A green, scalable, one-minute synthesis of benzimidazoles

Received:

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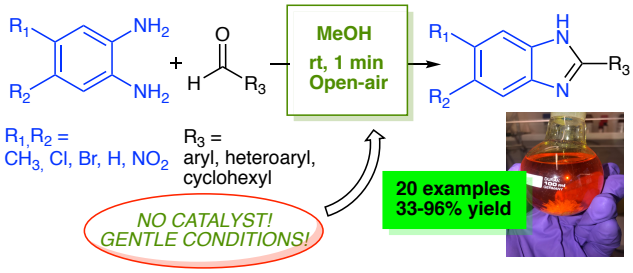


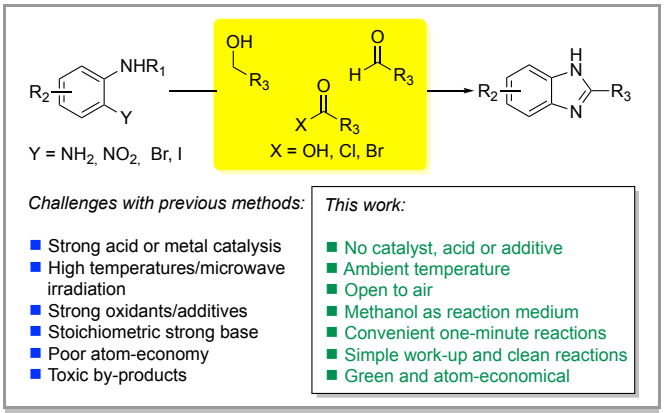
Accepted:
Published online:
DOI:

Abstract Herein is reported a substantially improved synthesis of 2-substituted benzimidazoles by condensation of 1,2-diaminoarenes and aldehydes using methanol as the reaction medium. The developed method afforded moderate to excellent yields (33-96%) at ambient temperature, displays high functional group tolerance, is conducted open to air, and requires only one-minute reaction time under catalyst- and additive-free conditions. Moreover, the efficient protocol permits scale-up to multi-gram scale synthesis of benzimidazoles and will become a method of choice when constructing such heterocyclic systems.

Key words Benzimidazoles. Green synthesis. Rapid condensation. Heterocyclization. 1,2-diaminoarenes. Catalyst-free

Introduction

Benzimidazole is a central heterocyclic structural motif in numerous natural products and a crucial building block in several drug candidates[1]. Benzimidazoles display a range of interesting biological properties such as, anti-viral,[2] anti-cancer,[3] anti-bacterial,[4] anti-inflammatory,[5] anti-fungal,[6] anti-ulcer,[7] anti-hypertensive[8] activities. Chemical methods for generating benzimidazoles are numerous in the literature going back as far as 140 years (Scheme 1).[9] Among them, a classical approach involving condensation of diamines and aldehydes is one of the most common methods for the synthesis of 2-substituted benzimidazoles. These reactions are typically conducted at high temperatures over several hours or days at reflux,[10] and in the presence of an added Lewis or Brønsted acid catalyst,[11] metal catalyst[12,13] or photocatalyst.[14] Despite their efficiency, these methods still employ expensive catalysts, additives and require relatively long reaction times and harsh conditions. The development of even more efficient, environmentally benign and atom-economical methods is desired because of the versatile applications of the benzimidazole heterocycle. We have particularly utilized the condensation between aldehydes and 1,2-diaminobenzenes under catalyst- and additive-free conditions at ambient temperature and with very short reaction

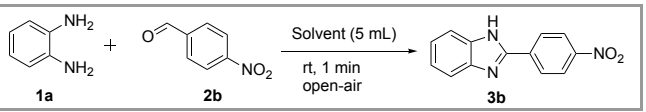


Scheme 1 Previous synthetic approaches and challenges

times. We are struggling to find reports of the use of milder conditions, even though that would be desirable, and are surprised that these mild conditions have not been reported earlier. In this letter, we report on the discovery of these extremely mild and green reaction conditions affording benzimidazoles in medium to excellent yields.

