ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

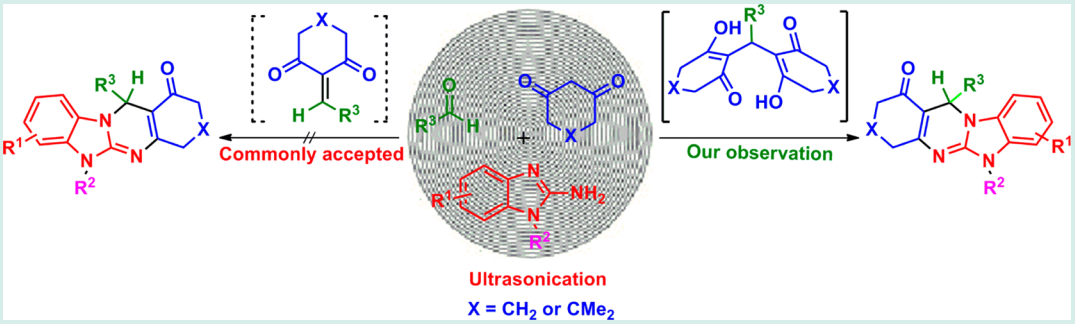
A Novel Mechanistic Study on Ultrasound-Assisted, One-Pot Synthesis of Functionalized Benzimidazo[2,1-*b*]quinazolin-1(1*H*)-ones

Li-Hsun Chen,[†] Tsai-Wen Chung,[†] Bharat D. Narhe,[†] 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: Ultrasound-assisted synthesis of benzimidazo[2,1-*b*]quinazolin-1(1*H*)-ones was achieved via piperidine-catalyzed three-component reaction of 2-aminobenzimidazoles, an aromatic aldehyde, and 1,3-dione in aqueous isopropanol. This mechanism was first suspected following our identification of unusual reaction intermediates in a one-pot reaction. An unprecedented coupling reaction, it involved a nucleophilic attack by 2-aminobenzimidazole on in situ generated Michael adduct, followed by electrocyclic ring formation reaction. In contrast to the commonly accepted mechanism, that the direct reaction of 2-amino benzimidazole with a Knoevenagel adduct cannot deliver target compounds.

KEYWORDS: *ultrasonication, multicomponent reaction, benzimidazo[2,1-b]quinazolin-1(1H)-ones*

INTRODUCTION

Multicomponent reactions (MCRs) greatly accelerate chemical synthesis, converting three or more components into complex molecules via simple one-pot routes.[1] MCRs are frequently associated with high atom economy since all the reactants are incorporated in the final products. This effectively contributes to make MCRs cost-effective, time-efficient, and eco-friendly as compared to conventional multistep synthesis.

Fused-ring heterocyclic compounds containing nitrogen are frequently studied owing to their diverse biological properties.[2] MCRs utilizing functionalized imidazoles[3] and benzimidazole[4] are often employed for the synthesis of polyazaheterocycles. Pyramido-benzimidazoles as a class of azaheterocycles are widely investigated for their assorted biological properties, such as antihypertensive,[5] anti-inflammatory,[6] antioxidant,[7] and immunosuppressive[8] activity and DNA gyrase inhibitor.[9] For example, bicyclic pyrimidinone **I** is a potent HIV integrase inhibitor;[11] compound **II** acts as an HIF prolyl hydroxylase inhibitor;[12,13] benzimidazoquinazolinone **III** is an immune-suppressive agent;[8] and quinazolinone **IV** shows antiproliferative activity[10] (Figure 1).

A three-component MCR involving 3-aminotriazole, an aldehyde and 1,3-dicarbonyl compounds was first reported by Kappe et al. for microwave assisted synthesis of triazole fused pyrimidine-6-carboxamides.[14] Similar multicomponent reactions using benzimidazole was adapted for the synthesis of pyrimido-benzimidazoles and benzimidazo-quinazoline derivatives.[14] Earlier we reported a rapid reaction of polymer-bound *N*-alkylated 2-amino benzimidazoles, aldehydes, and 1,3-diones under microwave irradiation generated triazafluor-enes.[16] This transformation still remains an attraction in synthesis and in medicinal chemistry as it produces biologically interesting benzimidazo-dihydropyrimidine skeleton. Our search for directed green synthesis of diverse drug-like azaheterocycles prompted us to apply ultrasound irradiation for current three-component coupling reaction. The results of our study reveal new insights into the reaction mechanism. Ultrasound wave causes "acoustic cavitations" to trounce molecular attractive forces and to promote molecular mixing which increases intimate contact between different molecules to form highly reactive species. These activation results in acceleration of reaction and improved product yields.[16,17]

In continuation of our research on the use of benzimidazole skeletons to synthesize drug-like compounds, we studied a mild reaction condition to provide a simple access toward

Received: December 13, 2015
Revised: January 29, 2016

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

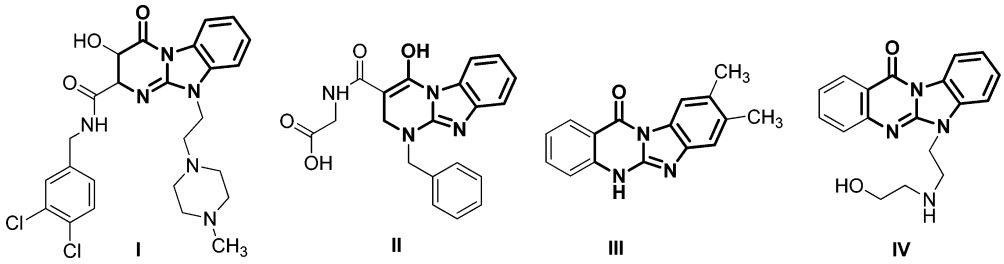
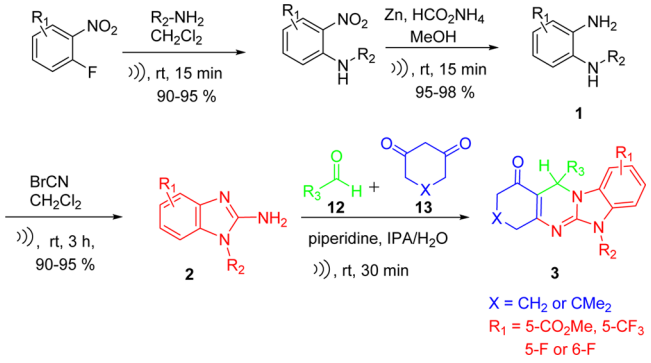


Figure 1. Biologically active pyrimido-benzimidazoles and benzimidazo-quinazolines.

