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Microwave Irradiation for Accelerating Synthesis of Diarylimidizo[1,5-*a*]pyrimidine Based on Isoflavones

Zhang, Zunting*,[a](张尊听) Zhang, Pengfei[a](张鹏飞) Kang, Taoying[a,b](康桃英) Zhu, Mulin[a](祝木林)

[a] *Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, Shaanxi 710062, China*
[b] *College of Chemical Engineering, Qinghai University, Xining, Qinghai 710062, China*

Microwave irradiation was used to accelerate the cyclocondensation of isoflavones and 5-amino-1*H*-imidazole-4-carboxamide in the presence of sodium hydroxide to produce 3,4-diphenyl-imidazo[1,5-*a*]pyrimidines in good to moderate yields.

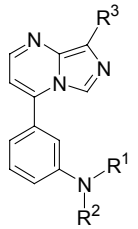
Keywords isoflavone, imidazo[1,5-*a*]pyrimidine, 5-amino-1*H*-imidazole-4-carboxamide, cyclocondensation

Introduction

Fused heteroaromatic compounds containing ring-junction nitrogen atoms are important for the preparation of biologically active molecules.[1,2] Imidazo[1,5-*a*]pyrimidine is an important pharmaceutical target (Scheme 1). Imidazo[1,5-*a*]pyrimidine exhibited biological activities, such as treatment and prevention of diseases mediated by $GABA_A$ receptor α-1 and α-2 subnuits;[3] and metabotropic glutamate receptor antagonist.[4]

Numerous methods for the synthesis of imidazo-[1,5-*a*]pyrimidine have been reported in the last decades, which involved the reaction between aminoimidazos and 1,3-biselectrophilic compounds, such as α,β-unsaturated carbonyl,[3] β-dicarbonyl,[4] α-cyano acrylonitrile with β-thioalkoxy, β-alkoxy, or β-chloro leaving group compounds.[5] It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent in the presence of alkali, which readily reacts with amidines,[6] guanidine,[7] hydrazine,[8] to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently we have reported the 2-aminobenzimidazole,[9] triazole,[10] and 3-amino-5-hydroxypyrazole,[11] condensed with isoflavones to get pyrimido[1,2-*a*]benzimidazoles, triazolopyrimidines, pyrazolo[3,4-*b*]pridines, respectively. To the best of our knowledge, there is no report on the synthesis of 3,4-diphenylimidazo[1,5-*a*]-pyrimidine. Herein, we report a new strategy for the preparation of the unknown class of 3,4-diphenyl-imidazo[1,5-*a*]pyrimidines from isoflavones.

Scheme 1 Chemical structure of an imidazo[1,5-*a*]pyrimidines pharmaceutical target



Experimental

Microwave irradiation was carried out using the commercial microwave oven MCR-3 (Zhengzhuo China). Melting points were measured on X-5 micro melting point apparatus, which are uncorrected. IR spectra were recorded on Fourier transform Infrared Spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on Bruker DRX-300 Advance spectrometer; chemical shifts (δ scale) are reported downfield from Me_4Si which was used as the internal standard for all NMR spectra. ^{1}H NMR spectra are reported in order: multiplicity and approximate coupling constant (*J* value) in hertz (Hz), number of protons; signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad signal). The ^{13}C NMR spectra were recorded at 75 MHz. The elemental analyses were performed with an Elementar Analysensyteme GmbH Vario EL III. All the products are new compounds, which were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. All other commercially obtained reagents were used as received. Thin layer chromatogra-

* E-mail: zhangzt@snnu.edu.cn; Tel.: 0086-029-85303940; Fax: 0086-029-85303940
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phy (TLC): silica gel 60 GF254 plate; and the eluant of column chromatography was the mixture of petroleum ether and ethyl acetate at volume ratio of 1∶1.

