J. Indian Inst. Sci., July–Aug. 2001, **81**, 431–452

Progress in the chemistry of heteroisobenzofurans†

SANKAR BASAK, SUNIL K. GHOSH AND TARUN K. SARKAR*
Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India.
email: tksr@chem.iitkgp.ernet.in; Phone: 91-3222-873330; Fax: 91-3222-755303

Received on December 19, 2000.

Abstract

Recent trend in the chemistry of heteroisobenzofurans such as furo[3,4-*b*]furans, furo[3,4-*b*]indoles, furo[3-4-*c*] pyridines including their methods of generation, trapping of these species as partners in [4+2] cycloaddition, and their applications in the synthesis of some natural and non-natural products of biological significance is reviewed.

Keywords: Heteroisobenzofuran, Diels–Alder reaction, ellipticine, heterolignan, constrained anabasine, murrayaquinone A, thiamarmelerin and thiafarfugin A.

1. Introduction

Isobenzofurans, represented by the parent benzo[*c*]furan (**1**), have long been recognized as an interesting class of reactive intermediates in organic synthesis. Several excellent reviews on the chemistry of these species have been published.[1–10] As highly reactive *o*-quinodimethanes, they can participate in both inter- and intramolecular cycloaddition reactions. Suitably substituted isobenzofurans have served as useful intermediates for the synthesis of natural products such as resistomycin[11] and anthracyclinones,[12] inner-functionalized cavity molecules,[13,14] steroid analogues,[15] oxasteroid analogues,[16] azasteroid analogues,[17] polycyclic nitrogen heterocycles[18–20] and others.[21–24]

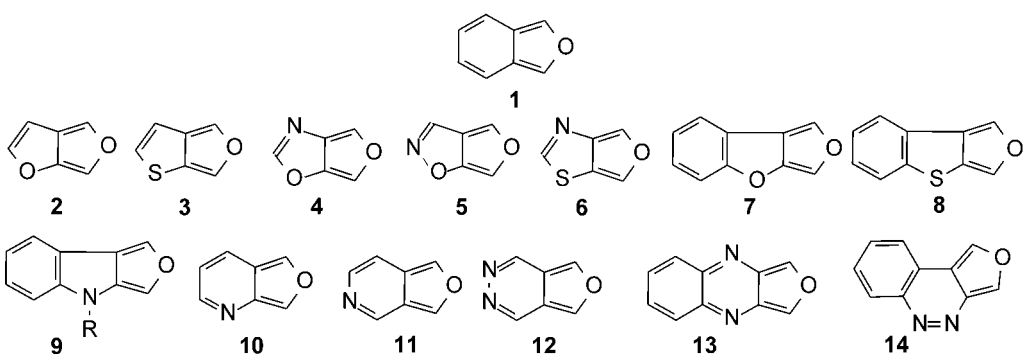


Fig.1. Parent members of known heteroaromatic isobenzofurans.

In contrast, heteroanalogues of isobenzofuran have received much less attention, although this situation is rapidly changing in recent years. The heteroaromatic isobenzofurans reported so far include furo[3,4-*b*]furan (**2**), thieno[2,3-*c*]furan (**3**), furo[3,4-*d*]oxazole (**4**), furo[3,4-*d*]isooxazole

† Dedicated to Prof. S. C. Bhattacharyya.
* Author for correspondence.

(**5**), furo[3,4-*d*]thiazole (**6**), furo[3,4-*b*]benzofuran (**7**), benzo[4,5]thieno[2,3-*c*]furan (**8**), furo[3,4-*b*]indole (**9**), furo[3,4-*b*]pyridine (**10**), furo[3,4-*c*]pyridine (**11**), furo[3,4-*d*]pyridazine (**12**), furo[3,4-*d*]quinoxaline (**13**) and furo[3,4-*c*]cinnoline (**14**)-based systems (Fig. 1). It seems that heteroisobenzofurans should have wider applicability since they can provide an attractive route to polycyclic heteroaromatics of biological interest. In this article, we will focus on the chemistry of heteroaromatic isobenzofurans including their methods of generation, reactivity profile as well as their applications in natural and non-natural product synthesis. This review is essentially comprehensive with the exception that early reports on **12**,[25–32] **13**[33] and **14**[34–37] have been left out from the purview of our discussion.

2. Generation of heteroaromatic isobenzofurans

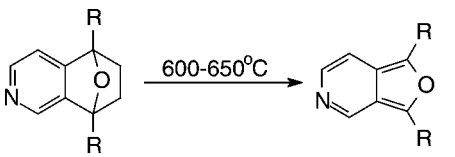
The parent members of most heteroaromatic isobenzofurans as pictured in Fig. 1 are as yet unknown except **11**[38] and **12**.[28] However, stable derivatives of a number of heteroisobenzofurans have been made. The choice of a particular synthetic method for the preparation of a heteroaromatic isobenzofuran not only depends on the availability of the starting materials and the overall yields of the process, but also on the ease with which the method can be carried out. The currently available methods for the generation of heteroaromatic isobenzofurans are discussed hereinunder.

2.1. *By thermolysis*

Heteroaromatic isobenzofurans can be generated by flash vacuum thermolysis (FVT) of suitable substrates.[38–43] This process requires very high temperatures usually in the range of 450–650°C. In general, two variations of this method have been reported in the literature, one using thermolysis of 1,4-epoxides, the other involving epoxyhexynes.

2.1.1. *From 1,4-epoxides*

The generation of the parent furo[3,4-*c*]pyridine (**16**, R = H) by FVT of 5,8-epoxy-5,6,7,8-tetrahydroisoquinoline (**15**, R = H) and its reactivity in a Diels–Alder reaction was first reported by Wiersum *et al.* (Scheme 1).[38] These authors isolated it as a white crystalline material, stable only at low temperature, but undergoing rapid polymerization at about room temperature. Structural assignments for **16** (R = H) came from its ^{1}H NMR as well as trapping experiments with maleic anhydride or *N*-phenylmaleimide. An application of Wiersum's FVT technique is found in a synthesis of the dimethyl analogue of **16** (R = Me).[39]



15 **16** (R = H, Me)

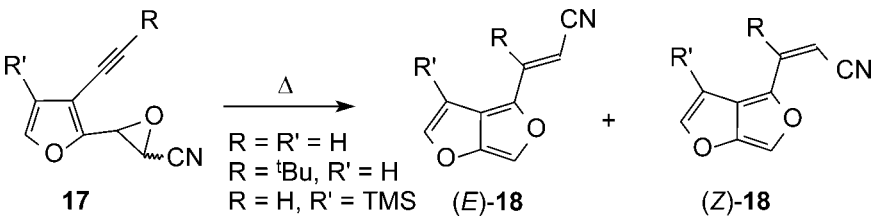
Scheme 1. Generation of furo[3,4-*c*]pyridines.[38,39]

2.1.2. *From epoxyhexynes*

A number of heteroaromatic isobenzofurans are available by FVT or short-time thermal treatment of epoxyhexynes.[40–42] For example, furan-based epoxyhexyne **(17)** under short-time thermolysis

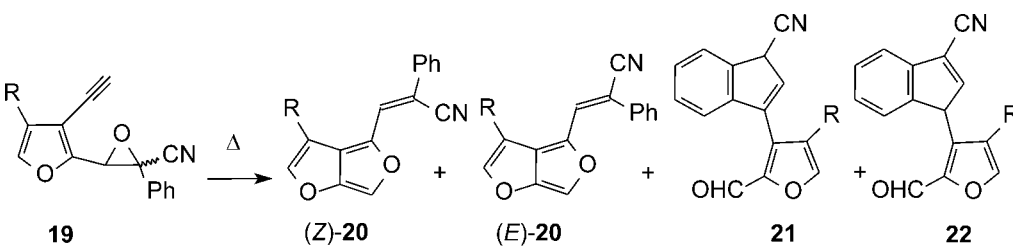
or FVT conditions (STT: 350°C, ca 10s; FVT: 450°C, ca 10^{-6} torr) gives an isomeric mixture of furo[3,4-*b*]furans (*E*)- and (*Z*)-**18** (Scheme 2).[40, 41] *E*-**18** ($R^1 = R^2 = H$ or $R^1 = H$, $R^2 = TMS$) exists as a stable yellow crystalline material.

