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

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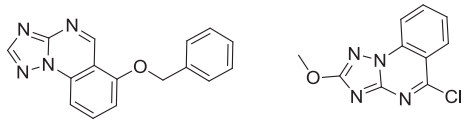
ABSTRACT

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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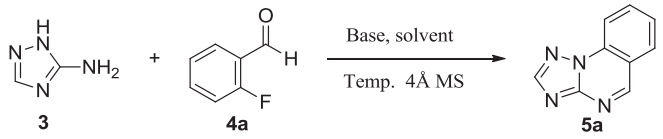
Table 1
Optimization of reaction conditions[a]



3 4a 5a

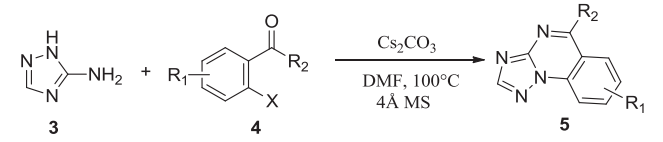
Entry	Base	Solvent	*T* (°C)	Time (h)	Yield (%)[c]
1	K_2CO_3	DMF	100	2	75
2	**Cs_2CO_3**	**DMF**	**100**	**2**	**84**
3	NaOH	DMF	100	2	62
4	*t*-BuOK	DMF	100	2	34
5	Cs_2CO_3	DMSO	100	2	67
6	Cs_2CO_3	NMP	100	2	52
7	Cs_2CO_3	CH_3CN	Reflux	2	Trace
8	Cs_2CO_3	Toluene	Reflux	2	n.d
9	Cs_2CO_3	DMF	50	2	54
10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

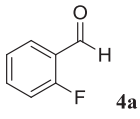
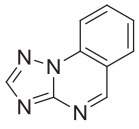
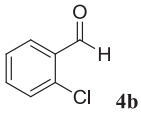
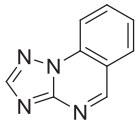
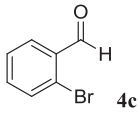
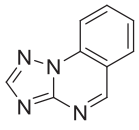
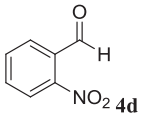
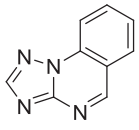
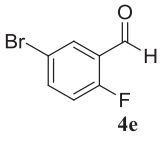
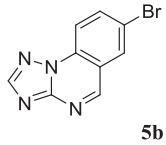
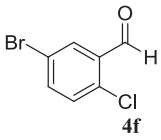
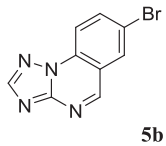
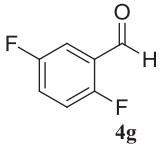
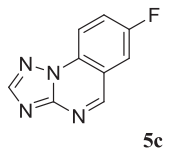
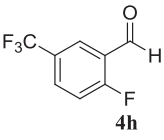
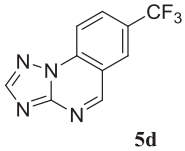
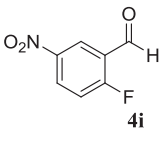
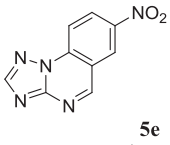
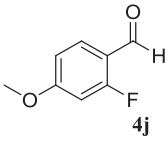
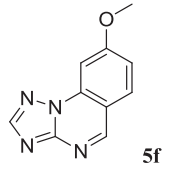
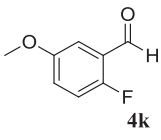
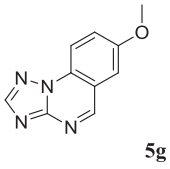
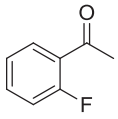
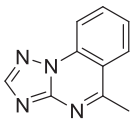
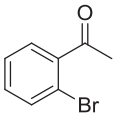
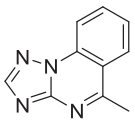
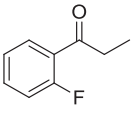
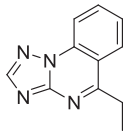
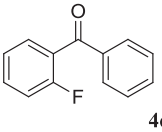
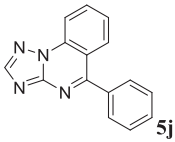
Moderate yield was achieved in NMP (entry 6), and trace amount of product was detected in CH_3CN (entry 7). Moreover, the yield decreased to 54% at 50 °C (entry 10). Without 4 Å molecular sieves, only 74% of the product was obtained (entry 13). Finally we found the reaction was most efficient when conducted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



