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A mild, highly selective and remarkably easy procedure for deprotection of aromatic acetates using ammonium acetate as a neutral catalyst in aqueous medium☆

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Abstract—Ammonium acetate was found to catalyze efficiently the selective deprotection of aromatic acetates in the presence of various sensitive functionalities in aqueous methanol under neutral conditions at room temperature to yield the corresponding phenols in excellent yields. The method has been utilized for deprotection of acetates of several naturally occurring bioactive phenolic compounds and for preparation of venkatasin, a natural coumarino-lignan, from the anticancer compound cleomiscosin A. © 2003 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Phenolic hydroxyl groups are frequently observed in various bioactive natural products. The modifications and synthesis of these compounds generally require the protection of these hydroxyl groups.[2] This protection is usually carried out by making the acetates of the compounds as the acetates can easily be prepared and again be converted into the parent hydroxyl compounds. Deprotection of aromatic acetates can classically be carried out under acidic or basic conditions, or by hydrogenolysis.[2] However, these deprotection methods may effect several sensitive functional groups present in the molecules. Different methods are also now known for the deprotection of aromatic acetates but the number of processes for selective deprotection of these groups are limited.[3] However, selective deprotection of aromatic acetates is very useful in synthetic organic chemistry. Several manipulations can be carried out on the regenerated phenolic hydroxyl groups of a molecule in the presence of alkyl acetate groups and other sensitive functionalities and this method can be utilized in multistep organic transformations and synthesis. Moreover, some bioactive natural products contain alkyl acetate groups with the free phenolic hydroxyl groups.[4] For preparation of these compounds selective deacetylation of aromatic acetates in the presence of aliphatic acetates will be highly valuable. The methods involving specific micelles,[5a] Zn–MeOH,[5b] cyclodextrin,[5c] metalloenzymes,[5d] metal complexes[5e–g] and antibodies[5h] have earlier been utilized for selective deprotection of aryl acetates in the presence of alkyl acetates. However, most of these methods suffer from certain drawbacks including drastic reaction conditions, tedious experimental procedures, use of nonavailable and expensive reagents, long reaction times and unsatisfactory yields. Recently aromatic thiols in the presence of catalytic amount of K_2CO_3 have been utilized for deprotection of aryl acetates but the utility of the methods in the presence of aliphatic acetates has not properly been studied.[3] Moreover, the reaction mixture should be refluxed at a very high temperature. More recently a mild procedure has applied natural kaolinitic clay as a catalyst but this clay is not commercially available and it was collected from a specific geographic region.[6] The catalyst also worked at a very high temperature and the time required was high. Thus, there is a need to develop a mild, efficient and practical procedure for the selective deprotection of aromatic acetates using an easily available, inexpensive and neutral reagent. Here, we wish to report a very suitable procedure by applying ammonium acetate as catalyst.

2. Results and discussion

In continuation of our work on the development on novel synthetic methodologies we have discovered that ammonium acetate is a highly efficient catalyst for the selective deprotection of aromatic acetates at room temperature and in neutral conditions. The catalyst worked efficiently in aqueous medium. Several aromatic acetates underwent deprotection in the presence of the catalyst to produce the corresponding phenols (Table 1) in excellent yields.

☆ For Part 18 see Ref. 1.

Keywords: aromatic acetates; ammonium acetate; deprotection; bioactive phenolic compounds; venkatasin.

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Table 1. Deprotection of aromatic acetates using ammonium acetate

