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A cascade formation of *N*-pyridylacrylamides from pyrido[1,2-*a*]pyrimidine diones and chromene aldehydes

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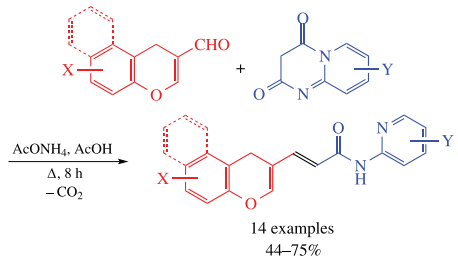
Various *N*-(pyridin-2-yl)acrylamides bearing 4*H*-chromene fragment were synthesized *via* the condensation of 4*H*-chromene-3-carbaldehydes and their fused analogues with 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones employing NH_4OAc/AcOH system. Possible mechanism of this hetero-domino reaction involves the consecutive Knoevenagel condensation, oxa-6π-electrocyclization, aza-6π-electrocyclic ring-opening, nucleophilic addition, retro-Alder-ene reaction and oxa-6π-electrocyclic ring-disclosure.



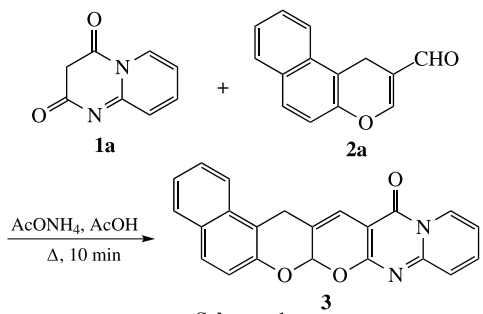
Keywords: chromene-3-carbaldehydes, pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones, *N*-(pyridin-2-yl)acrylamides, acrylamides, cascade reaction, electrocyclization, pericyclic reactions.

2*H*-Pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione derivatives are of interest as starting compounds for the preparation of fluorescent whitening agents,[1] dyes[2] as well as different polyfused heterocycles with valuable biological properties.[3–11] Among these derivatives, representatives with antimicrobial,[5,12,13] bronchodilatory,[7] urease inhibition,[14] anticancer and anti-oxidant[15] activities were found. Being rather strong CH-acids, they are capable of entering into condensation at the methylene group with electrophilic agents. In this case, as a rule, these reactions retain the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one fragment. In very rare cases, the opening of this heterocyclic system occurs.[16,17] When aldehydes were used as electrophiles, the Knoevenagel adducts,[5,7,18,19] 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano[2,3-*d*]pyrido[1,2-*a*]pyrimidine-2,5-diones[20] and pentacyclic pyrido[1,2-*a*]pyrido[1′′,2′′:1′,2′]pyrimido[5′,4′:5,6]-pyrano[2,3-*d*]pyrimidines[19] were obtained. We have previously shown[21] that short-term boiling of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione **1a** and 1*H*-benzo[*f*]chromene-2-carbaldehyde **2a** in AcOH in the presence of ammonium acetate gave pyrido[1,2-*a*]pyrimidinone **3** (Scheme 1).

In this work, we report that the prolonged heating of an equimolar mixture of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones **1a–c** and 1*H*-benzo[*f*]chromene-2-carbaldehydes **2a–c** or 4*H*-chromene-3-carbaldehydes **5a–f** leads to *N*-(pyridin-2-yl)-acrylamide derivatives **4a–f** and **6a–g** as individual *trans*-isomers in 44–75% yields (Scheme 2). 4-Methyl-2-oxo-2*H*,10*H*-pyrano[2,3-*f*]chromene-9-carbaldehyde **7** can also be introduced into the condensation to afford product **8**.† The reactions were carried out in AcOH under reflux for 8 h in the presence of 1.0 equiv. of ammonium acetate. When piperidine was used instead of $AcONH_4$, the yield of product **4a** was only 20%, apparently due to the Michael addition of piperidine to aldehyde **2a**.[22,23] Increase in the quantity of $AcONH_4$ (>1 equiv.) as well as prolongation of the reaction up to 15 h did not substantially affect the product yield. In boiling acetonitrile or DMF as well as in the absence of $AcONH_4$ the reaction did not proceed. Apparently, the base is necessary to promote the Knoevenagel condensation. At the same time, the method does not require strong bases for successful annulation, perhaps owing to the high acidity of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones. 4*H*-Chromene-3-carbaldehydes containing electron-donating (Bu^t, 1-adamantyl) and electron-withdrawing (NO_2, Br) substituents in the benzene ring are good substrates for this cascade reaction.

