ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

Microwave-Assisted Multicomponent Synthesis of Dihydroquinoxalinones on Soluble Polymer Support

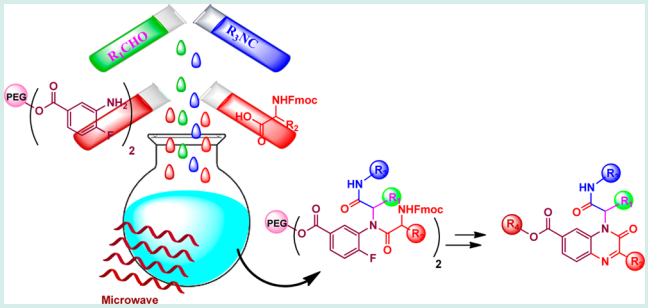
Prashant B. Dalvi,[†] Shu-Fen Lin,[†,‡] Vijaykumar Paike,[†] and Chung-Ming Sun*[,†,‡]

[†]Department of Applied Chemistry, National Chiao-Tung University, 1001 Ta-Hseuh Road, Hsinchu 300-10, Taiwan

[‡]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, 100, Shih-Chuan First Road, Kaohsiung 807-08, Taiwan

Supporting Information

ABSTRACT: A one-pot and two-step reaction of four components, including aldehydes, Fmoc-protected α-amino acid, isocyanide, and soluble polymer-supported 4-fluoro-3-amino benzoate ester, was developed for an efficient synthesis of dihydroquinoxalinones under microwave irradiation. Fmoc deprotection followed by intramolecular cyclization of the diamide gave a facile access to novel bicyclic quinoxalin-2-ones. On the basis of this approach, a new route to synthesize this privileged scaffold from the diamide intermediate was designed and accomplished with high yields. Use of multicomponent reaction (MCR) has been shown to display a good functional group tolerance, while the product isolation and purification is straightforward by precipitation and washings. Current library discusses the synthesis and diversification of 21 compounds produced using this strategy.



KEYWORDS: *dihydroquinoxalin-2-ones, microwave chemistry, soluble supported synthesis, multicomponent reaction (MCR)*

INTRODUCTION

Nitrogen-containing heterocyclic molecules are essential and frequently used in the pharmaceutical and agricultural industries as building blocks to design more potent compounds.[1−3] Accordingly, small molecules containing the quinoxalinone scaffold, an important structural motif, has been studied extensively for their biological properties. For examples, pyridoquinoxalinone **I** shows anticancer activities against various cancer cells, such as leukemia, nonsmall cell lung cancer, and colon cancer.[4] Quinoxalinone-hydrazone prototypes **II** is a potent antifungal agent.[5] Heteroaryl sulfonyl quinoxaline **III** is a potential HIV-1 reverse transcriptase inhibitor with submicromolar activity.[6] Amidino-phenoxyquinolone **IV** is a novel antithrombotic compound with in vitro activity (IC_{50} = 0.008 μM).[7] Therefore, efforts have been made to construct a diversified and efficient synthesis of these N-containing heterocycles with various potential biological applications.

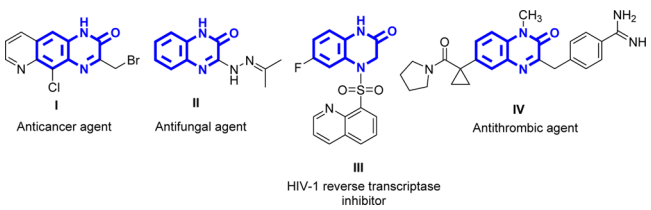


Figure 1. Biologically active quinoxalinone derivatives.

MCRs play an important role in the synthesis of structurally diverse molecular scaffolds and increase the efficiency of reactions by combining several operational steps together without the isolation of intermediates. In MCRs, three or more components are reacted in a one-pot to generate products with high atom economy and selectivity under mild reaction conditions.[8] They can be used to produce combinatorial libraries for screening purposes since the number of new chemical entities can be synthesized to fulfill the demands of medicinal research. MCRs, such as Passerini, Ugi, Groebke−Bienaymé−Blackburn, and Orru reactions are widely recognized methods for the rapid synthesis of biologically important heterocycles.[9,10] Among the MCRs, the Ugi-4CR is highly versatile in terms of potential library size and diversity because it can afford a wide variety of substitution patterns.[11−14] This well-known MCR involves the coupling of a Schiff base or an imine with an acid and an isocyanide, followed by a Mumm rearrangement to deliver diamides.

