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

Indrajeet J. Barve, Chih-Hau Chen, Chih-Hsien Kao, and Chung-Ming Sun*

Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan

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 triazine 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 benzimidazotriazines.

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. 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.

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). However, the biological profiles of the new scaffolds 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, 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. 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. 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. 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. 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. 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. Abbiati et al. 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-1H-[1,3,5]triazin-2-ones and 3,4-dihydro-1H-[1,3,5]triazin-2-thiones, respectively. Furthermore, Ward et al. 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,
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 and cycloaddition reactions of diazabutadienes with isocyanates, we envisioned a possible route that utilizes a tandem imination–isocyanate-mediated annulation to afford 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. 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 fluoride atom with various amines. This was achieved by reacting 3 with various amines 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.
In this stage 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, 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 (R2). 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 H2O. Finally, the formation of diazabutadiene conjugates 9 is achieved by expulsion of piperidine. 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 benzoimidatzotriazines 11 in quantitative yield. An additional point of diversity (R3) 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 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 benzoimidatzotriazine 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.
The upfield shift of the \( \alpha \)-methylene protons from \( \delta 4.3 \) 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

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

support. The upfield shift of the \( \alpha \)-methylene protons from \( \delta 4.3 \) 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
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 benzoimidazothiadiazines 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 benzoimidazothiadiazines 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 (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. Afterformation 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...
benzimidazotriazine 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 x 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)).** 1H NMR (300 MHz, CDCl3) δ 8.55 (d, J = 1.6 Hz, 1H), 8.24 (d, J = 8.7 Hz, 2H), 7.89 (dd, J = 8.7, 2H), 6.09 (s, 1H), 4.71 (m, 1H), 3.91 (m, 1H), 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);13C NMR (75 MHz, CDCl3) 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); 2954, 2871, 1710; MS (ESI-MS) m/z 492 [M + H]+; HRMS calc for C28H30N5O5 [M + H]+ m/z 491.2169, found 492.2250.

**ASSOCIATED CONTENT**

Supporting Information
Spectral data (1H and 13C 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.

**AUTHOR INFORMATION**

*Corresponding Author*

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

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


