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MCRs reshaped into a switchable microwave-assisted protocol toward 5-aminoimidazoles and dihydrotriazines

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Abstract

A tunable microwave-assisted protocol for the synthesis of two biologically relevant families of heterocycles has been designed. Via a simple switch of reaction conditions, the same starting materials can be engaged in either an improved synthesis of the dihydrotriazine scaffold or a novel, first-in-class MCR to render the challenging 5-aminoimidazole nucleus in a single step. An additional first in class MCR is also reported utilizing guanidines to afford 2,5-aminoimidazoles.

Keywords

Imidazole; Multicomponent Reaction; Strecker; Trimethylsilylcyanide

1. Introduction

Imidazoles are one of the most common ring systems in heterocyclic chemistry, with a significant amount of scientific literature covering their preparations, properties and a broad range of applications in many different fields. For example, in marine natural products, imidazoles are common structural motifs that offer significant synthetic challenges and represent key moieties responsible for observed biological activities.¹ Indeed, the imidazole ring constitutes a privileged structure in medicinal chemistry and can be found in a large number of therapeutic agents, such as angiotensin II inhibitors, anti-inflammatory and anticancer agents, to cite just a few.² This motif is also commonly employed in material science, where it is widely used to generate high temperature-resistant polymers and liquid crystals.³ In particular, 5-aminoimidazoles exhibit a distinctly attractive utility profile. This scaffold is found, inter alia, in pharmaceuticals for the treatment of cancer, HIV and hepatitis B, with many other applications also reported.⁴ Consequently, the utility is reflected in the numerous reported syntheses of this nucleus.⁵ However, lengthy procedures, poor yields and access to limited substitution patterns make these methodologies unsuitable for high-throughput synthesis and library generation.

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Multicomponent reactions (MCRs) are a valuable synthetic tool for the efficient assembly of structurally diverse molecules in one synthetic operation^{6,7} and we were thus attracted by the possibility of developing new MCR methodology to efficiently synthesize diverse arrays of 5-aminoimidazoles. Indeed, the well-known advantages of MCRs, e.g., high efficiency, generality and step and atom economy,⁸ are ideal to address the limitations of existing methods to prepare this chemotype.

2. Results and discussion

Initially it was envisioned the most convenient strategy to the 5-aminoimidazole **6**, could feasibly utilize the versatile reactivity of isonitriles.⁹ Akin to the the Groebke-Blackburn-Bienaymé (GBB) condensation¹⁰ that render bicyclic systems **4** (Scheme 1), it was postulated that the replacement of the heterocyclic input **3** with an amidine **5** would be sufficient to afford the desired chemotype **6**. However, after preliminary investigation of acid catalyzed promotion of this MCR, production of **6** was observed in only nominal yields <5% (Scheme 1).¹¹

Subsequently, it was hypothesized that **6** could be synthesized from aldehydes **2**, amidines **5** and a cyanide source **8** (Scheme 2), somewhat similar to a “Strecker variant” of the GBB MCR where trimethylsilyl cyanide (TMSCN) proved a fruitful replacement for classical isonitriles, affording bicyclic structures **4** in good yield ($R_1=H$).¹² Mechanistically, aldehyde **2** and amidine **5** were expected to form the corresponding Schiff base **7**, which is prone to interception by nucleophilic attack of cyanide **8** in a Strecker-like fashion.¹³ Thereafter, intermediate **9** undergoes intramolecular cyclization to the five-membered ring **10**.¹⁴ After tautomerization to free amine **11**, and on the basis of prior published reactivity observations of **4** ($R_1=H$),¹⁵ **11** was thought susceptible to further reaction with a second equivalent of aldehyde **2** to generate 5-aminoimidazole **12**, endowing the final product with a further diversity point. Thus, TMSCN was employed in conjunction with benzaldehyde **2a** and benzamidine **5a**, coupled with relatively mild microwave irradiation (Table 1).^{16,17} Initially, this failed to produce the desired 5-aminoimidazole **12a** (Table 1, entries 1 and 2), interestingly affording the dihydrotriazine **13a** as the sole product.¹⁸ This finding was not completely new, as preparation of dihydrotriazines via similar methodology was reported over 40 years ago.¹⁹ Encouragingly, at elevated temperatures (150 °C and 180 °C) **12a** was observed in modest yields, although **13a** remained the major product. Nevertheless, this expedited route to **13a** was not undesirable, since the dihydrotriazine core is known to display antiparasitic and antimicrobial activity.²⁰

Having developed an efficient single-step MCR that simultaneously generates two medicinally relevant scaffolds, the task of identifying conditions capable of enabling complete control over what appeared to be two distinct chemical pathways was undertaken. Sodium sulfate has been previously used to facilitate Strecker-type reactions,²¹ and interestingly when added to the reaction, an improvement in 5-aminoimidazole **12a** yield (36%) was seen with complete suppression of dihydrotriazine **13a** formation (Table 2, entry 1). Stoichiometry of the reactants was further studied, and doubling the amount of TMSCN employed (4 equiv.) resulted in a distinct drop in the yield of **12a** (entry 2). Conversely, an analogous increase in benzaldehyde (four equiv.) afforded a satisfactory 55% yield of **12a** (entry 3). Subsequently, various desiccants were evaluated (entries 4–6), resulting in only slightly lower yields of **12a**.

