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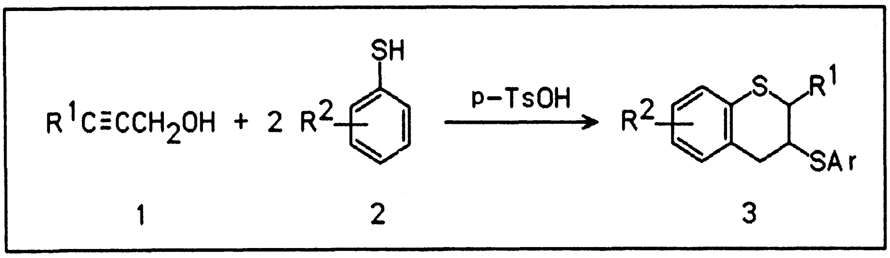
A Novel Synthesis of 3,4-Dihydro-2H-1-benzothiopyrans. Acid-Catalyzed Intermolecular Cycloaddition of Acetylenic Alcohols with Arenethiols

Yoshio ISHINO,* Toshihiro MASAOKA, and Tsuneaki HIRASHIMA
Osaka Municipal Technical Research Institute,
Morinomiya, Joto-ku, Osaka 536

Reaction of the acetylenic alcohols with arenethiols in the presence of p-toluenesulfonic acid (p-TsOH) gave 3,4-dihydro-2H-1-benzothiopyrans (thiochromans) in good to excellent yields, the reaction of which may involve intermolecular cycloaddition via cationic intermediates.

In our earlier work,$^{1)}$ we showed that acetylenediols, especially 2-butynediol, react with arenethiols in the presence of zinc iodide to give the seven-membered intermolecular cycloaddition products, 4,5-bis-(arylthio)- 2,3,4,5-tetrahydro-1-benzothiepins. Herein we wish to report further applications of the acid-catalyzed cycloaddition of acetylenic alcohols, 3-substituted-propargyl alcohols (1), and arenethiols (2) which provides 3,4-dihydro-2H-1-benzothiopyrans (thiochromans) (3) in good to excellent yields. Although numerous methods have been known for the synthesis of thiochromans by the reactions of phenyl-allylsulfides,$^{2)}$ α-thiochlorosulfides,$^{3)}$ and so on,$^{4)}$ to our knowledge, one-pot and convenient synthesis of 3 by the acid catalyzed intermolecular cycloaddition of acetylene alcohols and arenethiols has not yet been reported.



When a mixture of the phenylpropargyl alcohol (1a) and phenylthiol (2a) was heated with p-TsOH (0.3 equiv.) in dichloroethane at 80 °C for 4 h, 2-phenyl-3-phenylthio-1-thiochroman (3a) was obtained in 85% yield as an almost sole product (Method A).$^{5)}$ The reaction of 1a with 2a was found to be largely influenced by the reaction conditions, especially the nature of the solvent and the acid catalyst. As shown in Table 1 (Entry i-k), formation of the by-products, 3-phenyl-2-phenylthio-propionaldehyde (4a), 3-phenyl-2-phenylthio-2-propene-1-ol (5a), and 3-phenyl-1,3-diphenylthio-2-propene (6a), was promoted by the use of 10% THF/dichloroethane as solvent and/or zinc iodide as catalyst (Method A', B, and B'[7]).

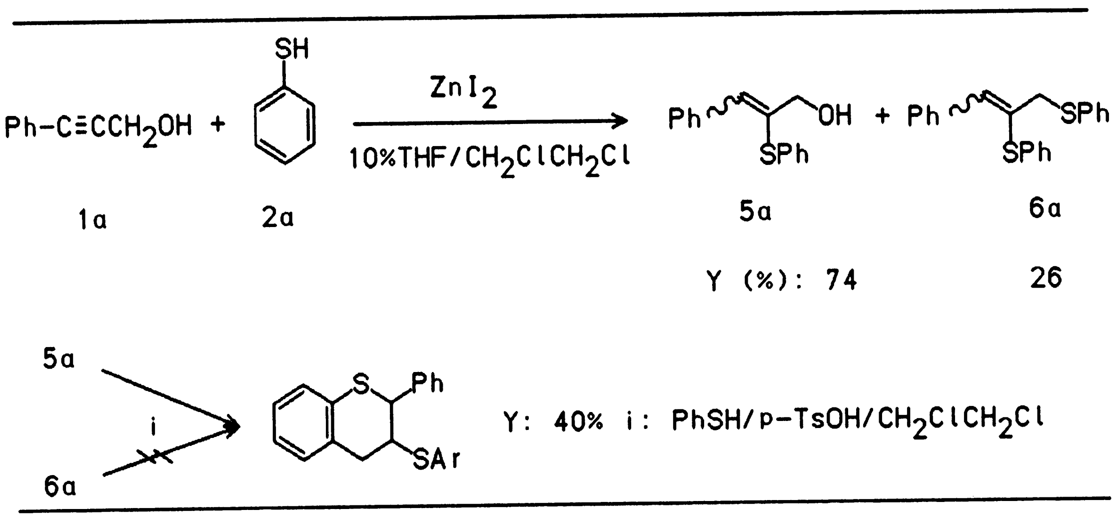
Under similar reaction conditions, the cycloaddition of 1a and related acetylenic compounds (2-pentyn-1-ol 1f and 2-heptyn-1-ol 1h) with a variety of arenethiols in the presence of acid easily took place to give the corresponding thiochromans (3) in good to excellent yields (Table 1).

