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ORIGINAL PAPER

Catalyst-free rapid synthesis of benzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamides via four-component coupling in one pot

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Abstract A new class of fused tricyclic benzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamide derivatives was synthesized *via* an environmentally benign one pot sequential four-component condensation reaction of an amine, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, an aldehyde and 1*H*-benzo[*d*]imidazol-2-amine without using catalyst in good yields.

Keywords Catalyst-free · Multicomponent reaction · 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one · 1*H*-Benzo[*d*]imidazol-2-amine

Introduction

Recently, much attention has been devoted towards dihydropyrimidine derivatives due to their significant therapeutic and medicinal properties [1–3]. Several marine alkaloids having the dihydropyrimidine core unit were found to show interesting biological activities such as antiviral, antibacterial and anti-inflammatory activities [4, 5]. Many functionalized derivatives are used as calcium channel blockers, antihypertensive agents and α-la antagonists [6, 7]. Numerous heterocyclic systems fused with pyrimidines are known for their important biological activities [8]. Benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives can be used as inhibitor of cell proliferation [9], lymphocyte specific kinase [10], DNA-topoisomerase and protein kinase [11, 12].

The rapid assembly of molecular diversity and complexity is widely regarded as one of the most important aspects in modern organic synthesis, and is also a key paradigm in the design of libraries of bioactive molecules (for selected reviews of diversity-oriented synthesis and its impact in the discovery of bioactive compounds, see: [13–19]). One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined sequentially together in a single reaction flask to generate a product in such a way that all the starting materials significantly contribute atoms to the newly formed product, are particularly promising for the construction of libraries of compounds (for selected recent reviews on multicomponent reactions, see: [20–26]). Another two important aspects are the development the catalyst-free synthesis in a greener solvent such as water or under solvent-free conditions [27–34]. The combination of these three aspects is highly challenging and will provide the more benefits for chemical transformations.

In continuing of our studies toward the synthesis of organic compounds *via* multicomponent reactions (MCRs) [35–39], we report an environmentally friendly synthesis of various dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamide derivatives **5** *via* a one pot sequential four-component condensation of amines **1**, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **2**, aldehydes **3** and 1*H*-benzo[*d*]imidazol-2-amine **4** in good yields under solvent-free and in water as a green solvent without using any catalyst within 35–60 min, respectively (Scheme 1).

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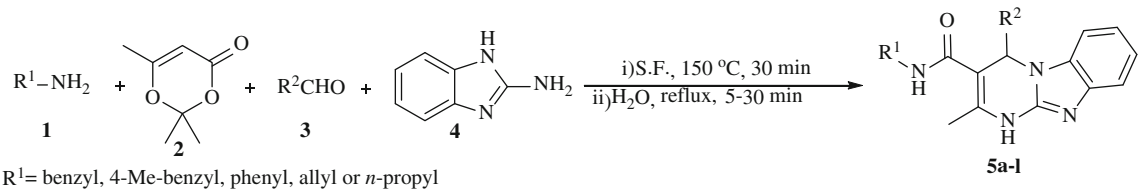


R^1= benzyl, 4-Me-benzyl, phenyl, allyl or *n*-propyl

R^2= Ph, 4-ClC_6H_4, 3-ClC_6H_4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$OMeC_6H_4$ or *n*-propyl

Scheme 1 Synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamides **5a–l**

Experimental

Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz; ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 100.65 MHz, respectively. The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. All the products are new compounds, which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra and elemental analyses data.

Typical procedure for the synthesis of *N*-benzyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenz[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxamide (**5a**)

