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Selective endo and exo Iodocyclizations in the Synthesis of Quinolines and Indoles

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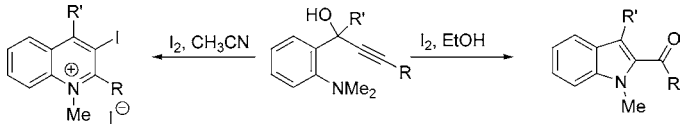
ABSTRACT



A simple, efficient method for a divergent synthesis of indoles, quinolines, and quinolinones using a highly selective endo/exo iodocyclization procedure is described.

The iodocyclization of heteroatoms such as oxygen, nitrogen, and sulfur with tethered alkynes has proven to be an effective method of preparing a large variety of heterocyclic-ring systems.[1−7] Important heterocycles such as furans,[1] pyrroles,[2] thiophenes,[3] indoles,[4] benzo[*b*]furans,[5] and benzo[*b*]thiophenes,[6] among others,[7] have been accessed using this protocol. We have employed this protocol in structure−activity relationship studies of some novel tubulin polymerization inhibitors in a manner that provides judicious and convenient modification of both the substituents and the scaffold, for example, **1** and **2** (Figure 1).[8] Herein, we report highly selective 5-exo- and 6-endo-digonal iodocyclization protocols that give direct access to a variety of indoles and quinolines and their application to the synthesis of analogues of **1** and **2**.

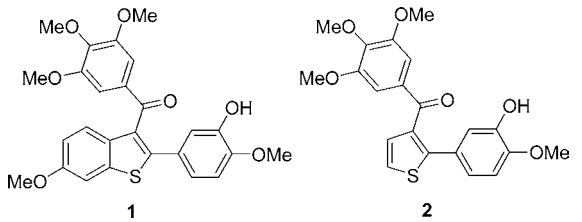


Figure 1. Potent heterocyclic tubulin polymerization inhibitors.[3a,6a]

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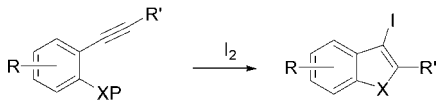
Studies by both Larock and our group have shown that 5-endo-digonal iodocyclization of readily available alkyl(2-alkynylphenyl) sulfides **3a** is an effective method for constructing 3-iodobenzo[*b*]thiophenes **4a**, which are activated toward C-3 substitution by virtue of the functionality of the iodo group (Scheme 1).[6] Larock and Noltes have

Scheme 1. 3-Iodobenzo[*b*]thiophenes and 3-Iodoindoles from 5-endo-Digonal Iodocyclization.



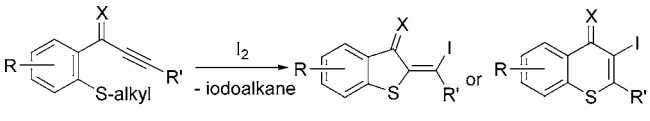
3a (X = S, P = alkyl)
3b (X = NMe, P = Me)

4a (X = S)
4b (X = NMe)

shown that equivalent 2-alkynyldimethylanilines **3b** can also participate in related iodocyclizations to give 3-iodoindoles **4b**.[4a,d]

Recently, we reported the preparation and iodocyclization of systems where the tether between the sulfide and the alkyne had been extended by one carbon, in particular, of 1-(2-alkylthiophenyl)alk-2-yn-1-ones **5a** and 1-(2-alkylthiophenyl)alk-2-yn-1-ols **5b** systems (Scheme 2).[6c] Interestingly,

Scheme 2. 5-exo-Digonal and 6-endo-Digonal Cyclization of **5**



5a (X = O)
5b (X = R",OH)

5-*exo*-digonal
6a (major)
6b (only)

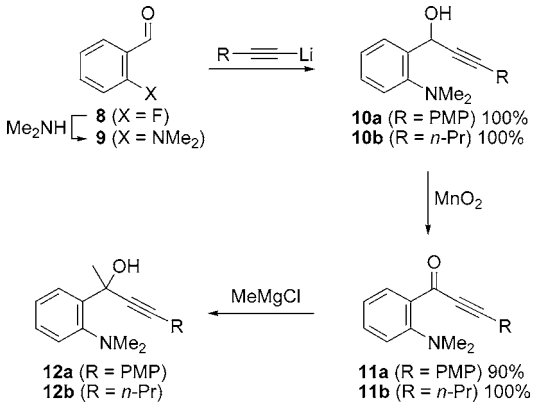
6-*endo*-digonal
7a (trace)
7b (none)

the possible 5-exo-digonal and 6-endo-digonal iodocyclization pathways of such systems are not predicted by Baldwin's rules and may provide for either or both products.[3a,9]