Thus with an optimized and expeditious route to **12a** in place, which to the best of our knowledge compared favorably to existing routes, the scope of the process was evaluated. Ten compounds were prepared (Table 3) from a pool of six aromatic aldehydes and four aromatic amidines. Note that aliphatic aldehydes proved incompatible with this method, the

only other reaction failure being observed with 4-nitrophenylbenzaldehyde (entry 2, **12b**). Note that this was somewhat surprising as based on relative electrophilicity one would have expected the substrate to be highly reactive. Indeed the substrate has been reported to react in high yield in TMSCN mediated Strecker reactions.²² For the amidine component, aromatic inputs were highly compatible, while aliphatic congeners were not evaluated due to their scarce commercial availability and lack synthetic accessibility. Of note, benzamidine and 3-nitrobenzamidine hydrochloride are commercially available, and other amidines were prepared by means of a reported procedure.²³ In summary, the new imidazole-forming MCR is an example of a 3-component-4-center reaction.

Post-condensation modification of MCR adducts is a useful strategy to enhance diversity,^{6b,24} and the imino group embedded in **12** clearly offers functionalization opportunities. Simple hydrolysis of **12a** under acidic conditions affords the 5-aminoimidazole **14** in 87% yield (Scheme 3).²⁵

Interestingly, a second new MCR, a 3-component-5-center reaction, was also developed from guanidine **15** using the conditions employed for the one-pot formation of **12**. As such, exposure of guanidine to aldehyde, TMSCN and desiccant, with concomitant microwave irradiation, delivered the 2,5-diaminoimidazole **16** in one pot, with yields ranging from 30% to 39% (entries 1–4, Table 4). The 2,5-diaminoimidazole core is another member of the imidazole family found in biologically active compounds.²⁶

With protocols in-hand favoring the exclusive formation of the imidazole core, switching pathways to deliver dihydrotriazines **13** was achieved by removal of TMSCN from the reaction. Interestingly, Zavatskii et. al. conducted only nominal studies on the scope of this reaction (Table 5) and MAOS (microwave assisted organic synthesis) was not available in 1969.¹⁹ Thus, irradiation at 100 °C (40 min) was determined to be optimal for formation of **13a** (entry 3, Table 5, 73%). Additional irradiation (~60 min) resulted in negligible improvements in yield with enhanced side-product formation, negating the slight yield advantage (entry 4). The methodology also proved optimal in polar aprotic solvents such as DMF and DMSO (entries 1–5), while the polar protic solvent i-propanol afforded reduced yields (57%, entry 6).

The preparation of dihydrotriazines (13a-13g, Table 6) highlights the range of inputs that may be used in this MCR. Note that X-ray structural assignment of **13b** unambiguously confirmed the observed substitution pattern.²⁷ In summary, the microwave assisted protocol proved more general and efficient than earlier published routes.¹⁹

3. Conclusions

Methodology is described herein leading to three chemotypes, namely 5-aminoimidazoles, 2,5-aminoimidazoles and dihydrotriazines. By altering reaction conditions, either scaffold can be exclusively obtained from the same amidine and aldehyde starting materials. Overall, a novel, first-in-class, 3-component-4-center MCR from reaction of aldehydes, amidines and TMSCN has been established, enabling an operationally friendly new portal to the 5-aminoimidazole core. An extension introduces a first-in-class 3-component-5-center MCR affording 2,5-diaminoimidazoles from guanidine **15**. This new efficient protocol strategically positions a versatile imino group offering functionalization opportunities, exemplified by the preparation of **12**. Alternatively, the dihydrotriazine moiety **13** can be accessed in the absence of TMSCN. Opportunities also exist for design of additional secondary modifications with subsequent biological evaluation of new products.²⁸ Supporting information containing all ¹H and ¹³C spectra, additional optimization tables and crystal structures of 13a and 13b are available on-line.

