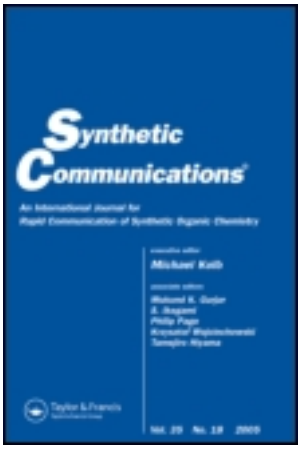


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# Synthesis of 2-Alkyl-Substituted Benzimidazoles by Thermal Decomposition of 2-Azidobenzenamines in thePresence of an Aldehyde

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# Synthesis of 2-Alkyl-Substituted Benzimidazoles by Thermal Decomposition of 2-Azidobenzenamines in the Presence of an Aldehyde

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**Abstract:** 2-Substituted benzimidazoles were prepared by reaction of 2-azidoaminobenzenes with aldehydes under thermal conditions. The reaction probably proceeds via a sequential imine formation, azide decomposition forming a nitrene, and electrocyclization.

**Keywords:** Alkaloids, azide, benzimidazole, nitrene

## INTRODUCTION

Thermal decomposition of organic azides is known to produce highly reactive nitrene intermediates. The nitrenes subsequently undergo a variety of reactions including carbon-hydrogen bond insertions and electrocyclic reactions forming nitrogen-containing heterocycles.[1] Thermolysis of imines formed from 2-azidobenzenamines and aromatic aldehydes has been shown to produce 2-aryl-substituted benzimidazoles.[2,3] In a related fashion, indazoles, indoles, and triazoles are formed from 2-azidobenzaldehyde imines,[4,5] 2-azidostyrenes, and 2-azidophenylazo compounds, respectively.[6] An example of a thermal decomposition of a 2-azidobenzeneamine

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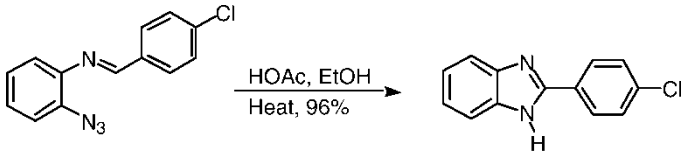


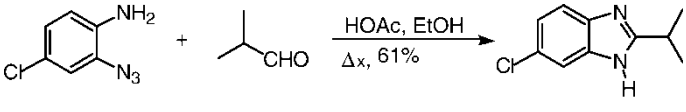

**1** **2**

***Scheme 1.***



imine is shown in Scheme 1. Thus, reaction of **1** in a refluxing mixture of HOAc–ethanol furnished benzimidazole **2** in excellent yield. No examples of substituted 2-azidobenzenamines or the use of aliphatic aldehydes were reported by the authors.[2] To the best of our knowledge, only the imine formed from reaction of 2-azidobenzenamine with 2,2-diphenylethanal has been isolated.[3] However, thermal decomposition of this imine failed to furnish the expected benzimidazole. The absence of additional examples of aliphatic aldehydes is probably a reflection of the instability of the corresponding imines.

We have previously reported a synthesis of enamines via reaction of 2-nitrobenzenamines with aliphatic aldehydes in the presence of molecular sieves. The isolated enamines were cyclized using a palladium-catalyzed reductive *N*-heteroannulation to give quinoxaline derivatives.[7] In an effort to probe the mechanism of the latter reaction, attempts were made to prepare the corresponding enamines derived from 2-azidobenzenamines. However, a complex mixture of products, in addition to starting material, was isolated using molecular sieves. Employing the conditions used to prepare the imines discussed in the preceding paragraph, we isolated benzimidazole **4**, in 61% yield, from reaction of 2-azido-4-chlorobenzenamine (**3**) with 2-methylpropanal (Scheme 2). The benzimidazole is probably derived from a sequential imine formation–thermal nitrene formation–electrocyclization. This result is surprising in light of previously reported difficulties with the imine formation from aliphatic aldehydes, and that formation of benzimidazoles from 2-azidobenzenamine imines was observed at substantially higher reaction temperatures, 130–140°C.




