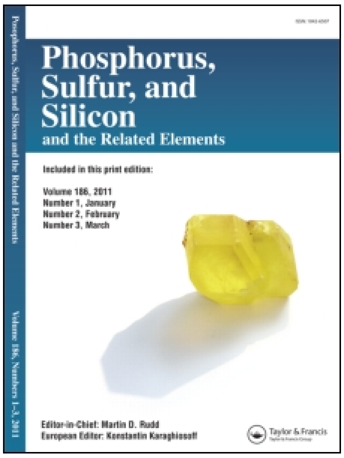

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BENZYLATION OF BENZO[*b*]THIOPHENE USING $ZnCl_2$-MODIFIED MONTMORILLONITE CLAY

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Benzylation of benzo[*b*]thiophene (1) with benzyl chloride catalyzed by metal-doped K-10 montmorillonite clays is described. Whereas $ZnCl_2$ dissolved in either nitromethane or nitrobenzene solution promoted benzylation of (1) only very slowly and resulted in a mixture of mono- and poly-substituted products, $ZnCl_2$-modified K-10 resulted in rapid benzylation at −17°C giving the 3-benzyl isomer in 74% isolated yield. This constitutes one of the most selective alkylations of (1) yet reported.

Key words: Benzylation, benzothiophene, K-10 montmorillonite, zinc chloride, catalysis.

INTRODUCTION

Alkyl-, aryl-, and alkylaryl-substituted benzo[*b*]thiophenes (**1**) occur in minor amounts in most sulfur-containing crude petroleums.[1] However, the complexity of these materials and the elaborate separation procedures required to separate individual compounds preclude isolation of (**1**) and its derivatives on a useful scale. Consequently, a variety of methods, based on cyclization of appropriately substituted benzene or thiophene derivatives, have been developed for the synthesis of benzothiophene compounds.[2,3] Direct electrophilic substitution of the parent heterocycle using standard Friedel-Crafts procedures leads to a complex mixture of mono-, di- and poly-substituted products, often in low yield. In some cases,[4,5] moderate yields of a mixture of 2- and 3-alkyl substituted products can be obtained, but the general sensitivity of (**1**) and its derivatives to Bronsted acid conditions render Friedel-Crafts alkylation an impractical synthetic method for most alkyl derivatives.

Recent work in our laboratories has shown that thiophene can be benzylated selectively at the 2-position in high isolated yields (>90%) using $ZnCl_2$-modified montmorillonite clay catalysts.[6] Physical characterization of catalysts prepared from K-10 montmorillonite clay has shown the presence of a mesoporous structure (20–100 Å) and a large surface area (up to 250 m^2 per gram).[7] When the clay is impregnated with 2 mmol of $ZnCl_2$ per gram, a mono-layer of $ZnCl_2$ covers the clay surface and provides, predominantly, Lewis-acid sites.[7] It has been suggested that the mesopores within the clay preclude reactions having large transition states, and, in particular, prevent acid catalyzed polymerization of substances such as thiophene and (**1**).[6] This limitation may apply particularly to reactions involving polar transition states with their attendant solvation spheres. For example, it can be estimated that a pore with a width of at least 20 Å would be required to

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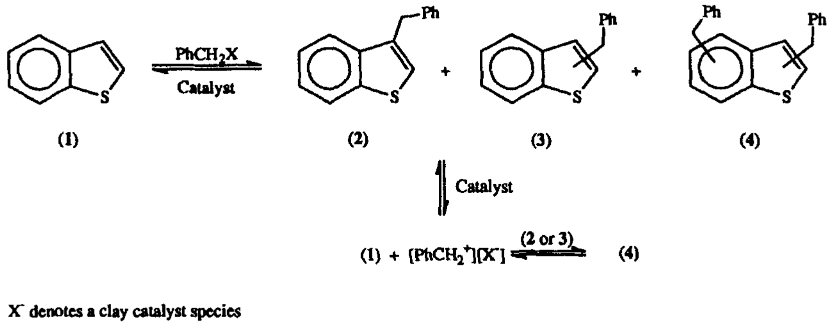

SCHEME I Benzylation of (1) using K-10/$ZnCl_2$.

accommodate the transition state of the reaction of (**1**) with benzyl chloride in nitrobenzene solution.

