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Microwave-assisted green construction of imidazole-fused hybrid scaffolds using 2-aminobenzimidazoles as building blocks†

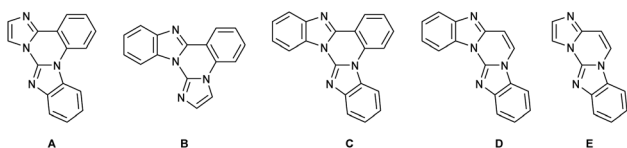
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A class of trinuclear imidazole-fused hybrid scaffolds was constructed by the reaction of 2-(2-bromoaryl)- and 2-(2-bromovinyl)imidazoles with 2-aminobenzimidazoles as building blocks in the presence of a base under microwave irradiation. A nucleophilic aromatic substitution followed by cyclization is proposed as a reaction pathway of this green process.

Introduction

Diverse synthetic methods for the construction of N-fused hybrid scaffolds have been developed due to their characteristic properties that are not shown in each homonuclear heterocycle.¹ In connection with this report, it is known that trinuclear N-fused hybrid structure **A**, benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline, exhibits biological activities and photoelectronic properties (Scheme 1).^{2,3} However, in contrast to well-known synthetic methods of each homonuclear quinazoline, imidazole and benzimidazole, several synthetic methods are reported for their trinuclear N-fused hybrid structures with a limited substrate scope.⁴ It is reported that bis(*o*-haloaryl)carbodiimides react with imidazole in the presence of CuI and 1,10-phenanthroline as a ligand along with a base to afford such a trinuclear compound *via* several sequential processes such as nucleophilic addition, tautomerization, intramolecular Ullmann-type C–N coupling, and intramolecular sp² C–H arylation (Scheme 2, route a).⁵ Kumar and co-workers demonstrated that 2-(2-bromophenyl)imidazoles are C–N coupled and oxidatively cyclized with benzimidazole by subsequent

treatment of CuI and Pd(OAc)₂/Cu(OAc)₂ (or Cu(OAc)₂) to give such a trinuclear compound (Scheme 2, route b).^{2,6} Such a similar coupling and cyclization for the construction of such a trinuclear compound was also exemplified by multistep processes starting from 1-benzyl-4,5-diphenyl-1*H*-imidazole/2-chlorobenzimidazole and 2-fluorobenzonitrile/benzimidazole, respectively (Scheme 2, routes c and d).³ However, these precedents still have some drawbacks such as limitation of substrate scope, the requirement of transition metal catalysts and contamination of residual metals in products, and tedious multistep processes. As part of our continuing studies directed toward transition metal-catalyzed and transition metal-free synthesis of polynuclear N-fused hybrid scaffolds,⁷ we recently reported that compounds **B–D** can be formed by double nucleophilic aromatic substitution of 2-(2-bromoaryl)- and 2-(2-bromovinyl)benzimidazoles with 2-aminoazoles in the presence of a base (Scheme 1).^{8,9} This work started during the course of the extension of such a transition metal-free double nucleophilic aromatic substitution to synthesize polynuclear N-fused hybrid scaffolds. This report shows an example of the green construction of trinuclear N-fused hybrid structure **A** by transition metal-free double C(sp²)-N coupling between 2-(2-bromoaryl)-4,5-diaryl-1*H*-imidazoles and 2-aminobenzimidazoles under microwave irradiation (Scheme 2, route e).^{10,11} The present protocol can also be extended to the reaction of 2-(2-bromovinyl)imidazoles with 2-aminobenzimidazole to produce trinuclear N-fused hybrid structure **E** (Scheme 2, route f).



Scheme 1 Trinuclear N-fused hybrid scaffolds.

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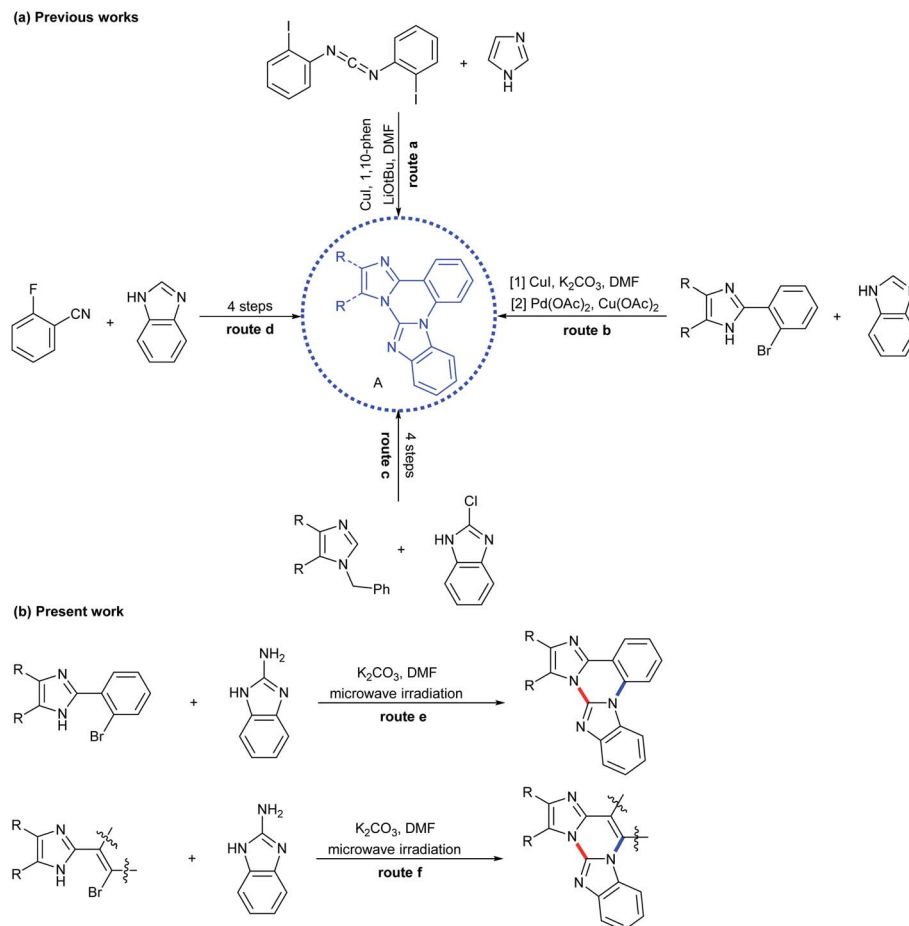
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Results and discussion

Based on our recent report on transition metal-free coupling and cyclization of 2-(2-bromoaryl)- and 2-(2-bromovinyl)benzimidazoles with 2-aminoazoles leading to trinuclear N-fused hybrid scaffolds, we optimized the reaction conditions with 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**1a**) and 2-aminobenzimidazole (**2a**) as model substrates to produce trinuclear N-fused hybrid compound **3a** effectively (Table 1).⁸ Treatment of





Scheme 2 Synthetic routes for trinuclear N-fused hybrid scaffolds.

