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Synthesis of Optically Active Michael Adducts Via Chiral Enamines

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Chiral enamines, obtained by *Schiff* base condensation from 1,3-dicarbonyl compounds and (*R*)-(+)-1-phenylethylamine, were found to undergo diastereoselective *Michael* reactions with α,β-unsaturated carbonyl compounds. After removal of the chiral auxiliary (*R*)-(+)-1-phenylethylamine by hydrolysis, the *Michael* adducts were isolated in 59–95% optical yield.

(Keywords: Michael Addition; Enamines; 1,3-Dicarbonyl compounds; Optical induction)

Synthese von optisch aktiven Michaeladdukten via chirale Enamine

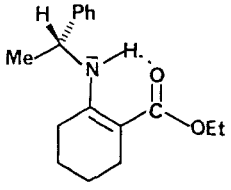
Chirale Enamine, durch *Schiff*basenkondensation aus 1,3-Dicarbonylverbindungen und (*R*)-(+)-1-Phenylethylamin erhalten, gehen mit α,β-ungesättigten Carbonylverbindungen diastereoselektive *Michael*reaktionen ein. Nach hydrolytischer Abspaltung des chiralen Hilfsstoffs (*R*)-(+)-1-Phenylethylamin werden die *Michael*addukte in 59—95% optischer Ausbeute isoliert.

Introduction

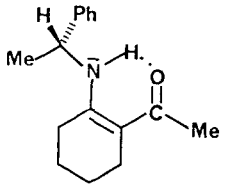
In the last years it has been found that chiral enamines give excellent results in *Michael* reactions concerning the diastereoselectivity of the newly formed asymmetric centers. Easy removal of the chiral auxiliary provided optically active products with more than 90% ee [1–4]. In a continuation of our efforts to study the stereochemistry of the *Michael* addition of 1,3-dicarbonyl compounds to α,β-unsaturated systems [5, 6], we extended our methodology from optically active transition metal catalysts to the enamine route, using (*R*)-(+)-1-phenylethylamine as the chiral auxiliary.

As 1,3-dicarbonyl compounds ethyl cyclohexanone-2-carboxylate and 2-acetylcyclohexanone were used. *Schiff* base condensation with (*R*)-(+)-1-phenylethylamine in the presence of *p*-toluenesulfonic acid afforded the corresponding enamines **1a** and **1b**, the enamine/ketimine equilibrium

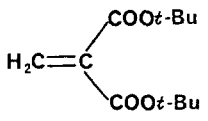
being completely shifted to the enamine side according to the ^{1}H NMR spectra. In the case of 2-acetylcyclohexanone, leading to **1b**, it is not yet clear, which of the two carbonyl groups is attacked by the amine. Therefore, the configuration of enamine **1b** is assigned arbitrarily in the formula scheme. As *Michael* acceptors di-*tert*-butyl methylenemalonate (**2a**), methyl vinyl ketone (**2b**) and ethyl acrylate (**2c**) were chosen. The *Michael* donors and acceptors which have been used and the *Michael* adducts **3a–3d** which have been isolated are shown in the formula scheme. Reaction conditions as well as chemical and optical yields are given in Table 1.



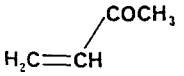
1a



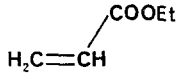
1b



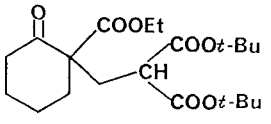
2a



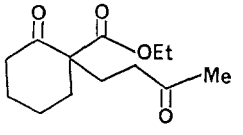
2b



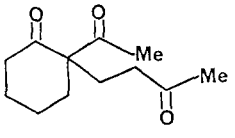
2c



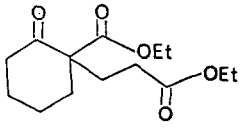
3a



3b



3c



3d

Table 1. *Enantioselective Michael reaction of the enamines* **1a** *and* **1b** *with the Michael acceptors* **2a–2c** *to give the Michael adducts* **3a–3d** *(solvent toluene, if not stated otherwise)*

