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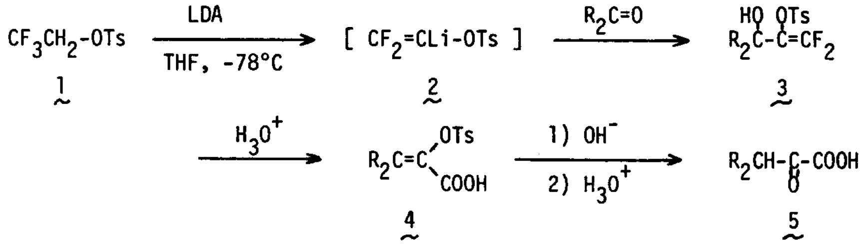
2,2-DIFLUORO-1-TOSYLOXYVINYLLITHIUM: A NOVEL, EFFECTIVE REAGENT FOR THE PREPARATION OF α-KETO ACIDS FROM CARBONYL COMPOUNDS[1]

Kiyoshi TANAKA, Takeshi NAKAI*, and Nobuo ISHIKAWA

Department of Chemical Technology, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Carbanions stabilized by β-fluorine atom(s) are the most frequently encountered intermediates in organofluorine reactions and hence may serve as nucleophiles in carbon-carbon bond formations.[2] However, such β-fluorine stabilized carbanions have been of extremely limited use in organic synthesis. In our continuing investigation of new applications of organofluorine reagents in organic synthesis,[3,4] we now wish to demonstrate the synthetic potentiality of the title reagent (2), readily generated from 2,2,2-trifluoroethyl tosylate (1) and 2 equiv of lithium diisopropylamide(LDA), which provides a facile synthetic route to α-keto acids (5) from various carbonyl compounds, as depicted below.



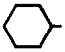
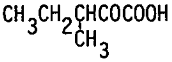
$$\underset{1}{CF_3CH_2\text{-}OTs} \xrightarrow[\text{THF, -78°C}]{\text{LDA}} \underset{2}{[\ CF_2\text{=}CLi\text{-}OTs\ ]} \xrightarrow{R_2C\text{=}O} \underset{3}{R_2C(OH)\text{-}C(OTs)\text{=}CF_2}$$

$$\xrightarrow{H_3O^+} \underset{4}{R_2C\text{=}C(OTs)COOH} \xrightarrow[2)\ H_3O^+]{1)\ OH^-} \underset{5}{R_2CH\text{-}C(=O)\text{-}COOH}$$

The generation of 2 was best carried out by treatment of 1 with 2 equiv of LDA in THF at -78°C under nitrogen.[5] At that temperature, carbonyl compounds were added and the mixtures were allowed to warm to 0°C providing quantitative yields of the corresponding carbinols (3). The crude products were then hydrolyzed with 95% sulfuric acid (0°C, 20 min) to the unsaturated acids (4) which were fully characterized. Hydrolysis of 4 with 10% aqueous sodium hydroxide (reflux, 2 hr) followed by acidification afforded the corresponding α-keto acids (5) in good yields. Alternatively, direct hydrolysis of 3 with 10% aqueous sodium hydroxide (reflux, 12 hr) also yielded 5; however, the one-step procedure, though more convenient, led to lower yields of products. Several examples of the preparation of α-keto acids are listed in Table I.

Notable advantages of the present method for the bishomologation of carbonyl compounds to α-keto acids compared with previous ones[6] are (i) the easy availability of the starting material (1),[7] (ii) good overall yields, (iii) the simplicity of the procedure requiring no purification of intermediates, and (iv) the applicability to both aldehydes and ketones. Although crotonaldehyde was converted to the acid 4 (R_2 = H, $CH{=}CHCH_3$), its conversion to the corresponding α-keto acid was not successful. This work serves to illustrate an example of the potential applications of organofluorine reagents in organic synthesis.

Table I. Synthesis of α-Keto Acids (5)

Carbonyl Compound	Acid 4[a] Yield,%[b]	α-Keto Acid 5[a]	Yield,%[b]	Mp,°C (Lit.)
Acetone	76	$(CH_3)_2CHCOCOOH$	95 (57[c])	Oil[d]
Cyclohexanone	76	-COCOOH	91	48-49 (45-49[e])
2-Butanone	60[f]	 $CH_3CH_2\underset{CH_3}{C}HCOCOOH$	92	39-40 (40[g])
n-Heptanal	71[h]	$CH_3(CH_2)_6COCOOH$	98	43-44 (43-44[i])
Benzaldehyde	78[h]	$PhCH_2COCOOH$[j]	89	154-156 (156 [k]) dec. dec.
Crotonaldehyde	73[h]	1		

[a] All products exhibited spectral (ir and nmr) data in accord with the assigned structures. [b] Isolated yields based on 1 and 4 for 4 and 5, respectively. [c] Overall yield based on 1 by the one-step procedure (see text). [d] Its 2,4-dinitrophenylhydrazone, mp, 197-198°C [lit. mp, 197°C: L. N. Owen, J. Chem. Soc., 236(1949)]. [e] D. D. E. Newman and L. N. Owen, J. Chem. Soc., 4713 (1952). [f] A 45:55 mixture of the E and Z isomers (by nmr analysis). [g] M. Igarashi and H. Midorikawa, J. Org. Chem., 28, 3088 (1963). [h] Only Z isomer. For a full discussion of stereochemistry of related systems, see ref. 3. [i] F. Adickes and G. Andresen, Liebigs Ann. Chem., 555, 41 (1944). [j] Obtained as a 2:7 mixture of the enol and keto tautomers (by nmr assay). [k] Mp for the enol tautomer: M. Bergmann and A. Miekeley, Liebigs Ann. Chem., 458, 40 (1927). [l] The corresponding α-keto acid was not obtained under general conditions (see text).

References and Notes

1) Part IV on the series of new applications of organofluorine reagents in organic synthesis. Part III: K. Tanaka, S. Shiraishi, T. Nakai, and N. Ishikawa, Tetrahedron Lett., 3103(1978). This work was supported in part by the Grant-in-Aid from the Ministry of Education, Japan.

2) M. Hudlicky, "Chemistry of Organic Fluorine Compounds", Ellis Horwood, New York, N. Y., 1976; W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", Benjamin, New York, N. Y.,1969.

3) K. Tanaka, T. Nakai, and N. Ishikawa, Chem. Lett., 1379 (1977); ibid., 1263 (1976).

4) For recent papers on generations and reactions of halogenated 2,2-difluorovinyllithiums, see R. Sauvetre, D. Masure, C. Chuit, and J. F. Normant, Synthesis, 128 (1978).

5) The formation of the anionic reagent 2 was further verified by its characteristic behavior toward deuterium oxide and methyl iodide.

6) G. Neef and U. Eder, Tetrahedron Lett., 2825 (1977); P. Coutrot and C. Legris, Synthesis, 118 (1975); D. R. White and D. K. Wu, J. Chem. Soc., Chem. Commun., 988 (1974), and references cited therein.

7) Available from Aldrich Co. and easily prepared from 2,2,2-trifluoroethanol: mp, 36-38°C.

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