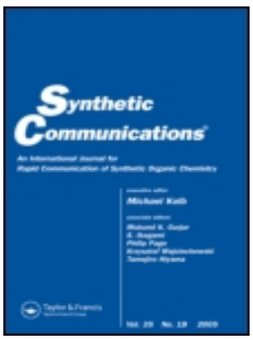

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REGIOSELECTIVE SYNTHESIS OF INDOLIZINES, PYRROLO[2,1-*a*]ISOQUINOLINES, AND QUINOLINES

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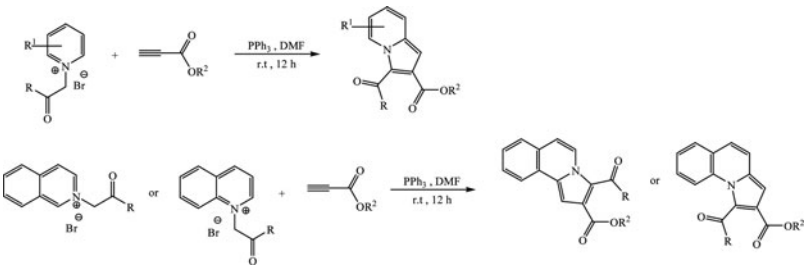
GRAPHICAL ABSTRACT



Abstract *Convenient and regioselective synthesis of indolizine and pyrrolo[2,1-a] isoquinoline/quinoline derivatives by one-pot multicomponent reaction of* N*-substituted pyridinium and isoquinolinum/quinolinium salts with alkyl propiolates in the presence triphenylphosphine is described.*

Keywords Indolizine; pyrrolo[2,1-a]isoquinoline; pyrrolo[2,1-a]quinoline; regioselective synthesis

INTRODUCTION

The development of efficient and versatile strategies for the synthesis of heterocycles is one of the top challenges in organic synthesis because most of the biologically active compounds produced by nature contain a heterocyclic scaffold as a fundamental unit in their structure.[1] Of these heterocycles, the indolizine motif is a bicyclic system in natural products, pharmaceuticals, and biologically active molecules such as aromatase inhibitory,[2] anti-inflammatory,[3] antitumor,[4] and antitubercular pharmaceuticals.[5] On the other hand, these azabicyclic compounds exhibit interesting electronic properties and are attractive molecules in theoretical chemistry.[6] Indolizines have emerged as important synthetic targets because of their potential applications. As a consequence, the development of new and general

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methods for their preparation is of significant interest.[7] The most important methods for the preparation of indolizine rings can be classified mainly as the cycloaddition reaction,[8] Tschirschibabin reaction,[9] and transition-metal-catalyzed cycloisomerization.[10] Among the currently used strategies to develop the new heterocyclic compounds, multicomponent condensation reactions offer a valuable solution for this area because of their inherent atom efficiency, time and energy savings, diversity with minimum waste, and ease of implementation.[11] Of the previously reported methods for the synthesis of indolizines and pyrrolo[2,1-*a*]isoquinolines/quinolines, the reaction pyridinium, isoquinolinum, or quinolinium salts with alkenes using ion-exchange resin as the base in the presence of oxidizing agent in a one-pot reaction is one of the most attractive routes because of biological applications of this new reaction products.[12] Therefore, in continuation of our interest in the development of new methods for the synthesis of these heterocyclic systems, we now describe a regioselective synthesis of the functionalized indolizines, pyrrolo[1,2-*a*]isoquinolines, and pyrrolo[2,1-*a*]quinolines in a new multicomponent reaction from simple starting materials, which proceeds in good yields.

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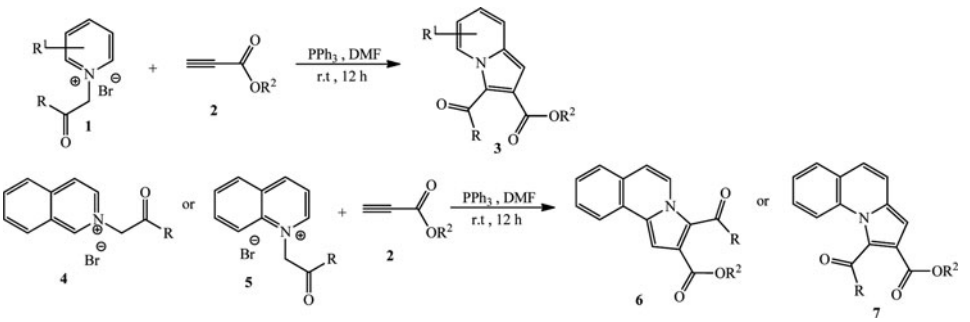
RESULTS AND DISCUSSION

