Synthesis of 2-Imino-3-aminobenzofurans via Multicomponent Reactions from TosMIC

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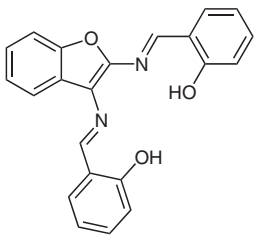
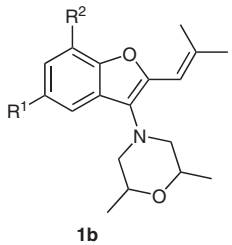
Abstract: A simple synthesis of 2-imino-3-aminobenzofurans was developed based on multicomponent reactions from *p*-toluenesulfonylmethylisocyanide, salicylaldehyde, and substituted anilines. The crystal structures of two of the aminobenzofurans were established by X-ray crystal structure analysis.

Key words: multicomponent reactions, imines, furans, TosMIC, isocyanide

To date, several synthetic routes to aminobenzofurans have been reported. Among the earlier examples, the synthesis of 2,3-diaminobenzofurans **1a** (Figure 1) using an excess of salicylaldehyde, concentrated ammonia, and aqueous potassium cyanide can be mentioned.[1] Later, Harhash prepared several 2-amino-3-arylaminobenzofurans[2] by treatment of Schiff bases with potassium cyanide in acetic acid followed by reaction with salicylaldehyde in the presence of catalytic amounts of piperidine. Also, 3-aminobenzofurans **1b** have been synthesized from 2,6-dimethylmorpholine, salicylaldehyde, and terminal acetylenes in the presence of copper(I) iodide[3] or the $Cu(OTf)_2$–CuCl-catalyzed coupling of salicyladehyde derivatives with alkynylsilanes and secondary amines followed by intramolecular cyclization.[4]



1a



1b

R^1 = H, NO_2, Cl, Br
R^2 = H, Cl, Br

Figure 1

A different approach is the isocyanide-based multicomponent reactions (IMCR) that comprise the Passerini three-component reaction (P-3CR), and the Ugi three- and four-component reactions (U-3CR, and U-4CR).[5] This methodology has been applied to the synthesis of structurally diverse molecules,[5] including benzofuran derivatives.[6] Thus, the reaction between phenols, aldehydes, and isocyanides affords 2-aminobenzofurans in a one-pot process via Mannich adducts;[7] 2-alkylamino- and 2-arylamino-3[(2-hydroxybenzylidene)amino]benzofurans can be generated from salicylaldehyde, isocyanides, and ammonium formate,[6a] and 2,3-diaminobenzofurans can be obtained using electron-poor 2-hydroxybenzaldehyde derivates, isocyanides, and secondary amines.[8]

In continuation with these studies, involved a multicomponent reaction, we envisioned the one-pot synthesis of benzofurans from the condensation of *p*-toluenesulfonylmethyl isocyanide (TosMIC) with salicylaldehyde and anilines by means of MCR. The later compounds are of interest and pharmacological importance due to their potential applications as anticonvulsant, anti-inflammatory,[9] antitumor,[10] and antimycobacterial[11] agents, they have also been shown to inhibit β-fibril formation.[12]

The present methodology provides selectively 2-imino-3-aminobenzofurans **5a–f** from a 2-hydroxybenzaldehyde (**2**), an amine **3**, and *p*-toluenesulfonylmethyl isocyanide (**4**, Scheme 1), in a one-pot process under mild reaction conditions in 39–71% yield,[13] adding a new derivative to the list of the formidable van Leusen reaction which provides a broad diversity of heterocycles, such as oxazoles,[14] imidazoles,[14,15] indoles,[16] triazoles,[17] and pyrroles.[18]

The ^{1}H NMR and ^{13}C NMR spectra evidenced the formation of the new heterocycle; selected spectroscopic data

Table 1 Selected ^{1}H, ^{13}C NMR (ppm), and IR (cm^{-1}) Data for Compound **5a–f**

Compound	^{1}H NMR (H-7)	^{13}C NMR (C-7)	IR (C=N)	Yield (%)
5a	8.98	156.2	1595	61
5b	9.04	155.0	1599	61
5c	9.00	156.2	1590	69
5d	9.05	155.9	1595	58
5e	9.05	155.8	1600	39
5f	8.94	154.1	1604	71