We observed that the different sulfides **5** all exhibited a strong bias toward the 5-exo-digonal pathway to give **6** rather than the 6-endo-digonal pathway to give **7** (Scheme 2).[6c] This was consistent with the earlier observations of Ren et al. on equivalent, nonbenzofused systems.[3b] In this report, we describe the iodocyclizations of dimethylamino equivalents of **5**, which exhibit somewhat different endo/exo selectivities. The dimethylamino containing iodocyclization precursors **10**−**12** were prepared in an almost identical manner to that previously described for some of the alkylthio systems **5** (Scheme 2).

Readily available 2-fluorobenzaldehyde (**8**) was converted to **9** by nucleophilic aromatic substitution.[10] This aldehyde was converted into the iodocyclization precursors **10**−**12** by reaction with lithium acetylides to give **10**, followed by oxidation to give **11** and 1,2-addition of MeMgCl to the ketone **11** to give **12** (Scheme 3).[6c] The tertiary alcohols **12**

Scheme 3. Preparation of Iodocyclization Precursors

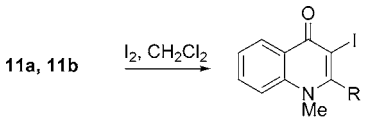


PMP = *para*-methoxyphenyl

were not purified but were used as crude reaction mixtures in the iodocyclization step (see below).

Unlike the ketone-linked sulfides **5a**, which underwent highly selective 5-exo-digonal iodocyclization, the equivalent dimethylamino systems **11** proved highly selective for the 6-endo-digonal pathway to give quinolinones **13** (Scheme 4).[11] The variations in reaction conditions that we have

Scheme 4. Iodocyclization of **11** in Dichloromethane



13a (R = PMP) 94%
13b (R = *n*-Pr) 86%

6-*endo*-digonal

employed to date (change in solvent and change in the $I^{\delta+}$ source) have not affected the endo/exo selectivity of these iodocyclization reactions.[12]

When the secondary and tertiary alcohols **10** and **12**, respectively, were subjected to iodocyclization, it was revealed that these systems could be directed down either a 6-endo-digonal or a 5-exo-digonal pathway depending on the nature of the reaction conditions (Scheme 5). When iodocyclization of the alcohols **10** and **12** was performed in

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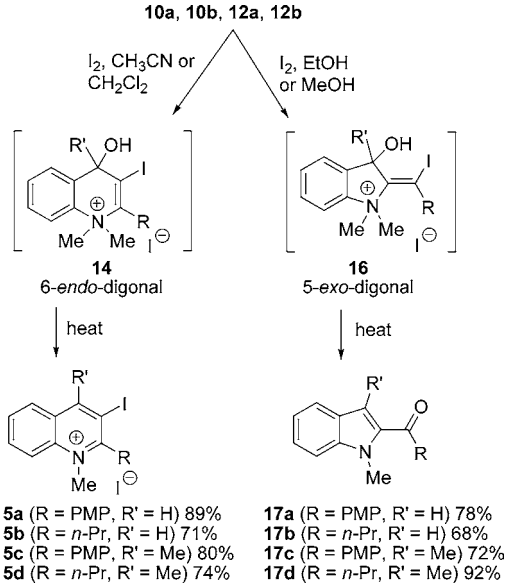
(10) Damhaut, P. *Tetrahedron* **1997**, *53*, 5785.

(11) No 5-exo digonal product could be detected in the ^{1}H NMR spectra of the crude reaction mixtures. The endo nature of this iodocyclization reaction was based on the characterization of **13a** using HMBC (see Supporting Information).

(12) Iodocyclizations were also performed in ethanol and acetonitrile using iodine. ICl and *N*-iodosuccinimide were used as alternative iodonium sources in dichloromethane and acetonitrile.

