Regioselective Piperidine-Catalyzed Tandem Imination−Isocyanate Annulation to Fused Tricyclic Triazines

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Ⓢ *Supporting Information*

ABSTRACT: A novel tandem imination−isocyanate-mediated annulation was explored. Ionic liquid-immobilized 2-aminobenzimidazoles react sequentially with aldehydes and isocyanates to give highly functionalized benzimidazole-embedded triazines. The second-stage transformation revealed that the formation of triazinone functionality is entirely regioselective to allow rapid assembly of biologically interesting tricyclic skeletons. In conjunction with the application of microwave irradiation and IL support, this method provides an efficient route to access substituted benzoimidazotriazines.

KEYWORDS: *tandem reaction, imination, isocyanate-mediated annulation, benzoimidazotriazine, ionic liquid, microwave*
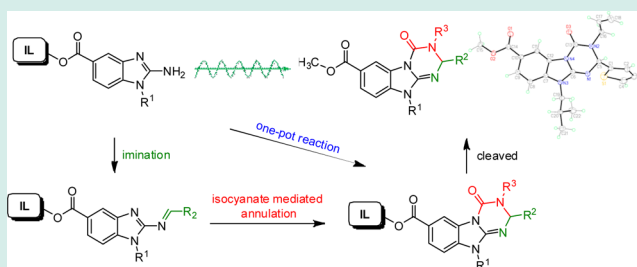
■ INTRODUCTION

Fused polyheterocyclic ring systems have played a crucial role in medicinal chemistry. Utilization of these types of molecules may facilitate the discovery of novel biologically active molecules.[1] To understand how small molecules modulate the functions of receptors or enzymes in living systems, the incorporation of privileged scaffolds into novel core skeletons is important to study biology and their treatment of disease.[2] Benzimidazole and triazine compounds have been reported as nociceptin/orphanin FQ receptor agonists, pan class I phosphatidylinositol 3-kinase (PI3K) inhibitors, and thymidine phosphorylase inhibitors (Figure 1).[3−6] However, the biological profiles of the new scaffolds incorporating other versatile pharmacophores are unexplored, which might be due to the lack of general methods for the synthesis of these compounds. Although some synthetic routes toward these hybrid cores are known,[7] novel approaches for the efficient construction of heterocycles comprising chimeric cores with various substitutions are unexplored.

Tandem reactions are multistep reactions combined into one synthetic operation to provide rapid access to natural and synthetic fused polycyclic skeletons.[8] Furthermore, these reactions are also consistent with the principles of green chemistry in that they are time- and cost-effective and more environmentally friendly, consuming less material and generating less waste.[9] The use of imination and isocyanate-mediated cyclization as a domino process has not been explored in the literature. The purpose of this work is to demonstrate a three-component cascade reaction for rapid assembly of complex compounds. The key step of the sequence consists of regioselective isocyanate-mediated cyclization.

Recently, ionic liquids (ILs) have attracted broad interest as novel green reaction media and reagents for various chemical reactions because of their unique physical properties.[10] Apart from the homogeneous reaction conditions and high loading capacity, the progress of IL-supported reactions can be monitored by proton NMR spectroscopy without cleavage of the IL support. All of the IL-supported intermediates can be purified by precipitation and filtration to remove excess reagents.[11] These promising features make ILs suitable as soluble supports in high-throughput synthesis. The advent of microwave-assisted organic synthesis has contributed significantly to the development of eco-compatible methods.[12,13] The use of microwave irradiation in combination with IL supports enhances energy dissipation and greatly speeds up the reaction.

