An Improved Synthesis of Benzo[*b*]thiophene and Its Derivatives Using Modified Montmorillonite Clay Catalysts[†]

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Methods for the preparation of benzothiophene (**3**) and its derivatives by cyclization of phenylthioacetals (**1**) over $ZnCl_2$-promoted montmorillonite clay are described. Reactions in solution resulted in only moderate (ca. 50%) yields of **3** and the formation of diphenyl disulfide (**4**) and uncharacterized products. The production of **4** was explained by coordination of **1** via its oxygen atom to active sites of the catalyst and subsequent bimolecular processes. Good to excellent yields (67−98%) of **3** and its derivatives were obtained using vapor phase techniques at 200−300 °C to promote the desired intramolecular cyclizations.

Introduction

Benzo[*b*]thiophene (**3**) and its derivatives are an important class of compounds which find use in the synthesis of pesticides and in general synthesis.[1,2] Although **3** and its alkyl derivatives are found in almost all sulfur-containing crude petroleum, separation procedures are too complex and laborious to enable isolation of the pure compounds in useful quantities.[1,2] A variety of methods have been developed to make the parent heterocycle and its alkyl derivatives,[1,2] one being based on the cyclization of **1** under acidic conditions.

Many acids have been used to promote these cyclizations, but in most cases only moderate yields of **3** are obtained because of the sensitivity of both **1** and **3** products to acid-catalyzed side reactions. In particular, proton-addition of the 2,3-bond of **3** and reaction of the resultant carbocation with another aromatic substance can lead to a complex mixture of products.[3-6] Previously, it has been shown that cyclization of **1** is best accomplished using excess polyphosphoric acid (PPA) under conditions (100−200 °C) which allow vacuum distillation of the product from the reaction mixture.[1] This method is difficult to control due to foaming of the PPA and gives very variable yields (20−80%). Use of chlorobenzene solvent with PPA[7] offers an alternative with yields as high as 81%, but as low as 0% for the methoxy-substituted precursor. With or without this solvent phase, handling and disposal of acid residues presents significant difficulty.

In this paper, we describe the use of montmorillonite clays modified with $ZnCl_2$ to cyclize **1** to various benzo[*b*]thiophene derivatives. These catalysts, particularly one based on K-10 montmorillonite, have been used to promote Friedel−Crafts and other related reactions, avoiding the formation of polymeric products so often associated with this type of process.[8-13] In a recent summary article,[14] Clark and co-workers describe data which show that K-10 impregnated with $ZnCl_2$ (2 mmol g^{-1}) has a high surface area (125−200 $m^2\ g^{-1}$) and a mesoporous structure (pore diameters 25−100 Å) with a preponderance of Lewis acid sites. Recent studies in our laboratories[15] have demonstrated that thiophene can be benzylated in high yield (>90%) and selectively (95% 2-isomer) using $ZnCl_2$-modified montmorillonite clays. These observations are significant because standard Friedel−Crafts alkylation reagents result in extensive polymerization of thiophene. It is probable that the restricted pore sizes within the clay limit polymerization reactions to some extent, although the rapidity of the reaction, allowing product isolation within 15 min, is, no doubt, a major factor contributing to the high isolated yields.

Clearly, $ZnCl_2$ modified K-10 clay is a good candidate to promote the desired cyclization to **3** as unwanted polymerization reactions may be limited and the desired intramolecular processes may be favored by the restricted pore sizes. Both solution and vapor phase cyclization of **1** to **3** over montmorillonite clays is described.

Results and Discussions

Attempted Cyclization of (1,R′ = H) to 3 in Solution. Moderate isolated yields (40−50%) of **3** were obtained from reactions carried out in chlorobenzene solution at 132 °C using the K10−$ZnCl_2$ catalyst but little benzo[*b*]thiophene was observed when K10 containing no added $ZnCl_2$ was used (Scheme 1). Small amounts (<5%) of diphenyl disulfide **4** were observed when a catalyst/reagent ratio of 5 was employed but, when using a much

