Molecular Catalysis 434 (2017) 134–139

Contents lists available at ScienceDirect

Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

MCAT

Editor's choice paper

Controllable Brønsted acid-promoted aerobic oxidation via solvation-induced proton transfer: Metal-free construction of quinazolinones and dihydroquinazolinones

Zhi-Yu Yu[a], Mei-Ying Chen[b], Jun-Xiong He[b], Duan-Jian Tao[b,*], Jian-Jun Yuan[c], Yi-Yuan Peng[a], Zhi-Bin Song[a,*]

[a] Key Laboratory of Functional Small Organic Molecules, Ministry of Education, Jiangxi Normal University, Nanchang 330022, PR China
[b] College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, PR China
[c] Center of Analysis and Testing, Jiangxi Normal University, Nanchang 330022, PR China

ARTICLE INFO

Article history:
Received 10 January 2017
Received in revised form 28 February 2017
Accepted 6 March 2017

Keywords:
Aerobic oxidation
Brønsted acid
Ionic liquids
Tunable synthesis
Quinazolinones

ABSTRACT

A controllable Brønsted acid-driven aerobic oxidation strategy for the efficient and convenient construction of quinazolinone ring system has been developed using bi-SO_3H-functionalized ionic liquids as catalyst under air atmosphere. The tunable syntheses of dihydroquinazolinones and quinazolinones have been achieved using the same catalyst in different reation meduim via solvation-induced proton transfer. The bi-SO_3H-functionalized ionic liquids (ILs) catalyst can be readily recovered and reused for the gram-scale application for at least three runs without any significant impact on the yields of the products. The operational simplicity and environmentally benign procedure are synthetically useful features.

1. Introduction

Aerobic oxidation is an important conversion in the preparation of fine chemicals and a lot of important organic compounds such as aldehydes, ketones and aromatic heterocyclics [1]. Although a number of efficient oxidants have been developed, molecular oxygen can be regarded as the best oxidants compatible with current environmental concerns. However, air is rarely used alone and transition metals were generally required for further activation [2]. In addition, the selective control of oxidation by using molecular oxygen or air as oxidant often become the bottleneck in the regulation of products formation [3].

Quinazolinone ring system represents a very attractive scaffold in a variety of synthetic drugs and natural products [4]. Quinazolinones as well as the 1,2-dihydroquinazolinones are widely used as antibacterial, antiinflammatory, antileishmanial and anti-tumor agents [5–8]. Recently, 2-substituted quinazolin-4(3H)-one and dihydroquinazolinones were used as sensors for detection of amine vapors and Cu^{2+} ions [9,10]. These special utilities of quinazolinone and dihydroquinazolinone derivatives highlight their synthetic necessity [11]. In most cases, the preparation of quinazolinones is achieved through the oxidation of dihydroquinazolinones [12]. Although a number of methodologies to construct quinazolinones via aerobic oxidation have been developed, metal co-catalysts were generally used [13]. Recently, metal-free protocols via aerobic oxidation in wet DMSO and aerobic oxidative amination for syntheses of 2-hetarylquinazolinones have been reported [14,15]. But tunable syntheses of dihydroquinazolinones and quinazolinones via controlled oxidation under such aerobic condition are inadequately addressed.