In this report, we disclose a novel IL-supported synthesis of benzoimidazotriazines via tandem imination−isocyanate annulation under microwave irradiation. Several synthetic strategies have been established to synthesize triazine derivatives. Houghten and co-workers reported the synthesis of 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles using a tandem aza-Wittig/heterocumulene-mediated annulation reaction of 2-aminobenzimidazole with alkyl isocyanates.[7] Abbiati et al.[14] employed cycloaddition reactions of 2,4-diphenyl-1,3-diazabuta-1,3-dienes with a variety of isocyanates and isothiocyanates to obtain 3,4-dihydro-1*H*-[1,3,5]triazin-2-ones and 3,4-dihydro-1*H*-[1,3,5]triazin-2-thiones, respectively. Furthermore, Ward et al.[15] reported the cyclization of 2-aminobenzimidazole with dialkyl ketones, alkyl isocyanates, and alkyl isothiocyanates to deliver 1,2,3,4-tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles. These synthetic methods typically suffer from a number of limitations, including lengthy synthetic sequences, low yields,
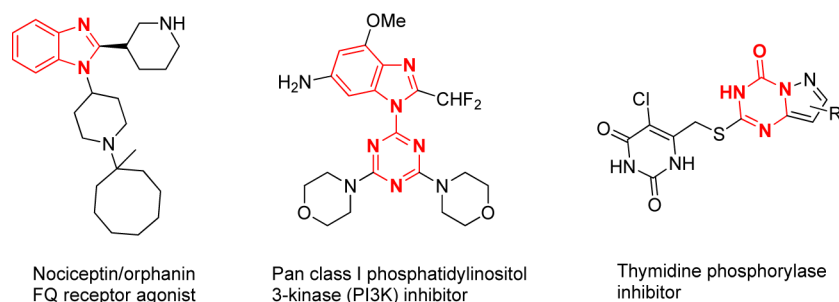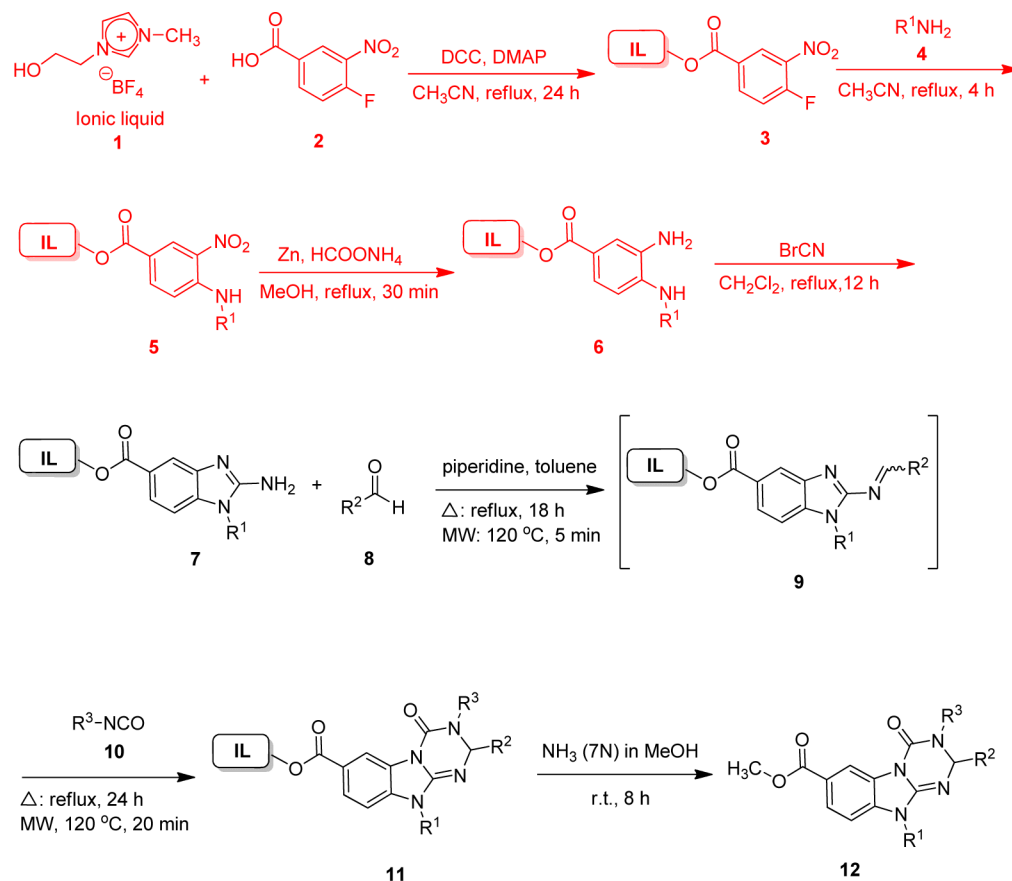
Figure 1. Several interesting heterocycles containing benzimidazole and triazine frameworks.

Scheme 1. Synthesis of Benzo[4,5]imidazo[1,2-a][1,3,5]triazines 12


and narrow substrate scope. Obviously, there is no efficient method to access these privileged scaffolds from commercially available substrates. Thus, we were enticed to investigate the possible utilization of imination and isocyanate-mediated cyclization to afford benzoimidazotriazines in a concise route.