**3** **4**

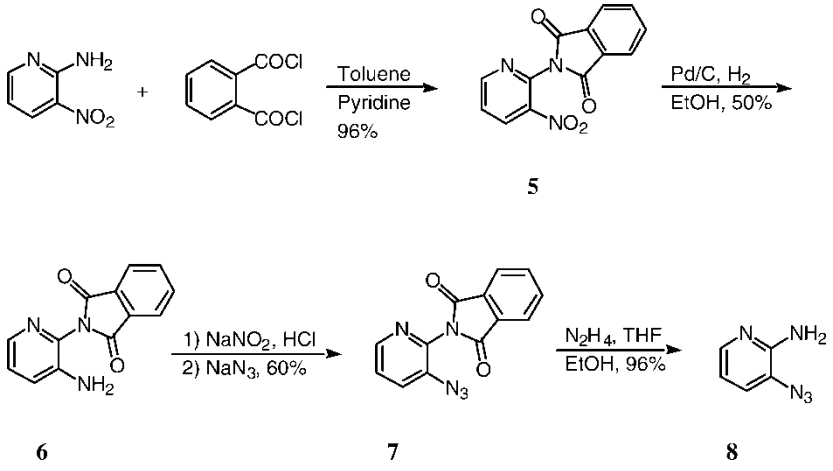
***Scheme 2.***

2-Substituted benzimidazoles are usually prepared from reaction of 1,2-diaminobenzenes with aldehydes,[8] carboxylic acids, esters, or amides under a variety of conditions.[9–11] Some more recently developed methodologies include a titanium dioxide–mediated photochemically promoted reaction of 1,2-dinitroaryls with alcohol solvents,[12] zinc[13]—or indium[14]—2-bromo-2-nitropropane mediated reductive cyclizations of 2-nitrobenzenamine-derived aromatic imines, palladium-catalyzed intramolecular amination of amidines derived from 2-halobenzenamines,[15] palladium-catalyzed reaction of 1,2-diaminobenzenes with aromatic iodides in the presence of carbon monoxide,[16] and cobalt-catalyzed direct 2-arylation of benzimidazole,[17] to name only a few.

Based on our initial result, described here is a relatively mild route to 2-substituted benzimidazoles via a sequential in situ imine formation–thermal nitrene formation–electrocyclization.

## RESULTS AND DISCUSSION

The 2-azidobenzenamines (**8**–**13**) required for the cyclizations were prepared according to the procedure of Hall and Patterson or by slight modifications thereof.[18] The general synthetic sequence is outlined in Scheme 3 for the preparation of the novel 3-azido-2-aminopyridine (**8**). Thus, reaction of 2-amino-3-nitropyridine with phthaloyl chloride gave **5** in excellent yield. The nitro group was reduced to an amine (**6**), and the amine was further transformed to an azide (**7**) via the corresponding diazonium salt. The phthalimido group was removed using hydrazine to give the expected 2-azidobenzenamine **8**.




*Scheme 3.*

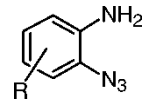
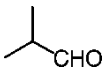
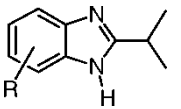
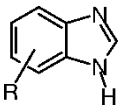
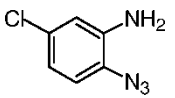
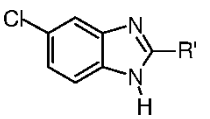
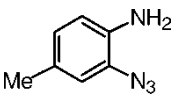
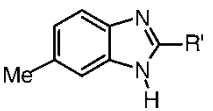
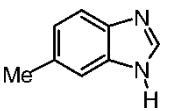
The isolated 2-azidobenzenamines were reacted with a selection of aliphatic and aromatic aldehydes, and the results are summarized in Table 1. In a typical experiment, an ethanol solution containing the azide and a slight excess (20%) of the aldehyde was heated at reflux for 24 h. The crude product mixtures were purified by chromatography on silica gel using gradient elution. A number of colored streaking bands were observed, but no other products were identified apart from those discussed in the subsequent paragraphs. Initially, HOAc was added to the reaction mixture but it was later shown to afford slightly lower yield of products from aliphatic aldehydes. For example, reaction of 2-azido-5-chlorobenzenamine (**9**) with 2-methylpropanal gave the expected benzimidazole **15** in 76% in the absence and in 67% in the presence of HOAc (entry 1).

Thermal decomposition of the 2-azidobenzenamines, occurring at ca. 65°C for the parent compound[3] prior to condensation, and the relatively slow condensation to form the imines are two factors negatively affecting the yield of benzimidazole. Benzimidazoles derived from formal loss of the 2-substituent were observed in some cases (entries 1, 4, 10, 11). This was particularly pronounced using 2-phenylethanal where the major product obtained was 5-methylbenzimidazole (**26**) and not the expected 2-benzyl-5-methylbenzimidazole (**25**). The ratio of **25** to **26** was increased slightly from 1 : 4 to 2 : 3 in the presence of added HOAc, but the overall yield remained the same. It is presently unclear how the alkyl group is lost during the reaction. Attempts to trap radical intermediate using 1,4-cyclohexadiene failed to provide any additional information regarding the mechanism (entry 11).

For the methoxy-substituted aminoazide **13**, the starting material decomposed rapidly as evidenced by a color change from yellow to dark brown. This does not appear to be a light-driven process because the same color change was observed after carefully wrapping the reaction vessel with aluminum foil prior to addition of solvent and the aldehyde. An almost identical yield of benzimidazole was realized in the absence of light.

