Monatshefte für Chemie 136, 1757–1761 (2005)
DOI 10.1007/s00706-005-0367-y

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Regioselective Reaction of N^1-Benzyl-N^2-(4-nitrophenyl)ethanediamide and Acetylenic Esters

Issa Yavari*, **Loghman Moradi, Farough Nasiri,** and **Hoorieh Djahaniani**

Department of Chemistry, Tarbiat Modarres University, P.O. Box 14115-175, Tehran, Iran

Received January 25, 2005; accepted March 15, 2005
Published online September 26, 2005

Summary. The regioselective reaction of N^1-benzyl-N^2-(4-nitrophenyl)ethanediamide with dialkyl acetylenedicarboxylates or alkyl propiolates in the presence of triphenylphosphine leads to dialkyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates or alkyl 4-benzylamino-1-(4-nitrophenyl)-2-oxo-5-pyrrolidinecarboxylates in good yields.

Keywords. Intramolecular *Wittig* reaction; Acetylenic esters; Triphenylphosphine; 2-Oxo-5-pyrrolidines; 5-Oxo-2,5-dihydro-1*H*-pyrroles.

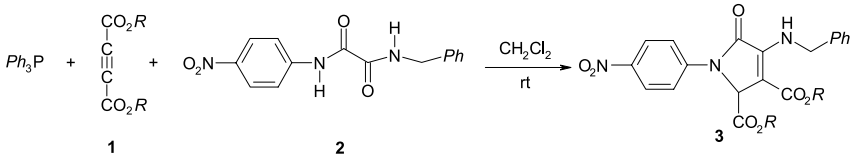
Introduction

Five-membered ring lactams have successfully been used in routes to various alkaloids [1, 2] and are suitable precursors for unusual γ-amino acids such as statine and its analogues [3, 4]. There are also many examples of pyrroline-containing natural products with pharmacological activities. Typical examples are the antitumor alkaloide Jatropham [5] and the platelet aggregation inhibitor PI-091 [6]. As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems [7], we report a simple, one-pot, and regioselective synthesis of highly functionalized 5-oxo-2,5-dihydro-1*H*-pyrroles **3**.

Results and Discussion

The reaction of acetylenic esters **1** with N^1-benzyl-N^2-(4-nitrophenyl)ethanediamide (**2**) in the presence of triphenylphosphine at ambient temperature in CH_2Cl_2 leads to dialkyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **3** in good yields (Scheme 1). The structures of compounds

* Corresponding author. E-mail: yavarisa@modares.ac.ir

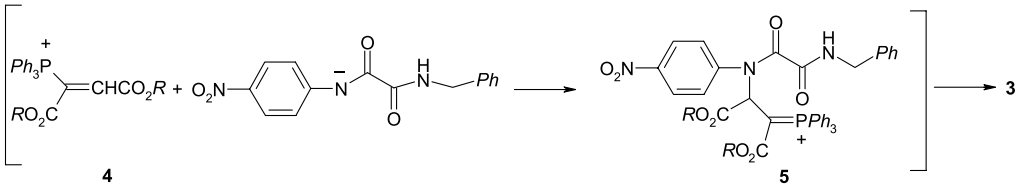


1,3	R	Yield of 3 (%)
a	*Me*	80
b	*Et*	78
c	*iPr*	79
d	*t*Bu	82

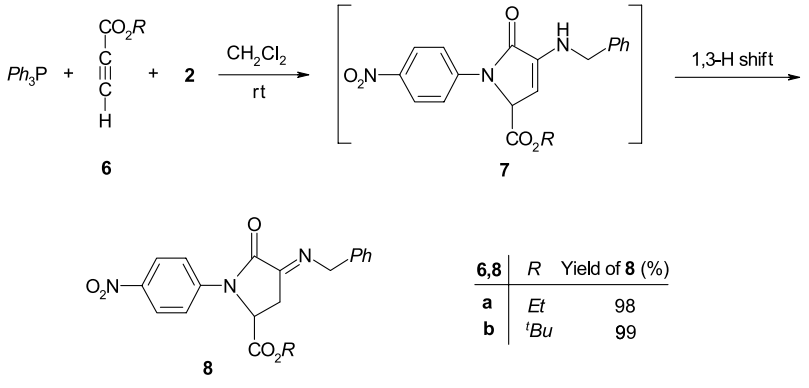
Scheme 1

3a–**3d** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. For example, the ^{1}H NMR spectrum of **3a** exhibited four singlets identified as methoxy ($\delta = 3.66$ and 3.73 ppm), methine ($\delta = 4.70$ ppm), and NH ($\delta = 8.59$ ppm) protons along with multiplets ($\delta = 7.26$–8.21 ppm) for the aromatic protons. The methylene protons of the benzyl group in **3a** are diastereotopic and exhibit an AX system ($^2J_{AX} = 15$ Hz, $\delta_A = 4.23$ ppm, and $\delta_X = 4.99$ ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed seventeen distinct resonances in agreement with the proposed structure.

