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Trifluoromethylcyclohexane as a new solvent? Limits of use

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This paper is dedicated to the memory of Professor Milos Hudlickú

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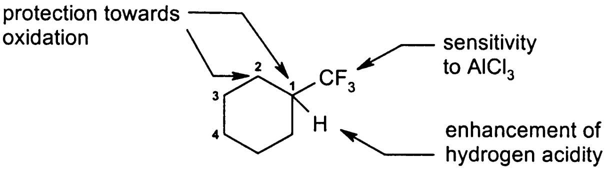
Abstract—Reactivity and stability of trifluoromethylcyclohexane (TFMC) has been investigated towards various reagents, in order to evaluate its possible use as solvent. TFMC is stable in most oxidizing conditions, indicating the protective effect of a fluoroalkyl substituent towards oxidation, and surprisingly, it is also very stable towards strong bases. TFMC has also been assessed as a chlorinated solvent substitute in some reactions. It is clearly adapted as a CCl_4 substitute in allylic bromination reaction. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Despite their disastrous implication in the depletion of the ozone layer, chlorinated solvents are still extensively used to perform common reactions in organic chemistry such as oxidation and halogenation. In view to replace them, fluorinated solvents could appear to be good substitutes, because of their excellent thermic and chemical stability.[1] However, due to the low solubility of most compounds in the fluorous phase, hybrid organic/fluorous solvents are possibly more convenient. In this line, trifluorotoluene has been proved to be a useful solvent.[2] Although it can undergo oxidation,[3] it is generally robust and suitable for various classical reactions. Trifluoromethylcyclohexane[4] (TFMC, bp: 106–107°C) (Scheme 1), which is now industrially developed,[5] could also appear as another good candidate. Herein we report some preliminary experiments performed in order to evaluate the potential use of TFMC as a solvent in organic synthesis. In a first step, we had to assess its chemical stability. Considering its structure, some evident limitations were expected (Scheme 1). First, like trifluorotoluene, TFMC can react with aluminium chloride ($AlCl_3$) by halogen exchange.[6] Second, the high electronwithdrawing character of the CF_3 is expected to enhance the acidity of the hydrogen at C-1,[1] thus favoring a deprotonation at this site under basic conditions. The resulting carbanion could undergo dehydrofluorination or trap an electrophile. At last, strong oxidative systems can allow the oxidation of the cyclohexyl carbons. However, a protection by the CF_3 substituent is expected.[7] In these experiments TFMC was used as substrate. In a second part, we have illustrated its use as replacement of chlorocarbon solvents in two typical organic reactions, oxidation of alcohol and allylic bromination.



Scheme 1. Trifluoromethylcyclohexane (TFMC): reactivity and expected effects of CF_3.

2. Results and discussion

2.1. Reactivity of trifluoromethylcyclohexane

As expected TFMC could react with $AlCl_3$. In an experiment performed with TFMC and $AlCl_3$ (in an equimolar amount) in benzene, GC/MS analysis showed a 95% conversion of the substrate into a mixture of chloro and fluoro compounds.

We then investigated the reaction of TFMC with bases. With aq. NaOH (2N) (2 equiv.) at reflux of benzene, no reaction occurred. By using *t*-BuOK or *n*-BuLi in Et_2O, from −78°C to room temperature, no dehydrofluorination product could be detected, and MeI, when added at −78°C, could not be trapped. With the stronger base, *t*-BuLi in presence of tetramethylethylenediamine (TMEDA), TFMC remained unchanged, even at reflux of pentane. In

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Keywords: hydrocarbon oxidation; selective functionnalization; trifluoromethyl compound; chlorinated solvent substitute.

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all experiments, TFMC was recovered quantitatively. Those experiments show the high stability of TFMC towards bases, higher than that of trifluorotoluene. This latter has been described to undergo lithiation[8] when reacting with *n*-BuLi, and electrophilic substitution reactions.[9] The use of TFMC in carbanionic chemistry, for instance as a substitute of hexanes, can thus be envisaged, and this study is now under investigation.

