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Direct Synthesis of Functional Azaxanthones by Using a Domino Three-Component Reaction

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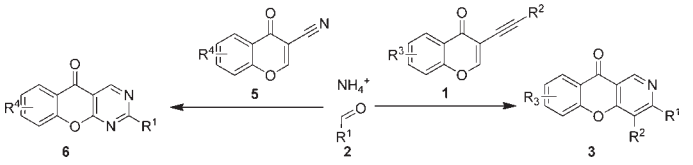
ABSTRACT



NH aldimines, generated in situ from the corresponding aldehydes by reaction with ammonium acetate, serve as nitrogen nucleophiles in reactions with 3-(1-alkynyl)chromones and 3-cyanochromones that generate functionalized azaxanthones. These processes take place under mild conditions that do not require dry solvents. The products of the reactions described represent new chemical entities. We believe that the newly developed cascade process will serve as a potent method for the synthesis of N-heterocycles and in diversity-oriented synthesis.

One pot, multicomponent reactions (MCRs) are powerful tools for the preparation of biologically relevant, natural product-like molecular frameworks.[1] Based on the properties of unique intermediates, these processes can be rationally designed so that they serve as ideal approaches for the efficient synthesis of structurally complex and functionally diverse molecules that play the role of lead compounds in drug discovery efforts.[2] In this regard, 2-(1-alkynyl)-2-alken-1-ones are attractive starting materials for multicomponent processes because they undergo transition metal, Lewis acid,[3] and electrophile-induced cascade cyclization reactions[4] promoted by nucleophiles to form highly substituted furans. Also, cascade reactions of these substances, initiated by additions of carbon and oxygen nucleophiles under base conditions, are known to proceed through domino-type Michael addition−cyclization sequences to form pyrans[3j,5] and carbocycles[3q,6].

Recent studies in our group have focused on the development of cascade reactions of 3-(1-alkynyl) chromones that have been utilized to generate diverse molecular scaffolds. Due to their propensity to undergo ring-opening and secondary cyclization reactions, chromones take part

(1) For examples of recent reviews, see: (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472. (b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (c) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234–6246.

(2) (a) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402–13404. (b) Ko, S. K.; Jang, H. J.; Kim, E.; Park, S. B. *Chem. Commun.* **2006**, 2962–2964. (c) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296–3298. (d) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900–6905.

(3) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (b) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531–4534. (c) Liu, X.; Pan, Z.; Shu, X.; Duan, X.; Liang, Y. *Synlett* **2006**, 1962–1964. (d) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307–5310. (e) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903–1906. (f) Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 617–629. (g) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505–5508. (h) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594–3596. (i) Liu, R.; Zhang, J. *Chem.—Eur. J.* **2009**, *15*, 9303–9306. (j) Gao, H.; Zhao, X.; Yu, Y.; Zhang, J. *Chem.—Eur. J.* **2010**, *16*, 456–459. (k) Liu, F.; Qian, D.; Li, L.; Zhao, X.; Zhang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6669–6672. (l) Li, W.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8839–8841. (m) Liu, R.; Zhang, J. *Adv. Synth. Catal.* **2011**, *353*, 36–40. (n) Krafft, M. E.; Vidhani, D. V.; Cran, J. W.; Manoharan, M. *Chem. Commun.* **2011**, *47*, 6707–6709. (o) Xie, X.; Du, X.; Chen, Y.; Liu, Y. *J. Org. Chem.* **2011**, *76*, 9175–9181. (p) Rauniyar, V.; Wang, Z. J.; Burks, H. E.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 8486–8489.

(4) (a) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609–4611. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679–7685. (c) Cho, C.-H.; Larock, R. C. *Tetrahedron Lett.* **2010**, *51*, 3417–3421. (d) Cho, C.-H.; Larock, R. C. *ACS Comb. Sci.* **2011**, *13*, 272–279.

(5) (a) Hu, J.; Liu, L.; Yang, S.; Liang, Y.-M. *Org. Biomol. Chem.* **2011**, *9*, 3375–3379. (b) Yu, X.; Cao, Z.; Zhang, J. *Org. Biomol. Chem.* **2010**, *8*, 5059–5061.

