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An efficient one-pot synthesis of 1,2,4-triazoloquinoxalines

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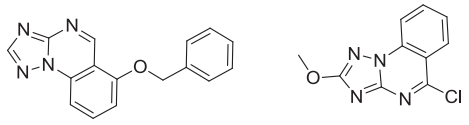
ABSTRACT

A transition metal-free tandem process for the synthesis of 1,2,4-triazoloquinoxalines was described. The construction of this tricyclic system went through a one-pot condensation/nucleophilic aromatic substitution approach. This methodology applied to a broad range of substrates, which included 2-halogenated or 2-nitro aryl aldehydes and ketones.

1. Introduction

1,2,4-Triazoloquinoxaline derivatives have attracted considerable attention due to their medicinal activities. For instance, compound **1** exhibits positive anticonvulsant activity with the 50% effective dose (ED_{50}) of 78.9 mg/kg, which is evaluated by Maximal Electroshock Test.[1] Meanwhile, compound **2** is able to perform as an effective adenosine receptor antagonist (Fig. 1).[2] Structures with the 1,2,4-triazoloquinoxaline scaffold are tested to display remarkable activity against coxsackievirus B4, adenovirus type 7 and mycobacterium tuberculosis.[3,4] Besides, anti-HCV, anti-inflammatory and antimalarial properties are studied through extensively exploring the tricyclic heteroaromatic system.[5–8]

As a class of privileged substructures, 1,2,4-triazoloquinoxalines' synthesis has attracted enormous attention. Charushin's group proposed a procedure of acylation of 3-amino-1,2,4-triazoles with tetrafluorobenzoyl chloride in refluxing toluene, followed by heating for 5 h.[9] Quan and co-workers developed a three-component and five-step protocol, while the products were obtained in relatively low yield.[1] Substituted 2-hydrazinobenzoic acids and *N*-cyanoimidocarbonates were prepared by Al-Salahi as the reactants, which reacted with each other in the presence of triethylamine using an ice water cooling bath. The target compound was isolated after treatment with phosphorus oxychloride in refluxing benzene for 2 h.[10,11]



1 2

Fig. 1. Structures of some biologically important 1,2,4-triazoloquinoxalines.

The existing methods are not effective and economical since multiple steps and harsh conditions were required in these systems. We have been engaged in the development of economical syntheses of heterocyclic systems.[12,13] Herein, we provide a novel approach to prepare a series of 1,2,4-triazoloquinoxalines, which are obtained in a reaction of 1*H*-1,2,4-triazol-5-amines with substituted aryl aldehydes and ketones.

2. Results and discussion

To optimize the conditions, 1*H*-1,2,4-triazol-5-amine **3** and 2-fluorobenzaldehyde **4a** were selected as the model substrates (Table 1). Several bases were screened, and Cs_2CO_3 was relatively efficient with 84% yield of **5a** (entry 2). K_2CO_3 and NaOH behaved less successfully (entries 1 and 3), while *t*-BuOK gave the product in relatively low yield (entry 4). Solvent was investigated and DMF was found to be more effective than DMSO (entries 4 and 5).

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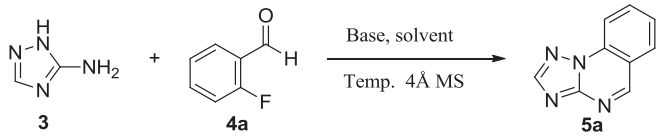
Table 1
Optimization of reaction conditions[a]



3 4a 5a

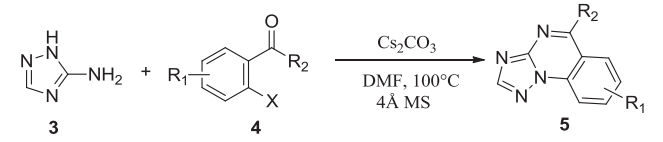
Entry	Base	Solvent	*T* (°C)	Time (h)	Yield (%)[c]
1	K_2CO_3	DMF	100	2	75
2	**Cs_2CO_3**	**DMF**	**100**	**2**	**84**
3	NaOH	DMF	100	2	62
4	*t*-BuOK	DMF	100	2	34
5	Cs_2CO_3	DMSO	100	2	67
6	Cs_2CO_3	NMP	100	2	52
7	Cs_2CO_3	CH_3CN	Reflux	2	Trace
8	Cs_2CO_3	Toluene	Reflux	2	n.d
9	Cs_2CO_3	DMF	50	2	54
10	Cs_2CO_3	DMF	135	2	80
11	Cs_2CO_3	DMF	100	1	58
12	Cs_2CO_3	DMF	100	3	77
13	Cs_2CO_3	DMF	100	2	74[b]

The bold values are represents the optimized reaction conidition after the screening.
[a] Reaction conditions: 1*H*-1,2,4-triazol-5-amine **3** (1.0 equiv), 2-fluorobenzal dehyde **4a** (1.2 equiv), base (3.0 equiv), molecular sieves 4 Å (0.4 g).
[b] Reaction conditions: 1*H*-1,2,4-triazol-5-amine **3** (1.0 equiv), 2-fluorobenzal dehyde **4a** (1.2 equiv), base (3.0 equiv).
[c] Isolated yield.