4. Experimental Section

4.1 General

^1H and ^{13}C NMR were recorded on a Varian 400 spectrometer at 400 and 100 MHz respectively. ^1H NMR and ^{13}C NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Coupling constants are measured in Hertz (Hz). HPLC-MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Restek Ultra C18 column (reverse phase, 3 μm , 50 $\times$ 2.1 mm); a linear gradient from 10% water and 90% acetonitrile to 95% acetonitrile and 5% water over 4.0 min; flow rate of 1 mL/min; UV photodiode array detection from 200 to 300 nm. High resolution mass spectra (HRMS) were acquired with a 9.4 Tesla Bruker FT/ICR-MS instrument. Melting points were measured on a MEL-TEMP II apparatus in an open glass capillary tube and are uncorrected. The products were purified either by Teledyne Isco CombiFlash Rf and *n*-hexane/EtOAc solvent systems or by HPLC system (reverse phase) using the conditions mentioned above. All reagents and solvents were obtained from commercial sources and used without further purification. All microwave irradiation experiments were carried out in a CEM-Discover SP-D microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 220 W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to r.t. with gas jet cooling.

4.2 General Procedure for the synthesis of scaffold 12, exemplified for 12a

In a sealed vessel, benzamidine (60 mg, 0.5 mmol) and sodium sulfate (284 mg, 2 mmol) were dissolved in 2.5 mL anhydrous DMF. Benzaldehyde (204 μL , 2 mmol) and TMSCN (133 μL , 1 mmol) were then added. The solution was microwave irradiated at 150 $^{\circ}\text{C}$ for 10 minutes. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography employing either a Teledyne – Isco chromatographic system (Hex/EtOAc) or a HPLC purification system (reverse phase, water/acetonitrile). Note: when compounds of generic structure **12** were purified by HPLC, acetonitrile traces were sometimes observed in the ^1H -NMR spectra (s, 2.10 ppm) and could not be removed despite prolonged rotary evaporation and oven-drying under vacuum.

4.2.1 N-Benzylidene-2,4-diphenyl-1H-imidazol-5-amine (12a)—A yellow powder was obtained (89 mg, 55% yield). m.p. 224 – 225 $^{\circ}\text{C}$; R_f = 0.43 (silica gel, 7:3 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.60 (s, 1H), 9.24 (s, 1H), 8.19 (d, J = 7.7 Hz, 2H), 8.14 (d, J = 7.8 Hz, 2H), 7.99 (d, J = 6.9 Hz, 2H), 7.51 (m, 7H), 7.42 (t, J = 7.3 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.5, 144.9, 144.8, 135.9, 131.9, 131.4, 130.2, 129.8, 129.0, 128.9, 128.7, 128.6, 125.7, 124.6, 124.1, 120.0; $[\text{M}+\text{H}]^+ = 324$; HRMS: m/z calculated for $\text{C}_{23}\text{H}_{18}\text{N}_4$ $[\text{M}+\text{H}]^+$: 324.1422; found 324.1421.

4.2.2. N-(4-Bromobenzylidene)-4-(4-bromophenyl)-2-phenyl-1H-imidazol-5-amine (12c)—A yellow solid was obtained (167 mg, 69% yield). m.p. 102 – 110 $^{\circ}\text{C}$; R_f = 0.35 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.68 (br, s, 1H), 9.15 (br, s, 1H), 8.13 (d, J = 9.2 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) 154.5, 144.9, 144.8, 135.9, 131.9, 131.4, 130.2, 129.8, 129.0, 128.9, 128.7, 128.6, 125.7, 124.6, 124.2, 120.0; $[\text{M}+\text{H}]^+ = 482$; HRMS: m/z calculated for $\text{C}_{22}\text{H}_{16}\text{Br}_2\text{N}_3$ $[\text{M}+\text{H}]^+$: 479.9633; found 479.9638, 481.9634 and 483.9635.

4.2.3 N-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-2-phenyl-1H-imidazol-5-amine (12d)—A dark orange viscous oil was obtained (106 mg, 55% yield). R_f = 0.35 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.42 (s, 1H), 9.14 (s, 1H), 8.13 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.13 – 7.03 (m, 4H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 161.7, 158.7, 154.5, 144.5, 144.0, 130.7, 130.3, 129.1, 128.9, 128.4, 125.9, 125.1, 123.2, 114.8, 114.4, 55.8, 55.6; $[\text{M}+\text{H}]^+$ = 384; HRMS: m/z calculated for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 384.1634; found 384.1637.