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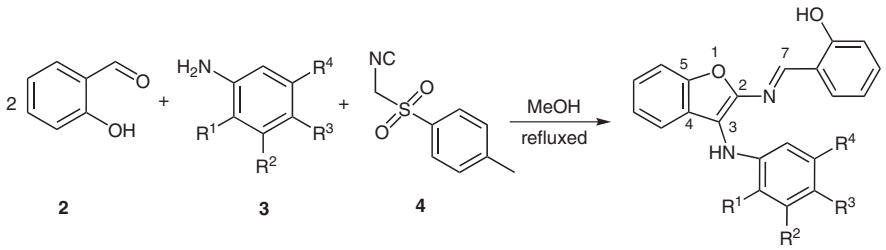

	R^1	R^2	R^3	R^4	Yield (%)
5a	OH	H	NO_2	H	61
5b	H	H	NO_2	H	61
5c	OH	H	NO_2	Cl	69
5d	OMe	H	NO_2	H	58
5e	NO_2	H	OMe	H	39
5f	H	NO_2	H	H	71

Scheme 1 Synthesis of 2-imino-3-aminobenzofurans

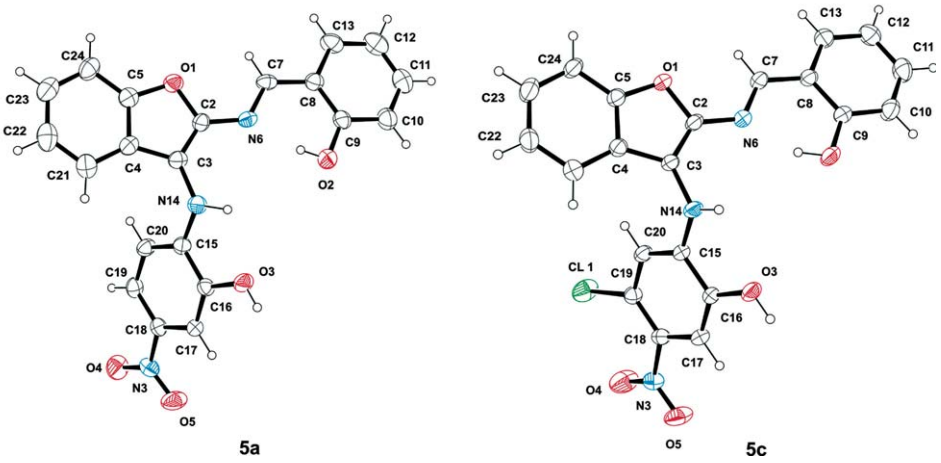

Figure 2 X-ray molecular structures and perspective view of compounds **5a** and **5c**

are summarized in Table 1. All of the compounds showed a low field signal around δ = 9.00 ppm attributed to H-7 that correlates with the ^{13}C NMR around δ = 156.0 ppm. The IR spectra revealed absorptions characteristic for N=C group from 1590–1604 cm^{-1}. Accordingly, the N–C2 fragment derived from TosMIC remains in the final product incorporating two molecules of aldehyde and amine.

The structures of **5a** and **5c** were corroborated by X-ray diffraction (Figure 2). Both compounds crystallized in the space group *C2/c* of the monoclinic system.[19]

A possible reaction sequence that accounts for the formation of the 2-imino-3-aminobenzofurans is depicted in Scheme 2. Condensation of 2-hydroxybenzaldehyde (**2**) with aminophenol **3** gives the Schiff base **6**. Subsequent attack of the TosMIC anion **7** gives the intermediate **8** which undergoes van Leusen reaction pathway to give the intermediate **9**,[15] tautomerization of **9** followed by nucleophilic attack of phenolic OH will result in the formation of **11**. Elimination of TsH, as is common in the van Leusen reaction, will generate the benzofuran **12**, which on hydrolysis affords the intermediate **13**. Finally, the amine **13** with the second molecule of 2-hydroxybenzaldehyde (**2**) yields the new heterocycle **5**.