However, thermolysis of phenylcyano-substituted epoxyhexynes **(19)** gives furylindenes **21** and **22** in addition to furo[3,4-*b*]furans (*E*)- and (*Z*)-**20** Table I. [41]



Scheme 2. Generation of furo[3,4-*b*]furans.[40, 41]

Table I
Product distribution in the thermolysis of phenylcyano-substituted epoxyhexynes



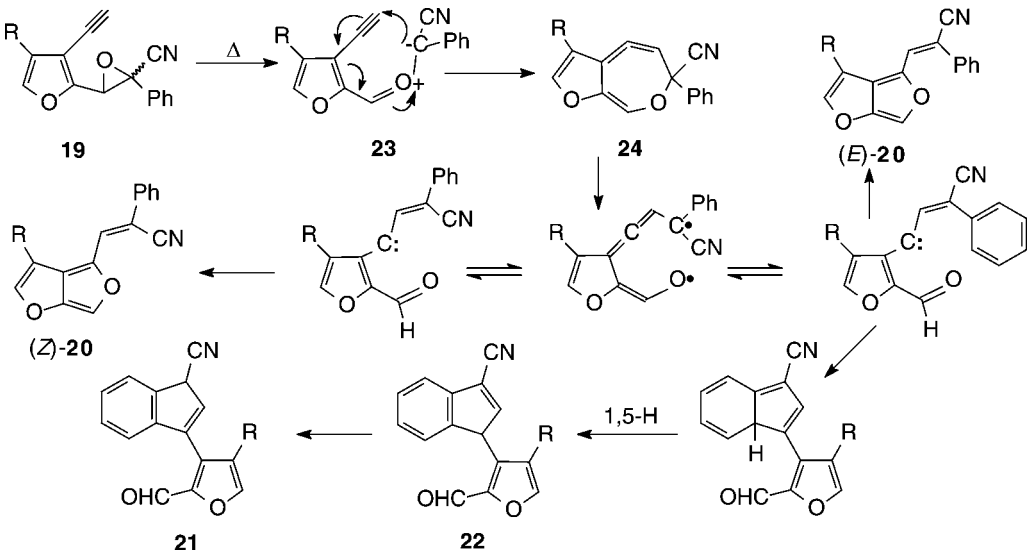
ratio of the products	R = H	22 : 0 : 30 : 22
	R = TMS	28 : 3 : 48 : 0

These reactions presumably proceed via a 1,7-dipolar cyclization of carbonyl ylide **23** to cycloallene derivative **24**, the latter subsequently rearranging to furo[3,4-*b*]furans via a pathway involving carbene intermediates (Scheme 3).[41]

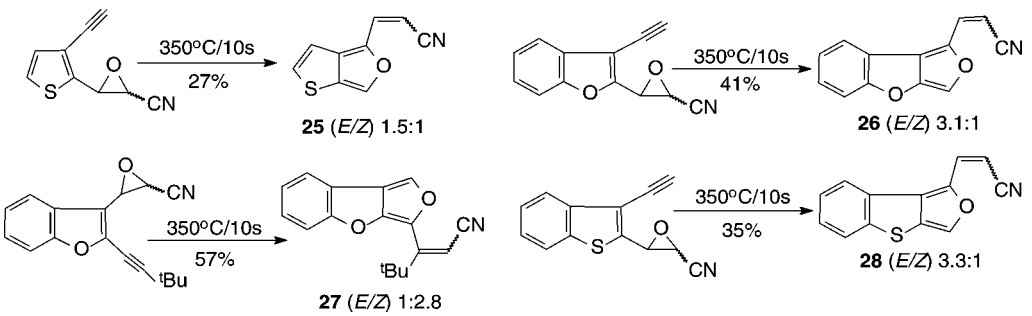
This short-time thermolysis method is equally useful for the synthesis of thieno[2,3-*c*]furans, furo[3,4-*b*]benzofurans as well as benzo[4,5]thieno[2,3-*c*]furans, e.g. the formation of **25**, **26**, **27** and **28** (Scheme 4).[41,42]

2.2. *By acid-catalyzed cyclization*

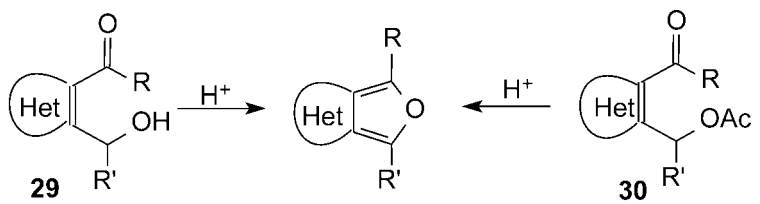
Another strategy for the generation of heteroaromatic isobenzofurans involves acidic treatment of suitable hydroxy-carbonyl or acetoxy-carbonyl compounds as represented by the structural motifs **29** or **30** (Scheme 5).[44–54] This method has been extensively used in the synthesis of ellipticine,[45, 48] isoellipticine[45] as well as hetero analogues of 1-arylnaphthalene lignans.[54] Although this method works well for **29** or **30**, the acidic treatment of the corresponding hydroxy-acetal precursors provides the desired products in very low yields.[54]



Scheme 3. Mechanistic rationale.[41]



Scheme 4. Synthesis of thienofurans, furobenzofurans and benzothienofurans.[41, 42]



Scheme 5. Heteroaromatic isobenzofurans by acid-catalyzed cyclization.[44–54]

2.2.1. *From hydroxy-carbonyl precursors*

Acid-catalyzed cyclization of hydroxy-carbonyl precursors provides a direct route to heteroaromatic isobenzofurans.[44–52] Gribble's group has established the utility of this method for the preparation of several furo[3,4-*b*]indoles **31**–**37** (Fig. 2).[44, 45, 48]

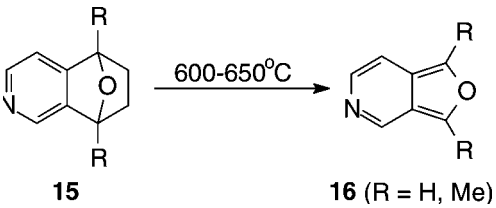
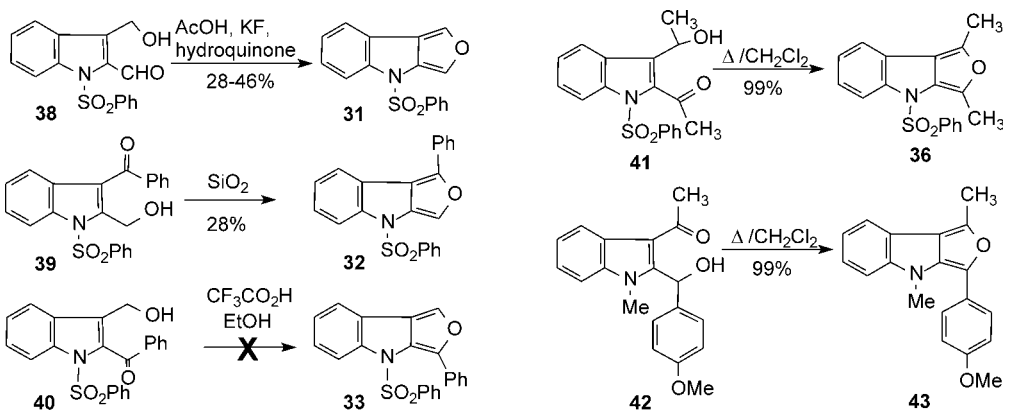


FIG. 2. Several examples of furo[3,4-*b*]indole derivatives.

The synthesis of the parent compound **31** has proven to be the most difficult in this series.[48] Nonetheless, it has been achieved by the treatment of hydroxy-carbonyl precursor **38** with potassium fluoride/hydroquinone/acetic acid in 28–46% yield (Scheme 6). In some cases, especially for hydroxy-carbonyl precursor **39**, the cyclization leading to furo[3,4-*b*]indole **(32)** was facilitated even during chromatographic purification of the crude product over silica gel. In contrast, cyclization of regioisomeric hydroxy-ketone **40** to **33** under a variety of conditions, such as CF_3CO_2H, HCl, etc. proved unsuccessful. However, the facile cyclization of **41**, even without acidic treatment, to dimethyl analogue **36** is noteworthy. This may be a consequence of the well-known Thorpe–Ingold Effect wherein cyclization is both kinetically as well as thermodynamically favoured by alkyl substitution in the open-chain substrate.

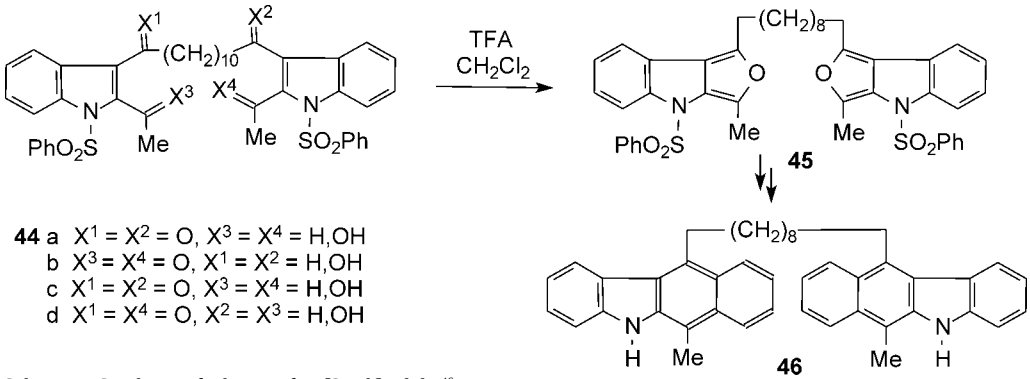


Scheme 6. Synthesis of 4H-furo[3,4-*b*]indoles from hydroxy-carbonyl compounds[44, 45, 48, 49]

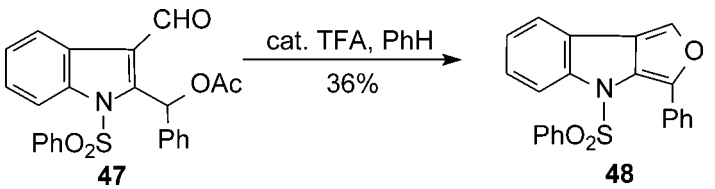
Related work by Shiue and Fang has also resulted in the synthesis of furo[3,4-*b*]indoles, e.g. the formation of **43**.[49–51] In this work, a number of precursors including **42** were prepared by a novel SmI_2-promoted hydroxyalkylation of indolo-3-carbonyl compounds. The same synthetic concept has been applied on **44** for the generation of a *bis*-4H-furo[3,4-*b*]indole **(45)**, a useful precursor in the synthesis of a DNA *bis*-intercalating agent **(46)** (Scheme 7).[46]

2.2.2. *From acetoxy-carbonyl precursors*

Acetoxy-carbonyl precursors can serve as an alternative source of heteroaromatic isobenzofurans. Iwasaki and coworkers reported the synthesis of furo[3,4-*b*]indoles by acidic treatment of the corresponding acetoxy-carbonyl precursors.[53, 54] Thus, treatment of acetoxy-aldehyde **(47)** with a catalytic amount of trifluoroacetic acid (TFA) in refluxing benzene gives **48** in 36% yield (Scheme 8).