New aldehydes **5a–e** can be easily obtained by a previously developed method[24,25] from salicylic alcohols as precursors of *o*-quinone methides[26] and 3-(diethylamino)acrylaldehyde.

The proposed mechanism of formation of products **4**, **6**, **8** comprises the Knoevenagel condensation between 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-diones **1** and aldehydes **2**, **5**, **7** followed by the disrotatory 6π-electrocyclization of the 1-oxatriene intermediates **A** formed (Scheme 3). Apparently, the presence of $AcONH_4$ is necessary for the activation of the



Scheme 1

† *Synthesis of* N*-(pyridin-2-yl)acrylamides* **4a–f**, **6a–g**, **8** *(general procedure)*. A mixture of chromenecarbaldehyde **2a–c**, **5a–f**, **7** (1 mmol), 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione **1a–c** (1 mmol) and $AcONH_4$ (77 mg, 1 mmol) in AcOH (4 ml) was stirred under reflux for 8 h. When the reaction was complete, the mixture was stored at 10 °C for 1 h, the solid formed was filtered off, washed with AcOH (1 ml) and ice-cold MeOH (2×3 ml) and dried at 120 °C for 10 h.

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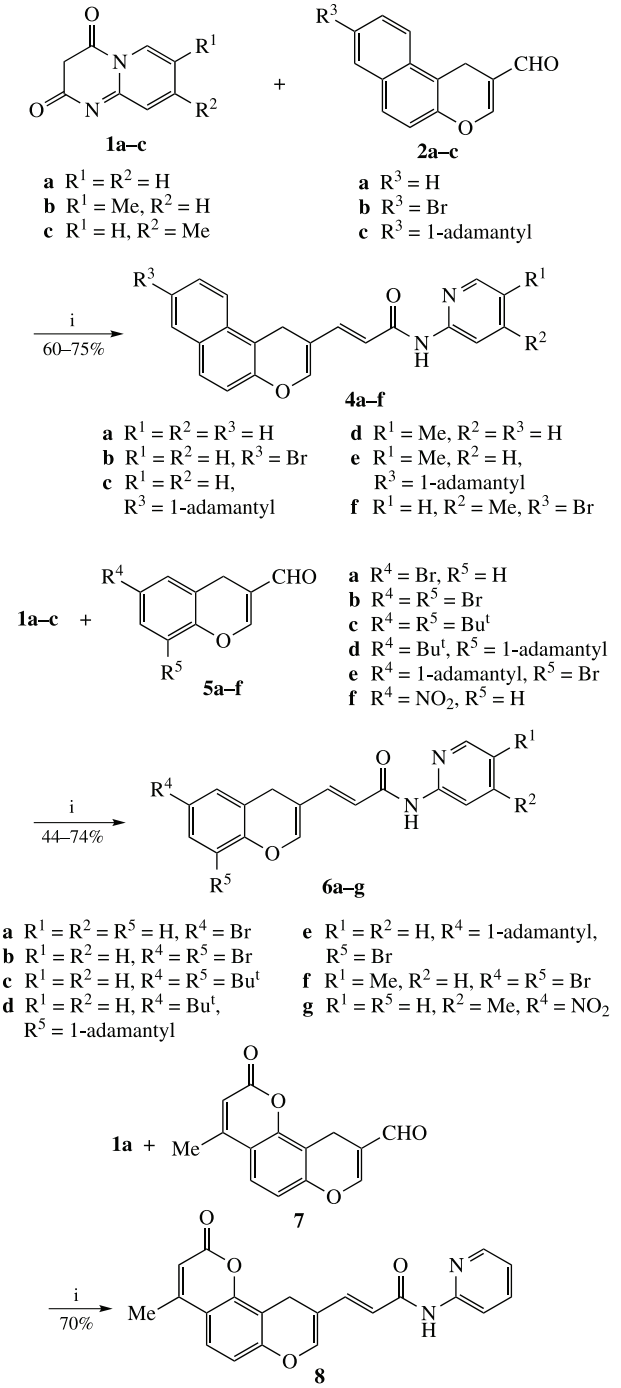