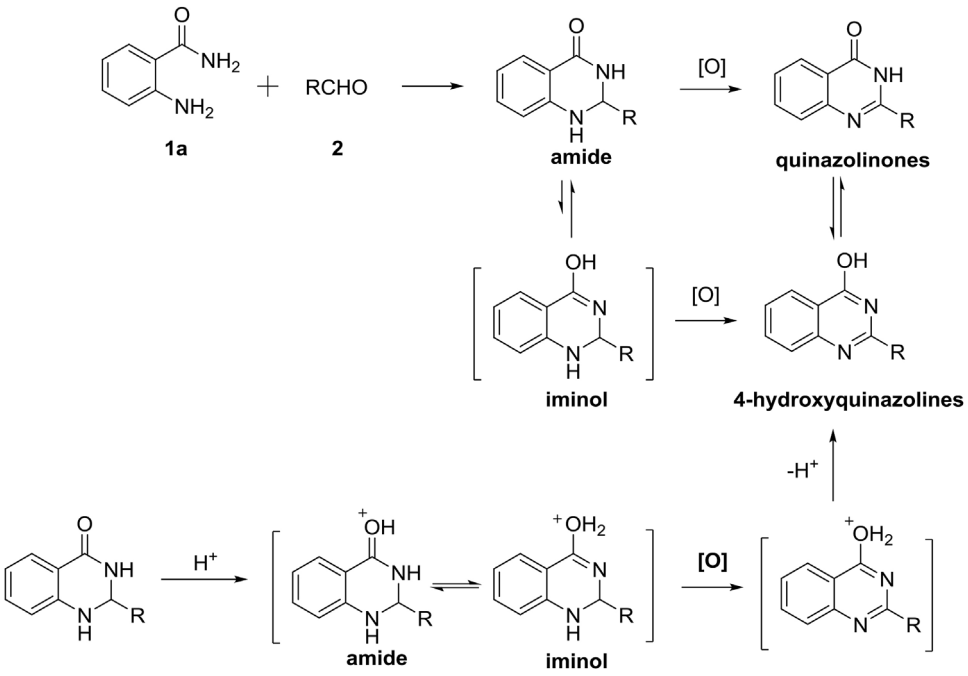
Herein, we disclosed an example of controllable metal-free Brønsted acid-promoted aerobic oxidation for constructing quinazolinone scaffolds from *o*-anthranilamides with aldehydes under air atmosphere by using bis-sulfonated ILs as catalyst. The tunable syntheses of dihydroquinazolinones and quinazolinones have been expediently achieved via modulation of the proton activity in different reaction medium.

2. Results and Discussion

In ring of quinazolinone, there is an amide-iminol tautomerism in quinazolinones or dihydroquinazolinones [16]. Generally, the amide tautomer of dihydroquinazolinone is more thermodynam-

* Corresponding authors.
E-mail addresses: djtao@jxnu.edu.cn (D.-J. Tao), zbsong@jxnu.edu.cn (Z.-B. Song).

http://dx.doi.org/10.1016/j.mcat.2017.03.006
2468-8231/



Scheme 1. Working hypothesis.

Table 1
Hammett acidity Function (H_0) values of different Brønsted acidic ionic liquids and H_2SO_4.

entry	acid	A_{max}	[I] %	$[HI]^+$ %	H_0
1	–	0.565	100	0	–
2	C1	0.523	92.50	7.50	2.08
3	C2	0.492	87.07	12.93	1.81
4	C3	0.359	63.53	36.47	1.231
5	H_2SO_4	0.510	90.26	9.73	1.95

ically stable than the iminol tautomer. Anticipating that the iminol tautomer of dihydroquinazolinones could convert to iminol tautomer of quinazolinones (4-hydroxyquinazolines) more easily through oxidation-dehydroaromatization in air (Scheme 1), we realized that the controlled syntheses of dihydroquinazolinones and quinazolinones under aerobic condition might be able to be achieved through the control of amide-iminol tautomerism. To a certain extent, acid can promote the formation of iminol tautomer [16]. Therefore, we resorted to acid-driven aerobic oxidation strategy.

Due to the remarkable properties of ILs such as designable structure and good compatibility in water and organic solvent, tuning the acidity of ILs can be achieved by the structure design and modification. In order to test our working hypothesis, three SO_3H-functionalized acidic ILs (Fig. 1) with different acidity were designed and synthesized. Hammett function (H_0) [17], which can be calculated by the formula ($H_0 = 0.99 + \lg[I]/[HI]^+$), was used to assess the acidity of ILs catalysts in organic solvents (Table 1). C3 showed strongest acidity in selected acids (Table 1, entry 4). We began our efforts on examining the model reaction between 2-aminobenzamide (1a) and benzaldehyde (2a) in the presence of acid using air as oxidant. The results are summarized in Table 2. The addition of acid could promote the aerobic oxidation using EtOH as solvent. And strong acid did better results on the formation of quinazolinone (4a). The C3 which was the strongest acidity in EtOH showed the best catalytic activity in this aerobic oxidation (Table 2, entry 7 and 8). In addition, the yield of quinazolinone (4a) could be reached 85% in the presence of C2 when the reaction time increased to 12 h (Table 2, entry 6). In consideration of the efficiency of catalysts, we choose C3 for further investigation. The following examination on the catalyst loading of C3 and reaction temperature was performed. The results showed that the reaction time needed to be prolonged to get a better yield when the catalyst loading of C3 or reaction temperature was decreased (Table 2, entries 9–13). The effect of organic solvents on this aerobic oxidation was also investigated (Table 2, entries 14–18). Polar solvents were favourable for the formation of quinazolinone 4a. For instance, the yield of quinazolinone 4a was 98% in ethanol (Table 2, entry 8), 80% in DMF (Table 2, entry 18). The green solvent such as PEG-400 also afforded a good yield (89%) of 4a (Table 2, entry 17). It is probably because the iminol tautomer can be stabilized through hydrogen bonding formation in the polarity condition.