functionalized benzimidazo-quinazolinones by one pot multi-component reaction. The substrates, substituted 2-amino-benzimidazoles were synthesized via aromatic nucleophilic substitution of *o*-nitrofluoroarenes with various amines, followed by nitro reduction to furnish diamines **1**. The diamines **1** on cyclization with cyanogen bromide gave 2-aminobenzimidazoles **2**. All these transformations were performed under ultra-sonication to give better yields in shorter reaction time compared to those under conventional heating conditions (Scheme 1).[18a]

Scheme 1. Ultrasonic Synthesis of Benzimidazo[2,1-*b*]-quinazolin-1(*1H*)-ones

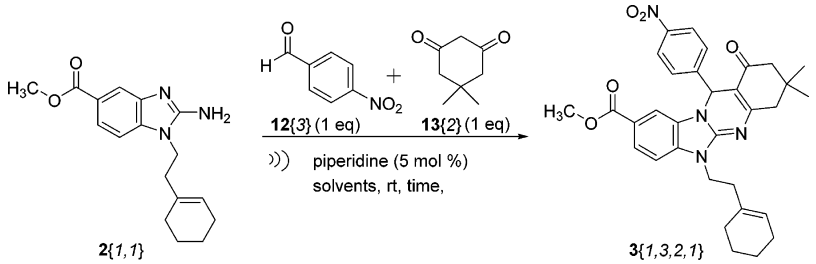


We initiated a MCR study by treatment of 2-aminobenzimdazole **2**{*1,1*} (R_1 = 5-CO_2Me, R_2 = 2-(1-cyclohexenyl)ethyl)) with equimolar quantities of 4-nitrobenzaldehyde **12**{*3*}, 5,5-dimethyl-1,3-hexadione **13**{*2*}, and a catalytic amount of piperidine (5 mol %). When the reaction was first tested under ultrasound in dichloromethane for 2 h, it gave only a trace amount of the desired product benzimidazo[2,1-*b*]quinazoli-none **3**{1,3,2,1} (Table 1, entry 1). We quickly screened solvents for this trans-formation and found that the best conversion (92% yield) was achieved in isopropanol. When aqueous isopropanol (IPA/H_2O = 9:1) was used, this resulted in precipitation of the coupling product upon its formation within 30 min (90%, entry 12).

The product was then obtained in pure form simply by washing the crude reaction mixture with cold ether. For the same reaction stoichiometry using aqueous isopropanol, the coupling reaction took 17 h to go to completion. However, at room temperature the reaction never went to completion, even after 72 h, to obtain the coupling product and only imine inter-mediate was detected.

With the optimized conditions in hand, the scope of the three-component reaction was studied with a number of 2-aminobenzimidazoles, substituted benzaldehydes and 1,3-diketones (Figure 2). An electron withdrawing substituent on benzaldehyde dramatically enhances the yields of benzimidazoquinazolinones (e.g., **3**{*1,1,1,1*} vs **3**{*1,3,2,1*} in Table 2). However, an electron

Table 1. Reaction Optimization Studies of Three-Component Reaction[a]



entry	solvent	time	yield of **3**{*1,3,2,1*} (%)
1	CH_2Cl_2	2 h	<5
2	CH_2Cl_2	12 h	46
3	MeOH	2 h	82
4	THF	2 h	<10
5	toluene	2 h	20
6	CH_3CN	2 h	13
7	DMF	2 h	<10
8	IPA	2 h	92
9	H_2O	30 min	trace
10	MeOH	30 min	78
11	IPA	30 min	90
12	IPA/H_2O	30 min	90

[a]All reactions were performed on 1.0 mmol scale with equimolar quantities of benzimidazole, diketone, and benzaldehyde.

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

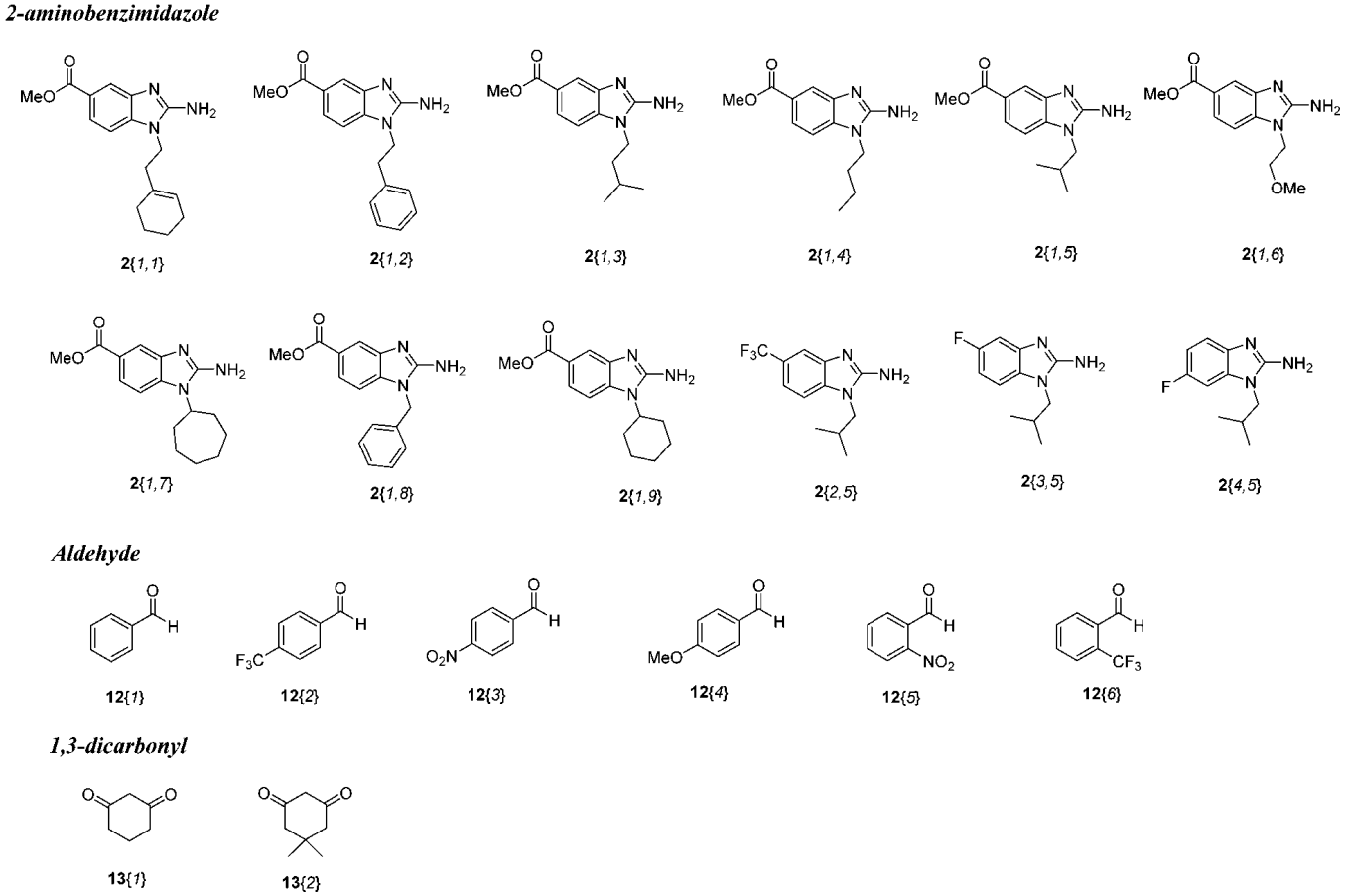


Figure 2. Diversity elements employed for library synthesis. 2-aminobenzimidazole **2**{*1,1*}−**2**{*1,9*}, **2**{*2,5*}, **2**{*3,5*}, **2**{*4,5*}, aldehyde **12**{*1*−*6*}, and 1,3-dicarbonyl **13**{*1*−*2*}.

