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A simple synthesis of benzofurans by acid-catalyzed domino reaction of salicyl alcohols with *N*-tosylfurfurylamine

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ABSTRACT

A simple route to polysubstituted benzofurans based on the domino reaction of commercial or easily available salicyl alcohols with *N*-protected furfurylamine has been designed and developed. The reaction was found to proceed with reasonable yields under heating of substrates in acetic acid in the presence of catalytic amount of conc. HCl when tosyl was used as protecting group.

1. Introduction

An increasing attention towards furan chemistry during past few decades is dictated by several reasons. Firstly, the furan core is the key structural element of a large number of organic materials, natural products and drugs.[1] Secondly, simple furans are easily available via processing of renewable sources such as agricultural wastes and other carbohydrate-containing raw materials.[2] This allows one to use furans as inexpensive starting materials for the synthesis of various useful products. The huge diversity of such products is provided by the versatile reactivity of the furan ring; thereby furans can serve as unique building blocks in organic and medicinal chemistry research.[3] They are widely used as synthetic equivalents of 1,4-dicarbonyl compounds for the preparation of various acyclic, carbocyclic and heterocyclic compounds.[4] What is more, processes wherein only a single masked carbonyl groups is involved into new ring formation, second one being released in a free form, were developed for the synthesis of diverse heterocyclic products.[5] Similarly, containing two C=C bonds, furans can react as either 2π- or 4π-component depending on the reaction partner and conditions. Namely, furans appear as activated alkenes in [2 + 4]-, [2 + 3]-, [2 + 2]-, and [2 + 1]-cycloadditions.[6] At the same time, furans exhibit the reactivity of 1,3-dienes in [4 + 2]-, [4 + 3]- and [4 + 4]-cycloadditions[7] as well as affording 1,4-addition products in reaction with methanolic bromine and some other electrophiles.[8]

Bearing a leaving group at the α-position of the side chain, furans can behave as synthetic equivalents of 1,3-dienes also in reactions with nucleophiles affording products of nucleophilic attack at the C(5) atom of the furan ring rather than typical nucleophilic substitution (Scheme 1a). Since the first announcement of this abnormal reactivity almost 90 years ago,[9] a number of examples of such reactions with various nucleophiles (alkoxide, phenoxide, sodium diethyl phosphite, CH-acids, ketene S,S-acetals, indoles etc.) were reported.[10] It was shown that this reaction proceeds through the initial leaving group departure followed by attack of nucleophile onto the furan C(5) atom producing 2-methylene-2,5-dihydrofuran intermediate.[11] The same two steps are also involved in the Piancatelli rearrangement.[12] The intramolecular version of this anomalous nucleophilic substitution furnishing substituted spirans was also investigated (Scheme 1b).[13] In some cases, the

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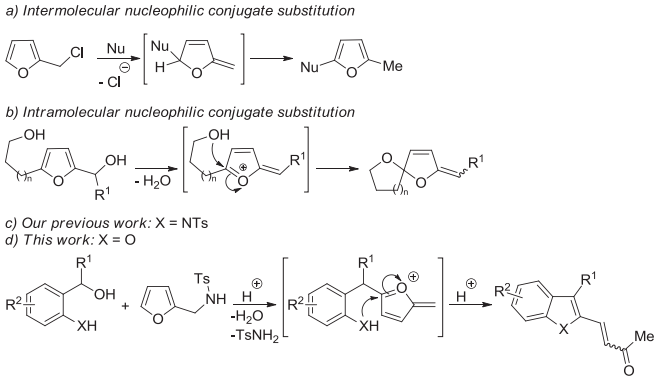


Scheme 1. Nucleophilic Conjugate Substitution of furfuryl derivatives.

corresponding spiroketal derivatives were isolated and it was showed that under acidic conditions they undergo further rearrangement producing the corresponding Piancatelli products.[14] Wu and Yin used this transformation in the total synthesis of antifeeding natural compound tonghaosu and its structural analogues.[15]

Recently, we described an unusual domino reaction of *N*-tosylfurfurylamine with 2-(tosylamino)benzyl alcohols providing direct access to 2-(2-acylvinyl)indoles,[16] an important class of organic molecules, which could be used as versatile building blocks for the synthesis of bioactive compounds (Scheme 1c). This reaction proceeds through the acid-induced elimination of tosylamide, intramolecular nucleophilic attack on the formed oxonium providing 5-methylene-5*H*-spiro[furan-2,2′-indoline], subsequent acid-promoted furan ring opening, and aromatization of the indole core. We proposed that the use of 2-hydroxybenzyl alcohols in this domino reaction should provide benzofurans that would allow for further extending the synthetic concept toward another class of internal nucleophiles. Herein we report our development of the general protocol for the synthesis of densely substituted 2-(2-acylvinyl)benzofurans in a highly stereoselective manner.

