

Synthesis of Polyfunctionalized Pyrroles by a PPh₃-Promoted Condensation Reaction between Ammonium Acetate, Dialkyl Acetylenedicarboxylate and Arylglyoxals

Nikomanesh, Parisa; Anaraki-Ardakani, Hossein⁺*

Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, I.R. IRAN

ABSTRACT: A simple and efficient synthesis of some polyfunctionalized pyrrole derivatives by a triphenylphosphine-promoted condensation reaction between dialkyl acetylenedicarboxylates, arylglyoxals, and ammonium acetate is described. This present method carries several advantages, such as good yields, a simple procedure, non-hazardous reaction conditions and starting from easily accessible substrates.

KEYWORDS: Dialkyl acetylene dicarboxylates; Triphenylphosphine; Ammonium acetate; Intramolecular Wittig reaction; Arylglyoxals.

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]. A diverse range of pharmacological properties, including antibacterial, antitumor, anti-inflammatory, antioxidant, antianginal and antifungal activities of this important class of heterocycles has been reported in the literature [4].

Recently, syntheses of polysubstituted pyrroles have been reported from conjugate addition reactions [5],

transition metal intermediates [6], reductive coupling [7], aza Wittig reactions [8], isocyanide-based reactions [9], utilizing the sila-Stetter/Paal-Knorr sequence strategy [10] and other pathways [11]. However, some of these methods have some drawbacks, such as harsh reaction conditions, lengthy reaction times, expensive catalysts and low yields. Therefore, it is clearly evident that developing new and flexible methods of synthesis is required.

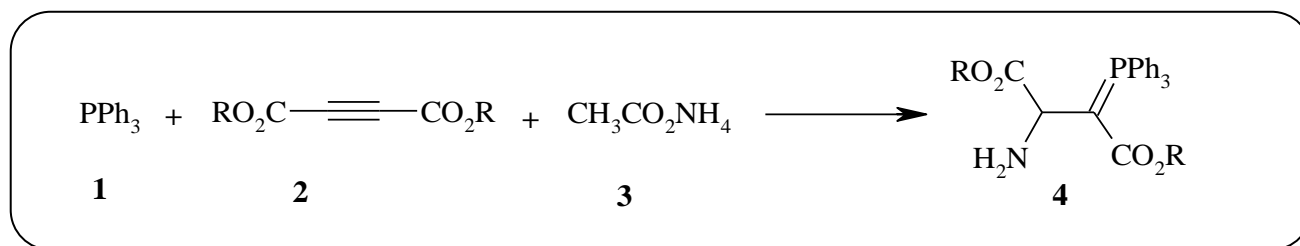
Addition reaction between phosphines or triphenylphosphite and activated carbon-carbon triple bonds is well known to produce a reactive zwitterionic intermediate, which may be trapped by various electrophiles [11-17]. The reaction of triphenylphosphine with dialkyl acetylenedicarboxylates (DAAD) has been studied in the presence of a variety of organic acidic compounds, in order to trap the zwitterionic intermediate.

* To whom correspondence should be addressed.

+ E-mail: hosseinanaraki@yahoo.com

1021-9986/2017/5/17-22

6/\$/5.60



Scheme 1: Synthesis of some α -aminophosphorous ylide.

Trapping of PPh_3 -DAAD zwitterion by an organic acidic compound containing a carbonyl group has been used as a one-pot and efficient route for the synthesis of a variety of heterocyclic and carbocyclic compounds [16-19]. Treatment of triphenylphosphine with DAAD in the presence of ammonium acetate has been reported to produce α -aminophosphorous ylide **4** [20- 22] (Scheme 1).

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 [18, 19, 23], herein we report a very simple and highly efficient one-pot method for the synthesis of polyfunctionalized pyrrole derivatives through the reaction of dialkyl acetylene dicarboxylates, ammonium acetate and arylglyoxals in the presence of triphenylphosphine under catalyst-free conditions. (Scheme 2).

