Progress in the chemistry of heteroisobenzofurans†

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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, murrayquinone 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 \(\sigma\)-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 resistomycin11 and anthracyclinones,12 inner-functionalized cavity molecules,13,14 steroid analogues,15 oxasteroid analogues,16 azasteroid analogues,17 polycyclic nitrogen heterocycles18–20 and others.21–24

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

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(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 1434–37 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 1138 and 1228. 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 hereunder.

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 1H 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

![Scheme 1. Generation of furo[3,4-c]pyridines.](image)

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).\textsuperscript{40, 41} E-18 (R\textsuperscript{1} = R\textsuperscript{2} = H or R\textsuperscript{1} = H, R\textsuperscript{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).\textsuperscript{41}

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).\textsuperscript{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).\textsuperscript{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).\textsuperscript{44-54} This method has been extensively used in the synthesis of ellipticine,\textsuperscript{45,48} isoeellipticine\textsuperscript{48} as well as hetero analogues of 1-arylnaphthalene lignans.\textsuperscript{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.\textsuperscript{54}
Scheme 3. Mechanistic rationale.\textsuperscript{41}

Scheme 4. Synthesis of thienofurans, furobenzofurans and benzothienofurans.\textsuperscript{41, 42}

Scheme 5. Heteroaromatic isobenzofurans by acid-catalyzed cyclization.\textsuperscript{44-54}

2.2.1. \textit{From hydroxy-carbonyl precursors}

Acid-catalyzed cyclization of hydroxy-carbonyl precursors provides a direct route to heteroaromatic isobenzofurans.\textsuperscript{44-52} Gribble’s group has established the utility of this method for the preparation of several furo[3,4-\textit{b}]indoles 31–37 (Fig. 2).\textsuperscript{44, 45, 48}
The synthesis of the parent compound 31 has proven to be the most difficult in this series. 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-\textit{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 CF₃CO₂H, 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.

Related work by Shiue and Fang has also resulted in the synthesis of furo[3,4-\textit{b}]indoles, e.g. the formation of 43. In this work, a number of precursors including 42 were prepared by a novel SmI₂-promoted hydroxyalkylation of indolo-3-carbonyl compounds. The same synthetic concept has been applied on 44 for the generation of a \textit{bis}-4H-furo[3,4-\textit{b}]indole (45), a useful precursor in the synthesis of a DNA \textit{bis}-intercalating agent (46) (Scheme 7).

2.2.2. \textit{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-\textit{b}]indoles by acidic treatment of the corresponding acetoxy-carbonyl precursors. Thus, treatment of acetoxy-aldehyde (47) with a catalytic amount of trifluoroacetic acid (TFA) in refluxing benzene gives 48 in 36% yield (Scheme 8).
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]furan. 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).

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 \( \omega \)-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 \( \text{[Rh}_2(\text{OAc})_4 \text{]} \)-catalyzed decomposition of \( \text{51} \) gives furoisoxazole \( \text{52} \) (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 (\( \text{53} \)) to 1 mol\% \( \text{Rh}_2(\text{OAc})_4 \) in \( \text{CH}_2\text{Cl}_2 \) at rt for 1 h yields azaisobenzofuran (\( \text{54} \)) in 50\% yield (Scheme 11).\(^{67,68}\) Another recent report on the synthesis of furo[3,4-\( b \)]benzofurans, such as \( \text{55} \) 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 \( \omega \)-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 \( \alpha \)-thiocarbocation and its interception by a neighbouring carbonyl group to give thio-substituted heteroaromatic isobenzofurans.\(^{70}\) Thus, exposure of thiophene-derived ketosulfoxide (\( \text{56} \)) to the classical Pummerer conditions, i.e. refluxing acetic anhydride gives a mixture of products containing 23\% of the desired thienofuran (\( \text{57} \)) (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 (\( \text{58} \) and \( \text{59} \)) (Scheme 13).\(^{70}\) Furo[3,4-\( c \)]indole (\( \text{58} \), which is not as stable as the thienofuran (\( \text{57} \)), 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
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.

