ELSEVIER

Journal of Fluorine Chemistry 101 (2000) 199–202

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Preparation of 3-trifluoromethyl-2-cycloalkenones by the oxidative rearrangement of trifluoromethylated tertiary allylic alcohols with pyridinium chlorochromate☆

G.K. Surya Prakash*, Emily C. Tongco, Thomas Mathew, Yashwant D. Vankar[1], George A. Olah

Department of Chemistry, Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90089-1661, USA

Received 9 May 1999; received in revised form 11 June 1999; accepted 14 June 1999

Abstract

Trifluoromethylated tertiary allylic alcohols, obtained from trifluoromethylation of several conjugated enones, undergo oxidative rearrangements to 3-trifluoromethyl-2-cycloalkenones with pyridinium chlorochromate in the presence of a small amount of concentrated H_2SO_4.

Keywords: Trifluoromethyltrimethylsilane; Trifluoromethylated tertiary allylic alcohols; Pyridinium chlorochromate; 3-trifluoromethyl-2-cycloalkenones

1. Introduction

Organofluorine compounds have found rapidly increasing use in the areas of agrochemicals, pharmaceuticals and fluoropolymers [1–4]. In addition to the introduction of elemental fluorine, incorporation of a trifluoromethyl group in organic compounds has received considerable attention in recent years [1–5]. In connection with our ongoing studies to develop synthetic methodologies for the synthesis of novel compounds containing trifluoromethyl groups [6–8], we now report the synthesis of 3-trifluoromethyl-2-cycloalkenones by oxidative rearrangement of the corresponding trifluoromethylated tertiary allylic alcohols. Conjugated enones have been used in (2 + 2) [9] and (2 + 3) [10,11] cycloadditions to rapidly build up polycylic molecules. It was, therefore, of interest to us to develop a general synthetic method which allows preparation of conjugated enones containing a trifluoromethyl group on the double bond. Such materials can also be used to prepare polycyclic compounds containing angular trifluoromethyl groups and are of particular interest in steroid chemistry. Of the several possibilites, we considered oxidative rearrangement of tertiary allylic alcohols as a viable route to this effect (Dauben rearrangement). This mainly stems from the fact that trifluoromethylated tertiary allylic alcohols are readily available by the addition of CF_3SiMe_3 to conjugated enones. The use of oxochromium (VI) reagents for oxidative rearrangement of tertiary allylic alcohols has been studied [12–14] for the past two decades and has found diverse applications in natural product synthesis [15]. This reaction has been extended to include oxidative rearrangements of enynols [16], dienols [17], vinylclopropylcarbinols [18], phosphorus-containing tertiary allylic alcohols [19–21], and substrates bearing sulfur substituents [15]. However, to our knowledge, oxidative rearrangement of tertiary allylic trifluoromethyl alcohols has not been studied.

2. Experimental

^1H, ^{13}C and ^{19}F NMR spectra were obtained in $CDCl_3$ solutions on a Varian unity 300 (300 MHz) instrument and the chemical shifts referenced to TMS (for ^1H, ^{13}C NMR) and $CFCl_3$ (for ^{19}F NMR). GC/MS data were obtained from a Hewlett–Packard 5890 series spectrometer. HRMS data

☆Considered Synthetic Methods and Reactions, Part. 204. For Part 203, see, G.A. Olah, E.R. Marinez, G.K.S. Prakash, Synlett, submitted for publication. The work was presented at the International Conference on Fluorine Chemistry 1999 Tokyo, 9–11 May 1999, Yokohama, Japan.

*Corresponding author. Fax: +1-213-740-66679.

E-mail address: prakash@methyl.usc.edu (G.K.S. Prakash)

[1]Present address: Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India.

0022-1139/00/$ – see front matter
PII: S0022-1139(99)00159-1

were obtained using chemical or electron ionization, and performed by the Southern California Mass Spectroscopy Facility at University of California Riverside. All starting ketones were commercially available, and used without further purification. All solvents were freshly distilled prior to use.

2.1. General procedure for the synthesis of trifluoromethylated alcohols

To a Schlenk flask equipped with a magnetic stirrer was placed 2.5 mmol of the ketone in 5 ml THF, followed by addition of CF_3TMS (1.2 eq). Tetrabutylammonium fluoride (TBAF, 1.0 M in THF solution) was added dropwise until reaction becomes exothermic and the reaction mixture becomes dark brown. The reaction was monitored by TLC. Hydrolysis of the corresponding trifluoromethyl silyl ethers was carried out either in 5 N HCl solution, or in 1 eq TBAF solution. After hydrolysis is complete as shown by TLC, the solvent was evaporated and the crude product filtered through silica gel. The trifluoromethylated alcohols were used in the subsequent oxidation step.

