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# AMINO ACIDS AND PEPTIDES—XIV[1]

## A SIMPLE AND CONVENIENT METHOD FOR PREPARATION OF α-SUBSTITUTED α-DIAZO ESTERS[2]

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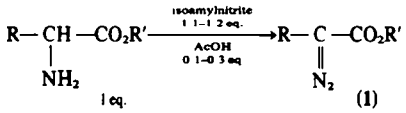
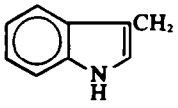
**Abstract**—Treatment of 16 α-amino acid esters with isoamyl nitrite in the presence of a small amount of organic acid in chloroform or benzene, followed by chromatographic purification on alumina was found to afford the corresponding α-substituted-α-diazo esters (1) in fairly good yields.

THE first synthesis of diazo esters by direct diazotization of amino acid esters was reported by Curtius.[3,4] This method, in which amino acid esters are diazotized with $HNO_2$, is well suited for the preparation of diazoacetic ester and convenient laboratory procedures of this method have long been in practice,[5] but it is generally inapplicable to synthesis of α-substituted-α-diazo esters (1) because of low yields and contamination with by-products.[4] Some other indirect routes (decomposition of a nitrosoamide derivative with base,[6] pyrolysis of a nitrosoamide derivative,[7] and acid treatment of a triazene derivative[8]) have also been reported for preparation of 1 from amino acid ester derivatives as starting materials. However, not only are these methods tedious and

Table 1

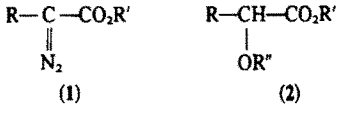



| (1) | R | R' | Solvent | Reflux (min) | Yield (%) |
|---|---|---|---|---|---|
| a | Me | $CH_2C_6H_5$ | $CHCl_3$ | 30 | 61 |
| b | $Me_2CH$ | Et | $CHCl_3$ | 15 | 64 |
| c | $Me_2CHCH_2$ | Et | $CHCl_3$ | 15 | 69 |
| d | $EtO_2CCH_2CH_2$ | Et | $C_6H_6$ | 60 | 59 |
| e | $MeSCH_2CH_2$ | Me | $CHCl_3$ | 60 | 64 |
| f | $PhCH_2OCONH(CH_2)_4$ | Et | $CHCl_3$ | 50 | 77 |
| g | $PhCH_2OCH_2$ | Me | $CHCl_3$ | 60 | 26 |
| h | Ph | Me | $CHCl_3$ | 15 | 31 |
| i | $PhCH_2$ | Me | $CHCl_3$ | 20 | 74 |
| j | $PhCH_2$ | Et | $C_6H_6$ | 60 | 86 |
| k | $PhCH_2$ | $(CH_2)_3Me$ | $CHCl_3$ | 20 | 71 |
| l | $PhCH_2$ | $C_6H_4$-*p*-$NO_2$ | $CHCl_3$ | 25 | 26 |
| m | *p*-$HOC_6H_4CH_2$ | Me | $CHCl_3$ | 45 | 41 |
| n | *p*-$MeOC_6H_4CH_2$ | Et | $CHCl_3$ | 20 | 74 |
| o | *p*-$O_2NC_6H_4CH_2$ | Et | $CHCl_3$ | 30 | 77 |
| p |  | Me | $C_6H_6$ | 50 | 62 |

wasteful, but they have been attempted only for a limited number of amino acid derivatives, such as glycine or alanine ester.

We now wish to report a simpler and more convenient synthesis of **1**. When amino acid esters dissolved in chloroform or benzene are refluxed with isoamyl nitrite in the presence of a small amount of acid, **1** is obtained in fairly good yields as shown in Table 1. Purification of the products is effected by chromatography on alumina which easily removes slight amounts of the by-products, $\alpha$-hydroxy acid derivatives (**2**).

The diazo esters (**1**) obtained after evaporation of the eluent were analytically pure and their structures were

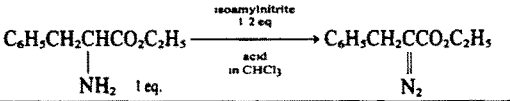


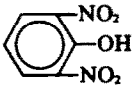
(**1**) (**2**)

