CHEMISTRY LETTERS, pp. 95-98, 1976. Published by the Chemical Society of Japan

REGIOSPECIFIC ALDOL SYNTHESIS. THE GENERATION OF ACTIVE ENOLATES BY THE REDUCTION OF 2,2,2-TRICHLOROETHYL ESTERS OF α-SUBSTITUTED-β-KETO ACIDS WITH Zn

Teruaki MUKAIYAMA*, Toshio SATO**, Seiji SUZUKI**,
Tan INOUE**, and Hideo NAKAMURA**

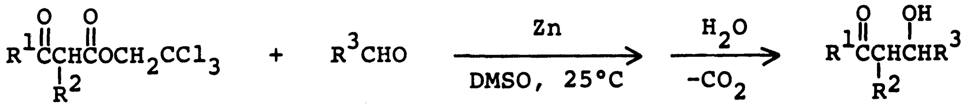
* Department of Chemistry, Faculty of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113

** Laboratory of Organic Chemistry, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152

α-Substituted-β-keto acid 2,2,2-trichloroethyl esters reacted with aldehydes regiospecifically at α-carbon to the ester carbonyl in the presence of Zn to give the corresponding aldols in good yields.

The aldol condensation reaction has been widely used as one of the most convenient methods for the formation of a new carbon-carbon bond. Concerning regiospecific aldol synthesis, several works were recently reported. Some of the intriguing examples utilize the reaction of carbonyl compounds with enolate anions generated regiospecifically by the combined use of enol silyl ethers and methyllithium (lithium enolates and metal salts), 1) that of methyl ketones and lithium diisopropylamide,2) and that of α-bromoketones and Zn.3) In a recent publication we reported the convenient method for the preparation of various cross aldols by the $TiCl_4$-promoted reaction, in which nucleophilic center was created from various enol ethers under acidic conditions.4) Considering importance of cross aldols in organic synthesis, it is also desired that active enolates can be generated under neutral conditions. In order to realize this idea we thought of incorporation of reduction process for the generation of active enolates. Here we would like to describe the generation of active enolates by the reduction of 2,2,2-trichloroethyl esters of α-substituted-β-keto acids5) with Zn.

Under mild conditions in the presence of Zn, α-substituted-β-keto acid 2,2,2-trichloroethyl esters [1]6) reacted with aldehydes specifically at α-carbon to the ester carbonyl. After hydrolysis, the corresponding aldols [2]6) were obtained in good yields accompanying the evolution of carbon dioxide.



$$R^1\overset{O}{\overset{\|}{C}}\underset{R^2}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OCH_2CCl_3 + R^3CHO \xrightarrow[\text{DMSO, 25°C}]{Zn} \xrightarrow[-CO_2]{H_2O} R^1\overset{O}{\overset{\|}{C}}\underset{R^2}{\underset{|}{C}}H\overset{OH}{\overset{|}{C}}HR^3$$

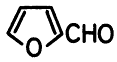
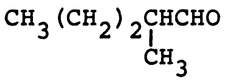
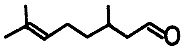
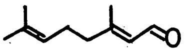
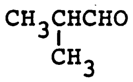
[1a, b, c] [2]

β-Keto esters[1a] (R^1=CH_3, R^2=H) and [1c] (R^1=CH_3CH_2, R^2=CH_3) were prepared by the reaction of diketene and methylketene dimer with 2,2,2-trichloroethanol at 80°C for 4 hr in the presence of a catalytic amount of sodium acetate in 65 and 80% yield, respectively. β-Keto ester [1b] (R^1=CH_3, R^2=n-Bu) was synthesized in 61% yield by the reaction of [1a] with n-butyl iodide using NaH in DMF at room temperature for 64 hr.

