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Title: An Efficient One-Pot Synthesis of 1,2,3-Triazole-Fused Chromenes/ Quinolines via Oxidative [3+2] Cycloaddition followed by Reductive Cyclization

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An Efficient One-Pot Synthesis of 1,2,3-Triazole-Fused Chromenes/ Quinolines *via* Oxidative [3+2] Cycloaddition followed by Reductive Cyclization

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Abstract. A convenient and efficient one-pot synthesis of 1,2,3-triazole-fused chromenes/ quinolines is developed. The methodology is based on oxidative azide-olefin [3+2] cycloaddition followed by intramolecular reductive cyclization. This methodology affords fast and simple access to 1,2,3-triazole-fused heterocycles in good to excellent yields without necessitating chromatographic purification.

Keywords: Fused 1,2,3-Triazoles; One-Pot Synthesis; Oxidative [3+2] Cycloaddition; Reductive Cyclization

Chromene and quinoline are two important structural scaffolds for pharmaceutical and biologically active natural products.[1-4] On the other hand, the 1,2,3-triazole moiety has its own importance in synthetic, medicinal and materials chemistry.[5-6] Especially, 1,2,3-triazole-fused heterocycles are found in a wide spectrum of bioactive molecules and pharmaceutical targets (Figure 1), such as benzodiazepine receptors, chemotherapeutic, GPR109A agonists and cardiovascular agents.[7-10] Hence, new strategies to synthesize this class of molecules are highly desirable. In this regard, different methods have been developed toward the synthesis of compounds containing fused triazoles.[11]

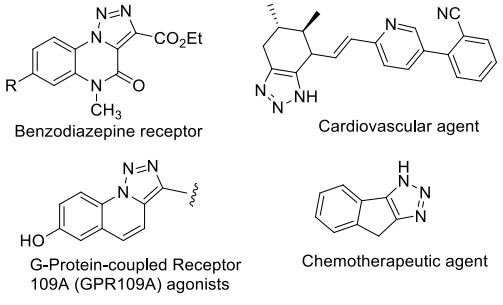
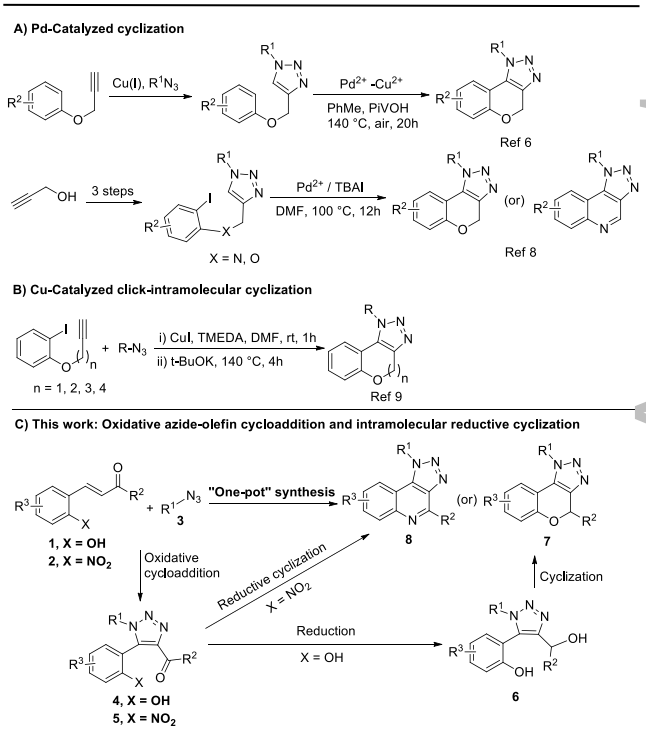


Figure 1. Pharmacologically active 1,2,3-triazole-fused heterocycles.

