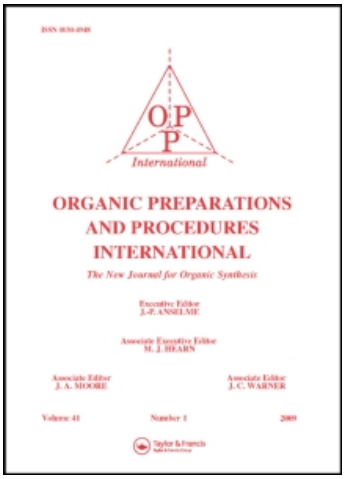

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N-(DIPHENYLMETHYLENE)-α,β-DIDEHYDROAMINO ACID ESTERS. THERMAL AND LEWIS ACID INDUCED DIMERIZATIONS

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Anal. Calcd. for $C_{21}H_{44}O_3$: C, 73.20; H, 12.87. Found: C, 72.90; H, 12.52

The spectral patterns (IR, ^1H NMR and MS) of 2b, 2c and 2d are similar to that of 2a.

REFERENCES

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1. H. K. Mangold, Angew. Chem. Int. Ed. Engl., 18, 493 (1973); Prog. Biochem. Pharmacol., 22, 1 (1988); F. Snyder in "Progress Chem. Fats and Other Lipids", Vol. 10 (part 3), p. 289, R. T. Holman, Ed., Pergamon Press, London, 1969.

2. F. Spener in "Ether Lipids: Biochemical and Biomedical Aspects", p. 239, H. K. Mangold and F. Paltauf, Eds., Academic Press, New York, 1983; G. Halperin, O. Stein, Y. Stein, in "Methods in Enzymology", Vol. 129, p. 816, J. J. Albers and J. P. Segrest, Eds., Academic Press, New York, 1986.

3. W. J. Baumann and H. K. Mangold, J. Org. Chem., 29, 3055 (1964); T. Kusumi, T. Ishitsuka, H. Iwashita, T. Konno and H. Kakisawa, Chemistry Lett., 1393 (1981); M. N. Do and K. L. Erickson, Tetrahedron Lett., 24, 5699 (1983).

4. K. Urata, S. Yano, A. Kawamata, N. Takaishi and Y. Inamoto, J. Am. Oil Chem. Soc., 65, 1299 (1988).

5. G. G. Davies, I. M. Heilbron and W. M. Owens, J. Chem. Soc., 2542 (1930); N. Kornblum and H. N. Holmes, J. Am. Chem. Soc., 64, 3045 (1942).

6. V. Bhushan, R. Rajendra and S. Chandrasekharan, Synthesis, 431 (1984).

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N-(DIPHENYLMETHYLENE)–α,β-DIDEHYDROAMINO ACID ESTERS. THERMAL AND LEWIS ACID INDUCED DIMERIZATIONS

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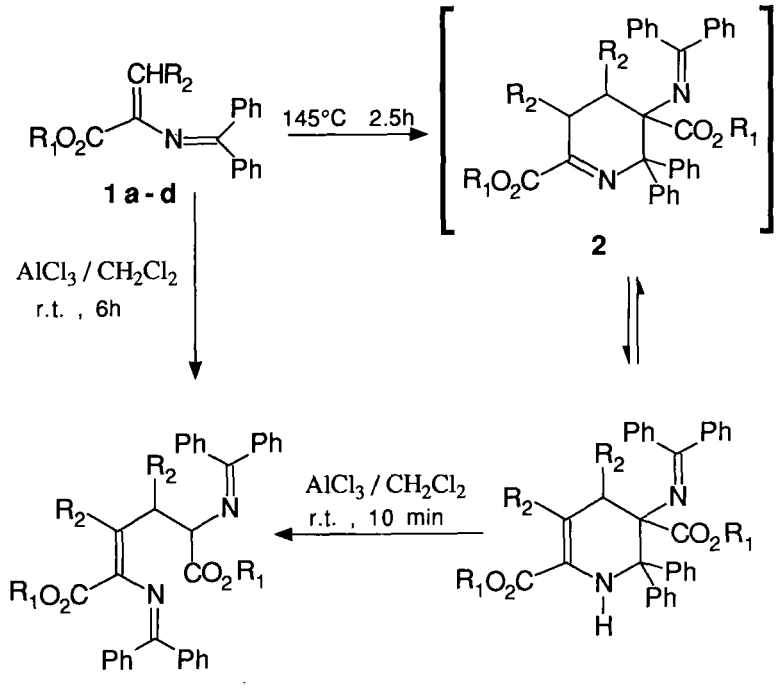
N-Protected α,β-didehydroamino acid esters are useful synthons in the synthesis of α-amino acids.[1] N-(Arylidene)-α,β-didehydroalaninates have been used as Michael acceptors