Scheme 5. Iodocyclization of **10** and **12** in Different Solvents



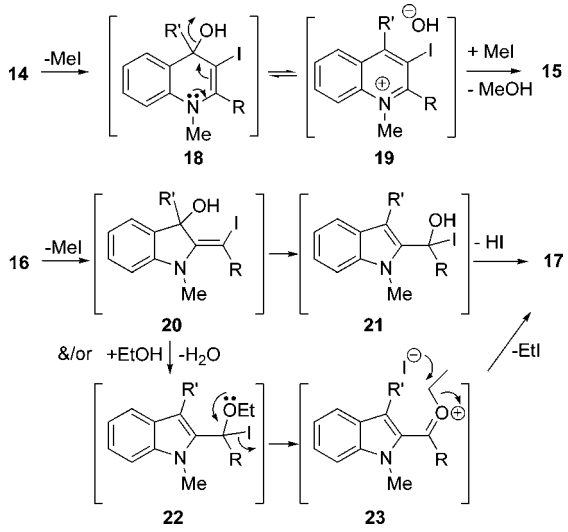
acetonitrile or dichloromethane using iodine, the 6-endo-product **14** was formed as a white precipitate. The quaternary ammonium salts **14** were often unstable and were generally not isolated but converted to the quinolinium salt **15** by direct heating of the reaction mixture.[13]

When iodocyclization of the alcohols **10** and **12** was performed in ethanol or methanol using iodine, the 5-exo-digonal product **16** was formed as a white precipitate. As with the quaternary ammonium salts **14**, the salts **16** were generally not isolated but converted to the 2-acylindoles **17** upon direct heating of the reaction mixture.[13] It should be noted that, for iodocyclizations involving tertiary alcohols of the type **12**, the alcohols are not isolated but are iodocyclized as crude reaction mixtures resulting from the alkylation of the relevant ketone **11**. Accordingly, the yields of **15c** and **15d** and **17c** and **17d** are calculated from the associated ketones **11a** and **11b**. It is also noteworthy that the *N*-methylquinolinium salts of the type **15** can be conveniently demethylated to give the parent quinolines (see below).[14]

At this stage, we are not able to offer a completely satisfactory explanation for the alternation of the endo/exo selectivity observed for the iodocyclizations of systems **10** and **12** in different solvents. The key difference at this stage appears to be in the protic nature of the solvent rather than in its polarity because both dichloromethane and acetonitrile gave **15** as the product and **17** was only formed in ethanol or methanol.

It also appears that the formation of **14** and **16** is under kinetic control because they both form quickly at room temperature, precipitate from the reaction mixtures, and do not interconvert when subsequently dissolved in the same solvent (dilute solutions in acetonitrile).[15] How the protic nature of the solvent affects the endo/exo selectivity of the iodocyclization pathway is uncertain. A proposed mechanism for the conversion of **14** and **16** to **15** and **17**, respectively, is given in Scheme 6. Loss of iodomethane from **14** to give

Scheme 6. Proposed Mechanism for the Conversion of **14** and **16** to **15** and **17**, Respectively



18 is followed by expulsion of the hydroxyl in **18** to give **19**. Because only one equivalent of iodine is used in these reactions, the hydroxide counterion in **19** presumably displaces the iodo group in iodomethane to give the observed iodide salt **15**. Loss of iodomethane from **16** gives **20**. As previously proposed for the equivalent benzo[*b*]thiophenes **6b**,[6c] these systems can be converted to the 2-acylindoles **17** either by 1,3-allylic migration of the hydroxyl group to give **21** and elimination of HI or by allylic substitution of the hydroxyl group in **20** with ethanol to give **22** (for reactions performed in ethanol), which loses iodoethane from the oxonium species **23** to give **17**.

The 5-exo-digonal iodocyclization reaction can also be used to access 2-[(*Z*)-1-iodoalkenyl]indoles **24** (Scheme 7) on the basis of observations made during our work on benzo-[*b*]thiophenes **6b** (R′ = CH_2R'''), which could be directed to give rise to the equivalent 2-[(*Z*)-1-iodoalkenyl]benzo[*b*]-thiophenes.[6c] This required the formation of the acetates **10b-Ac** and **12b-Ac**, respectively, which were conveniently formed by addition of acetic anhydride to the alkoxide resulting from nucleophilic addition to the aldehyde and ketones of **9** and **11b**, respectively (Scheme 7).

