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A novel domino condensation–intramolecular nucleophilic cyclization approach towards annulated thiochromenes

Leonid G. Voskressensky *, Ekaterina A. Sokolova, Alexey A. Festa, Alexey V. Varlamov

Organic Chemistry Department of the Peoples' Friendship University of Russia, 6, Miklukho-Maklaya St., Moscow 117198, Russia

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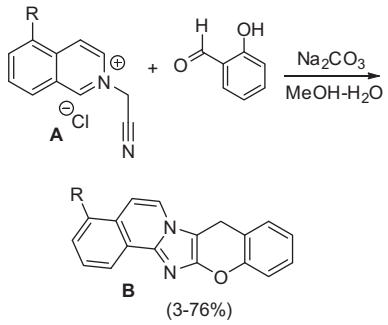
ABSTRACT

A one-pot protocol towards previously unreported derivatives of thiochromeno [2′,3′:4,5] imidazo[2,1-*a*]isoquinoline via a domino reaction of isoquinoline-derived iminium salts and α-mercapto benzaldehydes is elaborated.

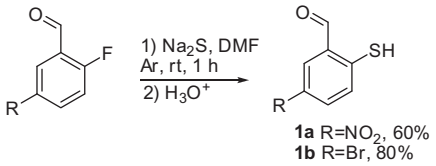
Critical objectives in modern organic chemistry and drug discovery are the improvement of efficiency, avoidance of toxic reagents, reduction of waste and the responsible treatment of resources.[1] Domino reactions have emerged as a powerful tool for the effective creation and expansion of molecular diversity.[2] Carbon–carbon and carbon–heteroatom bond-forming reactions are crucial to organic synthesis. Domino processes are important for generating high levels of diversity and complexity giving rise to complex structures by simultaneous formation of two or more bonds from simple substrates. These advantages are of particular interest in pharmaceutical research for the construction of libraries of biologically active compounds. Thus, developing new, environmentally benign domino reactions is an important topic of green chemistry.[3]

We recently reported a new domino pathway towards previously unknown chromeno [2′,3′:4,5] imidazo[2,1-*a*]isoquinolines **B** based on the reaction of isoquinoline derived cycloiminium salts **A** with salicylic aldehydes (Scheme 1).[4]

Herein, we present a novel reaction which provides an easy access towards functionalized thiochromeno [2′,3′:4,5] imidazo[2,1-*a*]isoquinoline derivatives, which, to the best of our knowledge have not been described. Thiochromene derivatives and their fused analogues are of interest because they represent an important class of heterocycles, many of which exhibit useful biological activities, and some have been tested and applied as drugs.[5]To our disappointment the *ortho*-mercaptobenzaldehydes **1**, prerequisite for the present study, were not commercially available and we had to plan their synthesis. A careful literature search[6] revealed, that the only procedure compatible with the presence of NO_2 and Br substituents in **1** is that involving nucleophilic displacement of an *ortho*-halogen atom in the corresponding benzaldehyde as described earlier.[7] The choice of the substituents is



Scheme 1. Previously reported domino reaction of salicylic aldehyde.



Scheme 2. Preparation of thiosalicylic aldehydes.

* Corresponding author. Tel.: +7 495 955 07 57; fax: +7 495 955 07 79.
E-mail address: lvoskressensky@sci.pfu.edu.ru (L.G. Voskressensky).

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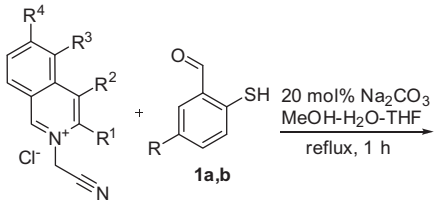
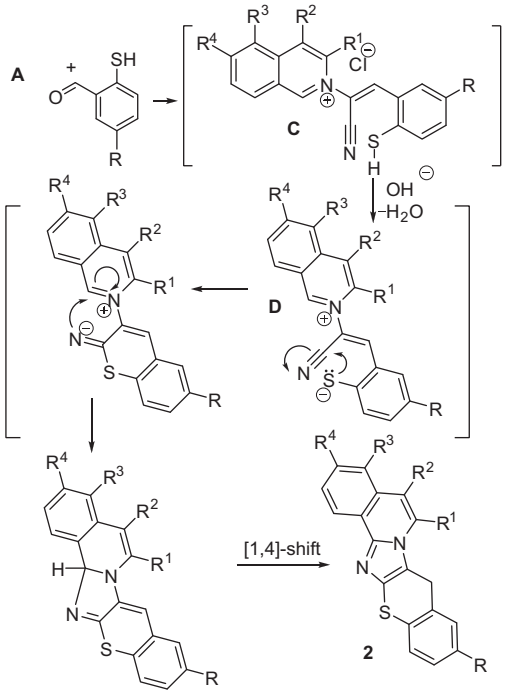


