A facile route to the synthesis of polyfunctionalized pyrroles

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DOI: http://dx.doi.org/10.3998/ark.5550190.0011.b27

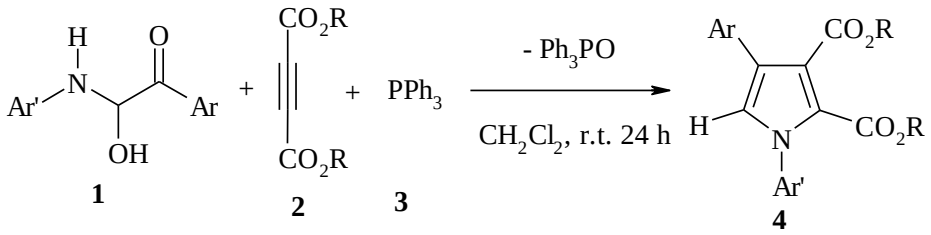
Abstract
A simple and efficient synthesis of some polyfunctionalized pyrrole derivatives by triphenylphosphine-promoted condensation reaction between dialkyl acetylenedicarboxylates and 1-aryl-2-(arylamino)-2-hydroxyethanones is described.

Keywords: Dialkyl acetylenedicarboxylates, pyrrole, triphenylphosphine, intramolecular Wittig reaction

Introduction

N-Heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores.[1] Of these heterocycles, the pyrrole ring is one of the most fundamental. It is a widely distributed structural unit in a variety of natural and biologically important molecules such as porphyrins, bile pigments, coenzymes, and alkaloids.[2] Therefore, it is not surprising that many methods for the syntheses of substituted and functionalized pyrroles have been reported in the literature.[3] Recently, syntheses of polysubstituted pyrroles have been reported from conjugate addition reactions,[4] transition metal intermediates,[5] reductive coupling,[6] aza Wittig reactions,[7] isocyanide-based reactions,[8] utilizing the sila-Stetter/Paal-Knorr sequence strategy[9] and other useful pathways.[10] Three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylates (DAAD's) and organic acidic compounds is well known to produce phosphorus ylides.[11] If the starting acidic compound possesses a carbonyl group in an appropriate position, these ylide intermediates may be converted to cyclic compounds by intramolecular Wittig reaction.[12-15] This strategy has been recently utilized for the synthesis of a variety of heterocyclic and carbocylic compounds. In

continuation of our previous work on the reaction between trivalent phosphorus nucleophiles and acetylene diesters in the presence of acidic organic compounds,[16-17] in this letter we report a simple and efficient synthesis of some functionalized pyrrole derivatives. Thus, the reaction between 2-hydroxy-1-aryl-2-(arylamino)ethanones[18] **1** and dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine **3** at ambient temperature in dichloromethane, leads to substituted pyrrole derivatives **4** in good yields (Scheme 1).



4	R	Ar	Ar'	Yield [a] %
a	Me	4-BrC_6H_4	4-$NO_2C_6H_4$	90
b	Me	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	85
c	Et	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	80
d	t-Bu	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	88
e	Me	4-ClC_6H_4	4-$NO_2C_6H_4$	85
f	t-Bu	4-ClC_6H_4	4-$NO_2C_6H_4$	80
g	Et	4-ClC_6H_4	3-$NO_2C_6H_4$	82

[a]Isolated Yield

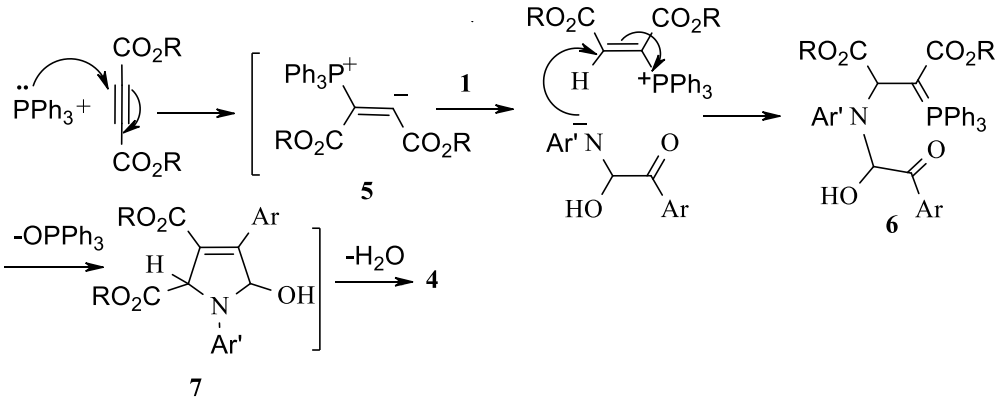
Scheme 1. One-pot synthesis of some polyfunctionalized pyrroles.

Results and Discussion

The structures of compounds **4a-g** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** was very simple including two sharp singlets for methoxycarbonyl groups (δ= 3.78, 3.89 ppm) supported by the absorption band at 1732 cm^{-1} in IR the spectrum of **4a**. A single signal was observed at δ 7.06 for pyrrole hydrogen and four doublets were appeared at δ 7.34, 7.54, 7.56 and 8.36 ppm for two para-substituted

phenyl rings. ^{13}C NMR spectrum of **4a** exhibited sixteen distinct signals in consistent with the proposed structure.

