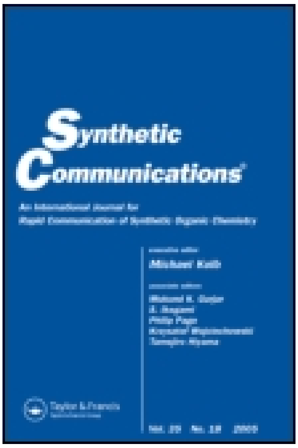

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Facile Synthesis of 2-Substituted Benzo[b]thiophen-3-ols in Water

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FACILE SYNTHESIS OF 2-SUBSTITUTED BENZO[b]THIOPHEN-3-OLS IN WATER

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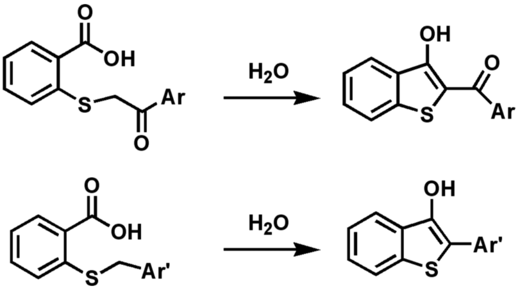
GRAPHICAL ABSTRACT



Abstract *A facile synthesis of 2-substituted benzo[b]thiophen-3-ols in a simple reaction system is reported with water as the only media. Density functional theory (DFT) investigations suggest two pathways comparable in energetics: A neutral pathway with concerted C-C bond formation and hydrogen transfer and an anionic pathway with anion attack to the carbonyl group. Studies indicate that water plays crucial mechanistic roles in both cases.*

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Keywords Benzo[b]thiophen-3-ol; DFT; mechanism; water-catalyzed

INTRODUCTION

Benzothiophenes are considered as important tools in synthetic medicinal chemistry and form the core structure in drugs such as raloxifene.[1–3] Benzo[b]-thiophene derivatives also exhibit a wide spectrum of biological activities, such as antibacterial and antifungal activity,[4] anabolic activity,[5] anxiolytic activity,[6] and anticancer activity,[7] and have potential as enzyme inhibitors[8] and selective estrogen receptor modulators.[9]

Conjugated 2-substituents are important in the exhibition of biological activities of benzo[b]thiophenes,[4,5,10] and thus functionalization on this position

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has attracted much attention, either from open-chain starting materials[11–15] or by functionalizing the benzothiophene framework.[16,17] For a benzo[b]thiophene carrying acyl function in the 2-position, when the 3-position is occupied by a hydroxy group, the resulting hydroxy ketone may also act as an important intermediate in the formation of other biological active heterocyclic compounds such as benzothieno[3,2-b]-pyranones.[18,19] Thus the 3-hydroxybenzo[b] thiophenes also become interesting targets for chemists.[20,21]

In our investigation of the coordination capability of 2-(pyridin-2-ylmethylsulfanyl)benzoic acid, we were deeply attracted by the serendipitous observation that 2-pyridin-2-yl-benzo[b]thiophen-3-ol was formed in good yield in the sole media of water. To gain deeper understanding of the scope and the plausible mechanism of this interesting conversion, we extended the reaction to a series of starting materials containing 2-oxo-2-arylethylthio or pyridinylmethylsulfanyl groups.

RESULTS AND DISCUSSION

A series of 2-[(2-oxo-2-phenylethyl)thio]-benzoic acids **1a–1f** were synthesized from corresponding α-bromoacetophenone derivatives and 2-mercapto-benzoic acid.[22] 2-Pyridinylsulfanyl-benzoic acids **1g** and **1h** were obtained in a similar way from 2-mercapto-benzoic acid and chloromethylpyridine HCl.