Microwave-assisted synthesis increases the efficiency of particular reaction sequences and in combination with this technique, soluble polymer supported synthesis of targeted compounds are performed easily with reduced efforts since product isolation is straightforward by precipitation.[15−17] PEG-supported intermediates are quite stable under harsh microwave, flash-heating conditions. Hence, great strides have been

Received: April 5, 2015
Revised: May 31, 2015
Published: June 23, 2015

DOI: 10.1021/acscombsci.5b00053
ACS Comb. Sci. 2015, 17, 421−425

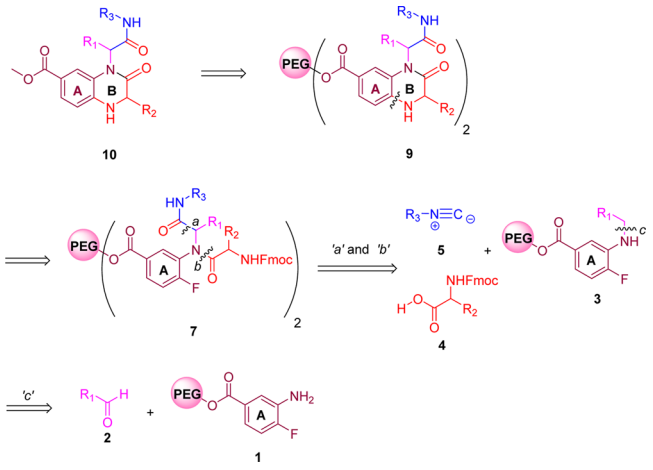
made to utilize the power of microwave and soluble polymer support for diversity-oriented synthesis (DOS).[18,19] Therefore, construction of an efficient synthetic route for the synthesis of quinoxalinones using microwave flash heating on a soluble polymer support has been designed by employing Ugi MCR. Several established protocols for the synthesis of quinoxalinone heterocycles frequently employ 1-fluoro-2-nitrobenzene as a synthon.[20−24]

Recently, Tanimori has reported a one pot, solution phase synthesis of chiral quinoxalinones using copper(I) catalyst and potassium phosphate in DMSO at 110 °C for 24 h.[25] Krchňák et al. published a solid phase synthesis of dihydroquinoxalin-2-ones with different amide linkers and substituted *o*-nitro fluoro benzenes to give target compounds in medium yields (18−58%).[26]

RESULTS AND DISCUSSION

Retrosynthetic analysis of targeted compound **10** is depicted in Scheme 1. Final product could be obtained through the

Scheme 1. Retrosynthetic Analysis of Dihydroquinoxalin-2-ones 10



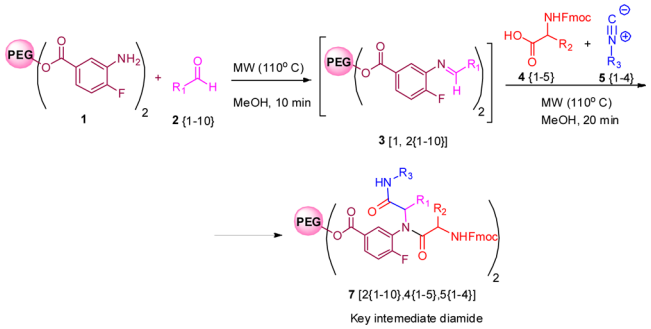
removal of the soluble polymer support from compound **9**. However, strategic C−N bond disconnection of ring B in **9** suggests that the bicyclic system could be constructed through nucleophilic attack of diamide intermediate **7** on the fluorinated carbon atom. The disconnection "b" between nitrogen and carbonyl group clearly indicates the amino acid **4** is one of the possible synthetic equivalence of this route. The disconnection "a" between carbonyl group and the carbon atom in intermediate **7** shows a second synthon as an isocyanide **5** to release intermediate **3** with ring A. Disconnection "c" between C−N bond of intermediate **3** indicates one of the synthetic reagents is the aldehyde **2**, while other one is PEG supported ring A, which is constructed from 3-fluoro-4-nitro benzoic acid.