donating substituent on benzaldehyde has an adverse effect and causes a very slow reaction to give desired product in low yields (**3**{*1,4,1,8*} and **3**{*1,4,2,9*}). The low yields with electron donating aldehyde is a result of a competing Cannizzaro reaction which produces 4-methoxybenzyl alcohol and 4-methoxybenzoic acid as side products. In view of fluorinated molecules playing an important role in development of biologically more active and selective agents,[19] we used 5-fluoro, 5-trifluoromethyl and 6-fluoro substituted benzimidazoles to obtain fluorine containing benzimidazo[2,1-*b*]quinazolin-6-ones (**3**{*2,3,2,5*}−**3**{*4,3,2,5*}) in good isolated yields. The tetracyclic triaza guanidine skeleton of the product was confirmed unambiguously by X-ray single crystal structure analysis (Figure 3).[20]

A widely accepted mechanism for such MCRs involves formation of 3-benzylidene-2,4-pentanedione **4** via Knoevenagel condensation of an aldehyde with 1,3-dicarbonyl compound.[15] Piperidine promotes the first transformation by forming iminium hydroxide intermediate with the aldehyde.[18] In the next step, nucleophlic attack of benzimidazole sp^2 nitrogen on β-carbon of enone **4** yields adduct **5** that subsequently undergoes cyclization to generate intermediate 6 which after dehydration yields observed product **3** (Scheme 2).

To be able to confirm this plausible mechanism, we planned to study a stepwise reaction between Knoevenagel adduct, 3-benzylidene-2,4-pentanedione (**4**) with 2-aminobenzimidazole (**2**). However, treatment of benzaldehyde (1 equiv) with 5,5-dimethylcyclohexane-1,3-dione (1 equiv) for 10 min in isopropanol under ultrasonication gave only Michael adduct **7** rather than Knoevenagel adduct **4** as suggested by a broad singlet at δ 11.80 (−O<u>H</u>) and other singlet at δ 5.50 (Ph−C<u>H</u>) in proton NMR. Our observation was supported by Kaupp's work on Knoevenagel condensation.[21] The structure of Michael adduct **7** was further confirmed by single crystal X-ray analysis (Figure 4).[20] The "Y" shape of the three-dimensional structure of **7** is characterized by strong intramolecular hydrogen bonding between the hydroxyl group of enol and the carbonyl function on the neighboring ring. Thus, the benzylidene enone **4** is too short-lived under current reaction conditions and undergoes 1,4 conjugate addition with enolizable ketone, that is, 1,3-dione instantly. Further addition of dimidone (1 equiv) resulted in complete consumption of benzaldehyde to yield **7** exclusively.

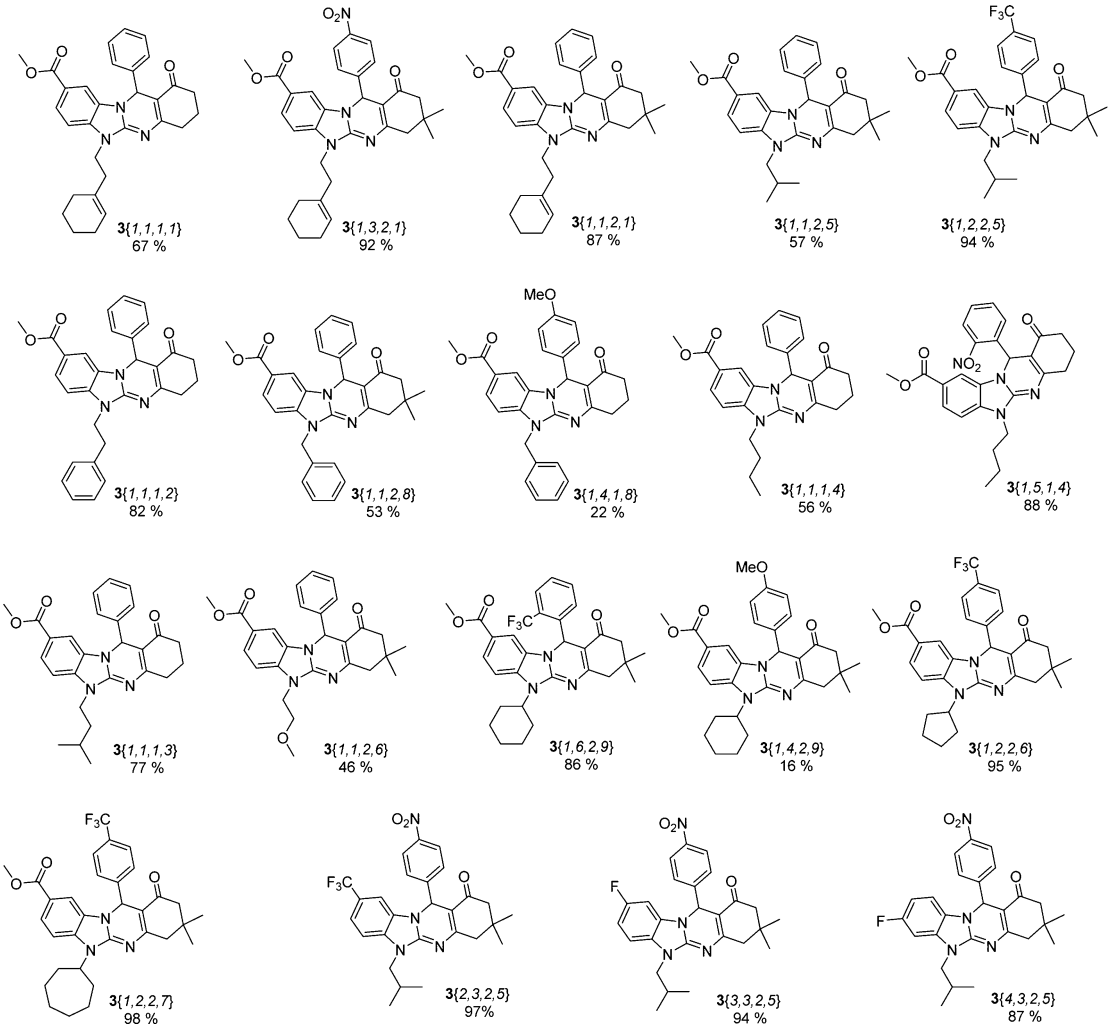
Silica gel column purification gave Michael adduct **7** as a major product in 90% yield along with small quantity of 1,8-dioxooctahydroxanthenes **8** (∼5%) as a result of cyclization **7** with elimination of a water molecule[22] (Scheme 5). The structure of 1,8-dioxooctahydroxanthenes **8** was also confirmed by single crystal X-ray analysis (Figure 5).[20]