■ RESULTS AND DISCUSSION

Encouraged by the recent reports of the tandem aza-Wittig/heterocyclization reaction of iminophosphorane[18] and cycloaddition reactions of diazabutadienes with isocyanates,[16] we envisioned a possible route that utilizes a tandem imination–isocyanate-mediated annulation to afford tetrasubstituted benzoimidazotriazines. The synthetic strategy toward benzo-[4,5]imidazo[1,2-a][1,3,5]triazine derivatives was designed to study IL-supported synthesis under microwave irradiation. A synthetic route for the preparation of benzo[4,5]imidazo[1,2-a][1,3,5]triazines 12 is described in Scheme 1. The IL support, 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate

([hydemim][BF$_4$], 1), was prepared in two steps according to the method reported in the literature.[17] Coupling of commercially available 4-fluoro-3-nitrobenzoic acid (2) with IL support 1 was carried out in refluxing acetonitrile using N,N'-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP) to provide IL-anchored 4-fluoro-3-nitrobenzoate (3) in excellent yield. The first position of diversity (R^1) was introduced by nucleophilic displacement of the fluorine atom with various amines. This was achieved by reacting 3 with various amines 4 in refluxing acetonitrile, affording IL-supported nitroamines 5 in good yields. In the next step, the nitro group of IL-supported nitroamines 5 was reduced by zinc and ammonium formate in refluxing methanol. This zinc reduction reaction proceeded smoothly to furnish IL-linked diamines 6 in excellent yields. Treatment of IL-immobilized diamines 6 with cyanogen bromide in refluxing dichloromethane provided IL-supported 2-aminobenzimidazoles 7 in good yields.

**Scheme 2. Catalytic Cycle for the Piperidine-Induced Imination**
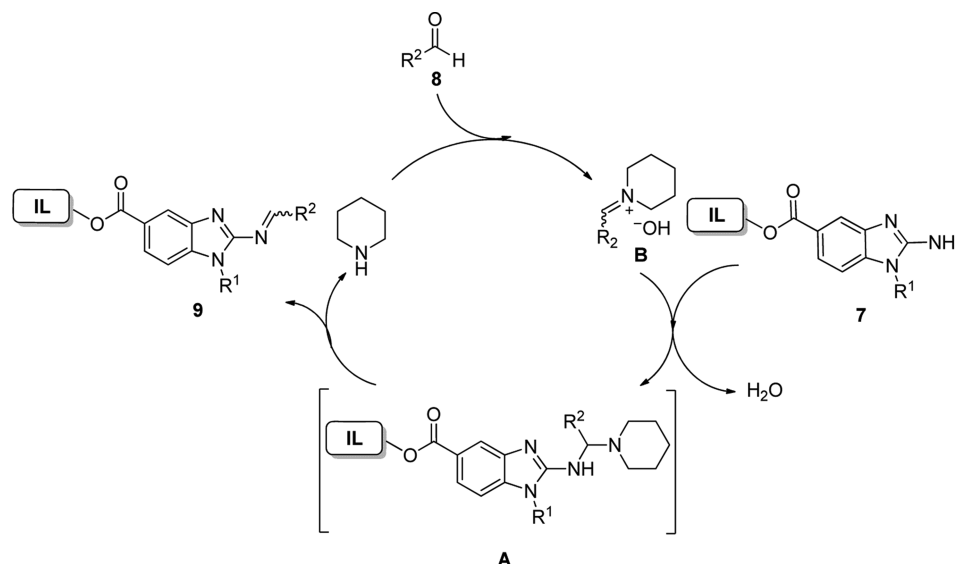
In the key step of the proposed synthetic sequence, we planned to prepare triazines **11** from 2-aminobenzimidazoles **7** by tandem imination–isocyanate-mediated annulation. Initially we attempted imination of IL-tagged 2-aminobenzimidazoles **7** with aldehydes **8** in the presence of Brønsted or Lewis acids, but incomplete conversion was observed under either reflux or microwave conditions. On the basis of a previous literature example,[19] we attempted to employ piperidine as a basic catalyst for imine formation. Condensation of IL-supported 2-aminobenzimidazoles **7** with aldehydes **8** in the presence of a catalytic amount of piperidine in toluene under microwave irradiation at 120 °C for 5 min furnished diazabutadiene conjugates **9**, affording the second point of structural diversity (R^2). This imine bond formation required 18 h in refluxing toluene, which indicated the significant impact of the microwave irradiation. The reaction progress and stepwise transformations on the IL support were monitored by conventional proton NMR spectroscopy. Conjugate **7** was reacted with 2-thiophenecarboxaldehyde to yield the corresponding imine conjugate **9**. A comparative proton NMR spectrum analysis of the respective conjugates **7** and **9** revealed that the spectrum of **9** displayed a singlet at 9.75 ppm due to the imine proton, which was absent in the spectrum of **7**. In addition, the peaks corresponding to the protons of the thiophene ring were observed at 7.19 and 7.65 ppm, respectively in the spectrum of diazabutadiene conjugate **9**.