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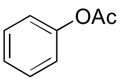
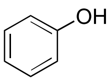
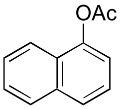
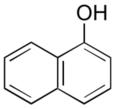
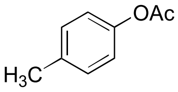
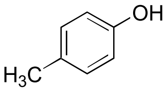
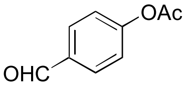
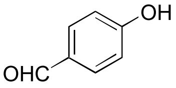
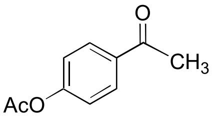
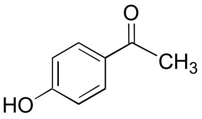
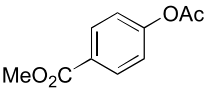
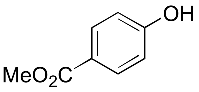
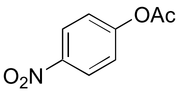
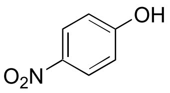
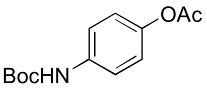
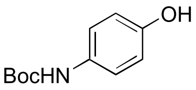
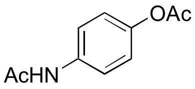
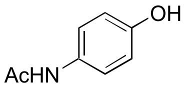
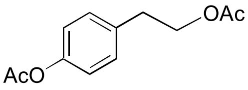
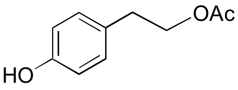
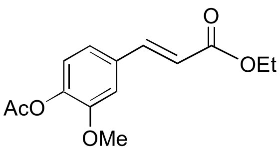
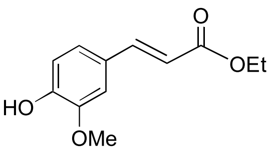
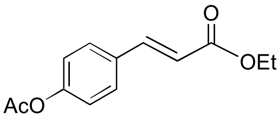
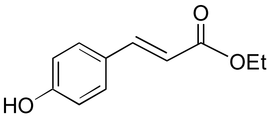
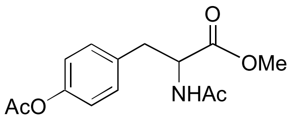
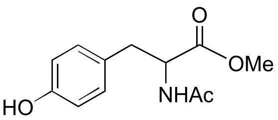
1		4		98
2		4		97
3		4.5		97
4		3		100
5		3.5		95
6		2.5		100
7		2		99
8		4		96
9		4.5		99
10		5		96
11		3.5		98
12		3.5		97
13		5		93

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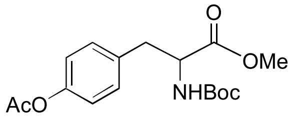
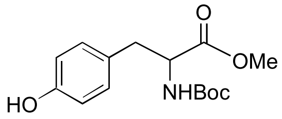
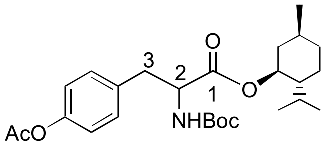
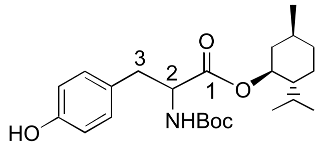
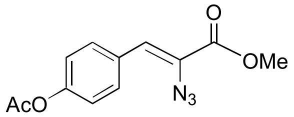
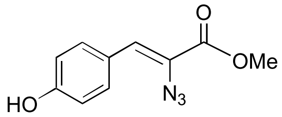
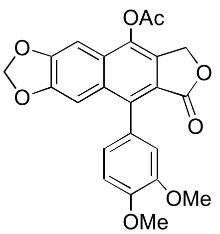
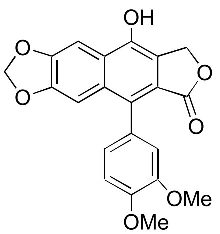
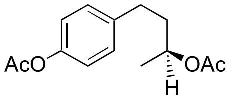
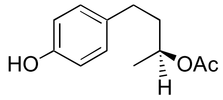
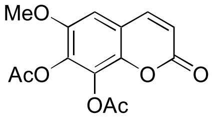
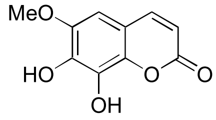
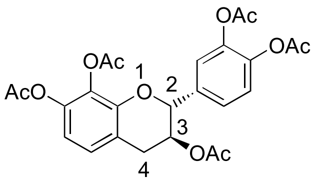
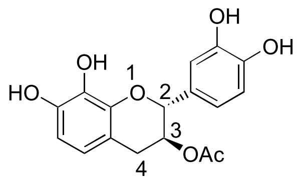
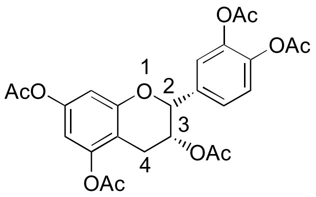
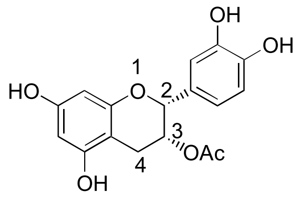
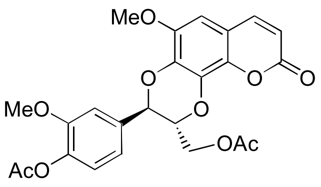
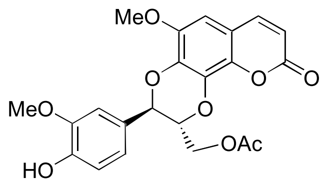
14		5		96
15		4.5		97
16		4		100
17		3		99
18		6		96
19		5		94
20		6		96
21		6		94
22		5		95

