Microwave Irradiation for Accelerating Synthesis of [1,2,4]Triazole[4,3-*a*]-pyrimidines Based on Isoflavones

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Abstract: Microwave irradiation was used to accelerate the cyclocondensation of isoflavones and 3-amino-1,2,4-triazoles in the presence of sodium methoxide to produce 6,7-diphenyl[1,2,4]-triazolo[4,3-*a*]pyrimidines in good to moderate yields.

Key words: isoflavone, triazole, [1,2,4]triazolo[4,3-*a*]pyrimidine, microwave

The 1,2,4-triazolopyrimidine skeleton, although virtually unknown as a component in natural products, is an important pharmaceutical target (Figure 1).[1] It has been reported that 1,2,4-triazolopyrimidine can show a broad spectrum of pharmacological and medicinal properties, such as antibacterial,[2] antifungal, antiviral,[1] antihypertension, and others.[3]

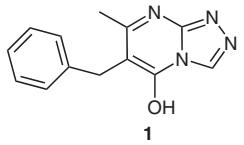

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Figure 1

The conventional synthesis of triazolopyrimidines involves cyclizations of 2-hydrazinopyrimidines with aliphatic carboxylic acids, their esters, anhydrides, and chlorides,[4–8] as well as with ortho esters,[9–11] or phosgene.[6] Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles, 4,5-diphenyl-2-pyrimidinylguanidine, and 2,3-diarylpyrimido[1,2-*a*]-benzimidazole by using one-step reaction of hydrazine,[12] biguanidine,[13] and 2-aminobenzimidazole[14] with isoflavones. To the best of our knowledge, there is no report on the synthesis of 6,7-diphenyl[1,2,4]triazolo-[4,3-*a*]pyrimidine. Herein, we report a new strategy for the preparation of 6,7-diphenyl[1,2,4]triazolo[4,3*a*]-pyrimidine (**3**) by cyclocondensation of isoflavones **1** with 3-amino-1,2,4-triazoles **2a** or 3-amino-5-hydroxy-1,2,4-triazoles **2b** by microwave irradiation.[15–17]

Treatment of ipriflavone (**1a**) with **2a** (1:1 equiv) in refluxing ethanol in the presence of NaOH (3 equiv) for 72 hours afforded 6-phenyl-7-(2-hydroxy-4-isopropoxyphenyl)-[1,2,4]trizolo[4,3-*a*]pyrimidine (**3a**) in 25% yield (Scheme 1).[18] On the other hand, treatment of **1a** with **2a** (1:1 equiv) in ethanol in the presence of NaOH (3 equiv) under microwave irradiation for 10 minutes afforded **3a** in slightly better yield (34%).

We then started to optimize the conditions by using **1a** and **2a** as model compounds (Table 1). First, NaOH was used as a base in different solvents such as MeOH, EtOH, *n*-BuOH, glycol, and DMSO, and DMSO was found to give the highest product yield (entry 5). A comparative study of different bases showed that NaOMe was the most effective (entry 8). Further studies using variable amount of NaOMe revealed that highest product yield could be obtained with 3 equivalents of base (entry 7). The ratio of **1a** and **2a** was also evaluated. With a ratio of **1a/2a** (1:1.4), the yield of **3a** was the highest (entry 11).

Table 1 Optimization of Cyclocondensation of Isoflavone **1a** with 3-Amino-1,2,4-triazoles **2a**[a]

Entry	Solvent	Base	Molar ratios **1a**/**2a**/base	Yield (%)[b] **3a**
1	MeOH	NaOH	1:1:3	17
2	EtOH	NaOH	1:1:3	34
3	*n*-BuOH	NaOH	1:1:3	38
4	glycol	NaOH	1:1:3	29
5	DMSO	NaOH	1:1:3	42
6	DMSO	K_2CO_3	1:1:3	29
7	DMSO	NaOMe	1:1:2	51
8	DMSO	NaOMe	1:1:3	64
9	DMSO	NaOMe	1:1:4	48
10	DMSO	NaOMe	1:1.2:3	66
11	DMSO	NaOMe	1:1.4:3	72
12	DMSO	NaOMe	1:1.6:3	69

