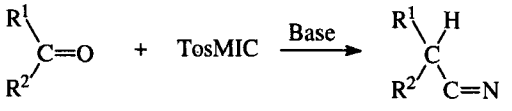
SCHEME 85

3. TOSMIC AS A SYNTHON IN OTHER ORGANIC REACTIONS

3.1. One-step Conversion of Ketones and Aldehydes into Cyanides

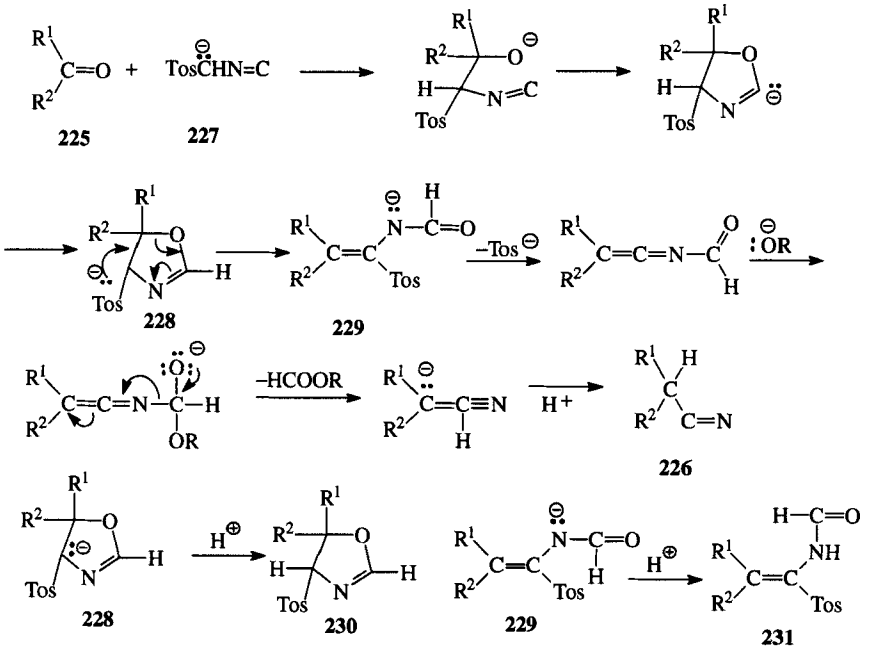
3.1.1. Reaction with Ketones

Ketones **225** are converted into nitriles **226** in one step between 0 and 45 °C by reaction with TosMIC and base (Scheme 86). The reductive cyanation is carried out in one step [79–81]. The mechanism proposed for conversion of ketones to nitriles is shown in Scheme 87 [80].



225 226

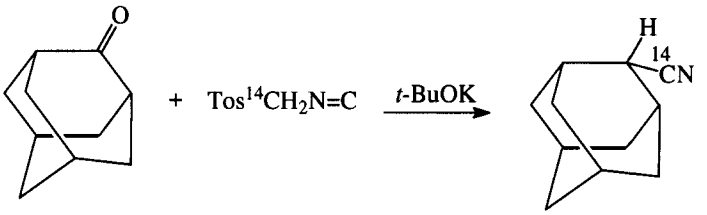
SCHEME 86



225 227 228 229 226 228 230 229 231

SCHEME 87

The first step is attack of the TosMIC anion **227** at the electrophilic carbon of **225** resulting in the formation of **228** which undergoes ring opening to form **229**. The cyano carbon of nitrile **226** is derived from the TosMIC methylene group. This is evident by reaction of adamantanone **232** with ^{14}C-labeled TosMIC **233**, leading to the formation of ^{14}C-labeled nitrile **234** (Scheme 88) [80]. The intermediates **228** and **229** can be converted under acidic conditions, leading to the formation of **230** and **231** respectively.



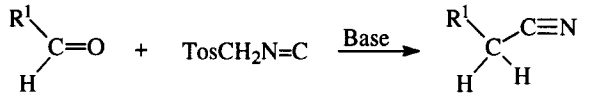
232 **233** **234**

SCHEME 88

The reduction cyanation of ketones is usually carried out with 1:1 equivalent of ketone and TosMIC and 2 equivalents or more of *t*-BuOK in DME [80]. THF, DMSO and HMPA have also been used as solvents or cosolvents. Replacement of *t*-BuOK with *n*-BuLi as a base in reductive cyanation of ketones leads to formation of oxazolines [81].

3.1.2. Reaction with Aldehydes

Compared with the reaction of ketones with TosMIC, which is performed between 5 and 45°C [80], the reaction of aldehydes **235** with TosMIC is carried out at much lower temperature (−50 to −60°C) in DME [82] (Scheme 89). The mechanism of reaction is similar to that outlined for ketones in Scheme 87. Nitriles **236** are formed in yields lower than nitriles **226** formed from ketones [82]. The crucial intermediate, the 4-tosyl-2-oxazoline anion **238**, formed from TosMIC anion

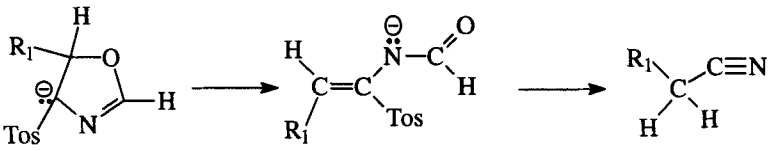


235 **236**

(R^1=C_6H_5, substituted phenyl, 2-naphthyl, 2-furyl, $CH_3(CH_2)_2$ etc.)

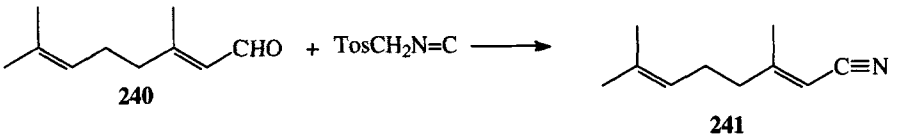
SCHEME 89

and aldehyde, undergoes electrocyclic ring opening to form the anion **239** which leads to formation of nitrile **237** [80,82].



238 239 237

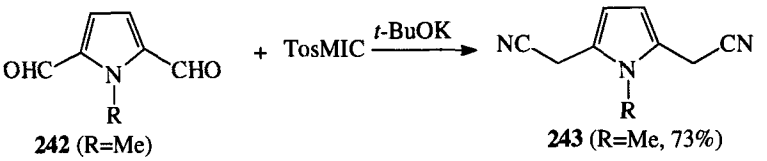
The α,β-unsaturated aldehyde citral **240** leads to formation of the α,β-unsaturated cyano compound **241** (Scheme 90).



SCHEME 90

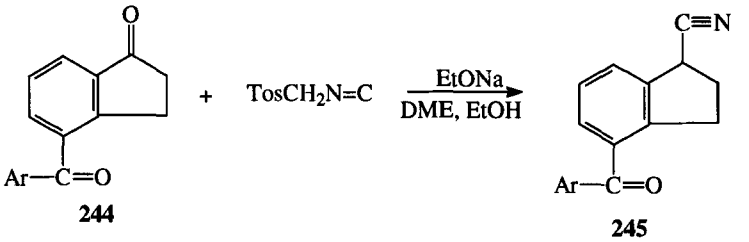
3.1.3. Reaction with Dialdehydes and Diketones

Symmetrical dialdehydes **242** have been converted into dinitriles **243** by reductive cyanation (Scheme 91) [83].



SCHEME 91

Unsymmetrical diketones **244** on reductive cyanation undergo reductive monocyanations to form cyanoketones **245** (Scheme 92) [84]. Similarly, the diketo group in steroids on reductive cyanation leads to selective reductive cyanation of one keto group only [80].



SCHEME 92

3.2. Synthesis of Ketones and Aldehydes

Hydrolysis of TosMIC and mono- and dialkylated TosMIC derivatives with acid results in formation of aldehydes or ketones via initial hydration of the isocyanide. The conversion of formaldehyde into TosMIC and the reverse reaction establish

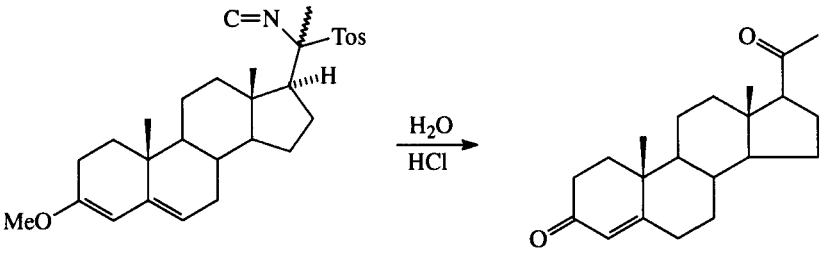
TosMIC as an *umpolung* of the $H_2C{=}O$ molecule [85] (Scheme 93). The geminal isocyano and tosyl group in TosMIC and its analogs behave as *N,S*-acetals and their reactions can be carried out accordingly.

TosMIC

SCHEME 93

3.2.1. Progesterone

The synthesis of progesterone **247** from the TosMIC derivative of 17-keto-3-methoxy-androsta-3,5-diene by reduction and alkylation affords **246** which on acid hydrolysis gives progesterone in excellent yield [86] (Scheme 94).

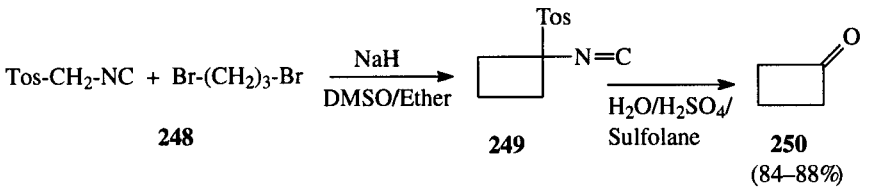


246 **247 Progesterone**

SCHEME 94

3.2.2. Cyclobutanones

Cyclobutanones were synthesized in two steps from TosMIC as shown in Scheme 95. Cyclodialkylation of TosMIC with 1,3-dibromopropane (**248**) leads to formation of 1-isocyano-1-tosylcyclobutanone **249**. On hydrolysis with 50% H_2SO_4 in sulfolane the compound **249** forms cyclobutanone **250** (Scheme 95) [87].

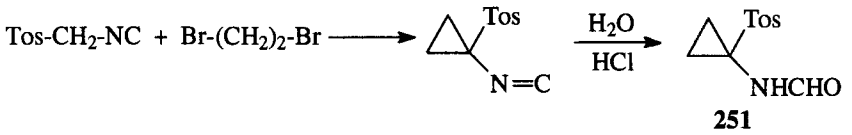


248 **249** **250** (84–88%)

SCHEME 95

2-Methyl and 3-methyl derivatives of **250**, i.e. 2-methylcyclobutanone and 3-methyl-cyclobutanone, were synthesized according to Scheme 95 from 1,3-dibromobutane and 1,3-dibromo-2-methylpropane respectively [87]. Acid hydrolysis of cycloadialkylated

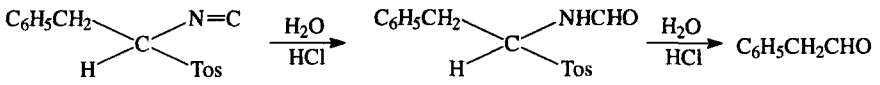
product obtained by reaction of 1,2-dibromoethane and TosMIC gave formamide **251** and no cyclopropane was formed [88]:



251

3.2.3. Phenylacetaldehyde

Phenylacetaldehyde **253** is obtained by hydrolysis of 2-phenyl-1-tosylethylisocyanide **252** prepared from TosMIC and benzyl bromide (Scheme 96) [89].

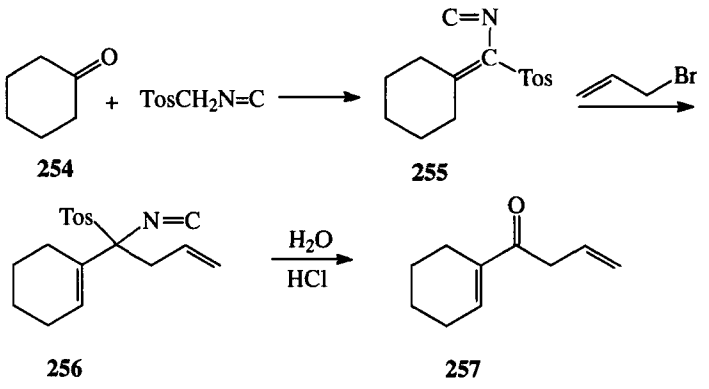


252 **253**

SCHEME 96

3.2.4. Enones

Alkylation of 1-isocyano-1-tosyl-1-alkenes and subsequent hydrolysis of the alkylated product leads to the formation of enones. Enone **257** has been synthesized from cyclohexanone **254** (Scheme 97) [90].