4.2.4. N-Benzylidene-2-(3-nitrophenyl)-4-phenyl-1H-imidazol-5-amine (12e)—An orange solid was obtained (48 mg, 26% yield). m.p. 240 – 241 °C; R_f = 0.40 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.97 (br, s, 1H), 9.23 (br, s, 1H), 9.00 (s, 1H), 8.56 (d, J = 7.9 Hz, 1H), 8.27 – 8.14 (m, 3H), 7.99 (d, J = 7.2 Hz, 2H), 7.80 (t, J = 8.0 Hz, 1H), 7.63–7.44 (m, J = 6.7 Hz, 5H), 7.33 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.4, 148.8, 142.6, 137.1, 132.1, 131.3, 130.9, 129.4, 129.0, 128.8, 127.6, 127.3, 123.5, 120.2; $[\text{M}+\text{H}]^+$ = 369; HRMS: m/z calculated for $\text{C}_{22}\text{H}_{17}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 369.1273; found 369.1270.

4.2.5. N-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-2-(3-nitrophenyl)-1H-imidazol-5-amine (12f)—An orange viscous oil was obtained (101 mg, 47% yield). R_f = 0.68 (silica gel, 1:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.79 (br, s, 1H), 9.16 (br, s, 1H), 8.97 (s, 1H), 8.53 (d, J = 7.9 Hz, 1H), 8.18 – 8.25 (m, 1H), 8.14 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.78 (t, J = 8.0 Hz, 1H), 7.23 – 6.96 (m, 4H), 3.80 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 161.9, 158.9, 155.2, 148.8, 144.9, 141.7, 132.2, 131.9, 130.8, 130.4, 130.1, 128.6, 126.0, 123.2, 122.8, 120.0, 114.8, 114.5, 55.8, 55.6; $[\text{M}+\text{H}]^+$ = 429; HRMS: m/z calculated for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 429.1485; found 429.1486.

4.2.6. N-Benzylidene-2-(4-methoxyphenyl)-4-phenyl-1H-imidazol-5-amine (12g)—An orange oil was obtained (97 mg, 55% yield). R_f = 0.19 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.43 (br, s, 1H), 9.19 (br, s, 1H), 8.17 (d, J = 7.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 6.9 Hz, 2H), 7.56 – 7.43 (m, 5H), 7.28 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.3, 155.1, 145.0, 137.3, 131.0, 129.3, 128.9, 128.6, 127.7, 127.1, 123.2, 114.6, 55.7; $[\text{M}+\text{H}]^+$ = 354; HRMS: m/z calculated for $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 354.1528; found 354.1530.

4.2.7. 2-(4-Methoxyphenyl)-4-(thiophen-2-yl)-N-(thiophen-2-ylmethylene)-1H-imidazol-5-amine (12h)—A yellow solid was obtained (112 mg, 61% yield). m.p. 118 – 120 °C; R_f = 0.15 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.50 (br, s, 1H), 9.18 (br, s, 1H), 8.00 (d, J = 7.7 Hz, 2H), 7.77 – 7.46 (m, 4H), 7.22 – 7.15 (m, 1H), 7.15 – 7.09 (m, 1H), 7.09 – 7.03 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.4, 147.8, 145.1, 144.3, 143.8, 132.5, 131.7, 130.7, 128.8, 127.6, 127.4, 123.8, 123.0, 122.0, 114.6, 110.0, 55.8; $[\text{M}+\text{H}]^+$ = 366; HRMS: m/z calculated for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{OS}_2$ $[\text{M}+\text{H}]^+$: 366.0657; found 366.0657.

4.2.8. N-(4-Bromobenzylidene)-4-(4-bromophenyl)-2-(4-chlorophenyl)-1H-imidazol-5-amine (12i)—An orange oil was obtained (287 mg, 57% yield). R_f = 0.36 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.76 (br, s, 1H), 9.15 (br, s, 1H), 8.26 – 8.04 (m, 4H), 7.87 – 8.00 (m, 2H), 7.65 – 7.82 (m, 4H), 7.65 – 7.53 (m, 2H); ^{13}C (100 MHz, DMSO- d_6) δ 155.1, 144.2, 136.2, 133.9, 132.4, 131.9, 130.6, 129.3, 129.2, 129.1, 127.8, 124.8, 120.6; $[\text{M}+\text{H}]^+$ = 516; HRMS: m/z calculated for $\text{C}_{22}\text{H}_{15}\text{Br}_2\text{ClN}_3$ $[\text{M}+\text{H}]^+$: 513.9243; found 513.9242, 515.9245 and 517.9245.