EXPERIMENTAL SECTION

Melting points were determined with an electrothermal 9100 apparatus. 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 the solution in CDCl_3 using TMS as an 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 PPh_3 (1 mmol) and, ammonium acetate (1 mmol) in CH_3CN (10 mL) was added dropwise a mixture of DAAD (1 mmol) in CH_3CN (3 mL) at room temperature over 2 min. The reaction mixture was then stirred for 20 min. After completion of the reaction (TLC), a mixture of

arylglyoxals (1 mmol) in CH_3CN (3 mL)) was added and the reaction mixture was stirred for more 24 h. The solvent was evaporated and the residue was purified by column chromatography on SiO_2 using EtOAc-hexane (1:4) mixture as eluent.

Dimethyl 4-phenyl-1H-pyrrole-2, 3-dicarboxylate (6a)

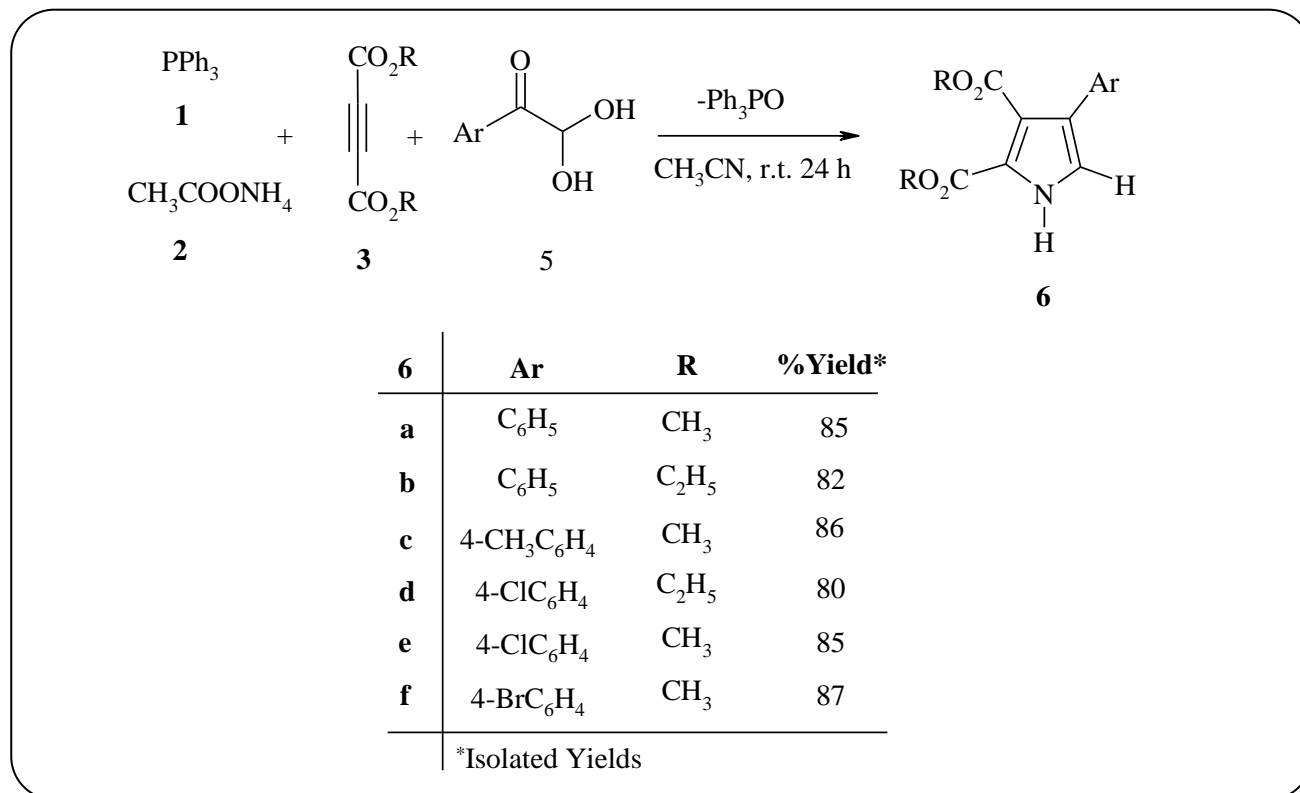
Yellow crystals, M.p. 135°C . IR (KBr) (ν_{max} , cm^{-1}): 3275(NH), 1669, 1729(C=O). ^1H NMR (500.1 MHz, CDCl_3) δ = 3.92 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 6.70-7.60(6 H, m, C_6H_5 and CH), 9.67(1H,br,NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ = 51.95 (OCH_3), 52.34 (OCH_3), 110.71, 121.43, 122.63, 124.90, 128.33, 129.09, 130.30, 135.05 (C arom), 160.93 (CO_2Me), 164.35 (CO_2Me). MS (m/z , %): 259 (M^+ , 9). Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_4$: C, 64.86; H, 5.05; N, 5.40 %. Found: C, 64.64; H, 5.21; N, 5.52 %.

