Novel chemistry of indole in the synthesis of heterocycles*,‡

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Abstract: Indoles that are substituted at the 2- or 3-position with electron-withdrawing groups (nitro, phenylsulfonyl) undergo nucleophilic addition, 1,3-dipolar cycloaddition, and Diels–Alder reactions to give a variety of indoles, pyrroloindoles, and carbazoles. New methods for the synthesis of furo[3,4-*b*]indoles and the novel ring system furo[3,4-*b*]pyrrole are described for the first time. Diels–Alder reactions of furo[3,4-*b*]pyrroles afford indoles after dehydration of the primary cycloadducts. Efficient syntheses of both 2- and 3-nitroindoles from indole are reported, and the first generation and successful electrophilic trapping of a 2,3-dilithioindole has been achieved.

INTRODUCTION

Although the chemistry of indole (**1**) has been investigated for more than 100 years, as summarized in Scheme 1 [1], recent times have seen the development of new indole chemistry, such as lithiated indoles and indole radicals for use in synthesis [2,3].
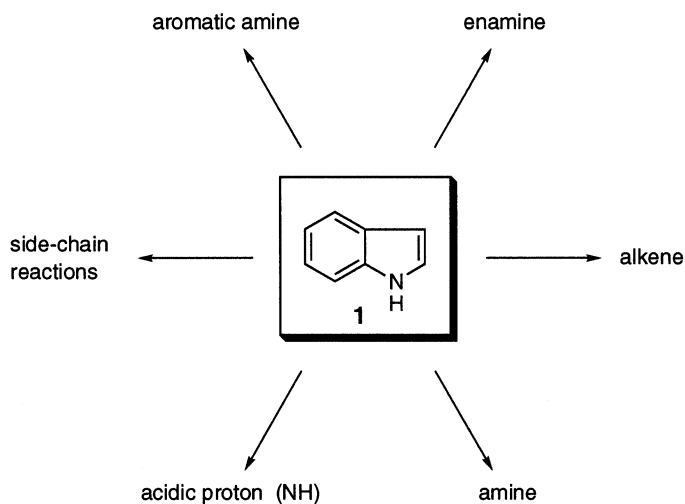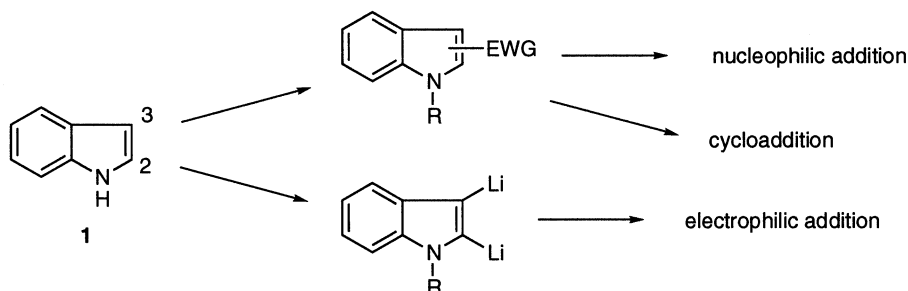

Scheme 1

In continuation of our own inveterate interest in the chemistry of indoles [4–6], we have begun to examine the chemistry of indoles that are substituted at the 2- or 3-position with a strong electron-withdrawing group (i.e., nitro, phenylsulfonyl, cyano), and also to generate and trap with electrophiles

2,3-dilithioindoles (Scheme 2). One important application of our work is the development of simple and efficient syntheses of fused ring systems, such as pyrrolo[3,4-*b*]indoles, pyrrolo[2,3-*b*]indoles, furo[3,4-*b*]indoles, furo[3,4-*b*]pyrroles, benzo[*b*]furo[2,3-*c*]pyrroles, and benzo[*b*]thieno[2,3-*c*]pyrroles, some of which can serve as synthetic analogs of indole-2,3-quinodimethane.
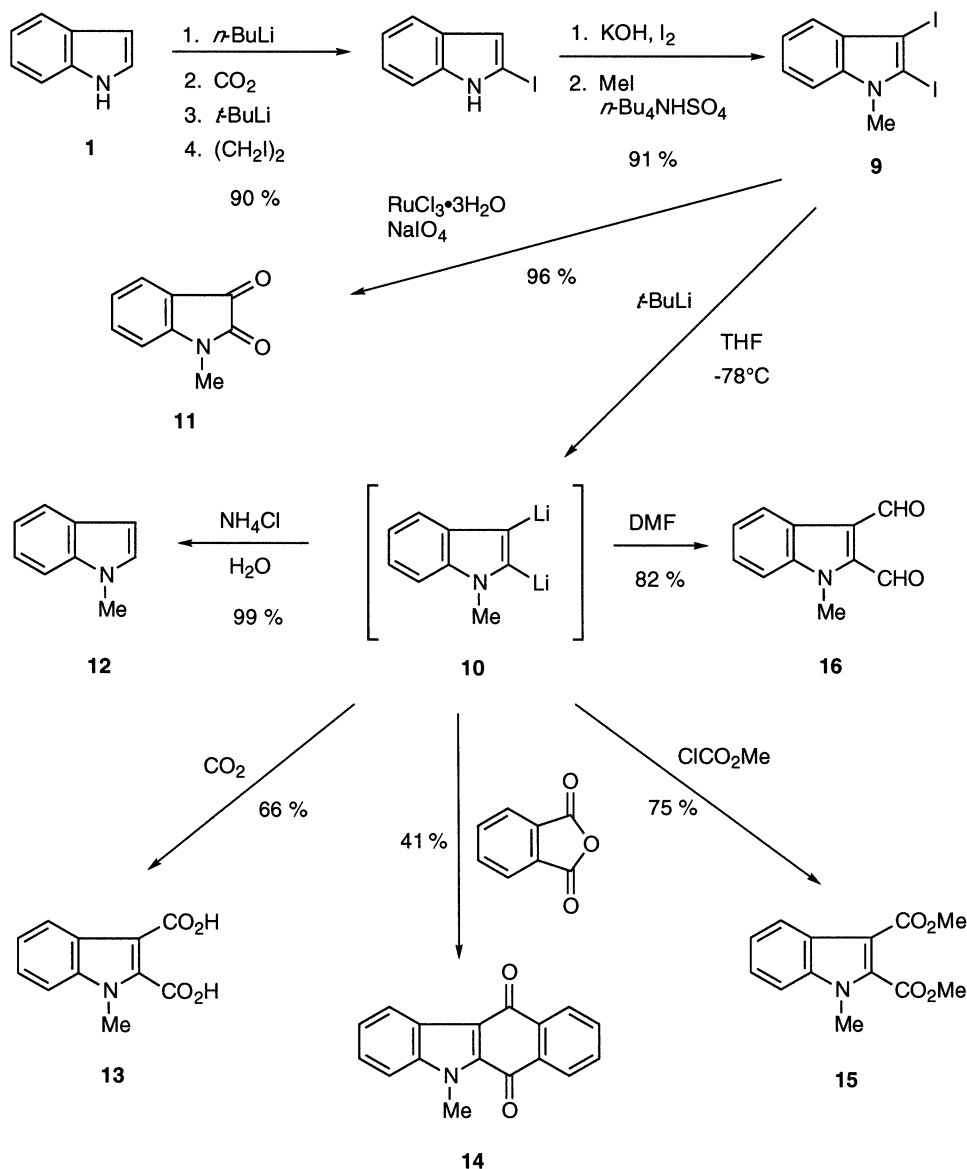