Scheme 7. Synthesis of a bis-4H-furo[3,4-*b*]indole.[46]

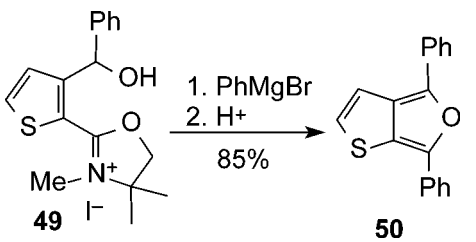


Scheme 8. Synthesis of a furo[3,4-*b*]indole from an acetoxy-carbonyl precursor.[53, 54]

Various other heteroaromatic acetoxy-aldehydes such as 2-(α-acetoxy-3,4-dimethoxybenzyl) pyridine-3-carbaldehyde, etc. are amenable to this protocol. However, in these cases the respective heteroisobenzofurans are formed only as transient species (see Section 4.4).

2.3. *By Grignard reagent-promoted cyclization*

A less-common but nevertheless a convenient procedure for the generation of heteroaromatic isobenzofurans involves Grignard reagent-mediated cyclization of a suitable precursor. In 1986, Friedrichsen and Schöning developed this methodology for the first time to synthesize thieno[2,3-*c*]furans.[55, 56] Thus, treatment of thienyl-2-oxazolinium iodide **(49)** with phenylmagnesium bromide followed by an acidic work-up yields thieno[2,3-*c*]furan **(50)** as tiny yellow needles in 85% yield (Scheme 9).

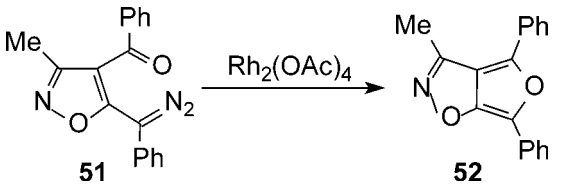


Scheme 9. Synthesis of 1,3-diphenylthieno[2,3-*c*]furan[55, 56]

2.4. *By Hamaguchi–Ibata reaction*

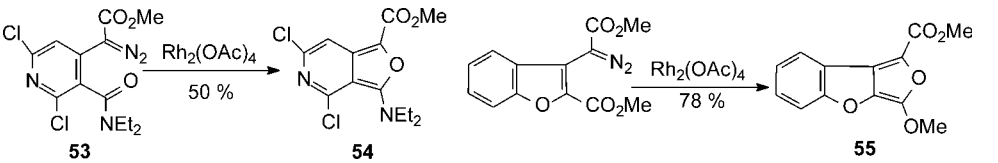
The Hamaguchi–Ibata reaction of *o*-amidodiazocarbonyl precursors has recently become a method of choice for the generation of heteroaromatic isobenzofurans.[57–69] This facile synthesis proceeds

by transition metal-catalyzed decomposition of *o*-amidodiazocarbonyl precursors and subsequent trapping of the resultant carbenoid intermediates by the adjacent carbonyl group. This approach seems to be of wide applicability and many functional groups are unaffected under reaction conditions. In 1986, Chen and Beak first applied this methodology for the transient generation of 1-amino-6-azaisobenzofuran.[57] In a related sequence, several furoisoxazoles have also been generated by Friedrichsen and coworkers.[58–61] For example, rhodium(II) acetate [$Rh_2(OAc)_4$]-catalyzed decomposition of **51** gives furoisoxazole **52** (Scheme 10).[60] Suitability of this protocol for the generation of furo[3,4-*b*]indole,[62, 63] furo[3,4-*d*]thiazoles[64, 65] as well as furo[3,4-*b*]-oxazoles[65,66] is of interest.



Scheme 10. Synthesis of a furo[3,4-*d*]isoxazole by Hamaguchi–Ibata reaction.[60]

Recently, we have also been able to prepare the first highly stable furo[3,4-*c*]pyridine by a Hamaguchi–Ibata reaction. Thus, exposure of substituted diazoacetic ester (**53**) to 1 mol% $Rh_2(OAc)_4$ in CH_2Cl_2 at rt for 1 h yields azaisobenzofuran (**54**) in 50% yield (Scheme 11).[67, 68] Another recent report on the synthesis of furo[3,4-*b*]benzofurans, such as **55** by a Hamaguchi–Ibata reaction is also noteworthy.[69]

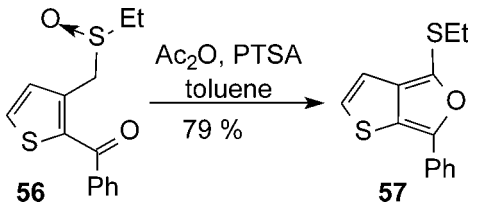


Scheme 11. Applications of Hamaguchi–Ibata reaction.[67–69]

2.5. *Via the Pummerer reaction*

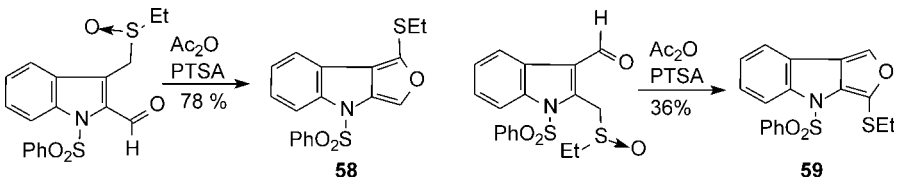
Pummerer reaction of heteroaromatic *o*-ketosulfoxides represents a promising synthetic tool for the synthesis of heteroisobenzofurans. This strategy developed recently by Kappe and Padwa[70] entails the generation of an α-thiocarbocation and its interception by a neighbouring carbonyl group to give thio-substituted heteroaromatic isobenzofurans.[70] Thus, exposure of thiophene-derived ketosulfoxide **(56)** to the classical Pummerer conditions, i.e. refluxing acetic anhydride gives a mixture of products containing 23% of the desired thienofuran **57** (Scheme 12). However, best results were obtained by employing a mixture of acetic anhydride, a catalytic amount of *p*-toluenesulfonic acid (PTSA) in refluxing toluene.

This possibility of generating heteroaromatic isobenzofurans has also been exploited in the synthesis of two regioisomeric furo[3,4-*c*]indoles **(58** and **59)** (Scheme 13).[70] Furo[3,4-*c*]indole **(58)**, which is not as stable as the thienofuran **(57)**, can be obtained in a high state of purity by rapid work-up and chromatographic purification of the reaction mixture. But if kept at room temperature for several days, significant decomposition is observed. Incidentally, the generation



Scheme 12. Thieno[2,3-*c*]furan via the Pummerer reaction.[70]

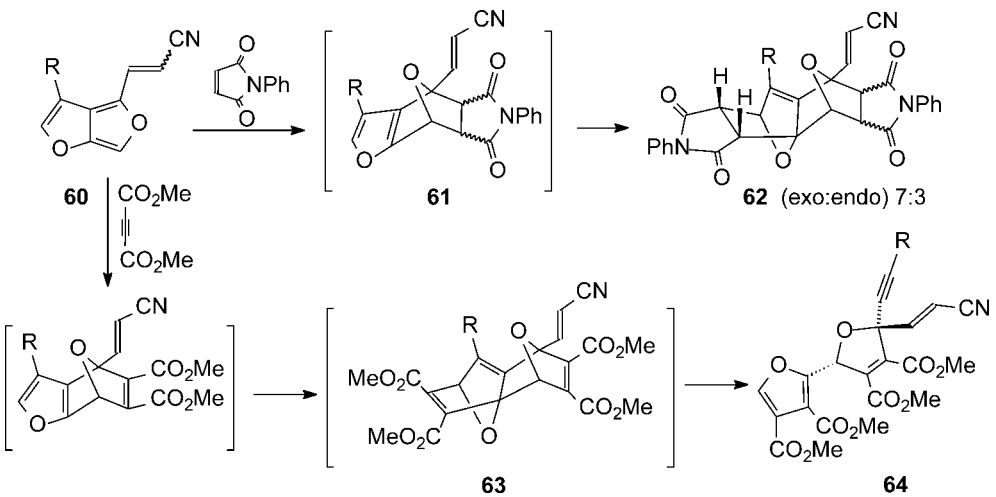
of furo[3,4-*c*]indole **(59)** is found to be less efficient than that of the regioisomeric furoindole **(58)**, the likely reason being steric crowding in **59**.



Scheme 13. Furo[3,4-*c*]indoles via the Pummerer reaction.[70]

3. Reactivity profile

The synthetic utility of heteroaromatic isobenzofurans stems from their ability to undergo Diels–Alder reactions with dienophiles. The nature of heteroaromatic isobenzofurans and dienophile partners plays a vital role in the cycloaddition reactions. In general, the two components should have complementary electronic character. Thus, the ease of cycloaddition with an unactivated dienophile depends particularly on the reactivity of the heteroaromatic isobenzofuran itself. In order to gain some insight into the reactivity of heteroaromatic isobenzofurans, some theoretical investigations on the transition state of Diels–Alder reactions have been carried out by Friedrichsen *et al.* In this section, Diels–Alder reactions of various heteroisobenzofurans are presented.



