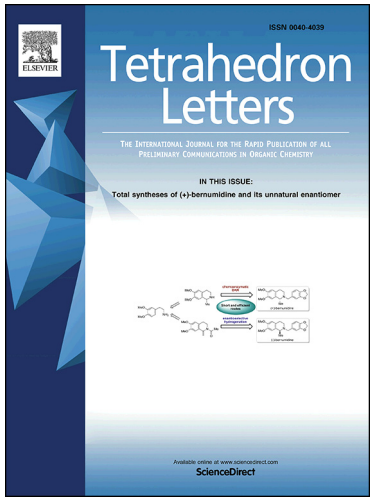

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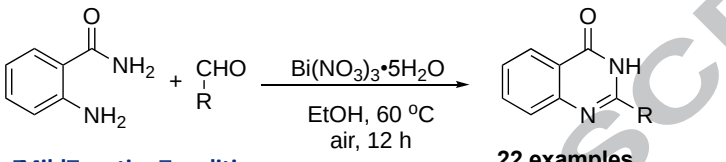
Sandeep R. Vemula,[a] Dinesh Kumar,[b] and Gregory R. Cook*[a]



- Mild reaction conditions
- Ethanol as the solvent
- Air as the sole oxidant

22 examples
68-95% yield

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Bismuth-Catalyzed Synthesis of 2-Substituted Quinazolinones

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ABSTRACT

The bismuth-catalyzed oxidative condensation of aldehydes with 2-aminobenzamide under aerobic conditions is reported using ethanol as the solvent. Good to excellent isolated yields (68-95%) of the corresponding 2-substituted quinazolinones were obtained under mild reaction conditions with excellent functional group tolerance. The quinazolinones were further functionalized to afford *N*-allylated quinazolinones, 2-aminopyridine derivatives, and annulated polyheterocyclic compounds *via* transition-metal catalyzed reactions.

1. Introduction

Quinazoline-4(3*H*)-ones represent a unique class of heterocycles that has attracted considerable attention due to their wide occurrence in natural products[1] and biologically active compounds (Fig. 1).[2] They exhibit a wide range of biological and pharmacological activities including antibacterial,[2b] antimalarial,[2c] antidiabetic,[2d] antiallergic,[2e] and antifungal properties.[2h] In view of the significant value of quinazolinones and their analogs, various methodologies for their synthesis have been developed. Although reported methods are effective in many instances, the development of general, efficient, simple and sustainable approaches is still desirable.

