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Facile Synthesis of Trifluoromethyl Carbinols and Trifluoromethyl-α,β-Unsaturated Ketones From the New CF_3CHO Synthetic Equivalent, 1,1-Bis(dimethylamino)-2,2,2-trifluoroethane

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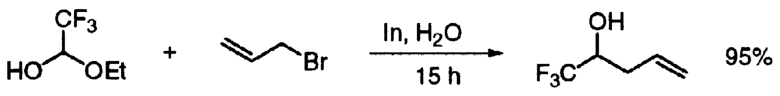
Abstract

1,1-Bis(dimethylamino)-2,2,2-trifluoroethane is an excellent synthetic building-block replacement for trifluoroacetaldehyde in condensation reactions with ketones using 36% aqueous HCl catalysis. Moderate to good yields (43-68%) of trifluoromethyl carbinols are obtained with symmetric and unsymmetric methyl ketones, with the latter undergoing reaction mainly at the methyl group. Its reactions with silyl enol ethers under anhydrous conditions, catalyzed by ZnI_2, lead directly to trifluoromethyl- α,β-unsaturated ketones.

Trifluoromethylated compounds continue to be of great industrial interest [1], and therefore the development of new methods to incorporate trifluoromethyl groups into organic compounds remains an important area of research [2]. Trifluoroacetaldehyde has always been recognized as a potentially very useful precursor to trifluoromethyl carbinols [3-5]. However, because of its volatility, high reactivity and commercial unavailability, trifluoroacetaldehyde almost never is used directly, but rather is usually generated *in situ* from its hydrate, hemiacetal, or acetal-type precursors, sometimes using Lewis acid catalysis [6-13]. Use of such methodology to generate a reactive electrophilic equivalent of CF_3CHO inevitably creates limitations with regard to the scope and effectiveness of its synthetic utility. One particularly useful recent application is shown below [7].



None of the previously reported CF_3CHO-equivalent methodologies has proved particularly useful for C-C direct bond-forming condensation reactions with ketones, an early report by Westheimer being typical [6].

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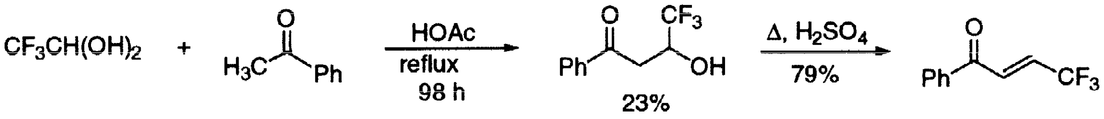
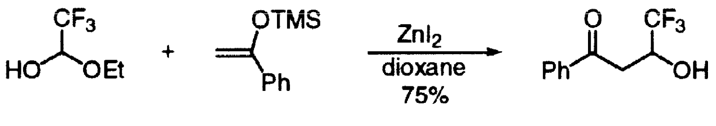


Kubota has recently reported the use of silyl enol ethers to accomplish this overall conversion, although the reaction seem limited in utility with respect to aliphatic ketones [8].



We report at this time that 1,1-bis(dimethylamino)-2,2,2-trifluoroethane [14], when treated with 30% aqueous HCl, acts as an effective *in situ* source of CF_3CHO in direct condensation reactions with ketones, yielding trifluoromethyl carbinols in moderate to good yield.