Scheme 2 *Reagents and conditions*: i, $AcONH_4$ (1 equiv.), AcOH, reflux, 8 h.

carbonyl group of the aldehyde by transforming it into a more electrophilic iminium salt,[21,27,28] although non-catalytic versions of the Knoevenagel condensation are also known.[29] In the resulting cyclic acetal **B**, an electrocyclic opening of the pyrimidinone fragment may occur with the formation of ketene intermediate **C** which would trap a water molecule to give carboxylic acid **D**. As a result of decarboxylation, which proceeds as a retro-Alder-ene reaction through a 6-membered transition state, a fused pyrano[2,3-*b*]pyran **E** is formed. Finally, electrocyclic opening of the 2*H*-pyran ring in it leads to thermodynamically more stable *trans*-isomers of *N*-(pyridin-2-yl)-acrylamides **4**, **6**, **8** (see Scheme 3).

In summary, we have developed a facile procedure for the synthesis of *trans*-*N*-(pyridin-2-yl)acrylamides bearing 4*H*-chromene fragment based on a cascade two-component reaction of 4*H*-chromene-3-carbaldehydes and 2*H*-pyrido[1,2-*a*]-pyrimidine-2,4(3*H*)-diones. The procedure is advantageous for easily accessible starting materials, good functional group tolerance, satisfactory yields, employment of very cheap and nontoxic catalyst, atom- and step-economy, simple reaction conditions, and easy isolation by a chromatography-free protocol.

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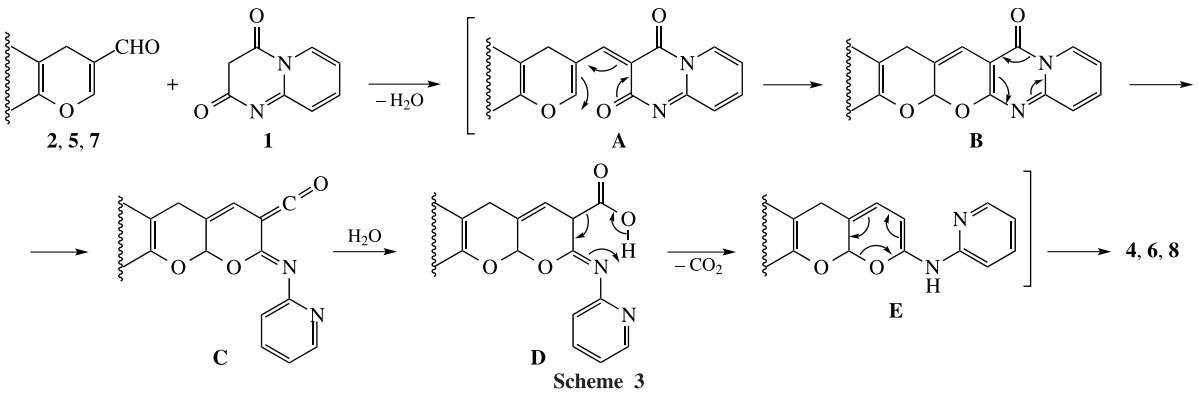
Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.030.