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Table 1 (*continued*)

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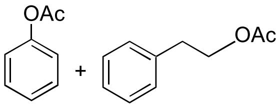
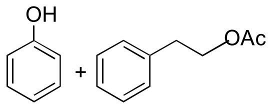
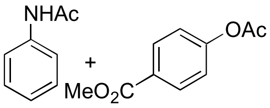
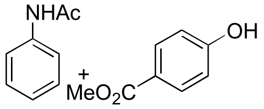
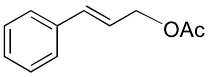
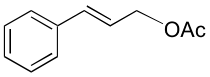
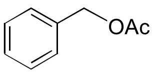
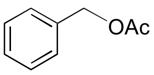
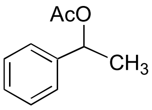
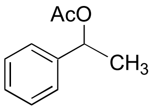
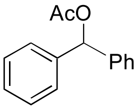
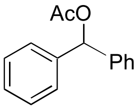
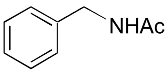
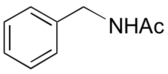
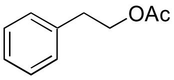
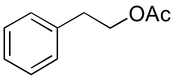
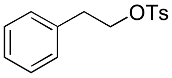
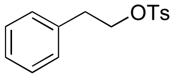
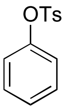
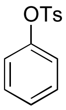
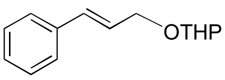
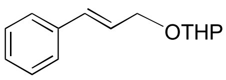
23		4		97+100 (respectively)
24		3.5		100+99 (respectively)
25		6		No reaction
26		6		No reaction
27		6		No reaction
28		6		No reaction
29		6		No reaction
30		6		No reaction
31		6		No reaction
32		6		No reaction
33		6		No reaction

Ammonium acetate is readily available and inexpensive. The experimental procedure is remarkably easy. Deprotection of aromatic acetates can be carried out in the presence of various functionalities like double bonds, aldehydes and azide groups, lactone rings and ether and dioxane linkages. Excellent chemoselectivity of the process was observed as several other protecting groups such as THP ether, tosyl and *t*-butoxycarbonyl (Boc) were unaffected under the experimental conditions. The method showed unique selectivity for deprotection of aryl acetates in the presence of benzoates, *N*-acetyl groups and alkyl acetates. Thus, 4-acetoxymethylbenzoate (entry 6), 4-acetoxyacetanilide (entry 9) and 4-acetoxyphenylethylacetate (entry 10), afforded 4-hydroxymethylbenzoate (100%), 4-hydroxyacetanilide (99%) and 4-hydroxyphenylethylacetate (96%), respectively. Fries rearrangement products or undesired side products were not obtained in any case. The presence of electron donating (e.g. $-$Me) or electron withdrawing group (e.g. $-NO_2$) in the aromatic ring did not show any change in the yields of the products. The structures of all the regenerated phenols were established from their analytical and spectral (IR, ^{1}H NMR and MS) data, and by direct comparison with available authentic samples.