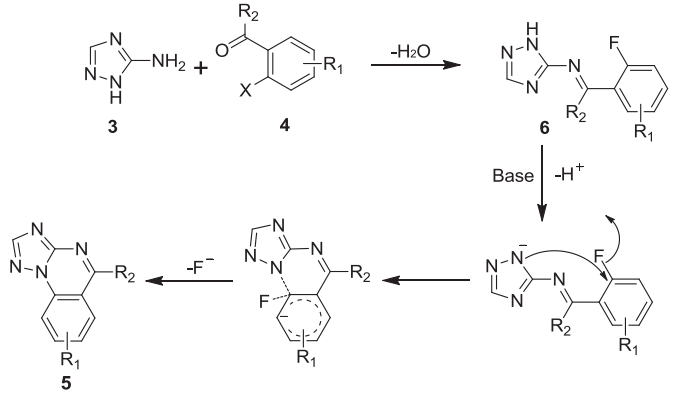
3 4 5

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

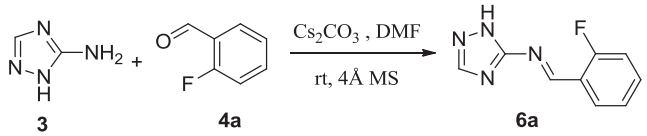
[a] Reaction conditions: 1*H*-1,2,4-triazol-5-amine **3** (1.0 equiv), compound **4** (1.2 equiv), Cs_2CO_3 (3.0 equiv), molecular sieves 4 Å (0.4 g), 100 °C, 2 h.
[b] Isolated yield.
[c] Reaction conditions: NaOH (3.0 equiv), molecular sieves 4 Å (0.4 g), 100 °C, 2 h.

aryl C–N coupling, metal catalyst and ligand are generally indispensable when bromine acts as the leaving group.[15] However, it could be realized in this metal-free system with moderate yield (entries 3 and 13). Compared with aldehyde, ketone is known to be less active in the synthesis of Schiff base.[16,17] Interestingly, varied aryl ketone performed as well as substituted 2-halobenzaldehyde in our work (entries 12–15). Substituted 2-fluorobenzaldehydes with electron-donating groups reacted better than those with withdrawing group (entries 5–11).

The possible mechanism was proposed in Scheme 1. Condensation of compound **3** and **4** provided the intermediate **6**. Subsequently, the Schiff base **6** underwent an intramolecular nucleophilic aromatic substitution (S_NAr), affording 1,2,4-triazoloquinoxalines **5**. To probe the above proposed mechanism, we reacted 1*H*-1,2,4-triazol-5-amine **3** with 2-fluorobenzaldehyde **4a** employing Cs_2CO_3 as base in DMF at room temperature (Scheme 2). The Schiff base **6a** was detected under the milder conditions after 0.5 h by high resolution mass spectrum (HRMS), which suggested that the first step was the formation of Schiff base **6**.

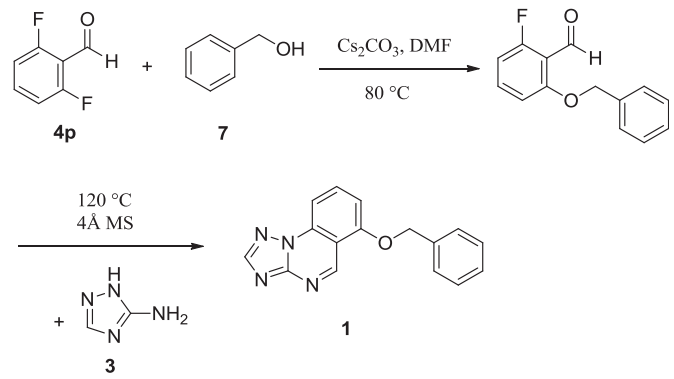


Scheme 1. Proposed mechanism for formation of **5**.



Scheme 2. Reaction of 1*H*-1,2,4-triazol-5-amine **3** and 2-fluorobenzaldehyde **4a**.

To demonstrate the application of this method, compound **1** shown in Fig. 1 was synthesized in one pot (Scheme 3). Phenylmethanol **7** and 2,6-difluorobenzaldehyde **4p** were stirred with Cs_2CO_3 in DMF at 80 °C for 2 h. Then 1*H*-1,2,4-triazol-5-amine **3** was added under the optimized conditions. Compound **1** was isolated by column chromatography.