In this study, we have examined the direct benzylation of (**1**) with a variety of benzylating agents and metal salt-promoted montmorillonite catalysts. Prior to our work, benzylation of (**1**) has been accomplished only in poor yield.[4,8] However, a report by A. V. Anisimov *et al.* recorded a 75% yield of 3-benzylation using benzyl alcohol in the presence of $ZnCl_2$ and HCl.[9] Repetition of this experiment in our laboratory showed non-selective benzylation to produce a mixture of mono and di-substituted products. The goal of our work was to improve procedures for the synthesis of benzylbenzothiophenes and examine factors controlling the activity of metal-promoted clay catalysts. Besides being of intrinsic interest, 2- and 3-benzylbenzo[*b*]thiophenes are useful precursors of diphenylethanes and propanes which find use in the synthesis of liquid crystals and fine chemicals.

EXPERIMENTAL

Reagents and Chemicals

(**1**), benzyl chloride, benzyl alcohol, benzyl sulfide and disulfide and other chemicals were obtained from the Aldrich Chemical Company and were used as received. K-10 montmorillonite clay was obtained from the Fluka Chemical Company and was used as received. This clay was manufactured by acid treatment of Tonsil-13 montmorillonite and had a surface area of 200 m^2g^{-1} of clay (measured in house on an ASDI surface characterization apparatus using nitrogen absorption methods). Powder X-ray diffraction data have shown that the acid treatment leads to a disordered structure in which some of the original layered structure has been broken down.[7] Metal salt-impregnated K-10 was prepared by adding a solution of the salt (60 mmol) in methanol (45 mL) to K-10 (30 g), stirring the resultant slurry for 24 h at 20°C, removing excess methanol by rotary evaporation and heating the "wet" clay cake at 250°C at reduced pressure (15 mmHg) for 24 h. This procedure was used to prepare clays modified with $ZnCl_2$, ZnF_2, $FeCl_3$, $RuCl_3$, $AlCl_3$, $ZrCl_4$, $LnCl_3$, $ErCl_3$, $YbCl_3$, $GdCl_3$ and $Yb(OSO_2CF_3)_3$. In most cases, the metal content of the clay was determined using AA spectroscopy and was found to be close to the predicted 2.0 $mmol \cdot g^{-1}$ level.

Benzylation Procedure

A solution of benzyl chloride, benzyl alcohol, benzyl sulfide or benzyl disulfide (8.99 mmol) in nitromethane or nitrobenzene (5 mL) was added dropwise to a stirred suspension of a modified clay (10 g) in a solution of (**1**) (1.0 g, 7.46 mmol) in the solvent (20 mL). The reaction mixtures were stirred under various conditions (see Tables) and were quenched with 6 M NaOH (50 mL) to stop further reaction. After dilution with dichloromethane (150 mL), the mixtures were filtered (Celite) and the organic layer was collected, washed with water and was dried ($MgSO_4$). Filtration and evaporation of the solvent left viscous, pale yellow oils, the compositions of which were determined by GC-MS analysis. In some experiments products were isolated by column chromatography (SiO_2-hexane/Et_2O (95:5) and were identified by comparison of their NMR spectra (200 MHz) to published information.[2] Since 2- and 3-benzylbenzo[*b*]thiophene display very similar NMR spectra, the structure of the 3-isomer was confirmed by desulfurization to 1-methyl-1,2-diphenylethane using nickel boride in refluxing ethanol.[10] 1,3-diphenylpropane would have been obtained if this material had been the 2-benzyl isomer. The desulfurization was carried out as follows.

$NiCl_2 \cdot 6H_2O$ (9.82 g, 49.3 mmol) and the isolated product suspected to be the 3-benzyl isomer (1.32 g, 5.9 mmol) were added to a 3:1 methanol-tetrahydrofuran mixture (150 mL). The mixture was stirred at 0°C while sodium borohydride (4.69 g, 123.9 mmol) was added slowly (1 h). The reaction mixture was stirred for an additional 0.5 h at 0°C and was filtered (Celite). The filtrate was evaporated, the residue was redissolved in ether (100 mL) and the resultant solution was washed (1M HCl, 3 × 50 mL and water, 2 × 50 mL), was dried ($MgSO_4$) and filtered, and was evaporated to afford a yellow oil (0.75 g, 65%), ^1H NMR (200 MHz): 1.15–1.25 (3H, d, —CH—CH_3, J = 6.25 Hz), 2.85–2.95 (2H, m, —CH_2—), 2.7 (1H, CH—CH_3) and 7.0–7.3 (m, aromatic H).[11]

RESULTS AND DISCUSSION

Reactions with Benzyl Chloride

Data obtained from the benzylation of (**1**) with benzyl chloride under a variety of conditions are summarized in Table I. As has been noted previously,[4] benzylation of (**1**) using free $ZnCl_2$, in this case dissolved in either nitromethane or nitrobenzene (entries 1 and 9 in Table I), results in slow conversion of (**1**) to a mixture mono- and dibenzylated products. The lack of selectivity and conversion of primary products to disubstituted material is typical of standard Friedel-Crafts chemistry on (**1**).

