Mendeleev Communications

Mendeleev Commun., 2025, **35**, 729–731

Synthesis of 3-acylindolizines based on β-nitro-substituted benzochromenes and carbonyl-stabilized pyridinium ylides

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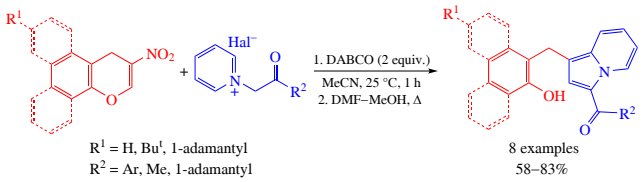
DOI: 10.71267/mencom.7789

3-Acylindolizines containing a (1-hydroxynaphthalen-2-yl)-methyl substituent at position 1 were obtained *via* the reaction of 2-nitro-1*H*-benzochromenes or 3-nitro-4*H*-benzo[*h*]chromene with carbonyl-stabilized pyridinium ylides. The proposed reaction mechanism includes the Michael addition of the pyridinium ylide, opening of the dihydropyran ring, 5-*endo-trig* cyclization, and elimination of nitrous acid.



Keywords: 2-nitro-1*H*-benzochromenes, 3-nitro-4*H*-benzo[*h*]chromene, pyridinium ylides, indolizines, Michael reaction.

Indolizines attract attention due to their wide spectrum of biological activity,[1–3] so the new methods for obtaining their derivatives are actively developed[4–10] and their further modification is studied.[8,11–13] Particular interest lies in 3-acylindolizines related to their ability to interact with various biological targets, high synthetic availability, and the possibility of easily modifying their structures. They demonstrate diverse pharmacological properties, including antibacterial,[14] anticonvulsant and anti-inflammatory effects,[15] antitubercular,[16] antimalarial[17] and anti-HIV[18] activities. One of the most studied aspects of indolizine biological activity is their antitumor potential[19–23] (for the structures, see Online Supplementary Materials, Figure S1).

Typically, 3-acylindolizines are obtained from pyridinium acylmethylides[24,25] which are generated *in situ* from the corresponding salts, and various Michael acceptors, including α,β-unsaturated nitro compounds. The use of α-chloro-,[20] α-bromo-,[26] α-fluoro nitroalkenes,[27] β-nitrostyrenes,[28,29] 1,1-diiodo-2,2-dinitroethylene,[30] 1-nitro-2,2-bis(methylthio)ethylene,[31,32] as well as 3-nitroindoles[33,34] for obtaining indolizines has been described.

Continuing the study of addition reactions involving β-nitro-substituted 4*H*-chromenes and their benzo analogues,[35–38] we investigated the reactions of 2-nitro-1*H*-benzochromenes **1a–c** and 3-nitro-4*H*-benzo[*h*]chromene **1d** with carbonyl-stabilized pyridinium ylides (generated *in situ* from the corresponding salts **2a–f**). The reactions were conducted at room temperature in MeCN in the presence of 2 equiv. of DABCO, followed by brief heating in a DMF–MeOH mixture. As a result, a series of 3-acylindolizines **3a–g** containing a (1-hydroxynaphthalen-2-yl)-methyl substituent at position 1 was obtained in 58–83% yields (Scheme 1).†

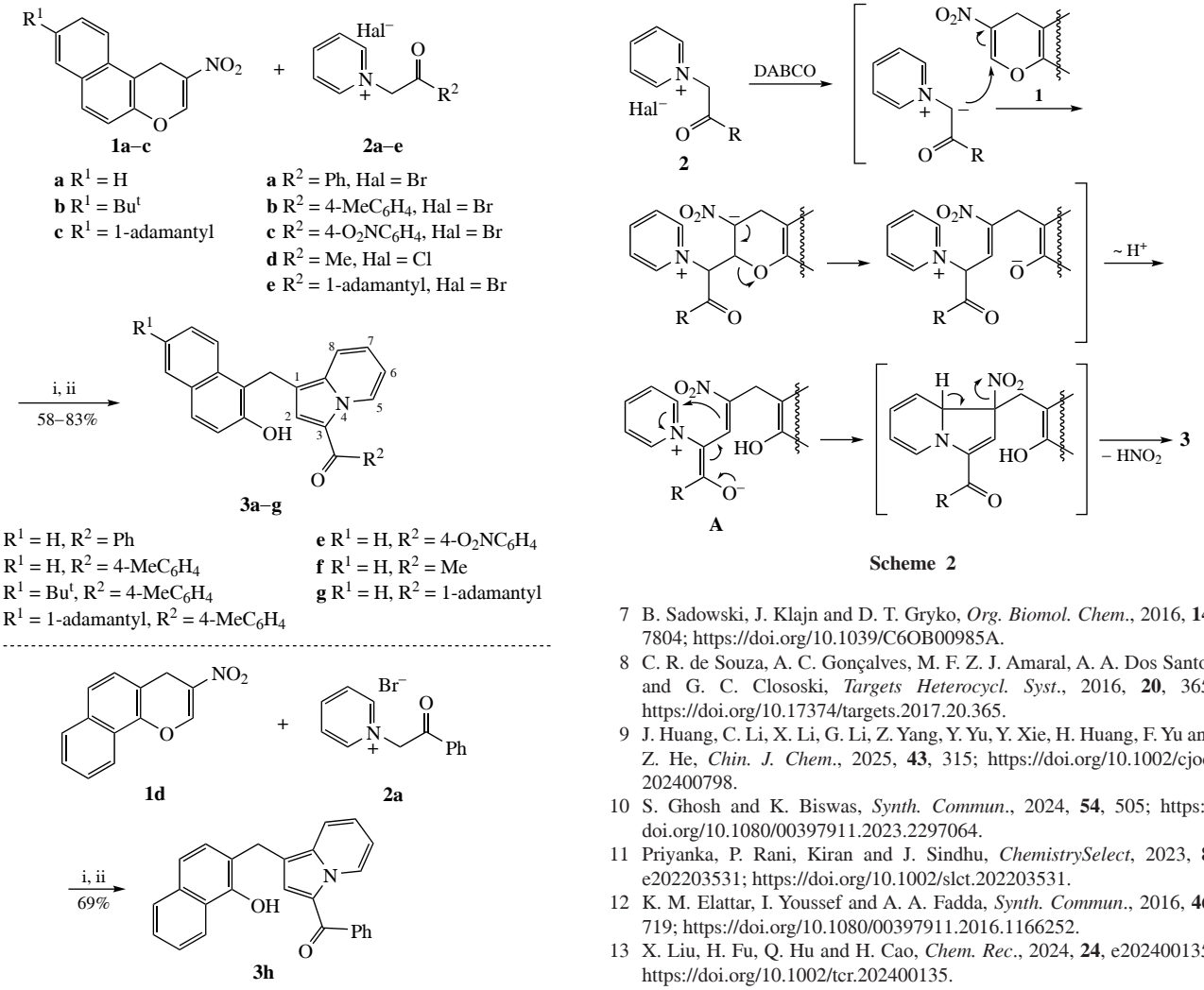
When Et_3N was tested as the base, a complex mixture of products was formed. The reaction can involve pyridinium salts derived from aryl bromomethyl ketone, chloroacetone and 1-adamantyl bromomethyl ketone (Scheme 1). The starting nitrobenzochromenes **1a–d** were synthesized according to a previously developed procedure.[39,40]

