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1,3-Dipolar Cycloadditions of Ethoxycarbonyl-nitrile Benzylimine, EtOOC C $\equiv \overset{+}{N}$ - $\overset{-}{N}$ $CH_2C_6H_5$, and Synthesis of β-Amino Acids. Synthesis and Reactions of Ethyl 2-Chloro-2-ethoxyacetate and 2-Chloro-2-ethoxyacetyl Chloride

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Abstract: The principles of 1,2-cyano-hydroxylation of olefins were applied to the preparation of 1,2-cyano-amines. The dipole component of this cycloaddition was nitrile imines, which formed pyrazolines with olefins. Ring cleavage was accomplished by thermolysis of 3-carboxypyrazolines, which gave 1,2-cyano-amines and subsequent hydrolysis gave β-amino acids. The syntheses of the title reagents were described. Ethyl 2-chloro-2-ethoxy-acetate gave selectively oximes, hydrazones, nitrones, and phosphonium salts with hydroxylamine, hydrazines, N-substituted hydroxylamines and triphenylphosphine respectively. The phosphonium salt was used in a Wittig reaction with aldehydes to give α-ketoesters. Treatment of the acid chloride with allyl alcohols and subsequently with a monosubstituted hydroxylamine gave the allylic ester nitrone, which underwent intramolecular cyclization. Similarly, intramolecular cyclizations were carried out with the allylic ester - nitrile oxide and allylic ester - nitrile imine systems.

INTRODUCTION

The present work describes our efforts to apply the principles of 1,2-carboxy-hydroxylation of olefins[1] to analogous 1,2-cyano-aminations, which eventually lead to the β-amino acid functionality. The dipole component of the cycloaddition is nitrile imines, which give pyrazolines with olefins.

We hypothesized that the pyrazoline cycloadducts **3** on thermal decarboxylation and subsequent acid catalysed hydrolysis could give the β-amino acids **5** via the nitriles **4**, Scheme 1. However, we have to face the fact that the N-N bonds of pyrazoles and pyrazolines are considerably stronger than the N-O bonds of corresponding isoxazoles and isoxazolines. Pyrazoles are not as readily cleaved as the isoxazoles by catalytic or $LiAlH_4$ reductions, nor does treatment of 3-H-pyrazolines with strong bases, e.g. KO-t-Bu, lead to ring cleavage.[2] This implies that protonation of the intermediate C-3 anion formed on thermolysis could conceivably compete with the ring cleavage.

Very few hydrazidoyl chlorides with a C-1 carbonyl substituent were known.[3] They were prepared by the Japp-Klingemann reaction and were principally restricted to N-aryl derivatives, which for our purpose were of more limited value. The N-benzyl group in **1** was more suitable since it could be reductively eliminated in a later step. In conjunction with the preparation of this target reagent the reactions of two

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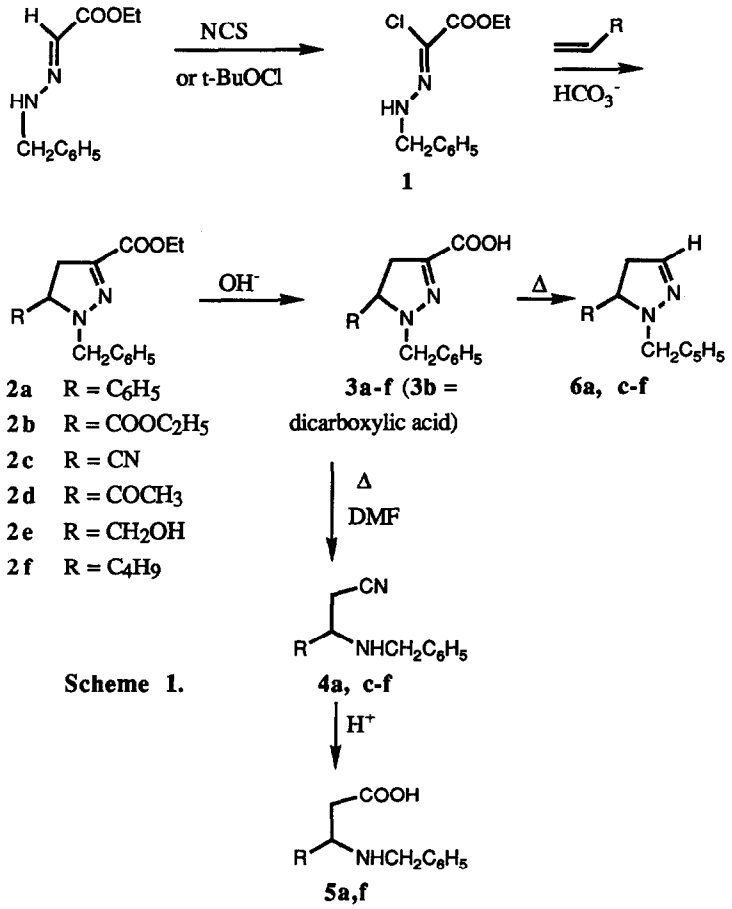


Scheme 1.

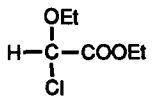
reactive bifunctional reagents: ethyl 2-chloro-2-ethoxyacetate **7** and 2-chloro-2-ethoxyacetyl chloride **8** were investigated. It was also of interest to investigate if the acylated derivative **12b** could be used for cycloadditions.

