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Technical Notes

Application of Heterogeneous Acid Catalysts to the Large-Scale Synthesis of 2- and 3-(*p*-Methoxyphenyl)-6-methoxybenzo[*b*]thiophenes

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Abstract:
2-(*p*-Methoxyphenyl)-6-methoxybenzothiophene (3) was synthesized by acid-catalyzed cyclization and rearrangement of the *β*-ketosulfide precursor 1. The use of Amberlyst 15 resin as a catalyst for the cyclization increased the isomer ratio from 75:25 to 88:12, compared to a conventional approach using polyphosphoric acid (PPA). Although solid acid catalysts were also evaluated for the rearrangement, a two-phase mixture of methanesulfonic acid in toluene was found to be the best alternative to the use of PPA for this reaction. The rearrangement, which was shown to be equilibrium controlled, was driven towards completion by crystallization of the product as it formed. An Amberlyst 15 catalyzed cyclization, combined with an MsOH-catalyzed rearrangement, raised the overall isolated yield from 70 to 80%, and difficulties associated with the use of PPA on a large scale were eliminated. This process has been successfully scaled to a pilot plant and manufacturing scale.

Introduction

2-(*p*-Methoxyphenyl)-6-methoxybenzo[*b*]thiophene (**3**) is an intermediate in the synthesis of raloxifene (Evista, Figure 1),[1] a drug recently introduced for the treatment of osteoporosis in postmenopausal women. This intermediate can be synthesized by electrophilic cyclization of a *β*-ketosulfide **1**, to yield the 3-*p*-methoxyphenyl isomer **2**, followed by rearrangement to the 2-isomer **3**.[1] A major undesired side reaction is the formation of the regioisomer **4** and its subsequently rearranged 2-isomer **5** (Figure 2).

In 1949, Werner reported the synthesis of several 3-alkyl- and 2,3-diakylbenzo[*b*]thiophenes by the cyclodehydration of arylthioacetones with phosphorus pentoxide or zinc chloride.[2] Since then, this reaction has been widely used and demonstrated to proceed most conveniently with polyphosphoric acid (PPA).[3] In this paper, we will compare the use of PPA to newly discovered conditions which utilize a solid acid catalyst in conjunction with methanesulfonic acid.[4] These new conditions provide a 10% increase in isolated yield and greatly reduced waste generation, and are more amenable to large-scale manufacturing.

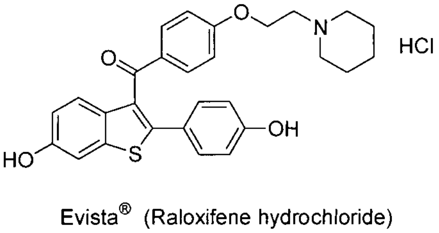

Figure 1.

Results and Discussion

Cyclization and Rearrangement with PPA. The cyclization and rearrangement of **1** occurred simultaneously in PPA at 90 °C, and the reaction was complete in less than 6 h, providing a 75:25 para:ortho isomer ratio. The product was precipitated as a crude isomeric mixture and was then recrystallized from toluene to yield the desired isomer **3** in 70% overall yield and greater than 99% purity. Varying the reaction temperature from 25 to 90 °C had no effect on the isomer ratio obtained. The addition of alternative soluble acid catalysts (glacial acetic, hydrochloric, sulfuric, and methanesulfonic acid) or the use of DMF as a cosolvent had no beneficial effects. Due to the high viscosity of PPA, 85% phosphoric acid was added to thin the reaction mixture, thereby making stirring easier on a large scale.[5] The use of more than a 1:3 ratio of phosphoric acid/PPA led to a very rapid drop in the reaction rate.

On a manufacturing scale, this process had several disadvantages, including difficulty in handling of PPA (due to high viscosity), slow filtration of the precipitated crude isomeric mixture, neutralization of large amounts of waste acid, subsequent disposal of a large quantity of phosphate wastes, and the need for a separate recrystallization to remove the undesired isomer. These practical concerns, as well as the possibility of increasing the yield, led us to explore alternatives to PPA to effect the desired transformations.