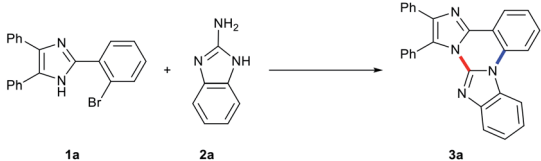
1a with 1.5 equiv. of **2a** in DMF in the presence of K_3PO_4 (1 equiv.) at 150 °C for 2 h under microwave irradiation (120 W of initial power) produced **3a** in 39% isolated yield with complete conversion of **1a** (Table 1, entry 1). Although it is still obscure why such an excess amount of base is needed for the effective formation of **3a**, the yield of **3a** gradually increased with an increase of the molar ratio of K_3PO_4 to **1a** up to 3 (Table 1, entries 2–4).^{9a} The yield of **3a** also increases on prolonging the reaction time up to 2 h and a lower yield of **3a** was observed with a short reaction time nevertheless complete conversion of **1a** (Table 1, entries 3, 5, and 6). Lower yield of **3a** was observed with incomplete conversion of **1a** under lower reaction temperature, and the yield increased with the increase in temperature up to 150 °C (Table 1, entries 3, 7, and 8). Among solvents examined in combination with K_3PO_4 under the employed conditions, DMF was found to be of choice in terms of both the yield of **3a** and complete conversion of **1a** (Table 1, entries 3, 9, and 10). No significant change of the yield of **3a** was observed with higher molar ratio of $[2a]/[1a]$ (Table 1, entry 11). The reaction also proceeded with other bases such as $KOtBu$, K_2CO_3 , and Cs_2CO_3 with complete conversion of **1a** and similar activities to that of K_3PO_4 under the employed conditions, and K_2CO_3 was shown to be the base of choice (Table 1, entries 3, 12–14). However, as is the case for our recent report on the reaction of 2-(2-bromoaryl)-

and 2-(2-bromovinyl)benzimidazoles with 2-aminoazoles, **3a** was not produced at all in the absence of base and no other spots were observed except for both substrates on TLC (Table 1, entry 15).⁸

Similar treatment of **1a** with **2a** under usual heating conditions screw-capped vial, 150 °C for 20 h resulted in only 33% yield of **3a** along with several unidentifiable side products with complete conversion of **1a** (Table 1, entry 16).

After the reaction conditions had been optimized, various 2-(2-bromoaryl)- and 2-(2-bromovinyl)imidazoles **1** were subjected to the reaction with 2-aminobenzimidazoles **2**, and the representative are shown in Table 2.^{12–14} 2-(2-Bromoaryl)imidazoles **1b–d** having electron-donating and withdrawing substituents on the bromoaryl moiety were also coupled and cyclized with **2a** to give the corresponding trinuclear N-fused hybrid scaffolds **3b–d** in 60–63% yields, irrespective of the electronic nature of such substituents. With 2-(2-bromophenyl)-4,5-diaryl-1H-imidazoles **1e–i** having electron-donating and withdrawing substituents on the phenyl moiety attached to imidazole ring, the corresponding trinuclear N-fused hybrid scaffolds **3e–i** were also formed in 63–71% yields. Prolonging the reaction time up to 4 h was needed for an allowable yield of **3e**, **3g** and **3h** from the reaction with the corresponding 2-(2-bromophenyl)imidazoles (**1e**, **1g** and **1h**). The reaction of 2-(2-bromophenyl)-4,5-



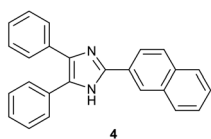
Table 1 Optimization of conditions for the reaction of **1a** with **2a**^a


| Entry | [Base]/[1a] | Base | Solvent | Temp. (°C) | Time (h) | Conv. of 1a (%) | Yield ^b (%) |
|-----------------|-------------|---------------------------------|---------|------------|----------|------------------------|------------------------|
| 1 | 1 | K ₃ PO ₄ | DMF | 150 | 2 | 100 | 39 |
| 2 | 2 | K ₃ PO ₄ | DMF | 150 | 2 | 100 | 54 |
| 3 | 3 | K ₃ PO ₄ | DMF | 150 | 2 | 100 | 65 |
| 4 | 4 | K ₃ PO ₄ | DMF | 150 | 2 | 100 | 66 |
| 5 | 3 | K ₃ PO ₄ | DMF | 150 | 3 | 100 | 66 |
| 6 | 3 | K ₃ PO ₄ | DMF | 150 | 1 | 100 | 29 |
| 7 | 3 | K ₃ PO ₄ | DMF | 100 | 2 | 66 | 34 |
| 8 | 3 | K ₃ PO ₄ | DMF | 125 | 2 | 85 | 41 |
| 9 | 3 | K ₃ PO ₄ | HMPA | 150 | 2 | 100 | 47 |
| 10 | 3 | K ₃ PO ₄ | DMSO | 150 | 2 | 97 | 0 |
| 11 ^c | 3 | K ₃ PO ₄ | DMF | 150 | 2 | 100 | 66 |
| 12 | 3 | KO ^t Bu | DMF | 150 | 2 | 100 | 58 |
| 13 | 3 | K ₂ CO ₃ | DMF | 150 | 2 | 100 | 76 |
| 14 | 3 | CS ₂ CO ₃ | DMF | 150 | 2 | 100 | 68 |
| 15 | 3 | — | DMF | 150 | 2 | 0 | 0 |
| 16 ^d | 3 | K ₂ CO ₃ | DMF | 150 | 20 | 100 | 33 |

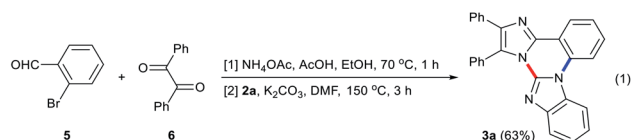
^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), base, DMF (3 mL), under microwave irradiation (120 W of initial power). ^b Isolated yield.