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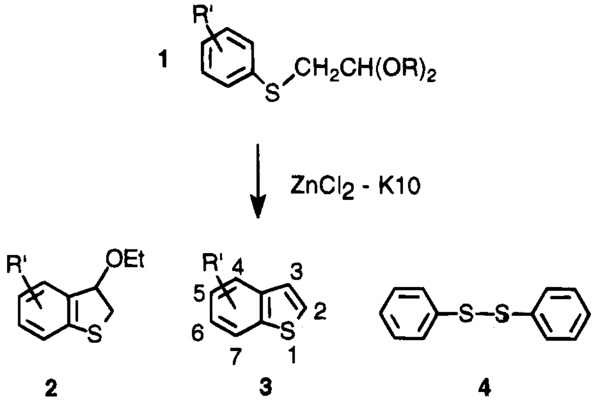
Table 1. Cyclization of (1, R′ = H) to Benzo[*b*]thiophene with K10−$ZnCl_2$

reaction conditions				products (%)				
solvent	catalyst/1 ratio	*T*, °C	time (h)	BT	1^c	2^c	3^c	4^c
		Method A (Solution Phase)						
PhCl	5^a	132	1.5	13^b	0	0	0	0
PhCl	5	132	0.6	46^b	0	0	<5	0
PhCl	0.1	132	0.25	50^b	13	0	32	0
$PhNO_2$	5	130	0.1	13^c	0	0	46	0
$ClCH_2CH_2Cl$	5	84	2	28^c	12	0	20	0
CH_2Cl_2	5	0	90	11^c	0	0	30	0
$CH_3(CH_2)_4CH_3$	5	69	5	3^c	0	0	34	0
		Method B (Vapor Phase)						
	5	200		69^b	0	30	1	0
	10	200		84^b	0	5	3	0
	15	200		82^b	0	<1	0	0
	0.2	300		12^b	40	46	0	0
	0.3	300		14^b	8	76	1	1
	0.4	300		26^b	19	44	0	2
	1	300		57^b	0	3	0	40
	5	300		84^b	0	0	1	0
	1^d	300		72^b	0	0	0	1
	0.2	400		0^b	28	60	<1	12

[a] Catalyst was K10-montmorillonite (Fluka) activated at 300 °C; all other experiments used K10−$ZnCl_2$ (2 mmol of $ZnCl_2$ per gram of clay). [b] Isolated yields. [c] Determined by GC-MS. [d] used (1, R = Me), all other experiments used (1, R = Et).

Scheme 1. Products from the Cyclization of 1 to Benzo[*b*]thiophene and Its Derivatives



smaller ratio (0.1), **4** became a major product (32%). A variety of other solvents and reaction conditions were tried (Table 1) but yields of **3** did not improve beyond those observed using chlorobenzene as solvent. In most cases, some polymeric product was observed.