1-Trifluoromethyl-2-cyclohexen-1-ol (**1a**): ^{1}H NMR (δ): 1.52–2.37 (7H, m); 5.73 (1H, br. d, $J = 10$ Hz); 6.17 (1H, m). ^{13}C NMR (δ): 17.2, 24.8, 28.9 (CH_2); 70.1 (C–CF_3, q, $J_{C–C–F} = 30$ Hz); 126.0 (CF_3, q, $J_{C–F} = 284$ Hz); 122.8, 136.4 (olefinic CH). ^{19}F NMR (δ): −83.3. Mass spectra, *m/z*: 166 (M^+, 0.4); 97 (100); 69 (16).

1-Trifluoromethyl-4,4-dimethyl-2-cyclohexen-1-ol (**1b**): ^{1}H NMR (δ): 1.04 (3H, s); 1.25 (3H, s); 1.51–1.97 (4H, m); 2.41 (1H, br); 5.55 (1H, br. d, $J = 10$ Hz); 5.84 (1H, br. d, $J = 10$ Hz). ^{13}C NMR (δ): 26.2 (CH_2); 26.9, 29.7 (CH_3); 31.6 (CH_2); 70.4 (C–CF_3, q, $J_{C–C–F} = 29$ Hz); 120.2 (CH); 125.8 (CF_3, q, $J_{C–F} = 284$ Hz); 146.1 (CH). ^{19}F NMR (δ): −83.1. Mass spectra, *m/z*: 176 (M−18, 13); 125 (100); 69 (11).

1-Trifluoromethyl-4-(2-propenyl)-2-cyclohexen-1-ol (**1c**): ^{1}H NMR (δ): 1.61–2.53 (m, 5H); 1.74 (3H, s); 1.82 (3H, s); 2.45 (1H, s); 4.75 (2H, d, $J = 8$ Hz); 5.81 (1H, br. m). ^{13}C NMR (δ): 17.4, 20.4 (CH_3); 30.7, 36.8 (CH_2); 37.4 (CH); 74.3 (C–CF_3, q, $J_{C–C–F} = 28$ Hz); 109.7 (CH_2); 125.8 (CF_3, q, $J_{C–F} = 287$ Hz); 129.8 (C_{quat}); 130.7 (CH); 147.7 (C_{quat}). ^{19}F NMR (δ): −76.2. Mass spectra, *m/z*: 220 (M^+, 0.7); 202 (100); 109 (89).

1-Trifluoromethyl-2-cyclohepten-1-ol (**1d**): ^{1}H NMR (δ): 1.53–2.30 (9H, m); 5.71 (1H, d, $J = 12$ Hz); 6.05–6.13 (1H, m). ^{13}C NMR (δ): 22.7, 26.8, 27.4, 31.3 (CH_2); 76.0 (C–CF_3, q, $J_{C–C–F} = 27$ Hz); 125.9 (CF_3, q, $J_{C–F} = 286$ Hz); 128.2 (CH); 137.9 (CH). ^{19}F NMR (δ): −83.4. Mass spectra, *m/z*: 180 (M^+, 0.6); 162 (79); 111 (100).

1-Trifluoromethyl-2-methyl-6,6-dimethyl-2,4-cycloheptadien-1-ol (**4**): ^{1}H NMR (δ): 1.14 (3H, s); 1.19 (3H, s); 1.97 (3H, s); 2.09 (1H, d, $J = 15$ Hz); 2.25 (1H, d, $J = 15$ Hz); 2.32 (1H, s); 5.53–5.59 (1H, m); 5.68 (1H, d, $J = 11$ Hz); 5.86 (1H, br. d, $J = 7$ Hz). ^{13}C NMR (δ): 21.6, 26.0, 32.3 (CH_3); 35.4 (C_{quat}); 48.9 (CH_2); 77.2 (C–CF_3, q, $J_{C–C–F} =$ 27 Hz); 121.2 (CH); 125.7 (CF_3, q, $J_{C–F} = 289$ Hz); 127.5 (CH); 136.1 (C_{quat}); 144.4 (CH). ^{19}F NMR (δ): −77.6. Mass spectra, *m/z*: 220 (M^+, 40); 109 (100); 91 (64).

