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An expedient multicomponent assembling of 1-azaxanthones

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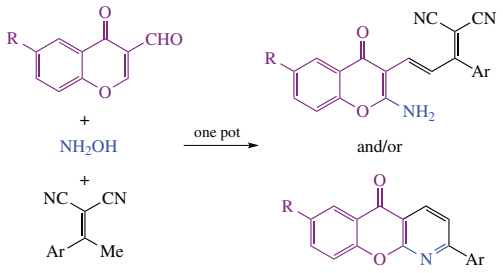
An efficient one-pot synthesis of 2-[3-(2-amino-4-oxo-4*H*-chromen-3-yl)-1-arylallylidene]malononitriles as intermediates and 2-aryl-5*H*-chromeno[2,3-*b*]pyridin-5-ones as final products comprises Et_3N-catalyzed condensation of alkylidenemalononitriles, 3-formylchromones and hydroxylamine hydrochloride. The transformation involves stages of 1,4-nucleophilic addition, phenolate–nitrile coupling and Mannich-type heterocyclization reactions.



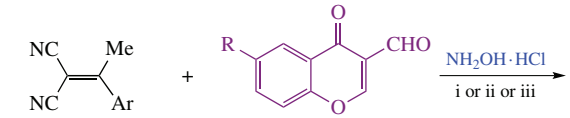
Keywords: 3-formylchromones, alkylidenemalononitriles, hydroxylamine hydrochloride, heterocyclization, 1-azaxanthones.

1-Azaxanthones (chromeno[2,3-*b*]pyridin-5-ones) are valuable medicinal compounds[1] with a wide range of biological activities.[2] This structural motif can be potent for inhibitors of passive cutaneous anaphylaxis[3] and can be regarded for anti-inflammatory drugs for rheumatoid diseases.[4] Such compounds suppress rat adjuvant arthritis,[5] exhibit anti-allergic, and antiulcer activities,[6] and are effective in treating bronchitis and asthma.[7] Accordingly, the development of efficient syntheses of these structures is valuable. To date, efforts have been attained in this area using metal-catalyzed[8,9] or metal-free cyclization reactions.[10]

Some documented syntheses of chromenopyridines suffer from limitations.[11] In the intramolecular Friedel–Crafts cyclization, expensive materials were used, and side reactions took place.[12] Also, in CH-activation-type arylation of 2-chloro diaryl ketones using the palladium catalyst, 1-azaxanthone was obtained as the by-product.[8] The treatment of active methylene compounds with cyanochromones was performed in the presence of bases such as piperidine, DABCO, and DBU under refluxing conditions.[13] The condensation of 1,3-bis-silyl enol ethers with 3-cyanobenzopyrylium triflates under mild conditions afforded 1-azaxanthones *via* retro-Michael–lactonization–aldol reactions.[14] Ultrasound irradiation with stoichiometric amount of DABCO improved the product yield.[15]

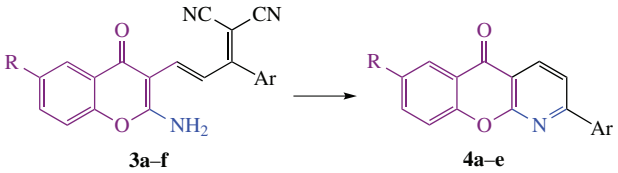
On the other hand, addition of vinylogous alkylidenemalononitriles to various electrophiles such as four-carbon ones in [4+2] annulation[16] and three-carbon components in [3+2] and [3+3] annulations led to various carbocyclic compounds.[17] To the best of our knowledge, the role of alkylidenemalononitrile as a 2-carbon nucleophile-electrophile compound has attained less attention in the synthesis of pyridines.[18] Herein, we describe a new synthesis of 1-azaxanthones using Et_3N-catalyzed tandem assembling of (1-arylethylidene)malononitriles **1**, 3-formylchromones and hydroxylamine under mild conditions (Scheme 1).

