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Base-catalyzed one-step synthesis of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines

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1,2,4-Triazolo[1,5-*a*]pyrimidines

Cyclocondensation

Chalcone

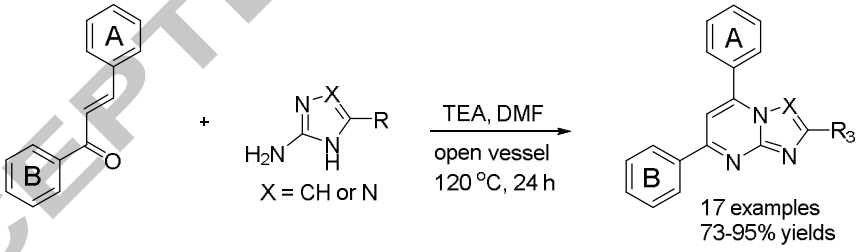
1,2,4-Triazol-3-amine

Imidazo[1,2-*a*]pyrimidines

Abstract

We report a practical high-yield synthesis of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines using a base-assisted cyclocondensation of chalcone and 1,2,4-triazol-3-amine in an open reaction vessel. The same conditions can also be used for the preparation of novel imidazo[1,2-*a*]pyrimidine derivatives.

Graphic Abstract



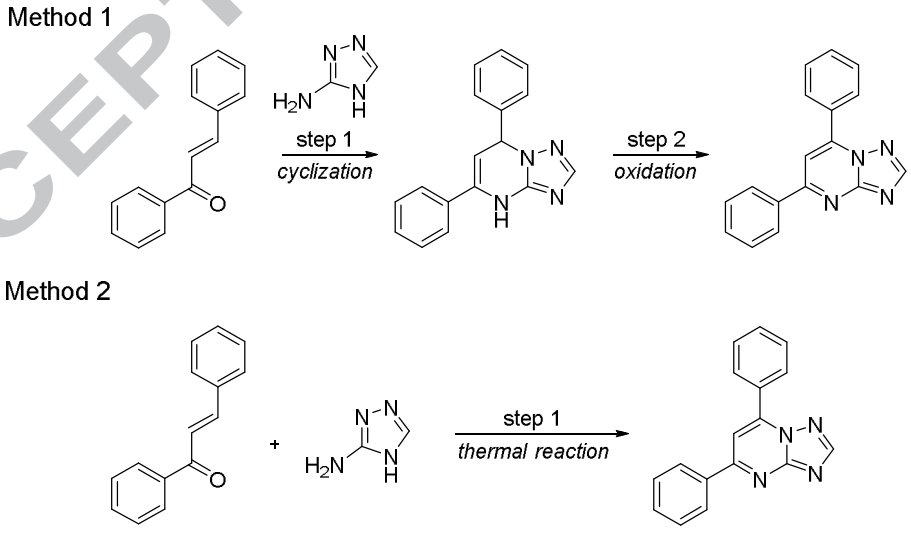
5,7-Disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidine is a privileged structure with a broad range of biological applications. They have shown superior *in vitro* cytotoxicity than the anti-cancer drug doxorubicin.[1] The organotin(IV) and platinum(II) complexes of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines demonstrate dose-dependent cytotoxic activity in multiple cancer cell lines.[2] Moreover, 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines are inhibitors of the casein kinase 1δ a potential treatment for neurological disorders.[3] From a high throughput screen, analogs of 1,2,4-triazolo[1,5-*a*]pyrimidine have been identified with neuroactive activities as potential therapeutic agents for neurodegenerative diseases.[4] In addition, 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines have shown promising inhibitory activities for cellular secretion of the hepatitis B virus surface antigen as potential treatment for HBV infection.[5] Furthermore, 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines have shown antileishmanial activity against *L. donovani* promastigotes,[6] and antibacterial activities against *S. marcescens*.[7] Therefore, the synthesis of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines has received significant attention.

Two synthetic methods are known for the preparation of 1,2,4-triazolo[1,5-*a*]pyrimidines (Scheme 1). The first method involves a two-step procedure beginning with chalcone and 1,2,4-triazol-3-amine. Cyclocondensation of chalcone with 1,2,4-triazol-3-amine provides the dihydro-triazolo-pyrimidine analogue,[5] which can be oxidized using either *N*-bromosuccinimide (NBS)[8] or Br_2 to give 1,2,4-triazolo[1,5-*a*]pyrimidines.[9] Considering NBS and Br_2 are highly reactive and cannot tolerate functionalities such as benzyl groups, allyl groups, olefins, hydroxyl groups, nor α-hydrogens of a carbonyl,[10] this method can only be used to prepare 1,2,4-triazolo[1,5-*a*]pyrimidines with limited substitutions. The other method includes a thermal reaction between chalcone and 1,2,4-triazol-3-amine either at high temperature (e.g., >220 °C in ethylene glycol[7]

and 190 °C in 1-methyl-2-pyrrolidinone[11]) or neat at 160 °C.[12] It is also reported that 1,2,4-triazolo[1,5-*a*]pyrimidines can be prepared in refluxing *t*-BuOH in the presence of the strong base *t*-BuOK.[13]

