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Benzimidazoles and benzoxazoles *via* the nucleophilic addition of anilines to nitroalkanes†

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PPA-induced umpolung triggers efficient nucleophilic addition of unactivated anilines to nitroalkanes to produce *N*-hydroxyimidamides. The latter undergo sequential acid-promoted cyclocondensation with *ortho*-OH or *ortho*-NHR moieties to afford benzoxazoles and benzimidazoles, respectively.

Introduction

It is hard to overstate the importance of benzimidazole and benzoxazole scaffolds for modern bioorganic and medicinal chemistry. Out of over 1.2 million and 300 000 benzimidazoles and benzoxazoles, respectively, listed in the SciFinder database, more than 400 000 were used in biological studies. Several best-selling drugs, such as antiulcerants Nexium (esomeprazole),[1] Prevacid (lansoprazole),[2] and Aciphex (rabeprazole);[3] antihypertensives Micardis (telmisartan)[4] and Bendazol;[5] anticoagulant agent Pradaxa (dabigartan);[6] and anticancer drug Treanda (bendamustine)[7] possess this versatile pharmacophore (Fig. 1).

Classical approaches to imidazoles and oxazoles involve cyclocondensations of carboxylic acid derivatives (esters, *ortho*-esters, acyl chlorides, *etc.*) with 1,2-phenylenediamines or 2-aminophenols, respectively.[8] These approaches rely on the efficiency of initial nucleophilic attack by the aniline moiety at an activated carbonyl group. Alternative routes *via* oxidative cyclocondensation with aldehydes take advantage of the enhanced reactivity of these electrophiles.[9] Condensations with less electrophilic carbonyl species, such as carboxylic acids can also be carried out in concentrated organic or mineral acids, although the require harsh conditions.[10] Herein we wish to report an alternative efficient approach to benzimidazole and benzoxazole heterocyclic cores employing unusual electrophilic behaviour of nitroalkanes activated with polyphosphoric acid.

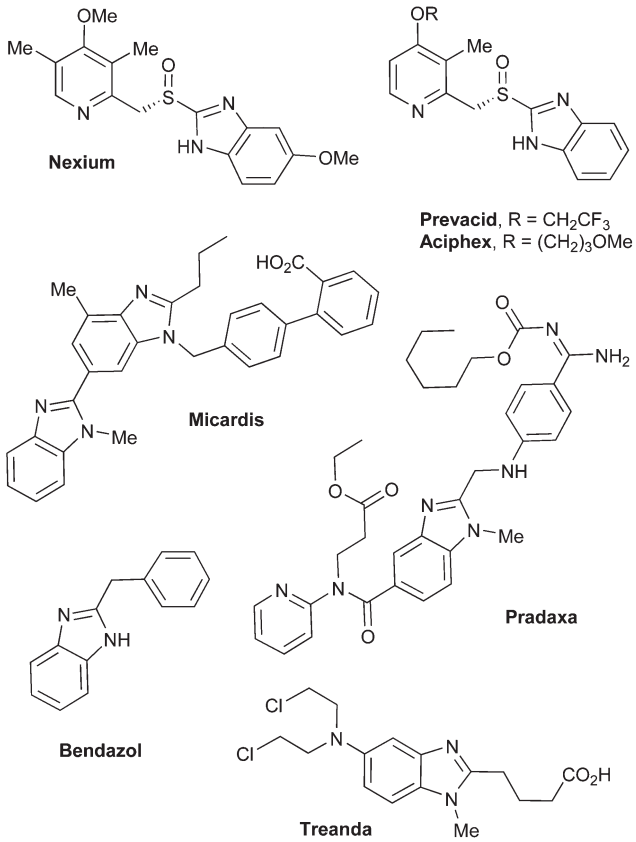

Fig. 1 Best-selling drugs with benzimidazole cores.

Results and discussion

In our prior research we have studied the behavior of nitro compounds in polyphosphoric acid (PPA)[11] and came across unusual reactivity of nitroalkanes **1** in reactions with electron-rich arenes. Treatment of **1** with PPA converted these normally

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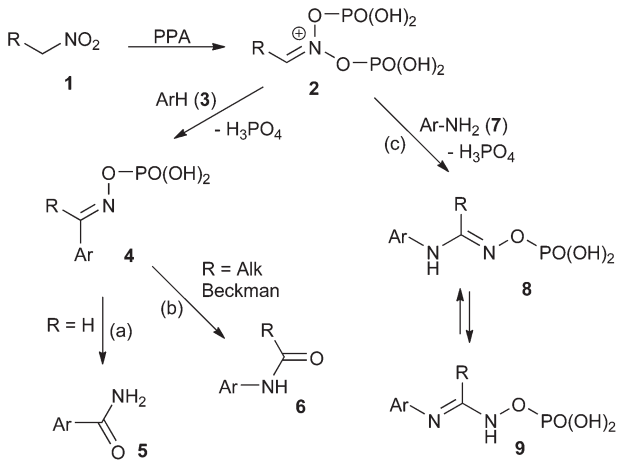
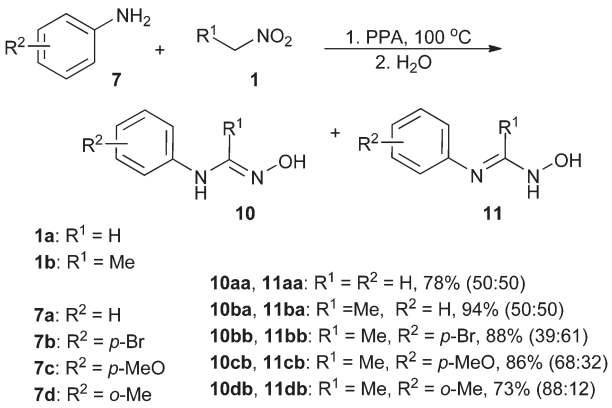