4.2.9. 2-(4-Chlorophenyl)-N-(2-methylbenzylidene)-4-(o-tolyl)-1H-imidazol-5-amine (12j)—A yellow solid was obtained (131 mg, 68% yield). m.p. 197 – 199 °C; R_f = 0.54 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.78 (br, s, 1H), 9.42 (br, s, 1H), 8.08 (m, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.63 – 7.51 (m, 2H), 7.45 (d, J = 6.7 Hz, 1H), 7.41 – 7.15 (m, 6H), 2.54 (s, 3H), 2.39 (s, 3H); ^{13}C (100 MHz, DMSO- d_6) δ 152.9, 145.2, 142.9, 137.9, 136.9, 134.4, 133.0, 131.0, 130.3, 130.1, 129.6, 129.2, 128.8, 128.2, 126.9, 126.7, 126.1, 125.4, 20.4, 19.1; $[\text{M}+\text{H}]^+ = 386$; HRMS: m/z calculated for $\text{C}_{24}\text{H}_{21}\text{ClN}_3$ $[\text{M}+\text{H}]^+$: 386.1346; found 386.1345.

4.2.10. 2-(4-Chlorophenyl)-N-(3-fluorobenzylidene)-4-(3-fluorophenyl)-1H-imidazol-5-amine (12k)—A yellow solid was obtained (130 mg, 66 % yield). m.p. 78 – 79 °C; R_f = 0.50 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.75 (br, s, 1H), 9.21 (br, s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 8.09 – 7.96 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 9.5 Hz, 1H), 7.64 – 7.48 (m, 4H), 7.34 (t, J = 8.7 Hz, 1H), 7.14 (t, J = 8.9 Hz, 1H); ^{13}C (100 MHz, DMSO- d_6) δ 163.6 (d, J = 25.0 Hz), 161.2 (d, J = 23 Hz), 154.8, 143.8, 137.9 (d, J = 7.6 Hz), 133.4, 129.8 (d, J = 8.0 Hz), 129.4 (d, J = 8.5 Hz), 127.7, 127.5, 126.3, 123.5 (d, J = 2.9 Hz), 121.6 (d, J = 2.9 Hz), 116.5 (d, J = 21.7 Hz), 112.8 (d, J = 21.7 Hz), 112.4 (d, J = 21.0 Hz), 111.8 (d, J = 23.4 Hz); $[\text{M}+\text{H}]^+ = 394$; HRMS: m/z calculated for $\text{C}_{22}\text{H}_{15}\text{ClF}_2\text{N}_3$ $[\text{M}+\text{H}]^+$: 394.0844; found 394.0846.

4.3. Synthesis of 2,4-Diphenyl-1H-imidazol-5-ammonium chloride 14

Imidazole **12a** (103 mg, 0.319 mmol) was dissolved in 5 mL EtOAc. Therefore, 10 drops of concentrated HCl were added to the solution, and a yellow precipitate was immediately observed. The reaction mixture was heated at 50 °C in an oil bath for 4 hours and then cooled to room temperature. The precipitate was collected on a fritted filter and washed with DCM. A yellow powder was obtained (75 mg, 87 % yield). m.p. 180 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (d, J = 7.7 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.52 (m, 5H), 7.30 (t, J = 7.4 Hz, 1H); ^{13}C (100 MHz, DMSO- d_6) δ 138.3, 136.9, 130.9, 129.6, 129.2, 129.0, 127.1, 126.4, 126.1, 125.1, 112.6; $[\text{M}+\text{H}]^+ = 236$; HRMS: m/z calculated for $\text{C}_{15}\text{H}_{14}\text{N}_3$ $[\text{M}+\text{H}]^+$: 236.1822; found 236.1821.

4.4. General Procedure for the synthesis of 16, exemplified for 16a

In a sealed vessel, guanidine hydrochloride (48 mg, 0.5 mmol) and sodium sulfate (284 mg, 2 mmol) were suspended in 2.5 mL anhydrous DMF. Benzaldehyde (408 μL , 2 mmol) and TMSCN (133 μL , 1 mmol) were added, and the solution was microwave irradiated at 150 °C for 10 minutes. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography employing a Teledyne – Isco chromatographic system (Hex/EtOAc).

4.4.1 N²,N⁵-Dibenzylidene-4-phenyl-1H-imidazole-2,5-diamine (16a)—A yellow oil was obtained (68 mg, 39 % yield). R_f = 0.79 (silica gel, 4:1 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 12.93 (br, s, 1H), 9.29 (s, 1H), 9.16 (br, s, 1H), 8.20 (d, J = 7.5 Hz, 2H), 8.07 – 8.00 (m, 2H), 7.98 (d, J = 6.7 Hz, 2H), 7.64 – 7.40 (m, 8H), 7.28 (t, J = 7.4 Hz, 1H); ^{13}C (100 MHz, DMSO- d_6) δ 161.6, 149.5, 137.2, 136.0, 132.6, 131.2, 129.5, 129.5, 129.4, 129.0, 128.7, 127.2, 126.8; $[\text{M}+\text{H}]^+ = 351$; HRMS: m/z calculated for $\text{C}_{23}\text{H}_{19}\text{N}_4$ $[\text{M}+\text{H}]^+$: 351.1531; found 351.1533.