A solution of benzylamine (0.11 g, 1.0 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.14 g, 1.0 mmol) was heated under solvent-free conditions at 150 °C for 30 min. Then, 2-nitrobenzaldehyde (0.15 g, 1.0 mmol) and 1*H*-benzo[*d*]imidazol-2-amine (0.13 g, 1.0 mmol) in 5 ml H_2O were added simultaneously. The reaction mixture was allowed to reflux for 15 min until the precipitate was appeared. After completion of the reaction, as indicated by TLC (EtOAc:*n*-hexane, 1:2), the reaction mixture was filtered off and the residue was washed with ethanol and then with ethanol to give **5a** as a pure product. Yellow powder (0.39 g, 89%): mp 260–262 °C. IR (KBr) cm^{-1}: 3,270, 3,051, 2,930, 1,670, 1,626, 1,580, 1,512, 1,459. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.15 (3H, s, CH_3), 3.96 (H*a*, d, $^2J_{HH}$ = 14.7 Hz, CH_aH_b), 4.42 (H_b, dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 6.5 Hz, CH_aH_b), 6.87–6.91 (3H, m, CH, H-Ar), 7.05 (1H, t, $^3J_{HH}$ = 6.5 Hz, H-Ar), 7.10–7.20 (5H, m, H-Ar), 7.27 (1H, d, $^3J_{HH}$ = 7.3 Hz, H-Ar), 7.36 (1H, d, $^3J_{HH}$ = 7.3 Hz, H-Ar), 7.49–7.59 (2H, m, H-Ar), 7.91 (1H, d, $^3J_{HH}$ = 7.4 Hz, H-Ar), 8.12 (1H, br s, NHCO), 10.26 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.9, 38.3, 48.4 (CH_3, CH_2, and CH), 99.9, 105.3, 112.8, 116.2, 118.1, 120.3, 122.8, 123.1, 124.3, 125.4, 125.6, 128.0, 130.0, 131.0, 131.7, 135.5, 138.6, 142.7, 144.4 (C-Ar, C=C and C=N), 162.3 (CO). Anal. Calcd for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94; found C, 68.39; H, 4.76; N, 15.86.

N-Benzyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5b**)

Yellow powder (0.37 g, 85%): mp 249 °C (dec.). IR (KBr) cm^{-1}: 3,246, 3,063, 2,918, 1,673, 1,628, 1,579, 1,531, 1,461. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.23 (3H, s, CH_3), 4.18 (H_a, br s, CH_aH_b), 4.35 (H_b, br s, CH_aH_b), 6.75 (1H, s, CH), 6.86–8.20 (13H, m, H-Ar), 8.33 (1H, br s, NHCO), 10.29 (1H, br s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.8, 38.3, 52.4 (CH_3, CH_2, and CH), 99.3, 105.7, 112.7, 116.1, 117.9, 118.1, 119.3, 122.8, 123.0, 124.1, 124.4, 124.9, 126.6, 127.7, 130.0, 131.8, 135.5, 138.6, 139.1, 142.4, 143.9 (C-Ar and C=C, C=N), 162.1 (CO). Anal. Calcd for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94; found C, 68.29; H, 4.89; N, 15.99.

N-Benzyl-2-methyl-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5c**)

White powder (0.37 g, 86%): mp 280–282 °C. IR (KBr) cm^{-1}: 3,307, 3,027, 2,918, 1,670, 1,627, 1,579, 1,512, 1,451. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.17 (3H, s, CH_3), 4.12 (H_a, m, CH_aH_b), 4.38 (H_b, m, CH_aH_b), 6.54 (1H, s, CH), 6.84–7.32 (13H, m, H-Ar), 8.27 (1H, br s, NHCO), 10.14 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.8, 38.3, 52.6 (CH_3, CH_2, and CH), 99.8, 105.6, 112.6, 115.8, 117.8, 122.7, 123.0, 124.2, 124.8, 125.3, 127.8, 128.8, 131.1, 135.6, 135.9, 138.6, 142.6, 144.4 (C-Ar, C=C and C=N), 162.3 (CO). Anal. Calcd for $C_{25}H_{21}ClN_4O$: C, 70.01; H, 4.93; N, 13.06; found C, 70.09; H, 4.86; N, 13.13.

N-Benzyl-2-methyl-4-(4-methylphenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5d**)

White powder (0.32 g, 79%): mp 292–294 °C. IR (KBr) cm^{-1}: 3,307, 3,039, 2,918, 1,671, 1,626, 1,582, 1,514, 1,449. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.18 (3H, s, CH_3), 2.25 (3H, s, CH_3), 4.16 (H_a, dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 4.7 Hz, CH_aH_b), 4.37 (H_b, dd, $^2J_{HH}$ = 15.4 Hz,

$^{3}J_{HH}$ = 6.6 Hz, CH_aH_b), 6.50 (1H, s, CH), 6.83–7.32 (13H, m, H-Ar), 8.27 (1H, br s, NHCO), 10.06 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 16.9, 38.3, 52.9 (CH_3, CH_2, and CH), 100.2, 105.7, 112.4, 115.7, 117.6, 122.7, 123.1, 123.3, 124.2, 125.3, 127.9, 130.9, 133.4, 134.0, 135.6, 138.7, 142.8 (C-Ar, C=C and C=N), 162.4 (CO). Anal. Calcd for $C_{26}H_{24}N_4O$: C, 76.45; H, 5.92; N, 13.72; found C, 76.53; H, 5.86; N, 13.65.