Scheme 1

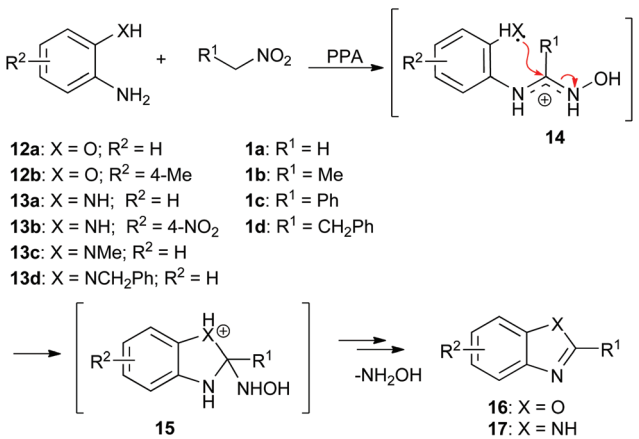


Scheme 2

nucleophilic species into electrophilic phosphorylated *aci* forms **2**. This umpolung activated nitroalkane towards attack by electron-rich arene **3**. Subsequent elimination of H_3PO_4 provided oxime intermediates **4**. Aldoximes **4** (R = H) obtained in reactions with nitromethane typically undergo elimination of a second molecule of H_3PO_4 to form nitriles which, after acid-mediated hydrolysis, provide primary amides **5** or parent carboxylic acids (path **a**, Scheme 1).[12] Ketoximes **4** (R = Alk) resulted from reactions with higher nitroalkanes undergo a Beckman rearrangement to afford the corresponding anilides **6** (path **b**, Scheme 1).[13] We rationalized that anilines can also be employed in a similar transformation as nitrogen-based nucleophiles to produce imidamides **8–9** (Scheme 1), which can further be employed as convenient building blocks for the synthesis of heterocyclic compounds.

This idea was realized upon heating a mixture of aniline (**7a**) with 5 equiv. of nitromethane (**1a**) in 86% PPA at 100 °C for 14 h. The expected transformation proceeded smoothly affording, after quenching with aqueous ammonia, crystalline *N*-phenylformimidamide in good yield. Next, we examined the reactivity of anilines towards higher nitroalkanes. To this end, mixtures of anilines **7a–d** and nitroethane (**1b**, 1.25 equiv.) were stirred in PPA at 105 °C for 5 h. In all these cases the corresponding *N*-phenylacetimidamides were obtained in good to excellent yields as crystalline solids upon simple dilution of the reaction mixtures with aqueous ammonia (Scheme 2). Interestingly, NMR spectra of the products in DMSO-d_6 showed mixtures of slowly exchanging tautomers **10** and **11** (Scheme 2), which averaged out upon heating of the sample to 110 °C or in the presence of TFA. We also found that the tautomeric ratio **10** : **11** was dependent on the electronic properties of the aromatic ring in the aniline reagent. Thus, the parent aniline (**7a**) provided a 1 : 1 tautomeric mixture of **10ba**/**11ba**. Introduction of electron withdrawing (Br) and electron-donating (OMe) substituents shifted the equilibria towards tautomers **11** (**10bb** : **11bb** = 39 : 61) or **10** (**10cb** : **11cb** = 68 : 32), respectively (Scheme 2). Employment of aniline **7d** with the sterically demanding methyl substituent in the *ortho*-position of the aromatic rings afforded nearly pure tautomer **10db** (Scheme 2).

Having optimized the nucleophilic amination step, we attempted to incorporate it into a heteroannulation cascade. Accordingly, substrates **12** or **13** possessing heteroatom-based nucleophilic *ortho*- substituents (XH = OH or NH_2, Scheme 3) were subjected to the standard reaction conditions. It was anticipated that the initially-formed imidamide **14** (in proto-



16aa: X = O; R1 = H; R2 = H (14 h at 100 °C - 88%)
16ba: X = O; R1 = Me; R2 = H (3 h at 110 °C - 91%)
16bb: X = O; R1 = Me; R2 = 5-Me (3 h at 110 °C - 89%)
16ca: X = O; R1 = Ph; R2 = H (7 h at 150 °C - 86%)
16db: X = O; R1 = CH2Ph; R2 = 5-Me (7 h at 150 °C - 83%)

