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Microwave-assisted preparation of trifluoroacetaldehyde (fluoral): isolation and applications

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Abstract—A novel method for the preparation of trifluoroacetaldehyde (fluoral, TFAc, CF_3CHO) from commercially available trifluoroacetaldehyde ethylhemiacetal (TFAE) by microwave irradiation is described. The isolation, characterization and reaction of fluoral with various nucleophiles were studied to verify the diverse applicability of this new method.

1. Introduction

The synthesis of organofluorine compounds has attracted extensive attention over the years.[1,2] Their unique properties make them invaluable in life and material sciences. Their importance is especially observable in the pharmaceutical sector, approximately 20% of all drugs contain at least one fluorine atom. Indeed, three of the current top 10 best sellers are organofluorine products.[3] The synthesis of these compounds, however, often raises unexpected difficulties.[4]

Trifluoroacetaldehyde (TFAc, fluoral) is one of the most important synthons from which compounds containing trifluoromethyl group can be prepared.[5] TFAc is also frequently utilized in asymmetric synthesis of trifluoromethylated compounds.[6] Synthetic methodologies using TFAc have considerable limitations[2a] due to its troublesome handling, harsh preparation conditions, and low boiling point (−18.8 °C to −17.5 °C).[7] Trifluoroacetaldehyde ethylhemiacetal (TFAE) is often used as a precursor for TFAc, though, only in limited applications.[8]

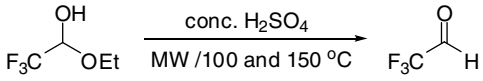
Over the years, several methods were reported for the preparation of TFAc from TFAE: (i) H_3PO_4/polyphosphoric acid (PPA);[9] (ii) P_2O_5;[10] (iii) H_2SO_4.[11] Other approaches involved the reduction of trifluoroacetic acid or its esters;[12] fluorination of trichloroacetaldehyde;[13] oxidation of trifluoroethanol;[14] oxidative nitration of trifluoropropane;[15] and reduction of trifluoroacetyl chloride.[16] Most of these methods required high temperatures (~400–450 °C)[17] and were carried out in the vapor phase. Considering the synthetic importance of TFAc, developing a low temperature, rapid, and easy to handle method is highly desirable.

A new synthetic tool, microwave-assisted organic synthesis,[18] appears to be a useful synthetic method to reach the above goal.

Continuing our efforts in the field of microwave-assisted reactions[19] and organofluorine chemistry,[20] herein, we report an effective and convenient method for the preparation of TFAc using microwave irradiation. The efficiency of the TFAc generation is also demonstrated in several reactions.

2. Results and discussion

Preparation of fluoral (TFAc) from trifluoroacetaldehyde ethylhemiacetal (Scheme 1) was carried out in a simple apparatus illustrated in Figure 1. TFAE was mixed with concd H_2SO_4, then the reaction vessel was placed into the microwave reactor and irradiated at



Scheme 1. Synthesis of trifluoroacetaldehyde from its ethyl hemiacetal.

Keywords: Trifluoroacetaldehyde; Fluoral; Microwave irradiation; Trifluoromethylated alcohols.
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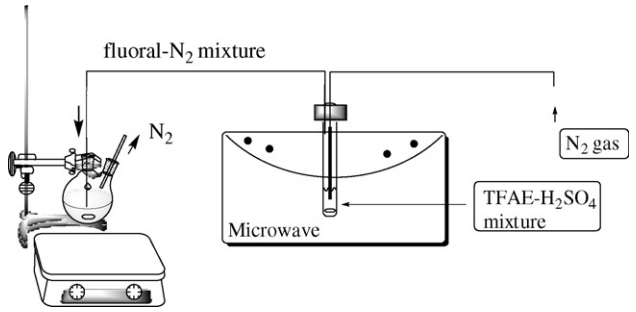
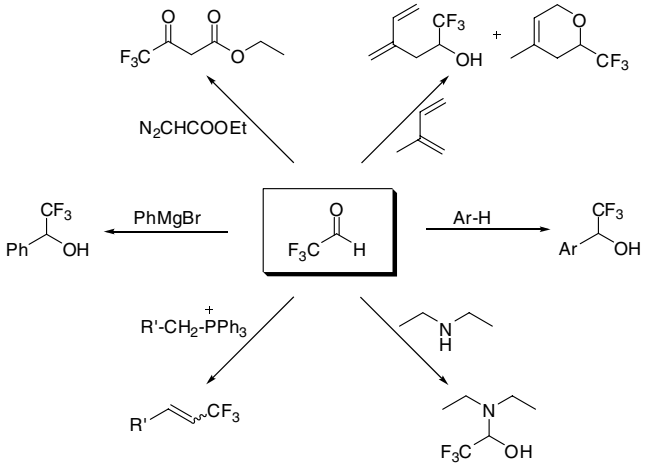


Figure 1. Schematic representation of the apparatus used for the preparation of TFAc and its immediate reaction with nucleophiles.