N-Benzyl-2-methyl-4-(4-methoxyphenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-]pyrimidine-3-carboxamide (**5e**)

White powder (0.32 g, 76%): mp 290–292 °C. IR (KBr) cm^{-1}: 3,295, 3,051, 2,918, 1,672, 1,623, 1,584, 1,512, 1,459. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.19 (3H, s, CH_3), 3.71 (3H, s, OCH3), 4.16 (H_a, m, CH_aH_b), 4.35 (H_b, dd,, $^{2}J_{HH}$ = 15.0 Hz, $^{3}J_{HH}$ = 5.7 Hz, CH_aH_b), 6.50 (1H, s, CH), 6.86–8.20 (13H, m, H-Ar),.8.33 (1H, br s, NHCO), 10.29 (1H, br s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 38.3, 51.3, 52.6 (CH_3, CH_2, and CH), 100.4, 105.7, 110.0, 112.4, 115.7, 117.6, 122.7, 123.1, 124.2, 124.7, 128.0, 129.1, 130.8, 135.7, 138.7, 142.8, 155.1 (C-Ar, C=C and C=N), 162.4 (CO). Anal. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20; found C, 73.49; H, 5.76; N, 13.25.

N-Benzyl-2-methyl-4-(4-ethyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5f**)

White powder (0.27 g, 80%): mp 275–277 °C. IR (KBr) cm^{-1}: 3,308, 3,060, 2,968, 1,677, 1,638, 1,614, 1,517, 1,459. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.56 (3H, t, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.49–1.59 (1H, m, CH_2), 1.98–2.10 (1H, m, CH_2), 2.13 (3H, s, CH_3), 4.38 (2H, m, CH_2), 5.64 (1H, br s, CH),.6.97–7.37 (9H, m, H-Ar), 8.40(1H, t, $^{3}J_{HH}$ = 5.0 Hz, NHCO), 9.75 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 3.1, 13.5, 22.0, 38.6, 49.4 (CH_3, CH_2, and CH), 97.7, 105.2, 112.5, 115.7, 117.6, 122.9, 123.5, 124.5, 127.7, 133.0, 136.0, 138.6, 144.0 (C-Ar, C=C and C=N), 163.0 (CO). Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17; found C, 72.89; H, 6.46; N, 16.25.

N-(4-Methylbenzyl)-2-methyl-4-(3-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5g**)

White powder (0.38 g, 87%): mp 271–273 °C. IR (KBr) cm^{-1}: 3,319, 3,051, 2,918, 1,671, 1,635, 1,579, 1,512, 1,457. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.18 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.71 (3H, s, CH3), 4.12 (H_a, dd, $^{2}J_{HH}$ = 15.2 Hz, $^{3}J_{HH}$ = 4.6 Hz, CH_aH_b), 4.32 (H_b, dd, $^{2}J_{HH}$ = 15.3 Hz, $^{3}J_{HH}$ = 6 Hz, CH_aH_b), 6.49 (1H, s, CH), 6.76–7.05 (9H, m, H-Ar), 7.22 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, H-Ar), 7.29 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, H-Ar), 8.22 (1H, t, $^{3}J_{HH}$ = 5.6 Hz, NHCO), 10.03 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 16.9, 38.0, 51.2, 52.6 (CH_3, CH_2, and CH), 100.4, 105.7, 110.0, 112.4, 115.6, 117.6, 123.1, 124.6, 124.8, 127.9, 129.0, 130.7, 131.6, 132.6, 138.7, 142.8, 155.0 (C-Ar, C=C and C=N), 162.3 (CO). Anal. Calcd for $C_{26}H_{23}ClN_4O$: C, 70.50; H, 5.23; N, 12.65; found C, 70.59; H, 5.26; N, 12.73.

