

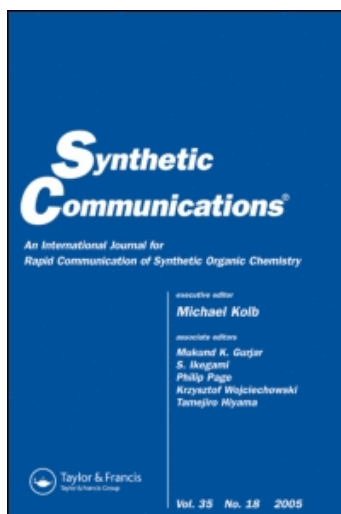
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Online publication date: 17 June 2010

To cite this Article Asghari, Sakineh and Qandalee, Mohammad(2010) 'Three-Component, One-Pot Synthesis of New Functionalized Pyrrolines', Synthetic Communications, 40: 14, 2172 – 2177

To link to this Article: DOI: 10.1080/00397910903219583

URL: <http://dx.doi.org/10.1080/00397910903219583>

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THREE-COMPONENT, ONE-POT SYNTHESIS OF NEW FUNCTIONALIZED PYRROLINES

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The addition of acetylenic esters to diethyl acetamidomalonate in the presence of tert-butyl isocyanide leads to highly functionalized 1-pyrrolines and 2-pyrroline.

Keywords: Acetylenic esters; diethyl acetamidomalonate; 1-pyrroline; 2-pyrroline *tert*-butyl isocyanide

INTRODUCTION

Three isomers are possible for pyrrolines: 1-pyrrolines, 2-pyrrolines, and 3-pyrrolines. These kinds of nitrogen (N)-containing rings are common structural scaffolds in natural products and pharmaceutical agents.^[1,2] Examples of medically important pyrroline-based compounds are protein kinase inhibitor staurosporine^[3] and geranylgeranyltransferase inhibitor.^[4] However, among these three groups of heterocycles, the 1-pyrrolines are the most interesting; they are present in biologically active compounds such as hemes,^[5] chlorophylls,^[5] and alkaloids.^[6] Furthermore, 1-pyrrolines have been used as templates in the structures of new drugs.^[7]

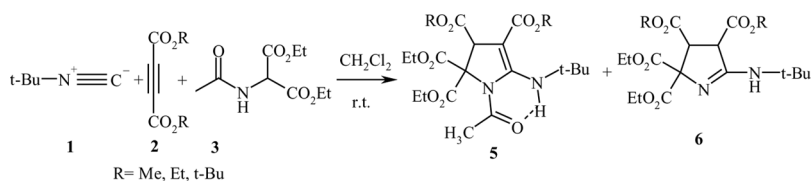
Several methods have been reported for synthesis of pyrrolines from acyclic, alicyclic, and heterocyclic compounds.^[8] As part of an effort aimed at developing multicomponent reactions leading to useful medicinal scaffolds,^[9] we carried out the reaction of *tert*-butyl isocyanide **1** and acetylenic esters **2** in the presence of diethyl acetamidomalonate **3**, which leads to highly functionalized 1-pyrrolines **6** and 2-pyrroline **5** (Scheme 1, Table 1).

RESULTS AND DISCUSSION

On the basis of the well-established chemistry of isocyanides,^[10–13] it is reasonable to assume that pyrrolines **5** and **6a–c** are the result of the nucleophilic addition of *tert*-butyl isocyanide to dialkyl acetylenedicarboxylate, subsequent protonation of the reactive 1:1 adduct by diethyl acetamidomalonate, and attack of the conjugated base of the CH-acid to generate intermediate **4**. This intermediate undergoes an

Received May 24, 2009.

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Scheme 1. Synthesis of pyrrolines through three-component reaction.

