Organic LETTERS

Letter

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Stereoselective Synthesis of Spiro[tetrahydropyran-3,3′-oxindole] Derivatives Employing Prins Cascade Strategy

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Supporting Information

ABSTRACT: A variety of aldehydes undergo smooth coupling with 4-hydroxy-*N*-methyl-2-methylene-*N*-phenylbutanamide in the presence of $BF_3{\cdot}OEt_2$ under ambient conditions to produce the corresponding spiro-oxindole derivatives in good yields with excellent selectivity. It is an entirely new strategy to construct the spirocycles in a one-pot operation through a Prins cascade process.

The spiro-oxindoles are important synthetic targets that are often found in various biologically active molecules (Figure 1).[1] They are considered to be privileged scaffolds in medicinal chemistry due to their broad range of biological activities including anticancer, antimalarial, antituberculosis, growth hormone secretagogue, and progesterone receptor agonists.[2] Consequently, several approaches have been developed for the stereoselective synthesis of spiro-oxindole derivatives, which are being used as broad and promising synthetic scaffolds in several therapeutic areas.[3−5] However, a few methods are reported for the synthesis of tetrahydrospiro-[indoline-3,4′-pyran]-2-one derivatives.[6−9]

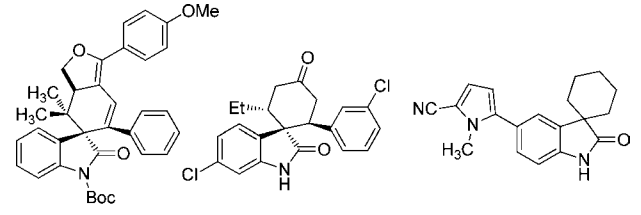
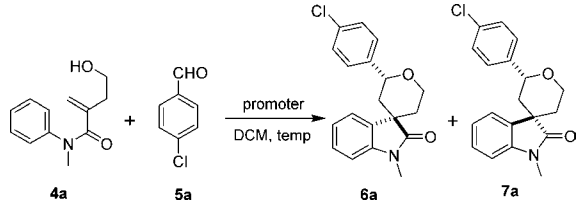


Figure 1. Examples of biologically active spiro-oxindoles.

Table 1. Study of Promoters in the Formation of 6a/7a



entry	promoter	equiv	temp (°C)	time (h)	yield (%)[a]	dr (6a/7a)[b]
a	$In(OTf)_3$	0.3	rt	24		
b	$In(OTf)_3$	1.2	rt	24		
c	$Sc(OTf)_3$	0.3	rt	24		
d	TMSOTf	1.2	rt	10	90	85:15
e	TMSOTf	1.2	0 to rt	12	90	90:10
f	$BF_3{\cdot}OEt_2$	1.2	rt	10	95	89:11
g	$BF_3{\cdot}OEt_2$	1.2	0 to rt	12	92	96:04
h	$BF_3{\cdot}OEt_2$	1.2	−20	24		

[a]Yield refers to pure product after column chromatography. [b]Ratio was determined by ^1H NMR.

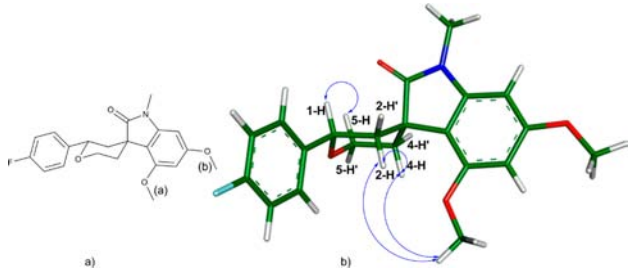


Figure 2. Schematic structure of major product **6m** (a) and the observed characteristic NOEs (b).

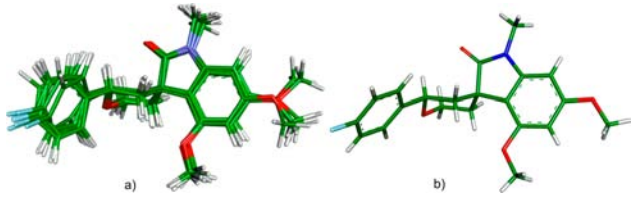


Figure 3. Overlay of the lowest energy NMR structures in solution state (a) and X-ray crystal structure (b) of major product **6m**.