Scheme 2

GENERATION AND CHEMISTRY OF 2,3-DILITHIOINDOLES

Several years ago, we attempted to generate and trap 2,3-dilithio-1-(phenylsulfonyl)indole (**4**) with electrophiles to give 2,3-disubstituted indoles **8**. Unfortunately, although we could synthesize 2,3-di-iodoindole **3** in very good yield from indole (**1**), via 3-iodoindole **2** [7], bis-halogen lithium exchange of **3** to generate **4** and subsequent addition of electrophiles gave mainly the products of indole ring fragmentation, i.e., **6** and **7** (Scheme 3) [8]. This ring-opening path to **5** is presumably due not only to C-2,C-3 anionic repulsion, but also to the formation of stabilized phenylsulfonamide and phenylacetylide anions.
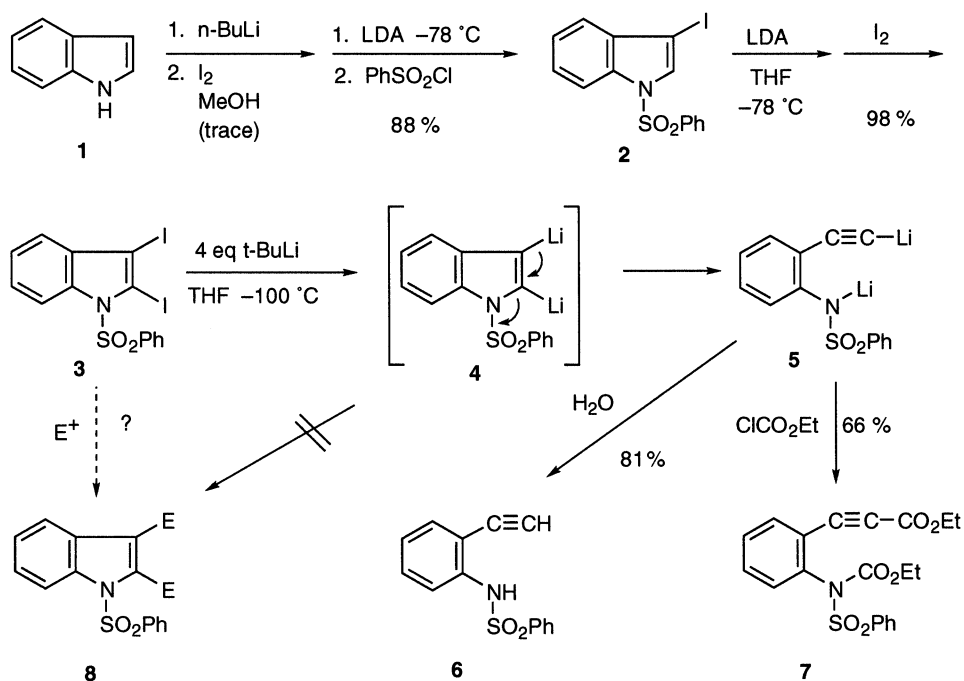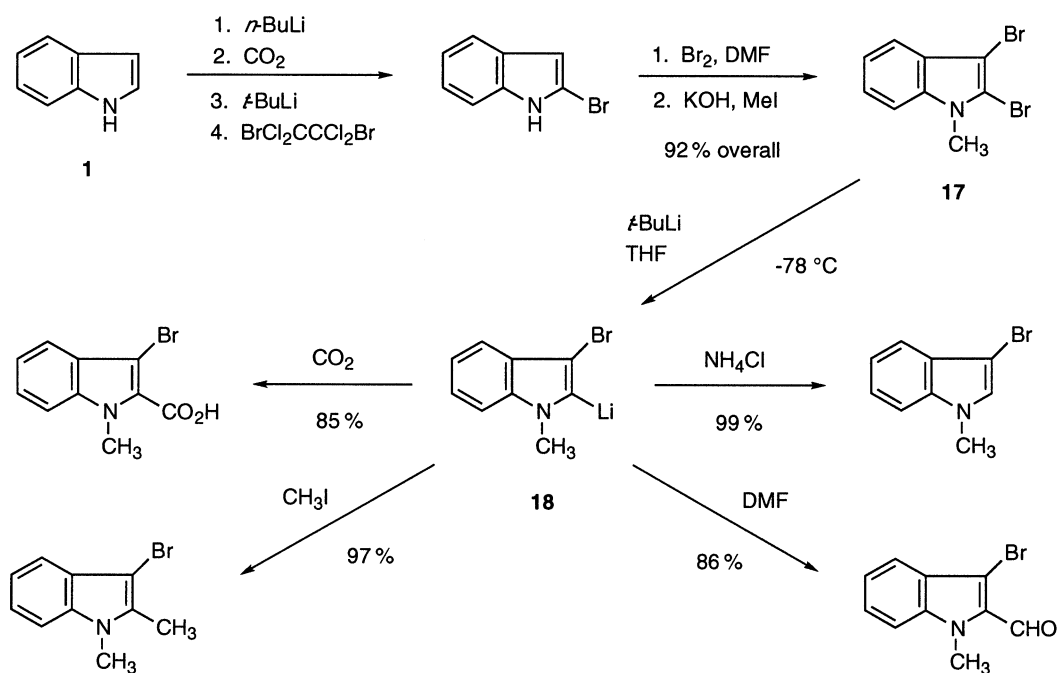

Scheme 3

We reasoned that an *N*-substituted electron-donating or neutral group would mitigate this **4 → 5** ring fragmentation. Indeed, the readily synthesized 2,3-diiodo-1-methylindole (**9**) undergoes halogen-metal exchange with *tert*-butyllithium to give the relatively stable 2,3-dilithio-1-methylindole (**10**) (Scheme 4) [9]. Interestingly, diiodoindole **9** is converted to *N*-methylisatin (**11**) in excellent yield upon treatment with ruthenium [10]. Treatment of dilithioindole **10** with several electrophiles affords the expected 2,3-disubstituted products **12–16** (Scheme 4) [9].
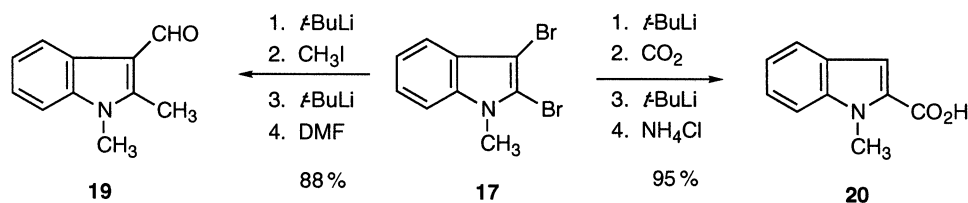