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [8, 9] it is reasonable to assume that **4** results from an initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the more acidic arylamino NH group (Scheme 2). Then, the positively charged ion might be attacked by the conjugate base of the NH-acid



Scheme 2



6,8	R	Yield of 8 (%)
a	*Et*	98
b	*t*Bu	99

Scheme 3

to produce the ylide **5**, which undergoes intramolecular *Wittig* reaction [10] to produce **3**.

The reaction of ethyl or *tert*-butyl propiolate with **2** in the presence of triphenylphosphine afforded alkyl 4-benzylamino-1-(4-nitrophenyl)-2-oxo-5-pyrrolidinecarboxylates **8** in high yields (Scheme 3). The structures of **8a** and **8b** were deduced from their ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of these compounds show characteristic ABX spin systems for the CH_2–CH moieties. Partial assignment of the NMR spectral data is given in the experimental section.

In conclusion, the presented reactions provide a simple one-pot entry into the regioselective synthesis of polyfunctionalized 2-oxopyrrolidines and 5-oxo-2,5-dihydro-1*H*-pyrroles of potential interest.

Experimental

Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses (C, H, N) were performed using a Heraeus CHN–O-Rapid analyzer. Their results agreed favorably with the calculated values. IR spectra were measured with a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz. Mass spectra were recorded with a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. 4-Nitroaniline, benzylamine, ethyl oxalyl chloride, and acetylenic esters were obtained from Fluka and used without further purification.

N^1-Benzyl-N^2-(4-nitrophenyl)ethanediamide (**2**, $C_{15}H_{13}N_3O_4$)
To a stirred solution of ethyl 2-(4-nitroanilino)-2-oxoacetate [11] (2.38 g, 10 mmol) in 20 cm^3 CH_2Cl_2 were added 1.07 g of benzylamine (10 mmol). The reaction mixture was stirred for 4 h. The product precipitates as a white powder, which was filtered off and washed with Et_2O. Product **2** was obtained as white powder, yield 2.93 g (98%), mp 169–170°C.

*General Procedure for Preparation of **3** and **8** (exemplified by **3a**)*
To a stirred solution of 0.57 g of triphenylphosphine (2.2 mmol) and 0.58 g of N^1-benzyl-N^2-(4-nitrophenyl)ethanediamide (2 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise a mixture of 0.31 g of dimethyl acetylenedicarboxylate (2.2 mmol) in 4 cm^3 CH_2Cl_2 at 0°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane-*Et*O*Ac* as eluent.

Dimethyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate
(**3a**, $C_{21}H_{19}N_3O_7$)
White powder, yield 0.68 g (80%), mp 134–138°C; IR (KBr): $\bar{\nu} = 3295$ (NH), 1735 and 1699 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.66$ (s, OMe), 3.73 (s, OMe), 4.23 (d, $^2J_{HH} = 15$ Hz, CH), 4.70 (s, CH), 4.99 (d, $^2J_{HH} = 15$ Hz, CH), 7.28–7.36 (m, 5CH of C_6H_5 and 2CH of C_6H_4), 8.20 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.59 (br s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 46.0$ (NCH_2), 51.9 (OMe), 53.0 (OMe), 60.3 (CH), 109.6 (N–C=*C*), 121.5 (2CH), 124.5 (2CH), 128.3 (CH), 128.7 (2CH), 128.9 (2CH), 135.2, 143.9, and 144.1 (3C), 144.6 (N–*C*=C), 163.8 and 164.6 (2C=O, ester), 167.8 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 425 (M^+, 20), 366 (90), 334 (30), 91 (100).

Diethyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate
(**3b**, $C_{23}H_{23}N_3O_7$)
White powder, yield 0.71 g (78%), mp 116–118°C; IR (KBr): $\bar{\nu} = 3290$ (NH), 1730 and 1689 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.20$ (t, $^3J_{HH} = 7$ Hz, CH_3), 1.26 (t, $^3J_{HH} = 7$ Hz,

CH_3), 4.10–4.22 (m, $2CH_2$), 4.25 (d, $^2J_{HH} = 15$ Hz, CH), 4.61 (s, CH), 5.02 (d, $^2J_{HH} = 15$ Hz, CH), 7.25–7.36 (m, 5CH of C_6H_5 and 2CH of C_6H_4), 8.17 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.64 (br s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 14.3 (CH_3), 45.9 (NCH_2), 60.5 (OCH_2), 60.9 (CH), 62.2 (OCH_2), 108.6 (N–C=*C*), 121.2 (2CH), 124.5 (2CH), 128.2 (CH), 128.6 (2CH), 128.0 (2CH), 135.3, 143.2, and 143.5 (3C), 144.2 (N–*C*=C), 163.7 and 164.4 (2C=O, ester), 167.7 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 453 (M^+, 5), 408 (100), 346 (65), 91 (85).

Diisopropyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**3c**, $C_{25}H_{27}N_3O_7$)
White powder, yield 0.79 g (82%), mp 175–177°C; IR (KBr): $\bar{\nu} = 3415$ (NH), 1724 and 1685 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.28$ (d, $^3J_{HH} = 6$ Hz, CH_3), 1.30 (d, $^3J_{HH} = 6$ Hz, CH_3), 1.31 (d, $^3J_{HH} = 6$ Hz, CH_3), 1.33 (d, $^3J_{HH} = 6$ Hz, CH_3), 4.12 (d, $^2J_{HH} = 15$ Hz, CH), 4.59 (s, CH), 5.01 (septet, $^3J_{HH} = 6$ Hz, CH), 5.08 (d, $^2J_{HH} = 15$ Hz, CH), 5.11 (septet, $^3J_{HH} = 6$ Hz, CH), 7.31–7.39 (m, 5CH of C_6H_5 and 2CH of C_6H_4), 8.22 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.87 (br s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 21.7$ and 21.7 ($4CH_3$), 45.8 (NCH_2), 60.9 (CH), 69.2 and 70.5 (2OCH), 109.8 (N–C=*C*), 121.5 and 125.0 (4CH), 128.7 (CH), 129.1 and 129.4 (4CH), 136.0, 143.8, and 143.8 (3C), 144.9 (N–*C*=C), 164.1 and 165.1 (2C=O, ester), 167.9 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 481 (M^+, 5), 422 (60), 391 (20), 91 (100).

Di-tert-butyl 4-benzylamino-1-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**3d**, $C_{27}H_{31}N_3O_7$)
White powder, yield 0.80 g (79%), mp 138–140°C; IR (KBr): $\bar{\nu} = 3305$ (NH), 1717 and 1686 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.51$ (s, CMe_3), 1.52 (s, CMe_3), 4.05 (d, $^2J_{HH} = 15$ Hz, CH), 4.48 (s, CH), 5.16 (d, $^2J_{HH} = 15$ Hz, CH), 7.31–7.38 (m, 5CH of C_6H_5 and 2CH of C_6H_4), 8.22 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.83 (br s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 27.8$ (C*Me*$_3$), 28.1 (C*Me*$_3$), 43.9 (NCH_2), 54.0 (CH), 81.4 (O*C*Me$_3$), 82.3 (O*C*Me$_3$), 108.6 (N–C=*C*), 121.2 (2CH), 124.8 (2CH), 128.2 (CH), 128.6 (2CH), 128.8 (2CH), 135.4, 143.2, and 143.6 (3C), 144.4 (N–*C*=C), 164.2 and 165.1 (2C=O, ester), 167.8 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 509 (M^+, 3), 436 (70), 418 (40), 91 (100).

Ethyl 4-benzylimino-1-(4-nitrophenyl)-5-oxo-2-pyrrolidinecarboxylate (**8a**, $C_{20}H_{19}N_3O_5$)
White powder, yield 0.75 g (98%), mp 151–154°C; IR (KBr): $\bar{\nu} = 1737$ and 1669 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.25$ (t, $^3J_{HH} = 7$ Hz, CH_3), 4.08 (q, $^3J_{HH} = 7$ Hz, OCH_2), 4.13 (m, CH_2), 4.24 (d, $^2J_{HH} = 15$ Hz, NCH_2), 4.36 (dd, $^2J_{HH} = 10$ Hz, $J_{AX} = 2$ Hz, CH), 5.23 (d, $^2J_{HH} = 15$ Hz, NCH_2), 7.24–7.28 (m, 5CH of C_6H_5), 7.46 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.14 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 49.9 and 50.3 (CH_2 and NCH_2), 55.7 (NCH), 62.9 (OCH_2), 124.6 (2CH), 124.7 (CH), 124.7 (CH), 128.4 (CH), 128.8 (2CH), 129.0 (2CH), 134.7, 145.6, and 145.7 (3C), 155.8 (N=C), 157.0 (C=O, ester), 168.6 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 381 (M^+, 6), 380 (50), 334 (20), 91 (100).

