ACS Combinatorial Science

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Rapid Two-Step Synthesis of Benzimidazo[1′,2′:1,5]-pyrrolo[2,3-*c*]isoquinolines by a Three-Component Coupling Reaction

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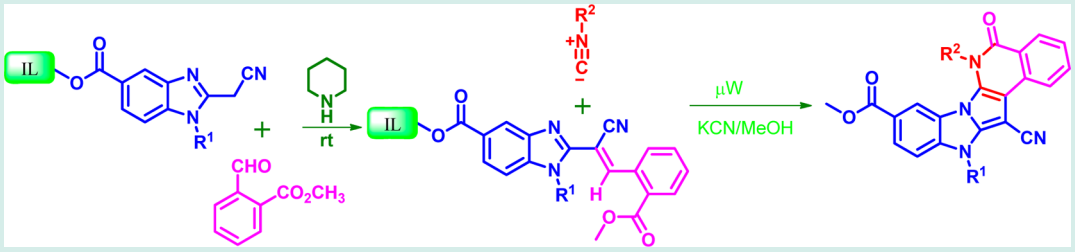
Supporting Information



ABSTRACT: A two-step, three-component coupling reaction on ionic liquid supported 2-cyanomethylbenzimidazoles, methyl 2-formylbenzoate, and isocyanides under microwave activation is explored. Knoevenagel condensation of 2-cyanomethylbenzimidazole with methyl-2-formylbenzoate in the presence of piperidine catalyst is followed by [4 + 1] cycloaddition with an isocyanide in the next step. Consequent intramolecular δ-lactam formation allows rapid construction of novel aza-pentacycles, benzimidazo[1′,2′:1,5]pyrrolo[2,3-*c*]isoquinolines.

KEYWORDS: *microwave, ionic liquid support, pyrrolo[1,2-a]benzimidazole, benzimidazo[1′,2′:1,5]pyrrolo[2,3-c]isoquinolines*

INTRODUCTION

Diversity-oriented and effective synthesis of structurally complex molecules by simple synthetic transformations are much needed for acceleration of combinatorial drug discovery process.[1] Advanced techniques like ionic-liquid supported synthesis, polymer-supported synthesis, microwave irradiation, and ultrasonication-assisted synthesis have proved as promising tools to speed up several synthetic transformations.[2] The reactions under microwave activation proceed in dramatically shortened reaction time as compared to that of reactions under conventional heating because of rapid and uniform dielectric heating. This may lead to cleaner reactions with lesser side products. Reactions which employ ionic liquid support simplifies the work up and purification process as the product can be obtained in pure form just by precipitation and solvents washing. Synergy of microwave irradiation and ionic liquid support has greatly enhanced parallel synthesis of novel molecular frameworks with potential biological activities that may result in acceleration of drug discovery.[2]

Benzimidazole represents an important class of azaheterocycles and is rightly considered as a "privileged scaffold" because of their widespread biological properties. It has been applied as a building block in the synthesis of polyazaheterocycles.[3] A large number of research efforts are focused on the synthesis and pharmacological studies of benzimidzole fused/linked polyazaheterocycles.[4] Similarly, isoquinoline-based heterocycles both of natural and synthetic origin are ubiquitous pharmacophores that are studied for their distinguished biological properties such as dopamine D_1 agonist and selective inhibition of DNA-PK in human tumor cell.[5] Polyazaheterocyclic frameworks containing benzimidazole and isoquinoline moieties are the molecules of choice in search of drug targets with unique pharmacological properties.[6] Recently, many variations in Ugi multicomponent reaction of heterocyclic aromatic amines with 2-formyl benzoic acid or 2-formylbenzoates and isocyanides or KCN have been used for the synthesis of benzimidazole-fused isoquinolines and their biological studies.[6a,7] Yang et al. designed and synthesized tetracyclic isoquinolinones as a potential CDK kinase inhibitor employing three-component reaction on 2-amionopyridine, 2-formylbenzoate and isonitrile.[7a] Choo and co-workers used similar reaction for the synthesis of polyheterocyclic isoquinolines with potent poly(ADP-ribose)polymerase-1 inhibition activity.[6b] Guchhait and Madaan used microwave assisted reaction in aqueous tetrafluoroboric acid to create isoquinolinones with free amide nitrogen.[7b] However, these reports are limited to the synthesis of tetracyclic skeletons. The synthetic and biological studies of fused pentacyclic aza heterocycles are largely undiscovered due to the lack of short and simple routes leading to these unique scaffolds. Few examples, Rutaecarpine **I** is an indolopyridoquinazolinone alkaloid with antithrombotic, anticancer, anti-inflammatory, and analgesic activities.[8] Its synthetic analogue **II** is an antiobesity compound that inhibits adipogenesis to reduce lipid accumulation in adipocytes.[9]

