A Phosphine-mediated Synthesis of 2,3,4,5-tetra-substituted N-hydroxypyrroles from α-oximino Ketones and Dialkyl Acetylenedicarboxylates under Ionic Liquid Green-media

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Abstract: Background: The development of multicomponent reactions (MCRs) in the presence of task-specific ionic liquids (ILs), used not only as environmentally benign reaction media, but also as catalysts, is a new approach that meet with the requirements of sustainable chemistry. In recent years, the use of ionic liquids as a green media for organic synthesis has become a chief study area. This is due to their unique properties such as non-volatility, non-flammability, chemical and thermal stability, immiscibility with both organic compounds and water and recyclability. Ionic liquids are used as environmentally friendly solvents instead of hazardous organic solvents.

Objective: We report the condensation reaction between α-oximino ketone and dialkyl acetylenedicarboxylate in the presence of triphenylphosphine to afford substituted pyrrolyl acetylenedicarboxylates under ionic liquid conditions in good yields.

Result: Densely functionalized pyrrolyl acetylenedicarboxylates was easily prepared from reaction of α-oximino ketones, dialkyl acetylenedicarboxylate in the presence of triphenylphosphine in a quantitative yield under ionic liquid conditions at room temperature.

Conclusion: In conclusion, ionic liquids are indicated as a useful and novel reaction medium for the selective synthesis of functionalized pyrroles. This reaction medium can replace the use of hazardous organic solvents. Easy work-up, synthesis of polyfunctional compounds, decreased reaction time, having easily available-recyclable ionic liquids, and good to high yields are advantages of present method.

Keywords: Dialkyl acetylenedicarboxylate, α-oximino ketone, N-hydroxypyrroles, ionic liquid, tandem reaction, β-dicarbonyl compounds, green media, phosphine-mediated synthesis.

1. INTRODUCTION

Pyrole nuclei are important chemical cores found in natural products [1] and pharmaceuticals [2]. They are useful as reagents, catalysts, and substances in the context of organic synthesis [3]. The pyrrole scaffold has received much attention in material science because of its special optical and electronic properties [4]. Polysubstituted pyrroles play important roles as promising pharmacophores in medicinal chemistry [5].

Accordingly, substantial attention is paid to develop efficient methods for their synthesis. The commonly used methods are Hantzsch [6], Knorr [7], Paal–Knorr [8] and Clausen Kaas condensation reactions [9]. Moreover, the application of multi-component reactions for the synthesis of pyrrole derivatives has been recently reviewed [10]. Although, many of these methods are quite useful, a general facile and regioselective approach to generate pyrroles with a wide functional group tolerance from readily available precursors is still lacking. Reactions of oxime and dialkyl acetylenedicarboxylate in the presence of various nucleophiles have recently been reported for the synthesis of poly-functionalized pyrroles [11]. In continuation of our studies in using according to green chemistry for the synthesis of organic compounds [12], herein, we report the condensation reaction between α-oximino ketone [13] and dialkyl acetylenedicarboxylate in the presence of triphenylphosphine to afford substituted pyrrolyl acetylenedicarboxylates under ionic liquid conditions in good yields. The advantages of the present procedure are decrease reaction time, high yield products, green and recyclable solvent for the synthesis of oximes and pyrroles.
2. MATERIALS AND METHODS

2.1. Experimental

Oximes 2a-m were generated from nitrosation of β-dicarbonyl compounds by NaNO2 under acidic ionic liquid conditions. Sodium nitrite, β-dicarbonyl compounds, triphenylphosphine and dialkyl acetylenedicarboxylates were obtained from fluka and were used without further purification. The ILs 1-methyl-3-butylimidazolium bromide ([mbim] Br) and 1-methyl-3-carboxymethylimidazolium chloride, used in this study, were synthesized according to the procedure reported in the literature [14].

To a stirred solution of 1 mmol of β-dicarbonyl compounds 1 in 1 mL 1-methyl-3-carboxymethylimidazolium chloride, NaNO2 (1 mmol in 1 mL of water) was added dropwise. The reaction mixture was further stirred at room temperature for 0.5 h. After completion of the reaction, the product was extracted with EtOAc (3× 10 mL). After drying (ethyl acetate) over sodium sulfate and solvent evaporation under reduced pressure, oxime 2 was obtained and used in the next step without further purification. The ionic liquid can be extracted from the aqueous phase with methylene dichloride and dried at room temperature for 0.5 h. After completion of the reaction, 5 mL of water was added and the mixture was extracted from the aqueous phase with ethyl acetate (3× 10 mL). After drying (ethyl acetate) over sodium sulfate and solvent evaporation under reduced pressure, oxime 2 as an oily residue was obtained and used in the next step without further purification. The liquid ion can be reused after extraction from the aqueous phase.