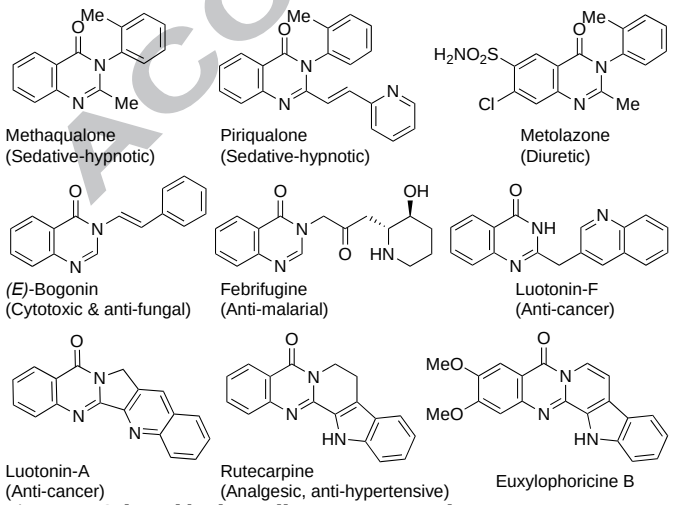

Figure 1. Selected biologically active quinazolinones

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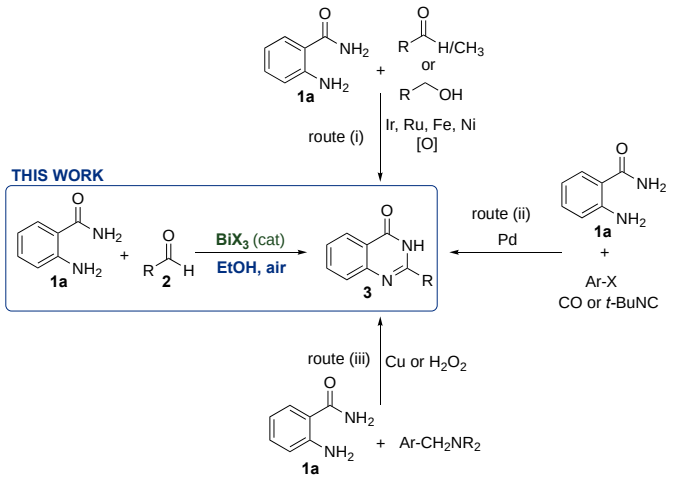
Classical routes for the synthesis of quinazolinones have relied on condensation reactions involving a variety of substrates including, but not limited to, 2-aminobenzamides,[3-9] 2-halobenzamides,[10] 2-halobenzonitriles or 2-nitrobenzonitriles,[11] amidines[12] and isatoic anhydrides,[13] among which 2-aminobenzamides are the most explored. As part of our on-going contributions towards benign Lewis acid catalysis[14,17] and sustainable organic synthesis,[18] we wish to report the synthesis of 2-substituted quinazolinones *via* oxidative cyclocondensation of 2-aminobenzamides with aldehydes catalyzed by a non-toxic and cost-effective bismuth salt in ethanol under mild aerobic conditions.

Synthetic strategies employed for the generation of 2-arylquinazoline-4(3*H*)-ones from 2-aminobenzamide (**1a**) can be summarized into three general routes (Scheme 1): (i) oxidative cyclocondensation of **1a** with aldehydes,[3] alcohols,[4] and methyl ketones;[5] (ii) Pd-catalyzed carbonylative reaction of **1a** with aryl halides in the presence of carbon monoxide[6] or isocyanides;[7] and (iii) copper or hydrogen peroxide-promoted domino oxidative cyclocondensation of **1a** with tertiary amines[8] or benzylamine.[9] Although most of these methods yield quinazolinones in modest to high yields, they usually require elevated temperatures in excess of 100 °C or a large excess of oxidant and non-renewable solvents.[4] Recently, an iron nitrate/TEMPO catalyzed approach for the synthesis of quinazolinones was reported by Li and co-workers.[4e] Although an improvement over previous methods, it still required stoichiometric amounts of oxidant. Transition metals, for example Ir, Ru, Pd, and Pt, have also been employed for the synthesis of quinazolinones.[19] In 2016, Gao and co-workers reported a $VO(acac)_2$-catalyzed coupling of **1a** with aldehydes or alcohols using O_2 as the oxidant, however DCE was used as the solvent and the reaction was carried out at 80 °C.[4f] In 2017, Li and co-workers, utilized an expensive Ir-catalyst for the synthesis of quinazolinones *via* the dehydrogenative coupling of aminobenzamides and unsaturated aldehydes.[3g] At the same time

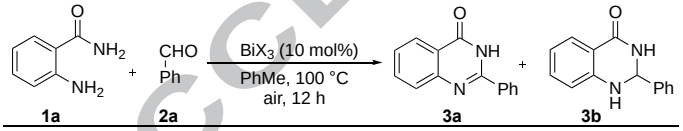
Paul and co-workers utilized a specially designed Ni-catalyst for the synthesis of 2-substituted quinazolinones.[4g] Both of these methods, although very effective, require elevated temperatures (120 °C) and non-renewable, toxic solvents (toluene). More recently, in 2018, Sun and co-workers reported a TBHP-mediated oxidative cyclization of **1a** with alcohols and aldehydes at 110 °C.[4h] Despite these advances, there remains a significant need for simple, efficient and green processes for the synthesis of quinazolinones.[20]



Scheme 1. Routes for the synthesis of 2-arylquinazoline-4(3*H*)-ones from 2-aminobenzamide (**1a**).