Literature reports infer that 1,2,3-triazole-fused heterocycles can be synthesized primarily by two strategic approaches. First strategy involves intermolecular regioselective 1,3-dipolar cycloaddition between azide and terminal alkyne followed by metal catalyzed arylation (coupling) of the resulting 1,2,3-triazole (Scheme 1, A). With this strategy Ackermann[12] synthesized 1,2,3-triazole-fused chromenes by a click reaction then followed by an intramolecular dehydrogenative arylation using a Pd^{2+}–Cu^{2+} catalytic system under air. More recently,



Scheme 1. Synthetic routes to access 1,2,3-triazole-fused heterocycles.

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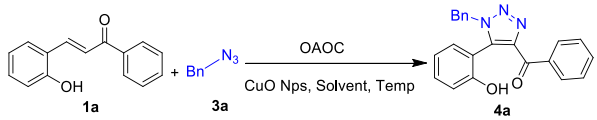
Lautens[13] developed an elegant palladium-catalyzed, intramolecular cyclization of 5-iodotriazoles to afford a number of 1,2,3-triazole-fused chromenes. Later, in 2013 Wang[14] reported palladium catalyzed synthesis of 1,2,3-triazole-fused chromenes/ quinolones. The second strategy involves thermal or metal-catalyzed regioselective intramolecular azide-alkyne cycloaddition (IAAC) of the azido-alkyne substrates (Scheme 1, B). In this regard, Swamy[15] described a copper-catalyzed tandem, one-pot click-intramolecular arylation sequence to generate several 1,2,3-triazole-fused chromenes. Cai and Gong reported Cu(I)-catalyzed cascade reactions of 1,1,1-trifluoro-*N*-(2-iodophenyl)but-3-yn-2-imines and *N*-(2-iodophenyl) propiolamides with sodium azide to achieve tricyclic 4-(trifluoromethyl)-[1,2,3]triazolo [1,5-a] quinoxalines and 1,2,3-triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones through cycloaddition and intramolecular Ullmann coupling.[16-17] In 2011, Yao described copper-catalyzed [3+2] cycloaddition, followed by *N*-arylation to access indoline- and thiophene-fused triazolothiadiazepine 1,1-dioxide derivatives.[18]

In continuation of our work on azide-olefin [3+2] cycloaddition reactions,[19-22] we have developed an alternative methodology based on oxidative azide-olefin [3+2] cycloaddition of organic azides with 2-hydroxychalcones (**1**) and 2-nitrochalcones (**2**) respectively, followed by reductive cyclization (Scheme 1, C) to access 1,2,3-triazole-fused heterocycles. This straightforward one-pot synthesis of 1,2,3-triazole-fused chromenes/ quinolones constitutes an important alternative strategy to the reported multistep route (Scheme 1, A and B).

At the outset, we have started our investigations with 2-hydroxychalcone (**1a**) and benzyl azide (**3a**) as model substrates for optimizing the oxidative azide-olefin cycloaddition (OAOC) reaction by using CuO nanoparticles (NPs) catalyst chosen from our previous report.[19] Initially the reaction was performed with 1.0 mmol of **3a** at 90 °C in DMF, producing 64% yield of **4a** (Table 1, entry 1). Exclusively, one regio-isomeric[19, 23-24] 1,2,3-triazole **4a** was achieved in DMF and toluene (Table 1) and no other products were observed. The screening of solvent, azide (equiv), catalyst load (equiv) and temperature was also examined. However, DMF was chosen for the OAOC of 2-hydroxychalcone since it accomplished higher yield (81%) of triazole **4a** than toluene (Table 1, entries 4-5) with azide (1.2 equiv) and CuO NPs (20 mol%) at 100 °C.

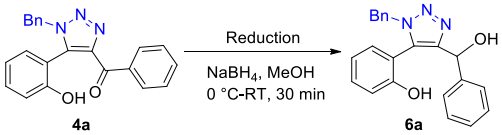
Table 1. Optimization of OAOC with 2-hydroxychalcones.[a]



Entry	Azide (equiv.)	CuO NPs (mol%)	Solvent	T (°C)	Yield of 4a (%)[b]
1	1.0	20	DMF	90	64
2	1.2	20	DMF	90	70
3	1.0	20	DMF	100	66
4	**1.2**	**20**	**DMF**	**100**	**81**
5	1.2	20	Toluene	100	53
6	1.2	15	DMF	100	72
7	1.5	20	DMF	100	80

[a] Reaction conditions: 2-hydroxychalcone **1a** (1.0 mmol), benzyl azide **3a** (1.2mol),CuO NPs (20 mol%) and solvent (4 mL) were heated for 12h. [b] Isolated Yields.

