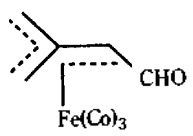
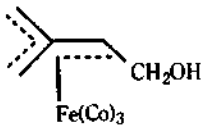
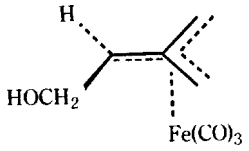


1



2



3

agent mentioned above, the ee of the obtained aldehyde ($[\alpha]_D$ +248°; c = 0.45, CH_2Cl_2) was found to be 89%. The alcohol obtained by the enzymic reduction was recrystallised several times in pentane and after two recrystallisations, the melting point and specific rotation remained constant on further recristallisations : mp. 64–65 °and $[\alpha]_D$ +47 °(c = 0.4, CH_2Cl_2). Thus HLADH catalyses the reduction of both enantiomers of aldehyde **1** with a kinetic sufficiently different so that partial resolution can be achieved during the enzymic reduction (17).

Since its substrate specificity has been related to its tridimensional structure in the diamond lattice[18,19] and the cubic space model[20], we attempted to explain with these models the enantioselective reduction of aldehyde **1**. The HLADH molecular model of the substrate was built with the bond lengths and angles published for phenyl trimethylenemethane iron tricarbonyl[21,22]. The two enantiomers of aldehyde **1** were built in the cubic-space model and the Kendrew model of the active site was used. We assumed that hydride is delivered to the Re face of the carbonyl group for both enantiomers. We analyzed the (1-S) 1-formyl trimethylene methane iron tricarbonyl forms a complex with fewer violations of forbidden regions than the (1-R) enantiomer dose. On the basis of this analysis, the (+) 1-hydroxymethyl trimethylene methane iron tricarbonyl ($[\alpha]_D$ +47 °), produced more rapidly in the enzyme reduction of (±) aldehyde **1**, is tentatively proposed to be of (1-S) chirality as presented in formula **3**. Enantioselective hydrolysis by pig liver esterase and enantioselective reduction by baker's yeast of organometallic compounds has been described[23-26].

The work illustrates the preparative use of horse liver alcohol dehydrogenase in microemulsion for the stereoselective reduction of carbonyl compounds of low water solubility with cofactor recycling.

Acknowledgement. This work was supported in part by ELF Aquitaine.