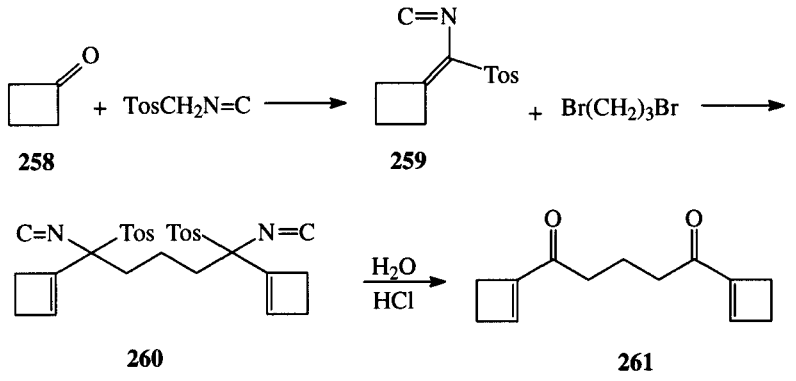
254 **255**

256 **257**

SCHEME 97

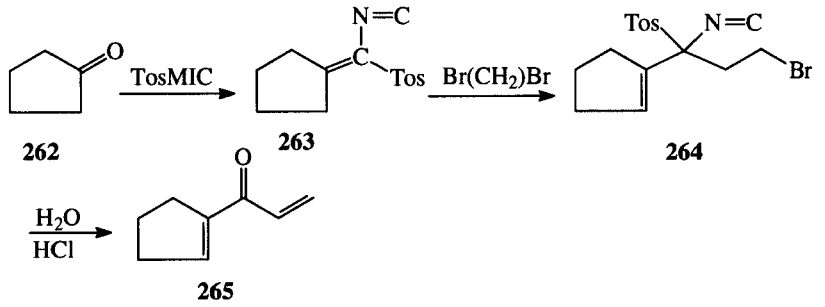
The Knoevenagel-type condensation product **255** was formed from cyclohexanone **254** which on alkylation with allylbromide and subsequent hydrolysis of **256** leads to the formation of **257**.

Bis-enone **261** was synthesized by an analogous reaction of cyclobutanone **258** with TosMIC leading to formation of **259** which on alkylation and further hydrolysis with acid formed bis-enone **261** (Scheme 98) [91].



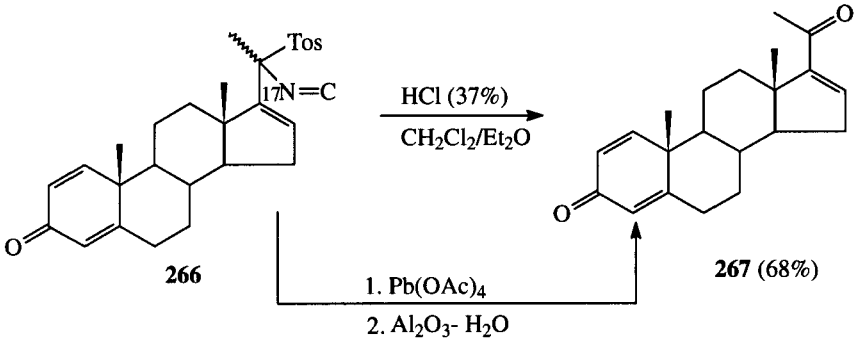
SCHEME 98

Enone **265** was obtained from cyclopentanone **262** by analogous reaction as shown in Scheme 97. Instead of a β-bromoenone the dienone **265** (divinyl ketone) was obtained [92] (Scheme 99).



SCHEME 99

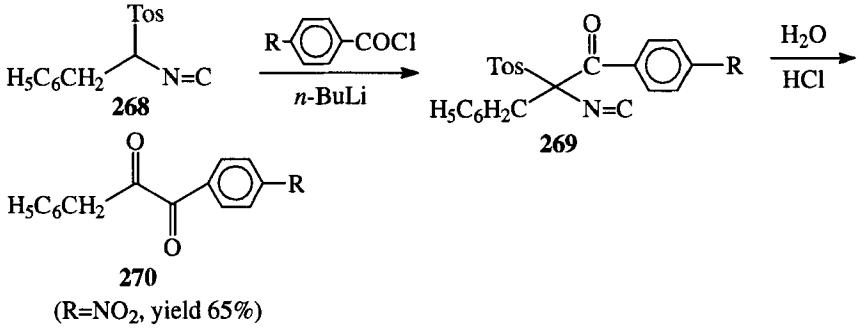
The above method has been used for introduction of the C-17 side chain in steroids (conversion of **266** to **267**; Scheme 100) [90]. Instead of acid hydrolysis, the isocyano group in **266** was oxidized with $Pb(OAc)_4$ to an isocyanate and then hydrolyzed with Al_2O_3 (Scheme 100).



SCHEME 100

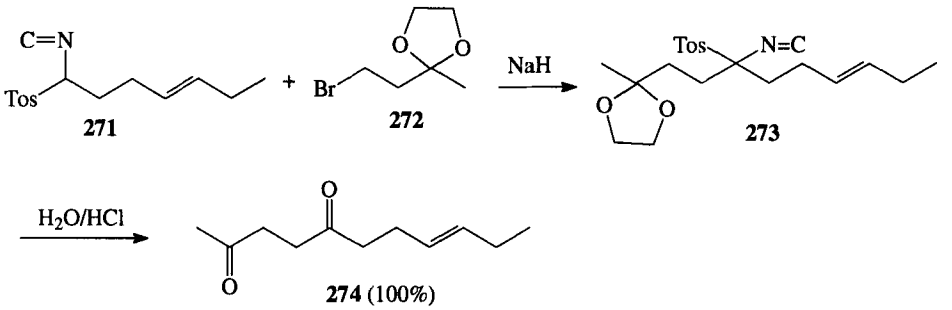
3.2.5. Diketones

1,2-Diketones can be synthesized by acylation of mono-substituted TosMIC derivative **268** to yield disubstituted TosMIC derivative **269** which on further hydrolysis with acid forms 1,2-diketones [92,93] (Scheme 101).



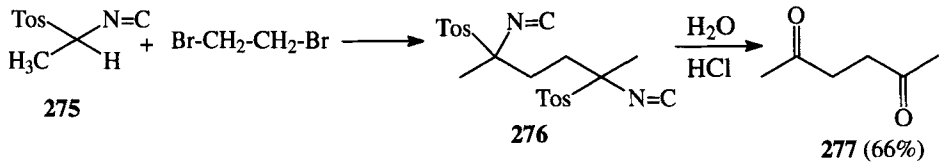
SCHEME 101

The synthesis of 1,3- and 1,4-diketones requires protection of one keto group. The 1-isocyano-1-tosyl-heptene derivative **271** reacted with protected bromoketone **272** to form **273** which on hydrolysis formed the 1,4-diketone **274** [17] (Scheme 102).

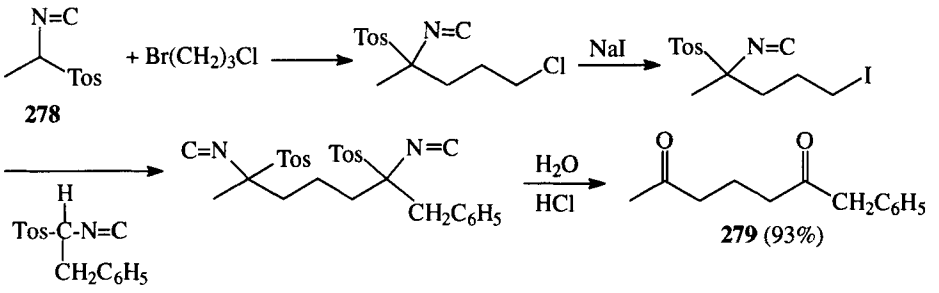


SCHEME 102

2,5-Hexanedione **277**, a 1,4-diketone, is formed from 1-tosyl ethyl isocyanide **275** by reaction with 1,2-dibromoethane. The product **276** thus formed on acid hydrolysis leads to formation of **277** (Scheme 103) [92]. 1,5-Diketones **279** can be synthesized from 1-tosyl ethyl isocyanide **278** as shown in Scheme 104 [90].

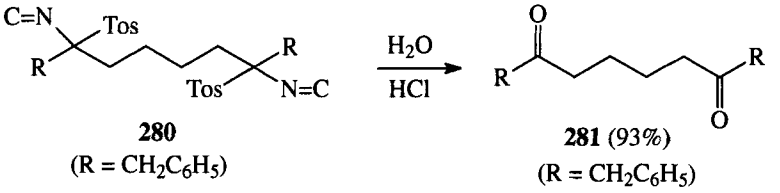


SCHEME 103



SCHEME 104

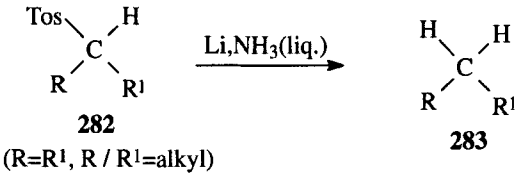
1,6-Diketones **281** can be synthesized from **280** by hydrolysis under acidic conditions (Scheme 105) [90].



SCHEME 105

3.3. Alkanes

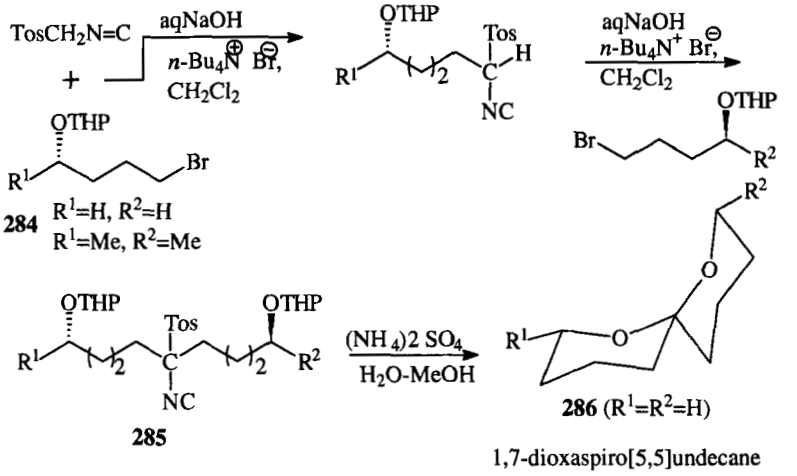
Both the tosyl and the isocyano groups can be reductively removed by reaction with Li and liquid NH_3 [16]. Thus dialkylated TosMIC derivatives **282** form the corresponding alkane derivatives **283** (Scheme 106).



SCHEME 106

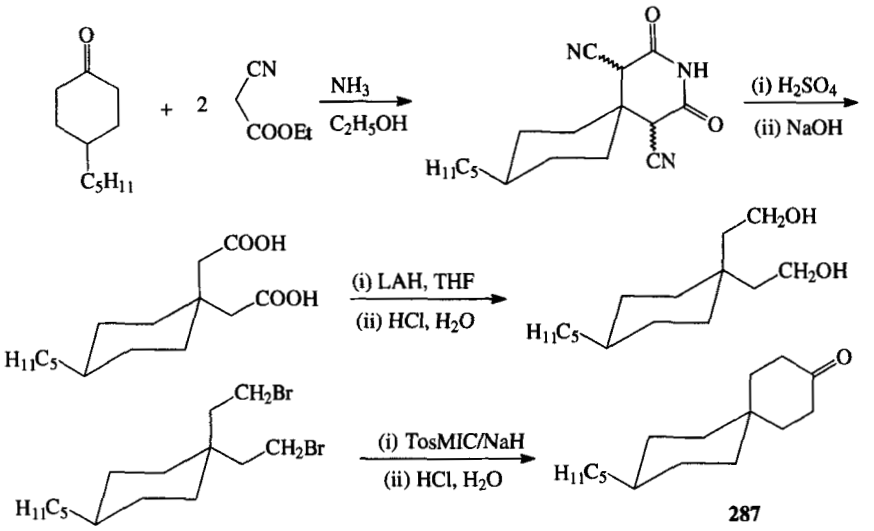
3.4. Synthesis of Spiroacetals

Spiroacetals constitute structural features of naturally occurring compounds [13]. The dialkylated TosMIC derivatives **285** obtained by alkylation of TosMIC with halohydrin derivatives **284** on hydrolysis with acid lead to the formation of 1,7-dioxaspiroalkanes **286** (Scheme 107) [13].



SCHEME 107

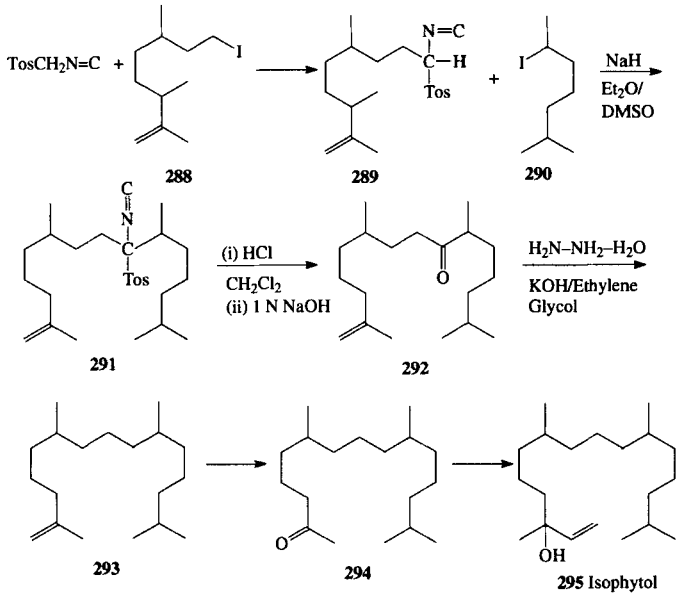
Terminally substituted spiro[5,5]undecanes have been used as building blocks in thermotropic liquid crystals. Synthesis of terminally substituted spiranes was carried out from 9-pentyl-3-spiro[5,5]undecanone **287** which could be obtained starting from 4-pentylcyclohexanone using an intramolecular cyclization with TosMIC as a key step (Scheme 108) [13].