On the basis of the well established three-component reaction between acetylene diesters and triphenylphosphine in the presence of organic NH acids, it is reasonable to propose that reaction between triphenylphosphine, DAAD and 2-hydroxy-1-aryl-2-(arylamino)ethanone afforded ylide intermediate **6**, which converted to 2,5-dihydropyrrole intermediate **7**. This intermediate loses a molecule of water and aromatizes to product **4** under reaction condition (Scheme 2).



Scheme 2. Suggested mechanism for formation of compound **4**.

Conclusions

In summary, here we report an efficient method for the synthesis of some functionalized pyrrole derivatives by condensation reaction between acetylene diesters and 2-hydroxy-1-aryl-2-(arylamino)ethanones promoted by triphenylphosphine. The advantages of the suggested method are simple reaction conditions, good yields and using starting materials without any activation or modification.

Experimental Section

General. Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal

standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of dialkyl acetylenedicarboxylate (1 mmol) and 2-hydroxy-1-aryl-2-(arylamino)ethanones (1 mmol) in dichloromethane (10 mL) was added a solution of triphenylphosphine (0.26 g, 1 mmol) in dichloromethane (5 mL) at room temperature over 2 min. The reaction mixture was then stirred for 24 hours. Solvent was evaporated and the residue was purified by column chromatography on silica-gel using ethyl acetate-hexane (1:4) mixture as eluent.

Dimethyl 4-(4-bromophenyl)-1-(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4a). Yellow crystals, yield 90 %, 0.41 g, mp 202-204 °C, IR (KBr) (ν_{max}, cm^{-1}): 1732 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ = 3.78 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.06 (1 H, s, CH), 7.34 (2 H, d, $^3J_{HH}$ = 8.35 Hz, 2 CH of 4-Br C_6H_4), 7.54 (2 H, d, $^3J_{HH}$ = 8.35 Hz, 2 CH of 4-Br C_6H_4), 7.56 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.36 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 52.82 (OCH_3), 53.17 (OCH_3), 122.27, 123.66, 123.71, 125.04, 125.38, 125.92, 127.52, 129.82, 131.95, 132.41, 144.90, 147.96 (C arom), 160.48 (CO_2Me), 166.50 (CO_2Me). MS (*m/z*, %): 458 (M^+, 7). Anal. Calcd for $C_{20}H_{15}BrN_2O_6$ (458): C, 52.31; H, 17.40; N, 6.10%. Found: C, 52.39; H, 17.68; N, 6.21%.

Dimethyl 1,4-bis(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate(4b). Yellow crystals, yield 85%, 0.36 g, mp 205-206 °C, IR (KBr) (ν_{max}, cm^{-1}): 1708 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ = 3.58 (3 H, s, OCH_3), 3.69 (3 H, s, OCH_3), 7.06 (1 H, s, CH), 7.40 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$), 7.44 (2 H, d, $^3J_{HH}$ = 8.5 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.05 (2 H, d, $^3J_{HH}$ = 8.5 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.17 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 52.70 (OCH_3), 52.99 (OCH_3), 122.99, 123.88, 124.24, 124.40, 124.84, 126.51, 127.27, 128.60, 139.70, 144.32, 147.18, 147.78 (C arom), 160.12 (CO_2Me), 165.12 (CO_2Me). MS (*m/z*, %): 425 (M^+, 11). Anal. Calcd. for $C_{20}H_{15}N_3O_8$ (425): C, 56.47; H, 3.55; N, 9.88%. Found: C, 56.32; H, 3.63; N, 9.72%.

Diethyl 1,4-bis(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4c). Yellow crystals, yield 80%, 0.36 g, mp 172-173 °C, IR (KBr) (ν_{max}, cm^{-1}): 1741 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ = 1.22 (3H, t, $^3J_{HH}$ = 7.1 Hz, $OCH_2C\mathit{H}_3$), 1.32 (3H, t, $^3J_{HH}$ = 7.1 Hz, $OCH_2C\mathit{H}_3$), 4.22 (2H, q, $^3J_{HH}$ = 7.1 Hz, $OC\mathit{H}_2CH_3$), 4.33 (2H, q, $^3J_{HH}$ = 7.1 Hz, $OC\mathit{H}_2CH_3$), 7.14 (1 H, s, CH), 7.56 (2 H, d, $^3J_{HH}$ = 8.9 Hz, 2 CH of 4-$NO_2C_6H_4$), 7.61 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.24 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.36 (2 H, d, $^3J_{HH}$ = 8.9 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 13.92, 14.05 ($2OCH_2\mathit{C}H_3$), 61.58, 61.90 ($2O\mathit{C}H_2\mathit{C}H_3$), 122.99, 123.11, 123.58, 123.99, 124.53, 125.79, 127.06, 128.25, 139.41, 144.18, 146.93, 147.51 (C arom), 159.36 (CO_2 Et), 165.21 (CO_2Et). MS (*m/z*, %): 453 (M^+, 11). Anal. Calcd. for $C_{22}H_{19}N_3O_8$ (453): C, 58.28; H, 4.22; N, 9.27%. Found: C, 58.42; H, 4.39; N, 9.12%.

