# Synthesis of Indoles upon Sequential Reaction of 3-Alkynylpyrrole-2-carboxaldehydes with Iodonium Ions and Alkenes. Preparation of Related Benzofuran and Benzothiophene Derivatives

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Dedicated to Prof. Javier de Mendoza on the occasion of his 60th birthday

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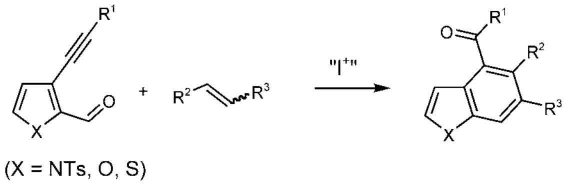
**Abstract:** Di- and trisusbstituted indoles **2** have been prepared by reaction of pyrroles **1** with alkenes *via* iodonium-induced benzannulation reaction. Enamines and enol ethers are also useful partners in that cyclisation process. This regioselective transformation can be easily adapted to prepare related benzofuran and benzothiophene skeletons.

**Keywords:** alkenes; enamines; indoles; iodine; pyrroles

The discovery of synthetic alternatives for a regioselective assembly of the basic core of heterocyclic compounds is of prime interest due to the many interesting biological profiles associated with these compounds and their ubiquitous prevalence in medicinal chemistry. The indole skeleton is a relevant target, thus the search for new methodologies to obtain this scaffold with different substitution patterns is a subject of much current interest.[1,2] However, only a few of these alternatives are well suited to obtain benzo-functionalised derivatives featuring a 2,3-unsubstituted indole ring motif.[3,4] In particular, the synthetic sequence involving the fusion of a benzene ring onto a pyrrole *en route* to generate the related indole has been hardly considered.[5]

Herein we present our preliminary results on a novel entry to the synthesis of different 2,3-unsubstituted indoles from pyrrole derivatives, and on its compatibility to obtain related benzofurans and benzothiophenes. Our approach is briefly outlined in Scheme 1.



**Scheme 1.** Iodonium-mediated benzoannulation approach for preparing benzo-fused heterocycles.

This strategy was established on the basis of our early observation on the key role that iodonium ions play as efficient promoters of an interesting reaction of *o*-alkynylbenzaldehyde, involving initial iodine-promoted cyclisation followed by *in situ* trapping of the resulting intermediate with silyl-masked C-nucleophiles.[6] Alternatively, a subsequent and stepwise cycloaddition reaction of that intermediate to either alkynes or alkenes led to substituted naphthalenes.[7] This iodination approach nicely complements recent work showing the merit of metal electrophiles, such as $AuCl_3$[8] or $Cu(OTf)_2$,[9] to assemble naphthalene or related skeletons from the same kind of precursors. Remarkably, although many research efforts have been focused in this area, no attempts to implement this interesting synthetic approach to target relevant benzo-fused heterocycles such as, for instance, indole have so far been disclosed.

Exploratory studies conducted on *N*-tosyl-protected 3-alkynylpyrrole-2-carboxaldehydes **1a** ($R^1 = n$-Bu) and **1b** ($R^1 = Ph$) proved the feasibility of the proposed iodination-mediated entry to both 4,5-disubstituted and 4,5,6-trisubstituted indoles **2**, depending on the degree of substitution of the starting olefin. Thus, indoles were regioselectively obtained upon treatment of **1** with the iodonium ions provided by the powerful and nicely storable iodinating reagent, the tetrafluoroborate of bis(pyridinium)iodonium ($IPy_2BF_4$),[10] and further reaction with the corresponding alkene (see Scheme 2 for indole structures and reaction details). In a typical experiment, the iodinating reagent and $HBF_4$ were mixed at 0 °C, the acid being added to speed the process by gently liberating into solution the active iodonium ions that would eventually trigger the cyclisation step. Both, simple alkyl and aryl model substituents on the alkyne are compatible with the process yielding the de-