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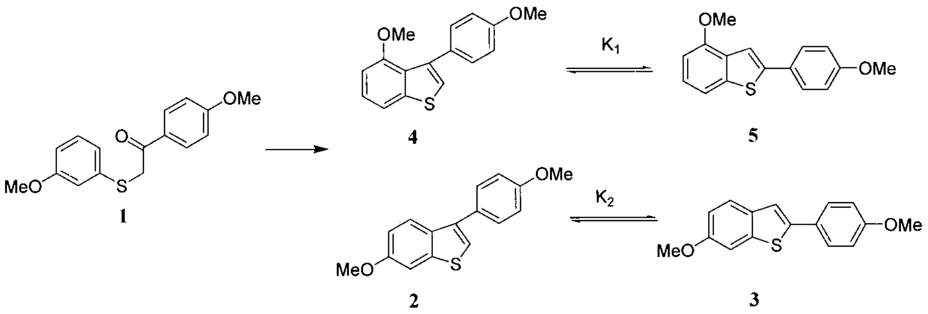

Figure 2.

Table 1. **Rearrangements catalyzed by solid acid catalysts**

catalyst	catalyst description	relative rate	% desmethyl
A15[a]	sulfonic acid/polystyrene	100	4
XN1010[a]	sulfonic acid/polystyrene	30	4
A36[a]	sulfonic acid/polystyrene	100	4
XE586[a]	sulfonic acid/polystyrene	100	2
HPK25[b]	sulfonic acid/polystyrene	10	
IRC76[a]	carboxylic acid/ polymethacrylate	<1	
DHC-32[c]	amorphous silica/alumina	100	4
DHC-8[c]	amorphous silica/alumina	50	6
CCS-10[c]	amorphous silica/alumina	<2	
LZY-74[c]	molecular sieve	0	
LZY-84[c]	molecular sieve	0	
SPA-2[c]	ortho and pyrophosporic acid on silica	5	0
CRP-200[b]	phosphonic acid/polystyrene	0	

[a] Obtained from Rohm and Haas. [b] Obtained from Mitsubishi. [c] Obtained from Universal Oil Products (UOP).

Cyclization and Rearrangement with Solid Acid Catalysts. With a 10 wt % loading of polymeric sulfonic acid resins such as Amberlyst 15,[6] the cyclization proceeded to completion in 2 h in refluxing toluene to give an 88:12 para/ortho isomeric ratio. Under these conditions, the rearrangement reaction was ~50−100 times slower than the cyclization, and hence the 3-isomer analogues (**2** and **4**) could be isolated if desired. Similar results were obtained with a number of different polymeric sulfonic acid resins, and we also found that the catalyst could be recycled directly without any need for regeneration. The isomer ratio of the product was not affected by temperature (60−110 °C), catalyst load (10−500 wt %), or choice of solvent. The reaction proceeded at a reasonable rate only in nonpolar aprotic solvents such as toluene, xylene, chlorobenzene, heptane, and chloroalkanes. No reaction was observed in alcohols, acetonitrile, or DMF. With SPA-2,[7] a catalyst consisting of ortho and pyrophosphoric acid adsorbed onto silica, a 75:25 para:ortho isomer ratio was obtained in toluene at reflux, identical to that obtained with PPA.

While the cyclization was readily catalyzed by solid acids, the rearrangement reaction required much more forcing conditions. With polymeric sulfonic acid resins, a 500 wt % loading of catalyst was required in order to drive the reaction to completion in 3 h in toluene at reflux. Under these conditions, the rearrangement of the para-cyclized intermediate **2** reached an equilibrium composition of 90% of 2-isomer **3** and 10% of 3-isomer **2**. This was demonstrated to be a true equilibrium by subjecting pure **3** to the reaction conditions and observing its rapid equilibration to a 90:10 isomeric mixture of **3** and **2**. Interestingly, the equilibrium of the ortho-cyclized intermediate **4** lies much further toward the 2-isomer **5**. This phenomenon may be rationalized through the higher energy of **4** resulting from steric interaction between the 4-methoxy and the 3-aryl groups. The equilibrium constant, K_1, for the ortho-cyclized product is estimated to be >100, while the equilibrium constant for the para-cyclized product, K_2, is estimated to be 8−9. These equilibria were not apparent in the PPA-catalyzed reaction, where the insolubility of the product under the reaction conditions drove the reaction to completion. Although it was possible to shift the equilibrium of the solid acid-catalyzed reaction by operating in solvents such as heptane, where the product precipitated as it formed, separation of the insoluble product from the insoluble catalyst complicated product isolation and made scale-up difficult.

