



Lewis acid-mediated nucleophilic reaction of 2-alkoxychromanes with silyl enol ethers

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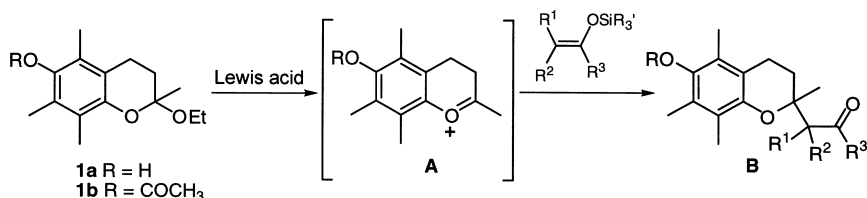
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Abstract

The synthesis of 2,2-disubstituted chromanes was achieved by the nucleophilic reaction of 2-alkoxychromanes with silyl enol ethers in the presence of a Lewis acid. © 2000 Published by Elsevier Science Ltd.

Keywords: chromanes; silyl enol ethers; Lewis acid.

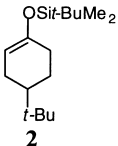
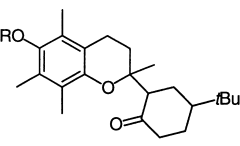
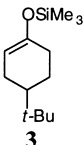
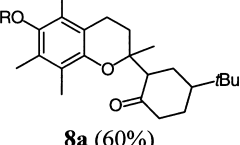
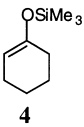
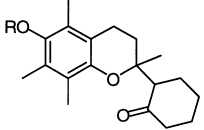
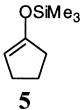
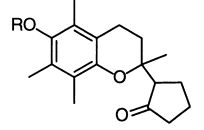
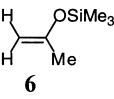
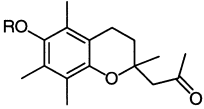
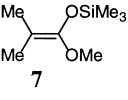
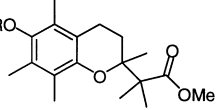
2*H*-1-Benzopyrans (2*H*-chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromanes) are important classes of oxygenated heterocyclic compounds¹ that have attracted much synthetic interest because of the biological activity^{2,3} of naturally occurring representatives. In the course of our work on the synthesis of therapeutically valuable compounds with antioxidizing properties, we needed to access chromanes bearing various 2-oxoalkyl groups at the C-2 position. Although the number of reported syntheses of substituted 2*H*-chromenes has grown rapidly,^{4–7} there are comparatively few synthetic methods available for the synthesis of 2,2-disubstituted chromanes⁸ and particularly those with 2-oxoalkyl groups.



In view of the ready availability of acetals **1** (R = H or COCH₃) it occurred to us that the introduction of a 2-oxoalkyl group at the C-2 position would require only the direct treatment of acetal of type **1** with silyl enol ethers in the presence of a Lewis acid to give products of type **B**. Such processes, which have precedent in related studies with simple acetals,^{9,10} probably proceed through oxonium intermediates of type **A**.

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Table 1
 Synthesis of 2,2-disubstituted chromanes from 2-ethoxychromanes **1**

Entry	Silyl enol ether	a R = H (yield; ratio) b R = Ac (yield; ratio)
1a	 2	 8a (20%)
2a	 3	 8a (60%) 8b (61%)
3a	 4	 9a (63%; 90/10, ^c 70/30 ^d) 9b (60%; 90/10, ^c 70/30 ^d)
4a	 5	 10a (80%; 70/30, ^c 55/45 ^d) 10b (77%; 70/30, ^c 55/45 ^d)
5a	 6	 11a (84%) 11b (87%)
6b	 7	 12a (40%) 12b (35%)

a) Conditions: SnCl₄ in CH₂Cl₂ at -50 °C for 1 h; b) Conditions: SnCl₄ in CH₂Cl₂ at -78 °C, 1 h; c) Ratio before chromatography; d) Ratio after chromatography.

Our initial studies were performed with 2-ethoxy-2,5,7,8-tetramethylchroman-6-ol **1a** (R = H), readily available in good yield (72%) via the cyclocondensation of trimethylhydroquinone with methyl vinyl ketone under acidic conditions (cat. H₂SO₄) in the presence of ethyl orthoformate.⁸ The results of these reactions with different silyl enol ethers in the presence of SnCl₄ as Lewis acid are presented in Table 1.

When **1a** was treated with *tert*-butyldimethylsilyl enol ether **2** (entry 1) in the presence of SnCl₄, ketone **8a** was obtained in 20% yield. Compound **8a** was obtained in a higher yield (60%) when trimethylsilyl enol ether **3** was used under similar conditions (entry 2), presumably because of decreased steric interactions in the transition state. It is noteworthy that only one isomer was detected by ¹H NMR (300 MHz) of the crude reaction mixture. This reaction seems to be general. When **1a** was treated with 1-(trimethylsilyloxy)cyclohexene **4** (entry 3), ketone **9a** was obtained (63%) as a mixture of two isomers, in a 90:10 ratio. Attempts to achieve separation of the two isomers by flash chromatography on silica gel failed. Moreover, the 90:10 mixture was converted to a 70:30 mixture on the silica gel column. When **1a** was treated with 1-(trimethylsilyloxy)cyclopentene **5** (entry 4) compound **10a** was isolated (80%) as a mixture of two isomers (70:30 and 55:45 after chromatography). Exposure of **1a** to 2-(trimethylsilyloxy)propene **6** (entry 5) gave ketone **11a** (84%). Silyl enol ethers prepared from esters also react with chromane **1a**. For example, when compound **1a** was treated with 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene **7** (entry 6), ester **12a** was isolated in 40% yield. Finally, treatment of 6-acetoxychromane **1b** (R = COCH₃) with silyl enol ethers led to the corresponding acetoxychromanes of type **B** (R = COCH₃) in similar yields and ratios.

In summary, 2,2-disubstituted 3,4-dihydro-2*H*-1-benzopyrans of type **B** can be obtained in modest to good yield from 2-alkoxychromanes on treatment with silyl enol ethers in the presence of SnCl₄. Further transformations of compounds of type **B** are under investigation.

Acknowledgements

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