Our attempts to synthesize Knoevenagel adduct using earlier reports also resulted into the formation of corresponding Michael adduct only. Since Knoevenagel adduct is highly reactive, it continues to proceed by 1,4-conjugated addition preferentially with 1,3-dicarbonyl compounds.[22−24]

We next attempted to synthesize the Knoevenagel adduct 3-benzylidene-2,4-pentanedione **4** by slow addition of 5,5-dimethylcyclohexane-1,3-dione **13**{*2*} (1 equiv) into an ethanolic solution of 4-methoxy benzaldehyde **12**{*4*} (1.2 equiv) with piperidine under ultrasonic activation for 1 h (Scheme 3). Once a Knoevenagel adduct is isolated and purified (SI: P. 48−51),

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

Table 2. Combinatorial Library of Benzimidazo[2,1-*b*]quinazolin-1(*1H*)-ones[a]



[a]All reactions were perfomed on 1.0 mmol scale with equimolar quanities of three reactants for 30 min under sonication in the presence of piperidine catalyst. Isolated yields after precipitation in ether.

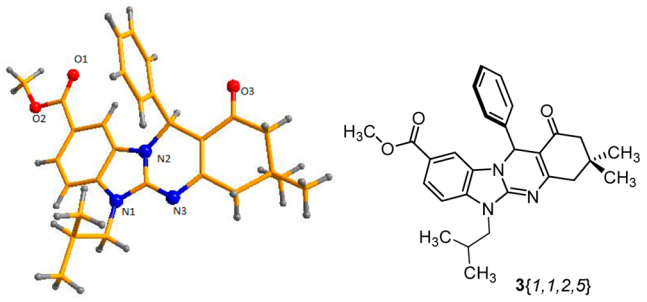


Figure 3. X-ray crystal structure of 3{*1,1,2,5*}.

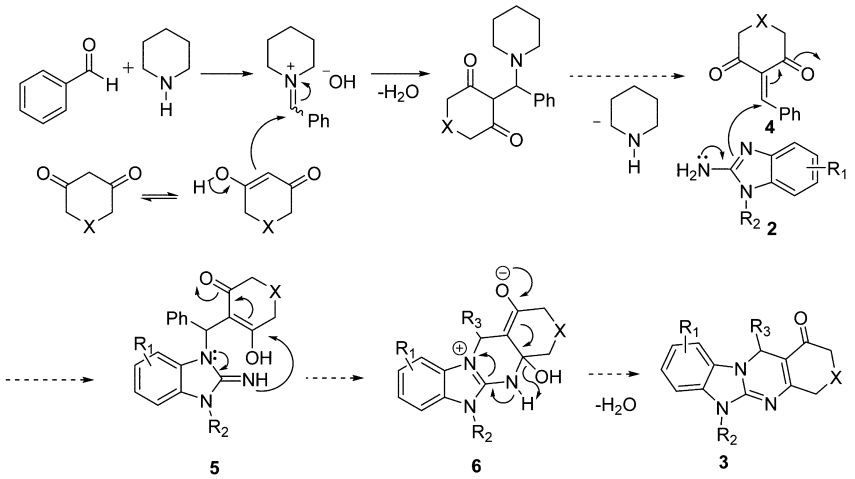
we treated it immediately with various 2-aminobenzimidazoles by the same reaction conditions. But to our surprise, none of reactions yielded MCR product. The results clearly show no nucleophilic addition of the 2-benzimidazole on Knoevenagel adduct and finally it was decomposed to aldehydes as well as dimidone in all cases (Scheme 4).

This encouraged us to treat Michael adduct **7** with 2-aminobenzimidazole **2**{*1,1*} under the same reaction conditions. Smooth reaction progress was observed to deliver the expected benzimidazoquinolinone 3{*1,1,2,1*} in 87% isolated yield within 30 min. A similar reaction of **2**{*1,1*} with 9-phenyl-1,8-dioxooctahydroxanthene **8** was unrewarding since no conversion was detected either under sonication or reflux conditions (Scheme 5). Tolerance of **8** to nucleophilic addition of 2-aminobenzimidazole is attributed to its higher stability under current reaction conditions. These observations confirmed that the true intermediate in this MCR is Michael adduct **7** instead of the claimed Knoevenagel adduct **4**. Michael adduct **7** cannot convert to Knoevenagel product **4** in ultrasonic condition.

The mechanism for the formation of tetracyclic triazafluorene by the reaction between 2-aminobenzimidazole and Michael adduct could be proposed as follows. Initial nucleophilic attack of primary sp^3 nitrogen of 2-aminobenzimidazole on enol of Michael adduct **7** yields the intermediate **9** that after dehydration gives enaminone **10a**. The intramolecular hydrogen bonding of Michael adduct **7** activates the enone toward nuleophilic attack of 2-amino-benzimidazole. Iminoenol **10b** undergoes retro Michael type reaction via keto tautomer **10c** to produce diazatriene **11** and 1,3-diketone. The diazatriene **11** then undergoes six electrons thermal electocyclic ring closure to produce observed product **3**. The sp^3 nitrogen of benzimidazole ring provides a driving force for electrocyclization (Scheme 6).[25]

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

Scheme 2. Commonly Proposed Mechanism of MCR



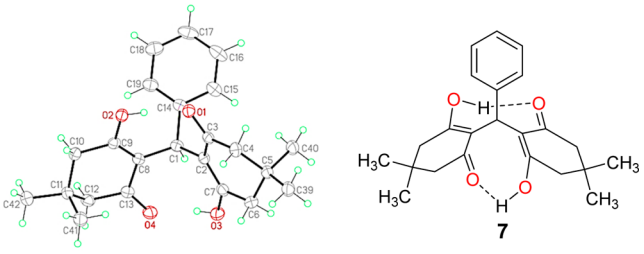


Figure 4. X-ray crystal structure of **7** with intramolecular hydrogen bonding.