A troublesome side reaction generating 1−5% demethylated products was observed with solid acid catalysts but not with PPA. Attempts to remove these side products through selective extraction, adsorption, or crystallization were only partially successful. A comparison of the activity and selectivity of a wide range of different solid acid catalysts tested in the rearrangement reaction is given in Table 1. In summary, no solid acid catalyst was found to demonstrate the desired combination of activity and selectivity as PPA.

Rearrangement with Alternative Soluble Acids. Since the cyclization with solid acid catalysts looked very attractive, but the rearrangement did not, we sought to develop a hybrid process involving cyclization with a polystyrenic sulfonic acid, followed by rearrangement with a soluble acid. For instance, cyclization with Amberlyst 15 resin, followed by rearrangement with PPA, increased the isolated yield from 70 to 80%, attributable to the enhanced isomer ratios obtained in the cyclization. However, this reintroduced the previously highlighted difficulties associated with using PPA on a large scale. Therefore, several alternative soluble acids were tested in the rearrangement reaction (see Table 2). Of particular interest were results obtained with methanesulfonic acid (MsOH) at 0.2 and 0.4 M concentrations. The 15-fold increase in reaction rate observed at 0.4 M compared to

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(6) Amberlyst is a trademark of Rohm and Haas Co., Philadelphia, PA.

(7) SPA-2 catalyst was obtained from Universal Oil Products (UOP) Corp., Des Plains, IL.

Table 2. **Rearrangements catalyzed by soluble acid catalysts**

acid	concn	solvent	temp, °C	relative rate
PPA	neat	none	90	100
TsOH	0.2 M	toluene	110	2
MsOH	0.2 M	toluene	110	30
MsOH	0.4 M	toluene	110	500
MsOH	1.0 M	toluene	90	100
HCl (gas)	40 psi	xylene	110	0
$PhPO_3H$	0.6 M	toluene	110	0
Cl_3CCO_2H	0.6 M	toluene	110	0

that at 0.2 M is believed to be related to the separation of a small, immiscible MsOH phase at concentrations above 0.2 M in toluene. This observation, and our observation that the rearrangement was very rapid if conducted in pure MsOH, suggests that the majority of the reaction actually occurred in the small, concentrated MsOH phase, with a minor percentage occurring in the bulk toluene phase. As expected for reactions involving multiple phases, we found that good agitation was necessary for successful large-scale operation.

As observed with the solid acid catalysts, the MsOH-catalyzed rearrangement reaction in toluene reached an equilibrium isomer ratio of 90:10. However, by lowering the temperature from 90 to 80 °C, and by adding heptane towards the end of the reaction, a majority of the product crystallized, thereby driving the equilibrium to a 98:2 ratio of 2- to 3-isomers. Unlike the situation with the solid acid catalysts discussed previously, precipitation of the product does not complicate product isolation, since the MsOH catalyst is readily solubilized and removed at the end of the reaction by the addition of 2-propanol. As observed with the solid acid catalysts, the rearrangement only proceeded in nonpolar, aprotic solvents. It was possible to run the reaction in pure heptane rather than a toluene/heptane mixture, but this resulted in discoloration, increased demethylation, and gummy product crystals. Under the optimum conditions given in the Experimental Section, less than 0.5% of the demethylation products was observed.

It was possible to catalyze both cyclization and rearrangement with MsOH in toluene, but due to poor isomer ratios in the cyclization, the overall yield was comparable to that of the PPA-catalyzed process.

Conclusions

The best overall process involved cyclization with a polystyrenic sulfonic acid resin in toluene, followed by rearrangement with MsOH in toluene under conditions where the reaction equilibrium was driven by precipitation of product. When the rearrangement was complete, the reaction mixture was quenched with *i*-PrOH, and the crystalline product **3** was isolated directly in 80% yield, >99% purity, and with < 0.1% demethylated impurities. In addition to a 10% yield increase in yield, the difficulties associated with the use of PPA were eliminated.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance studies were performed on a Bruker ARX 500 spectrometer. The mass spectra, infrared spectra, and elemental analyses were performed by Molecular Structure Research at Eli Lilly and Co. HPLC analysis utilized a 4.6-mm × 25-cm Zorbax RX-C18 column withan acetonitrile/0.1% phosphoric acid gradient elution at 1 mL/min and detection at 290 nm. The gradient was linear from 64 to 94% acetonitrile over 15 min. The retention times were 6.2 (**1**), 10.62 (**4**), 10.94 (**2**), 13.3 (**3**), and 13.6 min (**5**). The mono-demethylated products related to **5** and **3** had retention times of 5.4, 5.5, 6.0, and 6.1 min.

