Synthesis of 1,2,3 Trisubstituted Indolizine Derivatives by Multicomponent Reaction of Pyridine, Activated Acetylenes and Phenylsulfonyl Acetophenone

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The 1:1 intermediates generated by addition of pyridine to activated acetylenes were trapped by phenylsulfonyl acetophenone to yield indolizine derivatives.

Keywords: indolizine, pyridine, activated acetylenes, phenylsulfonyl acetophenone, multicomponent reactions

Pyrrolo[1,2-α]pyridine, known as indolizine, is an important structural motif frequently found in nature [1-4]. Among these functionalized indolizines (especially at 1, 2 or 3 positions) (fig. 1) are common substructures found in biologically important natural products and synthetic pharmaceuticals.

Due to the various biological functions associated with this skeleton, it has been frequently employed as a key scaffold in the drug industry. Accordingly, many synthetic methods have been reported in the literature [5-7] including Gevorgyan’s cycloisomerization approach [8]. However, in many cases they have drawbacks such as: expensive and toxic metals, extended reaction times, or high reaction temperatures providing opportunity for the further development of milder protocols. In continuation of our interest on the facile synthesis of heterocycles using mild and environment-friendly conditions [9-12] we found a very convenient route to indolizine core structures using MCRs reaction.

Experimental part

Compounds 1-3 were obtained from Merck and used without further purification. M.p.: Electrothermal 9100 apparatus; uncorrected. IR spectra: Shimadzu IR-460 spectrometer; in cm⁻¹. ¹H- and ¹³C- Spectra: Bruker DRX-500-Avance instrument; in CDCl₃ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: Finnigan-MAT-8430 mass spectrometer, at 70 eV; in m/z. Elemental analyses (C, H, N): Heraeus CHN-O-Rapid analyzer.

General procedure for synthesis of compounds 4

To a stirred mixture of 0.47 g of 1 (2 mmol) and activated acetylenes 2 (2 mmol) in 5 cm³ of CHCl₃, was added 0.16 g of pyridine (2 mmol) at r.t. reaction mixture was then stirred for 12-16 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230-400 mesh) flash column chromatography using n-hexane-EtOAc (4:1) mixture as eluent to get pure product 4.
1H- and 13C-NMR spectra of the pure products clearly indicated the formation of dialky 1-benzoyl-2,3-indolizindicarboxylate (4) in 91-94% yield (scheme 1).

The structures of compounds 4a-4e were deduced from their IR, 1H-NMR, and 13C-NMR spectra. For example, the 1H-NMR spectrum of 4a exhibited methoxy groups (δ 3.30 and 3.87), along with multiplets for the aromatic H-atoms. The 13C-NMR spectrum of 4a showed 17 distinct signals that confirms the proposed structure. The IR spectrum of 4a displayed characteristic carbonyl and aromatic bands. The 1H- and 13C-NMR spectra of 4b-4d are similar to those of 4a except for the ester moieties (or aliphatic and ester moieties in the case of 4e) which exhibited characteristic resonances in appropriate regions of the spectrum.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterionic intermediate [13-15] formed from pyridine and the dialkyl acetylenedicarboxylate, is protonated by 3 to furnish intermediate 6, which is attacked by carbanion 7, to produce 8. This intermediate is converted into 9 via a 1,3-proton shift and cyclization, which then undergoes elimination of PhSO2H, and H, and via intermediates 10 converted to product 4. (scheme 2)

**Conclusions**

In summary, we report synthesis of 1,2,3-trisubstituted indolizine derivatives by MCRs in excellent yield under mild condition. The present procedure has the advantage that the reaction takes place under non-catalytic conditions and that the reactants can be mixed without any prior activation or modification.

**References**

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**Results and discussions**

The reaction of pyridine derivatives (1), activated acetylenes (2), and phenylsulfonyl acetonophenone (3) proceeded smoothly and was complete within 8-12 h. The