Facile Synthesis of Spiropyrans from Chromene Hemiacetal Esters and Bifunctional Nucleophiles

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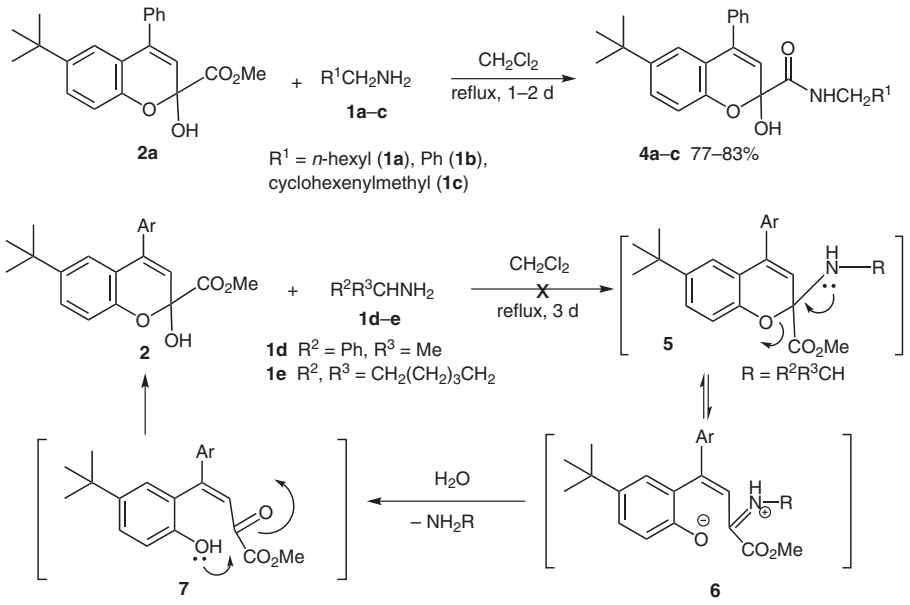
Abstract: Facile synthesis of several new kinds of spiropyrans has been accomplished through the condensation of chromene hemiacetal esters with bifunctional nuclephiles, in which previously non-practical amination and amidation processes help each other and all become practical processes of the corresponding tandem reactions.

Key words: spiropyran, tandem reaction, hemiacetal ester, chromene, bifunctional nucleophile

Spiropyrans have attracted increasing attention in the area of molecular sensors, switches, and information processors due to the reversible structural transformations between neutral spiropyran (SP) forms and zwitterionic merocyanine (MR) forms that accompanied significant changes of characteristic photochemical and photophysical properties in response to external chemical,[1] thermal,[2] and optical[3] stimulation. Herein, we would like to report that the condensation of chromene hemiacetal esters with bifunctional nuclephiles could afford several new kinds of spiropyrans.

During our ongoing interest aiming at the synthesis of functional heterocycles,[4] we observed that treatment of simple amines **1a–c** with hemiacetal ester **2a** in refluxing dichloromethane afforded the corresponding amides **4a–c** in good yields (Scheme 1).[5] However, when modestly sterically hindered amines such as cyclohexylamine (**1d**) and α-methylbenzylamine (**1e**) were used, no reaction products were detected, and the starting materials were recovered, even with an excess of amines **1d**,**e** as nucleophiles, indicating that the steric factor affects the amide formation.[5] It is reasonable to suggest that the potential adducts **5**, which was supposed to be formed from the amination of hemiacetals **2** with amines **1d**,**e**, are probably unstable in refluxing dichloromethane. The nitrogen's lone pair of electrons, in aliphatic amines **5**, is likely to cause the transformation of **5** into α-ketoesters **7**, which underwent intramolecular cyclization to convert back to the hemiacetals **2** (Scheme 1). In contrast to the nitrogen's lone pair of electrons in *N*,*O*-acetals **5**, the oxygen's lone pair of electrons in acetal **8** (Figure 1) display relatively