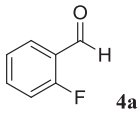
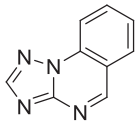
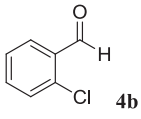
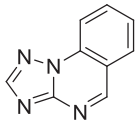
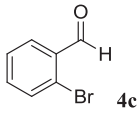
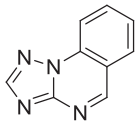
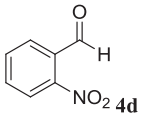
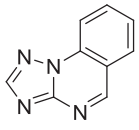
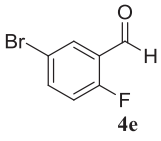
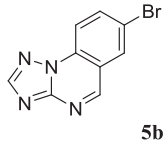
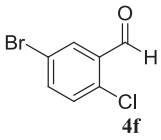
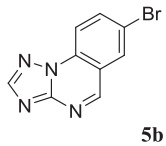
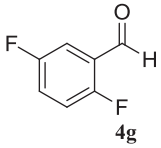
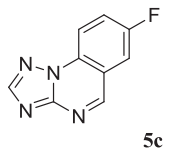
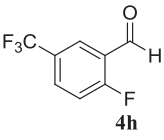
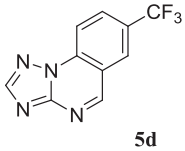
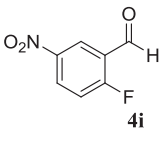
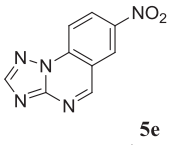
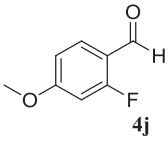
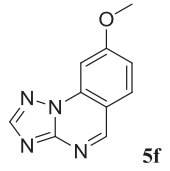
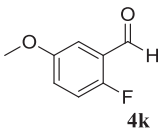
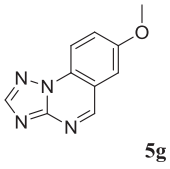
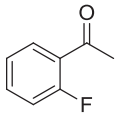
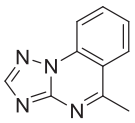
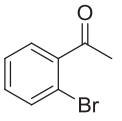
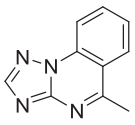
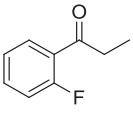
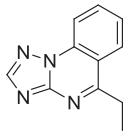
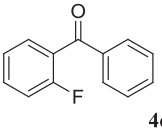
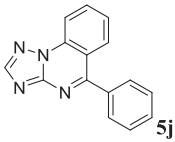
Moderate yield was achieved in NMP (entry 6), and trace amount of product was detected in CH_3CN (entry 7). Moreover, the yield decreased to 54% at 50 °C (entry 10). Without 4 Å molecular sieves, only 74% of the product was obtained (entry 13). Finally we found the reaction was most efficient when conducted with Cs_2CO_3 in DMF at 100 °C in the presence of 4 Å molecular sieves.

With the optimized condition in hand, the scope of this methodology was examined. As shown in Table 2, not only 2-fluorobenzaldehyde but also 2-chloro, 2-bromo and even 2-nitro[14] substituent worked well (entries 1–4). To accomplish the

Table 2
Synthesis of 1,2,4-triazoloquinoxaline **5**[a]



3 4 5

Entry	Substrate **4**	Product **5**	Yield (%)[b]
1	 **4a**	 **5a**	84
2	 **4b**	 **5a**	65[c]
3	 **4c**	 **5a**	72[c]
4	 **4d**	 **5a**	78
5	 **4e**	 **5b**	51
6	 **4f**	 **5b**	42[c]
7	 **4g**	 **5c**	62
8	 **4h**	 **5d**	37
9	 **4i**	 **5e**	Trace
10	 **4j**	 **5f**	80
11	 **4k**	 **5g**	77
12	 **4l**	 **5h**	72
13	 **4m**	 **5h**	53[c]
14	 **4n**	 **5i**	58
15	 **4o**	 **5j**	60

[a] Reaction conditions: 1*H*-1,2,4-triazol-5-amine **3** (1.0 equiv), compound **4** (1.2 equiv), Cs_2CO_3 (3.0 equiv), molecular sieves 4 Å (0.4 g), 100 °C, 2 h.
[b] Isolated yield.
[c] Reaction conditions: NaOH (3.0 equiv), molecular sieves 4 Å (0.4 g), 100 °C, 2 h.