^c [2a]/[1a] = 2. ^d Usual heating (5 mL screw-capped vial).

diheteroarylimidazole **1j** with **2a** also proceeded to give the corresponding trinuclear N-fused compound **3j** in similar yield. Performing the reaction of **1a** with dimethyl- and dichloro-substituted 2-aminobenzimidazoles (**2b** and **2c**) also afforded the corresponding trinuclear N-fused hybrid scaffolds (**3k** and **3l**). Here again, prolonging the reaction time was necessary for the effective formation of **3l** from the reaction of **1a** and **2c**. However, no expected cyclized product was observed with the reaction of 2-(1-bromonaphthalen-2-yl)-4,5-diphenyl-1H-imidazole (**1k**) and **2a**, a considerable amount of 2-(naphthalen-2-yl)-4,5-diphenyl-1H-imidazole **4** by debromination of **1k** being produced in 57% yield with 59% conversion of **1k**. It is known that aryl bromides were reduced to the corresponding arenes in the presence of a base by DMF as hydrogen source.¹⁵ Similar treatment of 2-(2-bromovinyl)imidazoles **1l–p** having alkyl and phenyl substituents on vinyl moiety with 2-aminobenzimidazoles **2a–c** under the employed conditions also afforded the corresponding imidazole-fused hybrid compounds **3m–s** irrespective of the identity of such substituents. To the best of our knowledge, there are no reports on the synthetic method and biological activity of such a scaffold.

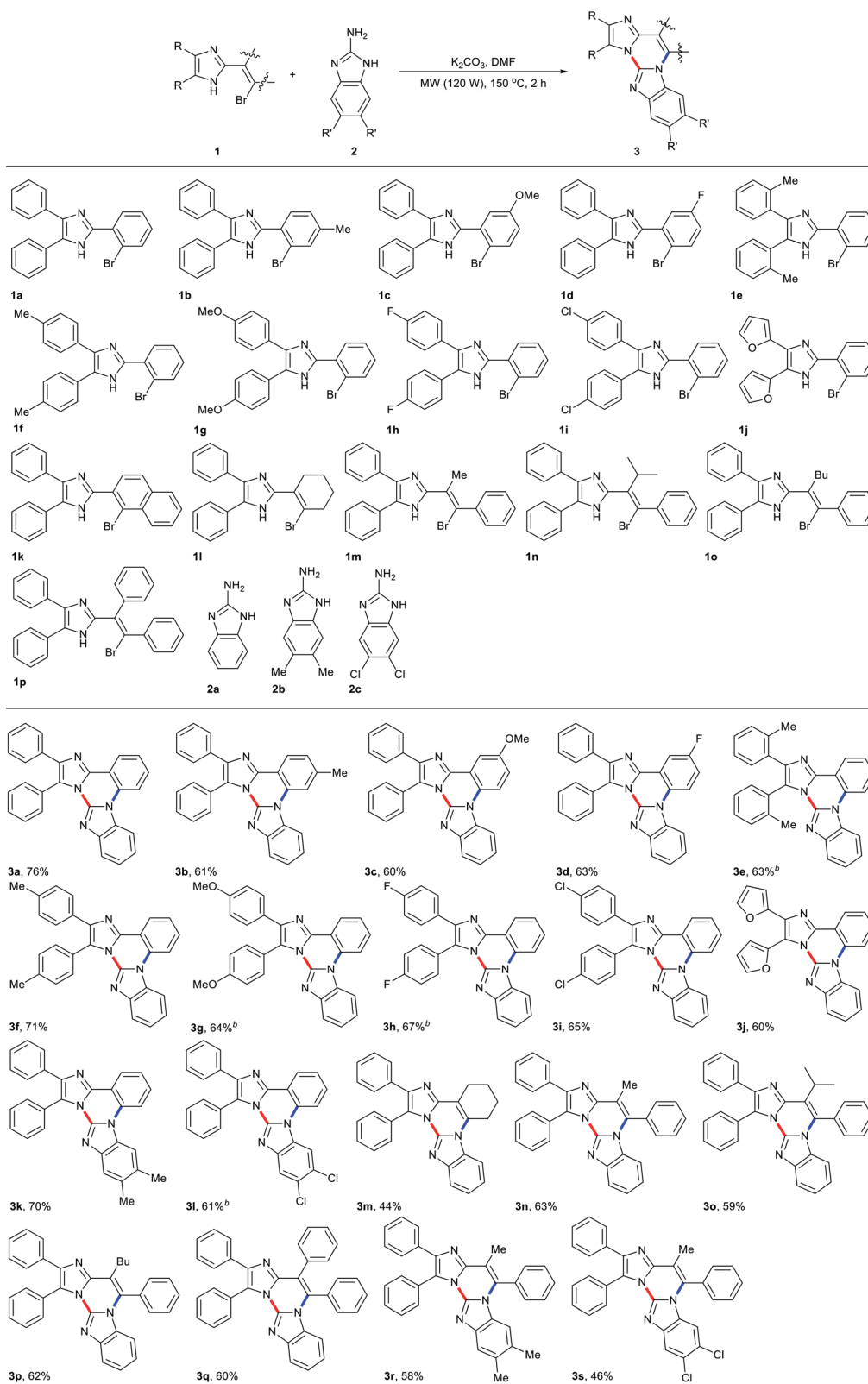


On the other hand, a one-pot reaction starting from 2-bromobenzaldehyde (**5**) and benzil (**6**) under microwave irradiation renders the synthesis of **3a** practical.¹³ Treatment of **5** with equimolar amount of **6** in the presence of NH₄OAc and AcOH in EtOH at 70 °C under microwave irradiation followed by removal of solvent afforded a white solid. Subsequent addition of **2a**, K₂CO₃ and DMF to the microwave reaction tube containing a white solid and heating at 150 °C for 3 h produced **3a** in 63% yield (eqn (1)).



