CHEMISTRY LETTERS, pp. 1165 - 1168, 1984.

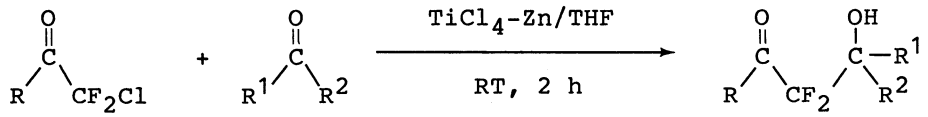
NEW LOW-VALENT TITANIUM CATALYZED REACTION OF CHLORODIFLUOROMETHYL KETONES LEADING TO α,α-DIFLUORINATED β-HYDROXY KETONES

Takashi ISHIHARA,* Tohru YAMANAKA, and Teiichi ANDO
Department of Industrial Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Kyoto 606

Various chlorodifluoromethyl ketones underwent the aldol-type reaction with aldehydes or ketones by the action of titanium tetrachloride and zinc reagent in tetrahydrofuran at room temperature to give moderate to good yields of α,α-difluorinated β-hydroxy ketones.

The aldol reaction is one of the most important, fundamental reactions in organic synthesis. Although a variety of methods[1] have been developed so far for effecting such a transformation, there exist few or no reports on the aldol reaction of fluorine-containing carbonyl compounds occurring at their fluorinated carbon terminus. In our continuing studies[2] to develop new methods for the introduction of fluorine or fluoroalkyl substituent(s) into organic molecules, which often brings about unique physiological activities,[3] titanium tetrachloride-zinc reagent was found to be effective for the synthesis of α,α-difluoro-β-hydroxy ketones from chlorodifluoromethyl ketones.

This communication describes a new method of regiospecific aldol synthesis from chlorodifluoromethyl ketones or ordinary α-chloro ketones, which provides the first example demonstrating that the low-valent titanium[4] can serve as an efficient catalyst for the aldol formation.



1 2

To a black-colored suspension, prepared by the treatment of titanium tetrachloride (0.1 equiv.) with zinc dust (3 equiv.) in anhydrous tetrahydrofuran (THF) at room temperature for 15 min, was dropwise added a solution of chlorodifluoromethyl ketone **1**[8] (1 equiv.) and a carbonyl compound (1.5 equiv.) in THF at 0 °C under nitrogen. The whole mixture was stirred at room temperature for 2 h. Quenching with an aqueous NH_4Cl solution, followed by extraction, drying, evaporation in vacuo, and silica gel column chromatography afforded analytically pure α,α-difluoro-β-hydroxy ketones (**2**).[9] The results of the reaction are summarized in Table 1.

Table 1. Aldol Synthesis from Chlorodifluoromethyl Ketones (1)

Ketone **1**	Carbonyl compd	Yield of aldol **2**/%
$CH_3(CH_2)_5COCF_2Cl$	$CH_3(CH_2)_2CHO$	95
	$CH_3(CH_2)_5CHO$	63
	$(CH_3)_2CHCHO$	75
	cyclo-$C_6H_{11}CHO$	38
	$CH_3CH_2COCH_2CH_3$	55
	cyclohexanone	58
	$CH_3CO(CH_2)_2COOEt$	54[a,b,c]
	$CH_3CO(CH_2)_3COOEt$	50[a,d]
	$CH_3COCH_2CH(OCH_3)_2$	47[a,d,e]
cyclo-$C_6H_{11}COCF_2Cl$	$CH_3(CH_2)_2CHO$	60
	$CH_3(CH_2)_5CHO$	61
	$(CH_3)_2CHCHO$	88
	cyclo-$C_6H_{11}CHO$	47
	$CH_3CH_2COCH_2CH_3$	50
	cyclohexanone	52
CH_3COCF_2Cl	$CH_3(CH_2)_2CHO$	62
$PhCH_2COCF_2Cl$	$CH_3(CH_2)_2CHO$	50

