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Unprecedented acetylation of phenols using a catalytic amount of magnesium powder

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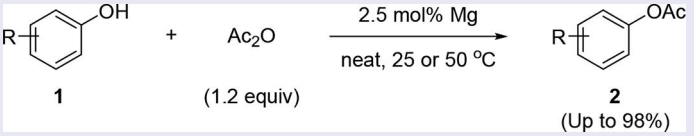
ABSTRACT

The acetylation of phenols with acetic anhydride was achieved using a catalytic amount of magnesium metal powder under air and solvent-free conditions to afford corresponding phenyl acetates in excellent yield (up to 98%).

GRAPHICAL ABSTRACT



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KEYWORDS
Acetylation; free radical mechanism; magnesium; phenyl acetates

Introduction

Acylation (or acetylation) is a fundamental process in organic chemistry for the protection of –OH, –SH, and $–NH_2$ groups, which is usually achieved using acetic anhydride during oxidation, peptide coupling, and glycosidation reactions to construct polyfunctional molecules such as peptides, nucleosides, oligonucleotides, carbohydrates, steroids, and other natural products.[1]

Classically, alcohols and phenols are acylated in the presence of a base (such as NaOH, Na_2CO_3, pyridine, DMAP, Et_3N, etc.) or an acid (such as H_2SO_4, H_3PO_4, *p*-TsOH, etc.).[2] Mechanistically, the base used abstracts the acidic proton from alcohol or phenol to generate enolate, which then attacks electrophilic carbon of the acylating agent. In the latter case, protonation of acylating agent occurs with the aid of an acid and subsequently generates acylium ion, which then electrophilically attacks the partner. In the past two decades, some Lewis acids such as $Ce(OTf)_3$,[3a] $Bi(OTf)_3$,[3b,3c] $Li(OTf)_3$,[3d] $Cu(OTf)_2$,[3d] Me_3SiOTf,[3e] $Fe(OTs)_3 \cdot 6H_2O$,[3f] $LiClO_4$,[3g] $BiOClO_4$,[3h] $RuCl_3$,[3i] LiCl,[3j] $FePO_4$,[3k] $Cu(BF_4) \cdot 6H_2O$,[3l] Mn(bis(2-hydroxyanil)acetylacetonato)Cl,[3m] V(tetraphenylporphyrinato)$(OTf)_2$,[3n] etc. have been used to achieve acetylation of phenols with acetic anhydride. Solid acid catalysts such as monomorillonite K-10[4a] and zeolite HSZ-360,[4b] ionic liquid,[5] heteropolyacid,[6] iodine,[7] and CBr_4[8] are also known to promote the reaction. Despite several catalysts have been reported, but some demerits associated in

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Supplemental data (^{1}H- and ^{13}C-NMR spectra of compound 2j, along with literature references) can be accessed on the publisher's website.

these transformations are (a) hazardous condition, (b) compromising yield, (c) expensive and readily unavailable catalyst, (d) anhydrous reaction condition, (e) additional solvent and acylating reagent, and/or (f) tedious purification process. Therefore, the development of inexpensive, simple, and eco-friendly acylation processes has still a great demand. Herein, we report an efficient and convenient protocol for the acetylation of phenols with acetic anhydride in the presence of catalytic amount of magnesium metal powder under neat condition.