To test the viability of this approach, we carried out the synthesis of benzoate ester **1** by linking commercially available 4-fluoro-3-nitrobenzoic acid (FNBA) to polyethylene glycol (PEG) via an esterification followed by an aromatic nitro reduction.[27]

The PEG-supported amino ester **1** was condensed with aldehydes **2**, Fmoc protected *α*-amino acids **4** and isocyanides **5** in methanol at either room temperature (10 h) or reflux (5 h) to obtain key intermediate **7** in moderate yields (40−55%). To check the feasibility of Ugi MCRs on PEG support under microwave conditions, a coupling reaction was performed in the microwave cavity for 25 min at 110 °C to afford the diamide **7**{*4,1,1*} in 63% yield. Presumably, the lack of an efficient imine formation could be the reason for moderate yield. The formation of the diamide and the intramolecular cyclization in the construction of dihydroquinoxalinones is one of the major challenges and aims of this work. Consequently, in order to enhance the reaction efficiency and yield, a stepwise one-pot, four-component reaction strategy was planned by microwave heating. In attempt to facilitate the formation of the desired intermediate diamide **7**{*4,1,1*}, the systematic study of the imine formation was carried out to find better conditions.

To our delight, the PEG-supported amino ester **1** was condensed with aldehyde **2**{4} under microwave irradiation (110 °C) for 10 min, leading to an imine **3**{*1,4*} followed by addition of amino acids **4**{*1*} and isocyanides **5**{*1*} for an additional 20 min irradiation (see Scheme 2). After the

Scheme 2. Two-Step, One-Pot Synthesis of PEG Supported Diamide 7 via Ugi-4CR



completion of the reaction, the coupling product was precipitated and washed with cold ether to yield the PEG-linked intermediate **7**{*4,1,1*}. Diamide **7**{*4,1,1*} was obtained in 86% yield under the modified two-step one-pot U-4CR.

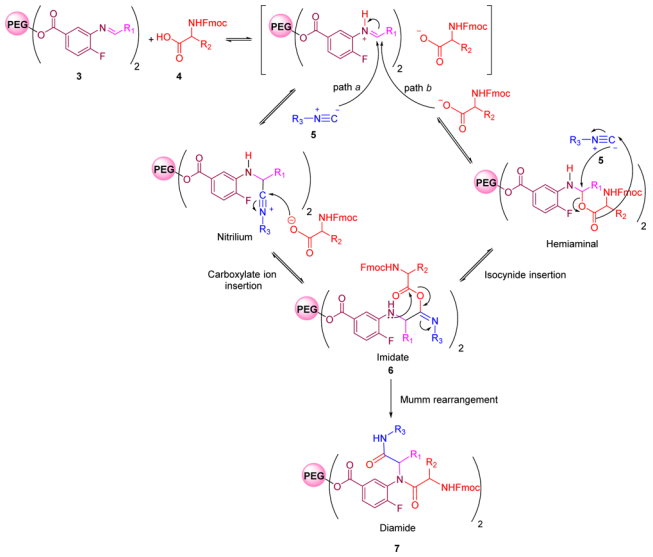
This particular screening envisaged that aliphatic, aromatic, and heteroaromatic aldehydes **2** reacted smoothly to give imines **3** with complete consumption of PEG-bound 4-fluoro-3-aminobenzene carboxylate **1**. Schiff base **3** generated in the first step of Ugi MCRs can be further subjected to various amino acids **4** and isocyanides **5** in one pot to afford key intermediate diamide **7** in good yields. The best outcome for the synthesis of **7** was obtained by microwave flash heating. The efficiency of microwave heating enhances the rate of reactions on the support with reduced reaction time.