for the preparation of either alkyl or phenyl β-substituted alaninates;[2] a similar procedure using advantageously the alkyl N-(diphenylmethylene)-α,β-didehydroalaninates **1a,b** has been reported.[3] The didehydro-α-imino acids **1a-d** contain a 2-aza-1,3-diene system, which is known to give readily electrocyclic reactions yielding pyridine derivatives.[4] Actually, in the course of the cited synthetic studies,[2,3] [4+2] cyclodimerizations of the imino acid synthons were observed and the derived tetrahydropyridines have been isolated on occasion. These cyclodimerizations were considered as troublesome side-reactions, since they might limit the synthetic use of didehydroamino acids. In fact, the methyl N-(arylidene)didehydroalaninates have been reported to dimerize even at very low temperatures;[2] besides, the tetrahydropyridine derivative **3a** had already been isolated as a by-product from the synthesis of **1a** (<5%). Thus, we decided to investigate these cyclodimerizations further both in order to use more properly **1a-d** in the synthesis of amino acids and to explore the synthetic potential of these reactions. The results of our work are summarized as follows.



a) $R_1 = CH_3$; $R_2 = H$

b) $R_1 = C_2H_5$; $R_2 = H$

c) $R_1 = CH_3$; $R_2 = CH_3$ (E and Z)

d) $R_1 = CH_3$; $R_2 = C_6H_5$ (E and Z)

The thermal cyclization of **1a,b** at 145° and the subsequent prototropic equilibria gave

the 2,2-diphenyl-3-(N-diphenylmethylenamino)-1,2,3,4-tetrahydropyridine-3,6-dicarboxylates **3a,b** in good yields. Below 110°, the rate of the reactions was very slow. At 145°, **(Z)-1c** and **(Z)-1d** did not give any detectable amount of the cycloadducts and the **(E)-1c** and **(E)-1d** rapidly isomerized to the **Z** isomers.[5] Using $AlCl_3$, a typical catalyst of the Diels-Alder reaction, we surprisingly obtained from **1a,b** the acylic dimers, dialkyl 2,5-di-(N-diphenylmethylenamino)-2-hexen-1,6-dicarboxylates (**4a** and**4b**). Compound **4a** was also isolated as a by-product (18%) in the thermal dimerization of **1a**. The course of the Lewis acid catalyzed reaction of **1a,b** to **4a,b** may be rationalized by invoking the highly sterically congested tetrahydropyridines **3a,b** as intermediates. This hypothesis is supported by the very rapid rearrangement of **3a,b** to **4a,b** when they were treated with $AlCl_3$. Accordingly, under the same reaction conditions, **(Z)-1c,d** and **(E)-1c,d** were unreactive. In conclusion, it has been demonstrated that the cyclodimerization of **1a,b** has some limited, albeit interesting, applications in the synthesis of both tetrahydropyridines **3** and hexendioic amino acids **4**. It has also been shown that the cyclodimerizations of **1a,b** can compete with other synthetic procedures only at temperatures above 110° or in the presence of a Lewis acid. These results have prompted the study of the [4+2]-cycloadditions of dienophiles to the 2-aza-1,3-diene system of **1a-d**, in the perspective defined by Ghosez and others.[4] Work is in progress to assess the scope of these reactions in the synthesis of dihydro- and tetrahydropyridines.[6]