(6) Li, W.; Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 3083–3088.

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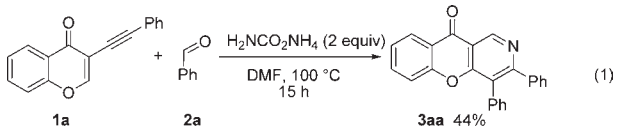
in base promoted cascade reactions that afford a diverse array of xanthones,[7] a structural unit found in a large number of naturally occurring and synthetic bioactive compounds.[8] Introduction of a nitrogen atom in the xanthone framework with a pyridine or pyrimidine core would lead to a more drug-like skeleton with the hope that it can be employed in the discovery of lead compounds. Below, we describe the results of a recent study that has led to the development of a direct method for the synthesis of diverse functionalized azaxanthones that employs a domino, three-component reaction.

Prior to the current investigation, a few examples involving reactions initiated by Michael addition of nitrogen to 2-(1-alkynyl)-2-alken-1-ones[9] had been described. We envisaged that in situ generated N-unsubstituted aryl aldimines[10] would act as nucleophiles[11] in Michael addition reactions with 3-(1-alkynyl)chromones that would initiate a novel cascade sequence to produce azaxanthones. In order to test this proposal, a mixture of 3-(1-alkynyl)-chromone (**1a**), benzaldehyde (**2a**) (1.5 equiv), and $H_2NCO_2NH_4$ (2 equiv) in DMF was stirred at 100 °C for 15 h (eq 1). The process occurring under these conditions did indeed generate the azaxanthone **3aa** in 44% yield. The structure of **3aa** was assigned by using X-ray crystallographic analysis.[12]

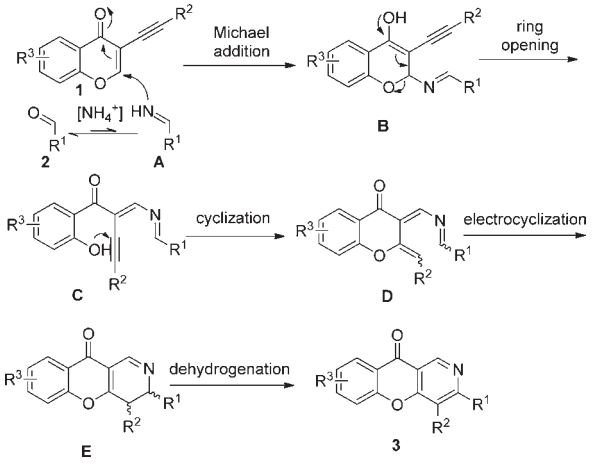


1a **2a** **3aa** 44% (1)

The proposed mechanism for this process, depicted in Scheme 1, begins with the addition of the NH aldimine **A**, formed in situ by condensation of the aldehyde with ammonia, to 3-(1-alkynyl)chromone serving as a Michael acceptor. This step is followed by the opening of the pyrone ring in **B** to afford intermediate **C**, which then undergoes regioselective intramolecular cyclization to produce 2-azatriene intermediate **D**. Finally, 6π-electrocyclization of **D** followed by dehydrogenation[13] of the dihydropyridine ring in **E** affords 2-azaxanthone **3**. To the best of our knowledge, this is the first example of a process that forms an azaxanthone through a domino sequence initiated by reaction of a 3-(1-alkynyl)chromone with an NH aldimine. Moreover, this new cascade reaction represents a concise method for the construction of the natural product-like, functionallized 2-azaxanthone framework.[14]

Studies were carried out to determine the optimal conditions for the 2-azaxanthone forming reaction. The results obtained from screening several ammonia sources showed that $NH_2CO_2NH_4$, $AcONH_4$, HCO_2NH_4, and NH_4HCO_3 all promote the tandem process with 3 equiv of $AcONH_4$ giving optimal results (Table 1, entries 1–6, 9–10). A poor efficiency was observed for the reaction in which NH_4Cl or $(NH_4)_2SO_4$ was employed (Table 1, entries 7–8). DMF was found to be a superior solvent for the reaction in contrast to ethanol, DMSO, toluene, and dioxane