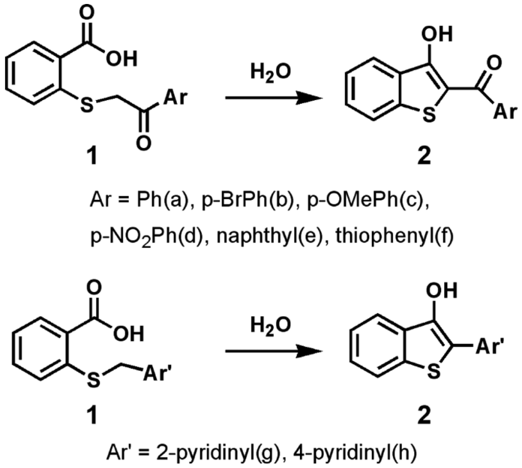
When S-substituted 2-mercapto-benzoic acids **1** were heated to a temperature above 100 °C in water as the sole media, 2-substituted benzo[b]thiophen-3-ols **2** were formed as exclusive products. Zinc powder was able to accelerate the reaction, though it was not indispensable for the formation of 2-substituted benzo[b]thiophen-3-ols as the only products.

Reaction conditions were examined to understand the influencing factors and optimized for the formation of **2a** as listed in Table 1. At a temperature of 130 °C, **2a** was obtained quantatively after 12 h in the presence of zinc powder while a pretty high isolated yield of 84% was still achieved without zinc in the reaction system. When the temperature decreased, the reaction took place at a lower rate while the recovery of unreacted starting material proved that **2a** was still the only product. This decrease in reaction speed could be offset by the presence of zinc powder, which was proved by the formation of **2a** in a yield of 81% when the reaction system was refluxed for 12 h. Because refluxing in water could be considered with a facile

Table 1. Condition optimization for the formation of **2a**

Temperature (°C)	Presence of Zn	Isolated yield (%)
130[a]	Y	99
	N	84
110[a]	Y	94
	N	45
100[a]	Y	95
	N	37
100[b]	Y	81

[a]All the reactions were carried out in a hydrothermal bomb for 12 h.
[b]The reaction was refluxed for 12 h.



Scheme 1. Formation of 2-substituted benzo[b]thiophen-3-ols.

condition for a reaction, it was adopted in the following experiments to gain the target 2-substituted benzo[b]thiophen-3-ols.

Sulfanyl benzoic acids **1** can be converted smoothly into 2-substituted benzo[b]thiophen-3-ols **2** (Scheme 1) in moderate to good yields under these conditions, as shown in Table 2. Products are obtained in satisfactory purity after a simple workup of washing with water several times. Taking into account the simplicity of the reaction system, this is not unexpected.

In solution, products exist in enol form as benzo[b]thiophen-3-ols, which can be deduced from the appearance of the hydroxy group at above 13 ppm in ^{1}H NMR. The highlighted low-field chemical shift values also suggest the existence of intramolecular hydrogen bonding between the hydroxy proton and the carbonyl oxygen or pyridine nitrogen. The explaination is verified with corroborative evidence that in **2h** the signal of the hydroxy proton shifts to about 11 ppm, owing to the loss of this intramolecular hydrogen bonding when the nitrogen atom occupies the *para*-position.

Though no keto tautomer is detected in solution, it is observed in solid state by x-ray crystallography. The crystal structure of **2h** in Fig. 1. indicates the existence of

Table 2. Formation of 2-substituted benzo[b]thiophen-3-ols **2**[a]

Starting material	Ar/Ar′	Isolated yield (%)	Product
1a	Ph	81	**2a**
1b	*p*-BrPh	96	**2b**
1c	*p*-OMePh	79	**2c**
1d	*p*-NO_2Ph	88	**2d**
1e	naphthyl	77	**2e**
1f	thiophenyl	79	**2f**
1g	2-pyridinyl	69	**2g**
1h	4-pyridinyl	71	**2h**

[a] All the reactions were carried out by refluxing for 12 h in the presence of zinc powder.

