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First General Method for Direct Formylation of Kinetically-Generated Ketone Enolates†

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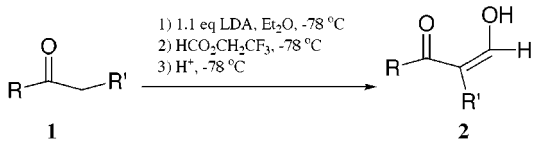
ABSTRACT



1 **2**

2,2,2-Trifluoroethyl formate reacts rapidly at −78 °C with preformed ketone enolates to give α-formyl ketones in good yields. In addition, this procedure allows for complete reversal of the regioselectivity of the classical Claisen reaction and provides a superior method for the α′-formylation of α,β-unsaturated ketones.

α-Formyl ketones (hydroxymethylene ketones) are critically important and versatile synthetic intermediates.[1] Nonetheless, the method introduced by Ludwig Claisen in 1888 (i.e., base-induced condensation of a ketone and a formate ester) remains the only general method for their preparation.[2] The classic Claisen formylation reaction is always run under equilibrating conditions and succeeds, ultimately, only because the resonance-stabilized salt of the α-formyl ketone product forms. The fact that success has always been contingent on such thermodynamic control imposes several serious limitations on the scope of the reaction including the inability to use strong base (e.g., LDA) to stereoselectively preform desired enolates of unsymmetrical ketones, poor yields when deprotonation at a site other than an α-positon gives a more stablized anion (e.g., γ-deprotonation of an α,β-unsaturated ketone), and complete failure in the formylation of tertiary α-carbons where the requisite salts cannot form. α-Formylation under conditions of kinetic control would overcome each of these limitations but has been heretofore impracticable due in large part to the poor reactivity between ketone enolates and typical formate esters (e.g., ethyl formate). To date, formylation remains the only condensation which has not yet been successfully applied to kinetically-generated ketone enolates.[3]

We present herein the first general method for achieving kinetic formylation of ketones, the success of which does not depend on formation of a salt. The key is use of a very reactive formate ester. 2,2,2-Trifluoroethyl formate (TFEF) is a known,[4] stable compound which can be easily prepared in about 67% yield from 2,2,2-trifluoroethanol and formic acid, commercially available and inexpensive precursors.[5] We have found that TFEF reacts rapidly at −78 °C with preformed ketone enolates to give α-formyl ketones in good yields.[6] The enolates can be generated either directly from

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(1) (a) As precursors to α-diazo ketones, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; pp 11−14 and references therein. (b) As precursors to enol thioethers, enamino ketones, enol ethers, α-formyl-α,β-unsaturated ketones, α-methylene ketones, and hydroxymethyl ketones, see: Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 837−838 and references therein.

(2) For reviews, see: (a) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59−196. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; Chapter 11.

(3) Successful condensations include esterifications (Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428), acylations (Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339−1340), and trifluoroacetylations (Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1995**, *73*, 134−143).

(4) Blackburn, G. M.; Dodds, H. L. H. *J. Chem. Soc. B* **1971**, 826−831.

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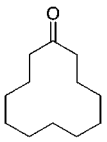
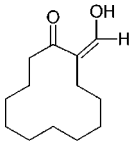
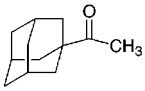
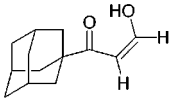
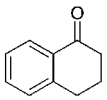
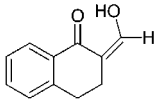
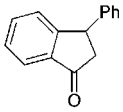
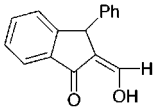
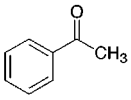
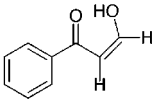
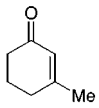
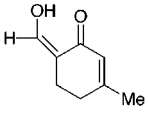
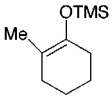
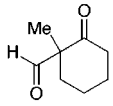
the ketones using LDA or indirectly from silyl enol ethers using methyllithium.

All major types of ketones have been examined (Table 1); the reaction is quite general.[7] The yields given in the table are of pure products obtained after appropriate purification—either extraction into dilute aqueous base (entries 1−6) or silica gel chromatography (entry 7).[8]

Table 1. α-Formylation of Kinetically-Generated Ketone Enolates with 2,2,2-Trifluoroethyl Formate.

