Silver Acetate Mediated Acetoxylations of Alkyl Halides

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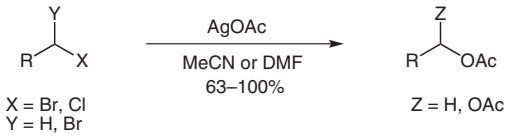
Abstract: Silver acetate promotes the acetoxylation of alkyl halides under neutral reaction conditions. The reaction is applicable to primary and activated secondary alkyl halides, and 2,2-dibromoacetophenones for preparing the corresponding acetates in good yields. The presence of ester, amide, nitrile, hydroxy, and OTBDMS functions on the substrate is tolerated.

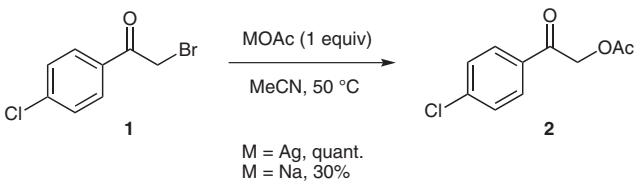
Key words: alkyl halides, substitution, acetoxylation, silver acetate, isomerization



Scheme 1 Acetoxylation of alkyl halides with silver acetate

Acetates are cheap and efficient protecting groups of alcohols. One of their advantages is that they can be gently removed by enzymes, which in addition opens the opportunity to procure enantioenriched substrates.[1] Usually acetates are prepared starting from the corresponding alcohols;[1] however, when the free hydroxyl group is not directly available an alternative way to introduce this functionality is the replacement of a halogen by an acetoxy group. This second alternative has been less investigated, and typically is carried out by heating the corresponding alkyl halide in AcOH,[2] or treating the alkyl halide with KOAc or NaOAc in the presence of 18-crown-6,[3] or with KOAc in ionic liquids.[4] The first method is only suitable for substrates not sensitive to acid mediums, the second one gives good yields just when the alkyl halide is activated, and the third one suffers from the inconveniences associated to ionic liquids such as high cost and viscosity. Given the utility of acetates and in order to further develop methodologies that do not use alcohols as starting materials, we decided to explore the possibility of synthesizing them by using AgOAc as the acetoxy supplier under neutral conditions (Scheme 1). Silver salts have been used in organic chemistry to facilitate substitution reactions thanks to their high affinity for halogens.[5] Nonetheless, there exits only a few reports where silver salts have been employed to promote the replacement of a halogen by an acetoxy group. In the major part of these reports the main interest is not synthetic but mechanistic and the transformation is achieved by adding AgOAc, Ag_2O, or Ag_2CO_3 to a solution of the corresponding alkyl halide in acetic acid.[6] Closely related to these substitutions, the transformation of primary iodides and bromides into alcohols by oxygen transfer from bis(tributyltin)oxide with silver salts,[7] and the replacement of a secondary iodide by OMe, or ONO_3 with AgOTf and $AgNO_3$ have also been, respectively, described.[8] Taking into account these precedents we wanted to test the applicability of the substitution promoted by AgOAc under neutral conditions on a wide range of alkyl halides.

The difference in reactivity between AgOAc and NaOAc on an activated α-bromo ketone **1** was examined first in a polar aprotic solvent. Performing the reaction in acetonitrile at room temperature with 1 equivalent of AgOAc, the acetate **2** was cleanly obtained after 5 hours in 93% yield. Increasing the temperature to 50 °C reduced the reaction time to 1.5 hours and the isolated yield was almost 100% (Scheme 2). Under these conditions, AcOH or less polar solvents gave lower yield,[9] whereas NaOAc instead of AgOAc led only to 30% of conversion.



Scheme 2 Acetoxylation of 2-bromo-4′-chloroacetophenone

With this result, the generality of the method was examined next on a variety of alkyl halides (Scheme 1, Table 1). In general, the reaction takes place very efficiently with yields ranging from 63 to 100% in acetonitrile or DMF for less reactive substrates (Table 1, entries 11–14).