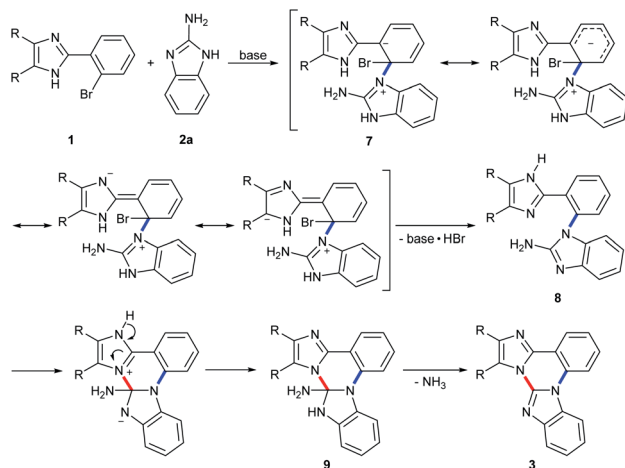
The present reaction seems to proceed *via* an initial formation of a C–N coupled intermediate **8** by an addition–elimination nucleophilic aromatic substitution by way of a resonance-stabilized carbanion, Meisenheimer complex **7** generated by a nucleophilic attack of **2a** to the carbon attached to Br in **1** (Scheme 3).¹⁶ The *ortho*-substituted imidazole group of **1** facilitates the formation of such a Meisenheimer complex **7** by further electron delocalization over phenyl and imidazole rings. Fortunately, a C–N coupled intermediate **8a** could be isolated in 18% yield from the reaction of **1c** with **2a** under the optimized conditions (eqn (2)). Performing the reaction of **1c** with **2a** for 4 h under the employed conditions resulted in 68% yield of **3c** with complete disappearance of **8a**. The intermediate **8a** thus



Table 2 Scope of reaction^a

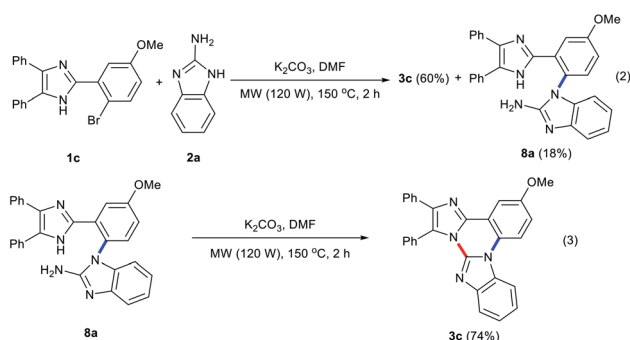
^a Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), K_2CO_3 (0.9 mmol), DMF (3 mL), under microwave irradiation (120 W of initial power) at 150 °C, for 2 h. ^b For 4 h.





Scheme 3 A plausible reaction pathway.

isolated was readily cyclized under the optimized conditions to give **3c** in 74% yield (eqn (3)). These results indicate a doubtless evidence for the formation of such a C–N coupled intermediate **8** during the reaction course between **1** and **2**. Subsequent intramolecular nucleophilic addition in intermediate **8** produces an intermediate **9**, which triggers β -elimination to give **3** with the evolution of ammonia (Scheme 3).¹⁷ The evolution of ammonia was testified by the color change of Nessler's reagent, an alkali solution of K_2HgI_4 .¹⁸



Conclusions

In summary, we developed a transition metal-free synthesis of trinuclear imidazole-fused hybrid scaffolds by K_2CO_3 -mediated coupling and cyclization of 2-(2-bromoaryl)- and 2-(2-bromovinyl)imidazoles with 2-aminobenzimidazoles as building blocks under microwave irradiation. The present protocol provides a green synthetic method for such trinuclear N-fused hybrid scaffolds. Further challenges on the green construction of polynuclear N-fused hybrid scaffolds *via* transition metal-free C(sp²)-N coupling are in progress.

Experimental

General information

¹H (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded on a Bruker Avance Digital 500 spectrometer. Melting points were

determined on a microscopic melting point apparatus (Stanford Research Inc. MPA 100 automated melting point apparatus). High-resolution mass data were recorded using electronic ionization (HRMS-ESI, magnetic sector-electric sector double focusing mass analyzer) at Korea Basic Science Institute, Daegu Center, Korea. All reactions were carried out in a sealed tube under microwave irradiation (CEM, Discover LabMate) and the reaction temperature was maintained by an external infrared sensor. The products were isolated by TLC (a glass plate coated with Kieselgel 60 GF₂₅₄, Merck). 2-(2-Bromoaryl)- and 2-(2-bromovinyl)-4,5-diaryl-1H-imidazoles **1** were synthesized from the corresponding aldehydes and 1,2-diarylethane-1,2-diones (see ESI†).^{12,13} 2-Aminobenzimidazoles **2** were prepared from 1,2-phenylenediamines and cyanogen bromide by known methods.¹⁹ Other commercially available organic and inorganic reagents were used without further purification.

General procedure for the synthesis of 3. To a 10 mL microwave reaction tube, **1** (0.3 mmol), **2** (0.45 mmol), K_2CO_3 (0.124 g, 0.9 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 150 °C for 2–4 h under microwave irradiation (120 W of initial power). The reaction mixture was cooled down to room temperature and filtered through a short silica gel column to eliminate inorganic residue using chloroform/MeOH = 7/3. Removal of the eluent under reduced pressure left a crude mixture, which was purified by thin layer chromatography (dichloromethane/MeOH = 99/1 or dichloromethane/hexane = 1/1) to obtain **3**. All new products were characterized spectroscopically.

1,2-Diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3a).^{7g} Yield 76% (94 mg), white solid, mp 289–291 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.78 (dd, J = 7.9 and 1.5 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.78–7.74 (m, 1H), 7.67–7.50 (m, 9H), 7.44–7.36 (m, 2H), 7.32–7.24 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 142.1, 133.5, 132.8, 132.1, 130.5, 128.9, 128.3, 128.1, 128.0, 127.5, 125.5, 125.3, 124.0, 123.2, 120.8, 115.2, 114.8, 112.8.