Table 1. Acid-catalyzed Intermolecular Cycloaddition of Acetylene Alcohols and Arenethiols

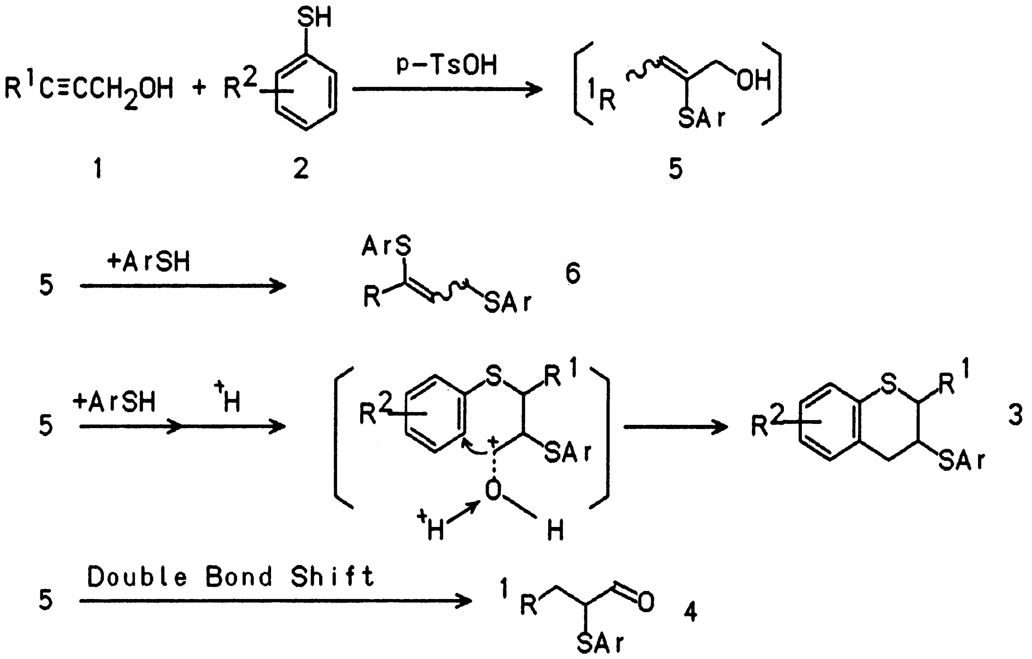
Run	R in 1	2	Reaction conditions	Yield/%[a), 8)] 3	4a	5a	6a
a	C_6H_5	C_6H_5SH	A	85			
b	C_6H_5	$p\text{-}CH_3C_6H_4SH$	A	83			
c	C_6H_5	$o\text{-}CH_3C_6H_4SH$	A	98			
d	C_6H_5	$p\text{-}ClC_6H_4SH$	A	71			
e	C_6H_5	$p\text{-}t\text{-}C_4H_9C_6H_4SH$	A	62			
f	C_2H_5	C_6H_5SH	A	52			
g	C_2H_5	$p\text{-}ClC_6H_4SH$	A	64			
h	$n\text{-}C_4H_9$	$p\text{-}ClC_6H_4SH$	A	78			
i	C_6H_5	C_6H_5SH	A'	18	41		
j	C_6H_5	C_6H_5SH	B			15	37
k	C_6H_5	C_6H_5SH	B'			74	26

a) Isolated yields after column chromatography by silica gel.