100 °C and 150 °C for 5 min each to produce the gaseous TFAc. To ensure that all TFAc produced was transferred to another vessel for isolation or further reaction, dry N_2 gas was continuously passed through the system.

The inert atmosphere protected TFAc from moisture and hydrate formation. TFAc was condensed and isolated at −78 °C. It was characterized as CF_3CHO by NMR spectroscopy. Both ^1H and ^{19}F NMR spectra indicated the presence of the underivatized trifluoroacetaldehyde. The expected quartet was observed for the formyl H, while a doublet appeared for the CF_3 in the ^{19}F NMR spectrum (see Section 4). Our method made possible the exact determination of the NMR data of unprotected TFAc that hitherto was known only from mixtures.[21]

We also intended to verify our TFAc preparation method via chemical reactions. The TFAc/N_2 gas mixture obtained during the irradiation was directly passed into the adjacent reaction vessel containing a nucleophilic substrate (Fig. 1). Several nucleophilic substrates were chosen for these reactions (Scheme 2). The Friedel–Crafts hydroxyalkylation of pyrrole was selected as a test reaction. First, we studied the effect of the temperature on the formation of TFAc from TFAE. The results are summarized in Table 1.



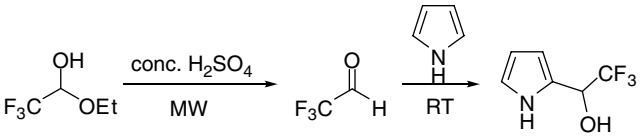
Scheme 2. Reaction of trifluoroacetaldehyde with various nucleophiles.

The data indicated that gradual increase in temperature provided the best yield. Using this temperature program, we studied the effect of pyrrole/TFAE (used for TFAc generation) ratios on the probe reaction (Table 2). The results showed that 1:2 ratio provided the best performance, although, the 1:1, 1:3 and 1:4 ratios also gave very similar yields. As a result, this ratio was chosen for further reactions. It is worth noting that the 92% yield obtained at 1:1 ratio indicates that the yield of TFAc generation is close to quantitative.

After optimization of the experimental conditions for the TFAc generation, we tested our method by carrying out reactions of TFAc with various nucleophiles. The above optimized conditions (gradual microwave heating, and 1:2 nucleophile–TFAE ratio) were applied. The results are summarized in Table 3.

Further reactions involved Friedel–Crafts hydroxyalkylation with activated heteroaromatics, couplings with Grignard reagent, Wittig phosphonium salts, ethyl diazoacetate, and hydroxyalkylation of anilines. The reactions provided excellent yields in most cases. In few cases the yields were only moderate due to significant side reactions. The conversion of the starting material, however, was always excellent indicating that the original attempt of producing free TFAc was successful.

Table 1. Effect of temperature on generation of TFAc probed by its reaction with pyrrole[a]



Entry	Temperature (°C)	Yield (%)[b]
1	70	23
2	100	68
3	130	70
4	150	83
5	70–100–130–150	94[c]

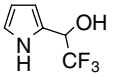
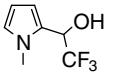
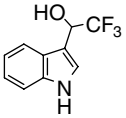
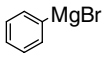
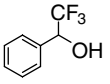
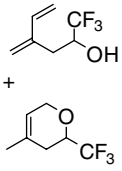
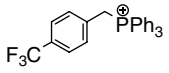
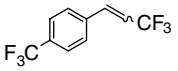
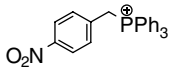
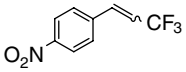
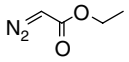
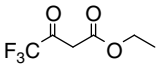
[a] TFAE (2.0 mmol), $H_2SO_4 = 2$ ml, $CH_2Cl_2 = 1$ ml, $t = 5$ min, MW power = 200 W; Reaction conditions: pyrrole (1.0 mmol), $CH_2Cl_2 = 1$ ml, rt.
[b] Based on pyrrole, GC yield.
[c] Gradual increase of temperature in 2 min increments.

