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Catalyst/ligand-free synthesis of benzimidazoles and quinazolinones from amidines via intramolecular transamination reaction

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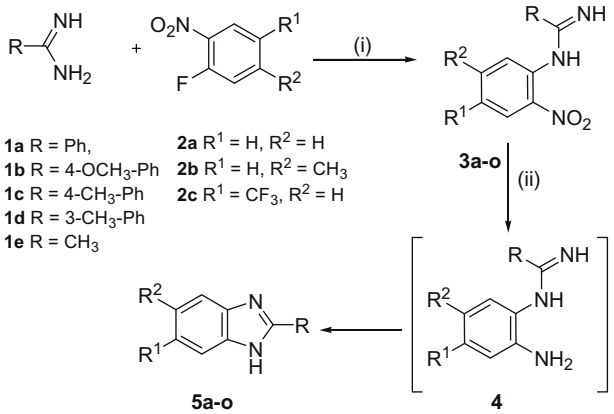
ABSTRACT

An efficient catalyst/ligand-free synthesis of benzimidazoles and quinazolinones from amidines in quantitative yields has been described.

N-Heterocycles have always remained a major source for therapeutic drugs with benzimidazoles[1] and quinazolinones[2] being the ones receiving significant attention. The synthesis of these heterocyclic structures is pivotal for the success of implementation of organic synthesis in the drug discovery process. Although a number of methods dealing with the synthesis of these heterocycles have appeared, new routes from new set of monomers remain the subject of continuous investigation.

In recent years syntheses of benzimidazoles and quinazolinones have been affected using amidines as a building block albeit in the presence of catalysts and/or ligands as additive. Brain and Brunton[3] described the synthesis of benzimidazoles using (*o*-bromophenyl) amidine precursor but the strategy suffers from the disadvantage that the product gets contaminated with the ligand and an extra step is involved in the purification. Brasche and Buchwald[4] used *N*-phenylbenzamidine for the copper-catalyzed synthesis of benzimidazoles, however, in the case of 2-alkylbenzimidazole it was limited to amidines bearing a bulky *tert*-butyl group. Hu and coworkers[5] synthesized benzimidazoles via cascade reactions of *o*-haloacetoanilide derivatives with amidine hydrochlorides using 10 mol % CuBr as catalyst. Deng et al.[6] reported a facile synthesis of benzimidazoles by treating dihalobenzenes with guanidines or amidines in the presence of CuI and L5 (*N*,*N*-dimethylethylenediamine). Similarly, for the synthesis of quinazolinones, Fu and coworkers[7] treated amidines with 2-bromobenzoic acid in the presence of copper followed by intramolecular cyclization. Thus, all the above strategies involved the use of either a catalyst and/or a ligand for the C–N bond formation thereby leading to the synthesis of benzimidazoles and quinazolinones. In this Letter, we report a simple and efficient method for the synthesis of benzimidazoles and quinazolinones from amidines without involving the use of catalysts and/or ligands for the C–N bond formation.

Our synthesis (Scheme 1) commenced with the N-arylation of amidine **1a** by treating it with 2-fluoronitrobenzene **2a** resulting in a key intermediate *N*-(2-nitrophenyl)benzene-carboximidamide **3a** via nucleophilic substitution reaction in 30 min under microwave conditions. Under conventional heating conditions the yield of *N*-(2-nitrophenyl)benzenecarboximidamide **3a** was poor and required longer reaction time. In order to increase the variation in **3**, the strategy was then successfully applied to the synthesis of 14 N-arylated substrates **3b–o** by treating several aliphatic/aromatic amidines with 2-fluoronitrobenzene derivatives. In general the compounds **3** were obtained in >90% isolated yields and were characterized using NMR and ESMS.[8] In the next step, the nitro group of *N*-(2-nitrophenyl)benzenecarboximidamide **3a** was initially subjected to reduction via hydrogenation using 10% Pd/C in ethanol and progress of the reaction was monitored by both TLC and HPLC. The conversion of the nitro derivative **3a** was found to be complete within 15 min and the product even after 24 h of stirring at rt



Scheme 1. Reagents and conditions: (i) K_2CO_3, DMSO, 110 °C, μW, 30 min; (ii) 10% Pd–C, $HCOONH_4$, CH_3COOH, 80 °C, 1 h.