A typical procedure of the reaction of [1] with aldehydes is as follows: To a mixture of Zn (0.08 g, 1.22 mmol) and benzaldehyde (0.075 g, 0.71 mmol) in 2 ml of dry DMSO, [1c] (0.218 g. 0.83 mmol) in 2 ml of DMSO was added with stirring during 5 min at 25°C under argon. After the reaction mixture was stirred for 11 hr, it was poured into 10 ml of a saturated aqueous solution of NaCl at 0°C and extracted with ether. The extract was dried over anhydrous Na_2SO_4. After removal of the solvents, 5-hydroxy-4-methyl-5-phenyl-3-pentanone was isolated in 92% yield by silica gel chromatography. In a similar manner, [1] reacted with various aldehydes to afford the corresponding aldols [2] in good yields as shown in Table 1.

When [1b] was treated with Zn in DMSO-d6,the nmr spectrum7) of the reaction mixture showed the signal of methyl adjacent to olefin at δ2.10 and the signal of the methine proton at the α-carbon disappeared. Most of the carbon dioxide was evolved on quenching the reaction mixture with H_2O. Based on these facts, the reaction might have proceeded as sketched in the following Scheme 1. A trichloroethyl ester is first reduced by Zn8) to produce presumably zinc salt [3] with concomitant elimination of dichloroethylene. The chelate intermediate [4] would likely be formed after elimination of hydrogen chloride from[3]. Chelate[4] would react with aldehydes to afford the proposed intermediate [5]. Hydrolysis of [5]

Table 1. Synthesis of Aldols from [1a, b, c] and Aldehydes.

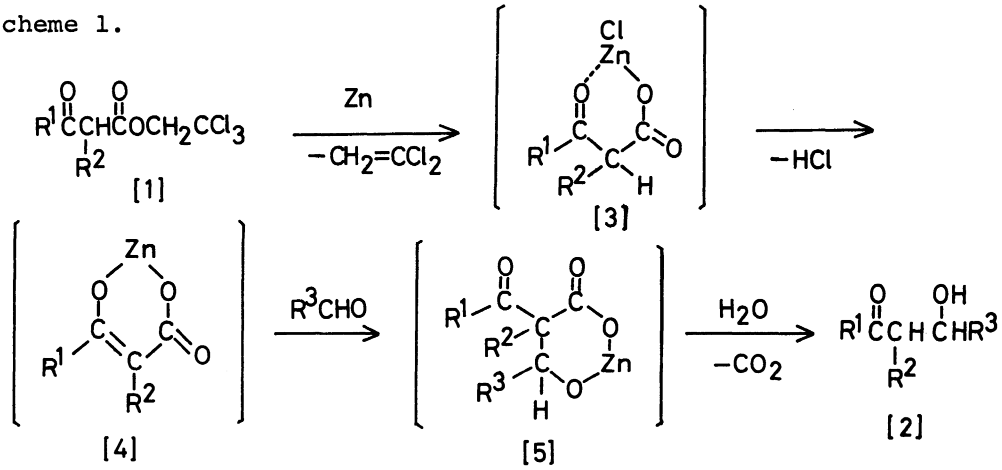
Run	Reactants[a] β-Keto Esters	Reactants[a] Aldehydes	Reaction Time(hr)	Yields of Aldols [2], %[a] (Ratio of Isomers[f]:Threo/Erythro)
1	[1a]	$C_6H_5CH_2CH_2CHO$	4.5	48[b]
2	[1b]	$C_6H_5CH_2CH_2CHO$	8	82
3	[1b]	C_6H_5CHO	8	86 (1.0)[g]
4	[1b]	$p\text{-}ClC_6H_4CHO$	1.2	92 (0.74)
5	[1b]	$p\text{-}CH_3OC_6H_4CHO$	1.2	80
6	[1b]	$p\text{-}NO_2C_6H_4CHO$	6	70
7	[1b]		5	80 (3.0)
8	[1b]	CH_3CHO	19	90[c]
9	[1b]	CH_3CH_2CHO	16	89[c]
10	[1b]	 $CH_3(CH_2)_2\underset{\mid \atop CH_3}{CH}CHO$	19	72
11	[1b]		16	82
12	[1b]		1.2	79 (1.6)
13	[1c]	$C_6H_5CH_2CH_2CHO$	11	70[d]
14	[1c]	C_6H_5CHO	11	92
15	[1c]	 $CH_3\underset{\mid \atop CH_3}{CH}CHO$	9	61[e]