Scheme 14. Cycloaddition reactions of substituted furo[3,4-*b*]furans.[40, 41]

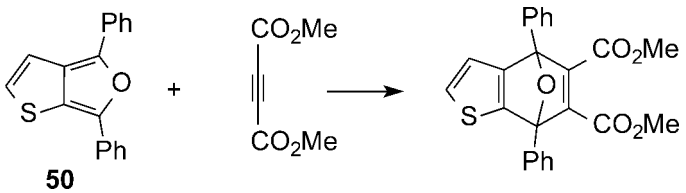
3.1. *Furo[3,4-b]furans*

The utility of furo[3,4-*b*]furans in synthesis is evident from their Diels–Alder reactivity. In 1988, Eberbach *et al*.[40, 41] prepared the first substituted furo[3,4-*b*]furans and found the systems to be sufficiently reactive to participate in [4+2]-cycloaddition reactions. For example, in the reaction of furo[3,4-*b*]furan **(60)** (R = TMS) with *N*-phenylmaleimide, only the 1:2 addition compound **62** (R = TMS) is formed via the corresponding 1:1 adduct **61** (R = TMS) (Scheme 14).[40, 41]

However, the adduct **63** (R = TMS) obtained from the Diels–Alder reaction of furo[3,4-*b*]furans **(60)** (R = TMS) and dimethyl acetylenedicarboxylate is not stable under the reaction conditions and undergoes a Diels–Alder reversion to give the furylbistetrahydrofuran derivative **(64)** (R = TMS) in 70% yield.[40, 41] Interestingly, the corresponding bisadduct **63** (R = H) from a similar reaction of **60** (R = H) is found to be somewhat more stable, though the overall reaction is less clean.

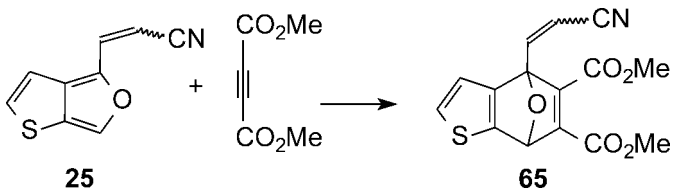
3.2. *Thieno[2,3-c]furans*

Thieno[2,3-*c*]furans have been shown to be useful dienes in Diels–Alder reactions. Friedrichsen and Schöning have observed that 4,6-diphenylthieno[2,3-*c*]furan **(50)** and dimethyl acetylenedicarboxylate undergo a [4+2] cycloaddition reaction at a rate comparable with the corresponding diphenyl substituted isobenzofuran (Scheme 15).[55] But when thienofuran **(50)** is treated with unsymmetrical dienophiles such as methyl acrylate, no regioselectivity is observed.[70]



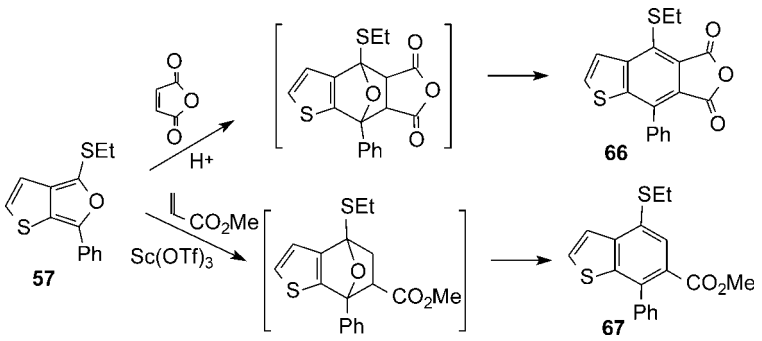
Scheme 15. Diels–Alder reaction of 4,6-diphenylthieno[2,3-*c*]furan.[55]

Eberbach *et al.*[41] have found that cyanovinyl-substituted thienofurans may participate in a [4+2] cycloaddition reaction, e.g. the formation of **65** (Scheme 16).



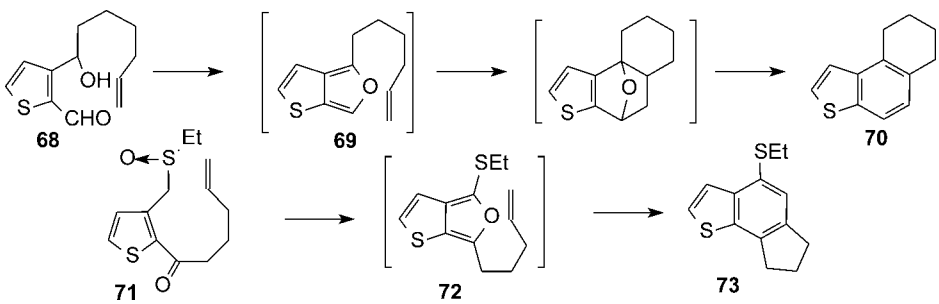
Scheme 16. Trapping of a cyanovinyl substituted-thienofuran.[41]

In recent studies, Kappe and Padwa[70] trapped thio-substituted thienofurans with dienophiles such as maleic anhydride or N-phenylmaleimide in the presence of *p*-toluenesulfonic acid, e.g. the formation of 66 (Scheme 17).[70] With the somewhat less reactive methyl acrylate ethylthio-substituted thienofuran (**57**) gives a single regioisomer **67** in the presence of $Sc(OTf)_3$. The use of $Sc(OTf)_3$ is not mandatory here, although its presence improves the yield.



Scheme 17. Reactivity profile of ethylthio-substituted thienofuran.[70]

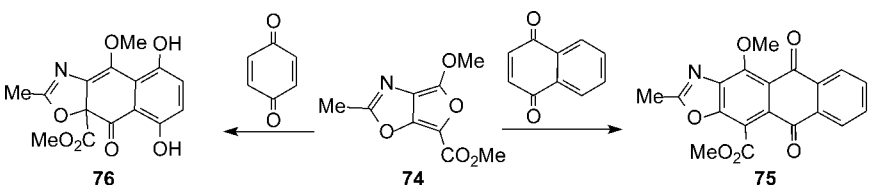
Schöning and Friedrichsen have described the *in-situ* generation of thieno[2,3-*c*]furans by the acid-catalyzed cyclization protocol.[52, 71, 72] When hydroxy-carbonyl precursor **68** is treated with 2% acetic acid in refluxing toluene, tricyclic product **70** is formed via *in-situ* generation of thieno[2,3-*c*]furan **(69)** and subsequent intramolecular cycloaddition followed by ring-opening and dehydration (Scheme 18).[52] Thienofuran **72** with a built-in olefinic tether, and generated as a transient intermediate from **71** by a Pummerer reaction, undergoes an intramolecular Diels–Alder reaction followed by ring-opening–dehydration to give the tricyclic product **73**.[70]



Scheme 18. Intramolecular trapping of transient thieno[2,3-*c*]furans.[52,70]

3.3. *Furo[3,4-d]oxazoles*

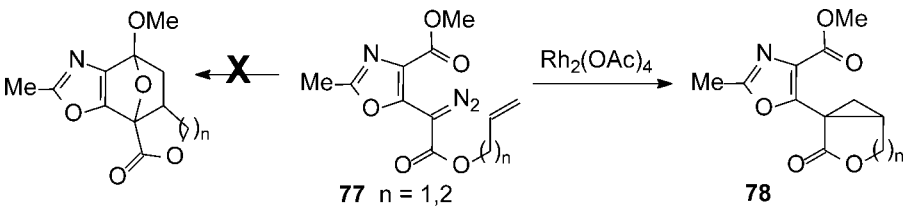
Density functional theoretical (DFT) studies show that the furo[3,4-*d*]oxazole (**4**) is less reactive in Diels–Alder reactions as compared to isobenzofuran **1**.[66] Interestingly, 1-alkoxy-3-alkoxycarbonyl-substituted furo[3,4-*d*]oxazoles are less reactive than their unsubstituted counterparts. Despite low reactivity, furo[3,4-*d*]oxazole reacts with typical dienophiles such as *N*-phenylmaleimide and 1,4-naphthoquinone, e. g. the formation of **75**[66] (Scheme 19). Thus, furo[3,4-



Scheme 19. Furooxazoles in intermolecular Diels–Alder reaction.[66]

d]oxazoles offer a convenient route to a variety of annulated benzoxazoles. Incidentally, exposure of **74** to *p*-benzoquinone takes an interesting course leading to **76**.[66]

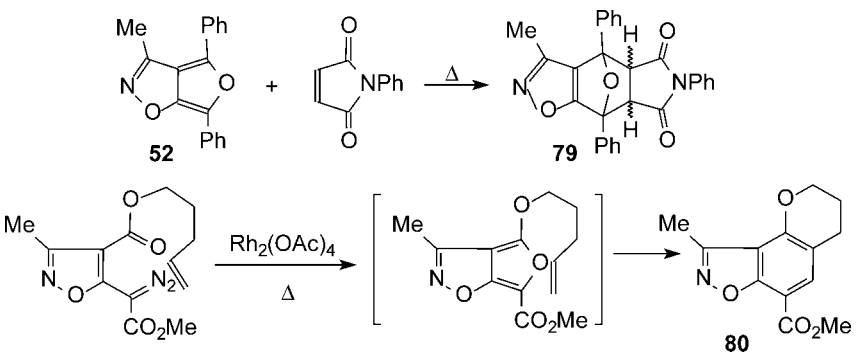
In order to explore the synthetic utility of furo[3,4-*d*]oxazoles in intramolecular cycloaddition with unactivated dienophiles, Reck and Friedrichsen[66] subjected **77** to metal-catalyzed decomposition using rhodium(II) acetate (Scheme 20).[66] However, this reaction yielded only some cyclopropane derivatives **78** in low yield indicating that these substrates are not reactive enough to undergo intramolecular cycloaddition reaction with an unactivated olefin.