Diethyl 4-phenyl-1H-pyrrole-2,3-dicarboxylate (6b)

Yellow crystals, M.p. 141°C . IR (KBr) (ν_{max} , cm^{-1}): 3280(NH), 1681, 1729 (C=O). ^1H NMR (500.1 MHz, CDCl_3) δ = 1.19 (3H, t, $^3J_{\text{HH}} = 7.2$ Hz, OCH_2CH_3), 1.35 (3H, t, $^3J_{\text{HH}} = 7.2$ Hz OCH_2CH_3), 4.23 (2H, q, $^3J_{\text{HH}} = 7.2$ Hz, OCH_2CH_3), 4.34 (2H, q, $^3J_{\text{HH}} = 7.2$ Hz, OCH_2CH_3), 7.01 (1 H, s, CH), 7.33-7.39 (5H, m, arom), 9.46(1H, br, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ = 14.35, 14.61 ($2\text{OCH}_2\text{CH}_3$), 61.42, 61.64 ($2\text{OCH}_2\text{CH}_3$), 118.61, 120.43, 123.46, 123.67, 128.12, 129.22, 130.30, 133.82 (C arom), 160.71 (CO_2Et), 164.25 (CO_2Et). MS (m/z , %): 287(M^+ , 11). Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_4$: C, 66.89; H, 5.96; N, 4.88%. Found: C, 66.74; H, 5.69; N, 4.96%.

Dimethyl 4-p-tolyl-1H-pyrrole-2, 3-dicarboxylate (6c)

Yellow oil, IR (KBr) (ν_{max} , cm^{-1}): 3295(NH), 1713(C=O). ^1H NMR (500.1 MHz, CDCl_3) δ = 2.49 (3H, s, CH_3), 3.86 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3),



Scheme 2: One-pot synthesis of some functionalized pyrrole derivatives.

6.87-7.57(5 H, m, arom and CH), 9.76 (1H, br, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 21.15(CH₃), 52.15 (OCH₃), 52.41 (OCH₃), 120.04, 121.13, 126.33, 127.29, 128.43, 129.24, 130.20, 130.46 (C arom), 160.61 (CO₂Me), 165.35 (CO₂Me). MS (m/z, %): 273 (M⁺, 20). Anal. Calcd. for C₁₅H₁₅NO₄: C, 65.92; H, 5.53; N, 5.13%. Found: C, 66.08; H, 5.41; N, 5.36%.

Diethyl 4-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate (6d)