The chloro-hydrazidoyl chlorides **10**, i.e. hydrazones of phosgene were tested as precursors for chloronitrile imines in cycloaddition. They were prepared by decarboxylative chlorination of hydrazones of glyoxylic acid, **9**, in analogy to the chlorination of the corresponding oxime, eqn. (1). The chemistry of these compounds is very little known. Pyrazoline **11a** could conceivably be reductively cleaved to the 1-cyano-2-amino derivative in analogy to the corresponding 3-chloroisoxazole derivatives.[4]

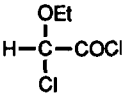
RESULTS AND DISCUSSION

Synthesis of ethyl 2-chloro-2-ethoxyacetate, **7** *and 2-chloro-2-ethoxyacetyl chloride* **8**: Commercially available ethyl glyoxylate diethylacetal (ethyl 2,2-diethoxy-acetate) was chlorinated with one equivalent of

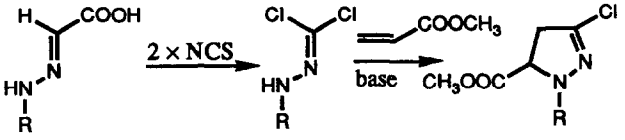
acetyl chloride to give **7**. The reaction proceeded slowly but was catalysed by small amounts of iodine. It has previously been synthesised by reacting the acetal with PCl_5.[5] The highly reactive bifunctional **8** was prepared earlier by a rather laborious method.[6] We found that **8** could be prepared by reacting the acetal with an excess of PCl_5 at 100 °C using iodine as a coreactant. The excess of I_2 was finally complexed with PCl_5 and **8**, $POCl_3$ and ethyl chloride were fractionally distilled. The acid chloride **8** gave selectively esters with alcohols. These esters and **7** reacted selectively with hydrazines, and hydroxylamine to give hydrazones, and oximes respectively, e.g. **21**. Further reactions of **7** and **8** are discussed below.



7



8



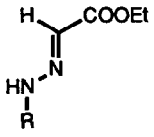
(1)

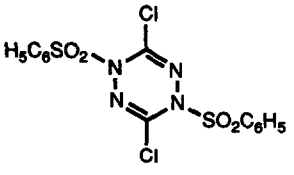
9a R = $CH_2C_6H_5$

9b R = $SO_2C_6H_5$

10a,b

11a

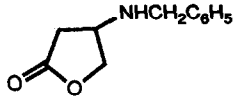


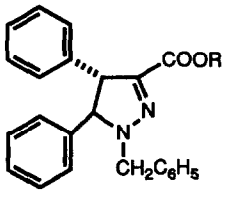


12a R = $CH_2C_6H_5$

12b R = CO-t-Bu

13





14

15a R = C_2H_5

15b R = H

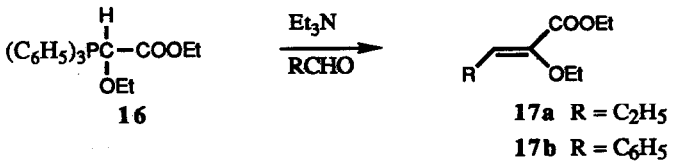
Synthesis of hydrazidoyl chlorides. Dipolar cycloadditions: The chlorination of **12a** to give **1** with NCS or t-BuOCl proceeded as anticipated. The = CH absorption vanished rapidly in the ^{1}H NMR spectrum of **12a** on chlorination and treatment of **1** with sodium hydrogencarbonate in the presence of vinylic olefins with electron withdrawing groups gave **2** in good yields, Scheme 1. Vinylic olefins with electron donating groups e.g. 1-hexene and 1,2- disubstituted olefins reacted sluggishly. Thus ethoxycarbonyl-nitrile benzylimine from **1** appeared to be less reactive than the corresponding ethoxy-carbonylnitrile oxide. *trans*-Stilbene gave only 25 % yield of the cycloadduct **15a.** No pyrazoline derivates were detected in the crude product when **12b** was chlorinated and reacted with olefins under the same conditions.

When **9a** was reacted with NCS, methyl acrylate and potassium hydrogencarbonate in a one-pot reaction the pyrazoline **11a** was obtained in 33 % yield proving the intermediacy of **10a**, (1). The phenylsulfonyl hydrazone **9b** gave under the same conditions no pyrazoline derivates. Instead a compound analyzing for the dihydrotetrazine **13** was obtained. The high dimerization tendency of N-nitrile sulfonyl-imines has been noted before.[7]

Cleavage of the pyrazoline ring. Cyano-amination of alkenes. β-Amino acids: Ring cleavage was not observed when the 3-chloro compound **11a** was heated with $Fe(CO)_5$ in acetic acid. We therefore turned our interest to the thermolysis of the 3-carboxy-pyrazolines **3** obtained by alkaline hydrolysis of **2.** When solid **3a** was heated to ca. 140 °C decarboxylation started but the yield of **4a** was disappointingly low. The principle product was the 3-H derivative **6**, R = C_6H_5, i.e. protonation of the intermediate 3-carbanion proceeded faster than ring cleavage. Use of DMF (dimethylformamide) as solvent at 140 °C changed the reaction course and gave a high yield of the desired cyano compound **4a** together with less than 10 % of **6.** Subsequent acid hydrolysis gave the β-N-benzylamino acid **5a.** Compound **4e** gave directly 3-benzylamino-butyrolactone **14** on acid hydrolysis.

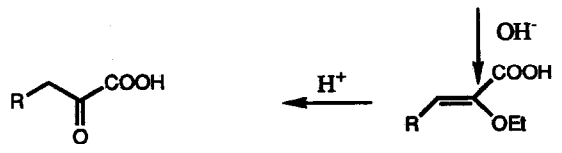
The dicarboxylic acid **3b** was stable in refluxing DMF at 150 °C for 2 h but decomposed when thermolyzed without solvent at 160 °C or in refluxing DMSO. The expected N-benzyl-β-cyano-alanine was not observed. The acetyl derivative **3d** was interesting, because it could conceivably be a precursor for 3-aminolevulinic acid **5d.** It gave **4d** on thermal decarboxylation but subsequent acid hydrolysis did not give the desired amino acid **5d.** Pyrazoline **2f** was transformed into **5f** in a modest yield. However, we feel that the procedure can be optimized and turned into a promising β-amino acid synthesis especially by using milder enzymatic hydrolysis of the cyano group.

Further reactions of compounds **7** *and* **8**: Ethyl glyoxylate diethylacetal did not directly give the oxime and hydrazones with hydroxylamine and hydrazines but the activated chloro-ethoxy derivative **7** formed the desired products **12.** The ester **7** gave the phosphonium salt **16,** which was used in a Wittig reaction to give 2-ethoxy-2-enoates with aldehydes in the presence of triethylamine. This reaction has been performed previously in the presence of strong bases such as NaH.[8] The complete sequence leading to α-ketoacids **19** was worked out, equation (2).



