SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201402157

Prins Spirocyclization for the Synthesis of Spiro[isobenzofuran-pyran] Derivatives

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Keywords: Spiro compounds / Cyclization / Lewis acids / Aldehydes / Ketones

A Prins cascade process was developed for the synthesis of tetrahydro-3*H*-spiro[isobenzofuran-pyran] derivatives in good yields and selectivity by the condensation of 3-[2-(hydroxymethyl)phenyl]but-3-en-1-ols with aldehydes or ketones. The reaction proceeds smoothly in the presence of indium(III) trifluoromethanesulfonate (30 mol-%) in dichloroethane at 80 °C. This is the first report on the synthesis of tetrahydro-3*H*-spiro[isobenzofuran-pyran] scaffolds through a Prins cascade reaction.

Introduction

The "Prins cyclization" is one of the most versatile approaches for the synthesis of the tetrahydropyran ring system, which is a core structure in many natural products.[1] Prins bicyclization is a cascade process that provides a wide range of heterobicycles such as bicyclo[3.3.1]nonanes, oxaspirobicycles, azaspiro[4,4]nonanes, bicyclo[3,2,1]octanes, and dioxaspirodecanes.[2,3] Therefore, the Prins cascade process has emerged as a powerful synthetic route for the stereoselective construction of fused tetrahydropyran systems.[4] In spite of its potential application in natural products synthesis,[5,6] the scope of the Prins cascade process has not yet been explored for the synthesis of spiro[isobenzofuran-pyrans] from a readily accessible trifunctional substrate, that is, 3-[2-(hydroxymethyl)phenyl]but-3-en-1-ol and aldehydes or ketones. In addition, isobenzofuran derivatives are privileged scaffolds in medicinal chemistry (Figure 1).[7]

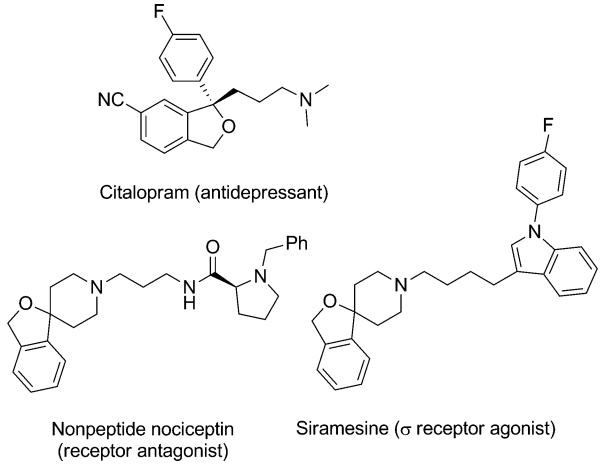

Figure 1. Biologically active isobenzofuranyl derivatives.

Results and Discussion

Following our interest in Prins and related cyclizations for the synthesis of tetrahydropyran scaffolds,[8] we herein report a novel strategy for the stereoselective synthesis of spiro[isobenzofuran-pyran] derivatives through a Prins cascade reaction. At first we attempted the spirocyclization of 3-[2-(hydroxymethyl)phenyl]but-3-en-1-ol (**1x**) with benzaldehyde (**2**) in the presence of an acid catalyst. To optimize the reaction conditions, the above reaction was performed with various acid catalysts, and the results are presented in Table 1. Of the various catalysts screened, indium(III) trifluoromethanesulfonate ($InCl_3$) or $BF_3{\cdot}OEt_2$ (20 mol-%) at 80 °C gave desired product **3a** in 25 and 30% yield, respectively (Table 1, entries 1 and 2). Similarly, $Sc(OTf)_3$ (10 mol-%) in dichloroethane at 80 °C also gave product **3a** only in 30% yield (Table 1, entry 3). To our surprise, no cyclization was observed with *para*-toluenesulfonic acid (TsOH, 1 equiv.; Table 1, entry 4). Furthermore, the combination of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH also gave required product **3a** in low yield (42%; Table 1, entry 5). To our delight, the yield was slightly improved with the use of $In(OTf)_3$ (20 mol-%; Table 1, en-

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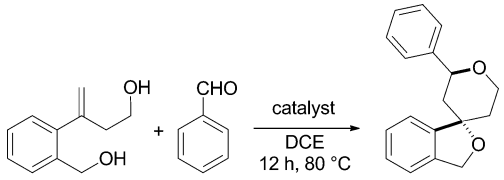
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402157.