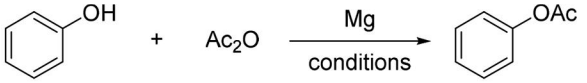
Results and discussion

In search of a suitable catalyst for the acetylation of phenols, the reactions of phenol (**1a**) with 1.2 equiv. of an acetylating agent (AcOH or EtOAc or Ac_2O) in the presence of 10 mol% of several catalysts (such as $AlCl_3$, $Ca_3(PO_4)_2$, $CaCl_2$, $Ce(SO_4)_2 \cdot 4H_2O$, $Cu(OAc)_2 \cdot H_2O$, $CoCl_2$, Cu, $CuCl_2 \cdot 2H_2O$, $CuSO_4 \cdot 5H_2O$, Fe, Fe_2O_3, $FeCl_3$, $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$, $FeSO_4 \cdot 7H_2O$, $K_2Cr_2O_7$, $KBrO_3$, KI, KIO_3, Mg, $MgCl_2 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$, MnO_2, $MnSO_4 \cdot H_2O$, K_2MnO_4, $NaAsO_3$, $NaWo \cdot 2H_2O$, $(NH_4)_2S_2O_8$, $(NH_4)_2Ni(SO_4)_2 \cdot 6H_2O$, NH_4Cl, $NH_4Fe(SO_4)_2 \cdot 12H_2O$, NH_4SCN, $NiCl_2$, $NiCO_3 \cdot 2Ni(OH)_2$, $NiSO_4 \cdot 6H_2O$, $SnCl_2 \cdot 2H_2O$, Zn, $ZnCl_2$, $ZnCO_3$, ZnO, and $ZnSO_4$) were performed under neat conditions at 25 °C for 6 h. The use of either AcOH or EtOAc as an acetylating agent was failed to promote the acetylation, while the use of Ac_2O could promote the reaction producing phenyl acetate (**2a**) with incomplete conversion. After careful analysis, we decided to focus on the use of magnesium (a fine metallic powder) as a catalyst for further optimization, since magnesium could be a cheap (US$ 28 for 500 g from Himedia), less hazardous, and novel catalyst for the acylation of phenols. From extensive literature survey, we were gratified to know that magnesium has never been used for the acylation, except single example of acetylation of *t*-BuOH.[9] Since *t*-BuOH is a unique and highly reactive substrate that prone to generate *tert*-butyl radical, it underwent acetylation in the presence of magnesium powder under reflux conditions. Pasha et al. have used metallic zinc dust as a reusable catalyst for the acylation of phenols with acyl chlorides.[10] In this reaction, acyl chlorides perhaps react with zinc dust to produce $ZnCl_2$ *in situ*. Acetylation of *t*-BuOH with acetic anhydride using $ZnCl_2$ is known.[11] Spassow also reported acetylation of *t*-BuOH with acetyl chloride using sub-stoichiometric amount of Mg.[12] Vedejs and Daugulis have reported $MgBr_2$-catalyzed acylation of alcohols with acyl chlorides.[13] In the above examples, $ZnCl_2$ and $MgBr_2$ were active Lewis acid catalysts for acylations.

Next, systematic optimization of the reaction conditions was performed and the results are summarized in Table 1. The reaction of phenol (**1a**) with 1.2 equiv. of acetic anhydride in the presence of 10 mol% of magnesium metal powder, at 25 °C for 18 h, afforded phenyl acetate (**2a**) in 95% isolated yield (entry 1). Additional amount of acetic anhydride was unnecessary (entries 2 and 3). The amount of magnesium can be effectively reduced to 2.5 mol% (entries 4–6). The increase in reaction temperature to 50 °C could reduce the reaction time as shown in entries 7–9.

After obtaining optimized reaction conditions on hand, we studied the scope and limitation of the present acetylation reaction (Table 2). 1-Naphthol (**1b**) was successfully acetylated forming naphthalene-1-yl-acetate (**2b**). Phenols bearing electron-donating group as in *o*-cresol (**1c**), *m*-cresol (**1d**), and thymol (**1e**) were acetylated to give corresponding products **2c–e** with excellent yields. A substrate vanillin (**1f**), possessing

Table 1. Optimization of reaction conditions for the acetylation of phenol (**1a**).

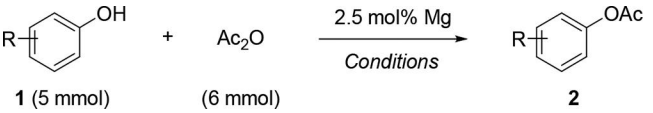


1a (5 mmol) **2a**

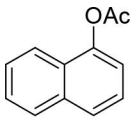
Entry	Mg (mol%)	Ac_2O (equiv.)	Temp (°C)	Time (h)	Isolated yield (%)
1	10	1.2	25	18	95
2	10	1.8	25	18	96
3	10	2.4	25	18	95
4	5	1.2	25	18	95
5	2.5	1.2	25	18	94
6	1	1.2	25	21	88
7	5	1.2	50	4.5	96
8	2.5	1.2	50	4.5	94
9	1	1.2	50	4.5	82

both electron-donating and electron-withdrawing groups, was acetylated providing 4-formyl-2-methoxyphenyl acetate (**2f**). Both the hydroxyl groups in hydroquinone (**1g**), resorcinol (**1h**), and 2-methyl resorcinol (**1i**) were acetylated under optimized reaction conditions to yield the corresponding products **2g–i** in high yields. The reaction of 2-hydroxy acetophenone was halted even after prolonged heating at 50 °C and a significant amount of the substrate (>85%) was recovered indicating intervention of hydrogen bonding between the phenolic proton and the keto group. This protocol is equally effective in

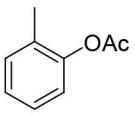
Table 2. Scope of the acetylation reaction using magnesium metal powder.