ORTEP diagram for **5g**; summary of data: The Cambridge Crystallographic Data Center (CCDC) no.: 907238; unit cell parameters: a 13.5701(5) b 8.9746(5) c 18.6211(9) beta 99.062(4); space group P 21/n.

N-Phenyl-2-methyl-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5h**)

White powder (0.34 g, 83%): mp 258–260 °C. IR (KBr) cm^{-1}: 3,319, 3,015, 2,942, 1,667, 1,626, 1,600, 1,514, 1,442. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.22 (3H, s, CH_3), 6.68 (1H, s, CH), 6.90–7.57 (13H, m, H-Ar), 9.77 (1H, br s, NHCO), 10.36 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 52.6 (CH_3 and CH), 100.4, 105.9, 112.4, 115.9, 116.4, 118.2, 119.6, 124.9, 125.6, 127.4, 128.8, 132.2, 135.1, 135.7, 137.5, 142.3 (C-Ar, C=C and C=N), 161.0 (CO). MS *m/z*: 417 (M^++1, ^{37}Cl, 4), 416 (M^+, ^{37}Cl, 18), 415 (M^++1, ^{35}Cl, 16), 414 (M^+, ^{35}Cl, 46), 399 (3), 322 (100), 294 (32), 184 (80), 158 (52), 119 (31), 65 (39). Anal. Calcd for $C_{24}H_{19}ClN_4O$: C, 69.48; H, 4.62; N, 13.50; found C, 69.41; H, 4.66; N, 13.57.

N-Phenyl-2-methyl-4-(phenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5i**)

Yellow powder (0.31 g, 81%): mp 266–268 °C. IR (KBr) cm^{-1}: 3,246, 3,051, 2,918, 1,670, 1,620, 1,578, 1,516, 1,441. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.22 (3H, s, CH_3), 6.66 (1H, s, CH), 6.86–7.57 (14H, m, H-Ar), 9.75 (1H, s, NHCO), 10.28 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 53.2 (CH3 and CH), 100.5, 105.7, 112.6, 115.8, 115.9, 117.8, 119.5, 122.9, 124.2, 124.8, 124.9, 127.9, 132.4, 135.3, 137.0, 138.7, 142.9 (C-Ar, C=C and C=N), 161.2 (CO). Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73; found C, 75.71; H, 5.36; N, 14.67.

N-Phenyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5j**)

Yellow powder (0.36 g, 85%): mp 245–247 °C. IR (KBr) cm^{-1}: 3,426, 3,051, 2,923, 1,661, 1,628, 1,594, 1,527,

1,439. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.22 (3H, s, CH_3), 6.66 (1H, s, CH), 6.86–7.57 (14H, m, H-Ar), 9.75 (1H, s, NHCO), 10.28 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.9, 52.4 (CH_3 and CH), 99.7, 105.7, 112.8, 115.9, 116.2, 117.4, 118.1, 119.3, 119.6, 124.8, 126.6, 127.6, 129.6, 133.1, 135.1, 138.6, 139.3, 142.6, 144.1 (C-Ar, C=C and C=N), 161.1 (CO). Anal. Calcd for $C_{24}H_{19}N_5O_3$: C, 67.76; H, 4.50; N, 16.46; found C, 67.71; H, 4.46; N, 16.51.

N-Propyl-2-methyl-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5k**)

White powder (0.33 g, 87%): mp 292–294 °C. IR (KBr) cm^{-1}: 3,331, 3,064, 2,955, 2,877, 1,676, 1,627, 1,512, 1,457. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.70 (3H, t, $^{3}J_{HH} = 7.2$ Hz, CH_3), 1.27–1.37 (2H, m, CH_2), 2.15 (3H, s, CH_3), 2.96–3.01 (2H, m, CH_2), 6.52 (1H, s, CH), 6.84–6.92 (1H, m, H-Ar), 6.97–7.05 (2H, m, H-Ar), 7.22–7.37 (5H, m, H-Ar), 7.77 (1H, br s, NHCO), 10.10 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 7.5, 13.6, 18.5, 36.7, 52.4 (CH_3, CH_2, and CH), 100.1, 105.6, 112.5, 115.8, 117.8, 124.7, 124.9, 127.8, 128.6, 130.7, 136.0, 138.7, 142.9 (C-Ar, C=C and C=N), 162.0 (CO). Anal. Calcd for $C_{21}H_{21}ClN_4O$: C, 66.22; H, 5.56; N, 14.71; found C, 66.16; H, 5.48; N, 14.66.