Entry	*Michael* donor	*Michael* acceptor	Molar ratio donor/acceptor	*t* [h]	*T* [°C]	Number of runs	Isol. prod.	Chem. yield [%]	$[\alpha]_\lambda^T$ [°][a] (*c* [g/100 ml])	Optical induction ee[b] [%]
1	(−)-**1a**	**2a**	1/1.04	22	+ 20	2	**3a**	60, 65	+ 52.6, 54.4 (2.05)	⩾ 95 (*R*)
2	(−)-**1a**	**2a**	1/1.01	66.5	+ 20	1	**3a**	67	+ 54.1 (2.00)	⩾ 95 (*R*)
3	(−)-**1a**	**2a**	1/0.99[c]	66	+ 20	1	**3a**	77	+ 22.9 (2.01)	40.7[d] (*R*)
4	(−)-**1a**	**2b**	1/1.03	118	+ 40	1	**3b**	18	+ 59.0 (2.05)	72.8 (*R*)
5	(−)-**1a**	**2b**	1/3.30	306	+ 40	1	**3b**	50	+ 64.1 (2.07)	79.1 (*R*)
6	(−)-**1b**	**2b**	1/1.14	233	+ 20	1	**3c**	6	+ 54.4 (1.51)	46.0
7	(−)-**1b**	**2b**	1/1.16	69.5	+ 60	2	**3c**	56, 58	+ 69.2[e] (1.53)	59.0, 65.0
8	(−)-**1a**	**2c**	1/1.97[f]	92	+ 81	1	**3d**	29	+ 69.5 (2.00)	89 (*R*)

[a] The optical rotations were measured for **3a** and **3d** in $CHCl_3$ (25 °C and 20 °C, respectively) at D line, for **3b** in CCl_4 (20 °C) at 578 nm, and for **3c** in benzene (20 °C) at 578 nm

[b] The enantiomeric excess was determined for **3a** by means of ^1H NMR spectroscopy with Eu(*hfc*)$_3$ in CCl_4, for **3b** by comparison of the optical rotation with the maximum rotation $[\alpha]_{578}^{20}$ + 81° (*c* 2.1, CCl_4 [7]), for **3c** by means of ^1H NMR spectroscopy with Eu(*tfc*)$_3$ in $CDCl_3$ after cyclization to spiro[5,5]undec-2-ene-3-methyl-1,7-dione [6], and for **3d** by comparison of the optical rotation with the maximum rotation $[\alpha]_D^{20}$ + 78.5° (*c* 2.0, $CHCl_3$) obtained after converting optically pure **3a** into **3d** (see discussion). For the absolute configuration of **3a** and **3b** see Refs. [2] and [7], respectively

[c] Carried out in *THF* as the solvent

[d] Calculated by comparison of the optical rotation with 54.4°

[e] Corresponding to 59% ee

[f] Carried out in CH_3CN as the solvent in the presence of Co(*acac*)$_2$

Results and Discussion

The optical rotation of **3a** obtained by the *Michael* reaction via the chiral enamine **1a** (Table 1, entry 1) exceeded the maximum value $[\alpha]_D^{25}$ $-49.2°$ ($CHCl_3$), reported for **3a** in the literature [2].

Since for the literature value no concentration was given, we diluted a sample from *c* 2.00 to *c* 0.24. The decrease of the optical rotation from $[\alpha]_D^{25} + 54.1°$ to $[\alpha]_D^{25} + 52.7°$ showed that solutions of **3a** exhibited only little concentration dependence [8].

Therefore we had to reinvestigate the optical purity of **3a**: A sample obtained in the *Michael* reaction with $[\alpha]_D^{25} + 53.0 \pm 0.4°$ (*c* 2.05) was purified by chromatography and distillation, having $[\alpha]_D^{25} + 54.1 \pm 0.1°$ (*c* 2.00). Gas chromatography and elemental analysis showed the sample to be chemically pure [9].

The optical purity of **3a** was determined by ^1H NMR studies in the presence of the optishift reagent Eu(*hfc*)$_3$ (*d*-camphorato isomer) in CCl_4. Focussing on both the ethyl group (molar ratio Eu(*hfc*)$_3$: **3a** = 1 : 6.13) and the *tert*-butyl groups [Eu(*hfc*)$_3$: **3a** = 1.01 : 1 − 1.78 : 1], we could not detect the (*S*)-enantiomer in purified samples of **3a** from experiments summarized in the first two entries of Table 1 [9]. The diastereoselectivity of the *Michael* reaction leading to **3a** was strongly solvent-dependent. By changing the solvent from toluene to *THF*, a slight enhancement of the chemical yield is accompanied by a strong decrease of the optical yield (entry 3).