Scheme 20. Intramolecular cycloaddition of furo[3,4-*d*]oxazoles.[66]

3.4. *Furo[2,3-d]isoxazoles*

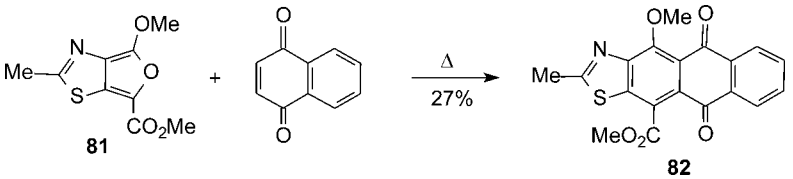
From a theoretical point of view, relative reactivity studies predict that the parent furo[2,3-*d*]-isoxazole is the most reactive heteroaromatic isobenzofuran when compared to furo[3,4-*d*]- oxazole, furo[3,4-*d*]thiazole or furo[3,4-*b*]indole.[66] Thus, Friedrichsen and coworkers [58, 59] showed that substituted furo[3,4-*d*]isoxazoles can take part both in inter- and intramolecular cycloaddition reactions, e. g. the formation of **79** and **80** (Scheme 21).



Scheme 21. Furo[3,4-*d*]isoxazoles in inter- and intramolecular cycloaddition reactions.[58,59]

3.5. *Furo[3,4-d]thiazoles*

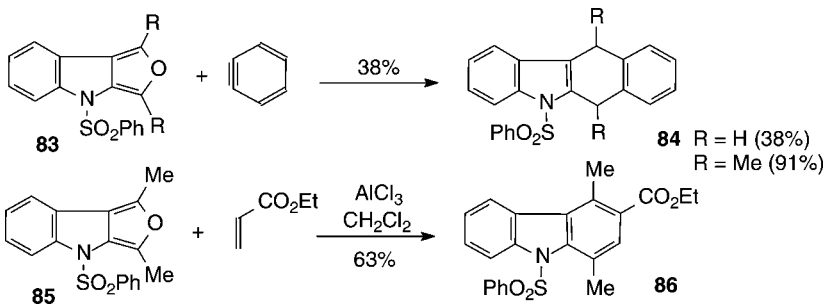
Computational studies on furo[3,4-*d*]thiazole indicate that this system is entirely planar and less reactive than isobenzofuran itself.[64] Substituted furo[3,4-*d*]thiazoles like furo[3,4-*d*]oxazoles have been shown to undergo Diels–Alder reactions with dienophiles, though they have been investigated much less. For example, the cycloaddition reaction of **81** with 1,4-naphthoquinone gives yellow needles of **82** in a moderate yield (Scheme 22).[64]



Scheme 22. Diels–Alder reactivity of a furo[3,4-*d*]thiazole.[64]

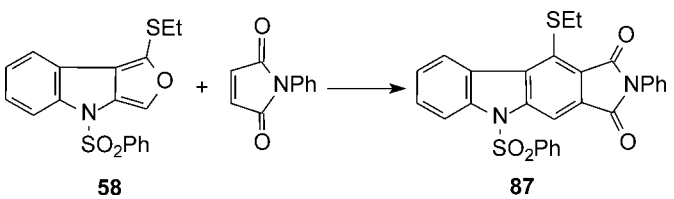
3.6. *Furo[3,4-b]indoles*

1-(Phenylsulfonyl)-4*H*-furo[3,4-*b*]indoles, e. g. **83** (R = H, Me) behave as reactive dienes in Diels–Alder reactions.[44–48, 70] Theoretical investigation suggests that the reactivity of the parent furo[3,4-*b*]indole is lower than that of isobenzofuran and furo[3,4-*d*]isoxazole.[66] With highly reactive dienophiles such as benzyne, generated from 2-fluorobromobenzene and magnesium, furoindole **83** (R = H) gives 5*H*-benzo[*b*]carbazole **84** (R = H), albeit in a poor yield (Scheme 23).[44, 48] Gribble and coworkers[44, 45, 48] explained that the low yield in this reaction is due to competing exchange metallation at C-3 (or C-1) because a similar reaction with 1,3-dimethylfuroindole **83** (R=Me) proceeds with excellent yield. Reaction of furoindoles with an unsymmetrical dienophile can, in principle, gives two regioisomeric adducts. Theoretical studies indicate that in the HOMO of **85**, C-3, has a higher coefficient than at C-1. If this result is matched with the coefficients for the LUMO of α,β-unsaturated carbonyl compounds like methyl acrylate, one can predict which regioisomer should form. Thus, treatment of furoindoles such as **85** with methyl acrylate in the presence of $AlCl_3$ gives a single isomer **86**.[48]



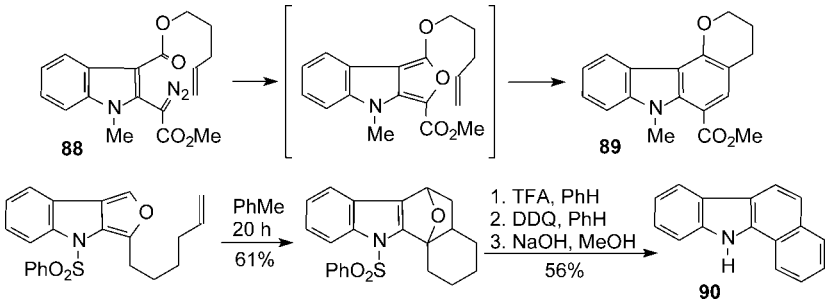
Scheme 23. Furoindoles in intermolecular Diels–Alder reaction.[44, 45, 48]

Kappe and Padwa[70] have also studied the Diels–Alder reactivity of some thio-substituted furoindoles. For example, a synthesis of pyrrolocarbazole **87** was achieved by a Diels–Alder reaction of **58** with *N*-phenylmaleimide (Scheme 24).[70]



Scheme 24. Utility of an ethylthio-substituted furoindole.[70]

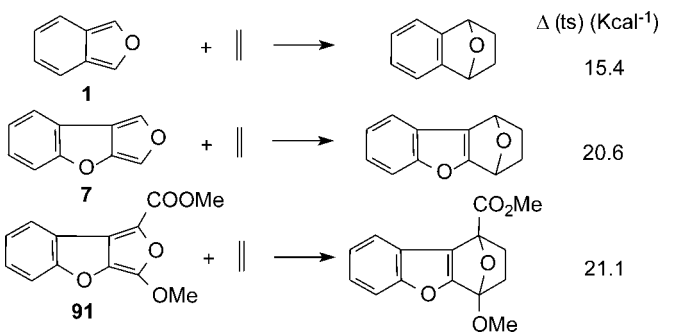
The most pioneering example of the intramolecular cycloaddition chemistry of furoindoles involves the $Cu(acacF_6)_2$-catalyzed decomposition of **88** in refluxing toluene giving pyrano[3,2-*c*]carbazole **89** in 32% yield (Scheme 25).[62] Recently, Gribble *et al.*[73] synthesized benzo[*a*]carbazole and benzo[*c*]carbazole ring systems via the intramolecular Diels–Alder reaction of furoindoles, e. g. the formation of **90**.



Scheme 25. Furoindole in intramolecular cycloaddition reactions.[62, 73]

3.7. *Furo[3,4-b]benzofurans*

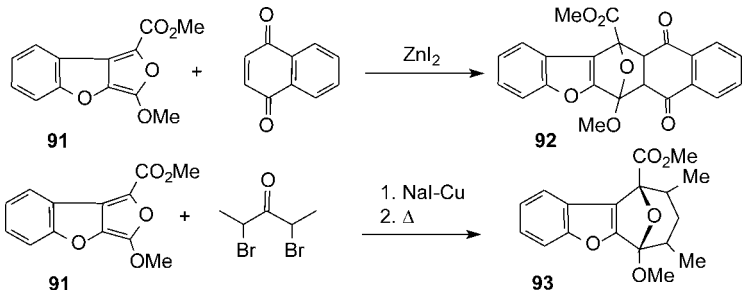
From a theoretical aspect, it has been found that the transition state energies [ΔE(ts)] for the intermolecular Diels–Alder reactions of furo[3,4-*b*]benzofurans **(7** and **91)** are 5–6 kcal mol^{-1} higher than that for isobenzofuran **1** and, therefore, furo[3,4 *b*]benzofurans should be less reactive than the corresponding isobenzofurans (Scheme 26).[69]



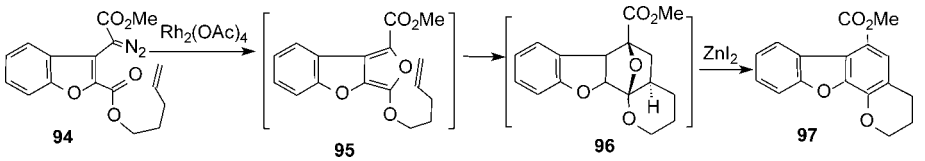
Scheme 26. Theoretical investigation on furo[3,4-*b*]benzofurans.[69]

Although less reactive than isobenzofuran, furo[3,4-*b*]benzofuran **(91)** can undergo Diels–Alder reactions with *N*-phenylmaleimide, 1,4-naphthoquinone and 1,4-benzoquinone in the presence of ZnI_2 as a Lewis acid catalyst, e. g. the formation of **92** (Scheme 27).[69] With oxyallyl species, generated from 2,4-dibromopentanone with NaI-Cu, a [4+3] cycloaddition reaction of **91** is observed and compound **93** is obtained as a mixture of isomers.[69]

From a computational point of view, the intramolecular cycloaddition reaction of **95** is expected to proceed preferably in an exo-fashion because of the higher transition state energy for the formation of the endo adduct than for the corresponding exo adduct.[69] Thus, on treatment of **94** with $Rh_2(OAc)_4$ and subsequently with ZnI_2, dioxabenzo[a]fluorene **(97)** is formed probably via an exo-cycloaddition reaction with subsequent loss of water (Scheme 28).