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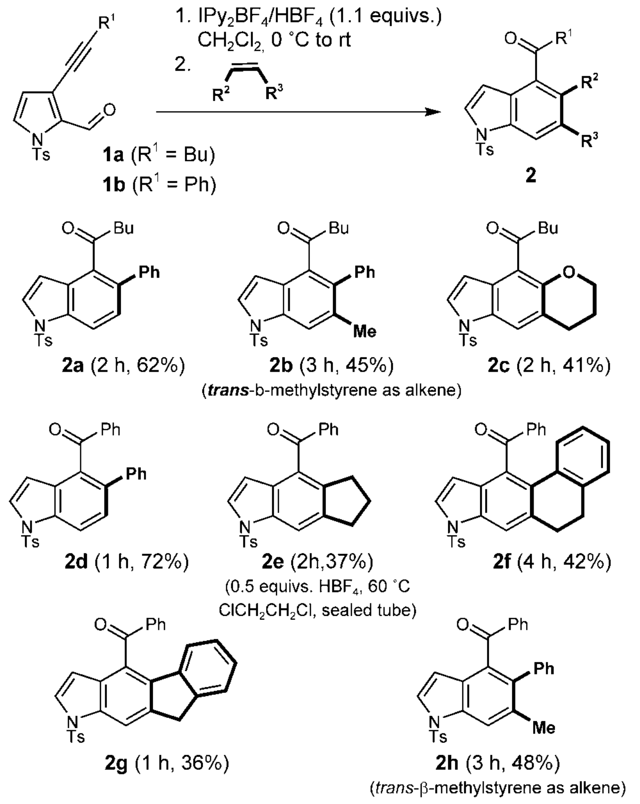
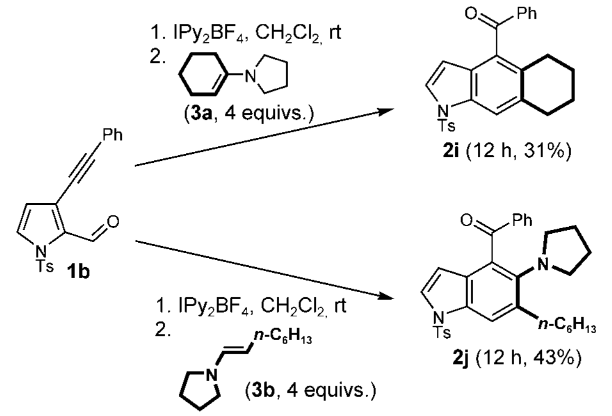


**Scheme 2.** Indoles **2** from reaction of pyrroles **1**, alkenes and $IPy_2BF_4$ in acid media.



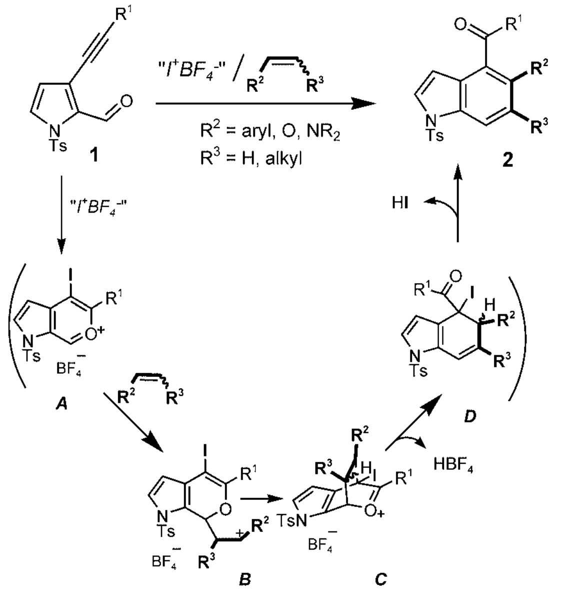
**Scheme 3.** Enamines, efficient partners in the iodonium-triggered entry to indoles **2** from pyrroles **1**.

sired indoles. As a rule, 1.2 equivs. of the corresponding alkene were added with the single exception of the reaction using cyclopentene (4 equivs. were used for this olefin).

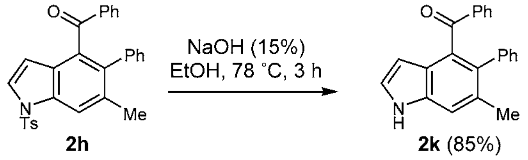
The reported reaction gives indoles showing nice substitution patterns in moderate to satisfactory isolated yields. So far, no attempts have been made to optimise the process and, in general, the reaction time has been established as a function of the disappearance of the starting pyrrole. Some cyclic olefins also undergo this transformation leading to tri- and tetracyclic compounds, among them 2,3-dihydropyran, indene and 1,2-dihydronaphthalene. For simple cycloalkenes, it was found that cyclopentene can enter the reaction under slightly modified conditions (reducing the amount of acid, changing to 1,2-dichloroethane as the solvent, increasing the reaction temperature up to 60 °C, see Scheme 2). However, under the same modified conditions, cyclohexene fails to react. We have also tested these alternative reaction conditions on a different alkene. Thus, **2h** can be prepared in 61% yield when **1b** was reacted with $IPy_2BF_4$ and *trans*-β-methylstyrene under the modified protocol, improving the yield previously obtained under standard reaction conditions and suggesting a simple alternative for future optimisation studies. Most interestingly, we have also tested the outcome for reaction partners that might render access to those indoles resulting from cycloalkenes other than cyclopentene, which represents a limitation for the direct reaction from the corresponding parent cycloalkene. Terminal aliphatic alkenes, such as 1-hexene, are also reluctant substrates under the standard conditions. Interestingly, the use of enamines opens up powerful opportunities for this approach to assemble the corresponding indoles arising from such alkene precursors (Scheme 3).