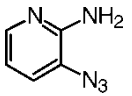
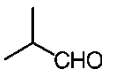
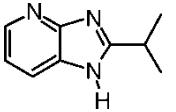
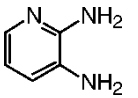
For the successful examples in the two previously published studies,[2,3] the overall yield of benzimidazole starting from 2-azidoaminobenzene ranged from 24 to 84%. The present one-pot methodology affords 2-substituted benzimidazoles in similar yields and compares favorably in some cases. The yield of 2-phenyl-substituted benzimidazole **22** was the highest, substantially higher compared to related literature examples. Furfural has previously been reported to fail to form an imine with 2-azidobenzeneamines.[3] In contrast, a 37% yield of 2-(2-furyl)-5-methylbenzimidazole (**30**) was realized using our one-pot procedure presumably via the corresponding imine (entry 16). Aza-benzimidazoles (imidazopyridines) are also of synthetic interest. However, reaction of 2-amino-3-azidopyridine (**8**) with 2-methylpropanal gave a very disappointing yield of the expected 3-azabenzimidazole (entry 17). The major product was 2,3-diaminopyridine (**32**), obtained from reduction of the starting material. Related reductions of aromatic azides under acidic conditions have been reported.[19–21]

***Table 1.*** Formation of 2-alkyl-substituted benzimidazoles

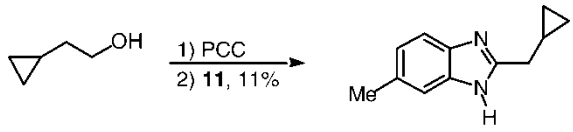
| Entry[a] | Azide[b] | Aldehyde | Benzimidazole (s)[c] | |
|---|---|---|---|---|
| |  |  |  |  |
| 1 | **9**, R = 5-Cl | | **15**, R = 5-Cl (76%, 67%) | **16** (6%)[d] |
| 2 | **10**, R = 4-Cl | | **15**, R = 5-Cl (66%, 61%) | |
| 3 | **11**, R = 4-Me | | **17**, R = 5-Me (71%, 50%) | |
| 4 | **12**, R = 6-Me | | **18**, R = 4-Me (69%) | **19** (8%) |
| 5 | **13**, R = 4-OMe | | **20**, R = 5-OMe (44%) | |
| |  | R′CHO |  | |
| 6 | **10** | $R' = C_6H_{13}$ | **21** (63%, 64%) | |
| 7 | **10** | R′ = Ph | **22** (82%)[d] | |
| |  | R′CHO |  |  |
| 8 | **11** | $R' = n\text{-}C_6H_{13}$ | **23** (75%, 46%) | |
| 9 | | $R' = n\text{-}C_{16}H_{33}$ | **24** (67%) | |

(*continued*)

***Table 1.*** Continued

| Entry[a] | Azide[b] | Aldehyde | Benzimidazole (s)[c] | |
|---|---|---|---|---|
| 10 | | $R' = PhCH_2$ | **25** (10%, 19%) | **26** (40%, 30%) |
| 11 | | $R' = PhCH_2$ | **25** (27%)[e] | **26** (27%) |
| 12 | | $R' = Me$ | **27** (33%) | |
| 13 | | $R' = t\text{-}Bu$ | **28** (25%) | |
| 14 | | $R' = H$ | **26** (18%) | |
| 15 | | $R' = MeCH = CH$ | **29** (14%) | |
| 16 | | $R' = 2\text{-furyl}$ | **30** (37%, 54%[f]) | |
| |  |  |  |  |
| 17 | **8** | | **31** (7%) | **32** (33%) |

[a]For reaction conditions and details see the experimental section.
[b]The compounds are numbered from the amino group having the azido group in the 2-position.
[c]Isolated yields of pure products. The second yield in the parentheses corresponds to reactions with added HOAc.
[d]In the presence of HOAc.
[e]With HOAc and 2 equiv. of 1,4-cyclohexadiene.
[f]With HOAc and 3 equiv. of aldehyde.




33

*Scheme 4.*

As a final example, reaction of cyclopropylethanal, prepared in situ by pyridinium chlorochromate (PCC) oxidation of cyclopropylethanol, with **11** furnished the cyclopropylmethyl-substituted benzimidazole **33** in low yield (Scheme 4).

In conclusion, a simple methodology for the preparation of 2-alkylbenzimidazoles via reaction of 2-azidobenzenamines with aldehydes has been developed.