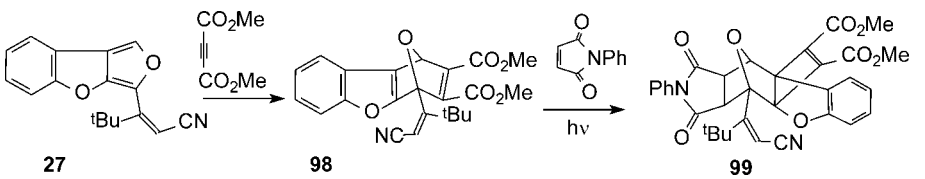


Scheme 27. Substituted furo[3,4-*b*]benzofurans in intermolecular cycloaddition reactions.[69]



Scheme 28. Intramolecular Diels–Alder reaction of a furo[3,4-*b*]benzofuran.[69]

Eberbach and coworkers[42] have also studied the Diels–Alder reactivity of furo[3,4-*c*]-benzofurans and presented an interesting photochemical reaction of benzofuro-annulated oxanorbornadiene **98** (Scheme 29). For example, irradiation of **98** in the presence of *N*-phenyl-maleimide gives the polycyclic compound **99** presumably via [2+2] photocycloaddition, 1,3-dipolar cycloreversion and subsequent endo-selective trapping by *N*-phenylmaleimide.

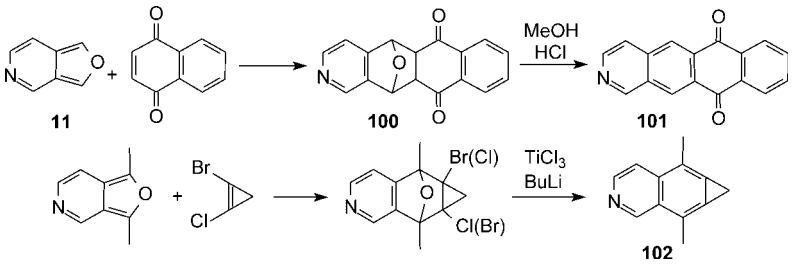


Scheme 29. Photochemical reaction of benzofuro-annulated oxanorbornadiene.[42]

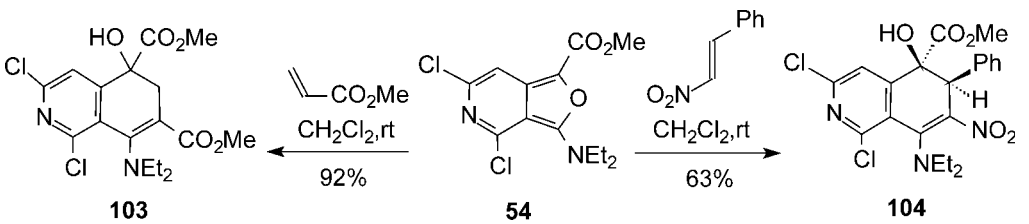
3.8. *Furo[3,4-c]pyridines*

The parent furo[3,4-*c*]pyridine (**11**) shows similar reactivity in Diels–Alder reaction as to open isobenzofuran itself.[74] Wiersum *et al*.[38] first reported the synthetic potential of furo[3,4-*c*]pyridine (**11**) in the synthesis of substituted isoquinolines and polycyclic aza-aromatics. For example, treatment of furopyridine **11** with 1,4-naphthaquinone gives the corresponding adduct **100** which on exposure to methanolic HCl gives **101** as a yellow-orange solid (Scheme 30). Another interesting application of furopyridine is found in a synthesis of 4-aza-2,7-dimethylcyclopropane[*b*]naph-thalene **102**.[39]

Recently, we have found that Diels–Alder reaction of the exceptionally stable azaisobenzofuran **(54)** with unsymmetrical dienophiles such as methyl acrylate, acrylonitrile, *trans* β-nitrostyrene, etc. proceeds with high regio- and stereoselectivity, e. g. the formation of **103** and **104** (Scheme 31).[67, 68] Frontier molecular orbital (FMO) studies have fully corroborated these stereochemical results.[68]

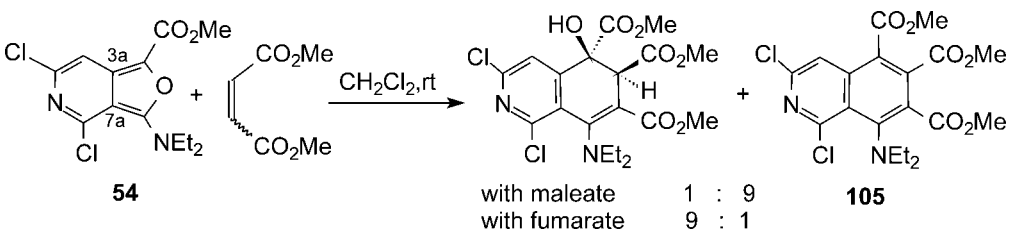


Scheme 30. Furo[3,4-*c*]pyridines in intermolecular Diels–Alder reactions.[38,39]



Scheme 31. Regioselective cycloaddition reactions of a furo[3,4-*c*]pyridine.[68]

However, with dimethyl maleate and fumarate, cycloaddition of furopyridine **54** also gives interesting stereochemical results. For dimethyl maleate, the major endo-adduct simply eliminated a water molecule on standing to give the fully aromatic species **105**, which is the minor product from dimethyl fumarate addition (Scheme 32).[68] (FMO studies indicate that the secondary orbital effect between C_{3a} of **54** and the C(O) of dimethyl fumarate will be stronger than C_{7a} of **54** and the C(O) of dimethyl fumarate.[68] Thus, in the transition state, one of the ester groups of dimethyl fumarate is oriented closer to the diethylamino group of **54**).



Scheme 32. Stereochemical results in the cycloaddition reactions of a furo[3,4-*c*]pyridine.[68]

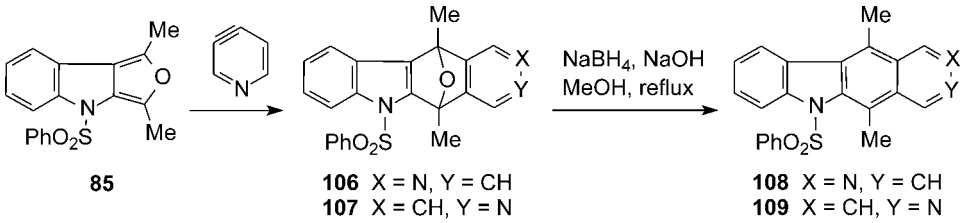
4. Applications of heteroisobenzofurans in natural and non-natural product synthesis

In contrast to isobenzofurans, heteroisobenzofurans have not found much use in the synthesis of natural and non-natural products. However, the limited works published in the literature are summrized in this section.

4.1. *Ellipticine*

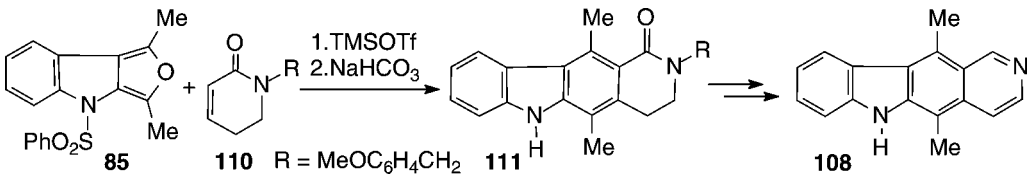
One of the most interesting applications of heteroisobenzofurans is found in a synthesis of the potent anticancer pyridocarbazole alkaloid ellipticine (**108**). In an initial attempt, Gribble *et al.*[45] utilized the cycloaddition of 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**85**) with 3,4-

pyridyne as the key step of synthesis (Scheme 33). However, the adduct was formed essentially as an inseparable 1:1 mixture of two regioisomeric products **106** and **107** in 38% yield; treatment of the mixture with $NaBH_4$/NaOH/MeOH gave ellipticine **108** and isoellipticine **109** in 23% and 29% yield, respectively.



Scheme 33. Synthesis of ellipticine and isoellipticine.[45]

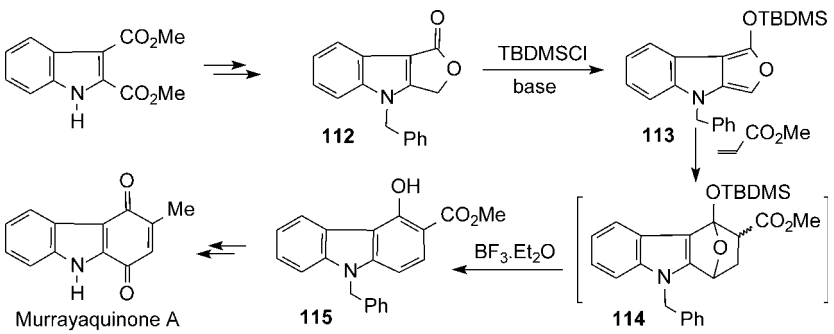
However, the trimethylsilyl trifluoromethanesulfonate-induced reaction of furoindole **85** and dihydropyridone **110** gave lactam **111** regioselectively in 89% yield (Scheme 34).[48] Subsequent reduction of **111** with $LiAlH_4$ and Pd/C-catalyzed tandem dehydrogenation/ debenzylation yielded ellipticine **108**, but in 18% yield. Incidentally, Guitián's synthesis of ellipticine is an improvement of the first approach of Gribble and coworkers (see Scheme 33).[75] There is a little strategic novelty in the 3,4-pyridyne cycloaddition step; indeed, they took advantage of the polar effect of the chloro-substituent present in position 2 of 3,4-pyridyne.