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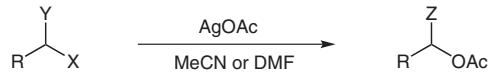
As in the case of **1**, 2-bromoacetophenones **3a–d** were converted into their acetoxy derivatives **4a–d** in excellent yields (entries 1–4). α-Acetoxy ketones can be prepared by a variety of methods but most of them involve the direct oxidation of ketones[10] or the oxidation of an enol intermediate[11] using an excess of the oxidant. Interestingly, it was possible to perform a double substitution onto 2,2-dibromoacetophenones **3e–h** to furnish the corresponding 1,1-diacetates (entries 5–8). 1,1-Diacetates are valuable protecting group of aldehydes under basic conditions,[12] they are usually synthesized from aldehydes[13] and to the best of our knowledge this is the first time that a substitution over a 1,1-dibromide has been used as method for their preparation. Secondary α-bromo ketones were also converted into α-acetoxy ketones, although higher temperatures were required (entries 11 and 12). As expected primary and secondary benzyl bromides were readily acetoxylated in good yields (entries, 9 and 10). Primary substrates like bromooctane or 3-phenylpropargyl bromide, were properly transformed into their acetoxy derivatives using DMF as solvent (entries 13 and 14). Nonetheless, cyclohexyl iodide and 3-bromocyclohexene, both secondary alkyl halides, gave mainly the elimination products under all the conditions examined.

Table 1 Scope of the Acetoxylation Reaction with AgOAc



3a–t **4a–t**

X = Br, Cl
Y = H, Br

Z = H, OAc

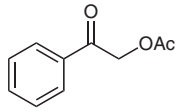
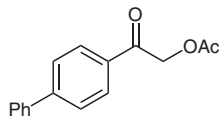
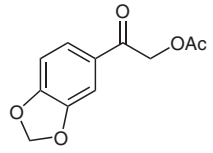
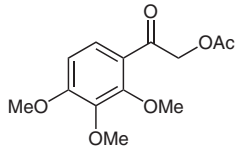
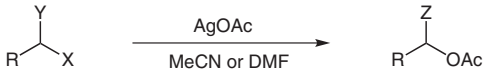
Entry[a]	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1	 **4a**	MeCN	50	2.5	94
2	 **4b**	MeCN	50	1.5	99
3	 **4c**	MeCN	50	1.5	98
4	 **4d**	MeCN	50	2.5	90

Table 1 Scope of the Acetoxylation Reaction with AgOAc (continued)



3a–t **4a–t**

X = Br, Cl
Y = H, Br

Z = H, OAc

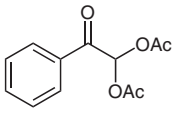
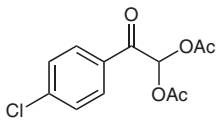
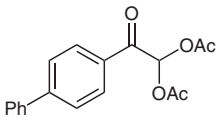
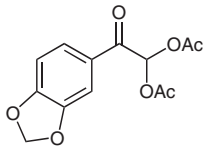
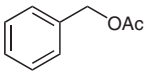
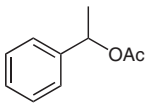
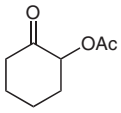
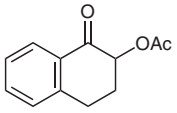
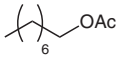
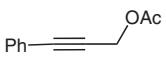
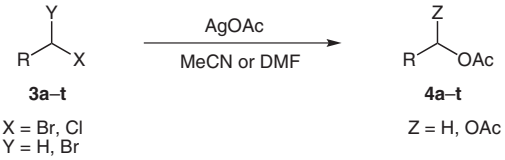
Entry[a]	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
5	 **4e**	MeCN	70	15	98
6	 **4f**	MeCN	70	20	93
7	 **4g**	MeCN	70	20	99
8	 **4h**	MeCN	70	15	96
9	 **4i**	MeCN	50	4	90
10	 **4j**	MeCN	50	2	91
11	 **4k**	DMF	70	2	91
12	 **4l**	DMF	70	36	63
13	 **4m**	DMF	70	24	93
14	 **4n**	DMF	25	2	100