2.1.5. Diethyl 5-benzoyl-1-hydroxy-4-methyl-1H-pyrrole-2,3-dicarboxylate (5b)

White powder, mp 99-101ºC; yield: 0.37 g (92%). IR (KBr) (νmax/cm−1): 3437, 1724, 1676, 1516, 1370, 1216, 1194. 1H NMR (300 MHz, CDCl3): δ = 1.33 (3 H, t, , J = 7.1, Me), 1.42 (3 H, t, J = 7.1, Me), 4.30 (2 H, q, J = 7.1, OCH2), 12.35 (1H, brs, NOH). 13C NMR (75 MHz, CDCl3): δ = 25.8 (CH), 129.7 (C), 128.2 (2 CH), 128.5 (2 CH), 129.0(CH), 130.1 (2 CH), 130.4 (2 CH), 132.1 (C), 133.6 (CH), 137.2 (C), 165.2 (C=O), 187.0 (C=O). MS (m/z, %): 379, 363, 348, 347, 333, 317, 273, 245. Anal. Calcd for C21H19NO6: C, 66.22; H, 4.65; N, 3.83. Found: C, 66.22; H, 4.52; N, 3.69.

2.1.6. Dimethyl 5-benzoyl-1-hydroxy-4-phenyl-1H-pyrrole-2,3-dicarboxylate (5c)

White powder, mp 98-99ºC; yield: 0.26 g (92%). IR (KBr) (νmax/cm−1): 3347, 1726, 1686, 1542, 1307, 1226. 1H NMR (300 MHz, CDCl3): δ = 2.10 (3 H, s, Me), 3.84 (3 H, s, OMe), 4.01 (3 H, s, OMe), 7.52 (2 H, t, J = 7.6, 2 CH), 7.65 (1 H, t, J = 7.6, CH), 7.73 (2 H, d, , J = 7.6, 2 CH), 12.84 (1 H, brs, NOH). 13C NMR (75 MHz, CDCl3): δ = 13.1 (Me), 52.2 (OMe), 53.6 (OMe), 112.0 (C), 124.1 (C), 124.4 (C), 126.7 (C), 129.0 (2 CH), 129.4 (2 CH), 133.6 (CH), 138.0 (C), 161.1 (C=O), 164.1 (C=O), 190.2 (C=O). Anal. Calcd for C18H16NO6: C, 70.97; H, 5.47; N, 4.45. Found: C, 70.52; H, 5.46; N, 4.45.

2.1.7. Diethyl 5-benzoyl-1-hydroxy-4-phenyl-1H-pyrrole-2,3-dicarboxylate (5d)

White powder, mp 99-101ºC; yield: 0.37 g (94%). IR (KBr) (νmax/cm−1): 3297, 1734, 1665, 1607, 1432, 1370, 1216. 1H NMR (300 MHz, CDCl3): δ = 1.33 (3 H, t, , J = 7.1, Me), 1.42 (3 H, t, J = 7.1, Me), 4.30 (2 H, q, J = 7.1, OCH2), 4.43 (2 H, q, J = 7.1, OCH2), 7.07-7.64 (10 H, m, 10 CH), 12.95 (1H, brs, NOH). 13C NMR (75 MHz, CDCl3): δ = 14.4 (Me), 14.6 (Me), 61.0 (OCH2), 62.9 (OCH2), 112.0 (C), 124.6 (C), 126.5 (C), 129.0 (C), 129.4 (2 CH), 133.4 (2 CH), 138.1 (CH), 138.6 (C), 160.9 (C=O), 163.7 (C=O), 190.0 (C=O). MS (m/z, %): 285, 238, 237, 206, 162, 133. MS (m/z, %): 345, 300, 299, 254, 214, 186. Anal. Calcd for C19H18NO6: C, 70.97; H, 5.47; N, 4.45. Found: C, 70.52; H, 5.46; N, 4.45.
2.1.9. Triethyl 1-hydroxy-4-methyl-1H-pyrrole-2,3,5-tricarboxylate (5f)