16

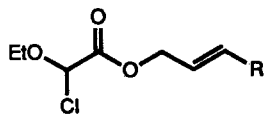
17a R = C_2H_5
17b R = C_6H_5



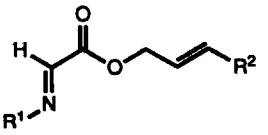
(2)

19a
19b

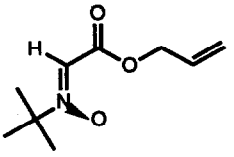
18a
18b



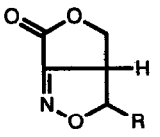
20a R = H
20b R = C_6H_5



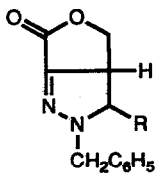
21a R^1 = OH, R^2 = H
21b R^1 = $NHCH_2C_6H_5$, R^2 = H
21c R^1 = $NHCH_2C_6H_5$, R^2 = C_6H_5
21d R^1 = OH, R^2 = C_6H_5



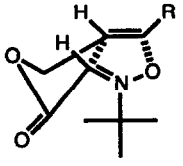
22



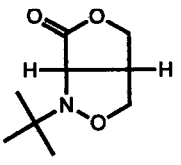
23a R = H
23b R = C_6H_5



24a R = H
24b R = C_6H_5



25



26

Of interest was the esterification of **8** with unsaturated alcohols and subsequent transformation of the chloro-ethoxy group to dipoles. This will give access to novel condensed heterocycles with regio- and stereoselective control as depicted by the transition state **25**. The intramolecular cyclization of nitrile oxides and nitrile imines from **21a,b,d** gave in our hands poor yields of impure **23a,b** and **24a** as concluded by inspection of the ^{1}H NMR and MS spectra of the crude cyclisation products and purified TLC fractions. However, the pyrazoline **24b** was formed in 55 % yield from **21c**. It is worth noting that the intramolecular cycloaddition of the allyl ester was regioselective and occurred in a direction opposite to the formation of **2e**. The intramolecular cycloadditions of the nitrone **22**, which only appeared as an intermediate, gave the bicyclic compound **26** in a moderate yield. Nitrone **22** was prepared by reacting **20a** with equimolecular amounts of t-butylhydroxylamine. The cycloaddition of similar allyloxycarbonyl nitrones, previously available by laborious routes, have recently been studied.[9] These cycloadducts are attractive from a synthetic point of view. Reductive ring cleavage will e.g. lead to functionalized α-amino acids.

Experimental

^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 MHz spectrometer and the MS spectra with a MicroMass 7070 F spectrometer. Preparative TLC was carried out on silica glass plates, 20 × 20 × 1.8 mm, Kieselgel 60, $Pf_{254+366}$, Merck and silica, Kieselgel 60, 63-200 μm, Merck was used for column chromatography.

Preparation of **1**: The crude benzylhydrazone of ethyl glyoxylate **12a** obtained from benzylhydrazine dihydrochloride (6.8 g) was dissolved in ethyl acetate (20 ml) and chlorinated with NCS (3.5 g) at 60 °C for ca. 1 h. The reaction was followed by TLC. The solvent was evaporated *in vacuo* and the residue extracted with CCl_4, filtered and the solvent was evaporated *in vacuo* to give crude **1**. It was chromatographed on a silica column with petroleum ether : diethyl ether, 3:1, as eluent. The yield of **1** was 5.1 g, 61 %, viscous yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, *J* 7 Hz), 4.32 (2 H, q, *J* 7 Hz), 4.70 (2 H, d, *J* 5.5 Hz), 6.7 (1 H, brt, *J* 5.5 Hz), 7.3 (5 H, m).

1-Benzyl-3-ethoxycarbonyl-5-phenyl-2-pyrazoline, **2a** : The hydrazone **12a** (1.0 g, 4.8 mmol) was chlorinated with NCS (0.71 g, 5.3 mmol) in ethyl acetate (8 ml) at 60 °C for 1 h. Styrene (1.0 g, 9.7 mmol), $KHCO_3$ (2.4 g) and a few drops of water were added and the mixture was kept at 70 °C for 20 h with stirring. Most of the succinimide formed was precipitated by addition of CCl_4. Filtration and evaporation of the solvent gave **2a** as a viscous yellow oil, which was chromatographed on a silica column (petroleum ether, 10 % ethylacetate), 0.92 g, 62 %. ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, *J* 7.1 Hz), 2.89 (1 H, dd, *J* 12.8 and 17.2 Hz), 3.32 (1 H, dd, *J* 13.0 and 17.2 Hz), 4.02 (1 H, d, *J* 14.8 Hz), 4.29 (2 H, q, *J* 7.1 Hz), 4.43 (1 H, dd, *J* 12.8 and 13.0 Hz), 4.77 (1 H, d, *J* 14.8 Hz), 7.1-7.4 (10 H, m). ^{13}C NMR ($CDCl_3$): δ 14.62, 41.56, 55.14, 61.24, 68.37, 128.02, 128.17, 128.70, 128.94, 129.40, 129.60, 136.09, 138.27, 140.14, 163.41.

1-Benzyl-3,5-diethoxycarbonyl-2-pyrazoline, **2b,** was prepared from **12a** and ethyl acrylate as described for **2a** in a yield of 76 %. It was purified by chromatography on silica (petroleum ether : diethyl ether, 3:2), light yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (3 H, t, *J* 7.5 Hz), 1.26 (3 H, t, *J* 7.3 Hz), 3.11 (2 H, d, *J* 12.5 Hz), 3.95 (1 H, t, *J* 12.5 Hz), 4.03 (2 H, q, *J* 7.5 Hz), 4.13 (2 H, q, *J* 7.3 Hz), 4.39 (1 H, d, *J* 14 Hz), 4.85 (1 H, d, *J* 14 Hz), 7.15-7.41 (5 H, m).

