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Synthesis of 1-Substituted Isoquinolines by Heterocyclization of TosMIC Derivatives: Total Synthesis of Cassiarin A

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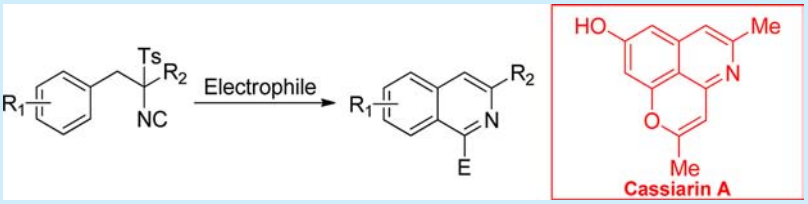
Supporting Information



ABSTRACT: A new method for the synthesis of 1-substituted isoquinolines by a heterocyclization that involves α-benzyl TosMIC derivatives and different electrophiles has been developed. This methodology has been successfully applied to a total synthesis of cassiarin A, an alkaloid with potent antiplasmodial activity against *Plasmodium falciparum*.

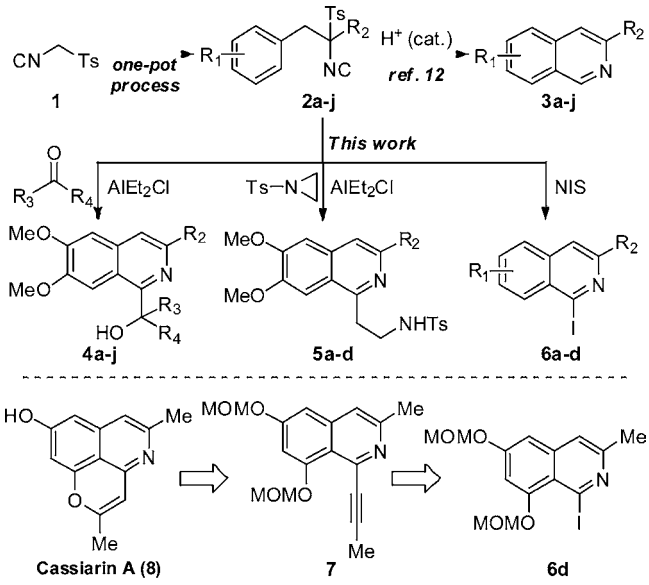
Isoquinolines and their reduced derivatives can be found as substructures in many relevant natural products[1] and fine chemicals, such as pharmaceuticals[2] and organic materials.[3] Consequently, diverse synthetic methods for their preparation have been developed.[4] Classical synthetic routes, such as the Pictet–Spengler,[5] Bischler–Napieralski,[6] and Pomeranz–Fritsch[7] reactions, suffer from some drawbacks, mainly the use of harsh reaction conditions.[8] For this reason, the development of efficient methods for the preparation of these important heterocycles is still of great interest.[9]

As part of a research project aimed at expanding tosylmethyl isocyanide (TosMIC) chemistry[10] to the preparation of six-membered heterocycles,[11] our group has very recently developed a new method for the synthesis of isoquinolines through a catalytic acid-mediated cyclization of α-benzyl TosMIC derivatives.[12] This cyclization takes place through an electrophilic aromatic substitution process and works efficiently when electron-donating substituents are present in the benzene ring. Moreover, the validity of this new methodology has been demonstrated by applying it in the total synthesis of mansouramycin B.

We have explored this strategy in relation to a heterocyclization that involves α-benzyl TosMIC derivatives and different electrophiles. This reaction takes advantage of the capacity of isocyanides to act both as nucleophiles and electrophiles, which means that cyclization of a TosMIC derivative by electrophilic aromatic substitution and attack of the isocyanide to the corresponding electrophile would occur as a tandem process.

