

One-Pot Synthesis of 3-Triazolyl-2-iminochromenes via a Catalytic Three Component Cascade Reaction

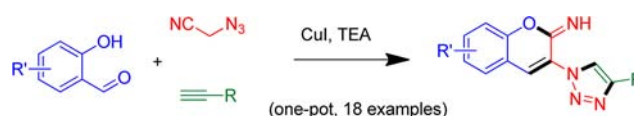
Wenyuan Qian,* Albert Amegadzie, David Winternheimer, and Jennifer Allen

Therapeutic Discovery, Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, United States

wqian@amgen.com

Received April 24, 2013

ABSTRACT



A variety of 3-triazolyl-2-iminochromenes were synthesized in a one-pot, catalytic, three component condensation. In this event, a Cu(I)-catalyzed cycloaddition between 2-azidoacetonitrile and an alkyne formed a triazole and activated the neighboring methylene group, inducing an aldol–cyclization–dehydration sequence in the presence of a salicylaldehyde. Further elaboration led to more complex polyheterocycles.

The efficient construction of diverse and elaborated heterocycles from simple starting materials is highly desirable in medicinal chemistry and material sciences yet remains a continuing challenge in organic synthesis. Multiple component reactions (MCRs), due to their convergent nature, are ideal tools to address this demand.^{1,2} Combining a series of “two-component” reactions in a reaction vessel can be operationally efficient. However, many of these one-pot, stepwise procedures require a specific order of addition of components/reagents or different conditions for each individual transformation. In contrast, “ideal” MCRs are conducted under the same conditions by adding all starting materials at the same time.^{2a,e} Therefore, better control of interactions among components/intermediates and, thus, more organized reaction pathways are essential in the design of new MCRs from existing reactions of lower dimensions. In principle, there are two requirements in “ideal” three-component reactions: (1) the direct product of the first two component reaction should be able to react with the next component automatically; (2) the third component

does not react irreversibly with the first two components to complicate the outcome of the condensation.^{2e,f}

In efforts to develop new MCRs, we were interested in exploiting the high chemoselectivity of the Cu(I) catalyzed azide–alkyne cycloaddition (CuAAC) reaction. This “click chemistry” has found many applications in drug discovery, bioconjugation and material sciences in the past decade.^{3–5} CuAAC reaction is attractive for participation in multiple component assembly processes due to its superior selectivity, reliability, and efficiency. In addition, alkyne and azide groups have a unique window of reactivity that makes them compatible with many other reactants. Utilizing these characteristics, some groups have successfully combined triazole formation with other reactions to construct more complex structures.⁶ Nevertheless, the utility of the *electronic outcome* of this powerful transformation has received little attention. We reasoned that switching from the azide group to the triazole group could have an impact on the reactivity of its neighboring groups in subsequent transformations. In accord with the design principles mentioned before, this

(1) *Multicomponent reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley: Weinheim, 2005.

(2) For reviews, see: (a) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371. (b) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (e) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 3, 366. (f) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

(3) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(4) For recent reviews on click chemistry, see: (a) Themed issue: *Click chemistry: Function follows form*; Finn, M. G.; Fokin, V. V., Eds. *Chem. Soc. Rev.* **2010**, *39*, 1221–1408. (b) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem.—Asian J.* **2011**, *6*, 2696.

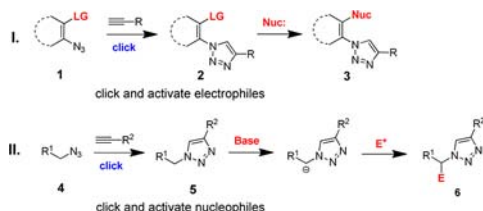
(5) *Click Chemistry for Biotechnology and Materials Science*; Lahann, J., Ed.; John Wiley & Sons: Hoboken, NJ, 2009.

aspect of the CuAAC reaction provides opportunities to construct new “ideal” MCRs.