17aa: X = NH; R1 = R2 = H (13 h at 100 °C - 86%)
17ba: X = NH; R1 = Me; R2 = H (3 h at 110 °C - 91%)
17bb: X = NH; R1 = Me; R2 = 5-NO2 (6 h at 110 °C - 93%)
17ca: X = NH; R1 = Ph; R2 = H (8 h at 150 °C - 83%)
17da: X = NH; R1 = CH2Ph; R2 = H (11 h at 140 °C - 84%)
17ac: X = NMe; R1 = R2 = H (13 h at 100 °C - 83%)
17bc: X = NMe; R1 = Me; R2 = H (3 h at 110 °C - 91%)
17bd: X = NCH2Ph; R1 = Me; R2 = H (3 h at 110 °C - 88%)

Scheme 3

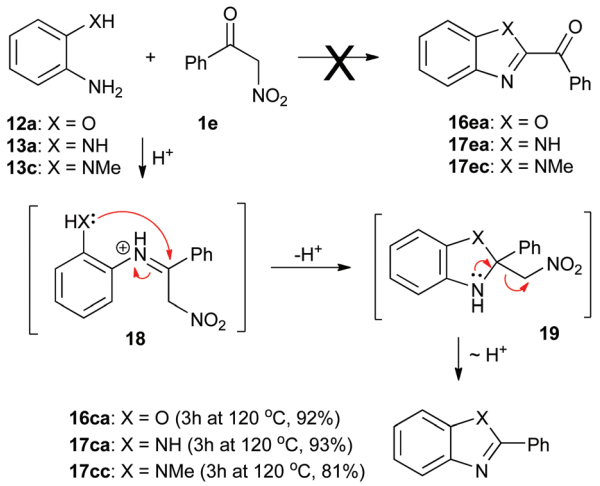
nated form) would undergo a nucleophilic ring closure to furnish cyclic aminal **15**, which after subsequent acid-promoted elimination of hydroxylamine would afford the corresponding heterocyclic products, benzoxazoles **16** (X = O) or benzimidazoles **17** (X = NH), respectively (Scheme 3).

This strategy proved to be very fruitful. Thus, the reaction between 2-aminophenol (**12a**) and nitromethane (**1a**) in PPA produced benzoxazole (**16aa**) in high yield. 1,2-Diaminobenzene (**13a**) afforded benzimidazole (**17aa**) under the same conditions (Scheme 3). It should be pointed out that the large excess of nitromethane (5 equiv.) used in both cases was necessary to compensate for significant loss of reagent due to evaporation in the employed reaction set up.[14] Less volatile nitroalkanes were used in only 10% excess, which was sufficient for ensuring complete conversions. It also allowed for carrying out the reaction at higher temperatures, which further improved the reaction efficiency. Treatment of aminophenols **12a,b** and diaminobenzenes **13a,b** with nitroethane **1b** afforded the corresponding benzoxazoles **16ba**, **16bb** and benzimidazoles **17ba**, **17bb** in excellent yields (Scheme 3). Further increase of reaction temperature to 140–150 °C was necessary to engage of the less reactive, sterically demanding (nitromethyl)benzene (**1c**) and (2-nitroethyl)benzene (**1d**) to obtain the corresponding 2-phenyl- (**16ca**, **17ca**) and 2-benzyl-substituted products **16da** and bendazole (**17da**) in high yields.

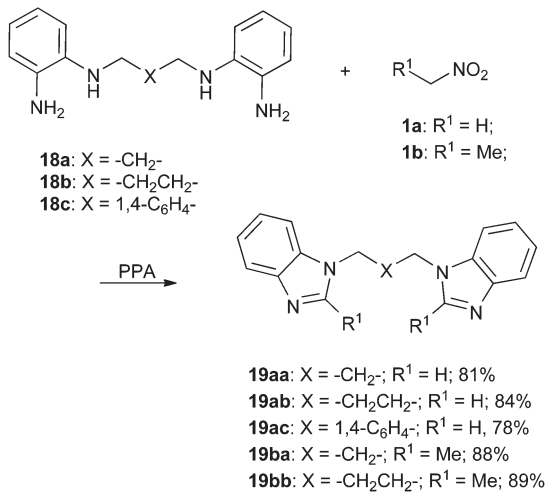
To further showcase the synthetic usefulness of the developed method and its competitiveness with existing protocols, we attempted synthesis of *N*-substituted benzimidazoles. First, we probed the reaction of nitromethane (**1a**) and nitroethane (**1b**) with *N*-monomethylated phenylenediamine (**13c**). Both reactions afforded *N*-methylbenzimidazoles (**17ac** and **17bc**) in high yields (Scheme 3). Under the same conditions a more sterically hindered **13d** efficiently provided the corresponding *N*-benzylated product **17bd** (Scheme 3).

Interestingly, attempts to synthesize 2-acylsubstituted azoles by reacting anilines **12a**, **13a**, and **13c** with 2-nitro-1-phenylethan-1-one (**1e**) did not provide the expected products **16ea**, **17ea**, and **17ec**. Instead, 2-phenylsubstituted azoles **16ca**, **17ca**, and **17cc** were obtained in excellent yields (Scheme 4). We believe that this transformation proceeded *via* the initial formation of iminium intermediate **18**, followed by intramolecular nucleophilic attack to give cyclic aminal **19**. The latter further undergoes nucleofugal cleavage of nitromethane to produce **16ca** and **17ca** (Scheme 4). Apparently, this alternative reactivity results from the superior electrophilicity of the ketone carbonyl function compared to the *aci* form of the nitroalkane.