We envisioned that non-toxic and relatively benign bismuth salts[14] under aerobic conditions could function as more sustainable alternatives for the preparation of quinazolinones *via* oxidative cyclization. To test our hypothesis the cyclocondensation of **1a** with benzaldehyde **2a** was carried out in the presence of various bismuth salts (10 mol%) at 100 °C in toluene (PhMe) for 12 h (Table 1). We anticipated that the formation of **3a** would proceed *via* intermediate dihydroquinazolinone **3b**, hence the reaction mixture was monitored by GC-MS for both **3a** and **3b**. As expected we observed both in variable amounts under different catalyst conditions.

Table 1. Investigation of bismuth Lewis acids for the oxidative cyclization of **1a** with **2a** in toluene.[a]



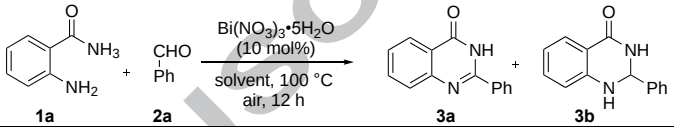
Entry	BiX_3	Conversion (%)	**3a**/**3b**[b]	Yield **3a** (%)[c]
1	$Bi(OTf)_3$	>99	85/15	78
2	$Bi(NO_3)_3$•$5H_2O$	>99	82/18	75
3	$Bi(OAc)_3$	82	56/44	36
4	$Bi(O^iPr)_3$	>99	42/56	31
5	BiF_3	92	31/69	18
6	$BiBr_3$	97	78/22	66
7	Ph_3Bi	71	36/64	17
8	None	44	20/78	< 5

[a] Reagents and conditions: **1a** (0.5 mmol), **2a** (0.75 mmol, 1.5 equiv.), bismuth salt (10 mol%), PhMe (2 mL), 100 °C, 12 h, open air. [b]Based on GC-MS. [c]Isolated yield of **3a**.

To our delight, nearly all bismuth(III) salts demonstrated promising potential to promote the oxidative cyclocondensation of **1a** with **2a** to form **3a** *via* **3b** (17-78%; Entries 1-7, Table 1). However, $Bi(OTf)_3$ and $Bi(NO_3)_3$•$5H_2O$ were found to be superior for the selective formation of **3a** in good isolated yield (78% and 75%, respectively, Entries 1 and 2). Slightly lower selectivity and yields were obtained with $Bi(OAc)_3$ and $BiBr_3$ (Entries 3 and 6). Poor selectivity and yield of **3a** was obtained in the absence of catalyst (Entry 8). For additional investigation, we opted to employ $Bi(NO_3)_3$•$5H_2O$ as the catalyst of choice due of its lower cost and toxicity compared to $Bi(OTf)_3$.[23]

To further optimize the reaction for the complete oxidation of intermediate **3b** to **3a**, and to develop a more sustainable process, we examined the effect of solvents for the oxidative cyclization of **1a** with **2a** in presence of $Bi(NO_3)_3$•$5H_2O$ (10 mol%) (Table 2). The reaction was found to be compatible with a diverse range of solvents including hydrocarbon, halogenated hydrocarbon, ethers, protic polar and aprotic polar solvents. However, in general, alcoholic solvents (Entries 8-10) were found to be optimal for maximizing the oxidation of **3b** to **3a**. Ethanol afforded complete conversion to **3a** and was chosen for further studies (Entry 9).