6-Methyl-1,2-diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3b). Yield 61% (78 mg), white solid, mp 268–270 °C. ¹H NMR (500 MHz, CD₂Cl₂) δ 8.60 (d, J = 8.0 Hz, 1H), 8.27–8.25 (m, 2H), 7.62–7.59 (m, 5H), 7.58–7.51 (m, 3H), 7.46–7.38 (m, 3H), 7.29–7.23 (m, 3H), 2.66 (s, 3H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 142.4, 142.2, 142.1, 142.0, 141.4, 134.3, 133.3, 132.5, 130.9, 130.7, 129.2, 128.6, 128.5, 128.3, 127.8, 127.0, 125.7, 125.4, 124.4, 123.4, 120.5, 115.6, 113.5, 113.2, 22.5. HRMS (EI): m/z [M^+] calcd for C₂₉H₂₀N₄: 424.1688, found 424.1686.

5-Methoxy-1,2-diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3c). Yield 60% (79 mg), pale yellow solid, mp 273–275 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.32 (d, J = 9.1 Hz, 1H), 8.20 (d, J = 2.7 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.65–7.61 (m, 5H), 7.56–7.49 (m, 3H), 7.41–7.28 (m, 6H), 4.04 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.0, 142.1, 142.0, 133.6, 132.1, 130.0, 128.9, 128.3, 128.1 (128.12), 128.1 (128.07), 127.5, 127.0, 125.9, 123.7, 122.9, 120.8, 119.1, 116.3, 112.5, 107.1 56.1. HRMS (EI): m/z [M^+] calcd for C₂₉H₂₀N₄O: 440.1637, found 440.1637.

5-Fluoro-1,2-diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3d). Yield 63% (81 mg), white solid, mp 311–



312 °C. ^1H NMR (500 MHz, CD_2Cl_2) δ 8.44–8.40 (m, 2H), 8.19 (d, $J = 8.1$ Hz, 1H), 7.63–7.49 (m, 9H), 7.47–7.44 (m, 1H), 7.42–7.40 (m, 1H), 7.31–7.26 (m, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.7 (d, $^1J_{\text{C-F}} = 244.7$ Hz), 142.4, 142.0, 141.0, 139.9, 133.4, 132.0, 130.0, 129.8, 129.3, 129.0, 128.3, 128.2, 128.0, 127.7, 126.2, 124.1, 123.3, 121.0, 117.9, 117.7 (d, $^4J_{\text{C-F}} = 3.9$ Hz), 116.6 (d, $^3J_{\text{C-F}} = 8.3$ Hz), 112.4, 111.5 (d, $^2J_{\text{C-F}} = 25$ Hz). HRMS (EI): m/z [M^+] calcd for $\text{C}_{28}\text{H}_{17}\text{FN}_4$: 428.1437, found 428.1433.

1,2-Di-*o*-tolylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3e). Yield 63% (83 mg), pale yellow solid, mp 250–253 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.72 (dd, $J = 7.9$ and 1.3 Hz, 1H), 8.37 (d, $J = 8.4$ Hz, 1H), 8.16–8.14 (m, 1H), 7.72–7.69 (m, 1H), 7.64–7.62 (m, 1H), 7.54–7.51 (m, 1H), 7.40–7.33 (m, 3H), 7.30–7.27 (m, 2H), 7.21–7.17 (m, 4H), 7.09–7.05 (m, 1H), 2.34 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.6, 142.3, 141.2, 140.5, 139.3, 137.5, 133.0, 132.8, 132.1, 130.8, 130.4, 130.3 (130.28), 130.3 (130.27), 129.7, 129.4, 128.9, 128.0, 126.2, 125.4, 125.3 (125.32), 125.3 (125.29), 125.2, 123.9, 123.0, 120.8, 115.4, 114.8, 112.7, 20.5, 20.4. HRMS (EI): m/z [M^+] calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4$: 438.1844, found 438.1841.

1,2-Di-*p*-tolylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3f). Yield 71% (93 mg), white solid, mp 300–302 °C. ^1H NMR (500 MHz, CD_2Cl_2) δ 8.71 (dd, $J = 7.9$ and 1.2 Hz, 1H), 8.42 (d, $J = 8.4$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 7.78–7.75 (m, 1H), 7.64–7.62 (m, 1H), 7.59–7.56 (m, 1H), 7.50–7.47 (m, 4H), 7.45–7.38 (m, 2H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.10 (d, $J = 7.9$ Hz, 2H), 2.52 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 142.4, 141.9, 140.9, 139.4, 137.8, 133.2, 132.3, 130.9, 130.7, 129.3 (129.27), 129.3 (129.25), 128.2, 127.7, 125.8, 125.7, 125.6, 124.5, 123.5, 120.5, 115.6, 115.3, 113.4, 21.7, 21.3. HRMS (EI): m/z [M^+] calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4$: 438.1844, found 438.1842.

1,2-Bis(4-methoxyphenyl)benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3g).⁶ Yield 64% (90 mg), pale yellow solid, mp 250–253 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.75 (dd, $J = 7.9$ and 1.2 Hz, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 8.17 (d, $J = 7.5$ Hz, 1H), 7.74–7.71 (m, 1H), 7.69–7.67 (m, 1H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.56–7.51 (m, 3H), 7.42–7.35 (m, 2H), 7.04 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 3.94 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.0, 159.1, 142.2, 141.8, 141.5, 140.4, 133.4, 132.7, 130.2, 129.2, 126.4, 125.4, 125.2, 124.7, 123.9, 123.0, 122.3, 120.8, 115.3, 114.7, 114.3, 113.8, 113.7, 112.8, 55.3, 55.2.

1,2-Bis(4-fluorophenyl)benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3h).⁶ Yield 67% (90 mg), white solid, mp 308–309 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.75 (d, $J = 7.9$ Hz, 1H), 8.41 (d, $J = 8.5$ Hz, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.78–7.75 (m, 1H), 7.67 (d, $J = 7.4$ Hz, 1H), 7.62–7.56 (m, 5H), 7.44–7.38 (m, 2H), 7.21 (t, $J = 8.7$ Hz, 2H), 7.00 (t, $J = 8.7$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.3 (d, $^1J_{\text{C-F}} = 247.1$ Hz), 162.4 (d, $^1J_{\text{C-F}} = 245.7$ Hz), 142.0, 141.4, 141.2, 140.8, 133.0 (d, $^3J_{\text{C-F}} = 8.4$ Hz), 132.8, 130.2, 129.7 (d, $^3J_{\text{C-F}} = 8.1$ Hz), 129.6 (d, $^4J_{\text{C-F}} = 3.3$ Hz), 125.8 (d, $^4J_{\text{C-F}} = 3.9$ Hz), 125.5, 125.4, 124.4, 124.1, 123.3, 120.8, 115.4 (d, $^2J_{\text{C-F}} = 21.7$ Hz), 115.3 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 115.1, 114.8, 112.8.

