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C. Wade Downey

University of Richmond, wdowney@richmond.edu

Miles W. Johnson

Daniel H. Lawrence

Alan S. Fleisher

Kathryn J. Tracy

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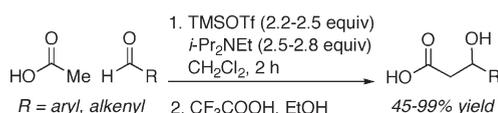
Acetic Acid Aldol Reactions in the Presence of Trimethylsilyl Trifluoromethanesulfonate

C. Wade Downey,* Miles W. Johnson,
Daniel H. Lawrence, Alan S. Fleisher, and Kathryn J. Tracy

Gottwald Center for the Sciences, University of Richmond,
Richmond, Virginia 23173

wdowney@richmond.edu

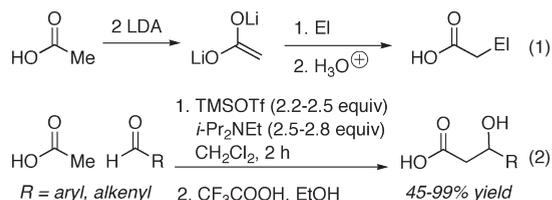
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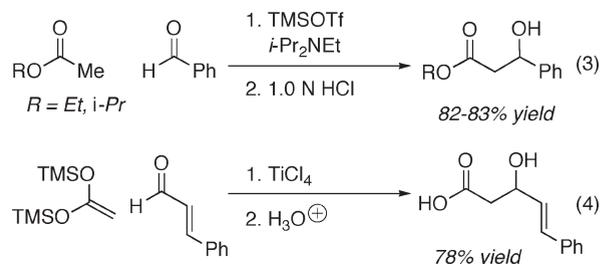
In the presence of TMSOTf and a trialkylamine base, acetic acid undergoes aldol addition to non-enolizable aldehydes under exceptionally mild conditions. Acidic workup yields the β -hydroxy carboxylic acid. The reaction appears to proceed via a three-step, one-pot process, including in situ trimethylsilyl ester formation, bis-silyl ketene acetal formation, and TMSOTf-catalyzed Mukaiyama aldol addition. Independently synthesized TMSOAc also undergoes aldol additions under similar conditions.

The use of carboxylic acid derivatives in α -substitution reactions, including aldol addition reactions, is well developed.¹ The parent carboxylic acids, however, are seldom employed in aldol reactions because their inherent Brønsted acidity results in deprotonation of the acid proton rather than the α -carbon. A second deprotonation to yield the dianion is possible, but harshly basic conditions are required and the highly reactive dianion is difficult to control (eq 1).² The development of a mild and general aldol reaction of carboxylic acids would be a desirable addition to the field of organic synthesis because of the synthetic versatility of the carboxylic acid group, which can be easily converted to the corresponding ester, anhydride, or acid halide. We now report that acetic acid undergoes one-pot bis-silyl ketene acetal formation–Mukaiyama aldol reactions in the presence of trimethylsilyl trifluoromethanesulfonate

(TMSOTf) and an amine base, yielding β -hydroxy carboxylic acids (eq 2). Syntheses of these products are exceedingly rare, as illustrated by the fact that only two of the 13 products described in this manuscript have ever been fully characterized in the literature.³



Motivated by our interest in silylation-driven additions to carbonyl compounds,⁴ we recently reported the one-pot enol silane formation–Mukaiyama aldol addition of esters to nonenolizable aldehydes, in which TMSOTf served as both silylating agent and Lewis acid catalyst (eq 3).^{4a,5} We speculated that silyl esters would also be effective enolate precursors under similar reaction conditions and would give rise to carboxylic acid aldol products after desilylative workup. Bellassoued has pioneered Lewis acid catalyzed Mukaiyama aldol reactions of bis-silyl ketene acetals but describes only a single example of the addition of an acetate nucleophile to an aldehyde, and the reaction requires preformation and purification of the nucleophile (eq 4).⁶ Accordingly, we set out to apply our one-pot enol silane formation–Mukaiyama aldol strategy to this problem.



We began our investigation by treating commercially available trimethylsilyl acetate (TMSOAc) with *i*-Pr₂NEt, benzaldehyde, and TMSOTf in CH₂Cl₂ for 2 h at room temperature and were pleased to observe >95% conversion to aldol addition adducts (eq 5). No α,β -unsaturated aldol condensation products were observed. Although the unpurified reaction mixture included products silylated at one,

(1) For recent reviews, see: (a) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131–173. (b) Abiko, A. *Org. Synth.* **2002**, *79*, 116–124. (c) Zappia, G.; Cancelliere, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Synth.* **2007**, *4*, 238–307. (d) Kimball, D. B.; Silks, L. A., III *Curr. Org. Chem.* **2006**, *10*, 1975–1992.