Received: March 24, 2014
Revised: May 24, 2014
Published: June 11, 2014

Luotonin A **III** is a pyrroloquinazolinoquinoline alkaloid to work against leukemia by inducing DNA topoisomerase I-dependent cytotoxicity (Figure 1).[10]

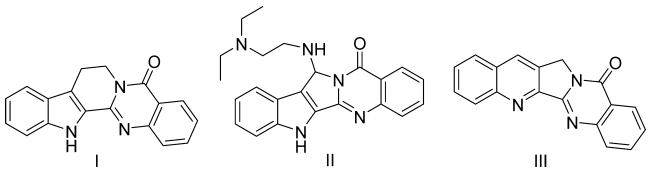


Figure 1. Biologically active pentacyclic azaheterocycles.

Recently, we developed multicomponent reactions utilizing 2-cyanomethylbenzimidazoles for the synthesis of pyrrolo[1,2-*a*]-benzimidazoles[11] and benzimidazole-linked 2-aminothiophenes.[12] In continuation with our efforts to establish facile reactions using functionalized benzimidazoles for the synthesis of biologically interesting polyazaheterocycles, we report a two step protocol for the synthesis of novel benzimidazo[1′,2′:1,5]pyrrolo[2,3-*c*]-isoquinolines (BPIs) that contains a benzimidazole and an isoquinolinone pharmacophore fused through a pyrrole ring.

RESULTS AND DISCUSSION

Our study began with the synthesis of various N-alkylated 2-cyanomethyl benzimidazoles (Scheme 1). Treatment of 3-nitro-4-fluorobenzoates with various amines and reduction of the nitro group yielded corresponding 3,4-diaminobenzoates **1**. The condensation of primary amine of **1** with cyanoacetic acid gave a cyanoacetamide **2** that was cyclized under acidic conditions with TFA to obtain the desired 2-cyanomethyl benzimidazoles **3** in good yields.[11,12]

Initially, we studied a one pot reaction on 2-cyanomethylbenzinmidazole **3**{*1*}, methyl 2-formyl benzoate, and cyclohexylisonitrile. Heating a dichloroethane solution of reactants in the presence of piperidine catalyst (30 mol %) at 180 °C for 12 h in a sealed tube yielded the desired pentacyclic benzimidazoisoquinolinone **6**{*1, 1,1*} in low yield (25%) along with pyrrolobenzimidazole (35%, PBI) **7** (Scheme 2).

The postulated mechanism of this MCR involves Knoevenagel condensation of 2-cyanomethylbenzimidazole with 2-formylbenzoate catalyzed by piperidine to yield azadiene **9**{*1,1*}. The Knoevenagel condensation is believed to yield a *s-trans*-diene **9**{*1,1*} that on thermal activation at higher temperature isomerizes to *s-cis*-diene **9**{*1,1*}, which then undergoes [4 + 1] cycloaddition with an isocyanide leading to pyrrolo[1,2-*a*]-benzimidazole (PBI) **11**{*1,1,1*} after aromatization. The intramolecular nucleophilic attack of secondary amine functionality of PBI **11**{*1,1,1*} on the benzoate carbonyl group delivers the BPI **6**{*1,1,1*} accompanied by a loss of methanol (Scheme 3).