Compared to **2a** the *Michael* acceptor **2b** turned out to be much less reactive: Consequently, the synthesis of optically active **3b**, whose optical purity and absolute configuration were already reported in the literature [7], required an elevated reaction temperature (40 °C) and an excess of **2b** to obtain a chemical yield of 50% and an optical induction of 79.1% ee (*R*) (entries 4, 5).

For adduct **3c**, acceptable chemical yields could only be obtained at even higher temperatures (entries 6, 7). By means of ^1H NMR spectroscopy in the presence of optishift Eu(*tfc*)$_3$ in $CDCl_3$, an enantiomeric excess of up to 65% could be calculated for optically active **3c** after cyclization to spiro[5,5]undec-2-ene-3-methyl-1,7-dione [6]. Unlike the preceeding reactions, the *Michael* addition leading to **3d** was carried out in boiling acetonitrile in the presence of Co(*acac*)$_2$ [5, 6, 10]. Although the chemical yield was rather low, the optical yield was 89% ee (entry 8). The optical purity was determined by comparing its optical rotation with that of a sample of **3d** prepared from optically pure **3a** by decarboxylation and transesterification with a chemical yield of 88% [$[\alpha]_D^{20} + 78.5°$ (*c* 2.0, $CHCl_3$)], using a mixture of glacial acetic acid, acetic anhydride, *p*-toluenesulfonic acid, and ethanol [10].

Summarizing the results, optically active 1-phenylethylamine turned out to be a valuable chiral auxiliary in the stereoselective *Michael* reaction via the enamine route with regard to availability and stereodifferentiation. For the synthesis of **3a**, which could be obtained optically pure, our method proved to be superior to *Koga*'s procedure [2], in which the *tert*-butyl valinate derived enamine had to be lithiated with *LDA* at low temperatures.

Experimental

IR spectra: Beckman Acculab 3.—^{1}H NMR spectra: Varian EM 360 L (60 MHz).—MS: Varian MAT CH5.—Optical rotation: Perkin-Elmer polarimeter 241.—GC: Perkin-Elmer F20. Detector: FID. Integrator: Spectra Physics SP4000/SP. Column: 8 m OV 101-CB, 0.32 mm $\varnothing_i$, 0.2 μm coat. T_C: 160–180 °C. Carrier gas: N_2. T_I: 255 °C.

Eu(*hfc*)$_3$ and ethyl cyclohexanone-2-carboxylate were purchased from Aldrich, methyl vinyl ketone from Merck, and ethyl acrylate from Fluka. (*R*)-(+)-1-phenylethylamine was a gift of BASF. 2-Acetylcyclohexanone [11] and di-*tert*-butyl methylenemalonate [12] were synthesized by procedures described in the literature. All *Michael* reactions were carried out under nitrogen.

General Procedure for the Synthesis of the Enamines **1a** *and* **1b**

15.7 mmol of the 1,3-dicarbonyl compound and 15.5 mmol of (*R*)-(+)-1-phenylethylamine [$[\alpha]_D^{22.5}$ + 39.2° (neat)] were dissolved in 40 ml of benzene. After addition of a small amount of *p*-toluenesulfonic acid, the mixture was heated under reflux using a water separator. On cooling to room temperature and removal of the benzene, oily residues remained which were dissolved in ether and filtered. Evaporation of the ether, followed by a *Kugelrohr* distillation in high vacuum, gave the products **1a** and **1b**, respectively.

Ethyl (−)-N-[(R)-1-phenylethyl]-1-aminocyclohexene-2-carboxylate (**1a**)

Reaction time: 1 h. Yield: 78%. Colourless oil which crystallized at low temperatures (recrystallized from ethanol). M.p. 35.5–36 °C. IR (KBr): 3260, 3170 (νNH); 1655, 1605 (νCO) cm^{-1}. ^{1}H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.30–1.82 (m, 4 H, CH_2, H-4, 5), 1.47 (d, J = 7 Hz, 3 H, CH_3), 1.82–2.56 (m, 4 H, CH_2, H-3, 6), 4.16 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.61 (m, 1 H, CH), 7.28 (s, 5 H, H aromat.), 9.43 (br. d, J = 7 Hz, 1 H, NH). Specific rotations: $[\alpha]_D^{20}$ − 496 ± 1° (*c* 2.0, benzene) ($[\alpha]_{578}^{20}$ − 524°, $[\alpha]_{546}^{20}$ − 622°, $[\alpha]_{436}^{20}$ − 1399°, $[\alpha]_{365}^{20}$ − 3531°). $C_{17}H_{23}NO_3$: Found C 74.52, H 8.25, N 5.13. Calcd. C 74.52, H 8.48, N 5.12.