The reaction of the enamine **3a** derived from pyrrolidine and cyclohexanone offers an attractive solution to overcome the lack of reactivity evidenced by cyclohexene. Thus, sequential reaction of **1b** in $CH_2Cl_2$, at room temperature, first with $IPy_2BF_4$ and then with the enamine **3a**, afforded **2i**. Interestingly, under the same reaction conditions, **1b** reacted with the enamine **3b** (from pyrrolidine and 1-octanal) to furnish indole **2j** that now retains the amine fragment attached to the obtained heterocyclic skeleton.

A mechanistic proposal to account for the formation of the obtained products is outlined in Scheme 4. An interaction of the alkynyl fragment with iodonium ions liberated from the iodinating reagent would be reasonably involved in the first stage of the reaction, leading to intermediate ***A***. Stepwise reaction through intermediate ***B***, resulting from the nucleophilic attack onto ***A*** of an alkene (or the corresponding enol ether or enamine), followed by intramolecular trapping of the resulting cationic species by the β-iodoenol ether fragment would led to ***C***. In this frame, the ability of the substituents to stabilise the developing positive charge along the reaction path would explain the noticed regioselectivity for the overall process.[11] The simple loss of a proton to give a conjugate double bond affords ***D***, and from there aromatisation, by elimination of HI, furnishes indoles **2**. Interestingly when the enamine **3a** was used the indole **2i** was formed, losing the amine functionality and acting as a more reactive surrogate for cyclohexene. In this case, intermediate ***D*** would be lacking the required hydrogen in a β-position to iodine to give rise to the other-



**Scheme 4.** Proposed mechanism to account for the formation of **2**, upon reaction of **1** with iodonium ions and alkenes.

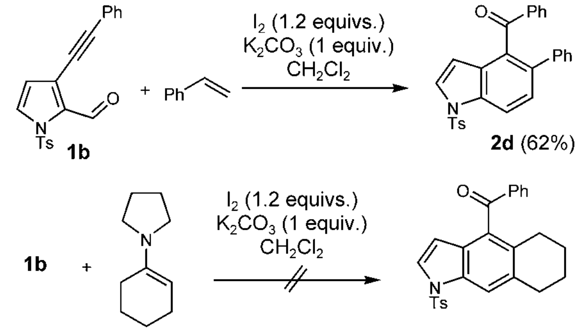


**Scheme 5.** Experimental conditions for deprotecting *N*-tosylated indoles.

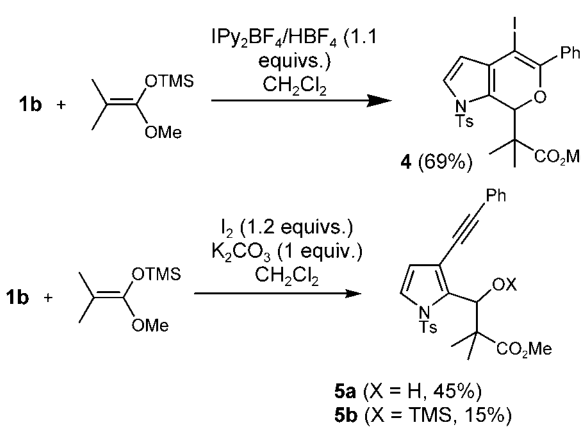
wise observed final aromatisation step, thus forcing an alternative cleavage of the β-amino functionality and affording **2i**.

