The increase in "local bulkiness" at the aldehyde α-carbon going from tetradecanal to phenylacetaldehyde to benzaldehyde to pivaldehyde results in a shift from 1:1 erythro/threo to exclusively erythro products. The observed shift toward erythro selectivity can be rationalized by either the acyclic anti-A or cyclic syn-A transition states (Figure 1). However, syn-A should be unfavorable relative to syn-B for large "R", and thus anti-A best explains the shift to higher erythro/threo ratios with increasing bulkiness. An analogous anti transition state was proposed by Yamamoto[14b] to account for the erythro selectivity of the reaction of crotyltrialkyltins with aldehydes. If R is small or if a divalent cation is added, the cyclic syn transition states can become energetically more favorable than the more charge-separated acyclic anti transition states. When this occurs for R small, little selectivity will result, and erythro/threo ratios near 1:1 will be observed. To summarize, as R increases in bulk, a cyclic transition state would result in a shift to threo (syn-B) with the R group pseudoequatorial. We believe that the observed shift to erythro selectivity is best rationalized by the minimization of steric interactions and maximal separation of negative charge provided by the acyclic anti-A transition state, although a pseudoboat cyclic transition state[15] is not strictly excluded by our results. Application of these data to 1,2- and 1,3-asymmetric induction of chirality in natural products synthesis will be reported in due course.

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Registry No. **3a**, 78987-06-1; **4**, 78986-53-5; **5a**, 78986-54-6; **5b**, 79005-32-6; **5c**, 78986-55-7; **5d**, 78986-56-8; **5e**, 78986-57-9; **6a**, 78986-58-0; **6b**, 78986-59-1; **6c**, 78986-60-4; **6d**, 78986-61-5; **7a**, 79081-93-9; **7b**, 79081-94-0; **7d**, 79055-74-6; benzaldehyde, 100-52-7; phenylacetaldehyde, 122-78-1; pivaldehyde, 630-19-3; tetradecanal, 124-25-4; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; 3-methylbut-3-enyl bromide, 20038-12-4; 1-hexadecanol methanesulfonate, 20779-14-0; allyl bromide, 106-95-6; benzyl bromide, 100-39-0.

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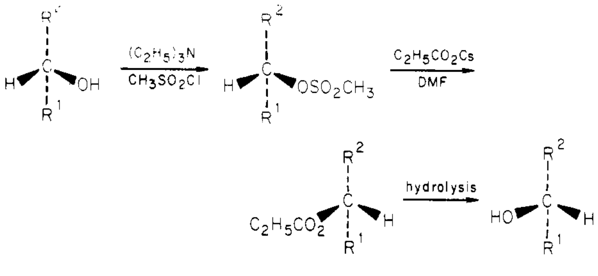
Cesium Carboxylates in Dimethylformamide. Reagents for Introduction of Hydroxyl Groups by Nucleophilic Substitution and for Inversion of Configuration of Secondary Alcohols

Summary: Cesium carboxylates, in particular the propionates, in dimethylformamide solvent give clean S_N2 substitutions on a variety of compounds.

Sir: Cesium carboxylates in dimethylformamide (DMF) are good nucleophiles.[1] In this solvent the large and polarizable cesium ion lends to the ion pair properties including nucleophilicity that lie at the heart of a recently described method for ring closure of ω-halo cesium carboxylates to macrolides.[2] We anticipated on the basis of this work that cesium carboxylates also would be useful for introduction of hydroxy substituents by intermolecular S_N2 nucleophilic substitution.

The nucleophile chosen for investigation is cesium propionate, prepared from Cs_2CO_3 and propionic acid;[3] this is a powder that can be readily dried and which is soluble (0.1 M) in DMF. Results for a variety of substitution reactions are given in Table I.

The overall scheme for alcohol inversion (entries 1–7) is given in eq 1. This approach complements two other



(1)

frequently used methods, namely, reaction of the alcohol with $RO_2CN{=}NCO_2R/(C_6H_5)_3P/RCO_2H$ to afford the inverted alcohol ester of RCO_2H[4] or treatment of the mesylate with KO_2/crown ether.[5] The inversion of (*S*)-2-octanol to the enantiomerically pure *R* enantiomer using the cesium propionate method (entry 1) proceeds in 86% overall isolated yield without detectable amounts of elimination. Inversion of (*S*)-2-octanol with $C_2H_5O_2CN{=}NCO_2C_2H_5/(C_6H_5)_3P/C_6H_5CO_2H$ is reported to afford the inverted benzoate in 20% yield[6] whereas reaction of (*S*)-2-octyl mesylate with KO_2/dibenzo-18-crown-6 gives (*R*)-2-octanol in 75% yield with 23% elimination (GLC yields).[7]