General procedure for the synthesis of diarylimidazo[1,5-*a*]pyrimidine 3

The isoflavone **1a**—**1i** (1.5 mmol), 5-amino-1*H*-imidazole-4-carboxamide **2** (2.4 mmol), and sodium hydrooxide (4.5, 6.0 and 7.5 mmol were used for 0, 1 and 2 free hydroxyl group of **1**) were refluxed in DMF (8 mL) by microwave irradiation for 12—30 min at 100 ℃ with microwave output 240 W. All reactions were monitored by TLC, which showed the disappearance of the starting materials. The reaction mixture was poured into water (100 mL) and acidified with 10% HCl/H_2O to the neutral pH and a light yellow precipitate formed. The precipitated yellow solid was filtered off and was purified on silica gel column (chloroform/methanol, 40∶1) to give the corresponding product **3**.

8-Carbomoyl-4-(2-hydroxy-4-isopropoxyphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (3a) m.p. 305—307 ℃. IR (KBr) *v*: 3428, 1665, 1609, 1501, 1379, 993, 858, 542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 1.27 (s, 6H), 4.56 (s, 1H), 6.39 (s, 1H), 6.53 (s, 1H), 6.93 (s, 1H), 7.32 (s, 6H), 7.62 (s, 1H), 7.79 (s, 1H), 8.60 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 22.2, 70.0, 103.3, 107.6, 109.0, 122.5, 122.9, 125.8, 128.3, 128.9, 129.8, 132.4, 134.8, 138.2, 138.9, 152.5, 157.3, 161.0, 163.6. Anal. calcd for $C_{22}H_{20}N_4O_3$: C 68.29, H 5.22, N 12.56; found C 68.03, H 5.19, N 12.60.

8-Carbomoyl-4-(2-hydroxy-4-methoxy-6-methylphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (3b) m.p. 303—305 ℃. IR (KBr) *v*: 3486, 2959, 1652, 1501, 1350, 1206, 979, 856, 542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 1.72 (s, 3H), 3.73 (s, 3H), 6.33 (s, 1H), 6.45 (s, 1H), 7.34—7.68 (m, 8H), 8.65 (s, 1H), 10.2 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 19.4, 55.5, 99.5, 107.5, 109.4, 123.1, 123.5, 125.2, 128.5, 128.9, 129.2, 134.8, 137.9, 138.2, 138.7, 152.2, 157.6, 162.1, 163.5. Anal. calcd for $C_{21}H_{18}N_4O_3$: C 67.50, H 5.02, N 15.11; found C 67.37, H 4.85, N 14.96.

8-Carbomoyl-4-(2-hydroxy-4-methoxyphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (3c) m.p. 301—302 ℃. IR (KBr) *v*: 3418, 1668, 1610, 1503, 1443, 1380, 944, 856, 543 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.70 (s, 3H), 6.41—7.77 (m, 11H), 8.62 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.6, 102.0, 106.3, 122.8, 125.2, 128.9, 132.3, 134.6, 138.6, 148.6, 152.3, 157.5, 162.6, 163.5. Anal. calcd for $C_{20}H_{16}N_4O_3$: C 66.82, H 4.52, N 15.62; found C 66.66, H 4.48, N 15.55.

8-Carbomoyl-4-(2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)imidazo[1,5-*a*]pyrimidine (3d) m.p. 318—319 ℃. IR (KBr) *v*: 3438, 1665, 1609, 1501, 1379, 993, 858, 542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.75 (s, 6H), 6.43—7.74 (m, 10H), 8.59 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.7, 102.1, 106.4, 109.7, 114.4, 122.5, 122.8, 125.5, 126.9, 131.0, 132.3, 138.2, 152.5, 157.4, 162.5, 163.5. Anal. calcd for $C_{21}H_{18}N_4O_4$: C 64.72, H 4.72, N 14.45; found C 64.61, H 4.65, N 14.35.

8-Carbomoyl-4-(2-hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)imidazo[1,5-*a*]pyrimidine (3e) m.p. 304—305 ℃. IR (KBr) *v*: 3455, 1642, 1504, 1350, 993, 857, 542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.54 (s, 3H), 3.75 (s, 6H), 6.15 (d, J=6.0 Hz, 2H), 6.90 (d, J=6.0 Hz, 2H), 7.20—7.35 (m, 3H), 7.58 (s, 1H), 7.74 (s, 1H), 8.58 (s, 1H), 10.1 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.6, 56.2, 56.5, 90.9, 94.4, 98.8, 114.3, 122.8, 123.8, 125.3, 127.4, 130.3, 135.4, 138.2, 152.2, 157.5, 159.3, 159.4, 163.4, 163.5. Anal. calcd for $C_{22}H_{20}N_4O_5$: C 62.97, H 4.89, N 13.52; found C 62.85, H 4.79, N 13.33.