Entry	Starting Ketone **1**	Product **2**	Isolated Yield (%)
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	75
3	 **1c**	 **2c**	79
4	 **1d**	 **2d**	82
5	 **1e**	 **2e**	51[a]
6	 **1f**	 **2f**	83
7	 **1g**	 **2g**	60[b]

[a] **2e** rapidly trimerizes to give 1,3,5-tribenzoylbenzene and is isolated in comparable yields of 40−50% using classical methodology. [b] Yield also includes $LiAlH_4$ reduction of the crude as the resultant diols were more easily purified.

Typically, a 6-fold excess of TFEF was employed to achieve high conversions, although this is probably more than necessary.

To put the reactivity of TFEF into a useful perspective, we note that while cyclododecanone (**1a**) was formylated in 75% yield using the new method, essentially no reaction occurred (<4%) when either ethyl formate or 4-nitrophenyl formate was used as the electrophile under otherwise identical conditions. When hexafluoroisopropyl formate was used in place of TFEF, a complicated mixture resulted, but the desired **2a** was not among the many compounds formed.

The α-formyl ketone products in entries 1−6 are acidic enough (pK_a ~10) to protonate starting enolate essentially irreversibly under the kinetic conditions employed. However, an excess of base is not required. To account for this, we believe that the rate of formation of the initial tetrahedral intermediates is faster than the rate of their subsequent collapse; as a result, the acidic proton of a product is not revealed until all (or most) of the enolate has already been consumed.

The α′-formylation of α,β-unsaturated ketones using classical Claisen methodology is generally a difficult, low-yielding affair. Few examples are documented, and even fewer are satisfactory.[2a] Thermodynamically favored γ-deprotonation probably confuses the issue. However, because the α′-carbon is the kinetically-favored site of deprotonation,[9] our methodology using kinetically-generated enolates provides an attractive solution to this problem. Thus, formylation of 3-methyl-2-cyclohexen-1-one (entry 6) gave α-formyl ketone **2f** in 83% isolated yield, whereas the classical method gave this product in only about 35% yield.[7f]

Using our method, it is possible to completely reverse the regioselectivity of the classical Claisen and attach a formyl

(5) The procedure is a modification of that given in ref 4. 2,2,2-Trifluoroethanol (Aldrich, 99.5%, 101 g, 1.01 mol) and formic acid (Aldrich, 96%, 186 g, 4.04 mol) were reluxed under N_2 for 24 h in a 500-mL, round-bottomed flask equipped with an Allihn condenser and stir bar. The mixture was cooled to room temperature and the condenser replaced with a 24-cm Vigreux column and distillation head. A colorless distillate (120 g, bp 55−61 °C) was collected. This was redistilled twice from P_2O_5 to remove starting materials giving TFEF (86.6 g, 67%), pure by ^{1}H NMR: bp 60 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.11 (s, 1H, HC═O), 4.56 (q, J = 8.4 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.0 (C═O), 122.9 (q, J = 277.0 Hz, CF_3), 59.6 (q, J = 37.1 Hz, CH_2).

(6) **Representative Experimental Procedure:** Synthesis of hydroxymethylenemethyl 1-adamantyl ketone (**2b**). A solution of *n*-BuLi in hexanes (3.88 mL, 1.60 M, 6.21 mmol) was cooled to −40 °C in a 100-mL, three-necked, round-bottomed flask equipped with a stir bar, N_2 inlet, and septum. Ether (7.3 mL) was added followed by the dropwise addition of diisopropylamine (0.870 mL, 6.21 mmol). After 15 min, the solution was cooled to −78 °C. A solution of **1b** (Aldrich, 99%, 1.00 g, 5.62 mmol) in ether (6 mL) was added dropwise over ca. 4 min. The solution was stirred at −78 °C for an additional 45 min. Neat TFEF (3.22 mL, 33.7 mmol) was added rapidly (ca. 2 s), and the mixture was stirred at −78 °C for 2 h. Neat H_2SO_4 (1.10 g, 11.2 mmol) was added at −78 °C in 1 portion. The mixture was transferred to a separatory funnel with ether (20 mL) and water (20 mL). The layers were separated, and the aqueous phase was extracted with ether (1 × 20 mL). The combined organic extract was washed with saturated aqueous NH_4Cl (1 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil was dissolved in ether (50 mL) and extracted with 1% aqueous NaOH (6 × 10 mL). The yellow extract was kept cold in an ice/water bath. The cooled extract was acidifed to pH = 1 by dropwise addition of 10% hydrochloric acid and then extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo to furnish **2b** as a yellow, sweet-smelling oil (871 mg, 75%), a mixture of enol (93%) and keto (7%) isomers by ^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$, TMS, enol) δ 15.02 (bs, 1H, C═COH), 8.13 (d, J = 4.4 Hz, 1H, C═CH−OH), 5.63 (d, J = 4.4 Hz, 1H, HC═COH), 2.05 (m, 3H, CH), 1.83−1.68 (m, 12H, CH_2); ^{1}H NMR (keto) δ 9.77 (t, J = 2.8 Hz, 1H, HC═O), 3.56 (d, J = 2.8 Hz, 2H, CH_2—CH═O), highfield absorptions same as for enol; ^{13}C NMR (100.6 MHz, $CDCl_3$, enol) δ 203.9 (C═O), 178.5 (CH═COH), 97.6 (CH═COH), 42.0, 38.8, 36.6, 28.1.

