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Short Note

trans-2-Phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran

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Abstract: Iodine-catalyzed cyclocondensation of cinnamaldehyde and thiophenol yields rapidly *trans*-2-phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran in excellent yield with very high diastereoselectivity.

Keywords: cinnamaldehyde; thiophenol; iodine; *trans*-2-phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran

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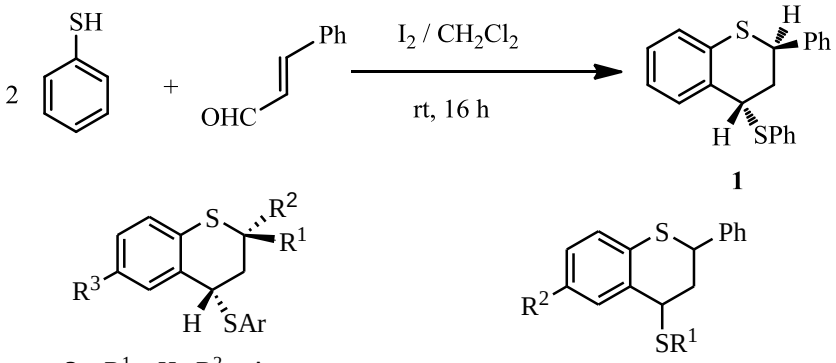
Introduction

3,4-Dihydro-2*H*-1-benzothiopyran derivatives (thiochromans) exhibit a wide range of biological activities, which include anti-bacterial, anti-inflammatory, anti-psychotic, anti-hyperplasia and anti-cancer activities [1]. Therefore, development of new and facile synthetic routes leading to such heterocycles for assessment of their biological potential is of considerable interest. A survey of the literature shows that there are a variety of methods available for the synthesis of these compounds, among which the reaction of thiophenols with α,β-unsaturated aldehydes [2,3] or allyl alcohols [4] in presence of various acidic catalysts are particularly important. Iodine is known to show Lewis acid properties [5-7] and in recent years these are being nicely exploited for achieving varieties of addition, elimination and condensation reactions. Thus, the conjugate addition of thiophenol to α,β-unsaturated ketones has been reported to be catalyzed by iodine [5]. Our endeavor to synthesize 3,4-dihydro-2*H*-1-benzothiopyrans started by taking two readily available fragments, *viz*., thiophenol and cinnamaldehyde and using iodine as catalyst, the interesting results of which are presented herein.

Results and Discussion

In the present study, when a mixture of thiophenol and cinnamaldehyde in CH_2Cl_2 was stirred at room temperature for 16 hours, only one product was obtained in excellent yield (90%). Characterization of the product from its spectral (IR, ^{1}H and ^{13}C NMR including HMBC and HMQC, and MS) data showed it to be *trans*-2-phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran (**1**). The *trans* configuration was ascertained from a comparison of the *J*-values of the four aliphatic protons of the product with the reported *J*-values for the aliphatic protons of *cis* and *trans* isomers of 4-acetoxy-2-alkylchromans [8] and 4-methoxyflavans [9] and those for *cis*-1,3-diarylthiochromans [10]. Confirmation of the said structure was finally obtained from X-ray crystallographic studies (ORTEP diagram shown in Figure 1) [11].

Scheme 1. Synthetic route to the title compound **1**.

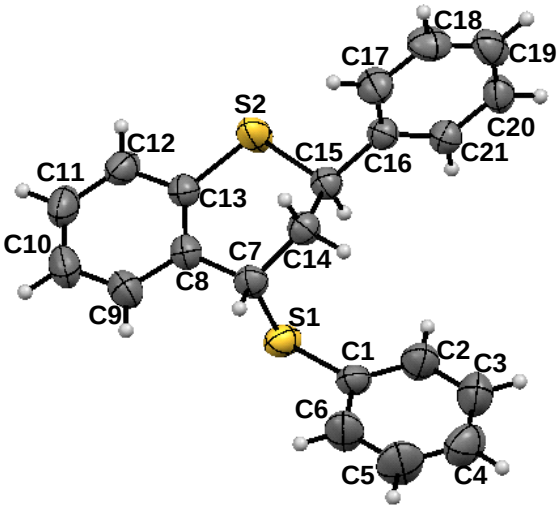


2a: R^1 = H, R^2 = Ar
b: R^1 = Ar, R^2 = H
3a: R^1 =H, R^2 = Alkyl
b: R^1 = Alkyl, R^2 = H

4a: R^1 = Ph, R^2 = H
b: R^1 = *p*-Br-C_6H_4, R^2 = Br

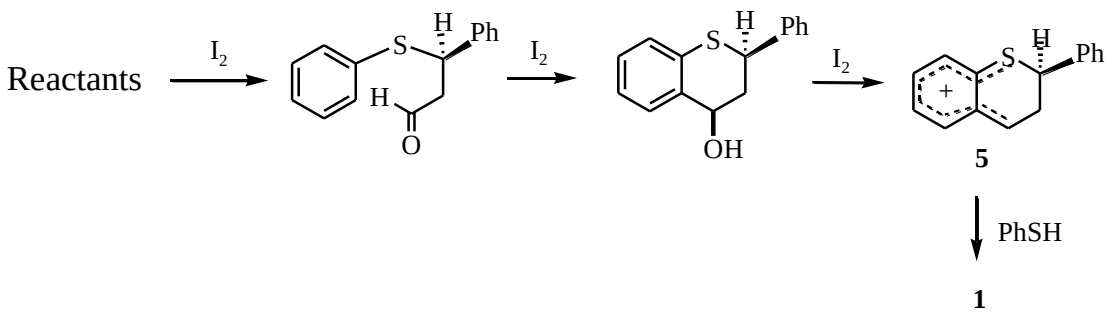
Our attempt to reduce the reaction time by carrying out the reaction at the boiling temperature of CH_2Cl_2 was not very successful, because the product was not at all clean, possibly due to some polymerization reactions.