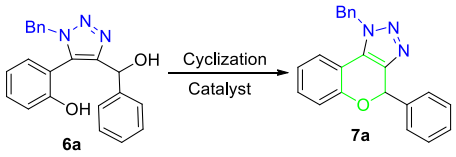
Synthesis of flavans and quinolines through reduction cyclization of 2-hydroxychalcones and 2-nitrochalcones respectively,[25-26] prompted us to investigate the synthesis of 1,2,3-triazole-fused heterocycles. Reduction of keto group of the triazole (**4a**) was examined upon treatment with $NaBH_4$ in methanol at RT which affords the corresponding alcohol **6a** in 98% yield (Scheme 2).



Scheme 2. Reduction of keto group of the 1,2,3-triazole **4a**.

Initially cyclization of alcohol **6a** was examined with acetic acid at 80 °C for 2 h, excellent yield of the corresponding 1,2,3-triazole-fused chromene (**7a**) was obtained (Table 2, entry 1). The effect of catalyst, solvent and temperature were also studied (Table 2, entries 1-6). However acetic acid was chosen for the cyclization of alcohol **6a** since it accomplished higher yield of **7a** than PTSA and HCl. It was found that the synthesis of **4a**, 6**a** and 7**a** proceeded without necessitating the chromatographic purification.

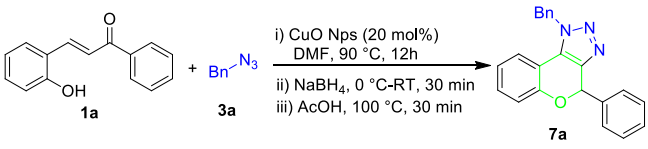
Table 2. Optimization for the cyclization of alcohol **6a.**[a]



Entry	Catalyst (equiv.)	Solvent	T (°C)	Time (h)	Yield of **7a** (%)[b]
1	AcOH	-	80	2	90
2	AcOH	-	100	0.5	90
3	**AcOH**	**DMF**	**100**	**0.5**	**90**
4	PTSA (1.0)	DMF	100	1	83
5	HCl(1.0)	DMF	100	5	66
6	HCl(2.0)	DMF	100	5	78

[a] Reaction conditions: Alcohol **6a** (1.0 mmol), acetic acid (3 mL) and DMF (3 mL) were heated at 100 °C for 0.5h. [b] Isolated yields.

With these excellent initial results in hand, a three-step, "one-pot" procedure was attempted. Since the oxidative [3+2] cycloaddition was carried out in DMF solvent, we reasoned that by optimizing the second



Scheme 3. One-pot synthesis of 1,2,3-triazole-fused chromene **7a**.

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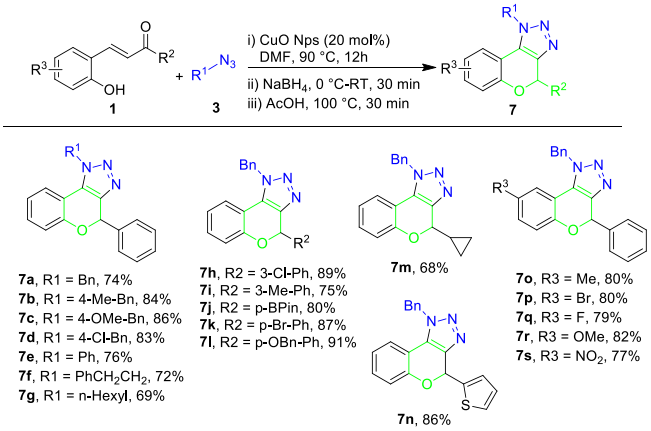
and third steps (reduction and cyclization respectively) using DMF, which enables us to carry out the entire synthetic sequence in a one-pot procedure. This definitely proved to be highly efficient process in our test experiment as outlined in Scheme 3.