Table 2. Effect of solvents on the oxidative cyclization of **1a** with **2a** in the presence of $Bi(NO_3)_3$•$5H_2O$.[a]



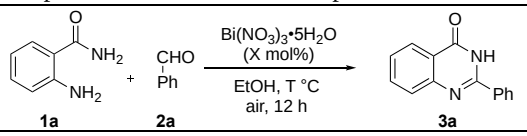
Entry	Solvent	Conversion (%)	**3a**/**3b**[b]	Yield, **3a** (%)[c]
1	PhMe	> 99	84/16	75
2	1,4-Dioxane	> 99	75/25	66
3	DMF	94	60/40	49
4	THF	> 99	82/18	71
5	DCE	> 99	83/17	72
6	DMC	> 99	81/19	70
7	CH_3NO_2	> 99	95/5	86
8	MeOH	> 99	96/4	88
9	EtOH	> 99	100/0	91
10	^{i}PrOH	> 99	97/3	88

[a]Reagents and conditions: **1a** (0.5 mmol), **2a** (0.75 mmol, 1.5 equiv), $Bi(NO_3)_3$•$5H_2O$ (10 mol%), solvent (2 mL), 100 °C, 12 h, open air. [b]Based on GC-MS. [c]Isolated yield of **3a**

In order to further optimize the reaction conditions, the model reaction using $Bi(NO_2)_3$•$5H_2O$ as catalyst in EtOH was performed while varying other reaction parameters such as the temperature, catalyst loading, and molar equivalent of **2a** (Table 3). The most efficient catalyst loading was found to be 10 mol% (Entry 1). No improvement was seen with increased catalyst loading (15 mol%, Entry 2) and the yield of **3b** declined significantly with lower catalyst loadings (5 mol%, 62%; 2.5 mol%, 37%; Entries 3 and 4, respectively). Lowering the temperature to 60 °C had no deleterious effect on the reaction (Entries 6 and 7). However, lower temperatures resulted in incomplete oxidation of **3a** to the desired **3b** (Entries 7 and 8). When the reaction was performed under an inert atmosphere (Entry 11), dihydroquinazolinone was formed as the major product (70% yield), indicating the necessity of air for the oxidation.

With the optimized conditions in hand (Table 3, Entry 9), the scope of the oxidative cyclocondensation was explored for the synthesis of a variety of 2-substituted quinazolinones by varying the aldehyde and 2-aminobenzamide reactants (Table 4). Aromatic aldehydes possessing both electron donating and electron withdrawing groups performed well in all cases affording excellent yields of the desired quinazolinones. 1,4-Benzenedialdehyde afforded the mono-quinazolinone product exclusively in high yield (82%, Entry 6). More sterically encumbered aldehydes also reacted well to afford good yields; the yields for these substrates were further improved at slightly higher temperatures (Entries 9, 13, 15, 16 and 17). The reaction also proceeded in good yields with non-aromatic and aliphatic aldehydes. Chloroaminobenzamide (81%, Entry 10) and aminothiophenecarboxamide (70%, Entry 18) were also effective and gave the corresponding products in good yields.

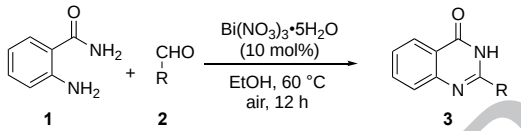
Table 3. Optimization of the reaction parameters.[a]

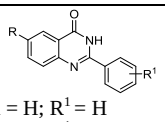
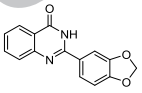
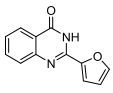
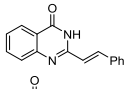
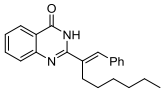
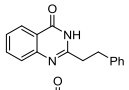
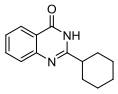
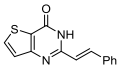


Entry	Catalyst (mol%)	T (°C)	**2a** (equiv)	Yield, **3a** (%)[c]
1	10	100	1.5	91
2	15	100	1.5	91
3	5	100	1.5	62
4	2.5	100	1.5	37
5	10	80	1.5	91
6	10	60	1.5	92
7	10	40	1.5	28[c]
8	10	rt	1.5	16[c]
9	10	60	1.2	91
10	10	60	1.0	77
11	10	60	1.2	17[d,e]
12	none	60	1.2	12