The above approach proved to be successful, and we report here a remarkable and effective synthesis of 1-substituted isoquinolines. Moreover, we applied this new methodology to a synthesis of the natural product cassiarin A (Scheme 1). This aromatic alkaloid, which has a tricyclic skeleton, was isolated from the leaves of *Cassia siamea*,[13] a common plant in Southeast Asia, and has attracted the widespread attention of

Scheme 1. General Approach to Isoquinoline Derivatives and Retrosynthetic Pathway for Cassiarin A



synthetic chemists[14] and pharmacologists[15] due to its potent antiplasmodial activity against *Plasmodium falciparum* (IC_{50} 0.005 μg/mL).[13]

Our initial attempts to carry out the heterocyclization of α-benzyl TosMIC derivative **2a**, which was obtained from TosMIC in a single one-pot, phase-transfer catalyst (PTC) process (Scheme 2),[12] employed benzaldehyde as the electrophile. Different Lewis acids [$AlCl_3$, $AlEt_2Cl$, $Yb(OTf)_3$] were also added to the reaction to enhance the electrophilicity of the

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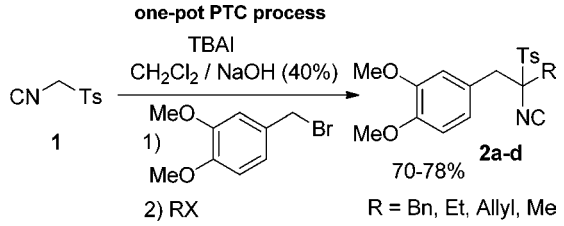
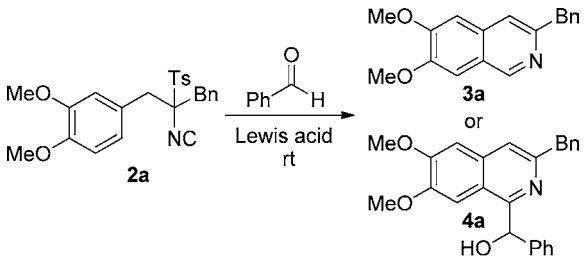
Scheme 2. Synthesis of TosMIC Derivatives 2a−d



aldehyde. It was found that the use of $AlCl_3$ or $Yb(OTf)_3$ led to the formation of 3-benzyl-6,7-dimethoxyisoquinoline **3a** following a known mechanism[12] in which the aldehyde is not involved (Table 1).

Table 1. Optimization of the Reaction Conditions for 4a



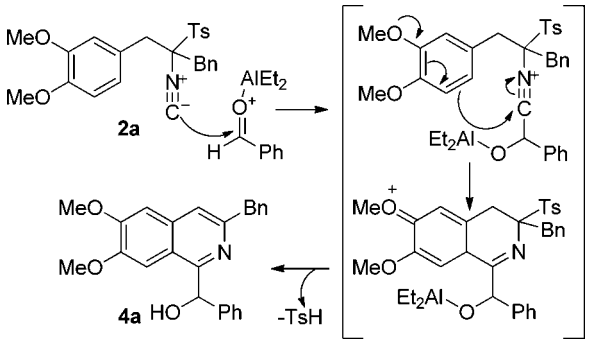
	Lewis acid	equiv	solvent	yield **3a**/**4a** (%)
1	$AlEt_2Cl$	1.4	THF	0/0[a]
2	$AlEt_2Cl$	1.4	CH_3CN	0/35
3	$AlEt_2Cl$	2.0	CH_3CN	0/37
4	$AlEt_2Cl$	2.0	CH_2Cl_2	0/80
5	$AlCl_3$	1.0	CH_2Cl_2	55/0
6	$Yb(OTf)_3$	1.0	CH_2Cl_2	43/0

[a]Starting material was recovered.

Nevertheless, the use of $AlEt_2Cl$ in CH_3CN afforded the desired 1-substituted isoquinoline **4a** as the only reaction product. In this sense, when 2 equiv of this Lewis acid was used with CH_2Cl_2 as solvent, the reaction achieved 80% yield.