Three step, one-pot synthesis of 1,2,3-triazole-fused chromene (**7a**) was examined from the above optimized conditions. Initially OAOC was carried out with 2-hydroxychalcone **1a** (1.0 mmol) and benzyl azide **3a** (1.2 mmol) using CuO NPs (20 mol%) in DMF (3 mL) at 90 °C for 12 h. Completion of reaction was monitored by the TLC, $NaBH_4$ (5.0 mmol) was added in small portions at 0 °C and stirred at RT for 0.5 h to afford the corresponding alcohol **6a**, which on treatment with acetic acid (3 mL) at 100 °C, cleanly produces the desired 1,2,3-triazole-fused chromene (**7a**) in 74% overall yield (Scheme 3).

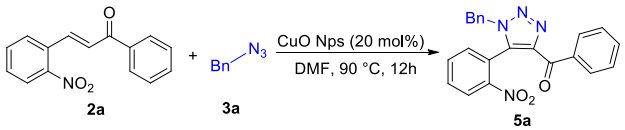
Under the optimized reaction conditions, we further investigated the scope of the reaction (Table 3). A wide range of 2-hydroxychalcones (**1**) were treated with organic azides (**3**) which led to the 1,2,3-triazole-fused chromenes (**7**) in moderate to excellent yields in one-pot. In all the cases single product (**7**) was obtained without necessitating chromatographic purification. Substrates bearing both electron-donating and electron-withdrawing groups were tolerated (Table 3, entries 7a-7s).

Table 3. Reaction scope for 1,2,3-triazole-fused chromenes **7**.[a-b]



[a] Reaction conditions: i) **1** (1.0 mmol), azide **3** (1.2 mmol), CuO Nps (20 mol%) and DMF (3 mL) were heated at 90 °C for 12h. ii) NaBH4 (5.0 mmol) added 0 °C and stirred at RT for 30 min. iii) Acetic acid (3 mL) added and heated at 100 °C for 30 min.
[b] Isolated over all yields.

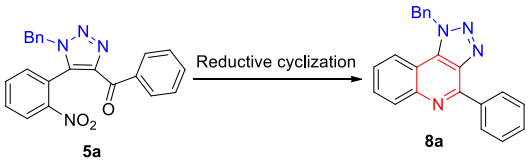
Azide-olefin cycloaddition and reductive cyclization strategy was extended for the construction of 1,2,3-triazole-fused quinolines. With the success of triazole (**4a**) derivatives in hand, the optimized reaction condition adopted from Table 2 is applied to perform the oxidative cycloaddition reaction of 2-nitrochalcone (**2a**) with benzyl azide (**3a**) using CuO NPs (20 mol%), in DMF and the reaction underwent smooth conversion to obtain the desired 1,4,5-tri-substituted-1,2,3-triazole (**5a**) in 86% yield.



Scheme 4. OAOC of 2-nitrochalcone with benzyl azide.

Initially reductive cyclization of triazole **5a** was examined with Iron powder (5.0 mmol), ammonium chloride (5.0 mmol) in MeOH were refluxed for 5 h, the corresponding 1,2,3-triazole-fused quinoline (8**a**) was obtained in 88% yield (Table 4, entry1). The effect of additive (acid catalyst) and reductant was also studied (Table 4, entries 1-5). However Iron powder and acetic acid combination was chosen for the reductive cyclization of triazole **5a** since it accomplished higher yield (90%) of **8a** in relatively shorter duration than other combinations (Table 4, entry 2).