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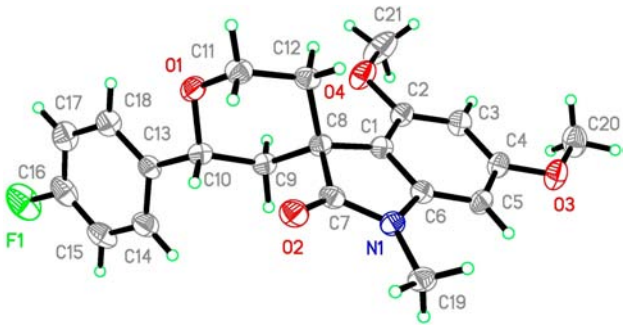
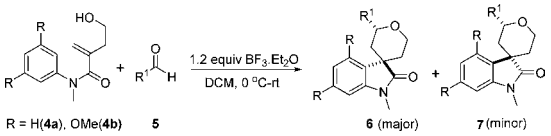
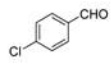
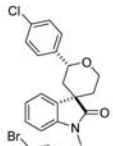
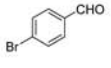
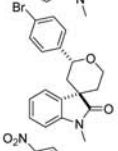
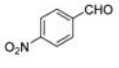
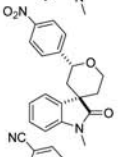
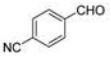
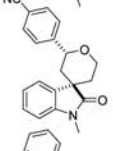
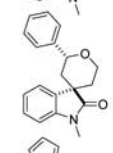
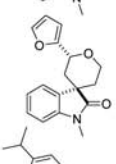
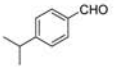
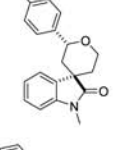
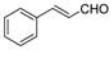
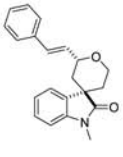
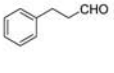
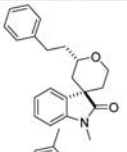
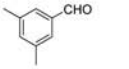
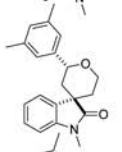
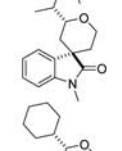
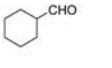
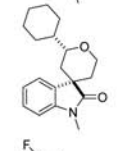
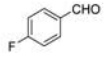
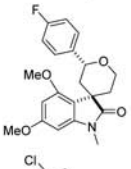
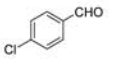
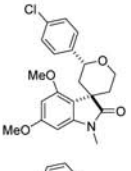
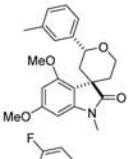
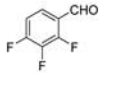
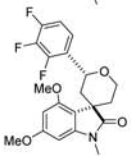


Figure 4. ORTEP diagram of **6m**.

Following our interest in spirocycles,[10] we herein report a novel strategy for the stereoselective synthesis of tetrahydrospiro[indoline-3,4′-pyran]-2-one derivatives through a Prins cascade cyclization.[11] Initially, we attempted the coupling of 4-hydroxy-*N*-methyl-2-methylene-*N*-phenylbutanamide (**4**) with *p*-chlorobenzaldehyde (**5**) in the presence of 0.3 equiv of $In(OTf)_3$ in dichloromethane at 0 °C (Table 1, entry a). However, no cyclization was observed under these conditions. A similar result was also observed with 0.3 equiv of $Sc(OTf)_3$ (Table 1, entry c). Even 1.2 equiv of $In(OTf)_3$ was found to be insufficient in promoting the cyclization reaction (Table 1, entry b). Next, we performed the reaction using 1.2 equiv of TMSOTf at room temperature. Interestingly, the desired product was obtained in 90% yield as a mixture of

Table 2. Preparation of Spiro-oxindoles[a]



entry	homoallylic alcohol (**4**)	aldehyde (**5**)	product (**6**)[a]	time (h)	yield (%)[b]	dr (**6**:**7**)[c]
a	4a			10	90	97:3
b	4a			12	95	98:2
c	4a			08	92	99:1
d	4a			08	91	97:3
e	4a			14	82	98:2
f	4a			10	95	99:1
g	4a			12	92	97:3
h	4a			10	90	94:6
i	4a			12	90	93:7
j	4a			10	93	95:5
k	4a			10	95	99:1
l	4a			10	95	99:1
m	4b			08	91	99:1
n	4b			08	92	97:3
o	4b			16	82	90:10
p	4b			12	91	95:5

[a]Products were characterized by NMR, IR, and mass spectrometry. [b]Yield refers to the pure product after column chromatography. [b]Ratio of the product was determined by ^{1}H NMR.

