

Study on the effect of di- and trifluoromethyl groups on the Baeyer–Villiger reaction

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Abstract

Case studies of the Baeyer–Villiger reaction applied to di- and trifluoromethylketone derivatives and the effect of the fluoromethyl groups on the Baeyer–Villiger reaction, are described.

Keywords: Baeyer–villiger reaction; Di- and trifluoromethylketones

1. Introduction

Comparative studies on the chemical behavior of non-fluorinated and/or partially fluorinated compounds has attracted intense interest [1–3]. Clearly, mechanistic and theoretical studies for the chemical behavior of materials modified by fluorine(s), at a specific position in the molecule, remain an important chemical challenge.

Accordingly, we have devoted our attention to the study of the difference in the reactivity of non-fluorinated, difluorinated and trifluorinated ketones using the Baeyer–Villiger reaction with *m*-chloroperoxybenzoic acid (*m*CPBA). In the literature [4], Smismann and co-workers have reported that the Baeyer–Villiger reaction of trifluoromethyl phenyl ketone with trifluoroperoxyacetic acid in CHCl_3 gave benzoic acid (67%) based on the migration of the CF_3 group and phenol (5%) based on the migration of the phenyl group. However, our experimental result (Entry 2) shown in Table 1, support that the migration of the phenyl group from carbon to oxygen occurs to give the corresponding phenyl trifluoroacetate in 93% yield.

In general, a two-step mechanism is accepted for the Baeyer–Villiger reaction based on kinetic, isotopic substitution, stereochemical and substituent effect studies [5]. In the second step, which is usually rate determining, the stereoelectronic requirements proposed for the migration step are an antiperiplanar arrangement of the C–R bond and the breaking O–O bond [6]. It has been further suggested that one of the hydroxy nonbonding electron pairs must be antiperiplanar to

the migrating carbon atom, as in Scheme 1. Further, it is known that the migrating group contributes to stabilize the cationic oxygen atom produced in a Criegee intermediate 1, and that the usual migratory preference for alkyl groups in Baeyer–Villiger reactions is tertiary > secondary >

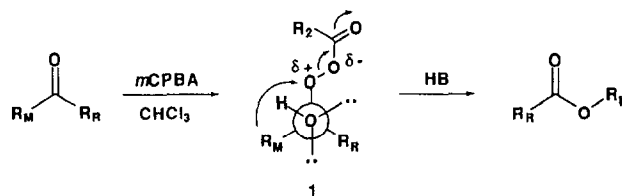
Table 1
Baeyer–Villiger reaction of various fluoroketones with *m*CPBA ^a

Entry	R_F	R_2	Time (h)	Yield (%) ^b		
				2	3	4
1 ^c	CH_3	Ph	3.5	12	70	18
2	CHF_2	Ph	1	6	94	0
3	CF_3	Ph	1	6	93	0
4	CH_3	<i>n</i> - C_6H_{13}	6	0	99	0
5	CHF_2	<i>n</i> - C_8H_{17}	10	10	87	0
6	CHF_2	<i>n</i> - C_8H_{17}	11	2	93	0
7	CF_3	<i>n</i> - C_6H_{13}	24	26	64	0
8	CF_3	<i>n</i> - C_8H_{17}	23	26	40	0
9	CF_2CF_2	<i>n</i> - C_6H_{13}	21	94	6	0

^a Unless otherwise noted, all reactions were performed under reflux conditions.

^b Determined by ^{19}F NMR with PhCF_3 as an internal standard.

^c Reaction was carried out at room temperature.



Scheme 1. Criegee intermediate.

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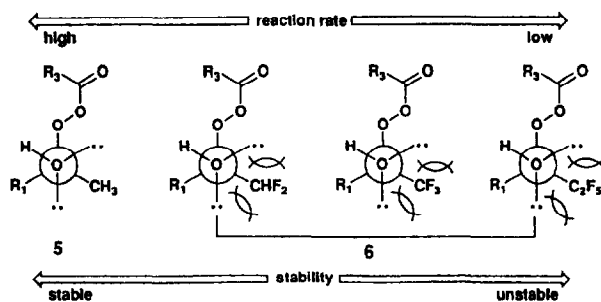
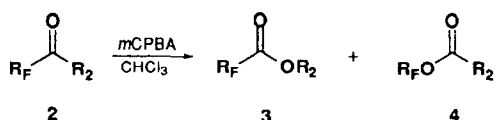


Fig. 1.

primary > methyl, which has been attributed to the greater electron-releasing power of, or to steric acceleration of migration by the large group.