4.4.2 N²,N⁵-Bis(3-fluorobenzylidene)-4-(3-fluorophenyl)-1H-imidazole-2,5-diamine (16b)—An orange viscous oil was obtained (60 mg, 30% yield). R_f = 0.68 (silica gel, 8:2 hexanes/EtOAc); ^1H NMR (400 MHz, DMSO- d_6) δ 13.07 (br, s, 1H), 9.21 (s, 1H), 9.06 (s, 1H), 7.96 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.74 (m, 2H), 7.68 (d, J = 9.9 Hz, 1H), 7.60 – 7.41 (m, 3H), 7.37 (m, 1H), 7.29 (m, 1H), 7.10 – 7.00 (m, 1H); ^{13}C NMR (100 MHz,

DMSO- d_6) δ 164.1 (d, J = 11.5 Hz) 164.0, 161.8 (d, J = 12.3), 161.6, 160.9, 155.3, 149.4, 139.5 (d, J = 7.3 Hz), 138.3 (d, J = 7.5 Hz), 131.6 (d, J = 8.6), 131.5 (d, J = 8.8 Hz), 131.1 (d, J = 8.8 Hz), 125.9 (d, J = 3.0 Hz), 125.2 (d, J = 2.5 Hz), 122.9, 119.5 (d, J = 22.0 Hz), 118.2 (d, J = 22.0 Hz), 115.2 (d, J = 23.0 Hz), 114.4 (d, J = 22.0 Hz), 113.9 (d, J = 22.0 Hz), 113.2 (d, J = 22.5 Hz); $[M+H]^+$ = 405; HRMS: m/z calculated for $C_{23}H_{16}F_3N_4$ $[M+H]^+$: 405.1249; found 405.1251.

4.4.3. N^2,N^5 -Bis(3-(trifluoromethyl)benzylidene)-4-(3-(trifluoromethyl)phenyl)-1H-imidazole-2,5-diamine (16c)—An orange viscous oil was obtained (97 mg, 35% yield). R_f = 0.36 (silica gel, 8:2 hexanes/EtOAc); 1H NMR (400 MHz, DMSO- d_6) δ 13.24 (br, s, 1H), 9.31 (s, 1H), 9.13 (s, 1H), 8.75 (s, 1H), 8.31 (s, 1H), 8.27 (m, 2H), 8.22 (d, J = 7.7 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.7, 154.9, 149.6, 137.9, 136.7, 133.6, 133.29, 130.8, 130.7, 130.5, 130.4, 130.2, 130.1, 130.1, 129.7 (m), 128.8 (m), 127.6 (m), 126.1, 125.8, 125.8, 125.1 (m), 123.8 (m), 123.5 (m), 123.4, 123.1, 123.0; $[M+H]^+$ = 555; HRMS: m/z calculated for $C_{26}H_{16}F_9N_4$ $[M+H]^+$: 555.1153; found 555.1149.

4.4.4. 4-(Thiophen-2-yl)- N^2,N^5 -bis(thiophen-2-ylmethylene)-1H-imidazole-2,5-diamine (16d)—A red foam was obtained (68 mg, 37%). R_f = 0.17 (silica gel, 8:2 hexanes/EtOAc); 1H NMR (400 MHz, DMSO- d_6) δ 12.99 (br, s, 1H), 9.34 (s, 1H), 9.11 (br, s, 1H), 8.06 – 7.81 (m, 2H), 7.79 – 7.71 (m, 1H), 7.65 (br, s, 1H), 7.54 (br, s, 2H), 7.27 (dd, J = 8.6, 4.9 Hz, 1H), 7.19 (dd, J = 8.6, 4.9 Hz, 1H), 7.08 (dd, J = 8.6, 4.9 Hz, 1H); ^{13}C (100 MHz, DMSO- d_6) δ 154.7, 149.2, 148.1, 144.1, 142.2, 136.2, 132.9, 132.7, 131.1, 129.3, 128.9, 127.5, 123.7; $[M+H]^+$ = 369; HRMS: m/z calculated for $C_{17}H_{13}N_4S_3$ $[M+H]^+$: 369.0224; found 369.0222.

