



CHEMOSELECTIVE ACYLATION OF AMINES, ALCOHOLS AND PHENOLS USING MAGNESIUM CHLORIDE UNDER SOLVENT FREE CONDITION

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ABSTRACT

Magnesium chloride was used as a heterogeneous catalyst for the acylation of a variety of aromatic amines, alcohols and phenols using acetic anhydride under solvent free conditions at room temperature. Deactivated substrates are also acylated rapidly.

Key words: Acylation, $MgCl_2 \cdot 5H_2O$, Solvent-free.

INTRODUCTION

The protection of amino group of amines and hydroxyl group of alcohols and phenols is often necessary during the various transformations in synthetic sequences especially in the preparation of various natural products, which includes perfumes, flavors, food additives, cosmetics and polymers^{1,2}.

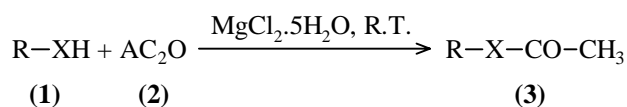
A variety of procedures are developed for the preparation of acyl derivatives of amines, alcohols and phenols. These include use of acetic anhydride in presence of homogeneous or heterogeneous catalysts. Such reactions are required to proceed rapidly, quantitatively, cost effective and environment friendly.

A number of methods are developed for the preparation of acetates from the corresponding amines, alcohols and phenols using various metal catalysts such as CuO , $anhydr.NiCl_2$ ^{3,4}, $RuCl_3$ ⁵, $Sc(OTf)_3$ ⁶, some triflates such as $In[OTf]_3$ ⁷, $Cu(OTf)_2$ ^{8,9}. In some cases $Cp_2Sm(thf)_2$ ¹⁰ and vinyl carboxylate¹¹ are used as catalysts for the acylation of amines

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and alcohols. Some methods involve use of supported catalysts such as $\text{FeCl}_3\text{-SiO}_2$ ¹², $\text{ZnCl}_2/\text{AlCl}_3/\text{Silica}$ ^{13,14}, $\text{SiO}_2\text{-H}_2\text{SO}_4$ ^{15,16}, Fe_2O_3 -activated carbon¹⁷. Some synthetic pathways involve use of costly reagents such as ammonium salt of 12-tungstophosphoric acid¹⁸, zinc per chlorate hexahydrate¹⁹, sulphated zirconia²⁰, bromodimethyl sulphonium bromide²¹.

However, the methods have limitations in respect of stability, cost availability, yields and hazardous nature of catalysts. Thus, there is still a need to develop new and mild method for the acylation in the presence of inexpensive, heterogeneous catalyst. In continuation of efforts to develop an efficient, easy, cost effective and environment friendly pathways for acylation of amines, alcohols and phenols, we report a simple, mild, clean and efficient method for the acylation of amine, alcohols and phenols with acetic anhydride in presence of $\text{MgCl}_2\cdot 5\text{H}_2\text{O}$ as a heterogeneous catalyst under solvent-free conditions.



X = -O-, -NH-; R = Alkyl, Phenyl

Scheme 1

EXPERIMENTAL

The catalytic activity of $\text{MgCl}_2\cdot 5\text{H}_2\text{O}$ was investigated with respect to the loadings. It was observed that when less than 0.1 mole% $\text{MgCl}_2\cdot 5\text{H}_2\text{O}$ was used more time was required to get corresponding products with considerable yield (Table 1, entries 1 and 2). On the other hand a catalyst more than 0.1 mole % gives excellent yields and requires less time (Table 1, entries 3 and 4).

Table 1: Catalytic effect of $\text{MgCl}_2\cdot 5\text{H}_2\text{O}$ in acylation of aniline with acetic anhydride at room temperature

Entry	$\text{MgCl}_2\cdot 5\text{H}_2\text{O}$ [mol %]	Time (min.)	Yield ^a (%)
1	0.01	70	50
2	0.05	70	60
3	0.10	30	96
4	0.15	30	96
5	0.20	30	96

^aIsolated yield

All required chemicals were purchased from reputed chemical companies and used without further purification. Products were characterized by spectral techniques such as IR and ^1H NMR.

General experimental procedure

To evaluate the efficiency of $\text{MgCl}_2 \cdot 5\text{H}_2\text{O}$ for acylation of aromatic amines, alcohols and phenols, aniline was selected as a model substrate. A reaction mixture was prepared by mixing aniline (1 mmol), AC_2O (2.0 mmol) and $\text{MgCl}_2 \cdot 5\text{H}_2\text{O}$ (0.1 mmol %). It was stirred at room temperature in solvent-free condition. The progress of reaction was monitored by TLC.

After the completion of reaction, CHCl_3 (10 mL) was added, the reaction mixture was filtered and water (10 mL) was added. It was allowed to stand and organic layer was separated. Thus, product was extracted in CHCl_3 . It was evaporated and dried over Na_2CO_3 . A product was purified by recrystallization using ethyl alcohol. The procedure was repeated for other substrates and corresponding products were obtained. The products were analyzed by IR and ^1H NMR.

