82. Asymmetric Aldol Condensation of 1-Naphtol and Pyruvates in the Presence of *Lewis* Acids

Preliminary Communication

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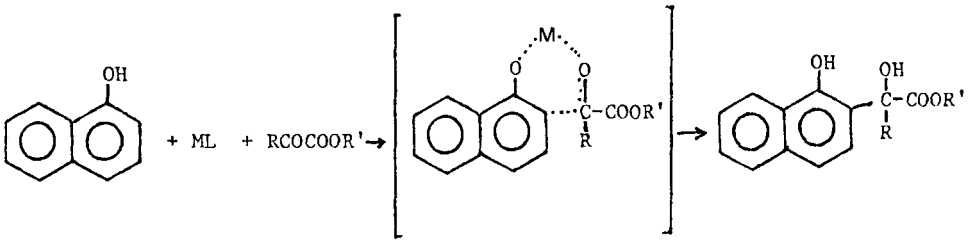
Summary

Lewis acids catalyze the condensation of menthyl pyruvate and 1-naphtol to give menthyl 2-hydroxy-2-(1-hydroxy-2-naphtyl)propionate in a ratio of up 96:4 in favor of the levorotatory diastereoisomer. Epimerization, at 25°C for five days, occurs on benzylic carbon atom to give a 30:70 mixture enriched with the dextrorotatory isomer.

Recently we have developed an efficient route for the preparation of 2-(*o*-hydroxyaryl)-2-hydroxyalkanoic acids or their esters using phenols, pyruvic derivatives and different *Lewis* acids as catalysts, the most effective ones being titanium, zirconium and tin tetrahalides [1] *(Scheme)*.

Scheme



This process can be considered as a *Lewis*-acid-catalyzed aldol condensation of two carbonyl derivatives. The fact that one of them, the phenol, exists in a stabilized enol form, accounts for the high *ortho*-selective C–C bond formation in this reaction. In the cyclic transition state [2] the metal should be tightly bonded to the phenolic and the carbonyl oxygen atoms, while the extent of the interaction between the alkoxycarbonyl group and the metal would depend on the coordination ability of the latter and on the metal-oxygen bond lengths.

Ojima et al. have observed fair asymmetric induction (e.e. up to 66%) in the $TiCl_4$-catalyzed reaction of menthyl pyruvate with some enol silyl ethers [3] and the extremely high stereoselectivity (up to 98% diastereomeric purity) in the asymmetric synthesis of β-lactams by means of the 'titanium template' [4]. Considering the analogies between the possible transition states of *Ojima*'s reactions and ours, we expected that an efficient asymmetric induction could be obtained in the reactions of the type shown in the *Scheme*, either by using α-keto esters derived from optically active alcohols, or by using *Lewis* acids containing chiral ligands. In the preliminary investigation described here, we chose 1-naphtol as a phenolic model compound. With respect to its high reactivity in this type of reactions [1], it should be possible to obtain good yields also while working at very low temperature. The results summarized in the *Table* show that a very high excess of the levorotatory diastereoisomer (A) is obtained by using $TiCl_4$; it is further increased by lowering the temperature (entry 2) and by partially reducing the acidity of the medium (entry 3 and 4).

Table. *Asymmetric Condensation of 1-Naphtol and Menthyl Pyruvate to Diastereoisomers* A *and* B[a])

Entry[a])	*Lewis* acid	Reaction conditions (temp./time)	Yield of A + B (ratio of A : B)	d.e.
1	$TiCl_4$	25°/0.2 h	98 (86:14)	72
2	$TiCl_4$	−60°/0.2 h	97 (92:8)	83
3[c])	$TiCl_4$	−60°/0.2 h	87 (96:4)	92
4[d])	$TiCl_4$	−60°/0.2 h	93 (96:4)	92
5	$TiCl_4$	25°/120 h	60 (30:70)	40
6	$SnCl_4$	−60°/0.2 h	80 (86:14)	68
7	$ZrCl_4$	−50°/0.4 h	92 (87:13)	74
8[e])	BCl_3	−40°/2.0 h	82 (43:57)	14

[a]) Equimolar amounts of 1-naphtol, *Lewis* acids and menthyl pyruvate were added in the order.
[b]) The diastereoisomeric ratio of products was determined by HPLC.
[c]) HCl was eliminated by removing ⅓ of the solvent by distillation.
[d]) Reaction was carried out in the presence of 50% molar excess (relative to substrate) of sodium carbonate.
[e]) *Lewis* acid was added as 1M solution in CH_2Cl_2.