EXPERIMENTAL SECTION

Dimethyl 2,2-Diphenyl-3-(N-diphenylmethylenamino)-1,2,3,4-tetrahydropyridine-3,6-dicarboxylate (3a).- Methyl N-(diphenylmethylene)-α,β-didehydroalaninate (**1a**)[3] (2.65 g, 10 mmol) was heated without any solvent and in the normal atmosphere at 145° for 2.5 hrs in an open pyrex glass tube. The resulting mixture was purified by flash-chromatography (silica gel; cyclohexane-ethyl acetate 95:5) and crystallization, thus giving 2.06 g (78%) of **3a**, mp. 210° (ethyl acetate-hexane). IR ($CDCl_3$): 3360, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1-2.46 (Part of ABX system, 2 H, CH_2, J_{AB} = 12.06 Hz; J_{AX} = 3.33 Hz); 3.38 (s, 3H, OCH_3); 3.49 (s, 1H, NH); 3.59 (s, 3H, OCH_3); 4.62 (t, 1H, vinyl H, J_{AX} = 3.33 Hz); 6.96-7.90 (m, 20ArH).
Anal. Calcd for $C_{34}H_{30}N_2O_4$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.74; H, 5.76; N, 5.19
Diethyl 2,2-Diphenyl-3-(N-diphenylmethylenamino)-1,2,3,4-tetrahydropyridine-3,6-dicarboxylate (3b).- Following the procedure described for **3a**, from 2.79 g (10 mmol) of ethyl N-(diphenylmethylene)-α,β-didehydroalaninate (**1b**),[3] 1.80 g (65%) of **3b** was obtained, mp. 147-149° (CH_2Cl_2-hexane). Spectroscopic data (IR, NMR) and melting point are identical to those of a sample obtained according to ref. 3.
Dimethyl 2,5-di-(N-Diphenylmethylenamino)-2-hexen-1,6-dicarboxylate (4a). From 1a.- A solution of **1a** (0.27 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was stirred for 6 hrs at r.t. in presence of an equimolecular amount of $AlCl_3$, with the exclusion of moisture. The mixture was then

poured into an ice-cold $NaHCO_3$ sat. solution (10 mL); the suspension of aluminum hydroxide was filtered on Celite, the organic layer was separated, washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated. **4a** was obtained by flash chromatography (silica gel; cyclohexane-ethyl acetate 95:5) and crystallization (0.15 g, 57%).

From 3a.- A solution of **3a** (0.53 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was stirred for 10 min. with $AlCl_3$ (1 mmol). Work-up as in the procedure from **1a** gave 0.45 g (85%) of **4a**, mp. 128-129° (ethyl acetate-hexane). IR (nujol): 1740; 1720; 1635; 1615 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.75 and 4.20 (2m, ABX system, 3H, =N-CH-CH_2); 3.55 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 5.92 (t, 1H, vinyl H); 7.00-7.80 (m, 20ArH).

Anal. Calcd for $C_{34}H_{30}N_2O_4$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.80; H, 5.81; N, 5.21

Diethyl 2,5-di-(N-diphenylmethylenamino)-2-hexen-1,6-dicarboxylate (4b) From 1b.- As in the procedure from **1a**, 0.28 g of **1b** (1 mmol) afforded 0.20 g (72%) of **4b**.

From 3b.- As in the procedure from **3a**, but in presence of 2 mmol of $AlCl_3$, 0.56 g of **3b** (1 mmol) afforded 0.53 g (96%) of **4b**, mp. 141° (ether-hexane). IR (nujol): 1735; 1710; 1640; 1615 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 1.22 (t, 3H, CH_2-CH_3), 1.23 (t, 3H, CH_2-CH_3); 2.65-2.72 (m, 2H, CH_2); 4.02 (q, 2H, CH_2-CH_3); 4.09 (q, 2H, CH_2-CH_3); 4.22 (m, 1H, H-5); 5.93 (t, 1H, vinyl H); 7.11-7.42 (m, 20ArH).

Anal. Calcd for $C_{36}H_{34}N_2O_4$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.22; H, 6.31; N, 4.89

REFERENCES

1. U. Schmidt, A. Lieberknecht and J. Wild, Synthesis, 159 (1988).

2. G. Wulff and H. Bohnke, Angew. Chem. Int. Ed. Engl., 25, 90 (1986); G. Wulff, H. Bohnke and H. T. Klinken, Ann., 501 (1988).

3. G. Tarzia, C. Balsamini, G. Spadoni and E. Duranti, Synthesis, 514 (1988).

4. Ph. Bayard, F. Sainte, R. Beaudegnies and L. Ghosez, Tetrahedron Lett., 3799 (1988) and references cited therein.

5. For the synthesis of (Z)- and (E)-1c,d, see: C. Balsamini, E. Duranti, L. Mariani, A. Salvatori and G. Spadoni, Synthesis, 779 (1990).

6. In preliminary cycloaddition experiments (toluene, reflux, 8 hrs), **1a** and dimethyl acetylenedicarboxylate reacted to give the expected trimethyl 2,2-diphenyl-1,2-dihydropyridine-3,4,6-tricarboxylate in about 50% yield, mp. 214-215° (toluene). This structure was confirmed by spectroscopic (IR, NMR) and microanalysis data.