1-Benzyl-3-ethoxycarbonyl-5-cyano-2-pyrazoline, **2c,** was prepared as a viscous oil in a yield of 86 % from **12a** and acrylonitrile. The cycloaddition temperature was 60 °C, the reaction time 16 h and the chromatographic eluent was petroleum ether : diethyl ether, 3:2. ^{1}H NMR ($CDCl_3$): δ 1.29 (3 H, t, *J* 7.2 Hz), 3.18 (1 H, dd, *J* 10.0 and 17.0 Hz), 3.26 (1 H, dd, *J* 6.5 and 17.0 Hz), 4.21 (1 H, dd, *J* 6.5 and 10.0 Hz), 4.30 (2 H, q, *J* 7.2 Hz), 4.36 (1 H, d, *J* 14,4 Hz), 4.95 (2 H, d, *J* 14.4 Hz), 7.33 (5 H, br s).

1-Benzyl-3-ethoxycarbonyl-5-acetyl-2-pyrazoline, **2d** : The hydrazone **12a** (0.43 g, 2.1 mmol) was chlorinated with *t* -BuOCl (0.25 g, 2.3 mmol) at 0 °C in ethyl acetate (4 ml). Methyl vinyl ketone (0.35 ml, 4.3 mmol), $KHCO_3$ (1 g) and 3 drops of water were added and the mixture was kept for 20 h at 60 °C with stirring. Work-up as for **2a** (eluent, petroleum ether : EtOAc, 2.3:1) gave **2d** as a yellow, viscous oil, 0.25 g, 51 %. ^{1}H NMR ($CDCl_3$): δ 1.34 (3 H, t, *J* 7.2 Hz), 2.01 (3 H, s), 2.93 (1 H, dd, *J* 12.7 and 17.3 Hz), 3.25 (1 H, dd, *J* 13.1 and 17.3 Hz), 4.03 (1 H, d, *J* 14.4 Hz), 4.29 (2 H, q, *J* 7.2 Hz), 4.51 (1 H, t, *J* 12.8 Hz), 4.66 (1 H, d, *J* 14.4 Hz), 7.22-7.34 (5 H, m).

1-Benzyl-3-ethoxycarbonyl-5-hydroxymethyl-2-pyrazoline, **2e,** was prepared from **12a** and allyl alcohol (1.7 eqv.) according to the procedure described for **2a**. The crude product, **2e,** 58 %, brownish oil, was difficult to purify by TLC. It was directly hydrolyzed to the carboxylic acid **3e**. ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, *J* 7.2 Hz), 2.93 (1 H, dd, *J* 12.8 and 17.4 Hz), 3.04 (1 H, dd, *J* 11.6 and 17.4 Hz), 3.45-3.77 (3 H, m), 4.32 (2 H, q, *J* 7.2 Hz), 4.60 (2 H, s), 7.3 (5 H, br s).

1-Benzyl-3-ethoxycarbonyl-5-butyl-2-pyrazoline, **2f**: 1-Hexene (1 ml) in ethyl acetate (1 ml) was stirred with **1** (0.72 g) and K_2CO_3 (1 g) at 25 °C for 3 days. Filtration, evaporation and purification on preparative TLC (SiO_2, petroleum ether : diethyl ether, 4:1) gave **2f**, 0.56 g, 64 %. ^{1}H NMR ($CDCl_3$): δ 0.80 (3 H, t, *J* 6.8 Hz), 1.1-1.8 (9 H, m), 2.50 (1 H, dd, *J* 14.6 and 17.4 Hz), 2.94 (1 H, dd, *J* 11.0 and 17.4 Hz), 3.41 (1 H, m), 4.24 (2 H, q, *J* 7 Hz), 4.39 (1 H, d, *J* 15.1 Hz), 4.70 (1 H, d, *J* 15.1 Hz), 7.3 (5 H, m). When triethylamine was used as base the yield was 29 % and $KHCO_3$ gave a still lower yield.

General procedure for the hydrolysis of **2** *to* **3:** The ester **2** (1 mmol) was dissolved in methanol (3 ml) and aqueous NaOH (1 M, 1.6 ml) was added. The reaction mixture was stirred for 2 h at 25 °C under N_2, then diluted with water (10 ml) and washed with diethyl ether and separated. Neutralization of the aqueous phase with hydrochloric acid to pH 3-4 and extraction with chloroform gave after evaporation of the solvent the crude acid **3** in a good yield.

3a: yield 92 %, white needles, m.p. 85-87 °C from isopropanol. ^{1}H NMR ($CDCl_3$): δ 2.93 (1 H, dd, *J* 13.3 and 17.2 Hz), 3.35 (1 H, dd, *J* 12.4 and 17.2 Hz), 4.05 (1 H, d, *J* 14.8 Hz), 4.58 (1 H, dd, *J* 12.4 and 13.3 Hz), 4.80 (1 H, d, *J* 14.8 Hz), 7.15-7.43 (5 H, m).

3b: dicarboxylic acid, yield 94 %, from CC on silica, $CHCl_3$: CH_3OH, 4:1, yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.11 (2 H, d, *J* 12.5 Hz), 4.09 (1 H, t, *J* 12.5 Hz), 4.25 (1 H, d, *J* 14 Hz), 5.04 (1 H, d, *J* 14 Hz), 7.2 (5 H, br s). IR, film, 1745, 1710 cm^{-1}.

3c: yield 85 %, yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.08 (2 H, d, *J* 12.5 Hz), 4.02 (1 H, t, *J* 12.5 Hz), 4.51 (1 H, d, *J* 16 Hz), 5.04 (1 H, d, *J* 16 Hz), 7.2 (5 H, br s). ^{13}C NMR ($CDCl_3$): δ 37.11, 53.39, 56.77, 116.05, 129.16, 129.53, 129.66, 134.28, 139.83, 166.01.

3d: The ester **2d** (1.0 mmol) was dissolved in dioxane (5 ml) and 12 ml of 0.1 M aqueous NaOH was added dropwise with stirring and cooling with tapwater. After 20 min. the solution was acidified with aqueous HCl to pH 3 and extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl, dried over $MgSO_4$ and evaporated. The carboxylic acid **3d** was obtained as a light yellow solid, yield 82 %. ^{1}H NMR ($CDCl_3$): δ 2.05 (3 H, s), 294 (1 H, dd, *J* 13.4 and 17.4 Hz), 3.26 (1 H, dd, *J* 12.4 and 17.4 Hz), 4.14 (1 H, dd, *J* 12.4 and 13.4 Hz), 4.48 (1 H, d, *J* 14.6 Hz), 4.75 (1 H, d, *J* 14.6 Hz), 7.27 (5 H, br s). The compound was purified by precipitation with water from a methanolic solution, m.p. 57-59°C.