Table 2: Spectral data of product compounds

Entry	IR (KBr, cm^{-1})	^1H NMR (CDCl_3 , ppm)
1	1698 (-CO-NH-), 1614 (Ar), 1275 (-COCH ₃)	2.2 (s, 3H, CH ₃), 6.5 (m, 5H, Ar-H), 7.2 (s, -NH-)
3	1702 (-CO-NH-), 1605 (Ar), 1259 (-COCH ₃)	5.7 (s, 1H, -NH-), 7.1 (d, 1H, Ar-H) 7.2 (d, 1H, Ar-H), 7.3 (d, 1H, Ar-H) 2.1 (s, 3H, CH ₃).
6	1766 (-OCO-), 1595 (Ar), 1197 (-OCOCH ₃).	6.9 (s, 5H, Ar-H), 1.8 (s, 3H, -COCH ₃), 4.7 (s, 2H, -CH ₂ -)
7	1741 (-OCO-), 1613 (Ar), 1176 (-OCOCH ₃), 1234 (-COCH ₃)	2.08 (s, 3H, -COCH ₃), 3.81 (s, 3H, OCH ₃), 5.04 (s, 2H, Ar-CH ₂ O), 6.92 (d, 2H, J=6, Ar-H), 7.32 (d, 2H, J=6, Ar-H)
11	1725 (-OCO-), 1618 (Ar), 1215 (-OCOCH ₃).	2.03 (s, 3H, -COCH ₃), 4.03 (s, 1H, -O-CH-), 7.15 (m, 10H, 2xAr-H)
13	1720 (-OCO-), 1593 (Ar), 1198 (-OCOCH ₃).	7.04 (s, 5H, Ar-H), 2.2 (s, 3H, -COCH ₃)
16	1710 (-OCO-), 1605 (Ar), 1197 (-OCOCH ₃).	7.15 (m, 7H, Ar-H), 2.5 (s, 3H, -COCH ₃)

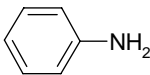
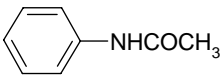
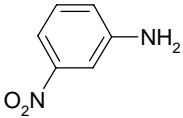
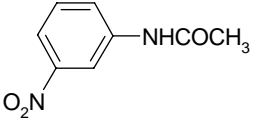
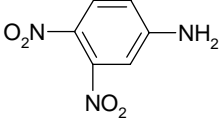
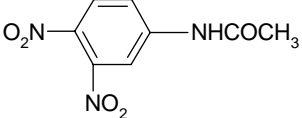
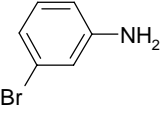
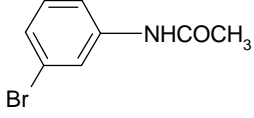
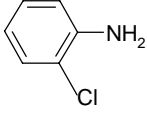
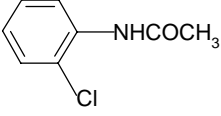
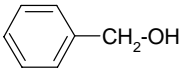
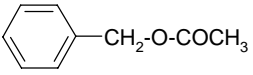
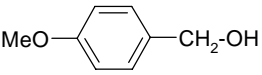
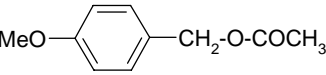
^as, singlet; d, doublet; m, multiplet

RESULTS AND DISCUSSION

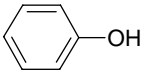
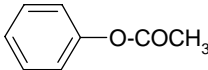
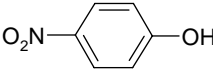
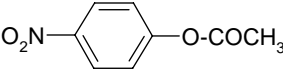
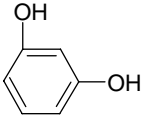
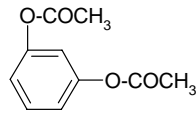
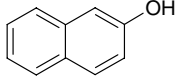
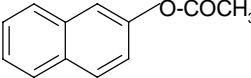
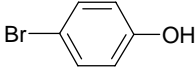
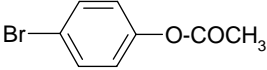
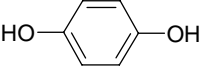
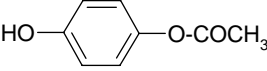
The scope of this acylation with acetic anhydride in presence of $MgCl_2 \cdot 5H_2O$ was checked by performing it on a variety of substrates which includes primary, benzylic, hindered and unhindered secondary and sterically hindered tertiary amines, phenols and alcohols.

The results are summarized in the Table 3.

Table 3:

Entry	Substrate	Product ^b	Time (min.)	Yield ^c (%)
Amines				
1			30	96
2			40	92
3			40	92
4			35	95
5			35	95
Alcohols				
6			30	96
7			30	96

Cont...