The remarkable selectivity of the present procedure was also demonstrated by intermolecular competition experiments. Thus, when a mixture (1:1) of phenylacetate and phenylethylacetate was treated with ammonium acetate in aqueous MeOH under the experimental conditions the latter was totally recovered unchanged along with phenol (97%). Similarly, when the reaction was carried out with a mixture (1:1) of acetanilide and 4-acetoxymethylbenzoate the first compound remained totally intact while the other compound afforded the product, 4-hydroxymethylbenzoate (99%).

The interesting point is that the present methodology has been applied to the acetyl derivatives of several bioactive natural products (entries 17–22). Thus, rhododendrol diacetate[7] (entry 18) afforded rhododendrol monoacetate (96%) with selective regeneration of phenolic hydroxyl group. Both the diphyllin acetate[8] (entry17) and fraxetin diacetate[9] (entry 19) underwent deacetylation to form the parent phenols, diphyllin (99%) and fraxetin (94%), respectively. (+) Mesquitol[10] and (−) epicatechin[11] contain five hydroxyl groups, four of them aromatic and one is aliphatic. Penta acetates of these compounds (entries 20 and 21) afforded tetrahydroxymonoacetate (having intact the aliphatic acetate group) under experimental conditions. Finally the method has been utilized for conversion of the anticancer compound, cleomiscosin A into venkatasin, both are naturally occurring coumarino-lignoids.[4] The former contains one aliphatic and one phenolic hydroxyl groups while venkatasin contains only the phenolic hydroxyl group along with aliphatic acetate. The diacetate of cleomiscosin A (entry 22) was treated with ammonium acetate to produce venkatasin (95%) directly.

3. Conclusion

In conclusion, we have developed a very simple, mild and highly efficient practical protocol with remarkable selectivity for deprotection of aromatic acetates. The catalyst is cheap, readily available and neutral. It works at room temperature and in aqueous medium. The present procedure is thus environmentally benign. The yields of the regenerated phenols are excellent. The method is quite suitable for deprotection of acetates of several naturally occurring complex bioactive phenols (both chiral and nonchiral) having different sensitive functionalities. For direct preparation of some of the natural phenols the present protocol will be highly useful.

4. Experimental

4.1. General methods

All the phenols and amines, except the naturally occurring compounds, were obtained commercially. The natural products were isolated earlier from the reported plant sources and were available in our laboratory. NH_4OAc was obtained from Rankem laboratories, India. The spectra were run on the following instruments: IR, Perkin–Elmer (RX1 FT-IR), ^1H NMR: Varion Gemini 200 MHz and EIMS: VG Micromass 7070 H (70 eV).

4.2. Typical experimental procedure

To a solution of 4-acetoxymethylbenzoate (194 mg, 1.0 mmol) in aqueous MeOH (1:4, 10 ml) NH_4OAc (618 mg, 8.0 mmol) was added. The resulting mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After 2.5 h the mixture was concentrated and the residue was extracted with EtOAc (3× 10 ml). Evaporation of the solvent afforded the deprotected product, 4-hydroxymethylbenzoate (152 mg, 1.0 mmol, 100%).

The characterization data of some compounds (which are unknown or whose spectral data are not completely known) prepared by following the above method is given below.

4.2.1. *N*-Acetyl-*p*-aminophenol (entry 9). Pale yellow solid, mp 152–154°C; [Found: C, 63.24; H, 5.92; N, 9.12. $C_8H_9NO_2$ requires C, 63.56; H, 6.00; N, 9.27%]; ν_{max} (KBr) 3324, 3165, 1653, 1562, 1508 cm^{-1}; δ_H (DMSO-d_6) 9.24 (brs, 1H, −OH), 8.76 (1H, brs, −NH−), 7.26 (2H, d, J=8.0 Hz, Ar-H), 6.64 (2H, d, J=8.0 Hz, Ar-H), 2.02 (3H, s, −Ac); EIMS: m/z 151 ($M^{+\cdot}$), 109, 80.