TABLE I

Friedel-Crafts alkylation of benzo[*b*]thiophene with 1.2 eq. of benzyl chloride

Solvent	Catalyst :BT	Time (h)	Temp (°C)	BT%[d]	3-BBT%	BBT%[e]	DiBBT%[f]
1. $MeNO_2$	[a]	2	20	15	28	15	43
2. $MeNO_2$	[b]	24	20	35	22	20	23
3. $MeNO_2$	[b]	2	100	24	18	25	32
4. $MeNO_2$	10:1	0.5	20	24	37	29	10
5. $MeNO_2$	10:1	2	−14	29	36	11	25
6. $MeNO_2$	10:1[c]	3.5	−17	22	58	7	13
7. $MeNO_2$	20:1[c]	3.5	−17	23	37	9	31
8. $MeNO_2$	10:1	6.5	−22	24	35	7	34
9. $PhNO_2$	10:1[a]	6	20	11	30	10	48
10. $PhNO_2$	10:1[b]	48	20	70	16	15	—
11. $PhNO_2$	1:1[b]	2	100	30	28	21	21
12. $PhNO_2$	10:1	1	10	22	33	17	28
13. $PhNO_2$	1:1	0.083	100	28	29	23	20
14. $PhNO_2$	1:10	3	80	29	28	20	23

Note: BBT = benzylbenzo[*b*]thiophene.

[a] No clay present. $ZnCl_2$ was used in quantities equivalent to the amounts present in experiments using a 10:1 clay catalyst BT experiment.

[b] No $ZnCl_2$ present.

[c] Reactions done with 1.5 eq. of benzyl chloride.

[d] % calculated by GC with *n*-decane as the internal standard.

[e] Other mono-benzylated benzo[*b*]thiophene.

[f] Dibenzylated benzo[*b*]thiophene products.

The K-10 montmorillonite clay used in the work, although having undergone an acid washing procedure, contains a small quantity of Fe (3.15 wt.%) that was originally present in Tonsil 13.[12] Despite this Fe-content and the Bronsted/Lewis character that may be associated with other components of the clay, K-10 has only low activity in catalyzing the benzylation of (**1**) and leads to a complex mixture of products in either nitromethane or nitrobenzene (entries 2, 3 and 10, 11 in Table I).

Use of the $ZnCl_2$-impregnated K-10 in nitromethane at 20°C (entry 4, Table I) resulted in a much more rapid benzylation of (**1**) with some selectivity to the 3-benzyl isomer (**2**). A significant amount of (**1**) remained after 0.5 h (24%), but, if the reaction was allowed to continue beyond 0.5 h, a much more complex mixture of products was obtained containing smaller quantities of (**2**) and di- and trisubstituted products. Electron density calculations predict that (**1**) should undergo electrophilic substitution at the 3-position, with the 2- and 5- or 6-positions being the next most reactive.[3] However, as expected, mono-benzylated products are more reactive than the parent heterocycle, and, as the data discussed so far show, are consumed to form disubstituted products.

In an attempt to obtain the kinetically favored 3-benzyl isomer (**2**), reactions were carried out at lower temperatures (−14 to −22°C) and with different K-10/$ZnCl_2$: (**1**) ratios (entries 5–8 in Table I). The most successful of these reactions, carried out at −17°C in nitromethane solution over 3.5 h (entry 6), resulted in a 58% isolated yield of (**2**) and 7% of other mono-benzylated products and 13% of dibenzylated products. Based on recycle of unconsumed (**1**), which can be recovered by column chromatography of the reaction mixture, this reaction gave a 74% yield of (**2**), a considerably higher yield than has been recorded to date for the benzylation of (**1**).[4,8,9]

Attempts to improve the yield of (**2**) further by increasing the amount of catalyst (at −17°C) or by extending the reaction time, but using a lower temperature (−22°C), resulted in similar conversions of (**1**) but less selectivity to (**2**). Likewise use of nitrobenzene as solvent at various conditions (entries 12–14) did not improve selectivity towards (**2**) and, generally, gave more complex reaction mixtures.