3e: crude yield 64 %, brownish oil, which was used directly for the decarboxylation. ^{1}H NMR ($CDCl_3$): δ 2.91 (1 H, dd, *J* 13.0 and 17.5 Hz), 3.01 (1 H, dd, *J* 12.0 and 17.5 Hz), 3.5-3.9 (3 H, m), 4.54 (1 H, d, *J* 14.5 Hz), 4.67 (1 H, d, *J* 14.5 Hz), 7.3 (5 H, m).

3f: yield 92 %, oil. ^{1}H NMR ($CDCl_3$): δ 0.82 (3 H, t, *J* 7.0 Hz), 1.1-1.8 (6 H, m), 2.62 (1 H, dd, *J* 14.0 and 16.8 Hz), 2.96 (1 H, dd, *J* 11.4 and 16.8 Hz), 3.54 (1 H, m), 4.40 (1 H, d, *J* 14.8 Hz), 4.74 (1 H, d, *J* 14.8 Hz), 7.3 (5 H, m).

General procedure for decarboxylation of **3** *to the cyano compounds* **4**: The 3-carboxypyrazoline **3** (1 mmol) was heated in dry DMF (3 ml) at 140-150 C for 1 h. The solvent was evaporated *in vacuo* and the residue was purified on a small silica column or by TLC.

4a: yield 71 %, colourless oil, silica gel, diethyl ether : CH_2Cl_2, 1:20. It gave a crystalline HCl-salt, white needles, m.p. 145-149 °C from water. ^{1}H NMR ($CDCl_3$): δ 1.93 (1 H, br s), 2.70 (2 H, d, *J* 6.5 Hz), 3.64 (1 H, d, *J* 13.2 Hz), 3.75 (1 H, d, *J* 13.2 Hz), 4.02 (1 H, t, *J* 6.5 Hz), 7.3-7.4 (10 H, m).

A small amount of **6**, R = C_6H_5, was also isolated, ca. 10 %. The 3-H was located at δ 6.75, narrow triplet.

4c: yield 34 %, oil, silica gel, Et_2O : CH_2Cl_2, 5:95. ^1H NMR ($CDCl_3$): δ 2.69 (2 H, d, *J* 6.5 Hz), 3.54 (1 H, t, *J* 6.5 Hz), 3.77 (1 H, *J* 13.5 Hz), 3.87 (1 H, *J* 13.5 Hz), 7.3 (6 H, m). Minor amounts of **6**, R = CN was visible in the ^1H NMR spectrum of the crude product, δ 6.77.

4d: yield 73 %, light yellow viscous oil, which decomposed on standing at 25 °C or by TLC purification. It was purified on a small silica column (CH_2Cl_2). Ca. 12 % of the pyrazoline **6**, R = $COCH_3$ was isolated. The 3-H of **6** was located at δ 6.69 narrow triplet in the ^1H NMR spectrum,. ^1H NMR ($CDCl_3$): **4d** δ 2.27 (3 H, s), 2.67 (2 H, d, *J* 6.2 Hz), 3.58 (1 H, t, *J* 6.2 Hz), 3.79 (1 H, d, *J* 13.2 Hz), 3.83 (1 H, d, *J* 13.2 Hz). IR (film): 2200, 1730 cm^{-1}.

4e: yield 38 %, brownish oil, TLC (SiO_2, CH_2Cl_2: CH_3OH, 10:1). ^1H NMR ($CDCl_3$): δ 2.57 (2 H, d, *J* 6.5 Hz), 3.1 (1 H, m), 3.58 (1 H, dd, *J* 5.5 and 11.0 Hz), 3.71 (1 H, dd, *J* 4.5 and 11.0 Hz), 3.82 (1 H, d, *J* 15 Hz), 3.86 (1 H, d, *J* 15 Hz), 7.3 (5 H,m). ^{13}C NMR: δ 20.67, 51.47, 55.25, 63.20, 118.22, 127.97, 128.54, 129.16, 139.69. A minute amount of **6**, R = CH_2OH was observed in the ^1H NMR spectrum of the crude product, δ 6.73 (3 H).

4f: yield 83 %, oil, silica gel, Et_2O:CH_2Cl_2, 5:95. ^1H NMR ($CDCl_3$): δ 0.84 (3 H, t, *J* 7.0 Hz), 1.2-1.7 (6 H, m), 2.37 (1 H, dd, *J* 5.07 and 16.8 Hz), 2.47 (1 H, dd, *J* 4.93 and 16.8 Hz), 2.80 (1 H, sext, *J* 5 Hz), 3.66 (1 H, d, *J* 13.6 Hz), 3.85 (1 H, d, *J* 13.6 Hz), 7.25 (5 H, m).

A minute amount of **6**, R = C_4H_9, was isolated. The 3-H was located at δ 6.73, narrow triplet, in the ^1H NMR spectrum.

3-Phenyl-3-N-benzylaminopropionic acid, **5a**: The nitrile **4a** (65 mg) was heated in 20 % sulfuric acid (2 ml) for 4 h at 100 °C. Water (10 ml) was added and the solution neutralized with $CaCO_3$. The $CaSO_4$ was filtered off and washed with water. The filtrate was evaporated *in vacuo* and the residue was recrystallized from methanol to give **5a**, 25 mg, as white needles, m.p. 190-191 °C (lit.[10] 187-188 °C).

3-N-Benzylaminoheptanoic acid, **5f**: The nitrile **4f** (304 mg) was hydrolyzed in 20 % sulfuric acid (3 ml) worked up as described for **4a**. The residue (170 mg) was recrystallized from a small amount of water (ca. 1 ml) to give pure **5f**, 80 mg, m.p. 150-155 °C. ^1H NMR ($CDCl_3$): δ 0.87 (3 H, t), 1.26 (4 H, m), 1.65 (2 H, m), 2.40 (2 H, m), 3.01 (1 H, m), 4.00 (1 H, d, *J* 13.5 Hz), 4.13 (1 H, d, *J* 13.5 Hz), 7.3 (5 H, m). The lines are broad.