The cesium propionate method is also compatible with other functional groups as shown by the remarkably clean conversion without detectable amounts of elimination or racemization of ethyl (*S*)-lactate (entry 4) to its *R* enantiomer (isolated as propionate; hydrolysis to (*R*)-lactic acid involves loss of material owing to isolation difficulties). The problem of base-catalyzed enolization occurs, however, for ethyl (*S*)-mandelate (entry 5), the propionate of which, prepared independently, racemized completely within 24 h at 50 °C with $CsO_2CC_2H_5$/DMF. Racemization is slower for the corresponding *N,N*-dimethyl amide (entry 6), which has a lesser tendency to form an enolate. Use of the amide together with the less basic cesium benzoate (entry 7) leads to the desired *R* enantiomer in 93% optical purity.

For the cases of the mesylates of menthol and cholestanol (entries 2 and 3) some elimination occurs in competition with the desired substitution. The inversion of cholestanol using the Mitsunobu method is reported to give a quantitative yield of inverted benzoate.[8] Other leaving groups can be used with cesium propionate (entries 9–12).

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(1) Wang, S. S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.

(2) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.*, in press; *J. Chem. Soc., Chem. Commun.* **1979**, 286.

(3) The preparation of $CsO_2CC_2H_5$ is carried out by dissolving Cs_2CO_3 (5 mmol) in 40 mL of dry CH_3OH. To this solution is added dropwise propionic acid (15 mmol) in 10 mL of dry CH_3OH. An excess of propionic acid is necessary to obtain complete reaction. After 30 min the CH_3OH is removed, and the white powder remaining is washed on a filter thoroughly with $(C_2H_5)_2O$.

(4) Review: Mitsunobu, O. *Synthesis* **1981**, 1.

(5) (a) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183. (b) See also: Sawyer, D. T.; Gibian, M. J. *Tetrahedron* **1979**, *35*, 1471.

(6) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.

(7) San Filippo, J., Jr.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1678.

(8) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.

0022-3263/81/1946-4321$01.25/0

Table I. Substitution Reaction with Cesium Propionate[a]