In a pilot experiment, a solution of alkyl propiolates **2** and *N*-substituted pyridinium (**1**), isoquinolinum (**4**), or quinolinium (**5**) salts in dimethylformamide (DMF) were reacted with a stoichiometric amount of triphenylphosphine at room temperature for 12 h (Scheme 1). After screening with various amounts of triphenylphosphine, the best results were obtained in DMF at rt for 12 h in the presence of stoichiometric amounts of PPh_3. Purification of the reaction mixtures by SiO_2 column chromatography afforded the functionalized indolizines **3**, pyrrolo[2,1-*a*]isoquinolines **6,** or pyrrolo[1,2-*a*]quinolines **7** (Fig. 1). The structures of the indolizines and pyrrolo[1,2-*a*]isoquinoline/quinoline derivatives were established on the basis of their infrared (IR), ^{1}H NMR, and ^{13}C NMR spectra. For example, the IR spectrum of **3a** exhibited characteristic ester carbonyl bands at 1725 cm^{-1}. Characteristic signals in ^{1}H NMR spectrum of **3a** showed ethoxy group at 4.28 as a quartet (^3J = 7.2 Hz) and methoxy group at 3.83 as singlet. The aryl protons exhibited characteristic signals in the aromatic region of the spectrum. The ^{13}C resonance signals of the



Scheme 1.

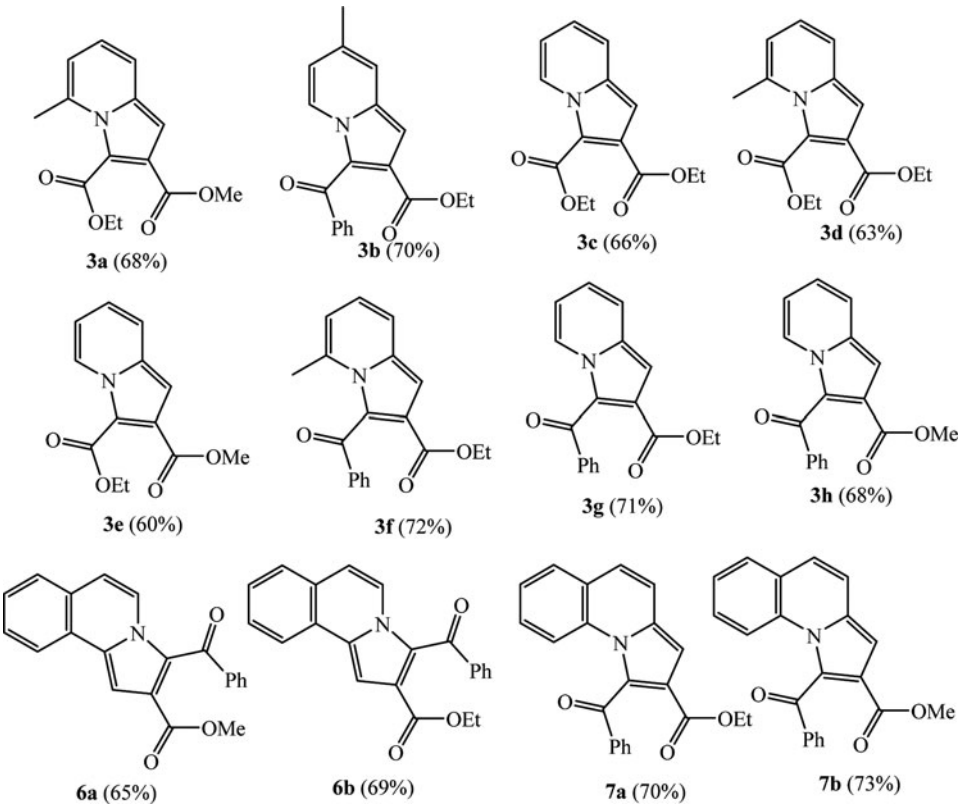


Figure 1.

two carbonyl groups were seen at δ 160.7 and 164.5 whereas the methyl signal was observed at 22.6 ppm. Partial assignment of these data is given in the experimental section.