try 6). Remarkably, $In(OTf)_3$ (30 mol-%) gave **3a** in excellent yield (85%; Table 1, entry 7). Under the optimized conditions, the reaction proceeded smoothly in the presence of $In(OTf)_3$ (30 mol-%) at 80 °C in dichloroethane (DCE). Under the above conditions, product **3a** was obtained with high selectivity (96:4; Table 2, entry 1). Though $In(OTf)_3$ is known to give the dihydropyran as a side product in the Prins cyclization,[9] no such product was detected in the present reaction because intramolecular cyclizations are highly favourable. The starting material was recovered for cases in which the yields were low (Table 1). Furthermore, no incorporation of F was observed if the reaction was performed with $BF_3{\cdot}OEt_2$ (Table 1, entry 2).

Table 1. Screening of various acid catalysts in the formation of **3a**.[a]



1x **2** **3a**

Entry	Catalyst	Yield [%][b]
1	$InCl_3$ (20 mol-%)	25
2	$BF_3{\cdot}OEt_2$ (20 mol-%)	30
3	$Sc(OTf)_3$ (10 mol-%)	30
4	TsOH (1 equiv.)	trace
5	$Sc(OTf)_3$ (10 mol-%)/TsOH (1 equiv.)	42
6	$In(OTf)_3$ (20 mol-%)	58
7	$In(OTf)_3$ (30 mol-%)	85

[a] Reaction was performed on 0.5 mmol scale. [b] Yield refers to the pure product after chromatography.

The ratio of products was determined by analysis of the crude mixture by ^1H NMR spectroscopy. The relative stereochemistry of **3c** was established by 1D and 2D NMR spectroscopy experiments. The scalar coupling constants for H2, $^3J_{H2,H3(eq)}$ = 5.5 Hz and $^3J_{H2,H3'(ax)}$ = 8.4 Hz, and the presence of NOE cross-peaks between H2/H6(ax) and H3(ax)/H5(ax) indicate that the six-membered ring adopts a $^1C_4$ chair conformation with the substituent at C2 in the equatorial position, as depicted in Figure 2. The stereochemistry at the spiro center (C4) was determined on the basis of the appearance of NOE cross-peaks between H8/H5(ax) and H8/H3(ax), which suggests that the O atom of the five-membered ring is in the axial position and that the C7 atom is in the equatorial position.

Next, we examined the effect of solvents such as tetrahydrofuran, DCE, and dimethoxyethane. Of these, DCE gave the best results in terms of yield. The scope of the reaction was further evaluated with respect to various aldehydes and ketones, and the results are presented in Table 2. Accordingly a variety of aldehydes were subjected to Prins spirocyclization with 3-[2-(hydroxymethyl)phenyl]but-3-en-1-ol under the influence of $In(OTf)_3$ in DCE. The corresponding 3*H*-spiro[isobenzofuran-1,4′-pyran] derivatives were obtained in good yields, and the results are presented in Table 2. The substituents present on the aromatic system showed some effect on the conversion. In the case of electron-deficient aldehydes, the yields gradually increased as the electron-withdrawing ability of the substituents increased. For instance, *p*-nitrobenzaldehyde gave **3i** in excellent yield (92%; Table 2, entry 10). Furthermore, chloro- and bromobenzaldehydes also afforded the respective products in high yields (Table 2, entries 2, 4, and 8). Similarly, alkyl-substituted aryl aldehydes gave spiro[isobenzofuran-pyran] derivatives **3c** and **3e** in 84 and 85% yield, respectively (Table 2, entries 3 and 5). This method was equally effective with aliphatic aldehydes to provide corresponding alkyl-substituted spirocycles **3j** and **3k** in good yields (Table 2, entries 10 and 11). Remarkably, a sterically hindered naphthaaldehyde also participated well in this reaction (Table 2, entry 7). Thus, the present method works not only with aromatic aldehydes but also with aliphatic aldehydes. In contrast, aromatic aldehydes gave the products in higher yields than their aliphatic counterparts. Further exploration of the substrate scope revealed that the reaction took slightly longer for cyclohexanone (Table 2, entry 6), but the desired product was obtained in good yield. Therefore, Prins spirocyclization was successful with all kinds of carbonyl compounds in good yields.