Scheme 34. Synthesis of ellipticine.[48]

4.2. *Murrayaquinone A*

Another application of heteroisobenzofurans is found in a synthesis of the carbazole alkaloid Murrayaquinone A, which was isolated from *Murraya euchrestifolia* Hayata. In 1993, Miki and Hachiken accomplished a synthesis of Murrayaquinone A via the regioselective cycloaddition reaction of furo[3,4-*b*]indole **113** with methyl acrylate (Scheme 35).[76] Their strategy involves the

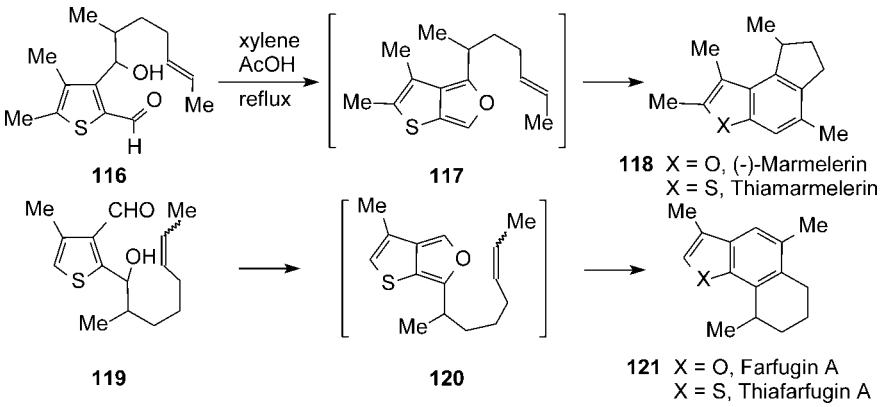


Scheme 35. Synthesis of murrayaquinone A.[78]

generation of 4-benzyl-1-tert-butyldimethylsiloxy-4H-furo[3,4-b]indole (**113**) by lithium tris(trimethylsilyl)amide-mediated deprotonation of lactone **112** followed by o-silylation with tert-butyldimethylsilyl chloride (TBDMSCl) and regioselective trapping of this in-situ-generated furoindole by methyl acrylate. The adduct **114**, thus formed, on treatment with boron trifluoride etherate gave methyl 9-benzyl-4-hydroxycarbazole-3-carboxylate (**115**) which was further transformed into murrayaquinone A.

4.3. *Thiamarmelerin and thiafarfugin A*

Thiamarmelerin and thiafarfugin A represent two sulfur analogues of the furanosesquiterpenes (–)–marmelerin **118** (X = O) and farfugin A **121** (X = O), respectively. In connection with the synthesis of thieno[2,3-*c*]furans, Schöning and Friedrichsen[71,72] have carried out the syntheses of these analogues. Their approach is based on the intramolecular cycloaddition reaction of alkenyl thieno[2,3-*c*]furans (**117** and **120**) (Scheme 36).[71,72] Here, the desired thieno[2,3-*c*]furans were generated by acid-catalyzed cyclization of corresponding hydroxy-carbonyl precursors **116** and **119**, respectively.



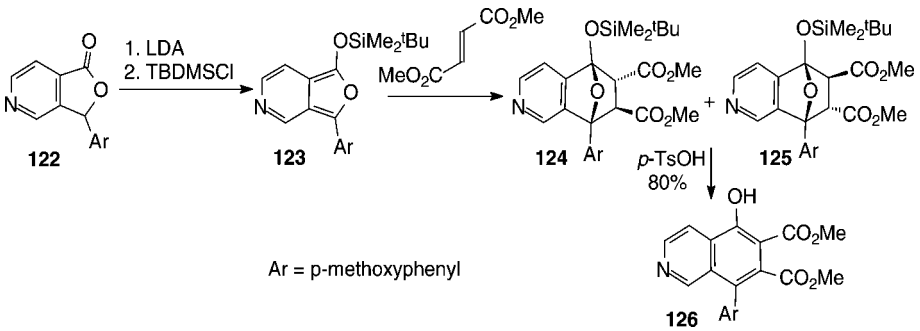
Scheme 36. Synthesis of thiamarmelerin and thiafarfugin A.[71,72]

4.4. *Heterolignans*

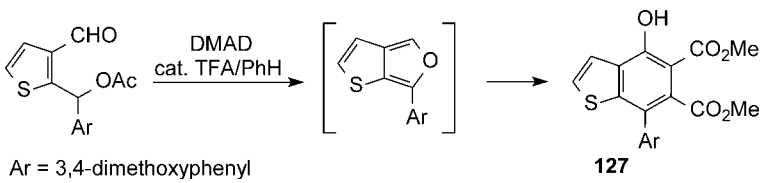
In 1984, Iwao *et al*.[77] reported a synthetic approach to the heterolignans as described in Scheme 37. Sequential lithiation of pyridine–phthalide **122** with LDA and subsequent *o*-silylation with TBDMSCl generates 3-(silyloxy)pyrido[3,4-*c*]furan **(123)** as a transient intermediate, the interception of which with dimethyl fumarate gives adducts **124** and **125** stereoselectively, but in poor yields. Treatment of adduct **124** with *p*-toluenesulfonic acid in refluxing benzene afforded the corresponding heterolignan **126**.

Iwasaki and coworkers have also described the synthesis of heteroanalogues of 1-arylnaphthalene lignans by acidic treatment of an acetoxy-carbonyl compound and subsequent trapping with dimethyl acetylenedicarboxylate.[54] Examples include the preparation of heterolignan **127** (Scheme 38). The compound **127** shows strong antihyperlipidemic activity.

Kappe and Padwa[70] have also attempted to synthesize heterolignans by a Pummerer reaction-based methodology.[70] For examples of this approach, see Scheme 17.



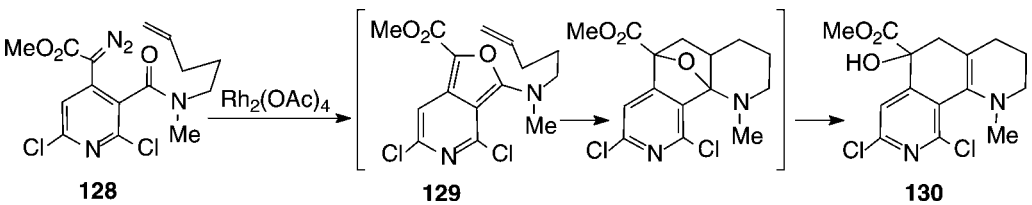
Scheme 37. Synthesis of a isoquinoline lignan.[77]



Scheme 38. Synthesis of a heterolignan.[54]

4.5. *Conformationally restricted analogues of nicotine and anabasine*

We have applied the unique advantage of intramolecular Diels–Alder chemistry of furo[3,4-*c*]-pyridines in the synthesis of conformationally restricted analogues of nicotine and anabasine.[78] Such compounds have assumed increasing importance in recent years in view of their importance as neuronal acetylcholine receptors (nAChRs).[79–86] Thus, exposure of diazoacetic ester **128** to 1 mol% $Rh_2(OAc)_4$ in refluxing benzene for 1 h gives the bridged anabasine **130** via intramolecular cycloaddition followed by ring opening of **129** and subsequent proton transfer (Scheme 39).



Scheme 39. Synthesis of a conformationally restricted analogue of anabasine.[78]

5. Outlook

The foregoing compilation clearly demonstrates the potential of heteroisobenzofurans for the synthesis of polycyclic heteroaromatics. In comparison to the chemistry of isobenzofurans, heteroaromatic isobenzofurans still remain at an infant stage and a number of possible hetero-isobenzofurans are yet to be developed. It is hoped that the challenge for the coming years will lie not only in developing new heteroisobenzofurans, but also in designing novel heteroaromatic assemblies of biological significance. Thus, interest in this area will continue presumably via the development of innovative new processes.

Acknowledgement

TKS is thankful to the Council of Scientific and Industrial Research (CSIR) [No. 1(1602) 99-EMR-II], Government of India, for financial support. SB thanks the same organization for Senior Research fellowship.

References

1. Haddadin, M. J. — *Heterocycles*, 1978, **9**, 865.
2. Friedrichsen, W. — *Adv. Heterocyclc. Chem.*, 1980, **26**, 135.
3. Wiersum, U. E. — *Aldrichimica Acta*, 1981, **14**, 53.
4. Rodrigo, R. — *Tetrahedron*, 1988, **44**, 2093–2135.
5. Rickborn, B. — In *Advances in theoretically interesting molecules*, Vol. 1 (Thummel, R. P., ed.), JAI Press, Greenwich, 1989, pp. 1–134.
6. Friedrichsen, W. — In *Methoden der organischen chemie (Houben-Weyl*), Vol. E6b1, (Kreher, R., ed.), Thieme, 1994, pp. 163.
7. Peters, O. and Friedrichsen, W. — *Trends in heterocyclic chemistry*, 1995, **4**, 217–259.
8. Wege, D. — *Aust. J. Chem.*, 1998, **51**, 1–52.
9. Traulsen, T. and Friedrichsen, W. — *Targets in heterocyclic systems:chemistry and properties*, Vol. 2, Societa Chimica Italiana, 1998, pp. 59–99.
10. Friedrichsen, W. — *Adv. Heterocyclc. Chem.*, 1999, **73**, 1–96.
11. Keay, B. A. and Rodrigo, R. — *J. Am. Chem. Soc.*, 1982, **104**, 4725–4727.
12. Kende, A. S., Curran, D. P., Tsay, Y. and Mills, J. E. — *Tetrahedron Lett*., 1977, 3537–3540.
13. Warrener, R. N., Wang, S. and Russell, R. A. — *Tetrahedron*, 1997, **53**, 3975.
14. Warrener, R. N., Wang, S., Butler, D. N. and Russell, R. A. — *Synlett*, 1997, 44.
15. König, B. M. and Friedrichsen, W. — *Tetrahedron Lett.*, 1987, **28**, 4279–4282.
16. Hildebrandt, K., Debaerdemaeker, T. and Friedrichsen,W. — *Tetrahedron Lett.*, 1988, **29**, 2045–2046.
17. Peters, O. and Friedrichsen, W. — Unpublished.
18. Peters, O. and Friedrichsen, W. — *Tetrahedron Lett.*, 1995, **36**, 8581–8582.
19. Kappe, C. O., Cochran, J. E. and Padwa, A. — *Tetrahedron Lett.*, 1995, **36**, 9285–9288.
20. Padwa, A., Kappe, C. O., Cochran, J. E. and Snyder, J. P. — *J. Org. Chem.*, 1997, **62**, 2786–2797.
21. Leong-Neumann, S., Derrick, S. D. and Dibble, P. W. — *Tetrahedron Lett.*, 1995, **36**, 4181–4184.