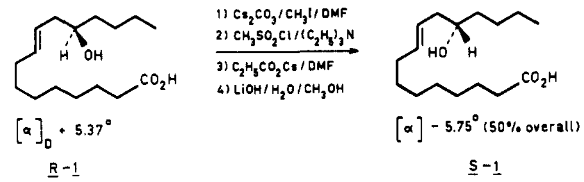
entry	starting matl ([α])	reaction conditions (yield, %)	product ([α])	overall isolated yield, %
1	(*S*)-2-octanol [[α]$^{20}_{D}$ +9° (*c* 10, $CHCl_3$)]	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (96), (b) $CsO_2CC_2H_5$/DMF/40 °C/24 h (100), (c) 5% $KOH/CH_3OH/H_2O$ (90)	(*R*)-2-octanol ([α]$^{20}_{D}$ −8.9° (*c* 10, $CHCl_3$))[b]	86
2	(1*R*)-menthol	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (96), (b) $CsO_2CC_2H_5$/DMF/100 °C/48 h (50), (c) 5% $KOH/CH_3OH/H_2O$ (100)	(1*R*)-neomenthol[c,d]	48
3	5α-cholestan-3β-ol	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (90), (b) $CsO_2CC_2H_5$/DMF/90 °C/24 h (90), (c) 5% $KOH/CH_3OH/H_2O$ (100)	5α-cholestan-3α-ol[e,d]	81
4	ethyl (*S*)-2-hydroxypropionate [[α]$^{20}_{D}$ −41.8° (*c* 5, $CHCl_3$)][f]	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (74), (b) $CsO_2CC_2H_5$/DMF/90 °C/3 h (90)	ethyl (*R*)-2-propionoxypropionate ([α]$^{20}_{D}$ +41.9° (*c* 5, $CHCl_3$))[g,h]	67
5	methyl (*S*)-2-hydroxy-2-phenylacetate [[α]$^{20}_{D}$ +130° (*c* 1, CH_3OH)]	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (70), (b) $CsO_2CC_2H_5$/DMF/50 °C/24 h (75), (c) $KOH/CH_3OH/H_2O$ (100)	methyl 2-hydroxy-2-phenylacetate ([α]$^{20}_{D}$ 0° (*c* 1, CH_3OH))	53
6	(*S*)-2-hydroxy-2-phenyl-*N,N*-dimethylacetamide [[α]$^{20}_{578}$ +143° (*c* 1, $C_2H_2Cl_4$)][i]	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (87), (b) $CsO_2CC_2H_5$/DMF/40 °C/24 h (83), (c) 5% $KOH/CH_3OH/H_2O$ (100)	(*R*)-2-hydroxy-2-phenyl-*N,N*-dimethylacetamide ([α]$^{20}_{578}$ −108° (*c* 1, $C_2H_2Cl_4$))[j]	73
7	same as entry 6	same as entry 6 but with $CsO_2CC_6H_5$/DMF/40 °C/21 h (70)	(*R*)-2-(benzoyloxy)-2-phenyl-*N,N*-dimethylacetamide ([α]$^{20}_{D}$ −166° (*c* 0.6, $CHCl_3$))[k]	70
8	benzyl methanesulfonate	(a) $CsO_2CC_2H_5$/DMF/20 °C/24 h (100), (b) 5% $KOH/CH_3OH/H_2O$ (80)	benzyl alcohol	80
9	(*RS*)-2-bromooctane	(a) $CsO_2CC_2H_5$/DMF/20 °C/24 h (98), (b) 5% $KOH/CH_3OH/H_2O$ (100)	(*RS*)-2-octanol[l]	96
10	*trans*-3-hexen-1-ol	(a) $CH_3SO_2Cl/(C_2H_5)_3N$ (90), (b) $CsO_2CC_2H_5$/DMF/40 °C/24 h (90), (c) 5% $KOH/CH_3OH/H_2O$ (100)	*trans*-3-hexen-1-ol	81
11	1-iodoheptane	(a) $CsO_2CC_2H_5$/DMF/60 °C/24 h (100), (b) 5% $KOH/CH_3OH/H_2O$ (100)	1-heptanol	100
12	ethyl 2-bromopropionate	(a) $CsO_2CC_2H_5$/DMF/20 °C/24 h (84)	ethyl (*RS*)-2-propionoxypropionate[m]	84

[a] For the S_N2 substitutions the concentrations are 0.1 M in both reactants. All yields reported are those of isolated products although in most cases intermediates were used in crude form to reduce loss of material. [b] No octenes could be detected by GLC. [c] 50% elimination to form menthene occurs. [d] Physical constants were identical with those of authentic material. [e] 8% elimination occurs. [f] This is the rotation of ethyl (*S*)-2-propionoxypropionate prepared by reaction of ethyl (*S*)-2-hydroxypropionate with propionyl chloride. [g] No elimination products detected. [h] In control experiments it was established that racemization occurs in the substitution step rather than during hydrolysis of the ester. [i] Starting material not optically pure: lit. (Freudenberg, K.; Todd, J.; Seidler, R. *Justus Liebigs Ann. Chem.* **1933**, *501*, 199) [α]$^{20}_{578}$ −162° (*c* 1, $C_2H_2Cl_4$) for the *R* enantiomer. [j] This corresponds to an optically purity of 76%. [k] (*S*)-2-(Benzoyloxy)-2-phenyl-*N,N*-dimethylacetamide prepared by treatment of alcohol with benzoyl chloride has [α]$^{20}_{D}$ +178° (*c*3, $CHCl_3$); this corresponds to an optical purity of 93%. [l] Alkene (4%) could be detected by GLC. [m] No acrylate could be detected.

In our hands no detectable amounts of elimination occurred in the reactions (not listed in Table I) of methyl (*RS*)-2-chloropropionate, 3-chloro-2-butanone, and ethyl 2-bromobutanoate. Elimination was the only reaction observed, however, with ethyl (*RS*)-3-bromobutanoate, the mesylate of diethyl malate, or the acetate of 2-hydroxysuccinic anhydride (malic acid anhydride).