With these expected results in hand, we subsequently investigated the possibility of blocking oxidation process via proton salvation effect to reduced proton activity under such aerobic oxidation using the same catalyst. To pursue this goal, water was added to reaction mixture. It was observed that the yield of 4a decreased from 82% to 17% with increasing water fractions from 10 to 90 vol% (Table 2, entries 19–21). Pure water gave 90% yield of 3a instead of 4a (Table 2, entry 22). Dihydroquinazolinone 3a could also be obtained at a yield of 88% even at room temperature (Table 2, entry 23). The yields of the 4a decreased in the presence of water probably due to the formation of the hydrated proton (H_3O^+) from Brønsted acid catalyst and water which reduces catalytic activity of C3 [20]. Thus, we have successfully achieved the regulation of aerobic oxidation.

Next, the scope and generality of this controlled Brønsted acid-promoted aerobic oxidation was explored under such operational condition. In consideration of the solubility of the catalyst and substrates, shorten reaction time, high yield and environmental acceptance, the operational condition we chose for syntheses of quinazolinones was the treatment of anthranilamides and aldehydes in the presence of C3 at 80 °C in EtOH. It was observed that the reactions of substituted 2-aminobenzamide with aldehydes proceeded smoothly and most of pure products were obtained by simple washing and recrystallization without using silica gel column chromatography. Aromatic aldehydes with electron withdrawing or electron donating groups can be successfully converted

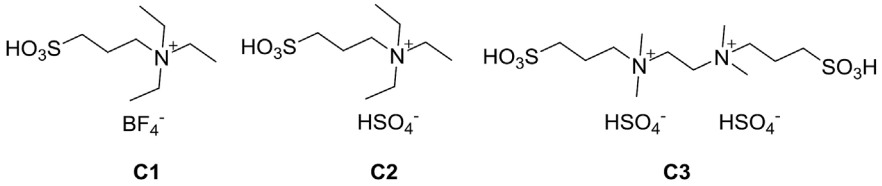
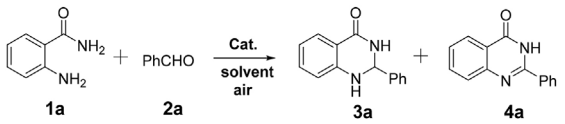


Fig. 1. The structures of SO_3H-functionalized ionic liquids catalysts.

Table 2
Optimization of the Reaction Conditions.[a]