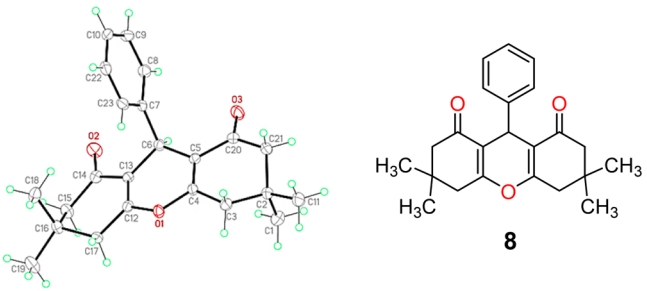
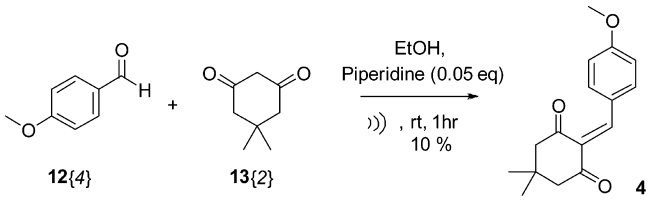


Figure 5. X-ray crystal structure of 1,8-dioxooctahydroxanthene **8**.

Scheme 3. Preparation of Knoevenagel Adduct 4



A regioisomeric product **3′** which could result from nucleophlic attack of sp^2 ring nitrogen of benzimidazole on Michael adduct **7** is not observed. The regioselective formation of **3** over **3′** is attributed to minimum steric crowding during the nucleophlic attack of primary amine as compared to that of secondary sp^2 ring nitrogen of 2-aminobenzimidazole.

Finally, we have successfully synthesized possible intermediates **9**{*1,1*}, **9**{*2,2*}, and **9**{*2,3*} by trapping reaction of Michael adduct **7** with various 2-aminobenzimidazoles (Supporting Information, pp 52−54) (Scheme 7)

CONCLUSIONS

We disclose here a novel three-component coupling reaction mechanism of substituted 2-aminobenzimidazoles, aromatic aldehydes and 1,3-cyclohexadiones under ultrasonic acceleration to synthesize benzimidazoquinazolinones. The detailed mechanistic investigation of the MCR allowed us to isolate and identify the true reaction intermediates Michael adducts **7** for the first time in the literature. It is contrary to common belief that the key step of the reaction is regioselective nucleophilic attack of primary amino group of 2-aminobenzimidazole on Michael adduct instead of nucleophilic attack of sp^2 nitrogen of 2-aminobezimidazole ring on Knoevenagel adduct **4**. Our observation is expected to broaden the mechanistic understanding of MCRs that proposed to involve highly reactive Knoevenagel adducts, eventually leading to development of better synthetic strategies for other biologically interesting compounds.

EXPERIMENTAL SECTION

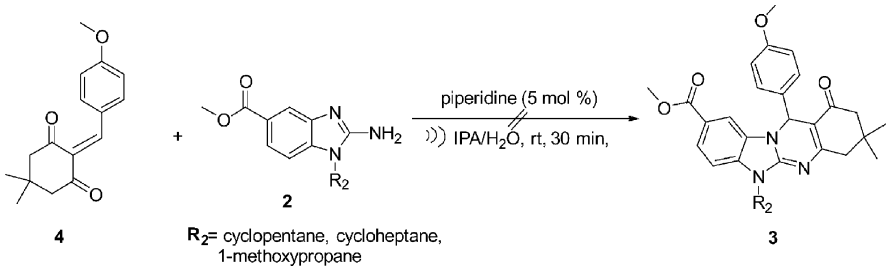
General Procedure for the Synthesis of MCR Products (3{*2,3,2,5*}) under Ultrasonic Irradiation. A 50 mL round-bottom flask was charged with 1-isobutyl-5-(trifluoromethyl)-1*H*-benzo[*d*]-imidazol-2-amine **2**{*2,5*} (200 mg, 1.0 equiv) in the isopropanol/water solvent mixture (9:1, 10 mL) and 4-nitrobenzaldehyde **12**{*3*} (117 mg, 1.0 equiv), 5,5-dimethylcyclohexane-1,3-dione **13**{*2*} (109 mg, 1.0 equiv), and piperidine (5 μL, 0.05 mmol) was added to the reaction mass. The mixture was subjected to ultrasound irradiation for 30 min. The progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled in ice cold water and filtered under vacuum. The residue was washed by cold diethyl ether (3 × 10 mL). The isolated product 6-isobutyl-3,3-dimethyl-12-(4-nitrophenyl)-9-(trifluoromethyl)-3,4,6,12-tetrahydro-benzo[4,5]imidazo[2,1-*b*]quinazolin-1(2*H*)-one (**3**{*2,3,2,5*}) was obtained 386 mg in 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.14 (s, 1H), 6.59 (s, 1H), 4.11−3.80 (m, 2H), 2.56 (d, J = 18.2 Hz, 1H), 2.47 (d, J = 18.2 Hz, 1H), 2.42−2.27 (m, 1H), 2.20 (d, J = 16.4 Hz, 2H), 2.16 (d, J = 16.4 Hz, 2H), 1.05 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7, 163.8, 151.1, 148.1, 147.8, 134.0, 129.1, 128.2, 125.3, 124.4, 121.1, 109.6, 107.7, 106.9, 55.4, 50.5, 46.7, 45.0, 32.9, 29.6, 28.3, 27.7, 22.7, 20.4, 20.4. HRMS (ESI) Calcd m/z for $C_{27}H_{28}F_3N_4O_3$ $[M + H]^+$: 513.2113. Found: 513.2114