[a] Reagents and conditions: **1a** (0.5 mmol), **2a**, $Bi(NO_3)_3$•$5H_2O$, EtOH (2 mL), 12 h, open air. [b]Isolated yield of **3a**. [c]**3b** was the major product (GC-MS). [d] reaction carried under N_2, [e]**3b** was isolated in 70% yield

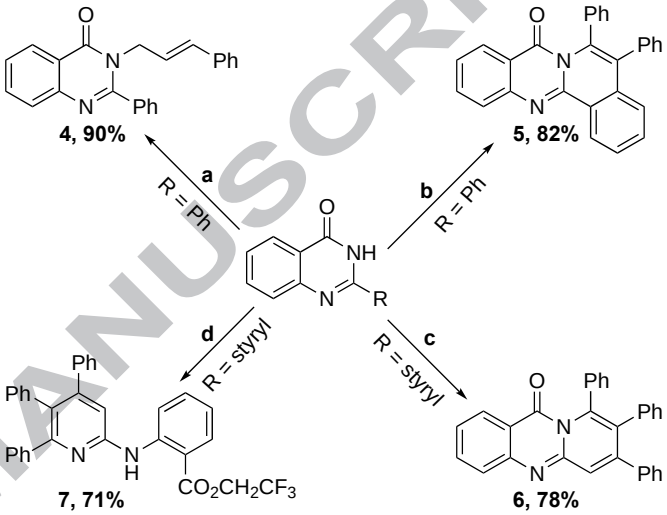
Table 4. Bismuth nitrate-catalyzed synthesis of 2-susbstituted quinazolinones in EtOH.[a]



Entry	Product	Yield (%)[b]
		
1	R = H; R^1 = H	91
2	R = H; R^1 = 4-OMe	90
3	R = H; R^1 = 4-NMe_2	89
4	R = H; R^1 = 4-CF_3	78
5	R = H; R^1 = 4-Cl	88
6	R = H; R^1 = 4-CHO	82
7	R = H; R^1 = 4-C(O)Me	78
8	R = H; R^1 = 4-CN	77
9	R = H; R^1 = 2-F	71 (88)[c]
10	R = Cl; R^1 = H	81
11		88
12		91
13		72 (95)[c]
14		68[c]
15		70 (92)[c]
16		71 (89)[c]
17[d]		69 (85)[c]
18		70

[a]Reagents and conditions: 2-aminobenzamide (0.5 mmol), aldehyde (0.6 mmol, 1.2 equiv), $Bi(NO_3)_3$•$5H_2O$ (5 mol%), EtOH (2 mL), 60 °C, 12 h, open air. [b]Isolated yield. [c]Reaction performed at 100 °C. [d]2.5 equiv. of acetaldehyde was used.

The selective functionalization and derivatization of 2-substituted quinazolinones to generate high value compounds is of significance.[20] In this context, we further demonstrated the late-stage functionalization of the cyclocondensation products *via* transition metal-catalyzed allylations, and annulations.[18,22] Thus, the preparation of synthetically useful *N*-allyl quinazolinone **4**, fused quinazolinones **5** and **6**, and 2-arylaminopyridine **7** have been demonstrated (Scheme 2).



Scheme 2. Functionalization of quinazolones. Reagents and conditions: (a) cinnamyl alcohol, $Pd(PPh_3)_4$ (5 mol%), DMC, 100 °C, 12 h; (b) diphenyl acetylene, $[RuCl_2(p\text{-cymene})]_2$) (5 mol%), $Cu(OAc)_2$ (2.2 equiv.), Na_2CO_3 (2.0 equiv.), PhCl, 90 °C, 16 h; (c) diphenyl acetylene, $[RuCl_2(p\text{-cymene})]_2$) (5 mol%), AgOAc (0.2 equiv.), $Cu(OAc)_2$ (1 equiv.), TFA (1 equiv.), 1,4-dioxane, 100 °C, 12 h; (d) diphenyl acetylene, $[RuCl_2(p\text{-cymene})]_2$) (5 mol%), AgOAc (0.2 equiv.), $Cu(OAc)_2$ (1 equiv.), TFA (1 equiv.), 1,4-dioxane-TFE, 100 °C, 12 h.