confirmed by NMR, IR and UV spectra (Table 5). **1p** was obtained as yellow prisms (mp 64–5°, on recrystallization from benzene-hexane), whereas the others were golden yellow oils at room temperature. Although Chiles and Noyes[9] reported that **1d**, when prepared from diethyl L-glutamate by the Curtius method, showed some optical rotation ($\alpha_D^{20} = +1{\cdot}68$ (1, 1·0, neat)), the compound obtained by the present method was completely optically inactive, as expected from the chemical property of aliphatic diazo compounds. None of **1** obtained by this method had any optical activity. The low yields of **1g** and **1h** might be due to the high reactivity of their diazo groups toward AcOH. In the case of **1g** (IR: 2100, 1705 $cm^{-1}$, UV: 257 m$\mu$) or **1h** (IR: 2100, 1710 $cm^{-1}$, UV: 248 m$\mu$), the spectral data, when compared with those of others (IR; 2075–2085, 1680–1695 $cm^{-1}$ UV: 260–264 m$\mu$) show that the resonance between the diazo group and the ester group of **1g** or **1h** is weakened by the effect of an $\alpha$-substituent and reactivity of the diazo group is consequently enhanced. The poor yield of **1l** is unavoidable, because *p*-nitrophenylester of amino acid is an active ester[10] and affords peptide derivatives as by-products under these reaction conditions. The crude products of **1m** and **1p** were slightly contaminated by by-products, O-nitroso-**1m** and N-nitroso-**1p** respectively.

The present method, as shown in Table 2, requires acid as a catalyst. But the acid also reacts slowly with **1** to afford **2** in chloroform or benzene. Thus, an insufficient amount of the acid discontinues the reaction, while a relatively large amount of the catalyst increases the formation of the by-product **2**. A 0·1–0·3 equivalent

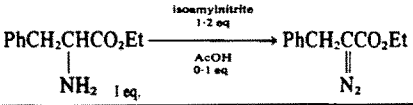
Table 2



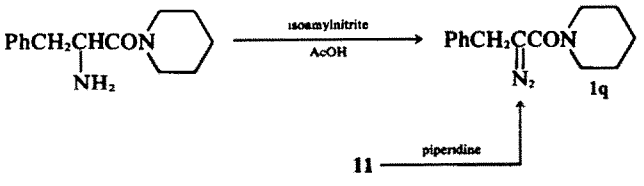

| Acid | Acid (eq) | Condition (min) | Yield (%) |
|---|---|---|---|
| — | — | reflux 120 | 0 |
| AcOH | 0·03 | reflux 45 | 7 |
| AcOH | 0·1 | reflux 45 | 88 |
| AcOH | 0·3 | reflux 15 | 81 |
| AcOH | 0·5 | reflux 15 | 77 |
| $CF_3COOH$ | 0·1 | reflux 45 | 33 |
| $CF_3COOH$ | 0·3 | reflux 45 | 59* |
| PhCOOH | 0·1 | reflux 45 | 85 |
| $Me_3CCOOH$ | 0·1 | reflux 45 | 49 |
|  | 0·1 | reflux 45 | 53† |
| HCl | 1 | room temp 60 | 0 |

*Contaminated by a slight amount of ethyl cinnamate.
†Contaminated by a slight amount of by-product, probably o-nitroso-2,6-dinitrophenol.

Table 3




| Solvent | Condition | Yield |
|---|---|---|
| $CHCl_3$ | reflux 45 min | 88 |
| $C_6H_6$ | reflux 1 h | 86 |
| EtOH | reflux 6 h | < 10 |
| Ether | reflux 24 h | < 10 |
| DMF | 80–90°C 4 h | 0 |



amount of the acid was found to be preferable. Of the several organic acids tested, AcOH or PhCOOH gave the best results. Use of stronger acids such as $CF_3COOH$ or HCl was rather unsatisfactory.

This diazotization reaction proceeded very slowly in ethanol or ether which may scavenge acidic protons in the reaction mixture, and as a result, a considerable amount of unreacted amino acid ester was recovered. DMF, as used for a solvent, also gave a poor result because **1** reacts with this solvent under these conditions. Thus, chloroform or benzene was found to be most suitable as solvent, as shown in Table 3.

An attempted application of the present method for synthesis of the α-diazoamide or diazopeptide derivatives was unsuccessful in most cases, but α-diazo-β-phenyl-propionic acid piperidine amide (**1q**) was obtained in poor yield. Although **1l** easily reacts with peperidine to afford **1q** in good yield, coupling of **1l** and amino acid esters was unsuccessful.