To determine the effect of (or need for) cesium ions, we investigated the substitution of menthol mesylate using Na^+, K^+, Rb^+, and Cs^+ propionates. As reported in Table I (entry 2) a clean reaction affording 50% propionate and 50% Δ^3-menthene was obtained by using cesium propionate. Under similar conditions (DMF/100 °C/72 h) complex product mixtures were isolated in 60%, 57%, and 51% crude yields using, respectively, Rb^+, K^+, and Na^+ propionates. Only in the rubidium reaction was an appreciable amount of propionate present. These mixtures were not investigated further. The difference among the salts is less pronounced, however, for 2-octyl mesylate, which is more easily displaced. By use of the procedure of Table I, entry 1, (*R*)-2-octanol was obtained in 74%, 81%, and 74% overall isolated yields, respectively, by using Rb^+, K^+, and Na^+ propionates. For sodium propionate the enantiomeric excess of (*R*)-2-octanol dropped to 83%. Substitution on the mesylate of ethyl (*S*)-lactate goes cleanly with sodium propionate in DMF, but in no instance could acceptable inversions on derivatives of ethyl (*S*)-mandelate be obtained by using this reagent. Our general experience has been that reactions of cesium salts are by far the cleanest and fastest, owing in part to the good solubility of cesium propionate in DMF.

Another application of cesium propionate is illustrated in eq 2 in which the homoallylic alcohol functionality of (*R*)-ricinealaidic acid ((*R*)-1) is converted to the *S* enantiomer in 51% overall yield. About 30% elimination occurs together with the desired substitution. Neither KO_2/crown



(2)

ether nor $C_2H_5O_2CNNCO_2C_2H_5/(C_6H_5)_3P/C_6H_5CO_2H$ gave acceptable results.[9,10]

Acknowledgment. We thank Professor D. Seebach, ETH Zürich, for providing us with an unpublished method for the transesterification of propionate esters.[11]

Registry No. (*R*)-1, 540-12-5; (*S*)-2-octanol, 6169-06-8; (1*R*)-menthol, 2216-51-5; 5α-cholestan-3β-ol, 80-97-7; ethyl (*S*)-2-hydroxypropionate, 687-47-8; methyl (*S*)-2-hydroxy-2-phenylacetate, 21210-43-5; (*S*)-2-hydroxy-2-phenyl-*N*,*N*-dimethylacetamide, 79043-43-9; benzyl methanesulfonate, 55791-06-5; (*RS*)-2-bromooctane, 60251-57-2; *trans*-3-hexen-1-ol, 928-97-2; 1-iodoheptane, 4282-40-0; ethyl-(*RS*)-2-bromopropionate, 41978-69-2; cesium propionate, 38869-24-8; cesium benzoate, 17265-04-2.

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[9] In the reaction of the methyl ester of (*R*)-1 with $C_2H_5O_2CN{=}NCO_2C_2H_5/(C_6H_5)_3P/C_6H_5CO_2H$ the benzoate obtained was almost completely racemic. The cause of the racemization has not been determined. The mesylate of the methyl ester of (*R*)-1 with excess KO_2/dibenzo-18-crown-6 gave impure methyl ester of (*S*)-1 in poor yield; separation from the large excess of crown ether was difficult.

[10] For a recent report on the use of cesium fluoride in DMF as a catalyst see: (a) Mukaiyama, T.; Murakami, M.; Yamaguchi, M. *Chem. Lett.* **1980**, 529. (b) Mukaiyama, T.; Pai, F.-C.; Onaka, M.; Narasaka, K. *Ibid.* **1980**, 563.

[11] Seebach, D.; Hungerbühler, E.; Schnurrenberger, P.; Weidmann, B.; Züger, M., submitted for publication in *Synthesis*.

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Preparation of Highly Reactive Metal Powders. A New Procedure for the Preparation of Highly Reactive Zinc and Magnesium Metal Powders

Summary: Highly reactive zinc and magnesium metal powders can be prepared by the lithium reduction of the corresponding metal salt with a catalytic amount of naphthalene as an electron carrier. Applications to the Reformatsky reaction, the Grignard reaction, and cyclopropanation (with dibromomethane) are described.

Sir: Earlier we had reported the preparation of highly reactive zinc and magnesium metal powders from the potassium or sodium reduction of the corresponding metal salt.[1–4] We now report a new general approach for the preparation of these highly reactive metal powders, using lithium as a reducing agent.[5] In the case of zinc, this results in far more reactive metal powders which can be used in several reactions with special advantage.