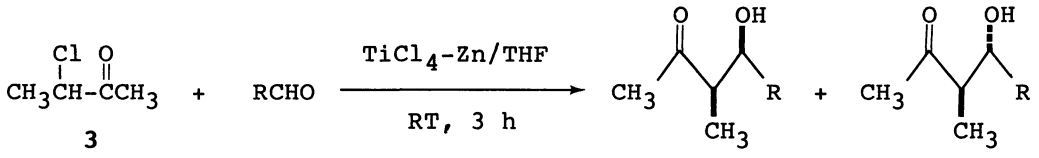
a) A 0.15 equiv. of titanium tetrachloride was used. b) Reaction time, 5 h. c) 4-(1,1-Difluoro-2-oxooctyl)-4-methyl-γ-butyrolactone was obtained instead of the corresponding aldol. d) Reaction time, 3 h. e) Worked up with an aqueous $NaHCO_3$ solution.

A variety of aliphatic aldehydes and ketones were subjected to the reaction to give the corresponding β-hydroxy ketones **2** in moderate to good yields. The reaction with aromatic or α,β-unsaturated carbonyl compounds such as benzaldehyde, acetophenone, and 2-butenal, however, gave no more than 20% yields of the desired products, which could not be improved at all in spite of the reaction conditions being varied. As shown in Table 1, keto esters, e.g., ethyl 4-oxopentanoate and ethyl 5-oxohexanoate, selectively underwent the aldol-type reaction at their ketonic carbonyl group to form the products **2**.[10] Only 4-(1,1-difluoro-2-oxooctyl)-4-methyl-γ-butyrolactone[11] was obtained from the reaction of 1-chloro-1,1-difluoro-2-octanone with ethyl 4-oxopentanoate; the ^{19}F NMR analysis of the reaction revealed that it was formed by successive cyclization of the initially formed aldol adduct. The acetal function did not react under the reaction conditions used; the treatment of 4,4-dimethoxy-2-butanone with 1-chloro-1,1-difluoro-2-octanone, followed by alkaline hydrolysis, afforded 4,4-difluoro-3-hydroxy-3-methyl-1,1-dimethoxy-5-undecanone.[12,13]

The use of titanium tetrachloride is essential to effect the reaction, since in its absence the result was the mere recovery of the unchanged carbonyl

compounds. Of more significance is that only a catalytic amount of titanium tetrachloride is sufficient as far as it is used with zinc.[14] Very probably, the real active species in this reaction is a bivalent titanium compound,[15] which attacks the chlorine atom of chlorodifluoromethyl ketones **1** to give the corresponding enolates.

It has been found, moreover, that ordinary α-chloro ketones are also as susceptible to the reaction described here as are chlorodifluoromethyl ketones. Thus, the treatment of 3-chloro-2-butanone (**3**) with butanal or 2-methylpropanal in the presence of zinc and a catalytic amount of titanium tetrachloride in THF gave the corresponding β-hydroxy ketones[9] as a mixture of stereoisomers **4e** and **4t**. Their ratios were determined by ^{13}C NMR,[16] indicating the erythro selectivity in these reactions.



R=$CH_3(CH_2)_2$, 50% (**4e**/**4t**=78/22)
R=$(CH_3)_2CH$, 49% (**4e**/**4t**=68/32)

Further studies on the application of the present reaction and its mechanism are now underway.

References

1) For a recent review, T. Mukaiyama, Org. React., **28**, 203 (1982).

2) M. Yamana, T. Ishihara, and T. Ando, Tetrahedron Lett., **24**, 507 (1983); T. Ishihara, T. Maekawa, and T. Ando, ibid., **24**, 4229 (1983); T. Ishihara, M. Yamana, and T. Ando, ibid., **24**, 5657 (1983).

3) For example, R. Filler, Chemtech, **1974**, 752; W. G. Taylor, Synthesis, **1980**, 554; D. Arlt, M. Jautelat, and R. Lantzsch, Angew. Chem., Int. Ed. Engl., **20**, 703 (1981); R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Elsevier Biomedical Press, Amsterdam, 1982.