22. Berkowitz, D. B., Maeng, J.–H., Dantzig, A. H., Shepard, R. L. and Norman, B. H. — *J. Am. Chem. Soc*., 1996, **118**, 9426–9427.
23. Berkowitz, D. B. and Maeng, J. H. — *Tetrahedron: Asymmetry*, 1996, **7**, 1577–1580.
24. Padwa, A., Cochran, J. E. and Kappe, C. O. — *J. Org. Chem*., 1996, **61**, 3706–3714.
25. Keller, H. and von Halban, H. — *Helv. Chim. Acta*, 1944, **27**, 1253–1275.
26. Bradley, W. and Watkinson, L. J. — *J. Chem. Soc*., 1956, 319–327.
27. Mosby, W. L. — *J. Chem. Soc*., 1957, 3997–4003.
28. Robba, M. and Zaluski, M. -C. — *C. R. Hebd. Seances Acad. Sci. Ser. C*, 1966, **263**, 301–303.
29. Lomme, L. and Lepage, Y. — *Bull. Soc. Chim. Fr*., 1969, 4183.
30. Le Guillanton, G. and Daver, A. — *C. R. Hebd. Seances Acad. Sci. Ser. C*, 1969, **268**, 643–646.
31. Adembri, G. A., de Sio, F., Nesi, R. and Scotton, M. — *J. Chem. Soc. C*, 1970, 1536–1540.
32. Lepage, Y. and Villessot, C. R. — *C. R. Hebd. Seances Acad. Sci. Ser. C*, 1972, **274**, 1466.
33. Haddadin, M. J., Yavrouian, A. and Issidorides, C. H. — *Tetrahedron Lett*., 1970, 1409–1410.
34. Angelico, F. — *Atti Accad. Naz. Lincei C1. Sci. Fis. Mat. Nat. Rend*., 1908, **17II**, 662.
35. Angelico, F. — *Gazz. Chim. Ital*., 1909, **39II**, 142.
36. Angelico, F. and Labisi, C. — *Gazz. Chim. Ital*., 1910, **40I**, 413.
37. Ames, D. E. *et al*. — *J. Chem. Soc. C*, 1969, 1795–1798.
38. Wiersum, U. E., Eldred, C. D., Vrijhof, P. and ven der Plas, H. C. — *Tetrahedron Lett*., 1977, 1741–1742.
39. Müller, P. and Schaller, J.-P. — *Tetrahedron Lett*., 1989, **30**, 1507–1510.
40. Eberbach, W., Fritz, H. and Laber, N. — *Angew. Chem. Int. Ed. Engl*., 1988, **27**, 568–569.
41. Eberbach, W., Laber, N., Bussenius, J., Fritz, H. and Rihs, G. — *Chem. Ber*., 1993, **126**, 975–995.
42. Bussenius, J., Keller, M. and Eberbach, W. — *Liebigs Ann*., 1995, 1503–1507.
43. Shafiee, A. and Behnam, E. — *J. Heterocyclc. Chem*., 1978, **15**, 1459.
44. Saulnier, M. G. and Gribble, G. W. — *Tetrahedron Lett*., 1983, **24**, 5435–5438.
45. Gribble, G. W., Saulnier, M. G., Sibi, M. P. and Obaza-Nutaitis, J. A. — *J. Org. Chem*., 1984, **49**, 4518–4523.
46. Gribble, G. W. and Saulnier, M. G. — *J. Chem. Soc., Chem. Commun.*, 1984, 168–169.
47. Davis, D. A. and Gribble, G. W. — *Tetrahedron Lett*., 1990, **31**, 1081–1084.
48. Gribble, G. W. *et al*. — *J. Org. Chem*., 1992, **57**, 5878–5891.

49. Shiue, J. S. and Fang, J. -M. *J. Chem. Soc., Chem. Commun.*, 1993, 1277–1278.

50. Yang, S. -M. and Fang, J. -M. *J. Org. Chem.*, 1999, **64**, 394–399.

51. Fang, J. -M. *J. Org. Chem.*, 1998, **63**, 2909–2917.

52. Schöning, A. and Friedrichsen, W. *Tetrahedron Lett.*, 1988, **29**, 1137–1138.

53. Kuroda, T. *et al.* *J. Chem. Soc., Chem. Commun.*, 1991, 1635–1636.

54. Kuroda, T. *et al.* *J. Org. Chem.*, 1994, **59**, 7353–7357.

55. Friedrichsen, W. and Schöning, A. *Heterocycles*, 1986, **24**, 307–308.

56. Schöning, A., Debaerdemaeker, T., Zander, M. and Friedrichsen, W. *Chem. Ber.*, 1989, **122**, 1119–1131.

57. Chen, C.-W. and Beak, P. *J. Org. Chem.*, 1986, **51**, 3325–3334.

58. Aßmann, L. and Friedrichsen, W. *Heterocycles*, 1989, **29**, 1003–1004.

59. Aßmann, L., Debaerdemaeker, T. and Friedrichsen, W. *Tetrahedron Lett.*, 1991, **32**, 1161–1164.

60. Aßmann, L., Palm, L., Zander, M. and Friedrichsen, W. *Chem. Ber.*, 1991, **124**, 2481–2488.

61. Reck, S. *et al.* *Heterocycles*, 1996, **43**, 1165–1170.

62. Nagel, J., Friedrichsen, W. and Debaerdemaeker, T. *Z. Naturforsch.* ***B***, 1993, **48**, 213–223.

63. Peters, O. and Friedrichsen, W. *Heterocyclc. Commun.*, 1996, **2**, 203–212.

64. Reck, S., Näther, C. and Friedrichsen, W. *Heterocycles*, 1998, **48**, 853–860.

65. Reck, S., Näther, C. and Friedrichsen, W. *Heterocycles*, 1999, **51**, 1225.

66. Reck, S. and Friedrichsen, W. *J. Org. Chem.*, 1998, **63**, 7680–7686.

67. Sarkar, T. K., Ghosh, S. K., Nandy, S. K. and Chow, T. J. *Tetrahedron Lett.*, 1999, **40**, 397–398.

68. Sarkar, T. K., Ghosh, S. K. and Chow, T. J. *J. Org. Chem.*, 2000, **65**, 3111–3115.

69. Traulsen, T. and Friedrichsen, W. *J. Chem. Soc., Perkin Trans.1*, 2000, 1387–1398.

70. Kappe, C. O. and Padwa, A. *J. Org. Chem.*, 1996, **61**, 6166–6174.

71. Schöning, A. and Friedrichsen, W. *Liebigs Ann. Chem.*, 1989, 405–408.

72. Schöning, A. and Friedrichsen, W. *Z. Naturforsch. B*, 1989, **44**, 825–833.

73. Gribble, G. W., Silva, R. A. and Saulnier, M. G. *Synth. Commun.*, 1999, 729–747.

74. Friedrichsen, W. *Comprehensive heterocycle chemistry*, Vol. 4 (Katritzky, A. R. and Rees, C. W., eds), Pergamon Press, 1984, pp. 973–1036.

75. Díaz, M. T., Cobas, A., Guitián, E. and Castedo, L. — *Synlett*, 1998, 157–158.

76. Miki, Y. and Hachiken, H. — *Synlett*, 1993, 333.

77. Iwao, M., Inoue, H. and Kuraishi, T. — *Chem. Lett*., 1984, 1263–1266.

78. Sarkar, T. K., Basak, S. and Ghosh, S. K. — *Tetrahedron Lett.*, 2000, **41**, 759–762.

79. Catka, T. E. and Leete, E. — *J. Org. Chem.*, 1978, **43**, 2125–2127.

80. Chavdarian, C. G., Seeman, J. I. and Wooten, J. B. — *J. Org. Chem.*, 1983, **48**, 492–494.

81. Glassco, W., Suchocki, J., George, C., Martin, B. R. and May, E. L. — *J. Med. Chem.*, 1993, **36**, 3381–3385.

82. Kanne, D. B., Ashworth, D. J., Cheng, M. T., Mutter, L. C. and Abood, L. G. — *J. Am. Chem. Soc*., 1986, **108**, 7864–7865.

83. Kanne, D. B. and Abood, L. G. — *J. Med. Chem*., 1988, **31**, 506–509.

84. Vernier, J.-M. *et al*. — *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2173–2178.

85. Xu, Y.-Z., Choi, J., Calaza, M. I., Turner, S. and Rapoport, H. — *J. Org. Chem.*, 1999, **64**, 4069–4078.

86. Lindström, S., Ripa, L. and Hallberg, A. — *Org. Lett*., 2000, **2**, 2291–2293.