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

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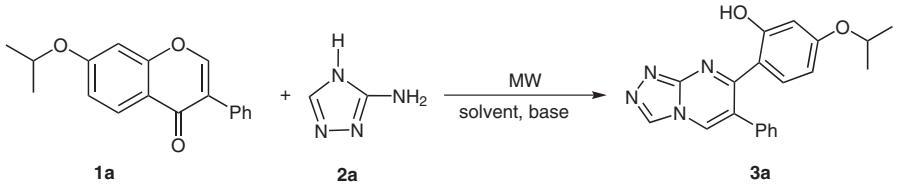
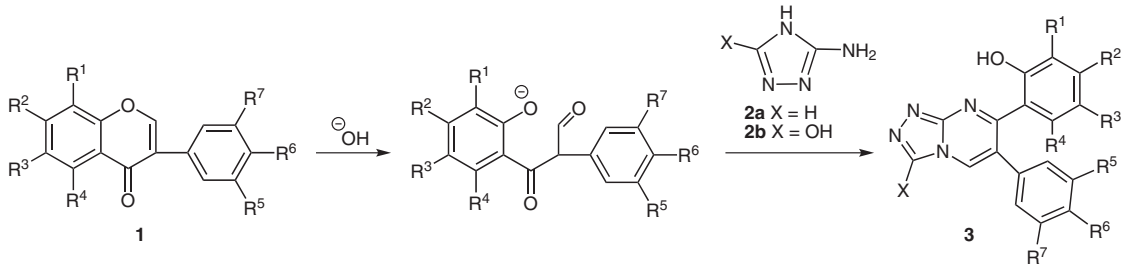


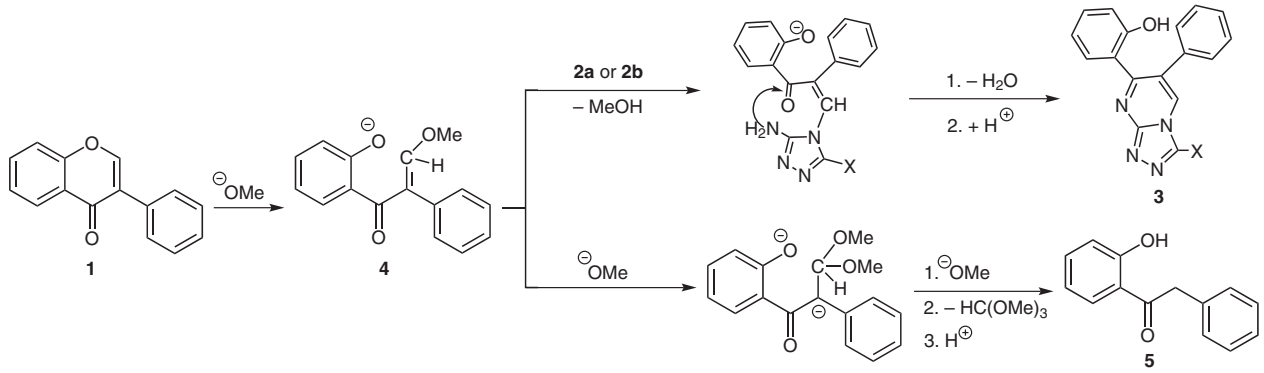
Scheme 1

Table 2 Synthesis of [1,2,4]Triazolo[4,3-*a*]pyrimidine by Cyclocondensation of Various Isoflavones with 3-Amino-1,2,4-triazole **2a** or 3-Amino-5-hydroxy-1,2,4-triazole **2b** in DMSO[a]



Entry	Product[b]	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Time (min)	Yield (%)[c]
1	**3a**	H	O*i*-Pr	H	H	H	H	H	10	72
2	**3b**	H	OMe	H	OMe	H	OMe	H	10	74
3	**3c**	H	OMe	H	H	H	OMe	H	10	68
4	**3d**	H	OMe	H	Me	H	H	H	12	54
5	**3e**	H	O*s*-Bu	H	H	H	OMe	H	12	69
6	**3f**	H	OMe	H	H	^{i}Pr	OMe	*i*-Pr	15	52
7	**3g**	Br	O*i*-Pr	H	H	H	H	H	12	67
8	**3h**	H	OBn	H	H	H	OMe	H	12	70
9	**3i**	H	OMe	Br	H	Br	OMe	H	10	58
10	**3j**	H	OMe	H	H	H	OH	H	15	47
11	**3k**	H	OMe	H	H	*i*-Pr	OH	^{i}Pr	15	43
12	**3l**	H	OMe	H	OMe	H	OMe	H	10	65
13	**3m**	H	OMe	H	H	H	OMe	H	10	62
14	**3n**	H	OMe	H	Me	H	H	H	15	50
15	**3o**	H	OMe	H	H	H	H	H	10	56
16	**3p**	Br	O*i*-Pr	H	H	H	H	H	10	64
17	**3q**	H	OMe	H	H	*i*-Pr	OMe	*i*-Pr	15	47
18	**3r**	H	OBn	H	H	H	OMe	H	10	62
19	**3s**	H	O*i*-Pr	H	H	H	H	H	10	67
20	**3t**	H	OMe	H	H	H	OH	H	15	38

