Improve Method for Synthesis of 4-Thioaryl-2,3,4-trihydro-1-benzothiopyrans: Acid-induced Stereoselective Intermolecular Cycloaddition of α,β-Unsaturated Aldehydes with Arenethiols

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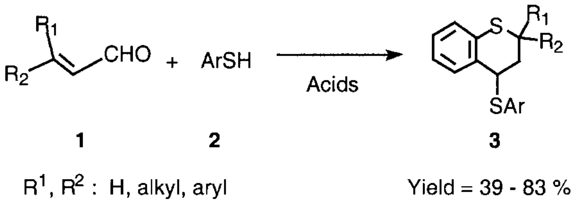
Abstract: A catalytic amount of acids catalyzed reaction of α,β-unsaturated aldehydes with arenethiols in 1,2-dichloroethane brought about intermolecular cycloaddition to give the corresponding 4-thioaryl-2,3,4-trihydro-1-benzothiopyrans (thiochromans) in good to excellent yield. These reactions are assumed to proceed through allylic cationic intermediates generated in site.

Key words: benzothiopyrans, acids catalysts, unsaturated aldehydes, arenethiols, intermolecular cycloaddition

Fused thiochromans are interesting and useful synthetic intermediates because of their strong activity toward many kinds of reagents; a thiochroman's ring system is also found in many naturally occurring biologically active compounds.[1] A number of methods for the preparation of thiochromans have been reported. The thio-Claisen rearrangement and its modified version represent a highly effective and general method for the intermolecular cycloaddition products from α,β-unsaturated compounds.[2 - 7] Synthetic utility of these methods may be, however, considerably limited because of the use of a large excess of protonic acids or Lewis acids, high temperature, multistep, and so on. To our knowledge, intermolecular cycloaddition of α,β-unsaturated aldehydes and arenethiols to thiochromans by using a catalytic amount of acids have not been reported.

Herein, we wish to describe an improved method for selective ring formation through intermolecular cycloaddition of α,β-unsaturated aldehydes with arenethiols in the presence of a catalytic amount of acids to give the corresponding 4-thioaryl-2,3,4-trihydro-1-benzotiopyrans (thio-chromans, **3**) in good to excellent yields (Scheme 1). The present method may be characterized by use of a catalytic amount of acids, highly simplicity and convenience of reaction procedure, mild reaction conditions, selective ring formation by easily available substrates, and good yields of the products.



Scheme 1

The reactions were usually carried out at 80 8 °C for 3 h in anhydrous dichloroethane containing a catalytic amount of acids, α,β-unsaturated aldehydes, and arenethiols.[8] Detailed studies on the reaction of crotyl aldehyde (**1a**) with thiophenol (**2a**) to 2-methyl-4-thiophenyl-1-benzothiopyran (**3a**) showed that this catalytic intermolecular cycloaddition is considerably influenced by the kinds of acids, the molar ratio of *p*-TsOH, and the solvents used, as shown in Table 1.

Table 1 Catalytic Activities of Acids in the Reaction of Crotyl Aldehyde (**1a**) and Thiophenol (**2a**)

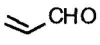
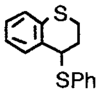
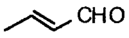
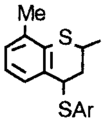
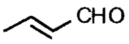
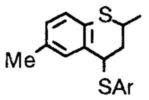
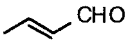
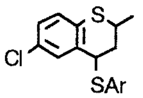
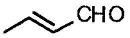
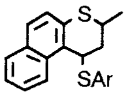
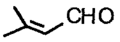
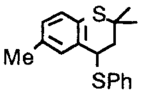
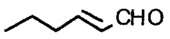
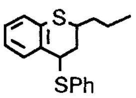
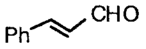
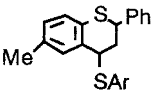
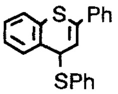
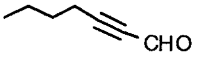
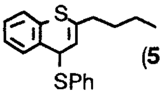
entry	Cat (mol. eq.)	Yield of **3a**(%) [a]
1	non	0
2	p-TsOH (0.01)	52
3	p-TsOH (0.05)	69
4	p-TsOH (0.10)	76
5	CH_3CH_2COOH (0.27)	0[b]
6	H_2SO_4 (2 drops)	79
7	$AlCl_3$ (2.0)	0
8	$FeCl_3$ (2.0)	0
9	ZnI_2 (2.0)	36[c]

[a] Isolated yield based on **1a**. 2-Methyl-1-benzothiopyran (**4**) was additionally obtained at entry 2-5 in the yield of 7%, 2%, 4%, and 10%, respectively.
[b] 3-Phenylthio-butanal was obtained in the yield of 46%.
[c] Crotyl-dithiophenyl acetal was also obtained in 63%.