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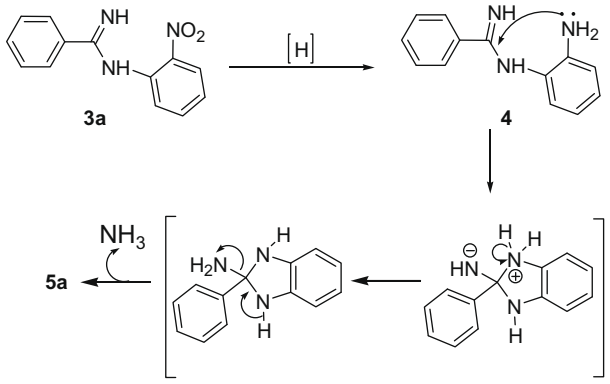


Figure 1. Proposed mechanism for the synthesis of **5a**.

Table 2
Synthesis of benzimidazoles **5a–o**

Entry	Substrate	R	R^1	R^2	Product	Yield (%)
1	**3a**	C_6H_5–	H	H	**5a**	96
2	**3b**	C_6H_5–	H	CH_3	**5b**	97
3	**3c**	C_6H_5–	CF_3	H	**5c**	91
4	**3d**	4-(OCH_3)–C_6H_4–	H	H	**5d**	95
5	**3e**	4-(OCH_3)–C_6H_4–	H	CH_3	**5e**	93
6	**3f**	4-(OCH_3)–C_6H_4–	CF_3	H	**5f**	94
7	**3g**	4-(CH_3)–C_6H_4–	H	H	**5g**	97
8	**3h**	4-(CH_3)–C_6H_4–	H	CH_3	**5h**	95
9	**3i**	4-(CH_3)–C_6H_4–	CF_3	H	**5i**	90
10	**3j**	3-(CH_3)–C_6H_4–	H	H	**5j**	92
11	**3k**	3-(CH_3)–C_6H_4–	H	CH_3	**5k**	93
12	**3l**	3-(CH_3)–C_6H_4–	CF_3	H	**5l**	97
13	**3m**	CH_3	H	H	**5m**	96
14	**3n**	CH_3	H	CH_3	**5n**	93
15	**3°**	CH_3	CF_3	H	**5o**	91

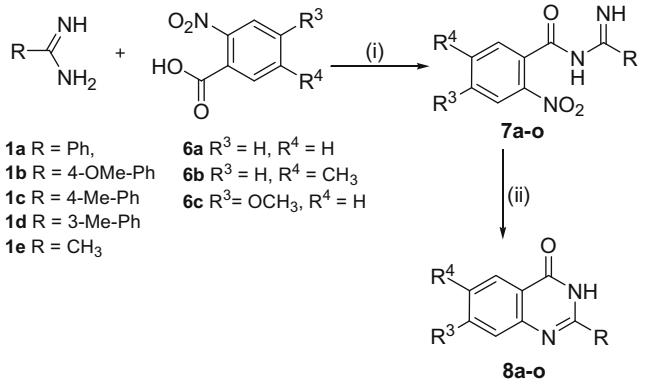
remained a mixture of two components. The HPLC exhibited a major peak in 51% yield (area under the curve) and the second component in 43% yield. The two components were separated by column chromatography and characterized by ESMS and NMR. One of the components with higher R_f on TLC was obtained in 42% isolated yield (mass of 194.2 Da) and was found to be benzimidazole derivative **5a.** The second component with the lower R_f and mass of 211.2 Da corresponded to the mass of amino component **4** but could not be characterized by the NMR as it had tendency to undergo slow cyclization to **5a**. The formation of the product **5a** may have occurred from an intramolecular cyclization via sequential C–N bond formation and dissociation resulting in benzimidazole. A plausible mechanism for the intramolecular cyclization following reduction of the aryl nitro group in **3a** has been depicted in Figure 1. The reaction commences with the nucleophilic attack of the aryl amino function **4** on to the electrophilic carbon of the amidine followed by an intramolecular transamination (addition–elimination of NH_2) reaction. The aromatization then occurred with the elimination of ammonia to yield benzimidazole.