We began our study with model reactants **1a** and **2a**. The acid-mediated synthesis involving 3-formylchromone and



a Ar = Ph
b Ar = 4-ClC_6H_4
c Ar = 4-$MeOC_6H_4$
d Ar = 4-MeC_6H_4
e Ar = 2-Oxochromen-3-yl

a R = H
b R = Me



3a Ar = Ph, R = H, 85% (i)
3f Ar = Ph, R = Me, 84% (i or iii)

a Ar = Ph, R = H, 58% (ii)
b Ar = 4-ClC_6H_4, R = H, 73% (i), 0% (iii)
c Ar = 4-$MeOC_6H_4$, R = H, 59% (i)
d Ar = 4-MeC_6H_4, R = H, 63% (i)
e Ar = 2-Oxochromen-3-yl, R = H, 70% (i)

Scheme 1 *Reagents and conditions*: i, Et_3N (30 mol%), EtOH, reflux, 12 h; ii, the same, with 50 mol% Et_3N; iii, the same, with 100 mol% Et_3N.

hydroxylamine hydrochloride under reflux is known.[19] We found that the resulting 3-cyanochalcone could *in situ* react with the carbanion formed from the activated methylene group of **1a** and triethylamine as a mild base. To improve efficiency, a screening of the amount of triethylamine was performed, which showed that 30 mol% provided good (85%) yield of linear product **3a**. It meant that the final cyclization did not occur. A noticeable improvement in the reaction progress was achieved with the use of a 50 mol% catalyst, which led to the desired azaxanthine **4a**. It is important to note that changing the polar solvent with the non-polar one had no significant effect on the reaction outcome. Under optimal conditions in hand, we examined the generality of

this Et_3N-catalyzed tandem reaction to synthesize a seires of 1-azaxanthones **4a–e** under the mild conditions (see Scheme 1).

The structures of products were characterized by IR, ^1H and ^{13}C NMR spectroscopic analyses. For example, the IR spectrum of 1-azaxanthone **4a** confirmed the change in the functional group nature, the elimination of malononitrile moiety from the structure, and the formation of a non-polar product. In the spectrum of **3a**, absorptions at 3315 and 2214 cm^{-1} indicated the presence of amine and nitrile functionalities. Also, in the mass spectrum, the molecular ion peak at 303 *m/z* was in agreement with a 1 : 1 of the starting materials minus malononitrile. In the ^1H NMR spectrum of **4a**, two doublets at δ 8.09 and 8.15 were attributed to pyridine protons. The presence of 19 distinct signals in the ^{13}C NMR spectrum of **4a** was consistent with the proposed structure. As compound **4a** has been previously documented,[20] the proximity of ^{13}C NMR chemical shift assignments was one of the evidences of 1-azaxanthone formation. Ultimately, the structure of product **4c** was established from single-crystal X-ray analysis (Figure 1).†

We investigated the reaction of 3-formylchromone **2a** with substituted alkylidenemalononitriles that contain both electron-withdrawing (4-Cl) and donating (4-MeO, 4-Me) substituents on the benzene ring. To our surprise, the reactions provided 73, 59, and 63% yields of 1-azaxanthones **4b–d**, respectively. The reason for attaining the highest yield of product **4b** in the case of chlorophenyl derivative of alkylidene malononitrile **1b** may be the electron-withdrawing property of the chlorine group. In determination of scope and limitations we found that, in cases of 2,4-dibromophenyl and 4-bromophenyl analogues, the reaction did not lead to 1-azaxanthones, and starting materials were recovered. Also, the treatment 6-chloro-3-formylchromone with alkylidene malononitriles of type **1** caused only the hydrolysis of the nitrile group giving imidic acid. An attempt also was made to perform the reaction of 6-methyl-3-formylchromone **2b** with alkylidenemalononitrile **1a** under optimized conditions. However, even with application of 1.0 equivalent of catalyst and after 24 h, the linear intermediate **3f** was isolated as the final product in 84% yield (see Scheme 1).