## EXPERIMENTAL

IR spectra were obtained with Hitachi EPI-G2 and Hitachi 215 spectrophotometers. UV spectra were measured on Hitachi 323 and Hitachi EPS-2U spectrophotometers. NMR spectra were recorded at 60 Mc on a Japan Electron Optical Models JNM-60 NMR spectrometer, (Abbreviation; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

*Preparation of α-substituted-α-diazo esters* (**1a-p**)

*General procedure.* A mixture of 10 mmoles of α-amino acid ester, 1–3 mmoles of AcOH (or benzoic acid) and 11–12 mmoles of isoamyl-nitrite in 50 ml chloroform (or benzene) was gently refluxed till the nihydrin positive spot of a starting material on TLC had almost diminished. The yellow soln obtained was cooled and washed successively with cold 1 N $H_2SO_4$, cold water, cold sat. $NaHCO_3$ and water and then dried over $Na_2SO_4$. The dried soln was filtered and chloroform and isoamyl alcohol were completely distilled off *in vacuo* to afford crude **1**. The oil was chromatographed over alumina (100 g, active grade, 2–3. eluent, see Table 4). The fractions required were combined and evaporated to dryness *in vacuo* to give **1** as a golden yellow oil, whose IR, UV and NMR spectral data showed the product to be pure **1** (Table 5). Elemental analysis of **1** was performed without further purification (Table 4).

*α-Diazo-β-phenyl-propionic acid piperidine amide* (**1q**)

(a) *From phenylalanine piperidine amide.* A soln of phenylalanine piperidine amide (2·0 g, 8·62 mmoles) AcOH (0·16 g, 2·60 mmoles) and isoamyl nitrite (1·21 g, 10·34 mmoles) in $CHCl_3$ (50 ml) was refluxed for 15 min. The cooled soln was worked up as described to give a yellow oil (1·56 g), which was purified on column chromatography using alumina (80 g, eluent: hexane 3-benzene 1) to give **1q** as a yellow oil (0·35 g,

Table 4

| (1) | Eluent | Formula | | C | H | N | S |
|---|---|---|---|---|---|---|---|
| **a** | hexane 2: benzene 1 | $C_{10}H_{10}O_2N_2$ | Calcd | 63·15 | 5·30 | 14·73 | |
| | | | Found | 62·91 | 5·30 | 14·78 | |
| **b** | hexane 10: benzene 1 | $C_7H_{12}O_2N_2$ | | volatile | | | |
| **c** | hexane 10: benzene 1 | $C_8H_{14}O_2N_2$ | | volatile | | | |
| **d** | benzene | $C_9H_{14}O_4N_2$ | Calcd | 50·46 | 6·59 | 13·08 | |
| | | | Found | 50·07 | 6·26 | 12·98 | |
| **e** | hexane 1: benzene 1 | $C_6H_{10}O_2N_2S$ | Calcd | 41·36 | 5·78 | 16·08 | 18·41 |
| | | | Found | 41·24 | 5·52 | 15·13 | 18·16 |
| **f** | benzene 1: chloroform 1 | $C_{16}H_{21}O_4N_3$ | Calcd | 60·17 | 6·63 | 13·16 | |
| | | | Found | 60·21 | 6·62 | 12·97 | |
| **g** | hexane 1: benzene 1 | $C_{11}H_{12}O_3N_2$ | Calcd | 59·99 | 5·49 | 12·72 | |
| | | | Found | 60·14 | 5·50 | 11·90 | |
| **h** | hexane 10: benzene 1 | $C_9H_8O_2N_2$ | Calcd | 61·36 | 4·58 | 15·90 | |
| | | | Found | 61·46 | 4·58 | 15·81 | |
| **i** | hexane 5: benzene 1 | $C_{10}H_{10}O_2N_2$ | Calcd | 63·15 | 5·30 | 14·73 | |
| | | | Found | 63·47 | 5·25 | 14·54 | |
| **j** | hexane 10: benzene 1 | $C_{11}H_{12}O_2N_2$ | Calcd | 64·69 | 5·92 | 13·72 | |
| | | | Found | 65·28 | 5·89 | 13·13 | |
| **k** | hexane 5: benzene 1 | $C_{13}H_{16}O_2N_2$ | Calcd | 67·22 | 6·94 | 12·06 | |
| | | | Found | 66·94 | 6·87 | 11·83 | |
| **l** | benzene | $C_{15}H_{11}O_4N_3$ | Calcd | 60·60 | 3·73 | 14·14 | |
| | | | Found | 60·83 | 3·80 | 13·51 | |
| **m** | chloroform | $C_{10}H_{10}O_3N_2$ | Calcd | 58·25 | 4·89 | 13·58 | |
| | | | Found | 57·45 | 4·72 | 13·58 | |
| **n** | hexane 3: benzene 1 | $C_{12}H_{14}O_3N_2$ | Calcd | 61·52 | 6·02 | 11·96 | |
| | | | Found | 62·18 | 6·00 | 11·96 | |
| **o** | hexane 3: benzene 2 | $C_{11}H_{11}O_4N_3$ | Calcd | 53·01 | 4·45 | 16·86 | |
| | | | Found | 53·36 | 4·48 | 16·31 | |
| **p** | hexane 1: benzene 3 | $C_{12}H_{11}O_2N_3$ | Calcd | 62·87 | 4·84 | 18·33 | |
| | | | Found | 62·70 | 4·87 | 18·46 | |