Use of zinc iodide as a catalyst instead of p-TsOH led to the formation of a mixture of 5a and 6a. Furthermore, additional treatment of each of the isolated products (5a and 6a) with phenylthiol in the presence of p-TsOH was also examined. 3-Phenyl-2-phenylthio-2-propene-1-ol (5a) was efficiently transformed into 3a with 40% yield. In the case of the reaction with 6a, 3a was not obtain at all. These results strongly suggest that after formation of 5a by the addition of phenylthiol to acetylene alcohols, 3a may be formed via acid-catalyzed intramolecular cyclization of 5a.



Although a detailed mechanism of the present reaction has not yet been clear, it may be assumed, as shown in the below Scheme, that 5 is initially formed and that the compound 3 is then formed by intramolecular cyclization of cationic intermediates generated by electrophilic attack of p-TsOH to the hydroxyl groups of 5.[9] The compounds 4 and 6 may be formed by double bond-shift of 5 to the terminal position and by the further reaction with arenethiols of 5, respectively.



The present one-pot reaction thus provides a new and convenient method for synthesis of a thiochroman ring system which have hitherto been difficult to synthesize,[10] and also a new-type of acid-catalyzed cycloaddition of acetylenic alcohols with arenethiols.

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5)The isolated 3 were an almost sole product (checked by TLC and GC). The stereochemical assignment of 4 are not enough to make definite for either cis or trans isomer and/or their mixture.6)

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7)Reaction conditions **A'**, **B**, and **B'** are as follows: **A'**: p-TsOH(0.3 equiv.)/10%THF-dichloroethane(30 mL) at 60 °C for 4 h, **B** : Zinc iodide(2 equiv.)/dichloroethane(30 mL) at 60 °C for 4 h, **B'**: Zinc iodide(2 equiv.)/10 %THF-dichloroethane(30 mL) at 60 °C for 4 h.

8)Spectral data: (^{1}H and ^{13}C-NMR at 90 MHz, in CDCl$_3$, ppm), 3A: 7.18(m, 14H), 4.56(d,J=3.6 Hz, 2H), 3.57(m, 2H), 2.85(m, 1H) ^{13}C-NMR: 129(m), 63.7, 56.4, 37.1, 3b: 7.23(m, 12H), 4.45(d, J=3.4 Hz, 1H),3.55(m, 1H), 2.90(m, 1H), 2.38(s, 3H), 2.32(s, 3H), 3c: 7.23(m, 12H), 4.49(d, J=3.2 Hz, 1H), 3.60(m, 2H), 2.88(m, 1H), 2.41(s, 3H), 2.15(s, 3H), 3d: 7.24(m, 15H), 4.42(d, J=3.0 Hz, 1H), 3.50(m, 2H), 2.93(m, 1H), 3e: 7.20(m, 12H), 4.49(d, J=2.2 Hz, 1H), 3.50(m, 2H), 2.82(m, 1H), 1.31(s, 18H), 3f: 7.20(m, 9H), 4.49(d, J=3.5 Hz, 1H), 3.37(m, 2H), 2.15(m, 1H), 1.60(m, 3H), 0.92(t, J=7.2 Hz, 3H), ^{13}C-NMR: 130(m), 65.1, 54.0, 31.5, 27.1, 13.8, 3g: 7.20(m, 9H), 4.48(d, J=3.6 Hz, 1H), 3.35(m, 2H), 2.22(m, 2H), 1.30(m, 6H), 0.87(t, J=5.0 Hz, 3H), 3h: 7.18(m, 9H), 4.28(d, J=3.3 Hz, 1H), 3.24(m, 1H), 2.10(m, 1H), 1.30(m, 3H), 0.90(t, J=6.5 Hz, 3H), 4a: 9.52(d, J=3.6 Hz, 1H), 7.34(m, 10H), 3.82(m, 1H), 3.15(d, J=2.9 Hz, 2H), $\nu_{C=O}$: 1719 cm^{-1}, 5a: 7.24(m, 10H), 6.88(s, 1H), 4.32(s, 2H), 2.12(bs, 1H), ν_{OH}: 3350 cm^{-1}, 6a: 7.24(m, 15H), 6.13(s, 1H), 3.70(s, 2H).

9)For analogous cationic intermolecular cycloaddition, see H. Ishibashi, H. Nakatani, H.Sasashita, and M. Ikeda, J. Chem. Soc., Chem Commun., **1987**, 338 and references therein.

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