Scheme 1 Reactions of hemiacetal esters **2** with amines **1a–e**

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weak electron-transfer ability, and thus avoid the similar decomposition (Scheme 1). Indeed, compound **8** is a stable molecule whose structure has been determined by single-crystal X-ray analysis.[6]

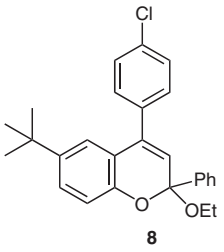

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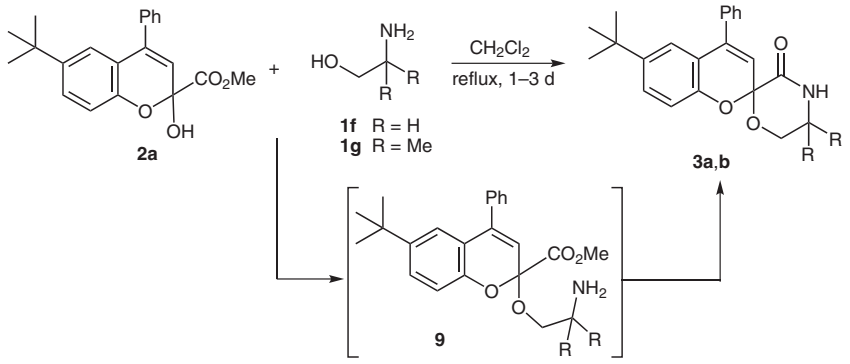
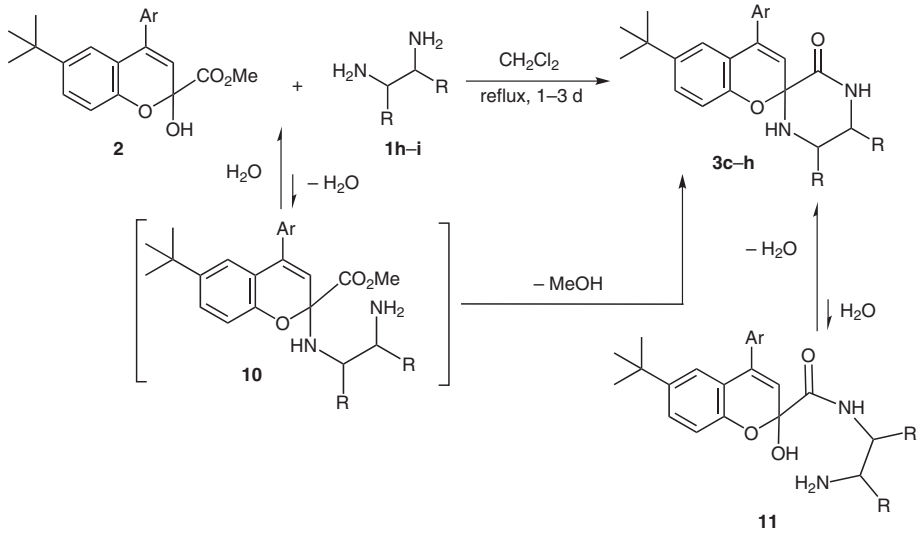
Figure 1 Structure of compound **8**

Based on the above results and analysis, simple β-hydroxy amine **1f** was selected for the exploration of the potential double nucleophilic substitutions of hemiacetal ester **2a** (Scheme 2). As expected, condensation of **1f** with **2a** in dichloromethane under reflux for 1 day in the absence of any catalyst and additives afforded 2*H*-chromene-morpholin-3-one spiropyran **3a** in 98% yield (Scheme 2, entry 1 in Table 1). The commercially available sterically hindered β-hydroxy amine **1g** was also used, which reacted smoothly with **2a** to afford 2*H*-chromene-morpholin-3-one spiropyran **3b** in 84% yield (Scheme 2, entry 2 in Table 1).