Scheme 4

Although we have been unable to effect selective *mono*-halogen metal exchange on 2,3-diiodo-1-methylindole (**9**), we have successfully accomplished such chemistry with 2,3-dibromo-1-methylindole (**17**), which is prepared in 92 % yield from indole (Scheme 5) [11]. Thus, selective conversion of **17** to 3-bromo-2-lithio-1-methylindole (**18**) and subsequent trapping with electrophiles gives the corresponding 3-bromo-2-substituted indoles (Scheme 5).
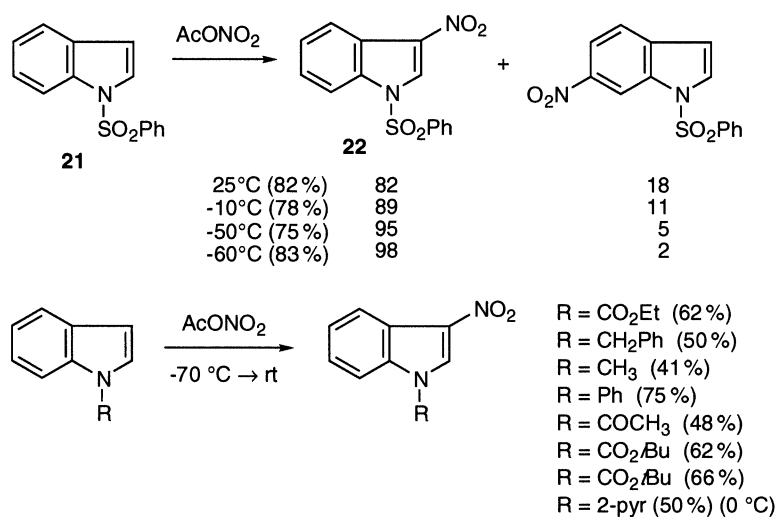
Scheme 5

Furthermore, we have found in a one-pot operation that both bromines of **17** can be sequentially replaced by electrophiles to give indoles **19** and **20** (Scheme 6) [11]. Subsequent bromination of **17**, depending on the conditions, affords the naturally occurring 2,3,6-tribromo-1-methylindole and 2,3,5,6-tetrabromo-1-methylindole (not shown) [12].
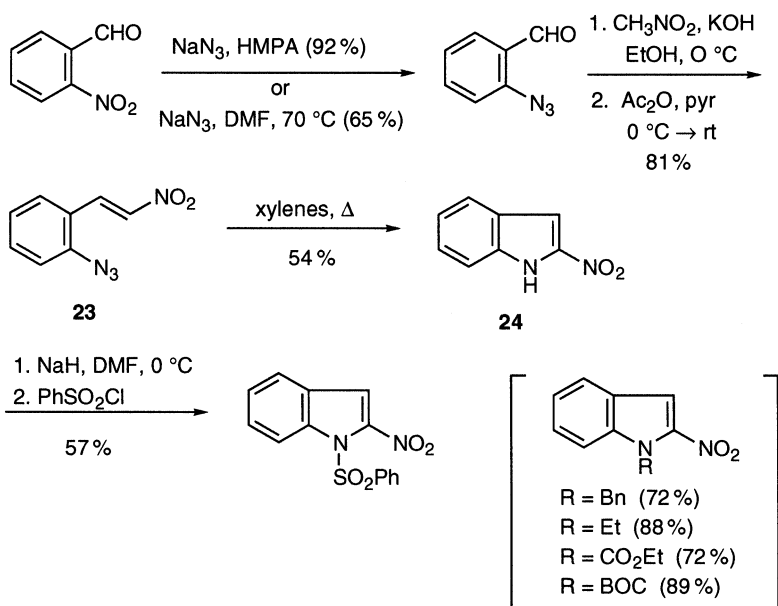
Scheme 6

SYNTHESIS OF 2- AND 3-NITROINDOLES

Because the nitro group is a very powerful electron-withdrawing group, this was our first choice with which to investigate the chemistry of electron-deficient indoles. Although 3-nitroindole can be prepared by direct nitration of indole, the yield is low [13]. Alternatively, we have found that the C-3 nitration of *N*-protected indoles is a very efficient method to access 3-nitroindoles (Scheme 7) [14] and is far superior to direct nitration of indole itself. Low temperature is necessary to minimize the formation of 6-nitroindoles. Under these conditions, 3-nitro-1-(phenylsulfonyl)indole (**22**) is now readily available.
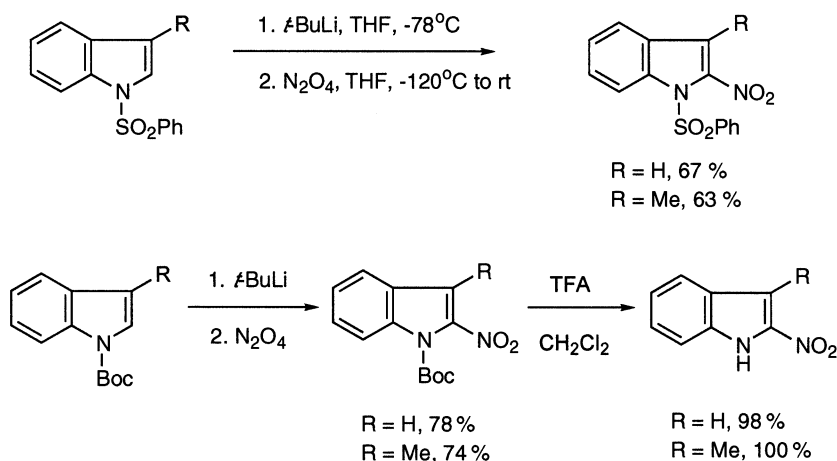
Scheme 7

	22	
25 °C (82 %)	82	18
-10 °C (78 %)	89	11
-50 °C (75 %)	95	5
-60 °C (83 %)	98	2

R = CO$_2$Et (62 %)
R = CH$_2$Ph (50 %)
R = CH$_3$ (41 %)
R = Ph (75 %)
R = COCH$_3$ (48 %)
R = CO$_2$*t*Bu (62 %)
R = CO$_2$*t*Bu (66 %)
R = 2-pyr (50 %) (0 °C)