8-Carbomoyl-4-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)imidazo[1,5-*a*]pyrimidine (3f) m.p. 305—306 ℃. IR (KBr) *v*: 3409, 1613, 1506, 1423, 1377, 1251, 987, 858,542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.74 (s, 3H), 6.23 (s, 1H), 6.48 (s, 1H), 6.82—7.35 (m, 6H), 7.60 (s, 1H), 7.74 (s, 1H), 8.58 (s, 1H), 9.89 (s, 1H), 10.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.6, 103.3, 107.9, 108.1, 114.4, 122.3, 122.7, 125.6, 127.0, 131.1, 132.2, 138.1, 138.8, 152.5, 157.4, 159.2, 161.0, 163.5. Anal. calcd for $C_{20}H_{16}N_4O_4$: C 63.89, H 4.35, N 14.92; found C 63.82, H 4.28, N 14.89.

8-Carbomoyl-4-(2,4-dihydroxyphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (3g) m.p. 306—307 ℃. IR (KBr) *v*: 3367, 3187, 1651, 1053, 1012, 833, 541 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 6.19 (s, 1H), 6.46 (s, 1H), 6.82 (d, J=9.0 Hz, 1H), 7.30 (d, J=9.0 Hz, 6H), 7.58 (s, 1H), 7.77 (s, 1H), 8.60 (s, 1H), 9.77 (s, 1H), 10.87 (s, 1H) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 103.3, 107.8, 108.0, 122.7, 125.8, 127.9, 128.0, 128.9,129.9, 132.2, 135.1, 138.2, 139.3, 152.3, 157.5, 161.1, 163.5. Anal. calcd for $C_{19}H_{14}N_4O_3$: C 65.93, H 4.15, N 16.24; found C 65.89, H 4.07, N 16.18.

8-Carbomoyl-4-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)imidazo[1,5-*a*]pyrimidine (3h) m.p. 306—307 ℃. IR (KBr) *v*: 3578, 1568, 1539, 1542, 1388, 980, 852, 536 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 6.23 (d, J=9.0 Hz, 1H), 6.55 (s, 1H), 6.71—6.81 (m, 3H), 7.06 (d, J=9.0Hz, 2H), 7.39 (s, 1H), 7.63—7.72 (m, 2H), 8.57 (s, 1H), 9.75 (s, 1H), 10.82 (s, 1H), 11.73 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 103.4, 105.8, 108.0, 115.8, 122.4, 122.7, 125.2, 125.6, 131.0, 132.1, 138.1, 138.7, 152.8, 157.5, 157.6, 161.1, 163.8. Anal. calcd for $C_{19}H_{14}N_4O_4$: C 63.05, H 4.02, N 15.54; found C 62.98, H 3.89, N 15.46.

8-Carbomoyl-4-(2-hydroxyphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (3i) m.p. 310—311 ℃. IR (KBr) *v*: 3428, 1668, 1602, 1504, 1379, 997, 858, 527 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 6.80—6.85 (m, 1H), 7.03—7.11 (m, 2H), 7.31—7.40 (m, 8H), 7.72 (s, 1H), 8.65 (s, 1H), 10.32 (s, 1H) ; ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 116.7, 116.9, 120.1, 122.8, 122.9, 125.5, 128.4, 128.9, 129.8, 131.3, 132.7, 134.6, 138.1, 138.7, 152.3, 156.1, 163.4. Anal. calcd for $C_{19}H_{14}N_4O_2$: C 69.13, H 4.32, N 17.02; found C 69.08, H 4.27, N 16.96.