SCHEME 108

3.5. Synthesis of Isophytol

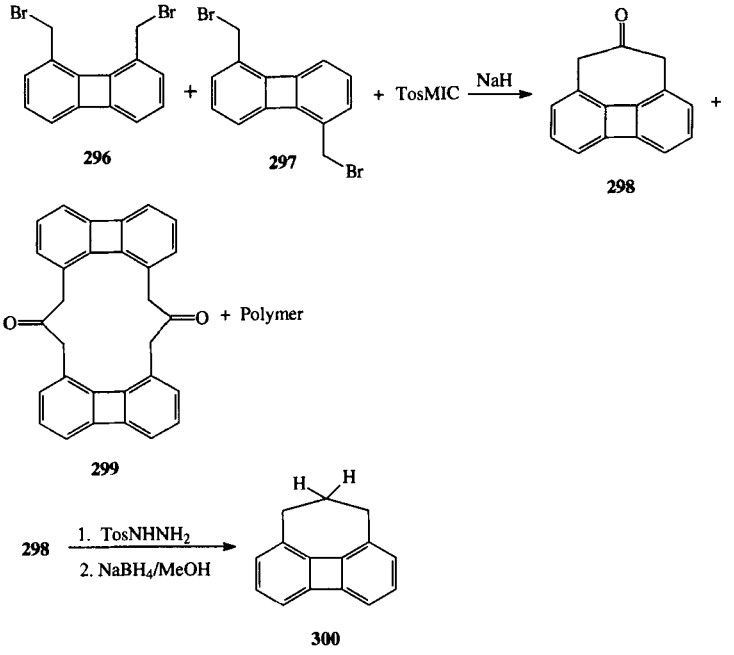
Isophytol **295** has been synthesized from TosMIC according to Scheme 109 [94]. The key intermediate, 2,6,10,14-tetramethyl-1-pentadecen-9-one, has been obtained via two successive alkylations of TosMIC with rhodinyliodide **288** and 2-iodo-6-methyl-heptane **290**, followed by acid hydrolysis of the product **291**. Huang–Minlon reduction of **292** affords norphylene **293** which is converted into isophytol **295** via **294**.



SCHEME 109

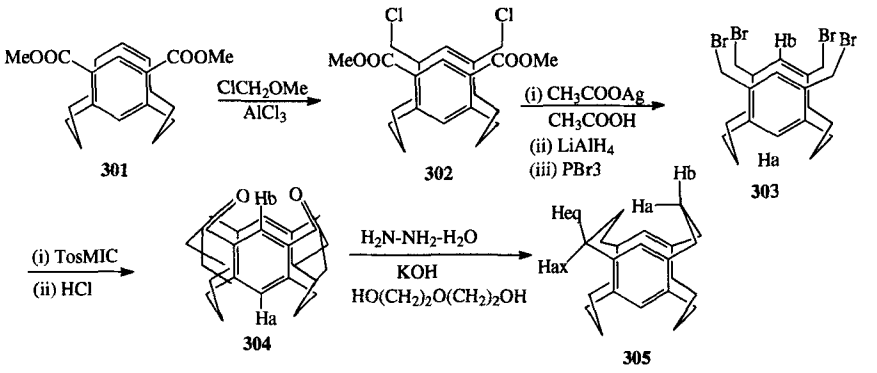
3.6. Synthesis of Cyclophanes

2-Oxo[3][1,8]biphenylenophane **298** was synthesized along with 2,13-dioxo[3,3](1,8)-biphenylenophane **299** by reaction of a mixture of dibromides **296** and **297** with TosMIC in the presence of NaH [94,95]. [3,1,8]Biphenylenophane **300** was obtained by reduction of hydrazone of **298** with $NaBH_4$ (Scheme 110).



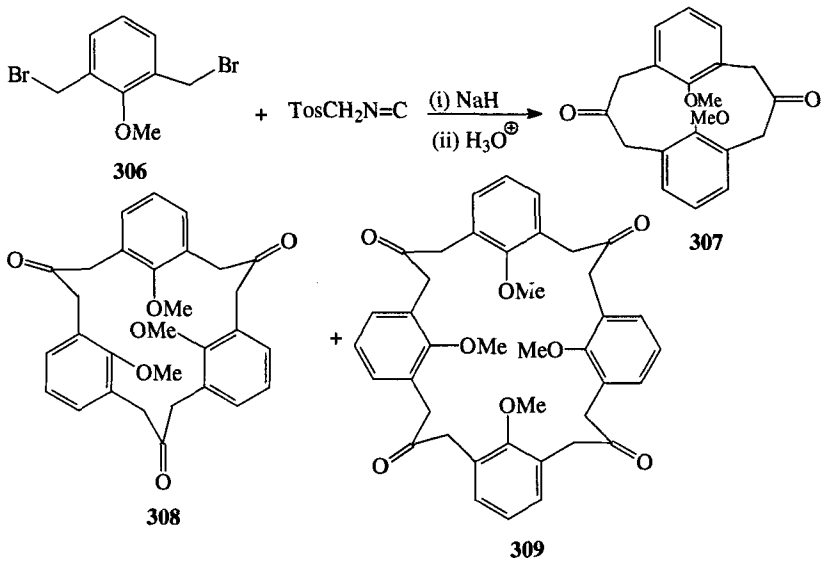
SCHEME 110

[3$_4$](1,2,4,5)Cyclophane **305** was synthesized from [3,3]metacyclophane-5,7-dicarboxylate **301** which on reaction with $ClCH_2OMe$ and $AlCl_3$ gave the bis(chloromethyl) compound **302**. Acetylation followed by reduction with LAH and reaction with PBr_3 gave tetrakis(bromomethyl)[3,3]metacyclophane **303**. A one-step TosMIC coupling reaction of **303** and subsequent hydrolysis afforded diketone the **304** which was converted into **305** by Wolf–Kishner reduction (Scheme 111) [96].



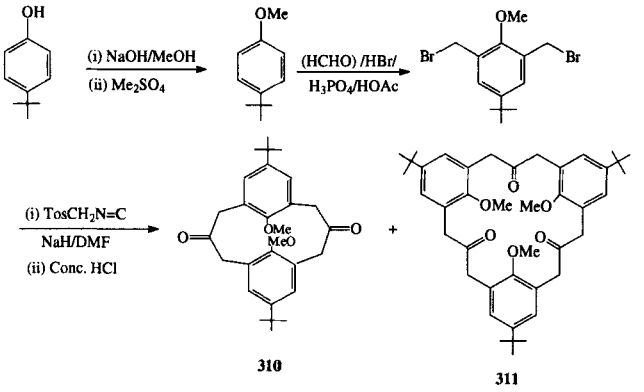
SCHEME 111

A mixture of cyclophanedione **307**, trione **308** and tetraketone **309** has been prepared by Breitenbach and Vogtle [97] according to Scheme 112 by condensation of TosMIC and **306** followed by acid hydrolysis.



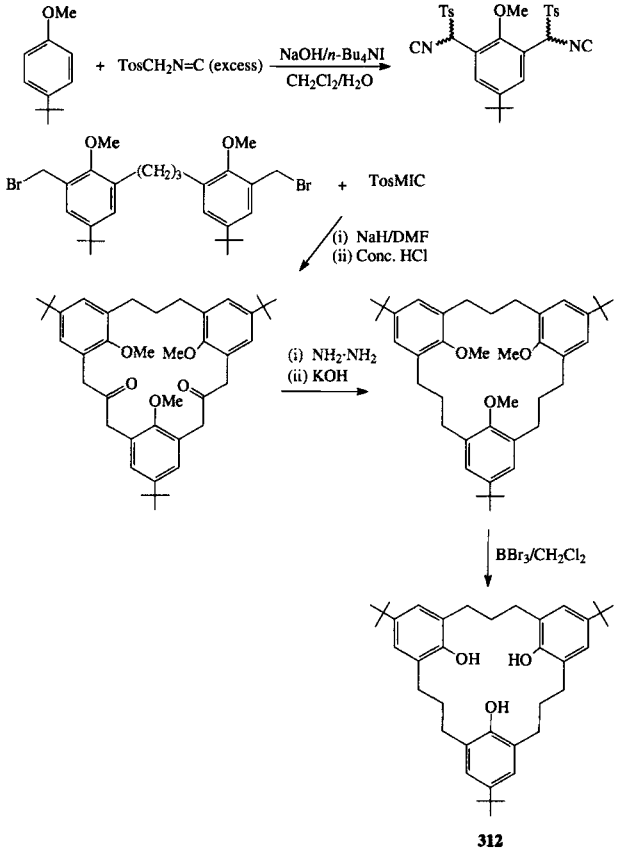
SCHEME 112

[3*n*]Metacyclophanes **311** have been synthesized from TosMIC in 22% yield. Thus 6,15,24-tri-*tert*-butyl-9,18,27-trimethoxy[3,3,3]metacyclophane-2,11,20-trione **311** has been synthesized along with dimer, anti-6,15-di-*tert*-butyl-9,18-dimethoxy[3,3]metacyclophane-2,11-dione (anti **310**) in 10% yield starting from 4-*tert*-butylphenol according to Scheme 113 [98].



SCHEME 113

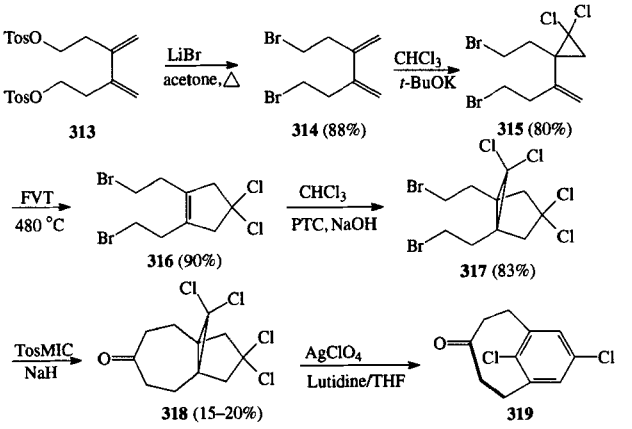
Tri-*tert*-butyltrihydroxy[3,3,3]metacyclophane **312** was synthesized from *p*-*tert*-butylanisole in 25% overall yield and in six steps by reaction with TosMIC according to Scheme 114 [98].



SCHEME 114

The highly reactive [5]metacyclophane derivative, 8,11-dichloro[5]metacyclophan-3-one **319** has been synthesized from ditosylate **313**. Reaction of **313** with LiBr yielded

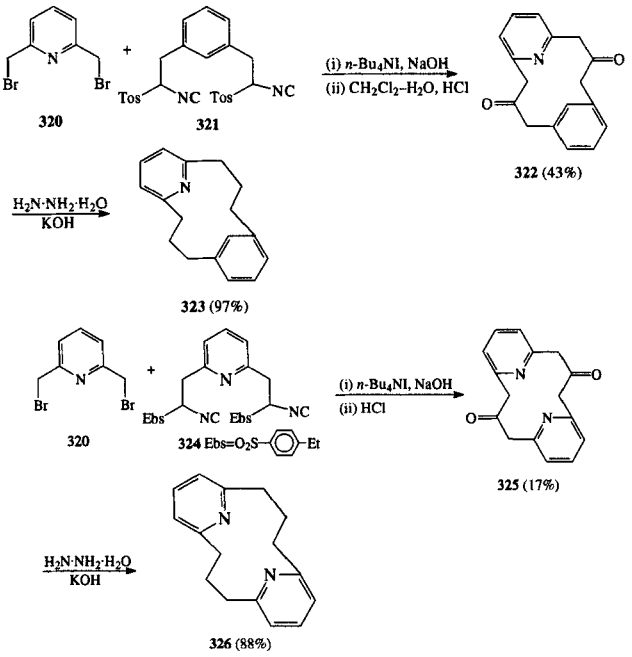
314. Dichlorocarbene addition to **314** gave **315** which was converted to **316** by flash vacuum thermolysis. Dichlorocarbene addition to **316** gave **317** which was cyclized with TosMIC to give propellane **318**. Cyclophanone **319** was prepared from **318** by double HCl elimination with $AgClO_4$ and lutidine in THF (Scheme 115) [99].



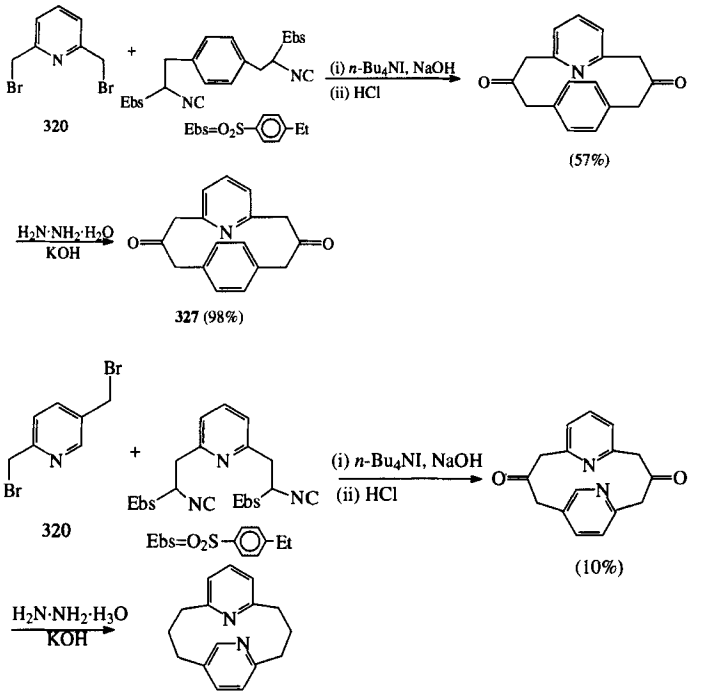
SCHEME 115

3.7. Synthesis of Heterocyclophanes

[3]Metacyclo[3](2,6)pyridinophane **323** has been prepared by a coupling reaction of 2,6-bis(bromomethyl)pyridine **320** and the TosMIC derivative **321** under phase-transfer conditions followed by acid treatment to afford ketone **322**. Diketone **322** was converted into **323** by Wolff–Kishner reduction (Scheme 116) [100].