While investigating solvent effects on the benzimidazole formation between equimolar amounts of *o*-phenylenediamine **1a** and *p*-nitrobenzaldehyde **2b**, it was discovered that high conversion was achieved already a few minutes after mixing the reactants in many solvents at ambient temperature. A closer look revealed that one minute was sufficient reaction time to achieve full conversion of the starting materials. Concerning solvent effects (Table 1), no product could be observed when using water, whereas ethanol, dioxane and acetonitrile gave comparably good yields (GC-yields of 73%, 77% and 78% respectively). Methanol appeared to be a superior solvent for the reaction as 99% GC-yield was observed (entry 1) and was therefore further utilized as the medium for studying the generality of this approach. Adding an oxidant H_2O_2 (entry 4) did not change the outcome in an observable way. Doubling

Table 1 Influence of solvent, equivalency and oxidant on chemical yield of benzimidazole formation.



1a 2b 3b

Entry	Solvent	Yield (%)[a,b]
1	MeOH	99
2	EtOH	73
3	H_2O	0
4	MeOH	99[c]
5	Dioxane	77
6	MeCN	78
7	MeOH	88[d]
8	MeOH	73[e]
9	MeOH	64[f]

[a] Procedure: To a stirred solution of diamine **1a** in MeOH (5 mL/mmol), aldehyde **2b** was added and stirred at ambient temperature for 1 min.

[b] GC-yield.

[c] H_2O_2 (1mmol) was used as oxidant

[d] 2 equivalents of aldehyde (2 mmol) was used

[e] In a microwave vial (10 mL), diamine **1a** (1 mmol) and aldehyde **2b** (1mmol) was added and the tube was sealed and flushed with N_2. Degassed MeOH (5 mL) was added and the solution stirred at ambient temperature for 1 min.

[f] To a stirred solution of diamine **1a** (1 mmol) in MeOH (5 mL), aldehyde **2b** (1 mmol) and Na_2CO_3 (0.5 eq) was added and stirred at ambient temperature for 1 min.

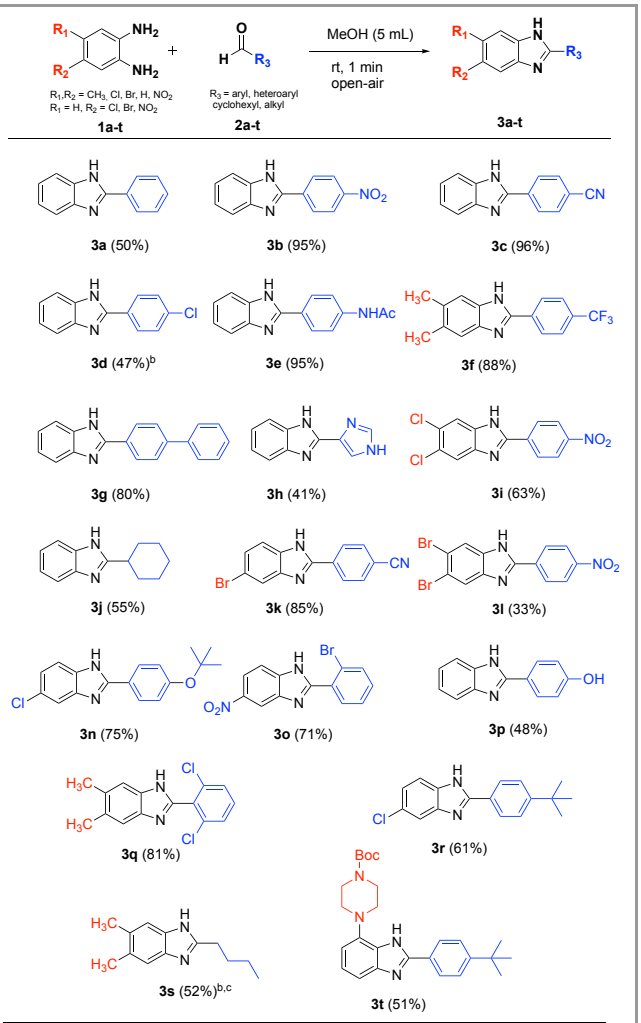
the equivalency of benzaldehyde led to a drop in the yield by 11%. These reaction conditions are remarkably simple and convenient (stir at room temperature and open to air) with a very short reaction time of only one minute.

The rapid rate of conversion to product observed in this reaction prompted us to conduct some control experiments to shed light on the chemistry. The standard reaction between **1a** and **2b** was conducted in a sealed tube under nitrogen atmosphere and with strictly degassed solvent (entry 8). A reduction in yield from 99% to 73% (GC-yield) was observed, thus demonstrating that oxygen is important for the performance of the reaction, likely in the oxidation of the saturated ring-closed intermediate. Another puzzling aspect of the reaction is the absence of an acid or metal catalyst, which is very commonly employed. Activation of the intermediate imine towards nucleophilic attack by the second aromatic amine is usually considered necessary. It is conceivable that small amounts of oxidized aldehydes could be present and effect acid catalysis. Addition of sodium carbonate in order to sequester any minute acid present in solution afforded diminished yield (64%) of **3b** (entry 9), which may suggest the reaction is enhanced by acid catalysis.