From the results shown in Table 1, the migratory preference of the groups is phenyl > alkyl > methyl > CHF₂ > CF₃ ≫ C₂F₅. This order has been attributed to the greater electron-releasing power. In an attempt to obtain information about the present order of migration, the PM3 calculation was carried out for the Criegee intermediates (Fig. 1). Calculations were performed by MOPAC v 6.10 (PM 3) included in CACHE Worksystem (SONY/Tektronix Corporation) for the conformers obtained from the rigid search method with the key word 'PERCISE' and the eigenvector following minimization (EF) method, final gradient norm being less than 0.01 kcal Å⁻¹. Comparison of the LUMO energy level in the most stable conformers of each of the Criegee intermediates predicts the order of the migration. A large LUMO energy level at the reaction site gives a greater propensity for the migration of a nonfluorinated group than a small one [LUMO energy level: methyl (2.317 eV), CHF₂ (1.646 eV), CF₃ (0.988 eV), C₂F₅ (0.156 eV)]. MOPAC results shown in Fig. 1 demonstrate that the order of migration is methyl > CHF₂ > CF₃ ≫ C₂F₅. Furthermore, in the Criegee intermediate (5 or 6) of the fluoroalkyl ketones, conformer 5 is more stable than conformer 6 based on the electric repulsion between the lone pair of the oxygen atom and the fluoroalkyl group. However, the contribution effect of a nonfluorinated group to stabilize the cationic oxygen atom is greater than for a fluoroalkyl group.

These calculation results and the consideration of Criegee intermediates (5 or 6) conveniently and qualitatively explains the experimental results of the Baeyer–Villiger reaction.

2. General procedure

The ¹H (200 or 500 MHz; internal Me₄Si) and ¹⁹F (470 MHz; internal C₆F₆₆) NMR spectra were recorded using Varian Gemini 200 or VXR 500 in CDCl₃.

2.1. General procedure for di- and trifluoromethylketones

2.1.1. 1,1,1-Trifluoro-2-decanone [7,8]

Octylgrignard reagent prepared from octyl bromide (100 mmol) and magnesium in diethyl ether (200 ml) was added slowly to a solution of ethyl trifluoroacetate (13.1 ml, 10 mmol) in diethyl ether (110 ml) at –78 °C under nitrogen atmosphere. After 5 h of stirring at –40 °C, the mixture was quenched with 1 N HCl. Oil materials were then extracted with diethyl ether. The ethereal extract was washed with brine, then dried over MgSO₄. On removal of the solvent, distillation afforded 1,1,1-trifluoro-2-decanone.

1,1,1-Trifluoro-2-octanone and trifluoromethyl phenyl ketone were synthesized in the same manner using ethyl trifluoroacetate and the corresponding Grignard reagent as described above [8,7].

2.2. Difluoromethyl phenyl ketone [9]

Into a solution of ethyl difluoroacetate (4.9 g, 40 mmol) in freshly dried diethyl ether (50 ml), phenyl magnesium bromide (44 mmol) was added dropwise at a temperature below –70 °C. After 4 h of stirring, the mixture was quenched with saturated NH₄Cl. Oily materials were extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave difluoromethyl phenyl ketone in a yield of 83%.

1,1,1-Difluoro-2-octanone and 1,1,1-difluoro-2-decanone were synthesized in the same manner using ethyl trifluoroacetate and the corresponding Grignard reagent as described above [9].

2.3. General procedure of Baeyer–Villiger reaction

A mixture of trifluoromethyl octyl ketone (0.42 g, 2 mmol), *m*-chloro-peroxybenzoic acid (*m*CPBA; 1.04 g, 6 mmol) and benzotrifluoride (BTF; 1 mmol) in CHCl₃ (10 ml) was refluxed for 23 h. The ratios of trifluoromethyl octyl ketone (¹⁹F NMR chemical shift appears in the downfield compared to the corresponding esters) and the corresponding esters [10] were determined by ¹⁹F NMR integral intensities as shown in Table 1.

References

- [1] W.W. Wilkerson, *Drugs of the Future*, 15 (1990) 140.
- [2] M. Waite, *J. Lipid. Res.*, 26 (1985) 1379.
- [3] I. Kudo, H.W. Chang, S. Hara, M. Murakami and K. Inoue, *Dermatologica*, 179 (1989) 72.
- [4] E.E. Smisman, P.J. Li and Z.H. Israili, *J. Org. Chem.*, 33 (1968) 4235.
- [5] B. Plesnicar, *Oxidation in Organic Chemistry*, in W.S. Trahanovsky (ed.), Academic Press, New York, 1978.
- [6] G.R. Krow, *Tetrahedron*, 37 (1981) 2697.
- [7] P.V. Ramachandran, A.v. Teodorovic, B. Gong and H.C. Brown, *Tetrahedron; Asymmetry*, 5 (1994) 1075.
- [8] J.-T. Lin, T. Yamazaki and T. Kitazume, *J. Org. Chem.*, 52 (1987) 3211.
- [9] T. Kitazume, M. Asai, T. Tsukamoto and T. Yamazaki, *J. Fluorine Chem.*, 56 (1992) 271.
- [10] J.M. Emsley, J. Feeney and L.H. Sutcliffe (eds.), *Progress in Nuclear Magnetic Resonance Spectroscopy*, Vol. 7, Pergamon, Oxford, 1971.