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Note

Chloroacetylation of arenes using chloroacetyl chloride in the presence of $FeCl_3$ modified montmorillonite K10

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Chloroacetylation reaction of arenes using chloroacetyl chloride has been studied in the presence of Fe-modified montmorillonite K10 catalysts in a liquid phase. The catalysts have been prepared by treating montmorillonite K10 with aqueous solution of $FeCl_3$. Good yields and selectivity are observed for the acylated product.

Keywords: Friedel-Crafts reaction, chloroacetyl chloride, Montmorillonite K10, Fe-modified K10

Chloroacetyl derivatives of arenes have attracted the attention of synthetic chemists because they serve as intermediates in the preparation of a variety of organic compounds, *e.g.* synthesis of 3-cyano-5-[(dimethylamino)methylene]-2-(5*H*)-furanones, which are used as algaecides, bactericides, *etc*., and includes use of chloroacetyl derivatives at intermediate steps[1a]. Further, they themselves also show fungicidal properties, *e.g.* 2-chloro-(4-methoxy-1-phenyl) ethanone is fungicidal in nature[1b]. Thiazepines and their hydrochlorides used as coronary blood vessel dilators are prepared in 85% yield by reaction of spiro compounds with chloroacetyl derivatives[2a]. Likewise, numerous pharmaceutical intermediates involve the use of chloroacetyl derivatives at the intermediate step[2b,2c]. They also find application in the preparation of dyes, *e.g.* basic imidazolinine dyes[3], and serve as warfare agents as they are potent lachrymators[4], Recently, they have been found to be non-ATP competitive inhibitors of glycogen synthase kinase (GSK-3ß). GSK-3ß plays a crucial role in Alzheimer’s disease and its inhibition is a valid approach to the treatment of AD[5].

In general, chloroacetyl derivatives of aromatic compounds can be prepared by two routes: (i) Chlorination of acetophenones[6]. However, it involves two steps, *i.e.*, Friedel-Crafts acetylation of benzene derivatives followed by α-chlorination of the resulting acetophenones. (ii) Friedel-Crafts acylation of benzene derivatives using chloroacetyl chloride.

Chloroacetyl chloride is a versatile reagent and has been extensively used in organic synthesis[7]. It is primarily used as an acylating agent. The multi-functional nature of chloroacetyl chloride has made it a suitable two-carbon building block for cyclization. By using chloroacetyl chloride for acylation, two steps are combined into one, *i.e.* (1) Friedel-Crafts acetylation of arenes and (2) Chlorination of the resulting acetophenones.

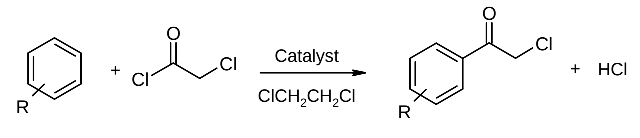
Chloroacetylation using chloroacetyl chloride is generally carried out under Friedel-Crafts reaction conditions in a solvent like carbon disulphide, nitromethane and sulfolane using aluminum chloride as a catalyst, although other Lewis acids have also been employed[8]. The use of metal halides causes problems associated with the strong complex formed between the ketone product and the metal halide itself, which provokes the use of more than stoichiometric amounts of catalyst. The work-up commonly requires hydrolysis of the complex leading to the loss of the catalyst and resulting in a large amount of corrosive waste streams[9].

Due to the above mentioned reasons and with the growing environmental concerns, solid acids have gained considerable importance in the recent years. They possess the advantages like environmental compatibility, low cost, operational simplicity, and environmental friendliness. Clays have intrinsic acidity and act as both Brønsted and Lewis acids in their natural and ion-exchanged forms[10]. The high activity of Fe-exchanged montmorillonite clay has been recently reported towards Beckmann rearrangement[11], acylation of sulphonamides[12], *t*-butylation of phenols using *t*-butyl alcohol[13], and Friedel-Crafts benzylation of arenes with benzyl chlorides[14].

In this paper is reported the use of Fe-modified montmorillonite clay for Friedel-Crafts chloroacetylation of arenes using chloroacetyl chloride (**Scheme I**).