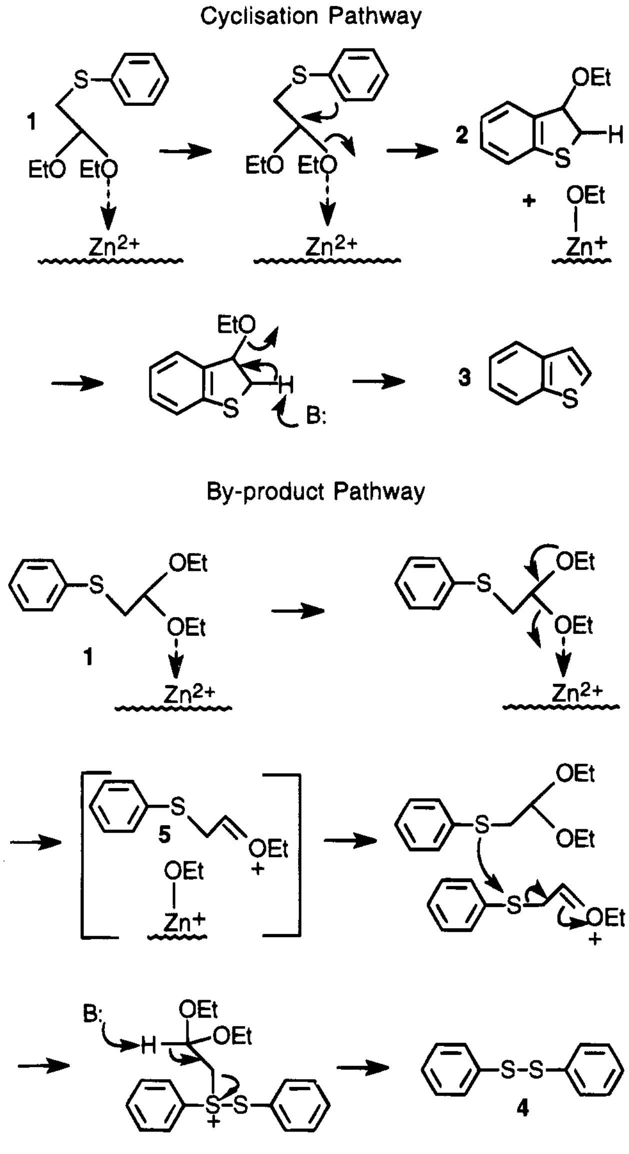
Our conclusions from these results are that the desired cyclization **3** does occur in solution but that competing side-reactions, leading to polymeric products and **4**, occur to a significant degree. The observation of **4** as a major byproduct is interesting as it can be explained by attack of sulfur of a phenylthioacetal molecule in bulk solution at the sulfur atom of another phenylthioacetal molecule which has already undergone elimination of an ethoxy group to the catalyst (Scheme 2). Coordination of **2** via oxygen results in the desired cyclization to **3**. An important observation was that **4** was formed in greatest amounts in chlorobenzene solution using a low catalyst/reagent ratio (0.1). Under these circumstances, the number of active catalytic sites to coordinate **1** would be limited and the chance of bimolecular processes leading to **4** would be enhanced. At higher catalyst/reagent ratios, less **1** should be available in free solution and the chance of cyclization of **1** improved.

Overall, products can be envisaged to arise by reaction of **1** coordinated at active sites by oxygen atoms, the formation of **2** or **4** depending on the result of a competitive reaction involving the intramolecular cyclization to **3** or intermolecular attack by another phenylthioacetal molecule in the solution phase to give **4**. Formation of **4** would be favored under two circumstances; when cyclization of **5** is slow, which is perhaps the case using most of the solvents listed in Table 1, and when **1** is in high concentration. Clearly, formation of **3** should be favored by working in solvents at high dilution or by carrying out the reactions in the vapor phase. We choose to work in the vapor phase in order to achieve a nonsolvent synthetic method for benzo[*b*]thiophene derivatives.

Vapor Phase Cyclization of Phenylthioacetal to Benzo[*b*]thiophene. This approach was very successful (Table 1, method B) using K10−$ZnCl_2$ at either 200 or 300 °C although the catalyst/reagent ratio affected both the yields and the type of product obtained. Using a ratio of 5 at 200 °C, a significant amount of **3** was obtained together with **2** in reasonable yield (69%). Clearly, cyclization is the major process occurring under these conditions, but it would appear that there was insufficient residence time in the clay for elimination of the final ethanol molecule. Increasing the ratio to 10 and 15 at 200 °C gave **3** in an isolated yields of 84 and 82%, respectively. Clearly, the larger amount of catalyst increased the overall residence time sufficiently for conversion of **1** and **2** to **3**.

Similar results were obtained at 300 °C; although, in general, lesser amounts of catalyst were required for complete conversion to **3**. Interestingly, ethyl phenyl sulfide (**6**) was obtained in significant yields (40%) when cyclization was attempted at 300 °C with a 1:1 catalyst/reagent ratio. This product could arise by reaction of **1** with ethanol (formed in a previous cyclization reaction) coordinated at active sites on the catalyst surface. The amount of **6** produced should depend on the amount of ethanol retained by the catalyst and hence on the catalyst/reagent/product ratios and the flow of these materials through the catalyst. None of these factors was rigorously controlled in this study, although the source of the ethyl group in **6** was proven by using the dimethoxy phenylthioacetal ($PhSCH_2CH(OMe)_2$) as reagent, in which case, methyl phenyl sulfide was obtained as a byproduct in minor amounts. Clearly thioether byproducts and **4**, which was only formed in very minor amounts in the vapor phase experiments, are limited by using a high

Scheme 2. Suggested Mechanism for Thioacetal Cyclization and Byproduct Formation



B: = Surface or Solution Species

Table 2. Preparation of Substituted Benzo[*b*]thiophenes in the Vapor Phase (Method B) at 300 °C

product BT[a], R′ =	isolated yield (%)
5-Me	81
7-Me	85
4-/6-Me	98
5-Cl	82
5-Br	87
4-/6-OMe	67

[a] Product purity and identity determined by use of GC-MS and referenced to published NMR spectra.

catalyst to reagent ratio. Some reactions at 400 °C were attempted, but, in general, lower yields of desired products were obtained.