1,2-Bis(4-chlorophenyl)benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3i). Yield 65% (93 mg), white solid, mp 302–303 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.73 (d, $J = 7.9$ Hz, 1H), 8.40 (d, $J = 8.4$ Hz, 1H), 8.18 (d, $J = 8.1$ Hz, 1H), 7.78–7.74 (m, 1H), 7.69–7.68 (m, 1H), 7.58–7.48 (m, 7H), 7.44–7.38 (m, 2H), 7.28 (d,

$J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.0, 141.3, 141.1, 141.0, 135.2, 133.6, 133.4, 132.8, 131.8, 130.7, 130.1, 129.2, 128.6 (128.61), 128.6 (128.59), 128.2, 125.5, 125.4, 124.5, 124.2, 123.4, 120.8, 114.9, 114.8, 112.8. HRMS (EI): m/z [M^+] calcd for $\text{C}_{28}\text{H}_{16}\text{Cl}_2\text{N}_4$: 478.0752, found 478.0751.

1,2-Di(furan-2-yl)benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3j). Yield 60% (70 mg), pale yellow solid, mp 245–247 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.76 (dd, $J = 7.9$ and 1.4 Hz, 1H), 8.37 (d, $J = 8.4$ Hz, 1H), 8.16–8.14 (m, 1H), 7.79–7.73 (m, 3H), 7.56–7.53 (m, 2H), 7.43–7.38 (m, 2H), 6.91 (dd, $J = 3.3$ and 0.8 Hz, 1H), 6.72 (dd, $J = 3.3$ and 1.9 Hz, 1H), 6.58 (dd, $J = 3.4$ and 0.7 Hz, 1H), 6.40 (dd, $J = 3.4$ and 1.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.7, 143.9, 142.9, 142.2, 142.1, 141.2, 140.5, 137.6, 133.1, 131.1, 130.3, 125.9, 125.3, 124.2, 123.3, 120.9, 114.8, 114.7, 114.5, 114.2, 112.8, 111.4, 111.3, 108.9. HRMS (EI): m/z [M^+] calcd for $\text{C}_{24}\text{H}_{14}\text{N}_4\text{O}_2$: 390.1117, found 390.1118.

10,11-Dimethyl-1,2-diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3k). Yield 70% (92 mg), white solid, mp 311–313 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.76 (dd, $J = 7.9$ and 1.4 Hz, 1H), 8.38 (d, $J = 8.4$ Hz, 1H), 7.93 (s, 1H), 7.76–7.73 (m, 1H), 7.64–7.59 (m, 4H), 7.56–7.48 (m, 4H), 7.42 (s, 1H), 7.30–7.27 (m, 2H), 7.25–7.22 (m, 1H), 2.48 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.9, 140.7, 140.5, 133.7, 133.2, 132.9 (132.94), 132.9 (132.91), 132.1, 130.1, 129.3, 128.9, 128.8, 128.3, 128.1, 128.0, 127.4, 125.6, 125.4, 125.0, 121.0, 115.1, 114.7, 113.2, 20.9, 20.1. HRMS (EI): m/z [M^+] calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4$: 438.1844, found 438.1847.

10,11-Dichloro-1,2-diphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3l). Yield 61% (88 mg), white solid, mp 304–306 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.78 (dd, $J = 7.9$ and 1.2 Hz, 1H), 8.28 (s, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 7.80–7.76 (m, 1H), 7.74 (s, 1H), 7.64–7.49 (m, 8H), 7.31–7.27 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.6, 142.3, 141.6, 140.5, 133.2, 132.1, 132.0, 130.7, 129.7, 129.3, 129.2, 129.1, 128.3, 128.2 (128.2463), 128.2 (128.17), 127.9, 127.7, 126.8, 126.0, 125.7, 121.7, 115.3, 114.5, 114.2. HRMS (EI): m/z [M^+] calcd for $\text{C}_{28}\text{H}_{16}\text{Cl}_2\text{N}_4$: 478.0752, found 478.0750.

1,2-Diphenyl-4,5,6,7-tetrahydrobenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (3m). Yield 44% (55 mg), white solid, mp 290–292 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.94 (d, $J = 8.3$ Hz, 1H), 7.63–7.61 (m, 1H), 7.59–7.57 (m, 4H), 7.51–7.46 (m, 3H), 7.34–7.30 (m, 1H), 7.28–7.21 (m, 4H), 3.41–3.39 (m, 2H), 3.15–3.12 (m, 2H), 2.14–2.11 (m, 2H), 2.01–1.96 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.8, 142.1, 141.8, 141.6, 133.9 (133.92), 133.9 (133.86), 132.2, 130.1, 129.8, 128.6, 128.2, 128.0, 127.3, 124.2, 123.7, 121.8, 120.4, 113.4, 109.8, 27.0, 23.1, 22.4, 21.1. HRMS (EI): m/z [M^+] calcd for $\text{C}_{28}\text{H}_{22}\text{N}_4$: 414.1844, found 414.1843.

4-Methyl-1,2,5-triphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3n). Yield 63% (85 mg), pale yellow solid, mp 200–202 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.70–7.60 (m, 7H), 7.56–7.48 (m, 6H), 7.30–7.22 (m, 3H), 7.20–7.17 (m, 1H), 6.86–6.83 (m, 1H), 5.90 (d, $J = 8.4$ Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.3, 142.5, 141.7, 134.0, 133.9, 132.2 (132.19), 132.2 (132.16), 130.2, 130.1, 130.0, 129.5, 128.7, 128.3, 128.2, 128.0, 127.4, 124.9, 123.6, 121.5, 120.0, 112.8, 109.7, 12.7. HRMS (EI): m/z [M^+] calcd for $\text{C}_{31}\text{H}_{22}\text{N}_4$: 450.1844, found 450.1846.