Results and Discussion

Since mesitylene was found to be very active in this reaction and it would give only one product, it



1 2 (R = -OCH$_3$, -CH$_3$, H) 3

Scheme I — Chloroacetylation of arenes using chloroacetyl chloride in the presence of FeCl$_3$ modified montmorillonite K10

was used to optimize the conditions. Based on earlier reports[15], Fe-exchanged K-10 catalyst (K10-Fe-A) was selected initially for the reaction. Chloroacetylation of mesitylene using equimolar quantity of chloroacetyl chloride showed low conversion of mesitylene. Hence for further reactions, an excess chloroacetyl chloride was used (200 mol %). Using excess of chloroacetyl chloride, 95% yield of the product was obtained. Chloroacetylation of mesitylene was subsequently attempted using different modified K10 catalysts activated at 120°C including K10 **(Table I)**.

The reaction was possible with all catalysts. However, the yields varied considerably. K10-Fe-A was found to be the most active, while K10-Zr-O was found to be the least active catalyst for the reaction.

ZnCl$_2$ is a mild Lewis acid under homogeneous conditions. However, the activity increases manifold on supporting it on clay, as is exhibited by Clayzic[15]. However, in the present case the Zn based catalysts showed poor activity. Its O-type catalyst was inferior to the A-type catalyst. Since sulphated zirconia is known as a super acid, it was thought of studying the efficacy of ZrCl$_4$ modified K10 catalysts in the reaction. Unfortunately, K10-Zr also gave poor yield. SnCl$_4$ is a poor catalyst in homogeneous Friedel-Crafts acylation reaction[16] and the use of SnCl$_4$ in a benzoylation reaction is much inferior to that of AlCl$_3$ (Ref. 17). Recently, it is reported that a very active acidic catalyst can be prepared by supporting SnCl$_4$ on Hβ (Ref. 18). The observation led to the employment of K10-Sn catalysts. However, K10-Sn catalysts also gave poor yield of the product. Among all the catalysts, K10-Fe-A was found to be the best catalyst for the reaction.

Table I — Reaction of mesitylene with chloroacetyl chloride in the presence of different K10 catalysts activated at 120°C[a]

No.	Catalyst	Yield of **3a**[b] (%)
1	K10[c]	20
2	K10-Zn-A120	38
3	K10-Zr-A120	16
4	K10-Sn-A120	15
5	K10-Zn-O120	15
6	K10-Zr-O120	09
7	K10-Sn-O120	20
8	K10-Fe-A120	95
9	K10- Fe-O120	95

[a]Mesitylene: 5 mmol, chloroacetyl chloride: 10 mmol, catalyst: 0.1 g, ethylene dichloride: 3 mL, Time: 5hr, [c]: 0.2g. [b]Yields were calculated by GC analysis using nitrobenzene as an internal standard.

It is known that the activity of a metal exchanged K10 catalyst depends on the activation temperature[19]. Hence, K10-Fe-A was activated at 120°, 280° and 550°C, to obtain catalysts K10-Fe-A120, K10-Fe-A280 and K10-Fe-A550, respectively. The reaction was carried out using these catalysts **(Table II)**.

K10-Fe-A120 was found to be most active and as the activation temperature increased the activity decreased. The reaction was carried out with different quantities of K10-Fe-A120 **(Table III)** and also at different temperatures **(Table IV)**.

The reaction carried out at RT (30°C) gave low yield, even after increasing the reaction time. Maximum yield was obtained at the reflux temperature (80°C). The optimum quantity of the catalyst was found to be 17 weight % (0.01 mol % of

Table II — Reaction of mesitylene with chloroacetyl chloride in the presence of K10-Fe-A catalysts activated at different temperatures[a]

No.	Activation temp. (°C)	Reaction time (hr)	Yield of **3a**[b] (%)
1	120	1	95
2	280	3	96
3	550	3	96

[a]Mesitylene: 5 mmol, chloroacetyl chloride: 10 mmol, catalyst: 0.1 g, ethylene dichloride: 3mL. [b]Yield was calculated by GC analysis using nitrobenzene as an internal standard.

