Benzylation of thiophene using zinc and iron chloride modified montmorillinite clay

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Montmorillinite clays, modified with either Zn(II) or Fe(III) chlorides have been used to catalyze the Friedel–Crafts alkylation of thiophene. High yields (ca. 80%) of 2- and 3-benzylthiophene mixtures were obtained using either catalyst in chlorobenzene or nitrobenzene solvent at 80°C. The ratio of 2-/3-products was found to be controlled by their relative stability. Reactions were most rapid in nitrobenzene solution (< 5 min) and resulted in formation of the 2-isomer as the only mono-substituted product. This is believed to be the first example in which an alkylation of thiophene has been limited to one regio-isomer.

Keywords: Thiophene; benzylation; iron/zinc chlorides; modified montmorillinite; Friedel–Crafts

1. Introduction

Seminal work by Laszlo [1], Clark [2], Brown [3], their co-workers and other researchers [4] has shown that benzene and simple aromatic molecules can be alkylated using modified clays. The method has considerable advantage over standard Friedel–Crafts alkylation procedures using $AlCl_3$, $SnCl_4$ and $ZnCl_2$ in organic solvents as no aqueous inorganic wastes are produced during product isolation. Consequently, clay-alkylations have been adopted for the large-scale synthesis of some benzene derivatives [4].

Synthesis of alkylthiophenes using Friedel–Crafts procedures has been studied in detail [5] but is viable in only a few cases. Besides difficulties in limiting polyalkylation of the reactive thiophene nucleus, polymerization of thiophene, which is catalyzed by either Lewis or Brønsted acid sites, results in very poor yields of mono-alkylated products. Several studies have been published for the alkylation of thiophene using various natural and synthetic alumino-silicates [6–8] but the work

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was limited to high temperature, vapour phase procedures and, to our knowledge, was not used on an industrial scale because of the poor yields (< 50%) obtained.

In this letter, we describe the controlled benzylation of thiophene under very mild conditions using K_{10}-montmorillinite clay (ex Fluka) impregnated with either $ZnCl_2$ of $FeCl_3$. Comments on the effect of using thiophene as a limiting reagent and the influence of kinetic/thermodynamic control on the product distribution are included in the discussion.

2. Experimental

2.1. CATALYST PREPARATION

Metal impregnated clay catalysts were prepared by adding a solution of the desired metal chloride (99.9% purity) in methanol to K_{10}-montmorillinite (Fluka Chemical Company, used as received) and evaporating the methanol by means of a rotary evaporator over 30 min. The catalyst was activated by heating the clay at 150°C over 2 h and the actual metal content of the clay was determined by atomic absorption analysis (see table 1).

2.2. ALKYLATION PROCEDURE

In a typical reaction, a clay catalyst (1.0 g) was added to a solution of thiophene (3.3 g, 29.5 mmol) and benzyl chloride (1.0 g, 7.9 mmol) in the desired solvent

Table 1
Benzylation of thiophene with $K_{10}/ZnCl_2$ and $K_{10}/FeCl_3$ catalysts at 80°C

Catalyst[a]	Clay/MCl_x loading (mmol g^{-1} clay)	Time for complete consumption of $PhCH_2Cl$ (h)	% monobenzylated products[b,c]	% dibenzylated products[b]
1 $ZnCl_2$	2.0	>30	80 (3.1)	10
2 K_{10}-clay	–	>25	79 (<3.0)	11
3 $K_{10}/ZnCl_2$	2.06	0.25	81 (3.1)	9
4 $K_{10}/ZnCl_2$	1.34	0.25	75 (3.1)	15
5 $K_{10}/ZnCl_2$	0.73	0.25	80 (3.1)	10
6 $K_{10}/ZnCl_2$	0.5	0.33	73 (nr)	17
7 $K_{10}/ZnCl_2$	0.1	7.0	70 (nr)	20
8 $K_{10}/ZnCl_2$	0.01	>25	65 (nr)	25
9 $FeCl_3$	2.0	0.20	73 (2.8)	13
10 $K_{10}/FeCl_3$	2.0	<0.1	70 (2.0)	15
11 $K_{10}/FeCl_3$	0.2	2.0	71 (2.0)	16
12 $K_{10}/ZnCl_2$	2.0	1.5	90 (2.1)	9
13 $K_{10}/ZnCl_2$	2.0	<0.1	91 (>100)	9

[a] Experiments 1–11 were conducted in chlorobenzene solution; experiments 12 and 13 were carried out in dichloromethane and nitrobenzene respectively.