Recently, we disclosed a general “click-and-activate” protocol in Scheme 1: a click reaction on azide **1** provided triazole **2** which led to activation of the leaving group substituted conjugated double bond toward nucleophilic attack to give **3** in one pot.⁷ This concept was demonstrated in a facile synthesis of a triazolyl-pyridazinone library^{7a} and, later, in a one-pot assembly of triazole-fused pyrazinopyridazindione tricycles.^{7b}

Here we propose a conceptually different “click-and-activate” protocol in Scheme 1: CuAAC of azide **4** should make the methylene group in the resulting triazole **5** more acidic and easily deprotonated by a base. Consequently, the stabilized carbanion should be a good substrate to be captured by a variety of electrophiles to afford **6** in one pot. Compared to the first “click-and-activate electrophiles” (CAE) protocol, this second “click-and-activate nucleophiles” (CAN) strategy should have even broader application in terms of both the substrate scope and reaction types involving stabilized carbanions.

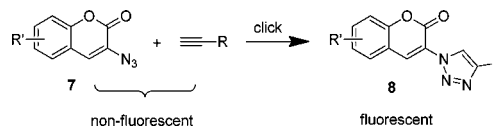
Scheme 1. “Click and Activate” in Two Different Ways



Coumarins and chromenes are interesting biocompatible heterocycles.^{8,9} Recently, 3-triazolylcoumarins **8** have attracted particular attention after Wang's group reported an elegant fluorogenic CuAAC reaction between 3-azidocoumarins **7** (as the profluorophore) and acetylenes (Scheme 2).¹⁰ This fluorogenic chemistry has found many

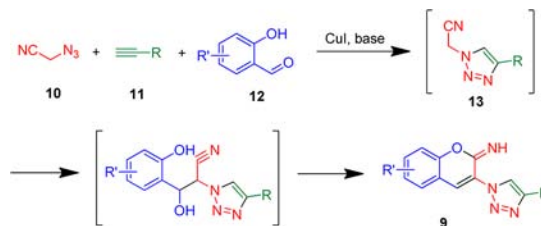
applications in the fields of drug discovery,¹¹ bioconjugation, and sensors.^{12,13}

Scheme 2. Wang's Fluorogenic Click Reaction



Nevertheless, the existing preparations of 3-azidocoumarins **7** require several synthetic steps involving strongly acidic conditions to install the azide group.¹⁰ Apparently, these procedures are tedious and particularly unsuitable for the synthesis of acid labile 3-triazolyl-2-iminochromenes which have not been reported in the literature. Here we report a facile, one-pot synthesis of 3-triazolyl-2-iminochromene **9** directly from the condensation of 2-azidoacetonitrile **10**, acetylene **11**, and salicylaldehyde **12** in a tandem “CuAAC–aldol–cyclization–dehydration” sequence (Scheme 3) as the first case study of our “click-and-activate nucleophiles” (CAN) approach toward MCRs.

Scheme 3. One-Pot Synthesis of 3-Triazolyl-2-iminochromenes



In the literature, the CuI/NR₃ combination has been a convenient catalytic system for CuAAC reactions in organic solvents. Meanwhile, efficient deprotonation of the activated methylene group is also desirable in an aldol reaction. Therefore, it would be possible and beneficial to use the same weak base to facilitate both steps in one pot.

Here we were also curious to see if the third component, salicylaldehyde, had any effect on the CuAAC step (Table 1). When 0.1 equiv of 5-methylsalicylaldehyde **12a** was added to a 0.5 M ethanol solution of 2-azidoacetonitrile **10**,¹⁴ 1.0 equiv of phenylacetylene **11a**, and 5 mol % of CuI,

(12) Droumaguet, C. L.; Wang, C.; Wang, Q. *Chem. Soc. Rev.* **2010**, 39, 1233 and the references therein.

(13) For some recent examples in bioconjugation and sensors, see: (a) Hong, V.; Presolski, S. I.; Ma, C.; Finn, M. G. *Angew. Chem., Int. Ed.* **2009**, 48, 9879. (b) Du, L.; Ni, N.; Li, M.; Wang, B. *Tetrahedron Lett.* **2010**, 51, 1152. (c) Kamaruddin, M. A.; Ung, P.; Hossain, M. I.; Jarasrassamee, B.; O'Malley, W.; Thompson, P.; Scanlon, D.; Cheng, H.-C.; Graham, B. *Bioorg. Med. Chem. Lett.* **2011**, 21, 329. (d) Zhou, Y.; Liu, K.; Li, J.-Y.; Fang, Y.; Zhao, T.-C.; Yao, C. *Org. Lett.* **2011**, 13, 1290. (e) Morris, J. C.; McMurtrie, J. C.; Bottle, S. E.; Fairfull-Smith, K. E. *J. Org. Chem.* **2011**, 76, 4964.