Thus, the controlling factors in this MCR are isomerization of *s-trans* azadiene **9**{*1,1*} to *s-cis*-azadiene **9**{*1,1*} and δ-lactam ring formation in PBI **11**{*1,1,1*} using its secondary amine function which can be affected by bulk of the substituent (R^3) in parent isonitriles.

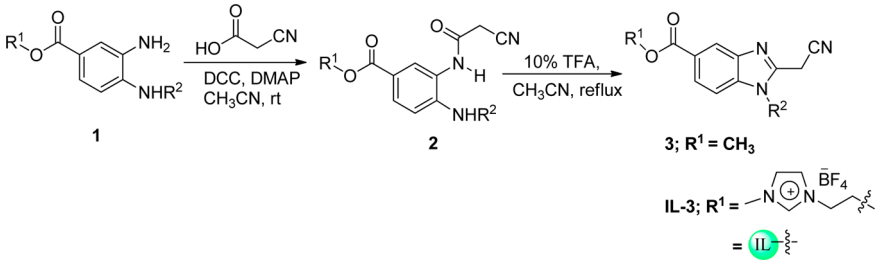
Unexpected formation of PBI **7** is the result of participation of solvent, 1,2-dichloroethane, in the reaction. Nucleophilic displacement of a chloride from $ClCH_2CH_2Cl$ by the 2-cyanomethylbenzimidazole and subsequent β-elimination of HCl, then double bond isomerization generates azadiene **14** that on [4 + 1] cycloaddition with an isocyanide and aromatization yields PBI **7** (Scheme 4).

To avoid solvent interference, we studied the same one pot transformation in various organic solvents, such as MeOH, IPA, THF, toluene, ACN, and DMF. The reactions did not progress well in MeOH, IPA, DMF, and THF. However, only moderate improvements in the yield (~40%) were achieved in either toluene or ACN. This led us to study this MCR in conventional stepwise manner. The piperidine catalyzed Knoevenagel condensation of 2-cyanomethylbenzimidazole **3**{*1*} with methyl 2-formylbenzoate in toluene at room temperature gave *s-trans*-azadiene **9**{*1,1*} in very good yields. The *s-trans* conformation of **9**{*1,1*} in both liquid and solid state were assigned unambiguously by NOE analysis and single crystal X-ray studies respectively (Figure 1). Irradiation of olefinic proton at δ 8.76 led to 2% enhancement in the signal for the methylene protons at δ 4.65 of 3-methoxypropyl substituent on benzimidazole to confirm their special vicinity and *s-trans* geometry of the diene. Such NOE enhancement is clearly not possible in *s-cis* confirmation.

The azadiene **9**{*1,1*} was then treated with benzyl isocyanide **5**{*2*} to minimize the steric influence of R^3 on lactamization. Sealed tube heating of **9**{*1,1*} and benzyl isonitrile **5**{*2*} in toluene at 180 °C for 12 h with piperidine by a telescoped reaction approach gave benzimidazoisoquinolinone **6**{*1,1,2*} along with PBI **16** as a result of reaction of piperidine with the ester carbonyl group. The formation of PBI **16** was eliminated by performing the reaction without piperidine which gave an improved 60% yield of **6**{*1,1,2*}. To achieve better *cis*−*trans* isomerization and overall conversion, we turned to microwave activation that produces an effective and uniform heating. Microwave irradiation at 150 °C gave better isolated yield of 70% as well as reduced reaction time to only 15 min (Scheme 5).

Knowledge of synergy of ionic liquid (IL)-support with microwave heating to speed up isolation and purification of products by precipitation and solvent washing motivated us to study reactions of IL-bound 2-cyanomethylbenzimidazoles.[2,13] Room temperature condensation of IL-bound 2-cyanomethyl-bemzimidazole **IL-3**{*1*} with 2-formyl benzoate in CH_3CN using piperidine catalyst gave IL-bound *s-trans*-azadiene IL-**17**{*1,1*}.