A possible mechanistic pathway for the formation of products **3** is shown in Scheme 2. The initial addition results in the formation of zwitterion **8** from the triphenylphosphine and alkyl propiolate **2**, which is subsequently protonated by pyridinium salt **1**. Next, the positively charged ion **10** is attacked by nucleophilic addition of pyridinium ylide **9** to form **11**, which then undergoes cyclization to produce the primary adduct **13** by eliminiation of PPh_3 and proton from cation **12**. The aromatization completes the reaction sequence, leading to the final product **3** via elimination of hydrogen molecule.

In conclusion, we have devised a novel synthesis of functionalized indolizines and pyrrolo[1,2-*a*]isoquinolines/quinolines by triphenylphosphine-mediate reaction of *N*- functionalized pyridinium, isoquinolinum, or quinolinium salts with alkyl propiolates. The simple purification, high regioselectivity, and good yield of products are advantages of this new method. It is conceivable that the regioselective synthesis of substituted indolizine derivatives may be amenable to a number of potentially useful synthetic transformations.

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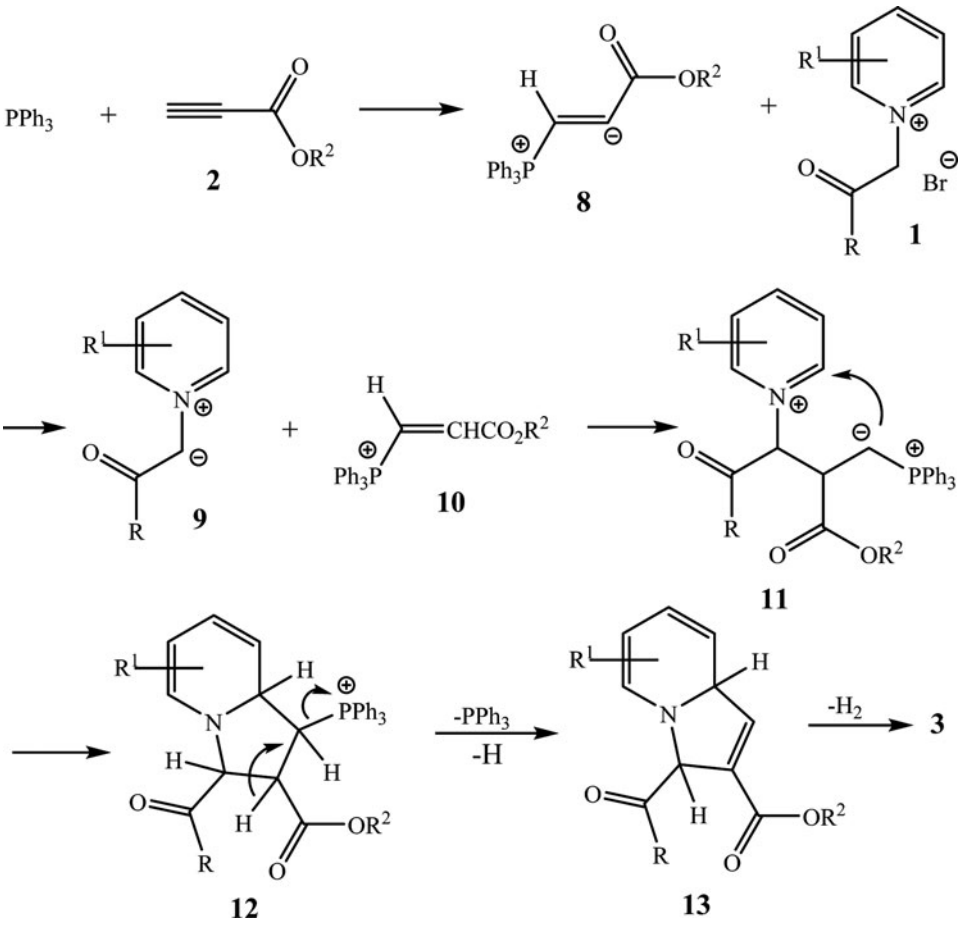

Scheme 2.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware. Progress of the reaction was monitored by thin-layer chromatography (TLC), while the reaction mixture was purified by column chromatography, using silica gel (Merck 230–240 mesh). Melting points were determined on an Electrothermal-9100 apparatus. IR spectra were recorded on a Shimadzu-IR-460 spectrometer, absorbances are reported in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solvent) with a Bruker DRX-400 Avance instrument at 400.1 and 100.6 MHz, respectively. Elemental analysis was carried out using a Vario EL III CHNOS elemental analyzer. Mass spectra were recorded on a Finnigan-MAT-8430EI-MS mass spectrometer.

