

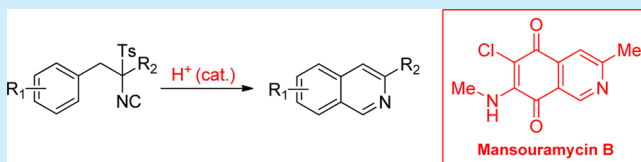
Isoquinoline Synthesis by Heterocyclization of Tosylmethyl Isocyanide Derivatives: Total Synthesis of Mansouramycin B

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S Supporting Information

ABSTRACT: A new method for the synthesis of isoquinolines through a catalytic acid-mediated cyclization of α -benzyl TosMIC derivatives has been developed. This methodology has been successfully applied to the total synthesis of mansouramycin B. This is the first total synthesis of this compound to be reported in the literature.



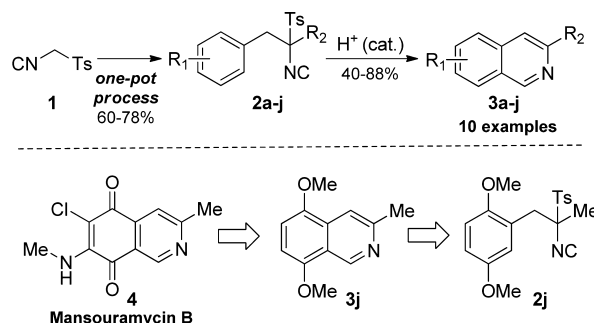
The isoquinoline core is an important structural motif that is found in many natural products,¹ pharmaceutically relevant molecules,² and organic materials.³ Due to the significance of this core, diverse synthetic methods for its preparation have been developed.⁴ Classically, isoquinolines have been synthesized using the Pictet–Spengler,⁵ Bischler–Napieralski,⁶ and Pomeranz–Fritsch⁷ reactions. However, these methods are often limited due to the use of harsh reaction conditions.⁸ For this reason, the development of efficient methods for the preparation of isoquinoline derivatives is of great interest and recently reported annulation reactions to generate the isoquinoline system are promoted by different metallic catalysts such as rhodium (I and III), manganese, and palladium.⁹

Tosylmethyl isocyanide (TosMIC)¹⁰ is a densely functionalized building block with three groups that can engage in a multitude of reactions, although its most important application has been in the synthesis of five-membered heterocycles.¹¹

In the course of our research aimed at expanding TosMIC chemistry to the preparation of six-membered heterocycles,¹² we attempted the heterocyclization reaction of bromobenzyl TosMIC derivatives in the presence of *t*-BuLi. However, the expected isoquinoline derivative was not obtained, and an unexpected rearrangement gave 2-vinylbenzonitriles in high yields.^{12a} Here, we report a successful approach to the isoquinoline system from α -benzyl TosMIC derivatives that are able to undergo an annulation reaction to give isoquinolines under metal-free conditions. The heterocyclization occurs on substrates bearing electron-donating substituents in the benzene ring under catalytic acid conditions.

Moreover, in order to prove the validity of this new methodology, we have applied it in the first total synthesis of mansouramycin B (Scheme 1). This alkaloid belongs to the mansouramycin family, a group of five isoquinolinequinones isolated in 2009 from the marine-derived *Streptomyces* sp. isolate Mei37. These compounds have shown cytotoxicity against 36 cancer cell lines and were found to have significant activity against nonsmall cell lung cancer, breast cancer, melanoma, and prostate cancer cells. Specifically, high cytotoxicity was shown against many human cancer cell lines,

Scheme 1. General Approach to Isoquinoline Derivatives and Retrosynthetic Pathway for Mansouramycin B



with an IC₅₀ value up to 0.089 μ M for lung cancer.¹³ Due to the biological importance of this group of alkaloids, the first total synthesis of mansouramycin D has recently been published.¹⁴ However, the successful synthesis of mansouramycin B has not been reported to date.