2.2. General procedure for oxidation of trifluoromethylated alcohols with PCC

The alcohol (2.5 mmol) was dissolved in CH_2Cl_2 (20 ml) followed by addition of PCC (1.075 g, 5 mmol). To this reaction mixture was added several drops (∼8 drops) of concentrated sulfuric acid until the solution becomes brownish-black. Progress of the reaction was monitored by TLC and GC/MS, but in all cases, complete conversion to the rearranged ketone was not achieved. After overnight stirring at room temperature, the reaction mixture was diluted with diethyl ether, and carefully quenched with saturated $NaHCO_3$. The organic layer was extracted several times with ether. The collected organic layer was washed with $NaHCO_3$, and with brine, and dried over $MgSO_4$. Evaporation of solvent gave the product as a mixture of starting trifluoromethyl alcohol and the β-trifluoromethyl carbonyl compound, which was purified through column chromatography on silica gel (hexane-methylene chloride).

3-Trifluoromethyl-2-cyclohexen-1-one (**2a**): Oil, ^{1}H NMR (δ): 2.02 (2H, q, $J = 6$ Hz); 2.37 (4H, t, $J = 6$ Hz); 6.24 (1H, s). ^{13}C NMR (δ): 21.8, 22.7, 37.2 (CH_2); 122.7 (CF_3, q, $J_{C–F} = 274$ Hz); 128.1 (CH, q, $J_{C–C–C–F} = 5$ Hz); 147.4 (C–CF_3, q, $J_{C–C–F} = 32$ Hz); 197.9 (CO). ^{19}F NMR (δ): −71.4. IR (cm^{-1}): 1711 (CO). Mass spectra, *m/z*: 164 (M^+, 22); 136 (100); 67 (40). HRMS, *m/z*: Calc. 164.0449 (M^+); Found 164.0449.

3-Trifluoromethyl-6,6-dimethyl-2-cyclohexen-1-one (**2b**): Oil, ^{1}H NMR (δ): 1.11 (6H, s); 1.91 (2H, t, $J = 6$ Hz); 2.47 (2H, br. t, $J = 6$ Hz); 6.25 (1H, s). ^{13}C NMR (δ): 20.2 (CH_2); 23.5 (CH_3); 35.2 (CH_2); 41.1 (C_{quat}); 124.3 (CF_3, q, $J_{C–F} =$ 274 Hz); 126.8 (CH, q, $J_{C–C–C–F} = 5$ Hz); 145.6 (C–CF_3, q, $J_{C–C–F} = 32$ Hz); 202.8 (CO). ^{19}F NMR (δ): −71.1. IR (cm^{-1}): 1695 (CO). Mass spectra, *m/z*: 192 (M^+, 14); 136 (100); 67 (19). HRMS, *m/z*: Calc. 192.0762 (M^+); Found 192.0760.

3-Trifluoromethyl-6-(2-propenyl)-2-cyclohexen-1-one (**2c**): Oil, ^{1}H NMR (δ): 1.76 (3H, s); 1.93–1.95 (2H, m); 2.33–2.45 (2H, m); 2.60–2.67 (3H, m); 4.78 (1H, s); 4.85 (1H, s). ^{13}C NMR (δ): 11.3, 20.3 (CH_3); 30.0 (CH_2); 40.5 (CH); 42.1, 111.4 (CH_2); 123.8 (CF_3, q, $J_{C–F} = 277$ Hz); 137.4 (C_{quat}); 140.5 (C–CF_3, q, $J_{C–C–F} = 30$ Hz); 145.3 (C_{quat}); 198.3 (CO). ^{19}F NMR (δ): −63.3. IR (cm^{-1}): 1689 (CO). Mass spectra, *m/z*: 218 (M^+, 3); 150 (100); 122 (34). HRMS, *m/z*: Calc. 219.0997 (M + 1); Found 219.1008 (M + 1).

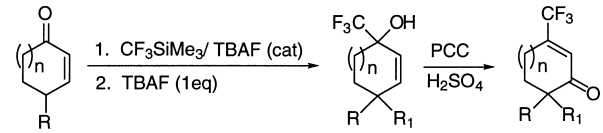
3-Trifluoromethyl-2-cyclohepten-1-one (**2d**): Oil, ^{1}H NMR (δ): 1.71–1.93 (4H, m); 2.52–2.67 (4H, m); 6.43 (1H, s). ^{13}C NMR (δ): 21.2, 24.9, 26.2, 42.5 (CH_2); 123.7 (CF_3, q, $J_{C–F} = 274$ Hz); 131.9 (CH, q, $J_{C–C–C–F} =$ 5 Hz); 142.8 (C–CF_3, q, $J_{C–C–F} = 29$ Hz); 202.5 (CO). ^{19}F NMR (δ): −70.9. IR (cm^{-1})1682 (CO). Mass spectra, *m/z*:

178 (M^+, 26); 136 (71); 109 (100); 81 (72). HRMS, *m/z*: Calc. 178.0605 (M^+); Found 178.0602.