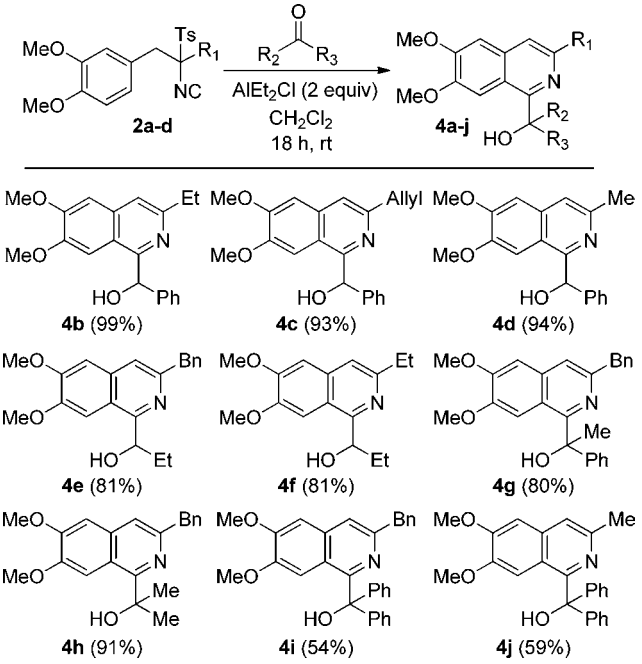
This result was rationalized through a plausible mechanistic hypothesis that involves cyclization of the TosMIC derivative by an electrophilic aromatic substitution and attack of the isocyanide to the aldehyde in a single process. The subsequent elimination of *p*-toluenesulfonic acid would afford the final product **4a** (Scheme 3). It is noteworthy that this method is only efficient when electron-donating substituents are present in the benzene ring. Thus, the dibenzyl TosMIC derivative was unable to produce the cyclization reaction.

Scheme 3. Mechanistic Hypothesis for the Cyclization of 4a



Once the best reaction conditions for the formation of **4a** had been identified (2 equiv of the electrophile, 2 equiv of $AlEt_2Cl$, CH_2Cl_2 as solvent, room temperature for 18 h), we studied the reaction with other *α*-benzyl TosMIC derivatives with electron-donating methoxy substituents in the benzene ring, such as the previously described *α*-ethyl and *α*-allyl compounds (**2b** and **2c**, respectively)[12] as well as with *α*-methyl derivative **2d**. The reaction was carried out in the presence of different carbonyl electrophiles, namely an aromatic and an alkylic aldehyde and three different ketones. In this way, compounds **4b−h** were formed in excellent yield (80−99%), whereas **4i** and **4j**, obtained both in this process in the presence of benzophenone, were isolated in more moderate yields (Scheme 4).

Scheme 4. Synthesis of 1-Substituted Isoquinolines 4a−j



In order to determine the scope of this new isoquinoline synthesis, we tested the cyclization with other kinds of electrophiles, including Michael acceptors, epoxides, aziridines and halogenating agents. Attempts with the first two types of reagents were unsuccessful. The addition to the *α*-benzyl TosMIC derivative **2a** of $AlEt_2Cl$ and *tert*-butyl acrylate, *β*-nitrostyrene, or propylene oxide only led to the recovery of starting material.

However, the reaction of **2a** with *N*-tosylaziridine and $AlEt_2Cl$ was successful and yielded isoquinoline **5a** in 68% yield. Similar results were obtained in the reaction of *N*-tosyl aziridine and the *α*-benzyl TosMIC derivatives **2b−d** (Scheme 5).

The use of *N*-iodosuccinimide as the electrophile also led to the desired heterocyclization. However, the addition of a Lewis acid was not necessary in this case, and a second step was required under strongly basic conditions (LiHMDS instead $NaHCO_3$) to promote the elimination of *p*-toluenesulfonic acid and the corresponding aromatization. In this sense, the addition of 2 equiv of NIS to the *α*-benzyl TosMIC derivative **2a** and a subsequent treatment at 0 °C with LiHMDS in *tert*-butyl methyl ether solution yielded isoquinoline **6a** in 96% yield.