tert-Butyl 4-benzylimino-1-(4-nitrophenyl)-5-oxo-2-pyrrolidinecarboxylate (**8b**, $C_{22}H_{23}N_3O_5$)
White powder, yield 0.81 g (99%), mp 183–185°C; IR (KBr): $\bar{\nu} = 1720$ and 1685 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.31$ (s, CMe_3), 4.04 (m, OCH_2), 4.34 (d, $^2J_{HH} = 15$ Hz, NCH_2), 4.37 (dd, $^2J_{HH} = 9$ Hz, $J_{AX} = 3$ Hz, CH), 5.15 (d, $J_{AB} = 15$ Hz, NCH_2), 7.24–7.35 (m, 5CH of C_6H_5), 7.50 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4), 8.19 (d, $^3J_{HH} = 9$ Hz, 2CH of C_6H_4) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 27.7$ (C*Me*$_3$), 50.3 and 50.5 (CH_2 and NCH_2), 56.5 (NCH), 84.6 (*C*Me$_3$), 124.5 (2CH), 124.6 (2CH), 128.5 (CH), 129.0 (2CH), 129.1 (2CH), 134.7, 145.6, and 145.8 (3C), 156.0 (N=C), 157.2 (C=O, ester), 168.2 (C=O, lactam) ppm; MS (EI, 70 eV): m/z (%) = 409 (M^+, 4), 336 (20), 318 (50), 91 (100).

References

[1] Casiraghi G, Spanu P, Rassu G, Pinna L, Ulgheri F (1994) J Org Chem **59**: 2906
[2] Griffart BD, Langois N (1994) Tetrahedron Lett **35**: 119
[3] Jouin P, Castro B (1987) J Chem Soc Perkin Trans 1, 1177
[4] Ma D, Ma J, Ding W, Dal L (1996) Tetrahedron Asymm **7**: 2365
[5] Dittami JP, Xu F, Qi H, Martin MW (1995) Tetrahedron Lett **36**: 4210
[6] Iwasawa N, Maeyama K (1997) J Org Chem **62**: 1918
[7] Yavari I, Alizadeh A (2004) Synthesis 237; Mosslemin MH, Yavari I, Anari-Abbasinejad M, Nateghi MR (2004) Synthesis 1029; Yavari I, Anari-Abbasinejad M, Hossaini Z (2003) Org Biomol Chem **1**: 560; Yavari I, Bayat M (2003) Monatsh Chem **134**: 1221; Yavari I, Adib M, Abdolmohammadi Sh, Aghazadeh M (2003) Monatsh Chem **134**: 1093; Yavari I, Adib M, Sayahi MH (2002) Tetrahedron Lett **43**: 2927; Yavari I, Adib M, Jahani-Moghaddam F (2002) Monatsh Chem **133**: 1431; Yavari I, Adib M, Sayahi MH (2002) J Chem Soc Perkin Trans 1, l517; Yavari I, Adib M, Hojabri L (2001) Tetrahedron **57**: 7537; Yavari I, Adib M (2001) Tetrahedron **57**: 5873; Yavari I, Nourmohammadian F (2000) Tetrahedron **56**: 5221; Yavari I, Asghari S (1999) Tetrahedron **55**: 11853; Yavari I, Samzadeh-Kermani AR (1998) Tetrahedron Lett **39**: 6343
[8] Kolodiazhnyi OI (1996) Tetrahedron **52**: 1855
[9] Johnson AW (1993) Ylides and Imines of Phosphorus. Wiley, New York
[10] Zbiral E (1974) Synthesis 775; Becker KB (1987) Tetrahedron **36**: 1717; Heron M (1995) Heterocycles **41**: 2357
[11] Yavari I, Aghazadeh M, Tafazzoli M (2002) Phosph Sulf Silic **177**: 1101