Preparation of Substituted Benzo[*b*]thiophenes. As can be seen from data in Table 2, halo- and alkyl-substituted derivatives of **3** were obtained in good isolated yields using the vapor phase method. GC-MS and NMR analysis showed that the products were obtained in high purity (>99%). Low catalyst/reagent ratios resulted in the same type of byproducts as observed in the preparation of **3**, but use of ratios >5 gave the good isolated yields quoted in Table 2. Cyclization of the *m*-methyl-substituted phenylthioacetal gave a mixture of 4- and 6-methyl derivatives of **3** in very similar ratio to that observed in PPA-promoted reactions. Thus, although the K10–$ZnCl_2$ catalyst gives superior yields to those obtained using to PPA,[1] its mesoporous structure gives no selectivity to either 4- or 6-substituted products.

Lower isolated yields (67%) were observed in the preparation of 4- and 6-methoxy benzo[*b*]thiophene. The lower yields may be due to competing coordination of the aromatic methoxy oxygen at the active sites of the catalyst. A similar suggestion has been advanced to explain the unreactivity of benzyl chloride in the alkylation of aromatics when benzyl alcohol was also present.[11] In this work, it was concluded that the oxygen of the benzyl alcohol occupied the reactive sites of the catalyst preventing reaction of benzyl chloride. In our work, the aromatic methoxy oxygen may bind preferentially in comparison to the ethoxy oxygen and, as a consequence, inhibits the cyclization process.

Conclusion

It has been shown that $ZnCl_2$-promoted montmorillonite clay is an effective catalyst for promoting the cyclization of phenylthioacetals to derivatives of **3**. Good to excellent yields of desired products were obtained using vapor phase methods in which the ratio reactant to catalyst was limited to prevent bimolecular processes.

Experimental Section

Catalyst Preparation and Characterization. $ZnCl_2$-modified K10-montmorillonite (Fluka Chemical Co., used as received) containing 2 mmol of $ZnCl_2$(per gram of clay) was prepared as described previously[15] and was activated by heating at either 150 or 300 °C for 2 h.

Cyclization Procedures. Method A. The phenylthioacetals (4.4 mmol), prepared by the method of Tilak and coworkers,[16] were added to a stirred mixture of K10–$ZnCl_2$ (5 g, activated at 150 °C) in either chlorobenzene, dichloromethane, nitrobenzene, or nitromethane (50 mL) at various temperatures (See Table 1). Aliquots of the reaction mixtures were withdrawn and were analyzed by GC-MS at various time intervals. The reactions were stopped by filtering off the catalyst when the analyses indicated either complete consumption of **1** or optimum yields of benzo[*b*]thiophenes. After removal of solvent by rotary evaporation, products were isolated by column chromatography (SiO_2/hexane–CH_2Cl_2).

Method B. Cyclizations were conducted in the vapor phase by drawing **1** through a plug of K10–$ZnCl_2$ (activated at 300 °C) heated to 200–300 °C in an apparatus held at a pressure of 0.05 mmHg). The reagent flask was warmed to 100–150 °C to facilitate vaporization of **1**, and the flask receiving the products was cooled by liquid nitrogen. In a typical experiment, 0.5 g of K10–$ZnCl_2$ was held in a tube (12 mm i.d.) and 0.3 g of **1** was drawn through the catalyst over 0.25 h. In most cases, products were isolated directly from the receiving flask and their structures confirmed by a combination of GC-MS and references to published NMR spectra (references 1 and 2 and articles cited therein). Further conditions of each experiment and any byproducts are noted in Tables 1 and 2.

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