4.5. General Procedure for the synthesis of 13, exemplified for 13a

In a sealed vessel, benzamidine (120 mg, 1 mmol) and benzaldehyde (101 μ L, 1 mmol) was dissolved in 1.5 mL anhydrous DMF. The solution was microwave irradiated at 100 °C for 40 minutes. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography employing a Teledyne – Isco chromatographic system (Hex/EtOAc). Note: Notwithstanding multiple attempts to remove them by chromatographic techniques, recrystallization from different solvents and scavenging, small traces of the starting aldehydes were sometimes detectable in the final compounds.

4.5.1 2,4,6-Triphenyl-1,2-dihydro-1,3,5-triazine (13a)—A white crystalline solid was obtained (110 mg, 71% yield). R_f = 0.41 (silica gel, 1:1 hexanes/EtOAc) m.p. 177 – 178 °C; 1H NMR (400 MHz, DMSO- d_6) δ 9.17 (br, s, 1H), 8.16 (br, s, 4H), 7.58 – 7.15 (m, 11H), 6.10 (br, s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.0, 159.2, 144.5, 138.0, 133.5, 132.6, 130.5, 129.0, 128.7, 128.5, 128.4, 127.9, 127.2, 126.6, 68.8; $[M+H]^+$ = 312; HRMS: m/z calculated for $C_{21}H_{18}N_3$ $[M+H]^+$: 312.1422; found 312.1422.

4.5.2. 2-Phenethyl-4,6-diphenyl-1,2-dihydro-1,3,5-triazine (13b)—A white crystalline solid was obtained (95 mg, 56% yield). R_f = 0.39 (silica gel, 1:1 hexanes/EtOAc); m.p. 155 – 156 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.27 (br, s, 1H), 8.13 (d, J = 7.1 Hz, 4H), 7.56 – 7.42 (m, 6H), 7.33 – 7.21 (m, 4H), 7.21 – 7.08 (m, 1H), 5.13 (t, J = 5.5 Hz, 1H), 2.89 – 2.76 (m, 2H), 2.15 – 2.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.5, 159.28, 141.8, 133.3, 132.0, 129.8, 128.4, 128.3, , 127.8, 127.5, 127.4, 125.7, 109.3, 68.7, 66.2, 29.5; $[M+H]^+$ = 340; HRMS: m/z calculated for $C_{23}H_{22}N_3$ $[M+H]^+$: 340.1735; found 340.1734.

4.5.3. 2-(2,3-Dimethoxyphenyl)-4,6-diphenyl-1,2-dihydro-1,3,5-triazine (13c)—A white crystalline solid was obtained (166 mg, 89% yield). R_f = 0.42 (silica gel, 1:1 hexanes/EtOAc) m.p. 170 – 171 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.85 (s, 1H), 8.26 – 8.18 (m, 2H), 8.11 (d, J = 6.7 Hz, 2H), 7.70 – 7.33 (m, 6H), 7.15 – 6.88 (m, 3H), 6.47 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.4, 158.8, 153.0, 146.0, 138.1, 137.9, 132.5, 130.4, 128.9, 128.7, 128.3, 127.8, 127.7, 124.6, 119.6, 113.0, 64.8, 61.4, 56.3; $[\text{M}+\text{H}]^+ = 372$; HRMS: m/z calculated for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 372.1634; found 372.1637.

4.5.4. 2-Cyclopropyl-4,6-bis(3-nitrophenyl)-1,2-dihydro-1,3,5-triazine (13e)—A yellow solid was obtained (112 mg, 61% yield). R_f = 0.42 (silica gel, 1:1 hexanes/EtOAc); m.p. 154 – 155 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 9.23 (br, s, 1H), 8.90 (s, 2H), 8.57 (d, J = 7.8 Hz, 2H), 8.38 (d, J = 7.9 Hz, 2H), 7.80 (t, J = 7.9 Hz, 2H), 4.80 (d, J = 6.7 Hz, 1H), 1.43 – 1.22 (m, 1H), 0.57 – 0.49 (m, 4H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 181.5, 168.4, 148.2, 147.8, 136.6, 134.5, 133.6, 130.7, 130.0, 127.9, 125.7, 122.6, 121.8, 70.1, 17.8, 12.5, 1.5; $[\text{M}+\text{H}]^+ = 366$; HRMS: m/z calculated for $\text{C}_{18}\text{H}_{16}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$: 366.1124; found 366.1127.

4.5.5 3-(4,6-Bis(4-methoxyphenyl)-1,2-dihydro-1,3,5-triazin-2-yl)phenol (13f)—A white solid was obtained (171 mg, 88 % yield). R_f = 0.14 (silica gel, EtOAc); m.p. 207 – 209 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (br, s, 1H), 8.25 – 7.98 (m, 4H), 7.24 – 7.09 (m, 2H), 7.05 – 6.99 (m, 4H), 6.92 – 6.86 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 6.04 (s, 1H), 3.84 – 3.80 (m, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 163.5, 162.1, 157.9, 146.2, 129.8, 129.7, 117.3, 115.2, 114.0, 113.6, 55.81, 55.78; $[\text{M}+\text{H}]^+ = 388$; HRMS: m/z calculated for $\text{C}_{23}\text{H}_{22}\text{N}_4$ $[\text{M}+\text{H}]^+$: 388.1583; found 388.1581.