References and Notes

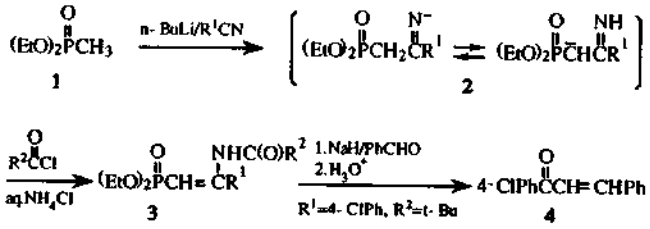
1. P. L. Luisi, *Angew. Chem. Int. Ed. Engl.* **24**, 439 (1985).
2. K. Martinek, A. V. Levashov, N. L. Klyachko, Y. L. Khmelnitske, and I. V. Berezin, *Eur. J. Biochem.* **155**, 453 (1986).
3. M. Waks, *Proteins* **1**, 4 (1986).
4. K. M. Lee and J. F. Biellmann, *Bioorg. Chem.* **14**, 262–273 (1986).
5. L. M. Lee and J. F. Biellmann, *Nouv. J. Chimie*, **10**, 675 (1986).
6. K. M. Lee and J. F. Biellmann, *Tetrahedron*, **44**, 1135–1139 (1988).
7. C. I. Branden, H. Jornvall, H. Eklund, and B. Furngren, The Enzymes, Vol. 11, Boyer R. Ed., Academic Press, p. 104 (1975).
8. J. P. Samama, K. M. Lee and J. F. Biellmann, *Eur. J. Biochem.* **163**, 609–617 (1987).
9. K. M. Lee, and J. F. Biellmann, *FEBS Letters*, **223**, 33–36 (1987)
10. K. M. Larsson, C. Oldfield and R. B. Freedman, *Eurl. J. Biochem.* **183**, 357–361 (1989).
11. B. R. Bonazza, C. P. Lillya, E. S. Magyar, and G. Scholes, *J. Amer. Chem. Soc.* **101**, 4100 (1979).
12. K. Ehrlich and F. G. Emerson, *J. Amer. Chem. Soc.* **94**, 2464 (1972).
13. M. P. Heitz, Thèse de Doctorat, Université Louis Pasteur, Strabourg, 1983; M. Franck-Neumann, D. Martina and M. P. Heitz, *Tet. Let.*, 6679 (1989).
14. R. Einarsson, L. Wallen and M. Zeppezaure, *Chemica Scripta*, **2**, 84 (1972).
15. Enzyme and NAD$^+$ were purchased from Boehringer-Mannheim. We used commercial enzyme directly without purification.
16. The ^{1}H-NMR of aldehyde 1 is given in ref. 11. The aldehydic proton of aldehyde **1** δ = 8.96 ppm (d, J = 7.5 Hz; $CDCl_3$) was shifted and gave two doublets when 0.3 eq. of the chiral agent (M. D. McCreary, D. W. Lwis, D. L. Wernick, and G. M. Whitesides, *J. Amer. Chem. Soc.* **96**, 1038–1054) was added. The ee was determined from area ratio. (1974).
17. Both enantiomers of 2-octanol are oxidised by the same enzyme: F. M. Dickinson and K. Daiziel, *Biochem. J.* **104**, 165 (1967).
18. V. Prelog, *Pure Appl. Chem.* **9**, 119 (1964).
19. H. Dutle and C. I. Branden, *Bioorg. Chem.* **10**, 1 (1981).
20. J. B. Jones and I. J. Jakovac, *Canad. J. Chem.* **60**, 19–28 (1982).
21. M. R. Churchill and K. Gold, *J. Chem. Soc. Chem. Comm.* 693 (1968)
22. M. R. Churchill and K. Gold, *Inorg. Chem.* **8**, 401 (1969).
23. N. W. Alcock, D. H. G. Crout, C. M. Henderson, and S. E. Thomas, *J. Chem. Soc. Chem. Comm.* 746–747 (1988).
24. J. Gillois D. Buisson, R. Azerad, and G. Jaouen, *J. Chem. Soc. Chem. Comm.* 1224–1225 (1988).
25. S. Top, G. Jaouen, J. Gillois, C. Baldoli, and Maiorana, S. *J. Chem. soc. Chem. Comm.* 1284–1285 (1988).
26. Y. Yamazaki, M. Uebayasi and K. Hosono, *Eur. J. Biochem.* **184**, 671–680 (1989).

Tandem Addition of α-Lithiomethane Phosphonate to Nitriles–N-Acylation: A Convenient Route to Enamine Phosphonates

Kilsung Lee and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science & Technology, Seoul 130–650

Received June 12, 1990



Scheme 1.

Table 1. Preparation of Enamine Phosphonates **3**

Product	R^1	R^2	Yield (%)[a]	^{1}H NMR[b] O ‖ P CH = C
3a	Ph	Ph	67(16)	5.03, d, J = 11Hz
3b	Ph	4-ClPh	78(10)	4.98, d, J = 12Hz
3c[c]	Ph	$N(Me)_2$	36(27)	4.80, d, J = 11Hz
3b	Ph	t-Bu	76(10)	5.00, d, J = 12Hz
3e	4-ClPh	Ph	75(12)	5.08, d, J = 11Hz
3f	4-ClPh	t-Bu	82(10)	4.95, d, J = 11Hz
3g	4-MePh	Ph	60(13)	4.84, d, J = 10Hz

[a]Isolated yield, the values given in parenthesis are yield of the corresponding β-keto phosphonates. [b]Obtained in $CDCl_3$ and expressed in δ (ppm) downfield from TMS, d = doublet. [c]The reaction time was 3 h at room temperature after the addition of dimethylcarbamyl chloride.

In the course of our investigations into synthetic utility of nitrile group,[1] we have further studied the nucleophilic addition of α-lithioanion of diethyl methylphosphonate to nitriles followed by subsequent acylation and isomerization to give enamine phosphonates, which is used as the basis for an efficient synthesis of α,β-unsaturated ketones and β-ketophosphonates.[2]

As shown in Scheme 1, α-lithiomethane phosphonates react with nitriles to give ketimine intermediates **2**, which react with acyl halides and subsequently isomerized in saturated NH_4Cl solution to give enamine phosphonates **3**. Our results are summarized in the Table 1. All but one of the acyl derivatives studied gave satisfactory yields along with a small amount of corresponding β-ketophosphonates (10–27%).