Table 5.

| (1) | IR(liq)cm$^{-1}$ | UV(EtOH)m$\mu$ | NMR($CDCl_3$)$\tau$ |
|---|---|---|---|
| a | 2075, 1695 | 262, 406 | 8·08(3H, s), 4·83(2H, s), 2·70(5H, s) |
| b | 2075, 1695 | 263, 415 | 8·85(8H, d, 7Hz), 8·73(3H, t, 7Hz)<br>7·21(1H, m), 5·73(2H, q, 7 Hz) |
| c | 2075, 1690 | 262, 406 | 9·04(6H, d, 6Hz), 8·74(3H, t, 7Hz)<br>7·50~8·50(3H, m), 5·76(2H, q, 7Hz) |
| d | 2080, 1735, 1690 | 262, 404 | 8·75(6H, t, 7Hz), 7·43(4H, s)<br>5·83(2H, q, 7Hz), 5·77(2H, q, 7Hz) |
| e | 2075, 1690 | 262, 410 | 7·85(3H, s), 7·25 ~ 7·40(4H, m)<br>6·22(3H, s)' |
| f | 2080, 1725(sh), 1695 | 264, 412 | 8·74(3H, t, 7Hz), 8·10 ~ 8·66(4H, m)<br>7·40 ~ 8·00(2H, m), 6·50 ~ 7·00(2H, m)<br>5·75(2H, q, 7Hz), 4·90(1H, broad s)<br>4·85(2H, s), 2·58(5H, s) |
| g | 2100, 1705 | 257, 388 | 6·22(3H, s), 5·57(2H, s), 5·44(2H, s)<br>2·60(5H, s) |
| h | 2100, 1710 | 248, 278, 440 | 6·10(3H, s), 2·20 ~ 3·00(5H, m) |
| i | 2075, 1690 | 261, 408 | 6·43(2H, s), 6·28(3H, s), 2·78(5H, s) |
| j | 2085, 1690 | 263, 410 | 8·75(3H, t, 7Hz), 6·39(2H, s)<br>5·77(2H, q, 7Hz), 2·71(5H, s) |
| k | 2075, 1695 | 261, 409 | 8·00 ~ 9·30(7H, m), 6·41(2H, s)<br>5·84(2H, t, 6Hz), 2·78(5H, s) |
| l | 2085, 1715 | 273 | 6·31(2H, s), 2·75(2H, d, 9Hz)<br>2·73(5H, s), 1·82(2H, d, 9Hz) |
| m | 2080, 1690(sh), 1660 | 263, 360(sh) | 6·44(2H, s), 6·22(3H, s)<br>4·15(1H, broad s), 3·23(2H, d, 9Hz)<br>2·91(2H, d, 9Hz) |
| n | 2075, 1685 | 260, 410 | 8·78(3H, t, 7Hz), 6·52(2H, s)<br>6·32(3H, s), 5·86(2H, q, 7Hz)<br>3·30(2H, d, 9Hz), 2·96(2H, d, 9Hz) |
| o | 2075, 1685 | 260 | 8·76(3H, t, 7Hz), 6·35(2H, s)<br>5·85(2H, q, 7Hz), 2·75(2H, d, 9Hz)<br>1·96(2H, d, 9Hz) |
| p | 2080, 1680* | 220, 262, 278(sh)<br>283(sh), 291,<br>410(sh) | 6·21(5H, s), 1·60 ~ 3·10(6H, m) |

*IR (nujol)cm$^{-1}$: 2075, 1665

17%). Found: C, 68·56; H, 7·14; N, 17·02. Calcd. for $C_{14}H_{17}ON_3$: C, 69·11; H, 7·04; N, 17·27. IR $\nu_{max}^{liq}$ cm$^{-1}$ 2055, 1620; NMR (in $CDCl_3$) $\tau$: 8·10–8·80 (6H, m), 6·40–6·90 (4H, m), 6·36 (2H, s), 2·77 (5H, s).

(b) *From α-diazo-β-phenyl-propionic acid p-nitrophenylester* (1l). A soln of 1l (0·5 g) and piperidine (0·5 ml) in $CH_2Cl_2$ (5 ml) was kept standing for 24 h at room temp. The mixture was diluted with $CH_2Cl_2$ (50 ml), washed with cold 1 N $H_2SO_4$, $H_2O$ sat $NaHCO_3$ and $H_2O$, and then dried over $Na_2SO_4$. Filtration and evaporation gave a yellow oil (0·38 g, 93%). IR and NMR spectra of this oil were identical with those of authentic 1q.

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