White powder, mp 84-86ºC; yield: 0.24 g (95%). IR (KBr) (ν max/cm⁻¹): 3320, 1730, 1712, 1645, 1542, 1307, 1226. 1H NMR (300 MHz, CDCl₃): δ = 1.36 (3 H, t, J = 7.1, Me), 1.39 (3 H, t, J = 7.1, Me), 1.43 (3 H, t, J = 7.1, Me), 2.48 (3 H, s, Me), 4.28 (2 H, q, J = 7.1, OCH₂), 4.34-4.48 (4 H, m, OCH₂), 12.50 (1H, brs, OH). 13C NMR (75 MHz, CDCl₃): δ = 11.7 (Me), 14.4 (Me), 14.5 (Me), 25.6 (Me), 61.0 (OCH₂), 62.4 (OCH₂), 62.7 (OCH₂), 111.2 (C), 114.4 (C), 124.2 (C), 126.1 (C), 160.3 (C=O), 164.0 (C=O), 164.9 (C=O). MS (m/z, %): 255, 267, 251, 206, 178. Anal. Calcd for C₁₃H₂₈NO₈ (313.12): C, 55.12; H, 6.05; N, 4.47. Found: C, 53.20; H, 6.07; N, 4.77.

2.1.10. Dimethyl 5-acyl-1-hydroxy-4-methyl -1H-pyrrole-2,3-dicarboxylate (5g)

White powder, mp 84-86ºC; yield: 0.24 g (95%). IR (KBr) (ν max/cm⁻¹): 3452, 1724, 1638, 1418, 1575, 1227. 1H NMR (300 MHz, CDCl₃): δ = 2.58 (3 H, s, Me), 2.59 (3 H, s, Me), 3.82 (3 H, s, OMe), 3.96 (3 H, s, OMe), 14.16 (1H, brs, OH). 13C NMR (75 MHz, CDCl₃): δ = 12.7 (Me), 29.5 (Me), 52.2 (OMe), 53.5 (Ome), 111.3 (C), 122.8 (C), 124.6 (C), 126.9 (C), 160.5 (C=O), 164.0 (C=O), 194.0 (C=O). MS (m/z, %): 255, 239, 224, 207, 192, 176. Anal. Calcd for C₁₃H₂₈NO₈ (329.09): C, 52.5 (OMe), 53.1 (OMe), 114.5 (C), 122.7 (CH), 123.2 (C), 125.2 (CH), 128.8 (CH), 132.8 (CH), 134.9 (CH), 136.8 (C), 137.2 (C), 141.3 (C=O), 160.8 (C=O), 162.8 (C=O), 205.6 (C=O).MS (m/z, %): 301, 285, 270, 253, 238, 222. Anal. Calcd for C₁₃H₂₈NO₈ (313.12): C, 59.80; H, 3.68; N, 4.65. Found: C, 59.45; H, 3.77; N, 4.54.

3. RESULTS AND DISCUSSION

Densely functionalized pyrroles were easily prepared from the reaction of α-oximinoketones, dialkyl acetylenedicarboxylate in the presence of trialkylphosphine from the reaction of δ = 12.7, Me), 2.59 (3 H, s, Me), 2.60 (3 H, s, Me), 4.29 (2 H, q, J = 7.0, OCH₂), 4.43 (2 H, q, J = 7.0, OCH₂), 14.12 (1H, brs, OH). 13C NMR (75 MHz, CDCl₃): δ = 12.6 (Me), 14.4 (Me), 14.5 (Me), 29.5 (Me), 61.0 (OCH₂), 62.8 (OCH₂), 112.5 (C), 122.7 (C), 124.8 (C), 126.9 (C), 160.2 (C=O), 163.6 (C=O), 193.8 (C=O). MS (m/z, %): 283, 266, 238, 206, 192, 179. Anal. Calcd for C₁₃H₂₈NO₈ (283.11): C, 55.12; H, 6.05; N, 4.94. Found: C, 55.20; H, 6.07; N, 4.77.