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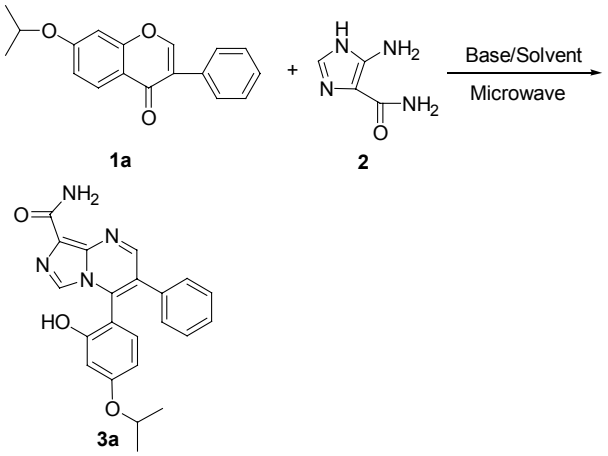
Results and Discussion

Treatment of ipriflavone (**1a**) with 5-amino-1*H*-imidazole-4-carboxamide **2** (1∶1 equiv.) in refluxing ethanol in the presence of NaOH (1 equiv.) for 20 h afforded 8-carbomoyl-4-(2-hydroxy-4-isopropoxyphenyl)-3-phenylimidazo[1,5-*a*]pyrimidine (**3a**) in 25% yield. On the other hand, treatment of **1a** with **2** (1∶1 equiv.) in ethanol in the presence of NaOH (1 equiv.) under microwave irradiation for 10 min afforded **3a** in better yield (34%) (Table 1, Entry 1). Then we started to optimize the conditions by using **1a** and **2** as model reaction (Table 1). First, NaOH was used as a base in different solvents such as MeOH, EtOH, DMF, glycol, and DMSO, and DMF was found to give the highest product yield (Entry 3). A comparative study of different bases showed that NaOH was the most effective (Entry 3). Further studies using variable amount of NaOH revealed that highest product yield could be obtained with 3 equivalents of base (Entry 10). The ratio of **1a** and **2** was also evaluated. With a ratio of **1a**/**2** (1∶1.6), the yield of **3a** was the highest (Entry 14). Our optimized conditions were suitable for the condensation of a variety of structurally divergent isoflavones **1a**—**1i** with 5-amino-1*H*-imidazole-4-carboxamide **2** [**1**∶**2**∶NaOH (1∶1.6∶3)/DMF/10—30 min/microwave] affording the corresponding 3,4-diphenylimidazo[1,5-*a*]pyrimidines **3a**—**3i** in moderate to good yields (58%—88%, Table 2). The yields were lower when the hydroxyl group was present in ring A (58%—82%, Table 2 Entries 6, 7, 8). It seems possible that the hydroxyl groups of the isoflavones can generate phenolates under basic reaction conditions, increasing the electron-donating ability of the hydroxyl-isoflavones more than the corresponding alkoxyiso-flavones. All products were characterized by spectroscopic techniques and elemental analysis.

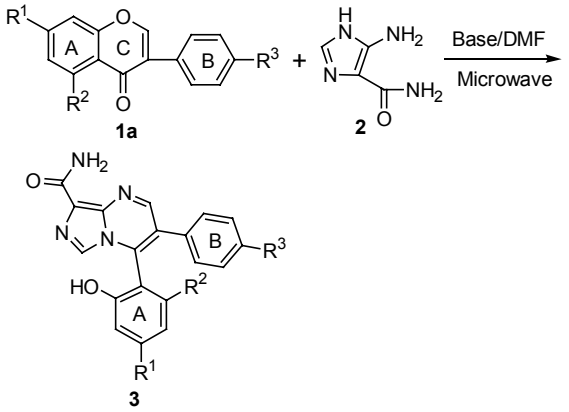
Table 1 Optimization of cyclocondensation of isoflavone **1a** with 5-amino-1*H*-imidazole-4-carboxamide **2**[a]



Entry	Solvent	Base	Molar ratios (**1a**∶**2**∶base)	Yield (**3a**)[b]/%
1	EtOH	NaOH	1∶1∶1	34
2	MeOH	NaOH	1∶1∶1	23
3	DMF	NaOH	1∶1∶1	65
4	$HOCH_2CH_2OH$	NaOH	1∶1∶1	41
5	DMSO	NaOH	1:1∶1	50
6	DMF	Et_3N	1∶1∶1	trace
7	DMF	CH_3ONa	1∶1∶1	15
8	DMF	K_2CO_3	1∶1∶1	30
9	DMF	NaOH	1∶1∶2	71
10	DMF	NaOH	1∶1∶3	75
11	DMF	NaOH	1∶1∶4	70
12	DMF	NaOH	1∶1.2∶3	79
13	DMF	NaOH	1∶1.4∶3	84
14	DMF	NaOH	1∶1.6∶3	89
15	DMF	NaOH	1∶1.7∶3	85