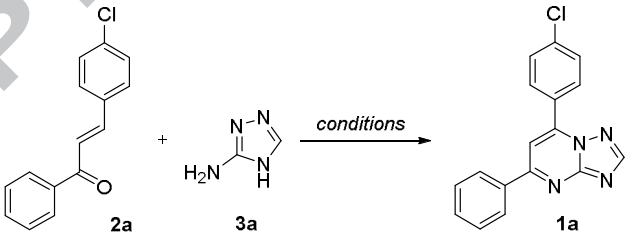
In the course of our research program on novel therapeutics for diffuse large B-cell lymphoma (DLBCL) and triple-negative breast cancer (TNBC), we performed a series of reactions intended to synthesize a collection of compounds based on a 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidine core. Motivated by the fact that dihydro-triazolo-pyrimidines can be oxidized by atmospheric O_2,[7, 11] while cyclocondensation reactions can be accelerated in presence of a base catalyst, we hypothesized that the formation of a 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidine can be achieved by base-catalyzed cyclocondensation of chalcone and 1,2,4-triazol-3-amine in an open reaction vessel.

Scheme 1. Previous synthesis of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines.



To test this idea, we first tried the reactions of (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**2a**) and 4*H*-1,2,4-triazol-3-amine (**3a**) in either ethanol (Table 1, entry 1) or DMF (entry 2) at 120 °C in an open flask. No significant reaction was observed under either condition after 24 h. However, we were pleased to find that addition of one equiv of KOH to the reaction mixture in DMF led to the formation of 1,2,4-triazolo[1,5-*a*]pyrimidine in good yields after 24 h (entry 3). With this encouraging result, we sought to screen bases used in the reaction (entries 4-10), and found that while inorganic bases (entries 3-5) gave modest yields, tertiary amines, such as TEA (entry 6) and DIPEA (entry 7), are more efficient with almost quantitative yields. Similarly good yields were detected when DMAP was used as the base (entry 8). When weaker bases such as NMM (entry 9) and pyridine (entry 10) were used, the reaction gave decreased yields. We also studied the effect of the equiv of the base, and found that < 1 equiv of TEA gave incomplete reactions (entries 11 and 12). When 2 equiv of TEA was used (entry 13), the reaction yields started to drop due to the complicated reaction mixture.

Table 1. Optimization of Reaction Conditions for 1a[a]



Entry	Base[b], equiv	Solvent	yield **1a**, %[c]
1	no base	ethanol	< 5
2	no base	DMF	< 5
3	KOH, 1.0	DMF	83

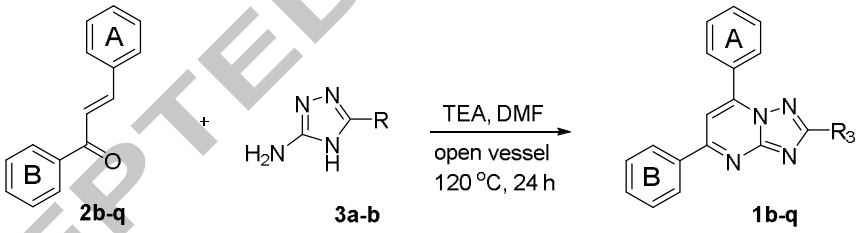
4	Cs_2CO_3, 1.0	DMF	66
5	K_2CO_3, 1.0	DMF	77
6	TEA, 1.0	DMF	95
7	DIPEA, 1.0	DMF	95
8	DMAP, 1.0	DMF	86
9	NMM, 1.0	DMF	36
10	Pyridine, 1.0	DMF	61
11	TEA, 0.25	DMF	74
12	TEA, 0.5	DMF	72
13	TEA, 2.0[d]	DMF	84

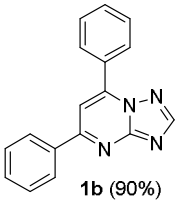
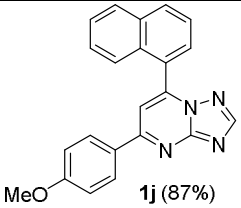
[a]The reaction was carried out in an open vessel at 120 ℃ with 1.0 mmol of **2a**, 2.0 mmol of **3a** and 1.0 mmol of base in 2.0 mL of solvent for 24 h. [b]KOH = potassium hydroxide, Cs_2CO_3 = cesium carbonate, K_2CO_3 = potassium carbonate, TEA = triethylamine, DMAP = 4-(dimethylamino)pyridine, DIPEA = diisopropyl ethylamine, NMM = 4-methylmorpholine. [c]Determined by ^{1}H NMR. [d]TLC indicated a complicated reaction in which significant amounts of side products were observed.

