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Simple Stereoselective Synthesis of (1*E*,3*Z*)-4-(Substituted)amino 1,3-diethoxycarbonyl-1,3-butadienes.

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Abstract: Ethyl propynoate reacted with esters of amino acids in methanolic solutions containing sodium acetate to yield the title compounds **1a-d** in 40-52% yields. Some aromatic amines similarly reacted with ethyl propynoate to yield the dienes **3a-h** in relatively poor yields (17-45%). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: vinylogous 1,3-butadienes, ethyl propynoate , amino acids, aromatic amines

We have previously studied the conjugate addition of β-alanine ester[1] and other amino acid esters[2] to α,β-unsaturated sulphoxides. We sought to synthesise α-amino acid-derived chiral enaminoates by way of conjugate addition of L-α-amino acid esters to propynoates. According to the literature, primary and secondary alkyl amines add readily to alkynoates in diethyl ether or benzene to give mainly the (*Z*)-enamines whereas cyclic secondary amines (and aromatic amines) add to give mainly the (*E*)-isomers.[3,4] In our hands these reactions of amino-acid esters in the given solvents failed to yield any of the expected mono-addition products. In this report we now disclose the formation of the hitherto unknown Michael products by the conjugate addition of α-amino acid esters and aromatic amines to ethyl propynoate.

In a simple one pot reaction between equimolar amounts of an amino acid ester hydrochloride, ethyl propynoate and anhydrous sodium acetate in dry methanol at 65°C , the (1*E*,3*Z*)-1,3-diethoxycarbonyl butadienes **1a-d** were produced as the sole reaction products as shown in Fig. 1.[5] The reactions are reproducible on a multi-gram scale and the dienes **1a-d** are all stable at room temperature. In all the cases **1a-d** the formation of mono-addition product was not detected. However, in the case of proline methyl ester hydrochloride the sole reaction product isolated in almost quantitative yield was the normal mono-addition product (*E*)-**2**. A single crystal X-ray analysis of compound **1a** complemented the deduced structure of the product (Fig. 2).[6] The aromatic amines reacted with ethyl propynoate in ethanol at room temperature (~24h) or at 70°C (overnight) to yield a mixture consisting of the (*E*)-mono-addition product, the (1*E*,3*Z*)-butadienes **3a-h**[5] and one or two other products which could not be identified after isolation by flash chromatography. We are currently investigating the scope and limitations of these electron deficient vinylogous dienes **1a-d** and **3a-h** in cycloaddition reactions.

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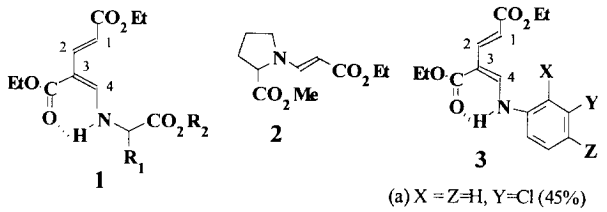
Fig. 1



1

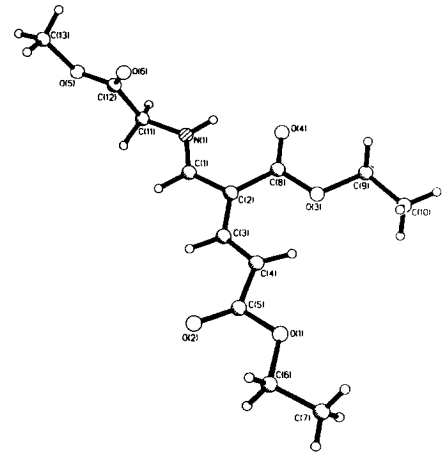
(a) R_1 = H, R_2 = Me (40%)
(b) R_1 = Me, R_2 = Me (49-56%)
(c) R_1 = $CHMe_2$, R_2 = Me (52%)
(d) R_1 = CH_2Ph, R_2 = Me (28%)

2

3

(a) X = Z=H, Y=Cl (45%)
(b) X = Z=H, Y= Br (38%)
(c) X = Z=H, Y = CH_3 (35%)
(d) X = Y=H, Z=F (31%)
(e) X=Y=H, Z=Br (20%)
(f) X=Y=H, Z=CO $_2$Et (17%)
(g) X= *sec*-C_4H_9, Y=Z=H (36%)
(h) X=OMe, Y=Z=H (22%)

Fig. 2 X-ray diagram of **1a**



A typical experimental procedure is illustrated with the synthesis of (1*E*,3*Z*)-4-(methoxycarbonylmethyl) amino-1,3-diethoxycarbonyl-1,3-butadiene **1a:** A mixture of ethyl propynoate (5.0g, 51mmol), glycine methyl ester hydrochloride (6.50g, 51mmol) and anhydrous sodium acetate (4.24g, 51mmol) in dry methyl alcohol (80ml) was heated under stirring at 65°C for 20h. Water (150ml) was added and the mixture was extracted with ethyl acetate (2x 200ml). The organic layer after drying ($MgSO_4$) was filtered and evaporated to yield the crude product as a thick yellowish oil which was purified by flash chromatography [1:1, light petroleum: ethyl acetate] to give the pure product **1a** (5.79g, 40%) as a thick viscous yellowish oil which, on keeping, solidified.

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References and Notes

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5. All of the compounds **1a-d** and **3a-h** have been fully characterised. Selected spectroscopic data **1c:** δ 1.02 (6H, d, J 7.8 Hz, 2 x CH_3), 1.33 (3H, t, J 7.8 Hz, CH_3), 1.43 (3H, t, J 7.8Hz, CH_3), 2.18-2.36 (1H, m, >CH), 3.72-3.82 (1H, m, >NCH), 3.80 (3H, s, OCH_3), 4.22 (2H, q, J 7.8 Hz,OCH_2), 4.30 (2H, q, J 7.8 Hz, OCH_2), 6.12 (1H,d, J 13.8 Hz, 1-H), 7.15 (1H, d, J 11.5 Hz, 4-H),7.38 (1H, d, J 13.8Hz, 2-H), 9.05 (1H, dd, J 11.7,12.3 Hz, NH); Elemental Analysis: Found C, 58.89; H, 7.28; N, 3.95.$C_{16}H_{25}NO_6$ requires C,58.72; H, 7.65; N, 4.28%; HRMS: m/z = 327.1692 (M^+).$C_{16}H_{25}NO_6$ requires 327.1682 (M^+). **3d:** Rf 0.8 (ethyl acetate: light petroleum; 1:4); m.p. 74-78°C; 1.27 (3H, t, J 7.8Hz, CH_3), 1.33 (3H, t, J 7.8 Hz, CH_3), 4.14 (2H, q, J 7.8 Hz, OCH_2), 4.26 (2H, q, J 7.8 Hz, OCH_2), 6.15 (1H, d, J 14.5 Hz, 1-H), 6.9-7.1 (4H, m, Ar), 7.42 (1H, d, J 14.5 Hz, 2-H), 7.63 (1H, d, J 12.2 Hz, 4-H),10.7 (1H, d, J 12.2 Hz, NH); HRMS: m/z = 307.1222 (M^+). $C_{16}H_{18}FNO_4$ requires 361.1219 (M^+).
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