Scheme 1. A Proposed Reaction Mechanism



(7) (a) Zhao, L.; Xie, F.; Cheng, G.; Hu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6520–6523. (b) Xie, F.; Pan, X.; Lin, S.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1378–1381. (c) Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3086–3089. (d) Gong, J.; Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3848–3851. (e) Liu, Y.; Huang, L.; Xie, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 6304–6307. (f) Li, D.; Duan, S.; Hu, Y. *J. Comb. Chem.* **2010**, *12*, 895–899. (g) Liu, Y.; Huang, L.; Xie, F.; Chen, X.; Hu, Y. *Org. Biomol. Chem.* **2011**, *9*, 2680–2684.

(8) For examples of recent studies, see: (a) Kikuchi, H.; Ohtsuki, T.; Koyano, T.; Kowithayakorn, T.; Sakai, T.; Ishibashi, M. *J. Nat. Prod.* **2009**, *73*, 452–455. (b) Duan, Y.-H.; Dai, Y.; Wang, G.-H.; Zhang, X.; Chen, H.-F.; Chen, J.-B.; Yao, X.-S.; Zhang, X.-K. *J. Nat. Prod.* **2010**, *73*, 1283–1287. (c) Gobbi, S.; Zimmer, C.; Belluti, F.; Rampa, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2010**, *53*, 5347–5351. (d) Marks, K. M.; Park, E. S.; Arefolov, A.; Russo, K.; Ishihara, K.; Ring, J. E.; Clardy, J.; Clarke, A. S.; Pelish, H. E. *J. Nat. Prod.* **2011**, *74*, 567–573. (e) González-Andrade, M.; Rivera-Chávez, J.; Sosa-Peinado, A.; Figueroa, M.; Rodríguez-Sotres, R.; Mata, R. *J. Med. Chem.* **2011**, *54*, 3875–3884. (f) Ren, Y.; Matthew, S.; Lantvit, D. D.; Ninh, T. N.; Chai, H.; Fuchs, J. R.; Soejarto, D. D.; Carcache de Blanco, E. J.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2011**, *74*, 1117–1125. (g) Correia-da-Silva, M.; Sousa, E.; Duarte, B. R.; Marques, F.; Carvalho, F.; Cunha-Ribeiro, L. M.; Pinto, M. M. M. *J. Med. Chem.* **2011**, *54*, 5373–5384.

(9) (a) Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **2010**, *12*, 1876–1879. (b) Chen, W. L.; Li, J.; Zhu, Y. H.; Ye, L. T.; Hu, W.; Moa, W. M. *ARKIVOC* **2011**, *9*, 381–392.

(10) For discussions about the instability of NH aldimines, see: (a) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288–3295. (b) Nielsen, A. T.; Atkins, R. L.; DiPol, J.; Moore, D. W. *J. Org. Chem.* **1974**, *39*, 1349–1355. (c) Boyd, D. R.; Coulter, P. B.; Hamilton, R.; Thompson, N. T.; Sharma, N. D.; Stubbs, M. E. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2123–2127. (d) Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217–4218.

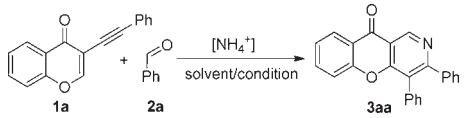
(11) (a) Vugts, D. J.; Jansen, H.; Schmitz, R. F.; de Kanter, F. J. J.; R. Orru, V. A. *Chem. Commun.* **2003**, 2594–2595. (b) Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369–5372. (c) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem.—Eur. J.* **2006**, *12*, 7178–7189.

(12) CCDC 883774 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/services/structure_deposit/.