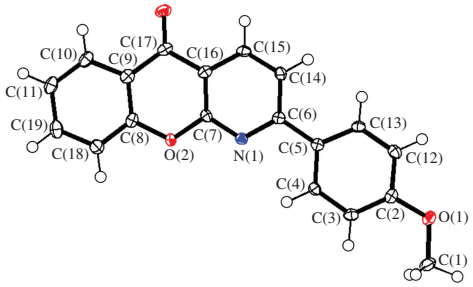
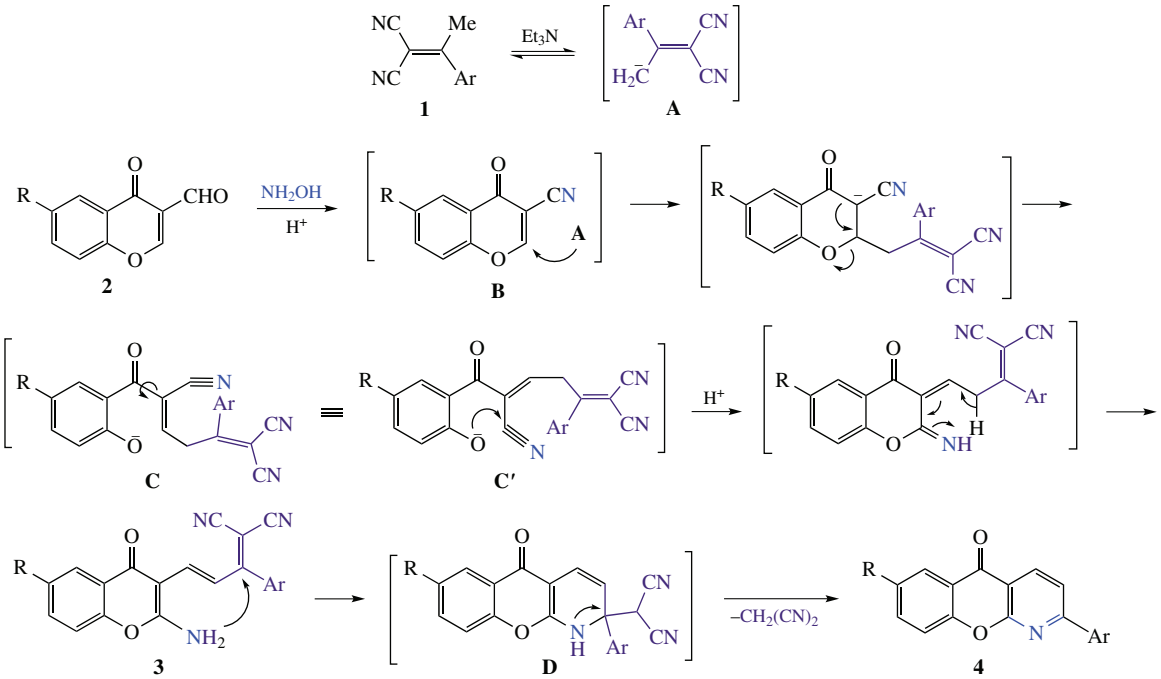


Figure 1 ORTEP diagram of azaxanthone **4c**.

The reaction between 3-formylchromones and alkylidene-malononitriles has been previously performed in the absence of NH_2OH, which gave the expected Knoevanagel products.[22] The presence of NH_2OH in our protocol has turned the process *via* a different pathway by converting the aldehyde functional group into carbonitrile.[13] Based on these results, the plausible mechanism of this tandem reaction is presented in Scheme 2.