## EXPERIMENTAL

All NMR spectra were determined in $CDCl_3$ at 270 or 600 MHz ($^1$H NMR) and at 67.5 or 150 MHz ($^{13}$C NMR) unless otherwise indicated. The chemical shifts are expressed in $\delta$ values relative to $Me_4Si$ (0.0 ppm, $^1$H and $^{13}$C) or $CDCl_3$ (77.0 ppm, $^{13}$C) internal standards. $^1$H-$^1$H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) and $^{13}$C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes $CH_3$ or CH and (+) denotes $CH_2$ or C.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Toluene, pyridine, hexanes, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under an argon atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Chromatography was performed on silica gel 60 (35–75 μm, VWR). High resolution mass spectra (HRMS) were performed at University of California Riverside Mass Spectrometry Center. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

**3-Nitro-2-phthalimidopyridine (5).** To a refluxing solution of phthaloyl chloride (4.0 mL, 27.7 mmol) in toluene (50 mL), a solution of 2-amino-3-nitropyridine (3.00 g, 21.6 mmol) and pyridine (6.0 mL, 74.2 mmol) in

toluene (50 mL) was added dropwise. The reaction was stirred at reflux for 42 h. The resulting mixture was filtered while hot through an oven-heated fritted funnel, and the solvent was removed under reduced pressure. Recrystallization of the crude product from acetic acid gave **5** (5.56 g, 20.7 mmol, 96%) as a yellow solid. Mp 171–173°C; $^1$H NMR (270 MHz) $\delta$ 8.94 (dd, $J = 4.9$ and 1.7 Hz, 1H), 8.56 (dd, $J = 8.2$ and 1.5 Hz, 1H), 8.03–7.98 (m, 2H), 7.90–7.80 (m, 2H), 7.65 (dd, $J = 8.2$ and 4.7 Hz, 1H); $^{13}$C NMR (67.5 MHz) $\delta$ 165.5 (+), 153.3 (−), 142.5 (+), 139.1 (+), 134.9 (−), 134.5 (−), 131.7 (+), 124.6 (−), 124.3 (−); IR (neat) 1786, 1735, 1592, 1541, 1355 cm$^{-1}$; HRMS (DCI, $NH_3$) calcd. for $C_{13}H_8N_3O_4$ ($MH^+$) 270.0515, found 270.0524; anal. cald. for $C_{13}H_7N_3O_4$: C, 58.00; H, 2.62. Found: C, 57.60; H, 2.56.

**3-Amino-2-phthalimidopyridine (6).** Compound **5** (3.50 g, 12.9 mmol), Pd/C (700 mg, 10% Pd), and ethanol (50 mL) were combined in a threaded pressure tube fitted with a Teflon® cap attached to a hydrogenation apparatus. The tube was flushed three times with hydrogen gas. The reaction flask was pressurized with hydrogen gas (4 atm) and stirred at 60°C for 15 h. After releasing the pressure, the open flask was heated gently to dissolve the solid product. The hot solution was filtered through an oven-heated fritted funnel packed with Celite® and washed with hot ethyl acetate. The solvent was removed at reduced pressure, and the crude residue was recrystallized from ethanol to give **6** (1.50 g, 6.4 mmol, 50%) as a yellow solid. Mp 204–206°C; $^1$H NMR (270 MHz) $\delta$ 8.10 (t, $J = 3.0$ Hz, 1H), 8.00–7.93 (m, 2H), 7.83–7.77 (m, 2 H), 7.23 (d, $J = 3.2$ Hz, 2H), 3.85 (br s, 2H); $^{13}$C NMR (67.5 MHz) $\delta$ 166.9 (+), 140.0 (+), 139.8 (−), 134.5 (−), 132.8 (+), 132.1 (+), 125.5 (−), 125.3 (−), 124.0 (−); IR (neat) 3434, 1716, 1469, 1377 cm$^{-1}$; HRMS (EI) calc. for $C_{13}H_9N_3O_2$ 239.0695; found 239.0703.

**3-Azido-2-phthalamidopyridine (7).** To a solution of **6** (1.50 g, 6.06 mmol) in $H_2O$ (60 mL) at 0°C, HCl (conc., 15 mL) was added. Small amounts of ice were added periodically to keep the solution at 0°C. The solution of the formed amine hydrochloride was stirred for 5 min. Sodium nitrite (500 mg, 7.25 mmol) dissolved in 10 mL of $H_2O$ was added to the cold solution, and the reaction was stirred for 3.5 h. The remaining insoluble solid was removed by rapid filtration. The filtrate was added to a beaker and cooled to 0°C in an ice bath. Sodium azide (485 mg, 7.46 mmol) dissolved in water (10 mL) was added together with small amounts of diethyl ether to stop the resulting foaming. The solution was stirred (2 h), and the resulting solid was removed by filtration and washed with cold diethyl ether to give **7** (970 mg, 3.66 mmol, 60%) as an off-white solid. Mp 167–169°C; $^1$H NMR (270 MHz) $\delta$ 8.47 (dd, $J = 1.5$ and 4.7 Hz, 1H), 8.00–7.94 (m, 2H), 7.85–7.78 (m, 2H), 7.68 (dd, $J = 8.2$ and 1.5 Hz, 1H), 7.50 (dd, $J = 8.2$ and 4.7 Hz, 1H); $^{13}$C NMR (67.5 MHz) $\delta$ 166.3, 145.6 (−), 137.2, 135.3, 134.5 (−), 132.0 (+), 127.9 (−), 125.6 (−), 124.0 (−); IR (neat) 2126,

1723, 1455, 1374 $cm^{-1}$; HRMS (DCI, $NH_3$) calcd. for $C_{13}H_8N_5O_2$ ($MH^+$) 266.0678; found 266.0683. Anal. cald. for $C_{13}H_7N_5O_2$: C, 58.87; H, 2.66. Found: C, 58.77; H, 2.77.