Scheme 1. Synthesis of 2-(Cyanomethyl)-*N*-alkyl Benzimidazoles



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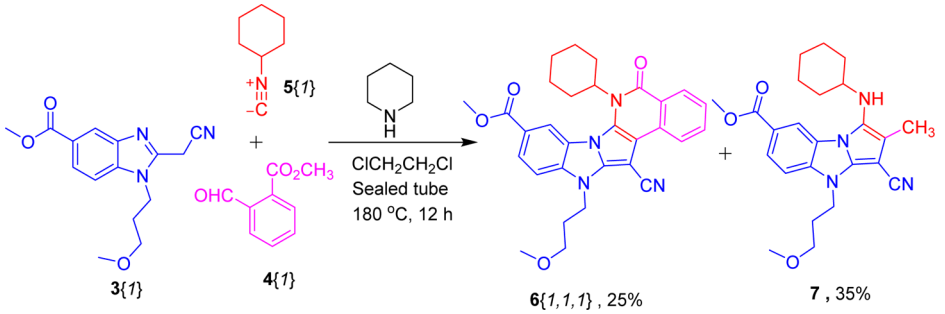
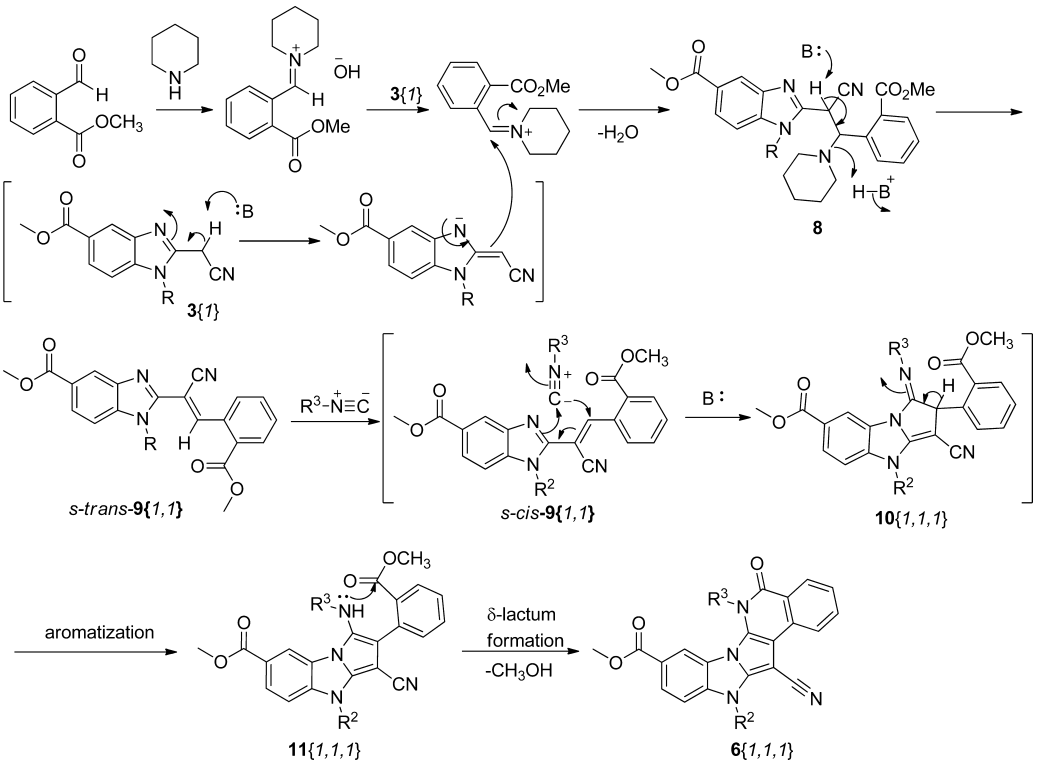
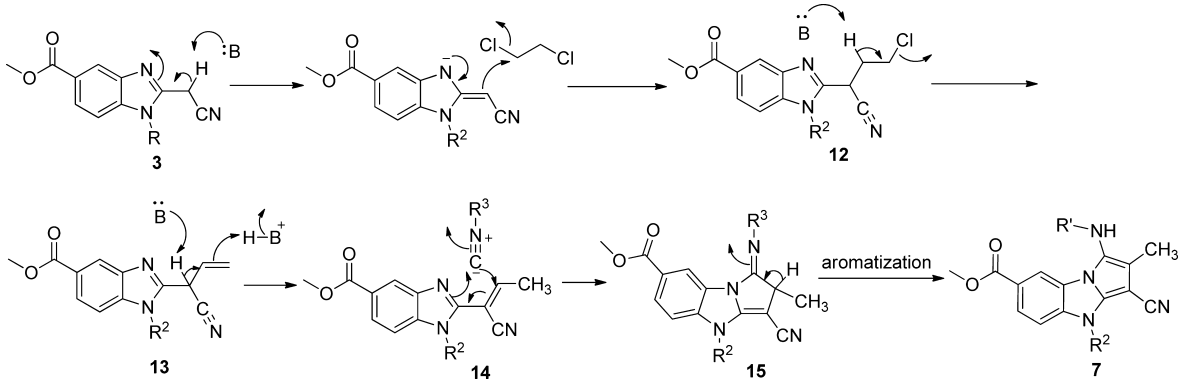
Scheme 2. Synthesis of Benzimidazo[1′,2′:1,5]pyrrolo[2,3-*c*]isoquinolinones



