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AN EFFICIENT SYNTHESIS OF (+)-8-PHENYLMENTHYL ISOCYANOACETATE.

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Abstract: *Optically pure (+)-8-phenylmenthyl isocyanoacetate* **1** *has been synthesized in 3 steps and 90% yield. The formamide* **4** *was obtained in 1 step by Pd/C-catalyzed hydrogenation of the corresponding azide in* HCO_2Et *as solvent.*

Racemic amino-hydroxy acids such as serine and threonine have been prepared in three to four steps upon condensation of ethyl isocyanoacetate with the desired aldehydes[1,2]. Recently amino-hydroxy acids with optical purities up to 95% have been obtained in the same way by using optically pure gold or silver complexes as catalysts[3,4]. Condensation of ethyl isocyanoacetate with chiral complexed aromatic aldehydes lead to complete diastereoselectivity when LDA (-78°) or TBAF (-15°) were used as bases[5]. Furthermore double induction during condensation of ethyl isocyanoacetate with a chiral aldehyde in the presence of an optically pure gold complex as catalyst lead to a cyclosporine N-methylamino-hydroxy acid with 80% diastereoselectivity in the 2*S*,3*R*,4*R*-isomer[6].

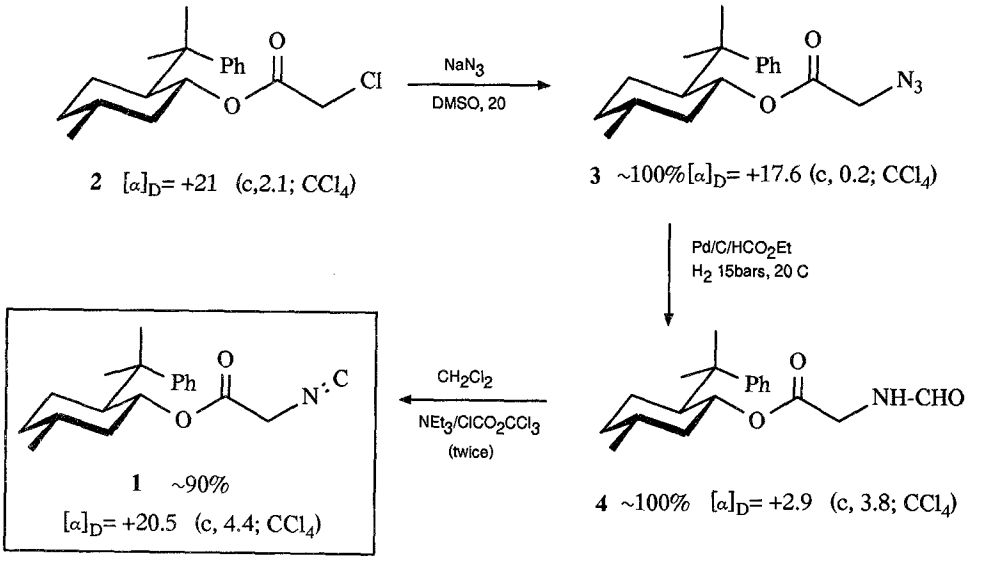
During work on the synthesis of optically active unusual amino-hydroxy acids[7,8] we became interested in 8-phenylmenthyl isocyanoacetate **1** as a route to these chiral compounds. We thus want to report here an efficient synthesis of 8-phenylmenthyl isocyanoacetate **1**.

As shown on the scheme, the (+)-8-phenylmenthyl isocyanoacetate **1** was synthesized from the (+)-phenylmenthyl chloroacetate **2** introduced by Ort[9] for the preparation of optically pure (-)-8-phenyl menthol.

Replacement of the chlorine by the azide group proceeded smoothly and quantitatively in DMSO at 20°C. Then the formamido ester **4** was obtained in quantitative yield and in one step by Pd/C-catalyzed hydrogenation of **3** in ethyl formate (HCO_2Et) as solvent[10]. According to Ugi's method[11], diphosgene was used for the last step and it was found that:

-the best ratios of reagents were: 2 equiv. of NEt_3 and 0.5 equiv. of diphosgene for 1 equiv. of the formamido ester **4**.

-the crude product thus obtained, which contained 55% of **1** and 45% of starting material **4**[12], had to be recycled in the same conditions.