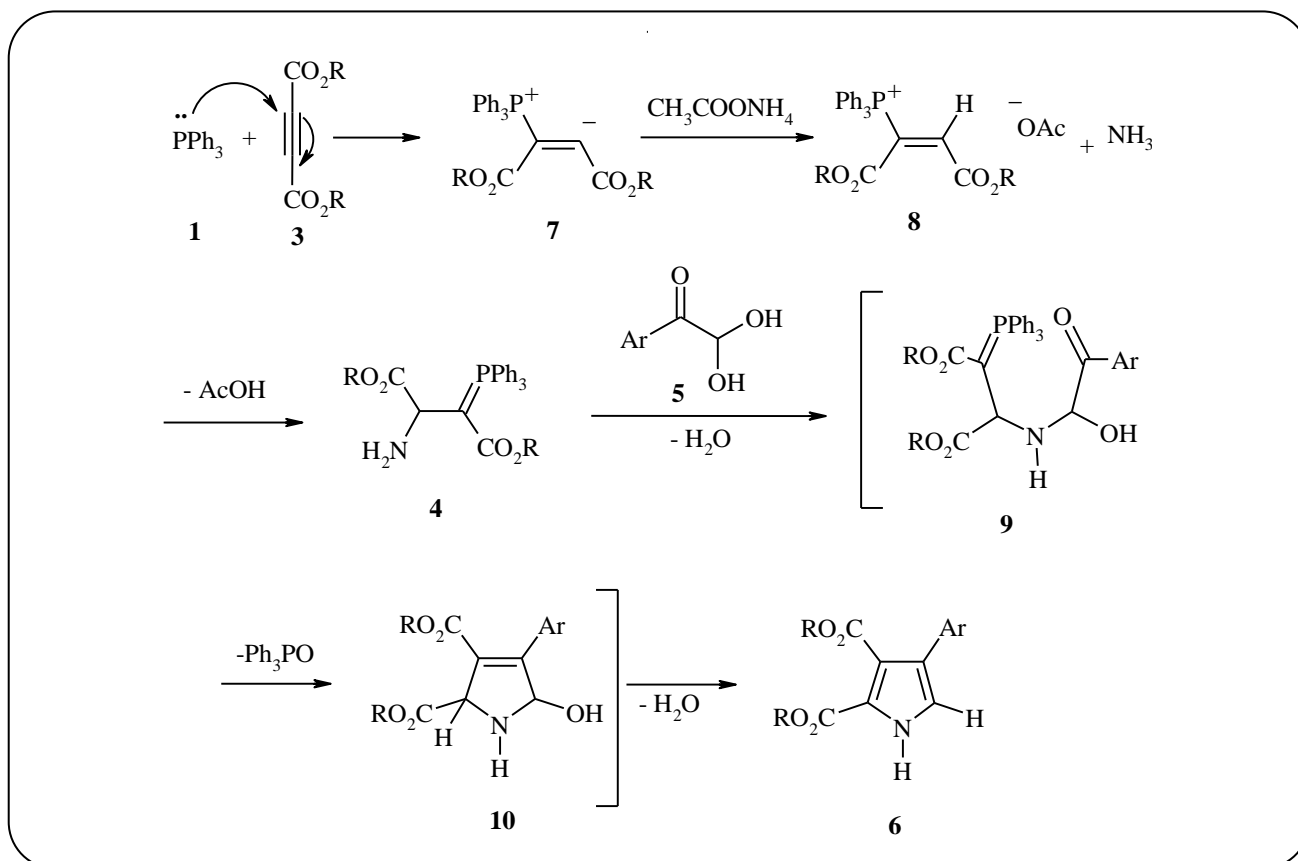
Yellow crystals, M.p. 137-139°C. IR (KBr) (ν_{max}, cm⁻¹): 3215 (NH), 1690, 1712 (C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 1.20 (3H, t, ³J_{HH} = 7.1 Hz, OCH₂CH₃), 1.32 (3H, t, ³J_{HH} = 7.1 Hz, OCH₂CH₃), 4.18 (2H, q, ³J_{HH} = 7.1 Hz, OCH₂CH₃), 4.32 (2H, q, ³J_{HH} = 7.1 Hz, OCH₂CH₃), 7.01 (1 H, s, CH), 7.33-7.39 (4H, m, 4-ClC₆H₄), 9.71(1H, br, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 14.34, 14.49 (2OCH₂CH₃), 61.68, 62.10 (2OCH₂CH₃), 122.08, 124.86, 125.98, 129.42, 130.18, 132.86, 133.87, 140.72 (C arom), 159.89 (CO₂ Et), 166.13 (CO₂Et). MS (m/z, %): 321 (M⁺, 15). Anal. Calcd. for C₁₆H₁₆ClNO₄: C, 59.73; H, 5.01; N, 4.35%. Found: C, 59.52; H, 5.27; N, 4.21%.