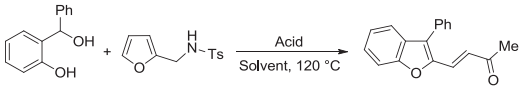
2. Results/discussion

The reaction of 2-hydroxybenzhydryl alcohol **1a** with *N*-tosylfurfurylamine **2a** was selected as a model process for the optimization of reaction conditions. Based on our previous findings, benzofuran **3a** was expected to be formed under acidic conditions.[16] The initial experiment showed that heating of starting compounds with H_3PO_4 in toluene under reflux afforded target product **3a** in low yield (Table 1, entry 1). Encouraged by this result, we have screened various Brønsted and Lewis acids using the same solvent and temperature regime and found that the yield of product could be improved to 40% when TMSCl was used (Table 1, entry 5).

Metal halides and trifluoromethanesulfonates were found to be less efficient in the initiation of the studied transformation (entries 6–10). In the attempt to achieve a better yield of the desired benzofuran **3a**, we have changed the solvent to acetic acid and screened several Bronsted acids again (entries 11–16). We found that the best yield of **3a** was observed when conc. HCl was applied for the transformation (entry 16). Further variation of the ratio of the reacting compounds, temperature and HCl loading had no positive influence on the yield of the target benzofuran **3a**.

Under the optimized conditions, we have screened a series of furans containing leaving groups of a different nature (Table 2). The furfurylamine **2b** and its derivatives **2c-e**, furfuryl alcohol **2f** and its derivatives **2g-j** and 5-(furan-2-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **2k** applied to this reaction. We have found that

Table 1
Screening of reaction conditions.



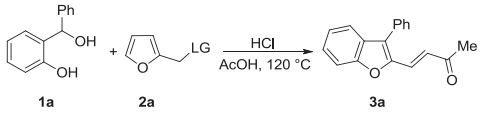
1a 2a 3a

Entry[a]	Acid	Solvent	Time (h)	Yield of **3a** (%)[b]
1	H_3PO_4	Toluene	0.5	16
2	AcOH	Toluene	12	25
3	TFA	Toluene	12	32
4	H_2SO_4	Toluene	0.5	22
5	TMSCl	Toluene	24	40
6[c]	$Yb(OTf)_3$	Toluene	6	33
7[c]	$CuBr_2$	Toluene	3	30
8[c]	$Cu(OTf)_2$	Toluene	0.5	28
9[c]	$PdCl_2$	Toluene	3	21
10[c]	AgOTf	Toluene	0.5	26
11	–	AcOH	1	16
12	$2\text{-}O_2NC_6H_4CO_2H$	AcOH	6	24
13	TSA	AcOH	0.5	27
14	Amberlyst 15	AcOH	6	25
15	H_2SO_4	AcOH	0.5	21
16	**HCl**	**AcOH**	**1**	**58**

[a] Reaction was performed at 0.1 mmol scale of **1a** with 1.2 eq. of **2a** and 1 eq. of acid.
[b] Conversion and yield was detected by GS-MS with an internal standard.
[c] 20 mol. % of catalyst was used.

only *N*-tosylfurfurylamine **2a** has a good balance between the stability in the first step of the domino reaction (Friedel-Crafts alkylation) and reactivity in the leaving group elimination. On the contrary, furans **2b-k** gave either products of Piancatelli rearrangement or significant tarring of the reaction mixture. Therefore, the optimal reaction procedure can be summarized as follows: 2-hydroxybenzyl alcohol **1** is heated under reflux with *N*-tosylfurfurylamine **2a** (1.2 eq.) in acetic acid containing conc. HCl (1 eq.) for 1 h under air atmosphere. Furthermore, we have successfully carried out the studied reaction using 1 mmol of starting alcohol **1** and

Table 2
Screening of leaving groups in furfuryl derivatives.



1a 2a 3a

Entry[a]	Furan **2**	LG	Yield of **3a** (%)[b]
1	**2a**	TsNH	58 (56[c])
2	**2b**	NH_2	traces
3	**2c**	PhNH	ND
4	**2d**	BnNH	traces
5	**2e**	Bn_2N	traces
6	**2f**	HO	20
7	**2g**	PhO	27
8	**2h**	$4\text{-}MeC_6H_4O$	29
9	**2i**	$4\text{-}ClC_6H_4O$	30
10	**2j**	TsO	ND
11	**2k**		ND

[a] Reaction was performed at 0.1 mmol scale of **1a** with 1.2 eq. of **2a** and 1 eq. of acid.
[b] Conversion and yield was detected by GS-MS with an internal standard.
[c] Reaction was performed at 1 mmol scale. Isolated yield.