N-Allyl-2-methyl-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxamide (**5l**)

White powder (0.32 g, 84%): mp 295–297 °C. IR (KBr) cm^{-1}: 3,331, 3,039, 2,917, 1,676, 1,615, 1,514, 1,458. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.18 (3H, s, CH_3), 3.68 (2H, br s, CH_2), 4.85 (H_a, d, $^{3}J_{HH(trans)} = 17.2$ Hz, $CH{=}CH_aH_b$), 4.94 (H_b, d, $^{3}J_{HH(cis)} = 10.2$ Hz, $CH = CH_aH_b$), 5.61–5.77 (1H, m, *CH*=CH_2) 6.54 (1H, s, CH), 6.85–6.93 (1H, m, H-Ar), 6.98–7.05 (2H, m, H-Ar), 7.24–7.37 (5H, m, H-Ar), 7.94 (1H, br s, NHCO), 10.12 (1H, s, NH). ^{13}C NMR (100.65 MHz, DMSO-d_6) δ: 13.7, 37.3, 52.3 (CH_3, CH_2, and CH), 99.8, 105.6, 111.1, 112.6, 115.9, 117.8, 124.8, 124.9, 127.7, 128.7, 131.4, 136.0, 138.7, 142.8 (C-Ar, C=C and C=N), 162.0 (CO). Anal. Calcd for $C_{21}H_{19}ClN_4O$: C, 66.58; H, 5.05; Cl, 9.36; N, 14.79; found C, 66.51; H, 5.12; N, 14.72.

Synthesis of *N*-(3-nitrobenzylidene)-1*H*-benzo[*d*]imidazol-2-amine (**7b**)

The mixture of 3-nitrobenzaldehyde (0.15 g, 1.0 mmol) and 1*H*-benzo[*d*]imidazol-2-amine (0.13 g, 1.0 mmol) in 5 ml H_2O was allowed to reflux for 5 min until the precipitate was appeared. After completion of the reaction, as indicated by TLC (EtOAc:*n*-hexane, 1:2), the reaction mixture was filtered off and the residue was further purified by recrystallization from ethanol to give **7b** as a pure product. Yellow powder (0.26 g, 97%): mp 177–179 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.17–7.22 (2H, m, H-Ar), 7.46 (1H, br s, H-Ar), 7.60 (1H, br s, H-Ar), 7.83 (1H, t, $^{3}J_{HH} = 7.9$ Hz, H-Ar), 8.37–8.46 (2H, m, H-Ar), 8.85 (1H, s, H-Ar), 9.59 (1H, s, CH), 12.85 (1H, s, NH). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04; found C, 63.11; H, 3.72; N, 21.01.

Results and discussion

In a pilot experiment, the reaction of *N*-alkyl-3-oxobutanamide **6**, which was derived from the nucleophilic reaction of benzyl amine **1** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one under solvent-free conditions at 150 °C for 30 min, with 2-nitrobenzaldehyde and 1*H*-benzo[*d*]imidazol-2-amine **4** without addition of catalyst proceeds in water at reflux temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product *N*-benzyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenz[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxamide **5a** was obtained in 89% yield.

We have shown that the use of a wide diversity of substituents in amines **1** and aldehydes **3** in this four-component reaction makes possible the synthesis of libraries under similar circumstances. The results revealed that not only electron-deficient and electron-rich aryl aldehydes but also aliphatic aldehydes in the multi-component reaction afforded the corresponding product efficiently under the same conditions. The results are shown in Table 1. As anticipated from our original results, these reactions proceeded very cleanly and no undesirable side reactions were observed. All compounds, described in the paper, were synthesized for the first time. The structures of products **5a–l** are shown in Fig. 1.