Dimethyl 4-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate (6e)

Yellow oil, IR (KBr) (ν_{max}, cm⁻¹): 3225(NH), 1668, 1735(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 3.86 (3 H, s, OCH₃), 3.88 (3 H, s, OCH₃), 7.06-7.43(5 H, m, arom and CH), 8.92 (1H, br, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 52.69 (OCH₃), 53.04 (OCH₃), 123.50, 124.91, 125.23, 125.87, 127.39, 129.40, 131.38, 133.99 (C arom), 160.38 (CO₂Me), 166.40 (CO₂Me). MS (m/z, %): 293 (M⁺, 11). Anal. Calcd. for C₁₄H₁₂ClNO₄: C, 57.25; H, 4.12; N, 4.77%. Found: C, 57.11; H, 4.32; N, 4.55%.

Dimethyl 4-(4-bromophenyl)-1H-pyrrole-2,3-dicarboxylate (6f)

Yellow crystals, M.p. 136-138°C. IR (KBr) (ν_{max}, cm⁻¹): 3275(NH), 1685, 1745(C=O). ¹H NMR (500.1 MHz, CDCl₃) δ = 3.79 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 7.27-7.80(5 H, m, arom and CH), 9.17(1H, br, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ = 52.33 (OCH₃), 52.83 (OCH₃), 110.39, 122.33, 129.23, 130.42, 132.22, 132.42, 133.40, 143.40 (C arom), 161.13 (CO₂Me), 170.38



Scheme 3: The suggested mechanism for the formation of functionalized pyrrole derivatives.

(CO₂Me). MS (*m/z*, %): 336 (M⁺, 29). Anal. Calcd. for C₁₄H₁₂BrNO₄: C, 49.73; H, 3.58; N, 4.14%. Found: C, 49.95; H, 3.31; N, 4.32%.

RESULTS AND DISCUSSION

The structures of compounds **6a-f** were deduced from their elemental analyses and their IR, ¹H NMR, ¹³C NMR spectra. For example, the mass spectrum of **6a** displayed the molecular-ion peak at *m/z* = 259. The 500.1 MHz ¹H NMR spectrum of **6a** exhibited two sharp signals at δ 3.92 and 3.96 ppm for two methoxy groups' protons. The aromatic protons were observed at 6.70-7.60 ppm. A broad singlet was observed at δ 9.67 ppm for NH proton. The ¹³C NMR spectrum of compound **6a** showed 12 distinct resonances in agreement with the proposed structure. The structural assignments made on the basis of the NMR spectra of compound **6a** were supported by its IR spectrum. NH group showed an absorption band at 3275 cm⁻¹ and carbonyl groups exhibited strong absorption bands at 1729, 1669 cm⁻¹.

A mechanistic rationalization for the reaction is given in Scheme 3. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [23-28], it is reasonable to assume that the initial event is the formation of the zwitterion **7** from the triphenylphosphine and the acetylenic ester. Next, the zwitterion is protonated by ammonium acetate. The resulting positively charged phosphonium ion **8** is attacked by the conjugate base of NH₃, leading to α-aminophosphorous ylide **4** [20, 21, 22], which then reacted with arylglyoxals **5** to produce intermediate **9** that underwent intramolecular Wittig reaction and then loses a molecule of water and aromatizes to product **6** under reaction condition (Scheme 3).

CONCLUSIONS

In conclusion here we report the reaction between dialkyl acetylene dicarboxylates, ammonium acetate 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 simple conditions but also that the substances can be mixed without any activation or modification.