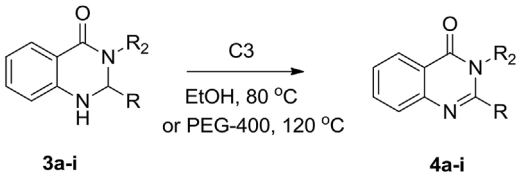


entry	catalyst (mol %)	solvent	temp (°C)	time (h)	Yield (%)[b]	
					3a	4a
1	Acetic acid (20)	EtOH	80	1	35	25
2	CH_3SO_3H(20)	EtOH	80	1	42	46
3	H_2SO_4(20)	EtOH	80	1	32	42
4	C1 (20)	EtOH	80	1	52	26
5	C2 (20)	EtOH	80	1	38	55
6	C2 (20)	EtOH	80	12	<10	85
7	C3 (20)	EtOH	80	1	<10	83
8	C3 (20)	EtOH	80	2	trace	98
9	C3 (10)	EtOH	80	5	trace	95
10	C3 (30)	EtOH	80	1.5	trace	97
11	C3 (20)	EtOH	60	8	trace	95
12	C3 (20)	EtOH	40	32	<5	90
13	C3 (20)	EtOH	r.t.	48	<10	88
14	C3 (20)	Toluene	80	2	20	30
15	C3 (20)	CH_3CN	80	2	16	70
16	C3 (20)	Dioxane	80	2	30	35
17	C3 (20)	PEG-400	80	2	<5	89
18	C3 (20)	DMF	80	2	15	80
19	C3 (20)	EtOH/H_2O (9:1, v/v)	80	2	12	82
20	C3 (20)	EtOH/H_2O (5:5, v/v)	80	2	45	50
21	C3 (20)	EtOH/H_2O (1:9, v/v)	80	2	75	17
22	C3 (20)	H_2O	80	2	90	<10
23	C3 (20)	H_2O	r.t.	12	88	<10

[a] Reaction conditions: *o*-aminobenzamide **1a** (1 mmol), benzaldehyde **2a** (1 mmol), catalyst based on **1a**, solvent (5 mL) under air.
[b] Isolated yield based on **2a**.

to the corresponding quinazolinones with good to excellent yield (73%–98%). The fused aryl (4f) and heteroaryl (4b, 4d and 4k) aldehydes were also well tolerated in this reaction, producing the corresponding products in yield from 77% to 93%. The synthesis of 2-alkyl substituted quinazolinones from 2-aminobenzamide with aliphatic aldehydes were more difficult in literatures [18]. To our delight, the aliphatic aldehydes (4i and 4l) can also be successfully converted to the corresponding products with good yield (76% and 84%). And the differently substituted anthranilamides such as methyl and bromide were also successfully used in this reaction to get quinazolinones (4k and 4m). When 2-Amino-*N*-methylbenzamide was used in this reaction to get 3-methyl quinazolinone, reaction temperature should be increased to 120 °C in PEG-400. This might be more difficult to form iminol tautomer of 3- substituted quinazolinones. The increase of temperature could make the transition easier. Subsequently, we used water instead of ethanol as reaction medium for syntheses of 1,2-dihydroquinazolinones. The corresponding products were also obtained in yield from 72% to 94%. The substrate compatibility is also good. In addition, quinazolinones were also obtained by direct dehydrogenation oxidation of their dihydroquinazolinone forms (Scheme 2).

In view of the simplicity of this controllable synthetic method, the reusability of catalyst for scale-up synthesis should also

