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Short Note

Methyl 3-(Quinolin-2-yl)indolizine-1-carboxylate

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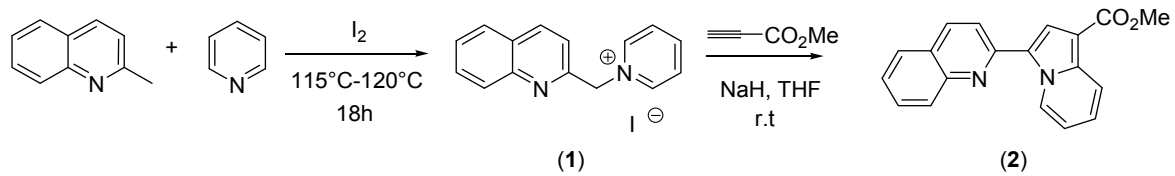
Abstract: A novel compound, methyl 3-(quinolin-2-yl)indolizine-1-carboxylate (**2**) has been synthesized by cycloaddition reaction of 1-(quinolin-2-ylmethyl)pyridinium ylide (**1**) with methyl propiolate in presence of sodium hydride in THF. The structure of this compound was established by IR, ^{1}H-NMR, ^{13}C-NMR and MS data.

Keywords: quinoline; cycloaddition; indolizine

1. Introduction

Indolizines are aromatic organic compounds containing condensed five and six-membered rings with bridging nitrogen (isomer of indole) [1]. Heterocycles, possessing indolizine core have also found numerous biological and pharmacological activities, such as anti-inflammatory [2,3], antiviral [4], aromatase inhibitory [5], analgestic [6], antitumor [7,8] activities. Some methods for the synthesis of various types of indolizines and benzoindolizines have been well reviewed in the literature, such as the condensation reactions [9], 1,3-dipolar cycloadditions [10,11], and 1,5-dipolar cyclizations [12]. Among these, the 1,3-dipolar cycloaddition of *N*-pyridinium ylide and related heteroaromatic ylides, e.g., quinolinium or isoquinolinium ylides, with various dipolarophiles, is one of the simplest approaches for the construction of indolizine ring [13–15].

In continuation of our research interest in heteroaromatic *N*-ylide [16,17], we report here our result concerning the reactivity of 1-((quinol-2-yl)methyl) pyridinium ylide toward methyl propiolate as dipolarophile. Indolizine derivative (**2**) containing a quinoline unit was achieved as a result of this reaction. The position of the ester group on the new heterocyclic ring could not be determined efficiently by NMR spectroscopy. However, it has been established by analogy and by comparison with previous reported compounds [17].



Scheme 1. The synthesis of methyl 3-(quinolin-2-yl)indolizine-1-carboxylate (**2**).

2. Experimental Section

2.1. General Information

The starting materials were generally used as received (Acros, Fontenay-sous-Bois, France) without any further purification. THF was freshly distilled from sodium/benzophenone. Melting point was determined on an Electrothermal Digital Melting Points Apparatus IA 9200 (Mentouri University, Constantine, Algeria) and is uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brüker Avance DPX250 spectrometers (Mentouri university, Constantine, Algeria). The purity of the final compound (greater than 95%) was determined by HPLC/MS on an Agilent 1290 system (Lyon 1 University, Lyon, France) using a Agilent 1290 Infinity ZORBAX Eclipse Plus C18 column (2.1 mm × 50 mm, 1.8 µm particle size) with a gradient mobile phase of H_2O/CH_3CN (90:10, *v*/*v*) with 0.1% of formic acid to H_2O/CH_3CN (10:90, *v*/*v*) with 0.1% of formic acid at a flow rate of 0.5 mL/min, with UV monitoring at the wavelength of 254 nm with a run time of 10 min. 1-((Quinol-2-yl)methyl) pyridinium iodide (**1**) was synthesized following a literature procedure starting from quinaldine and its structure has been confirmed by spectroscopic methods [18].

2.2. Synthesis of Methyl 3-(Quinolin-2-yl)indolizine-1-carboxylate (**2**)

To a suspension of 50 % sodium hydride dispersion in mineral oil (30 mg, 1.25 mmol) placed in 10 mL of tetrahydrofurane, was added, at 0 °C, 348 mg (1 mmol) of 1-((quinol-2-yl)methyl) pyridinium iodide (**1**) and 126 mg (1.5 mmol) of methyl propiolate. The ice bath was then removed, and the contents were allowed to cool to room temperature. The reaction mixture was kept, under stirring at room temperature, for 24 h (the progress of the reaction was monitored by TLC). Water was added and the residue was extracted threefold with CH_2Cl_2 (2 × 20 mL). The organic layers were separated and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel, using cyclohexane/AcOEt (2/1) as eluent.

Yellow solid; Yield: 40%; m.p. = 164 °C. MS (ES-API): *m*/*z* [M + H] = 303.1. Anal. calcd. for $C_{19}H_{14}N_2O_2$. 0.09 $CHCl_3$: C 73.24, H 4.54, N 8.95, found: C 73.20, H 4.11, N 8.85. IR(KBr) ν cm^{-1} : 3838, 2360, 1685, 1211, 740. ^{1}H-NMR δ (ppm) (250 MHz, $CDCl_3$): 10.63 (d, 1H, *J* = 7.2 Hz), 8.35 (dt, 1H, *J* = 9.0 Hz, *J* = 1.2 Hz), 8.10 (d, 2H, *J* = 8.7 Hz), 7.95 (s, 1H), 7.90–7.68 (m, 3H), 7.49 (td, 1H, *J* = 8.0 Hz, *J* = 1.1 Hz), 7.40–7.19 (m, 1H), 6.98 (td, 1H, *J* = 7.1 Hz, *J* = 1.4 Hz), 3.97 (s, 3H, COOMe). ^{13}C-NMR δ (ppm) (62.9 MHz, $CDCl_3$): 165.2 (C=O), 151.3, 147.3, 138.6, 136.2, 129.8, 128.9, 128.8, 127.6, 126.2, 125.9, 124.5, 123.6, 119.6, 119.5, 119.4, 113.6, 104.6 and 51.2 (CH_3). (see supplementary material for more details, Figures S1–S4).

Supplementary Materials: The molefiles and the other supplementary materials can be found at http://www.mdpi.com/1422-8599/2016/1/M883.

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Conflicts of Interest: The authors declare no conflict of interest.

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