As indicated above, modestly sterically hindered amines **1d**,**e** are not appropriate nucleophiles for the intermolecular amidations of ester **2a** (Scheme 1), the amidation of sterically hindered β-hydroxy amine **1g** with **2a** did not take place directly. Presumably, the hindered β-hydroxy amine **1g** can react with **2a** via its unhindered hydroxyl to form intermediate **9**, and the subsequent amidation is actually an intramolecular process and hence easier than the corresponding intermolecular amidation. With 1,2-diamines as nucleophiles, a small concentration of the adducts **10** would also potentially allow an otherwise unfavorable amidation to occur by an intramolecular pathway to afford spiropyrans **3c**–**h** (Scheme 3). Instead, with the original modestly hindered amines **1d**,**e** there is no opportunity for an intramolecular amidation and species related to **10** simply to hydrolyze back to **2a**. Similarly, spiropyrans **3c**–**h** are potentially hydrolyzed to compounds **11**. However, the irreversible amide formation would enable the intramolecular amination processes easier than the corresponding intermolecular ones, and thus facilitates the conversion of compounds **11** into spiropyrans **3c**–**h** (Scheme 3). This analysis suggests that these two previously nonpractical amination and amidation pro-



Scheme 2 Synthesis of spiropyrans **3a**,**b**

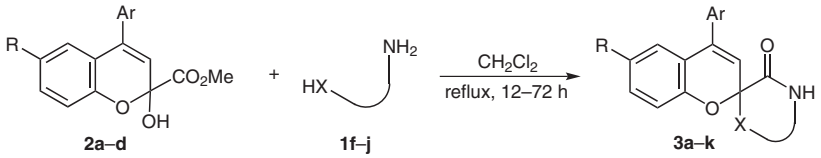


Scheme 3 Synthesis of spiropyrans **3c**–**h**

cesses might help each other and all become practical processes of these tandem reactions.

As expected, the treatment of hemiacetal ester **2a** with 1,2-diamine **1h** in dichloromethane under reflux for 3 days afforded spiropyran **3c** in 85% yield (Table 1, entry 3). The reactions of hemiacetal esters **2b**,**c** with **1h** under the same reaction conditions proceeded equally well to afford spiropyrans **3d**,**e** in 81–84% yields (Table 1, entries 4 and 5). 1,2-Diamine **1i** was also used, which reacted with hemiacetal esters **2a–c** uneventfully under the same reaction conditions to afford spiropyrans **3f–h** in 83–86% yields (Table 1, entries 6–8). The significance of spiropyrans inspired and encouraged us to further explore their preparations from hemiacetal esters **2**. Accordingly, treatment of hemiacetal esters **2a**,**b** and **2d** with naphthalen-1-amine (**1j**) in dichloromethane under reflux for 2 days afforded another new kind of spiropyrans **3i–k** in high yields (Scheme 4, Table 1, entries 9–11).

Table 1 Highly Selective Synthesis of Spiropyrans **3a–k** from Hemiacetal Esters **2a–d** and Amines **1f–j**[a]