**2-Amino-3-azidopyridine (8).** To a solution of **7** (840 mg, 3.2 mmol) dissolved in THF (20 mL) and ethanol (5 mL), hydrazine hydrate (85% aqueous, 1.5 mL) was added. The reaction was stirred at ambient temperature (26 h). The insoluble solid was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. To the resulting solid, HCl (10% aqueous, 100 mL), was added and the formed precipitate was removed by filtration. The filtrate was washed with diethyl ether (3 × 50 mL). The aqueous layer was made basic with NaOH (aqueous, 3 M) and was extracted with diethyl ether (4 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure, affording **8** (412 mg, 3.1 mmol, 96%) as a brown solid. Mp 71–73°C; $^1$H NMR (270 MHz) $\delta$ 7.86 (dd, $J = 4.9$ and 1.5 Hz, 1H), 7.23 (dd, $J = 7.7$ and 1.5 Hz, 1H), 6.70 (dd, $J = 7.7$ and 4.9 Hz, 1H), 4.74 (br s, 2H); $^{13}$C NMR (67.5 MHz) $\delta$ 150.9 (+), 143.4 (−), 124.5 (−), 120.3 (+), 113.4 (−); IR (neat) 3453, 2120, 1629, 1487, 1257 $cm^{-1}$; HRMS (EI) calc. for $C_5H_5N_5$ 135.0545; found 135.0542. Anal. cald. for $C_5H_5N_5$: C, 44.44; H, 3.73. Found: C, 44.11; H, 4.07.

**5-Chloro-2-(1-methylethyl)benzimidazole (15).**[22] To a refluxing solution of 2-azido-5-chlorobenzenamine (**9**)[23] (300 mg, 1.78 mmol) in ethanol (50 mL), a solution of 2-methylpropanal (195 μL, 2.15 mmol) in ethanol (20 mL) was added dropwise. The reaction was stirred at reflux for 24 h, followed by evaporation of the solvent at reduced pressure. The crude solid was purified by column chromatography (hexanes–EtOAc, in order 8 : 2, 7 : 3, 1 : 1, and 3 : 7) affording **15** (262 mg, 1.35 mmol, 76%) as a brown solid. Mp 189–190°C (lit.[24] 192–194°C); $^1$H NMR (600 MHz) $\delta$ 7.51 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.18 (dd, $J = 8.4$ and 1.8 Hz, 1H), 3.28 (septet, $J = 6.6$ Hz, 1H), 1.47 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (150 MHz) $\delta$ 161.2, 127.8, 122.7, 114.5 (br), 29.1, 21.5. Three carbons were not observed due to the slow exchange of the N-H proton, causing signal broadening.

Reaction of 2-azido-4-chlorobenzenamine (**10**)[18,25] (174 mg, 1.03 mmol) with 2-methylpropanal (115 μL, 1.27 mmol) in ethanol (70 mL), as described previously (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, and 3 : 7) gave **15** (132 mg, 0.68 mmol, 66%) as a brown solid.

**5-Chloro-2-(1-methylethyl)benzimidazole (15) and 5-chlorobenzimidazole (16).** Commercially available. Reaction of **9** (250 mg, 1.48 mmol) with 2-methylpropanal (400 μL, 4.40 mmol) and AcOH (500 μL) in ethanol (20 mL), as described for **15** (reflux, 21 h), after chromatography (hexanes–EtOAc, in order 8 : 2, 7 : 3, 1 : 1, 4 : 6, and 3 : 7) gave **15** (194 mg,

0.97 mmol, 67%) followed by **16** (13 mg, 0.085 mmol, 6%). Mp for **16** 118–121°C (lit.[24] 120–125°C).

**5-Methyl-2-(1-methylethyl)benzimidazole (17).**[26] Reaction of 2-azido-4-methylbenzenamine **11**[18] (300 mg, 2.02 mmol) with 2-methylpropanal (220 μL, 2.42 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **17** (249 mg, 1.43 mmol, 71%) as a brown solid. Mp 158–159°C (lit.[24] 154–157°C). $^1$H NMR (600 MHz) $\delta$ 7.44 (d, $J = 8.4$ Hz, 1H), 7.35 (s, 1H), 7.02 (dd, $J = 8.4$ and 1.8 Hz, 1H), 3.30 (septet, $J = 7.2$ Hz, 1H), 2.44 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (150 MHz) $\delta$ 160.0, 138.5 (broad signal), 137.0 (broad signal), 131.8, 123.4, 114.5 (broad signal), 114.0 (broad signal), 29.1, 21.7, 21.6.