4-Isopropyl-1,2,5-triphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3o). Yield 59% (85 mg), white solid, mp 284–286 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.71–7.63 (m, 7H), 7.59–7.46 (m, 6H), 7.32–7.21 (m, 3H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 5.67 (d, *J* = 8.4 Hz, 1H), 3.04 (q, *J* = 7.0 Hz, 1H), 1.59 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 141.8, 141.7, 141.6, 141.4, 134.1, 132.9, 132.6, 132.2, 130.5, 130.2, 130.0, 129.7, 129.6, 128.7, 128.1 (128.1470), 128.1 (128.08), 128.0, 127.3, 123.8, 123.5, 121.4, 119.9, 118.9, 112.8, 29.3, 21.3. HRMS (EI): *m/z* [M⁺] calcd for C₃₃H₂₆N₄: 478.2157, found 478.2155.

4-Butyl-1,2,5-triphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3p). Yield 62% (92 mg), pale yellow solid, mp 226–229 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.71–7.62 (m, 7H), 7.55–7.49 (m, 6H), 7.30–7.22 (m, 3H), 7.19–7.15 (m, 1H), 6.85–6.81 (m, 1H), 5.80 (d, *J* = 8.4 Hz, 1H), 2.78 (t, *J* = 7.9 Hz, 2H), 1.81–1.75 (m, 2H), 1.39–1.32 (m, 2H), 0.88–0.85 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 142.8, 142.3, 141.7, 141.6, 134.0, 133.9, 132.2, 132.0, 130.2 (130.22), 130.2 (130.20), 129.6, 129.4, 128.7, 128.2 (128.20), 128.2 (128.17), 128.0, 127.4, 124.5, 123.6, 121.4, 119.9, 114.5, 112.8, 32.0, 26.7, 22.7, 13.8. HRMS (EI): *m/z* [M⁺] calcd for C₃₄H₂₈N₄: 492.2314, found 492.2316.

1,2,4,5-Tetraphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3q). Yield 60% (92 mg), white solid, mp 308–309 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.67–7.65 (m, 2H), 7.58–7.48 (m, 7H), 7.46–7.39 (m, 6H), 7.30–7.26 (m, 3H), 7.24–7.17 (m, 4H), 6.87–6.84 (m, 1H), 5.90 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 142.9, 142.7, 142.0, 141.7, 134.8, 133.7, 132.4, 132.2, 131.7, 131.5, 130.8, 130.1, 129.9, 129.8, 128.9, 128.8, 128.2, 128.1 (128.08), 128.1 (128.06), 127.8, 127.6, 127.4, 124.7, 123.9, 121.6, 120.1, 115.6, 113.3. HRMS (EI): *m/z* [M⁺] calcd for C₃₆H₂₄N₄: 512.2001, found 512.2000.

4,8,9-Trimethyl-1,2,5-triphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3r). Yield 58% (83 mg), white solid, mp 283–286 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.70–7.58 (m, 7H), 7.54–7.47 (m, 6H), 7.33 (s, 1H), 7.29–7.23 (m, 2H), 5.59 (s, 1H), 2.40 (s, 3H), 2.22 (s, 3H), 2.01 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.3, 142.3, 141.1, 140.1, 134.1, 134.0, 132.6, 132.4, 132.2, 130.2, 130.1, 130.0, 129.6, 129.4, 128.8, 128.6, 128.2, 128.0, 127.8, 127.3, 124.7, 120.0, 113.2, 109.0, 20.6, 20.0, 12.6. HRMS (EI): *m/z* [M⁺] calcd for C₃₃H₂₆N₄: 478.2157, found 478.2155.

8,9-Dichloro-4-methyl-1,2,5-triphenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]pyrimidine (3s). Yield 46% (72 mg), white solid, mp 289–292 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.75–7.67 (m, 3H), 7.65 (s, 1H), 7.64–7.58 (m, 4H), 7.56–7.48 (m, 5H), 7.30–7.23 (m, 3H), 5.87 (s, 1H), 2.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 142.9, 141.2, 133.7, 133.6, 132.2, 131.4, 130.8, 130.1 (130.08), 130.1 (130.07), 130.0, 129.8, 129.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 125.2, 125.1, 121.0, 114.5, 114.4, 110.9, 12.8. HRMS (EI): *m/z* [M⁺] calcd for C₃₁H₂₀Cl₂N₄: 518.1065, found 518.1063.

1-(2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine (8a). Yield 18% (25 mg), white solid, mp 263–265 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.49 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.43–7.37 (m, 6H), 7.24 (d, *J* = 5.8 Hz, 1H), 7.17–7.09 (m, 6H), 6.95–6.92 (m, 1H), 6.76–6.73 (m, 1H), 6.53 (d, *J* = 6.0 Hz, 1H), 5.97 (s, 2H), 3.94 (s, 3H); ¹³C NMR (125

MHz, DMSO-*d*₆) δ 159.5, 155.4, 143.0, 142.3, 136.7, 136.5, 134.7, 132.0, 131.0, 129.8, 128.6, 128.5, 127.9, 127.8, 127.7, 126.6, 126.1, 124.3, 120.2, 118.2, 115.2, 114.5, 113.6, 107.5, 55.8. HRMS (EI): *m/z* [M⁺] calcd for C₂₉H₂₃N₅O: 457.1903, found 457.1903.

One-pot procedure for the synthesis of 3a. To a 10 mL microwave reaction tube, **5** (0.056 g, 0.3 mmol), **6** (0.063 g, 0.3 mmol), NH₄OAc (0.093 g, 1.2 mmol), AcOH (75 μL), and EtOH (3 mL) were added. After the reaction mixture was heated at 70 °C for 1 h under microwave irradiation (100 W of initial power), solvents were removed under reduced pressure, water soluble components were removed by decantation using H₂O several times, and organic residues were washed with EtOAc/hexane (1/15). To the reaction tube containing a white solid dried under vacuum, **2a** (0.060 g, 0.45 mmol), K₂CO₃ (0.124 g, 0.9 mmol), and DMF (3 mL) were added. The reaction mixture was stirred at 150 °C for 2 h under microwave irradiation (120 W of initial power). A workup procedure similar to that described above afforded **3a** (77 mg, 63%).

Cyclization of 8a to 3c. To a 10 mL microwave reaction tube, **8a** (0.030 g, 0.065 mmol), K₂CO₃ (0.026 g, 0.19 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 150 °C for 2 h under microwave irradiation (120 W of initial power). Similar work-up procedure described above afforded **3c** (21 mg, 74%).