In conclusion, a simple MCR is described for the synthesis of 2-imino-3-aminobenzofurans from three components by coupling of salicylaldehyde with various amines and *p*-toluenesulfonylmethyl isocyanide. The process is easy and demonstrates the versatility of isocyanide-based multicomponent reactions providing a different route to the existing conventional synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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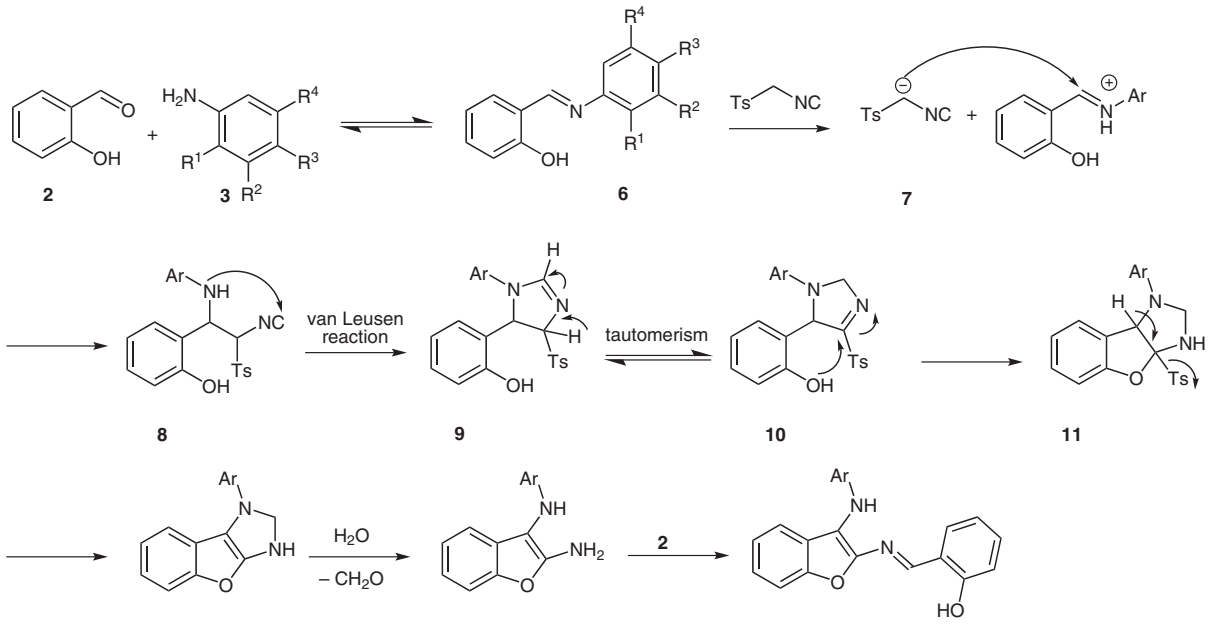

Scheme 2 Proposed mechanism

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(13) **General Procedure for the Preparation of 2-Imino-3-aminobenzofurans**
Salicylaldehyde **2** (2.00 mmol) was added to a solution of the amines **3a–f** (1.00 mmol) in MeOH (15 mL). The mixture was stirred for 30 min at r.t. and *p*-toluenesulfonylmethyl isocyanide (**4**, 1.20 mmol) was added. The reaction mixture was refluxed (3–24 h), and the solid precipitate was collected by filtration and washed with hexane.
Selected Data for Compound 5a
The product **5a** (0.450 g) was obtained as a red solid in 61% yield, mp 253–255 °C. IR: 3366 (OH), 1595 (C=N), 1310, 1275, 744 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.52 (1 H, br s, OH), 10.78 (1 H, br s, OH), 8.98 (1 H, s, H-7), 8.44 (1 H, br s, NH), 7.71–7.67 (2 H, m, ArH), 7.60–7.56 (2 H, m, ArH), 7.42–7.32 (3 H, m, ArH), 7.24 (1 H, t, *J* = 7.6 Hz, ArH), 6.93–6.87 (2 H, m, ArH), 6.61 (1 H, d, *J* = 9.04 Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.0, 156.2 (C=N), 151.0, 147.4, 144.8, 141.7, 138.4, 134.1, 132.1, 126.7, 126.4, 123.7, 120.7 (2 C), 120.1, 117.9, 117.2, 114.5, 111.9, 111.7, 109.2. MS (20 eV): *m/z* (%) = 389 (100) $[M]^+$, 372 (16), 342 (8), 268 (27), 236 (13), 211 (25), 122 (38). HRMS: *m/z* calcd for $C_{21}H_{16}N_3O_5$ $[M^+ + H]^+$: 390.1084; found: 390.1083.
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