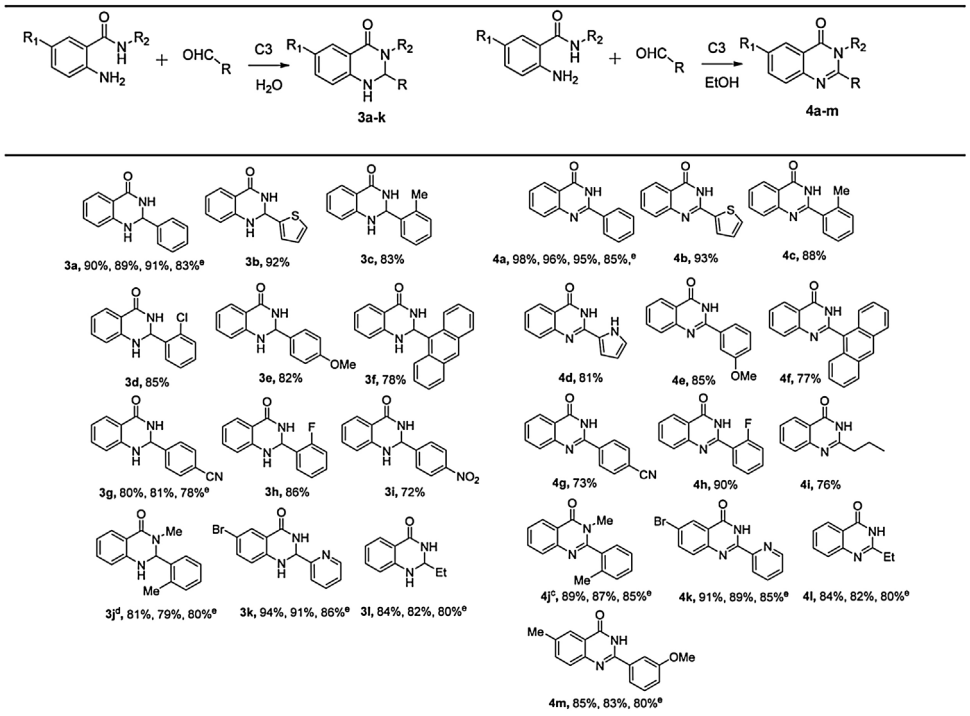


Scheme 2. Synthesis of quinazolinones via direct dehydrogenation oxidation of dihydroquinazolinones.

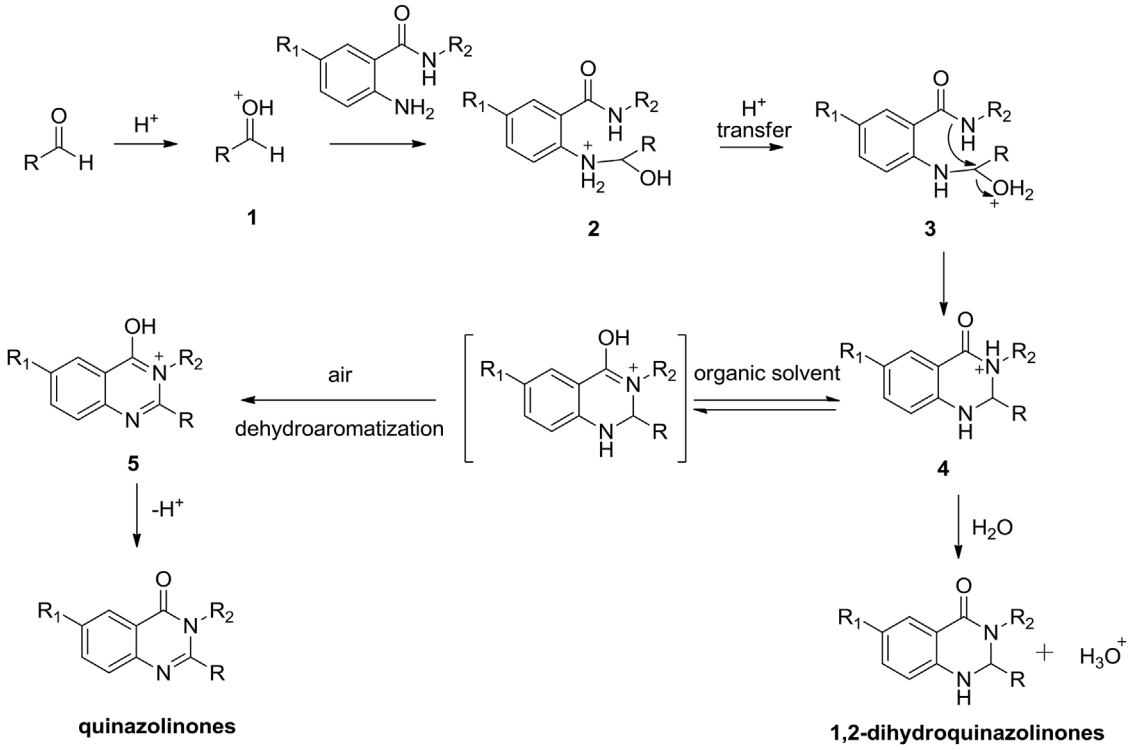
be checked so as to confirm the applicability of this protocol. Therefore, the several reactions were selected to examine the recyclability of the catalyst system. The results indicate that the catalyst system can be recycled for the muti-gram scale syntheses of quinazolinones and dihydroquinazolinones (Table 3). After three cycles, the yields of products were slightly decreased because of catalyst loss in the recycling process. The recycled C3 was also characterized by FT-IR and ^{1}H NMR. Compared with the fresh C3, the characteristic peaks of reused C3 were the same in the IR and ^{1}H NMR spectrum (see Supporting information).