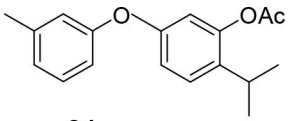
1 (5 mmol) (6 mmol) **2**



2b
24 h, 98%[a]
2.5 h, 94%[b]

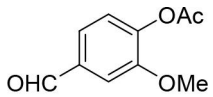


2c
18 h, 98%[a]
4 h, 90%[b]

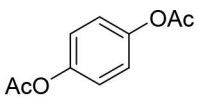


2d
18 h, 98%
2.5 h, 98%

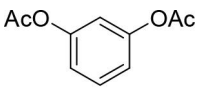
2e
18 h, 94%[a]
5 h, 93%[b]



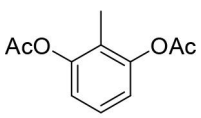
2f
24 h, 92%[a]
4.5 h, 88%[b]



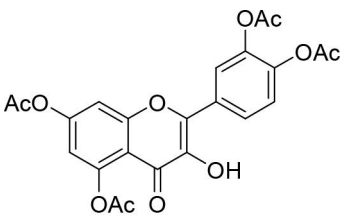
(**2g**)
18 h, 98%[a,c]
2.5 h, 93%[b,c]



(**2h**)
24 h, 98%[a,c]
2.5 h, 93%[b,c]



(**2i**)
18 h, 98%[a,c]
6.5 h, 93%[b,c]

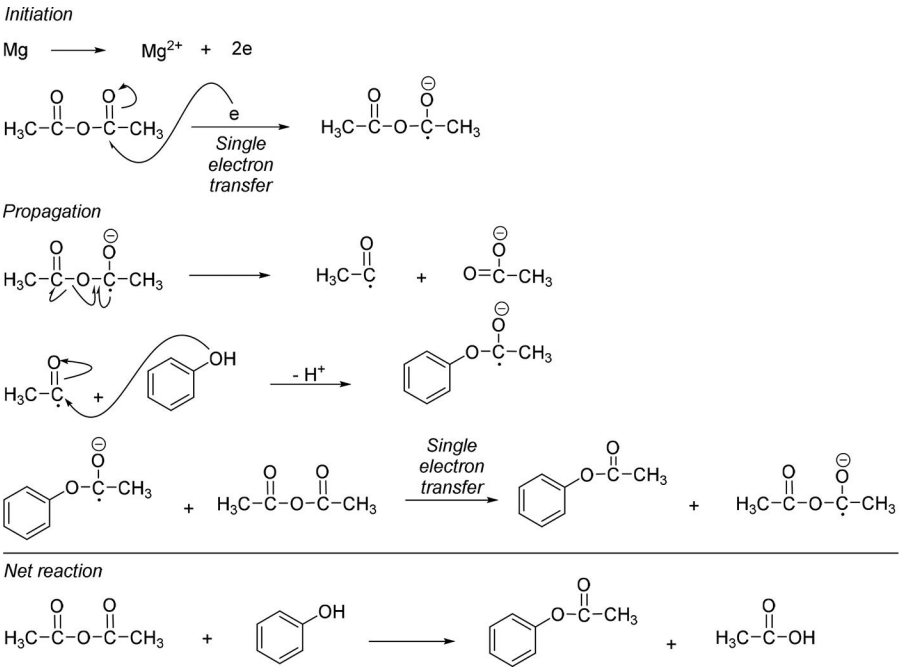


(**2j**)
3.5 h, 98%[a,d]
3.5 h, 95%[b,d]

[a]Temp 25 °C.
[b]Temp 50 °C.
[c]Substrate (5 mmol), Mg (0.25 mmol) and Ac_2O (12 mmol) were used.
[d]Quercetin (1 mmol), Mg (0.125 mmol) and Ac_2O (12 mmol) were used.

acetylation of polyphenolic natural products. For example, quercetin (**1j**) was tetraacetylated to afford quercetin-3′,4′,5,7-tetraacetate (**2j**) with a free 3-OH in excellent yields.