Table 2. Effect of pyrrole–TFAE initial molar ratios on the yield of the hydroxyalkylation reaction of pyrrole[a]

Entry	Pyrrole–TFAE	Yield (%)[b]
1	1:1	92
2	1:2	94
3	1:3	92
4	1:4	91

[a] Reaction conditions: pyrrole (1.0 mmol), $H_2SO_4 =$ 2 ml, $CH_2Cl_2 =$ 1 ml, $T = 70$–100–130–150 °C, $t =$ 2 min each step, MW power = 200 W.
[b] Based on pyrrole, determined by GC–MS.

Table 3. Microwave-assisted generation of TFAc and its reaction with nucleophiles[a]

	Substrate	T (°C)(solvent)	Yield (%)[b]	Product
1		rt (CH_2Cl_2)	94	
2		rt (CH_2Cl_2)	98	
3		rt (CH_2Cl_2)	33	
4		rt (Ether)	51	
5		0 °C (CH_3NO_2) $ZnCl_2$	91[c] (56:35)	
6		rt (CH_2Cl_2)	35[d] (60:40)[e]	
7		rt (CH_2Cl_2)	55[d] (75:25)[e]	
8		rt (CH_2Cl_2)	15[f] (81% conv)[g]	
9		−10 °C (THF)	60[h]	

[a] TFAc generation: TFAE (2.0 mmol), H_2SO_4 = 2 ml, T = 70–100–130–150 °C (gradual), t = 2 min each, MW power = 200 W; Reaction conditions: substrate (1.0 mmol), solvent = 1 ml.
[b] GC yield.
[c] 56% Trifluoromethylated alcohol, 35% Diels–Alder adduct.
[d] NaH was added to the benzyltriphenylphosphonium salt and stirred for 1 h prior to reaction with TFAc.
[e] *E*:*Z* ratio.
[f] Determined by ^{19}F NMR and GC–MS.
[g] Mixtures of products are formed.
[h] Determined by ^{19}F NMR.

3. Conclusion

In conclusion, a novel microwave-assisted protocol is developed for the preparation of trifluoroacetaldehyde. The method produces TFAc efficiently and rapidly, while it is convenient, easy to handle and operate, and reproducible. The TFAc generated may be utilized for the preparation of a wide array of trifluoromethylated compounds.

4. General procedures

4.1. Preparation of trifluoroacetaldehyde (TFAc)—general procedure

The reactions were carried out in a focused CEM Discover Benchmate microwave reactor, using the open vessel technique. The temperature was measured and increased gradually using an infrared temperature detector/controller.

Trifluoroacetaldehyde ethylhemiacetal (TFAE) (2 mmol) and 2 ml of concd H_2SO_4 were added to a nitrogen flushed vial. The vial was sealed with a plastic septum and inserted into the microwave cavity, where it was continuously stirred during the irradiation. The vial was equipped with an inlet to pass nitrogen gas through and an outlet for TFAc/N_2 gas mixture (Fig. 1). The outlet was connected to an adjacent reaction vessel containing a nucleophile. The reaction vessel was equipped with a N_2 outlet to avoid pressure build-up. The TFAE/H_2SO_4 mixture was then heated gradually from 70–100–130–150 °C, (power 200 W) for 2 min each. The flowing N_2 carried the TFAc gas produced, directly into the adjacent reaction vessel.

The isolation of TFAc was carried out using 3 mmol TFAE and 2 ml of concd H_2SO_4. The mixture was irradiated at a specified temperature (90 and 150 °C) for 5 min each. The colorless gas produced was passed through drying agent and condensed directly into an NMR tube at −78 °C. The isolated TFAc was immediately mixed with $CDCl_3$, and sealed under N_2 flow.

NMR spectra were recorded without delay. ^1H NMR (300.126 MHz, $CDCl_3$), δ (ppm) 9.39 (q, $J_{H-F} = 3.0$ Hz, 1H, CH). ^{19}F NMR(282.401 MHz, $CFCl_3$), δ (ppm) −81.79 (d, $J_{F-H} = 3.1$ Hz, 3F, CF_3).

4.2. Reaction of nucleophiles with TFAc—general procedure

In a typical reaction, a nucleophile (1 mmol) and 1 ml of solvent were placed into a 10 ml round-bottomed flask equipped with a magnetic stirring bar. The TFAc gas produced was passed into the vessel and was further stirred for 15 min. All reactions were carried out under nitrogen flow. The progress of the reaction was monitored by GC–MS. When the reaction was completed, the product was dissolved in CH_2Cl_2 and passed through a short silica column. The crude products were purified by flash chromatography.

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