We next checked TFMC stability towards harsh oxidative systems. Oxidation of cyclohexane derivatives has been of importance during the last decades because of its considerable industrial applications[10] and some strong oxidative systems have been described to be efficient for non-activated carbon oxidation. First, we have investigated the oxidation of TFMC using [Ru] and [Rh] catalyzed processes,[11,12] in particular Carlsen's method involving the powerful oxidizing agent RuO_4.[13] This catalyst is generated in situ from $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ in a mixture of CCl_4/MeCN/H_2O and has been shown to oxidize methylcyclohexane and *t*-butylcyclohexane with, respectively, 100 and 73% conversion rates after a 3–7 h reflux, with no particular regioselectivity.[13] Under the same conditions, TFMC was recovered unchanged, even after two days.

Next, we evaluated the stability of TFMC under the H_2O_2/trifluoroacetic acid system[14] (Table 1, entry 1). Cyclohexane has been shown to be oxidized with 1.2 equiv. of aq. H_2O_2 30%, after 24 h at 25°C, with 82% conversion rate. A mixture of cyclohexyl trifluoroacetate derivatives were obtained as major products. Under the same conditions, oxidation of TFMC occurred in 1 h, but with a low conversion rate (around 10%), which could not be improved even after a longer reaction time, and with 3 equiv. of H_2O_2. The reaction afforded a mixture of regioisomers of trifluoromethylcyclohexyl trifluoroacetates and traces of trifluoromethylcyclohexanols. Saponification of the crude mixture with a NaOH solution followed by oxidation with pyridinium chlorochromate (PCC) afforded a 1:1 mixture of ketones at C-3 and C-4 as only products (5% isolated yield).

We also investigated the GoAgg^{V} oxidation system,[15] which is generally considered as a radical process[16] (Table 1, entry 2). In the presence of $FeNO_3 \cdot 9H_2O$/picolinic acid and *t*-butyl hydroperoxyde (TBHP) in pyridine/acetic acid (25°C, 16 h), *t*-butylcyclohexane is described to be converted with a 21% rate into ketones (67% at C-3 and 25% at C-4) and alcohols (5% at C-3 and 1% at C-4).[15] Traces of ketone at C-2 were also observed (1%). The parallel reaction performed with TFMC afforded, after 16 h, a mixture of ketones and alcohols with a 15% conversion rate. After oxidation with PCC, ketones at C-3 and C-4 were obtained in a 2:1 ratio (11% isolated yields).

These experiments with oxidizing systems show that the presence of the CF_3 highly modifies the reactivity of the substrate. With all systems, oxidation of TFMC was much more difficult than that of cyclohexane derivatives, and when the reaction occurred, oxidation took place only at C-3 and C-4. Regioselectivity can be attributed to electronic or steric effect of the CF_3 group. The electron-withdrawing character of CF_3 substituent entails a great difficulty in developing a positive charge in α and β.[17] Furthermore, CF_3 is a bulky substituent, its steric hindrance is close to that of an isopropyl group.[18] The mechanism of the H_2O_2/TFA couple system (involving the trifluoroperoxyacetic acid, generated in situ), can be considered as electrophilic, and it is likely that the absence of oxidation at C-1 and C-2 is due to an electronic effect of CF_3. This also explains that C-3/C-4 oxidation ratio is 1:1, thus in favor of the C-4 site. Electronic effect of CF_3 can also explain, to a certain extent, the lack of oxidation with [Ru] catalyst. However, the complete protection of C-3 and C-4 is very striking. Concerning the GoAgg^{V} system, no oxidation occurred at C-1 and C-2. Ketone ratio (C-3/C-4, 2:1) shows that oxidation occurred as statistically expected. These results are very similar to those described for *t*-butylcyclohexane. The influence of the CF_3 on regioselectivity in this system can thus be assumed to be of steric nature.

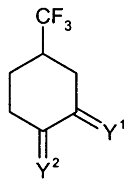
All these experiments show that TFMC exhibits a high stability, despite of a possible conversion in some extreme oxidative systems.

2.2. TFMC as substitute of chlorocarbon solvents

In order to evaluate the potential of TFMC as a solvent, we selected two representative reactions of organic chemistry involving dichloromethane or carbon tetrachloride. We first examined the classical oxidation reaction of alcohol into ketone with PCC. The reaction was performed with

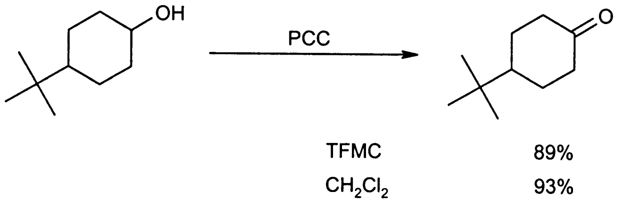
Table 1. Oxidation of TFMC with H_2O_2/TFA and GoAgg^{V} systems