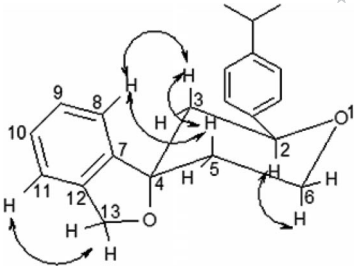
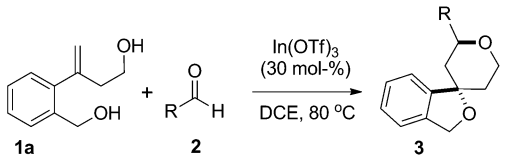


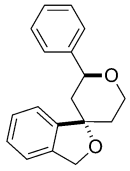
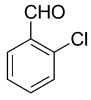
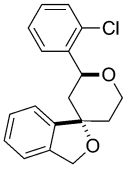
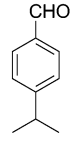
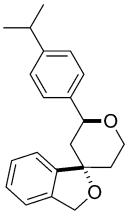
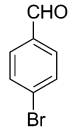
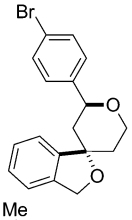
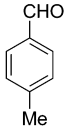
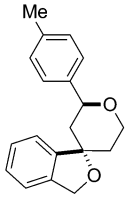
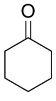
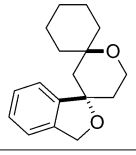
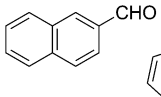
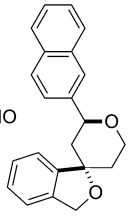
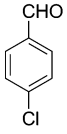
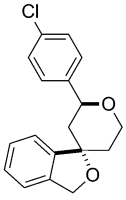
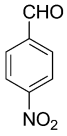
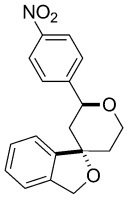
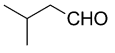
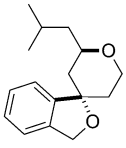
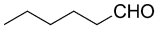
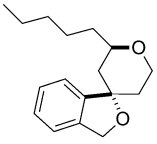
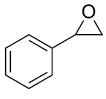
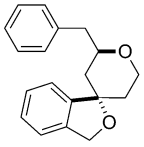
Figure 2. Characteristic NOEs of **3c**.

Encouraged by the results obtained with the carbonyl compounds, we next attempted the Prins bicyclization with epoxides and acetals. Interestingly, styrene oxide underwent smooth coupling with **1x** in the presence of $In(OTf)_3$ (30 mol-%) in DCE at 80 °C to afford desired product **3l** in 70% yield with 9:1 selectivity. In the above reaction, the epoxide initially undergoes rearrangement to give the corresponding phenylacetaldehyde,[10] which simultaneously participates in the Prins spirocyclization. However, benzaldehyde dimethylacetal failed to give the desired product under similar conditions.

Inspired by the above results, we extended this process to the aza-Prins cyclization by using various acid catalysts, but none of them were able to give product **4** (Table 3, entries 1–6). Interestingly, the reaction was successful with $FeCl_3$ (30 mol-%), which is a familiar catalyst for the aza-Prins cyclization.[11] For example, treatment of benzaldehyde (**2**) and *N*-{3-[2-(hydroxymethyl)phenyl]but-3-en-1-yl}-4-methylbenzenesulfonamide (**1y**) with $FeCl_3$ (30 mol-%) in DCE in the presence of molecular sieves (4 Å) afforded 2′-phenyl-

Table 2. $In(OTf)_3$-promoted synthesis of spiro(isobenzofuranyl) pyran derivatives.



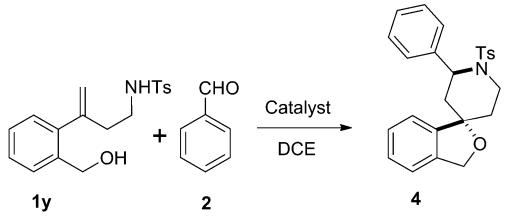
Entry	Aldehyde **2**	Product **3**[a]	Time [h]	Yield [%][b]	*dr*[c]
1			10	85	96:4
2			15	80	95:5
3			13	84	97:3
4			12	86	92:8
5			12	85	85:15
6			24	75	95:5
7			8	92	90:10
8			10	89	94:6
9			6	92	96:4
10			18	78	96:4
11			20	75	85:15
12			8	70	90:10

[a] All products were characterized by NMR and IR spectroscopy and mass spectrometry. [b] Yield refers to the pure product after chromatography. [c] Diastereomeric ratio was determined by NMR spectroscopy.

1′-tosyl-3*H*-spiro[isobenzofuran-1,4′-piperidine] (**4**) in 65% yield with high selectivity (Table 3, entry 7). Thus, this method is simple and convenient to generate the desired products in good yields with good to excellent diastereoselectivity.