We have also explored the possibility of furnishing bis-imidazoles **19**, potentially useful as precursors for chelating NHC ligands broadly used in transition metal catalysis and material science applications.[15] Using our methodology these scaffolds can be accessed *via* a double-fold nucleophilic cyclization of tethered bis(1,2-phenylenediamines) **18** with 2 equivalents of an appropriate nitroalkane (Scheme 5). Indeed, the corresponding tethered bis-imidazoles **19** were isolated in excellent yields (Scheme 5), although required extended reaction times as compared to single-fold cyclizations described above.



Scheme 4



Scheme 5

Conclusions

In conclusion, we demonstrated that PPA-induced umpolung activates the α-carbon of nitroalkanes towards addition of nitrogen-based nucleophiles. This transformation was used to design an efficient method for the synthesis of oxazoles and imidazoles. The synthetic usefulness of this method was demonstrated in a concise synthesis of antihypertensive drug bendazole (**17da**). A double-fold cyclization can be employed for efficient synthesis of tethered bis-imidazoles.

Experimental part

General information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with BBO probe in $CDCl_3$ or DMSO-d_6, using TMS as internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using HCO_2Na–HCO_2H for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried drum vials open to the atmosphere employing overhead stirring. Reaction progress and purity of isolated compounds were controlled by TLC on Silufol UV-254 plates, eluting with EtOAc. Flash column chromatography was performed on silica gel (32–63 μm, 60 Å pore size).

Nitroacetophenone (**1e**),[16] 2-phenylnitroethane (**1d**),[17] phenyitromethane (**1c**),[18] 1,3-bis(2-aminophenylamino)propane (**18a**),[19] 1,4-bis(2-aminophenylamino)butane (**18b**),[19] and *N*,*N*′-bis(2-aminophenyl)-1,4-benzenedimethanamine (**18c**)[20] were synthesized according to published procedures. All other reagents and solvents were purchased from commercial vendors and used as received.

***N*-Hydroxy-*N*′-arylformimidamides (10, 11) (general procedure).** Mixture of aniline (2 mmol) and nitroalkane (2.5 mmol of nitroethane or 10 mmol of nitromethane) in PPA (4 g, 86% P_2O_5) was vigorously stirred. Reactions with nitromethane and nitroethane were heated for 14 h at 100 °C or for 5 h at 110 °C, respectively. When TLC analysis confirmed consumption of starting aniline, the mixture was cooled down to 80 °C and diluted with water (10 mL). The mixture was neutralized with 20% aqueous ammonia (to pH ~ 9, *ca.* 25 mL), heated to reflux, and filtered. The filtrate was then cooled down to 0 °C, and formed crystalline precipitate was collected by suction filtration. Analytically pure samples were obtained by second crystallization from water.

***N*-Hydroxy-*N*′-phenylformimidamide (10aa, 11aa).**[21] This material was obtained as colorless crystalline solid, mp 127–129 °C (water) in a yield 212 mg (1.56 mmol, 78%); ^{1}H NMR (DMSO-d_6) δ, ppm: 9.83 (br. s, 1H), 8.52 (d, J = 10.4 Hz, 1H), 7.44 (d, J = 10.4 Hz, 1H), 7.12–7.21 (m, 4H), 6.83 (t, J = 7.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ, ppm: 147.6, 140.7, 129.1 (2C), 123.0, 122.7 (2C); NMR spectra are averaged at RT. IR, cm^{-1}: 3378, 3312, 3015, 1695, 1635, 1594, 1465, 1363, 1326, 911, 809, 765; HRMS calcd for $C_7H_9N_2O$ (M + H)$^+$: 137.0715, found 137.0712.

***N*′-Hydroxy-*N*-phenylacetimidamide (10ba, 11ba).**[22] This material was obtained as colorless crystalline solid, mp 114–115 °C (water) in a yield 282 mg (1.88 mmol, 94%); **10ba**: ^{1}H NMR (DMSO-d_6) δ, ppm: 9.11 (br. s, 1H), 7.85 (br. s, 1H), 7.25–7.24 (m, 2H), 7.09 (d, J = 7.13 Hz, 2H), 7.00 (t, J = 5.96 Hz, 1H), 1.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ, ppm: 151.9, 142.1, 128.3 (2C), 122.2, 117.5 (2C), 14.1. **11ba**: ^{1}H NMR (DMSO-d_6) δ, ppm: 9.49 (br. s, 1H), 7.99 (br. s, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.19–7.15 (m, 2H), 6.78 (t, J = 6.1 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 147.1, 140.2, 128.8 (2C), 122.6, 119.5 (2C), 16.1. ^{1}H NMR (DMSO-d_6, CF_3COOH) δ, ppm: 10.54 (s, 1H), 7.46–7.43 (m, 2H), 7.36–7.32 (m, 3H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6, CF_3COOH) δ, ppm: 157.3, 135.9, 129.3 (2C), 127.2, 126.0 (2C), 14.2; IR, cm^{-1}: 3373, 3312, 3004, 1669, 1631, 1594, 1494, 1363, 1314, 1236, 1030, 907, 806, 752, 686; HRMS calcd for $C_8H_{11}N_2O$ (M + H)$^+$: 151.0871, found 151.0869.