A plausible mechanism for the piperidine-catalyzed imination of 2-aminobenzimidazole conjugates **7** with aldehydes **8** is described in Scheme 2. Condensation of aldehydes **8** and piperidine gives piperidinium hydroxide salt **B**. Nucleophilic addition of 2-aminobenzimidazole conjugates **7** to **B** affords IL-supported intermediates **A** upon elimination of H$_2$O. Finally, the formation of diazabutadiene conjugates **9** is achieved by expulsion of piperidine.[20] The generated IL-bound diazabutadiene conjugates **9** were directly used for the next step without further purification.

Exposure of IL-bound intermediates **9** to various isocyanates **10** under microwave irradiation 120 °C for 20 min afforded IL-supported benzoimidazotriazines **11** in quantitative yield. An additional point of diversity (R^3) was introduced at this stage in the fused tricyclic scaffold. Upon completion of the reaction,

the IL-immobilized compounds **11** were purified by precipitation and filtration to remove excess reagents and side products. The success of the isocyanate-mediated annulation was also confirmed by proton NMR analysis of conjugates **9** and **11**, which indicated the disappearance of the imine proton at 9.75 ppm as well as the emergence of the proton at 6.21 ppm.

A plausible mechanistic route for piperidine-catalyzed [4 + 2] annulation with isocyanates to give the fused tricyclic heterocycles **11** is outlined in Scheme 3. The cyclization is

Scheme 3. Possible Mechanism of the Annulation To Give Diazabutadiene Conjugates 11
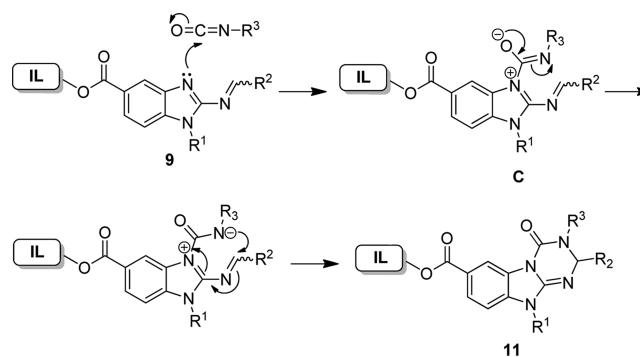
initiated by nucleophilic attack on the isocyanate by the benzimidazole nitrogen atom to form urea **C**. Subsequently, the resulting intermediate undergoes an intramolecular heterocyclization to generate the corresponding benzoimidazotriazine **11**. Therefore, the current tandem reaction provides a direct path for the rapid and regioselective synthesis of fused heterocycles with multiple sites of molecular diversity.

Finally, removal of the IL support from **11** was carried out in a solution of ammonia in methanol at room temperature for 8 h to provide benzo[4,5]imidazo[1,2-a][1,3,5]triazine methyl esters **12** in good yields. The IL support was then precipitated out with diethyl ether and removed by filtration. The filtrate containing final compound was dried and subjected to HPLC analysis (Table 1). The progress of the cleavage reaction was monitored by proton NMR spectroscopy of the recovered IL