[b] Yields determined by GC, the balance of the products was polymeric in nature.

[c] 2/3-isomer ratios are given in the parentheses. nr = not recorded.

(30 ml) (see table 1). The reaction mixtures were stirred to obtain good dispersion of the clay and the temperature was maintained at the desired value by means of a thermostated oil bath. Aliquots of the reaction mixtures were withdrawn and filtered to remove catalyst particles and were analyzed using GC-MS techniques. Consumption of reactants and product formation was determined assuming the mass detector gave equal responses for each compound. This assumption was justified by comparison of ^{1}H-NMR and GC-MS data for some product mixtures.

2- and 3-benzylthiophenes were isolated by filtration of the reaction mixtures, evaporation of the solvent, and a combination of vacuum distillation and column chromatography (SiO_2–hexane) of the crude products. In experiment 13 (see table 1), 2 M sodium hydroxide (50 ml) was added to the reaction mixture to quench further reaction. In this case, products were isolated from the dried organic phase using the procedures described previously. Since polymerization of thiophene is a major reason for the low yields obtained in using conventional Friedel–Crafts alkylation procedures, the clay catalyst recovered from the experiments was extracted with THF to determine if polar, non-volatile material had been formed. In all cases, minor quantities of residue were obtained indicating that polymerization of thiophene had been minimal.

3. Results and discussion

Initial experiments were conducted to determine the effectiveness of $ZnCl_2$/clay catalysts in comparison to free $ZnCl_2$ and the untreated clay. These experiments (entries 1–3 in table 1) demonstrate that free $ZnCl_2$ or untreated clay have little catalytic activity for the benzylation of thiophene in comparison to a $ZnCl_2$/clay catalyst containing 2 mmol $ZnCl_2$ g^{-1} clay. Use of a 3 : 1 ratio of thiophene to benzyl chloride limited the formation of dibenzylated products. Extraction of used clay catalyst with a variety of polar solvents confirmed that only minimal amounts of polymeric material had been formed in these experiments. As a result, it was possible to obtain isolated yields very similar to the GC yields reported in table 1. Further experiments (entries 3–8 in table 1) with reduced loadings of $ZnCl_2$ on the clay show that the catalyst remains very active until the loading was reduced below the cation exchange capacity of the clay (0.5 mmol g^{-1} clay).

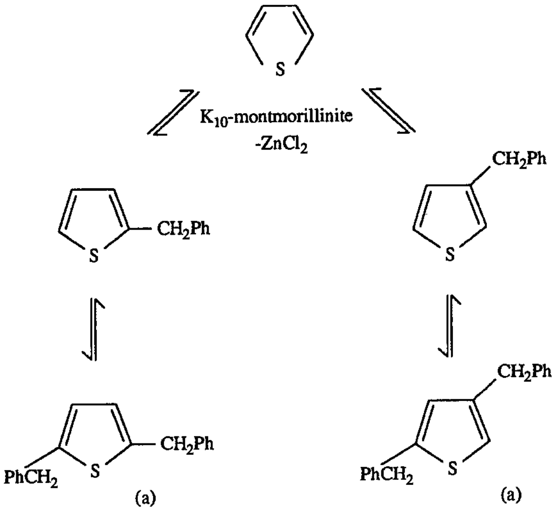
In general, similar results were obtained with $FeCl_3$/clay catalysts (entries 9–11 in table 1) although free $FeCl_3$ was substantially more reactive than $ZnCl_2$ (compared entries 9 and 1 in table 1). Overall, less control was observed with $FeCl_3$ or $FeCl_3$/clay catalysts as more di-substitution and conversion to polymer was noted in these experiments. Table 2 summarizes the effect of time on the benzylation of thiophene using an $FeCl_3$/clay catalyst conducted at 40°C. As expected from the predicted reactivity of the 2- and 3-positions of thiophene [5], the 2-isomer predominates. However, an interesting feature of these data is that the ratio of 2- to

Table 2
Effect of time on benzylation of thiophene using $K_{10}/FeCl_3$ (0.2 mmol $FeCl_3$ g^{-1} clay) at 40°C

Time (min)	% $PhCH_2Cl$ consumed[a]	% monobenzylated products	% dibenzylated products	2 : 3 isomer ratio
10	72	57	6	2.7
20	89	67	10	2.2
60	94	71	12	2.0
120	96	71	16	2.0

[a] 5 : 1 thiophene/$PhCH_2Cl$ mole ratio; $PhCH_2Cl/FeCl_3$ mole ratio = 40 : 1.