2-(*p*-Methoxyphenyl)-6-methoxybenzothiophene (3): PPA Procedure. A solution of the β-ketosulfide **1** (40 g, 0.139 mol), PPA (200 g), and 85% phosphoric acid (66 g) was stirred at 90 °C for 6 h. Water (60 mL) was slowly added, and the resulting fine precipitate was filtered and washed with water (100 mL). The resulting wet cake was suspended in toluene (300 mL), heated to reflux, and azeoptropically dried. A black oily layer was separated off the bottom of the hot toluene solution, which was cooled slowly to 0 °C, stirred for 1 h, filtered, washed with toluene (2 × 50 mL), and dried overnight at 60 °C to yield the desired product **3** (26.2 g, 70% yield, 99.7% purity versus HPLC reference standard, 0% desmethyl).

2-(*p*-Methoxyphenyl)-6-methoxybenzothiophene (3): Amberlyst 15/MsOH Procedure. *Laboratory Scale.* A slurry consisting of the β-ketosulfide **1** (40 g, 0.139 mol), toluene (120 mL), and dry Amberlyst 15 resin (4 g) was refluxed for 2 h while azeoptropically removing water. The catalyst was removed by filtration and washed with toluene (17 mL). Methanesulfonic acid (14 g, 0.146 mol) was added to the filtrate, and the mixture was stirred at 90 °C for 4 h. Heptane (56 mL), was added and the reaction mixture was stirred for 1 h at 90 °C, followed by 3 h at 80 °C. 2-Propanol (98 mL) was added, and the mixture was then cooled to 0 °C, stirred for 1 h, filtered, washed with toluene/2-propanol (2 × 75 mL, 70/30 v/v), and dried overnight at 60 °C under vacuum to yield the desired product **3**, mp 196−197 °C (30.0 g, 80% yield, 99.7% purity versus HPLC reference standard, 0.1% desmethyl). ^1H NMR ($CDCl_3$): δ 3.88 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 6.96−7.01 (m, 3H, ArH), 7.32 (d, 1H, ArH), 7.36 (s, 1H, ArH), 7.61−7.65 (m, 3H, ArH).

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.16; H, 5.26; S, 11.66.

Pilot Plant Scale. To a nitrogen-inerted, 50-gal, glass-lined, jacketed reactor equipped with a 12-in.-diameter retreat curve impeller and an overhead tantalum condenser were added toluene (49.5 L), β-ketosulfide **1** (16.5 kg), and Amberlyst 15 resin (1.65 kg). This mixture was refluxed at atmospheric pressure for 2 h, removing 1010 mL of water via a Dean Stark trap. After cooling to 75 °C, the reactor was pressurized to 20 psig with nitrogen, and the catalyst was removed by transferring the reaction mixture through a 316SS 100 mesh screen (8 in. diameter) followed by a 5 μm cotton cartridge filter (2 in. diameter × 12 in. long) over 5 min. The filtered catalyst was washed with toluene (8 L), and the filtrates and washes were combined in a second 50-gal reactor identical to the first. Methanesulfonic acid (5.8

kg) was charged, and the mixture was agitated at 115 rpm for 4 h at 90 °C. Heptane (23 L), was added, and the reaction mixture was stirred for 1 h at 90 °C, followed by 3 h at 80 °C. 2-Propanol (40.4 L) was charged, and the mixture was stirred for 30 min at 80−90 °C, followed by cooling to 0 °C over 2 h. The product was filtered under 30 psig nitrogen pressure over 15 min on a polypropylene filter cloth (10-μm pores) installed in a 16-in.-diameter pressure filter, followed by two washes with 70:30 toluene/2-propanol (31 L). The product was dried overnight under vacuum at 60 °C to yield the desired product **3** (12.3 kg, 79.6% yield, 99.8% purity versus HPLC reference standard, 0.08% desmethyl).

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