***N*-(4-Bromophenyl)-*N*′-hydroxyacetimidamide (10bb, 11bb).** This material was obtained as colorless crystalline solid, mp 143–144 °C (water) in a yield 403 mg (1.76 mmol, 88%); **10bb**: ^{1}H NMR (DMSO-d_6) δ, ppm: 9.26 (br. s, 1H), 8.21 (br. s, 1H), 7.45 (d, J = 8.90 Hz, 2H), 7.33 (d, J = 8.90 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 151.8, 141.4, 131.0 (2C), 119.4 (2C), 110.6, 14.1; **11bb**: ^{1}H NMR (DMSO-d_6) δ, ppm: 9.60 (br. s, 1H), 8.05 (br. s, 1H), 7.40 (d, J = 8.74 Hz, 2H), 7.06 (d, 8.74 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 146.6, 139.8, 131.4 (2C), 123.9 (2C), 114.2, 16.1; IR, cm^{-1}: 3383, 3111, 2976, 2360, 1659, 1585, 1543, 1491, 1421, 1387, 1341, 1313, 1299, 1275, 1261, 1236, 1212, 1073, 947, 914, 841, 822, 757; HRMS calcd for $C_8H_{10}BrN_2O$ (M + H)$^+$: 228.9977, found 228.9968.

***N*′-Hydroxy-*N*-(4-methoxyphenyl)acetimidamide (10cb, 11cb).**[23] This material was obtained as colorless crystalline solid, mp 150–152 °C (water) in a yield 310 mg (1.72 mmol, 86%); **10cb**: ^{1}H NMR (DMSO-d_6) δ, ppm: 9.30 (br. s, 1H), 7.60 (br. s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 156.2, 148.5, 133.6, 125.8 (2C), 114.4 (2C), 55.5, 16.2; **11cb**: ^{1}H NMR (DMSO-d_6) δ, ppm: 8.95 (br. s, 1H), 7.77 (br. s, 1H), 7.41 (d, J = 9.00 Hz, 2H), 6.77 (d, J = 9.0 Hz, 1H), 3.67 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 153.2, 152.5, 136.1, 119.4 (2C), 114.1 (2C), 55.6, 14.5; IR, cm^{-1}: 3386, 3314, 3216, 1636, 1560, 1491, 1441, 1420, 1370, 1333, 1300, 1260, 1229, 1182, 1034, 825, 811, 763, 712; HRMS calcd for $C_9H_{13}N_2O_2$ (M + H)$^+$: 181.0977, found 181.0976.

***N*′-Hydroxy-*N*-(*o*-tolyl)acetimidamide (10db, 11db).** This material was obtained as colorless crystalline solid, mp 104–105 °C (water) in a yield 240 mg (1.46 mmol, 73%); ^{1}H NMR (DMSO-d_6) δ, ppm: 9.37, (br. s, 1H), 7.60 (br. s, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.16 (dd, J = 7.4, 6.8 Hz, 1H), 7.08 (d, J = 6.8 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 2.20 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 148.5, 139.0, 133.5, 130.8, 126.7, 126.6, 125.2, 18.1, 16.1; IR, cm^{-1}: 3366, 3085, 2981, 2794, 1638, 1610, 1517, 1488, 1432, 1393, 1354, 1314, 1274, 1131, 1032, 931, 830, 807, 707; HRMS calcd for $C_9H_{13}N_2O$ (M + H)$^+$: 165.1028, found 165.1025.

Synthesis of benzoxazoles 16 (general procedure). A mixture of *o*-aminophenol (2 mmol) and nitroalkane (2.5 mmol) in PPA (4 g, 86% P_2O_5) was vigorously stirred and heated to the specified temperature. The reactions with nitromethane (**1a**, 10 mmol) were carried out at 100 °C for 14 h. Reactions with nitroethane (**1b**) were carried at 105–110 °C for 3 h. Reactions with 1-nitro-2-phenylethane and phenylnitromethane were carried out at 150 °C for 7 h. When TLC analysis confirmed the completion of the reaction the mixture was cooled down to 80 °C and diluted with water (25 mL) and neutralized with 20% aqueous ammonia (to pH ~ 9, *ca.* 25 mL), and then extracted with CH_2Cl_2 (4 × 15 mL). Combined organic phases

were dried with $CaCl_2$, filtered, and concentrated in vacuum. Flash column chromatography on Silica gel eluting with mixture of *n*-hexane and ethyl acetate (gradient from 9 : 1 to 5 : 5) afforded the corresponding product. Physical and spectral properties of all the synthesized materials were identical to those previously reported in literature.

Benzoxazole (16aa).[24] This material was obtained as colorless oil that solidified upon standing. Yield 210 mg (1.76 mmol, 88%); ^{1}H NMR ($CDCl_3$) δ, ppm: 7.30–7.40 (2H, m), 7.51–7.60 (1H, m), 7.74–7.83 (1H, m); 8.09 (1H, s); ^{13}C NMR ($CDCl_3$) δ, ppm: 111.0, 120.6, 124.7, 125.7, 140.0, 150.0, 152.6; HRMS calcd for C_7H_6NO $(M + H)^+$: 120.0449, found 120.0438.