(13) For discussions of electrocyclization and dehydrogenation reactions of azatrienes, see: (a) Barluenga, J.; Ferrero, M.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2193–2197. (b) Molina, P.; Pastor, A.; Vilaplana, M. J. *Tetrahedron* **1993**, *49*, 7769–7778. (c) Palacios, F.; Alonso, C.; Rubiales, G. *J. Org. Chem.* **1997**, *62*, 1146–1154. (d) Palacios, F.; Gil, M. J.; de Marigorta, E. M.; Rodríguez, M. *Tetrahedron* **2000**, *56*, 6319–6330. (e) Bonini, C.; D'Auria, M.; Funicello, M.; Romaniello, G. *Tetrahedron* **2002**, *58*, 3507–3512. (f) Palacios, F.; Alonso, C.; Rodríguez, M.; de Marigorta, E. M; Rubiales, G. *Eur. J. Org. Chem.* **2005**, 1795–1804.

(Table 1, entries 5, 11–14). In addition, the yield of the process is not sensitive to the presence of moisture (Table 1, entry 15). The findings arising in this exploratory study indicate that optimized conditions for the 2-azaxanthone forming reaction starting with **1a** (1 equiv) and the aldehyde (1.5 equiv) involve the use of 3 equiv of $AcONH_4$ in DMF at 100 °C for 15 h.

Table 1. Optimization of the 2-Azaxanthone Forming, Three-Component Reaction[a]



entry	solvent	$[NH_4^+]$ (equiv)	temp/time	yield (%)[b]
1	DMF	$NH_2CO_2NH_4$(2)	100 °C/15 h	44
2	DMF	$NH_2CO_2NH_4$(5)	100 °C/15 h	49
3	DMF	$NH_2CO_2NH_4$ (10)	100 °C/15 h	44
4	DMF	$AcONH_4$ (2)	100 °C/15 h	43
5	DMF	$AcONH_4$ (3)	100 °C/15 h	80
6	DMF	$AcONH_4$ (5)	100 °C/15 h	78
7	DMF	NH_4Cl (3)	100 °C/15 h	NR[c]
8	DMF	$(NH_4)_2SO_4$ (2)	100 °C/15 h	NR
9	DMF	NH_4HCO_3 (3)	100 °C/15 h	67
10	DMF	HCO_2NH_4 (3)	100 °C/15 h	64
11	EtOH	$AcONH_4$ (3)	80 °C/24 h	76
12	DMSO	$AcONH_4$ (3)	100 °C/24 h	57
13	PhMe	$AcONH_4$ (3)	100 °C/24 h	NR
14	dioxane	$AcONH_4$ (3)	100 °C/24 h	NR
15[d]	DMF	$AcONH_4$ (3)	100 °C/15 h	75

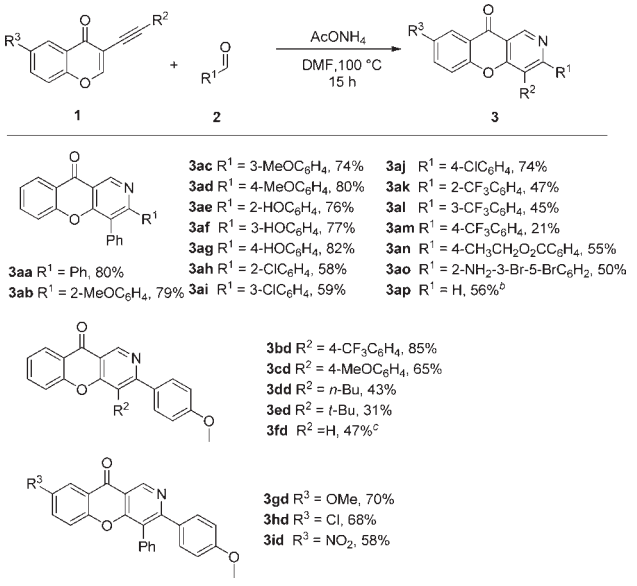
[a] Reaction conditions: a mixture of **1a** (0.5 mmol), **2a** (0.75 mmol), and ammonia source was stirred at the indicated temperature and time. [b] Isolated yields. [c] No reaction. [d] 4 Å molecular sieves were present.