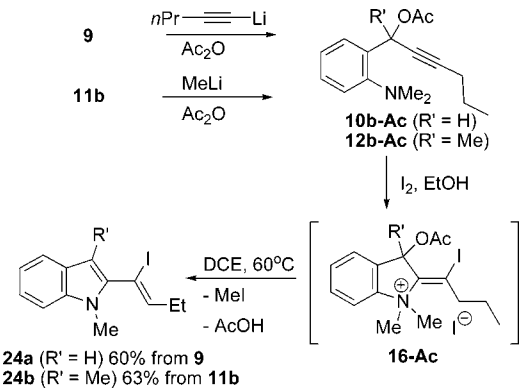
Iodocyclization of the acetates **10b-Ac** and **12b-Ac** in ethanol gives the intermediate acetates **16-Ac**. The reaction mixture is then evaporated to dryness to remove all traces

(13) Samples of **14** and **16** (R = *n*-Pr and R′ = H) were isolated, and an ^{1}H NMR spectrum and an LCMS were obtained on each (see Supporting Information).

(14) Deady, L. W.; Korytsky, O. L. *Tetrahedron Lett.* **1979**, *20*, 451.

(15) Similar iodocyclizations of sulfur and nitrogen heteroatoms involving alkenes often proceed in a 5-exo-digonal fashion but then undergo a 1,2-rearrangement to give a 6-endo-digonal-type product under thermal conditions. See: Gataullin, R. R.; Minnigulov, F. F.; Khakimova, T. V.; Fatykhov, A. A.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 1329 and ref 3a.

Scheme 7. Formation of 2-(1-Iodoalkenyl)indoles **24a** and **24b** by Iodocyclization of **10b-Ac** and **12b-Ac**



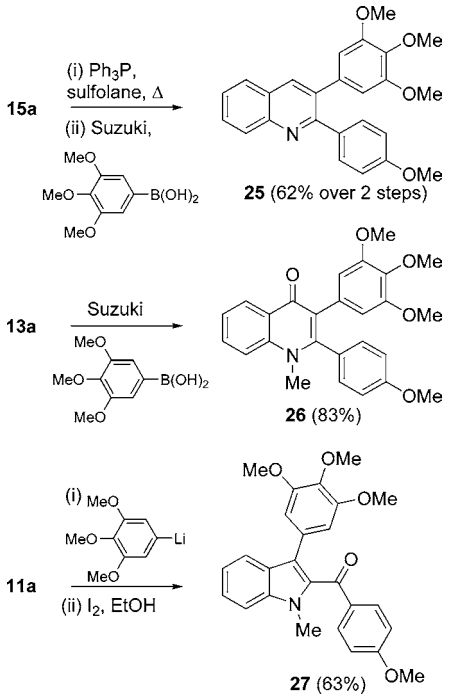
of ethanol, and the crude product **16-Ac** is heated in 1,2-dichloroethane (DCE) to give 2-[(*Z*)-1-iodoalkenyl]indoles **24a** and **24b** in good overall yields from **9** and **11b**, respectively (minor amounts of the *E*-isomer were observed upon standing). The exchange of ethanol for DCE as the solvent is required to avoid allylic substitution of the acetate for an ethoxy group, giving rise to an intermediate of the type **22**, which would lead to the formation of ketone **17** (Scheme 6). Likewise, the presence of the acetate groups in **10b-Ac** and **12b-Ac** prevents the possibility of any competing 1,3-allylic migration of the hydroxyl substituent in the equivalent intermediate of **20** (Scheme 6) leading to ketone **17**.[16]

We are currently using these selective iodocyclization reactions in our ongoing structure−activity relationship studies of tubulin polymerization inhibitors of the types **1** and **2**. In particular, we were interested in displaying the key pharmacophoric units, *para*-methoxyphenyl and 3,4,5-trimethoxyphenyl, over a range of different heterocyclic cores. For example, demethylation of **15a** followed by Suzuki coupling with 3,4,5-trimethoxyphenylboronic acid gives **25**.

(16) Evaporating the ethanol from the crude mixture of **16** (R = *n*-Pr, R′ = H) and adding acetonitrile and heating lead to a 1:2 mixture of indoles **17b** and **24a**.

Applying the same Suzuki coupling to **13a** gives analogue **26**. Finally, 1,2-addition of 3,4,5-trimethoxyphenyllithium to **11a** followed by iodocyclization of the crude tertiary alcohol in ethanol gives the indole **27** (Scheme 8).

Scheme 8. Synthesis of Analogues of **1** and **2**



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Supporting Information Available: Detailed synthetic procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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