2-Methylbenzoxazole (16ba).[25] This material was obtained as colorless oil, yield 242 mg (1.82 mmol, 91%). ^{1}H NMR ($CDCl_3$) δ, ppm: 2.61 (3H, s), 7.20–7.30 (2H, m), 7.39–7.47 (1H, m), 7.58–7.66 (1H, m); ^{13}C NMR (CDCl3) δ, ppm: 14.6, 110.3, 119.5, 124.3, 124.6, 141.4, 151.1, 164.0; HRMS calcd for C_8H_8NO $(M + H)^+$: 134.0606, found 134.0600.

2,5-Dimethylbenzoxazole (16bb).[26] This material was obtained as colorless oil, yield 262 mg (1.78 mmol, 89%). ^{1}H NMR ($CDCl_3$) δ, ppm: 2.44 (3H, s), 2.61 (3H, s), 7.08 (1H, d, J = 8.5 Hz), 7.32 (1H, d, J = 8.5 Hz), 7.43 (1H, s); ^{13}C NMR (CDCl3) δ, ppm: 14.6, 21.5, 109.7, 119.4, 125.6, 134.1, 141.6, 149.3, 164.1; HRMS calcd for $C_9H_{10}NO$ $(M + H)^+$: 148.0762, found 148.0767.

2-Phenylbenzoxazole (16ca).[25] This material was obtained as colorless oil, yield 335 mg (1.72 mmol, 86%). ^{1}H NMR (DMSO-d_6) δ, ppm: 7.37–7.46 (2H, m), 7.57–7.66 (3H, m), 7.75–7.84 (2H, m), 8.16–8.24 (2H, m); ^{13}C NMR (DMSO-d_6) δ, ppm: 110.9, 119.8, 124.9, 125.5, 126.4, 127.3 (2C), 129.3 (2C), 131.9, 141.5, 150.2, 162.2; HRMS calcd for $C_{13}H_{10}NO$ $(M + H)^+$: 196.0762, found 196.0758.

2-Benzyl-5-methylbenzoxazole (16db).[27] This material was obtained as colorless oil, yield 372 mg (1.66 mmol, 83%). ^{1}H NMR ($CDCl_3$) δ, ppm: 2.39 (3H, s), 4.20 (2H, s), 7.02–7.06 (1H, d, J = 8.5 Hz), 7.18–7.34 (6H, m), 7.42 (1H, s); ^{13}C NMR (CDCl3) δ, ppm: δ 21.6, 35.4, 110.0, 119.7, 126.0, 127.4, 129.0 (2C), 129.1 (2C), 134.3, 134.9, 141.2, 149.4, 165.5; HRMS calcd for $C_{15}H_{14}NO$ $(M + H)^+$: 224.1075, found 224.1067.

Synthesis of benzimidazoles 17 (general procedure). A mixture of *o*-phenylenediamine (2 mmol) and nitroalkane (2.5 mmol) in PPA (4 g, 86% P_2O_5) was vigorously stirred at specified temperature. The reaction progress was monitored by TLC. The reactions were carried out for 13 h at 100 °C with nitromethane, for 3 h at 110 °C with nitroethane, for 8 h at 150 °C with phenylnitromethane, and for 11 h at 150 °C with 1-nitro-2-phenylethane. After achieving full conversion the reaction mixture was cooled down to 80 °C and diluted with water (15 mL). Crude mixture was neutralized with 20% aqueous ammonia (25 mL), cooled down, and the formed crystalline precipitate was collected by suction filtration.

1*H*-Benzimidazole (17aa).[28] This material was obtained as colorless crystals, mp 170 °C (ethanol) in a yield 203 mg (1.72 mmol, 86%). ^{1}H NMR ($CDCl_3$) δ, ppm: 8.31 (br. s, 2H), 7.69 (dd, J = 5.9, 3.2 Hz, 2H), 7.31 (dd, J = 6.1, 3.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ, ppm: 140.5, 136.7 (2C), 123.6 (2C), 115.5 (2C); IR, cm^{-1}: 2355, 2342, 1460, 1411, 1274, 1245, 753, 745; HRMS calcd for $C_7H_7N_2$ $(M + H)^+$: 119.0609, found 119.0619.

2-Methyl-1*H*-benzimidazole (17ba).[29] This material was obtained as colorless crystals, mp 177–178 °C (ethanol) in a yield 240 mg (1.82 mmol, 91%). ^{1}H NMR ($CDCl_3$) δ, ppm: 7.56 (dd, J = 5.9, 3.2 Hz, 2H) 7.24 (dd, J = 6.0, 3.2 Hz, 2H), 6.0 (br. s, 1H), 2.68 (3H); ^{13}C NMR ($CDCl_3$) δ, ppm: 151.1, 137.6 (2C), 122.9 (2C), 114.5 (2C), 14.7; IR, cm^{-1}: 2685, 1557, 1446, 1437 1417, 1387, 1361, 1273, 1218, 1025, 848, 830, 730; HRMS calcd for $C_8H_9N_2$ $(M + H)^+$: 133.0766, found 133.0765.