The formation of an intermediate **7** can take place through path *a* or path *b* which may lead to either nitrillium or hemiaminal intermediate through attack of an isocyanide or carboxylate ion on the imminium ion, respectively. The nitrillium intermediate reacts with a carboxylate while hemiaminal reacts with an isocyanide to deliver imidate **6**.[28] This imidate undergoes intramolecular nucleophilic attack of amine on carbonyl to form unstable cyclic oxazolidine to produce key intermediate **7** through Mumm rearrangement (Scheme 3).

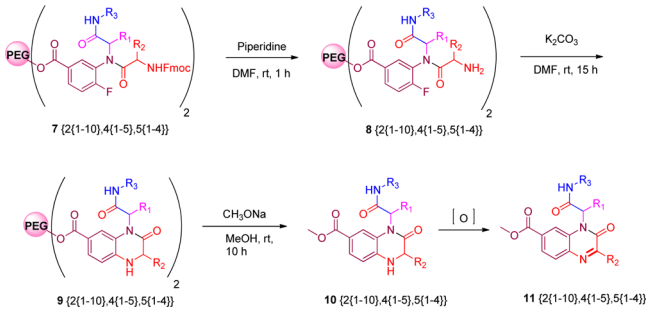
In subsequent steps, Fmoc deprotection was carried out with base followed by an intramolecular cyclization to obtain biheterocycles **9** in good yields (60−80%) as showed in Scheme 4. Therefore, with the crucial intermediate **7**{*4,1,1*} in hand, optimization of Fmoc group deprotection on the support was performed with two different tertiary amines (Et_3N or DIPEA) as well as a secondary amine (piperidine) with suitable

DOI: 10.1021/acscombsci.5b00053
ACS Comb. Sci. 2015, 17, 421−425

Scheme 3. Mechanism for Ugi-4CR



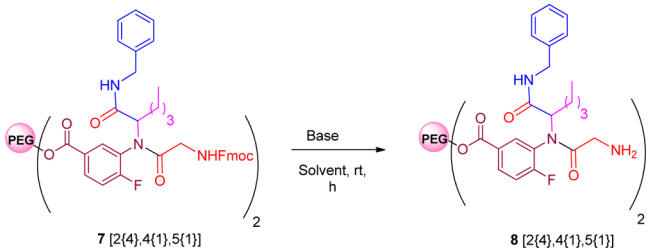
Scheme 4. Synthesis of Dihydroquinoxalin-2-ones 11



solvents at room temperature (Table 1). This study revealed that complete deprotection of Fmoc group was achieved with reduced time, using less equivalents of piperidine when solvent was switched to DMF (Table 1, entry 7).

Using these optimized conditions, the crude reaction mixture was subjected to an attempted, intramolecular cyclization via an ipso substitution of the fluoro atom to afford intermediate **9**{*4,1,1*}. Therefore, crude product **8**{*4,1,1*} (Table 1, entry 6) was continuously stirred under the same conditions for 3h but further conversion to **9**{*4,1,1*}was not observed. Addition of one more equivalent of piperidine to the same reaction mixture was resulted in little conversion to the PEG supported tetrahydroquinaxalinone **9**{*4,1,1*} after 3 h. However, under reflux the crude mixture (Table 1, entry 7) afforded 50% conversion to **9**{*4,1,1*}. Moreover many of our attempts to directly convert diamide **7**{*4,1,1*} to **9**{*4,1,1*} via the two-step, one-pot strategy failed. Accordingly, Fmoc-deprotected amine **8** was subjected to intramolecular cyclization using various bases in a stepwise manner (Scheme 4).

Table 1. Optimization of Fmoc Deprotection on the Support



entry	solvent	base	time (h)	% conversion[a]
1	DCM	Et_3N	2	50
2	DCM	Et_3N[b]	4	50
3	DCM	DIPEA	2	60
4	DCM	DIPEA[b]	4	70
5	DCM	piperidine	1	80
6	DCM	piperidine[b]	2	100
7	DMF	piperidine	1	100

[a]Conversion into product **8**{*4,1,1*} was checked with ^{1}H NMR, [b]Reaction was continued using 1 extra equivalent of base.