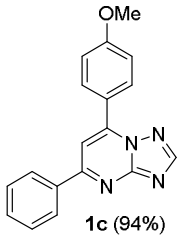
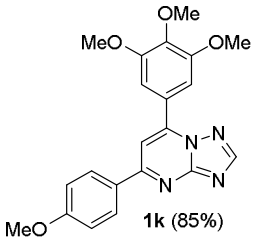
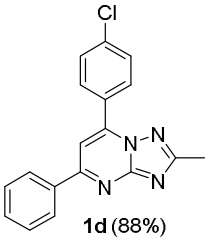
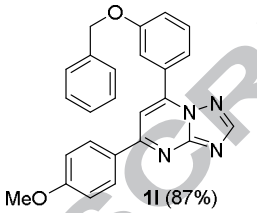
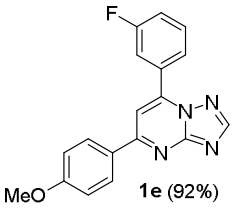
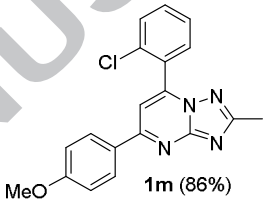
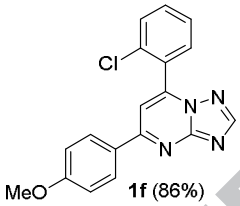
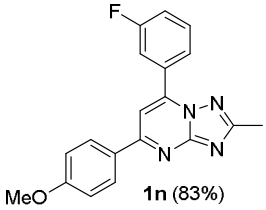
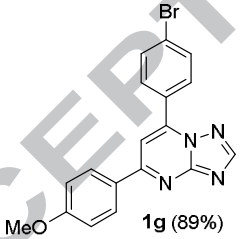
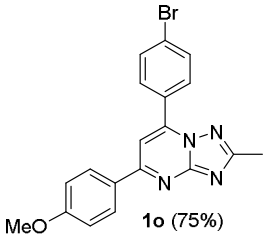
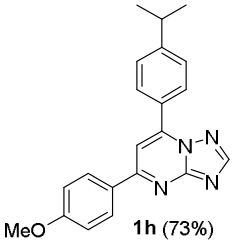
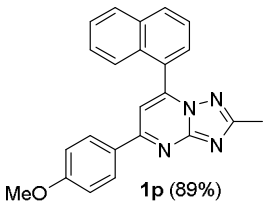
Utilizing the optimized conditions, we next studied the scope of the reaction (Table 2). Without further substitution, compound 1,3-diphenylpropan-1-one and 1,2,4-triazol-3-amine reacted with a decreased rate. However, we isolated the product 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine **1b** in very good yields after 48 h (entry 1). Using the same ketone starting material, both electron-donating (entry 2) and electron-withdrawing (entry 3) substituents on the A-ring reacted smoothly to give products **1c** and **1d**. Effects of the position of halogen substitutions on

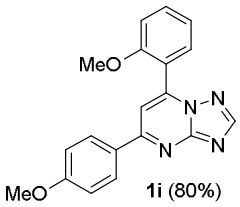
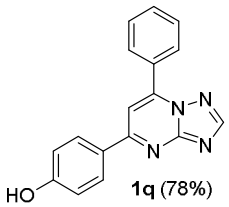
the A-ring were also studied (entries 4-6), and the reactions gave consistently good yields for compounds **1e**-**1g**. Using 3-(4-isopropylphenyl)-1-(4-methoxyphenyl)propan-1-one as the starting material, the reaction gave compound **1h** in modest yields (entry 7). Other electron-donating groups gave good yields (entries 8-11). It is noted that compound **1l** cannot be prepared using the procedure employing NBS/Br_2.[8-9] When 5-methyl-1,2,4-triazol-3-amine was used as the starting material, the reactions gave compounds **1m**-**1p** in good yields (entries 12-15). Using 1-(4-hydroxyphenyl)-3-phenylpropan-1-one, the reaction also proceeded smoothly with 1,2,4-triazol-3-amine (entry 16) to give compound **1q** in good yields, which cannot be synthesized using previously reported methods. It is worthwhile to point out that all the products were purified by a simple process of crystallization and filtration; no chromatography was involved.