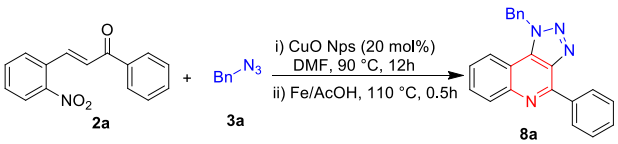
Table 4. Optimization for reductive cyclization of triazole 5**a**.[a]



Entry	Reductant	Solvent	Time (h)	Yield 29a(%)[b]
1	Fe[c]	MeOH	5	88
2	**Fe**	**AcOH**	**0.5**	**90**
3	Fe[d]	EtOH	1	86
4	Fe[d]	MeOH	1	62
5	Zn	AcOH	2	79

[a] Reaction conditions: Triazole **26a** (1.0 mmol), catalyst (5.0 mmol) and solvent (3 mL) were refluxed for particular time. [b] Isolated yields. [c] NH_4Cl (5.0 mmol). [d] Conc. HCl (1.0 mmol).

With these excellent initial results in hand, a two-step, "one-pot" procedure was attempted. Since the oxidative [3+2] cycloaddition of 2-nitrochalcone (**2a**) was carried out in DMF solvent, we reasoned that by optimizing the second step (reductive cyclization) using DMF and acetic acid, we should be able to carry out the entire synthetic sequence in a one-pot procedure.



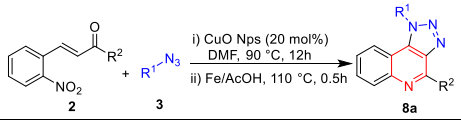
Scheme 5. One-pot synthesis of 1,2,3-triazole-fused quinoline **8a**.

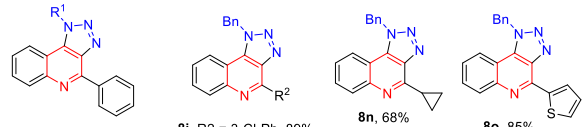
Two-step, one-pot synthesis of 1,2,3-triazole-fused quinoline (**8a**) was examined from the above optimized conditions. Initially OAOC was carried out with 2-nitrochalcone 2**a** (1.0 mmol) and benzyl azide **3a** (1.2 mmol) using CuO NPs (20 mol%) in DMF (3 mL) at 90 °C for 12 h. Completion of reaction was monitored by the TLC, Iron powder (5.0 mmol) and acetic acid (3 mL) were added and refluxed for 0.5 h to afford the desired 1,2,3-triazole-fused quinolone (**8a**) in 83% overall yield (Scheme 5).

Under the optimized reaction conditions, we further investigated the scope of the reaction (Table 5). A wide array of 2-nitrochalcones (**2**) reacted with organic azides (**3**) which led to the 1,2,3-triazole-fused quinolines (**8**) in moderate to excellent yields in

one-pot without necessitating chromatographic purification. Substrates bearing both electron-donating and electron-withdrawing groups were tolerated in this conversion (Table 5, entries 8a-8o).

Table 5. Reaction scope for 1,2,3-triazole-fused quinolines **8**.[a-b]





8a, R1 = Bn, 83%
8b, R1 = 4-Me-Bn, 86%
8c, R1 = 4-OMe-Bn, 89%
8d, R1 = 4-Cl-Bn, 84%
8e, R1 = Ph, 95%
8f, R1 = $PhCH_2CH_2$, 80%
8g, R1 = n-Hexyl, 78%
8h, R1 = CH_2CO_2Me, 80%

8i, R2 = 3-Cl-Ph, 89%
8j, R2 = 3-Me-Ph, 86%
8k, R2 = p-BPin, 82%
8l, R2 = p-Br-Ph, 83%
8m, R2 = p-OBn-Ph, 88%

8n, 68%

8o, 85%

[a] Reaction conditions: i) 2-nitrochalcone **2** (1.0 mmol), organic azide **3** (1.2 mmol), CuO NPs (20 mol%) and DMF (3 mL) were heated at 90 °C for 12h. ii) Iron powder (5.0 mmol) and acetic acid (3 mL) were added and heated at 110 °C for 0.5h.
[b] Isolated over all yields.

In conclusion, we have developed an easy and efficient one-pot protocol to synthesize novel 4-aryl substituted 1,2,3-triazole-fused chromenes and 4-aryl substituted 1,2,3-triazole-fused quinolines *via* oxidative [3+2] cycloaddition using CuO NPs, followed by an intramolecular reductive cyclization sequence. The precedent methods for synthesizing 1,2,3-triazole fused heterocycles often involve multi step synthesis, utilization of costly catalysts such as palladium and poor synthetic availability of the starting materials. But this method affords a fast and simple access to a diverse array of 1,2,3-triazole-fused heterocycles in good to excellent yields without necessitating chromatographic purification.