The aforementioned study revealed that K_2CO_3 was the preferred base for the ipso substitution to afford bicyclic compounds **9** at ambient temperature within 15 h. The PEG support was removed from bicyclic compounds **9** by treatment with sodium methoxide in methanol at room temperature for 10 h to generate tetrahydroquinoxalin-2-ones **10**, which were very unstable and readily underwent air oxidation to produce dihydroquinoxalin-2-one **11** in 60−80% yields (Table 2).

The building blocks used for the synthesis of target library are shown in the Figure 2. The variety of aldehydes **2**, isocyanides **5**, and amino acids **4** used not only to make this synthetic route more efficient but also to expand molecular diversity. The results of our study are summarized in Table 2. Use of different aldehydes, amino acids, and numerous isocyanides in this two-step, one-pot Ugi MCRs smoothly produced the respective dihydroquinoxalin-2-one **11** in moderate to good yields (Table 2). However, in two cases (entries 4 and 19, Table 2), we were able to isolate tetrahydroquinoxalin-2-ones **10**{*2,1,2*} and **10**{*8,1,3*} as crude products. However, products **10**{*2,1,2*} and **10**{*8,1,3*} underwent auto-oxidation to yield **11**{*2,1,2*} and **11**{*8,1,3*} when crude products were subjected to silica gel column chromatography.

CONCLUSION

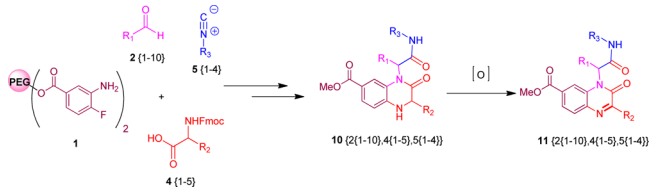
In conclusion, we developed a simple and efficient method toward synthesis of dihydroquinoxaline-2-one. The design and optimization of a microwave promoted multicomponent reaction on soluble polymer support has established to produce substituted dihydroquinoxalin-2-ones. The key intermediate diamide **7** was synthesized via modified one-pot two-step Ugi 4-CR and this has been used further for the planned synthetic route. These reactions proceeded stepwise via deprotection of Fmoc from diamide **7** followed by intramolecular cyclization through an ipso displacement to construct structurally diverse PEG supported bicyclic quinoxalinones **9**. Subsequently, PEG support was removed to deliver tetrahydroquinoxaline-2-one **10**, which readily underwent oxidation to produce bicyclic dihydroquinoxalinones **11**. Herein, we have reported 21 compounds with various diversities and scope of these compounds can be further extended. Present multicomponent reactions have shown high atom economy with good functional group tolerance and their studies are in progress to explore potential biological properties.

EXPERIMENTAL PROCEDURES

General Synthetic Procedure for the of Dihydroquinoxaline-2-one 11 on PEG Support. A PEG-bound 4-fluoro-3-aminobenzene carboxylate **1** (500 mg, 1 equiv) and

DOI: 10.1021/acscombsci.5b00053
ACS Comb. Sci. 2015, 17, 421−425

Table 2. Reaction Substrate Scope for Synthesis of Dihydroquinoxalin-2-one Molecular Library[a]



entry	product **11**	yield[b] (%)	entry	product **11**	yield[b] (%)	entry	product **11**	yield[b] (%)
1	**11**{*1,1,1*}	60	9	**11**{*3,3,1*}	73	17	**11**{*7,2,3*}	75
2	**11**{*1,2,2*}	75	10	**11**{*4,3,1*}	77	18	**11**{*4,1,1*}	69
3	**11**{*1,3,1*}	65	11	**11**{*5,1,1*}	65	19	**11**{*8,1,3*}	82
							10{*8,1,3*}	86[c]
4	**11**{*2,1,2*}	61	12	**11**{*5,4,3*}	75	20	**11**{*9,1,3*}	63
	10{*2,1,2*}	71[c]						
5	**11**{*2,1,3*}	63	13	**11**{*5,5,3*}	80	21	**11**{*10,1,3*}	79
6	**11**{*2,2,4*}	73	14	**11**{*6,1,4*}	62			
7	**11**{*2,4,1*}	71	15	**11**{*6,4,2*}	71			
8	**11**{*3,2,4*}	70	16	**11**{*7,1,4*}	72			

[a]Ugi MCRs were performed under MW irradiation (110 °C, 30 min). [b]Isolated yield after column purification. [c]Crude yield of product **10**{*2,1,2*} and **10**{*8,1,3*}.