1 $Y^1 = Y^2 = H_2$ (TFMC)
2 $Y^1 = O$; $Y^2 = H_2$
3 $Y^1 = H_2$; $Y^2 = O$



Entry	Oxidation system	Products[a]	Ketones[b]		Yield (%)[c]
			2	**3**	
1	H_2O_2/TFA	Trifluoroacetates and alcohols (traces)	1	1	5
2	GoAgg^{V}	Alcohols and ketones	2	1	11

[a] Products were identified by GC/MS analysis.
[b] Position of the carbonyl group was determined by ^{13}C NMR.
[c] Isolated yield.

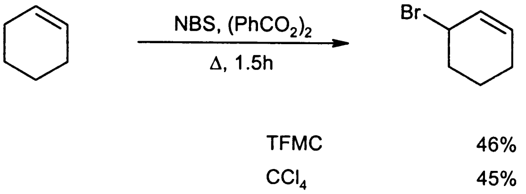


Scheme 2.

4-*t*-butylcyclohexanol as a substrate and 2 equiv. of PCC (Scheme 2).

The reaction occurred within 1 h in CH_2Cl_2 and within 3 days in TFMC at room temperature. Nevertheless, a total conversion could be obtained in 15 h in TFMC by heating the reaction mixture at 70°C. Yields were, respectively, 93 and 89% in CH_2Cl_2 and TFMC. Despite of this high yield, TFMC clearly shows less aptitude than CH_2Cl_2 for this reaction since a long reaction time is required. However, the ketone could be easily purified with a single filtration of the reaction mixture over a celite pad. Distillation of TFMC afforded pure 4-*t*-butylcyclohexanone. Conversely, when the reaction is performed in CH_2Cl_2, the addition of a large amount of another solvent (generally diethyl ether) is required in order to precipitate the resulting chromium salts, and the product is recovered with good purity only after a filtration over Florisil® or silica gel.[19a] Thus, it is worth noting that in TFMC, purification of the product is cheap and simple.

As a second example, we chose the allylic bromination reaction. The reaction was performed on cyclohexene with NBS and benzoyl peroxide using TFMC as solvent (at 70°C), instead of CCl_4 (reflux)[19b] (Scheme 3).



Scheme 3.

Results in both solvents are very similar. The reaction occurred within 1.5 h in each case and afforded 3-bromocyclohexene with, respectively, 46 and 45% in TFMC and in CCl_4. Purification of bromocyclohexene by fractionned distillation allowed the recovering of TFMC. In this reaction, TFMC could advantageously replace CCl_4.

3. Conclusion

Exploring experiments performed on TFMC, in order to check its stability, showed that this compound is quite unreactive under basic conditions, and exhibits only low reactivity towards harsh oxidative systems, with a maximum conversion of 15%. Results of oxidation experiments clearly show the protective effect of a fluoroalkyl substituent towards those reactions. Furthermore, two typical reactions (oxidation of alcohol with PCC, and allylic bromination) have been proved to be efficient when TFMC was used as solvent instead of chlorocarbons. These preliminary results, although insufficient to draw conclusions about the global scope of TFMC, are very encouraging for a possible replacement of these solvents. To evaluate in an appropriate way the potential of TFMC, more experiments must be performed. Moreover, investigations concerning its toxicity, and the environmental impact are necessary. Nevertheless, environment requirements should promote such design of new hybrid fluorous/organic compounds as chlorinated solvents alternative.

4. Experimental

^{19}F, ^{1}H and ^{13}C NMR were recorded on a Bruker AC-200 MHz multinuclear spectrometer. Chemical shifts (δ) are given in ppm relative to $CFCl_3$ for ^{19}F NMR, and relative to TMS for ^{1}H and ^{13}C NMR. In all measurements, $CDCl_3$ was used as a solvent. IR spectra were recorded on a Bruker Vector 22 spectrometer. GC analysis were performed on HP 4890 apparatus equipped with a SE 30 capillary column (l=30 m). In all experiments, TFMC was used as provided, without any purification procedure.