Thus our method, unlike the reported strategies[2–6] did not involve the use of either catalysts such as copper/$Pd(PPh_3)_4$ or ligands for the C–N bond formation. The Pd/C used on our methodology was involved in the functional group transformation from nitro to amine which in turn triggered the intramolecular transamination reaction. This led us to optimize the reaction conditions for the quantitative conversion of **3a** into **5a** by carrying out the reduction of the nitro group under other reducing conditions and the results have been summarized in Table 1. Reduction of **3a** in the presence of 10% Pd/C in ethanol at rt for 24 h furnished benzimidazole **5a** in 42% yield, in contrast, when the same reaction mixture was heated, **5a** could be isolated in 65% yield. Addition of acid to the reaction mixture followed by heating at 80 °C for 1 h improved the yield to 85% (entry 3). Similarly, reduction with $SnCl_2{\cdot}2H_2O$ at 80 °C in ethanol and with Fe/AcOH at 80 °C furnished **5a** in 72% and 77% yield, respectively within 1 h. However, the complete conversion of **3a** into **5a** was observed when reduction of the nitro group was carried out under catalytic transfer hydrogenation conditions involving 10% Pd/C in AcOH using ammonium formate as a hydrogen donor at 80 °C for 1 h.[9] The resulting crude product obtained after work-up exhibited >98% purity on HPLC and was therefore simply triturated with 5:1 hexane/ether to furnish benzimidazole **5a** in 96% isolated yield. In general, it appears that although the amine component was formed within 15 min under all reductive conditions, the transamination leading to the formation of **5a** required elevated temperatures and acidic conditions. To further substantiate this, in one of the experiments, the substrate **3a** was subjected to catalytic reduction by passing hydrogen in the presence of 10% Pd/C in EtOH–AcOH mixture (1:1). After 15 min Pd/C was removed by filtration and the filtrate was heated at 80 °C for 1 h which in turn furnished **5a** in quantitative yield. Once we optimized the reaction condition for the conversion of **3a**–**5a**, we next examined the scope and limitation of our strategy by synthesizing 14 benzimidazole derivatives **5b–o** using aromatic and aliphatic amidine-derived substrates **3b–o** and in all the cases the product was isolated in 90–97% yields after crystallization (Table 2). This is in contrast to catalyst- and/or ligand-driven reactions reported in the literature from amidines wherein yields of benzimidazole ranged between 60% and 80% and involved purification using column chromatography as an additional step. Of the fifteen benzimidazole derivatives synthesized, physico-chemical parameters of 12 compounds (**5a**–**h**, **5j**, and **5m**–**o**) matched with the ones reported in the literature.[10]

After establishing the methodology for benzimidazoles, we next focused our attention on the synthesis of yet another important six-membered N-heterocycle quinazolinones. The substrate *N*-[imino(phenyl)methyl]-2-nitrobenzamide **7a** required for the synthesis of quinazolinone was prepared (Scheme 2) by the coupling of benzenecarboximidamide **1a** and 2-nitrobenzoic acid **6a**. The strategy was then successfully used to synthesize 14 substrates **7b–o** by coupling several aliphatic/aromatic amidines with 2-nitrobenzoic acid derivatives. The resulting N-acylated compounds **7** after purification via either crystallization or column chromatography were characterized using NMR and ESMS.[11] It is worth mentioning that acylation

Table 1
Optimization of reaction conditions for the conversion of **3a** into **5a**

Entry	Reaction conditions	Temp (°C)	Time (h)	Yield of **5a** (%)
1	10% Pd/C, H_2, in ethanol	rt	24	42
2	10% Pd/C, H_2, in ethanol	80 °C	1	65
3	10% Pd/C, H_2, in 20% MeOH/AcOH	80 °C	1	85
4	Fe/AcOH	80 °C	1	77
5	$SnCl_2{\cdot}2H_2O$ in ethanol	80 °C	1	72
6	10% Pd/C in AcOH, $HCOONH_4$	rt	12	60
7	10% Pd/C in AcOH, $HCOONH_4$	80 °C	1	96



Scheme 2. Reagents and conditions: (i) DCC, HOBT, DMF, rt, 12 h; (ii) 10% Pd–C, $HCOONH_4$, CH_3COOH, 80 °C, 1 h.