[a] Isoflavones **1** (1.5 mmol), **2b** (2.1 mmol), NaOMe (4.5, 6.0, and 7.5 mmol are used for 0, 1, and 2 free hydroxyl groups in **1** and **2b**, respectively), 100 °C.
[b] Compounds **3a**–**k** compounds are synthesized with isoflavones **1** and 3-amino-1,2,4-triazole (**2a**), compounds **3i**–**t** are synthesized with isoflavones **1** and 3-amino-5-hydroxy-1,2,4-triazole (**2b**).
[c] Isolated yield after silica chromatography.



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

With the optimized reaction conditions in hand, condensation of a variety of structurally divergent **1** with **2a** were studied (Table 2).[19] Due to the presence of an unprotected acidic phenol functionalities in isoflavones **1j,k,t** and in compound **2b**, 4 or 5 equivalents of NaOMe were required in the synthesis of **3j–t**.[19] All substrates react smoothly to give compound **3** in high yields for 10–15 minutes. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

The reaction possible underwent a mechanism as shown in Scheme 2. It was reported that isoflavone underwent ring-opening reaction to form an α,β-unsaturated ketone intermediate **4** in the presence of a base. The nitrogen atom at position 4 of **2a** or **2b** then attacked the β-carbon in **4**. Ring-closure reaction between primary amine and the carbonyl carbon then afforded product **3**. On the other hand, intermediate **4** may eliminate $HC(OMe)_3$ to generate a byproduct **5**.[20]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) **6-Phenyl-7-(2-hydroxy-4-isopropoxyphenyl)[1,2,4]-triazolo[4,3-*a*]pyrimidine (3a)**
Mp 228–230 °C. IR (KBr): ν = 3083, 2982, 2679, 2586, 1610, 1504, 1440, 1381, 1292, 1264, 1180, 1115, 989, 921, 846, 791, 757, 703, 652, 573, 506, 461 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.26 (d, *J* = 5.9 Hz, 6 H), 4.56 (m, 1 H), 6.39 (d, *J* = 8.2 Hz, 2 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 7.33 (m, 5 H), 8.60 (s, 1 H), 8.95 (s, 1 H), 9.86 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.8, 69.4, 102.6, 106.4, 118.7, 125.0, 127.8, 128.3, 129.4, 131.6, 134.4, 144.2, 154.3, 155.5, 155.9, 156.9, 160.2 ppm. MS (EI): *m/z* (rel intensity) = 369 (62) [M + Na], 347 (100) [M + 1], 305 (66). Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.18; H, 5.31; N, 16.25.
(19) **Representative Procedure for the Preparation of 6-Phenyl-7-(2-hydroxy-4-isopropoxy-phenyl)[1,2,4]-triazolo[4,3-*a*]-pyrimidine (3a) and 3-Hydroxy-6-phenyl-7-(2-hydroxy-4-isopropoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyrimidine (3s)**
The ipriflavone (**1a**, 1.5 mmol, 420 mg), **2a** (2.1 mmol, 118 mg) and NaOMe (4.5 mmol, 3 equiv) were mixed in DMSO (8 mL). The mixture was heated by the microwave irradiation (output 240 W, 100 °C) for 10 min. Reaction was

monitored by TLC, in which the disappearance of **1a** indicated the completeness of reaction. The mixture was added into H_2O (30 mL) and adjusted to neutrality with the solution of 5% HCl. Precipitate appeared and was filtered. Finally, **3a** (374mg, 72%) was obtained by purifying the precipitate on silica gel column chromatography (PE 60–90–EtOAc = 2:1); **3s** was obtained by the same way, except that the equivalent of NaOMe (6.0 mmol, 4 equiv) was different when **2b** was instead of **2a**.

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