Ethyl 2-chloro-2-ethoxyacetate, **7**: To a mixture of acetyl chloride (2.5 g) and ethyl glyoxalate diethylacetal (5.3 g) iodine (12 mg) was added as catalyst. An exothermic reaction started and the mixture was heated at 50 °C for 1 h. Distillation *in vacuo* gave **7** (82 %), bp. 79 °C/10 mm Hg (lit.[5] bp. 79 °C/12 mm Hg). ^1H NMR ($CDCl_3$): δ 1.28 (6 H, m), 3.63 (1 H, dq, *J* 7 and 8 Hz), 3.99 (1 H, dq, *J* 7 and 8 Hz), 4.24 (2 H, q), 5.77 (1 H, s). ^{13}C NMR ($CDCl_3$): 14.39, 14.75, 62.95, 66.85, 88.97, 165.8. MS: m/z 131 $(M-Cl)^+$, 122, 94. IR (film): 1770 cm^{-1}.

2-Ethoxy-2-chloroacetyl chloride, **8**: To a mixture of PCl_5 (28.1 g) and iodine (1 g) was added dropwise ethyl glyoxalate diethylacetal (10.0 g) containing iodine (50 mg) with stirring. The flask was equipped with a drying tube and an air condenser. After the initial exothermal reaction evolving ethyl chloride has ceased, the temperature was kept at 100 °C for 17 h. Additional PCl_5 (ca. 3 g) was added at room temperature with stirring until the iodine coloured solution turned yellow. The mixture was distilled at 10 mm Hg and the PCl_5, which had sublimed into the distillate, was decomposed by adding methyl formate (1 ml). The crude product consisting principally of $POCl_3$ and **8** was fractionated over a Vigreux column at 50 mm Hg to give **8**, 4.1 g (47 %). bp. 77 °C (lit.[6] b.p. 49-51.5 °C/12 mm Hg). The product contained small amounts (5-10 %) of an unknown compound with an ethyl group absorbing at δ 1.4 (t) and 4.2 (q). ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t), 3.7 (1 H, m), 4.05 (1 H, m), 5.94 (1 H, s). The product was sufficiently pure for further reactions.

Benzylhydrazone of glyoxylic acid, **9a**, was obtained by reacting glyoxylic acid with benzylhydrazine · 2 HCl in ice water for 1 h. The hydrazone, **9a** precipitated and was filtered, washed with cold water and dried. The crude yield was 80 %. It could be recrystallized from acetonitrile : methanol, 3:1, m.p. 135-140 °C. ^{1}H NMR ($CDCl_3$): δ 4.22 (2 H, s), 6.53 (1 H, s), 7.1 (5 H, br s).

Benzenesulfonyl hydrazone of glyoxylic acid, **9b**: Benzenesulfonyl hydrazine (5 g) was suspended in methanol (8 ml) and glyoxylic acid (4.4 ml, 50 % aqueous solution) was added. The hydrazine went rapidly into solution and after 20 min. water (20 ml) was added in portions. Crystals of **9b** separated on the glass wall. They were filtered and dried in a desiccator, m.p. 96-102 °C, dec. A sample recrystallized from ether melted at 99-101 °C, dec. ^{1}H NMR ($CDCl_3$: CD_3CN, 2:1): δ 7.11 (1 H, s). The yield was 5.4 g, 92 %.

1-Benzyl-3-chloro-5-methoxycarbonylpyrazoline, **11a**: Compound **9a** (0.89 g), methyl acrylate (1.2 g) potassium hydrogencarbonate (1.0 g) and NCS (1.47 g) in ethyl acetate (5 ml + one drop of water) were stirred at 25 °C for 48 h. The solution was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica (diethyl ether : petroleum ether, 1:4) to give **11a**, viscous oil, 0.42 g, 33 %. MS: 254, 252 (M^+), 195, 193, 91. ^{1}H NMR ($CDCl_3$): δ 2.98 (1 H, dd, *J* 17.0 and 12.0 Hz), 3.21 (1 H, dd, *J* 17.0 and 12.5 Hz), 3.65 (3 H, s), 3.89 (1 H, dd, *J* 12.5 and 12.0 Hz), 4.25 (1 H, d, *J* 14.0 Hz), 4.37 (1 H, d, *J* 14.0 Hz), 7.30 (5 H, br s).

Benzylhydrazone of ethyl glyoxylate, **12a**: Benzylhydrazine dihydrochloride (4.23 g) was suspended in water (10 ml) and the pH was adjusted to ca. 4. Ethyl 2-chloro-2-ethoxyacetate (4.15 g) in dioxane (25 ml) was added in small portions with cooling with tap water and stirring. After 1 h the reaction mixture was neutralized to pH 8 with aqueous sodium hydroxide and evaporated *in vacuo* to half the volume. Water was added and the emulsion extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ filtered and evaporated *in vacuo* . The crude product (5.2 g) was subjected to column chromatography (SiO_2, diethyl ether : dichloromethane, 1:4) to give **12a**, 3.9 g, 76 %, as a yellow oil which slowly crystallized, m.p. 49-51 °C. A small sample was recrystallized from cyclohexane: carbontetrachloride, 10:1, m.p. 51-52 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (3 H, t, *J* 7.0 Hz), 4.23 (2 H, q, *J* 7.0 Hz), 4.37 (2 H, d, *J* 4.6 Hz), 6.74 (1 H, br t), 6.75 (1 H, s), 7.2-7.4 (5 H, m).

Boc-hydrazone of ethyl glyoxylate, **12b**, was obtained from ethyl glyoxylate and N-butyl carbazate in ethanol : acetic acid, 8:1, at 54 °C for 5 h. Evaporation of the solvent and column chromatography (SiO_2, ethyl acetate : petroleum ether, 2:3) gave **12b**, as an isomeric mixture, 70 %, m.p. 107-112 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (1 H, s, CH = N, major), 6.80 (1 H, s, CH = N, minor).