[a] All reactions were carried out in the appropriate solvent (8 mL) using **1a** (1.5 mmol), **2** and base until complete disappearance of **1a** (microwave irradiation for 10—20 min). Reaction temperature: MeOH, EtOH at boiling; DMF, glycol, DMSO at 100 ℃. Microwave output=240 W. [b] Isolated yield after silica chromatography.

Table 2 Synthesis of 3,4-diphenyl-imidazo[1,5-*a*]pyrimidine by the cyclocondensation of various isoflavones with 5-amino-1*H*-imidazole-4-carboxamide[a]



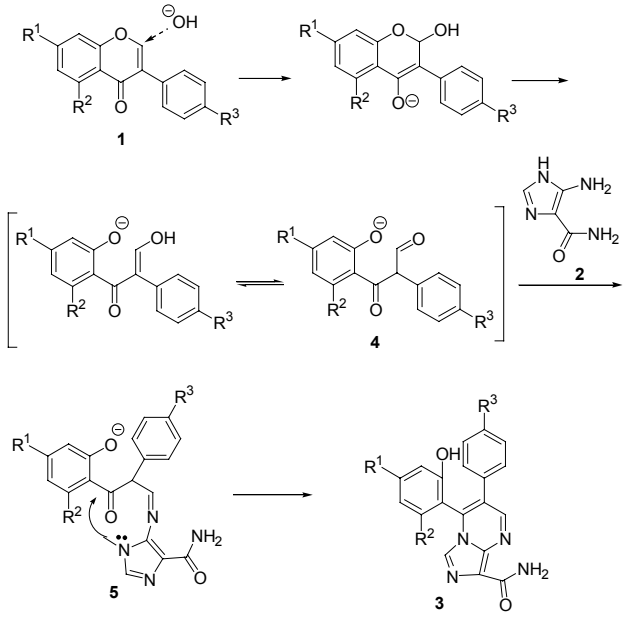
Entry	Compd.	R^1	R^2	R^3	Product **3**	Yield[b]/%	Time/min
1	**1a**	*i*-OPr	H	H	**3a**	88	10
2	**1b**	OMe	Me	H	**3b**	79	10
3	**1c**	OMe	H	H	**3c**	65	20
4	**1d**	OMe	H	OMe	**3d**	86	15
5	**1e**	OMe	OMe	OMe	**3e**	61	20
6	**1f**	OH	H	OMe	**3f**	82	10
7	**1g**	OH	H	H	**3g**	58	25
8	**1h**	OH	H	OH	**3h**	62	30
9	**1i**	H	H	H	**3i**	76	10

[a] Isoflavones **1** (1.5 mmol), **2** (2.4 mmol), NaOH (4.5, 6.0 and 7.5 mmol are used for 0, 1 and 2 free hydroxyl groups in **1** respectively), 100 ℃. Microwave output=240 W. [b] Isolated yield after silica chromatography.

Further experimentation and mechanistic studies are

required to fully understand the regioselectivity of the cyclocondensation of isoflavone **1** with imidazo **2**. It was reported that isoflavone may undergo ring opening reaction when refluxing in the presence of alkali forming a 1,3-diketo intermediate **4** (Scheme 2).[12] The primary amine of **2** attacked the *β*-carbon in **4**. Ring-closure reaction between nitrogen atom at position 1 of **2** and the carbonyl carbon then afforded product **3**.

Scheme 2 Proposed mechanism for the formation of **3**



Conclusions

In summary, we have developed a useful method for the construction of fused 3,4-diphenylimidazo-[1,5-*a*]pyrimidines derivatives by the cyclocondensation of 5-amino-1*H*-imidazole-4-carboxamide with isoflavone in DMF and the presence of sodium hydroxide by microwave irradiation. It is an efficient and regioselective approach toward the synthesis of 3,4-diphenylimidazo[1,5-*a*]pyrimidines.

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(Cheng, F.)