4.1. Oxidation of TFMC by H_2O_2/TFA system

To a solution of TFMC (1 g, 6.6 mmol) in TFA (40 mL), H_2O_2 30% in water (2.04 mL, 19.8 mmol) was added in three portions. After 1 h (reaction was monitored by GC), Et_2O (40 mL) was added and the reaction mixture was cooled to 0°C. The mixture was then treated with an aq. NaOH 10N solution until a pH 12 was obtained, extracted twice with Et_2O (30 mL each), washed with brine, dried over $MgSO_4$, and solvents were evaporated. This experiment was performed twice. Combined crude products were diluted in CH_2Cl_2, and PCC (347 mg, 1.6 mmol) was added. After 1.5 h stirring, pentane was added, and the product was filtered on celite. Solvents were evaporated and products were purified by chromatography on silica gel (pentane/Et_2O, 70:30) to afford ketones **2** and **3** (55 mg, 5%).

4.2. Oxidation of TFMC by GoAgg^{V} system

To a solution of TFMC (5 g, 32.9 mmol) in pyridine (22 mL) and acetic acid (2.2 mL) under stirring, $FeNO_3\cdot 9H_2O$ (1.3 g, 3.3 mmol), picolinic acid (1.2 g, 9.9 mmol) and 70% TBHP in water (9 mL, 65.8 mmol) were added. After 16 h at 25°C (reaction was monitored by GC), the mixture was acidified to pH 1 with a 25% H_2SO_4 solution and extracted three times with Et_2O (30 mL each). The combined organic phases were neutralized with an aqueous saturated $NaHCO_3$ solution, washed with brine, dried over $MgSO_4$ and solvents were evaporated. The crude mixture was diluted in CH_2Cl_2, and PCC (555 mg, 2.6 mmol) was added. After 1.5 h stirring, pentane was added, and the product was filtered on celite. The solvents were evaporated and products were purified by chromatography on silica gel (pentane/Et_2O, 70:30) to afford ketones **2** and **3** (608 mg, 11%). A further chromatography (pentane/Et$_2$O, 90:10 then 70:30) allowed the isolation of a sample of each pure ketone.

4.2.1. 3-Trifluoromethylcyclohexan-1-one (2).[20] Colorless liquid: IR ν (cm^{-1}) 1717; ^{19}F NMR δ −74.1 (d, $J_{\mathrm{H-F}}$=8.0 Hz), ^{1}H NMR δ 1.6–2.7 (m); ^{13}C NMR δ 207.2, 126.5 (q, $^{1}J_{\mathrm{C-F}}$=278 Hz, CF$_3$), 42.1 (q, $^{2}J_{\mathrm{C-F}}$=28 Hz, CF$_3$*C*H), 40.5, 39.7 (q, $^{3}J_{\mathrm{C-F}}$=2.0 Hz, CF$_3$CH*C*H$_2$CO), 23.5 (q, $^{3}J_{\mathrm{C-F}}$=2.5 Hz, CF$_3$CH*C*H$_2$), 23.4.

4.2.2. 4-Trifluoromethylcyclohexan-1-one (3).[20] Colorless liquid: IR ν (cm^{-1}) 1719; ^{19}F NMR δ −73.2 (d, $J_{\mathrm{H-F}}$=8.0 Hz), ^{1}H NMR δ 1.6–2.7 (m); ^{13}C NMR δ 208.9, 127.2 (q, $^{1}J_{\mathrm{C-F}}$=278 Hz, CF$_3$), 40.1 (q, $^{2}J_{\mathrm{C-F}}$=28 Hz, CF$_3$*C*H), 40.0, 24.7 (q, $^{3}J_{\mathrm{C-F}}$=2.5 Hz, CF$_3$CH*C*H$_2$).

