An Efficient Approach to the Synthesis of 4*H*-1-Benzothiopyran-4-ones *via* Intramolecular Wittig Reaction†

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The reaction of *S*-acyl(aroyl)thiosalicylic acids **2** with *N*-phenyl(triphenylphosphoranylidene)ethenimine **3** in stepwise fashion leads to the acylphosphoranes **5** which subsequently undergo intramolecular Wittig cyclization on the thiolester carbonyl to afford the 4*H*-1-benzothiopyran-4-ones **7** in excellent yields.

1-Benzothiopyran-4-ones are an important class of heterocycles and interest in their chemistry continues unabated because of their usefulness as synthons and/or as biologically active agents.[1] In connection with our studies on biologically active compounds possessing benzothiopyran and benzothiazepine skeletons, we became interested in developing a suitable methodology for the synthesis of 1-benzothiopyran-4-ones. In general, 1-benzothiopyran-4-ones are synthesized either by the condensation of a β-keto ester with a thiophenol in polyphosphoric acid[2] or by the cyclization of a β-substituted cinnamate, derived from the constituent thiophenol and an appropriate propiolate.[3] However, these methods could not be applied for the synthesis of many target molecules,[4] in particular methoxy-substituted thioflavone.[5] We now report a very simple and convenient route to 1-benzothiopyran-4-ones *via* intramolecular thiolester carbonyl olefination using *N*-phenyl(triphenylphosphoranylidene)ethenimine **3**. Compound **3** is a useful and versatile reagent.[6]

Thiosalicylic acid **1** was converted into its *S*-acyl (aroyl) derivatives **2** by treatment with the corresponding acid chloride or anhydride. When a mixture of compound **2** and *N*-phenyl (triphenylphosphoranylidene)ethenimine **3** was heated in refluxing toluene or dioxane, the desired 2-substituted, 4*H*-1-benzothiopyran-4-ones **7** were obtained in 80–

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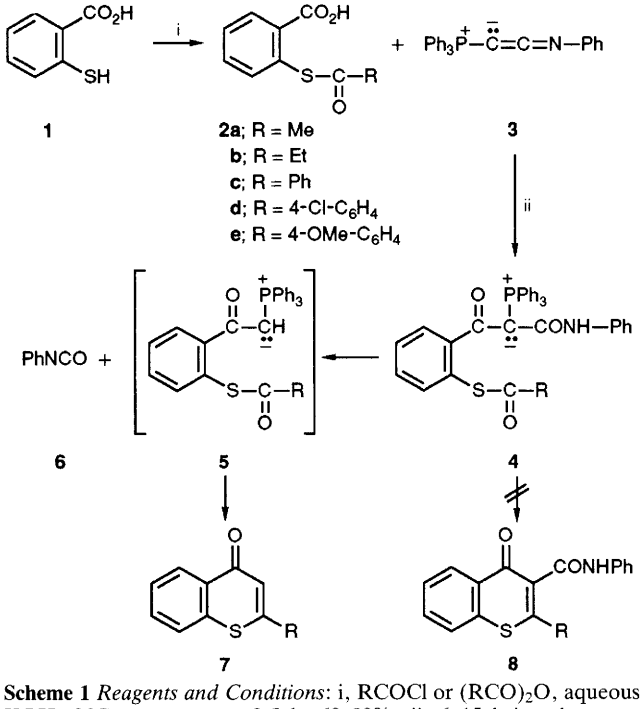
Table 1 One-pot synthesis of 2-substituted, 4*H*-1-benzothiopyran-4-ones 7 from **2** and **3** *via* intramolecular Wittig cyclization

Entry	Reaction time/h	Products[a]	Yield (%)[d]
1	10[b]	**7a**	85
2	12[b]	**7b**	83
3	8[b]	**7c**	89
4	6[c]	**7d**	91
5	15[c]	**7e**	80

[a] All products were characterized by their IR, ^{1}H NMR and mass spectral data and also by comparison with authentic samples. [b] Reaction performed in toluene. [c] Reaction performed in dioxane since the starting compounds **2d** and **2e** were not sufficiently soluble in toluene. [d] The products were purified by silica gel column chromatography using light petroleum–acetone 98 : 2 as eluent. Yields refer to isolated pure products.