(14) In all related experiments in this paper, the volatile and potentially hazardous 2-azidoacetonitrile **10** was prepared by treatment of a 10 M chloroacetonitrile solution in DMF with 1 equiv of sodium azide for 2 h and was then diluted with ethanol and used directly without isolation.

(6) For examples of combining triazole formation with other reactions to construct diverse structures, see: (a) Ramachary, D. B.; Barbas, C. F., III. *Chem.—Eur. J.* **2004**, 10, 5323. (b) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, 6, 884. (c) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, 45, 8439. (d) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, 46, 9053. (e) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, 10, 3081. (f) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, 13, 852. (g) Donald, J. R.; Wood, R. R.; Martin, S. F. *ACS Comb. Sci.* **2012**, 14, 135. (h) Groenendaal, B.; Ruijter, E.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Biomol. Chem.* **2008**, 6, 3158.

(7) (a) Qian, W.; Winternheimer, D.; Allen, J. *Org. Lett.* **2011**, 13, 1682. (b) Qian, W.; Winternheimer, D.; Amegadzie, A.; Allen, J. *Tetrahedron Lett.* **2012**, 53, 271.

(8) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications, and Mode of Action*; Wiley & Sons: Chichester, 1997.

(9) For a recent review on chromane derivatives, see: Masesane, I. B.; Desta, Z. Y. *Beilstein J. Org. Chem.* **2012**, 8, 2166.

(10) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, 6, 4603.

(11) (a) Peterson, L. B.; Blagg, B. S. J. *Bioorg. Med. Chem. Lett.* **2010**, 20, 3957. (b) Soto-Ortega, D. D.; Murphy, B. P.; Gonzalez-Velasquez, F. J.; Wilson, K. A.; Xie, F.; Wang, Q.; Moss, M. A. *Bioorg. Med. Chem.* **2011**, 19, 2596.

virtually no effect was observed on the rate of triazole formation (7% and 8% conversion at 2 h, entries 1 and 3, respectively). Interestingly, a combination of 0.1 equiv of **12a** and 0.1 equiv of triethylamine greatly accelerated the CuAAC reaction (entry 4, Table 1). The reaction rate under this condition is 2-fold faster than that in the presence of only triethylamine, and over 20-fold faster than that in the absence of the base, as indicated by the approximate $t_{1/2}$ of the three parallel reactions (~ 1 h, ~ 2 h, and > 24 h for entries 4, 2, and 1, respectively). It is known that deprotonated salicylaldehydes act as versatile bidentate ligands to form a wide variety of Cu complexes with different coordination numbers and geometries.¹⁵ In the literature, some ligands significantly accelerate the CuAAC reaction via activation or stabilization of the catalytic Cu(I) species.¹⁶ So it is feasible that deprotonated **12a** can play a similar chelating role to promote the reaction, albeit to a lesser extent. Another possible reason for this intriguing rate acceleration could be the ability of **12a** to buffer the basicity of the triethylamine and facilitate the protonation of the 5-cuprated 1,2,3-triazole key intermediate in the final stage of the CuAAC catalytic cycle.^{16f}

The “click-and-activate” concept was demonstrated in the following control experiments (Scheme 4). Treatment of triazole **13a** in ethanol with 1 equiv of **12a** and 1 equiv of triethylamine led to 85% conversion to 3-triazolyl-2-iminochromene **9a** in 24 h. In comparison, azide **10** failed to afford any amount of 3-azido-2-iminochromene **14** under the same conditions. Benzylnitrile was also tested, and only a trace of conversion to 3-phenyl-2-iminochromene **15** was detected after 24 h.