When we began our work, 2-nitroindole (**24**) was unknown. Our initial synthesis of **24** utilized the reliable Sundberg indole synthesis starting from 2-nitrobenzaldehyde (Scheme 8) [15].
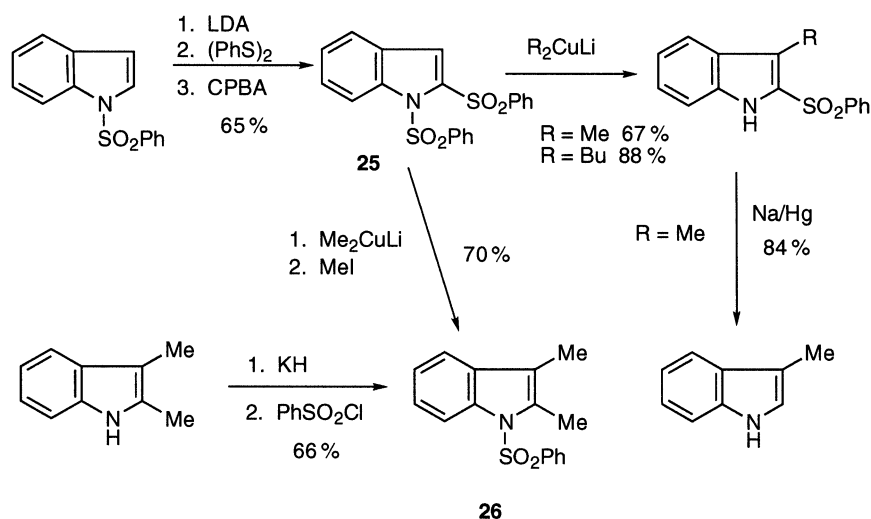
Scheme 8

Unfortunately, the intermediate 2-azidonitrostyrene **23** is a potent skin and eye irritant, not unlike "pepper spray" ("CS", *o*-chlorobenzalmalonitrile), and, as a result, we needed to find an alternative synthesis of 2-nitroindoles. Our earlier work with 2-lithioindoles [7,16] suggested that direct nitration of this species would afford 2-nitroindoles. After considerable experimentation with different sources of "NO$_2^+$" (nitronium triflate, nitronium boron tetrafluoride, acetyl nitrate, pivaloyl nitrate), we found that adding dinitrogen tetroxide onto a frozen THF reaction mixture [17] of a 2-lithioindole gives the corresponding 2-nitroindole in reasonable yields (Scheme 9) [18]. Deprotection of the *N*-Boc-2-nitroindoles affords the parent 2-nitroindoles.
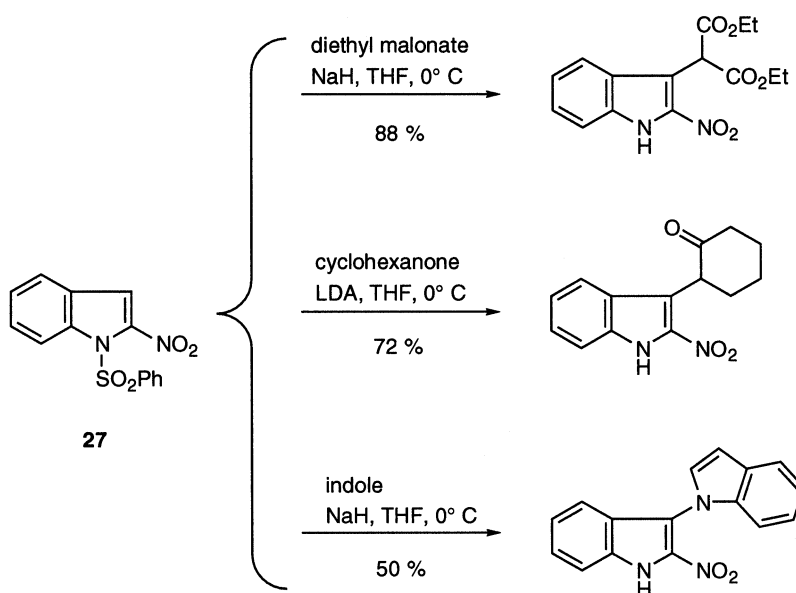
Scheme 9

NUCLEOPHILIC ADDITION REACTIONS

Although electrophilic additions to C-3 of indole are well established [1,2], nucleophilic addition reactions to the indole double bond are less well known [19]. Our initial work in this area involved 1,2-bis(phenylsulfonyl)indole (**25**), and we found that this compound undergoes smooth addition of lithium dialkylcuprates to yield the corresponding 3-alkyl-2-(phenylsulfonyl)indoles devoid of the *N*-phenylsulfonyl group (Scheme 10) [15,20,21]. Furthermore, we were able to intercept the presumed intermediate C-2 anion with methyl iodide to give 2,3-dimethyl-1-(phenylsulfonyl)indole (**26**) in 70 % yield. Independent synthesis or conversion to known compounds confirmed the structures of these cuprate addition products.
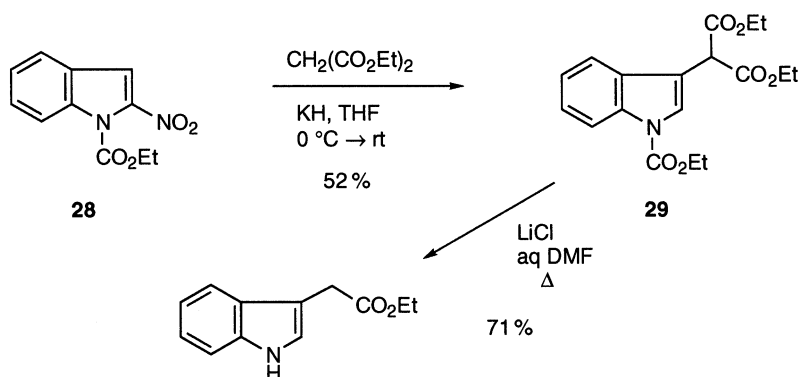