Di-tert-butyl 1,4-bis(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4d). Yellow crystals, yield 88%, 0.44 g, mp 168-169 °C, IR (KBr) (ν_{max}, cm^{-1}): 1714 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$),

δ = 1.37 (9 H, s, C(C*H*$_3$)$_3$), 1.47 (9 H, s, C(C*H*$_3$)$_3$), 7.02 (1 H, s, CH), 7.54 (2 H, d, $^3J_{HH}$ = 8.85 Hz, 2 CH 4-$NO_2C_6H_4$), 7.61 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.23 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.36 (2 H, d, $^3J_{HH}$ = 8.85 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 27.52, 27.96 (2 C(*C*H$_3$)$_3$), 82.45, 82.07(2 *C*(CH$_3$)$_3$), 122.77, 123.12, 123.62, 124.51, 124.68, 126.28, 126.73, 128.74, 140.11, 144.75, 146.73, 147.17 (C arom), 158.60 (CO_2Me), 163.72 (CO_2Me). MS (*m/z*, %): 509 (M^+, 5). Anal. Calcd. for $C_{26}H_{27}N_3O_8$ (509): C, 61.29; H, 5.34; N, 8.25%. Found: C, 61.11; H, 5.44; N, 8.31%.

Dimethyl 4-(4-chlorophenyl)-1-(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4e). Yellow crystals, yield 85%, 0.35 g, mp 174-175 °C, IR (KBr) (ν_{max}, cm^{-1}): 1738 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ = 3.74 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 7.02 (1 H, s, CH), 7.33-7.37(4 H, m, 4-Cl C_6H_4), 7.52 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.32 (2 H, d, $^3J_{HH}$ = 8.8 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 52.69 (OCH_3), 53.04 (OCH_3), 123.50, 123.63, 124.91, 125.23, 125.87, 127.39, 129.33, 129.40, 131.38, 133.99, 144.78, 147.81 (C arom), 160.38 (CO_2Me), 166.40 (CO_2Me). MS (*m/z*, %): 414 (M^+, 7). Anal. Calcd. for $C_{20}H_{15}ClN_2O_6$ (414): C, 57.91; H, 3.64; N, 6.75%. Found: C, 57.97; H, 3.52; N, 6.60%.

Di-tert-butyl 4-(4-chlorophenyl)-1-(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4f). Yellow crystals, yield 80%, 0.35 g, mp 162-163 °C, IR (KBr) (ν_{max}, cm^{-1}): 1714 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ = 1.36 (9 H, s, C(CH$_3$)$_3$), 1.43 (9 H, s, C(CH$_3$)$_3$), 6.87 (1 H, s, CH), 7.31-7.35 (4H, m, 4-Cl C_6H_4), 7.48 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$), 8.31 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 28.31, 28.41 (2 C(*C*H$_3$)$_3$), 82.51, 83.18 (2 *C*(CH$_3$)$_3$), 124.53, 124.85, 125.25, 125.71, 127.12, 128.87, 130.06, 130.53, 132.09, 133.66, 145.51, 147.49 (C arom), 159.22 (CO_2Me), 164.41 (CO_2Me). MS (*m/z*, %): 498 (M^+, 11). Anal. Calcd. for $C_{26}H_{27}ClN_2O_6$ (498): C, 62.59; H, 5.45; N, 5.61%. Found: C, 62.62; H, 5.49; N, 5.42%.

Diethyl 4-(4-chlorophenyl)-1-(3-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (4g). Yellow crystals, yield 82%, 0.36 g, mp 94-96 °C, IR (KBr) (ν_{max}, cm^{-1}): 1712 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$), δ =1.20 (3H, t, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 1.32 (3H, t, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 4.18 (2H, q, $^3J_{HH}$ = 7.1 H Hz, OCH_2CH_3), 4.32 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 7.01 (1 H, s, CH), 7.33-7.39 (4H, m, 4-ClC_6H_4), 7.63-7.71 (2H, m, 3-$NO_2C_6H_4$), 8.24-8.31 (2H, m, 3-$NO_2C_6H_4$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$), δ = 14.34, 14.49 ($2OCH_2CH_3$), 61.68, 62.10 ($2OCH_2CH_3$), 109.42, 122.08, 123.45, 123.82, 124.86, 125.98, 129.26, 129.42, 130.18, 131.55, 132.86, 133.87, 140.72, 148.69 (C arom), 159.89 (CO_2 Et), 166.13 (CO_2Et). MS (*m/z*, %): 442 (M^+, 9). Anal. Calcd. for $C_{22}H_{19}ClN_2O_6$(442): C, 59.67; H, 4.32; N, 6.33%. Found: C, 59.57; H, 4.17; N, 6.39%.

Acknowledgements

We gratefully acknowledge the financial support from the Young Researchers Club of Islamic Azad University, Yazd Branch

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