Tetrahedron Letters,Vol.30,No.40,pp 5437-5438,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

A NOVEL SYNTHESIS OF DIFLUOROMETHYL KETONES FROM 2,2,2-TRIFLUOROETHYL *p*-TOLUENESULFONATE *VIA* 2,2-DIFLUOROALKENYLBORANES

Junji Ichikawa, Takaaki Sonoda, and Hiroshi Kobayashi
Institute of Advanced Material Study, Kyushu University,
Kasuga, Fukuoka 816, Japan

Summary: Oxidation of 2,2-difluoroalkenylboranes can be achieved with alkaline hydrogen peroxide in the presence of sodium methoxide, which suppresses protonolysis, to afford difluoromethyl ketones in good yields.

Fluoromethyl ketones are versatile starting materials for introducing fluorinated moieties,[1] and have recently received considerable attention as transition-state analogue inhibitors for a variety of hydrolytic enzymes.[2,3] There appeared several methods concerning the preparation of fluoromethyl ketones. Most of these methods, however, are confined to the reaction of organolithium or Grignard reagent with fluoroacetic acids or their derivatives.[3,4]

In the previous paper,[5] we reported a novel synthesis of 1,1-difluoroolefins *via* 2,2-difluoroalkenylborane 1, which was easily generated from 2,2,2-trifluoroethyl *p*-toluenesulfonate (2) and trialkylborane. During the course of our synthetic studies on the application of 1, we found a new approach for preparing difluoromethyl ketones by oxidation of 1.

Treatment of 1 ($R=(CH_2)_4Ph$), generated in the reported way,[5] with alkaline hydrogen peroxide gave the desired difluoromethyl ketone 3 in 54% yield along with a 30% yield of the protonolyzed product, 1,1-difluoro-6-phenyl-1-hexene.[6] In order to avoid protonolysis, non-aqueous conditions were employed using an oxidant such as trimethylamine *N*-oxide, *m*-chloroperbenzoic acid (mCPBA), and pyridinium chlorochromate (PCC), but they resulted in failure. Several methods for inhibiting protonolysis were tried under the alkaline hydrogen-peroxide conditions. Finally, the addition of sodium methoxide suppressed protonolysis and the yield of 3 was raised up to 81%.[7]

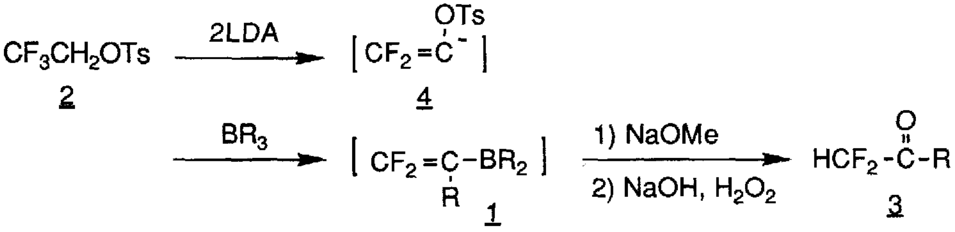

Table 1. Synthesis of Difluoromethyl Ketones[a]

Entry	R	BR_3/2	NaOMe/2	Yield of 3/%[b]
1	$-(CH_2)_4Ph$	1.1	1.4	81[c]
2	$-CH_2CH(CH_3)Ph$	1.5	1.1	77
3	10-Pinanyl	1.1	1.7	63
4	Cyclooctyl	1.1	2.8	63
5	Bicyclo[2.2.1]hept-2-yl	1.5	---	67[d]
6	$-C(^nPr)=CH^nPr$	1.1	1.2	27

[a] Unless otherwise noted, all reactions were carried out under conditions described in the text. [b] ^{19}F NMR yield relative to internal C_6F_6 standard. All products gave satisfactory ^1H, ^{19}F, ^{13}C NMR, and IR spectra. [c] Isolated yield. [d] Diastereomer ratio (*exo*:*endo* = 92:8) was determined by ^{19}F and ^{13}C NMR measurements.

The results of reaction with several other organoboranes are summarized in Table 1, which reveal that 2 functions as the synthetic equivalent of difluoroacetyl cation synthon.

A typical reaction procedure is as follows: To a tetrahydrofuran (THF, 2 ml) solution of 2,2-difluoro-1-tosyloxyvinyllithium (4) generated from 2 (84 mg, 0.33 mmol) and lithium diisopropylamide (LDA, 0.69 mmol) was added tris(4-phenylbutyl)borane (0.36 mmol) in THF (2 ml) at -78 °C under an argon atmosphere.[5] After 30 min at -78 °C, sodium methoxide (25 mg, 0.46 mmol) was added in solid form. The mixture was brought to room temperature, and stirred for 12 h. Aqueous sodium hydroxide (3N, 0.36 ml) and 30% hydrogen peroxide (0.33 ml) were added successively at 0 °C. The mixture was stirred for 1h and an additional 1h at room temperature, then quenched with saturated aqueous ammonium chloride. After usual workup, 1,1-difluoro-6-phenyl-2-hexanone (57 mg, 81%) was isolated by thin layer chromatography on silica gel (Et_2O-hexane 1:4).

References and Notes

1. M. Hudlicky, "Chemistry of Organic Fluorine Compounds," 2nd ed, Ellis Horwood, Chichester (1976).
2. B. Imperiali and R. H. Abeles, Tetrahedron Lett., 27, 135 (1986).
3. R. J. Linderman and M. S. Lonikar, J. Org. Chem., 53, 6013 (1988) and references cited therein.
4. S. -M. L. Chen and C. V. Grudzinskas, J. Org. Chem., 45, 2278 (1980).
5. J. Ichikawa, T. Sonoda, and H. Kobayashi, Tetrahedron Lett., 30, 1641 (1989).
6. 1 is susceptible to protonolysis as compared to the nonfluorinated counterpart.[5]
7. A similar effect of methoxide anion was reported by Levy and Brown, independently. A. B. Levy and S. J. Schwartz, Tetrahedron Lett., 1976, 2201; H. C. Brown and G. A. Molander, J. Org. Chem., 51, 4512 (1986).

(Received in Japan 23 June 1989)