A Facile Synthesis of Polysubstituted Pyrroles by One-Pot Three-Component Reaction

HOSSEIN ANARAKI-ARDAKANI^{1*}, MAZIAR NOEI¹, MINA KARBALAEI-HAROFTEH², SHAHAB ZOMORODBAKSH¹

¹Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran

²Department of Chemistry, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran
hosseinanaraki@yahoo.com

Received 28 October 2011; Acceptance 29 December 2011

Abstract: A new and efficient one-pot synthesis of polysubstituted pyrrole derivatives by three-component reaction between dialkyl acetylenedicarboxylates, triphenylphosphine, 2-aminopyridin derivatives in the presence of arylglyoxals is described. The reactions were performed in dichloromethane at room temperature and neutral conditions and afforded high yields of products.

Keywords: pyrrole, dialkyl acetylenedicarboxylates, 2-aminopyridin, triphenylphosphine, intramolecular Wittig reaction.

Introduction

Pyrroles¹ are among the most important heterocyclic compounds as they are structural elements of various bioactive natural products²⁻⁴ and pharmaceutical agents.⁵⁻⁷ They are also valuable intermediates in organic synthesis.^{2,8} Various pyrrole derivatives are widely used as organic conducting materials.⁹ Consequently, a wide range of procedures have been devised for the synthesis of pyrroles.¹⁰⁻¹³ However, many of the methods are associated with various drawbacks such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, and long reaction times. Moreover, the number of methods for the synthesis of polysubstituted pyrroles is relatively limited.

Addition reaction between phosphines and activated carbon-carbon triple bonds is well known to produce a reactive zwitterionic intermediate, which may be trapped by various electrophiles.¹⁴⁻¹⁸ Reaction of triphenylphosphine with dialkyl acetylenedicarboxylates (DAAD's) has been studied in the presence of a variety of organic acidic compounds, in order to trap the zwitterionic intermediate. Trapping of PPh₃-DAAD zwitterion by an organic acidic compound containing a carbonyl group have been used as a one-pot and efficient route for the synthesis of a variety of heterocyclic and carbocyclic compounds.¹⁹⁻²³

Keeping in mind the biological importance of pyrrole ring and in continuation of our current studies on the development of new routes in heterocyclic synthesis,²³⁻²⁴ in this letter we report a simple and efficient synthesis of some functionalized pyrrole. Thus, three-component reaction between triphenylphosphine **1**, 2-aminopyridin derivative **2**, dialkyl acetylenedicarboxylates **3** in the presence of arylglyoxals **4** at ambient temperature in dichloromethane, leads to substituted pyrrole derivatives **5** in good yields (Figure 1).

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

Experimental

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. ^1H 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 triphenylphosphine (1 mmol) and 2-aminopyridin derivatives (1 mmol) in dichloromethane (10 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate (1 mmol) in dichloromethane (3 mL) at room temperature over 5 min. The reaction mixture was then stirred for 10 minute. Arylglyoxal (1 mmol) was added and the reaction mixture was stirred for more 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.

Spectral data

Dimethyl 1-(5-bromopyridin-2-yl)-4-(4-nitrophenyl)-1H-pyrrole-2,3-dicarboxylate (4a):

Yellow oil (0.41 g, 90 %). IR (KBr) (ν_{max} , cm^{-1}): 1715($\text{C}=\text{O}$). ^1H NMR (500.1 MHz, CDCl_3) δ = 3.85(3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 7.35 (1 H, s, CH), 7.33 (1 H, d, $^3J_{\text{HH}}$ = 8.5 Hz, 1 CH of 4-Br $\text{C}_5\text{H}_3\text{N}$), 7.65 (2 H, d, $^3J_{\text{HH}}$ = 8.8 Hz, 2 CH of 4- $\text{NO}_2\text{C}_6\text{H}_4$), 7.99 (1 H, dd, $^3J_{\text{HH}}$ = 8.5 Hz, $^4J_{\text{HH}}$ = 2.4 Hz, 1 CH of 4-Br $\text{C}_5\text{H}_3\text{N}$), 8.26 (2 H, d, $^3J_{\text{HH}}$ = 8.8 Hz, 2 CH of 4- $\text{NO}_2\text{C}_6\text{H}_4$), 8.61 (1 H, d, $^3J_{\text{HH}}$ = 2.4 Hz, 1 CH of 4-Br $\text{C}_5\text{H}_3\text{N}$) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ = 52.77 (OCH_3), 53.03 (OCH_3), 119.55, 120.30, 121.05, 123.90, 124.12, 124.79, 129.33, 130.11, 140.26, 141.50, 147.40 149.41, 150.40 (C arom), 161.53 (CO_2Me),

165.25 (CO₂Me). MS (m/z, %): 459 (M⁺, 5). Anal. Calcd. for C₁₉H₁₄BrN₃O₆ (459): C, 49.58; H, 3.07; N, 9.13%. Found: C, 49.32; H, 3.18; N, 9.29%.