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References

1. *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.
2. Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450–451.
3. (a) Kaspel Vel Leitner, N.; Abdessalem, R. B.; Dore, M. *New J. Chem.* **1997**, *21*, 187–194. (b) Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn* **2000**, *73*, 951–956. (c) Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsuhara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* **1996**, *52*, 3889–3896.
4. Zalesskaya, I. M.; Blakitnyi, A. N.; Saenko, E. P.; Fialkov, Y. A.; Yagupol’skii, L. M. *Zh. Org. Khim. Engl. Trans.* **1980**, *16*, 1194–1202.
5. Negishi, J.; Sawai, M.Central Glass Co., Ltd, Japan *Jpn. Kokai Tokkyo Koho* **1988**, JP63051354.
6. (a) Henne, A. L.; Newman, M. S. *J. Am. Chem. Soc.* **1938**, *60*, 1697–1698. (b) Ramchandani, R. K.; Wakharkar, R. D.; Sudalai, A. *Tetrahedron Lett.* **1996**, *37*, 4063–4064.
7. (a) Paletta, O. *Chemistry of Organic Fluorine Compounds*; Hudlicky, M., Pavlath, A. E., Eds.; 1995; Vol. II, p 321. (b) For a comparative study on influence of CF$_3$ on oxidation, see: González-Núñez, M. E.; Castellano, G.; Andreu, C.; Royo, J.; Báguena, M.; Mello, R.; Asensio, G. *J. Am. Chem. Soc.* **2001**, *123*, 7487–7491. (c) A reaction of TFMC with F$_2$ is described to provide perfluoromethylcyclohexane: Okajima, H.; Nakano, T.; Ishii, F.; Sato, S. (Kanto Denka Kogyo Co., Ltd, Japan) *Jpn. Kokai Tokkyo Koho* **1989**, JP01180838.
8. Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Büker, H. H.; Nibbering, N. M. M. *Chem. Eur. J.* **1998**, *4*, 1281–1286.
9. (a) Sheppard, W. A. *J. Am. Chem. Soc.* **1965**, *87*, 2410–2420. (b) Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry*; Benjamin WA: New York, 1969. (c) Schiemann, G.; Cornils, B. *Chemie und Technologie Cyclischer Fluorverbidungen*, Enke: Stuttgart, 1969.
10. (a) Sheldon, R. A.; Dakka, J. *Catal. Today* **1994**, *19*, 215–245. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981. (c) Shilov, A. E. *Activation of Saturated Hydrocarbons by Transition Metal Complexes*; D. Reidel Publishing Co: Dordrecht, 1984. (d) Hill, C. L. *Activation and Functionalization of Alkanes*; Wiley: New York, 1989. (e) Schuchardt, U.; Cardoso, D.; Sercheli, R.; Pereira, R.; DaCruz, R. S.; Guereiro, M. C.; Mandelli, D.; Spinace, E. V.; Pues, E. L. *Appl. Catal. A* **2001**, *211*, 1–17. (f) Dugal, M.; Sankar, G.; Raja, R.; Thomas, J. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2310–2313.
11. Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599–2660.
12. Nomura, K.; Uemara, S. *J. Chem. Soc., Chem. Commun.* **1994**, 129–130.
13. Carlsen, H. *J. Synth. Commun.* **1987**, *17*, 19–23.
14. (a) Deno, N. C.; Jedziniak, E. J.; Messer, L. A.; Meyer, M. D.; Stroud, S. G.; Tomeszko, E. S. *Tetrahedron* **1977**, *33*, 2503–2508. (b) Deno, N. C.; Messer, L. A. *J. Chem. Soc., Chem. Commun.* **1976**, 1051.
15. Barton, D. H. R.; Chavasiri, W. *Tetrahedron* **1994**, *50*, 19–30.
16. (a) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.* **1994**, *35*, 3759–3762. (b) Minisci, F.; Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427–1430. (c) Barton, D. H. R. *Synlett* **1996**, 229–230.
17. (a) Charpentier-Morize, M.; Bonnet-Delpon, D. *Advances in Carbocation Chemistry*; Jai : Greenwich, 1989; p. 219. (b) The α-electron withdrawing effect of a CF$_3$ substituent is illustrated by the low values of pK_a of CF$_3$-substituted aliphatic amines, even in δ position: Podols’kii, A. V.; German, L. S.; Knuynants, I. L. *Izv. Akad. Nauk. SSR, Ser. Khim.* **1967**, *5*, 1134–1135.
18. Kumadaki, I. *Reviews on Heteroatom Chemistry* **1993**, *9*, 181–204.
19. (a) Vogel, A. I. *Vogel’s Textbook of Practical Organic Chemistry*; 5th ed.; Longman Scientific and Technical: Essex, UK, 1989; p. 590. (b) Vogel, A. I. *Vogel’s Textbook of Practical Organic Chemistry*; 5th ed.; Longman Scientific and Technical: Essex, UK, 1989; pp. 578–579.
20. Ojima, I.; Yatabe, M.; Fuchikami, T. *J. Org. Chem.* **1982**, *47*, 2051–2055.