GREEN PREPARATION OF ACETAMINOPHEN FROM THE CLAY-CATALYSED REACTION OF 4-AMINOPHENOL AND ACETIC ANHYDRIDE

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Introduction

Acetanilide, phenacetin, and acetaminophen are *N*-acetylated aromatic amines that are important in over-the-counter pain-relieving (analgesic) and fever-reducing (antipyretic) remedies (Bertolini *et al.*, 2006). Today acetaminophen has replaced phenacetin and acetanilide as pain-killers, and acetaminophen is marketed under the tradenames, Panadol, Paracetamol, Paracetol, Tylenol and Datril (Chiniwalla *et al.*, 1990).

Acetaminophen is customarily prepared by *N*-acetylating 4-aminophenol with acetic anhydride or acetic acid in the presence or absence of a mineral acid such as concentrated phosphoric acid at atmospheric pressure and temperatures ranging from room temperature to 130 °C. An unsatisfactory product is generally obtained due to the readily oxidizable nature of 4-aminophenol and the consequent formation of coloured impurities which are carried over to the acetylated product. Removal of colored impurities requires additional steps in the commercial production of acetaminophen. Phosphoric acid, which serves as a Brønsted acid catalyst in this reaction is a corrosive chemical.

Cation-exchanged montmorillonite clays can function as environmental-friendly solid acid catalysts in organic reactions (Lazlo and Balogh, 1993). Montmorillonite clay belongs to semectite family and has an expandable layer structure of aluminosilicate. The layered structure facilitates the uptake of cations such as Zn^{2+}, Al^{3+}, Fe^{3+} and ZrO^{2+}. Cation-exchanged clays show high Brønsted and Lewis acidity. We report here a green preparation of acetaminophen, in pure form as a colorless product, and other *N*-acetylated aromatic amines in high yield using ZrO^{2+}-exchanged montmorillonite (ZrO^{2+}-MMT) clay as a Brønsted/Lewis acid catalyst under mild conditions.

Materials and Methods

Preparation of catalyst

Na^{+}-Montmrillonite clay (5 g) was stirred overnight with a 0.5 M solution of zirconyl chloride (200 ml) to obtain ZrO^{2+}-MMT clay catalyst. The clay was then centrifuged and washed with distilled water repeatedly until washings showed negative test for chloride ions. The clay sample was then dried under ambient air for a week and ground to pass through a mesh of size 100. The clay sample was characterized using X-ray diffraction analysis (XRD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and Fourier-

Transform infrared (FTIR) spectroscopy. The catalyst was activated at 150 °C for 2 h prior to the study of its catalytic activity.

General procedure for N-acetylation of aminophenols

Acetic anhydride (0.31 g, 3 mmol), 4-aminophenol (0.11 g, 1 mmol), dichloromethane (5.0 ml) and ZrO^{2+}-MMT (0.01 g) were added to a 10-ml round-bottomed flask fixed with a Dean-Stark apparatus. The mixture was refluxed (40 °C) for 8 h under N_2 atmosphere, cooled, and centrifuged. The supernatant was washed with 5 % aqueous $NaHCO_3$ solution (20 mL, 5 mL × 4) in a separating funnel to remove carboxylic acid. The organic phase was concentrated on a rotary evaporator to obtain crude acetanilide. The product was re-crystallized from water to obtain pure **N-(4-hydroxyphenyl)acetamide** (acetaminophen) (0.13 g, 85 %) as colorless crystals, mp: 169-172 °C; *lit.*170 °C (Lide, 2009). ^{1}H-NMR, δ_H (300 MHz, acetone): 2.10 (3H, s, -CH_3), 6.6-7.6 (4H, m, Ar-H). 8.4 (1H, s, -NH-), 9.2 (1H, s, -OH), ^{13}C-NMR, δ_C (300 MHz, acetone): 23.3 (-CH_3), 115.3-131.7 (Ar-C), 153.8 (Ar-C), 168.3 (C=O st). FTIR (KBr), υ_{max} (cm^{-1}): 3600-3500 (O-H st), 3500-3100 (N-H st), 3100-3000 (Ar-H st), 1600, 1550 and 1400 (skeletal vibrations of the benzene ring), 1410-1310 (O-H in plane bend), 1680 (C=O st, amide I band), 1620 (amide II band, N-H in plane bend) and 1320 (amide III band, C-N st), 840 (C-H out-of-plane bend, p-disubstituted Ar-ring), 750 (N-H out-of-plane bend, amide V band) and 610 (OCN bend, amide IV and VI bands).

Using the above procedure, the aromatic amines, aniline, 4-bromoaniline, 4-chloroaniline and 4-methoxyaniline were acetylated to obtain *N*-phenylacetamide, *N*-(4-bromophenyl)actetamide, *N*-(4-chlorophenyl)actetamide and *N*-(4-methoxyphenyl)actetamide, respectively. The products were characterized using their melting points and NMR and FTIR data.

Results and Discussion

Some N-acetylated aromatic amines are analgesics and antipyretics important in pharmaceutical industry. We therefore studied the acetylation of aromatic amines using ZrO^{2+}-MMT. Acetylation was carried out with 4-aminophenol, aniline, 4-bromoaniline, 4-chloroaniline 4-methoxyaniline using acetic anhydride and ZrO^{2+}-MMT in refluxing (40 °C) dichloromethane, and the yields of the corresponding anilides were 85, 90, 91, 92 and 94 %, respectively. The acetaminophen sample obtained by this procedure did not have any colored impurities.

The yield of acetaminophen (85 %) was slightly low compared to that of the other anilides (91-94 %). This may be due to chelation of the OH group in 4-aminophenol with metal cations inside the clay layers, reducing the electron availability at the amine group. The chelation of OH group with metal ion inside the clay layers also explains the observation that in 4-aminophenol the NH_2 group rather than the OH group is preferentially acetylated. Alternatively, the formation of the *N*-acetyl linkage is thermodynamically more favorable than the O-acetyl linkage under the present conditions.

When the electron donating methoxy group was attached to the benzene ring the yield of the anilide (94 %) was slightly higher than with other amines. However 4-nitroaniline did not react with acetic anhydride in the presence of ZrO^{2+}-MMT. This is presumably due to the reduction of nucleophilicity of the amine group by the nitro group through mesomeric withdrawal of electrons.

The high yields (94-85 %) of acetanilides indicate that ZrO^{2+}-MMT is an efficient catalyst for the acetylation of amines using acetic anhydride. Using this method acetaminophen free of coloured-impurities was prepared in high yield (85 %) under mild conditions; the clay retains its catalytic efficiency even after several cycles of re-using.

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