(−)-N-[(R)-1-Phenylethyl]-1-amino-2-acetylcyclohex-1-ene (**1b**)

In this reaction an excess (13%) of optically active amine was used. Reaction time: 4 h. Yield: 56%, slight green oil. B.p. 105–107.5 °C/0.01 mm Hg. IR (film): 3160 (νNH); 1610, 1575 (νCO) cm^{-1}. ^{1}H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.21–1.84 (m, 4 H, CH_2, H-4, 5), 1.51 (d, J = 7 Hz, 3 H, CH_3), 1.84–2.59 (m, 4 H, CH_2, H-3, 6), 2.13 (s, 3 H, $COCH_3$), 4.65 (m, 1 H, CH), 7.25 (s, 5 H, H aromat.), 11.93 (br. d, J = 7 Hz, 1 H, NH). Specific rotations: $[\alpha]_D^{20}$ − 647 ± 3° (*c* 2.0, benzene) ($[\alpha]_{578}^{20}$ − 687°, $[\alpha]_{546}^{20}$ − 829°, $[\alpha]_{436}^{20}$ − 1399°). $C_{16}H_{21}NO$: Found C 78.92, H 8.73, N 6.54. Calcd. C 78.97, H 8.70, N 5.76.

Ethyl Cyclohexanone-2-(2,2-dicarbo-t-butoxy-ethyl)-2-carboxylate (**3a**)

1a (0.70 g, 2.56 mmol) was dissolved in 30 ml of toluene, followed by addition of di-*tert*-butyl methylenemalonate **2a** (0.6 ml, 2.59 mmol). The colourless solution was stirred for 66.5 h at room temperature, and then hydrolyzed with 30 ml of half-conc. HCl with stirring for 1 h at room temperature. The aqueous layer was extracted 2 × with 20 ml of toluene. The combined organic layers were washed with 30 ml of H_2O and dried over Na_2SO_4. After filtration and removal of the toluene the crude product was purified by *Kugelrohr* distillation, yielding **3a** (0.68 g, 67%) as a colourless oil. $[\alpha]_D^{25}$ + 53.0 ± 0.4° (*c* 2.05, $CHCl_3$). For further purification the product was chromatographed on silica gel (length 23 cm, 15 °C) with *n*-hexane/ether 18 : 1, being eluted after 270 ml of solvent had passed the column. Repeated distillation in a *Kugelrohr* apparatus gave **3a**, pure by GC [9]. $[\alpha]_D^{25}$ + 54.1 ± 0.1° (*c* 2.0, $CHCl_3$). B.p. 110–115 °C/0.01 mm Hg. IR (film): 1 745, 1 730 (*v*CO); 1 400, 1 375 (δ $C(CH_3)_3$) cm^{-1}. ^1H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.48 [s, 18 H, $OC(CH_3)_3$], 1.53–2.73 (2 m, 8 H, CH_2 ring), 2.39 (d, J = 5.5 Hz, 2 H, CH_2—CH), 3.37 (t, J = 5.5 Hz, 1 H, CH), 4.18 (q, J = 7 Hz, 2 H, CH_3). MS (70 eV): *m/e* (%) 398 ($M^{+\cdot}$, 1.5), 342 (6.8), 286 (45.9), 269 (35.3), 258 (13.2), 241 (13.2), 170 (47.7), 57 (100). $C_{21}H_{34}O_7$: Found C 63.56, H 8.76. Calcd. C 63.30, H 8.60.