2-Methyl-5-nitro-1*H*-benzimidazole (17bb).[30] This material was obtained as colorless crystals, mp 198–199 °C (ethanol) in a yield 329 mg (1.86 mmol, 93%). ^{1}H NMR ($CDCl_3$) δ, ppm: 8.36 (d, J = 2.1 Hz, 1H), 8.06 (dd, J = 8.8, 2.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ, ppm: 142.1, 117.2, 14.9; IR, cm^{-1}: 3108, 2974, 2784, 1633, 1544, 1514, 1473, 1419, 1383, 1337, 1309, 1270, 1220, 1124, 1065, 1028, 947, 879, 822, 738; HRMS calcd for $C_8H_8N_3O_2$ $(M + H)^+$: 178.0617, found 178.0612.

2-Phenyl-1*H*-benzimidazole (17ca).[31] This material was obtained as colorless crystals, mp 296–297 °C (ethanol) in a yield 322 mg (1.66 mmol, 83%). ^{1}H NMR (DMSO-d_6) δ, ppm: 12.91 (br. s, 1H), 8.19 (d, J = 7.35 Hz, 2H), 7.67–7.47 (m, 5H), 7.21 (d, J = 4.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ, ppm: 151.2 (2C), 130.2 (2C), 130.2, 128.9 (4C), 126.4 (4C); IR, cm^{-1}: 2366, 2342, 1464, 1445, 1410, 1372, 1315, 1276, 1226, 1119, 969, 740, 701, 684; HRMS calcd for $C_{13}H_{11}N_2$ $(M + H)^+$: 195.0922, found 195.0923.

2-Benzyl-1*H*-benzimidazole (bendazole, 17da).[32] This material was obtained as colorless crystals, mp 186–187 °C (benzene) in a yield 350 mg (1.68 mmol, 84%). ^{1}H NMR (DMSO-d_6) δ, ppm: 12.28 (br. s, 1H), 7.48 (dd, J = 5.2, 3.2 Hz, 2H), 7.36–7.29 (m, 4H), 7.25–7.20 (m, 1H), 7.14–7.10 (m, 2H), 4.17 (s, 2H); ^{13}C NMR (DMSO-d_6) δ, ppm: 153.5 (2C), 137.7 (2C), 128.8 (3C), 128.5 (3C), 126.5, 121.3 (2C), 34.9; IR, cm^{-1}: 2360, 2342, 1422, 1268, 1022, 1010, 927, 766, 745, 722, 692, 669; HRMS calcd for $C_{14}H_{13}N_2$ $(M + H)^+$: 209.1079, found 209.1076.

1-Methyl-1*H*-benzoimidazole (17ac). Mp 59–62 °C (hexane); ^{1}H NMR ($CDCl_3$) δ, ppm: 7.72–7.71 (m, 2H), 7.26–7.14 (m, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ, ppm: 143.4, 143.3, 122.8, 122.0, 119.8, 109.3, 30.8; IR, cm^{-1}: 2915, 2851, 1498, 1459, 1424, 1329, 1284, 1249, 1204, 1054, 1003, 886, 775, 739, 719; HRMS calcd for $C_8H_9N_2$ $(M + H)^+$: 133.0706, found 133.0761.

1,2-Dimethyl-1*H*-benzoimidazole (17bc). Mp 111–112 °C (hexane); ^{1}H NMR (DMSO-d_6) δ, ppm: 7.51 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.19–7.11 (m, 3H), 3.71 (s, 3H), 2. 51 (s, 3H); ^{13}C NMR (DMSO-d_6) δ, ppm: 152.0, 142.3, 135.8, 121.2, 121.0, 118.0, 109.5, 29.6, 13.4; IR, cm^{-1}: 3052, 2941, 1617, 1520, 1511, 1479, 1446, 1396, 1328, 1286, 1234, 1008, 995, 928, 858, 753, 732; HRMS calcd for $C_9H_{11}N_2$ $(M + H)^+$: 147.0922, found 147.0936.

1-Benzyl-2-methyl-1*H*-benzoimidazole (17bd). Mp 58–59 °C (petroleum ether); ^{1}H NMR (DMSO-d_6) δ, ppm: 7.56 (dd, J = 5.85, 2.95 Hz, 1H), 7.46 (dd, J = 5.58, 3.27 Hz, 1H), 7.34–7.25 (m, 3H), 7.16–7.12 (m, 4H), 5.47 (s, 3H), 3.38 (s, 2H); ^{13}C NMR

(DMSO-d_6) δ, ppm: 151.9, 142.4, 137.0, 135.4, 128.9 (2C), 127.5, 126.6 (2C), 121.6, 121.3, 118.3, 110.0, 46.2, 13.7; IR, cm^{-1}: 3033, 1619, 1525, 1465, 1452, 1401, 1354, 1330, 1283, 1248, 1227, 1154, 1013, 856, 726, 694; HRMS calcd for $C_{15}H_{14}N_2Na$ $(M + Na)^+$: 245.1055, found 245.1053.