4.5.6 4,6-Bis(4-chlorophenyl)-2-(o-tolyl)-1,2-dihydro-1,3,5-triazine (13g)—A white solid was obtained (100 mg, 51% yield). R_f = 0.87 (silica gel, 1:1 hexanes/EtOAc); m.p. 188 – 189 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.18 (br, s, 4H), 7.62 (d, J = 6.7 Hz, 2H), 7.45 (d, J = 6.8 Hz, 2H), 7.30 (d, J = 6.4 Hz, 1H), 7.21 (br, s, 3H), 6.38 (s, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 159.4, 157.5, 141.0, 137.0, 136.2, 135.2, 134.8, 131.7, 130.6, 129.3, 129.2, 128.6, 127.9, 127.8, 126.5, 126.1, 66.7, 18.8; $[\text{M}+\text{H}]^+ = 394$; HRMS: m/z calculated for $\text{C}_{22}\text{H}_{18}\text{Cl}_2\text{N}_3$ $[\text{M}+\text{H}]^+$: 394.0800 ; found 394.0804.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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27. X-ray structural assignment was also achieved for 13b. This unambiguously confirmed the substitution pattern of dihydrotriazine 13. Crystallographic data is available at CCDC 916050.
28. Four additional optimization tables are included within the attached experimental data.

Conventional application:

Application toward synthesis of 5-aminoimidazoles:

Scheme 1.
Groebke-Blackburn-Bienaymé MCR.

Scheme 2. Proposed mechanism of 5-aminoimidazole **12** formation.

Scheme 3.
Hydrolysis of 5-iminoimidazoles.

Table 1Original MCR protocol to **12a** and **13a**.

Entry	Temp. [°C]	Yield 12a	Yield 13a [%]
1	50	0	53
2	100	0	52
3	150	20	36
4	180	25	31

Table 2

Survey of stoichiometry and desiccating agents.

Entry	Equiv 2a	Equiv TMSCN	Desiccant	Yield 12a [%]
1	2	2	Na ₂ SO ₄	36
2	2	4	Na ₂ SO ₄	8
3	4	2	Na ₂ SO ₄	55
4	4	2	MgSO ₄	38
5	4	2	5 Å M.S.	48
6	4	2	CaCl ₂	51

Table 3

Exploration of the reactivity domain.

Entry	R ¹	R ²	Yield 12 [%]
1	phenyl	phenyl	12a , 55
2	4-nitrophenyl	phenyl	12b , 0
3	4-bromophenyl	phenyl	12c , 69
4	4-methoxyphenyl	phenyl	12d , 55
5	phenyl	3-nitrophenyl	12e , 26
6	4-methoxyphenyl	3-nitrophenyl	12f , 47
7	phenyl	4-methoxyphenyl	12g , 55
8	3-thiophene	4-methoxyphenyl	12h , 61
9	4-bromophenyl	4-chlorophenyl	12i , 57
10	2-methylphenyl	4-chlorophenyl	12j , 68
11	3-fluorophenyl	4-chlorophenyl	12k , 66

Table 4

A small collection of 2,5-diaminoimidazoles.

Entry	R	Yield 16 [%]
1	phenyl	16a , 39
2	3-fluorophenyl	16b , 30
3	3-(trifluoromethyl)-phenyl	16c , 35
4	3-thiophene	16d , 37

Table 5

Dihydrotriazine synthesis optimization.

Entry	Solvent	Temp. [°C]	<i>t</i> [min]	Yield 13a [%]
1	DMF	50	20	48
2	DMF	100	20	64
3	DMF	100	40	73
4	DMF	100	60	75
5	DMSO	100	40	68
6	<i>i</i> -PrOH	100	40	57
7	toluene	100	40	19

Table 6

Small library of dihydrotriazines.

Entry	R ¹	R ²	Yield 13 [%]
1	phenyl	phenyl	13a , 73
2	2-phenylethyl	phenyl	13b , 56
3	2,3-dimethoxyphenyl	phenyl	13c , 89
4	4-nitrophenyl	phenyl	13d , 0
5	cyclopropyl	3-nitrophenyl	13e , 61
6	3-hydroxyphenyl	4-methoxyphenyl	13f , 88
7	2-methylphenyl	4-chlorophenyl	13g , 51