It is noteworthy that a slow epimerization of the diastereomers occurs *in situ*, at room temperature, to give after five days, a diastereomeric mixture consisting of 30:70 ratio (entry 5). So, it is possible to isolate each diastereoisomer by flash chromatography by using the same natural source of chirality. The rate of epimerization was found to be strongly accelerated by working with an excess of $TiCl_4$.

Less satisfying results are obtained in the $ZrCl_4$- or $SnCl_4$-catalyzed reactions (d.e. = 70% at −50°C) and no significant asymmetric induction was observed using BCl_3 as *Lewis* acid (in the last case, also at low conversions, the same diastereoisomeric mixture was observed by HPLC). These results, in our opinion, can be derived from the fact that the M−O bond length in boron complex is shorter than the corresponding bond in the other metal complexes (B−O 1.36–1.47, *vs.* Ti−O 1.68–1.78, Zr−O 2.10–2.15, Sn−O 2.20 Å) [5] and therefore an efficient interaction of the metal with the carbonyl group of the ester bearing the asymmetric centre may be prevented or diastereomeric intermediates destabilized.

Very low or zero d.e.'s were found in preliminary experiments in the reactions of ethyl pyruvate and 1-naphtol catalyzed by titanium derivatives obtained from equimolar quantities of optically active 2,3-butandiol, ephedrine or alkyl tartrate and $TiCl_4$ or from 1 or 2 equivalent of menthol and $TiCl_4$.

At present we cannot exclude that, under these reaction conditions, optically active products or catalysts racemize. However, other effects, such as steric perturbation of remote substituents or structure changes of intermediate complexes, can play an unexpected role on the extent of carbonyl enantioface selection.

Work in progress is directed to further elucidate this and related 'aldol condensations' and to study the possible use of these optically active products as chiral ligands precursors in asymmetric synthesis.

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Experimental Part

General. All reactions were carried out under N_2 and the solvent (CH_2Cl_2) was dried according to standard methods immediately before use. Melting points (m.p.) were determined on a *Kofler* block and are uncorrected. Specific optical rotations $[\alpha]_D^{20}$ were measured at 20° in EtOH, concentration in parentheses. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$, on *Bruker CXP 300* (300 MHz for ^{1}H) and *Varian XL 100* (25.18 MHz for ^{13}C). Chemical shifts were reported in ppm downfield from TMS. MS were obtained with a *VG MICROMASS ZAB-2F,* direct inlet system, at 200°. HPLC analyses were performed with a *Jasco Uvidec-100-IV* apparatus using 0.4 × 25 cm column packed with *LiChrosorb* Diol (10 m), coupled to a *Chromatopac C-R1B* computing integrator.

Starting materials. Commercial products were obtained from *Fluka;* menthyl pyruvate was prepared according to [6] (b.p. 105–107°/3 mmHg; $[\alpha]_D^{20} = -84.764$ (1.887 EtOH)).