Therefore (+)-8-phenylmenthyl isocyanoacatate **1** *has thus been obtained in more than 90% yield, that is 2.6 times more than the 35% obtained in the synthesis proposed in 1978*[14].

Experimental part.

^1H and ^{13}C NMR have been recorded on an AC 200 Bruker (δ in ppm, J in Hz). Optical rotations were measured with a Perkin-Elmer polarimeter 241 MC. Infra-Red stectra were recorded on a Perkin-Elmer 257. Thin layer chromatographies were performed on Kieselgel 60 F_{254} plates purchassed from Merck. All the solvents were distilled before use. Anhydrous Et_2O was obtained by refluxing over $LiAlH_4$, anhydrous THF over sodium/benzophenone, anhydrous CH_2Cl_2 and DMSO over calcium hydride. NEt_3 was distilled over KOH.

(+)-8-phenylmenthyl chloroacetate (2). Was obtained in the usual way (cf ref. 9). Yield 58%; m.p. 83-84°C (lit. 82-83°C, ref. 9).

$[\alpha]_D^{25}$ = +21 (c, 2.1; CCl_4) (lit. +22.4; c=2.29, CCl_4, ref. 9).

^1H NMR ($CDCl_3$/TMS) δ: 0.90 (3H, d, J=6.5, Me); 1.20 (3H, s, Me); 1.31 (3H, s, Me); 0.85-2.25 (17H); 3.18 (2H, AB system, $\Delta\nu$=67Hz, J_{AB}=15, CH_2-Cl); 4.92 (1H, td, J_{aa}=10, J_{ae}=5, CH-O); 7.15 (1H, m, Harom.); 7.30 (4H, m, Harom.).

Displacement of the chlorine by an azide group. To (+)-8-phenylmenthyl chloroacatate 5g (16mmol, 1 equiv.) dissolved in DMSO (150ml) were added 1.52g (24mmol, 1.5 equiv.) of NaN_3. The mixture is stirred at 25°C for 16h. Then Et_2O (500ml) was added and the solution extracted with water (50mlx8). The organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude product (5.1g) was checked by ^1H NMR and used for the next step without purification.

(+)-8-phenylmenthyl azidoacetate (3). Uncoloured oil; yield 100%.

R_f=0.7 (Et_2O/hexane, 2/8)

$[\alpha]_D^{21}$= +17.6 (c, 0.2; CCl_4).
IR (neat): ν_{N3}, 2110cm-1; ν_{CO}, 1735cm-1
Anal. for $C_{18}H_{25}N_3O_2$: Cald. C, 68.54%; H, 7.99%; N, 13.32%. Found C, 68.68%; H, 8.22%; N, 13.37%.
^1H NMR ($CDCl_3$/TMS) δ:0.90 (3H, d, J=6.5, Me); 1.2 (3H, s, Me); 1.33 (3H, s, Me); 0.88-2.14 (17H); 2.91 (2H, AB system, $\Delta\nu$=87Hz, J_{AB}=17, CH_2-N_3); 4.94 (1H, td, J_{aa}= 10.5, J_{ae}=4.5, CH-O); 7.15 (1H, m, Harom.); 7.35 (4H, m, Harom.).
^{13}C NMR ($CDCl_3$/TMS) δ: 22.2 (Me); 22.8 (Me); 26.6 (CH_2); 30.4 (Me); 31.7 (CH); 34.8 (CH_2); 39.8 (C); 42.1 (CH_2); 50.0 (CH_2-N_3); 50.5 (CH); 75.5 (CH-O); 125.5 (CH arom.para); 125.7 (2CH arom.); 128.5 (2CH arom.); 152.1 (C arom.); 167.8 (CO).

