Efficient Synthesis of Imidazo[2,1-*b*][1,3]benzothiazoles and 9*H*-Imidazo-[1,2-*a*][1,3]benzimidazoles under Solvent-Free Conditions

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Abstract: An efficient synthesis of imidazo[2,1-*b*][1,3]benzothiazoles and 9*H*-imidazo[1,2-*a*][1,3]benzimidazoles is described from a novel multicomponent reaction between 2-aminobenzothiazoles or 2-aminobenzimidazole, benzaldehydes, and imidazoline-2,4,5-trione under solvent-free conditions.

Key words: imidazo[2,1-*b*][1,3]benzothiazoles, 9*H*-imidazo[1,2-*a*][1,3]benzimidazoles, imidazoline-2,4,5-trione, multicomponent reactions, solvent-free synthesis, heterocycles

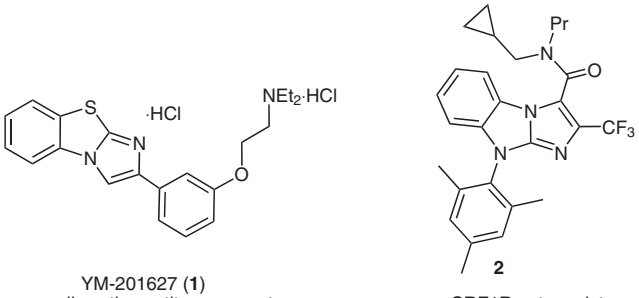
Multicomponent reactions (MCR) have become a significant part of today's arsenal of methods in combinatorial chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCR is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] Multicomponent reactions, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules.

In recent times, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity, and environmentally benign processes.[2]

Imidazo[2,1-*b*][1,3]benzothiazoles (IBT) and 9*H*-imidazo[1,2-*a*][1,3]benzimidazoles (9*H*-IBI), fused tricyclic 6-5-5 heterocyclic compounds, are of interest because of the occurrence of these heterocycles in biologically active compounds, some of which are used in pharmaceutical preparations.[3]

Some IBT have been reported as serotonin 5-HT_3 receptor antagonists.[4] YM-201627 (**1**, Figure 1) is an orally active antitumor agent with selective inhibition of vascular endothelial cell proliferation.[5]

Compounds having 9*H*-IBI ring system have been shown to possess hypotensive, antiaggregating, membrane-stabilizing,[6] hypoglycemic, hyperglycemic, spasmolytic,[7] antiarrhythmic, antioxidant,[8] membranotropic, anticalmodulin, antiulcer, antiproliferative,[9] hypnotic, anxiolytic, and anticonvulsant[10] activities. Furthermore, some 9*H*-IBI have been claimed to be serotonin 5-HT_2, 5-HT_3,[11] and corticotropin-releasing factor 1 receptor (CRF1R) antagonists (e.g., **2**, Figure 1).[12]



YM-201627 (**1**)
an orally active antitumor agent

2
a CRF1R antagonist

Figure 1 Examples of pharmacologically active IBT and 9*H*-IBI

So far, several synthetic routes have been reported for the preparation of these heterocycles. The most common approaches classified on the basis of the number of ring atoms in each of the components being cyclized involve: (i) single bond formation from [5+0] atom fragments and (ii) formation of two bonds from [4+1] or [3+2] atom fragments.[3,13–16]

As far as we know, there is no report concerning the synthesis of these heterocyclic systems by formation of three bonds. Considering the important biological properties of these fused tricyclic compounds, as part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[17] we report herein a novel synthesis of these nuclei from [3+1+1] atom fragments by formation of three bonds. Thus, 2-aminobenzothiazoles or 2-aminobenzimidazole **3**, benzaldehydes **4**, and imidazoline-2,4,5-trione **5** undergo a novel one-pot multicomponent addition reaction to produce IBT or 9*H*-IBI **6a**–**i** under solvent-free conditions (Scheme 1, Table 1).