Table 1. Substrate Scope for the Synthesis of Benzoimidazoletriazines 12
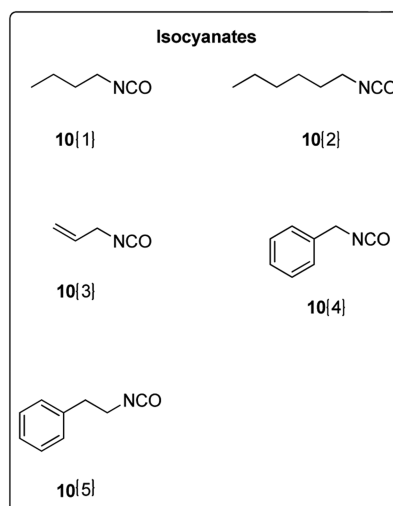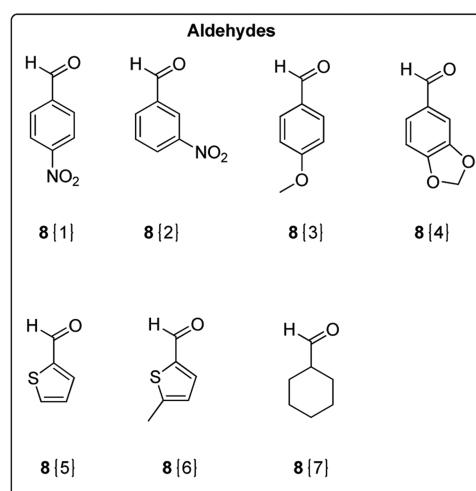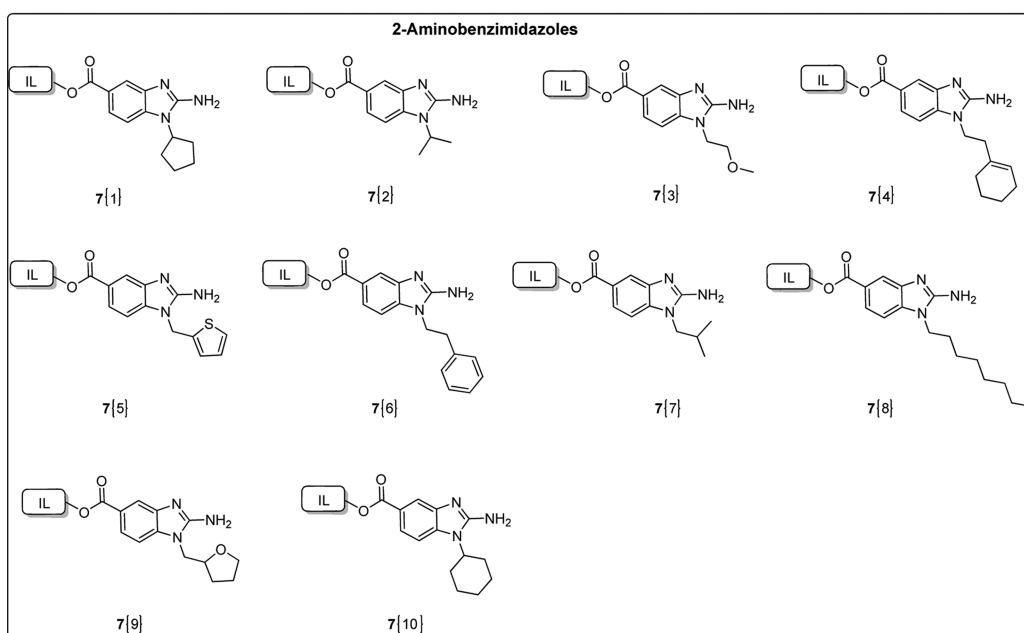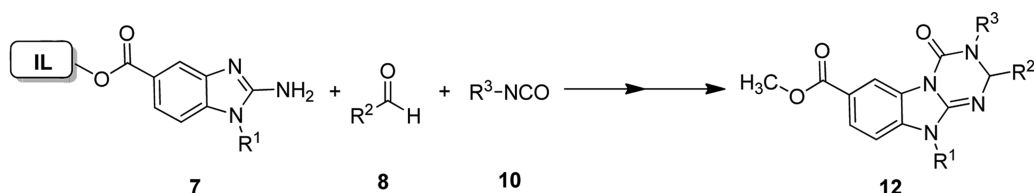
entry	product	isolated yield (%)^a	HPLC purity (%)^b	entry	product	isolated yield (%)^a	HPLC purity (%)^b	entry	product	isolated yield (%)^a	HPLC purity (%)^b
1	12{1,1,1}	92	86	8	12{7,5,2}	84	82	14	12{6,7,3}	90	97
2	12{2,2,1}	89	81	9	12{8,6,2}	82	85	15	12{7,5,3}	87	91
3	12{2,3,1}	85	97	10	12{6,2,3}	95	98	16	12{1,2,4}	80	81
4	12{3,4,1}	83	84	11	12{9,1,3}	92	93	17	12{5,1,4}	89	92
5	12{4,5,1}	80	81	12	12{6,3,3}	88	92	18	12{3,1,5}	90	94
6	12{5,2,2}	90	91	13	12{10,4,3}	71	72	19	12{8,2,5}	82	85
7	12{5,3,2}	83	82								

^{a}Determined from the weight of purified compound. ^{b}Determined on crude products by normal-phase HPLC analysis.

support. The upfield shift of the α-methylene protons from δ 4.3 to 3.6 confirmed the complete transformation.