Scheme 3. Plausible Mechanism for the Cascade Reaction



Scheme 4. Plausible Mechanism for the Formation of PBI 7



Benzyl isocyanate was added to CH_3CN solution of azadiene IL-**17**{*1,1*} and heated with microwave irradiation at 150 °C for 15 min. The reaction mixture was then treated with KCN/methanol to remove IL-support which afforded a 76% of BPI **6**{*1,1,2*} after flash column purification (Table 1, entry 2).

Delighted with this observation, we treated a number of IL-bound 2-cyanomethylbenzimidazoles with methyl 2-formyl

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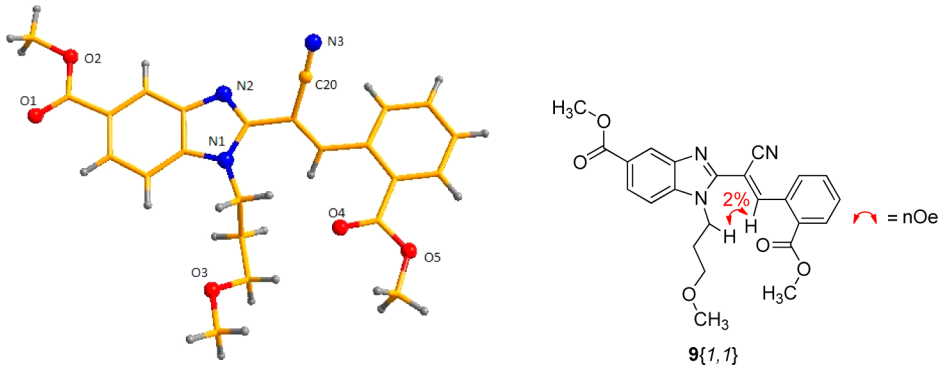
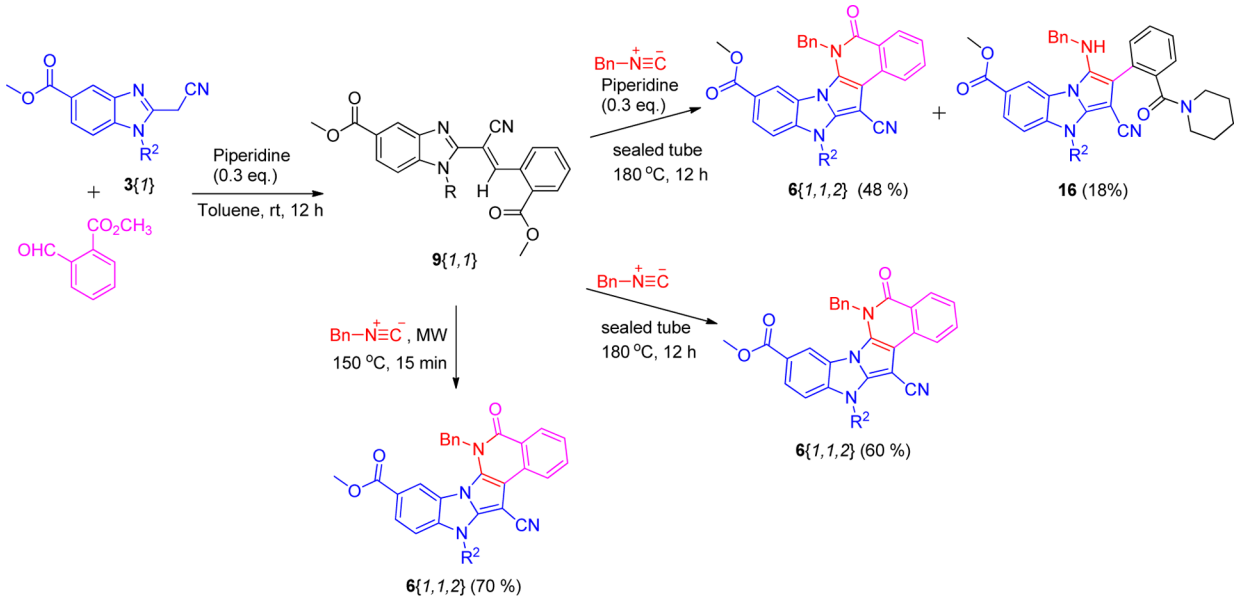