Reactions of 3-(1-alkynyl)chromone **1a** with various substituted aromatic aldehydes **2** were investigated using the optimized conditions (Scheme 2). The results show that although the efficiency of the reaction is not influenced by the steric bulkiness of the benzaldehyde derivatives, it is significantly sensitive to electronic properties of the aldehydes. Specifically, benzaldehydes containing strongly electron-donating groups, regardless of their position on the arene ring, react to give products (**3ab**–**3ag**) in high yields (Scheme 2). In contrast, electron-withdrawing group substituted benzaldehydes afford 2-azaxanthone products (**3ak**–**3am**) in only moderate yields (Scheme 2) with the dimeric byproduct of **1a**.[7b] The latter effect may be a consequence of the weak nucleophilicity of electron-poor NH aldimines. The results of this exploratory investigation demonstrate that the new cascade reaction is compatible with hydroxy, chlorine, bromine, amino, and ester substituted benzaldehydes that react to form products (**3ae**–**3ak** and **3an**–**3ao**) in acceptable yields (Scheme 2).

(14) Payne, D. J.; Hueso-Rodríguez, J. A.; Boyd, H.; Concha, N. O.; Janson, C. A.; Gilpin, M.; Bateson, J. H.; Cheever, C.; Niconovich, N. L.; Pearson, S.; Rittenhouse, S.; Tew, D.; Díez, E.; Pérez, P.; de la Fuente, J.; Rees, M.; Rivera-Sagredo, A. *Antimicrob. Agents Chemother.* **2002**, *46*, 1880–1886.

Finally, when paraformaldehyde is employed as the aldehyde starting material, reaction of **1a** produces the corresponding 2-azaxanthone **3ap** in 56% yield (Scheme 2). The enolizable aldehydes, such as phenylacetaldehyde and valeraldehyde, and α,β-unsaturated aldehydes, such as crotonaldehyde, all give complicated results due to the instability of their NH aldimines.[10]

Scheme 2. Synthesis of Substituted 2-Azaxanthones[a]



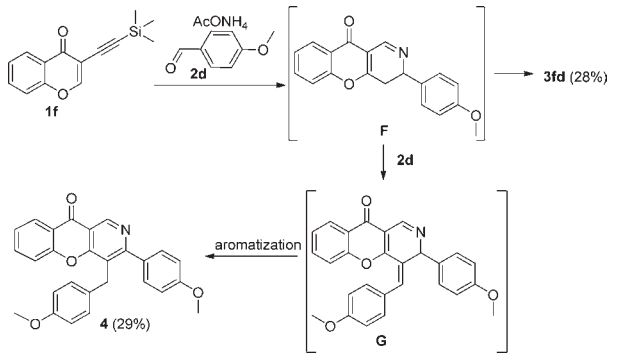
[a] Reaction conditions: a mixture of **1** (0.5 mmol), aldehyde (0.75 mmol), and ammonium acetate (1.5 mmol) in DMF (10 mL) was stirred at 100 °C for 15 h. [b]Paraformaldehyde (75 mg) was used. [c]1.05 equiv of 4-methoxybenzaldehyde was used.

Reactions utilizing various 3-(1-alkynyl)chromones were studied to explore the scope of the new domino reaction. Good yields of products were observed for reactions of 3-(1-alkynyl)chromone **1a** containing aromatic substituents (R^2) on the acetylene moiety (Scheme 2, **3aa**, **3bd**–**3cd**). However, when R^2 is a linear or sterically hindered (*tert*-butyl) alkyl group, reactions take place to form 2-azaxanthones (**3dd**–**3ed**) in lower yields with complicated byproducts (Scheme 2). The R^2 = trimethylsilyl substituted chromone (**1f**) undergoes reaction to generate the corresponding desilylated product **3fd** in 47% yield (Scheme 2). Finally, the process also tolerates various substituents (R^3) on the arene ring of the 3-(1-alkynyl)-chromone (Scheme 2, **3gd**–**3id**).