To get insight into the reaction mechanism of the present acetylation reaction, we set up two stoichiometric reactions. First, phenol (**1a**) was treated with 1 equiv. of magnesium powder at 50 °C. Both magnesium and **1a** were persisted in the mixture even after stirring for 24 h. Second, when acetic anhydride was stirred with 1 equiv. of magnesium powder at 25 °C, a white precipitate was gradually appeared indicating that acetic anhydride (not phenol) makes complexation with magnesium. To this complex was added 1 equiv. of **1a** and the mixture was stirred at 50 °C for 30 min. After usual workup, the product **2a** was obtained in 50.6% isolated yield. Since we were aware of the report of Norris and Rigby on acetylation of *t*-BuOH with the involvement of *tert*-butyl radical,[9] we have performed the present acetylation reaction in the presence of 2,2,6,6-tetrtamethyl-1-piperidinyloxy (TEMPO) free radical. The reactions of phenol (**1a**) with 1.2 equiv. of acetic anhydride and 2.5 mol% of magnesium at 25 °C for 24 h in the presence of 0.2, 0.5, 1, or 2 equiv. of TEMPO allowed us to isolate **2a** in 49, 1.3, 0.8, and 0.3% yields, respectively, after silica gel column chromatography. These results clearly indicated that the presence of another free radical hampered the transformation. Therefore, a free radical mechanism of the present acetylation reaction is proposed (Scheme 1). The reaction may proceed through SRN-1 process (substitution, radical-nucleophile, unimolecular). A single electron transfer from magnesium to acetic anhydride would form an anionic radical in the initiation step. In the propagation step, loss of the leaving group (CH_3COO^-) forms a neutral radical. Since phenols are prone to scavenge free radicals, this neutral radical would be attacked to form a new radical anion. This new radical anion serves as an electron source for the



Scheme 1. A plausible mechanism.

single electron transfer and forms the product together with formation of initial anionic radical.

Conclusion

In conclusion, we have developed a new catalytic and solvent-free route for the acetylation of phenols using magnesium metal powder. A plausible free radical mechanism of this transformation is given. Acetylation of alcohols, thiols, and amines are under progress in our laboratory.

Experimental

Materials and methods

Chemicals and solvents were obtained from Qualigens, Merck and Himedia, and were used as received. Magnesium metal powder (GRM726, Lot no. 0000138967) was procured from Himedia Laboratories Pvt. Ltd. Quercetin (**1j**) and TEMPO free radical was purchased from Aldrich. For thin-layer chromatography (TLC), precoated TLC plates (0.2 mm thickness, Kieselgel 60 F_{254}) were procured from Merck. Melting and boiling points were determined using a Thile's tube and were uncorrected. Gas chromatography–mass spectrometry was performed using an Agilent 7890A GC system coupled with a mass spectrometer (Agilent 5975 C). The separation was performed using a fused silica capillary column HP-5MS (5% phenyl methyl siloxane, Agilent 19091S-433, 30 m × 250 µm internal diameter, 0.25 µm film thickness). Helium was used as a carrier gas at a flow rate of 1 mL/min. ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL JMN ESC400 FT NMR spectrophotometer.

General procedure for acetylation

A mixture of phenol (**1a**, 470.5 mg, 5 mmol), acetic anhydride (0.6 mL, 1.2 equiv., 6 mmol), and 2.5 mol% of magnesium metal powder (3.0 mg, 0.125 mmol) was stirred at 25 °C for 18 h (or at 50 °C for 4.5 h in another experiment). After the completion of reaction, the mixture was diluted with EtOAc (60 mL). The reaction mixture was washed with saturated $NaHCO_3$ (30 mL × 2) and brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and finally vacuum dried. The product phenyl acetate (**2a**) was directly obtained in a pure form with the yield of 640.3 mg, 94% (the yield of the product **2a** at 50 °C reaction condition was 640.0 mg, 94%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 7.39–7.34 (m, 2H), 7.23–7.19 (m, 1H), 7.08 (d, $J = 7.6$ Hz, 2H), 2.27 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ ppm: 169.66, 150.86, 129.58, 125.98, 121.73, 21.27.

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