Table 1. Additive Effects on CuAAC Reaction

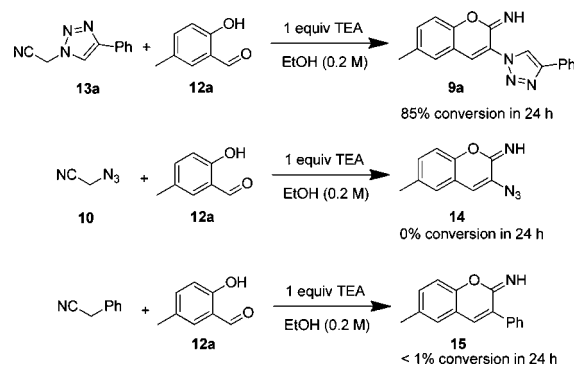
entry	TEA		conversion from 11a to 13a ^a		
			1 h	2 h	24 h
1	0	0	3%	7%	41%
2	0.1 equiv	0	29%	54%	89%
3	0	0.1 equiv	4%	8%	47%
4	0.1 equiv	0.1 equiv	54%	80%	100%

^a The conversion was calculated based on relative HPLC peak area integrations of **13a** and **11a** at 215 nm.

(15) (a) Perez, E.; Moreno-Manas, M.; Sebastian, R. M.; Vallribera, A.; Jutand, A. *Eur. J. Inorg. Chem.* **2010**, 7, 1013. (b) Guo, H.; Zhao, G. *Asian J. Chem.* **2008**, 20, 2781. (c) Gagne, R. R.; Spiro, C. L.; Smith, T. J.; Hamann, C. A.; Thies, W. R.; Shiemke, A. D. *J. Am. Chem. Soc.* **1981**, 103, 4073.

(16) For selected references, see: (a) Chan, R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, 6, 2853. (b) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, 129, 12696. (c) Rodionov, V. O.; Presolski, S. I.; Daz, D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, 129, 12705. (d) He, Y.; Bian, Z.; Kang, C.; Cheng, Y.; Gao, L. *Chem. Commun.* **2010**, 46, 3532. (e) Shao, C.; Wang, X.; Xu, J.; Zhao, J.; Zhang, Q.; Hu, Y. *J. Org. Chem.* **2010**, 75, 7002. (f) Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y. *J. Org. Chem.* **2011**, 76, 6832.

Scheme 4. Control Experiments on 2-Iminochromene Formation

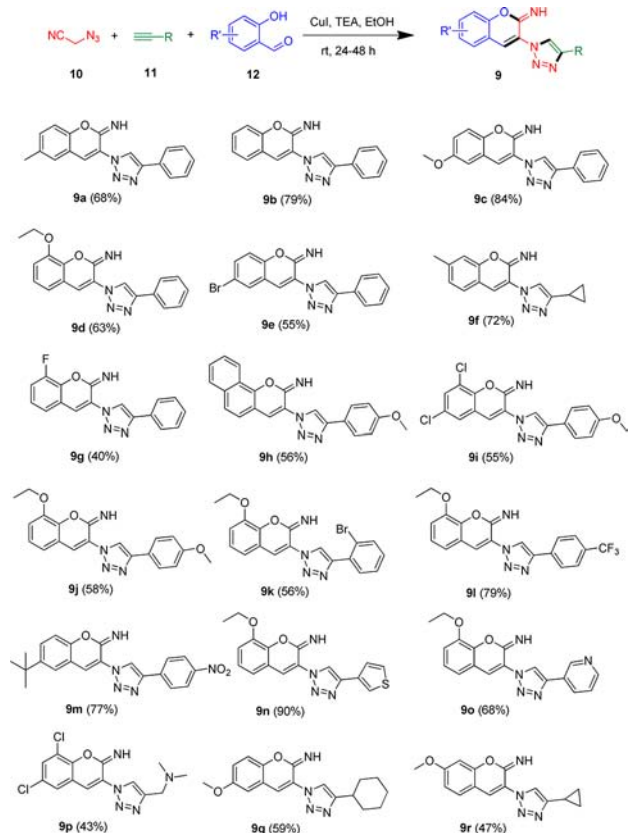


Since the same base and solvent can be used in both steps, it was convenient to run the entire three component condensation in one pot (**9a** in Scheme 5) as follows: To a 1 M ethanol solution of **10** were added **11a** (1.1 equiv), **12a** (1 equiv), and triethylamine (2 equiv). As expected from control experiments, no desired transformation was observed. Upon adding a catalytic amount of CuI (5 mol %), the mutually promoted CuAAC–aldol–cyclization–dehydration cascade was triggered. Both the intermediate **13a** and the final product **9a** were detected by HPLC in 5 min. After stirring for 24 h, the solvents were removed under reduced pressure and the residue was suspended in water and then filtered. The collected solid was sequentially washed with 2% of NH_4OH , water, and methanol and was air-dried on the filtering funnel for 1 h to give analytically pure product **9a** (68% yield). It should be mentioned that the easy purification by filtration and washing was critical not only for operational simplicity but also because attempts to purify the product by silica gel column led to partial hydrolysis of the 2-iminochromene to the corresponding coumarin.