Noteworthy is the fact that the reaction in the absence of acids did not give **3a**, while the presence of a catalytic amount of acids, especially *p*-TsOH and H_2SO_4, caused a smooth reaction to give product **3a** in good yields. As shown in Table 1, the optimum reaction condition for the formation of **3a** is attained when the molar ratio of **1a** : **2a**: *p*-TsOH is 1: 2.1: 0.1. A reaction with Lewis acids resulted in a low yield (36-0%). The use of propionic acid instead of *p*-TsOH gave no chroman products. 1,2-Dichloroethane is the best choice of solvents.

The intermolecular cycloaddition between α,β-unsaturated aldehydes with arenethiols led to stereoisomeric mix-

Table 2 Reaction of α,β-Unsaturated Aldehydes (**1**) with Arenethiols (**2**) in the Presence of *p*-Toluenesulfornic Acid

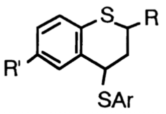
Entry	**1**	Ar in **2**	Yield of 3 (%)		
1		C_6H_5		(**3b**)	54
2		o-MeC_6H_4		(**3c**)	78
3		p-MeC_6H_4		(**3d**)	81
4		p-ClC_6H_4		(**3e**)	82
5		β-$C_{10}H_7$		(**3f**)	83
8		p-MeC_6H_4		(**3i**)	39
6		C_6H_5		(**3g**)	81
7		p-MeC_6H_4		(**3h**)	56
9	Ph—≡—CHO	C_6H_5		(**5a**)	79
10		C_6H_5		(**5b**)	53

tures of *cis* and *trans* isomer. A molar ratio of *cis* to *trans* isomer was determined by means of ^1H NMR and GLC analyses.[9] Representative examples are given in Tables 2 and 3.

A catalytic amount of acids has been found to promote smoothly the transformation of various unsaturated aldehydes with arenethiols to the corresponding intermolecular cycloaddition products, such as thiochromans **3** and thiochromens **4**, under mild reaction conditions. Several comments are worth noting: (1) Various type of α,β-unsaturated aldehydes reacted with **2**, except 2-substituted crotonaldehydes,[10] and gave thiochromans (**3**) in good to excellent yield; (2) the *cis* isomer was usually obtained as major isomer; and (3) acetylenic aldehydes also reacted smoothly with **2** under the same reaction conditions and gave thiochromenes (**5**) in good yields.

Table 3 Stereochemistry of 2,3,4-Trihydro-1-Benzothiopyrans (**3**)

Entry	R and R' in **3**		Cat	Ratio of *cis/trans*
1	Me	H (**3a**)	H_2SO_4	5.8/1.0
2	Me	H (**3a**)	*p*-TsOH	1.9/1.0
3	Me	H (**3a**)	ZnI_2	4.4/1.0
4	Me	Me (**3d**)	*p*-TsOH	13.3/1.0
5	n-C_3H_7	H (**3g**)	*p*-TsOH	0/1.0
6	Ph	H (**3h**)	*p*-TsOH	0.6/1.0



(**3**)

Although the details concerning the mechanism still remain ambiguous, the reaction may proceed through allylic cationic intermediates generated in site. These allylic cationic intermediates gave the products thiochromans **3** or **4** through a subsequent cross-condensation of arenethiols.[11]

In conclusion, the present method using easily available catalyzer is characterized by high operational simplicity and mild reaction conditions. These reactions provide a route to prepare 2,3,4-trihydro-1-benzothiopyrans with a high stereoselectivity in good-to-moderate yields. We believe that this intermolecular cycloaddition offers one of the most simple and very convenient methods for synthesis of 1-benzothiopyrans.