Experimental Section

General procedure for one-pot synthesis of 1,2,3-triazole-fused chromenes (7a-s)

A mixture of 2-hydroxychalcone **1** (1.0 mmol), organic azide **3** (1.2 mmol), CuO NPs (20 mol%) and DMF (3 mL) were heated at 90 °C for 12 h. Completion of reaction was monitored by the TLC and then $NaBH_4$ (5.0 mmol) was added in small portions at 0 °C and stirred at RT for 0.5 h to afford the corresponding alcohol (**6**). Following that acetic acid (3 mL) was added and the temperature was gradually raised to 100 °C and then heated for 0.5 h. The consumption of the starting materials was monitored by TLC. The reaction mixture was cooled to room temperature and poured into the ice water (50 mL) there by the precipitated solid was filtered and washed with hexane (10-20 mL) and dried under vacuum to obtain pure 1,2,3-triazole-fused chromenes (**7a-s**) in moderate to excellent yield.

General procedure for one-pot synthesis of 1,2,3-triazole-fused quinolines (8a-o)

A mixture of 2-nitrochalcone **2** (1.0 mmol), organic azide **3** (1.1 mmol), CuO NPs (20 mol%) and DMF (3 mL) were heated at 90 °C for 12 h. The completion of the reaction was monitored by TLC, and then Iron powder (5.0 mmol) and acetic acid (3 mL) were added and refluxed for 0.5 h. Completion of the reaction was monitored by TLC and the reaction mixture was cooled to room temperature. The black sludge was filtered through a bed of celite and washed with DCM (20 mL). The combined filtrates were washed with water (40 mL). The organic layer was dried ($NaSO_4$) and concentrated under vacuum to afford the pure 1,2,3-triazole-fused quinolones (**8a-o**) in moderate to excellent yield.

Acknowledgments

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References

1. R. Prathap, V. Ji Ram, *Chem. Rev.* **2014**, *114*, 10476-10526.
2. N. Thomas, S. M. Zachariah, *Asian J. Pharm. Clin. Res.* **2013**, *6*, 11-15.
3. S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal, H. D. Patel, *RSC Adv.* **2014**, *4*, 24463-24476.
4. S. Kumar, S. Bawa, H. Gupta, *Mini Rev. Med. Chem*. **2009**, *9*, 1648-1654.
5. *Chem. Soc. Rev*. **2010**, *39*, 1221-1408.
6. Y. L. Angell, K. Burgess, *Chem. Soc. Rev*. **2007**, *36*, 1674-1689.
7. G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, M. L. Trincavelli, *Eur. J. Med. Chem*. **2002**, *37*, 565-571.
8. L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D.Meek, G. A. Hofmann, C. K. Schulz-Pritchard, W.W. Smith, C. A. Janson, M. D. Ryan, G.-F. Zhang, K. O. Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson, M. J. Hansbury, J. D. Winkler, K. W. Ward, D. F. Veber, S. K. Thompson, *J. Med. Chem*. **2005**, *48*, 5644-5647.
9. H. C. Shen, F. Ding, Q. Deng, L. C. Wilsie, M. L. Krsmanovic, A. K. Taggart, E. Carballo-Jane, N. Ren, T. Cai, T. Wu, K. K. Wu, K. Cheng, Q. Chen, M. S. Wolff, X. Tong, T. G. Holt, M. G. Waters, M. L. Hammond, J. R. Tata, S. L. Colletti, *J. Med. Chem*. **2009**, *52*, 2587-2602.
10. D. Niculescu-Duvaz, I. Niculescu-Duvaz, B. M. J. M. Suijkerbuijk, D. Menard, A. Zambon, A. Nourry, L. Davies, H. A. Manne, F. Friedlos, L. Ogilvie, D. Hedley, A. K. Takle, D. M. Wilson, J.-F. Pons, T. Coulter, R. Kirk, N. Cantarino, S. Whittaker, R. Marais, C. J. Springer, *Bioorg. Med. Chem*. **2010**, *18*, 6934-6952.
11. E. A. Shafran, V. A. Bakulev, Y. A. Rozin, Y. M. Shafran, *Chem. Heterocycl. Compd*. **2008**, *44*, 1040-1069.
12. L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Novak, L. Buttner, *Org. lett*. **2010**, *12*, 2056-2059.
13. J. M. Schulman, A. A. Friedman, J. Panteleev, M. Lautens, *Chem. Commun*. **2012**, *48*, 55-57.
14. C.-Y. Chen, C.-H. Yang, W.-P. Hu, J. K. Vandavasi, M.-I.