Among several acylating agents tested in this study, trimethylacetyl chloride gave the best results. The β-keto phosphonates are derived from the unreacted ketimine intermediates, which is proved by TLC.

Although the anion **2** is more nucleophilic at carbon than it is at nitrogen, the acylation occurs only at nitrogen. The ketimine → enamine isomerization takes place very rapidly. The driving force for this isomerization may be attributed to the conjugation of the two activating groups with the amino group[3].

As an example for the synthesis of α,β-unsaturated ketones with N-acylated enamine phosphonates obtained by our procedure, we have treated that enamine phosphonate (**3f**) successively with NaH–PhCHO–hydrolysis (**3** → **4**). As expected, 4'-chlorochalcone was obtained in nearly quantitative yield (93%). In summary, the α-lithiomethane phosphonate addition–N-acylation–isomerization of nitriles to form enamine phosphonates has been established as an attractive synthetic method.

Experimental

General procedure for 1 → 3. To a stirred solution of diethylmethane phosphonate (1.1 mmol) in dry THF (3 m*l*), is added n-butyllithium (1.1 mmol, 1.6 M in hexane) at −78 °C under nitrogen atmosphere. After being stirred for 1 h at −78 °C, nitrile (1 mmol) is added and the reaction mixture is warmed to −5 °C for 2 h. Acyl halide (1 mmol) is added dropwise at −78 °C and stirred for 30 min at −78 °C. Usual work up with sat. aq. NH_4Cl give the crude enamine phosphonates, which is purified by short-path column chromatography on silica gel (8/2: hexane/ethylacetate).

Procedure for 3 → 4. To a suspension of NaH (1 mmol) in dry THF (3 m), is added 1 mmol of enamine phosphonate (3f, R^1=4-ClPh, R^2=t-Bu) at 0° under nitrogen atmosphere. The reaction mixture is stirred for additional 5 min at 0 °C to allow completion of the H_2 evolution. Benzaldehyde (1 mmol) is added and the solution is refluxed for 10 h. Hydrolysis is accomplished directly by addition of 10% oxalic acid (1 m*l*) for 8 h at room temperature. Normal work-up give the 4'-chlorochalcone, which is purified by short-path column chromatography on silica gel (10/1: hexane/ethylacetate). mp: 93–95 °C, ^{1}H-NMR (δ, $CDCl_3$): 7.17–8.10 (11H, m). IR (cm^{-1}, KBr): 1660 (C=O), 1590 (C=C). MS (%): 244 (M+2, 16.1), 242 (57.9), 241 (72.4), 207 (37.7), 179 (82.2), 139 (42.8), 111 (100), 77 (97.9).

References

1. K. Lee and D. Y. Oh, *Bull. Kor. Chem. Soc.*, **10**, 613 (1989)
2. (a) W. Nagata and Y. Hayase, *Tetrahedron Lett.* 4359 (1963). (b) N. A. Portnoy, C. J. Morrow, M. S. Chattha, J. C. Jr. Williams, and A. M. Aguiar, *Tetrahedron Lett.*, **18**, 1397 (1971). (c) *Idem*, **17**, 1401 (1971). (d) M. S. Chattha and A. M. Aguiar, *Tetrahedron Lett.*, 18, 1419 (1971). (e) M. S. Chattha and A. M. Aguiar, *J. Org. Chem.*, **38**, 2908 (1973).
3. In the case of the intramolecular nucleophilic addition to the nitrile group, the isomerization often has occurred, see (a) D. Taub, C. H. Kuo and N. L. Wendler, *J. Chem. Soc.* (b), 1558 (1967). (c) H. E. Schroeder and G. W. Rigby, *J. Am. Chem. Soc.*, **71**, 205 (1949).

Carbonylation of Benzal Chloride to Alkyl Phenylacetates using $Co_2(CO)_8$ Catalyst

Sang Chul Shim*, Chil Hoon Doh, and Chan Sik Cho

Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701

Received August 16, 1990

The technology of transition metal complexes catalyzed