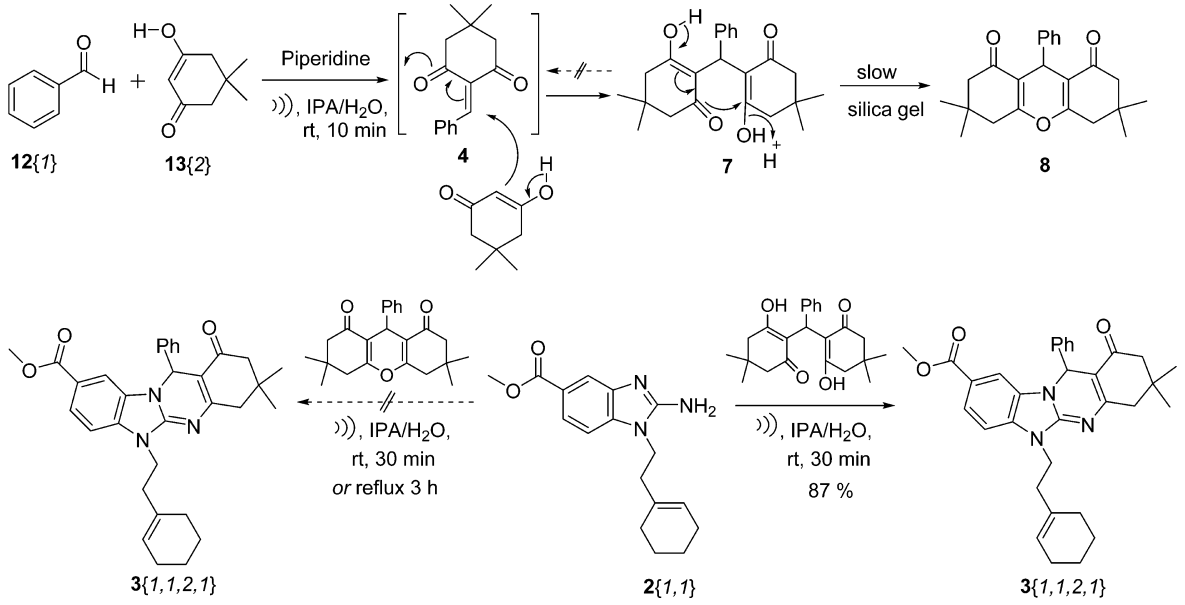
General Procedure for the Synthesis of Michael Adduct: 2,2′-(Phenylmethylene) Bis(3-Hydroxy-5,5-dimethylcyclohex-2-enone) (7). A 50 mL round-bottom flask was charged with benzaldehyde **12**{*1*} (1.0 g, 1 equiv), 5,5-dimethylcyclohexane-1,3-dione **13**{*2*} (1.32 g, 1.0 equiv), and piperidine (0.04 g, 0.05 equiv) in

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

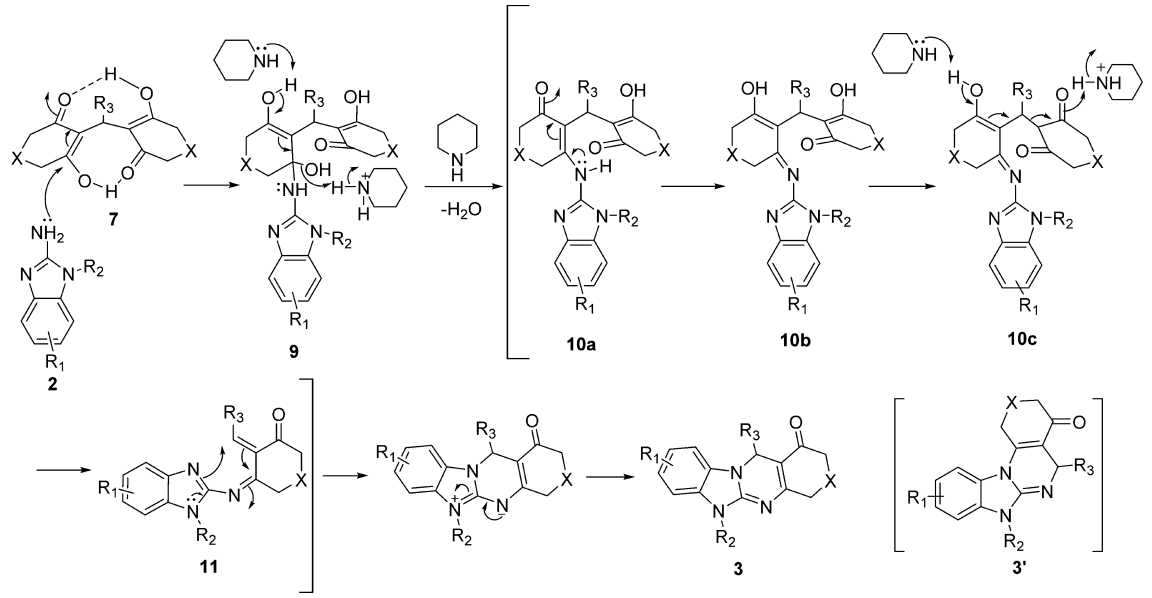
Scheme 4. Reaction of Knoevenagel Adduct and 2-Aminobenzimidazoles



Scheme 5. Verification of Mechanistic Course of MCR



Scheme 6. Probable Mechanism of Three-Component Reaction through Michael Adduct

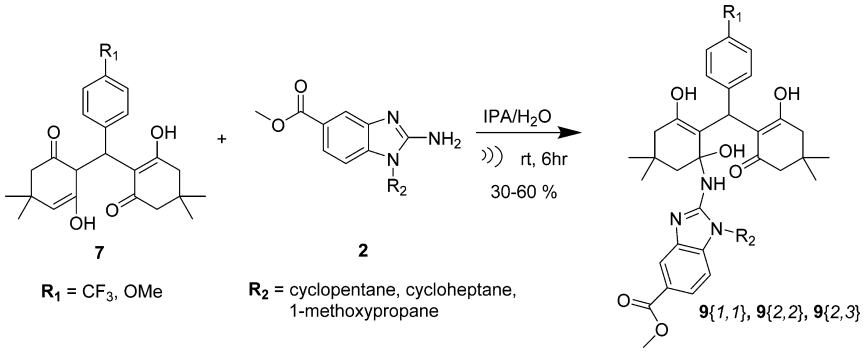


the isopropanol/water solvent mixture (9:1, 10 mL). The reaction mass was subjected to ultrasound irradiation for 10 min. The progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled in ice cold water and filtered under vacuum. The residue was washed by cold hexane (3 × 10 mL). The obtained product was dried under vacuum to give 2,2′-(phenylmethylene) bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**7**) 3.12 g in 90% yield. The residual filtrate was purified via column purification to give 1,8-dioxooctahydroxanthenes (**8**) (~5% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.97 (s, 1H), 10.30 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 5.57 (s, 1H), 2.55−2.25 (m, 8H), 1.24 (s, 6H), 1.10 (s, 6H). ^{13}C NMR

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

Scheme 7. Isolation of Intermediates 9{*1,1*}, 9{*2,2*}, and 9{*2,3*}



(101 MHz, $CDCl_3$): δ 190.4, 189.4, 138.1, 128.2, 126.8, 125.8, 115.6, 47.1, 46.4, 32.8, 31.4, 29.6, 27.4. MS (ESI): m/z 369 $[M + H]^+$; HRMS (ESI): calcd for $C_{23}H_{28}O_4$, 369.2060, found 369.2065 $[M + H]^+$.