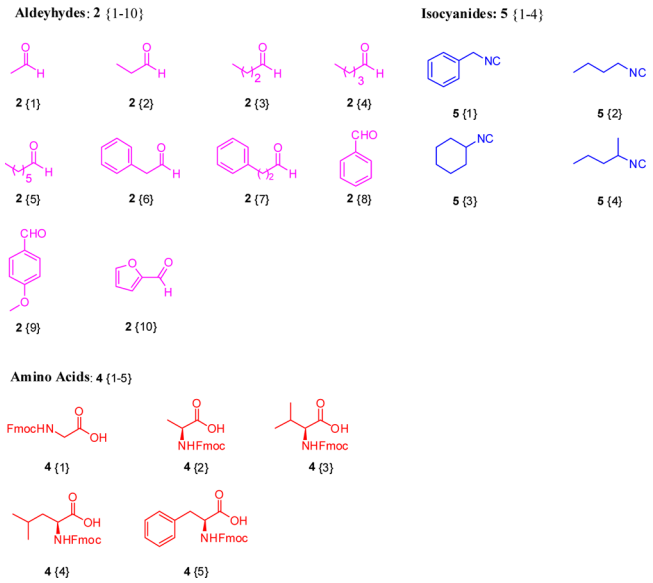


Figure 2. Library building blocks.

aldehyde **2** (1.2 equiv) were dissolved in methanol (4 mL) at ambient temperature. The reaction mixture was irradiated by microwave at 110 °C (150 W, 7 bar) for 10 min. After complete consumption of amine and aldehyde, reaction mixture was cooled to room temperature. Fmoc protected amino acid **4** (1.5 equiv) and isocyanides **5** (3.0 equiv) were added to the same reaction mixture. The resulted reaction mixture was irradiated at 110 °C with microwave (150 W, 7 bar) for 20 min. The organic solvent was removed under reduced pressure and residue was precipitated, as well as washed with cold ether (40 mL × 3), to give PEG-bound intermediate diamide **7.** Reaction progress on the support was monitored directly by proton NMR. To a solution of PEG-attached intermediate diamide **7** (500 mg, 1 equiv.) in dichloromethane (15 mL), piperidine (0.1 equiv) was added. The reaction mixture was stirred at room temperature for 1 h. The deprotection was also monitored by proton NMR analysis of crude sample directly. The crude product was purified by precipitation with cold ether followed by filtration. The solid obtained after filtration was dried under vacuum to give PEG-bound amine **8.** This PEG bound amine **8** (300 mg, 1 equiv) was dissolved in DMF (7 mL), K_2CO_3 (10 equiv) was added and resultant reaction mixture was allowed to stir at ambient temperature for 15 h. After completion of reaction, cold ether was added to precipitate out PEG-bound tetrahydroquinoxalin-2-ones **9.** In order to remove polymer support, PEG attached tetrahydroquinoxalin-2-ones **9** was further reacted with NaOMe (3 equiv) in MeOH (10 mL). The reaction mixture was stirred at room temperature until complete release of polymer support from PEG bound tetrahydroquinoxalin-2-ones **9** to support-free compound **10**. After completion of reaction, the mixture was filtered to remove polymer support and washed with cold ether (50 mL) and resulting crude residue dried over $MgSO_4$ to give crude support-free tetrahydroquinoxaline-2-one **10**. This crude product was readily converted to dihydroquinoxaline-2-one **11** as a final product through air oxidation. The crude residue was purified by silica column chromatography (eluent = 40% EA in hexane) to afford the corresponding dihydroquinoxaline-2-one **11** (60−80%).