To investigate the generality of this unprecedented tandem imination−isocyanate-mediated annulation, aldehydes having either electron-withdrawing or electron-donating groups and a variety of isocyanates were employed (Table 1). The electronic effects of the substituted aldehydes have a minor impact on the conversion. The yields were higher when electron-deficient
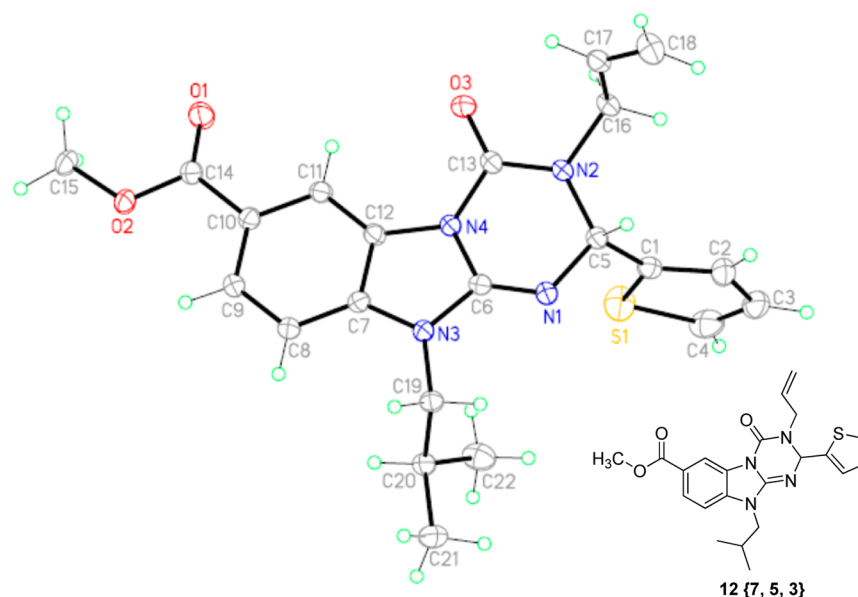
Figure 2. ORTEP diagram of compound **12**{7,5,3} (Table 1, entry 15).

aldehydes were used. These results are attributed to the higher reactivity of activated aldehydes. The feasibility of employing aliphatic aldehydes in the reaction was also investigated (compound **12**{6,7,3}; Table 1, entry 14).

Additionally, various types of isocyanates were examined to increase the diversity of benzoimidazotriazines **12**. The substituent on the isocyanate had no obvious influence on the yield. The significant cooperative effect of microwave conditions and IL support was proven to dramatically improve the efficiency of this telescopic imination–isocyanate-mediated cyclization. We attempted to extend this cascade reaction to isothiocyanates as well. The reactions of imines **9** with different isothiocyanates failed to generate benzoimidazothiotriazines under microwave irradiation. We speculated that the low electrophilicity of the isothiocyanates (R−N=C=S) inhibited the piperidine-catalyzed [4 + 2] cyclization.

In addition to spectroscopic studies, the structure of the representative compound **12**{7,5,3} (Table 1, entry 15) was further confirmed by single-crystal X-ray structure analysis. The ORTEP diagram of compound **12**{7,5,3} is presented in Figure 2. The tricyclic ring system is aligned in a linear conformation, and the planar thiophene ring is perpendicular to the plane of the fused tricycle. The allyl group on N2 and the sulfur atom of the thiophene ring are oriented in a relative anti position.

CONCLUSION

We have developed a highly regioselective cascade reaction for the synthesis of functionalized benzoimidazotriazines **12** employing 2-aminobenzimidazoles **7**, aldehydes **8**, and isocyanates **10**. This novel synthetic strategy utilizes an initial imination followed by an isocyanate-mediated annulation to deliver the tricyclic scaffold with three points of diversity. A synergistic effect of microwave heating and the ionic liquid support was exploited to speed up the tandem process. This strategy offers a concise route for the convergent synthesis of densely functionalized benzoimidazotriazines. It is anticipated that the current method could have potential utility in chemical synthesis and medicinal chemistry.

