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One-Pot, Two-Step Synthesis of Imidazo[1,2-*a*]benzimidazoles via A Multicomponent [4 + 1] Cycloaddition Reaction

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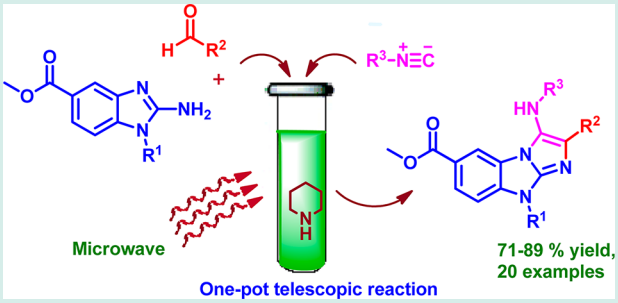
Supporting Information

ABSTRACT: A one-pot, two-step synthesis of imidazo[1,2-*a*]benzimidazoles has been achieved by a three-component reaction of 2-aminobenzimidazoles with an aromatic aldehyde and an isocyanide. The reaction involving condensation of 2-aminobenzimidazole with an aldehyde is run under microwave activation to generate an imine intermediate under basic conditions which then undergoes [4 + 1] cycloaddition with an isocyanide.



KEYWORDS: *microwave irradiation, [4 + 1] cycloaddition, imidazo[1,2-a]benzimidazoles, three-component reaction*

INTRODUCTION

Benzimidazoles are well established as "privileged scaffolds", since a large number of these molecular frameworks show interesting biological activities and are often part of various pharmaceutical compositions.[1] Imidazo[1,2-*a*]benzimidazoles, the fused tricyclic derivatives of benzimidazoles are also known for their medicinal properties. For example, tricyclic N-fused amino benzimidazoimidazole **I** shows anticancer activity by inhibition of topoisomerase IIα.[2] Other active compounds include antianxiety agent **II** and neuropsychotic compound **III** among few other medicinally important molecules of this class (Figure 1).[3,4]

In addition, these skeletons allow easy scaffold hopping with various bioactive molecules to permit diversity oriented synthesis of molecular libraries for further drug development.[5] Benzimidazoles are suitable substrates for synthesis of various polycyclic N-heterocycles. Commonly studied benzimidazole fused polycyclic heterocycles includes benzimidazo[1,2-*a*]-quinolines,[6] pyrrolo[1,2-*a*]benzimidazoles,[7] pyrido[1,2-*a*]-benzimidazoles,[8] pyrimido[1,2-*a*]benzimidazoles,[9] benzo[4,5]-imidazo[2,1-b]thiazoles,[10] and imidazo[1,2-*a*]-benzimidazoles.[2−4] However, common synthetic routes for various functionalized benzimidazo[1,2-*a*]imidazoles are rare in the literature, consequently, they are relatively less studied.

We have earlier reported a soluble polymer-supported regioselective synthesis of imidazo[1,2-*a*]benzimidazoles.[11] A similar protocol was used by Han and co-workers for the synthesis and SAR studies of imidazo[1,2-*a*]benzimidazoles as corticotrophin-releasing factor 1 receptor antagonists.[3] Langer et al. synthesized 2-aminoimidazo[1,2-*a*]imidazoles by [3 + 2] cycloaddition of dilithiated 2-methylbenzimidazole and oxaldiimidoyl dichlorides.[12] Hence, a simple strategy that allows the synthesis of substituted imidazobenzimidazoles is required for the study of biological and medicinal properties associated with this molecular framework.

Multicomponent reactions (MCRs) are reactions in which three or more components react to produce complicated molecules with high atom economy by incorporating all the starting materials. MCRs are cost and time effective as they produce desired products in good yields under simple and mild reaction conditions. These synthetic methods provide quick access to diverse molecular structures that are often very difficult to synthesize by conventional methods.[13] Additionally, the products of a MCR can be easily utilized as synthetic hub for diverse structures by incorporating orthogonal functional group into the starting materials that subsequently can be used in further transformations. Isocyanides are widely used substrates for multicomponent reactions, such as Passenini, Ugi, Groebke−Bienaymé−Blackburn, Orru, and Van Leusen reactions.[13a,14] Several variations of these reactions are widely used to afford scaffold diversity in the design of biologically active molecules. These reactions share a unique characteristic, that is, attack of isocyanide on a carbonyl function or an imine followed by subsequent transformations. MCRs are often aided by microwave activation as uniform heating and rapid transformation rate makes the process cleaner and more energy efficient.[15]

With this knowledge and our interest in development of novel multicomponent reactions utilizing benzimidazoles directed toward synthesis of biologically interesting polyheterocycles, we designed a three component reaction of 2-aminobenzimidazoles for synthesis of imidazobenzimidazoles.