Diethyl 1-(5-bromopyridin-2-yl)-4-(4-nitrophenyl)-1H-pyrrole-2,3-dicarboxylate (4b):

Yellow oil (0.41 g, 85 %). IR (KBr) ($\nu_{\max}$, cm⁻¹): 1726(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 1.32 (6 H, m, 2OCH₂CH₃), 4.22 (2 H, q, ³J_{HH} = 7.1 Hz, OCH₂CH₃), 4.33 (4H, m, 2OCH₂CH₃), 7.33 (1 H, s, CH), 7.34 (1 H, d, ³J_{HH} = 8.5 Hz, 1 CH of 4-Br C₅H₃N), 7.65 (2 H, d, ³J_{HH} = 8.8 Hz, 2 CH of 4-NO₂C₆H₄), 7.99 (1 H, dd, ³J_{HH} = 8.5 Hz, ⁴J_{HH} = 2.4 Hz, 1 CH of 4-Br C₅H₃N), 8.26 (2 H, d, ³J_{HH} = 8.8 Hz, 2 CH of 4-NO₂C₆H₄), 8.60 (1 H, d, ³J_{HH} = 2.4 Hz, 1 CH of 4-Br C₅H₃N) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 14.37, 14.44 (2OCH₂CH₃), 61.85, 62.13 (2OCH₂CH₃), 119.79, 120.25, 121.43, 123.88, 124.08, 124.62, 129.31, 131.30, 140.40, 141.41, 147.34, 149.55, 150.30 (C arom), 161.01 (CO₂Me), 164.91 (CO₂Me). MS (m/z, %): 487 (M⁺, 7). Anal. Calcd. for C₂₁H₁₈BrN₃O₆ (487): C, 51.65; H, 3.72; N, 8.61%. Found: C, 51.52; H, 3.62; N, 8.86%.

Dimethyl 4-(4-bromophenyl)-1-(5-chloropyridin-2-yl)-1H-pyrrole-2,3-dicarboxylate (4c):

Yellow oil (0.35 g, 80 %). IR (KBr) ($\nu_{\max}$, cm⁻¹): 1721(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 3.83 (3H, s, OCH₃), 3.84 (3 H, s, OCH₃), 7.32 (1H, s, CH), 7.35 (1 H, d, ³J_{HH} = 8.5 Hz, 1CH of 4-Cl C₅H₃N), 7.36 (2 H, d, ³J_{HH} = 8.3 Hz, 2 CH of 4-BrC₆H₄), 7.51 (2 H, d, ³J_{HH} = 8.3 Hz, 2CH of 4-BrC₆H₄), 7.85 (1 H, dd, ³J_{HH} = 8.5 Hz, ⁴J_{HH} = 2.4 Hz, 1CH of 4-Cl C₅H₃N), 8.48 (1H, d, ³J_{HH} = 2.4 Hz, 1CH of 4-Cl C₅H₃N) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 52.63 (OCH₃), 52.87(OCH₃), 119.32, 121.94, 121.05, 123.52, 124.12, 125.05, 125.67, 128.75, 130.27, 131.94, 137.97, 138.51, 139.10, 147.48, 148.00, 149.23 (C arom), 161.62 (CO₂Me), 65.71(CO₂Me). MS (m/z, %): 447 (M⁺, 9). Anal. Calcd. for C₁₉H₁₄BrClN₂O₄ (447): C, 50.75; H, 3.14; N, 6.23%. Found: C, 50.62; H, 3.31; N, 6.12%.