General Procedure for the Preparation of 3, 6, and 7

A solution of alkyl propiolate **2** (1 mmol) in 2 mL DMF was added to a magnetically stirred solution of *N*-functionalized pyridinium, isoquinolinum, or

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quinolinium salt **1, 4**, or **5** (1 mmol) and triphenylphosphine (1 mmol) in 3 mL DMF at −5 to 0 °C temperature. The reaction mixture was stirred for 12 h, and then the mixture was poured onto H_2O (5 mL), extracted with AcOEt (15 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–ethyl acetate mixture as eluent. In addition, Compounds **3 g, 3 h, 6,** and **7** have been reported in the literature.[12]

3-Ethyl 2-Methyl-5-methylindolizine-2,3-dicarboxylate (3a)

Colorless oil. yield: 0.17 g (68%). IR (KBr) (ν_{max}/cm^{-1}): 1725 (COO). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.34$ (3 H, t, $^3J = 7.2$ Hz, Me), 2.64 (3 H, s, Me), 3.83 (3 H, s, OMe), 4.28 (2 H, q, $^3J = 7.2$ Hz, OCH_2), 6.71 (1 H, d, $^3J = 7.2$ Hz, CH), 7.19–7.22 (1 H, m, CH), 7.89 (1 H, s, CH), 8.21 (1 H, d, $^3J = 8.8$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.3$ (Me), 22.6 (Me), 51.1 (OMe), 60.8 (OCH_2), 104.5 (C), 116.2 (CH), 117.2 (CH), 126.1 (CH), 126.7 (CH), 134.6 (C), 138.8 (C), 141.2 (C), 160.7 (C=O), 164.5 (C=O). MS m/z 261 (M^+, 28), 131 (38), 117(100). Anal. calcd. for $C_{14}H_{15}NO_4$(261.28): C 64.36, H 5.79, N 5.36%. Found: C 64.74, H 5.68, N 5.42%.

Ethyl 3-Benzoyl-7-methylindolizine-2-carboxylate (3b)

White powder, mp 87–89 °C. yield: 0.21 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 1714 (COO), 1675 (CO). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.41$ (3 H, t, $^3J = 7.2$ Hz, Me), 2.51 (3 H, s, Me), 4.40 (2 H, q, $^3J = 7.2$ Hz, OCH_2), 6.94 (1 H, dd, $^3J = 6.8$ Hz, $^4J = 2.4$ Hz, CH), 7.50-7.58 (3 H, m, 3 CH), 7.79 (1 H, s, CH), 7.82–7.84 (2 H, m, 2 CH), 8.21 (1 H, s, CH), 9.88 (1 H, d, $^3J = 6.8$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.5$ (Me), 22.7 (Me), 59.9 (OCH_2), 114.0 (C), 117.7 (CH), 118.2 (CH), 128.3 (2 CH), 128.6 (CH), 128.9 (2 CH), 129.2 (CH), 131.3 (CH), 139.2 (C), 139.4 (C), 140.0 (C), 140.4 (C), 164.2 (C=O), 185.2 (C=O). MS m/z 307 (M^+, 25), 262 (40), 77 (100). Anal. calcd. for $C_{19}H_{17}NO_3$(307.34): C 74.25, H 5.58, N 4.56%. Found: C 74.65, H 5.42, N 4.60%.

Diethylindolizine-2,3-dicarboxylate (3c)

Colorless oil. Yield: 0.17 g (66%). IR (KBr) (ν_{max}/cm^{-1}): 1709 (COO). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.32$–1.37 (6 H, m, 2 Me), 4.29–4.35 (4 H, m, 2 OCH_2), 6.88–6.92 (1 H, m, CH), 7.22–7.26 (1 H, m, CH), 7.92 (1 H, s, CH), 8.25–8.28 (1 H, m CH), 9.45 (1 H, d, $^3J = 7.2$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (Me), 14.2 (Me), 59.9 (OCH_2), 60.2 (OCH_2), 114.3 (CH), 119.5 (CH), 124.2 (CH), 125.5 (CH), 127.9 (CH), 132.0 (C), 133.0 (C), 139.0 (C), 161.2 (C=O), 164.2 (C=O). MS m/z 261 (M^+, 15), 117 (100). Anal. calcd. for $C_{14}H_{15}NO_4$(261.27): C 64.36, H 5.79, N 5.36%. Found: C 64.49, H 5.64, N 5.41%.