Scheme 10

Similarly, nucleophilic addition reactions of 2-nitro-1-(phenylsulfonyl)indole (**27**) result in the expulsion of the *N*-phenylsulfonyl group to give the corresponding 3-substituted 2-nitroindoles (Scheme 11) [20]. A minor product in the reaction of **27** with indole anion results from attack at C-3 to give a 3,3′-biindole.
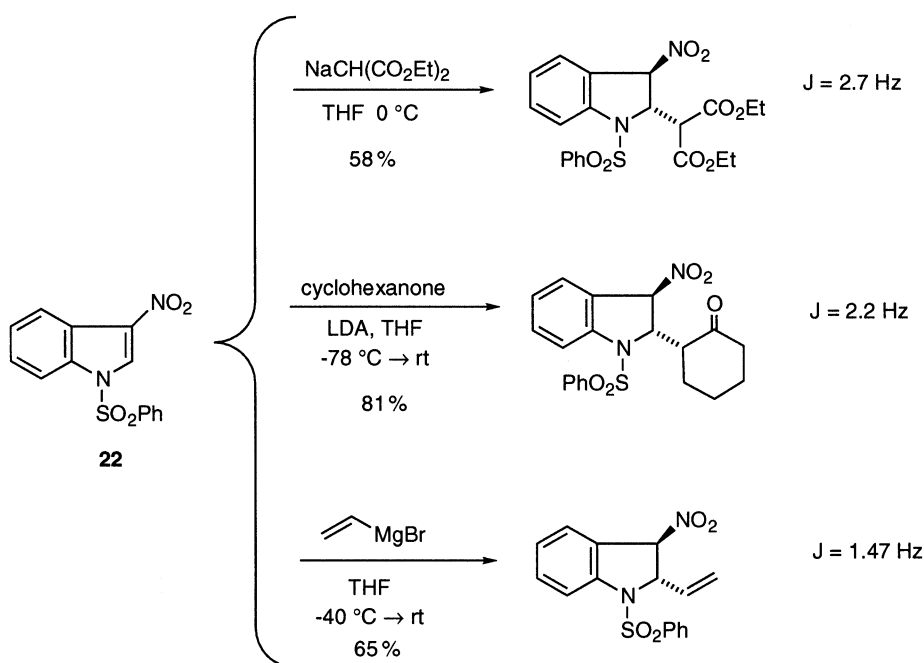
Scheme 11

In contrast to the behavior of **27**, 1-carboethoxy-2-nitroindole (**28**) reacts with the anion of diethyl malonate to give diester **29** with retention of the *N*-carboethoxy group and formal loss of nitrous acid (Scheme 12) [21]. Diester **29** was converted to the known ethyl 3-indoleacetate using a Krapcho decarboethoxylation.
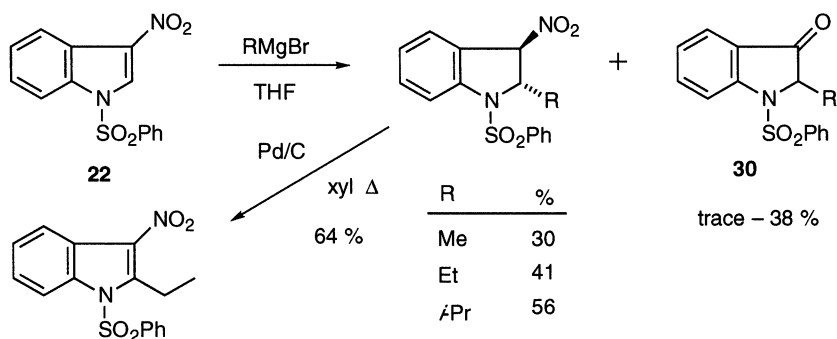
Scheme 12

Nucleophilic additions to 3-nitro-1-(phenylsulfonyl)indole (**22**) take a different course and result in *trans*-dihydroindole products (Scheme 13) [21].
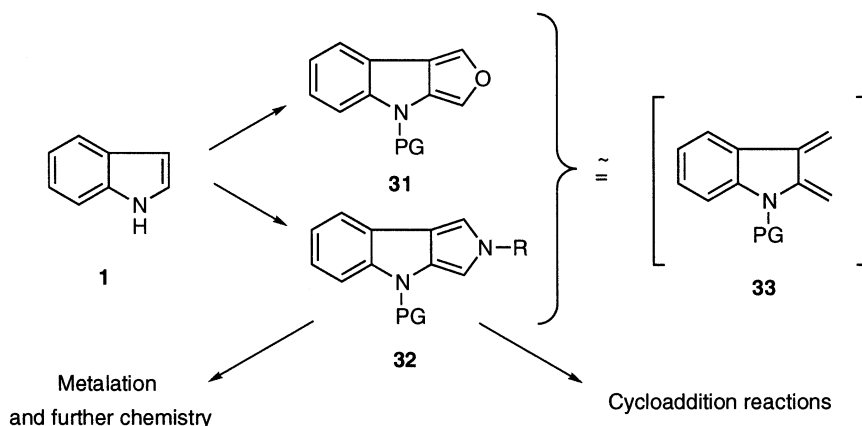
Scheme 13

A similar path is observed with nucleophilic additions to 1-Boc-3-nitroindole, but alkyl Grignards add to **22** to afford significant amounts of 2-alkylindoxyls **30**, the products of a formal Nef reaction, in addition to the *trans*-2-alkyl-3-nitroindolines, which are the major products (Scheme 14) [21]. Both 2-lithiopyridine and 2-lithiothiazole add to **22** to give the corresponding 2-heteroaryl-3-nitroindoles, following loss of phenylsulfinate.
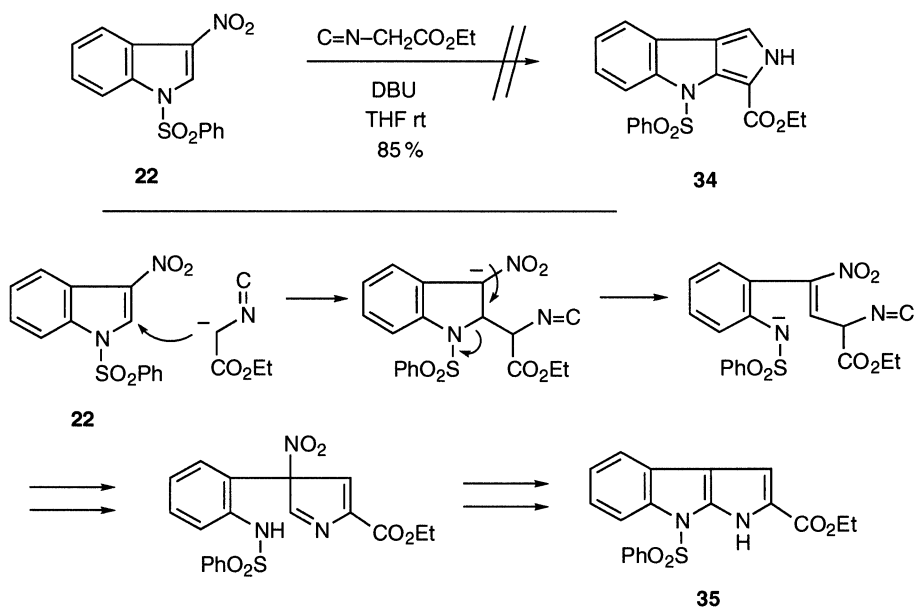