First, it was necessary to synthesize suitable TosMIC derivatives to explore catalytic acid-mediated cyclization. The preparation of the corresponding α -benzyl α -alkyl TosMIC derivatives **2a–h** was achieved by the addition of two different alkyl groups in a single one-pot phase transfer catalyst (PTC) process. It was found that TosMIC reagent **1** reacted sequentially with two different alkyl halides in a single two-phase medium [$\text{CH}_2\text{Cl}_2/\text{NaOH}$ (40%)] in the presence of tetrabutylammonium iodide (TBAI) as catalyst.^{12a} The first addition of 1 equiv of the substituted benzyl bromide to TosMIC at 0 °C, to avoid the formation of dibenzyl derivatives, was followed by a second addition of a simple alkyl halide at room temperature. This process gave isonitriles **2a–h** in high yields (Table 1). α -Benzyl α -phenyl TosMIC derivative **2i** was obtained in 85% yield by addition of 3,4-dimethoxybenzyl bromide to tosylbenzyl isocyanide¹⁵ in the presence of *n*-BuLi.

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Table 1. Synthesis of TosMIC Derivatives 2a–h

one-pot PTC process					
	R ₁	R ₂	R ₃	yield (%)	compd
1	OCH ₃	OCH ₃	Et	73	2a
2	OCH ₃	OCH ₃	Bn	70	2b
3	OCH ₃	OCH ₃	allyl	78	2c
4		OCH ₂ O	Et	70	2d
5		OCH ₂ O	Bn	68	2e
6	OCH ₃	H	Et	67 ^a	2f
7	OCH ₃	H	Bn	72 ^a	2g
8	NBn ₂	H	Et	60	2h

^aThese reactions were carried out in NaOH (30%) solution at 0 °C during the first addition.

With the aim of finding an efficient method to obtain isoquinolines from the TosMIC derivatives, α -3,4-dimethoxybenzyl α -ethyl TosMIC 2a was selected to study the viability of the planned cyclization reaction (Table 2). Initial attempts

Table 2. Optimization of the Reaction Conditions for 3a

	catalyst	equiv	solvent	time (h)	yield (%)
1	CH ₃ COCl	1	CH ₂ Cl ₂	18	31
2	^t BuCOCl	1	CH ₂ Cl ₂	24	40
3	^t BuCOCl	1	THF	48	36
4	^t BuCOCl	1	CH ₃ CN	48	35
5	CF ₃ SO ₃ H	0.1	CH ₂ Cl ₂	24	25
6	CF ₃ CO ₂ H	0.1	CH ₂ Cl ₂	18	73
7	AlEt ₂ Cl	0.3	CH ₂ Cl ₂	48	0 ^a
8	AlEt ₂ Cl	1	CH ₂ Cl ₂	18	0 ^a
9	Yt(OTf) ₃	0.3	CH ₂ Cl ₂	48	69
10	AlCl ₃	0.1	CH ₂ Cl ₂	18	22 ^a
11	AlCl ₃	0.3	CH ₂ Cl ₂	18	69
12	AgBF ₄	0.3	CH ₂ Cl ₂	24	0 ^a
13	CuI	0.1	CH ₂ Cl ₂	24	0 ^a
14	[P(Ph) ₃] ₂ AuCl	0.1	CH ₂ Cl ₂	24	0 ^a

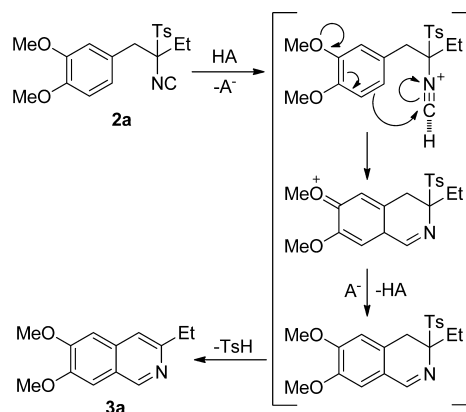
^aStarting material was recovered.