Table III — Reaction of mesitylene with chloroacetyl chloride in the presence of different quantity of K10-Fe-A activated at 120°C[a]

No.	Catalyst	Catalyst quantity (g)	Time (hr)	Yield of **3a**[b] (%)
1	K10-Fe-A	0.2	1	96
2	K10-Fe-A	0.1	1	95
3	K10-Fe-A	0.05	5	96

[a]Mesitylene: 5 mmol, chloroacetyl chloride: 10 mmol, ethylene dichloride: 3 mL. [b]Yields were calculated by GC analysis using nitrobenzene as an internal standard.

Table IV — The reaction of mesitylene with chloroacetyl chloride in the presence of K10-Fe-A catalyst activated at 120°C at different temperatures.[a]

No.	Reaction temp. (°C)	Time (hr)	Yield of **3a**[b] (%)
1	80	1	95
2	60	5	82
3	30	5	28

[a]Mesitylene: 5 mmol, Chloroacetyl chloride: 10 mmol, K10-Fe-A120: 0.1g, Ethylene dichloride: 3 mL. [b]Yield was calculated by GC analysis using nitrobenzene as an internal standard.

Fe). The catalyst was not recyclable, obviously due to leaching of the active species by the strong acid generated *in situ*.

Among all the catalysts, K10-Fe-A120 was found to be the best catalyst for the reaction, even though $FeCl_3$ as such is a poor acidic catalyst for Friedel-Crafts acylation reaction under conventional homogeneous conditions. In the Friedel-Crafts benzylation of arenes, Cseri[19a] has observed the same trend and has proposed a redox mechanism to account for the high activity of Fe^{3+} modified K10 catalysts containing reducible metal cations. The high activity was attributed to the easily reducible nature of the cation.

The Fe content of the three catalysts, K10, K10-Fe-O and K10-Fe-A, was found to be 2.12, 4.63 and 3.19%, respectively[14]. It should be noted that K10, which contained 2.12% Fe, could also catalyze the reaction; however, the activity of K10 was much lower than that of the other two catalysts. K10-Fe-A contained a lower concentration of Fe than that in K10-Fe-O. However, in the present reaction, K10-Fe-A was a better catalyst than K10-Fe-O. Thus, it was felt that the nature of the active species of Fe was important as far as the activity of the catalyst was concerned; such speciation has been reported earlier[20].

Under the optimized conditions, chloroacetylation of different benzene derivatives was carried out using chloroacetyl chloride in the presence of K10-Fe-A120 **(Table V)**. The reaction could also give alkylated product, phenylacetyl chloride derivatives. However, negligible amount of the alkylated product was obtained in each reaction. The trend observed in this reaction with all substrates was that, the reaction was fast in the initial stage, but became sluggish afterwards **(Figure 1)**. Good yields were obtained with activated substrates like mesitylene, durene, xylenes, but low yields with deactivated arenes.

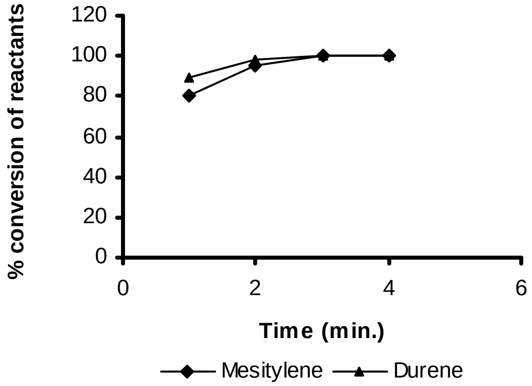


Figure 1 — The reaction of mesitylene and durene with chloroacetyl chloride in the presence K10-Fe-A

Experimental Section

Materials

Montmorillonite K10 was obtained from Aldrich (manufactured by M/s Sud-Chemie AG). The chemical composition (wt. %) of the clay (main elements) was: Al_2O_3: 14.6; SiO_2: 67.6; Fe_2O_3: 2.9; MgO: 1.8. The BET surface area was 220±20m^2/g and the micropore volume was 0.1 m^3/g. Prior to any further treatment, the clay was dried overnight at 120°C.