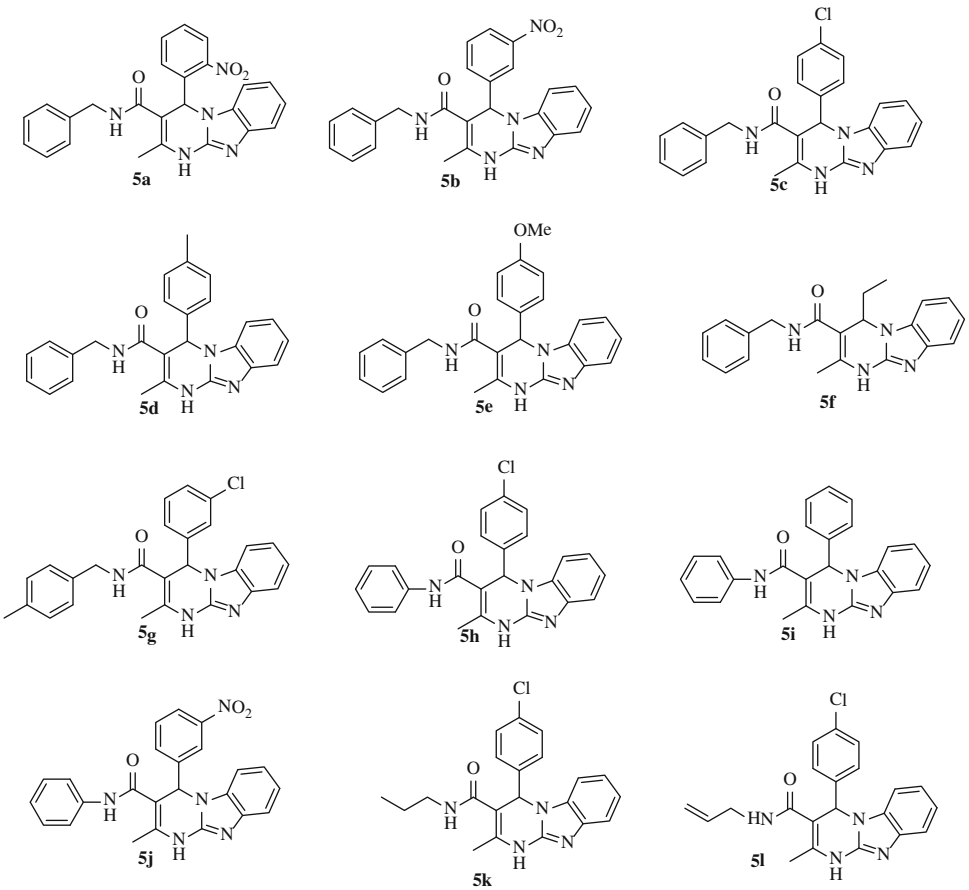
The nature of these compounds as 1:1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z values. Compounds **5a–l** are stable solids whose structures are fully supported by IR, ^{1}H, and ^{13}C NMR spectroscopies and elemental analysis. For example, the ^{1}H NMR spectrum of **5a** exhibited a singlet for the methyl group ($\delta = 2.15$), a doublet at 3.96 ppm ($^{2}J_{HH} = 14.7$ Hz) and a doublet of doublet at 4.42 ppm ($^{2}J_{HH} = 14.9$ Hz, $^{3}J_{HH} = 6.5$ Hz) for the methylene group. One multiplet ($\delta = 6.87$–6.91) was attributed to methine group (CHN) and phenyl moiety. Other 11 aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. The spectrum also contains a broad singlet

Table 1 Synthesis of dihydrobenzo[4,5]imidazo[1,2-a]-pyrimidine-3-carboxamides **5a–l**

Entry	R^1	Aldehyde	Product	Time (min)	Yield[a] (%)
1	Benzyl	2-Nitrobenzaldehyde	**5a**	45	89
2	Benzyl	3-Nitrobenzaldehyde	**5b**	35	85
3	Benzyl	4-Chlorobenzaldehyde	**5c**	50	86
4	Benzyl	4-Methylbenzaldehyde	**5d**	55	79
5	Benzyl	4-Methoxybenzaldehyde	**5e**	60	76
6	Benzyl	Propionaldehyde	**5f**	60	80
7	4-Methylbenzyl	3-Chlorobenzaldehyde	**5g**	40	87
8	Phenyl	4-Chlorobenzaldehyde	**5h**	50	83
9	Phenyl	Benzaldehyde	**5i**	60	81
10	Phenyl	3-Nitrobenzaldehyde	**5j**	45	85
11	*n*-Propyl	4-Chlorobenzaldehyde	**5k**	60	82
12	Allyl	4-Chlorobenzaldehyde	**5l**	55	84

[a] Isolated yield

Fig. 1 The structures of products **5a–l**



($\delta = 8.12$) which is attributed NHCO group. The signal corresponding to the NH group appears as a singlet at 10.26 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed 23 distinct resonances in agreement with the product structure. Furthermore, the structure of the product **5g** was confirmed unambiguously by single-crystal X-ray analysis (Fig. 2).

