

Ethyl 2-(Diphenylmethyleamino)acrylate as a Dienophile in the Synthesis of Alicyclic α -Amino Acids

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Synopsis. Ethyl 2-(diphenylmethyleamino)acrylate behaves as an excellent dienophile with cyclopentadiene. This reaction constitutes a new and improved procedure for the synthesis of 2-aminonorbornane-2-carboxylic acids.

Alicyclic amino acids with a norbornane skeleton are known to possess interesting biological properties that affect the transport of ions through biological membranes.^{1–3} These amino acids have been prepared from *N*-acyl- α,β -dehydroalanines by means of the Diels-Alder reaction with cyclopentadiene.^{4,5} It has been recently published⁶ that the methyl ester of 2-isocyanatopropenoic acid is a good dienophile and that the cycloadducts obtained by the reaction with cyclopentadiene can be converted into the above mentioned amino acids.

Alkyl 2-(diphenylmethyleamino)acrylates, which are easily prepared from glycine^{7–11} and whose amino groups can be selectively deprotected under mild conditions, were found to be stable derivatives of 2-aminoacrylic acid. These compounds were used in the synthesis of racemic α -amino acids via the Michael type reactions.¹¹

We would now like to report the ability of the easily available ethyl 2-(diphenylmethyleamino)acrylate to act as a dienophile in the reaction with cyclopentadiene, which opens a new route to 2-aminonorbornane-2-carboxylic acids. 2-(Diphenylmethyleamino)acrylate was found to be more stable than the previously reported methyl 2-(benzylideneamino)acrylate^{12,13} which is somewhat unstable and undergoes extensive dimerization.

using a Perkin-Elmer 240 element analyzer. IR spectra were obtained using a Perkin-Elmer 1600 spectrometer and ¹H NMR spectra were obtained using a Varian XL 200 MHz spectrometer using TMS as internal standard. Homonuclear NOE measurements were carried out in a Bruker 400 MHz spectrometer.

The Diels-Alder Reaction. General Procedure for the Synthesis of Adducts (2). To a stirred solution of ethyl 2-(diphenylmethyleamino)acrylate (134 mg, 0.5 mmol) in CH₂Cl₂ (35 ml) in a dried, argon-filled, round-bottomed flask at work temperature (Table 1), the corresponding amount of Lewis acid catalyst was added. After 10 min the corresponding amount of freshly distilled cyclopentadiene in CH₂Cl₂ (5 ml) was added at the same temperature and the solution was stirred under argon for the corresponding time (Table 1). Then solid Na₂CO₃ · 10H₂O (2 g) was added, and stirring was continued at the work temperature until the orange color had disappeared. The suspension was filtered, the solvent evaporated under reduced pressure, and the residue analyzed by ¹H NMR. The crude product (2) was chromatographed on a silica-gel column (20×1.5 cm, 230–400 mesh) using chloroform as an eluent giving pure samples of **2a** and **2b** which were recrystallized from EtOH. **2a**: mp 126–128 °C. Found: C, 79.71; H, 6.97; N, 3.84%. Calcd for C₂₃H₂₃NO₂: C, 79.97; H, 6.71; N, 4.05%. ¹H NMR (CDCl₃): δ =1.03 (t, 3H, OCH₂CH₃, 1.60–1.70 (m, 2H), 2.15–2.22 (m, 2H), 2.86 (brs, 1H), 3.24 (brs, 1H), 3.52 (m, 2H, OCH₂CH₃), 5.76 (dd, 1H_{vinyl}), 6.21 (dd, 1H_{vinyl}), 7.05–7.65 (m, 10H_{arom}). **2b**: mp 70–72 °C. Found: C, 79.69; H, 6.95; N, 3.88%. Calcd for C₂₃H₂₃NO₂: C, 79.97; H, 6.71; N, 4.05%. ¹H NMR (CDCl₃): δ =1.11 (t, 3H, OCH₂CH₃), 1.15–1.47 (m, 3H), 2.61 (dd, 1H), 2.81 (brs, 1H), 3.30 (brs, 1H), 3.81 (m, 2H, OCH₂CH₃), 6.40 (m, 2H_{vinyl}), 6.92–7.70 (m, 10 H_{arom}).