Methyl 4-(1-(Benzylamino)-1-oxopropan-2-yl)-3-oxo-3,4-dihydroquinoxaline-6-carboxylate ***11****{1,1,1}:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.11 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 8.3, 1.5 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.25 (m, 3H), 7.13 (m, 2H), 6.35 (dd, J = 5.5, 6.0 Hz), 5.92 (q, J = 7.2 Hz, 1H), 4.50 (dd, J = 14.7, 6.0 Hz, 1H), 4.38 (dd, J = 14.7, 5.5 Hz, 1H), 3.98 (s, 3H), 1.96 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.1, 155.1, 152.2, 137.9, 136.9, 132.3, 131.5, 131.4, 129.0, 128.2, 128.0, 125.3, 117.1, 53.3, 52.3, 44.4, 14.4; IR (cm^{-1}, neat) 3317, 2951, 1726, 1670; LRMS (ESI^+):m/z 388 $(M + Na)^+$; HRMS (ESI^+) calcd for $C_{20}H_{19}N_3O_4Na$ m/z 388.1123; Found 388.1122.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data (^{1}H and ^{13}C NMR, LRMS, HRMS, FT-IR) of compound **10**{*2,1,2*}, **10**{*8,1,3*}, and **11**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00053.

DOI: 10.1021/acscombsci.5b00053
ACS Comb. Sci. 2015, 17, 421−425

AUTHOR INFORMATION

Corresponding Author

*E-mail: cmsun@mail.nctu.edu.tw.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors wish to thank the National Science Council of Taiwan for financial support and the authorities of the National Chiao Tung University to provide the laboratory facilities. This study was particularly supported by the "Centre for Bioinformatics Research of Aiming for the Top University Plan" of the National Chiao Tung University and Ministry of Education, Taiwan.

REFERENCES

(1) El Ashry, S. H.; El Nemr, A. *Synthesis of Naturally Occurring Nitrogen Heterocycles from Carbohydrates*; Wiley-Blackwell: Oxford, U.K., 2005.

(2) Smil, D. V.; Manku, S.; Chantigny, Y. A.; Leit, S.; Wahhab, A.; Yan, T. P.; Fournel, M.; Maroun, C.; Li, Z.; Lemieux, A. M.; Nicolescu, A.; Rahil, J.; Lefebvre, S.; Panetta, A.; Besterman, J. M.; Daziel, R. Novel HDAC6 isoform selective chiral small molecule histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 688−692.

(3) Mori, Y.; Hirokawa, T.; Aoki, K.; Satomi, H.; Takeda, S.; Aburada, M.; Miyamoto, K. Structure activity relationships of quinoxalin-2-one derivatives as platelet-derived growth factor-β receptor (PDGFb R) inhibitors, derived from molecular modeling. *Chem. Pharm. Bull.* **2008**, *56*, 682−687.

(4) Carta, A.; Sanna, P.; Gherandini, L.; Usai, D.; Zanetti, S. Novel functionalized pyrido[2,3-*g*]quinoxalinones as antibacterial, antifungal, and anticancer agents. *IL Farmaco* **2001**, *56*, 933−938.

(5) Ajani, O. O.; Obafemi, C. A.; Nwinyi, O. C.; Akinpelu, D. A. Microwave assisted synthesis and antimicrobial activity of 2-quinoxalinone-3-hydrazone derivatives. *Bioorg. Med. Chem.* **2010**, *18*, 214−221.

(6) Bailing, X. B.; Xu, Y.; Sun, Y.; Guo, Y.; Cao, T. Y. Synthesis and biological evaluation of N4-(hetero)arylsulfonylquinoxalinones as HIV-1 reverse transcriptase inhibitors. *Bioorg. Med. Chem.* **2009**, *17*, 2767−2774.

(7) Ries, U. J.; Priepke, H. W. M.; Hauel, N. H.; Handschuh, S.; Mihm, G.; Stassen, J. M.; Wienen, W.; Nar, H. Heterocyclic thrombin inhibitors. Part 2: Quinoxalinone derivatives as novel, potent antithrombotic agents. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2297−2302.

(8) Dömling, A. Recent developments in isocyanide based multi-component reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17−89.