Acknowledgements

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

Received: Jun. 30, 2016; Accepted: Jan. 9, 2017

REFERENCES

- [1] Gribble G.W., In: "Comprehensive Heterocyclic Chemistry I", Vol. 2; Katritzky A. R., Rees C. W., Scriven E. F. V., Eds., Elsevier: Oxford, 207(1996).
- [2] Jones R.A., Bean G.P., "The Chemistry of Pyrroles"; Academic Press: London, 1(1977).
- [3] Bean G.P., In: "The Chemistry of Heterocyclic Compounds"; Jones A. R. Ed.; Wiley: New York, Vol. 48, Part 1, Chapter 2, p 105(1990).
- [4] (a) Fan H., Peng J., Hamann M.T., Hu J.F., [Lamellarins and Related Pyrrole-Derived Alkaloids From Marine Organisms](#), *Chem. Rev.*, **108**(1): 264-287(2008).
- (b) Estevez V., Villacampa M., Menendez J.C., [Multicomponent Reactions for the Synthesis of Pyrroles](#), *Chem. Soc. Rev.*, **39**: 4402-4421(2010).
- [5] Dieter R.K., Yu H., [A Facile Synthesis of Polysubstituted Pyrroles](#), *Org. Lett.*, **2**(15): 2283-2286 (2000).
- [6] Iwasawa N., Maeyama K., Saitou M., [Reactions of Propargyl Metallic Species Generated by the Addition of Alkynyllithiums to Fischer-Type Carbene Complexes](#), *J. Am. Chem. Soc.*, **119**(6): 1486-1487 (1997).
- [7] Furstner A., Weintritt H., Hupperts, A., [A New Titanium-Mediated Approach to Pyrroles: First Synthesis of Lukianol a and Lamellarin-o-Dimethyl Ether](#), *J. Org. Chem.*, **60**: 6637-6641(1995).
- [8] Katritzky A.R., Jiang J., Steel J., [1-Aza-1,3-Bis\(triphenylphosphoranylidene\)propane: A Novel: CHCH₂N: Synthone](#), *J. Org. Chem.*, **59**(16):4551-4555 (1994).
- [9] Chen N., Lu Y., Cadamasetti K., Hurt C.R., Norman M.K., Fotsch C., [A Short, Facile Synthesis of 5-Substituted 3-Amino-1H-pyrrole-2-carboxylates](#), *J. Org. Chem.*, **65**(8): 2603-2605 (2000).
- [10] Bharadwaj A.R., Scheidt K.A., [Catalytic Multicomponent Synthesis of Highly Substituted Pyrroles Utilizing a One-Pot Sila-Stetter/Paal-Knorr Strategy](#), *Org. Lett.*, **6**(23):2465-2468 (2004).
- [11] Chien T.C., Meade E.A., Hinkley J.M., Townsend L.B., [Facile Synthesis of 1-Substituted 2-Amino-3-Cyanopyrroles: New Synthetic Precursors for 5,6-Unsubstituted Pyrrolo\[2,3-d\]Pyrimidines](#), *Org. Lett.*, **6**(17) : 2857-2859 (2004).
- [12] Nair V., Nair J.S., Vinod A.U., Rath N.P., [Triphenylphosphine Promoted Addition of Dimethyl Acetylenedicarboxylate to 1, 2-Benzoquinones: Facile Synthesis of Novel \$\gamma\$ -Spirolactones](#), *J. Chem. Soc. Perkin Trans 1*, 3129-3130 (1997).
- [13] Anary-Abbasinejad M., Anaraki-Ardakani H., Hosseini-Mehdiabad H., [One-Pot Synthesis of Stable Phosphorus Ylides by Three-Component Reaction between Dimethyl Acetylenedicarboxylate, Semicarbazones, and Triphenylphosphine](#), *Phosphorus, Sulfur and Silicon*, **188**: 1440-1446 (2008).
- [14] Yavari I., Hekmat-Shoar R., Zonouzi A., [A New and Efficient Route to 4-Carboxymethylcoumarins Mediated by Vinyl Triphenylphosphonium Salt](#), *Tetrahedron Lett.*, **39**(16): 2391-2392 (1998).
- [15] Yavari I., Adib M., Hojabri L., [Vinyltriphenylphosphonium Salt Mediated Serendipitous Synthesis of Arylimin Ophosphoranes](#), *Tetrahedron*, **58**:7213-7219 (2002).
- [16] (a) Kamijo S., Kanazawa C., Yamamoto Y., [Copper- or Phosphine-Catalyzed Reaction of Alkynes with Isocyanides. Regioselective Synthesis of Substituted Pyrroles Controlled by the Catalyst](#), *J. Am. Chem. Soc.*, **127**(25):9260-9266 (2005).
- (b) Kamijo S., Kanazawa C., Yamamoto Y., [Phosphine-Catalyzed Regioselective Heteroaromatization between Activated Alkynes and Isocyanides Leading to Pyrroles](#), *Tetrahedron Letters*, **46**(52) :2563-2566 (2005).
- [17] Maghsoodlou M.T., Rostami Charati F., Habibi Khorassani S.M., Khosroshahrodi M., Makha M., [Synthesis of Pyrrole Phosphonate Esters: Emphasis on Pyrrole NH Acids and Dialkylacetylenic Esters Substitution](#), *Iran. J. Chem. Chem. Eng. (IJCCE)*, **27**(1): 105-113 (2008).