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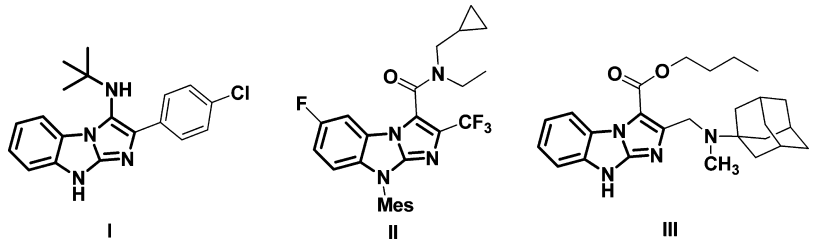
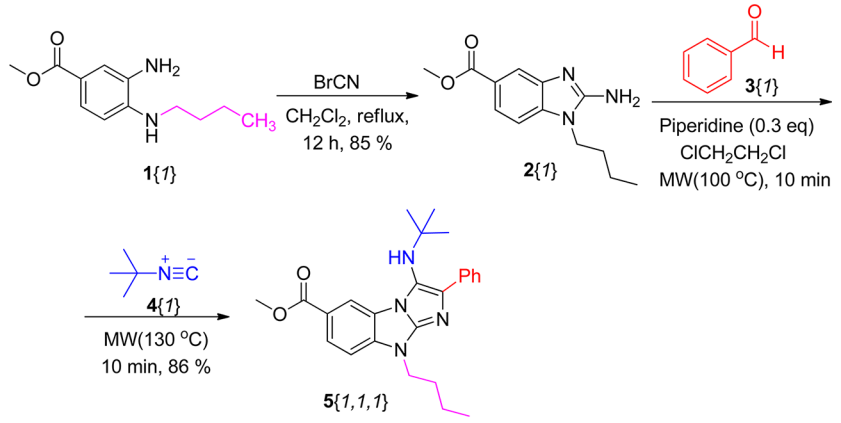
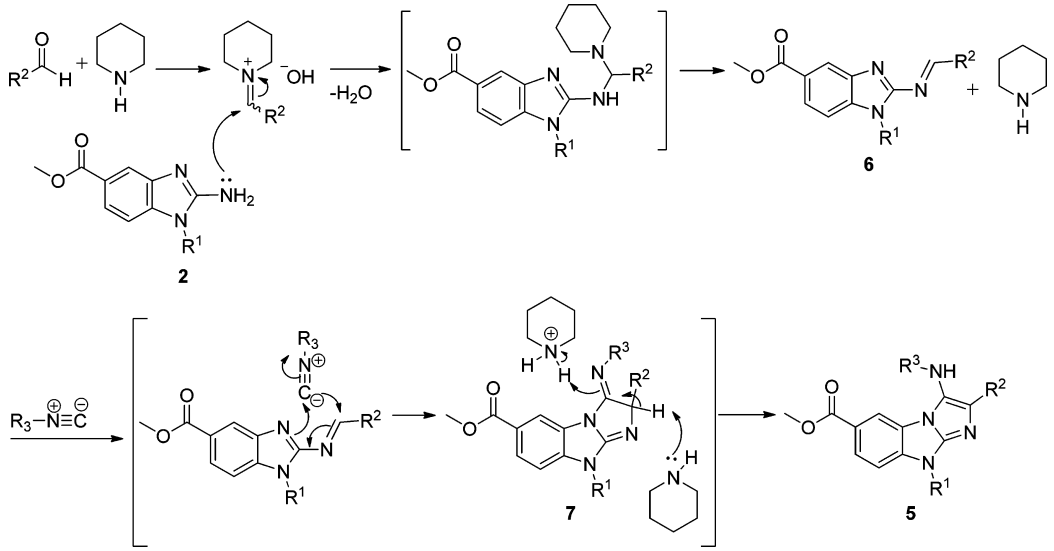


Figure 1. Biologically active imidazolo[1,2-*a*]benzimidazoles.