10.1002/adsc.201800908

Chung, J.-J. Wang, *RSC Adv.* **2013**, *3*, 2710-2719.
15. M. Nagarjuna Reddy, K. C. Kumara Swamy, *Eur. J. Org. Chem*. **2012**, *2012*, 2013-2022.
16. Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, *Adv. Synth. Catal*. **2010**, *352*, 1296-1300.
17. J. Yan, F. Zhou, D. Qin, T. Cai, K. Ding, Q. Cai, *Org. Lett*. **2012**, *14*, 1262-1265.
18. D. K. Barange, Y-C. Tu, V. Kavala, C-W. Kuo, C-F. Yao, *Adv. Synth. Catal*. **2011**, *353*, 41-48.
19. D. Gangaprasad, J. Paul Raj, T. Kiranmye, S. SagubarSadik, J. Elangovan, *RSC Adv*. **2015**, *5*, 63473-63477.
20. D. Gangaprasad, J. Paul Raj, T. Kiranmye, R. Sasikala, K. Karthikeyan, S. Kutti Rani, J. Elangovan, *Tetrahedron Lett*. **2016**, *57*, 3105-3108.
21. D. Gangaprasad, J. Paul Raj, T. Kiranmye, K. Karthikeyan, J. Elangovan, *Eur. J. Org. Chem*. **2016**, *2016*, 5642-5646.
22. J. Paul Raj, D. Gangaprasad, K. Karthikeyan, M. Vajjiravel, J. Elangovan, *J. Chem. Sci*. **2018**, *130*, 44-49.
23. D. Janreddy, V. Kavala, C.-W. Kuo, W.-C. Chen, C. Ramesh, T. Kotipalli, T.-S. Kuo, M.-L. Chen, C.-H. He, C.-F. Yao, *Adv. Synth. Catal*. **2013**, *355*, 2918-2927.
24. W. Yang, T. Miao, P. Li, L. Wang, *RSC Adv*. **2015**, *5*, 95833-95839.
25. O. Mazimba, I. B. Masesane, R. R. Majinda, *Tetrahedron Lett*. **2011**, *52*, 6716-6718.
26. W.-C. Chen, C.-C. Lin, V. Kavala, C.-W. Kuo, C.-Y. Huang and C.-F. Yao, *Molecules*, **2015**, *20*, 22499-22519.

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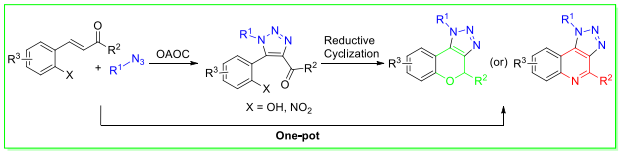
COMMUNICATION

An Efficient Synthesis of 1,2,3-Triazole-Fused Chromenes/ Quinolines *via* Oxidative [3+2] Cycloaddition Followed by Reductive Cyclization



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An easy and efficient one-pot synthesis of 1,2,3-triazole-fused chromenes/ quinolines is developed. The methodology is based on oxidative azide-olefin [3+2] cycloaddition followed by intramolecular reductive cyclization. This methodology affords fast and simple access to 1,2,3-triazole-fused heterocycles in good to excellent yields without necessitating chromatographic purification.