Figure 2. X-ray crystal structure for *s-trans*-azadiene **9**{*1,1*}.

Scheme 5. Synthesis of Benzimidazo[1′,2′:1,5]pyrrolo[2,3-*c*]isoquinolines



benzoate and various isonitriles by this two-step protocol (Figure 3). Various *N*-alkyl substitutents (R^2) on benzimidazole were abided and good yields of products were obtained with reactive heteroaromatic 2-furyl, 2-thiofuryl, endocyclic olefin and ether function on R^2 intact. As expected the yields with benzyl isocyanide were better than that of cyclohexyl or isopropyl isonitriles. The slightly lower yields with pentyl isocyanide may be result of steric factors associated with flexible alkyl chain. The planar pentacyclic structure of **6**{*1,1,1*} was confirmed by single crystal X-ray diffraction studies (Figure 4).

In conclusion, we have developed a short and rapid synthesis of novel benzimidazole-fused pentacyclic azaheterocycles. The two step protocol includes Knoevenagel condensation of 2-cyanomethylbenzimidazole with an aldehyde to deliver azadiene. These adducts undergo cis−trans isomerization, [4 + 1] cycloaddition with an isocyanide, aromatization, and δ-lactam formation reaction cascade on microwave activation.

EXPERIMENTAL SECTION

General Procedure for Reaction of IL-Bound 2-Cyanomethyl Benzimidazoles. Methyl 2-formylbenzoate (0.22 g, 1.32 mmol) and piperidine (13 μL, 0.13 mmol) were added to a solution of IL-bound 2-(cyanomethyl) benzimidazole IL-**3**{*1*} (0.17 g, 0.44 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at ambient temperature for 12 h. After completion, the reaction mixture, the precipitate was washed with cold ether (20 mL × 3). The precipitate was filtered and dried well to furnish the IL-bound (*E*)-methyl 2-(1-cyano-2-(2-(methoxycarbonyl) phenyl)vinyl)-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **IL-17**{*1,1*} in excellent yield. **IL-17**{*1,1*} was then treated with cyclohexyl isocyanide (164 μL, 1.30 mmol) in acetonitrile