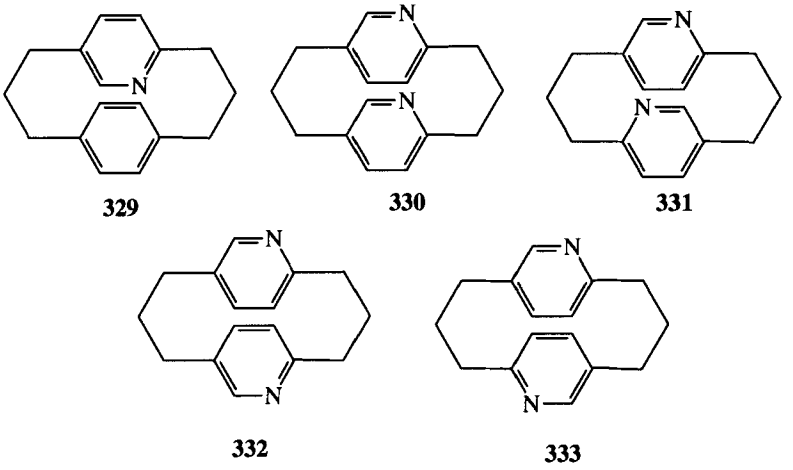
SCHEME 116



SCHEME 116 (Continued)

Similarly 2,6-bis(bromomethyl)pyridine **320** was coupled with **324** under similar conditions followed by acid treatment to afford ketone **325** which was converted to [3,3](2,6)pyridinophane **326** by Wolff–Kishner reduction (Scheme 116) [100]. [3]Paracyclo[3](2,6)pyridinophane **327** and [3](2,6)-pyridino[3](2,5)pyridinophane **328** were prepared by analogous routes (Scheme 116) [100]. **327** and **328** belong to the [3,3]metaparacyclophane system.

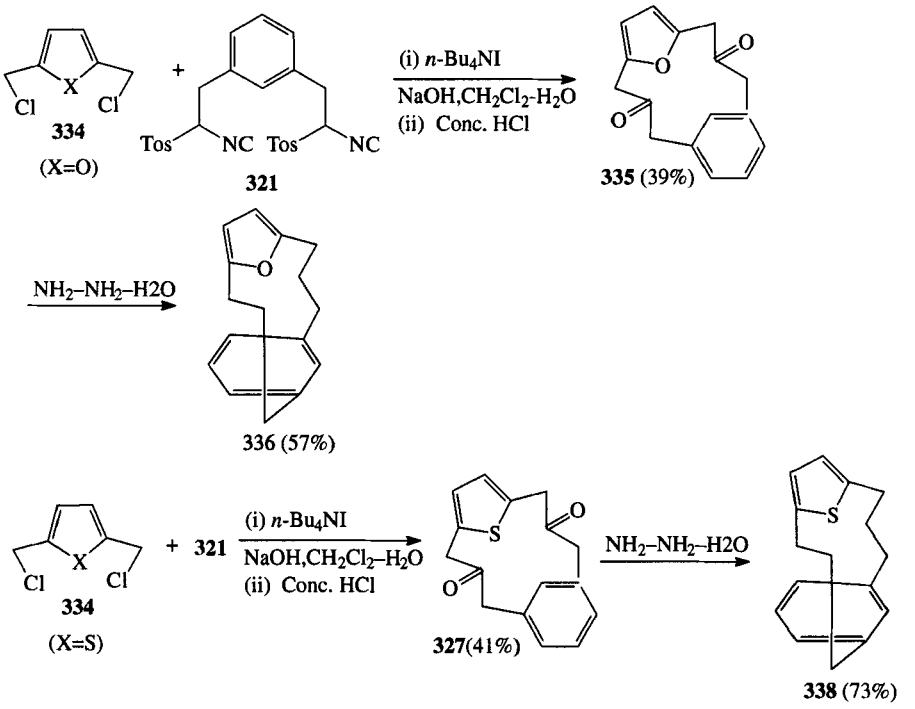
In the [3,3]paracyclophane system, [3]paracyclo[3]-(2,5)-pyridinophane **329** and isomeric **330**, **331**, **332** and **333** were prepared analogously (Scheme 116) [100].



329 **330** **331**

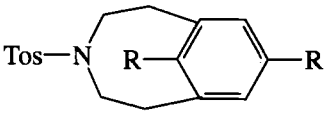
332 **333**

The TosMIC method was also applied successfully to other heterophanes. The coupling reaction of 2,5-bis(chloromethyl)furan **334** and **321** afforded the ketone **335** in 39% yield. Reduction of **335** gave furanophane **336** in 57% yield. Similarly, the coupling reaction of 2,5-bis(chloromethyl) thiophene **334** with **321** gave ketone **337** in 41% yield. **337** on subsequent reduction afforded thiophanophane **338** in 73% yield (Scheme 117) [100].



SCHEME 117

The *N*-tosyl protected 3-aza[5]metacyclophane derivative **339** has been synthesized. It was found that compound **339** had an unpredicted decrease in overall ring strain compared with the carbon analog **319** and this was reflected in its high thermal stability and very low chemical reactivity [101].

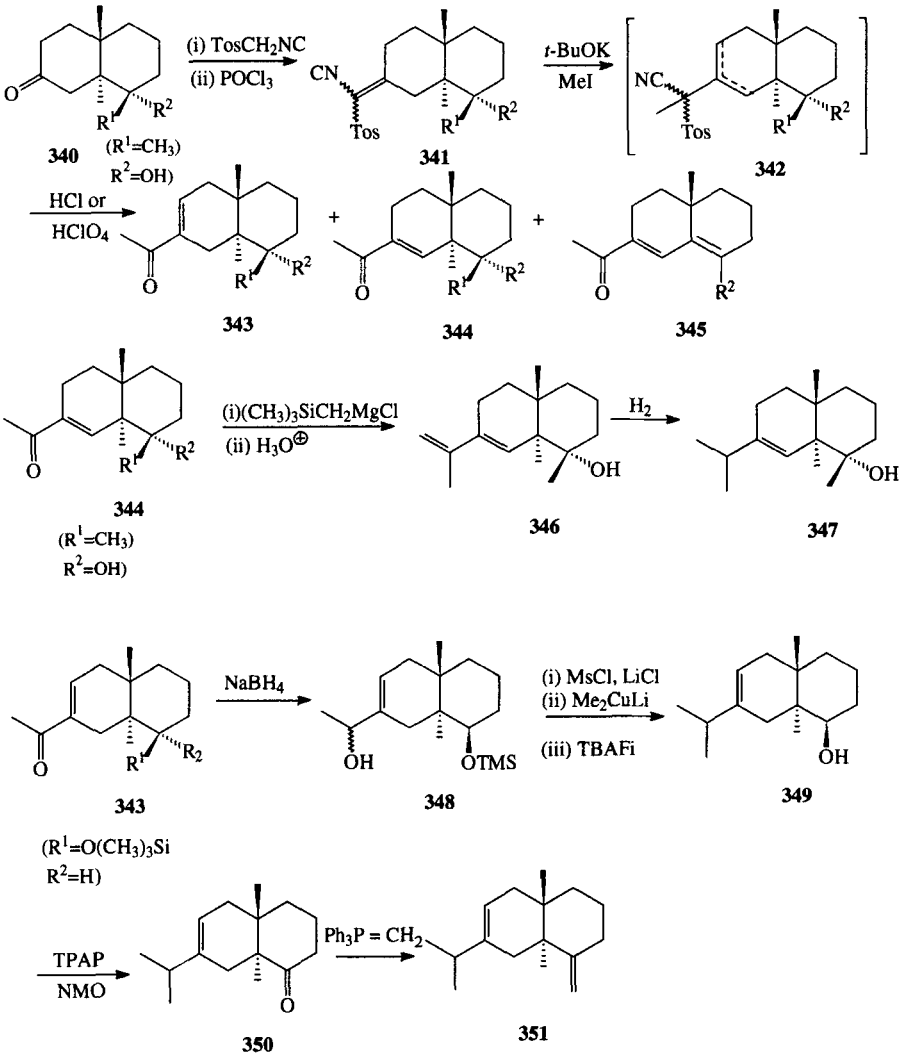


339

3.8. Synthesis of (±)-6-Eudesmen-4α-ol and (±)-Vetiselinene

Total synthesis of two important sesquiterpenes **347** and **351** has been described starting from TosMIC. Reaction of decalones **340** with TosMIC gave adducts **341** which on methylation with CH_3I and *t*-BuOK gave the methylated derivative **342**. Subsequent

acid-catalyzed hydrolysis of **342** gave a mixture of three isomers **343**, **344** and **345**. The major component **344** was converted into (±)-6-eudesmen-4α-ol **347** and **343** into (±)-vetiselinene **351** according to Scheme 118 [102].

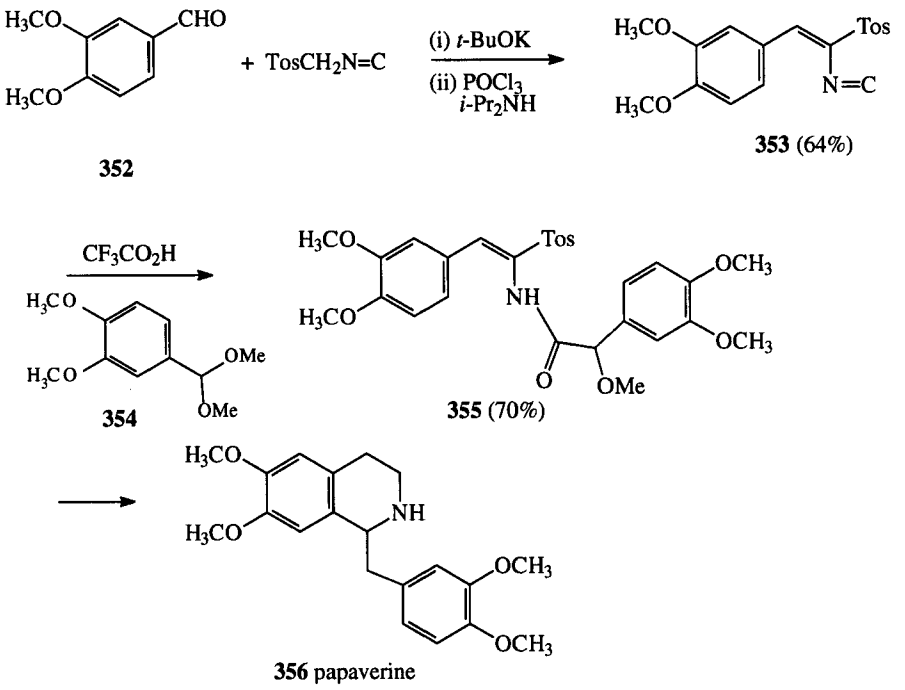


TPAP = tetrapropylammonium perruthenate
NMO = 4-methylmorpholine *N*-oxide

SCHEME 118

3.9. Synthesis of Papaverine

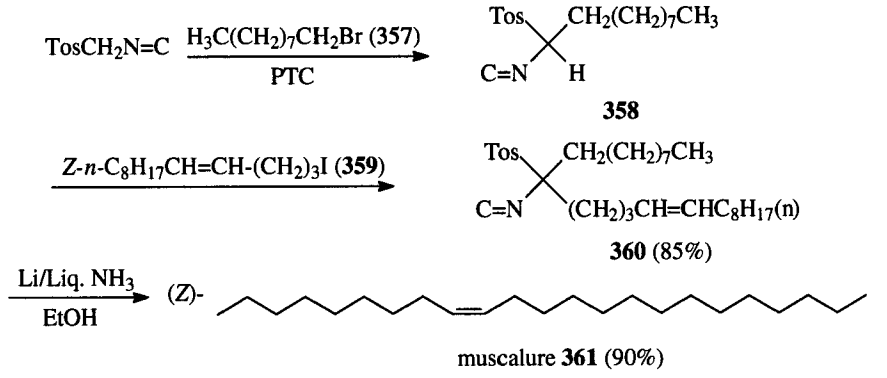
Veratraldehyde **352** was reacted with TosMIC to form the isonitrile derivative **353** which was reacted again with veratraldehyde acetal **354** in the presence of CF_3CO_2H to form amide derivative **355**. This was further converted into papaverine **356** according to Scheme 119 [103].



SCHEME 119

3.10. Synthesis of Muscalure

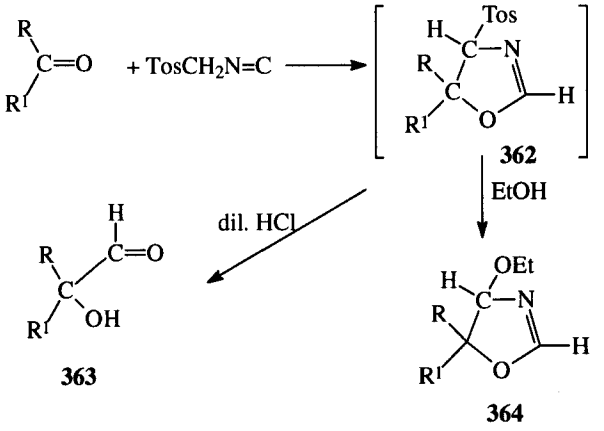
The TosMIC dialkylation procedure described earlier has been followed for the synthesis of muscalure **361**, a pheromone of the common housefly. The synthetic route is outlined in Scheme 120 [104]. The reaction of TosMIC with *n*-nonylbromide **357** under phase transfer conditions gave monoalkylated TosMIC derivative **358** which on further reaction with *(Z)*-tridec-4-enyl iodide **359** gave disubstituted TosMIC derivative **360** in 85% yield. Further reduction by Li/NH_3 resulted in an excellent yield of muscalure **361**.