Possible mechanisms for preparation of quinazolinones from *o*-anthranilamides with aldehydes have been reported before. Based on experimental observations and literature reports of similar reaction, a plausible reaction mechanism was proposed for

Table 3
Tunable synthesis of dihydroquinazolinones and quinazolinones.[a]



[a] Reaction conditions: *o*-aminobenzamide 1a (1 mmol), benzaldehyde 2a (1 mmol), catalyst based on 1a, EtOH or water (5 mL), 80 °C, 2 h under air; [b] Isolated yield, c 120 °C in PEG-400, 4 h, d 100 °C, 6 h, e Catalyst was recycled. Reactions performed at 20 mmol scale of all reactants.



Scheme 3. A possible mechanism for the formation of quinazolinone and 1,2-dihydroquinazolinone and derivatives.

this controllable metal-free Brønsted acid-promoted aerobic oxidation (Scheme 3). Firstly, aldehydes were activated by acid to give intermediate **1**. The next step involved nucleophilic addition with amino-group to generate tetrahedral intermediate **2**. Subsequently, cyclization resulted in another intermediate **4**. Finally, 1,2-dihydroquinazolinones were formed through proton transfer in

the reaction medium containing an appropriate amount of water. And quinazolinones were formed in organic solvent via oxidative dehydrogenation of the intermediate **5** and subsequent deprotonation.

3. Conclusions

In this work, we have described a successful controllable acid-driven aerobic oxidation strategy for the efficient and convenient construction of quinazolinones and dihydroquinazolinones using bis-sulfonated ILs as catalyst from *o*-anthranilamides with aldehydes in the air. It provides a tunable synthetic approach to afford the desired product. Particularly noteworthy is that the catalyst can be readily recovered and reused for muti-scale syntheses at least three runs without any significant impact on the yield of the products. This protocol offers several advantages such as the broad substrate scope, high yield, environmentally benign solvent and an easy experimental workup procedure. Further exploring the aerobic synthetic approach to the synthesis of N-containing heterocycles using functional Ionic Liquids is underway in our laboratory.

4. Experimental section

4.1. General methods

All commercial reagents were used without further purification unless otherwise noted. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC). Melting points were recorded in open capillaries and are uncorrected. The mass spectra were obtained from a Finnigan8230 instrument (ESI). High resolution mass spectrometry (HRMS) spectra analysis was performed by electrospray ionization (ESI-microTOF). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR by using CDCl3 or DMSO-d6 as solvents and TMS as an internal standard. UV–vis absorption spectra were measured on a Shimadzu UV-2450 spectrophotometer. FTIR spectrum was recorded on Thermo Nicolet 870, elemental analysis was recorded on Elementar Vario E1 III and thermal analysis was recorded on Netzsch STA 449C.

4.2. Preparation of sulfonic functionalized ionic liquids catalysts [19]

Ethanol (25 mL) and the corresponding amine was charged into a 100 mL round bottom flask. After that, 1,3-propyl sultone was added dropwise with stirring at 70 °C and the reaction was kept for 12 h; the intermediate product of internal salt was washed repeatedly with diethyl ether to remove non-ionic residues and further dried under vacuum at 80 °C for 8 h; Then the internal salt was loaded into a 250 mL round bottom flask, and an aqueous solution of acid was added dropwise with stirring at 70 °C and the reaction was kept for 8 h; resulted product was washed repeatedly with acetone to remove unreacted raw material and dried under vacuum at 80 °C for 12 h to afford sulfonic functionalized ionic liquids catalyst.

4.3. General procedure for the measurement of acidity

All experiments were carried out in 20 °C. To the mixture of p-nitroaniline (1 μmol/L) in anhydrous ethanol, the solution of acid (2 μmol/L) in anhydrous ethanol was added. The absorption value of the mixed solution at 360 nm was measured by UV–vis spectrophotometer.