During the exploratory study, we observed that treatment of chromone **1f** with an excess (2.5 equiv) of 4-methoxybenzaldehyde (**2d**) and $AcONH_4$ (3 equiv) in DMF at 100 °C leads to formation of the corresponding 2-azaxanthone **3fd**, along with the byproduct **4** in 29% yield (Scheme 3). It is likely that **4** is generated by a sequence in which the dihydropyridine intermediate **F** undergoes condensation with 4-methoxybenzaldehyde to generate **G**, which then aromatizes (Scheme 3).

The success of the new cascade reaction encouraged us to carry out the studies aimed at extending the scope of the

Scheme 3. In *Situ* Trapping of Dihydropyridine Intermediate **F**



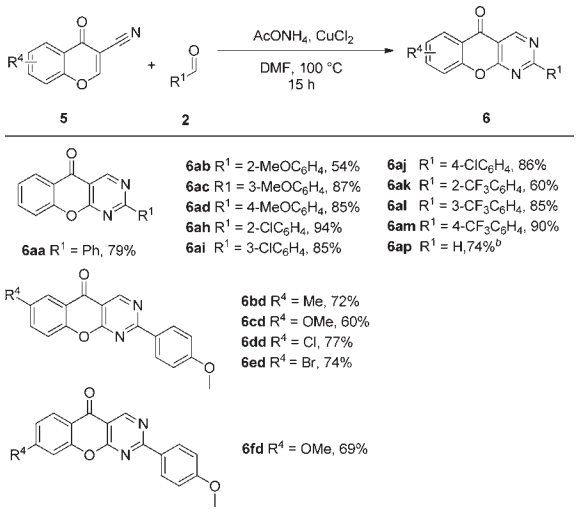
process to other Michael acceptors. The results of this effort showed that 3-cyanochromone **5** (R^4 = H) reacts with benzaldehyde derivative **2** (R^1 = 4-$MeOC_6H_4$) to form 2,4-diazaxanthones **6ad** (Table S1 in the Supporting Information). A brief optimization effort demonstrated that the yield of the 2,4-diazaxanthone forming reaction could be increased to 85% when 1.2 equiv of $CuCl_2$ was present as an oxidant in the reaction mixture.[15] Reactions of cyanochromone **5a** (R^4 = H) with a wide range of electron-rich, -neutral, and -deficient benzaldehydes **2**, under the optimized conditions, were found to generate the corresponding products **6aa**–**6am** in good to excellent yields (Scheme 4). When paraformaldehyde is employed as the aldehyde, the unsubstituted 2,4-diazaxanthone **6ap** is produced in 74% yield (Scheme 4). This process takes place efficiently when 3-cyanochromones containing a variety of arene ring substituents serve as starting materials (Scheme 4, **6bd**–**6fd**). The structure of **6ad** was unambiguously elucidated by using X-ray crystal structure analysis.[16]

In conclusion, the observations made in this investigation show that NH aldimines, generated in situ by condensations of the corresponding aldehydes with ammonium acetate, serve as nitrogen nucleophiles in efficient cascade reactions

(15) (a) Ciesielski, M.; Pufky, D.; Döring, M. *Tetrahedron* **2005**, *61*, 5942–5947. (b) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285–3287. (c) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732–4735.

(16) CCDC 883773 (**6ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/services/structure_deposit/.

Scheme 4. Synthesis of Substituted 2,4-Diazaxanthones[a]



[a] Reaction conditions: **5** (0.5 mmol), aldehyde (0.75 mmol), ammonium acetate (1.5 mmol), $CuCl_2$ (0.6 mmol), DMF (10 mL), 100 °C, 15 h. [b] Paraformaldehyde (75 mg) was used.

with 3-(1-alkynyl)chromones and 3-cyanochromones. Importantly, these processes, which generate diverse functionalized azaxanthones, take place under mild conditions and without the need for dry solvents. Moreover, the results open the door for the use of unsubstituted aldimines in other types of tandem processes. Further investigations probing the scope and synthetic applications of the reaction and the biological properties of new substances produced are underway and will be described in due course.

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Supporting Information Available. Experimental procedures and characterization data of compounds **3aa**–**3id**, **4**, and **6aa**–**6fd**; X-ray structure and crystallographic data in CIF format of compounds **3aa** and **6ad**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.