Table 3
Synthesis of quinazolinones **8a–o**

Entry	Substrate	R	R^3	R^4	Product	Yield (%)
1	**7a**	C_6H_5–	H	H	**8a**	96
2	**7b**	C_6H_5–	H	CH_3	**8b**	91
3	**7c**	C_6H_5–	OCH_3	H	**8c**	95
4	**7d**	4-(OCH_3)–C_6H_4–	H	H	**8d**	97
5	**7e**	4-(OCH_3)–C_6H_4–	H	CH_3	**8e**	92
6	**7f**	4-(OCH_3)–C_6H_4–	OCH_3	H	**8f**	96
7	**7g**	4-(CH_3)–C_6H_4–	H	H	**8g**	91
8	**7h**	4-(CH_3)–C_6H_4–	H	CH_3	**8h**	95
9	**7i**	4-(CH_3)–C_6H_4–	OCH_3	H	**8i**	93
10	**7j**	3-(CH_3)–C_6H_4–	H	H	**8j**	94
11	**7k**	3-(CH_3)–C_6H_4–	H	CH_3	**8k**	91
12	**7l**	3-(CH_3)–C_6H_4–	OCH_3	H	**8l**	94
13	**7m**	CH_3	H	H	**8m**	93
14	**7n**	CH_3	H	CH_3	**8n**	95
15	**7o**	CH_3	OCH_3	H	**8o**	96

with aryl amidines (yield >90%) was more favored than that with aliphatic amidines (yield 51–53%). Next, for the transamination reaction, the nitro group in the substrate **7a** was subjected to reduction with 10% Pd/C in AcOH using ammonium formate as a hydrogen donor at 80 °C for 1 h. The resulting crude product obtained after work-up was triturated with diethyl ether to furnish 2-phenylquinazolin-4(3*H*)-one **8a**[12] in 96% isolated yield. Of the 15 quinazolinone derivatives synthesized, physico-chemical parameters of 11 compounds (**8a–e**, **8g–h**, **8j**, and **8m–o**) matched with the ones reported in the literature.[7,13]

The scope and limitation of our strategy were established by synthesizing 14 compounds based on quinazolinone **8b–o** (Table 3) using a variety of aromatic and aliphatic amidine-derived substrates **7b–o** and in all the cases the product was obtained in 91–96% isolated yield after crystallization. In contrast, variable yields of 40–87% were reported for quinazolinones from amidines in the literature under copper-catalyzed conditions.[7]

In summary, we have developed a mild and efficient method for the synthesis of highly substituted benzimidazole and quinazolinone derivatives under catalyst and ligand-free conditions. In general the strategy involves N-arylation and N-benzoylation of amidines with *o*-nitro arenes followed by reduction of the nitro group and intramolecular transamination reaction. The work-up procedure was simple and isolation of the product without column chromatography proved to be an added advantage for the synthesis of benzimidazole and quinazolinone motifs. This procedure will be a value addition for the synthesis of benzimidazole and quinazolinone derivatives of academic and industrial importance.