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.
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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{55} But when thienofuran (50) is treated with unsymmetrical dienophiles such as methyl acrylate, no regioselectivity is observed.\textsuperscript{70}

\begin{equation}
\text{Scheme 15. Diels–Alder reaction of 4,6-diphenylthieno[2,3-c]furan.}\textsuperscript{55}
\end{equation}

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

\begin{equation}
\text{Scheme 16. Trapping of a cyanovinyl substituted-thienofuran.}\textsuperscript{41}
\end{equation}

In recent studies, Kappe and Padwa\textsuperscript{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).\textsuperscript{70} With the somewhat less reactive methyl acrylate ethylthio-substituted thienofuran (57) gives a single regioisomer 67 in the presence of Sc(OTf)\textsubscript{3}. The use of Sc(OTf)\textsubscript{3} is not mandatory here, although its presence improves the yield.
Schöning and Friedrichsen have described the in-situ generation of thieno[2,3-c]furans by the acid-catalyzed cyclization protocol. 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). 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.

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. Interestingly, 1-alkoxy-3-alkoxy-carbonyl-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 (Scheme 19). Thus, furo[3,4-
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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.

In order to explore the synthetic utility of furo[3,4-d]oxazoles in intramolecular cycloaddition with unactivated dienophiles, Reck and Friedrichsen subjected 77 to metal-catalyzed decomposition using rhodium(II) acetate (Scheme 20). 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.

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. Thus, Friedrichsen and coworkers 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.

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. 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).
3.6. Furo[3,4-\(b\)]indoles

1-(Phenylsulfonyl)-4\(H\)-furo[3,4-\(b\)]indoles, e. g. 83 (\(R = \text{H, Me}\)) 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 (\(R = \text{H}\)) gives 5\(H\)-benzo[\(b\)]carbazole 84 (\(R = \text{H}\)), 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-dimethyl-furoindole 83 (\(R = \text{Me}\)) proceeds with excellent yield. Reaction of furoindoles with an unsymmetrical dienophile can, in principle, give 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 \(\alpha,\beta\)-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 22. Diels–Alder reactivity of a furo[3,4-\(d\)]thiazole.\(^{64}\)](image)

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 23. Furoindoles in intermolecular Diels–Alder reaction.\(^{44, 45, 48}\)](image)

![Scheme 24. Utility of an ethylthio-substituted furoindole.\(^{70}\)](image)
The most pioneering example of the intramolecular cycloaddition chemistry of furoindoles involves the Cu(acacF)₂-catalyzed decomposition of 88 in refluxing toluene giving pyrano[3,2-c]carbazole 89 in 32% yield (Scheme 25). Recently, Gribble et al. 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.

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).

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

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 ZnI₂ as a Lewis acid catalyst, e.g. the formation of 92 (Scheme 27). 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.

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. Thus, on treatment of 94 with Rh₂(OAc)₄ and subsequently with ZnI₂, dioxabenzo[a]fluorene (97) is formed probably via an exo-cycloaddition reaction with subsequent loss of water (Scheme 28).
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. Wiersum et al. 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]naphthalene 102.

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). Frontier molecular orbital (FMO) studies have fully corroborated these stereochemical results.
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). 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. 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 summarized 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. utilized the cycloaddition of 1,3-dimethyl-4-(phenylsulfonyl)-4H-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 regiosomeric products 106 and 107 in 38% yield; treatment of the mixture with NaBH₄/NaOH/MeOH gave ellipticine 108 and isoellipticine 109 in 23% and 29% yield, respectively. 

![Scheme 33. Synthesis of ellipticine and isoellipticine.](image)

However, the trimethylsilyl trifluoromethanesulfonate-induced reaction of furoindole 85 and dihydropyridone 110 gave lactam 111 regioselectively in 89% yield (Scheme 34). Subsequent reduction of 111 with LiAlH₄ 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). 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.](image)

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). Their strategy involves the
generation of 4-benzyl-1-tert-butylidemethylsiloxy-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 (TBDMSCI) 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 TBDMSCI 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.
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. Such compounds have assumed increasing importance in recent years in view of their importance as neuronal acetylcholine receptors (nAChRs). Thus, exposure of diazoacetic ester 128 to 1 mol% \( \text{Rh}_2(\text{OAc})_4 \) 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).

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 heteroisobenzofurans 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.
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