After the reaction had been performed at equivalent ratios of 2-aminobenzothiazole (**3**, R = H and X = S), 4-methylbenzaldehyde (**4**, Ar = 4-MeC_6H_4) and **5**, the TLC and ^{1}H NMR analysis of the reaction mixture indicated the formation of the corresponding IBT **6a** at nearly 45% yield. Nearly half of 2-aminobenzothiazole was recovered unreacted at the end of the reaction, compared with the amount

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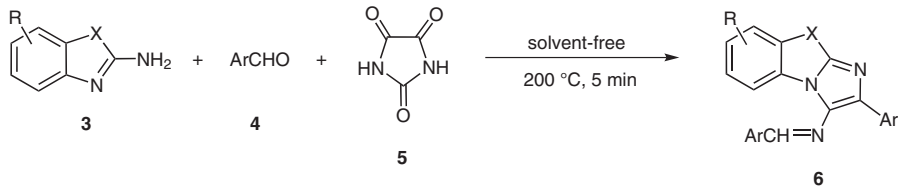


Scheme 1

initially added. Thus, the best results were obtained when the reactions were carried out using the three components at the 1:2.5:1.5 ratios, respectively (Table 1).[18]

The reactions were carried out by mixing the amine component **3**, the aldehyde **4**, and imidazoline-2,4,5-trione **5**. The reaction proceeded at 200 °C and was complete within a few minutes and afforded the corresponding IBT or 9*H*-IBI **6** in 90–97% yields.[18]

The structures of the isolated adducts **6a**–**i** were deduced by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **6a** displayed the molecular ion [M$^+$] peak at *m/z* 381, which was consistent with the adduct structure. The ^{1}H NMR spectrum of **6a** exhibited three sharp singlets, arising from the two methyl (δ = 2.37 and 2.44 ppm) and aldimine (δ = 8.67 ppm) groups along with characteristic multiplets with appropriate chemical shifts and coupling constants for the four H atoms of the the six-membered ring, as well as four doublets for the eigth H atoms of the two aryl substituents. The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 20 distinct resonances, in agreement with the suggested structure. Partial assignments of these resonances are given.[18] Single-crystal X-ray analysis conclusively confirmed the structure of the isolated products. An ORTEP diagram of **6a** is shown in Figure 2.[19]

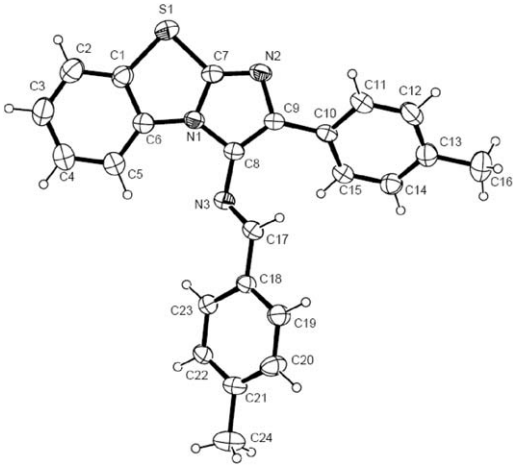
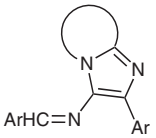
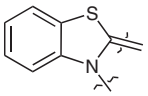
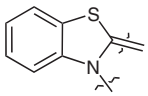
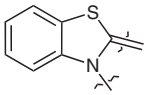
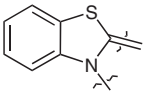
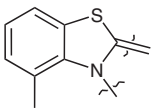
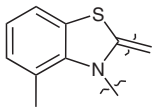
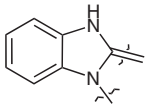
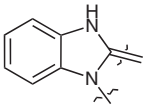
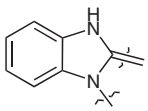


Figure 2 Molecular structure of **6a**

In summary, we have developed a novel, efficient, one-pot and multicomponent synthesis of imidazo[2,1-*b*][1,3]benzothiazoles and 9*H*-imidazo[1,2-*a*][1,3]benzimidazoles of potential synthetic and pharmacological interest. Solvent-free conditions, excellent yields of the products, and use of simple starting materials are the main