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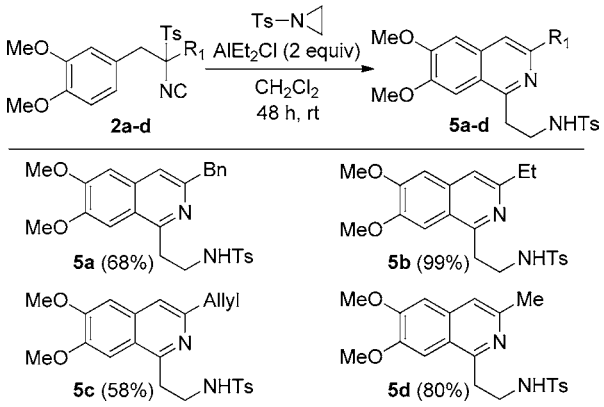
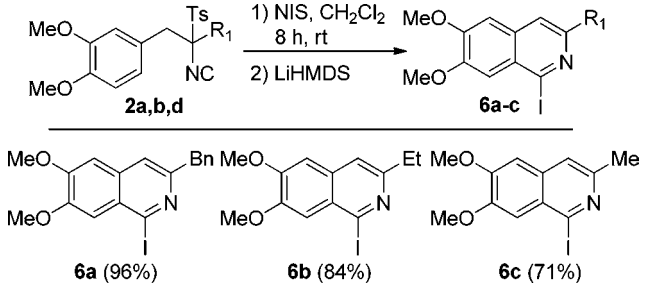
Scheme 5. Synthesis of 1-Substituted Isoquinolines 5a–d



Similar satisfactory results were obtained in the reactions of NIS and the α-benzyl TosMIC derivatives **2b** and **2d** (Scheme 6). The use of *N*-bromosuccinimide as the electrophile was also tested, but the starting materials **2a** and **2b** decomposed in all cases.

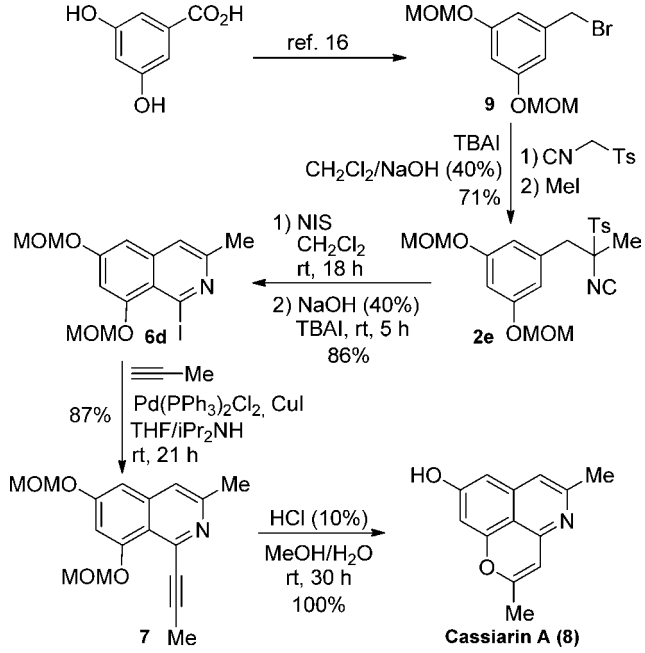
Scheme 6. Synthesis of 1-Substituted Isoquinolines 6a–c



Finally, the validity of this new methodology was demonstrated with a total synthesis of cassiarin A (**8**). The key step in this synthesis was the formation of 1-iodoisoquinoline **6d**, which subsequently could be transformed into the desired alkaloid (Scheme 7). The synthesis started with the preparation of benzyl bromide **9**,[16] and this was used in the preparation of α-benzyl TosMIC derivative **2e** through a PTC process. In this way, sequential addition to TosMIC of **9** and methyl iodide in a single two-phase medium [CH_2Cl_2/NaOH (40%)] afforded derivative **2e** in 71% yield. This compound was treated with 2 equiv of NIS to achieve cyclization and an aqueous solution of NaOH to force the aromatization, with the consequent formation of 1-iodoisoquinoline **6d** in 86% yield. Finally, Sonogashira coupling of **6d** with in situ generated propyne gave alkyne **7** in 87% yield. Compound **7** was converted quantitatively into the natural product cassiarin A (**8**) by treatment with 10% aq HCl in methanol.[14b]

In summary, a new method for the synthesis of 1-substituted isoquinolines has been developed through a heterocyclization that involves α-benzyl TosMIC derivatives and different electrophiles. This reaction works efficiently when electron-donating methoxy substituents are present in the benzene ring and takes advantage of the capacity of isocyanides to act both as a nucleophile and an electrophile. The validity of the new methodology was demonstrated by applying it in a total synthesis of cassiarin A (53% overall yield in four steps from commercially available TosMIC).

Scheme 7. Total Synthesis of Cassiarin A



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01521.

Experimental procedures and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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