---

[a] The molar ratio of [1], aldehyde and Zn was 1.1-1.2 : 1.0 :1.5, and yields were based on aldehydes except Runs 8,9,15. [b] In this case, the corresponding α,β-unsaturated ketone, 6-phenyl-3-hexen-2-one, and its Michael adduct with acetone produced, 4-phenethyl-2,6-heptanedione, were isolated in 29 and 11% yield, respectively. [c] The mole ratio of aldehyde/[1b] was 4.0. Yields were based on [1b]. [d] The corresponding α,β-unsaturated ketone, 4-methyl-7-phenyl-4-hepten-3-one, was isolated in 19% yield. [e] The mole ratio of aldehyde/[1c] was 1.5. The yield was based on [1c]. [f] The threo- and erythro- isomers were separated by silica gel chromatography, and the configuration of the stereo-isomers was determined by nmr spectrum. Each of the isomers has a doublet due to the proton (Ha) of the CH-O- group or the other tertiary hydrogen (Hb), and the comparison of the coupling constant (Jab) of the isomers suggests the configuration.[1)]

[g] The spectral properties of these isomers were identical with published data.[1)]

Scheme 1.



would then afford the corresponding aldols. In the case of the reaction of [1a], where R^2 is hydrogen, with 3-phenylpropanal, a considerable amount of the corresponding α,β-unsaturated ketone and Michael adduct were isolated (see Table 1). The elimination reaction to form the unsaturated ketone takes place readily from [5] having an acidic hydrogen atom.

It was also found that DMSO works better as a solvent than DMF, HMPA, and CH_3CN with respect to rate of reaction and yield of aldol. Examination of the effect of halogen functionality in the haloethyl esters showed that the yields of the aldol in the reaction of 2,2,2-tribromoethyl acetoacetate (12%) and 2-iodoethyl acetoacetate (36%) with 3-phenylpropanal were lower than that in the reaction of 2,2,2-trichloroethyl acetoacetate [1a] (48%).

Clearly, these results demonstrate that under very mild conditions, 2,2,2-trichloroethyl esters of β-keto acid can undergo efficient regiospecific replacement of trichloroethoxycarbonyl group with β-hydroxyalkyl group originated in aldehyde to produce α-substituted-β-hydroxy ketones.

References and Notes

1) H.O.House, O.S.Crumrine, A.Y.Teranishi, and H.D.Olmstead, J.Amer.Chem. Soc., 95 3310 (1973); G.Stork and P.F.Hudrlik, J.Amer.Chem.Soc., 90, 4462, 4464 (1968).
2) G.Stork, F.A.Kraus, and G.A.Garcia, J. Org. Chem., 39, 3459 (1974).
3) T.A.Spencer, R.W.Briton and D.S.Watt, J. Amer. Chem. Soc., 89, 5727 (1967).
4) T.Mukaiyama, K.Banno, and K.Narasaka, J. Amer. Chem. Soc., 96, 7503 (1974).
5) Although the aldol synthesis by the reaction of β-keto acid and aldehyde in pH 7~8 buffer solution was already known, the reaction period was long and the yield was low. C.Schöpf and K.Thierfelder, Ann., 518, 127 (1935); M.Stiles, D.Wolf, and G.V.Hudson, J. Amer. Chem. Soc., 81, 628 (1959); M.S.Schechter, N.Green, and F.B.LaForge, J. Amer. Chem. Soc., 71, 3165 (1949).
6) All new compounds in this paper showed satisfactory ir and nmr data.
7) The nmr spectrum of Ib (CCl_4): δ4.75 (2H, s, $-OCH_2CCl_3$), 3.45 (1H, triplet, J = 7 Hz, COCH<), 2.22 (3H, s, CH_3CO), 0.6~2.0 (9H, m, aliphatic CH).
8) Reduction with Zn has been effectively used in the removal of the trichloroethyl group from esters. E.Kasafirek, Tetrahedron Lett., 2021 (1972); M.F.Semmelhack and G.E.Heinsohn, J. Amer. Chem. Soc., 94, 5139 (1972).

(Received November 21, 1975)