Scheme 3. Synthesis of compound **1** in one pot.

3. Conclusion

A variety of 1,2,4-triazoloquinoxaline derivatives were synthesized by condensation and nucleophilic aromatic substitution in a one-pot transition metal-free tandem process. Not only aldehydes but also ketones worked well to afford the tricyclic products. Further studies on the application of this procedure to the synthesis of pharmaceutical compounds are in progress.

4. Experimental section

4.1. General

Reagents were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or 300 MHz, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were run in the same instrument at 100 or 75 MHz. Melting points were determined on an XD-4 digital micro melting point apparatus. HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent).

4.2. General procedure for the synthesis of compounds 5a

A mixture of 1*H*-1,2,4-triazol-5-amine **3** (1.0 mmol), 2-fluorobenzaldehyde **4a** (1.2 mmol) and Cs_2CO_3 (3.0 mmol) in DMF (10 mL) was heated to 100 °C, and TLC monitored the reaction. Then the mixture was cooled to room temperature and diluted with brine (60 mL) and extracted with dichloromethane twice (2×30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo to afford a residue. The residue was purified by column chromatography (silica gel, hexane/EtOAc=1:5) to afford **5a**.

*4.2.1. [1,2,4]Triazolo[1,5-a]quinazoline (**5a**).* White solid. Mp 172.1–173.5 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.53 (1H, s), 8.69 (1H, s), 8.42–8.38 (2H, m), 8.19–8.13 (1H, m), 7.81 (1H, t, J=7.5 Hz); ^{13}C NMR (75 M, DMSO-d_6): δ 158.99, 154.36, 153.17, 136.12, 135.64, 130.16, 127.18, 119.36, 115.02; HRMS calcd for $C_9H_6N_4$ $(M+H)^+$ 171.0626; found: 171.0682.

*4.2.2. 7-Bromo-[1,2,4]triazolo[1,5-a]quinazoline (**5b**).* Pale yellow solid. Mp 236.9–237.7 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.47 (1H, s), 8.71 (1H, s), 8.67 (1H, d, J=1.8 Hz), 8.35–8.36 (2H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 157.48, 154.09, 152.63, 138.11, 134.23, 131.77, 120.32, 118.66, 116.97; HRMS calcd for $C_9H_5BrN_4$ $(M+H)^+$ 248.9677; found: 248.9788.

*4.2.3. 7-Fluoro-[1,2,4]triazolo[1,5-a]quinazoline (**5c**).* Pale yellow solid. Mp 199.9–201.5 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.48 (1H, s), 8.69 (1H, s), 8.46 (1H, dd, J=9.0, 4.5 Hz), 8.26 (1H, dd, J=8.7, 3 Hz), 8.09–8.02 (1H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 159.24 (1C, d, J=243.8 Hz), 157.63 (1C, d, J=3.0 Hz), 153.87, 152.47, 132.26, 124.30 (1C, d, J=25.5 Hz), 119.94 (1C, d, J=9.0 Hz), 117.46 (1C, d, J=9 Hz), 114.17 (1C, d, J=23.3 Hz); HRMS calcd for $C_{10}H_5FN_4$ $(M+H)^+$ 189.0532; found: 189.0573.

*4.2.4. 7-(Trifluoromethyl)-[1,2,4]triazolo[1,5-a]quinazoline (**5d**).* White solid. Mp 193.4–193.9 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.63 (1H, s), 8.91 (1H, s), 8.77 (1H, s), 8.56 (1H, d, J=9.0 Hz), 8.43 (1H, dd, J=9.0, 1.2 Hz); ^{13}C NMR (100 M, DMSO-d_6): δ 159.12, 155.01, 153.75, 137.57, 131.78 (1C, d, J=4.0 Hz), 128.25 (1C, q, J=4.0 Hz),

127.16 (1C, q, J=33 Hz), 124.10 (1C, d, J=271 Hz), 119.02, 116.73; HRMS calcd for $C_{10}H_5F_3N_4$ $(M+H)^+$ 239.0500; found: 239.0518.

*4.2.5. 7-Nitro-[1,2,4]triazolo[1,5-a]quinazoline (**5e**).* Pale yellow solid. HRMS calcd for $C_9H_5N_5O_2$ $(M+H)^+$ 216.0516; found: 216.0500.