3-benzylated product decreases as the reaction proceeds. Two processes could explain this result: either the 2-benzyl product reacts more quickly than the 3-benzyl isomer to form di-benzylated products or, as a result of the general reversibility of Friedel–Crafts processes, the products re-distribute to the more thermodynamically stable product which, in this case, would have to be the 3-benzyl isomer (scheme 1). The suggestion that 3-substituted thiophenes are more stable than corresponding 2-isomers has been made previously [5] but does not appear to have been tested. We examined this hypothesis by treating 2-benzylthiophene (95% purity) in chlorobenzene solution over an active $ZnCl_2$/clay catalyst at 20 and 120°C. At 20°C, very little conversion of 2-benzylthiophene was observed after 90 h, but at 120°C, 24% of the 2-benzylthiophene was converted to the 3-isomer during a 120 h heating period. Although the 3-benzyl isomer was not available in pure form, treatment of a 1:1 2-/3-isomer mixture at 120°C in chlorobenzene solution resulted in conversion to a mixture containing a higher proportion of 3-benzylthiophene.



Scheme 1. Product distribution from the benzylation of thiophene. (a) Structures based on known chemistry of 2- and 3-benzylthiophene.

Since minor amounts of by-products arising from reaction of benzyl chloride with the solvent chlorobenzene could be detected in the GC-MS analysis of the crude product mixtures, experiments were conducted using dichloromethane and nitrobenzene as solvents (entries 12 and 13 in table 1). Use of dichloromethane at its boiling point resulted in good conversion to mono-substituted products (90%) and a high isolated yield of the 2-/3-isomer mixture (86%). When the reaction was carried out in nitrobenzene at 80°C, the benzyl chloride was consumed rapidly (<5 min) and by quenching the reaction mixture in aqueous sodium hydroxide to prevent further reaction, it was found that the 2-isomer was formed as the sole mono-substituted product. To our knowledge, this is the first example of an alkylation of thiophene in which reaction has been limited to the formation of one regio-isomer. In view of earlier observations, it seems reasonable to propose that 2-benzylthiophene was formed as the kinetic product with rearrangement to the more stable 3-isomer being curtailed by the rapidity of the reaction. Use of nitrobenzene also demonstrates that solvent effects are very important in mediating the alkylation reaction at the clay surface.

These observations represent a considerable advance over methods described for the alkylation of thiophene with methanol and isobutanol over clays and zeolites at high temperature [7,8] as in these cases it proved impossible to control the regio-selectivity of the reaction and prevent polyalkylation completely. Further work is being conducted in our laboratories to extend the use of promoted clays for the synthesis of thiophenes and related compounds.

4. Conclusions

Zn(II) and iron(III) chloride impregnated K_{10}-clays have been shown to be very effective materials to promote the benzylation of thiophene. The $ZnCl_2$ impregnated clay was especially useful in that polyalkylation and polymerization of thiophene was largely prevented. Most importantly, the rapidity of the clay promoted reactions allows preparation of kinetic favored 2-benzyl product. Future studies will examine extension of these findings to other alkylating agents and related reactions.

References

[1] P. Laszlo and A Mathy, Helv. Chim. Acta 70 (1987) 577.

[2] J.H. Clark, A.P. Kybett, D.J. Macquarrie, S.J. Barlow and P. Landon, J. Chem. Soc. Chem. Commun. (1989) 1353.

[3] D.R. Brown, C.N. Rhodes, M. Franks and G.M.B. Parkes, J. Chem. Soc. Chem. Commun. (1991) 804.

[4] T.W. Bastock, in: Abstract Proceedings of the Royal Society of Chemistry International Conference on Supported Reagent Chemistry, held at The University York, England, 2–5 July 1993, p. I3.

[5] R. Taylor, in: Electrophilic Substitution of Thiophene and Its Derivatives in Advances in Heterocyclic Compounds, *Thiophene and Its Derivatives*, Part II, ed. S. Gronowitz (Wiley, New York, 1986) ch. 1.
[6] H.D. Hartough, A.I. Kosak and J.J. Sardella, J. Am. Chem. Soc. 69 (1947) 1014.
[7] P.B. Venuto, L.A. Hamilton, P.S. Landis and J.J. Wise, J. Catal. 4 (1966) 81.
[8] V. Solinas, R. Monaci, G. Longu and L. Forni, Acta. Phys. Chem. 31 (1985) 291.