(9) Kalinski, C.; Umkehrer, M.; Weber, L.; Kolb, J.; Burdack, C.; Ross, G. On the industrial applications of MCRs: Molecular diversity in drug discovery and generic drug synthesis. *Mol. Diversity* **2010**, *14*, 513−522.

(10) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing synthetic efficiency: Multi-component trasformations lead the way. *Chem.—Eur. J.* **2000**, *6*, 3321−3329.

(11) Ugi, I. The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions. *Angew. Chem., Int. Ed.* **1962**, *1*, 8−21.

(12) Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(13) Wang, W.; Dömling, A. Efficient synthesis of arrays of amino acid derived Ugi products with subsequent amidation. *J. Comb. Chem.* **2009**, *11*, 403−409.

(14) Musonda, C. C.; Taylor, D.; Lehman, J.; Gut, J.; Rosenthal, P. J.; Chibale, K. Application of multi-component reactions to antimalarial drug discovery. Part 1: Parallel synthesis and antiplasmodial activity of new 4-aminoquinoline Ugi adducts. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3901−3905.

(15) Stadler, A.; Kappe, C. O. Automated library generation using sequential microwave-assisted chemistry. *J. Comb. Chem.* **2001**, *3*, 624−630.

(16) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. J. Increasing rates of reaction: Microwave-assisted organic synthesis for combinatorial chemistry. *J. Comb. Chem.* **2002**, *4*, 95−105.

(17) Swamy, K. M. K.; Lin, M. J.; Yeh, W. B.; Sun, C. M. Microwave-assisted polymer-supported combinatorial synthesis. *Curr. Med. Chem.* **2003**, *10*, 2403−2424.

(18) Dickerson, T. J.; Reed, N. N.; Janda, K. D. Soluble polymers as scaffolds for recoverable catalysts and reagents. *Chem. Rev.* **2002**, *102*, 3325−3344.

(19) Lu, J.; Toy, P. H. Organic polymer supports for synthesis and for reagent and catalyst immobilization. *Chem. Rev.* **2009**, *109*, 815−838.

(20) Lee, J.; Murray, W. V.; Rivero, R. A. Solid phase synthesis of 3,4-disubstituted-7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones. *J. Org. Chem.* **1997**, *62*, 3874−3879.

(21) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. Solid-phase synthesis of benzopiperazinones. *J. Org. Chem.* **1998**, *63*, 1172−1177.

(22) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Solid phase parallel synthesis of trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones. *Tetrahedron* **2002**, *58*, 221−225.

(23) Purandare, A. V.; Gao, A.; Poss, M. A. Solid-phase synthesis of "diverse" heterocycles. *Tetrahedron Lett.* **2002**, *43*, 3903−3906.

(24) Laborde, E.; Peterson, B. T.; Robinson, L. Traceless, self-cleaving solid- and solution-phase parallel synthesis of 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones. *J. Comb. Chem.* **2001**, *3*, 572−577.

(25) Tanimori, S.; Kashiwagi, H.; Nishimura, T.; Kirihata, M. A General and practical access to chiral quinoxalinones with low copper-catalyst loading. *Adv. Synth. Catal.* **2010**, *352*, 2531−2537.

(26) Neagoie, C.; Krchňák, V. Piperazine amide linker for cyclative cleavage from solid support: Traceless synthesis of dihydroquinoxalin-2-ones. *ACS Comb. Sci.* **2012**, *14*, 399−402.

(27) Chen, L. H.; Chang, C. M.; Salunke, D. B.; Sun, C. M. Divergent synthesis of unsymmetrical annulated biheterocyclic compound libraries: Benzimidazole linked indolo-benzodiazepines/quinoxaline. *ACS Comb. Sci.* **2011**, *13*, 391−398.

(28) Fleurat-Lessard, P.; Grimaud, L.; El Kaim, L.; Ramozzi, R.; Cheron, N. Challenging 50 years of established views on Ugi reaction: A theoretical approach. *J. Org. Chem.* **2012**, *77*, 1361−1366.

DOI: 10.1021/acscombsci.5b00053
ACS Comb. Sci. 2015, 17, 421−425