2.1.11. Diethyl 5- acetyl-1-hydroxy-4-methyl-1H-pyrrole-2,3-dicarboxylate (5h)

White powder, mp 88-90ºC; yield: 0.25 g (87%). IR (KBr) (ν max/cm⁻¹): 3456, 1738, 1698, 1643, 1542, 1307, 1226. 1H NMR (300 MHz, CDCl₃): δ = 1.33 (3 H, t, J = 7.1, Me), 1.40 (3 H, t, J = 7.1, Me), 2.59 (3 H, s, Me), 2.60 (3 H, s, Me), 4.29 (2 H, q, J = 7.1, OCH₂), 4.43 (2 H, q, J = 7.0, OCH₂), 14.12 (1H, brs, OH). 13C NMR (75 MHz, CDCl₃): δ = 12.6 (Me), 14.4 (Me), 14.5 (Me), 29.5 (Me), 61.0 (OCH₂), 62.8 (OCH₂), 112.5 (C), 122.7 (C), 124.8 (C), 126.9 (C), 160.2 (C=O), 163.6 (C=O), 193.8 (C=O). MS (m/z, %): 283, 266, 238, 206, 192, 179. Anal. Calcd for C₁₃H₂₈NO₈ (283.11): C, 55.12; H, 6.05; N, 4.94. Found: C, 55.20; H, 6.07; N, 4.77.

2.1.12. Dimethyl 1-hydroxy-8-oxo-1,8-dihydroindeno[2,1-b]pyrrole-2,3-dicarboxylate (5i)

White powder, mp 105-107ºC; yield: 0.26 g (86%). IR (KBr) (ν max/cm⁻¹): 3405, 1724, 1702, 1675, 1542, 1307, 1211. 1H NMR (300 MHz, CDCl₃): δ = 3.96 (3 H, s, OMe), 4.06 (3 H, s, OMe), 7.14 (1 H, t, J = 7.6, CH), 7.37 (1 H, t, J = 7.1, CH), 7.44 (1 H, d, J = 7.6, CH), 7.52 (1 H, d, J = 7.1, CH), 9.67 (1 H, brs, NOH). 13C NMR (75 MHz, CDCl₃): δ = 52.5 (OMe), 53.1 (OMe), 114.5 (C), 122.7 (CH), 123.2 (C), 125.2 (CH), 128.8 (CH), 132.8 (CH), 134.9 (CH), 136.8 (C), 137.2 (C), 141.3 (C=O), 160.8 (C=O), 162.8 (C=O), 205.6 (C=O).MS (m/z, %): 301, 285, 270, 253, 238, 222. Anal. Calcd for C₁₅H₁₄NO₈ (301.06): C, 59.80; H, 3.68; N, 4.65. Found: C, 59.45; H, 3.77; N, 4.54.
Scheme 1. Conversion of β-dicarbonyl compounds to tetrasubstituted N-hydroxypyrroles 5.

extensive intramolecular hydrogen-bond formation with the vicinal carbonyl group [17]. The $^{13}$C NMR spectrum of $\text{5a}$ appeared signals for methyl ($\delta = 13.1$ Me-pyrrole ring); and two methoxy at $\delta = 52.2$ and $53.6$ ppm, four signals at $\delta = 112.0, 123.6, 124.1$ and $124.4$ pyrrole ring Cs. along with four signals at $\delta = 129.0, 129.4, 133.4$ and $138.0$ ppm for phenyl group. The chemical shifts of the ester carbonyl groups at $161.1$ and $164.1$ proved the unsymmetrical structure of $\text{5a}$. The signal for ketone carbonyl group appeared at $\delta = 190.2$ ppm.
The mass spectrum of 5a displayed the molecular ion peak at m/z = 317. The 1H and 13C NMR spectra of 5b-5j were similar to those of 5a, except for the side chains, which exhibited characteristic signals with appropriate chemical shifts (See Experimental Section).

Finally, the recyclability of ionic liquid [bmim]Br was examined in the synthesis of 5-acetyl-1-hydroxy-4-methyl-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester 5g. It was recovered from the reaction mixture by extraction with water. After evaporation of the water under reduced pressure, it was reused three times for the synthesis of 5g. In the second run, 5g was obtained in 89% yield, and that reduced to 88% in the third run.

CONCLUSION

In conclusion, ionic liquids are indicated as a useful and novel reaction medium for the selective synthesis of functionalized pyrroles. This reaction medium can replace the use of organic solvents such as acetonitrile, dichloromethane, and chloroform. Easy work-up, synthesis of polyfunctional compounds, decreased reaction time, having easily available-recyclable ionic liquids, and good to high yields are advantages of the present method. We believe the chemistry will afford efficient production of more complex pyrrole derivatives.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