Entry	Substrate	Product ^b	Time (min.)	Yield ^c (%)
8	$\text{CH}_3-\text{CH}_2-\text{OH}$	$\text{CH}_3-\text{CH}_2-\text{O}-\text{COCH}_3$	30	94
9	$\text{CH}_3-\text{CH}_2-\underset{\text{OH}}{\text{CH}}-\text{CH}_3$	$\text{CH}_3-\text{CH}_2-\underset{\text{OCOCH}_3}{\text{CH}}-\text{CH}_3$	35	92
10	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{OH} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{O}-\text{COCH}_3 \\ \\ \text{CH}_3 \end{array}$	40	85
11	$\begin{array}{c} \text{Ph} \\ \\ \text{Ph}-\text{C}-\text{OH} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{Ph} \\ \\ \text{Ph}-\text{C}-\text{O}-\text{COCH}_3 \\ \\ \text{H} \end{array}$	40	90
12	$\begin{array}{c} \text{Ph} \\ \\ \text{Ph}-\text{C}-\text{OH} \\ \\ \text{Ph} \end{array}$	$\begin{array}{c} \text{Ph} \\ \\ \text{Ph}-\text{C}-\text{O}-\text{COCH}_3 \\ \\ \text{Ph} \end{array}$	40	85
Phenols				
13			30	95
14			35	90
15			30	94
16			30	95
17			30	94
18			30	92

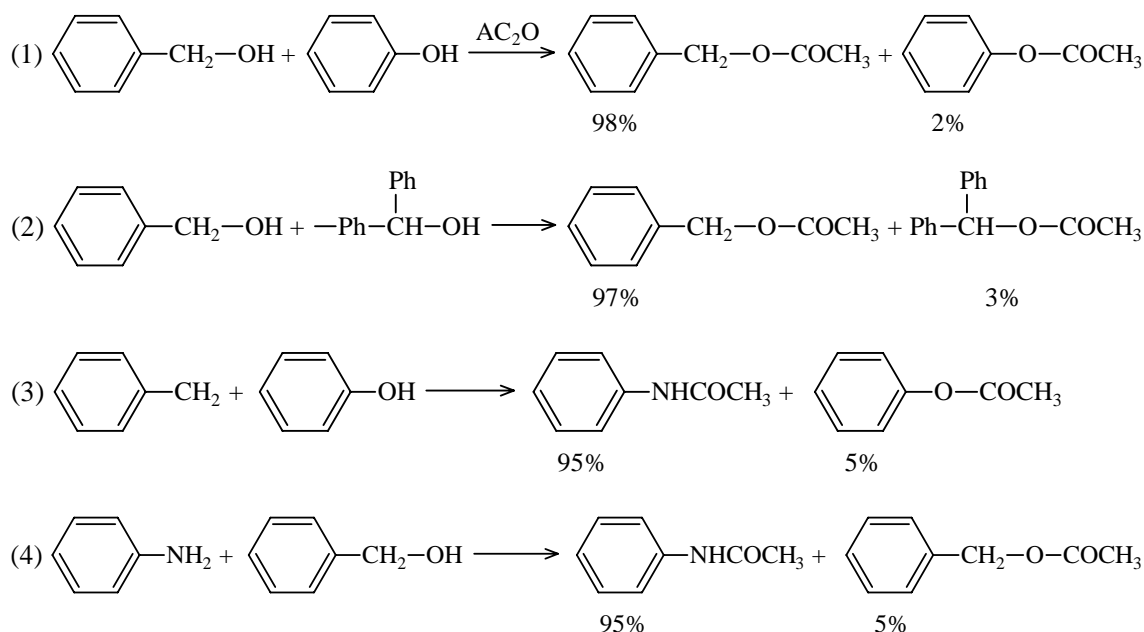
^bAll products were identified by their IR and ¹H NMR spectra

^cIsolated yields

The generality of catalyst $\text{MgCl}_2 \cdot 5\text{H}_2\text{O}$ was established by efficient acylation of aromatic amines containing both electron donating (Table 3, Entries 4 and 5) and electron withdrawing (Table 3, Entries 2 and 3) substituent giving excellent yields of the corresponding acetamides. In case of phenols, compounds containing electron withdrawing (Table 3, Entry 14) and electron donating (Table 3, Entries 17 and 18) substituents were acylated giving excellent yields.

Similarly, primary alcohols were acylated faster than secondary ones (Table 3, Entries 8 and 9). Even sterically hindered alcohols (Table 3, Entries 10, 11 and 12) are acylated in short time.

The chemo selectivity was observed during acylation in presence of $\text{MgCl}_2 \cdot 5\text{H}_2\text{O}$ with respect to amines, alcohols and amines (**Scheme 2**).



Scheme 2

CONCLUSION

In conclusion, this article describes a method, in which $\text{MgCl}_2 \cdot 5\text{H}_2\text{O}$ is an efficient catalyst for acylation of amines, alcohols and phenols. The advantages of this methodology include low cost, easy handling of catalyst, requirement of small amount of catalyst (0.1%). Further, mild reaction conditions, short reaction time, excellent yields are other

characteristics of this pathway. The solvent-free condition makes this methodology environment friendly.

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