Scheme 14

INDOLE-2,3-QUINODIMETHANE ANALOGS

A major interest in our indole research program has been to synthesize furo[3,4-*b*]indoles (**31**) and pyrrolo[3,4-*b*]indoles (**32**) as indole-2,3-quinodimethane (**33**) analogs, since the latter species is unstable and has never been isolated. Furthermore, fused heterocycles **31** and **32** can be modified prior to subsequent chemistry (Scheme 15).
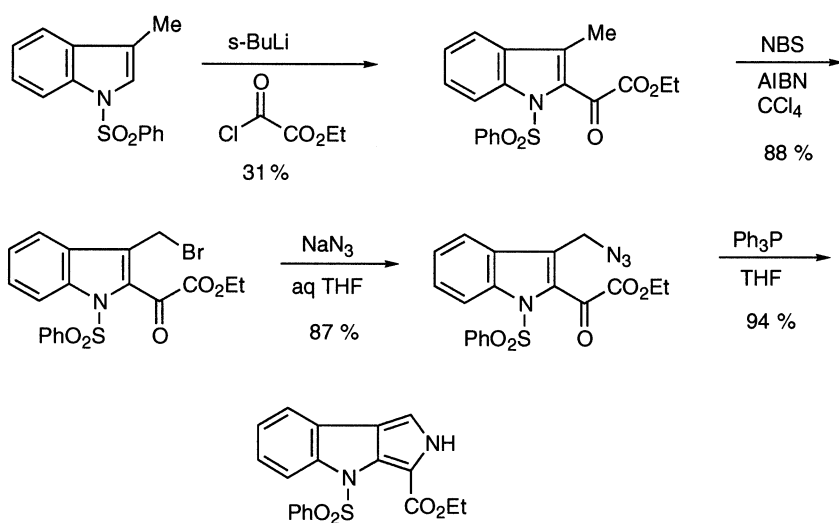
Scheme 15

Pyrrolo[3,4-*b*]indoles

Although pyrroloindoles **32** are well known, multistep pathways are usually involved in the synthesis of this ring system [22,23]. It seemed that a possible one-step route to these pyrroloindoles would be the Barton–Zard pyrrole synthesis involving the reaction between nitroalkenes and the anion of iso-cyanoacetate [24,25]. Much to our surprise, the reaction of 3-nitro-1-(phenylsulfonyl)indole (**22**) under Barton–Zard conditions gave the rearranged pyrrolo[2,3-*b*]indole **35** instead of the expected pyrrolo[3,4-*b*]indole **34** (Scheme 16) [26]. A possible pathway for this unexpected result is shown.
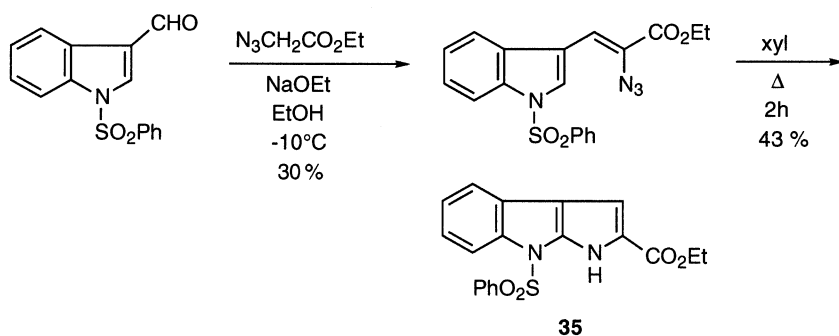

Scheme 16

The structures of both **34** and **35** were confirmed by independent synthesis (Schemes 17 and 18).
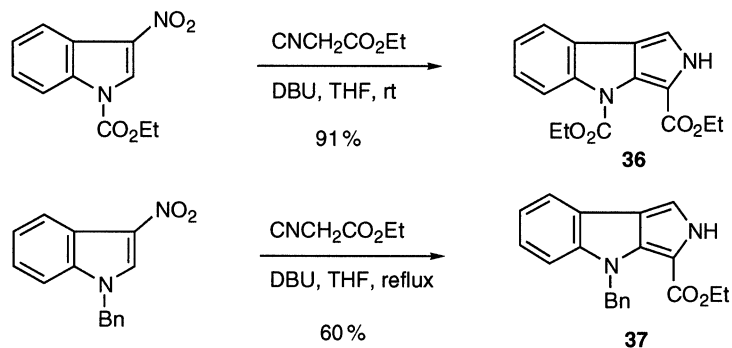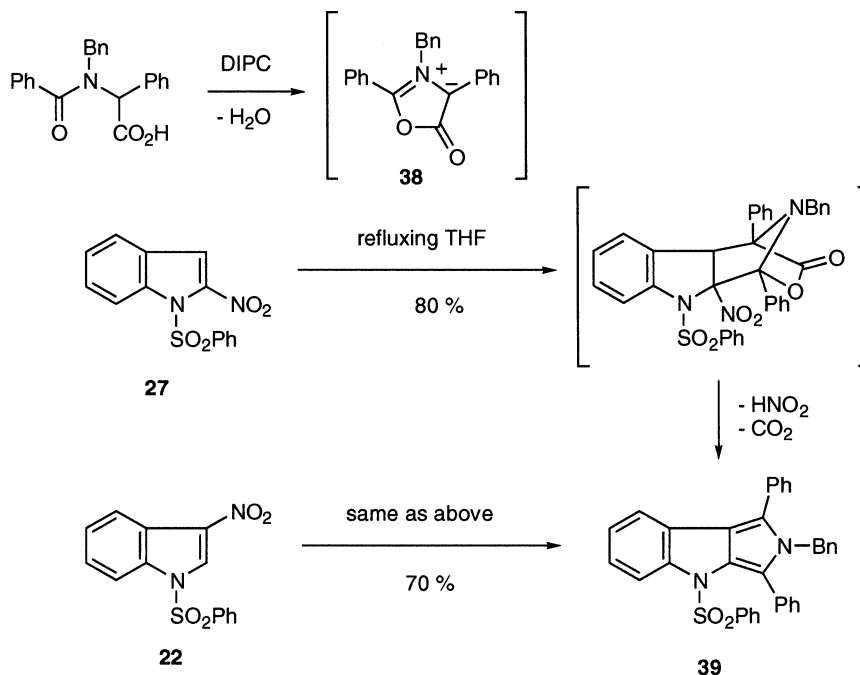
Scheme 17