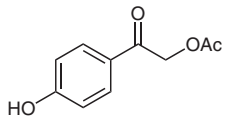
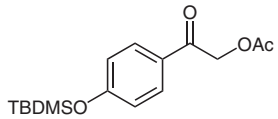
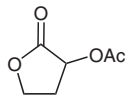
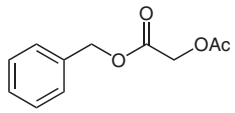
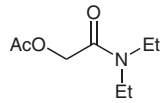
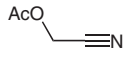
Table 1 Scope of the Acetoxylation Reaction with AgOAc (continued)



3a–t **4a–t**

X = Br, Cl
Y = H, Br

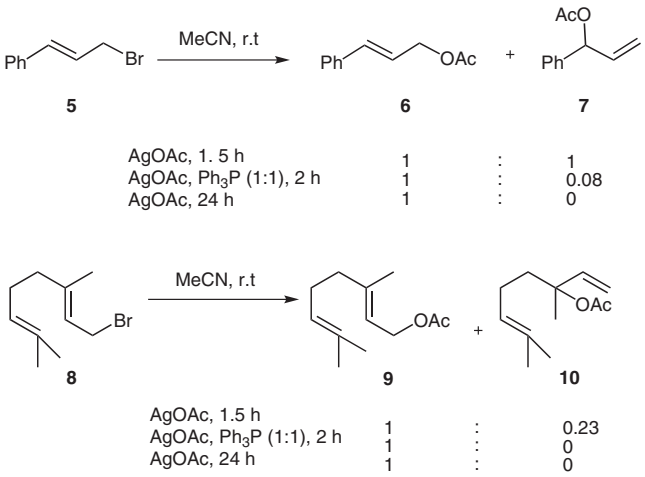
Z = H, OAc

Entry[a]	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
15	 **4o**	MeCN	50	3	96
16	 **4p**	MeCN	70	2	90
17	 **4q**	MeCN	70	24	93
18[b]	 **4r**	MeCN	50	16	95
19[b]	 **4s**	MeCN	50	48	96
20[c]	 **4t**	MeCN	50	60	91

[a] Reaction conditions: R–X (0.1 M); R–X/AgOAc = 1:1. Unless otherwise noted: R–X = R–Br.
[b] Reaction performed in the presence of Ph_3P. R–X/AgOAc/Ph_3P = 1:2:1; R–X = R–Cl.
[e] R–X/AgOAc = 1:2; R–X = R–Cl.

Aiming at studying the compatibility of the method over different functional groups, we tested the reaction in the presence of a hydroxyl, an OTBDMS, an ester, an amide, and a nitrile function. Satisfactorily the acetoxylation worked efficiently without affecting the different functionalities (entries 15–20). In the cases of ester **3r** and amide **3s**, the addition of 1 equivalent of Ph_3P was necessary to accelerate the reaction (entries 18 and 19).

Finally we decided to examine the regioselectivity of the substitution onto primary allylic substrates. At first instance, the reaction of allylic substrates like cinnamyl or geranyl bromides with silver acetate furnished a mixture of linear and branched acetoxy derivatives (Scheme 3). This is in line with an S_N1 process where the silver ion undergoes an electrophilic attack on the halogen group to produce an allylic cation intermediate. Nonetheless it was possible to obtain solely the linear acetoxy derivatives either by adding 1 equivalent of Ph_3P or with prolonged reaction times. The presence of Ph_3P decreases the electrophilicity of the silver cation causing a milder interaction with the halogen group and thus inhibiting the formation of the allylic cation. Under these conditions the acetate anion likely replaces the halogen by an S_N2 mechanism resulting in the exclusive formation of the linear derivative. On prolonged reaction times silver ion itself would promote an allylic isomerization reaction. This was supported by the observation that the addition of 1 equivalent of AgOAc to a 1:1 mixture of the linear **6** and branched **7** acetoxy derivatives of cinnamyl bromide furnished only the linear derivative **6** after 24 hours. As it has been previously reported mainly for palladium[14] and recently for gold carbenes[15] silver ions would promote the rearrangement by π coordination with the olefin.



Scheme 3 Acetoxylation of geranyl and cinnamyl bromide

In summary, we have found that silver acetate promotes the substitution reaction of primary and activated secondary alkyl halides under soft and neutral reaction conditions. The method described allows the preparation of 1,1-diacetates and linear allylic acetoxy compounds by careful tuning of the reaction conditions.