**4-Methyl-2-(1-methylethyl)benzimidazole (18)**[27] **and 4-methylbenzimidazole (19).**[28] Reaction of 2-azido-6-methylbenzenamine **12**[18] (280 mg, 1.89 mmol) with 2-methylpropanal (210 μL, 2.31 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), gave after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) **18** (226 mg, 1.30 mmol, 69%) as a brown solid and **19** (21 mg, 0.16 mmol, 8%) as an off-white solid. Data for **18**: mp 206–208°C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 7.28 (d, $J = 7.7$ Hz, 1H), 7.01 (t, $J = 7.3$ Hz, 1H), 6.91 (d, $J = 6.9$ Hz, 1H), 3.16 (septet, $J = 6.9$ Hz, 1H), 2.49 (s, 3H), 1.35 (s, $J = 6.9$ Hz, 6H). [Lit. for **18**:[27] $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.02 (br s, 1H), 7.26 (br s, 1H), 6.99 (dd, $J = 7.7$ and 7.4 Hz, 1H), 6.87 (ddt, $J = 7.4$, 1.1, and 0.8 Hz, 1H), 3.14 (septet, $J = 7.0$ Hz, 1H), 2.48 (s, 3H), 1.34 (d, $J = 7.0$ Hz, 6H).] Data for **19**: mp 118–121°C (lit.[24] 142–149°C). $^1$H NMR (270 MHz) $\delta$ 8.60 (br s, 1H), 8.12 (s, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 2.62 (s, 3H). [Lit. $^1$H NMR data for **19**:[29] $\delta$ 10.10 (s, 1H), 8.17 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 7.7$ Hz, 1H), 2.63 (s, 3H).]

**5-Methoxy-2-(1-methylethyl)benzimidazole (20)**.[30] Reaction of 2-azido-4-methoxybenzenamine **13**[18] (136 mg, 0.82 mmol) with 2-methylpropanal (130 μL, 1.42 mmol) in ethanol (70 mL), as described for **15** (reflux, 24.5 h), after chromatography (hexanes–EtOAc, in order of elution 1 : 1, and 2 : 8) gave **20** (69 mg, 0.36 mmol, 44%) as a faint brown solid. Mp 130–131°C, $^1$H NMR (600 MHz) $\delta$ 7.43 (br d, $J = 8.4$ Hz, 1H), 7.04 (br s, 1H), 6.85 (dd, $J = 7.8$ and 1.8 Hz, 1H), 3.82 (s, 3H), 3.22 (septet, $J = 7.2$ Hz, 1H), 1.44 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (150 MHz) $\delta$ 159.5, 156.1, 115 (br), 111.3, 108 (br), 55.9, 29.0, 21.5.

**5-Chloro-2-hexylbenzimidazole (21).** Reaction of **10** (302 mg, 1.79 mmol) with heptanal (290 μL, 2.08 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2,

and 7 : 3) gave **21** (266 mg, 1.12 mmol, 63%) as a brown solid. Mp 120–122°C; $^1$H NMR (270 MHz) $\delta$ 12.01 (br s, 1H), 7.53 (d, $J = 2.0$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.19 (dd, $J = 8.6$ and 2.0 Hz, 1H), 2.97 (t, $J = 7.6$ Hz, 2H), 1.85 (pentet, $J = 7.4$ Hz, 2H), 1.40–1.10 (m, 6H), 0.79 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (67.5 MHz) $\delta$ 157.3 (+), 139.3 (+), 137.0 (+), 127.7 (+), 122.6 (−), 115.1 (−), 114.4 (−), 31.3 (+), 29.3 (+), 28.9 (+), 28.4 (+), 22.3 (+), 13.8 (−); IR (neat) 2921, 2360, 1450, 1024 cm$^{-1}$; HRMS (EI) calc. for $C_{13}H_{17}C1\,N_2$ 236.1080; found 236.1071. Anal. calcd. for $C_{13}H_{17}ClN_2$: C, 65.95; H, 7.24. Found: C, 66.27, H, 7.52.

**5-Chloro-2-phenylbenzimidazole (22).**[16] Reaction of **10** (250 mg, 1.48 mmol) with benzaldehyde (450 μL, 4.43 mmol), and AcOH (500 μL) in ethanol (20 mL), as described for **15** (reflux, 21 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, and 1 : 1) gave **22** (268 mg, 1.21 mmol, 82%) as a faint brown solid. Mp 213–214°C (lit.[16] 209–210°C); $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 8.17 (dd, $J = 8.2$ and 2.0 Hz, 2H), 7.68–7.49 (m, 5H), 7.23 (dd, $J = 8.7$ and 2.0 Hz, 1H). [Lit.[16] $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.8 (br s, 1H), 8.18 (d, $J = 7.2$ Hz, 2H), 7.5 (m, 5H), 7.19 (dd, $J = 8.2$ and 1.0 Hz, 1H).]