Figure 1. ORTEP diagram of **1**.



In a report of synthesis of 2-aryl-4-thioaryloxy-3,4-dihydro-2*H*-1-benzothiopyrans and 2-alkyl-4-thioaryloxy-3,4-dihydro-2*H*-1-benzothiopyrans, Ishino *et al*. [2] reported that they obtained both the *cis* and *trans* isomers of these compounds (**2a**/**2b** and **3a**/**3b**) and they could not separate the diastereomers. Without isolating the pure diastereomers, they determined the composition of the mixtures from the ^{1}H NMR spectral data of the product mixtures. Subsequently, Jafarzadeh *et al*. [3] have reported the synthesis of such compounds without mentioning any stereochemistry (*i.e.*, the products having the structure **4**) by tungstophosphoric acid catalyzed cyclocondensation of α,β-unsaturated aldehydes and thiophenols, but the ^{1}H NMR spectral data reported by them corresponded neither with the data reported by Ishino *et al.* [2] nor with the data recorded by us. Moreover, the ^{1}H NMR spectral data for the aliphatic protons of two compounds (**4a** and **4b**) of the same series reported by them differed significantly [**4a**: δ 3.54 (1H, d, *J* = 7.3 Hz), 5.19 (1H, d, *J* = 9.3 Hz), 6.22 (1H, dd, *J* = 1.8 and 8.7 Hz), 6.39 (1H, dd, *J* = 1.9 and 8.9 Hz); **4b**: δ 4.98 (1H, d, *J* = 7.0 Hz), 6.18 (1H, d, *J* = 9.2 Hz), 6.41 (1H, dd, *J* = 1.7 and 8.5 Hz), 6.89 (1H, dd, *J* = 1.6 and 8.5 Hz)]. It was very difficult to understand why the data for these two closely related compounds differed so widely. This left some doubt about the identity of the compounds isolated by Jafarzadeh *et al*. [3]. The very high diastereoselectivity of the iodine-catalyzed reaction described here may be accounted for by considering that the stable cation **5** generated by initial combination of the two reactants followed by a cyclization is attacked very selectively from the side opposite of the existing phenyl (**Scheme 2**)

Scheme 2. Plausible mechanism for formation of **1**.



Experimental Section

To a mixture of cinnamaldehyde (1 mmol) and thiophenol (2 mmol) in dry dichloromethane (30 mL), iodine (64 mg, 0.25 mmol) was added and the reaction mixture was stirred in N_2 atmosphere at room temperature (30 ℃). When the reaction was complete after 16 h, the reaction mixture was diluted with dichloromethane (25 mL) and the resulting solution was washed with sodium thiosulphate solution (2 × 25 mL) and water (2 × 25 mL), successively. The solid material obtained after removal of the solvent showed one TLC spot and it was purified further by passing through a silica gel (100–200 mesh) column followed by crystallization from chloroform-petroleum ether, yield: 90%; mp. 102 ℃, colorless cubes.

IR (KBr) cm^{-1}: 3028, 2903, 1585, 1562, 1470, 1453, 1436, 1297, 1249, 1152, 1058, 960, 745. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43–2.51 (2H, m, H_2-3), 4.74 (1H, t, *J* = 3.1 Hz, H-4), 5.15 (1H, dd, *J* = 9.2 and 5.6 Hz, H-2), 7.00–7.06 (1H, m, H-6), 7.10–7.17 (2H, m), 7.28–7.38 (7H, m), 7.41–7.45 (2H, m), 7.49–7.52 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.69, 40.50, 49.15, 123.91, 125.89,

127.84, 127.90, 128.72, 129.16, 130.73, 131.55, 133.10, 134.25, 134.74, 140.72. MS (TOF MS ES$^+$): Calcd. for $C_{21}H_{18}S_2$ $(M+K)^+$: 373.0487; found 373.0115. Elemental analysis: Calcd. for $C_{21}H_{18}S_2$: C, 75.40; H, 5.42. Found: C, 75.12; H, 5.59%.

Conclusions

Thus, we report here a very simple and highly diastereoselective synthesis of *trans*-2-phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran which itself and its analogues are expected to find important applications.

Acknowledgements

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11. **X-ray crystallography:** X-Ray single crystal data were collected using Mo Kα (λ = 0.7107 Å) radiation on a SMART APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. The single crystal structure of **1** was solved by direct method and refined. The non hydrogen atoms were treated anisotropically. The positions of all hydrogen atoms were generated by their idealized geometry and refined using a riding model. Crystal dimension: 0.32 × 0.26 × 0.19 mm; T = 298(2) K; orthorhombic, space group Pccn ; a = 29.205(2), b = 9.3942(7), c = 12.8072(10) Å; V = 3513.8(5) $Å^3$; Z = 8, ρ_{calcd} = 1.265 gcm^{-3}; μ = 0.300 mm^{-1}; F(000) = 1408; θmin/max/° = 1.39/28.11; R_{int} = 0.0302; Range of h, k, l = -38/38, -11/12, -16/16; 36889 reflections collected of which 4268 were unique, 3273 observed [I > 2σ(I)] reflections, 208 parameters were refined; R_1 = 0.0410, wR_2 = 0.1032; Goodness of fit on F^2 = 1.006; CCDC - 799121 contains the supplementary crystallographic data 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.