4) The low-valent titanium is known to be capable of promoting such characteristic reactions as inter- or intramolecular reductive coupling,[5] reductive elimination,[6] and deoxygenation.[7]

5) a) T. Mukaiyama, T. Sato, and J. Hanna, Chem. Lett., **1973**, 1041; b) J. E. McMurry and M. P. Fleming, J. Am. Chem. Soc., **96**, 4708 (1974); c) E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, J. Org. Chem., **41**, 260 (1976); d) J. E. McMurry and M. P. Fleming, ibid., **41**, 896 (1976); e) J. E. McMurry and L. R. Krepski, ibid., **41**, 3929 (1976); f) H. M. Walborsky

and M. P. Murari, J. Am. Chem. Soc., **102**, 426 (1980); g) J. E. McMurry and J. R. Matz, Tetrahedron Lett., **23**, 2723 (1982); h) J. E. McMurry and D. D. Miller, ibid., **24**, 1885 (1983); i) Idem, J. Am. Chem. Soc., **105**, 1660, (1983).

6) a) J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, J. Org. Chem., **43**, 3255 (1978); b) H. M. Walborsky and H. H. Wüst, J. Am. Chem. Soc., **104**, 5807 (1982); c) F. Sato, T. Akiyama, K. Iida, and M. Sato, Synthesis, **1982**, 1025; d) V. Reutrakul and P. Poochaivatananon, Tetrahedron Lett., **24**, 531 (1983).

7) J. E. McMurry, M. G. Silvesti, M. P. Fleming, T. Hoz, and M. W. Grayston, J. Org. Chem., **43**, 3249 (1978); N. Z. Huang, Y. D. Xing, and D. Y. Ye, Synthesis, **1982**, 1041; Y. D. Xing, and N. Z. Huang, J. Org. Chem., **47**, 140 (1982).

8) Chlorodifluoromethyl ketones **1** were prepared from chlorodifluoroacetic acid and Grignard reagents according to the literature procedure. See, A. Sykes, J. C. Tatlow, and C. R. Thomas, J. Chem. Soc., **1956**, 835; R. A. Moore and R. Levine, J. Org. Chem., **29**, 1439 (1964).

9) All isolated compounds exhibited spectroscopic (IR, MS, ^{1}H, ^{19}F, and/or ^{13}C NMR) properties which are fully consistent with the assigned structures.

10) Ethyl 3-oxobutanoate did not react with **1** under the same reaction conditions, both carbonyl compounds being recovered unchanged.

11) ^{1}H NMR: δ 0.81 (t, J = 6 Hz, 3H), 1.1-2.1 (m, 10H), 1.44 (s, 3H), 2.4-3.0 (m, 4H); ^{19}F NMR: δ ($CFCl_3$) -116.8 (d, J = 270 Hz, 1F), -121.7 (d, J = 270 Hz, 1F); IR (neat): 1795, 1745, 1155, 1105, 1070, 1005 cm^{-1}; MS (m/e): 262 (M^+), 113 (100).

12) ^{1}H NMR: δ 0.87 (t, J = 6 Hz, 3H), 1.1-2.2 (m, 13H), 2.72 (m, 2H), 3.34 (s, 6H), 4.10 (s, 1H), 4.68 (t, J = 6 Hz, 1H); ^{19}F NMR: δ ($CFCl_3$) -117.4 (d, J = 254 Hz, 1F), -120.8 (d, J = 254 Hz, 1F); IR (neat): 3465, 1740, 1190, 1120, 1070 cm^{-1}; MS (m/e): 296 (M^+), 101 (100).

13) No self-condensation products from the ketones **1** or carbonyl compounds were detected in any of these reactions.

14) Titanium trichloride- or tetrachloride-lithium aluminium hydride did not give satisfactory results. Bis(cyclopentadienyl)titanium dichloride and zinc could be employed though an equimolar amount of the titanium reagent was needed for complete reaction.

15) The bivalent titanium compound has been suggested as an actual reactive species in some related reactions. For example, see references 5a, 5c, and 6d.

16) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., **44**, 4294 (1979).

(Received April 16, 1984)