To study the generality of these conditions, a survey of reactions between available substituted phenylenediamines and aryl/alkyl aldehydes was conducted using the simple conditions found above. The short reaction time of one minute was kept constant in order to demonstrate the rapid reaction performance even though there may be examples where conversion was not complete. In the case of unsubstituted phenylenediamine reacting with several *p*-substituted benzaldehydes, moderate to excellent yields were achieved (Scheme 2). Particularly high yields were obtained for *p*-nitro- (**2b**), *p*-cyano- (**2c**) and *p*-acetamido- (**2e**) substituted benzaldehydes (95-96% yields of **3b**, **3c** and **3e**). The reaction with benzaldehyde **2a** afforded 50% yield of **3a** and it was shown by GC-MS that the main remainder was the *N*-alkylated 1,2-disubstituted benzimidazole – a known by-product in this synthesis. In the case of *p*-chlorobenzaldehyde **2d** a moderate 47% yield was obtained of the expected benzimidazole **3d**. GC-MS analysis of the reaction mixture revealed that the *N*-4-chlorobenzyl-1,2-substituted benzimidazole was formed with 45% conversion (GC). The *N*-benzylated by-products likely arise from double imine formation and followed by a Cannizzaro-like hydride transfer to saturate the benzylic carbon.[15] The *p*-hydroxybenzaldehyde **2p** afforded moderate 48% yield of benzimidazole **3p**. Here, the unreacted starting material was the majority of the remainder. The heterocyclic aldehyde **2h** gave moderate 41% yield of the desired product **3h**. The *p*-phenyl benzaldehyde **2g** gave high yield of benzimidazole **3g** (80%). Aliphatic aldehydes were also demonstrated to work in the reaction through cyclohexyl aldehyde **2j** which afforded the 2-cyclohexylbenzimidazole **3j** in 55% yield. In case of linear aldehyde **2s**, we obtained both the desired 2-substituted benzimidazole **3s** (52% NMR-yield) and 1,2-disubstituted benzimidazoles (in overall 78% yield).

Next, substituted phenylenediamines were tested with various aldehydes. A series of 4-substituted phenylenediamines with bromo– (**1k**), chloro- (**1n**) and nitro-(**1o**) substituents were employed with various aldehydes to generate substituted 2-arylbenzimidazoles **3k**, **3n**, **3o** and **3r** in very good yields (71-85%). Simultaneous variations on the aldehyde substituent reveals that the reaction is compatible with both π-donor (*t*-butoxy) and π-acceptor (cyano) substituents in the *para*-position of the aryl group, and even an *ortho*-bromo substituent was well tolerated. The 4,5-dimethyl substituted phenylenediamine gave high yields of **3f** (88%) and **3q** (81%) and shows compatibility with the electron-withdrawing trifluoromethyl group on the aldehyde. The *ortho*-disubstituted 2,6-dichlorobenzaldehyde demonstrates the steric tolerance at these positions. Markedly lower yields were obtained with the 4,5-dihalogenated phenylenediamines **1i** and **1l** which afforded the 2-(*p*-nitrophenyl) benzimidazoles **3i** and **3l** in 55% and 33% yields respectively. It has been assumed that lowered yields are mainly from unreacted starting materials or formation of the benzylated benzimidazole by-product. A more thorough analysis of the formation of **3l** revealed that the yield is likely low due to solubility issues with the reactants, and it did not improve the reaction yield with longer reaction times (1-25 min.) or increased temperature (rt-70°C). Finally, we have used a more complex diamine **1t** to generate 4-(*N*-Boc-piperazinyl) benzimidazole **3t** in 51% yield (Scheme 3). This represents a formal synthesis of a Gonadotropin-releasing hormone receptor antagonist.[16] The previously reported method required 48 hours under reflux, whereas our conditions yields the target benzimidazole **3t** in one-minute in good yield. Overall, the studies herein demonstrate that the remarkably practical and mild reaction conditions appear to be general for the reaction.