Conclusion

In conclusion, we have developed a bismuth-catalyzed protocol for the efficient formation of 2-substituted quinazolinones. The present work demonstrates the first investigation of Bi(III) Lewis acids for the condensation of 2-aminobenzamides with aldehydes under aerobic conditions. $Bi(NO_2)_3$•$5H_2O$ was found to be a cost effective and nontoxic catalyst that can be used in ethanol as a solvent. The reaction displayed a diverse range of functional group tolerance and the mild conditions afford an efficient and practical method for the synthesis of biologically important functionalized heterocycles.

Acknowledgments

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References and notes

1 (a) A. Witt, J. Bergman. *Curr Org Chem.* 2003, **7**, 659 (b) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (c) A. Cagir, S. H. Jones, R. Gao and B. M. Eisenhauer, *J. Am. Chem. Soc.*, 2003, **125**, 13628; (d) S. Wang, K. Fang, G. Dong, S. Chen, N. Liu, Z. Miao, J. Yao, J. Li, W. Zhang and C. Sheng, *J. Med. Chem.*, 2015, **58**, 6678.

2 a) Antitumor: A. Nathubhai, P. J. Wood, M. D. Lloyd, A. S. Thompson and M. D. Threadgil, *ACS Med. Chem. Lett.*, 2013, **4**,

1173; (b) Antibacterial: R. Bouley, M. Kumarasiri, Z. Peng, L. H. Otero, W. Song, M. A. Suckow, V. A. Schroeder, W. R. Wolter, E. Lastochkin, N. T. Antunes, H. Pi, S. Vakulenko, J. A. Hermoso, M. Chang and S. Mobashery, *J. Am. Chem. Soc*., 2014, **137**, 1738; (c) Antimalarial: Y. Takaya, H. Tasaka, T. Chiba, K. Uwai, M.-a. Tanitsu, H.-S. Kim,Y. Wataya, M. Miura, M. Takeshita and Y. Oshima, *J. Med. Chem*., 1999, **42**, 3163; (d) Anti-diabetic: M. S. Malamas and J. Millen, *J. Med. Chem.*, 1991, **34**, 1492; (e) Anti-allergic: N. P. Peet, L. E. Baugh, S. Sunder, J. E. Lewis, E. H. Matthews, E. L. Olberding and D. N. Shah, *J. Med. Chem*., 1986, **29**, 2403; (f) Non-nucleoside reverse transcriptase inhibitor: J. W. Corbett, S. S. Ko, J. D. Rodgers, L.A. Gearhart, N. A. Magnus, L.T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson and S. K. Erickson-Viitanen, *J. Med. Chem*., 2000, ***43***, 2019; (g) CNS depressants: J. F. Wolfe, T. L. Rathman, M. C. Sleevi, J. A. Campbell and T. D. Greenwood, *J. Med.Chem.*, 1990, **33**, 161. (h) Antifungal: N. J. Liverton, D. J. Armstrong, D. A. Claremon, D. C. Remy, J. J. Baldwin, R. J. Lynch, G. Zhang and R. J. Gould, Bioorg. Med. Chem. Lett., 1998, 8, 483–487.