Initially, the reaction of aldehyde **2** with hydroxylamine hydrochloride gives in a standard way the corresponding carbonitrile **B**. The next 1,4-nucleophilic addition of preliminarily deprotonated akylidenemalononitrile **1** as carbanion **A** at position 2 of 3-cyanochromone **B** afforded species **C** upon opening the pyran ring. The further transformations can be readily rationalized from Scheme 2. Final heterocyclization occurred through intramolecular attack of amino group in linear intermediate **3** at



Scheme 2

† *Crystal data for* **4c**. $C_{19}H_{13}NO_3$, M_W = 303.30, orthorhombic, *Pbca*, *a* = 10.6856(11), *b* = 9.4219(6) and *c* = 27.671(3) Å, *V* = 2785.9(4) $Å^3$, *Z* = 8, d_{calc} = 1.446 g cm^{-3}, *F*(000) = 1264, crystal dimensions 0.20×0.10×0.10 mm, MoKα radiation (λ = 0.71073 Å), 2.94 ⩽ 2θ ⩽ 27.41, intensity data were collected at 100(2) K with a Bruker APEX area-detector diffractometer using $\omega/2\theta$ scanning technique, in the range of –12 ⩽ *h* ⩽ 12, –11 ⩽ *k* ⩽ 11, –32 ⩽ *l* ⩽ 32; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2457 observed reflections with R_{int} = 0.0908 by a full-matrix least-squares technique converged to R_1 = 0.0510, and wR_2 = 0.1354 [$I > 2\sigma(I)$].

CCDC 1955484 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://ccdc.cam.ac.uk.

the alkylidenemalononitrile moiety to afford species **D**. This species would liberate malononitrile molecule and undergo aromatization to generate the desired 1-azaxanthone **4**.

To better rationalize the results obtained, quantum chemical calculations were performed. The energy gap between HOMO and LUMO orbitals[21] characterizes the reactivity of a molecule, which is determined based on parameters such as electronegativity (μ), hardness (η), and softness (ζ). The quantum descriptors obtained from the HOMO–LUMO energy gap in **3a–f** were obtained by B3LYP/6-31G (d,p) basis set (for details, see Online Supplementary Materials). Compounds **3b** and **3e** could be referred to as soft molecules compared to other derivatives due to the smaller band space of the energy gap. Besides, compound **3b** with a higher electronegativity and a lesser chemical hardness was designated as the most reactive molecule. A comparison of experimental results and theoretical predictions suggested that electron-withdrawing substituent could increase the reactivity and accelerate the cyclization. The natural bond orbital of compound **3a** has been computed using B3LYP/6-31G (d,p). Results show that this molecule is polarized due to donor–acceptor interactions. The resonance can provide the needed energy to break the π bond, and it can be converted into a less stable conformer (*s-cis*) by rotation about a single bond. The interaction between the lone pair electrons of O(13) and the anti-bonding C(1)–N(16) can increase the electron density around the nitrogen atom, and the nucleophilic substitution reaction of N(16) to the C(23) (+0.076e), which is attached to the leaving group, can lead to the formation of the final product.

In conclusion, we have developed the convenient one-pot synthesis of functionalized 1-azachromones from available reactants. We believe that our findings will promote the use of compounds obtained in search for new biologically active substances.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.034.

References

1 (*a*) M. I. Hegab, A.-S. M. Abdel-Fattah, N. M. Yousef, H. F. Nour, A. M. Mostafa and M. Ellithey, *Arch. Pharm. Chem. Life Sci.*, 2007, **340**, 396; (*b*) P. C. Unangst, T. Capiris, D. T. Connor, T. G. Heffner, R. G. Mackenzie, S. R. Miller, T. A. Pugsley and L. D. Wise, *J. Med. Chem*., 1997, **40**, 2688; (*c*) V. Giannouli, I. K. Kostakis, N. Pouli, P. Marakos, O. C. Kousidou, G. N. Tzanakakis and N. K. Karamanos, *J. Med. Chem*., 2007, **50**, 1716.

2 M. A. Rashid, N. Rasool, B. Appel, M. Adeel, V. Karapetyan, S. Mkrtchyan, H. Reinke, C. Fischer and P. Langer, *Tetrahedron*, 2008, **64**, 5416.