SCHEME 120

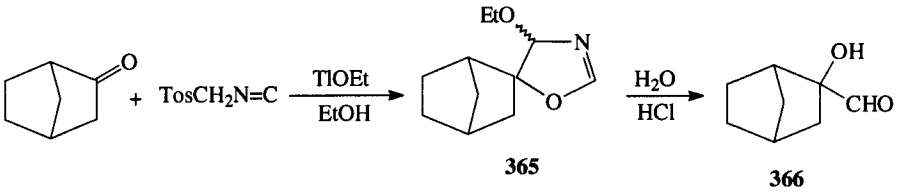
3.11. Synthesis of α-Hydroxy Aldehydes and α-Hydroxy Ketones

The reaction of TosMIC with ketones in alcoholic solvents leads to the formation of oxazolines **362** which on further hydrolysis give α-hydroxy aldehydes **363** [105] (Scheme 121).



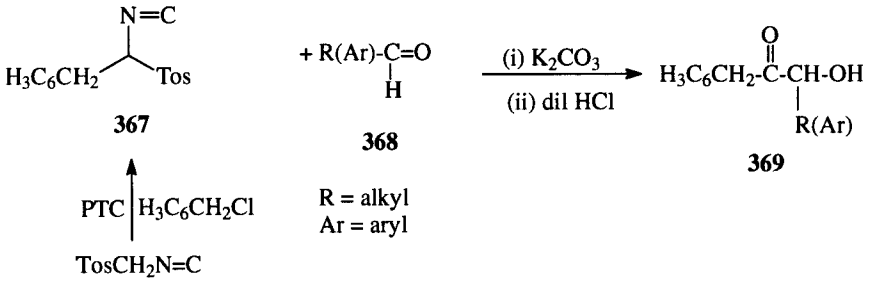
SCHEME 121

On using thallium ethoxide as a base oxazoline, **365** was isolated. Hydrolysis of **365** with dilute HCl in THF at room temperature gave the α-hydroxy aldehyde **366** [105] (Scheme 122).



SCHEME 122

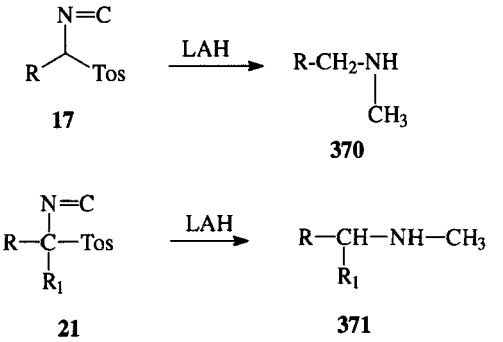
β-Hydroxyketones are synthesized from 2-phenyl-1-tosyl isocyanide **367** by reaction with an aldehyde **368** in a single pot to form 1,3-di-1-hydroxy-2-propanone **369** (Scheme 123) [88].



SCHEME 123

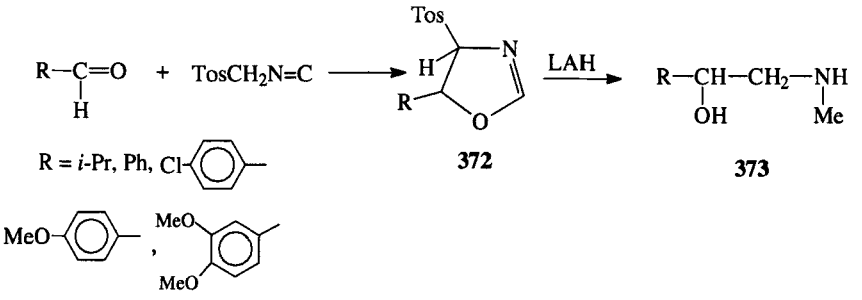
3.12. *N*-methylamines and β-Hydroxy *N*-methylamines

Mono- and disubstituted derivatives of TosMIC **17** and **21** can be reduced to *N*-methylamines **370** and **371**, respectively, by LAH (Scheme 124) [88].



SCHEME 124

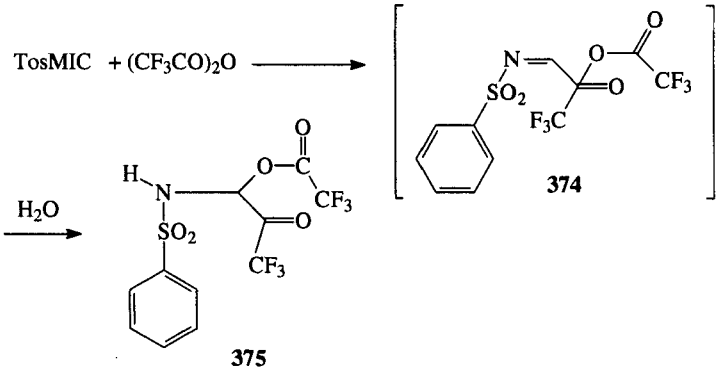
β-Hydroxy-*N*-methylamines **373** were synthesized from 4-tosyloxazolines **372** by reduction with LAH (Scheme 125) [88].



SCHEME 125

3.13. Synthesis of Trifluoropyruvamides

TosMIC reacts with trifluoroacetic anhydride to give adduct **374** which on hydrolysis yields trifluoropyruvamide **375** in quantitative yield (Scheme 126) [106].

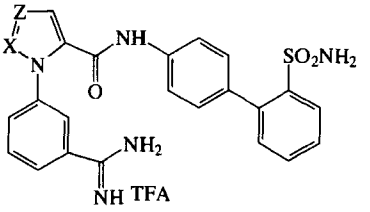


SCHEME 126

4. APPLICATION TO THE SYNTHESIS OF DRUGS AND INTERMEDIATES USED IN PHARMACOLOGICALLY ACTIVE COMPOUNDS

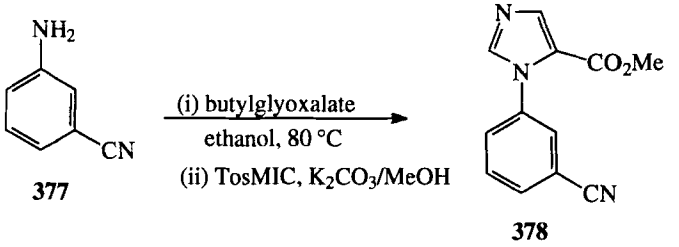
4.1. Benzamidine Factor Xa Inhibitors

TosMIC has been used for the synthesis of heterocyclic intermediates involved in the synthesis of benzamidine factor Xa inhibitors containing a vicinally substituted heterocyclic core **376** [107].



376 (X = CH, Z = N)

The core intermediates **378** containing an imidazole ring was prepared from 3-aminobenzonitrile **377** according to Scheme 127. Condensation of **377** with butylglyoxalate in refluxing ethanol gave an imine which on treatment with TosMIC and K_2CO_3 in MeOH underwent cyclization and transesterification to give imidazole methyl ester **378**.

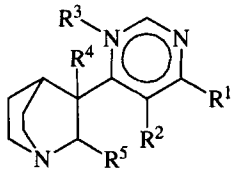


377 **378**

SCHEME 127

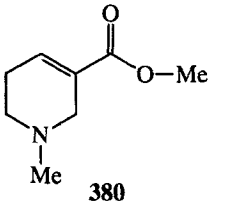
4.2. Muscarinic Agonists/Antagonists

A series of 3-(pyrazol-3-yl)-1-azabicyclo[2,2,2]octane derivatives **379** were synthesized. The compounds were found to possess potential muscarinic agonistic or antagonistic properties [108] on the basis of binding studies measuring their potencies to inhibit the binding of [^{3}H]oxotremorine-M (OXO-M) and [^{3}H]pirenzepine (PZ).



379

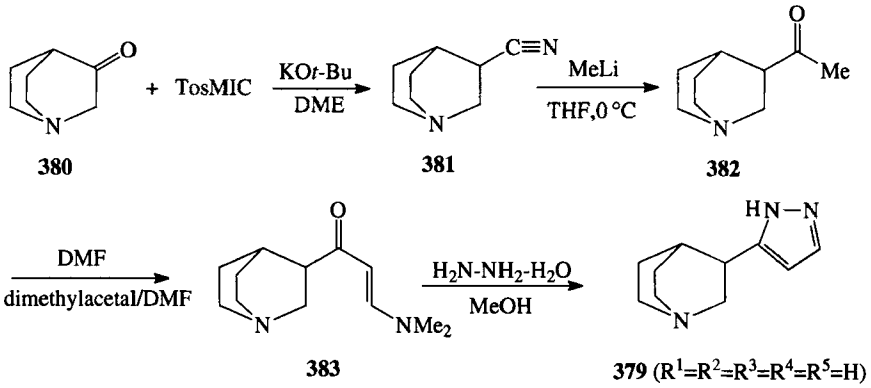
R^1 = H, Br
R^2 = H, Br
R^3 = H, Me
R^4 = H, OH
R^5 = H



380

Receptor binding affinity and muscarinic cholinergic activity of these compounds have been compared with arecoline **380** as outlined in Tables XIV and XV.

The compound **379** ($R^1 = R^2 = R^3 = R^4 = R^5 = H$) was found to have highest ratio of PZ and OXO-M (135) and is therefore a full M_3 agonist. Compounds **379** were prepared by reaction of 1-azabicyclo[2,2,2]octan-3-one **380** with TosMIC according to Scheme 128, resulting first in the formation of cyanide **381**.



SCHEME 128

Cyanide **381** on reaction with methyl lithium gave the 3-acetyl derivative **382** which on reaction with dimethylformamide dimethyl acetal as reagent gave the enamine derivative **383**. Finally, **383** on treatment with $H_2N–NH_2$ gave the desired pyrazole **379**.

TABLE XIV Receptor binding affinity and affinity ratios for assays using agonist, oxotremorine-M (OXO-M) and antagonist pirenzepine (PZ) ligands

Compound	*K_I for [^{3}H]-OMO-M* (μM)	*K_I for[^{3}H]PZ* (μM)	*[^{3}H]PZ:[^{3}H]OXO-M ratio*
Arecoline	0.0079	1.58	200
379 ($R^1 = R^2 = R^3 = R^4 = R^5 = H$)	0.79	40	50.6
379 (R^3 = Me, $R^1 = R^2 = R^4 = R^5 = H$)	0.63	6.3	10.0
379 (R^4 = OH, $R^1 = R^2 = R^3 = R^5 = H$)	3.1	40	12.9
379 (R^2 = Br, $R^1 = R^3 = H$, $R^4 + R^5$ = double bond)	0.063	0.15	2.38
379 (R^2 = Br, $R^1 = R^3 = R^4 = R^5 = H$)	0.012	1.63	135
379 (R^2 = I, $R^1 = R^3 = R^4 = R^5 = H$)	0.004	0.126	31.5
379 ($R^1 = R^2$ = Br, $R^3 = R^4 = R^5 = H$)	0.025	1.02	40.3

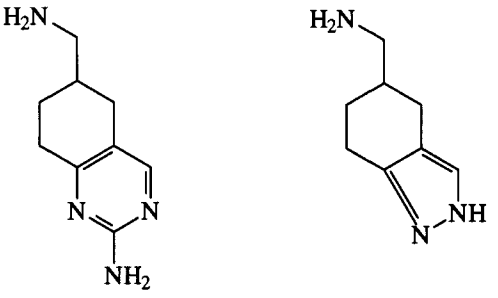
TABLE XV Muscarinic cholinergic activity in guinea pig ileum (MUGI) and rat left atrium (M_2LA)

Compound	*MUGI*			*M_2LA*		
	PD_2[a]	*α*	*PA_2*[b]	*PD_2*	*α*	*PA_2*
Arecoline	6.5	1.0				
379 ($R^1 = R^2 = R^3 = R^4 = R^5 = H$)	4.6	1.0	–	–	–	–
379(R^2 = Br, $R^1 = R^3 = H$, $R^4 + R^5$ = double bond)	–	–	5.7	–	–	–
379 (R^2 = Br, $R^1 = R^3 = R^4 = R^5 = H$)	5.7	1.0	–	<4	0	5.9
379 (R^2 = I, $R^1 = R^3 = R^4 = R^5 = H$)	6.2	0.7	5.7	6.3	0.5	6.2
379 ($R^1 = R^2$ = Br, $R^3 = R^4 = R^5 = H$)	–	–	5.2	–	–	–

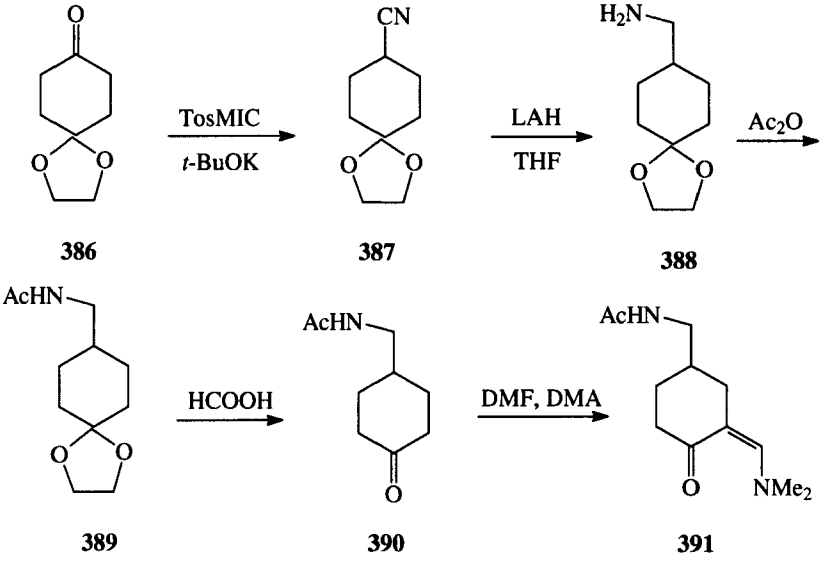
[a]Agonist values, PD_2; [b]Antagonist values in μM, PA_2; α = intrinsic activity.