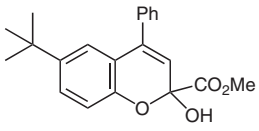
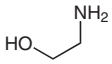
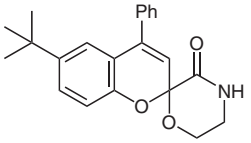
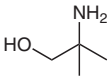
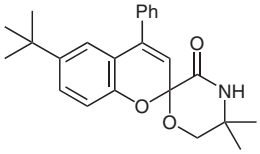
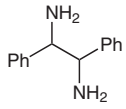
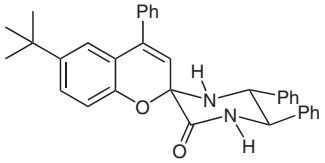
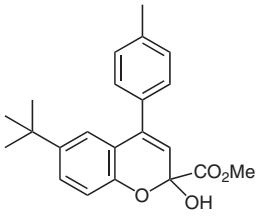
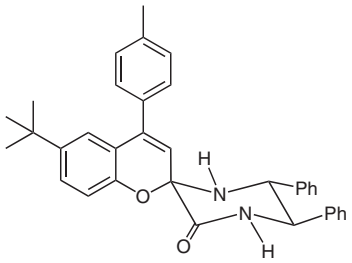
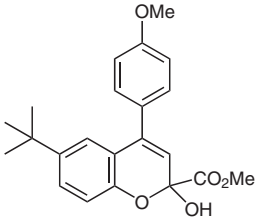
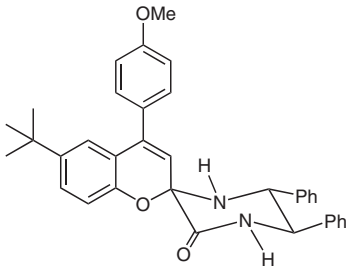
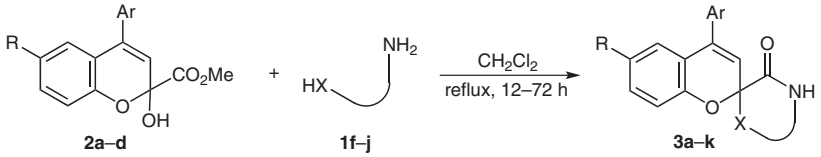
Entry	Hemiacetal esters **2**	Amines **1**	Time (h)	Spiropyrans **3**[8]	Yield (%)
1	 **2a**	 **1f**	24	 **3a**	98
2	**2a**	 **1g**	48	 **3b**	84
3	**2a**	 **1h**	72	 **3c**	85
4	 **2b**	**1h**	72	 **3d**	84
5	 **2c**	**1h**	72	 **3e**	81

Table 1 Highly Selective Synthesis of Spiropyrans **3a–k** from Hemiacetal Esters **2a–d** and Amines **1f–j**[a] (continued)



2a–d **1f–j** **3a–k**

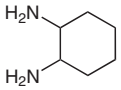
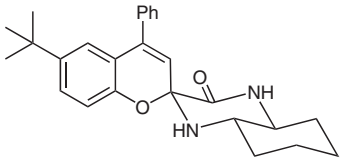
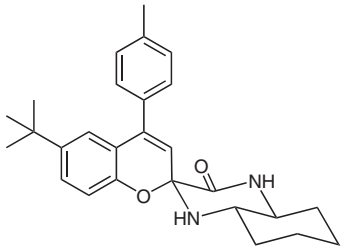
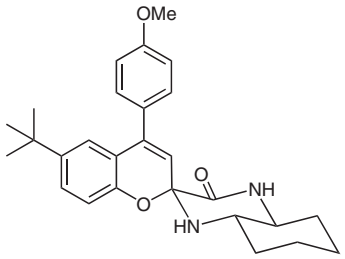
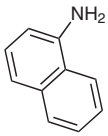
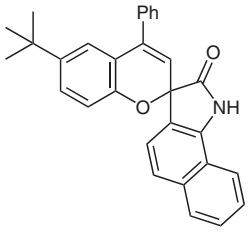
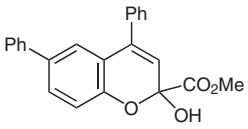
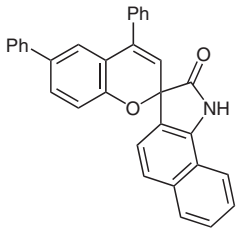
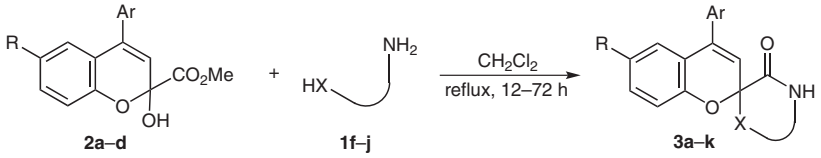
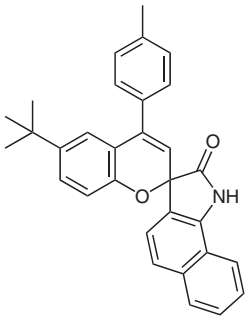
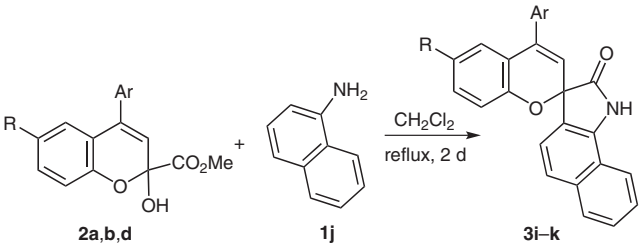
Entry	Hemiacetal esters **2**	Amines **1**	Time (h)	Spiropyrans **3**[8]	Yield (%)
6	**2a**	 **1i**	72	 **3f**	86
7	**2b**	**1i**	72	 **3g**	85
8	**2c**	**1i**	72	 **3h**	83
9	**2a**	 **1j**	48	 **3i**	91
10	 **2d**	**1j**	48	 **3j**	83