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of Compounds 12. To a stirred solution of 4-fluoro-3-nitrobenzoic acid (**2**) (1.12 mmol, 1.2 equiv) in acetonitrile was added DCC (1.12 mmol, 1.2 equiv), DMAP (0.04 mmol, 0.05 equiv), and IL support **1** (0.93 mmol, 1 equiv). The reaction mixture was refluxed for 16 h. After completion of the reaction, dicyclohexylurea was filtered off, and the filtrate was concentrated. The crude residue was washed with cold ether (50 mL × 3) and dried in vacuo to afford **3** in 96% yield. To a stirred solution of **3** (1.41 mmol, 1 equiv) in acetonitrile was added amine **4** (1.7 mmol, 1.2 equiv), and the reaction mixture was refluxed for 4 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was precipitated and washed with cold diethyl ether (50 mL × 3). The precipitate was dried to give **5** in good yield. To a stirred solution of **5** in methanol were added zinc (8.96 mmol, 7 equiv) and ammonium formate (19.2 mmol, 15 equiv), and the reaction mixture was refluxed for 30 min. After completion of the reaction, the reaction mixture was filtered through a Celite bed to remove zinc, and the filtrate was concentrated. Dichloromethane (30 mL) was added to the crude residue to precipitate ammonium formate, and the mixture was again passed through a Celite bed. The filtrate was concentrated to yield **6** in good yield. A solution of **6** (1.28 mmol, 1 equiv) and cyanogen bromide (2.56 mmol, 2 equiv) in dichloromethane (30 mL) was refluxed for 12 h. The crude material was washed with cold diethyl ether (50 mL × 3) to afford IL-bound 2-aminobenzimidazole **7** in good yield. Aldehyde **8** (0.44 mmol, 1.0 equiv) and piperidine (0.2 mmol, 0.5 equiv) were added to a solution of **7** (0.16 g, 0.44 mmol) in toluene. The reaction mixture was subjected to microwave irradiation at 120 °C for 5 min. After formation of iminium intermediate **9**, isocyanate **10** was added to the resulting reaction mixture, and the mixture was continuously microwave-irradiated at 120 °C for 20 min. The reaction progress was monitored by proton NMR spectroscopy. After completion of the reaction, the reaction mixture was washed and precipitated with diethyl ether (50 mL × 3). The precipitate was filtered and dried to furnish the IL-bound

benzoimidazotriazine **11** in excellent yield. A 7 M solution of ammonia in methanol was added to **11** (0.27 g, 0.44 mmol). The mixture was stirred at ambient temperature for 8 h. After completion of the cleavage reaction, the solvent was evaporated to dryness, and the polymer was precipitated with diethyl ether (50 mL × 3). The filtrate was concentrated in vacuo, and the crude product was subjected to HPLC analysis. The title compound **12** was obtained in excellent yield after purification by column chromatography.

Methyl 3-Butyl-10-cyclopentyl-2-(4-nitrophenyl)-4-oxo-2,3,4,10- tetrahydrobenzo[4,5]imidazo[1,2-a]-[1,3,5]triazin-7-ylcarboxylate (12{*1,1,1*}). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.55 (d, J = 1.6 Hz, 1H), 8.24 (d, J = 8.7 Hz, 2H), 7.89 (dd, J = 8.4, 1.6 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.09 (s, 1H), 4.71 (m, 1H), 3.91 (m, 1H), 3.91 (s, 3H), 2.87 (m, 1H), 2.01 (m, 4H), 1.69 (m, 2H), 1.55 (m, 4H), 1.30 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.2, 149.0, 148.6, 148.2, 148.1, 135.7, 127.7, 127.3, 126.8, 124.7, 123.7, 115.3, 108.2, 76.3, 54.4, 52.5, 45.2, 30.0, 28.3, 28.3, 25.3, 20.4, 14.1; IR (cm^{-1}, neat) 2954, 2871, 1710; MS (ESI-MS) m/z 492 [M + H]$^+$; HRMS calcd for C$_{26}$H$_{29}$N$_5$O$_5$ [M + H]$^+$ m/z 491.2169, found 492.2250.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Spectral data (^{1}H and ^{13}C NMR, IR, LRMS, HRMS) for compounds **12** and X-ray data for compound **12**{*7,5,3*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Reymond, J.-L.; Awale, M. Exploring chemical space for drug discovery using the chemical universe database. *ACS Chem. Neurosci.* **2012**, *3*, 649−657. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.* **2003**, *103*, 893−930.

(2) (a) Schreiber, S. L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **2000**, *287*, 1964−1969. (b) Arya, P.; Chou, D. T. H.; Baek, M. G. Diversity-based organic synthesis in the era of genomics and proteomics. *Angew. Chem., Int. Ed.* **2001**, *40*, 339−346.