The highly reactive zinc is readily prepared by the reduction of anhydrous zinc chloride with 2.1 equiv of lithium and a small amount of naphthalene (10% based on the number of moles of lithium) in freshly distilled glyme under an argon atmosphere.[8] The solution is stirred at room temperature for 15 h to complete the reduction. When the stirring is stopped, the very finely divided black zinc particles settle out, leaving a clear colorless solution above the black powder. In some cases, the solution may appear more or less green due to the presence of some lithium naphthalide. This causes no problems in further reactions and can be ignored or, if desired, the clear solution can be removed by syringe and replaced with fresh dry glyme (this process being repeated 2 or 3 times). In this manner, the naphthalene which acts as an electron carrier in the reduction can be removed and a variety of other solvents added if desired.[15] With regard to the solvent in which the reduction is carried out, glyme is definitely the best solvent. Use of tetrahydrofuran leads to a zinc powder of much reduced reactivity and reduction does not proceed at all in diethyl ether. Also, the anion is of critical importance, with chloride being clearly superior.

The exceptional reactivity of the zinc powders is clearly demonstrated by several reactions. The reduction of anhydrous zinc chloride with potassium in glyme yields a zinc powder which will react with bromobenzene.[10] When the solution is refluxed in glyme for 18 h, 41% of the bromobenzene reacted. In contrast, zinc prepared by lithium reduction of zinc chloride in glyme reacts with bromobenzene under reflux to give 73% reaction in only 10 h.

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[1] Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178.

[2] Rieke, R. D.; Hudnall, P. M.; Uhm, S. *J. Chem. Soc., Chem. Commun.* **1973**, 269.

[3] Rieke, R. D.; Bales, S. E. *J. Chem. Soc., Chem. Commun.* **1973**, 789.

[4] Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775.

[5] We had earlier reported using this approach to prepare highly reactive transition metals.[6,7]

[6] Rieke, R. D.; Kavaliunas, A. V.; Rhyne, L. D.; Fraser, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 246.

[7] Kavaliunas, A. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 5944.

[8] An example of a typical reduction for zinc is as follows. Into a 50-mL, two-necked, round-bottomed flask is placed 0.35 g (0.0504 mol) of lithium,[9] 3.27 g (0.0240 mol) of zinc chloride, 0.65 g (0.00507 mol) of naphthalene, and 16.0 mL (0.154 mol) of 1,2-dimethoxyethane. This is stirred at room temperature until the reduction is complete (about 15 h). The activated zinc appears as a fine black powder which settles out of the solution after the stirring is stopped for some time (about 1 h). The zinc chloride was purchased from Cerac, Inc., Milwaukee, WI, and was 99.5% pure and anhydrous. The combination Li (1.84 g, 0.265 mol), $ZnCl_2$ (17.21 g, 0.126 mol), naphthalene (2.23 g, 0.0174 mol), 1,2-dimethoxyethane (95 mL, 0.912 mol) in a 250-mL flask has also been successfully used.

[9] Lithium (99.9%, rod, 1.27-cm diameter) from Alfa has been used extensively in our studies. The lithium is cut under oil, rinsed in hexane, and trasferred to a tared 24/40 adapter with a stopcock and rubber septum which has been filled with argon. The adapter is evacuated to pump off the hexane, filled with argon, and weighed. The lithium is then transferred to the reaction vessel under an argon stream.

[10] For exact details for the preparation of zinc with potassium or sodium, see ref 11.

[11] Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.

[12] A 1:1 ratio of α-halo ester to aldehyde or ketone was normally employed. The ratio of zinc to α-halo ester was normally 1:0.9.

[13] A typical reaction follows. A 50-mL, two-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, rubber septum, and condenser connected to an argon inlet. The flask is charged with 0.224 g (0.033 mol) of freshly cut lithium,[9] 1.57 g (0.0165 mol) of anhydrous magnesium chloride (Cerac, Inc.), 0.436 g (0.0034 mol) of naphthalene and 10–20 mL of tetrahydrofuran. The mixture is stirred vigorously at room temperature for 24 h.[14] After complete reduction, the highly reactive magnesium appears as a dark gray to black powder, which slowly settles when stirring is stopped. In some cases, the tetrahydrofuran has a slight olive green color due to a small amount of lithium naphthalide. This can be ignored when the highly reactive magnesium is reacted. If desired this can be removed by syringing off the THF and adding fresh dry tetrahydrofuran or other solvent.

[14] It is important that the reaction be stirred vigorously and that the lithium make frequent contact with the stirring bar, as the lithium has a tendency to be coated with magnesium, stopping the reduction from continuing. If reduction does stop, it can be initiated again by gently rubbing the piece of lithium against the wall of the flask with a metal spatula. The rubber septum can be temporarily removed under a stream of argon to carry out this procedure.

[15] One can also remove the solvent and electron carrier by filtering through a medium frit under an argon atmosphere.

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