Catalyst preparation

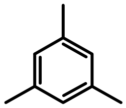
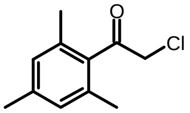
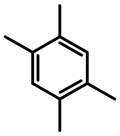
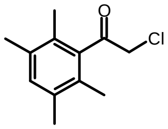
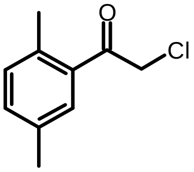
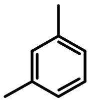
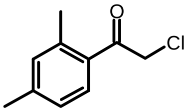
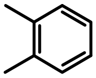
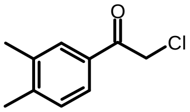
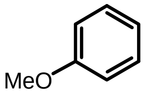
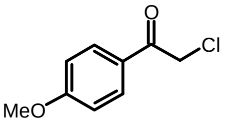
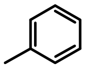
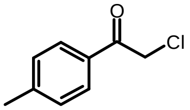
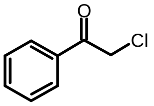
K10-Fe-A catalyst: To anhydrous $FeCl_3$ (15 g), dissolved in demineralised water (60 ml), montmorillonite K10 (10 g) was added over a period of 10 min and the resulting slurry was stirred at RT for 5 hr. The clay was filtered and washed with demineralised water until free from chloride ions.

K10-Fe-O catalyst*:* To anhydrous $FeCl_3$, dissolved in dry acetonitrile (60 mL), montmorillonite K10 (10 g) was added over a period of 10 min and the resulting slurry was stirred at RT for 5 hr. The clay was filtered, washed with acetonitrile (10 mL), and then with benzene (60 mL).

These catalysts were activated at 120°C overnight to obtain K10-Fe-A120 and K10-Fe-O120 catalysts respectively. The characterization of these catalysts is already reported[14].

The same procedure as above was followed to prepare other catalysts namely K10-Zn-A, K10-Zn-O, K10-Zr-A, K10-Zr-O, K10-Sn-A, K10-Sn-O, using anhydrous chlorides of the metals zinc, zirconium, and tin, respectively.

Table V — Reaction of substituted benzenes with chloroacetyl chloride in the presence of K10-Fe-A120 at 80°C[a]

No.	Substrate	Product	Time (hr)	Yield of **3**[b] (%)
1	 **1a**	 **2a**	1	95
2	 **1b**	 **2b**	3	97
3	 **1c**	 **2c**	5	73
4	 **1d**	 **2d**	5	55
5	 **1e**	 **2e**	5	13
6	 **1f**	 **2f**	5	15
7	 **1g**	 **2g**	5	12
8	 **1h**	 **2h**	5	10

[a] Arene: 5 mmol, Chloroacetyl chloride: 10 mmol, Catalyst: 0.1g, Ethylene dichloride: 3 mL.
[b] Yield was calculated by GC analysis using nitrobenzene as an internal standard.

Chloroacetylation of arenes

Each reaction was carried out in a 25 mL round bottom flask equipped with a reflux condenser, magnetic stirrer, and a $CaCl_2$ guard tube. The catalyst (0.1 g) was heated at 120°C overnight for activation in the reaction flask itself in open air. Arene (5 mmol), chloroacetyl chloride (0.8 mL, 10 mmol) and ethylene dichloride (EDC) (3mL) were added to the flask and the mixture was heated in a thermostatic oil bath at the reflux temperature.

The products were analyzed by GC with nitrobenzene as an internal standard, using a Chemito-2865 gas chromatograph (10% SE-30, 4.0 m) equipped with a flame ionization detector, by comparison with the authentic samples and confirmed by GC-MS. GC program (gradient): 100°C -1 min,-15°C/min, -180°C- 2min,-15°C/min, - 270°C -6 min.

Conclusion

Among Fe, Zn, Zr, Sn- modified K10 catalysts, the catalyst prepared by modification of K10 by $FeCl_3$ under aqueous conditions and activated at 120°C (K10-Fe-A) was found to be the best catalyst for chloroacetylation of activated benzene derivatives. Selectively *para* products were obtained. The catalyst being heterogeneous has the advantages such as mild reaction conditions, operational simplicity and higher yields.

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