4.3. Conformationally Restricted Arginine Side Chain Mimetics

6-(Aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (**384**) and 4,5,6,7-tetrahydro-2*H*-indazol-5-yl methanamine (**385**) were synthesized by Masic and Kikelj [109] as novel conformationally restricted arginine side chain mimetics using TosMIC as starting material. The key intermediate enaminoketone (**391**) was synthesized according to Scheme 129. Thus ketone **386** on reductive cyanation forms the nitrile **387** which on reduction with LAH forms the primary amine **388**. Acetylation of **388** gave the *N*-acetyl derivative **389**.



384 **385**

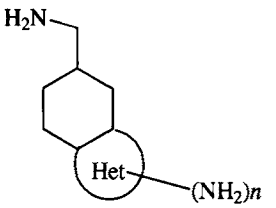


386 **387** **388**

389 **390** **391**

SCHEME 129

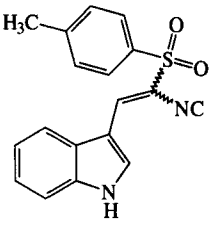
Cleavage of 1,3-dioxolane ring of **389** gave *N*-[(4-oxocyclohexyl)methyl] acetamide **390**. The ketone **390** was converted into the novel enaminoketone **391** by reaction with DMF/DMA. The enaminoketone **391** was used as a key intermediate for the synthesis of arginine side chain mimetics **392** [109].



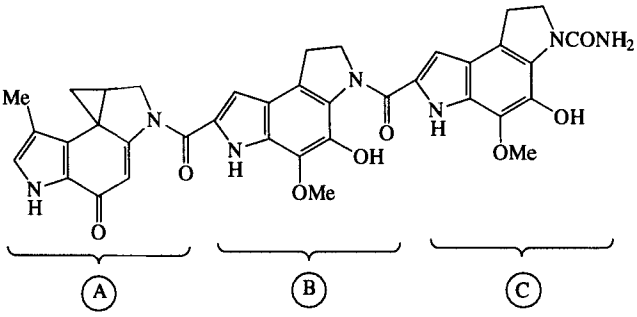
392

4.4. Anticancer and Antiviral Agents

Beck *et al.* in a program to discover novel anticancer drugs with new mechanisms of action recognized the presence of indole-3-ethenamide as a possible chromophore in many natural products [110]. Isocyanide **393** was synthesized by condensation of TosMIC with 3-formyl indole. Isocyanide **393** contains the essential indole-3-ethenamide chromophore in it.

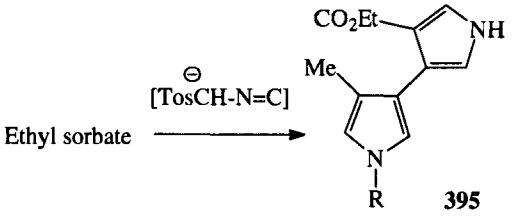


393



394

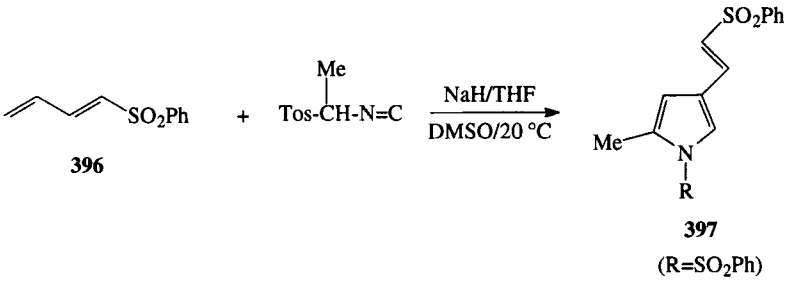
As part of a strategy towards total synthesis of the antitumor agent CC-1065 (**394**), 3,3′-bipyrrole (**395**) was synthesized by sequential conjugate addition of TosMIC anion to ethyl sorbate [111] (Scheme 130).



395

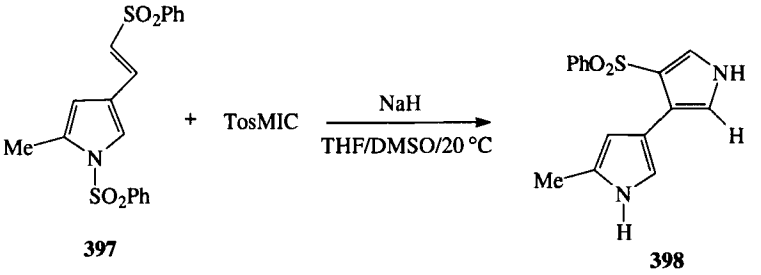
SCHEME 130

The synthesis of CC-1065 (**394**) comprises of synthesis of three fragments A, B and C [112]. Fragment A was synthesized by a similar route employed for **395**. For the synthesis of the B–C portion of **395**, 1-phenylsulfonyl-1,3-butadiene **396** was treated with TosCHMeNC and NaH to give 2,4-disubstituted pyrrole **397** (R=H) (Scheme 131).



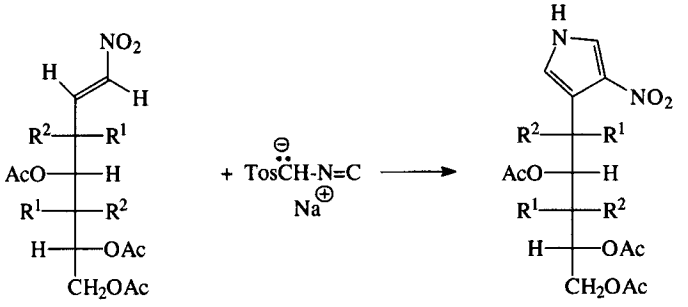
SCHEME 131

The vinyl sulfone **397** (R=SO_2Ph) was treated again with TosMIC in the presence of NaH to give 3,3′-bipyrrole **398** (Scheme 132) [113].



SCHEME 132

The sodium salt of TosMIC reacted with (*E*)-3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-*C*-nitro-*D*-galacto (**399**) and *D*-manno- (**400**) hept-1-enitol to give 3-(*D*-galacto- (**401**) and 3-(*D*-manno-(**402**)penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole respectively (Scheme 133).



R¹=OAc, R²=H, **399**
R¹=H, R²=OAc, **400**

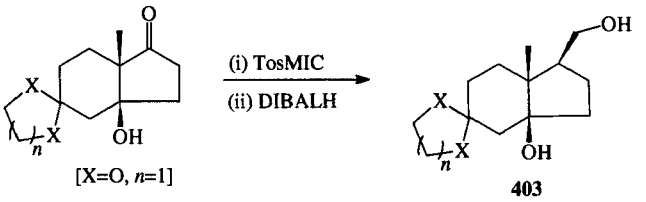
R¹=OAc, R²=H, **401**
R¹=H, R²=OAc, **402**

SCHEME 133

4.5. Cardiotonics

The intermediates **403** used for the synthesis of 1,5-disubstituted hydroindenes have been synthesized by TosMIC cyanation followed by DIBALH reduction. These are

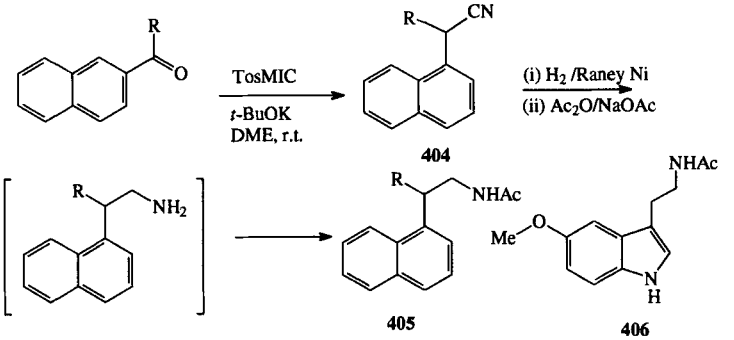
the simplest homocyclic skeletal base for the construction of either cardiotonics or negative inotropic agents [114] (Scheme 134).



SCHEME 134

4.6. Melatoninergic Agonists

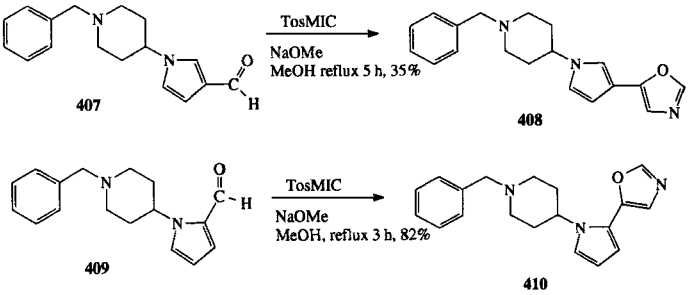
Synthesis of β-substituted naphth-1-yl ethylamido derivatives as melatoninergic agonists has been carried out using TosMIC for the synthesis of intermediate nitrile (**404**) [115]. Melatonin, chemically known as *N*-acetyl-5-methoxy tryptamine **406**, is the vertebrate pineal gland hormone secreted during darkness. It is known to alleviate jet-lag, to regulate delayed sleep phase syndrome and to induce sleep (Scheme 135).



SCHEME 135

4.7. Dopamine D_4 Receptor Ligands

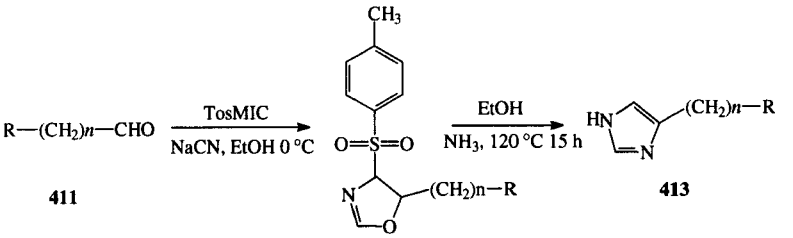
Novel dopamine D_4 receptor ligands, the piperidinyl pyrroles, **408** and **410**, have been synthesized by employing TosMIC and its reaction with carbaldehydes **407** and **409** [116] (Scheme 136).



SCHEME 136

4.8. Histamine H_3 Receptor Ligands

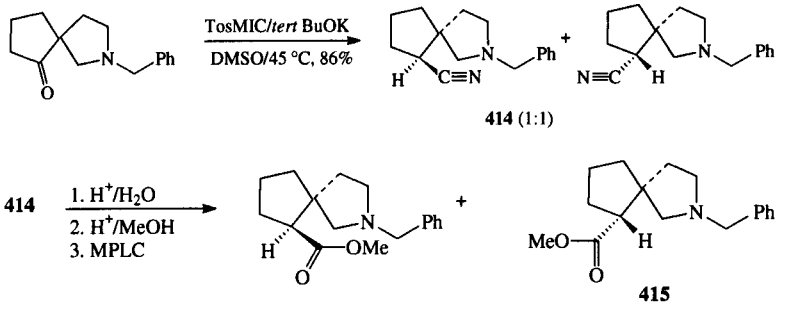
The effect of lipophilic moieties attached to a 4-1*H*-imidazole ring on the histamine H_3 receptor activity has been investigated by DeEsch *et al.* [117]. H_3 antagonists provide means for the treatment of Alzheimer's disease, narcolepsy, schizophrenia, epilepsy and obesity. 1*H*-imidazoles **413** were synthesized from aldehydes **411** by first reaction with TosMIC in a [3 + 2] anionic cycloaddition. The 4-tosyloxazolines **412** on reaction with NH_3 and EtOH form 1*H*-imidazoles **413** (Scheme 137).



SCHEME 137

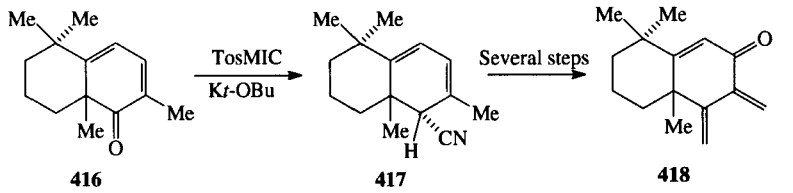
4.9. Neurotransmitter Inhibitors of the Central Nervous System

Spirocyclic analogs **415** of 4-aminobutyric acid, the most important inhibitory neurotransmitter in the central nervous system, have been synthesized using TosMIC for the synthesis of intermediates (**414**) involved in the synthesis of **415** [118] (Scheme 138).



SCHEME 138

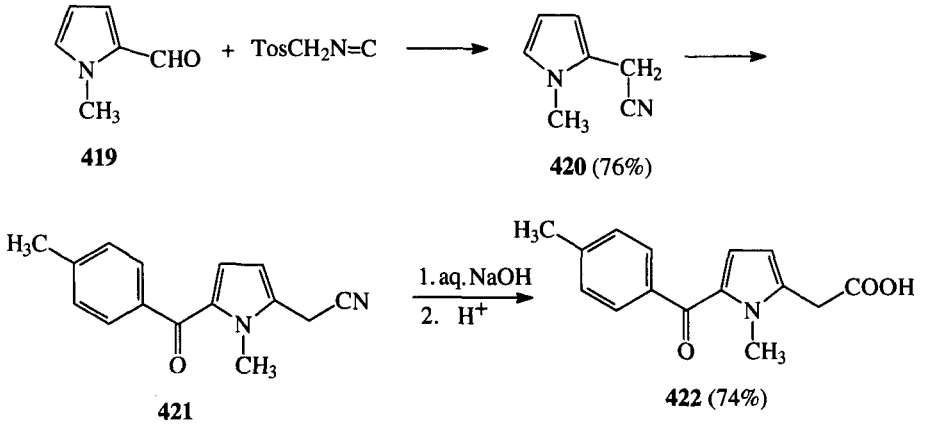
(±)-Herbertene (415), a sesquiterpene isolated from the liverwort *Herberta adma*, has been synthesized by reaction of dienone **416** with TosMIC in the presence of K*t*-OBu to form the nitrile **417**. Nitrile **417** on further reactions with suitable reagents formed **418** [119] (Scheme 139).