Scheme 1. Synthesis of Imidazo[1,2-*a*]benzimidazole



Scheme 2. Plausible Mechanism for Multicomponent [4 + 1] Cycloaddition



RESULT AND DISCUSSION

Our exploration starts with the synthesis of various *N*-alkyl-2-aminobenzimidazoles To obtain various *N*-alkyl-2-amino-benzimidazoles, we reacted methyl 4-fluoro-3-nitrobenzoate with various alkyl amines followed by reduction to the intermediate diamine **1**{*1*}. Reaction with cyanogen bromide afforded the 2-aminobenzimidazole **2**{*1*} in good yields (Scheme 1).[11,17]

The model study for the multicomponent reaction was performed on 2-amino-1-butylbenzimidazole **2**{*1*}, with benzaldehyde **3**{*1*} and *t*-butylisocyanate **4**{*1*} as the other reactants in dichloromethane. The reaction using catalytic amount of piperidine (0.3 equiv) under microwave irradiation at 100 °C for 10 min yielded the desired imidazo[1,2-*a*]benzimidazole **5**{*1,1,1*} in 47% yield. The reaction analysis revealed presence of unreacted starting materials. Mechanistically, the reaction proceeds via initial condensation of aldehyde with the free amine of 2-amino-1-butyl-benzimidazole **2**{*1*} to generate imine **6**{*1,1*}. Piperidine catalyzes the reaction by forming an iminium hydroxide intermediate with benzaldehyde that on nucleophilic attack of 2-amino-1-butyl-benzimidazole **2**{*1*} delivers imine **6**{*1,1*} with liberation of piperidine and water.[17] Imine **6**{*1,1*} is expected to exist in s-cis conformation for cycloaddition reactions, as in the s-trans conformation, there will be steric repulsion between R^1 and olefinic proton of imine double bond. Attack of reactive isocyanide carbon on imino carbon of *s-cis*-**4** initiates stepwise [4 + 1] cycloaddition to yield

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Table 1. Optimization of [4 + 1] Cycloaddition Reaction

entry	solvent	temperature	time	yield of 5{1,1,1} (%)[a]
1	CH_2CI_2	MW, 100 °C	10 min	43[b]
2	CH_2CI_2	MW, 100 °C	10 min	72
3	DCE	MW, 100 °C	10 min	88
4	THF	MW, 100 °C	10 min	60
5	toluene	MW, 100 °C	10 min	80
6	CH_3CN	MW, 100 °C	10 min	76
7	DMF	MW, 100 °C	10 min	72
8	DCE	MW, 110 °C	10 min	77
9	DCE	MW, 120 °C	10 min	84
10	DCE	MW, 130 °C	10 min	86
11	DCE	MW, 140 °C	10 min	77
12	DCE	MW, 150 °C	10 min	74
13	DCE	Sealed tube, 100 °C	12 h	20
14	DCE	Sealed tube, 130 °C	12 h	75
15	DCE	Sealed tube, 150 °C	12 h	60

[a]All reactions were performed using 1.0 mmol 6{1,1}imine, 1.1 mmol f-butyl isonitrile, 0.3 mmol piperidine in 5 mL of CH_2CI_2 solvent. [b]No piperidine base was added.

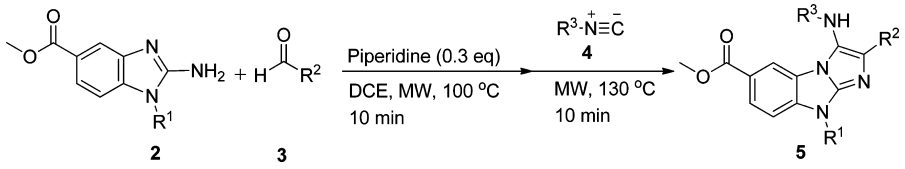
exocyclic imine intermediate **7** that aromatizes to deliver the observed tricyclic product, imidazo[1,2-*a*]benzimidazole **5** (Scheme 2).

Absence of imine in the reaction mixture as suggested by lack of olefin proton signal at 9.60 ppm in ^{1}H NMR spectrum clearly indicates that the success of this reaction is determined by formation and reactivity of an imine **6** under reaction conditions. This led us to study the conventional stepwise reaction over one-pot MCR.

The imine 6{1,1} was synthesized and isolated using piperidine as a catalyst under microwave heating at 100 °C for 10 min.[17] Preliminary studies on the [4 + 1] cycloaddition reaction were performed with imine 6{1,1} and *t*-butylisocyanate 4{1} (Table 1). The reaction of 6{1,1} and *t*-butylisonitrile in dichloromethane under microwave heating gave 43% of imidazo[1,2-*a*]benzimidazole 5{1,1,1} (entry 1) along with considerable amount of hydrolysis of unstable imine 6{1,1}. With knowledge of higher stability of imines **6** under the basic conditions of piperidine, a small amount of piperidine (0.3 equiv) was added to the reaction mixture that enhanced the yields of imidazo[1,2-*a*]benzimidazole 5{1,1,1} up to 70%. A quick screening for solvent and temperature optimization indicated that the best reaction condition by microwave heating is 130 °C for 10 min in dichloroethane. The reaction also progressed well under conventional heating in a sealed tube but required 12 h for good conversion to occur at 130 °C (entries 7–9).