(2) For examples of the successful execution of this strategy, see: (a) Parra, M.; Sotoca, E.; Gil, S. *Eur. J. Org. Chem.* **2003**, *8*, 1386–1388. (b) Galatsis, P.; Manwell, J. J.; Blackwell, J. M. *Can. J. Chem.* **1994**, *72*, 1656–1659. (c) Fringuelli, F.; Martinetti, E.; Permati, O.; Pizzo, F. *Gazz. Chim. Ital.* **1993**, *123*, 637–640. For an example of a soft enolization strategy similar to the one reported here, using Bu₂BOTf as the Lewis acid, see: (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

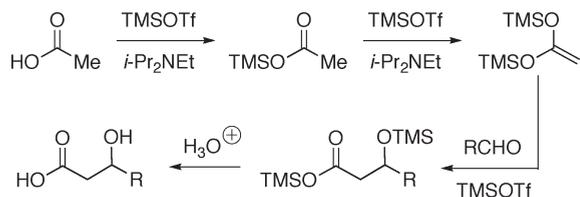
(3) (a) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704–8705. (b) Bietti, M.; Capone, A. *J. Org. Chem.* **2006**, *71*, 5260–5267.

(4) (a) Downey, C. W.; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559–3562. (b) Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299–3302. (c) Downey, C. W.; Mahoney, B. D.; Lipari, V. R. *J. Org. Chem.* **2009**, *74*, 2904–2906.

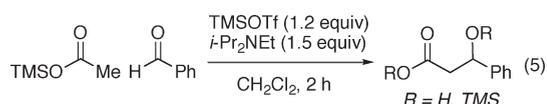
(5) For a similar strategy applied to intramolecular cases, see: (a) Hoye, T. R.; Dvornikov, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191–5194. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zombrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070–8075.

(6) (a) Bellassoued, M.; Gaudernar, M. *J. Organomet. Chem.* **1988**, *338*, 149–158. (b) Bellassoued, M.; Gaudernar, M. *J. Organomet. Chem.* **1990**, *393*, 19–25.

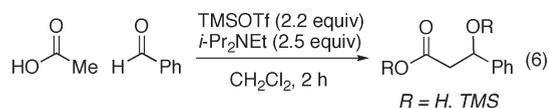
SCHEME 1. Proposed Mechanistic Scheme



both, or neither hydroxyl group, acid-catalyzed desilylation of the product mixture afforded a single β -hydroxy carboxylic acid.



Encouraged by this result, we next tested the reactivity of acetic acid itself under similar conditions. By changing the reaction conditions to include an extra 1 equiv of both TMSOTf and *i*-Pr₂NEt, one-pot conversion of acetic acid to the Mukaiyama aldol adduct was achieved (eq 6).



Our interpretation of the reaction mechanism is outlined in Scheme 1. First, *i*-Pr₂NEt and TMSOTf react with acetic acid to form TMSOAc in situ. A second equivalent of TMSOTf activates the silyl ester toward deprotonation, which is carried out by a second equivalent of *i*-Pr₂NEt, forming the bis-silyl ketene acetal. Finally, residual TMSOTf catalyzes Mukaiyama aldol addition of the bis-silyl ketene acetal to the aldehyde. In our hands, partial desilylation of the initial aldol product occurs either in situ or during a brief filtration through a pad of silica, resulting in a mixture of monosilylated, bis-silylated, and fully desilylated species. Subsequent treatment with trifluoroacetic acid (TFA) in 95% ethanol provides the final β -hydroxy carboxylic acid product. Control experiments confirm that TMSOTf is required for desired product formation; neither TMSOAc nor acetic acid provides aldol adducts in the absence of trimethylsilyl trifluoromethanesulfonate.

A brief survey of the reaction conditions verified that our standard one-pot Mukaiyama aldol procedure^{4a} was optimal for this one-pot, three-step process. Of the amines tested, *i*-Pr₂NEt performed more consistently than Et₃N and 2,6-lutidine when acetic acid was used as the enolate precursor. Toluene, THF, Et₂O, and acetonitrile were all notably inferior solvents compared to CH₂Cl₂. When TMSOTf was replaced with TESOTf, reactivity slowed considerably, affording less than 50% conversion after 24 h. Desilylation with 95% EtOH⁷ and TFA proved optimal, rendering aqueous workup unnecessary after removal of the solvent in vacuo. Attempts to isolate the products via acid–base extraction generally provided poor or irreproducible yields, but the products were easily purified by flash chromatography.

(7) Although methanol was also an effective solvent for the desilylation reaction, competing formation of the methyl ester via Fischer esterification was observed.