Table 2. Preparation of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines[a]



entry	product	yield, %[b]	entry	product	yield, %[b]
1	 **1b** (90%)	90	9	 MeO **1j** (87%)	87

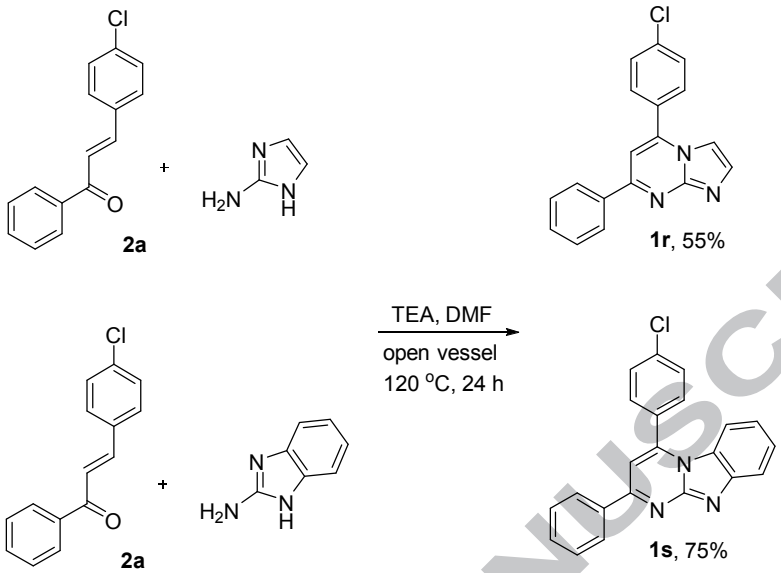
2	 **1c** (94%)	94	10	 **1k** (85%)	85
3	 **1d** (88%)	88	11	 **1l** (87%)	87
4	 **1e** (92%)	92	12	 **1m** (86%)	86
5	 **1f** (86%)	86	13	 **1n** (83%)	83
6	 **1g** (89%)	89	14	 **1o** (75%)	75
7	 **1h** (73%)	73	15	 **1p** (89%)	89

8	 1i (80%)	80	16	 1q (78%)	78

[a]The reaction was carried out at 120 ℃ with 1.0 mmol of **2a**, 2.0 mmol of **3a** and 1.0 mmol of base in 2.0 mL of DMF for 24 h. [b]Isolated yields. [c]The reaction was complete in 48 h.

We applied the optimized conditions to the preparation of imidazo[1,2-*a*]pyrimidines (Scheme 2). As a bioisostere of 1,2,4-triazolo[1,5-*a*]pyrimidines, imidazo[1,2-*a*]pyrimidines are also important in the pharmaceutical industry. They are employed, as the core structures, in several clinically used anxiolytic drugs such as fasiplon, taniplon, and divaplon.[14] We performed reactions using compound **1a** and imidazol-2-amine or 1*H*-benzo[*d*]imidazol-2-amine. Both reactions proceeded smoothly to generate 5-(4-chlorophenyl)-7-phenylimidazo[1,2-*a*]pyrimidine (**1r**) and 4-(4-chlorophenyl)-2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (**1s**) in modest to good yields (Scheme 2). Synthetic methods to benzimidazopyrimidines are known,[15] however, to the best of our knowledge, preparation of 5,7-diphenylimidazo[1,2-*a*]pyrimidines remains challenging. One available method described by Kiselyov involves a three-step one-pot synthesis beginning with *α*,*β*-unsaturated imines and amino heterocycles using strong base at -78 ℃.[16]

Scheme 2. Preparation of **1r** and **1s.**[a]



In summary, a facile one-step synthesis of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines have been discovered, by which a variety of 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines, as well as the imidazole analogs, have been prepared in good yields.[17]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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17. Typical procedure for the synthesis of compound **1a**: To a solution of (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (242 mg, 1.0 mmol) and 1,2,4-triazol-3-amine (168 mg, 2.0 mmol) in DMF (2.0 mL) was added TEA (140 μL, 1.0 mmol). The reaction mixture was allowed to stir at 120 ℃ until (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one was completely

consumed (TLC, ethyl acetate/hexanes = 1:4 (v/v)). The solvent was removed, and to the resulting residue was added water (10 mL). The mixture was ultrasonically agitated for 30 min and then filtered. The filtrate was washed using water (20 mL × 5) and dried to yield 7-(4-chlorophenyl)-5-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **1a** (291 mg, 0.95 mmol, 95%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (m, 3H), 7.74-7.76 (d, J = 8.4 Hz, 2H), 8.20 (s, 1H), 8.34-8.36 (d, J = 8.4 Hz, 2H), 8.39-8.41 (m, 2H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 107.3, 128.3, 129.1, 129.5, 130.3, 131.8, 132.2, 136.5, 136.9, 146.8, 156.3, 156.5, 161.1; LC-MS ($M+H^+$) calcd for $C_{17}H_{12}ClN_4$ 307, found 307.

Graphic Abstract