However, thia-Prins cyclization of [2-(4-mercaptobut-1-en-2-yl)phenyl]methanol (**1z**) with benzaldehyde failed to give the desired product under the present reaction conditions.

Table 3. Screening of various acid catalysts in the formation of **4**.[a]

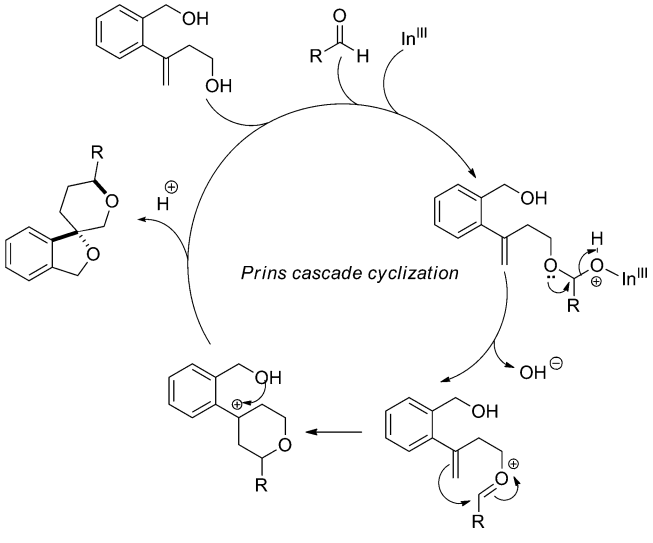


1y **2** **4**

Entry	Catalyst	Temp. [°C]	Time [h]	Yield[b] [%]
1	$InCl_3$ (20 mol-%)	80	24	n.d.
2	$BF_3{\cdot}OEt_2$ (20 mol-%)	80	48	n.d.
3	$Sc(OTf)_3$ (10 mol-%)	80	24	n.d.
4	TsOH (1 equiv.)	80	12	trace
5	$Sc(OTf)_3$ (10 mol-%)/TsOH (1 equiv.)	80	12	trace
6	$In(OTf)_3$ (30 mol-%)	80	24	n.d.
7	$FeCl_3$ (30 mol-%)	25	2	65

[a] Reaction was performed on 0.5 mmol scale. [b] Yield refers to the pure product after chromatography. n.d. = not detected.

A plausible mechanism for the Prins cascade process is proposed in Scheme 1. The reaction is assumed to proceed through the formation of an oxocarbenium ion generated in situ from the hemiacetal, which in turn is formed by the reaction of a homoallylic alcohol with the aldehyde under acidic conditions. The thus-formed oxocarbenium ion is attacked by the internal alkene to generate the carbocation, which is simultaneously trapped by a tethered benzylic alcohol to give the desired tetrahydro-3*H*-spiro[isobenzofuran-1,3′-pyran].



Scheme 1. A plausible mechanism.

Conclusions

In summary, a novel Prins spirocyclization was developed for the synthesis of tetrahydro-3*H*-spiro[isobenzofuran-1,3′-pyran] derivatives. The reaction is highly diastereoselective and proceeds in good yields in most cases. This method provides direct access to the synthesis of biologically interesting 1,3-dioxaspirocycles in a single-step process. These spirocycles may be useful for the discovery of novel antidepressants.

Experimental Section

Typical Procedure for the Prins Cascade Cyclization for the Synthesis of 3a–l: To a stirred solution of 2-arylethylbut-3-en-1-ol (**1x**; 0.5 mmol) and aldehyde (0.6 mmol) in dry dichloroethane (2 mL) was added $In(OTf)_3$ (30 mol-%). The resulting mixture was stirred at 80 °C under a nitrogen atmosphere for the specified time (Table 2). Upon completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (2.0 mL) and extracted with dichloromethane (2 × 6 mL). The organic layers were combined, washed with brine (6 mL), dried with Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) by using ethyl acetate/hexane as the eluent to afford the pure product. The same procedure was followed for the synthesis of all other compounds reported in this work.

Supporting Information (see footnote on the first page of this article): General experimental procedures and spectroscopic data (^{1}H NMR and ^{13}C NMR) for the corresponding products.

Acknowledgments

H. K. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of a fellowship. B. V. S. thanks the CSIR for financial support as a part of a XII five-year-plan program under title ORIGIN (CSC-0108).

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Received: March 27, 2014
Published Online: June 3, 2014