In this three component condensation, two rings and four bonds of three different types (one C–C, one C–O, and two C–N bonds) are formed in one pot. It is striking that all four new bonds are formed with 2-azidoacetonitrile (**10**) which comprises only six heavy atoms. This small molecule of remarkable bond-forming potential remains latent in the presence of the other two components *until a catalyst is introduced to stitch them together via our designed pathway*.

The easy execution of this three component reaction provides rapid access to substituent diversity on the 3-triazolyl-2-iminochromene scaffold by condensing a variety of salicylaldehydes **12** and alkynes **11** with **10** as shown in Scheme 5. Both electron-donating groups such as alkoxy- and electron-withdrawing groups such as bromo-, dichloro-, and fluoro- are tolerated at various positions on the salicylaldehyde component. On the other side, a range of alkynes bearing electron-rich (**9h–j**, **9n**) and electron-poor (**9k–m**, **9o**) aryl or heteroaryl groups can be easily incorporated. Several less reactive alkyl substituted acetylenes were also installed in decent yields (**9f**, **9p–r**).

Scheme 5. Reaction Scope

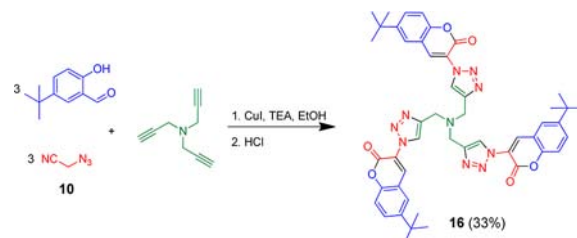


The bond-forming efficiency of this novel MCR was further showcased in a one-pot synthesis of a star-shaped coumarin trimer **16** by condensing tripropargylamine with an excess of **10** and 5-*tert*-butylsalicylaldehyde, followed by a facile hydrolysis in the same pot (Scheme 6). A total of 12 bonds were formed in this *pseudo*-seven component assembly process.

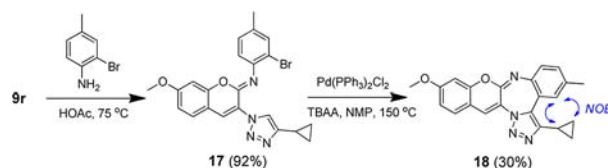
In addition, this three-component condensation generated new functionalizable sites on **9**. Further elaboration was quickly explored to afford a more complex scaffold (Scheme 7): Treatment of **9r** with 2-bromo-4-methylaniline provided **17**. Then, an intramolecular C–H functionalization on the triazole moiety led to a diazepine ring.¹⁷ Overall, a novel 6–6–7–5–6 pentacycle **18** was constructed in a very short reaction sequence.

(17) (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, 9, 2333. (b) Fiandanese, V.; Marchese, G.; Punzi, A.; Iannone, F.; Rafaschieri, G. G. *Tetrahedron* **2010**, 66, 8846.

Scheme 6. One-Pot Condensation Leading to Coumarin Trimer 16



Scheme 7. Further Elaboration



In conclusion, the “click-and-activate nucleophiles” (CAN) protocol is a simple and powerful strategy in the rational design of novel multiple component reactions. As exemplified in this early case study, this approach utilizes the subtle change in the electronic character following triazole formation, along with the narrow distribution of reactivity of azides and alkynes, to manage the reaction sequence in an orderly fashion in one pot. Future efforts will focus on the design of other catalytic MCRs employing this concept and postcondensation manipulations^{2b} to construct other complex scaffolds.

Acknowledgment. The authors thank Dr. Randy Jensen (Amgen) for help in 2D NMR studies and Dr. Iain Campuzano (Amgen) for supplying HRMS data. D.W. thanks Amgen Therapeutic Discovery for financial aid in a summer internship.

Supporting Information Available. Experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.