Menthyl (−)-2-hydroxy-2-(1-hydroxy-2-naphtyl)propionate (A). To a solution of 500 mg (3.5 mmol) of 1-naphtol in CH_2Cl_2 (20 ml), kept at −60°, was added 664 mg (3.5 mmol) of $TiCl_4$ and then stirred at the same temperature for 15 min. A solution of 840 mg (3.5 mmol) of menthyl pyruvate in CH_2Cl_2 (5 ml) was then slowly added (15 min). After 5 min at −60° the reaction was quenched with H_2O (30 ml) and extracted five times with 30 ml of Et_2O. The extracts were washed with H_2O, dried (Na_2SO_4) and evaporated. The oily residue (1.42 g) was chromatographed on silica gel with hexane/AcOEt (8:2, *v/v*) to yield 1.085 g (81%) of the pure, oily diastereoisomer (A). $[\alpha]_D^{20} = -196.769°$ (*c* = 2.043, EtOH). ^{1}H-NMR: 9.78 (*s*, 1H, ArO*H*); 8.30 (*m*, 1H, Ar*H*); 7.73 (*m*, 1H, Ar*H*); 7.46 (*m*, 2H, Ar*H*); 7.33 (*m*, 2H, Ar*H*); 4.82 (*dt*, 1H, CH); 4.50 (*s*, 1H, CO*H*); 1.89 (*s*, 3H, CH_3); 1.95–0.80 (*m*, 9H, C*H*, CH_2); 0.89 (*d*, 3H, CH_3); 0.85 (*d*, 3H, CH_3); 0.73 (*d*, 3H, CH_3). ^{13}C-NMR: 174.2, 151.8, 134.1, 126.9, 125.7, 125.0, 123.8, 122.7, 118.7, 117.4, 78.8, 77.4, 46.9, 40.2, 34.0, 31.3, 26.9, 26.2, 23.2, 21.8, 20.7, 16.0. MS: 370 (6, M^+), 352 (3), 232 (20), 214 (40), 196 (100), 186 (72), 171 (44), 168 (96), 139 (72), 123 (20), 115 (56), 95 (40), 83 (64), 81 (48).

Menthyl (−)- and (+)-2-hydroxy-2-(1-hydroxy-2-naphtyl)propionate (A and B, entry 5). To a solution of 1.312 g (9.1 mmol) of 1-naphtol in CH_2Cl_2 (50 ml), kept at 0°, was added of 1.726 g (9.1 mmol) of $TiCl_4$ and then stirred at the same temperature for 10 min. A solution of 2.205 g (9.1 mmol) of menthyl pyruvate in CH_2Cl_2 (10 ml) was slowly added (45 min). The reaction was allowed to run for five days and worked up as before to yield 879 mg (25%) of diastereoisomer A and 2.250 g (64%) of diastereoisomer B. An analytical sample of B was recrystallized from hexane at r.t. M.p. 138–140°. $[\alpha]_D^{20} = +74.159°$ (*c* = 2.180, EtOH). ^{1}H-NMR: 9.44 (*s*, 1H, ArO*H*); 8.32 (*m*, 1H, Ar*H*); 7.75 (*m*, 1H, Ar*H*); 7.48 (*m*, 2H, Ar*H*); 7.36 (*m*, 2H, Ar*H*); 4.72 (*dt*, 1H, C*H*); 4.38 (*s*, 1H, CO*H*); 2.10–0.70 (*m*, 9H, C*H*, CH_2); 1.92 (*s*, 3H, CH_3); 0.91 (*d*, 3H, CH_3); 0.48 (*d*, 3H, CH_3); 0.42 (*d*, 3H, CH_3). ^{13}C-NMR: 175.7, 152.1, 134.6, 127.1, 126.7, 125.3, 124.9, 124.5, 122.7, 118.9, 117.4, 78.2, 77.4, 47.1, 40.5, 34.2, 31.0, 26.8, 25.4, 23.0, 21.8, 20.3, 15.5. MS: 370 (6, M^+), 352 (2), 232 (16), 214 (29), 196 (100), 186 (21), 171 (26), 168 (91), 139 (52), 123 (12), 115 (26), 95 (36), 83 (26), 81 (36).

By using the conditions described in the *Table* (entries 1–8) for the condensation of 1-naphtol and menthyl pyruvate in the presence of some *Lewis* acids the hydrolyzed residues of the reactions were directly analyzed by HPLC to give the diastereoisomeric distribution reported in the *Table.*

REFERENCES

[1] EP Appl. 83200915.3 (1983); work submitted for publication.
[2] *H.E. Zimmermann & M.D. Traxler*, J. Am. Chem. Soc. *79*, 1920 (1957).
[3] *I. Ojima, K. Yoschida & S. Inaba*, Chem. Lett. *1977*, 429.
[4] *I. Ojima & S. Inaba*, Tetrahedron Lett. *1980*, 2081.
[5] a) *M.T. Reetz*, Top. Curr. Chem. *1982*, 106; b) *P.J. Wheatley*, J. Chem. Soc. *1961*, 5027.
[6] *K. Matsumoto & L. Harada*, J. Org. Chem. *31*, 1956 (1966).