TABLE 1. Aldol Addition of Acetic Acid to Various Aldehydes

entry	RCHO	conditions ^a	product	yield (%) ^b
1		X = H, A	1	99
2		X = Me, A	2	87
3		X = OMe, B	3	80
4		X = F, A	4	91
5		X = O, A	5	80
6		X = S, A	6	66
7		A	7	79
8		A	8	94
9		X = H, B	9	45
10		X = Me, A	10	71

^aConditions A: 1.0 mmol acetic acid, 2.5 mmol *i*-Pr₂NEt, 1.4 mmol RCHO, 2.2 mmol TMSOTf, 5.0 mL CH₂Cl₂, rt. Conditions B: 1.0 mmol acetic acid, 2.8 mmol *i*-Pr₂NEt, 1.4 mmol RCHO, 2.5 mmol TMSOTf, 5.0 mL CH₂Cl₂, rt. ^bIsolated yield after chromatography.

We tested the scope of the reaction by adding acetic acid to a variety of nonenolizable aldehydes (Table 1). Benzaldehyde derivatives were outstanding electrophiles, including both electron-rich and electron-poor acceptors (entries 1–4). One exception was *p*-nitrobenzaldehyde, which generally reacted with < 50% conversion.⁸ Heteroaromatic substrates (entries 5 and 6) and naphthyl substrates (entries 7 and 8) also provided good yields of the carboxylic acid aldol products. Cinnamaldehyde was a surprisingly poor substrate under our one-pot conditions (entry 9), but α -methylcinnamaldehyde reacted efficiently to yield the synthetically useful allylic alcohol (entry 10). Subjection of enolizable aldehydes to these conditions did not provide the desired products, presumably because of competing aldehyde–aldehyde condensation and polymerization reactions. Nonetheless, the success of this reaction is remarkable, as illustrated by the fact that only two of the adducts in Table 1 (entries 1^{3a} and 3^{3b}) have been characterized in the literature prior to this report.

We also tested the efficacy of carboxylate salts in this one-pot reaction. Sodium acetate was unreactive and appeared to be insoluble in the solvents tested under our reaction conditions.⁹ In contrast, tetrabutylammonium acetate dissolved rapidly and added to benzaldehyde to provide the aldol adduct in 78% yield (eq 7). In addition to providing a useful alternative to acetic acid, the results of the tetrabutylammonium acetate experiment are in accord with our proposed mechanism. Because deprotonation of the acetic acid

(8) We speculate that the nitro group may interact unfavorably with the TMSOTf catalyst, although addition of 1.4 equiv of nitrobenzene to the standard reaction with benzaldehyde does not affect conversion for that substrate. Note that the other electron-poor aromatic aldehyde tested, 4-fluorobenzaldehyde, reacts in high yield.

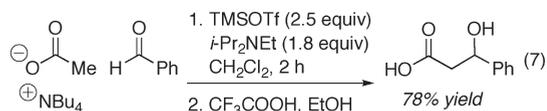
(9) Addition of tetrabutylammonium salts as phase transfer catalysts had no effect upon reaction conversion.

TABLE 2. Aldol Addition of TMSOAc to Various Aldehydes

entry	RCHO	conditions ^a	product	yield (%) ^b
1		X = H C	1	93
2		X = Me C	2	86
3		X = OMe D	3	85
4		X = F C	4	90
5		X = NO ₂ D	11	56
6		X = O C	5	78
7		X = S C	6	89
8		D	7	77
9		C	8	87
10		X = H D	9	54
11		X = Me C	10	71

^aConditions C: 1.0 mmol TMSOAc, 1.5 mmol *i*-Pr₂NEt, 1.4 mmol RCHO, 1.2 mmol TMSOTf, 5.0 mL CH₂Cl₂, rt. Conditions D: 1.0 mmol TMSOAc, 1.8 mmol *i*-Pr₂NEt, 1.4 mmol RCHO, 1.5 mmol TMSOTf, 5.0 mL CH₂Cl₂, rt. ^bIsolated yield after chromatography.

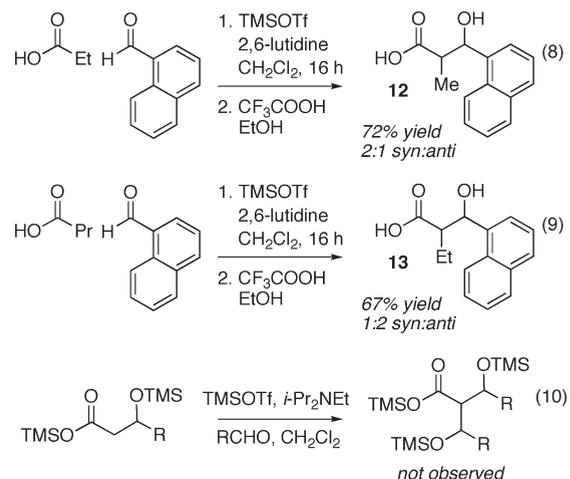
is unnecessary for this variant, less than 2 equiv *i*-Pr₂NEt was necessary to achieve full conversion, in contrast with our results with acetic acid itself.