Based on the scope study, it was postulated that the reaction conditions could also favor similar heterocyclizations in

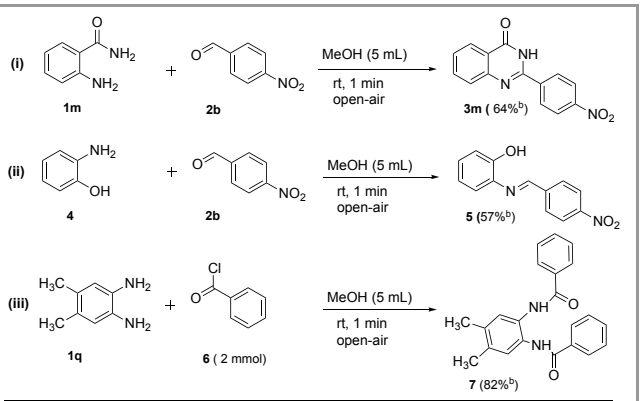


[a] Procedure: To a stirred solution of diamine 1a-t in MeOH (5 mL), aldehyde 2a-t was added and stirred at ambient temperature for 1 min.
[b] In addition to the desired product, *N*-alkyl substituted-1,2-disubstituted benzimidazole was observed as by-product (GC).
[c] NMR yield

Scheme 2 Synthesis of substituted benzimidazoles – scope and limitations.

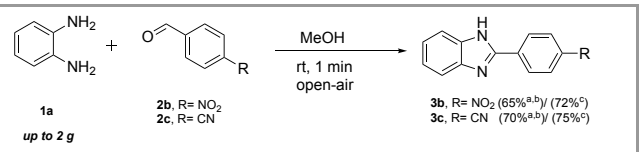
other dinucleophile systems reacting with aldehydes. Therefore, 2-aminobenzamide **1m** was employed as the dinucleophile source with *p*-nitrobenzaldehyde (Scheme 3i). The reaction afforded the quinazolinone **3m** in 64% isolated yield. This demonstrates that such simple reaction conditions can potentially be employed more generally or should at least be tested when similar condensations are conducted. A reaction between 2-aminophenol and 4-nitrobenzaldehyde afforded the imine **5** which could be isolated in 57% yield (Scheme 3ii). This observation supports that the first stage of the mechanism is likely imine formation. Furthermore, we tested the reaction conditions with carboxylic acid derivatives. No reaction occurred with phenylenediamine and benzoic acid whereas with benzoyl chloride **6** and diamine **1q** (Scheme 3iii), the reaction afforded diamide **7** in 82% yield. These could be important intermediates for various heterocyclic systems.[17]

In order to further probe the applicability of our reaction conditions, two reactions were conducted at up to 2 g scale. *p*-Nitro (**2b**) and *p*-cyanobenzaldehyde (**2c**) produced the anticipated benzimidazoles **3b** and **3c** in 65% and 70% isolated yields, respectively (Scheme 4). Both products were crystallized from the reaction mixture after work-up and did not require



[a] Procedure: (i) To a stirred solution of diamine 1m (1 mmol) in MeOH (5 mL), aldehyde 2b (1 mmol) was added and stirred at ambient temperature for 1 min. (ii) To a stirred solution of aminophenol 4 (1 mmol) in MeOH (5 mL), aldehyde 2b (1 mmol) was added and stirred at ambient temperature for 1 min. (iii) To a stirred solution of diamine 1q (1 mmol) in MeOH (5 mL), acid chloride 6 (1 mmol) was added and stirred at ambient temperature for 1 minute.
[b] Isolated-yield

Scheme 3 (i) Formation of quinazolinone from reaction with 2-aminobenzamide. (ii) Formation of imine in reaction with 2-aminophenol. (iii) Formation of bis-acylation product in the reaction with benzoyl chloride.

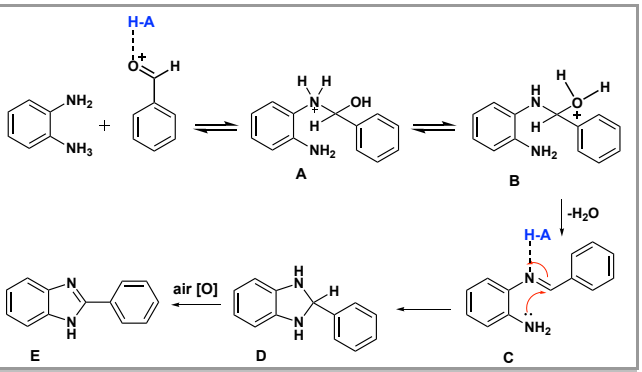


[a] Reaction Procedure: To a stirred solution of diamine 1 (18.5 mmol) in MeOH (50 mL), aldehyde 2b-c (18.5 mmol) was added and stirred at ambient temperature for 1 min. After the reaction time, H_2O (30 mL) was added and diluted with EtOAc (60 mL). The reaction solution was kept at room temperature for sometime. The crystals were slowly formed and finally filtered to obtain the desired benzimidazole derivatives 3b (dark-brown crystals) and 3c (yellow crystals).
[b] Isolated yield
[c] GC-yield was measured