Ethyl Cyclohexanone-2-(3-oxobutyl)-2-carboxylate (**3b**)

1a (1.02 g, 3.73 mmol) was dissolved in 40 ml of toluene. After addition of methyl vinyl ketone **2b** (1.0 ml, 12.32 mmol) the mixture was allowed to react 12 d at 40 °C. Then the unreacted methyl vinyl ketone was removed in vacuum, and the mixture was hydrolyzed with 30 ml of half-conc. HCl for 2 h at 40 °C. The aqueous layer was extracted 2 × with 30 ml of toluene and the combined toluene layers were dried over Na_2SO_4. After filtration and removal of the solvent, the residue was fractionally distilled in a short path distillation apparatus to give **2b** (0.45 g, 50%) as a colourless oil. $[\alpha]_{578}^{20}$ + 64.1° (*c* 2.07, CCl_4). B.p. 96–98 °C/0.01 mm Hg (Lit. 138–140 °C/0.4–0.5 mm Hg [13]). IR (film): 1 740, 1 725, 1 715 (*v*CO) cm^{-1}. ^1H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.28 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.49–2.71 (m, 12 H, 6 × CH_2), 2.13 (s, 3 H, $COCH_3$), 4.18 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$). $C_{25}H_{28}N_8O_{10}$ (the bis-2,4-dinitrophenylhydrazone derivative of **3b**, m.p. 160–162 °C): Found C 49.83, H 4.82, N 18.34. Calcd. C 50.00, H 4.70, N 18.66.

2-Acetyl-2-(3-oxobutyl)-cyclohexanone (**3c**)

1b (1.56 g, 6.41 mmol) was dissolved in 30 ml of toluene, followed by addition of methyl vinyl ketone **2b** (0.6 ml, 7.39 mmol). The mixture was stirred at 60 °C for 70 h. For hydrolysis, the toluene was completely evaporated and the resulting dark brown oil was treated with a solution of 5 g of sodium acetate in 10 ml of H_2O and 10 ml of acetic acid. After refluxing for 3 h, the mixture was extracted 3 × with 30 ml of $CHCl_3$. The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was fractionally distilled in a *Kugelrohr* distillation apparatus yielding **3c** (0.75 g, 56%) as a colourless oil. $[\alpha]_{578}^{20}$ + 69.2° (*c* 1.53, benzene). B.p. 90–95 °C/0.01 mm Hg. IR (film): 1 740, 1 700 (*v*CO) cm^{-1}. ^1H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.58–2.60 (2 m, 12 H, 6 × CH_2), 2.10 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$). UV: λ_{max} 278 nm (*Me*OH). $C_{12}H_{18}O_3$: Found C 68.50, H 8.91. Calcd. C 68.55, H 8.63.

Ethyl Cyclohexanone-2-(2-carboethoxy-ethyl)-2-carboxylate (**3 d**)

1 a (10.37 g, 37.39 mmol) and Co(*acac*)$_2$ (0.44 g, 1.71 mmol) were dissolved in 50 ml of acetonitrile, followed by addition of ethyl acrylate **2 c** (8.0 ml, 73.59 mmol). The solution was refluxed for 92 h, and then hydrolyzed with 100 ml of half-conc. HCl for 4 h at room temperature. The mixture was concentrated to 70 ml and extracted with ether. The organic layer was dried over Na_2SO_4. After filtration and removal of the ether, the crude product was purified by *Kugelrohr* distillation yielding **3 d** (2.99 g, 29%) as a colourless oil. $[\alpha]_D^{20}$ + 69.5 °C (*c* 2.0, $CHCl_3$). B.p. 150–152 °C/0.01 mm Hg (Lit. 150–152 °C/1 mm Hg [14]). IR (film): 1750, 1740 (*v*CO) cm^{-1}. ^{1}H NMR ($CDCl_3$/*i-TMS*): δ (ppm) 1.25 (t, J = 7 Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.28 (t, J = 7 Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.32–2.53 (m, 12 H, 6 × CH_2), 4.11 (q, J = 7 Hz, 2 H, $OCH_2\mathbf{CH_3}$), 4.21 (q, J = 7 Hz, 1 H, $OCH_2\mathbf{CH_3}$), 4.22 (q, J = 7 Hz, 1 H, $OCH_2\mathbf{CH_3}$). MS (70 eV): *m*/e (%) 242 ($M^{+\cdot}$, 23), 224 (100), 170 (100), 142 (46). $C_{14}H_{22}O_5$: Found C 62.14, H 8.01. Calcd. C 62.21, H 8.20.

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