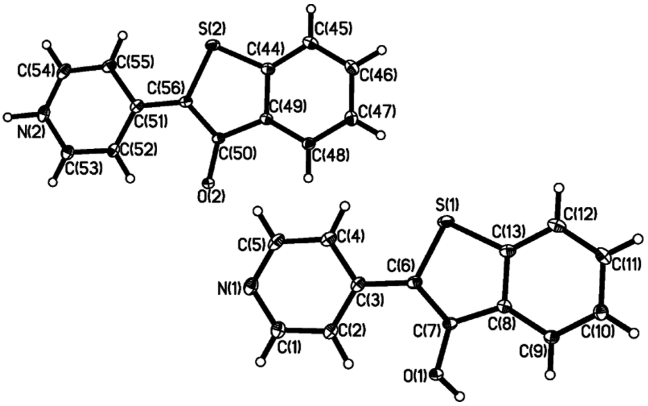
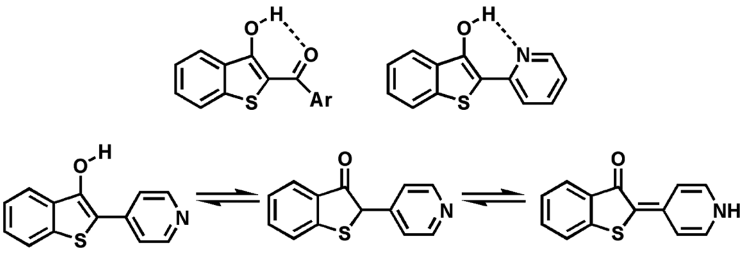


Figure 1. Crystal structure of **2h**.

both keto and enol isomers in the crystal packing. An interesting outcome of this tautomerization to keto isomer is the transfer of methine proton to the pyridine nitrogen to form a quinoid structure, as shown in Scheme 2, in all probability due to the fairly strong basicity of the nitrogen atom. Another feature of the crystal structure is the formation of 1-D linkage by strong intermolecular hydrogen bondings. The distances of 1.52(3) Å for O(1)-H(1)...O(2) and 1.63(3) Å for N(2)-H(2)...N(1) point out the strong interaction between the two moieties.

Besides serving as a proper solvent in certain organic reactions, water may also play important roles from the reaction mechanistic angles, especially when proton transfer might be involved in the reaction pathways.[23–25] To look into the mechanism of the reaction and the effect of water in this facile conversion to 2-substituted benzo[b]thiophen-3-ols, density functional theory (DFT) studies were carried out in B3LYP[26–30] calculations.

A net result of the conversion is the loss of water, which means a methylene hydrogen in the starting material must be transferred to the carboxylate oxygen in a certain step of the reaction. Two possible ways are shown in Fig. 2 as pathways A and B. This concerned hydrogen is directly transferred from methylene to oxygen via a four-membered transition state in pathway A. The crucial C-C bond forms in a concerted way at the same time as the hydrogen transfers. The energy barrier of



Scheme 2. Intramolecular hydrogen bonding and tautomerism in **2h**.