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- For reviews, see: (a) A. R. Katritzky, C. A. Ramsden, J. A. Joule and V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, Elsevier, 2010; (b) J. Alvarez-Builla and J. J. Vaquero, in *Modern Heterocyclic Chemistry*, ed. J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, Wiley-VHC, Weinheim, 2011, ch. 22, pp. 1989–2070; (c) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622; (d) S. K. Manna, T. Das and S. Samanta, *ChemistrySelect*, 2019, **4**, 8781.
- N. K. Nandwana, R. P. Singh, O. P. S. Patel, S. Dhiman, H. K. Saini, P. N. Jha and A. Kumar, *ACS Omega*, 2018, **3**, 16338.
- (a) D. B. Knowles, C. Lin, P. B. Mackenzie, J.-Y. Tsai, R. Walters, S. A. Beers, C. S. Brown, W. H. Yeager and E. Barron, *Utility Pat.*, 2008156879, 2008; Chem. Abstr., 2008, 150, 86349; (b) T. Y. Park, J. S. Bae, S. G. Hong, D. H. Lee, D. U. Lee, S. Y. Jeon and S. S. Kim, Korean patent 2010097797, 2010; Chem. Abstr., 2010, 153, 456673.
- For the synthesis of scaffold **B**, another N-fused mode of scaffold **A** (Scheme 1), see: (a) D. Chen, L. Huang, J. Yang, J. Ma, Y. Zheng, Y. Luo, Y. Shen, J. Wu, C. Feng and X. Lv,



- Tetrahedron Lett.*, 2018, **59**, 2005; (b) X. Guo, J. Hu, M. Zhang and L. Wang, *Asian J. Org. Chem.*, 2019, **8**, 417.
- 5 G. Yuan, H. Liu, J. Gao, K. Yang, Q. Niu, H. Mao, X. Wang and X. Lv, *J. Org. Chem.*, 2014, **79**, 1749.
- 6 N. K. Nandwana, K. Pericherla, P. Kaswan and A. Kumar, *Org. Biomol. Chem.*, 2015, **13**, 2947.
- 7 (a) P. D. Q. Dao, H. K. Lee, H.-S. Sohn, N. S. Yoon and C. S. Cho, *ACS Omega*, 2017, **2**, 2953; (b) H. K. Lee, P. D. Q. Dao, Y. Kim and C. S. Cho, *Synthesis*, 2018, **50**, 3243; (c) P. D. Q. Dao, S. L. Ho and C. S. Cho, *ACS Omega*, 2018, **3**, 5643; (d) D. Y. Kim, P. D. Q. Dao and C. S. Cho, *ACS Omega*, 2018, **3**, 17456; (e) T. D. Diep, P. D. Q. Dao and C. S. Cho, *Eur. J. Org. Chem.*, 2019, 4071; (f) D. Y. Kim, P. D. Q. Dao, N. S. Yoon and C. S. Cho, *Asian J. Org. Chem.*, 2019, **8**, 1726; (g) P. D. Q. Dao and C. S. Cho, *Eur. J. Org. Chem.*, 2020, 330; (h) T. D. Diep, P. D. Q. Dao, S. L. Ho and C. S. Cho, *Eur. J. Org. Chem.*, 2020, 2807; (i) J. P. Kwak, P. D. Q. Dao and C. S. Cho, *Eur. J. Org. Chem.*, 2020, 3468.
- 8 P. D. Q. Dao, H.-J. Lim and C. S. Cho, *Green Chem.*, 2019, **21**, 6590.
- 9 For our recent reports for transition metal-free cyclizations via homolytic aromatic substitution (HAS) type pathway, see: (a) P. D. Q. Dao, S. L. Ho, H.-J. Lim and C. S. Cho, *J. Org. Chem.*, 2018, **83**, 4140; (b) P. D. Q. Dao, H.-J. Lim and C. S. Cho, *ACS Omega*, 2018, **3**, 12114.
- 10 For recent reports on transition metal-free C(sp²)-N bond formation, see: (a) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (b) W. Liu, J. Li, P. Querard and C.-J. Li, *J. Am. Chem. Soc.*, 2019, **141**, 6755; (c) F. Diness and D. P. Fairlie, *Angew. Chem., Int. Ed.*, 2012, **51**, 8012; (d) F. Diness and M. Begtrup, *Org. Lett.*, 2014, **16**, 3130; (e) A. H. Sandtorv and D. R. Stuart, *Angew. Chem., Int. Ed.*, 2016, **55**, 15812; (f) C. B. Jacobson, M. Meldal and F. Diness, *Chem.-Eur. J.*, 2017, **23**, 846.
- 11 P. D. Q. Dao and C. S. Cho, *J. Org. Chem.*, 2020, **85**, 13354.
- 12 Y. Yuan and H. Zhu, *Eur. J. Org. Chem.*, 2012, 329.
- 13 M.-Y. Gang, J.-Q. Liu and X.-S. Wang, *Tetrahedron*, 2017, **73**, 4698.
- 14 For biological activities of imidazo[1,2-c]quinazolines, see: (a) G. Domány, T. Gizur, A. Gere, K. Takács-Novák, G. Farsang, G. G. Ferenczy, G. Tárkányi and M. Demeter, *Eur. J. Med. Chem.*, 1998, **33**, 181; (b) E. E. Korshin, L. A. Sabirova and Y. A. Levin, *Synthesis*, 2012, **44**, 3512.
- 15 H.-X. Zheng, X.-H. Shan, J.-P. Qu and Y.-B. Kang, *Org. Lett.*, 2017, **19**, 5114.
- 16 M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley & Sons, New Jersey, 2020, pp. 767–838.
- 17 Y. Ashida, K. Arashiba, K. Nakajima and Y. Nishibayashi, *Nature*, 2019, **568**, 536.
- 18 W. M. Haynes, *CRC Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, 97th edn, 2017, p. 91, section 8.
- 19 (a) M. Beesu, S. S. Malladi, L. M. Fox, C. D. Jones, A. Dixit and S. A. David, *J. Med. Chem.*, 2014, **57**, 7325; (b) X. Guida, H. Jianhua and L. Xiaomin, *Eur. J. Med. Chem.*, 2006, **41**, 1080.