Scheme 4 Multi-gram scale synthesis of benzimidazoles.

further purification. Although the yields are diminished compared to the small-scale reactions, they are still high. GC-MS analysis of the reaction mixture revealed that 72% of **3b** and 75% of **3c** were formed and the remainder was mainly unreacted substrates.

Based on literature studies and the experimental results, a mechanism is proposed for obtaining 2-arylbenzimidazoles as shown in Scheme 5. The first step involves the acid-catalysed condensation reaction between amine and aldehyde to form imine intermediate (C) via (B) by loss of water. Subsequent cyclization gives intermediate D, followed by air oxidation to obtain the observed product (E).



Scheme 5 A likely reaction mechanism with general acid catalysis.

In summary, we have re-discovered a classical heterocyclization reaction between phenylenediamines and aldehydes to generate

benzimidazoles utilizing extremely simple, practical and green conditions and without the explicit addition of acid- or metal catalyst. The simplicity of the conditions is remarkable and this should become a method of choice for *de novo* synthesis of a range of benzimidazoles.

Acknowledgment

The authors gratefully acknowledge funding for this work by the Research Council of Norway (Grant no. 275043 CasCat). The advanced *N*-Boc piperazinyl-substituted diamine **1t** was prepared and generously provided by Mr. Eirik A. L. Rustad.

Supporting Information

Electronic supporting information with detailed procedures, characterization data and NMR-spectra is available online. Representative procedures and characterization can be found in notes 18 and 19.[18,19]

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(18) **A Representative experimental procedure and characterization data: 2-([1,1'-biphenyl]-4-yl)-1H-benzo[d]imidazole (3g)**

In a RB-flask (25 mL), diamine **1g** (0.93 mmol) was dissolved in MeOH (5 mL). To the stirred solution, aldehyde **2g** (0.925 mmol) was added and stirred for 1 minute at ambient temperature. After the reaction time, the reaction was quenched with water (10 mL), diluted with ethyl acetate (50 mL), and washed with water (30 mL). The water layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was further isolated using flash chromatography [(EtOAc: Pentane, 20:80)] and afforded compound **3g** as a yellow solid (200 mg, 80%). R_f = 0.48 [(EtOAc:Pentane, 30:70)] ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.58 (s, 1H), 7.99 – 7.92 (m, 2H), 7.70 – 7.64 (m, 2H), 7.64 – 7.57 (m, 2H), 7.36 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.31 – 7.22 (m, 1H), 7.02 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.87 (td, *J* = 7.6, 1.4 Hz, 1H), 6.66 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.50 (td, *J* = 7.5, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 156.6, 144.7, 129.8, 129.7, 128.5, 128.3, 127.8, 127.6, 117.6, 117.5, 115.6. HR-MS Calcd $(M+H)^+$ for $C_{19}H_{15}N_2^+$ 271.1230; Found 271.1232.

(19) Gram-Scale Synthesis of 2-(4-nitrophenyl)-1*H*-benzo[d]imidazole (3b)

In a RB-flask (250 mL), benzene-1,2-diamine **1b** (2.00 g, 18.5 mmol) was dissolved in MeOH (50 mL). To the stirred solution, 4-nitrobenzaldehyde **2b** (2.80 g, 18.5 mmol) was added and stirred for 1 minute at ambient temperature. After the reaction time, the reaction was quenched with water (40 mL) and diluted with ethyl acetate (50 mL). After a while, crystals were formed in the reaction mixture at room temperature. The crystals were filtered and dried to obtain the compound **3b** (2.85 g, 65%) as a dark-brown crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.40 – 8.30 (m, 2H), 8.34 – 8.22 (m, 2H), 7.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.03 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 6.76 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.63 – 6.53 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.5, 148.3, 144.9, 142.4, 133.9, 129.4, 128.8, 123.9, 117.0, 116.0, 115.1. HR-MS Calcd $(M-H)^-$ for $C_{13}H_8N_3O_2^-$ 238.0622; Found 238.0623