(3) (a) Ognyanov, V. I.; Balan, C.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y. X.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. Design of potent, orally available antagonists of the transient receptor potential vanilloid 1. Structure−activity relationships of 2-piperazin-1-yl-1H-benzimidazoles. *J. Med. Chem.* **2006**, *49*, 3719−3742. (b) Krečmerová, M.; Holý, A.; Pískala, A.; Masojídkov, M.; Andrei, G.; Naesens, L.; Neyts, J.; Balzarini, J.; De Clercq, E.; Snoeck, R. Antiviral activity of triazine analogues of 1-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine (Cidofovir) and related compounds. *J. Med. Chem.* **2007**, *50*, 1069−1077.

(4) Hayashi, S.; Hirao, A.; Imai, A.; Nakamura, H.; Murata, Y.; Ohashi, K.; Nakata, E. Novel non-peptide nociceptin/orphanin FQ receptor agonist, 1-[-(1-methylcyclooctyl)-4-piperidinyl]-2-[(3R)-3-piperidinyl]-1H-benzimidazole: Design, synthesis, and structure−activity relationship of oral receptor occupancy in the brain for orally potent antianxiety drug. *J. Med. Chem.* **2009**, *52*, 610−625.

(5) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W. J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Shepherd, P. R. Synthesis and biological evalution of novel analogues of the pan class I phosphatidylinositol 3-kinase (PI3K) inhibitor 2-(difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (ZSTK474). *J. Med. Chem.* **2011**, *54*, 7105−7126.

(6) Sun, L.; Li, J.; Bera, H.; Dolzhenko, A. V.; Chiu, G. N. C.; Chui, W. K. Fragment-based approach to the design of 5-chlorouracil-linked-pyrazolo[1,5-a][1,3,5]triazines as thymidine phosphorylase inhibitors. *Eur. J. Org. Chem.* **2013**, *70*, 400−410.

(7) Hoesl, C. E.; Nefzi, A.; Houghten, R. A. Parallel solid-phase synthesis of 2-imino-4-oxo-1,3,5-triazino[1,2-a]benzimidazoles via tandem aza-Wittig/heterocumulene-mediated annulation reaction. *J. Comb. Chem.* **2003**, *5*, 155−160.

(8) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent tandem catalysis. *Chem. Rev.* **2005**, *105*, 1001−1020.

(9) Tietze, L. F. Domino reactions in organic synthesis. *Chem. Rev.* **1996**, *96*, 115−136.

(10) Zhang, Q.; Zhang, S.; Deng, Y. Recent advances in ionic liquid catalysis. *Green Chem.* **2011**, *13*, 2619−2637.

(11) Miao, W.; Chan, T. H. Ionic-liquid-supported synthesis: A novel liquid-phase strategy for organic synthesis. *Acc. Chem. Res.* **2006**, *39*, 897−908.

(12) Moseley, J. D.; Kappe, C. O. A critical assessment of the greenness and energy efficiency of microwave-assisted organic synthesis. *Green Chem.* **2011**, *13*, 794−806.

(13) Kappe, C. O.; Dallinger, D. The impact of microwave synthesis on drug discovery. *Nat. Rev. Drug Discovery* **2006**, *5*, 51−63.

(14) Abbiati, G.; de Carvalho, A. C.; Rossi, E. Cycloaddition reactions of 2,4-diphenyl-1,3-diazabuta-1,3-dienes with isocyanates and isothiocyanates. *Tetrahedron* **2003**, *59*, 7397−7402.

(15) Ward, C. E.; Berthold, R. V.; Koerwer, J. F.; Tomlin, J. B.; Manning, D. T. Synthesis and herbicidal activity of 1,2,3,4-tetrahydro-1,3,5-triazino[1,2-a]benzimidazoles. *J. Agric. Food Chem.* **1986**, *34*, 1005−1010.

(16) Klein, G.; Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Parallel solid-phase synthesis of trisubstituted triazinobenzimidazole-diones. *J. Comb. Chem.* **2002**, *4*, 345−351.

(17) Miao, W.; Chan, T. H. Exploration of ionic liquids as soluble supports for organic synthesis. Demonstration with a Suzuki coupling reaction. *Org. Lett.* **2003**, *5*, 5003−5005.

(18) Alvarez-Sarandés, R; Peinador, C.; Quintela, J. M. Iminophosphoranes in heterocyclic chemistry. A simple one-pot synthesis of pyridothienopyridazines and pyrimidothienopyridazines. *Tetrahedron* **2001**, *57*, 5413−5420.

(19) Correa, W. H.; Edwards, J. K.; McCluskey, A.; McKinnon, I.; Scott, J. L. A thermodynamic investigation of solvent-free reactions. *Green Chem.* **2003**, *5*, 30−33.

(20) 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.