All reactions were carried out under a N_2 atmosphere. Et_2O and $CHCl_3$ were dried by standard methods and freshly distilled prior to use. Anhydrous MeCN and DMF were purchased from Aldrich. Commercial reagents were used as received without further purification. Reactions containing AgOAc were protected from light in order to prevent its decomposition. NMR spectra were recorded at 25 °C on a Jeol Eclipse 300 MHz spectrometer. High-resolution mass spectra (HRMS) were recorded on a Jeol JMS-SX-102A spectrometer.

Acetoxylation of Alkyl Halides 3; General Procedure

To a suspension of AgOAc (42 mg, 0.25 mmol) in MeCN or DMF (2 mL) was added the respective alkyl halide **3** (0.25 mmol) dissolved in the corresponding solvent (1 mL). The reaction mixture was stirred at the temperature and time indicated in Table 1 until the starting material was consumed. After completion of the reaction,

sat. aq NH_4Cl (20 mL) was added and the crude mixture was extracted with EtOAc (3 × 20 mL). When necessary, the product was purified by column chromatography on silica gel (hexane–EtOAc).

2-Acetoxy-3′,4′-(methylenedioxy)acetophenone (4c)
Yield: 62.90 mg (98%); white solid; mp 75–77 °C.

IR (KBr): 1736, 1676, 1600 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.0 Hz, 1 H), 7.36 (s, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 6.03 (s, 2 H), 5.24 (s, 2 H), 2.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.25, 170.53, 152.47, 148.46, 128.95, 124.05, 108.19, 107.62, 102.09, 65.83, 20.66.

HRMS-FAB: *m*/*z* calcd for $C_{11}H_{11}O_5$ $[M + H]^+$: 222.0528; found: 222.0527.

2-Acetoxy-2′,3′,4′-trimethoxyacetophenone (4d)
Yield: 53.30 mg (90%); orange oil.

IR (KBr): 1748, 1685, 1589 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.9 Hz, 1 H), 6.67 (d, *J* = 9.0 Hz, 1 H), 5.14 (s, 2 H), 3.97 (s, 3 H), 3.35 (s, 3 H), 3.79 (s, 3 H), 2.14 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.84, 170.69, 154.61, 149.67, 141.62, 126.21, 122.17, 107.53, 69.41, 61.32, 60.91, 56.26, 20.75.

HRMS-FAB: *m*/*z* calcd for $C_{13}H_{17}O_6$ $[M + H]^+$: 269.1025; found: 269.1028.

2,2-Bisacetoxy-4′-chloroacetophenone (4f)
Yield: 56.00 mg (93%); yellowish oil.

IR (KBr): 1767, 1706, 1588 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.6 Hz, 2 H), 7.55 (s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 2.17 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.96, 168.78, 141.03, 131.61, 130.39, 129.43, 129.37, 86.37, 20.72.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{11}ClO_5$ + Na $[M + Na]^+$: 293.0193; found: 293.0178.

2,2-Bisacetoxy-4′-phenylacetophenone (4g)
Yield: 60.90 mg (99%); orange oil.

IR (KBr): 1770, 1703, 1603 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.3 Hz, 2 H), 7.82–757 (m, 5 H), 7.55–7.37 (m, 3 H), 2.02 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.49, 168.87, 147.09, 139.57, 131.91, 129.59, 129.15, 128.67, 127.61, 127.40, 86.38, 20.76.

HRMS-FAB: *m*/*z* calcd for $C_{18}H_{17}O_5$ $[M + H]^+$: 313.1076; found: 313.1067.

2,2-Bisacetoxy-3′,4′-(methylenedioxy)acetophenone (4h)
Yield: 58.40 (96%); light brown oil.

IR (KBr): 1750, 1687, 1601 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.51 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.40 (d, *J* = 1.6 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.05 (s, 2 H), 2.16 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.88, 168.81, 152.99, 148.56, 127.82, 125.70, 108.57, 108.35, 102.24, 86.17, 20.73.

HRMS-FAB: *m*/*z* calcd for $C_{13}H_{13}O_7$ $[M + H]^+$: 280.0583; found: 280.0591.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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