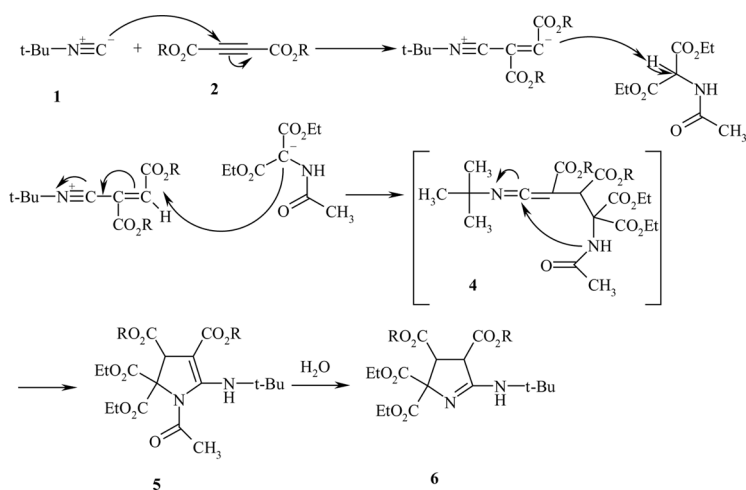
intramolecular reaction to form 2-pyrroline **5**, which gives 1-pyrrolines **6** by losing an acetyl group in the presence of water (Scheme 2).

The structures of **5** and **6a–c** were deduced from their ^1H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values and other fragmentations involved with the loss of the ester moieties. The infrared (IR) spectrum and elemental analysis support the proposed structures. Unambiguous evidence for the structure of **6a** was obtained from single-crystal X-ray analysis (Fig. 1).

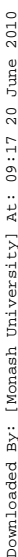
The ^1H and ^{13}C NMR spectra of **5** exhibited three sharp singlets for *tert*-butyl groups at 1.35, 1.43, and 1.45 ppm and three singlets for CH_3CO , CH , and NH groups at 2.19, 5.06, and 5.83 ppm, respectively. The proton-decoupled ^{13}C NMR spectrum of **5** showed 20 distinct resonances in agreement with the proposed structure.

Table 1. Synthesis of pyrrolines through three-component reaction

Compound	R	Yield (%)
5	t-Bu	35
6a	Me	88
6b	Et	90
6c	t-Bu	55



Scheme 2. Mechanism of the three-component reaction.



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commercial suppliers. All of the coupling constants are given in hertz. X-ray crystal data was carried out by Bruker, programs APEX II, SAINT, version 7.23A.

General Procedure

A mixture of dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in dichloromethane (3 ml) was added to a magnetically stirred solution of diethyl acetamidomalonate (0.43 g, 2 mmol) and *tert*-butyl isocyanide (0.22 ml, 2 mmol) in dichloromethane (20 ml) at -5°C for 10 min. Then, the reaction mixture was allowed to warm up to room temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/ethyl acetate (80:20) as eluent.

Analytical and Spectroscopic Data of Products

3,4-Di(*tert*-butyl)-2,2-diethyl-1-acetyl-5-(*tert*-butylamino)-1,3-dihydro-2H-pyrrole-2,2,3,4-tetracarboxylate (5). White powder, mp $80\text{--}82^{\circ}\text{C}$, 0.36 g, yield 35%; IR (KBr) ν : NH 3393, C=O 1750, 1729, 1714, 1690, C=N 1633 cm^{-1} . ^1H NMR (500.1 MHz, CDCl_3): δ 1.25 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.29 (t, CH_3 , $^3J_{\text{HH}}$ 7 Hz), 1.35 (s, 9H, CMe_3), 1.43 (s, 9H, CMe_3), 1.45 (s, 9H, CMe_3), 2.19 (s, 3H, CH_3CO), 4.18–4.28 (m, 4H, 2OCH_2), 5.06 (s, 1H, CH), 5.83 (s, 1H, NH); ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.9, 14.0 (2CH_3), 21.6 (CH_3CO), 27.8, 28.2 and 30.0 (3CMe_3), 55.6 (NCMe_3), 62.3 and 62.5 (2OCH_2), 67.9 (CH), 78.3 [$\text{C}(\text{CO}_2\text{Et})_2$], 80.4 and 81.6 (2OCMe_3), 98.3 (N-C=C), 148.8 (N-C=C), 163.2 (CO amide), 165.0, 165.7, 168.9 and 169.1 (4C=O ester); MS, m/z (%): 526 (M^+ , 10), 425 ($\text{M}^+ - \text{CO}_2\text{ t-Bu}$, 73), 369 [$\text{M}^+ - (\text{CO}_2\text{ t-Bu} + (\text{CH}_3)_2\text{C=CH}_2)$, 25], 313 [$\text{M}^+ - (\text{CO}_2\text{ t-Bu} + 2(\text{CH}_3)_2\text{C=CH}_2)$, 61], 271 [$\text{M}^+ - (\text{CO}_2 + 3(\text{CH}_3)_2\text{C=CH}_2 + \text{CH}_3\text{CO})$, 100], 57 (C_4H_9^+ , 75). Anal. calcd. for $\text{C}_{26}\text{H}_{42}\text{N}_2\text{O}_9$: C, 59.30; H, 8.03; N, 5.31. Found: C, 59.26; H, 8.08; N, 5.36.