Reactions with Other Benzylating Agents

Alcohols, sulfides, and disulfides in particular, are used less frequently as alkylating agents, but are of interest, as HCl is not produced as a by-product. In addition, since K-10/$ZnCl_2$ likely activates the benzylating agent by coordination of the heteroatom of the reagent to the zinc(II) site, these reagents can be expected to react with (**1**) at different rates and perhaps with different selectivities. Reactions using these other benzylating agents all proceeded more slowly in nitrobenzene solution than when using benzyl chloride as the alkylating agent (cf. data in Tables I and II), and, in general, required higher temperatures to proceed in reasonable reaction time. No advantage, in terms of product selectivity, was obtained by carrying out the reactions at lower temperatures or by using nitromethane as the solvent. The 3-isomer could be isolated from all of these reaction mixtures, but separation of other mono- and disubstituted products could not be achieved easily by column chromatography.

TABLE II

Friedel-Crafts alkylation of benzo[*b*]thiophene with other reagents

Solvent	Alkylating agent	Catalyst :BT	Time (h)	Temp (°C)	BT%[a]	3-BBT%	BBT%	DiBBT%
$PhNO_2$	BzOH	10:1	0.25	110	16	34	29	22
$PhNO_2$	BzOH	1:1	1	150	28	28	24	18
$PhNO_2$	DBDS	10:1	2	130–140	15	31	18	36
$PhNO_2$	DBDS	4:1	2	150	37	27	28	9
$PhNO_2$	BzS	10:1	1	170–180	8	31	21	40
$PhNO_2$	BzS	4:1	4.5	150	18	21	31	29

Note: BzOH = benzyl alcohol, DBDS = dibenzyl disulfide, BzS = benzyl sulfide.
[a]% calculated by GC with *n*-decane as the internal standard.

Benzylation with Other Metal Salt-Impregnated K-10 Catalysts

To date, very little work has been conducted which examines the use of lanthanide modified clays in Friedel-Crafts reaction although Yb triflate has been reported to catalyze the reaction of anisole with acetic anhydride.[13] Several lanthanide K-10 catalysts were prepared containing 2 mmol of La(III), Er(III), Yb(III) and Gd(III) chlorides and Yb triflate but none promoted the benzylation of (**1**) with benzyl chloride under a variety of conditions. K-10 impregnated with either Zr(IV) or Ru(III) also produced inactive catalysts but K-10 modified with either Fe(III) or Zn(II) (from ZnF_2) displayed similar ability to promote benzylation of (**1**) in comparison to the K-10/$ZnCl_2$ catalyst, but did not give any improvement in selectivity. A K-10/$AlCl_3$ catalyst displayed intermediate reactivity.

Surface area and pore volume distributions of the lanthanide catalysts were similar to the K-10 catalyst leading to the conclusion that it is the metal species on the clay (i.e. Zn(II), Fe(III), etc.) which determines the catalyst activity. It appears that lanthanide cations, in particular, have limited ability to coordinate benzyl chloride to produce carbocations at the clay surface, although other factors such as metal cation dispersion (not measured in this study) could affect catalyst activity.

Rationalization of Product Distribution

In general, the product distribution noted in Table I can be explained on the basis that the 3-benzyl isomer is the kinetic product, being favored at low temperatures, with (**2**) being consumed to form dibenzylated products or, perhaps, rearrange to thermodynamically more stable isomers. The relative stability of 4-, 5-, 6-, or 7-substituted isomers with respect to 2- and 3-substituted isomers has not been recorded, but it is known that 2-arylated benzothiophenes are more stable than 3-substituted compounds.

Some experiments were conducted to determine the relative stability of the monobenzylated products but no conclusive information was obtained. When (**2**) was heated under reflux in nitromethane with K-10/$ZnCl_2$, (**2**) was recovered unchanged after a 24 h treatment. A similar treatment in nitrobenzene over 24 h, however, yielded dibenzylated derivatives as the major products. Thus, although it is clear that the benzylation process can be reversed, as expected, the "benzyl carbocations" formed in this process react most rapidly with unreacted (**2**). Consequently, it has not been possible to determine the relative stability of monobenzylated products.

CONCLUSION

$ZnCl_2$-modified K-10 montmorillonite clay is an effective catalyst for the benzylation of (**1**) in comparison to standard Friedel-Crafts catalysts allowing some selectivity to the 3-benzyl product (**2**) at low temperatures. Complex product reaction mixtures obtained at higher temperatures or when using long reaction times probably result from rearrangement and further reaction of initial products.

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