3 A. Nohara, H. Kuriki, T. Sajio, H. Sugihara, M. Kanno and Y. Sanno, *J. Med. Chem*., 1977, **20**, 141.

4 S.-T. Chung, W.-H. Huang, C.-K. Huang, F.-C. Liu, R.-Y. Huang, C.-C. Wu and A.-R. Lee, *Res. Chem. Intermed.*, 2016, **42**, 1195.

5 K. Kubo, K. Ukawa, S. Kuzuna and A. Nohara, *Chem. Pharm. Bull*., 1986, **34**, 1108.

6 N. Akira, I. Toshihira and U. Kiyoshi, *J. Med. Chem*., 1985, **28**, 559.

7 D. T. Connor, P. C. Unangst, C. F. Schwender, R. J. Sorenson, M. E. Carethers, C. Puchalski and R. E. Brown, *J. Heterocycl. Chem*., 1984, **21**, 1561.

8 N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, V. Dorcet, A.-L. Gagez, S. Sable, L. Picot, V. Thiery, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron*, 2013, **69**, 10123.

9 (*a*) A. V. Dubrovskiy and R. C. Larock, *Org. Lett*., 2010, **12**, 3117; (*b*) M. F. Ibad, O.-ur-R. Abid, M. Adeel, M. Nawaz, V. Wolf, A. Villinger and P. Langer, *J. Org. Chem*., 2010, **75**, 8315.

10 V. Y. Sosnovskikh, R. A. Irgashev and I. A. Demkovich, *Russ. Chem. Bull., Int. Ed*., 2008, **57**, 2210 (*Izv. Akad. Nauk, Ser. Khim*., 2008, 2168).

11 M. A. Rashid, N. Rasool, B. Appel, M. Adeel, V. Karapetyan, S. Mkrtchyan, H. Reinke, C. Fischer and P. Langer, *Tetrahedron*, 2008, **64**, 5416.

12 F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L. L. Larca, M. J. Landon, W. Spivak, D. Vashi, S. Tozzi, G. Danko, M. del Prado and R. Lutz, *J. Med. Chem*., 1975, **18**, 1.

13 M. A. Ibrahim, *Synth. Commun.*, 2009, **39**, 3527.

14 P. Langer and B. Appel, *Tetrahedron. Lett*., 2003, **44**, 5133.

15 E. Dimitriadou, M. Raftopoulou, P. M. Kasapidou, C. A. Tsoleridis, J. Stephanidou-Stephanatou, D. J. Hadjipavlou-Litina, C. Kontogiorgis, A. Pritsa and A. Papadopoulos, *ARKIVOC*, 2014, (**iv**), 372.

16 D. M. Barnes, A. R. Haight, T. Hameury, M. A. McLaughlin, J. Mei, J. S. Tedrow and J. Dalla Riva Toma, *Tetrahedron*, 2006, **62**, 11311.

17 Z. Lu, S. Zheng, X. Zhang and X. Lu, *Org. Lett*., 2008, **10**, 3267.

18 R. Panwar, Shally, R. Shaw, A. Elagamy and R. Pratap, *Org. Biomol. Chem*., 2018, **16**, 8994.

19 G. J. Reddy, D. Latha, C. Thirupathaiah and K. S. Rao, *Org. Prep. Proced. Int*., 2004, **36**, 287.

20 H. Waldmann, G. V. Karunakar and K. Kumar, *Org. Lett*., 2008, **10**, 2159.

21 X.-H. Liu, P.-Q. Chen, B.-L. Wang, Y.-H. Li, S.-H. Wang and Z.-M. Li, *Bioorg. Med. Chem. Lett*., 2007, **17**, 3784.

22 V. Yu. Korotaev, A. Yu. Barkov, I. B. Kutyashev, A. V. Safrygin and V. Ya. Sosnovskikh, *Tetrahedron*, 2014, **70**, 3584.

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