**2-Hexyl-5-methylbenzimidazole (23).**[31] Reaction of **11** (305 mg, 2.06 mmol) with heptanal (330 μL, 2.36 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 8 : 2, 7:3, 1 : 1, 3 : 7, and EtOAc) gave **23** (334 mg, 1.54 mmol, 75%) as a brown solid. Mp 79–83°C (lit.[31] 79–80°C); $^1$H NMR (600 MHz) $\delta$ 7.43 (d, $J = 8.4$ Hz, 1H), 7.32 (s, 1H), 7.03 (dd, $J = 8.4$ and 1.8 Hz, 1H), 2.89 (t, $J = 7.8$ Hz, 2H), 2.44 (s, 3H), 1.82 (pentet, $J = 7.8$ Hz, 2H), 1.36 (pent, $J = 7.2$ Hz, 2H), 1.28–1.22 (m, 4H), 0.83 (t, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz) $\delta$ 155.0, 131.8, 123.5, 114.8 (broad signal), 31.4, 29.3, 29.0, 28.3, 22.5, 21.6, 14.0.[30]

**2-Hexadecyl-5-methylbenzimidazole (24).**[32] Reaction of **11** (114 mg, 0.77 mmol) with heptadecanal (297 mg, 1.16 mmol) in ethanol (70 mL), as described for **15** (reflux, 38.5 h), after chromatography (hexanes–EtOAc, in order 8 : 2, and 7 : 3) gave **24** (185 mg, 0.52 mmol, 67%) as a beige solid. Mp 72–73°C; $^1$H NMR (270 MHz) $\delta$ 8.33 (br s, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 7.31 (br s, 1H), 7.04 (dd, $J = 8.1$ and 1.0 Hz, 1H), 2.86 (t, $J = 5.8$ Hz, 2H), 2.45 (s, 3H), 2.37 (t, $J = 7.5$ Hz, 1H), 1.80 (pent, $J = 6.7$ Hz, 2H), 1.67 (pent, $J = 7.3$ Hz, 1H), 1.25 (brs, 24H) 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (150 MHz) $\delta$ 155.0, 137.3, 135.7, 132.2, 123.9, 114.2, 114.0, 36.0, 31.9, 29.70, 29.69, 29.66, 29.65, 29.63, 29.61, 29.51, 29.49, 29.35, 29.32, 29.30, 28.7, 28.3, 25.7, 22.7, 21.5, 14.1; IR (neat) 2916, 2849, 1706, 1467, 798, 721 cm$^{-1}$.

**2-Benzyl-5-methylbenzimidazole (25)**[33] **and 5-methylbenzimidazole (26).**[25] Reaction of **11** (300 mg, 2.02 mmol) with phenylethanal (280 μL,

2.39 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **25** (47 mg, 0.21 mmol, 10%) as a brown solid and **26** (107 mg, 0.81 mmol, 40%) as an off-white solid. Compound **25**: 139–140°C (lit.[34] mp 146–147°C). Compound **26**: mp 107–110°C (lit.[34] 114–117°C). Alternative procedure: Reaction of **11** (300 mg, 2.00 mmol), ethanol (70 mL total), phenylacetaldehyde (0.300 mL, 2.60 mmol), and glacial HOAc (25 μL, 0.44 mmol) as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **25** (87 mg, 0.39 mmol, 19%) as a brown solid and **26** (79 mg, 0.60 mmol, 30%). Alternative procedure for 26: Reaction of **11** (306 mg, 2.07 mmol) with paraformaldehyde (78 mg, 2.60 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 6 : 4, 1 : 1, 3 : 7, and EtOAc) gave **26** (49 mg, 0.37 mmol, 18%) as an off-white solid.

**2,5-Dimethylbenzimidazole (27)**.[25] Reaction of **11** (302 mg, 2.04 mmol) with ethanal (140 μL, 2.33 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **27** (99 mg, 0.67 mmol, 33%) as a brown solid. Mp 200–202°C (lit.[24] 202–204.5°C).

**5-Methyl-2-(1,1-dimethylethyl)benzimidazole (28)**.[35] Reaction of **11** (300 mg, 2.02 mmol) with 2,2-dimethylpropanal (270 μL, 2.97 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **28** (94 mg, 0.50 mmol, 25%) as a brown solid. Mp 239–242°C (lit.[35] 205–208°C); $^1$H NMR (DMSO-$d_6$, 270 MHz) $\delta$ 11.90 (br s, 1H), 7.40–7.12 (m, 2H), 6.91 (d, $J = 7.6$ Hz, 1H), 2.37 (s, 3H), 1.36 (s, 9H) [lit.[35] $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.40–7.10 (m, 2H), 6.95–6.85 (m, 1H), 2.38 (s, 3H), 1.39 (s, 9H).]