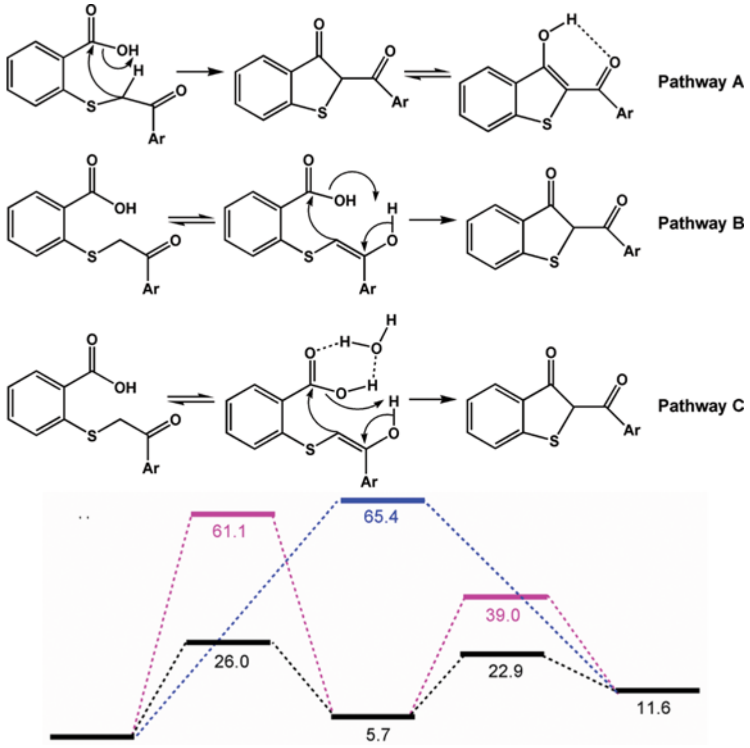


Figure 2. Energy profiles of neutral concerted pathways (B3LYP/6-31G**). Blue: ketone pathway (pathway A). Violet: enol pathway (pathway B). Black: enol pathway with water assistance (pathway C). (Figure is provided in color online.)

this process is suggested to be extremely high with a value of 65.4 kcal/mol. In the alternative pathway B, the hydrogen transfer happens after the enolization of ketone. The hydrogen transfer step itself has a six-membered transition state with an energy requirement of 39.0 kcal/mol. However, the barrier for enolization is 61.1 kcal/mol, which is too high to agree with the reaction conditions and implies the existence of certain types of catalysis. Taking into consideration the fact that reaction can happen at a certain rate without the presence of any other reagent but water, this catalysis should be directly related to water molecule. Thus the influence of water is examined as in pathway C, in which the proton transfer is facilitated by the coordination of a water molecule to the enol and the formation of the hydrogen bond to the carbonyl oxygen. As expected, the presence of water in the transition states changes the energy requirement dramatically, decreasing the barrier of hydrogen transfer by 16.1 kcal/mol. A more striking energy decrease is gained for the enolization, by a value of 35.1 kcal/mol. The resulting energy barrier for this step, still as the rate-determining step, is 26.0 kcal/mol and is in agreement with the reaction conditions.

In our studies on other influencing factors of the reaction, we noticed that reaction is also accelerated when zinc is replaced by zinc oxide. This observation implies

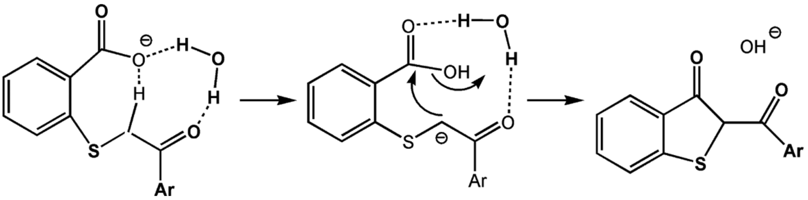


Figure 3. Anionic pathway with water assistance.

the possibility of involvement of an alkaline species, and thus an anionic mechanism as shown in Fig. 3 is also studied in comparison with the neutral pathway.

Keeping in mind the dramatic influence of water on the neutral pathway, it is reasonable to believe that water also plays significant roles in the anionic mechanism. This presumption is proved by the calculational results that show that without the stabilization of a water molecule, the energy of the anion intermediate is too high to connect two transition states. On the other hand, when a water molecule is introduced into the mechanism, the anion attack to the carbonyl carbon acts as the rate-determining step after a equilibrium proton transfer from the methylene to the carboxylate and the energy requirement of the whole reaction is proposed to be 25.1 kcal/mol, which is comparable to the energy barrier of the neutral pathway, as shown in Fig. 4. The comparability of the energy barrier of these two pathways indicates that both mechanisms play a part in the reaction process while in both cases water acts as a crucial participator.

In summary, we report here a facile synthesis of 2-substituted benzo[b]-thiophen-3-ols in a simple reaction system with water as the only media. Mechanistic studies in DFT calculations suggest two pathways comparable in energetics: a neutral pathway with concerted C-C bond formation and hydrogen transfer, and an anionic pathway with the anion attack to the carbonyl group as the rate-determining step. Water plays crucial mechanistic roles in both cases.