3-Benzylaminobutyrolactone, **14**, was obtained by heating **4e** (40 mg) in 4 M HCl (1 ml) for 10 h at 100 °C. The reaction mixture was neutralized to pH 7 with NaOH and extracted with CH_2Cl_2. Drying and evaporation of the solvent gave **14** as a colourless oil, 25 mg, 63 %. ^{1}H NMR ($CDCl_3$): δ 2.38 (1 H, dd, *J* 5.0 and 17.5 Hz), 2.69 (1 H, dd, *J* 7.5 and 17.5 Hz), 3.60-3.73 (1 H, m), 3.78 (2 H, s), 4.11 (1 H, dd, *J* 4.0 and 9.5 Hz), 4.35 (1 H, dd, *J* 6.5 and 9.5 Hz), 7.3 (5 H, m).

1-Benzyl-3-ethoxycarbonyl-4,5-diphenyl-2-pyrazoline, **15a**: *trans* -Stilbene (0.37 g, 2.0 mmol) was reacted with **1** (from 0.21 g of **12a**) and K_2CO_3 (0.35 g) for 22 h at 45 °C in ethyl acetate (4 ml) with stirring. Work-up gave **15a**, 96 mg, 25 %, as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.15 (3 H, t, *J* 7 Hz), 4.13 (1 H, d, *J* 14.7 Hz), 4.18 (2 H, q, *J* 7 Hz), 4.28 (1 H, d, *J* 10.4 Hz), 4.42 (1 H, d, *J* 10.4 Hz), 4.97 (1 H, d, *J* 14.7 Hz), 6.9-7.4 (15 H, m). ^{13}C NMR ($CDCl_3$): δ 14.64(q), 55.55 (t), 61.14(t), 61.18(d), 77.32(d), 127.56(d), 127.63(d), 128.13(d), 128.33(d), 128.76(d), 129.03(d), 129.11(d), 129.47(d), 129.52(d), 135.88(s), 139.04(s), 139.85(s) 141.57(s), 162.85(s).

15b: solid, m.p. 168-169 °C from CH_3OH:H_2O. ^{1}H NMR($CDCl_3$): δ 4.14 (1 H, d, *J* 14.7 Hz), 4.27 (1 H, d, *J* 9.7 Hz), 4.46 (1 H, d, *J* 9.7 Hz), 4.97 (1 H, d, *J* 14.7 Hz), 6.8-7.4 (15 H, m).

Ethoxy-ethoxycarbonylmethyl-triphenylphosphonium chloride, **16**: Triphenyl-phosphine (2.62 g) and **7** (1.67 g) was reacted in chloroform (5 ml) for 25 h at 25 °C. Most of the solvent was evaporated *in vacuo* and the salt **16** was precipitated by addition of diethyl ether, 3.6 g, 84 %, sufficiently pure for further synthesis, m.p. 137-139 °C. ^{1}H NMR ($CDCl_3$): δ 0.91 (3 H, t, *J* 7 Hz), 1.00 (3 H, t, *J* 7 Hz), 4.00 (2 H, q, *J* 7 Hz), 4.13 (2 H, q, *J* 7 Hz), 7.55-7.8 (9 H, m), 7.9-8.13 (6 H, m), 8.37 (1 H, d, *J* 16 Hz).

Preparation of **17a**: To the phosphonium salt **16** (2.14 g) and propanal (0.30 g) in chloroform (20 ml) was added triethylamine (0.55 g) at 0 °C. The mixture was stirred at 25 °C for 24 h then evaporated and diethyl ether was added to precipitate triphenylphosphine oxide, which was filtered off. The filtrate was evaporated *in vacuo* and the residue purified on TLC (SiO_2, CH_2Cl_2) to give **17a**, Z-isomer, 0.52 g, 60 % as an oil. ^{1}H NMR ($CDCl_3$): δ 1.01 (3 H, t, *J* 7 Hz), 1.3 (6 H, m), 2.22 (2 H, quint, *J* 7 Hz), 3.83 (2 H, q, *J* 7 Hz), 4.21 (2 H, q, *J* 7 Hz), 6.23 (1 H, t, *J* 8 Hz). Minute amounts of the E-isomer were formed, δ 5.22 (t, *J* 8 Hz).

The phenyl derivative **17b** was prepared according to the same method from benzaldehyde in a yield of 70 %, Z-isomer, oil. ^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, t, *J* 7 Hz), 4.02 (2 H, q, *J* 7 Hz), 4.30 (2 H, q, *J* 7 Hz), 6.93 (1 H, s), 7.25-7.45 (3 H, m), 7.75-7.85 (2 H, m).

Z-2-Ethoxy-2-pentenoic acid, **18a**: The ester **17a** (0.17 g, 1 mmol) was hydrolyzed in ethanol:water (2:1, 4 ml, 1 M NaOH) for 1 h at 25 °C. Water was added, the solution acidified and extracted with dichloromethane. Drying ($MgSO_4$) and evaporation of the solvent gave **18a**, 0.12 g, 84 %. ^{1}H NMR ($CDCl_3$): δ 1.03 (3 H, t, *J* 7 Hz), 1.29 (3 H, t, *J* 7 Hz), 2.29 (2 H, quint, *J* 7 Hz), 3.87 (2 H, q, *J* 7 Hz), 6.44 (1 H, t, *J* 7 Hz). The product contained ca. 10 % of the E-form, δ 5.38 (t, *J* 7 Hz).

Z-2-Ethoxy-cinnamic acid, **18b**, was prepared from **17b** according to the method described for **18a**. The emulsion became homogenous after ca. 15 min. Yield 90 %. ^{1}H NMR ($CDCl_3$): δ 1.41 (3 H, t, *J* 7 Hz), 4.04 (2 H, q, *J* 7 Hz), 7.18 (1 H, s), 7.2-7.5 (3 H, m), 7.8-7.9 (2 H, m). The product contained ca. 10 % of the E-form, δ 6.3 (s).