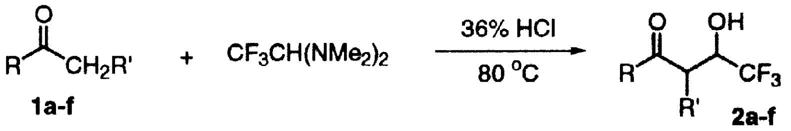


Table. Reactions of 1,1-bis(dimethylamino)-1,1,1-trifluoroethane with ketones

Ketone	*Conditions*	*Major Product*	*Isomer Ratio*	*Yield (%)*[a]
Acetone, **1a**	reflux, 11 h[b]	**2a**: R = CH_3, R' = H	-	68
Acetophenone, **1b**	EtOH, reflux, 14 h	**2b**: R = Ph, R' = H	-	46
3-pentanone, **1c**	85 °C, 30 h[b]	**2c**: R = C_2H_5, R' = CH_3	10 : 7[c]	43
Cyclohexanone, **1d**	80 °C, 18 h[b]	**2d**: R, R' = $(CH_2)_4$	2.5 : 1[c]	51
2-pentanone, **1e**	90 °C, 22 h[b]	**2e**: R = C_2H_5, R' = H	100 : (4 : 3)[c]	63
2-butanone, **1f**	90 °C, 22 h[b]	**2f**: R = C_3H_7, R' = H	4 : (1 : 1)[c]	56

[a] yields isolated by distillation; [b] no solvent; [c] mixture of diastereomers

In a typical procedure, 0.85 g of $CF_3CH(NMe_2)_2$, 2.0 g of cyclohexanone, and 0.5 mL of 36% HCl were heated at 80 °C. After 18 hours, the reaction was cooled, 20 mL of CH_2Cl_2 added, and the mixture washed with H_2O, dried and distilled (50-53 °C at 0.03 mm Hg) to give 0.50 g (51%) of a 2.5:1 mixture of diastereomers, **1d**.[1,2]

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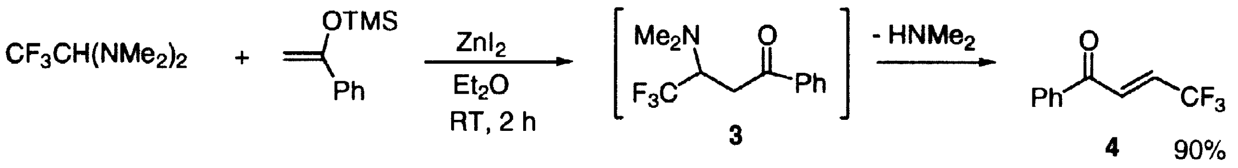
[1] Products **2a-e** were fully characterized by a combination of ^{1}H, ^{19}F, and ^{13}C NMR, and IR spectra, HRMS, and elemental analysis data.

In attempts to define the most advantageous conditions, optimization experiments were carried out using acetone as the substrate. The reaction was found to proceed quite cleanly, but much more slowly, without acid (63% product from **1a** after refluxing in H_2O for 35 hours). However, using no water, even with ZnI_2, $SnCl_4$, or $BF_3 \cdot Et_2O$ as catalysts, gave only complex mixtures of products. Using a larger excess of 36% HCl led to shorter reaction times, but at some sacrifice of yield.

Cyclohexanone and 3-pentanone gave a mixture of diastereomeric products, with little selectivity being exhibited, whereas unsymmetrical ketones such as 2-butanone and 2-pentanone, reacted with significant regioselectivity, with a preference for reaction at the methyl rather than the methylene site. In the case of 2-pentanone, a 14:1 preference for formation of 1,1,1-trifluoro-2-hydroxy-4-heptanone, **2e** was observed.[1,2]

Reactions with silyl enol ethers.

When one uses silyl enol ethers in the reaction with aminal **1**, under anhydrous conditions with ZnI_2 catalysis, the reaction proceeds directly to elimination products under the reaction conditions, presumably via an initial, amine-containing adduct, such as **3**, which can be detected in the crude product mixture. Complete conversion of **3** to **4** [6] occurs during silica gel flash chromatography.



When a silyl enol ether of an aliphatic ketone is used in the reaction, a more complex product mixture is formed, with multiple substitution dominating as shown below for cyclohexanone silyl enol ether. Such results are reminiscent of those obtained by Kubota in his condensations of silyl enol ethers with trifluoroacetaldehyde hemiacetals [8].