SCHEME 139

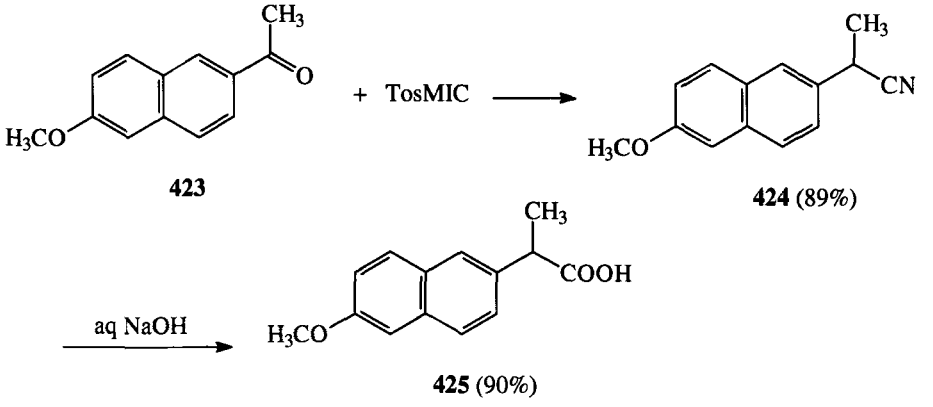
4.10. Non-steroidal Anti-inflammatory Agents

Nitrile precursors of two important clinically used non-steroidal anti-inflammatory agents, tolmetin and naproxen, have been synthesized from TosMIC according to Scheme 140. 1-Methylpyrrole-2-carboxaldehyde **419** was reacted with TosMIC to form 1-methylpyrrole-2-acetonitrile **420** which was converted to 1-methyl-5-(4-methylbenzoyl)pyrrole-2-acetonitrile **421**. Hydrolysis of **421** with aqueous NaOH led to the formation of tolmetin **422** [120].



SCHEME 140

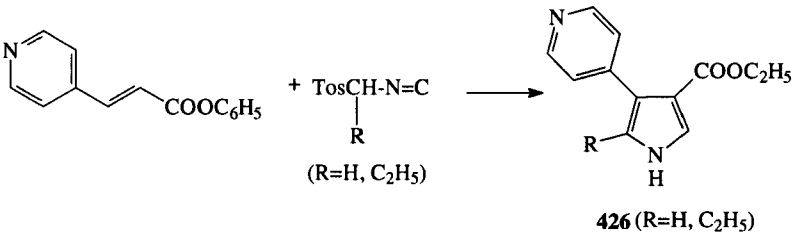
Naproxen **425** was synthesized from nitrile **424**, which was synthesized by reaction of 2-acetyl-6-methoxynaphthalene **423** with TosMIC followed by hydrolysis with alkali (Scheme 141) [120].



SCHEME 141

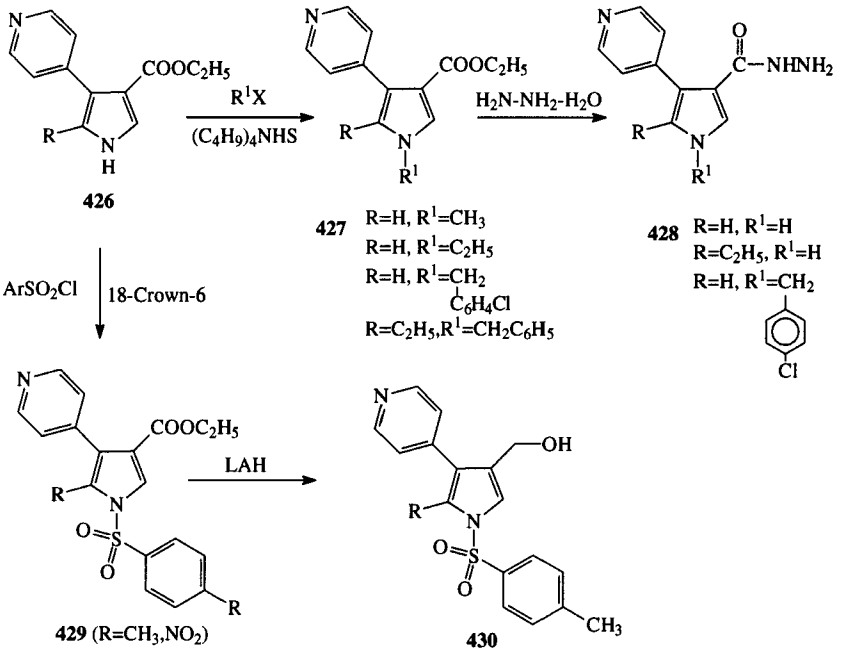
4.11. Antitubercular Agents

A set of pyrroles were synthesized and a 3D QSAR study was carried out on their antitubercular activities. Pyrrole derivatives **426** were synthesized according to Scheme 142 [121].



SCHEME 142

426 were *N*-alkylated and *N*-arylalkylated to form *N*-alkyl **426** and *N*-arylalkyl **427** derivatives which were further reacted with hydrazine hydrate to form carboxyhydrazide derivative **428**. On reaction with arylsulfonylchlorides compounds **426** formed the arylsulfonyl derivative **429**. Reduction of **429** with LAH formed the corresponding alcohol **430** [121] (Scheme 143).

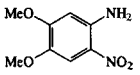
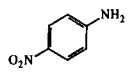
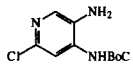
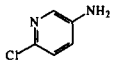


SCHEME 143

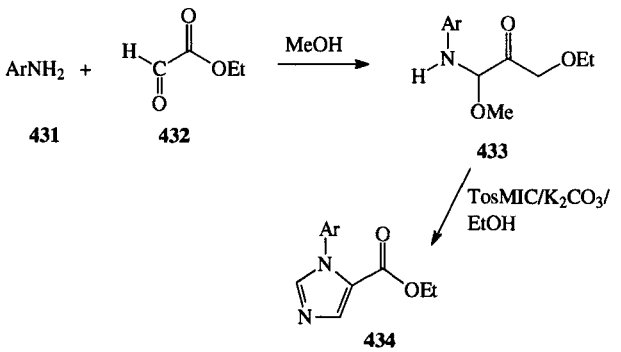
Compounds of the series **426–430** were subjected to a 3D QSAR study and a comparative molecular field analysis (CoMFA) was applied. A comparison between QSAR, CoMFA and mixed QSAR–CoMFA models was presented.

1-Arylimidazole-5-carboxylates **434** have been synthesized by a new method involving reaction of anilines (**431**) and ethyl glyoxylate **432** in methanol to give α-anilino α-methoxy acetates **433** followed by cyclization with TosMIC [109] (Scheme 144). Compounds **434** are an important class of intermediates involved in organic synthesis. These have been used in the synthesis of biologically active compounds such as fungicides, herbicides, plant growth regulators, analogs of histidine and histamine, factor Xa inhibitors. These have also been used in the synthesis of phenylimidazoles for treatment of cerebral disorders, amnesia and senile dementia (Scheme 144) [122].

TABLE XVI Synthesis of 1-arylimidazole-5-carboxylates 434 from $ArNH_2$

Entry	*$ArNH_2$*	*Conditions* **431**:**432**[a] (h)	*Yield of* **433** (%)	*Conditions* **43.3**: TosMIC:K_2Ca_3[a]	*Temperature* (°C)	*Time* (h)	*Yield of* **434** (%)
1		1.0:5.0 17	–	1.0:1.2:2.0	50	4	68
2		1.0:5.0 18	–	1.0:1.2:2.0	65	4	40
3		1.0:5.0 18	95%	1.0:1.2:2.0	65	3	89
4		1.0:1.3 5	98%	1.0:2.5:4.0	60	3	96
5		1.0:2.5 18	–	1.0:2.5:5.0	60	8	48

[a]Molar ratios.



SCHEME 144

This method is applicable to electron-rich anilines, electron-deficient anilines and heterocyclic anilines. The overall yield of 1-arylimidazole-5-carboxylates is 40–94% as reported in Table XVI.

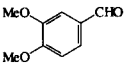
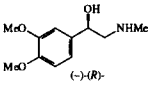
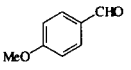
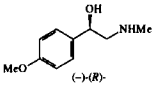
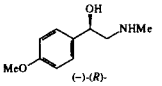
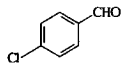
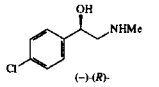
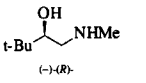
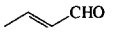
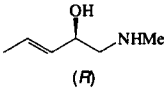
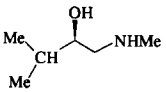
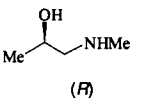
5. TOSMIC AND CHIRAL TOSMIC ANALOGS IN THE SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS

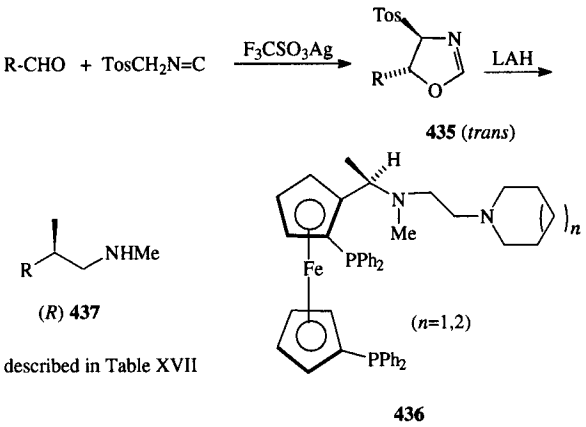
5.1. From TosMIC

5.1.1. Synthesis of (R)- and (S)-enantiomers of β-Hydroxy N-methylamines

(*R*)-β-hydroxy-*N*-methylamines (**437**) have been synthesized from TosMIC by reaction with aliphatic and aromatic aldehydes leading to formation of *trans*-4-tosyl oxazolines **435**. The enantiomeric efficiencies (EEs) range from 73% to 86% under the influence of a chiral silver catalyst from AgOTf and the *N*,*N*,*N*′,*N*′-tetraalkylethylene-diamino substituted bis(diphenylphosphine)ferrocene ligand **436** followed by reduction with LAH [123] (Scheme 145). The yields of **437** and EEs are described in Table XVII.

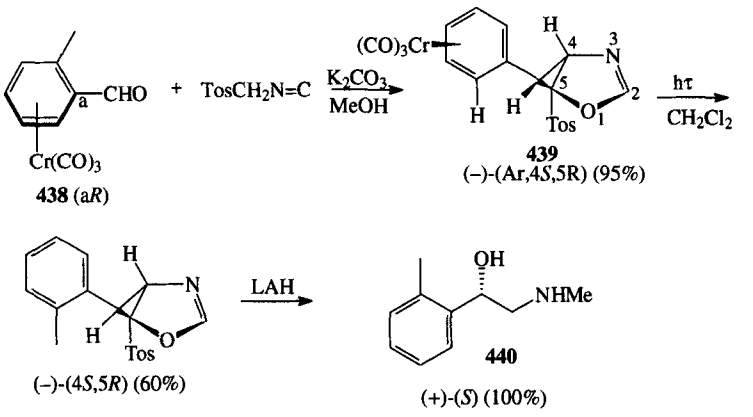
TABLE XVII Synthesis of (*R*)-β-hydroxy-*N*-methylamines 437 according to Scheme 145

Substrate (RCHO)	*Reaction conditions*	*Product* **437** *(absolute configuration)*	*Yield (%)*
	(i) **436** ($n=1$) CH_2Cl_2, RT, 2 h (ii) LAH, RT		83
	(i) **436** ($n=2$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		78
	(i) **436** ($n=2$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		86
	(i) **436** ($n=2$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		84
t-BuCHO	(i) **436** ($n=2$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		68
	(i) **436** ($n=2$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		63
i-PrCHO	(i) **436** ($n=1$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		58
MeCHO	(i) **436** ($n=1$) F_3CSO_3Ag, CH_2Cl_2, RT, 2 h (ii) LAH, RT		67



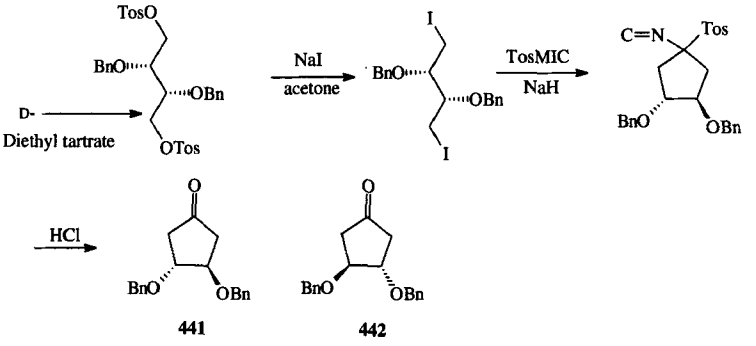
SCHEME 145

The (*S*)-enantiomer of β-hydroxy *N*-methylamines can be obtained by the reaction of the chiral metal carbonyl complex of aromatic aldehydes **438** with TosMIC under base-catalyzed conditions to form chiral oxazoline **439**. The complex **439** on photochemical reaction followed by reduction with $LiAlH_4$ forms (*S*)-β-hydroxy-*N*-methylamines **440** (Scheme 146) [124].