- [18] Anaraki-Ardakani H., Mosslemin M.H., Anary-Abbasinejad M., Mirhosseini S.H., Shams N., [A Facile Route to the Synthesis of Polyfunctionalized Pyrroles](#), *Arkivoc*, **xi**: 343-349(2010).
- [19] Anaraki-Ardakani H., Noei M., Tabarzad A., [Facile Synthesis of N-\(arylsulfonyl\)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylates by One-Pot Three-Component Reaction](#), *Chinese Chemical Letters*, **23**(1):45-48(2012).
- [20] Azizian J., Karimi A. R., Arefrad H., Mohammadi A.A., Mohammadizadeh M.R., [A Novel One-Pot, Four Component Synthesis of Some Densely Functionalized Pyrroles](#), *Molecular Diversity*, **6**: 223-226 (2003).
- [21] Kassae M.Z., Masrouri H., Movahedi F., Partovi T., [One-Pot Four-Component Synthesis of Tetrasubstituted Pyrroles](#), *Helvetica Chimica Acta*, **91**(2): 227-231 (2008).
- [22] Azizian J., Hosseini J., Mohammadi M. k., Sheikholeslami F., [Efficient Route for the Synthesis of Highly Substituted Pyrroles](#), *Synthetic Communications*, **40**(23): 3472-3479 (2010).
- [23] Anaraki-Ardakani H., Hassanabadi A., Fazilnia A., Tabarzad A., Heidari-Rakati T., [A Facile Route to the Synthesis of 2,5-Dihydropyrrole Derivatives](#), *Journal of Chemical Research*, **38**(1) 9-11(2014).
- [24] Anary-Abbasinejad M., Dehghanpour-Farashah H., Hassanabadi A., Anaraki-Ardakani, H., Shams N., [Three-Component Reaction of Triphenylphosphine, Dialkyl Acetylenedicarboxylate, and 2-Aminothiazole or 2-Aminobenzothiazole in the Presence of Arylglyoxals: An Efficient One-Pot Synthesis of Highly Functionalized Pyrroles](#), *Synth. Commun.*, **42**:1877-1884(2012).
- [25] Arduengo A.J., Stewart C.A., Low Coordinate Hypervalent Phosphorus, *Chem. Rev.*, **94**, 1215-1237(1994).
- [26] Yavari I., Khorramabadi-Zad A., Rashidi-Ranjbar P., Fallah-Bagher-Shaidaii H., [Reaction between Trimethyl Phosphite and Dimethyl Acetylenedicarboxylate in the Presence of 5,5-Dimethylcyclohexane-1,3-Dione](#), *J. Mol. Struct. (Theochem)* **389**(1):155-158 (1977).
- [27] Burgada R., Leroux Y., Khoshnieh Y.O.E., [Synthese et Structure d'un Trialkoxy-1,1,1 Phospholev Premier Modele Pentacoordine Contenant Le Cycle Phosphole](#), *Tetrahedron Lett.*, **22**:3533-3536 (1981).
- [28] Cadogan J.I.G., "Organophosphorus Reagents in Organic Synthesis", Academic Press, New York, (1979).