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8. The mixture of benzenecarboximidamide (0.50 g, 4.11 mmol), 1-fluoro-2-nitrobenzene (0.57 g, 4.11 mmol), and potassium carbonate (0.62 g, 4.52 mmol) in DMSO (5 ml) was taken in a microwave vial. The solution was heated at 110 °C for 30 min in microwave (Biotage). The reaction mixture was cooled to room temperature, water was added, and the compound was extracted with ethyl acetate (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to get the crude product which was triturated with 9:1 hexane–diethyl ether to afford a yellow compound which was used without further purification.
4-Methoxy-N-(5-methyl-2-nitrophenyl)benzene carboximidamide (**3e**): Yield = 0.87 g (92%), yellow oil, R_f = 0.48 (1:1 EtOAc–hexane), IR (KBr) ν_{max} 2920, 1639, 1388, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.96–7.91 (1H, m, ArH), 7.78 (2H, s, ArH), 6.98–6.93 (4H, m, ArH), 3.88 (3H, s, OCH_3), 2.41 (3H, s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.9, 145.7, 139.4, 129.8, 128.7, 127.6, 125.7, 124.8, 123.7, 114.3, 114.0, 55.5, 21.7; mass (ES^+) *m/z* 286.1 (M^++1); Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.28; N, 14.76.
9. To a stirred solution of *N*-(2-nitro-phenyl)-benzamidine (0.25 g, 1.04 mmol) in acetic acid (2 ml) under nitrogen atmosphere were added ammonium formate (0.40 g, 5.18 mmol) and palladium on carbon 10% wet (25 mg) at room temperature. The reaction mixture was heated at 80 °C for 1 h. It was filtered through Celite bed and washed with ethyl acetate. The filtrate was neutralized with satd sodium bicarbonate. The compound was extracted with ethyl acetate (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was triturated with 5:1 hexane–diethyl ether to afford pure compound as white solid.
2-Phenyl-1H-benzimidazole (**5a**): Yield = 0.19 g (96%), white solid, mp >250 °C [lit.[4] 286–289], R_f = 0.48 (2:3 EtOAc–hexane), IR (KBr) ν_{max} 3399, 1653, 1408, 1112 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 8.19–8.16 (2H, m, ArH), 7.61–7.47 (5H, m, ArH), 7.23–7.18 (2H, m, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 151.2, 130.1, 129.9, 128.9, 126.5, 122.1; mass (ES^+) *m/z* 195.3 (M^++1); Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.43; H, 5.16; N, 14.41.
2-(4-Methylphenyl)-5-(trifluoromethyl)-1H-benzimidazole (**5i**): Yield = 0.19 g (90%), white solid, mp 192–194 °C, R_f = 0.54 (2:3 EtOAc–hexane), IR (KBr) ν_{max} 3119, 1620, 1431, 1122 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 13.28 (1H, s, NH), 8.13 (2H, d, *J* = 8.2 Hz, ArH), 7.96 (1H, s, ArH), 7.79 (1H, d, *J* = 8.4 Hz, ArH), 7.56–7.54 (1H, m, ArH), 7.43 (2H, d, *J* = 8.0 Hz, ArH), 2.43 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 154.1, 140.4, 129.6, 126.8, 122.8(d, *J* = 33.7 Hz), 122.4, 118.7, 20.9; mass (ES^+) *m/z* 277.3 (M^++1); Anal. Calcd for $C_{15}H_{11}F_3N_2$: C, 65.21; H, 4.01; N, 10.14. Found: C, 65.18; H, 4.00; N, 10.17.
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11. To a stirred solution of 2-nitrobenzoic acid (1.0 g, 6.66 mmol) in DMF (10 ml) at 0 °C were added DCC (1.51 g, 7.33 mmol) and HOBT (0.99 g, 7.33 mmol) .The reaction mixture was stirred at 0 °C for 1 h to which 4-methoxy-benzamidine (1.22 g, 7.33 mmol) was added and allowed to stir at room temperature for 12 h. The reaction mixture was filtered through Celite bed and washed with ethyl acetate. The filtrate was washed with brine, dried over Na_2SO_4, and

concentrated to get the crude product, which was triturated with hexane and used without any purification.

N-[Imino(4-methoxyphenyl)methyl]-5-methyl-2-nitrobenzamide (**7e**): Yield = 0.70 g (90%), yellow oil, R_f = 0.38 (1:1 EtOAc–hexane), IR (KBr) ν_{max} 3434, 1656, 1524, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.56 (1H, br s, NH), 8.09 (1H, d, J = 8.5 Hz, ArH), 7.73 (1H, s, ArH), 7.69–7.66 (1H, m, ArH), 7.38–7.36 (2H, m, ArH), 7.11–7.06 (2H, m, ArH), 6.73 (1H, br s, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 163.5, 153.0, 143.4, 131.2, 130.8, 130.6, 129.9, 129.7, 129.2, 124.8, 123.6, 114.3, 55.6, 21.5; mass (ES^+) m/z 314.3 (M^++1); Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.37; H, 4.80; N, 13.43.

12. To a solution of *N*-[Imino-(4-methoxy-phenyl)-methyl]-2-nitro-benzamide (0.4 g, 0.333 mmol) in acetic acid (5 ml) under nitrogen atmosphere were added ammonium formate (0.42 g, 1.67 mmol) and palladium on carbon 10% wet (0.4 g) at room temperature. The reaction mixture was heated at 80 °C for 1 h. It was filtered through Celite bed and washed with ethyl acetate. The filtrate was neutralized with satd sodium bicarbonate. The compound was extracted with ethyl acetate (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was triturated with diethyl ether to afford pure compound as white solid.

2-(4-Methoxyphenyl)-6-methylquinazolin-4(3H)-one (**8e**): Yield = 0.2 g (92%), white solid, mp >250 °C [lit.[13d] 258–259] R_f = 0.57 (2:5 EtOAc–hexane), IR (KBr) ν_{max} 3089, 1672, 1598, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD) δ = 8.02 (3H, d, J = 7.0 Hz, ArH), 7.65 (2H, d, J = 16.2 Hz, ArH), 7.05 (2H, d, J = 6.7 Hz, CH), 3.90 (3H, s, OCH_3), 2.5 (3H, s, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 161.6, 135.6, 135.5, 129.2, 125.1, 124.8, 120.4, 113.8, 55.3, 20.8; mass (ES^+) m/z 267.3 (M^++1); Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.27; N, 10.53.

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