Table 1 Highly Selective Synthesis of Spiropyrans **3a–k** from Hemiacetal Esters **2a–d** and Amines **1f–j**[a] (continued)



Entry	Hemiacetal esters **2**	Amines **1**	Time (h)	Spiropyrans **3**[8]	Yield (%)
11	**2b**	**1j**	48	 **3k**	89

[a] Conditions: **1** (1.1 equiv) and **2** (1.0 equiv.) in CH_2Cl_2 (*c* 0.1 M) under reflux for 24–72 h.



Scheme 4 Synthesis of spiropyrans **3i–k**

The products were confirmed from their spectra and supported by the single-crystal X-ray analysis of **3i** (Figure 2).[7]

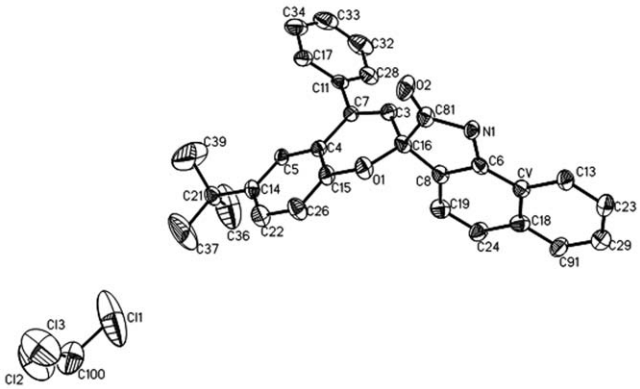


Figure 2 ORTEP plot of spiropyran **3i**

In conclusion, several new kinds of spiropyrans have been efficiently synthesized through the condensation of chromene hemiacetal esters with bifunctional nuclephiles, in which previously nonpractical amination and amidation processes help each other and all become practical processes of the corresponding tandem reactions. We envision that the above consideration would be explored for the development of various tandem reactions that might be difficult to obtain by usual methods.

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

Acknowledgment

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(7) CCDC 800884 contains the supplementary crystallographic data of spiropyran **3i** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) **Synthetic Procedure for Spiropyrans 3**
A solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (**1h**, 42.5mg, 0.2 mmol) and hemiacetal esters **2a** (67.7mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was stirred at reflux for 3 d. The mixture was concentrated, and the residue was purified by column chromatography over silica gel to afford 2*H*-chromene-piperazin-2-one spiropyran **3c** (85.1 mg) in 85% yield as a single diastereomer. White solid; mp 136–137 °C. $[\alpha]_D^{24}$ +101.27 (*c* 2.0, $MeCO_2Et$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.05 (m, 18 H), 5.95 (s, 2 H), 4.67 (s, 2 H), 2.98 (br s, 1 H), 1.18 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 148.1, 144.1, 138.0, 137.9, 137.8, 137.6, 129.0, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 127.7, 126.6, 123.3, 120.4, 120.2, 117.0, 86.9, 65.8, 58.6, 34.3, 31.4. FT-IR (KBr): 3350, 3033, 2361, 1693, 1489, 1245, 921, 700 cm^{-1}. Anal. Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44; N, 5.60. Found: C, 81.43; H, 6.67; N, 5.82.