3 (a) J. Jadhav, S. Khanapure, R. Salunkhe and G. Rashinkar, *Appl. Organometal. Chem.*, 2013, **27**, 486; (b) R. Cheng, T. Guo, D. Zhang-Negrerie, Y. Du and K. Zhao, *Synthesis*, 2013, **45**, 2998; (c) Y. Nagasawa, Y. Matsusaki, T. Nobuta, N. Tada, T. Miura and A. Itoh, *RSC Adv*., 2015, **5**, 63952; (d) Y.-H. Shang, L.-Y. Fan, X.-X. Li and M.-X. Liu, *Chin. Chem. Lett.*, 2015, **26**, 1355; (e) F. Li, L. Lu and J. Ma, *Org. Chem. Front.*, 2015, **2**, 1589; (f) N. Kausar, I. Roy, D. Chattopadhyay and A. R. Das, *RSC Adv*., 2016, **6**, 22320. (g) W. Zhao, W. Ma, T. Xiao, F. Li. *ChemistrySelect*, 2017, **2**, 3608. (h) L. Parashuram, S. Sreenivasa, S. Akshatha, V. Udaya Kumar, K. Sandeep. *Asian J. Org. Chem.* 2017, **6,** 1755. (i) B.-Q. Hu, J. Cui, L.-X. Wang, Y.-L. Tang, Yang, L. *RSC Adv*. 2016, **6**, 43950. (j) N. Y. Kim, C.-H. Cheon, *Tetrahedron Lett.* 2014, **55**, 2340.

4 (a) Zhou and J. Fang, *J. Org. Chem*., 2011, **76**, 7730; (b) J. A. Watson, A. C. Maxwell and Jonathan M. J. Williams, *Org. Biomol. Chem*., 2012, **10**, 240 (c) S. M. A. H. Siddiki, K. Kon, A. S. Touchy and K.-i. Shimizu, *Catal. Sci. Technol*., 2014, **4**, 1716; (d) Y. Nagasawa, Y. Matsusaki, T. Nobuta, N. Tada, T. Miura and A. Itoh, *RSC Adv*. 2015, **5**, 63952. (e) Y. Hu, L. Chen, B. Li *RSC Adv*, 2016, **6**, 65196 (f) Z. Bie, G. Li, L. Wang, Y. Lv, J. Niu, S. Gao, *Tetrahedron Lett.* 2016, **57**, 4935. (g) S. Parua, S. Das, R. Sikari, S. Sinha, N. D. Paul, *J. Org. Chem*, 2017, **82**, 7165. (h) J. Sun, T. Tao, D. Xu, H. Cao, Q. Kong, X. Wang, Y. Liu, J. Zhao, Y. Wang, Y. Pan *Tetrahedron Lett.* 2018, **59**, 2099 (i) Y. Wang, X. Meng, G. Chen, P. Zhao. *Catal. Commun.* 2018, **104**, 106. (j) Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu, F. Wang, *Chem. Commun*. **2015**, 9205 (k) D. Zhao, Y.-R. Zhou, Q. Shen, J.-X. Li, *RSC Adv*. 2014, **4**, 6486

5 S. Mohammed, R. A. Vishwakarma, and S. B. Bharate, *J. Org. Chem*., 2015, **80**, 6915.

6 X.-F. Wu, L. He, H. Neumann and M. Beller, *Chem. Eur. J*., 2013, **19**, 12635.

7 X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.M. Zhu, and S.-J. Ji, *J. Org. Chem*., 2014, **79**, 5082.

8 X. Chen, T. Chen, Y. Zhou, D. Han, L.-B. Han and S.-F. Yin, Org. *Biomol. Chem.*, 2014, **12**, 3802

9 X. -X. Qi, Z.-Z. Song, J.-L. Gong, Z.-Y. Fang and X.-F. Wu, *Chin. Chem. Lett.*, 2016, **27**, 21.

10 (a) W. Xu, Y. Jin, H. Liu, Y. Jiang and Hua Fu, *Org. Lett.*, 2011, **13**, 1274; (b) W. Xu and H. Fu, *J. Org. Chem.*, 2011, **76**, 3846; (c) L.-X. Wang, J.-F. Xiang and Y.-L. Tang, *Eur. J. Org. Chem*., 2014, 2682; (d) T. Li, M. Chen, L. Yang, Z. Xiong, Y. Wang, F. Li and D. Chen, *Tetrahedron*, 2016, **72**, 868.

11 (a) W. Zhao, P. Liu and F. Li, *ChemCatChem* **2016**, *8*, 1523; (b) L. Tang, X. Zhao, G. Zou, Y. Zhou and X. Yang, *Asian J. Org. Chem*. **2016**, *5*, 335.