A telescoped reaction involves sequential addition of reagents, one at a time without any workup in a multistep or multicomponent reaction.[16] This considerably reduces the number of purification processes often boosting reaction outcome. We performed our reaction by a telescoped approach. Condensation of 2-amino-1-butylbenzimidazole 2{1} with benzaldehyde under microwave heating in the presence of piperidine at 100 °C for 10 min and subsequent addition of *t*-butylisocyanide for further 10 min heating at 130 °C yielded imidazo[1,2-*a*]benzimidazole 5{1,1,1} in 86% yield. Delighted with this observation, we explored this telescopic transformation with different aromatic aldehydes and isonitriles

Table 2. Results of Telescopic One Pot 3-CR [4 + 1] Cycloaddition Reaction[a]



2 3 5

entry	product	yield (%)[a]	LRMS[b]	clogP[c]
1	5{1,1,1}	86	419	7.623
2	5{1,2,3}	83	490	8.183
3	5{1,2,2}	88	478	8.32
4	5{1,3,3}	73	451	7.69
5	5{2,1,3}	78	431	8.86
6	5{2,4,3}	80	481	7.12
7	5{2,5,1}	71	449	6.33
8	5{2,6,3}	89	476	8.62
9	5{2,7,3}	81	456	6.00
10	5{2,7,1}	77	430	6.35
11	5{2,8,3}	85	499	6.51
12	5{3,2,1}	86	480	8.25
13	5{3,2,2}	75	494	7.11
14	5{3,7,3}	84	486	5.74
15	5{3,4,3}	80	511	6.84
16	5{3,5,3}	77	505	9.21
17	5{4,7,1}	77	472	8.70
18	5{4,2,3}	83	518	8.26
19	5{5,2,3}	80	542	9.05
20	5{5,2,4}	82	550	8.57

[a]Isolated yields. [b]LRMS was recorded by ESI ionization method. [c]Estimated clogP by ChemBioOffice 2010.

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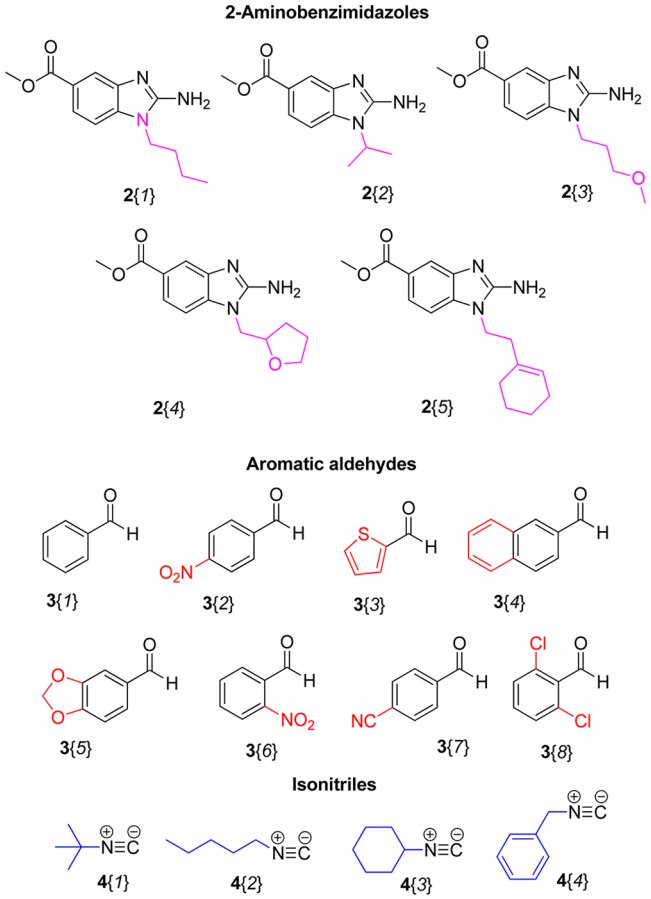

Figure 2. Substrate scope of the reaction.