2-Oxopentanoic acid, **19a**, was obtained in a yield of 72 % by hydrolyzing **18a** (1 mmol) in 1 M H_2SO_4 (3 ml) at 90 °C for 1 h. Extraction with dichloromethane, drying with $MgSO_4$ and evaporation gave **19a**. ^{1}H NMR ($CDCl_3$): δ 0.97 (3 H, t, *J* 7 Hz), 1.70 (2 H, sext, *J* 7 Hz), 2.91 (2 H, t, *J* 7 Hz).

Phenylpyruvic acid, **19b**: The cinnamic acid **18b** (1 mmol) was hydrolyzed in dioxane (2 ml) and 8 M HCl (8 ml) at 100 °C for 1 h. Extraction with dichloromethane gave **19b**, m.p. 159 °C from chloroform (lit.[11] 157-158 °C).

Allyl 2-chloro-2-ethylacetate, **20a**: The acid chloride **8** (0.75 g) in dichloromethane (5 ml) was slowly added to allyl alcohol (0.28 g) and triethylamine (0.50 g) in dichloromethane (5 ml) at 0 °C. The temperature was slowly raised to 25 °C (0.5 h) and the solution was washed twice with ice water, dried ($MgSO_4$) and evaporated to give pure **20a**, 0.72 g, 83 %, oil, sufficiently pure for further synthetic use. ^{1}H NMR ($CDCl_3$): δ 1.29 (3 H, t, *J* 7 Hz), 3.63 (1 H, m), 4.00 (1 H, m), 4.67 (2 H, d, *J* 7 Hz), 5.24 (1 H, d, *J* 11 Hz), 5.35 (1 H, d, *J* 16 Hz), 5.79 (1 H, s), 5.8-6.0 (1 H, m).

The cinnamyl ester, **20b**, was prepared according to the procedure described for **20a** in a yield of 92 % as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 1.34 (3 H, t, *J* 7 Hz), 3.70 (1 H, m), 4.05 (1 H, m), 4.90 (2 H, d, *J* 7 Hz), 5.88 (1 H, s), 6.31 (1 H, dt, *J* 16 and 7 Hz), 6.71 (1 H, d, *J* 16 Hz), 7.25-7.45 (5 H, m).

Oxime, **21a**: Hydroxylamine hydrochloride (0.21 g) in water (2 ml) was mixed with **20a** (0.54 g) in dioxane (3 ml) at 0 °C and stirred for 0.5 - 1 h at 25 °C. Water was added and **21a** was extracted with dichloromethane. The crude **21a** was purified by TLC (SiO_2, CH_2Cl_2: Et_2O, 95:5), yield 65 %. ^{1}H NMR ($CDCl_3$): δ 4.71 (2 H, d, *J* 7 Hz), 5.25 (1 H, d, *J* 11 Hz), 5.33 (1 H, d, *J* 16 Hz), 5.91 (1 H, m), 7.55 (1 H, s). ^{13}C NMR ($CDCl_3$): δ 66.81, 119.93, 131.57, 114.96, 162.68.

Hydrazone, **21b**: Benzylhydrazine dihydrochloride (1.60 g) in water (5 ml) was mixed with **20a** (1.46 g) in dioxane (10 ml) at 0 °C with stirring. The pH was kept at 3-4 by addition of solid sodium hydrogencarbonate. The temperature was slowly raised to 25 °C (0.5 h). Work-up as for **21a**. Chromatographic purification (SiO_2, CH_2Cl_2) gave 0.68 g, 38 %, of **21b**. ^{1}H NMR ($CDCl_3$): δ 4.40 (2

H, d, *J* 4 Hz), 4.67 (2 H, d, *J* 5.5 Hz), 5.23 (1 H, d, *J* 11 Hz), 5.32 (1 H, d, *J* 17 Hz), 5.95 (1 H, m), 6.77 (1 H, s), 6.9 (1 H, br s), 7.2-7.4 (5 H, m).

Hydrazone, **21c**, was prepared according to the procedure described for **12a** in a chromatographic yield of 26 % (5 % Et_2O in CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 4.40 (2 H, br s), 4.87 (2 H, d, *J* 5 Hz), 6.36 (1 H, dt, *J* 12.5 and 5 Hz), 6.8 (2 H, br s), 7.2-7.45 (10 H, m).

Oxime, **21d**, was prepared according to the procedure described for **21a** in a yield of 76 % (SiO_2, 5 % Et_2O in CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 4.92 (2 H, d, *J* 7 Hz), 6.33 (1 H, dt, *J* 16 and 7 Hz), 6.70 (1 H, d, *J* 16 Hz), 7.2-7.45 (5 H, m), 7.60 (1 H, s).

Synthesis of **24b**: The hydrazone **21c** (151 mg) was chlorinated with NCS (69 mg) in ethyl acetate (5 ml) at 60 °C (ca. 20 min). The solution was cooled to 0 °C and solid potassium carbonate (130 mg) was added. The mixture was stirred at room temperature for 40 h, filtrated, evaporated *in vacuo* and the residue purified by TLC (SiO_2, Et_2O : CH_2Cl_2, 5:95) to give **24b** as an oil, 82 mg, 55 % yield. ^1H NMR ($CDCl_3$): δ 3.83 (1 H, dt, *J* 14 and 8.5 Hz), 4.00 (1 H, d, *J* 14 Hz), 4.12 (1 H, t, *J* 8.5 Hz), 4.52 (1 H, d, *J* 14 Hz), 4.57 (1 H, t, *J* 8.5 Hz), 4.62 (1 H, d, *J* 14 Hz). MS: m/z 392 (M^+), 117, 91.

Synthesis of **26**: t-Butylhydroxylamine hydrochloride (0.25 g) and sodium bicarbonate (0.25 g) in water (2 ml) was added to **7** (0.33 g) in dioxane (3 ml) and the mixture was stirred for 20 h at 25 °C. Water was added and the product was extracted with dichloromethane. The organic phase was separated, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica, CH_2Cl_2: Et_2O, 98:2, to give **26**, 46 %. ^1H NMR ($CDCl_3$): δ 1.12 (9 H, s), 3.41 (1 H, m), 3.66 (1 H, m), 3.91 (1 H, d, *J* 8.5 Hz), 4.14 (2 H, m), 4.39 (1 H, m). MS: m/z 185 (M^+), 170, 129, 84, 70.

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