2,2-Diethyl-3,4-dimethyl-5-(*tert*-butylamino)-3,4-dihydro-2H-pyrrole-2,2,3,4-tetracarboxylate (6a)

Yellow powder, mp $85\text{--}87^{\circ}\text{C}$, 0.70 g, yield 88%; IR (KBr) ν NH 3488, C=O 1740, 1734, 1710, C=N 1628 cm^{-1} . ^1H NMR (500.1 MHz, CDCl_3): δ 1.18 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.26 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.33 (s, 9H, CMe_3), 3.67 and 3.73 (2s, 6H, 2OCH_3), 4.17 (d, CH, $^3J_{\text{HH}}$ 10.3 Hz), 4.19 (d, CH, $^3J_{\text{HH}}$ 10.3 Hz), 4.05–4.21 (m, 2H, OCH_2), 4.25–4.41 (m, 2H, OCH_2), 5.31 (br s, 1H, NH); ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.9, 14.0 (2CH_3), 28.4 (CMe_3), 50.7 (OMe), 52.0 (NHCMe_3), 52.4 (CH), 52.9 (CH), 54.0 (OMe), 61.7, 61.9 (OCH_2), 82.9 [$\text{C}(\text{CO}_2\text{Et})_2$], 159.3 (C=N), 169.0, 169.3, 169.7 and 170.8 (4CO); MS, m/z (%): 400 (M^+ , 13), 385 ($\text{M}^+ - \text{Me}$, 2.3), 355 ($\text{M}^+ - \text{OEt}$, 27), 341 ($\text{M}^+ - \text{CO}_2\text{Me}$, 76), 239 [$\text{M}^+ - (2\text{CO}_2\text{Et} + \text{CH}_3)$, 100], 211 [$\text{M}^+ - \text{CO}_2\text{Et} + \text{N}(\text{CMe}_3)_3 + \text{OEt}$, 65], 57 [$\text{C}(\text{Me}_3)_2$, 20]. Anal. calcd. for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_8$: C, 54.24; H, 7.04; N, 6.99. Found: C, 54.10; H, 7.06; N, 6.92.

X-Ray Crystal Data and Structure Refinement for 6a

The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 764099.

Empirical formula, $C_{18}H_{28}N_2O_8$; formula weight, 400.42; temperature, 100(2) K; wavelength, 0.71073 Å; crystal system, monoclinic; space group, P 21/c; unit cell dimensions, $a = 12.9033(19)$ Å, $\alpha = 90^\circ$; $b = 19.797(3)$ Å, $\beta = 91.134(3)^\circ$; $c = 8.2131(12)$ Å, $\gamma = 90^\circ$; volume, $2097.6(5)$ Å³; $Z = 4$, density (calculated), 1.268 mg/m³; absorption coefficient, 0.100 mm^{-1} ; $F(000)$, 856; crystal size, $0.55 \times 0.16 \times 0.11 \text{ mm}^3$; theta range for data collection, 1.88 to 28.00° ; index ranges, $-16 \leq h \leq 17$, $-26 \leq k \leq 26$, $-10 \leq l \leq 10$; reflections collected, 15206; independent reflections, 4992 [$R(\text{int}) = 0.0346$]; observed reflections [$I > 2 \sigma(I)$], 4036; completeness to $\theta = 28.00^\circ$, 98.7%; absorption correction, semi-empirical from equivalents; max. and min. transmission, 0.989 and 0.947; refinement method, full-matrix least-squares on F^2 , data/restraints/parameters 4992/0/260, goodness-of-fit on F^2 , 0.998, final R indices [$I > 2 \sigma(I)$], $R1 = 0.0626$, $wR2 = 0.1526$, R indices (all data), $R1 = 0.0757$, $wR2 = 0.1598$; largest diff. peak and hole, 0.584 and $-0.285 \text{ e. \AA}^{-3}$.