4.2.2. (*S*)-Menthyl ester of *N*-Boc-tyrosine (entry 15). Viscous; [Found: C, 68.32; H, 8.83; N, 3.22. $C_{24}H_{37}NO_5$ requires C, 68.71; H, 8.89; N, 3.34%]; $[\alpha]_D^{25}$=+18.2° (c 1.13, MeOH); ν_{max} (KBr) 3436, 1730, 1695, 1635, 1615, 1503, 1450 cm^{-1}; δ_H ($CDCl_3$): 6.97 (2H, d, J=8.0 Hz, Ar-H), 6.62 (2H, d, J=8.0 Hz, Ar-H), 4.86 (1H, m, carbinol proton from menthyl moiety), 4.64 (1H, brs, −NH−), 4.44 (1H, m, H-2), 3.04–2.77 (2H, m, H_2-3), 2.02–0.88 (9H, m, menthyl moiety), 1.24 (9H, s, −$OCMe_3$), 0.82, 0.80, 0.68 (3H, each, d, J=7.0 Hz, 3×−Me); LSIMS: m/z 419 ($M^{+\cdot}$), 420 (M+1).

4.2.3. 3-*O*-Acetyl-(+)-mesquitol (entry 20). White solid, mp 162–164°C; [Found: C, 61.32; H, 4.75. $C_{17}H_{16}O_7$ requires C, 61.44; H, 4.85%.]; $[\alpha]_D^{25}$=+73.1° (c 1.21, MeOH); ν_{max} (KBr) 3476, 3331, 1724, 1613, 1474 cm^{-1}; δ_H ($CDCl_3$+DMSO-d_6): 8.68, 8.22, 8.06, 7.78 (4H, brs each, 4×−OH), 6.82–6.60 (3H, m, Ar-H), 6.41–6.30 (2H, m, Ar-H), 5.22 (1H, m, H-3), 5.11 (1H, d, J=4.5 Hz, H-2), 2.94 (1H, dd, J=12.5, 4.5 Hz, H-4), 2.65 (1H, dd, J=12.5, 6.5 Hz, H-4), 2.00 (3H, s, −OAc); EIMS: m/z332 ($M^{+\cdot}$), 272, 176, 152.

4.3. 3-*O*-Acetyl-(−)-epicatechin (entry 21)

White solid, mp 140–142°C; [Found: C, 61.22; H, 4.67. $C_{17}H_{16}O_7$ requires C, 61.44; H, 4.85%]; $[\alpha]_D^{25}$=−40.4° (c 1.05, MeOH); ν_{max} (KBr) 3475, 3312, 1723, 1624, 1475 cm^{-1}; δ_H ($CDCl_3$+DMSO-d_6): 8.80, 8.62, 8.24, 7.98 (4H, brs each, 4×−OH), 6.96 (1H, m, Ar-H), 6.82–6.56 (2H, m, Ar-H), 6.24 (1H, d, J=1.5 Hz, Ar-H), 6.08 (1H, d, J=1.5 Hz, Ar-H) 5.24 (1H, m, H-3), 4.85 (1H, d, J=6.5 Hz, H-2), 3.04–2.52 (2H, m, H_2-4), 2.18 (3H, s, −OAc); EIMS: m/z 332 ($M^{+\cdot}$), 290, 272, 212, 123.

4.4. Competition experiment

A mixture of acetanilide (135 mg, 1.0 mmol) and 4-acetoxy methylbenzoate (194 mg, 1.0 mmol) was dissolved in aqueous MeOH (1:4, 20 ml). NH_4OAc (618 mg, 8.0 mmol) was added. The mixture was stirred at room temperature. After 3 h the mixture was concentrated to afford a residue which was extracted with EtOAc (3×20 ml). The extract was purified by column chromatography (15% EtOAc/hexane) over silica gel to obtain 4-hydroxymethylbenzoate (150 mg, 0.986 mmol, 99%) and the unchanged acetanilide (135 mg, 1.0 mmol, 100%).

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