Dimethyl 1-(5-chloropyridin-2-yl)-4-(4-nitrophenyl)-1H-pyrrole-2,3-dicarboxylate(4d):

Yellow oil (0.35 g, 85 %). IR (KBr) ($\nu_{\max}$, cm⁻¹): 1709(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 3.87(3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 7.29 (1 H, s, CH), 7.38 (1 H, d, ³J_{HH} = 8.5 Hz, 1 CH of 4-Cl C₅H₃N), 7.64 (2 H, d, ³J_{HH} = 8.7 Hz, 2 CH of 4-NO₂C₆H₄), 7.85 (1 H, dd, ³J_{HH} = 8.5 Hz, ⁴J_{HH} = 2.4 Hz, 1 CH of 4- Cl C₅H₃N), 8.26 (2 H, d, ³J_{HH} = 8.7 Hz, 2 CH of 4-NO₂C₆H₄), 8.50 (1 H, d, ³J_{HH} = 2.4 Hz, 1 CH of 4- Cl C₅H₃N) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 52.80 (OCH₃), 53.05 (OCH₃), 119.18, 120.320, 121.14, 124.02, 124.14, 124.73, 129.31, 132.05, 138.67, 140.26, 147.38, 148.14, 148.97 (C arom), 161.53 (CO₂Me), 165.25 (CO₂Me). MS (m/z, %): 415 (M⁺, 6). Anal. Calcd. for C₁₉H₁₄ClN₃O₆ (415): C, 54.89; H, 3.39; N, 10.11%. Found: C, 54.72; H, 3.16; N, 10.21%.

Dimethyl 4-(4-bromophenyl)-1-(4-methylpyridin-2-yl)-1H-pyrrole-2,3-dicarboxylate(4e):

Yellow oil (0.34 g, 80 %). IR (KBr) ($\nu_{\max}$, cm⁻¹): 1728(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 2.41(3 H, s, CH₃), 3.78 (3 H, s, OCH₃), 3.82 (3 H, s, OCH₃), 6.69 (1 H, d, ³J_{HH} = 5.2 Hz, 5- CH₃ C₅H₃N), 7.21(1 H, s, CH), 7.36 (2 H, d, ³J_{HH} = 8.3 Hz, 2 CH of 4-BrC₆H₄), 7.51 (2H, d, ³J_{HH} = 8.3 Hz, 2CH of 4-BrC₆H₄), 7.96 (1 H, d, ³J_{HH} = 5.2 Hz, 5- CH₃ C₅H₃N), 8.01 (1 H, s, 5- CH₃ C₅H₃N), ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 14.54(CH₃), 52.45 (OCH₃), 52.69 (OCH₃), 114.3, 121.6, 122.14, 124.11, 124.21, 124.61, 129.30, 132.14, 138.61, 140.22, 147.06, 149.61, 149.19 (C arom), 162.11 (CO₂Me), 166.05 (CO₂Me). MS (m/z, %): 428 (M⁺, 8). Anal. Calcd. for C₂₀H₁₇BrN₂O₄ (428): C, 55.96; H, 3.99; N, 6.53%. Found: C, 55.82; H, 3.78; N, 6.81%.

Results and Discussion

We first prepared Ylide **6** by the reaction between triphenylphosphine, dimethyl acetylenedicarboxylate (DMAD) and 5-bromo-2-aminopyridin by the previously reported procedure.²⁵ (Figure 1). When phosphorane **6** was stirred with an equimolar amount of phenylglyoxal in dichloromethane, a smooth reaction took place. After completion of the reaction (monitored by TLC) dimethyl 1-(5-bromopyridin-2-yl)-4-(4-nitrophenyl)-1H-pyrrole-2,3-dicarboxylate **5a** was obtained in 90% yield. As shown in Scheme 2, it is reasonable to assume that the Wittig reaction between phosphorane **4** and phenylglyoxal (**5**) affords intermediate **7** which then cyclizes to dihydropyrrole intermediate **8** that subsequently loses water to produce pyrrole derivative **5a**.

Figure 2 Suggested mechanism for formation of compound **5a**.

To explore the scope and limitations of this reaction further, we extended our studies to the reaction of various dialkyl acetylenedicarboxylates and 2-aminopyridin derivative with arylglyoxals (Table 1). As indicated in Table 1, the reactions proceeded very efficiently in relatively good yields.

Table 1. Three-component reaction between 2-aminopyridin, DAAD's and arylglyoxals promoted by PPh₃.