were carried out using acyl halides because there are examples of the reaction of isocyanides with acyl halides to provide α -ketoimidoyl halides, which can undergo silver(I)-mediated cyclizations to form 1-acyl-3,4-dihydroisoquinolines.¹¹ Thus, derivative 2a was treated with 1 equiv of acetyl chloride, but instead of the expected acylimidoyl chloride, isoquinoline 3a was obtained as the main isolated product (Table 2, entry 1). The same result was obtained on treatment of 2a with pivaloyl chloride in different solvents (entries 2–4), with the best yield obtained in CH₂Cl₂.

These results were rationalized as being due to the presence in the reaction medium of tiny amounts of hydrogen chloride, which could force an acid-mediated cyclization of TosMIC derivative 2a by an electrophilic aromatic substitution

process.¹⁶ The subsequent elimination of *p*-toluenesulfonic acid would afford isoquinoline 3a (Scheme 2). This mechanistic

Scheme 2. Mechanistic Hypothesis for the Cyclization of 2a



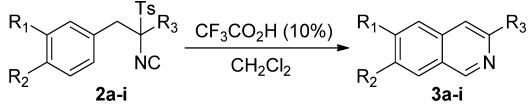
hypothesis was tested by adding to 2a catalytic amounts of different Brønsted and Lewis acids (Table 2, entries 5–11). Isoquinoline 3a was the only product of these reactions, and this result confirmed our assumption.

From the experiments listed in Table 2, it was found that treatment with 0.1 equiv of trifluoroacetic acid in CH₂Cl₂ at room temperature was the best condition for the cyclization of TosMIC derivative 2a. In this way, isoquinoline 3a was obtained in 73% yield. It is worth noting that this reaction was also tested using different metals as catalysts (Ag, Cu, Au, entries 12–14) but the reaction did not take place under these conditions.

In order to determine the scope of this new isoquinoline synthesis, the best conditions achieved for the cyclization of 2a were applied to other α -benzyl TosMIC derivatives. As a general conclusion, it was found that this method is efficient when electron-donating substituents are present in the benzene ring. The isoquinolines successfully obtained with this methodology are listed in Table 3. First, the catalytic acid-mediated cyclization was tested with different α -alkyl or aryl α -3,4-dimethoxybenzyl TosMIC derivatives, which gave in all cases the expected isoquinolines in high yields (entries 1–3, 15). However, if a substituent was not present in the C3 position of the isoquinoline, the elimination of *p*-toluenesulfonic acid did not occur and the tosyl group remained in the final product.

In the next step, the substituents present in the benzene ring were changed. The results showed that cyclizations on benzene derivatives with electron-withdrawing substituents, such as halogens, or those without a substituent did not take place. For this reason, the subsequent investigations were focused on benzenes with electron-donating substituents (entries 4–14). α -Piperonyl TosMIC derivatives 2d and 2e underwent the cyclization to give high yields, although it was necessary to lower the temperature of the reaction medium (entries 4–6). In α -3-methoxybenzyl TosMIC derivatives, cyclization was also successful despite the formation of a small amount of the other possible regioisomer of the reaction (3-alkyl-8-methoxyisoquinolines). In an effort to improve the selectivity of these reactions, the cyclization was tested at different temperatures. It was found that the selectivity of the reaction increased on decreasing the temperature, with the best reaction conditions achieved at –30 °C (entries 7–12). Finally, reaction of α -3-dibenzylaminobenzyl TosMIC derivative 2h with catalytic