Two suggested pathways for the formation of compound **5** are presented in Scheme 2. It is conceivable in pathway **I**, so that the initial event is the formation of Schiff base **7** by the condensation of an aldehyde **3** and 1*H*-benzo[*d*]imidazol-2-amine **4**. In the next step, intermediate **8** is obtained *via* Michael addition reaction between **7** and *N*-alkyl-3-oxobutanamide **6**, which derived from the reaction

of an amine **1** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **2**. Then, the intermediate **9** is produced by an elimination reaction. Finally, Michael addition between **9** and 1*H*-benzo[*d*]imidazol-2-amine **4** afforded the intermediate **10**, which upon isomerization, intramolecular cyclization and dehydration gave the product **5**. In the case of pathway **II**, a reaction between compound **6** and aldehyde **3** produces the intermediate **9**, which after reaction with **4** affords product **5**.

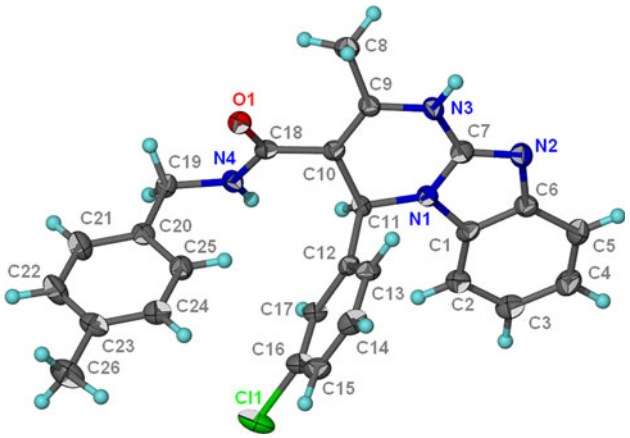
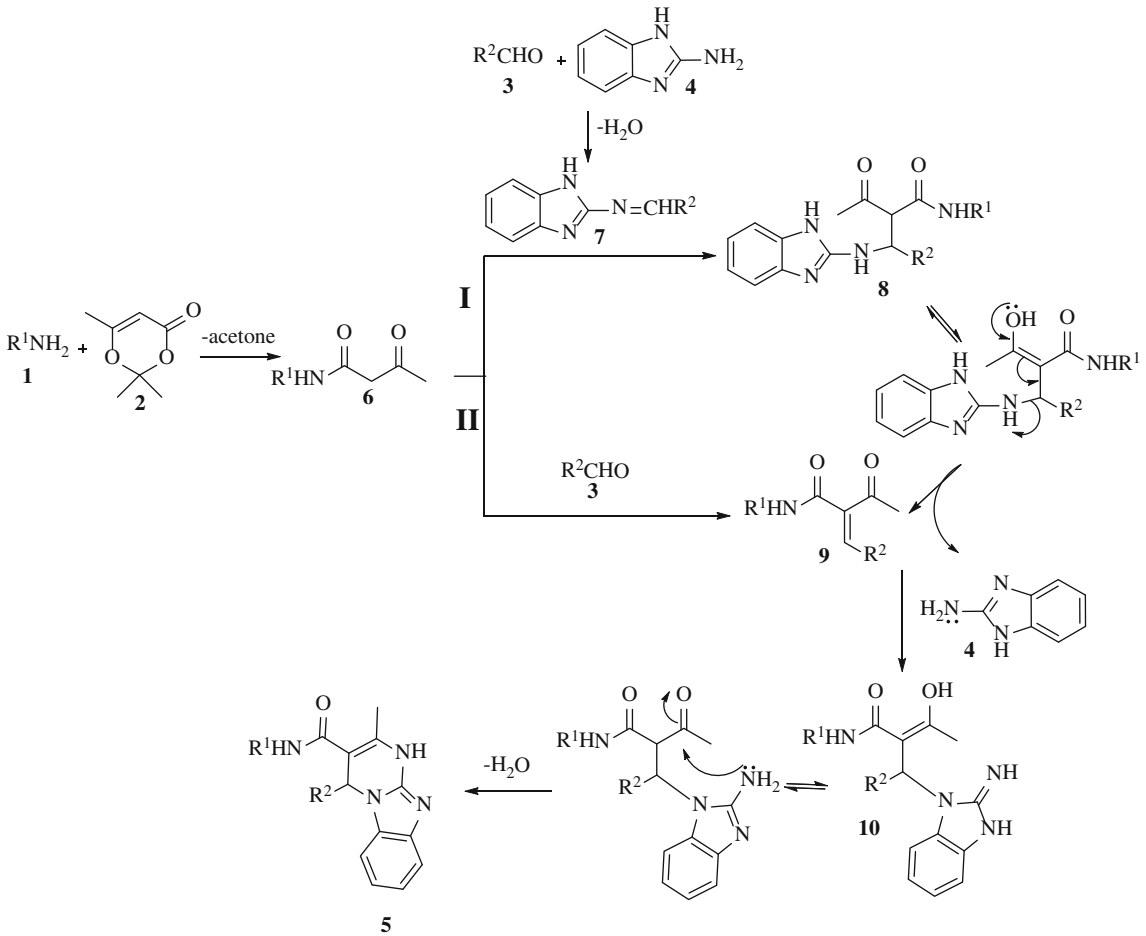