(7) All products are known compounds. (a) **2a**: Wilson, S. R.; Misra, R. N.; Georgiadis, G. M. *J. Org. Chem.* **1980**, *45*, 2460−2468. (b) **2b**: Fisnerova, L.; Nemecek, O.; Musil, V. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2681−2689. (c) **2c**: Bansal, R. C.; Browne, C. E.; Eisenbraun, E. J. *J. Org. Chem.* **1988**, *53*, 452−455. (d) **2d**: Johnson, W. S.; Shelberg, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 1745−1754. (e) **2e**: Pasteur, A.; Rivière, H.; Tchoubar, B. *Bull. Soc. Chim. Fr.* **1965**, 2328−2332. (f) **2f**: Labidalle, S.; Jean, E.; Moskowitz, H.; Miocque, M. *Tetrahedron Lett.* **1981**, *22*, 2869−2870. Boyer, F.; Décombe, J. *Bull. Soc. Chim. Fr.* **1967**, 281−285. (g) **2g**: Tsuboi, S.; Ono, T.; Takeda, A. *Heterocycles* **1986**, *24*, 2007−2014.

(8) α-Formyl ketones are sensitive materials (many extremely so). Careful handling, particularly in the workup and purification is essential.

(9) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 3rd ed.; Plenum: New York, 1990; p 7.

moiety to the more highly substituted α-carbon of an unsymmetrical ketone. The formylation of 2-methylcyclohexanone under thermodynamic conditions (e.g., NaOMe and ethyl formate) is an oft-cited example used to illustrate the strict regioselectivity of the classical Claisen: 2-formyl-6-methylcyclohexanone forms exclusively.[10] We have found that the regioisomeric product **2g** was obtained instead by treating **1g** with MeLi and reacting the resultant enolate with TFEF under conditions of kinetic control (entry 7). **2g**, unlike 2-formyl-6-methylcyclohexanone, cannot form a resonance-stabilized salt and thus violates the essential criterion of the thermodynamic reaction.

We have examined variations in base and solvent and found, in general, that the yields of α-formyl ketones increased and the reaction became cleaner as the enolates were made less "naked". Thus, enolates with a Li^+ counterion (formed by LDA) were superior to ones with a less tightly associated K^+ cation (generated with potassium bis(trimethylsilyl)amide). Further, the poorly-coordinating solvent diethyl ether was significantly better than THF which was better, in turn, than DME. And finally, virtually none of the desired α-formyl ketones were formed when the polar additive HMPA was added to the reaction mixture.

2,2,2-Trifluoroethyl esters merit investigation in other areas of condensation chemistry. For example, the reaction of TFEF and anions derived from substrates other than ketones (e.g., esters, acids, imines, nitriles, β-dicarbonyls) should be examined. In addition, 2,2,2-trifluoroethyl alkanoates, less toxic alternatives to acyl cyanides, might hold promise as reagents for the acylation of kinetically-generated enolates.

Acknowledgment. I gratefully acknowledge the receipt of a GAAN fellowship and intellectual and financial support from my Ph.D. advisor, Professor Philip E. Eaton. This work was funded by the U.S. Army Research Office (ASSERT program).

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(10) Boatman, S.; Harris, T. M.; Hauser, C. R. *Org. Synth.* **1968**, *48*, 40−44.