Scheme 18

Similar to what we saw earlier, a switch to a less electron-withdrawing *N*-protecting group changes the course of this reaction and prevents this abnormal Barton–Zard pathway, involving indole ring opening, and now affords the "normal" pyrrolo[3,4-*b*]indoles **36** and **37** (Scheme 19) [27].
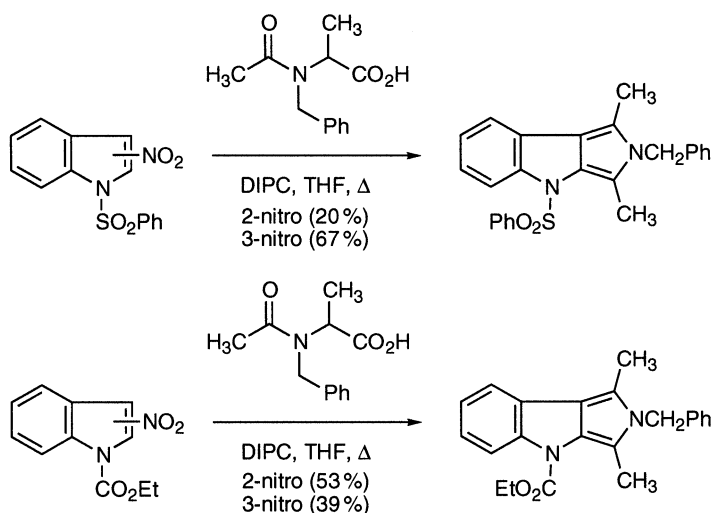

Scheme 19

Our earlier work with munchnone cycloaddition reactions [28] suggested that these mesoionic 1,3-dipoles could also react with electron-deficient indoles to afford pyrrolo[3,4-*b*]indoles in one operation. Indeed, this has proven to be the case. Both 2- and 3-nitro-1-(phenylsulfonyl)indoles (**27** and **22**) react with munchnone **38**, which is generated in situ by cyclodehydration of the appropriate *N*-acyl amino acid with 1,3-diisopropylcarbodiimide (DIPC), to give pyrroloindole **39** in very good yields (Scheme 20) [29].
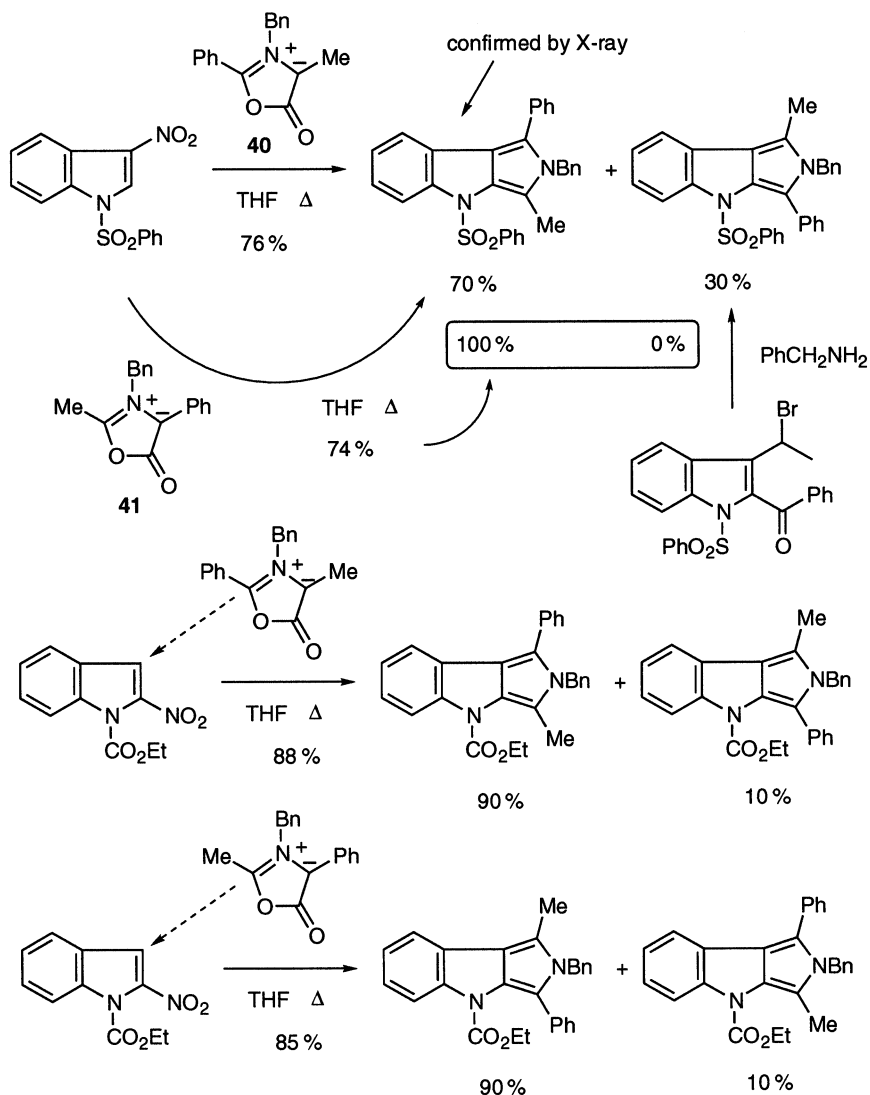
Scheme 20

The corresponding 1,3-dimethylpyrroloindoles can be crafted in similar fashion (Scheme 21) [29].

Scheme 21

Interestingly, the unsymmetrical munchnones **40** and **41** generally display anti-FMO regioselectivity in cycloaddition reactions with both 3- and 2-nitroindoles (Scheme 22) [30]. The isomeric pyrroloindoles were separated by chromatography and characterized by NMR (NOE), X-ray crystal structure determination [31], and/or independent synthesis.
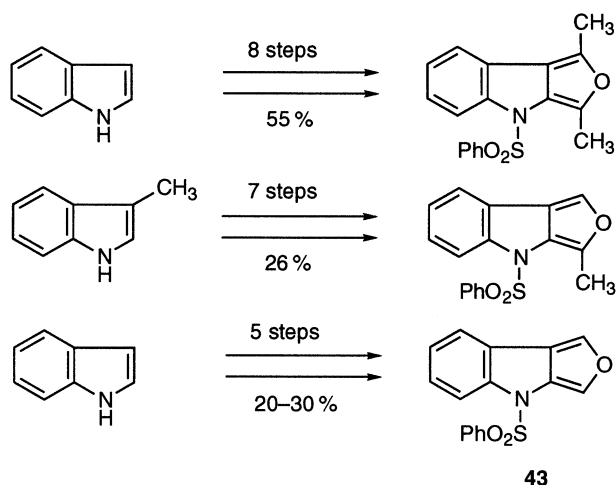