12 (a) C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun*., 2008, 6333; (b) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem. Int. Ed*., 2009, **48**, 348.

13 (a) J. Chen, D. Wu, F. He, M. Liu, H. Wu, J. Ding and W, Su, *Tetrahedron Lett*., 2008, **49**, 3814; (b) J. Zhang, D. Ren, Y. Ma, W. Wang and H. Wu, *Tetrahedron*, 2014, **70**, 5274; (c) R. Mekalaa, R. Akulaa, R. R. Kamarajua, C. K. Bannoth, S. Regati, J. Sarva, *Synlett*, 2014, **25**, 821; (d) D. Kumar, P. S. Jadhavar, M. Nautiyal, H. Sharma, P. K. Meena, L. Adane, S. Pancholia and A. K. Chakraborti, *RSC Adv*., 2015, **5**, 30819.

14 For recent reviews of bismuth Lewis acid, see: (a) T. Ollevier *Org. Biomol. Chem.* 2013, **11**, 2740. (b) J. M. Bothwell, S. W. Krabbe, and R. S. Mohan, *Chem. Soc. Rev.* 2011, **40**, 4649.

15 M. Poliakoff and P. Licence, *Nature*, 2007, **450**, 810.

16 C. Capello, U. Fischer and K. Hungerbühler, *Green Chem*., 2007, **9**, 927.

17 (a) R. Hayashi, J.-A Park and G. R. Cook, *Heterocycles*, 2014, **88**, 1477; (b) R. Hayashi and G. R. Cook, *Tetrahedron Lett.*, 2008, **49**, 3888; (c) M. Kaneko, R. Hayashi and G. R. Cook, *Tetrahedron Lett.*, 2007, **48**, 7085; (d) R. Hayashi and G. R. Cook, *Org. Lett*., 2007, **9**, 1311. (e) D. Kumar, S. R. Vemula, B. Narayanaganesh, G. R. Cook, *Acc. Chem. Res*., 2016, **49**, 2169.

18 (a) S. R. Vemula, D. Kumar and G. R. Cook, *Tetrahedron Lett.* 2015, **56**, 3322; (b) D. Kumar, S. R. Vemula and G. R. Cook, *Green Chem.*, 2015, **17**, 4300. (c) S. R. Vemula, D. Kumar, G. R. Cook, *ACS Catalysis*, 2016, **6,** 5295.

19 (a) J. Zhou, J. Fang, *J. Org. Chem*. 2011, **76**, 7730. (b) A. J. Watson, A. C. Maxwell, J. M. Williams, *Org. Biomol. Chem.* 2012, **10**, 240 (c) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.* 2012, **77**, 7046 (d) S. M. A. Hakim Siddiki, K. Kon, A. S. Touchy, K.-I. Shimizu, *Catal. Sci. Technol*. 2014, **4**, 1716 (e) F. Li, L. Lu, J. Ma, *Org. Chem. Front.* 2015, **2**, 1589.

20 P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem*., 2000, **72**, 1207.

21 J. Wencel-Delord and F. Glorius, *Nat. Chem*., 2013, **5**, 369.

22 (a) H. Lu, Q. Yang, Y. Zhou, Y. Guo, Z. Deng, Q. Dinga and Y. Peng, *Org. Biomol. Chem*., 2014, **12**, 758; (b) D. Kumar, S. R. Vemula and G. R. Cook, *ACS Catal*., 2016, **6**, 3531.

23 Sigma-Aldrich catalogue: $Bi(NO_3)_3 \cdot 5H_2O$ CAS No: 10035-06-0; $Bi(OTf)_3$ CAS No: 88189-03-1

Bismuth-Catalyzed Green Protocol for the Synthesis of 2-Substituted Quinazolinones

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Highlights:

Sustainable green protocol for the synthesis of quinazolinones.

Bismuth-catalysis for the synthesis of quinazolinones.

Simple and efficient green methodology.

Biorenewable solvents.

Non-toxic catalysts.