General Procedure for the Synthesis of Knoevenagel Adduct: 2-(4-Methoxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (4). A 50 mL round-bottom flask was charged with 4-methoxybenzaldehyde **12**{*4*} (0.9 g, 1.2 equiv), ethanol (9 mL), and piperidine (0.03 g, 0.05 equiv). The reaction mixture was added 5,5-dimethylcyclohexane-1,3-dione **13**{*2*} (1.0 g, 1.0 equiv) slowly portion by portion over 5−10 min and the mixture was subjected to ultrasound irradiation for 1 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold water and filtered under vacuum. The residue was purified via flash chromarograohy (gradient elution 10:1 to 6:1 in Hex/EtOAc). The product was obtained and dried under vacuum to give 2-(4-methoxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (**4**) was obtained 0.17 g in 10% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40−7.23 (m, 2H), 6.99−6.80 (m, 2H), 5.40 (s, 1H), 3.73 (s, 3H), 3.53−3.39 (m, 4H), 1.11 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 191.7, 159.5, 131.8, 128.1, 113.8, 101.2, 60.9, 55.5, 15.6. MS (ESI): m/z 259 $[M + H]^+$ for $C_{16}H_{18}O_3$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00186.

General experimental methods, ^{1}H and ^{13}C NMR spectra of the desired products, and X-ray characterizations (PDF)

X-ray data for 3{*1,1,2,5*} (CIF)

X-ray data for **7** (CIF)

X-ray data for **8** (CIF)

■ 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 Ministry of Science and Technology of Taiwan for financial support and the authorities of the National Chiao Tung University for providing 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) (a) Ruijter, E.; Orru, R. V. A. Multicomponent reactions - opportunities for the pharmaceutical industry. *Drug Discovery Today: Technol.* **2013**, *10*, e15−e20. (b) Dömling, A.; Wang, W.; Wang, K. Chemistry and Biology Of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083−3135. (c) Vaxelaire, C.; Winter, P.; Christmann, M. One- pot reactions accelerate the synthesis of active pharmaceutical ingredients. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607. (d) Touré, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.* **2009**, *109*, 4439−4486.

(2) (a) Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. Ultrasonic-Promoted Three- Component Synthesis of Some Biologically Active 1, 2, 5, 6- Tetrahydropyrimidines. *J. Comb. Chem.* **2007**, *9*, 797−803. (b) Bravo, J. L.; Lopez, I.; Cintas, P.; Silvero, G.; Arevalo, M. J. Sonochemical cycloadditions in ionic liquids. Lessons from model cases involving common dienes and carbonyl dienophiles. *Ultrason. Sonochem.* **2006**, *13*, 408−414. (c) Cravotto, G.; Cintas, P. Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large- scale applications. *Chem. Soc. Rev.* **2006**, *35*, 180−196. (d) Cella, R.; Stefani, H. A. *Ultrasonic Reactions in Green Techniques for Organic Synthesis and Medicinal Chemistry*; Zhang, W., Cue, B., Eds.; John Wiley & Sons, Ltd, 2012; Chapter 13, pp 343−362.

(3) (a) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. Copper- Catalyzed Domino Synthesis of Quinazolinones via Ullmann- Type Coupling and Aerobic Oxidative C- H Amidation. *Org. Lett.* **2011**, *13*, 1274−1277. (b) Zhu, M.; Kim, M. H.; Lee, S.; Bae, S. J.; Kim, S. H.; Park, S. B. Discovery of Novel Benzopyranyl Tetracycles that Act as Inhibitors of Osteoclastogenesis Induced by Receptor Activator of NF- κB Ligand. *J. Med. Chem.* **2010**, *53*, 8760−8764. (c) Wan, J. P.; Pan, Y. J. Chemo-/regioselective synthesis of 6- unsubstituted dihydropyrimidinones, 1, 3-thiazines and chromones via novel variants of Biginelli reaction. *Chem. Commun.* **2009**, *19*, 2768−2770. (d) Carpenter, R. D.; Lam, K. S.; Kurth, M. J. Microwave- Mediated Heterocyclization to Benzimidazo[2, 1- b] quinazolin- 12(5H) - ones. *J. Org. Chem.* **2007**, *72*, 284−287.

(4) (a) Pericherla, K.; Khedar, P.; Khungar, B.; Kumar, A. One- pot sequential C- N coupling and cross dehydrogenative couplings: synthesis of novel azole fused imidazo[1, 2- a] pyridines. *Chem. Commun.* **2013**, *49*, 2924−2926. (b) Yan, Y.; Zhang, Y.; Zha, Z.; Wang, Z. Mild Metal- Free Sequential Dual Oxidative Amination of C(sp3) - H bonds: Efficient Synthesis of Imidazo[1, 5- a] pyridines. *Org. Lett.* **2013**, *15*, 2274−2277. (c) Nagaraj, M.; Boominathan, M.; Perumal, D.; Muthusubramanian, M. S.; Bhuvanesh, N. Copper(I) - Catalyzed Cascade Sulfonimidate to Sulfonamide Rearrangement: Synthesis of Imidazo[1, 2- a] [1, 4] diazepin- 7(6H) - one. *J. Org. Chem.* **2012**, *77*, 6319−6326. (d) Krasavin, M.; Shkavrov, S.; Parchinsky, V.; Bukhryakov, K. Imidazo[1, 2- a] quinoxalines accessed via two sequential isocyanide-based multicomponent reactions. *J. Org. Chem.* **2009**, *74*, 2627−2629.

(5) (a) Liu, J.; Lei, M.; Hu, L. One- pot conversion of CO2 and glycerol to value- added products using propylene oxide as the coupling agent. *Green Chem.* **2012**, *14*, 840−846. (b) Dou, G.; Wang, M.; Shi, D. One-Pot Synthesis of Quinazolinone Derivatives from Nitro- Compounds with the Aid of Low- Valent Titanium. *J. Comb. Chem.* **2009**, *11*, 151−154.