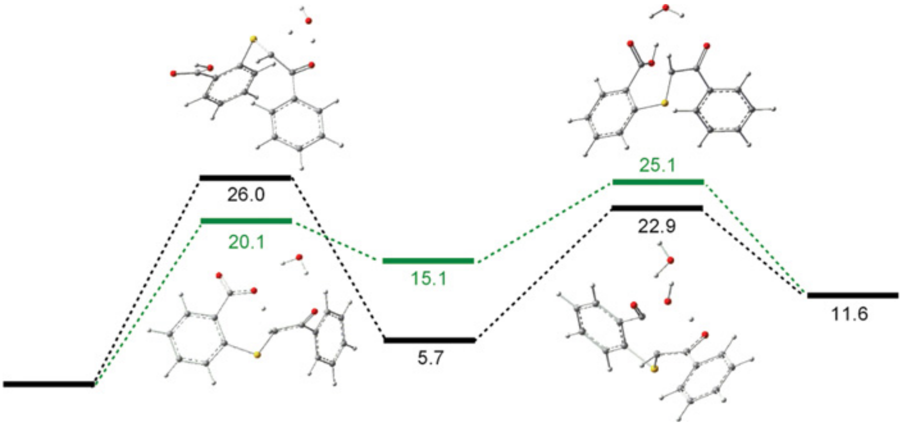


Figure 4. Energy profiles. Black: neutral pathway via enol from starting material (B3LYP/6-31G**). Gray: anionic pathway with water assistance (B3LYP/6-31++G**). (Figure is provided in color online.)

EXPERIMENTAL

Infrared (IR) spectra were obtained from a Nicolet 380 spectrometer as KBr discs. Multinuclear NMR spectra were recorded with a Bruker 400 spectrometer using $CDCl_3$ as solvent unless otherwise noted, and the chemical shifts were reported in parts per million (ppm) with respect to reference standards (internal $SiMe_4$ for ^1H NMR and ^{13}C NMR spectra). Electrospray ionization–mass spectra (ESI-MS) were recorded with a Thermofinnigan Trace DSQ spectrometer. Melting points were measured with an X-4 digital micro-melting-point apparatus and were uncorrected.

Preparation of Starting Materials

2-[(2-Oxo-2-phenylethyl)thio]-benzoic acids **1a–1f** were synthesized from corresponding α-bromoacetophenone derivatives and 2-mercapto-benzoic acid. α-Bromoacetophenone derivative (15 mmol) and 15 mmol of 2-mercapto-benzoic acid were mixed with 30 mmol of KOH in 90 mL of ethanol. The reaction mixture was stirred under reflux under an Ar atmosphere for 2 h and poured into a mixture of 10% HCl in ice water. The resulting solids were recrystallized from ethanol to gain pure acids.

2-Pyridinylsulfanyl-benzoic acids **1g** and **1h** were obtained in a similar way from 2-mercapto-benzoic acid and chloromethylpyridine HCl. 2-Mercapto-benzoic acid (0.1 mol) and 0.1 mol of chloromethylpyridine HCl were added to a mixture of 70 mL of ethanol, 14 mL of water, and 18.5 g of KOH. The reaction mixture was stirred at room temperature for 2 h before 100 mL of water was poured into the system and extracted with three times with 100 mL of ether. The aqueous layer was acidified with 2 M HCl to a pH value of 4 to allow the product to precipitate. The resulting solids were filtered off, washed with water, and recrystallized from methanol to gain pure acids of **1g** as white solids and **1h** as pink crystals.

Synthesis of 2-Substituted Benzo[b]thiophen-3-ols

2-[(2-Oxo-2-phenylethyl)thio]-benzoic acid or 2-pyridinylsulfanyl-benzoic acid (0.5 mmol) was mixed with 0.25 mmol of zinc powder in 10 mL of water and stirred under reflux for 12 h. The resulting product was cooled to room temperature and washed with water several times to obtain pure 2-substituted benzo[b]thiophen-3-ol **2**.

Further experimental details can be found online in the Supplementary Material.

ACKNOWLEDGMENTS

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