In the ^{1}H NMR spectra of indolizines **3a–h**, the hydroxy proton appears as a singlet in the range of 8.83–10.00 ppm, methylene protons are detected as singlets at 3.32 (for product **3h**) or 4.39–4.47 ppm (for **3a–g**). For compounds **3a–g**, the signal for the 5-positioned proton of the indolizine fragment is shifted downfield and resonates as a doublet with J = 6.9–7.3 Hz at 9.64–9.80 ppm. The proton at position 2 of the indolizine bicycle is detected as a singlet signal at 6.98–7.04 (for **3a–e**), 7.28 (for **3f**), or 7.63 ppm (for **3g**). In the ^{13}C NMR spectra of compounds **3a–h**, signals for methylene carbon atoms appear at 14.6–21.5 ppm. Carbonyl atoms resonate in the range of 176.7–194.4 ppm. In the IR spectra of indolizines **3a–h**, broad absorption bands are present in the range of 3400–2800 cm^{-1}, corresponding to O–H bond vibrations.

The proposed reaction mechanism includes the Michael addition of the pyridinium ylide, followed by dihydropyran ring opening and formation of zwitterionic salts **A**, which spontaneously transform into indolizine derivatives **3a–h** upon attempted recrystallization from a DMF–MeOH mixture, resulting from 5-*endo-trig* cyclization and HNO_2 elimination (Scheme 2). Salts **A** are poorly soluble in MeCN and precipitate out, but we were unable to obtain satisfactory spectral data for them due to rapid transformation in DMSO solution into the indolizines. We have previously observed zwitterionic salts of this type in reactions of 3-nitrobenzofurans with carbonyl-stabilized sulfur ylides.[41]

In summary, we have demonstrated that reactions of β-nitro-substituted benzochromenes with carbonyl-stabilized pyridinium ylides lead to the formation of the indolizine cycle. This protocol provides satisfactory yields, atom- and step-

† *Synthesis of 3-acylindolizines* **3a–h** *(general procedure).* To a suspension of 2-nitro-1*H*-benzo[*f*]chromene **1a–c** or 3-nitro-4*H*-benzo[*h*]chromene **1d** (0.5 mmol) and pyridinium salt **2a**–e (0.5 mmol) in MeCN (4 ml), DABCO (112 mg, 1 mmol) was added with stirring. The reaction mixture was stirred for 1 h, the precipitate was filtered off, washed with MeCN, and dried in air. The obtained zwitterionic salt of type **A** was dissolved in a hot DMF–MeOH mixture (1 : 5), then the solution was slowly cooled to room temperature and kept at –30 °C for 1 h. The precipitated solid was filtered off, washed with ice-cold MeOH, and dried in air to afford the title products **3**.



Scheme 1 *Reagents and conditions*: i, DABCO (2 equiv.), MeCN, 25 °C, 1 h; ii, DMF–MeOH (1 : 5), Δ.

economy, simple reaction conditions, and easy isolation avoiding chromatography.

The study was carried out with the support of The Russian Science Foundation (grant no. 22-73-10104, https://rscf.ru/project/22-73-10104/) using scientific equipment of the Center for Collective Use 'Investigation of the physicochemical properties of substances and materials' of the Samara State Technical University.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7789.

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Scheme 2

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Received: 4th April 2025; Com. 25/7789