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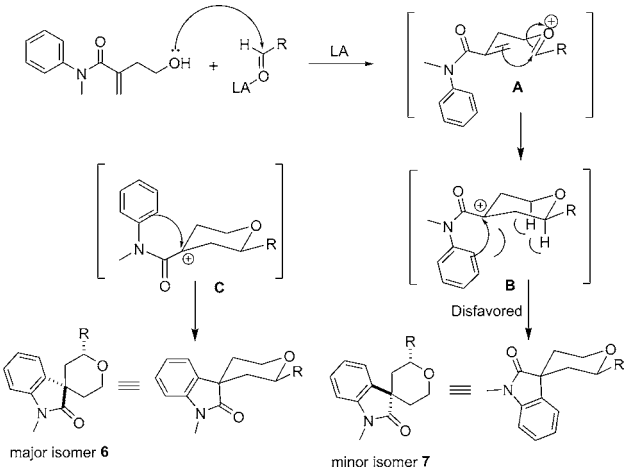
Scheme 1. Plausible Reaction Pathway



diastereomers **6a** and **7a** in 85:15 ratio (Table 1, entry d). The diastereomeric ratio was increased to 9:1 when the reaction was performed at 0 °C to room temperature (Table 1, entry e). Finally, the best results (92% yield and 96:04 ratio) were obtained with 1.2 equiv of $BF_3{\cdot}OEt_2$ at 0 °C to room temperature (Table 1, entry g). Surprisingly, no cyclization was observed at −20 °C (Table 1, entry h). Further, we screened the solvents for this spirocyclization. Among various solvents such as dichloromethane, acetonitrile, tetrahydrofuran, and toluene, DCM gave the best results in terms of conversion.

The solution state structure of the major product **6m** was derived by using detailed NMR studies such as 2D-NOESY, COSY, TOCSY, and *J*-coupling constants. The measured strong scalar coupling values, $^3J_{1\text{-H}/2\text{-H}}$ = 11.8 and $^3J_{4\text{-H}/5\text{-H}}$ = 13.8 Hz, from the one-dimensional ^{1}H NMR spectrum clearly indicate that the 1-H, 2-H, 4-H, and 5-H protons are in axial positions in the six-membered ring. The observed characteristic NOE correlations, 1-H/5-H, 2-H/4-H, 2-H/OCH_3(a) and 4-H/OCH_3(a), and the scalar coupling values confirm that the six-membered ring is in the chair conformation and exhibits the relative stereochemistry as shown in Figure 2.

The lowest energy structures of major product **6m**, derived from the NOE-restrained MD simulations, are compared with X-ray crystal structure and are found to be in excellent agreement with the solid state structure (Figures 3 and 4).

Inspired by the above results, we extended this method for different substrates bearing various substituents on the aromatic ring of the aldehyde. A variety of aldehydes including aromatic, heteroaromatic, and aliphatic aldehydes underwent smooth cyclization under the optimized conditions (Table 2).

A plausible mechanism for the Prins cascade process is proposed in Scheme 1. We assume that the reaction proceeds through an oxo-carbenium ion that is formed in situ from alkenol and aldehyde after likely activation with $BF_3{\cdot}OEt_2$. A subsequent attack of the olefin on the oxo-carbenium ion followed by the trapping of carbocation with a tethered aryl group would give the desired spirocycle.

Generally, the Prins cyclization proceeds with electron-rich olefins, whereas, in the present study, we showed that it also proceeds with electron-deficient olefins. This may be attributed to the formation of oxindole with simultaneous Prins-type cyclization.

In summary, we have developed a novel strategy for the stereoselective construction of spiro-oxindoles from 4-hydroxy-*N*-methyl-2-methylene-*N*-phenylbutanamide and aldehydes through a Prins cascade cyclization. This method offers significant advantages such as mild reaction conditions, broad substrate scope, high conversions, and excellent diastereoselectivity, which make it quite simple, more convenient, and practical. It provides the spirocycles that are of increasing interest to the pharmaceutical industry.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of products (**6a**−**6p**), NOESY, and DQFCOSY study of compounds (**6m**). 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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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 has been updated. The revised version was re-posted on December 19, 2014.