Table 1 Synthesis of Imidazo[2,1-*b*][1,3]benzothiazoles and 9*H*-Imidazo[1,2-*a*][1,3]benzimidazoles **6a**–**i**



6		Ar	Mp (°C)	Yield (%)[a]
6a		4-MeC$_6$H$_4$	144–145	92
6b		4-MeOC$_6$H$_4$	134–136	95
6c		3-MeC$_6$H$_4$	135	92
6d		4-FC$_6$H$_4$	175–176	97
6e		4-MeC$_6$H$_4$	194–195	94
6f		4-FC$_6$H$_4$	217–219	94
6g		4-FC$_6$H$_4$	264–265	92
6h		4-MeC$_6$H$_4$	235–238 (dec)	93
6i		3-MeC$_6$H$_4$	223–226 (dec)	90

[a] Isolated yields.

advantages of this method. The reactions have been performed under neutral conditions and the substances have been mixed without any activation or modification. The simplicity of this method makes it an interesting alternative to other approaches. Further investigations on the reaction mechanism, the scope, and the limitations of this reaction are under way.

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(18) **Procedure for the Preparation of 2-(4-Methylphenyl)-N^3-[(*E*)-1-(4-methylphenyl)methylidene]imidazo[2,1-*b*]-[1,3]benzothiazol-3-amine (6a)**

A mixture of 2-aminobenzothiazole (0.30 g, 2 mmol), 4-methylbenzaldehyde (0.60 g, 5 mmol), and imidazoline-2,4,5-trione (0.34 g, 3 mmol) was stirred at 200 °C for 5 min. Then, the reaction mixture was cooled to r.t. and the residue was purified by column chromatography using *n*-hexane–EtOAc (1:3) as eluent. The solvent was removed and the product was recrystallized from *n*-hexane–EtOAc (1:1). The product **6a** was obtained as yellow crystals; yield 0.70 g (92%, relative to 2-aminobenzothiazole). IR (KBr): 1603, 1495, 1479, 1379, 1352, 1315, 1175, 1146, 1109, 820, 748 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.37, 2.45 (2 × s, 6 H, 2 × CH_3), 7.19 (d, *J* = 7.4 Hz, 2 H, 2 × CH), 7.29–7.32 (m, 3 H, 3 × CH), 7.42 (dd, *J* = 7.9, 7.4 Hz, 1 H, CH), 7.64–7.68 (m, 3 H, 3 × CH), 7.76 (d, *J* = 7.4 Hz, 2 H, 2 × CH), 8.27 (d, *J* = 8.0 Hz, 1 H, CH), 8.74 (s, 1 H, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.30, 21.70 (2 × CH_3), 115.03, 123.79, 124.45, 126.18, 127.32, 128.60, 129.52, 129.70 (8 × CH), 130.27, 131.88, 133.25, 133.36, 133.61, 135.18, 137.10, 142.32, 144.98 (9 × C), 159.89 (CH). MS: *m/z* (%) = 381 (100) [M^+], 366 (10), 289 (4), 251 (85), 134 (16), 103 (7), 91 (14), 77 (7), 65 (5). Anal. Calcd (%) for $C_{24}H_{19}N_3S$ (381.50): C, 75.56; H, 5.02; N, 11.01. Found: C, 75.5; H, 5.2; N, 10.9.