*4.2.6. 8-Methoxy-[1,2,4]triazolo[1,5-a]quinazoline (**5f**).* White solid. Mp 193.6–194.3 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.35 (1H, s), 8.65 (1H, s), 8.27 (1H, d, J=9.0 Hz), 7.72 (1H, d, J=2.4 Hz), 7.36 (1H, dd, J=9.0, 2.7 Hz); ^{13}C NMR (75 M, DMSO-d_6): δ 164.83, 157.09, 153.87, 153.00, 137.30, 131.52, 116.94, 113.41, 95.98, 56.44; HRMS calcd for $C_{10}H_8N_4O$ $(M+H)^+$ 201.0771; found: 201.0751.

*4.2.7. 7-Methoxy-[1,2,4]triazolo[1,5-a]quinazoline (**5g**).* White solid. Mp 186.7–187.9 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 9.43 (1H, s), 8.63 (1H, s), 8.32 (1H, d, J=9.0 Hz), 7.87 (1H, d, J=2.7 Hz), 7.75 (1H, dd, J=9.0, 2.7 Hz); ^{13}C NMR (75 M, DMSO-d_6): δ 157.46, 157.24, 153.49, 152.01, 130.10, 125.60, 120.06, 116.20, 109.41, 55.92; HRMS calcd for $C_{10}H_8N_4O$ $(M+H)^+$ 201.0771; found: 201.0765.

*4.2.8. 5-Methyl-[1,2,4]triazolo[1,5-a]quinazoline (**5h**).* White solid. Mp 167.5–168.6 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 8.58 (1H, s), 8.42–8.37 (2H, m), 8.14–8.09 (1H, m), 7.80–7.75 (1H, m), 2.99 (3H, s); ^{13}C NMR (75 M, DMSO-d_6): δ 165.94, 153.62, 151.86, 135.15, 134.67, 128.12, 126.43, 118.21, 114.83, 22.73; HRMS calcd for $C_{10}H_8N_4$ $(M+H)^+$ 185.0822; found: 185.0828.

*4.2.9. 5-Ethyl-[1,2,4]triazolo[1,5-a]quinazoline (**5i**).* White solid. Mp 190.8–192.0 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 8.60 (1H, s), 8.46–8.38 (2H, m), 8.13–8.08 (1H, m), 7.80–7.74 (1H, m), 3.40 (2H, q, J=7.5 Hz), 1.41 (3H, t, J=7.5 Hz); ^{13}C NMR (75 M, DMSO-d_6): δ 169.38, 153.66, 151.96, 135.00, 134.76, 127.44, 126.47, 117.60, 114.99, 27.71, 11.55; HRMS calcd for $C_{11}H_{10}N_4$ $(M+H)^+$ 199.0978; found: 199.1018.

*4.2.10. 5-Phenyl-[1,2,4]triazolo[1,5-a]quinazoline (**5j**).* White solid. Mp 182.2–183.8 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 8.70 (1H, s), 8.49 (1H, d, J=8.4 Hz), 8.18–8.13 (1H, m), 8.09 (1H, d, J=8.4 Hz), 7.82–7.79 (2H, m), 7.77–7.72 (1H, m), 7.69–7.64 (3H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 165.94, 154.70, 152.37, 137.12, 136.23, 135.78, 130.65, 130.22, 129.90, 129.05, 127.11, 117.87, 115.63; HRMS calcd for $C_{15}H_{10}N_4$ $(M+H)^+$ 247.0978; found: 247.1025.

*4.2.11. N-(2-Fluorobenzylidene)-1H-1,2,4-triazol-5-amine (**6a**).* HRMS calcd for $C_9H_7N_5F$ $(M+H)^+$ 191.0728; found: 191.0748.

*4.2.12. 6-(Benzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**1**).* White solid. Mp 175.8–176.3 °C. ^{1}H NMR (400 M, DMSO-d_6): δ 9.59 (1H, s), 8.67 (1H, s), 8.07 (1H, d, J=1.2 Hz), 7.92 (1H, d, J=1.2 Hz), 7.61 (2H, d, J=1.2 Hz); ^{13}C NMR (100 M, DMSO-d_6): δ 156.97, 154.58, 153.32, 137.67, 136.64, 136.48, 129.10, 128.67, 128.19, 110.55, 109.02, 106.98, 70.94; HRMS calcd for $C_{16}H_{12}ON_4$ $(M+H)^+$ 277.1045; found: 277.1062.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.029.

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