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX

(c) Hranjec, M.; Kralj, M.; Piantanida, I.; Sedić, M.; Šuman, L.; Pavelić, K.; Karminski-Zamola, G. Novel Cyano- and Amidino- Substituted Derivatives of Styryl- 2- Benzimidazoles and Benzimidazo[1, 2- a] quinolines. Synthesis, Photochemical Synthesis, DNA Binding, and Antitumor Evaluation, Part 3. *J. Med. Chem.* **2007**, *50*, 5696−5711.
(6) Alagarsamy, V.; Solomon, V. R.; Murugan, M. Synthesis and pharmacological investigation of novel 4- benzyl- 1- substituted- 4H- [1, 2, 4] triazolo[4, 3- a] quinazolin- 5- ones as new class of H1- antihistaminic agents. *Bioorg. Med. Chem.* **2007**, *15*, 4009−4015.
(7) Sondhi, S. M.; Rajvanshi, S.; Johar, M.; Bharti, N.; Azam, A.; Singh, A. K. Anti- inflammatory, analgesic and antiamoebic activity evaluation of pyrimido[1, 6- a] benzimidazole derivatives synthesized by the reaction of ketoisothiocyanates with mono and diamines. *Eur. J. Med. Chem.* **2002**, *37*, 835−843.
(8) Neochoritis, C. G.; Zarganes-Tzitzikas, T.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J.; Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.; Choli Papadopoulou, T. One- pot microwave assisted synthesis under green chemistry conditions, antioxidant screening, and cytotoxicity assessments of benzimidazole Schiff bases and pyrimido[1, 2- a] benzimidazol- 3(4H) - ones. *Eur. J. Med. Chem.* **2011**, *46*, 297−306.
(9) Lunn, W. H. W.; Harper, R. W.; Stone, R. L. Benzimidazo[2, 1- b] quinazolin- 12- ones. New class of potent immunosuppressive compounds. *J. Med. Chem.* **1971**, *14*, 1069−1071.
(10) Hubschwerlen, C.; Pflieger, P.; Specklin, J. L.; Gubernator, K.; Gmunder, H.; Angehrn, P.; Kompis, I. Pyrimido[1, 6- a] benzimidazoles: a new class of DNA gyrase inhibitors. *J. Med. Chem.* **1992**, *35*, 1385−1392.
(11) Dalla Via, L.; Gia, O.; Marciani Magno, S.; Da Settimo, A.; Marini, A. M.; Primofiore, G.; Da Settimo, F.; Salerno, S. Synthesis, in vitro antiproliferative activity and DNA-interaction of benzimidazoquinazoline derivatives as potential anti-tumor agents. *Farmaco* **2001**, *56*, 159−167.
(12) Jones, E. D.; Coates, J. A. V.; Rhodes, D. I.; Deadman, J. J.; Vandegraff, N. A.; Winfield, L. J.; Thienthong, N.; Issa, W.; Choi, N.; MacFarlane, K. Preparation of bicyclic pyrimidinones and analogues for the treatment of viral infections, particularly HIV infections. WO 2008077188, 2008.
(13) Chai, D.; Fitch, D. M. Prolyl hydroxylase inhibitors. WO 2009039322, 2009.
(14) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. Microwave- Assisted Three- Component Synthesis of 7- Aryl- 2- alkylthio- 4, 7- dihydro- 1, 2, 4- triazolo[1, 5- a] - pyrimidine- 6- carboxamides and Their Selective Reduction. *J. Comb. Chem.* **2006**, *8*, 427−434.
(15) (a) Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Alimadadi, B.; Oskooie, H. A.; Bamoharram, F. F. A three component one- pot procedure for the synthesis of [1, 2, 4] triazolo /benzimidazoloquinazolinone derivatives in the presence of H6P2W18O62 · 18H2O as a green and reusable catalyst. *Mol. Diversity* **2008**, *12*, 181−185. (b) Shao, Q.; Tu, S.; Li, C.; Cao, L.; Zhou, D.; Wang, Q.; Jiang, B.; Zhang, Y.; Hao, W. Green and high efficient synthesis of triazabenzo[b] fluoren- 6- one derivatives in water under microwave irradiation. *J. Heterocycl. Chem.* **2008**, *45*, 411−416. (c) Shaabani, A.; Farhangi, E.; Rahmati, A. Synthesis of tetrahydrobenzimidazo[1, 2- b] quinazolin- 1(2H) - one and tetrahydro- 1, 2, 4- triazolo[5, 1- b] quinazolin- 8(4H) - one ring systems under solvent- free conditions. *Comb. Chem. High Throughput Screening* **2006**, *9*, 771−776. (d) Shaabani, A.; Rahmati, A.; Naderi, S. Bioorg. A novel one- pot three- component reaction: Synthesis of triheterocyclic 4H- pyrimido[2, 1- b] benzazoles ring systems. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5553−5557.
(16) Hsiao, Y. S.; Yellol, G. S.; Chen, L. H.; Sun, C. M. Multidisciplinary Synthetic Approach for Rapid Combinatorial Library Synthesis of Triaza- Fluorenes. *J. Comb. Chem.* **2010**, *12*, 723−732.
(17) Ryabukhin, S. V.; Plaskon, A. S.; Boron, S. Yu.; Volochnyuk, D. M.; Tolmachev, A. A. Aminoheterocycles as synthons for combinatorial Biginelli reactions. *Mol. Diversity* **2011**, *15*, 189−195.
(18) (a) Chen, C. H.; Yellol, G. S.; Lin, P. T.; Sun, C. M. Base-catalyzed Povarov reaction: an unusual [1, 3] sigmatropic rearrangement to dihydropyrimidobenzimidazoles. *Org. Lett.* **2011**, *13*, 5120−5123. (b) Correa, H.; Edwards, J. K.; McCluskey, A.; McKinnon, I.; Scott, J. L. A thermodynamic investigation of solvent- free reactions. *Green Chem.* **2003**, *5*, 30−33.
(19) (a) Ojima, I. Exploration of Fluorine Chemistry at the Multidisciplinary Interface of Chemistry and Biology. *J. Org. Chem.* **2013**, *78*, 6358−6383. (b) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369.
(20) The molecular structure of product (**3**{*1,1,2,5*}, **7**, **8**) was determined by X-ray crystallography. CCDC 978693−978696 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(21) Kaupp, G.; Reza Naimi-Jamal, M.; Schmeyers, J. Solvent- free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield. *Tetrahedron* **2003**, *59*, 3753−3760.
(22) (a) He, F.; Li, P.; Gu, Y.; Li, G. Glycerol as a promoting medium for electrophilic activation of aldehydes: catalyst- free synthesis of di(indolyl) methanes, xanthene- 1, 8(2H) - diones and 1- oxohexahydroxanthene derivatives. *Green Chem.* **2009**, *11*, 1767−1773. (b) Cravotto, G.; Demetri, A.; Nano, G. M.; Palmisano, G.; Penoni, A.; Tagliapietra, S. The aldol reaction under high- intensity ultrasound: A novel approach to an old reaction. *Eur. J. Org. Chem.* **2003**, *2003*, 4438−4444.
(23) Goswami, P.; Das, B. Efficient organocatalyzed solvent- free selective synthesis of conjugated enones. *Tetrahedron Lett.* **2009**, *50*, 897−900.
(24) Fuchs, K.; Paquette, L. A. Access to Protected 2- Alkylidene 1, 3-diones by Modified Knoevenagel Reaction in the Presence of Thiophenol. A New Approach to Spirocyclopentanol Construction. *J. Org. Chem.* **1994**, *59*, 528−532.
(25) Chung, T. W.; Narhe, B. D.; Lin, C. C.; Sun, C. M. Multicomponent Synthesis of Functionalized Tetrahydroacridinones: Insights into a Mechanistic Route. *Org. Lett.* **2015**, *17*, 5368−5371.

DOI: 10.1021/acscombsci.5b00186
ACS Comb. Sci. XXXX, XXX, XXX−XXX