5	R	Ar	X	Yield ^a %
a	Me	4-NO ₂ C ₆ H ₄	5-Br	90
b	Et	4-NO ₂ C ₆ H ₄	5-Br	85
c	Me	4-BrC ₆ H ₄	5-Cl	80
d	Me	4-NO ₂ C ₆ H ₄	5-Cl	85
e	Me	4-BrC ₆ H ₄	4-CH ₃	80

^aIsolated Yield

The structures of compounds **5a-e** were deduced from their elemental analyses and their IR, ¹H NMR, ¹³C NMR spectra. The ¹H NMR spectrum **5a** exhibited three sharp signals at δ = 3.85, 3.88 and 7.33 ppm for two methoxy groups protons and the proton of pyrrole ring, respectively. The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum. The ¹³C NMR spectrum of compound **6a** showed 17 distinct resonances in agreement with the proposed structure.

Conclusion

In conclusion here we reported a three-component reaction between dialkyl acetylenedicarboxylates, 2-aminopyridin derivatives and arylglyoxals promoted by triphenylphosphine, to produce functionalized pyrrole derivatives in high yields. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multi-step approaches.

Acknowledgements

We gratefully acknowledge the financial support from the Research Council of Islamic Azad University, Mahshahr Branch.

References

1. Part 283 in the series 'Studies on Novel Synthetic Methodologies'.
2. Finar I L, Organic Chemistry: Stereochemistry and Chemistry of Natural Products, 5th ed., Vol. 2; Longman: London, 1975, 885–913.
3. Hagan D O, *Nat Prod Rep.*, 2000, **17**, 435.
4. Walsh C T, Garneau-Tsodikova S, Howard-Jones A R, *Nat Prod Rep.*, 2006, **23**, 517.

5. Huffman J W, *Curr Med Chem.*, 1999, **6**, 705.
6. Kidwai M, Venkataramanan R, Mohan R, Sapra P, *Curr Med Chem.*, 2002, **9**, 1209.
7. LaRegina G, Silvestri R, Artico, Lavechia M, Novellino, A. Befani E, Turini O, Agostinelli E P, *J Med Chem.*, 2007, **50**, 922.
8. Abid M, Landge S M, Torok B, *Org Prep Proced Int.*, 2006, **38**, 495.
9. Facchetti A, Abboto A, Beverina L, vander Boom M E, Dutta P, Evmenenko G, Pagani G A, Marks T, *J Chem Mater.*, 2003, **15**, 1064.
10. Larionov O V, Meijere A, *Angew Chem Int Ed.*, 2005, **44**, 5664.
11. Minetto G, Raveglia L F, Sega A, Taddei M, *Eur J Org Chem.*, 2005, **24**, 5277.
12. Shiner C M, Laner T D, *Tetrahedron*, 2005, **61**, 11628.
13. Abid M, Teixeira L, Torok B, *Org Lett.*, 2008, **10**, 933.
14. Anaraki-Ardakani H, Mosslemin M H, Mohebat R, Barazandeh-Doust M, *J Chem Res.*, 2011, **1**, 32
15. Trost B M, Dake G R, *J Am Chem Soc.*, 1997, **119**, 7595.
16. Anary-Abbasinejad M, Anaraki-Ardakani H, Hosseini-Mehdiabad H, *Phosphorus, Sulfur and Silicon and the Relat. Elem.*, 2008, **183**, 1440
17. Yavari I, Hekmat-Shoar R, Zonouzi A, *Tetrahedron Lett.*, 1998, **39**, 2391.
18. Evans L A, Griffiths K E, Guthmann H, Murphy P J, *Tetrahedron Lett.*, 2002, **43**, 299.
19. Khabazzadeh H, Saidi K, Sheibani H, Islami M R, *Phosphorus, Sulfur and Silicon Relat. Elem.*, 2007, **182**, 2163.
20. Anary-Abbasinejad M, Mosslemin M H, Hassanabadi A, Tabatabaee M, *Synth Commun.*, 2008, **38**, 3700.
21. Mosslemin M H, Yavari I, Anary-abbasinejad M, Nateghi M R, *Synthesis*, 2004, **7**, 1029.
22. Nair V, Nair J S, Vinod A U, Rath N P, *J Chem Soc., Perkin Trans I*, 1997, 329.
23. Anaraki-Ardakani H, Mosslemin M H, Anary-Abbasinejad M, Shams N, Mirhosseini S H, *Arkivoc*, 2010, **(xi)**, 343.
24. Anary-Abbasinejad M, Anaraki-Ardakani H, Dehghan A, Hassanabadi A, Seyedmir M R, *J Chem Res.*, 2007, **10**, 574.
25. Yavari I, Adib M, Hojabri L, *Tetrahedron*, 2002, **58**, 7213.