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A novel cascade Kröhnke condensation—an intramolecular nucleophilic cyclization approach toward annulated chromenes

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ABSTRACT

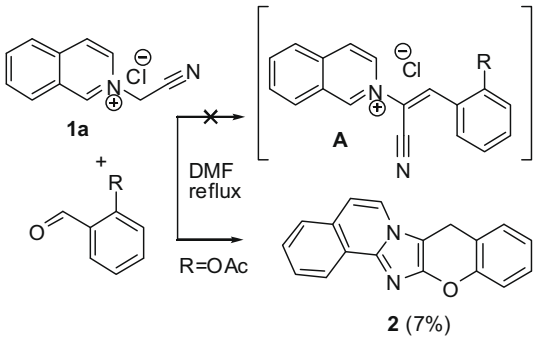
A one-pot protocol toward previously unreported derivatives of chromeno[2′,2′:4,5]imidazo[2,1-*a*]isoquinoline via a cascade reaction of isoquinoline-derived immonium salts and α-hydroxy aromatic aldehydes is elaborated.

Base-catalyzed or thermal condensation of cycloimmonium salts, bearing an active methylene group, with carbonyl compounds (Kröhnke condensation) has been used widely in the synthesis of annulated azines.[1] However, it was reported[2] that isoquinoline-derived immonium salts failed to yield the corresponding styryl derivatives of type **A** (Scheme 1) under 'classic' reaction conditions (refluxing in acetic anhydride).

Wanting to modify the reaction conditions to obtain salts **A**, we carried out the reaction of isoquinolinium salt **1a**[2] with *ortho*-substituted benzaldehydes (R = Me, OMe, OAc, Br) in refluxing DMF. To our disappointment, the target compounds **A** were not isolated in any of the reactions. In most cases a tar formed with no isolable products. However, the TLC of the reaction mixture in the case of 2-acetoxybenzaldehyde showed a distinct spot with a rather high R_f value (0.65, on Silufol plates in EtOAc/hexanes, 1:2) that could not be attributed to the isoquinoline salt **A**. The reaction mixture was purified by column chromatography to yield 8*H*-chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinoline (**2**) in low yield (7%).

This novel (to the best of our knowledge) heterocyclic system incorporates two units: an aminochromene and an imidazoisoquinoline. The continuing interest surrounding these two unique heterocyclic cores is aptly demonstrated by a number of recent publications.[3,4]

Critical objectives in modern organic chemistry are the improvement of efficiency, avoidance of toxic reagents, reduction of waste, and the responsible treatment of resources. Multi-step one-pot reactions, also known as cascade reactions, address many of these objectives. As they do not require work-up or isolation of intermediates, the cascade reactions are cleaner, quicker, and more efficient than the traditional 'step-by-step methods'. Therefore, the concept of increasing the molecular complexity, while decreasing the number of synthetic steps, is becoming more and more attractive.[5] In light of the above it seemed appropriate to us to investigate this new synthetic method further.



Scheme 1.

We presume that compound **2** is the product of a cascade reaction, starting with the Kröhnke condensation of 2-acetoxybenzaldehyde and isoquinolinium salt **1** to produce the styryl derivative **A** which upon thermally-induced cleavage of acetyl chloride forms zwitterion **B**. This then undergoes two consecutive nucleophilic cyclizations, followed by a [1,4]-proton shift to yield the pentacycle **2** (Scheme 2).

To check this presumption, we studied the reaction of **1a** with unprotected salicylaldehyde in the presence of K_2CO_3[6] which gave compound **2** in 55% yield.[7]

The generality of this approach was demonstrated using 2-hydroxy-2-naphthaldehyde along with various isoquinolinium salts.[8] (Scheme 3, Table 1).

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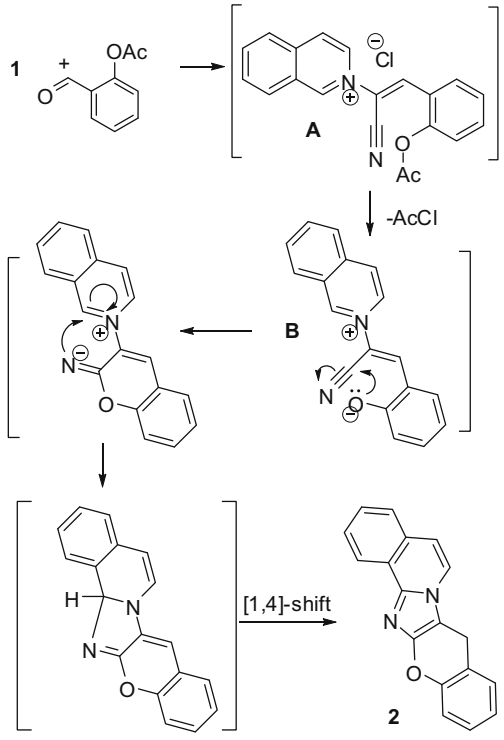
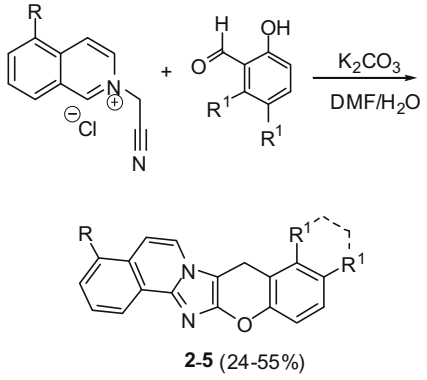


Scheme 2.