Hydrogenation-Formylation (one step). To the crude azidoacetate obtained above, 5.1g (16mmol), in HCO_2Et (100ml) was added Pd/C 10% (about 50mg) and the mixture was stirred at 25°C for 15h under 15bars of H_2. The catalyst was then filtered out and the solvent evaporated under vacuum. The crude compound was filtered over Silicagel (ϕ=2cm, h=15cm, Et_2O): 5.05g.
(+)-8-phenylmenthyl-formylamido acetate (4). Yield 100%
R_f= 0.35 (Et_2O)
$[\alpha]_D^{21}$ = +2.9 (c, 3.8; CCl_4)
IR (neat): ν_{NH}, 3330cm^{-1}; ν_{CO}ester, 1735cm^{-1}; ν_{CO}formyl, 1675cm^{-1}.
Anal. for $C_{19}H_{27}NO_3$: Calcd. C, 71.89%; H, 8.57%; N, 4.41%. Found C, 72.05%; H, 8.65%; N, 4.21%.
^1H NMR ($CDCl_3$/TMS) δ: 0.90 (3H, d, J=6.5, Me); 1.19 (3H, s, Me); 1.30 (3H, s, Me); 0.72-2.13 (17H); 3.34 (2H, AB part of an ABX, $\Delta\nu$= 54Hz, J_{AB}=18, J_{AX}=5, J_{BX}=5.5, CH_2-N); 4.89 (1H, td, J_{aa}=11, J_{ae}=4.5, CH-O); 6.25 (1H, broad t, X part of the ABX, NH); 7.20 (1H, m, Harom.); 7.30 (4H, m, Harom.); 8.01 (1H, s, CHO).
^{13}C NMR ($CDCl_3$/TMS) δ: 22.1 (Me); 23.3 (Me); 26.5 (CH_2); 29.9 (Me); 31.5 (CH); 34.7 (CH_2); 39.7, 40.1 and 41.8 ($2CH_2$ and C); 50.4 (CH); 75.3 (CH-O); 125.5 (CHarom. para); 125.6 (2CH arom.); 128.3 (2CH arom.); 152.1 (Carom.); 165.1 (CO); 168.8 (CO).

Formation of the isocyano group. To 480mg (1.51mmol) of 8-phenylmenthyl isocyanoacetate in anhydrous CH_2Cl_2 (15ml) was added 0.45ml (3.16mmol, 2 equiv.) of anhydrous NEt_3. The mixture was cooled to 0°C in an ice-bath and 0.096ml (0.8mmol, 1.1 equiv.) of trichloromethyl chloroformiate (diphosgene) dissolved in anhydrous CH_2Cl_2 (2ml) were added dropwise. After stirring at 25°C overnight, the mixture was washed with a 10% $NaHCO_3$ solution (5ml x 2) then with water untill pH=6-7. The organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude product, which is a mixture of the desired isocyano acetate **1** (55%) and of the starting material **4** (45%) as determined by ^1H NMR, was then recycled in the same conditions (with 2 equiv. of NEt_3 and 0.5 equiv. of diphosgene). After the same work-up the crude compound, a yellowish visquous liquid, 411mg (Y= 95%) was obtained.
(+)-8-phenylmenthyl isocyanoacetate (1). Yield 95%.
R_f= 0.6 (Et_2O/hexane, 1/1).

$[\alpha]_D^{21}$ = +20.5 (c, 4.4; CCl_4).
IR (neat): $\nu_{N=C}$, 2160cm^{-1}; ν_{CO}, 1750cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS) δ: 0.91 (3H, d, J=6.5, Me); 1.19 (3H, s, Me); 1.32 (3H, s, Me); 0.8-2.20 (17H); 3.18 (2H, AB system, $\Delta\nu$=110Hz, J_{AB}=19, CH_2-NC); 4.93 (1H, td, J_{aa}= 11, J_{ae}=4.5, CH-O); 7.15 (1H, m, Harom.); 7.30 (4H, m, Harom.).
^{13}C NMR ($CDCl_3$/TMS) δ: 22.3 (Me); 26.6 (CH_2); 31.2 (2Me); 31.9 (CH); 34.9 (CH_2); 39.9 (C); 42.1 (CH_2); 43.4 (CH_2); 50.7 (CH); 76.7 (CH-O); 125.8 (CHarom. para); 125.9 (2CH arom.); 128.7 (2CH arom.); 152.4 (Carom.); 161.2 (N=C); 163.8 (CO).

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12) As determined by ^{1}H NMR (200MHz) on the signals of the O=C-C**H$_2$**-N groups (which lead to an ABX system in **4** and to an AB in **1**), and of the C**H**O proton.
13) One must notice that further addition of excess of reagent (NEt_3/diphosgene) into the reaction-mixture without isolation of the product lead to degradation and very low yield in isocyanoacetate (<20%).
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