Scheme 1 *Reagents and Conditions*: i, RCOCl or $(RCO)_2O$, aqueous KOH, 0 °C–room temp., 0.5 h, 60–80%; ii, 6–15 h in toluene or dioxane, reflux, 80–91%

91% yields (Scheme 1).‡ The formation of product **7** could be explained by a sequence of reaction as illustrated in Scheme 1. A possible reaction pathway for the conversion of **2** into **7** involves protonation of *N*-phenyl(triphenylphosphoranylidene)ethenimine **3** by the **2** followed by nucleophilic attack of the carboxylate anion to the resulting vinylphosphonium salt. There is then a migration of the ester carbonyl group from O to C forming **4** followed by extrusion of phenyl isocyanate **6** and ultimately leading to the acylphosphorane **5** which subsequently undergoes ring closure *via* the intramolecular Wittig reaction on the thiolester carbonyl to form the desired 4*H*-1-benzothiopyran-4-one **7**. The extrusion of phenyl isocyanate during the reaction was detected by addition of ethanol to the reaction mixture. Thus, phenyl-isocyanate was trapped and isolated in the form of the carbamate. In none of the cases were we able to isolate 2-substituted, 4-oxo-4*H*-benzothiopyran-3-carboxanilide **8**. This result indicates that the cleavage of phenyl-isocyanate in **4** at higher temperatures is faster than the intramolecular Wittig reaction and thus eventually leads to the desired product **7**. Further, an electron withdrawing substituent in **2d** accelerates the rate of intramolecular Wittig reaction (Table 1, entry 4), whereas presence of a donor substituent in **2e** reduces the rate of reaction and hence, a slightly longer time is required for the completion of the reaction (Table 1, entry 5). It may be pertinent to mention here that the cyclization of cinnamate with an electron donating substituent such as methoxy by a usual process led to the formation of the corresponding coumarin instead of the desired 1-benzothiopyran-4-one.[5] Also, the reaction of methoxy-substituted benzenethiol with ethylbenzoyl acetate by a conventional method has been found to give a mixture of the corresponding thioflavone and isomeric thiocoumarin or only the thiocoumarin in very low yield.[7] In this connection, the present methodology for **2e** to **7e** is noteworthy.

With a view to ascertaining the reaction pathway, *S*-acetyl thiosalicylic acid **2a** was treated with **3** in toluene at room temperature, it yielded compound **4a** which was isolated and identified by its spectral data. Compound **4a**, on heating in refluxing toluene gave the desired 2-methyl-1-benzothiopyran-4-one **7a**. This finding indicates that compound **4a** which results from the reaction between **2a** and **3**, is one of the intermediates which, after cleavage of phenyl-isocyanate, undergoes subsequent intramolecular Wittig cyclization to afford the desired product **7a**. However, the same reaction under reflux condition led to 2-methyl-1-benzothiopyran-4-one **7a** as the only product.

Thus, we have synthesized a number of 2-substituted, 4*H*-1-benzothiopyran-4-ones from readily accessible starting materials[8] in excellent yields. This method offers a more general and one-pot synthesis of 1-benzothiopyran-4-one. Some of the synthesized compounds are precursors for thiochroman-4-ones which serve as key intermediates in the syntheses of a variety of compounds of biological interest.[9]

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‡ *Spectroscopic data* for **7b** (semisolid); IR ν_{max}/cm^{-1} ($CHCl_3$), 1640, 1600, 1340; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.2 (3 H, t), 2.5 (2 H, q), 6.7 (1 H, s), 7.13–7.45 (3 H, m) and 8.35 (1 H, m); satisfactory elemental analyses obtained for **7b**.

For **7e**, m.p. 126–127 °C (lit.[5] m.p. 127–128 °C); IR ν_{max}/cm^{-1} (Nujol), 1640, 1610, 1520, 1340; ^{1}H NMR (200 MHz; $CDCl_3$) δ 3.9 (3 H, s), 7.25 (1 H, s), 7.05 (2H, dd), 7.6 (5 H, m) and 8.1 (1 H, m).

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