under MW (150 °C) irradiation for 15 min. After completion of the reaction, the precipitate was washed with ether (20 mL × 3) and dried to yield IL-bound benzimidazopyrroloisoquinolinone that was dissolved in methanol (10 mL) and KCN (0.1 g) was added to the solution. The reaction mixture was stirred for 12 h. After the reaction completed, the precipitated ionic liquid was recovered by filtration and reused. The filtrate was concentrated and the crude product was purified by flash column chromatography to remove traces aliphatic impurities to yield methyl 5-cyano-12-cyclohexyl-6-(3-methoxypropyl)-13-oxo-12,13-dihydro-6*H*-benzimidazo[1′,2′:1,5]pyrrolo[2,3- *c*]isoquinoline-9-carboxylate **6**{*1,1,1*} (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41−8.36 (m, 3H), 8.18 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.73−7.68 (m, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 4.52 (t, *J* = 6.6 Hz, 2H), 4.36 (m, 1H), 4.00 (s, 3H), 3.45 (t, *J* = 5.7 Hz, 2H), 3.35 (s, 3H), 3.11−2.98 (m, 2H), 2.33−2.24 (m, 2H), 2.06−1,92 (m, 4H), 1.84−1.70 (m, 2H), 1.63−1.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 163.6, 143.6, 140.4, 133.4, 132.6, 129.3, 127.4, 126.5, 126.5,

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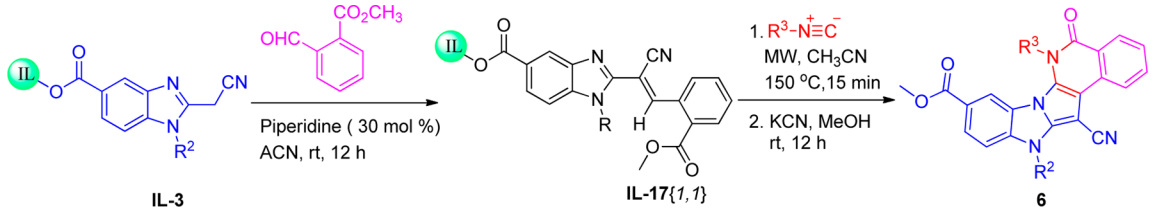
Table 1. Results of two step 3-CR cascade reactions[a]



entry	product	yield (%)[b]
1	**6**{*1,1,1*}	67
2	**6**{*1,1,2*}	76
3	**6**{2,1,1}	70
4	**6**{*2,1,3*}	61
5	**6**{*2,1,2*}	73
6	**6**{*3,1,1*}	68
7	**6**{*3,1,2*}	78
8	**6**{*4,1,1*}	67
9	**6**{*4,1,2*}	82
10	**6**{*4,1,3*}	62
11	**6**{*4,1,4*}	55
12	**6**{*5,1,1*}	73
13	**6**{*5,1,2*}	89
14	**6**{*5,1,3*}	67
15	**6**{*5,1,4*}	46
16	**6**{*6,1,2*}	74
17	**6**{*7,1,1*}	72
18	**6**{*7,1,2*}	82
19	**6**{*7,1,3*}	57
20	**6**{*8,1,1*}	68

[a]All reactions were performed using 0.44 mmol benzimidazole **IL-3**, 1.32 mmol methyl2-formylbenzoate, and 1.30 mmol isonitrile. [b]Overall yield of isolated product.