4.4. General procedure for preparation of dihydroquinazolinones

To a mixture of *o*-aminobenzamide (1 mmol), aldehyde (1 mmol) in distilled water (5 mL) was added C3 (0.2 mmol, 111 mg). The resulting mixture was stirred at 80 °C for 2 h in the open air. After completion of the reaction, the resulting solution was cooled to room temperature. The products were precipitated out, and the aqueous phase containing C3 was isolated simply by filtration. It can be recovered and reused in the next run after heat treatment to remove water under vacuum at 80 °C for 12 h. The pure products were obtained by recrystallization with DMF/water or silica gel column chromatography.

4.5. General procedure for preparation of quinazolinones

To a mixture of *o*-aminobenzamide (1 mmol), aldehyde (1 mmol) in EtOH (5 mL) was added C3 (0.2 mmol, 111 mg). The resulting mixture was stirred at 80 °C for 2 in the open air. After completion of the reaction, the resulting solution was cooled to room temperature. Deionized water (20 mL) was added to the reaction mixture. The products were precipitated out, and the aqueous phase containing C3 was isolated simply by filtration. It can be recovered and reused in the next run after heat treatment to remove water under vacuum at 80 °C for 12 h. The pure products were obtained by recrystallization with DMF/water or silica gel column chromatography.

Acknowledgements

We thank the financial support by the National Natural Science Foundations of China (No. 21606116), the Natural Science Foundations of Jiangxi Province (No. 20161BAB213070).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2017.03.006.

References

[1] (a) T. Mallat, A. Baiker, Chem. Rev. 104 (2004) 3037–3058;
(b) Z. Guo, B. Liu, Q.-H. Zhang, W.-P. Deng, Y. Wang, Y.-H. Yang, Chem. Soc. Rev. 43 (2014) 3480–3524;
(c) S.E. Davis, M.S. Ide, R.J. Davis, Green Chem. 15 (2013) 17–45;
(d) N. Gunasekaran, Adv. Synth. Catal. 357 (2015) 1990–2010;
(e) S.E. Allen, R.R. Walvoord, R. Padilla-Salinas, M.C. Kozlowski, Chem. Rev. 113 (2013) 6234–6458.
[2] Z.-Z. Shi, C. Zhang, C.-H. Tang, N. Jiao, Chem. Soc. Rev. 41 (2012) 3381–3430.
[3] P. Galletti, F. Funiciello, R. Soldati, D. Giacomini, Adv. Synth. Catal. 357 (2015) 1840–1848.
[4] U.A. Kshirsagar, Org. Biomol. Chem. 13 (2015) 9336–9352.
[5] R. Bouley, D. Ding, Z. Peng, M. Bastian, E. Lastochkin, W. Song, M.A. Suckow, V.A. Schroeder, W.R. Wolter, S. Mobashery, M. Chang, J. Med. Chem. 59 (2016) 5011–5021.
[6] K. Ozaki, Y. Yamada, T. Oine, T. Ishizuka, Y. Iwasawa, J. Med. Chem. 28 (1985) 568–576.
[7] M. Sharma, K. Chauhan, R. Shivahare, P. Vishwakarma, M.K. Suthar, A. Sharma, S. Gupta, J.K. Saxena, J. Lal, P. Chandra, B. Kumar, P.M.S. Chauhan, J. Med. Chem. 56 (2013) 4374–4392.
[8] L.H. Pettus, K.L. Andrews, S.K. Booker, J. Chen, V.J. Cee, F. ChavezJr, Y. Chen, H. Eastwood, N. Guerrero, B. Herberich, D. Hickman, B.A. Lanman, J. Laszlo III, M.R. Lee, J.R. Lipford, B. Mattson, C. Mohr, Y. Nguyen, M.H. Norman, D. Powers, A.B. Reed, K. Rex, C. Sastri, N. Tamayo, P. Wang, J.T. Winston, B. Wu, T. Wu, R.P. Wurz, Y. Xu, Y. Zhou, A.S. Tasker, H.-L. Wang, J. Med. Chem. 59 (2016) 6407–6430.
[9] M. Gao, S.-W. Li, Y.-H. Lin, Y. Geng, X. Ling, L.-C. Wang, A.-J. Qin, B.Z. Tang, ACS Sens. 1 (2016) 179–184.
[10] P.N. Borase, P.B. Thale, G.S. Shankarling, Dyes Pigm. 134 (2016) 276–284.
[11] (a) R.S. Rohokale, U.A. Kshirsagar, Synthesis 48 (2016) 1253–1268;
(b) L. He, H.-Q. Li, J.-B. Chen, X.-F. Wu, RSC Adv. 4 (2014) 12065–12077;
(c) J. Wu, X.-L. Du, J. Ma, Y.-P. Zhang, Q.-C. Shi, L.-J. Luo, B.-A. Song, S. Yang, D.-Y. Hu, Green Chem. 16 (2014) 3210–3217;