5-Trifluoromethyl-3, 3, 6-trimethyl-8-oxa-bicyclo[3.2.1]-octa-6-ene-2-one (**5**): Oil, ^{1}H NMR (δ): 1.19 (3H, s); 1.32 (3H, s); 1.80 (1H, d, $J = 14$ Hz); 1.93 (3H, s); 2.26 (1H, d, $J = 14$ Hz); 4.75 (1H, s); 5.93 (1H, s). ^{13}C NMR (δ): 12.0, 30.3, 30.8 (CH_3); 36.8 (CH_2); 42.5 (C_{quat}); 85.3 (CH); 87.2 (C–CF_3, q, $J = 32$ Hz); 123.3 (CF_3, q, $J_{C-F} = 281$ Hz); 126.1 (CH); 143.3 (C_{quat}); 206.3 (CO). ^{19}F NMR (δ): −79.2. IR (cm^{-1}): 1715.6 (CO). Mass spectra, *m/z*: 234 (M^+, 11); 150 (100); 81 (14). HRMS, *m/z*: Calc. 234.0878 (M^+); Found 234.0869 (M^+).

3. Results and discussion

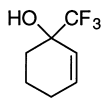
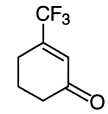
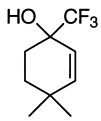
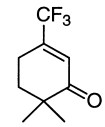
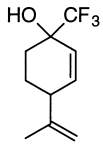
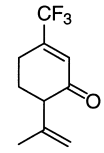
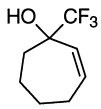
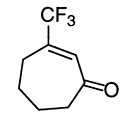
The required trifluoromethylated tertiary allylic alcohols were synthesized following the procedure developed by Prakash and Yudin [6]. Initial studies to effect the oxidative rearrangement with reagents like pyridinium chlorochromate (PCC) [22] pyridinium dichromate (PDC) [23], Collins [24] and Jones reagents [25], failed to give the expected enones. Use of PCC on alumina [26] or ultrasound promoted PCC oxidation [27] also gave no encouraging results. Interestingly, however, when the reaction was carried out with PCC in the presence of a small amount of concentrated sulfuric acid, the rearrangement took place leading to the formation of the expected 3-trifluoromethyl-2-cycloalkenones, albeit in preparatively low yields (Table 1). However, such low yields are still acceptable as valuable trifluoromethyl-substituted dienophiles are obtained in a one-pot procedure. It is noteworthy that PCC alone or only with a drop of H_2SO_4 did not give any rearranged products. On the other hand, one equivalent (or more) of H_2SO_4 led to excessive decomposition of PCC without any improvement in the yields of the final rearranged products. Substitution of sulfuric acid with Nafion-H (a solid polymeric sulfonic acid catalyst) [28,29] did not give any rearrangement product. Furthermore, the present reaction was found to be generally limited to cyclic enones. Thus, for example, trifluoromethylated allylic alcohols derived from chalcone, 4-phenyl-buten-2-one, α-ionone, and 4-hexen-3-one did not give the rearrangement products.



1a n=1, R, R_1= H
1b n=1, R, R_1= CH_3
1c n=1, R= H, R_1= 2-propenyl (diastereomeric mixture)
1d n=2, R, R_1= H

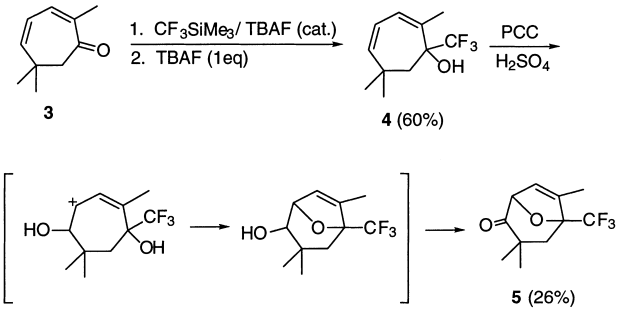
In an attempt to extend the scope of this reaction, eucarvone **3** was chosen as a substrate. Addition of CF_3SiMe_3 gave the expected trifluoromethylated alcohol **4** in 60% yield. Reaction of **4** with PCC under the above described conditions gave a product with an exact mass which was 16 masses higher than the expected oxidation product. Analyses of ^{1}H and ^{13}C NMR spectra show the likely product to have the dihydrofuran structure **5**. It is

Table 1
PCC oxidation of α,β-unsaturated trifluoromethylated alcohols

Entry	Starting alcohol		Product	Yields (%)[a]
1a		**2a**		28
1b		**2b**		25
1c[b]		**2c**		34
1d		**2d**		20

[a]Isolated yields.
[b]Diastereomeric mixture.

possible that PCC under acidic conditions hydroxylates the farthest double bond, creating a carbocationic center that is subsequently attacked by the hydroxyl geminal to the trifluoromethyl group. The resulting intermediate alcohol bearing the dihydrofuran ring is oxidized to the final product **5**.