Fig. 2 ORTEP diagram for **5g**

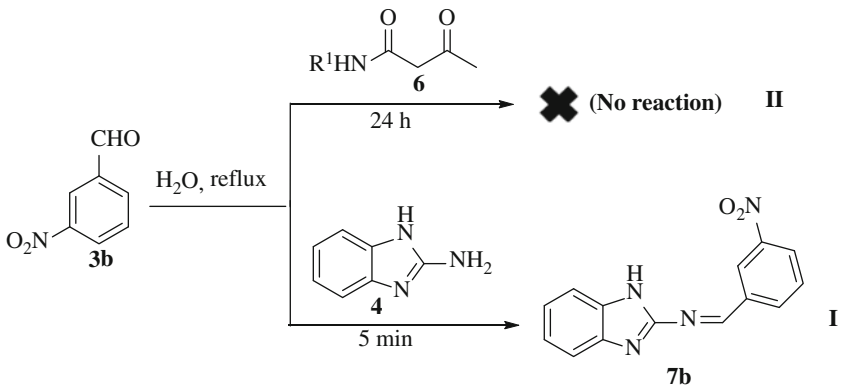
To distinguish the preferred pathway (pathway **I** or **II**), we carried out the condensation reaction between 3-nitrobenzaldehyde **3b** with *N*-alkyl-3-oxobutanamide **6** and the desired intermediate **9** was not obtained under reflux conditions in water. However, the intermediate *N*-(3-nitrobenzylidene)-1*H*-benzo[*d*]imidazol-2-amine **7b** was easily prepared *via* the condensation of 3-nitrobenzaldehyde **3b** and 1*H*-benzo[*d*]imidazol-2-amine **4** under the same reaction conditions (Scheme 3). This finding leads us to conclude that the preferred pathway to produce **5** is *via* route **I**.

In conclusion, we demonstrated an environmentally efficient four-component approach for the synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamide derivatives *via* cyclocondensation reaction of primary aliphatic or aromatic amines, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, 1*H*-benzo[*d*]imidazol-2-amine and aliphatic or aromatic aldehydes under catalyst-free conditions and in water. To the best of our knowledge, this new procedure provides the first example of the efficient synthetic method



Scheme 2 Proposed mechanism for the synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamides **5**

Scheme 3 Synthesis of *N*-(3-nitrobenzylidene)-1*H*-benzo[*d*]imidazol-2-amine **7b**



for dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carboxamides by a four-component reaction. The operational simplicity, short reaction time, high purity and good yield of products and minimal environmental impact are notable features of this procedure.

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