Experimental

Melting points were taken using a Mettler FP 61 apparatus and are uncorrected. Microanalyses were obtained

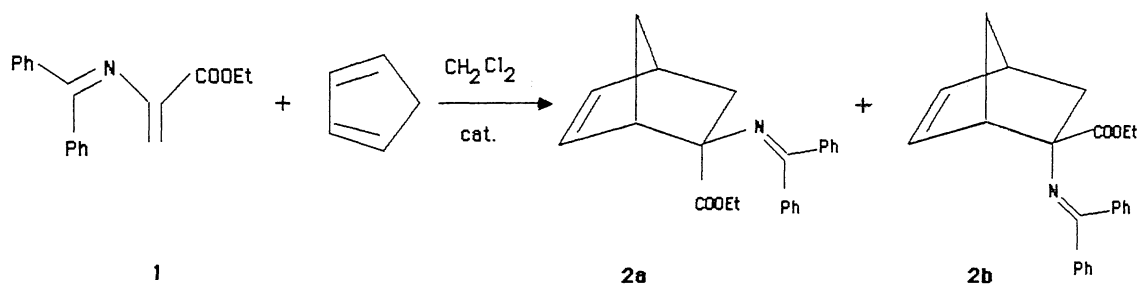
Results and Discussion

Ethyl 2-(diphenylmethyleamino)acrylate was easily prepared according to the previously reported

Table 1. Diels-Alder Reaction between **1** and Cyclopentadiene

Lewis acid (equiv)	Ratio diene/ 1	Temp °C	Reaction time/h	Yield % ^a	Ratio 2b / 2a ^a	Isolated yields/%	
						2b	2a
—	6:1	25	72	<<5	—	—	—
— ^b	6:1	25	96	53	1.6:1	—	—
AlCl ₃ (1.1)	3:1	25	9	92	1.2:1	40.3	38.2
AlCl ₃ (0.5)	3:1	25	9	76	1.5:1	—	—
AlCl ₃ (1.1)	6:1	0	1	100	2.3:1	59.3	26.3
AlCl ₃ (0.5)	6:1	0	6	67	1.3:1	—	—
AlCl ₃ (0.75)	6:1	−20	22	74	10.3:1	57.2	0
TiCl ₄ (1.1)	6:1	25	0.5	100	1.2:1	48.3	38.1
TiCl ₄ (0.5)	6:1	25	3	65	1.4:1	—	—
TiCl ₄ (0.75)	6:1	0	2	89	2.0:1	51.2	25.1
TiCl ₄ (0.75)	6:1	−20	5	100	1.8:1	53.7	30.5
TiCl ₄ (0.5)	6:1	−40	45	58	2.5:1	—	—

a) Determined by ¹H NMR. b) Reaction carried out in water.



Scheme 1.

procedure¹¹⁾ from commercially available ethyl *N*-(diphenylmethylene)glycinate and dimethyl(methylene)ammonium iodide¹⁴⁾ and allowed to react with cyclopentadiene (Scheme 1) in different conditions. The cycloadducts were separated by column chromatography, and the structural assignments were made on the basis of $H_{\text{aromatic ortho}}\{H-7\}$ and $H_{\text{vinyl}}\{H_{\text{methyl}}\}$ homonuclear NOE experiments performed for **2a**. These experiments yielded a 4.28% increase in the absorption of H -aromatic ortho at $\delta=7.09$ on pre-saturation of the H -7 protons at $\delta=1.63$ – 1.70 and a 0.39% increase in the absorption of the vinylic proton at $\delta=5.76$ on pre-saturation of the methyl protons at $\delta=1.03$. The **2b**:**2a** ratios obtained by the Diels-Alder reaction were determined by integration of the vinylic protons and are shown in Table 1.

As can be seen, high total conversion could be achieved by using a moderate excess of cyclopentadiene in several runs with $AlCl_3$ or $TiCl_4$ as a catalyst. In all cases moderate **2b**:**2a** ratios were obtained although **2b** was slightly favored in accordance with the previously reported reactions of cyclopentadiene with *N*-acyl- α,β -dehydroalaninates⁵⁾ and the methyl ester of the 2-isocyanatopropenoic acid.⁶⁾ High **2b**:**2a** ratios could be obtained carrying the reaction at low temperatures and using $AlCl_3$ as a catalyst.

Several authors have reported that the use of water greatly increases the rate of the Diels-Alder reactions;^{15–22)} together with this effect an increase in endo/exo selectivity is sometimes observed. In our case the use of water noticeably increased the reaction rate, but only a small modification in the ratio of cycloadducts (**2b**/**2a**) was observed.

In conclusion, ethyl 2-(diphenylmethyleneamino)-acrylate behaves as an excellent dienophile when a suitable catalyst is used and allows a new synthetic route to cycloaliphatic α -amino acids. The high selectivity obtained improves the results of the previously reported methods with *N*-acyl- α,β -dehydroalaninates and 2-isocyanato-2-alkenoates. Under the used conditions a better selectivity than those obtained with related dienophiles^{4–6)} is achieved.

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