Several additional aspects concerning this new transformation have been also explored, among them the deprotection of the *N*-tosyl-masked compound to afford the corresponding 1*H*-indole, the suitability of molecular iodine as an alternative iodonium donor and the possibility of extending this approach to prepare other types of benzo-fused heterocycles. Initially, the free indole was easily liberated upon a facile reaction in boiling ethanol with NaOH (see Scheme 5).[12]

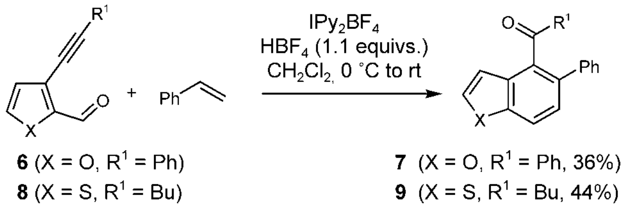
The use of iodine as a promoter for this kind of transformation was explored. It was found that it represents a true alternative for the reaction with conventional alkenes, such as styrene.[13] However, it fails to provide a useful triggering element to access the indole core when enamines were employed as an alternative to the olefin counterpart, see Scheme 6. In this case, a very sluggish process was observed, and after reaction for 24 hours and the usual aqueous work-up, **1b** was recovered unchanged to a great extent.[14] For iodine, like previously for the reaction using $IPy_2BF_4$, cyclohexene was also found to be unreactive to furnish indoles, under the standard protocol.



**Scheme 6.** Influence of the iodonium donor over the target indole synthesis.



**Scheme 7.** Different types of products for the reaction of **1** with silylketenes depending on the nature of the iodonium source.



**Scheme 8.** Synthesis of benzofuran **7** and benzothiophene **9** following a common approach.

Thus, for studies addressing the search for new transformations, $IPy_2BF_4$ represents for the moment a superior tool and offers the possibility of exerting an easy and tuneable control over the reaction, as several protocols have been already developed for its efficient use. In this sense, to further evaluate the robustness of the iodonium source and to test its influence over this class of one-pot but stepwise cyclisation processes involving labile C-nucleophiles, we have also gathered preliminary results concerning the reaction of pyrrole **1b** towards silylketenes. In these initial studies entirely different reaction pathways have been observed (see Scheme 7).

For this transformation, $IPy_2BF_4$ launches the desired iodocyclisation-nucleophilic trapping sequence leading, after the corresponding hydrolysis to **4**, providing additional support to the above proposed mechanism. The use of iodine triggers a different process such as the addition of the nucleophile to the carbonyl functionality, showing again a difference for the reaction pathway taking place as a function of the iodonium source.

Finally, we have also explored the convenience of this type of approach to tackle other but related heterocycles. The initial results are depicted in Scheme 8, showing the possibility of further use this transformation to prepare both benzofuran **7** from furan **6** and, similarly, benzothiophene **9** from the related thiophene **8**. This represents more than a nice addition to this study, because the number of methods available to prepare these heterocycles is more limited when compared to those for indoles.

Overall a new strategy to regioselectively prepare different types of benzo-fused heterocyclic scaffolds has been executed. Main emphasis has been devoted to the preparation of interesting patterns of di- and trisubstituted indoles featuring the 2,3-unsubstituted ring motif. The process is based on the reaction of a pyrrole precursor with an alkene mediated by iodonium ions, and has been found compatible with the replacement of the olefin by the more labile and reactive enol ethers and enamines, opening new expectations for these simple benzannulation operations. Further studies to optimise this transformation and to delineate its scope are in progress.

## Experimental Section

### Synthesis of the Indole 2a by Reaction of Pyrrole 1a, Styrene and $IPy_2BF_4$ in Acid Medium; Typical Procedure

$IPy_2BF_4$ (112 mg, 0.3 mmol, 1 equiv.) was dissolved in dry $CH_2Cl_2$ (5 mL). The solution was cooled at 0 °C and tetrafluoroboric acid (54% solution in diethyl ether; 45 μL, 0.33 mmol, 1.1 equivs.) was added. After 10 min, 3-(hex-1-ynyl)-*N*-tosylpyrrole-2-carboxaldehyde (**1a**; 99 mg, 0.3 mmol, 1 equiv.) was added and the solution was stirred during 30 min at room temperature. After this time, styrene (41 μL, 0.36 mmol, 1.2 equivs.) was added and the solution was further stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (20 mL) and water (20 mL); dried over sodium sulphate and concentrated. The crude material was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford the compound **2a**; yield: 80 mg (62%).

### Supporting Information

Experimental procedures, characterisation data and NMR spectral data of all compounds are contained in the Supporting Information.

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