Tetraethyl-5-(*tert*-butylamino)-3,4-dihydro-2*H*-pyrrole-2,2,3,4-tetracarboxylate (6b)

Viscous oil, 0.77 g, yield 90%; IR (KBr) ν ; NH 3438, C=O 1740, 1730, 1715, C=N 1630 cm^{-1} . ^1H NMR (500.1 MHz, CDCl_3): δ 1.08 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.10 (t, CH_3 , $^3J_{\text{HH}}$ 7.2 Hz), 1.14 (t, CH_3 , $^3J_{\text{HH}}$ 7.2 Hz), 1.15 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.23 (s, 9H, CMe_3), 3.96–4.00 (m, 2OCH_2), 4.01 (d, $^3J_{\text{HH}}$ 10.7 Hz, CH), 4.02 (d, $^3J_{\text{HH}}$ 10.7 Hz, CH), 4.13–4.18 (m, 4H, 2OCH_2), 5.20 (bs, 1H, NH); ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.8, 13.90, 13.92 and 13.93 (4CH_3), 28.2 (CMe_3), 50.7 (NCMe_3), 51.8 and 54.2 (CHCO_2Et), 61.0, 61.5, 61.6 and 61.8 (4OCH_2), 82.6 [$\text{C}(\text{CO}_2\text{Et})_2$], 159.4 (C=N), 168.6, 168.9, 169.6 and 170.2 ($4\text{C}=\text{O}$); MS, m/z (%): 429 ($\text{M}^+ + 1$, 45), 428 (M^+ , 23), 355 ($\text{M}^+ - \text{CO}_2\text{Et}$, 100), 309 [$\text{M}^+ - (\text{CO}_2\text{Et} + \text{EtOH})$, 40], 299 [$\text{M}^+ - (\text{CO}_2\text{Et} + (\text{CH}_3)_2\text{C}=\text{CH}_2)$, 27], 253 [$\text{M}^+ - (2\text{CO}_2\text{Et} + \text{Et})$, 89], 225 [$\text{M}^+ - (2\text{CO}_2\text{Et} + \text{C}_4\text{H}_9^+)$, 50], 57 (C_4H_9^+ , 17). Anal. calcd. for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_8$: C, 56.04; H, 7.52; N, 6.50. Found: C, 56.10; H, 7.55; N, 6.46.

3,4-Di(*tert*-butyl)-2,2-diethyl-5-(*tert*-butylamino)-3,4-dihydro-2*H*-pyrrole-2,2,3,4-tetracarboxylate (6c)

Viscous oil, 0.53 g, yield 55%; IR (KBr) ν ; NH 3433, C=O 1739, 1719, 1710, C=N 1622 cm^{-1} . ^1H NMR (500.1 MHz, CDCl_3): δ 1.18 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.26 (t, CH_3 , $^3J_{\text{HH}}$ 7.1 Hz), 1.33 (s, 9H, CMe_3), 1.38 (s, 9H, CMe_3), 1.42 (s, 9H, CMe_3), 3.96 (d, CH, $^3J_{\text{HH}}$ 10.2 Hz), 4.01 (d, CH, $^3J_{\text{HH}}$ 10.2 Hz), 4.08–4.10 (m, 2H, OCH_2), 4.22–4.28 (m, 2H, OCH_2), 5.21 (br s, 1H, NH); ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.9, 14.0 (2CH_3), 27.8, 27.9 and 28.4 (3CMe_3), 51.7 (NCMe_3), 51.79 and 55.3 (CH), 61.3 and 61.4 (OCH_2), 81.2 (OCMe_3), 82.4 [$\text{C}(\text{CO}_2\text{Et})_2$], 82.8 (OCMe_3), 159.9 (C=N), 167.9, 169.0, 169.2 and 169.9 ($4\text{C}=\text{O}$); MS, m/z (%): 484 ($\text{M}^+ + 1$, 92), 429 ($\text{M}^+ - (\text{CH}_3)_2\text{C}=\text{CH}_2$, 11), 411 ($\text{M}^+ - \text{NHCMe}_3$, 38), 383 ($\text{M}^+ - \text{CO}_2 \text{ t-Bu}$,

50), 327 [$M^+ - (CO_2\text{-}t\text{-Bu} + (CH_3)_2C=CH_2)$, 76], 57 ($C_4H_9^+$, 100). Anal. calcd. for $C_{24}H_{40}N_2O_8$: C, 59.50; H, 8.32; N, 5.80. Found: C, 59.46; H, 8.33; N, 5.83.

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