Compound **6d**: yellow crystals; yield 0.75 g (97%). IR (KBr): 1603, 1589, 1528, 1500, 1491, 1454, 1379, 1290, 1225, 1192, 1148, 1092, 845, 752 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.09 (dd, $^3J_{FH}$ = 8.6 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 7.20 (dd, $^3J_{FH}$ = 8.6 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 7.35 (dd, *J* = 8.1, 7.2 Hz, 1 H, CH), 7.45 (dd, *J* = 8.1, 7.2 Hz, 1 H, CH), 7.69 (d, *J* = 7.2 Hz, 1 H, CH), 7.72 (dd, $^4J_{FH}$ = 5.4 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 7.86 (dd, $^4J_{FH}$ = 5.5 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 8.24 (d, *J* = 8.1 Hz, 1 H, CH), 8.67 (s, 1 H, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 114.94 (CH), 115.87 (d, $^2J_{FC}$ = 21.5 Hz, CH), 116.27 (d, $^2J_{FC}$ = 22.1 Hz, CH), 123.93, 124.71, 126.29 (3 × CH), 129.34 (d, $^3J_{FC}$ = 7.9 Hz, CH), 130.30 (C), 130.56 (d, $^3J_{FC}$ = 8.8 Hz, CH), 130.82 (d, $^4J_{FC}$ = 3.3 Hz, C), 132.30 (d, $^4J_{FC}$ = 3.2 Hz, C), 132.56, 133.21, 134.89, 145.43 (4 × C), 158.47 (CH), 162.20 (d, $^1J_{FC}$ = 247.3 Hz, CF), 165.05 (d, $^1J_{FC}$ = 253.7 Hz, CF). MS: *m/z* (%) = 389 (98) [M^+], 350 (32), 326 (8), 255 (100), 229 (27), 201 (13), 134 (37), 107 (15), 90 (9). Anal. Calcd (%) for $C_{22}H_{13}F_2N_3S$ (389.43): C, 67.85; H, 3.36; N, 10.79. Found: C, 67.8; H, 3.4; N, 10.7.

Compound **6g**: yellow crystals; yield: 0.68 g (92%). IR (KBr): 3290 (NH), 1601, 1585, 1528, 1510, 1493, 1450, 1339, 1232, 1225, 1196, 1150, 1094, 839, 768 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 7.19 (dd, *J* = 7.8, 7.6 Hz, 1 H, CH), 7.25 (dd, $^3J_{FH}$ = 8.6 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 7.31 (dd, *J* = 7.8, 7.6 Hz, 1 H, CH), 7.37 (dd, $^3J_{FH}$ = 8.6 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 7.43 (d, *J* = 7.8 Hz, 1 H, CH), 7.71 (d, *J* = 8.0 Hz, 1 H, CH), 8.04 (dd, $^4J_{FH}$ = 5.3 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 8.19 (dd, $^4J_{FH}$ = 5.4 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH), 8.86 (s, 1 H, CH), 12.00 (br, 1 H, NH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 112.04, 112.36 (2 × CH), 115.04 (d, $^2J_{FC}$ = 21.4 Hz, CH), 116.00 (d, $^2J_{FC}$ = 22.0 Hz, CH), 119.84, 123.61 (2 × CH), 124.98, 127.37 (2 × C), 129.18 (d, $^3J_{FC}$ = 7.9 Hz, CH),

130.03 (d, $^3J_{FC}$ = 8.7 Hz, CH), 131.22 (d, $^4J_{FC}$ = 3.3 Hz, C), 133.29 (d, $^4J_{FC}$ = 3.2 Hz, C), 136.45, 138.98, 148.09 (3 × C), 150.49 (CH), 162.41 (d, $^1J_{FC}$ = 247.9 Hz, CF), 164.95 (d, $^1J_{FC}$ = 252.5 Hz, CF). MS: *m/z* (%) = 372 (19) [M$^+$], 360 (15), 326 (97), 238 (91), 229 (23), 196 (100), 133 (33), 118 (43), 107 (19), 95 (35), 79 (44), 69 (16). Anal. Calcd (%) for $C_{22}H_{14}F_2N_4$ (372.38): C, 70.96; H, 3.79; N, 15.05. Found: C, 71.0; H, 3.8; N, 14.9.

(19) **Selected X-ray Crystallographic Data for Compound 6a**
$C_{24}H_{19}N_3S$, monoclinic, space group = $P2_1/n$, a = 12.7579 (12) Å, b = 7.5112 (7) Å, c = 21.2243 (20) Å, β = 91.626 (2)°, V = 2033.03 (3) Å^3, T = 295 (2) K, Z = 4, D_{calcd} = 1.25 g cm^{-3}, μ = 0.173 mm^{-1}, 2245 observed reflections, final R_1 = 0.079, wR_2 = 0.149 and for all data R_1 = 0.137, wR_2 = 0.172. CCDC 671151 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.