SCHEME 146

Synthesis of *trans*-(3*R*,4*R*)-bis(benzyloxy)-cyclopentanone **441** and *trans*-(3*S*,4*S*)-bis(benzyloxy)-cyclopentanone **442** was carried out in seven steps starting from *D*- and *L*-diethyl tartrate respectively (Scheme 147) [125].



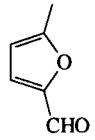
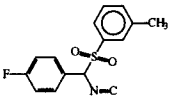
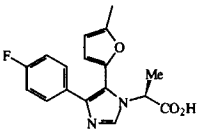
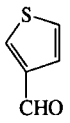
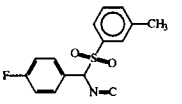
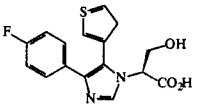
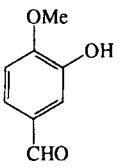
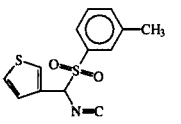
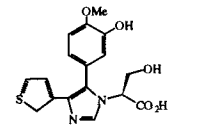
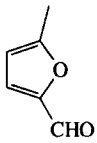
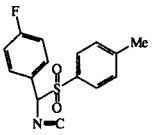
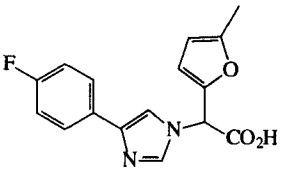
SCHEME 147

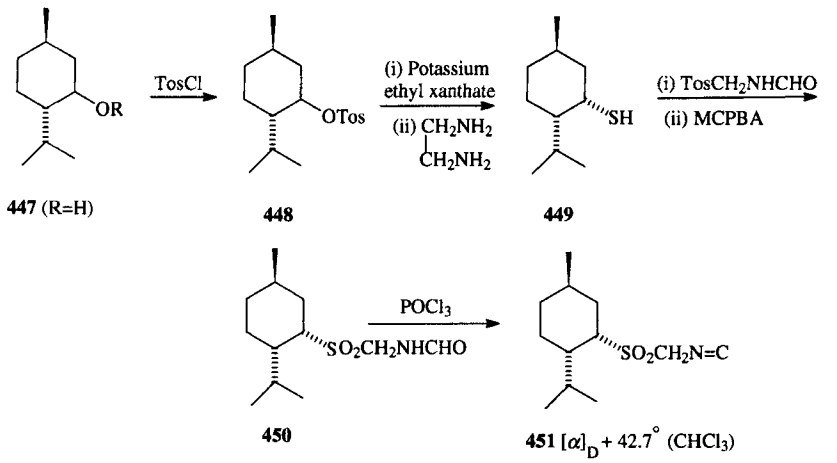
Chiral 1,4,5-trisubstituted imidazoles **443–445** in optically pure forms were prepared by reaction of the desired imines with a TosMIC reagent. Imines were prepared by reaction of an α-amino acid with an aldehyde in $MeOH:H_2O$ (10:1) and aqueous NaOH (1 equivalent) [35]. Homologated carboxylic acids **446** have been synthesized using β-alanine instead of α-amino acids (fourth row, Table XVIII). Chiral imidazoles **443–445** are obtained in high yield and with EE >99%.

5.2. Chiral TosMIC Analogs

The first chiral TosMIC analog (+)-(neomenthylsulfonyl) methyl isocyanide (NeSMIC) **451** was synthesized from (−)-menthol **447** according to Scheme 148 by Van Leusen *et al.* [126].

TABLE XVIII Synthesis of 1,4,5-trisubstituted imidazoles from tosylisonitriles and imines derived from α- and β-amino acids [35]

Aldehyde	*Amino acid*	*Tosyl isonitrile*	*Product (yield)*
	L-Alanine		 **443** (67%) EE > 99%
	L-Serine		 **444** (74%) EE > 99% ee
	L-Phenylalanine		 **445** (79%) EE > 99%
	β-Alanine		 **446** (67%)



SCHEME 148

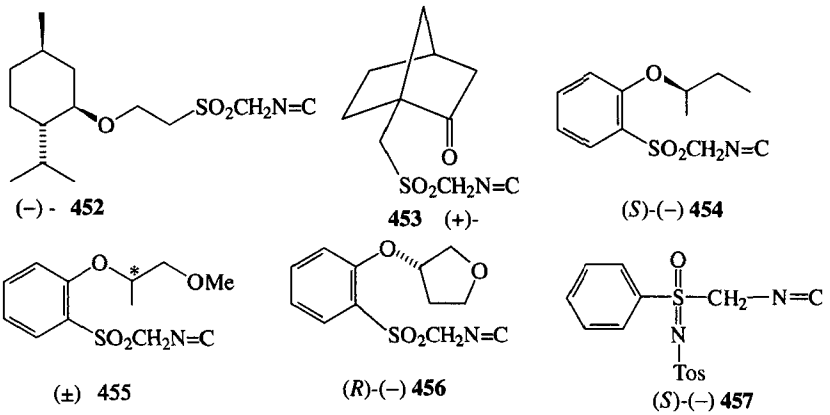


FIGURE 2

TABLE XIX

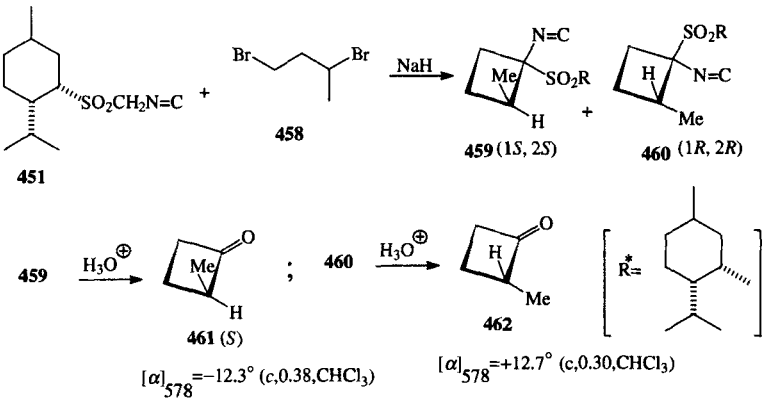
Chiral alcohol used as precursor	*Chiral isocyanide*	*Specific rotation* (deg)	*EE* (%)	*Absolute configuration*	*Literature reference*
(−)-Menthol	**452**	$[\alpha]_{578}^{20} = 51.6$ (*c*, 2.0,$CHCl_3$)	100	–	[127,128]
(+)-(10)-Camphor sulfonic acid	**453**	–		–	[127,128]
(*R*)-(+)-Sec-butanol	**454**	$[\alpha]_D^{20} = -35.3$ (*c*, 1.16, $CHCl_3$)	50	(*S*)	[127,128]
(+) 1-Methoxy-2-Propanol	**455**	–	–	–	[127,128]
(*S*)+3-hydroxy-tetrahydrofuran	**456**	$[\alpha]_D^{20} = -40.8$ (*c*, 2.0, $CHCl_3$)	47	(*R*)	[127,128]
–	**457**	$[\alpha]_D^{20} = +19.4$ (*c*, 1.4, $CHCl_3$)	34	(*S*)	[128–130]

The (+)-neomenthane thiol **449** was converted into **451** by well-known procedures described earlier for the preparation of TosMIC by Van Leusen and co-workers [6]. The structure of six other chiral TosMIC analogs **452–457** synthesized are given in Figure 2 [127]. The characteristic data for these chiral isocyanides **452–457** are given in Table XIX [127].

5.3. Application of Chiral TosMIC Analogs

5.3.1. Synthesis of (R)-(+)-2-methylcyclobutanone and (S)-(−)-2-methylcyclobutanone

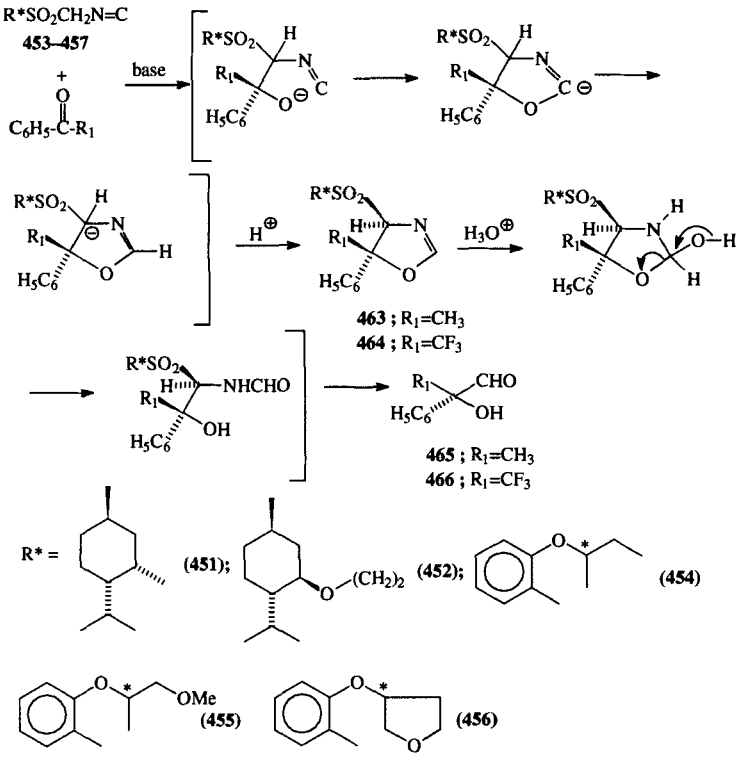
Reaction of NesMIC **451** with racemic 1,3-dibromobutane **458** leads to a 1 : 1 mixture of only two diastereomeric cyclobutane derivatives **459** and **460**. Hydrolysis of a mixture of **459** and **460** with sulfolane in H_2SO_4–water gave a mixture of diastereomers **461** and **462**. Separation of the diastereomers **459** and **460** was achieved by analytical high pressure liquid chromatography. Pure **459** on hydrolysis gave pure **461** whereas **460** gave the pure enantiomer **462** (Scheme 149) [126].



SCHEME 149

5.3.2 Synthesis of Optically Active α-Hydroxy Aldehydes

Seven chiral TosMIC analogs **451–457** were compared for their propensities in asymmetric induction by their reactions with acetophenone and trifluoroacetophenone. Intermediate 2-oxazolines **463** and **464** on hydrolysis gave optically active α-hydroxy aldehydes **465** and **466** (Scheme 150) [128]. The optical purity of the α-hydroxyaldehydes **465** and **466** and diastereomeric excess (DE) in 2-oxazolines **463** and **464** as a result of asymmetric induction are described in Tables XX and XXI [128].

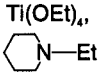
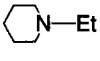


SCHEME 150

TABLE XX Reaction of chiral isocyanides **451**, **452–457** with acetophenone to give diastereomeric oxazolines **463** and hydrolysis to (*R*)-2-hydroxy-2-phenylpropanol **466** as shown in Scheme 150

Isocyanide	*EE* (%)	*Conditions*	*Oxazoline* **463** *DE* (%)	*α-Hydroxyaldehyde*	
				$[\alpha]^{20}$	*EE* (%)
451	90	PTC, benzene	18	−40.3	16
452	100	PTC, benzene	33	−80.2	31
454	50	I.I. equiv. BuLi, THF	40	−37.7	15
454	Racemic	2.2 equiv. BuLi, THF	15		
454	Racemic	PTC, benzene	40		
455	Racemic	PTC, benzene	17		
455	Racemic	2.2 equiv. BuLi,THF	33		
455	Racemic	PTC, toluene	17		
455	Racemic	PTC, toluene	20		
456	Racemic	PTC, benzene	7		
456	Racemic	PTC, toluene	20		
456	Racemic	1.1 equiv. BuLi,THF	40		
456	Racemic	MeMgI, Et_2O–THF	19		
456	47	1.1 equiv. BuLi,THF	38	−46.1	18

TABLE XXI Reaction of chiral isocyanides **451**, **456** and **457** with α,α,α-trifluoroacetophenone to oxazolines **464** according to Scheme 150

Isocyanide	*EE* (%)	*Conditions*	*Oxazolines* **464**	
			^1H *NMR DE* (%)	^{19}F *NMR DE* (%)
451	90	$Ti(OEt)_4$, $Ti(OEt)_4$, 	18	18
451	90	Triton B,THF	18	18
456	47	$Ti(OEt)_4$, $Ti(OEt)_4$, 	41	45
457	Racemic	$Ti(OEt)_4$, $Ti(OEt)_4$, 	80	80
457	Racemic	Triton B,THF	80	80
457	34	Triton B,THF	80	80

6. CONCLUSIONS

Although four brief reviews [1,51,85,131] on TosMIC have appeared prior to the last recent review published in *Organic Reactions* in 2001 [23], pioneering work by A.M. Van Leusen showed the versatility of TosMIC as a powerful synthon. Numerous workers have since sought to evaluate the potential of TosMIC in a wide variety of reactions for the preparation of heterocycles, complex natural products, drug intermediates and intermediates used in pharmacologically active compounds.

However, none of the review covers the literature on TosMIC from 1996 to 2001. This review specifically describes the extensive work carried out on TosMIC from 1996 to 2001. The emphasis is on reviewing the work carried out in the area of

medicinal chemistry during the past six years and the application of TosMIC and chiral TosMIC analogs in the synthesis of optically active compounds.

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