Table 3. Synthesis of Isoquinolines 3a–i



	R ₁	R ₂	R ₃	T (°C)	yield ^a (%)	compd
1	OCH ₃	OCH ₃	Et	rt	73 (0)	3a
2	OCH ₃	OCH ₃	Bn	rt	88 (0)	3b
3	OCH ₃	OCH ₃	allyl	rt	80 (0)	3c
4		OCH ₂ O	Et	rt	24 (0)	3d
5		OCH ₂ O	Et	−30	75 (0)	3d
6		OCH ₂ O	Bn	−30	73 (0)	3e
7	OCH ₃	H	Et	rt	70 (23)	3f
8	OCH ₃	H	Et	−30	82 (8)	3f
9	OCH ₃	H	Et	−78	68 (6)	3f
10	OCH ₃	H	Bn	rt	70 (16)	3g
11	OCH ₃	H	Bn	−30	73 (6)	3g
12	OCH ₃	H	Bn	−78	68 (5)	3g
13	NBn ₂	H	Et	rt	0 (0)	3h
14	NBn ₂	H	Et	rt	60 (0) ^b (AlCl ₃)	3h
15	OCH ₃	OCH ₃	Ph	rt	80 (0)	3i

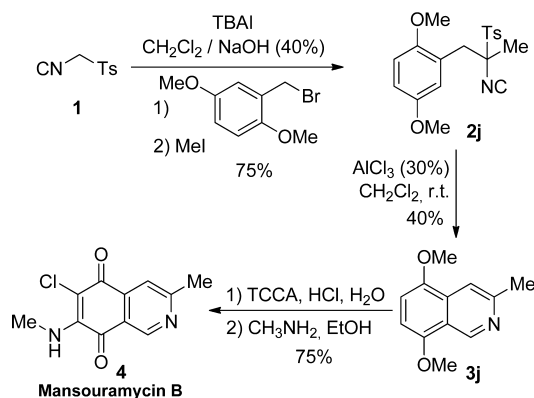
^aThe first number refers to the yield of the major regioisomer (3a–i); the number in parentheses refers to the yield of the minor regioisomer.

^bThis reaction was carried out with AlCl₃ (0.3 equiv) instead of CF₃CO₂H.

trifluoroacetic acid led to a complex mixture of products, but the same derivative was converted to isoquinoline 3h in 60% yield on using 0.3 equiv of AlCl₃ (entries 13 and 14).

The validity of this new methodology was demonstrated with the total synthesis of mansouramycin B (4). The key step in this synthesis is the formation of isoquinoline 3j, which can subsequently be transformed into the desired alkaloid (Scheme 3). Thus, the synthesis started with the preparation of TosMIC

Scheme 3. Synthesis of Mansouramycin B



derivative 2j by the method described in Table 1. Sequential addition of 2-(bromomethyl)-1,4-dimethoxybenzene¹⁷ and methyl iodide to TosMIC in a single two-phase medium [CH₂Cl₂/NaOH (40%)] afforded derivative 2j in 75% yield. This compound was treated with a catalytic acid medium to achieve the cyclization. Treatment with 0.1 equiv of trifluoroacetic acid in CH₂Cl₂ only led to the formation of isoquinoline 3j in poor yields. As a consequence, the conditions for the cyclization had to be modified slightly. The reaction of derivative 2j with 0.3 equiv of AlCl₃ in CH₂Cl₂ at room temperature yielded isoquinoline 3j in 40% yield. Finally,

isoquinoline 3j was converted to the alkaloid 4 by reaction with trichloroisocyanuric acid (TCCA) in H₂O/HCl at room temperature followed by the addition of methylamine in ethanol.¹⁸ In this way, mansouramycin B was obtained in 75% yield (23% overall yield).

In summary, a new method for the synthesis of isoquinolines through a catalytic acid-mediated cyclization of α-benzyl TosMIC derivatives has been developed. This cyclization takes place through an electrophilic aromatic substitution process and works efficiently when electron-donating substituents are present in the benzene ring. The validity of the new methodology was demonstrated by applying it in the total synthesis of mansouramycin B (23% overall yield in three steps from commercially available TosMIC). This is the first synthesis of this compound to be reported in the literature. Work is in progress to explore the potential of this reaction in the formation of more complex isoquinolines and to improve the synthesis of other relevant bioactive and pharmacologically interesting compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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