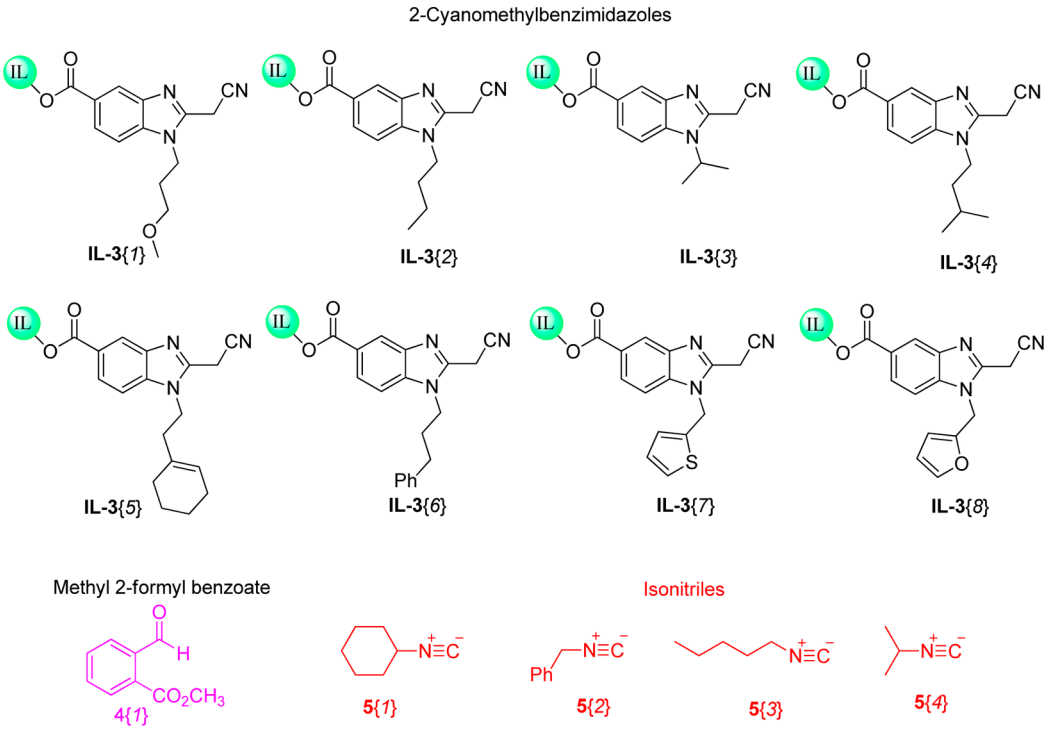


Figure 3. Substrate scope of the reactions.

125.5, 124.3, 123.1, 121.8, 117.5, 115.1, 109.3, 107.4, 68.9, 63.0, 59.1, 58.7, 52.8, 41.6, 30.0, 29.5, 26.4, 25.4. IR (cm^{-1}, neat): 2929, 2200, 1718. MS (EI-MS): 510.3. HRMS (EI) calcd. for $C_{30}H_{30}N_4O_4$ *m/z*: 510.2267; found 510.2258 (M^+).

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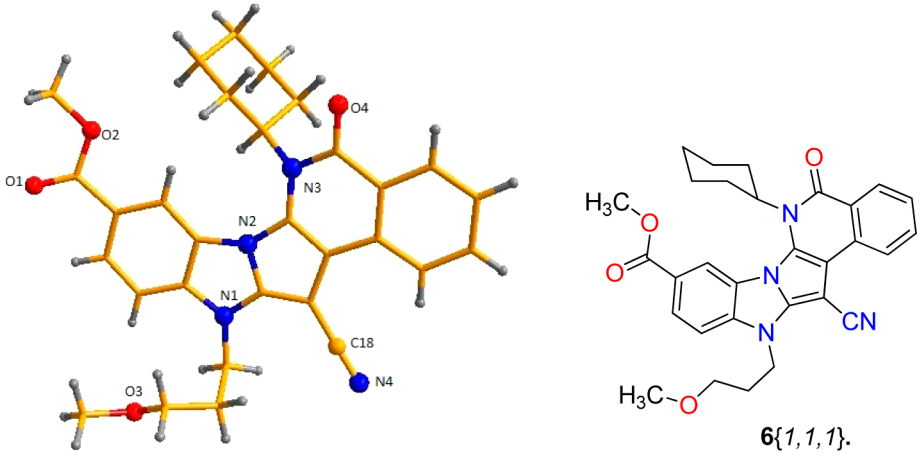

Figure 4. Single crystal X-ray structure of BPI **6**{*1,1,1*}.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, procedure for synthesis of **1**, **IL-3**, and **6**, and ^{1}H and ^{13}C NMR, IR, LRMS, and HRMS spectral data and spectra for **6**, **9**{*1,1*}, and **16**. 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

The authors wish to thank the National Science Council 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.

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