References and Notes

(1) For example, Katrizky, A. R.; Bonlton, A. J. *Advances in Heterocyclic Chemistry*; Academic Press: **1975**, 18, 76.

(2) Tilak, B.D.; Desai, H. S.; Deshande, C. V.; Jain, S. K.; Vaiaya, Y. M., *Tetrahedron* **1966**, 22, 7.

(3) Meters, C.Y.; Rineldi, C.; Bonali, L., *J. Org. Chem.* **1963**, 28, 2440.

(4) Tanaka, J.; Katagiri, T.; Takabe, K.; Takeshita, S., *J. Synth. Org. Chem, Japan* **1971**, 29, 788.

(5) Kwart, H.; Greoge, T. J., *J. Chem. Soc., Chem. Comm* **1970**, 433.

(6) Gopalan, B.; Rajagopalan, K.; Swaminathan, S., *Synthesis* **1976**, 409.

(7) Intermolecular cycloaddition catalyzed by aluminum chloride to thiochromans are known. Manimaran, T.; Thiruvengadim, T. K.; Ramakrishuan, V. T., *Synthesis* **1975**, 739.

(8) Typical reaction procedure: To a solution of **1a** (350 mg, 5 mmol) and *p*-TsOH-H_2O (100 mg, 0.5 mmol) in anhydrous dichloroethane (15 mL) was added a solution of **2a** (1.21 g, 11 mmol) in anhydrous dichloroethane (15 mL). The reaction mixture was stirred at 80 °C for 4 h. After the usual work-up of the reaction mixture, the crude products was purified by chromatography column on silica gel to afford 2-methyl-4-thiophnyl-2,3,4-trihydro-1-benzotiopyrans as a mixture of *cis* and *trans* isomers (**3a**, 76%, ratio of cis/trans = 1.9/1). All new compounds were fully characterized by ^{1}H and ^{13}C NMR (270 MHz; $CDCl_3$), IR and MS. Selected spectral data: **3a**-*cis*: ^{1}H NMR (270 Mz, $CDCl_3$): 6.98-7.78 (m, 9H), 4.56 (t, J = 3.15 Hz, 1H), 3.95 (m, 1H), 2.24 (m, 1H), 1.86 (m, 1H), 1.30 (d, J = 6.60 Hz. 3H); ^{13}C NMR (270 Mz, $CDCl_3$): 128-136, 48.8, 35.5, 30.8, 21.0; **3a**-*trans*: ^{1}H NMR (270 Mz, $CDCl_3$): 6.98-7.78 (m, 9H), 4.43 (m, 1H), 3.30 (m, 1H), 2.55 (m, 1H), 2.06 (m, 1H), 1.23 (d, J = 8.91 Hz. 3H); ^{13}C NMR (270 Mz, $CDCl_3$): 128-136, 47.7, 40.8, 36.3, 21.5; HRMS Calcd for $C_{16}H_{16}S_2$ 272.0693, Found 272.0690. **5a**: ^{1}H NMR (270 Mz, $CDCl_3$): 6.74-7.64 (m, 14H), 6.22 (d, J = 3.3 Hz, 1H), 5.92 (d, J = 3.3 Hz, 1H); HRMS Calcd for $C_{21}H_{16}S_2$ 332.0693, Found 332.0689.

(9) Assignment of the *cis* and *trans*-isomers of the products, and determination of the *cis/trans* ratio were accomplished by means of ^{1}H NMR and/or gas chromatography according to the reported assignment. For example; Cotterill, W. D.; France, C. J.; Livingstone, R.; Atkinson, J. R.; Cottan, J., *J. Chem. Soc., Perkin I* **1972**, 787.

(10) In the case of 2-substituted aldehydes, such as 2-ethyl-2-butanal, diphenylthioacetals (2-ethyl-2-buta-diphenylthioacetals) were obtained in 70% yield.

(11) For example, Ishino, Y.; Nakamura, M.; Nishiguchi, I.; Hirashima, T. *Synlett* **1991**, 633. Cossy, J.; Henin, F,; Leblanc, C., *Tetrahedron Lett.* **1987**, 28, 1417.

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