Readily available and inexpensive, acetic acid is an ideal building block for organic synthesis. Its trimethylsilyl ester, TMSOAc, is also readily available, inexpensive, and reactive under our conditions. This silyl ester is particularly attractive as a reaction partner because it requires fewer equivalents of TMSOTf and *i*-Pr₂NEt to be converted into the reactive bis-silyl ketene acetal intermediate. Accordingly, we surveyed the ability of TMSOAc to add to various aldehydes (Table 2). These results closely parallel the results for acetic acid illustrated in Table 1. Notably, however, the yield for cinnamaldehyde improved (entry 10), and even *p*-nitrobenzaldehyde reacted in moderate yield under these conditions (entry 5).

Finally, we turned to carboxylic acids other than acetic acid. Phenylacetic acid did not provide aldol products under our conditions, although bis-silyl ketene acetal formation was detectable by ¹H NMR spectroscopy. Presumably, the phenyl group reduces the nucleophilicity of the π bond both sterically and electronically. Similarly, the sterically hindered isobutyric acid was also unreactive. Initial experiments with propionic acid were promising but sluggish, providing about 50% conversion overnight. We speculated that the size of the nascent silyl propionate made it kinetically difficult to activate with TMSOTf and/or deprotonate with *i*-Pr₂NEt. When *i*-Pr₂NEt was replaced with the less sterically demanding 2,6-lutidine, however,

propionic acid added to 1-naphthaldehyde in 72% yield after 24 h (eq 8). Butyric acid behaved similarly under the same conditions (67% yield, 24 h, eq 9).^{10,11} Although it is clear that steric effects slow the reaction rate of this one-pot silylation–Mukaiyama aldol process, they may also provide a benefit by preventing the desired products from undergoing a second aldol addition (eq 10), which could be a competing pathway under our conditions.



In summary, this one-pot, three-step reaction allows acetic acid to be used directly as an enolate precursor in aldol reactions, providing versatile carboxylic acid products. Commercially available TMSOAc is a convenient and inexpensive surrogate. We anticipate the application of this strategy to other classical enolate reactions, including the development of asymmetric variants.

Experimental Section

Typical Procedure for the Addition of Acetic Acid to Aldehydes. Synthesis of Product 1.^{3a} To an oven-dried 10-mL round-bottomed flask under N₂ were added CH₂Cl₂ (5.0 mL), acetic acid (57 μ L, 60 mg, 0.996 mmol), *i*-Pr₂NEt (435 μ L, 323 mg, 2.50 mmol), benzaldehyde (142 μ L, 148 mg, 1.40 mmol), and TMSOTf (400 μ L, 491 mg, 2.21 mmol). The reaction was stirred at room temperature, and the colorless solution became pale yellow. After 2 h, the reaction mixture was added to a 25-mL round-bottomed flask with 10 mL of EtOH (95%) and 5–10 drops trifluoroacetic acid. The reaction mixture was concentrated by rotary evaporation. Flash chromatography (10–50% EtOAc/hex) afforded the pure product as a white solid (99%): mp 89–90 °C; IR (film) 3283, 2914, 2648, 1687, 1448, 1394, 1269, 1052, 1014, 883, 764, 710 cm⁻¹; ¹H NMR (500 MHz, acetone) δ 7.47–7.43 (m, 2H), 7.38–7.31 (m, 2H), 7.29–7.24 (m, 1H), 5.17 (dd, *J* = 5.4, 8.1 Hz, 1H), 2.74 (dd, *J* = 8.0, 15.5 Hz, 1H), 2.70 (dd, *J* = 5.3, 15.5 Hz, 1H); ¹³C NMR (125 MHz, acetone) δ 172.4, 144.4, 128.2, 127.2, 125.8, 70.1, 43.8; HRMS (ESI) exact mass calcd for C₉H₁₀O₃Na [M + Na]⁺ 189.0522, found 189.0517.

(10) The major diastereomer of product **12** is *syn*, as proven by conversion to the methyl ester (MeOH, TFA) and comparison to the known ¹H NMR spectrum. Configuration of the major diastereomer of compound **13** is assigned as *anti*, by analogy to the ¹H NMR spectra for the stereoisomers of compound **12**.

(11) Because of the symmetry of the bis-silyl ketene acetal derived from a carboxylic acid under these conditions, enolization can only produce a compound of *Z* geometry.

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Supporting Information Available: Experimental procedures, compound characterization data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.