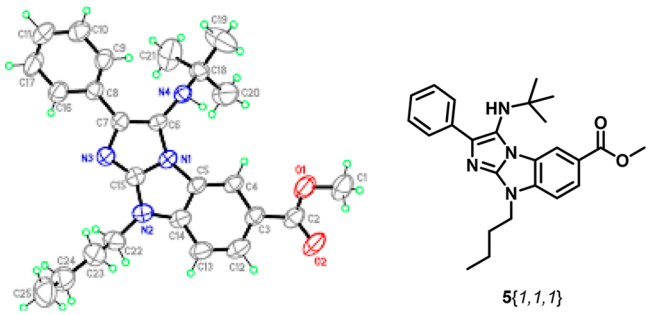

Figure 3. ORTEP diagram for X-ray crystal structure of **5**{*1,1,1*}.

under the optimized conditions. The results of our study are summarized in Table 2.

The effect of various substituents on benzimidazole nitrogen (R^1) was studied. Additional functional groups on R^1 such as ethers or endocyclic olefins were found to have no effect on the reaction output and comparable yields were obtained in all cases. The reaction worked very well with various aromatic aldehydes containing either electron withdrawing or electron donating groups. Heteroaromatic thiophene-2-aldehyde also reacted to give the cycloaddition product in good yield (entry 3d). A bulky (*t*-butyl, cyclohexyl) or linear (pentyl) substituents on isonitrile also had no effect on yields of the reaction possibly due to their remoteness from the reaction center. Thus, tolerance of the reaction to various substituents on each of the three reactants was studied. X-ray crystallographic analysis of product **5**{*1,1,1*} (R^1 = *n*-butyl, R^2 = Ph, and R^3 = *t*-butyl) confirmed its unique fused tricyclic ring system (Figure 3).

Importantly, the design of our present library is relying on the structure based approach where the basic skeleton imidazo[1,2-*a*]benzimidazole was adapted from the medicinally important scaffolds.[2−4] The calculated clogP (5.74−9.21) values for our library are very well matched with that of reported bioactive molecules of this class.[2−4] The clogP values for imidazo[1,2-*a*]benzimidazoles **I**, **II**, and **III** are 6.70, 7.17, and 6.29, respectively (Figure 1). The clogP values for **5**{*3,7,3*}, **5**{*2,7,3*}, and **5**{*2,5,1*} are 5.74, 6.00, and 6.33, respectively, which make them good candidates for further bioactivity study.

In conclusion, we have developed an efficient one-pot, two-step, multicomponent reaction for the synthesis of biologically interesting imidazo[1,2-*a*]benzimidazoles. Use of microwave irradiation effectively accelerates the reaction to proceed in short reaction times. The versatility and utility of this protocol is demonstrated for a variety of substituents on each of three reaction components. This simple, rapid, and efficient transformation is expected to enhance study of biological properties associated with these fused hetero tricyclic molecules.

EXPERIMENTAL PROCEDURES

Representative Procedure for Microwave Assisted Three Component Reaction. To a dichloroethane solution of **2**{*1*} (192 mg, 1.0 mmol) in a microwave absorbance vessel was added benzaldehyde (102 μL, 1.0 mmol) and piperidine (30 μL, 0.3 mmol). The reaction mixture was irradiated under microwave radiations (100 °C) for 10 min. The reaction mixture was cooled to room temperature, *t*-butylisocyanide (124 μL, 1.1 mmol) was added subsequently and reaction mixture was irradiated again for further 10 min at 130 °C. The solvent was removed by rotary evaporation and the product was purified by column chromatography to obtain **5**{*1,1,1*} (360 mg, 86% yield).

Methyl 9-Butyl-3-(tert-butylamino)-2-phenyl-9H-imidazo-[1,2-a]benzimidazole-6-carboxylate ***5****{1,1,1}*. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 1.4 Hz, 1H), 8.00 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.91 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.27−7.24 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 3.97 (s, 3H), 3.17 (s, 1H), 1.92 (quint, *J* = 7.5 Hz, 2H), 1.50−1.37 (m, 2H), 1.10 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 146.3, 139.5, 137.9, 136.1, 128.6, 128.1, 126.9, 125.1, 125.0, 123.2, 121.5, 113.7, 108.8, 56.7, 52.6, 43.2, 31.0, 30.5, 20.6, 14.1. IR (cm^{-1}, neat): 3332, 1714, 1277. MS (ESI) *m*/*z*: 419. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{31}N_5O_2$ $[M + H]^+$: 419.2447. Found: 419.2443.

ASSOCIATED CONTENT

Supporting Information

Further details are given about the experimental procedures and ^{1}H and ^{13}C NMR spectra of all the compounds; X-ray structure CIF file for **5**{*1,1,1*}. 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.

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