Benzoxazoles 16 and benzimidazoles 17 by the reaction with nitroacetophenone. A mixture of aniline (**12a**, **13a**, or **13c**, 2 mmol) and nitroacetophenone (**1e**, 2.2 mmol) in PPA (4 g, 87% P_2O_5) was vigorously stirred for 3 h at 120 °C monitoring the reaction progress by TLC. When the reaction was complete, the mixture was cooled down to 80 °C, diluted with water (25 mL), and neutralized with 20% aqueous ammonia (25 mL). The resulted solution was cooled down and the formed precipitate was collected by suction filtration. The physical and spectral properties of products **16ca**, **17ca** obtained in these experiments were identical to those described above.

1-Methyl-2-phenyl-1*H*-benzoimidazole (17cc). Mp 94–96 °C (hexane); ^1H NMR ($CDCl_3$) δ, ppm: 7.87 (m, 1H), 7.8–7.79 (m, 2H), 7.56–7.50 (m, 3H), 7.42–7.39 (m, 1H), 7.34–7.31 (m, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ, ppm: 153.9, 143.1, 136.7, 129.9, 129.6 (2C), 128.8 (2C), 122.9, 122.6, 120.0, 109.7, 31.8; IR, cm^{-1}: 2365, 2333, 1469, 1440, 1349, 1383, 1278, 1264, 776, 766, 755, 714, 703; HRMS calcd for $C_{14}H_{12}N_2Na$ $(M + Na)^+$: 231.0898, found 231.0895.

1,3-Bis(1*H*-benzoimidazol-1-yl)propane (19aa). Mp 135–136 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ, ppm: 7.89 (s, 1H), 7.81–7.79 (m, 1H), 7.28–7.23 (m, 3H), 4.16 (t, J = 6.9 Hz, 2H), 2.53–2.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ, ppm: 143.8 (2C), 142.7, 133.4, 123.5 (2C), 122.7 (2C), 120.7 (2C), 109.5 (2C), 41.8, 29.5; IR, cm^{-1}: 2363, 2342, 1495, 1459, 1442, 1357, 1322, 1287, 1252, 1199, 1180, 893, 875, 866, 772, 760, 743, 721; HRMS calcd for $C_{17}H_{17}N_4$ $(M + H)^+$: 277.1453, found 277.1455.

1,4-Bis(1*H*-benzoimidazol-1-yl)butane (19ab). Mp 174–175 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ, ppm: 7.8 (s, 1H), 7.78–7.76 (m, 1H), 7.29–7.22 (m, 3H), 4.10 (m, 2H), 1.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ, ppm: 143.9 (2C), 142.8133.6, 123.3 (2C), 122.5 (2C), 120.6 (2C), 109.5 (2C), 44.5, 27.3; IR, cm^{-1}: 2360, 1495, 1462, 1442, 1384, 1374, 1357, 1333, 1283, 1249, 1196, 1159, 1009, 1002, 880, 771, 752, 742, 736; HRMS calcd for $C_{18}H_{19}N_4$ $(M + H)^+$: 291.1610, found 291.1608.

1,4-Bis((1*H*-benzo[*d*]imidazol-1-yl)methyl)benzene (19ac). Mp 168–169 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ, ppm: 7.83 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.21–7.14 (m, 3H), 7.03 (s, 2H), 5.22 (s, 2H); ^{13}C NMR ($CDCl_3$) δ, ppm: 143.9, 143.1, 135.6, 133.8, 127.7, 123.2, 122.4, 120.5, 109.9, 48.33; IR, cm^{-1}: 2363, 2342, 1489, 1454, 1366, 1352, 1286, 1259, 1169, 777, 766, 744, 740, 731; HRMS calcd for $C_{22}H_{19}N_4$ $(M + H)^+$: 339.1610, found 339.1619.

1,3-Bis(2-methyl-1*H*-benzoimidazol-1-yl)propane (19ba). Mp 226–227 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ, ppm: 7.68 (dd, J = 4.8, 1.3 Hz, 1H), 7.23–7.18 (m, 3H), 4.05 (t, J = 4.3 Hz, 2H), 2.52 (s, 3H), 1.86–1.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ, ppm: 151.3, 142.8, 135.0, 122.3, 122.1, 119.4, 109.0, 43.4, 27.3, 14.1; IR, cm^{-1}: 2948, 1612, 1507, 1457, 1404, 1358, 1332, 1285, 1248, 1159, 1136, 1011, 853, 790, 768, 735; HRMS calcd for $C_{19}H_{21}N_4$ $(M + H)^+$: 305.1766, found 305.1761.

1,4-Bis(2-methyl-1*H*-benzoimidazol-1-yl)butane (19bb). Mp 196–197 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ, ppm: 7.68 (dd, J = 4.6, 1.3 Hz, 1H), 7.24–7.19 (m, 3H), 4.06 (t, J = 4.6 Hz, 2H), 2.53 (s, H), 1.86–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ, ppm: 151.3, 142.7, 135.0, 122.3, 122.1, 119.4, 109.0, 43.4, 27.3, 14.1; IR, cm^{-1}: 2369, 2336, 1457, 1403, 1360, 1288, 1248, 1008, 787, 738; HRMS calcd for $C_{20}H_{22}N_4Na$ $(M + Na)^+$: 341.1742, found 341.1737.

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