References

1 Y. Gawale and N. Sekar, *J. Lumin.*, 2018, **194**, 248.
2 Y. Gawale, A. Jadhav and N. Sekar, *Fibers Polym.*, 2018, **19**, 1678.
3 M. Abass and A. S. Mayas, *J. Chem. Res.*, 2009, 93.
4 M. Abass, M. M. Ismail, W. R. Abdel-Monem and A. S. Mayas, *Chem. Pap.*, 2010, **64**, 72.
5 A. Bishnoi, S. Singh, A. K. Tiwari, K. Srivastava, R. Raghuvir and C. M. Tripathi, *J. Chem. Sci.*, 2013, **125**, 305.
6 K. M. Elattar, R. Rabie and M. M. Hammouda, *Monatsh. Chem.*, 2017, **148**, 601.
7 P. Gupta, S. Gupta, A. Sachar and R. L. Sharma, *J. Heterocycl. Chem.*, 2010, **47**, 1188.
8 A. A. Esmaeili, F. Salehan, A. Habibi and A. R. Fakhari, *Tetrahedron Lett.*, 2016, **57**, 100.
9 N. F. H. Mahmoud and A. M. El-Saghiera, *J. Heterocycl. Chem.*, 2019, **56**, 1820.
10 P. Devi, A. Bishnoi and V. Singh, *Russ. J. Org. Chem.*, 2021, **57**, 265.
11 S. Jannati and A. A. Esmaeili, *Res. Chem. Intermed.*, 2017, **43**, 6817.
12 A. K. Verma, A. Bishnoi, S. Fatma, H. Parveen and V. Singh, *ChemistrySelect*, 2017, **2**, 4006.
13 S. M. Alwan and J. A.-S. Al-Kaabi, *Med. Chem.*, 2014, **4**, 635.
14 A. Rauf, S. Liaqat, A. M. Qureshi, M. Yaqub, A. U. Rehman, M. U. Hassan, Z. H. Chohan, F. U. H. Nasim and T. B. Hadda, *Med. Chem. Res.*, 2012, **21**, 60.
15 M. A. S. Gouda, M. A. I. Salem and N. F. H. Mahmoud, *J. Heterocycl. Chem.*, 2020, **57**, 3988.



Scheme 3

16 M. Abass and A. S. Mayas, *Heteroat. Chem*., 2007, **18**, 19.
17 H. R. Snyder and M. M. Robison, *J. Am. Chem. Soc.*, 1952, **74**, 4910.
18 M. A. Ibrahim and N. M. El-Gohary, *J. Heterocycl. Chem*., 2020, **57**, 2815.
19 A. A. Harutyunyan, *Russ. J. Org. Chem*., 2016, **52**, 916 (*Zh. Org. Khim.*, 2016, **52**, 920).
20 A. D. Dunn and R. Norrie, *Z. Chem*., 1990, **30**, 98.
21 V. A. Osyanin, D. V. Osipov, I. A. Semenova, K. S. Korzhenko, A. V. Lukashenko, O. P. Demidov and Yu. N. Klimochkin, *RSC Adv*., 2020, **10**, 34344.
22 V. A. Osyanin, D. V. Osipov, I. V. Melnikova, K. S. Korzhenko, I. A. Semenova and Yu. N. Klimochkin, *Synthesis*, 2020, **52**, 3604.
23 K. S. Korzhenko, V. A. Osyanin, D. V. Osipov and Yu. N. Klimochkin, *Mendeleev Commun*., 2021, **31**, 265.
24 D. V. Osipov, A. A. Artyomenko, V. A. Osyanin and Yu. N. Klimochkin, *Chem. Heterocycl. Compd*., 2019, **55**, 261 (*Khim. Geterotsikl. Soedin*., 2019, **55**, 261).
25 A. V. Lukashenko, V. A. Osyanin, D. V. Osipov and Yu. N. Klimochkin, *Chem. Heterocycl. Compd*., 2016, **52**, 711 (*Khim. Geterotsikl. Soedin*., 2016, **52**, 711).
26 V. A. Osyanin, A. V. Lukashenko and D. V. Osipov, *Russ. Chem. Rev*., 2021, **90**, 324.
27 I. A. Semenova, D. V. Osipov, Yu. V. Popova, V. A. Osyanin, O. P. Demidov and Yu. N. Klimochkin, *Chem. Heterocycl. Compd*., 2020, **56**, 1218 (*Khim. Geterotsikl. Soedin*., 2020, **56**, 1218).
28 I. A. Semenova, V. A. Osyanin, D. V. Osipov and Yu. N. Klimochkin, *Chem. Heterocycl. Compd*., 2021, **57**, 691 (*Khim. Geterotsikl. Soedin*., 2021, **57**, 691).
29 M. N. Elinson, A. N. Vereshchagin, Yu. E. Anisina, N. A. Leonova and M. P. Egorov, *Mendeleev Commun*., 2020, **30**, 15.

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