Diethyl 5-Methylindolizine-2,3-dicarboxylate (3d)

Colorless oil. yield: 0.17 g (63%). IR (KBr) (ν_{max}/cm^{-1}): 1709 (CO). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.34$ (6 H, t, $^3J = 7.2$ Hz, 2 Me), 2.63 (3 H, s, Me), 4.25–4.37

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(4 H, m, 2 OCH_2), 6.71 (1 H, d,$^3J = 6.8$ Hz, CH), 7.21 (1 H, t,$^3J = 7.2$ Hz, CH), 7.90 (1 H, s, CH), 8.23 (1 H, d,$^3J = 8.4$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.4$ (Me), 14.5 (Me), 22.6 (Me), 59.8 (OCH_2), 60.8 (OCH_2), 116.2 (CH), 117.2 (CH), 126.0 (CH), 126.7 (CH), 128.5 (C), 134.4 (C), 138.8 (C), 141.2 (C), 160.7 (C=O), 164.1 (C=O). MS m/z 275 (M^+, 18), 131 (45), 117 (100). Anal. calcd. for $C_{15}H_{17}NO_4$(275.30): C 65.44, H 6.22, N 5.09%. Found: C 65.71, H 6.27, N 5.13%.

3-Ethyl 2-Methylindolizine-2,3-dicarboxylate (3e)

Colorless oil. Yield: 0.14 g (60%). IR (KBr) (ν_{max}/cm^{-1}): 1715 (COO). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.33$ (3 H, t,$^3J = 7.2$ Hz, Me), 3.84 (3 H, s, OMe), 4.31 (2 H, q,$^3J = 7.2$ Hz, OCH_2), 6.89–6.92 (1 H, m, CH), 7.22–7.26 (1 H, m, CH), 7.92 (1 H, s, CH), 8.26 (1 H, d,$^3J = 8.8$ Hz, CH), 9.45 (1 H, d,$^3J = 7.2$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (Me), 51.2 (OMe), 60.3 (OCH_2), 114.4 (CH), 119.5 (CH), 124.2 (CH), 125.6 (CH), 127.9 (CH), 130.8 (C), 134.6 (C), 139.0 (C), 161.1 (C=O), 164.6 (C=O). MS m/z 247 (M^+, 20), 216 (35), 117 (100). Anal. calcd. for $C_{13}H_{13}NO_4$(247.25): C 63.15, H 5.30, N 5.67%. Found: C 63.26, H 5.24, N 5.72%.

Ethyl 3-Benzoyl-5-methylindolizine-2-carboxylate (3f)

White powder, mp 86–89 °C. Yield: 0.22 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1710 (COO), 1680 (CO). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.39$ (3 H, t,$^3J = 7.2$ Hz, Me), 2.62 (3 H, s, Me), 4.37 (2 H, q,$^3J = 7.2$ Hz, OCH_2), 6.93 (1 H, d,$^3J = 6.8$ Hz, CH), 7.28–7.44 (1 H, m, CH), 7.52–7.56 (2 H, m, 2 CH), 7.62–7.66 (1 H, m, CH), 7.75 (1 H, s, CH), 8.04–8.07 (2 H, m, 2 CH), 8.39 (1 H, d,$^3J = 8.4$ Hz, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.5$ (Me), 23.2 (Me), 59.9 (OCH_2), 105.4 (C), 116.7 (CH), 117.1 (CH), 125.4 (C), 127.4(CH), 128.4 (2 CH), 129.6 (CH), 130.2 (2 CH), 132.5 (CH), 138.5 (C), 139.8 (C), 141.8 (C), 164.1 (C=O), 182.9 (C=O). MS m/z 307 (M^+, 41), 77 (100). Anal. calcd. for $C_{19}H_{17}NO_3$(307.12): C 74.25, H 5.58, N 4.56%. Found: C 74.63, H 5.45, N 4.38%.

SUPPLEMENTAL MATERIAL

Full experimental details and ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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