2a R=NO_2, R^1=H, R^2=H, R^3=H, R^4=H; 66%
2b R=NO_2, R^1=H, R^2=H, R^3=H, R^4=OH; 29%
2c R=NO_2, R^1=H, R^2=H, R^3=OH, R^4=H; 22%
2d R=NO_2, R^1=Me, R^2=H, R^3=H, R^4=H; 21%
2e R=Br, R^1=H, R^2=H, R^3=H, R^4=OH; 30%

Scheme 3. The reaction of isoquinolinium salts with thiosalicylic aldehydes. Product **2e** was obtained without the addition of THF.



Scheme 4. A mechanistic proposal for the domino process.

determined by the possibility of further modification of the target molecules by cross- and aza-coupling reactions.

The targets **1a** and **1b** were obtained in 60% and 80% yields as judged by LC–MS analysis and were used without any further purification due to their instability (Scheme 2).

In a typical experiment the isoquinolinium salt (1 mmol), 20 mol % of sodium carbonate and 1.2 mmol of thiosalicylic aldehyde in a mixture of MeOH–H_2O–THF were stirred vigorously under reflux for 1 h. The resulting precipitate was filtered off, washed with MeOH and dried in air to yield compounds **2** (Scheme 3).[8] The structures of compounds **2** were determined similar to compounds **B**: the ^{1}H spectra of the following compounds are characterized by a singlet signal of the methylene group at 4.49–5.08 ppm and an absence of the C-1 proton of the isoquinoline ring. The mass spectra of the compounds **2** confirmed the presence of a sulfur atom. The structures are also confirmed by the data of ^{13}C, IR spectra and elemental analysis.

We presume that compound **2** is the product of an anionic domino-reaction, starting with condensation of thiosalicylic aldehyde and isoquinolinium salt **A** to produce the styryl derivative **C**. The base-catalysed deprotonation of the thiophenol SH yields zwitterion **D**. This then undergoes two consecutive nucleophilic cyclizations, followed by a [1,4] proton shift to yield the pentacycle **2** (Scheme 4).

Although the yields of the polycyclic thiochromenes were moderate, the simplicity of the procedure and the molecular complexity gained make this reaction very attractive. Further studies aimed at the optimization of the reaction conditions as well as at exploring the scope and limitations of this procedure are underway and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.040.

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8. *10-Nitro-8H-thiochromeno [2′,3′:4,5] imidazo[2,1-a]isoquinoline (**2a**).* Yield 220 mg (66%), yellow solid, mp 268–269 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$ + CF_3CO_2H): δ = 4.68 (s, 2H, H-8), 7.56 (d, J = 8.9 Hz, 1H, H-12), 7.83 (d, J = 6.9 Hz, 1H, H-5), 7.95–7.97 (m, 1H, H-2), 8.00–8.02 (m, 1H, H-3), 8.09–8.12 (m, 2H, H-6, H-1), 8.19 (dd, J = 8.9, 2.1 Hz, 1H, H-11) 8.35 (s, 1H, H-9), 8.45 (d, J = 8.3 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$ + CF_3CO_2H): δ = 25.8, 100.0, 116.3, 116.9, 118.9, 119.3, 122.8, 123.3, 123.4, 125.2, 126.0, 128.6, 128.8, 131.5, 133.6, 135.4, 139.2, 146.9; IR (KBr) 1517, 1335 cm^{-1}; EI MS: m/z (%) = 334 (12), 333 (100) $[M]^+$, 287 (22), 286 (46), 143 (12), 129 (11), 128 (22), 71 (12), 43 (17), 42 (11); $C_{18}H_{11}N_3O_2S$ (333.36): Calcd C, 64.85, H, 3.33, N, 12.60; found C, 64.72, H, 3.45, N, 12.53.