**(*E*)-5-Methyl-2-(1-propenyl)benzimidazole (29).**[36,37] Reaction of **11** (308 mg, 2.08 mmol) with trans-2-butenal (200 μL, 2.41 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 95 : 5, 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7, and EtOAc) gave **29** (50 mg, 0.29 mmol, 14%). Mp 185–196°C (lit.[37] 186.5°C).

**2-(2-Furyl)-5-methyl-benzimidazole (30).**[38] Reaction of **11** (147 mg, 1.00 mmol) with furfural (100 μL, 1.20 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 7 : 3, 1 : 1, and 2 : 8) gave **30** (73 mg, 0.37 mmol, 37%) as a yellow-orange solid. Mp 188–192°C (lit.[38] 196–197°C); $^1$H NMR (600 MHz) $\delta$ 7.50 (dd, $J = 8.4$ and 3.6 Hz, 1H), 7.37 (br s, 2H), 7.12 (t, $J = 3.6$ Hz, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 6.42 (dd, $J = 4.2$ and 1.8 Hz, 1H), 2.42 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 145.5, 144.1, 143.6, 138.4, 137.3, 132.8, 124.4,

115.1, 114.5, 112.1, 110.5, 21.6; IR 2923, 1522, 1422, 907, 731 $cm^{-1}$. Alternative procedure: Reaction of **11** (148 mg, 1.00 mmol) with furfural (250 μL, 3.02 mmol) and HOAc (0.4 mL) in ethanol (20 mL), as described for **15** (reflux, 48 h), after chromatography (hexanes–EtOAc, in order 7 : 3 and 1 : 1) gave **30** (106 mg, 0.54 mmol, 54%) as a yellow-orange solid.

**2-(1-Methylethyl)imidazo[4,5-*b*]pyridine (31)[39] and 2,3-diaminopyridine (32).**[25] Reaction of **8** (302 mg, 2.23 mmol) with 2-methylpropanal (250 μL, 2.75 mmol) in ethanol (70 mL), as described for **15** (reflux, 24 h), after chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, 3 : 7 and EtOAc) gave **31** (27 mg, 0.17 mmol, 8%) and **32** (81 mg, 0.74 mmol, 33%) as brown solids. Analytical data for **31**: mp 146–149°C (lit.[39] 157–159°C); $^1$H NMR (270 MHz) $\delta$ 8.36 (dd, $J = 4.9$ and 1.5 Hz, 1H), 8.07 (d, $J = 7.9$ Hz, 1H), 7.25 (dd, $J = 7.9$ and 4.9 Hz, 1H), 3.40 (septet, $J = 7.2$ Hz, 1H), 1.58 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (67.5 MHz) $\delta$ 162.4 (+), 149.2 (+), 141.6 (−), 136.0 (+), 127.1 (−), 117.7 (−), 29.7 (−), 21.3 (−); IR (neat) 2971, 2750, 1609, 1410, 1271 $cm^{-1}$. Data for **32**: mp 107–110°C (lit.[40] mp 110–115°C).

**2-Cyclopropylmethyl-5-methylbenzimidazole (33).** A mixture of 2-cyclopropylethanol (300 mg, 3.48 mmol) and pyridinium chlorochromate (980 mg, 4.55 mmol) dissolved in $CH_2Cl_2$ (50 mL) was stirred at ambient temperature (7 h). The resulting mixture was filtered through a fritted funnel packed with a thin layer of silica gel. The filtrate containing crude cyclopropylethanal[41] was added to a threaded ACE-glass pressure tube. To the solution was added **11** (310 mg, 2.09 mmol), and the tube was capped with a Teflon® screw cap. The reaction was stirred at 100°C (24 h), followed by evaporation of the solvents under reduced pressure. The crude product was purified by chromatography (hexanes–EtOAc, in order 9 : 1, 8 : 2, 7 : 3, 1 : 1, and 3 : 7) to give **33** (73 mg, 0.39 mmol, 11%). Mp 155–157°C; $^1$H NMR (270 MHz) $\delta$ 7.45 (d, $J = 8.2$ Hz, 1H), 7.34 (s, 1 H), 7.03 (d, $J = 8.2$ Hz, 1H), 2.87 (d, $J = 7.2$ Hz, 2H), 2.44 (s, 3H), 1.29–1.13 (m, 1H), 0.58–0.50 (m, 2H), 0.28–0.22 (m, 2H); $^{13}$C NMR (67.5 MHz) $\delta$ 154.8 (+), 138.5 (+), 137.0 (+), 131.6 (+), 123.3 (−), 114.4 (−), 114.1 (−), 34.0 (+), 21.5 (−), 9.5 (−), 4.8 (+); IR (neat) 3005, 2919, 2865, 1449, 1282 $cm^{-1}$; HRMS (EI) calc. for $C_{12}H_{14}N_2$ (M-H$^+$) 185.1079; found 185.1078.

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