Scheme 3.

Although the yields of the polycyclic chromenes were moderate (Table 1), the simplicity of the procedure as well as the ready availability of the starting materials makes this reaction very attractive. Preliminary experiments showed that this cascade reaction is applicable to pyridine and quinoline-derived quaternary salts as well. Work aimed at optimization of the reaction conditions as well as at exploring its scope and limitations is underway, and the results will be reported in due course.

Table 1
Yields of polycyclic chromene derivatives **2–5**

Product	R	R^1	Yield (%)
2	H	H	55
3	NO_2	H	24
4	H	–CH=CH–CH=CH–	48
5	Br	H	43

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6. *General experimental procedure*: To a solution of hydroxy-substituted aldehyde (1.47 mmol) and isoquinolinium salt (1.47 mmol) in DMF (5 ml) was added K_2CO_3 (0.4 g in 1 ml of H_2O) and the resulting mixture was heated at reflux for 1 h. After cooling, the reaction mixture was poured into H_2O (20 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The extract was washed with H_2O (50 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 using EtOAc/hexane (1:20) as an eluent. (Compound **4** precipitated after the addition of H_2O and was filtered, dried, and recrystallized from MeOH/DMF).
7. *8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline* (**2**). Yellow crystals, mp 172–173 °C (EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (s, 2H, CH_2-8), 6.98 (dd, 1H, *J* = 8.1, *J* = 1.2 Hz,H-12), 7.01 (d, 1H, *J* = 7.5 Hz, H-5), 7.07–7.12 (m, 2H, H-10 + H-9), 7.16 (dd, 1H, *J* = 8.1, *J* = 1.2 Hz, H-11), 7.40–7.45 (m, 1H, H-3), 7.48–7.53 (m, 1H, H-2), 7.55 (d, 1H, *J* = 7.5 Hz, H-4), 7.58 (d, 1H, *J* = 7.5 Hz, H-6), 8.47 (d, 1H, *J* = 8.1 Hz, H-1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2 (CH_2), 112.9 (CH), 117.8 (C_q), 118.1 (C_q), 118.3 (CH), 120.3 (CH), 123.1 (CH), 123.2 (C_q), 123.5 (CH), 127.1 (CH), 127.8 (CH), 128.2 (2 × CH), 129.1 (C_q), 130.3 (CH), 138.0 (C_q), 152.0 (C_q), 161.1 (C_q). EI MS: *m*/*z* (%) = 272 (70) [M^+], 136 (11), 128 (10). $C_{18}H_{12}N_2O$ (272.30): Calcd: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.13; H, 4.58; N, 10.53.
8. *16H-Benzo[5′,6′]chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline* (**4**). Brown crystals, mp 252 °C (dec) (MeOH/DMF). ^{1}H NMR, (400 MHz, DMSO-d_6) δ 4.69 (2H, s, CH_2-16), 7.40 (1H, d, *J* = 6.9 Hz, H-13), 7.45 (1H, d, *J* = 8.7 Hz, H-4), 7.56 (1H, t, *J* = 7.5 Hz, H-2), 7.60–7.74 (3H, m, H-5 + H-10 + H-11), 7.91 (1H, d, *J* = 8.1 Hz, H-3), 7.95 (1H, d, *J* = 8.7 Hz, H-6), 7.99 (1H, d, *J* = 8.1 Hz, H-1), 8.08 (1H, d, *J* = 8.1 Hz, H-12), 8.32 (1H, d, *J* = 7.5 Hz, H-9) 8.46 (1H, d, *J* = 7.5 Hz, H-14). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.7 (CH_2), 100.6 (C_q), 110.9 (CH), 112.3 (CH), 118.4 (C_q), 122.1 (C_q), 122.9 (CH), 124.7 (CH), 127.1 (CH), 127.2 (C_q), 127.7 (CH), 127.9 (2 × CH), 128.2 (C_q), 128.7 (CH), 128.8 (C_q), 129.9 (CH), 132.0 (CH), 136.7 (CH), 146.4 (C_q), 148.9 (C_q), 156.8 (C_q). EI MS: *m*/*z* (%) = 322 (48) [M^+], 321 (100), 139 (9). $C_{22}H_{14}N_2O$ (322.35): Calcd: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.63; H, 4.13; N, 8.99.