(d) P.N. Borase, P.B. Thale, G.S. Shankarling, RSC Adv. 6 (2016) 63078–63083;
(e) J. Safari, S. Gandomi-Ravandi, J. Mol. Catal. A 390 (2014) 1–6;
(f) A. Ghorbani-Choghamarani, M. Norouzi, J. Mol. Catal. A 395 (2014) 172–179;
(g) Y.-L. Luo, Y. Wu, Y.-Y. Wang, H.-M. Sun, Z.-Y. Xie, W.-Q. Zhang, Z.-W. Gao, RSC Adv. 6 (2016) 66074–66077;
(h) J. Safari, S. Gandomi-Ravandi, J. Mol. Catal. A: Chem. 371 (2013) 135–140;
(i) P. Kumar, A.K. Singh, V. Bahadur, C. Len, N.G.J. Richards, V.S. Parmar, E.V. Van der Eycken, B.K. Singh, ACS Sustain. Chem. Eng. 4 (2016) 2206–2210;
(j) P. Kumar, A. Matta, S. Singh, J. Van der Eycken, C. Len, V.S. Parmar, E.V. Van der Eycken, B.K. Singh, Synth. Commun. (2017) http://dx.doi.org/10.1080/00397911.2016.1277761.

[12] (a) X.-F. Wu, S. Oschatz, A. Block, A. Spannenberg, P. Langer, Org. Biomol. Chem. 12 (2014) 1865–1870;
(b) X.-L. Chen, T.-Q. Chen, Y.-B. Zhou, D.-Q. Han, L.-B. Han, S.-F. Yin, Org. Biomol. Chem. 12 (2014) 3802–3807;
(c) D. Zhao, T. Wang, J.-X. Li, Chem. Commun. 50 (2014) 6471–6474.

[13] (a) K. Upadhyaya, R.K. Thakur, S.K. Shukla, R.P. Tripathi, J. Org. Chem. 81 (2016) 5046–5055;
(b) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, J. Org. Chem. 77 (2012) 7046–7051;
(c) X.-L. Chen, T.-Q. Chen, F.-Y. Ji, Y.-B. Zhou, S.-F. Yin, Catal. Sci. Technol. 5 (2015) 2197–2202;
(d) Q. Li, Y. Huang, T.-Q. Chen, Y.-B. Zhou, Q. Xu, S.-F. Yin, L.-B. Han, Org. Lett. 16 (2014) 3672–3675.

[14] N.Y. Kim, C.-H. Cheon, Tetrahedron Lett. 55 (2014) 2340–2344.
[15] H.-H. Liu, T.-R. Zhai, S.-T. Ding, Y.-L. Hou, X.-Y. Zhang, L. Feng, C. Ma, Org. Chem. Front. 3 (2016) 1096–1099.
[16] E.D. Raczyńska, W. Kosińska, Chem. Rev. 105 (2005) 3561–3612.
[17] C. Thomazeau, H. Olivier-Bourbigou, L. Magna, S. Luts, B. Gilbert, J. Am. Chem. Soc. 125 (2003) 5264–5265.
[18] M. Sharif, J. Opalach, P. Langer, M. Beller, X.-F. Wu, RSC Adv. 4 (2014) 8–17.
[19] D.-J. Tao, Y. Dong, Z.-J. Cao, F.-F. Chen, X.-S. Chen, K. Huang, J. Ind. Eng. Chem. 41 (2016) 122–129.
[20] C.A. Reed, Acc. Chem. Res. 46 (2013) 2567–2575.