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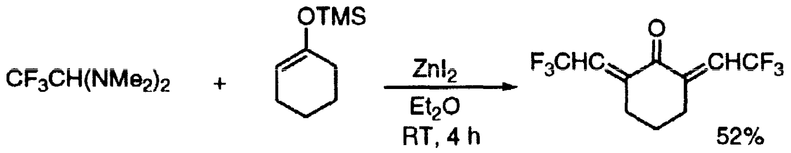
[2] Selective NMR spectra of products: **2a**: ^{1}H NMR δ2.23 (s,3H), 4.41-4.53 (m, 1H), 3.52-3.90 (bf, 1H), 2.70-2.92 (m, 2H). ^{19}FNMR δ -80.12 (d, J = 7.3 Hz). ^{13}C NMR δ 30.62, 42.82, 66.30 (q, (J = 32.2 Hz), 66.32 (q, J = 32.2 Hz), 124.64 (q, J = 280.5 Hz), 206.34. **2b**: ^{1}H NMR δ 3.25-3.48 (m, 2H), 3.80 (s, 1H), 4.72 (m, 1H), 7.50 (dd, J = 8.0, 7.1 Hz), 7.64 (dd, J = 7.4, 7.1 Hz), 7.97 (d, J = 7.4 Hz). ^{19}F NMR δ -79.76 (d, J = 7.3 Hz). ^{13}C NMR δ 38.26, 66.93 (q, J = 32.2 Hz), 124.79 (q, J = 280.5 Hz), 128.20, 128.85, 134.12, 135.97, 197.53). **2c**: ^{1}H NMR and ^{13}C NMR complex due to mixture of two diastereomers. ^{19}F NMR δ -77.22 (d, J = 7.3 Hz), -77.60 (d, J = 7.3 Hz) ratio, 7:10. **2d**: ^{1}H NMR and ^{13}C NMR complex due to mixture of two diastereomers. ^{19}F NMR δ - 76.21 (d, J = 7.4 Hz), -76.35 (d, J = 7.4 Hz) (ratio of signals, 1 : 2.5); **2e** (one major product): ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, 3H), 1.63 (sextet, J = 7.3, 2H), 2.46 (t, J = 7.3 Hz. 2H), 2.77 (m, 2H), 3.65-3.82 (m, 1H), 4.40-4.56 (m, 1H); ^{19}F NMR δ -80.07 (d, 7.3 Hz); ^{13}C NMR δ 13.47, 16.90, 41.79, 45.53, 66.61 (q, J = 32.2 Hz), 124.66 (q, J = 280.5 Hz). **2f**: ^{1}H NMR and ^{13}C NMR complex due to mixture of three isomers. ^{19}F NMR δ -77.21 (d, J = 7.3 Hz), -77.25 (d, J = 7.3 Hz), -80.11 (d, J = 7.3 Hz) ratio, 1:1:4.



In a typical procedure, 0.34 g (2.0 mmol) of $CF_3CH(NMe_2)_2$, 0.38 g (2.0 mmol) of the trimethylsilyl enol ether of acetophenone, 0.64 g of ZnI_2 and 5 mL of Et_2O were stirred at RT for two hours, after which time starting materials were gone and two new signals deriving from products **3** and **4** were observed in the ^{19}F NMR at - 70.5 and - 65.5 ppm, respectively. Addition of 20 mL of Et_2O, washing with water, drying over $MgSO_4$, evaporation followed by flash chromatography [silica gel, (10:1) hexane:ethyl acetate] led to isolation of 0.36 g (90%) of **4**.

In conclusion, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane **1** has been found to be a good trifluoroacetaldehyde synthetic equivalent, perhaps the best one for use in direct acid catalyzed condensation reactions with ketones to form β-keto trifluoromethylcarbinols of the general structure, $RCOCHR'CHOHCF_3$. Silyl enol ethers are found to undergo a ZnI_2-catalyzed condensation with **1** to form α,β-unsaturated products of the general structure, $CF_3CH{=}CR'COR$.

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