Scheme 22

Both 2-nitrobenzofuran and 3-nitrobenzothiophene undergo similar reactions with munchnones to give the novel fused heterocycles shown (Scheme 23) [29].
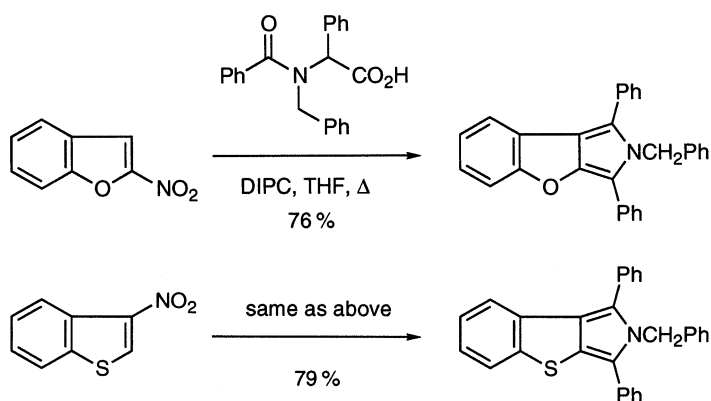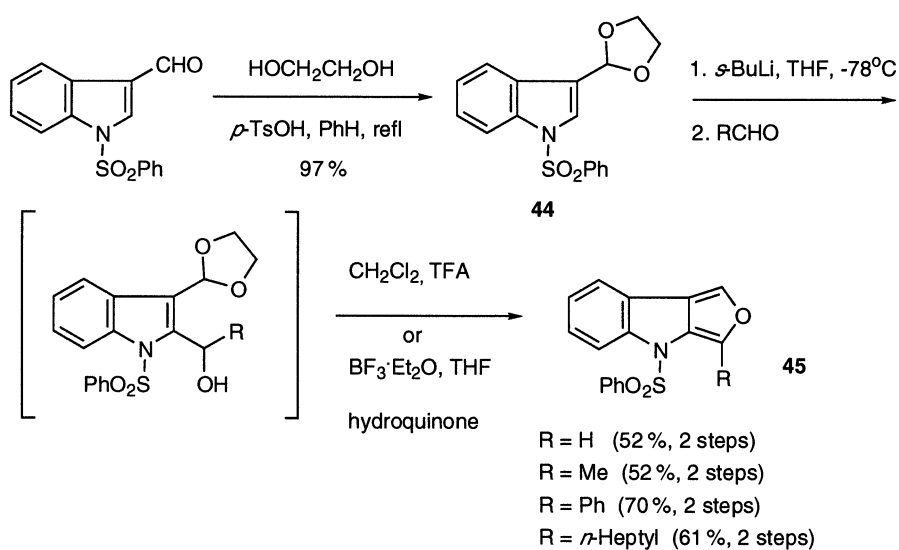
Scheme 23

Furo[3,4-*b*]indoles

The fused heterocycle 4*H*-furo[3,4-*b*]indole has played an important role in our research program for 20 years [32–37]. Nevertheless, the syntheses of this ring system typically involve several steps and, especially for the unsubstituted compound **43**, are often erratic (Scheme 24).
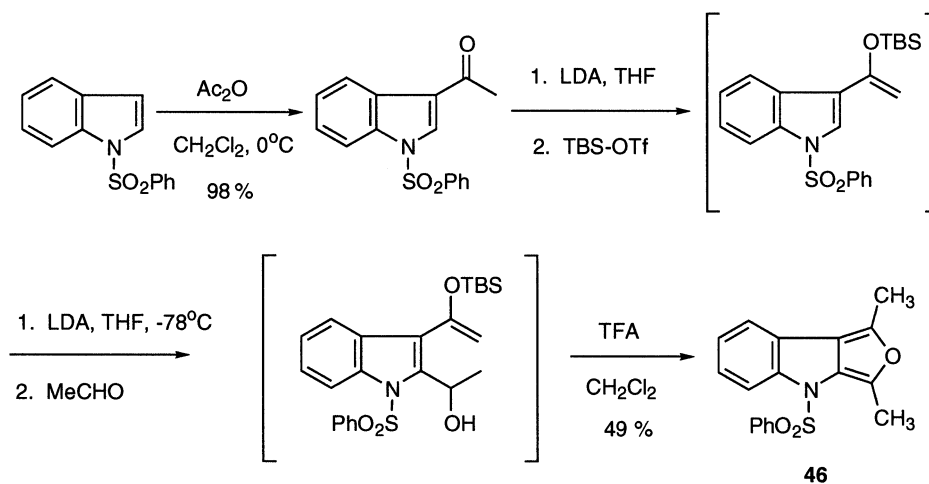
Scheme 24

In view of the importance of furo[3,4-*b*]indoles as indole-2,3-quinodimethane analogs, we needed to develop shorter, more efficient routes to this ring system. Indeed, we have found that C-2 lithiation of acetal **44**, subsequent quenching with an aldehyde, and acid-induced cyclization affords good to very good overall yields of furoindoles **45** (Scheme 25) [38].
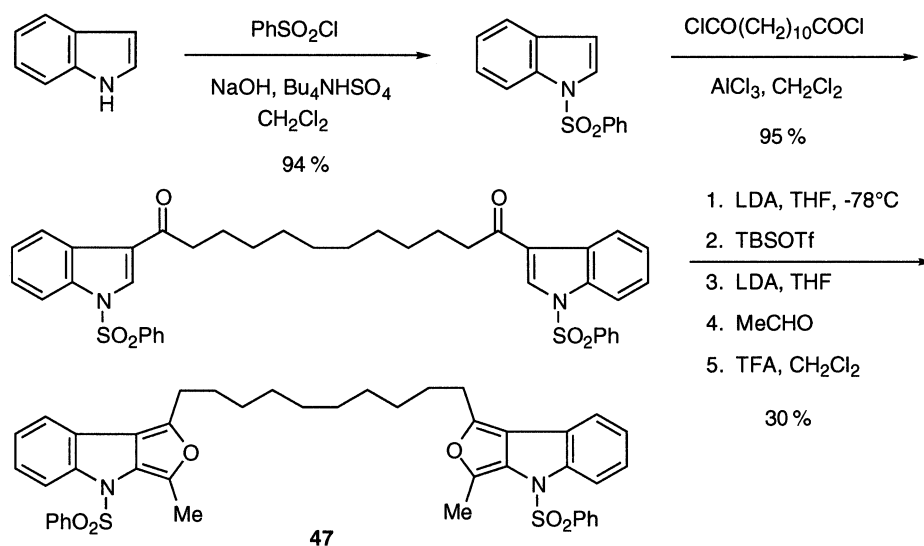
Scheme 25

Slightly different tactics provide an efficient synthesis of the important 1,3-dimethylfuroindole **46** (Scheme 26) [39].

Scheme 26

This same strategy has afforded bis-furoindole **47** (Scheme 27) [21], a compound that we previously synthesized in very poor overall yield [34].

Scheme 27

CONCLUSION

Despite the intense scrutiny that indoles have undergone for the past 100 years, new chemistry of this fascinating heterocycle continues to be revealed. In particular, C-2 and C-3 electron-withdrawing substituents on the indole ring allow for a variety of nucleophilic addition and cycloaddition reactions to proceed, the course of which often depends on the *N*-protecting group. Space does not allow the presentation of our work involving Diels–Alder reactions with 2- and 3-nitroindoles leading to carbazoles [40] and the synthesis and Diels–Alder reactions of furo[3,4-*b*]pyrroles affording indoles [41].

ACKNOWLEDGMENTS

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