In summary, we report a relatively simple route to 3-trifluoromethyl-2-cycloalkenones by the oxidative rearrangement of trifluoromethylated tertiary allylic alcohols, obtained from trifluoromethylation of several conjugated enones with pyridinium chlorochromate in the presence of a small amount of concentrated H_2SO_4. This reaction is, however, limited to cyclic enones.

Acknowledgements

Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

References

[1] J.T. Welch, S. Eshwarakrishnan (Eds.), Fluorine in Bioorganic Chemistry, Wiley, New York, 1991.
[2] J.F. Liebman, J.A. Greenberg, W.R. Dolbier, Jr. (Eds.), Fluorine-containing Molecules. Structure, Reactivity, Synthesis, and Applications, VCH, New York, 1988.
[3] R. Filler, Y. Kobayashi (Eds.), Biomedical Aspects of Organofluorine Chemistry, Elsevier, Amsterdam, 1983.
[4] F.A. Smith, Handbook of Experimental Pharmacology, vol. XX, part 2, Springer, Berlin, 1970, p. 166.
[5] R.E. Banks (Ed.), Organofluorine Compounds and Their Industrial Applications, Ellis Horwood, Chichester, UK, 1979.
[6] G.K.S. Prakash, A. Yudin, Chem. Rev. 97 (1997) 757.
[7] E.C. Tongco, G.K.S. Prakash, G.A. Olah, Synlett (1997) 1193.
[8] J. Weidemann, T. Heiner, G. Mloston, G.K.S. Prakash, G.A. Olah, Angew. Chem. Int. Ed. Engl. 37 (1998) 820.
[9] Y. Yamada, H. Uda, K. Nakanishi, J. Chem. Soc., Chem. Commun. (1966) 423.
[10] B.M. Trost, Angew. Chem. Int. Ed. Engl. 25 (1986) 1.
[11] B.M. Trost, Pure Appl. Chem. 60 (1988) 1615.
[12] W.G. Dauben, D.M. Michno, J. Org. Chem. 42 (1977) 682.
[13] J.H. Babler, M.J. Coghlin, Synth. Commun. 6 (1976) 469.
[14] P. Sundararaman, W. Herz, J. Org. Chem. 42 (1977) 813.
[15] F.A. Luzzio, W.J. Moore, J. Org. Chem. 58 (1993) 2966 and references cited therein.
[16] D. Liotta, D. Brown, W. Hoekstra, R. Monihan, Tetrahedron Lett. (1987) 1069.
[17] G. Majetich, S. Condon, K. Hull, S. Ahmad, Tetrahedron Lett. (1989) 1033.
[18] E. Wada, M. Okawara, T. Nakai, J. Org. Chem. 44 (1979) 2952.
[19] E. Öhler, E. Zbiral, Synthesis (1991) 357.
[20] P.S. Brown, A.B. McElroy, S. Warren, Tetrahedron Lett. (1985) 249.
[21] A.B. McElroy, S. Warren, Tetrahedron Lett. (1985) 1677.
[22] E.J. Corey, J.W. Suggs, Tetrahedron Lett. (1975) 2647.
[23] E.J. Corey, G. Schmidt, Tetrahedron Lett. (1979) 399.
[24] J.C. Collins, W.W. Hess, F.J. Frank, Tetrahedron Lett. (1968) 3363.
[25] R.G. Curtis, I. Heilbron, E.R.H. Jones, G.F. Woods, J. Chem. Soc. (1953) 457.
[26] Y. Cheng, W. Liu, S. Chen, Synthesis (1980) 223.
[27] F.A. Luzzio, L.L. Adams, J. Org. Chem. 54 (1989) 5387.
[28] G.A. Olah, P.S. Iyer, G.K.S. Prakash, Synthesis (1986) 513.
[29] M. Hachoumy, T. Mathew, E.C. Tongco, Y.D. Vankar, G.K.S. Prakash, G.A. Olah, Synlett. (1999) 363.