Synthesis of Tetrahydropyrrolo[1,2-*a*]quinoxalines and Tetrahydropyrido[1,2-*a*]quinoxalines via a One-Pot CuI-Catalyzed Aryl Amination–Hydrolysis–Condensation Process

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Abstract: CuI-catalyzed coupling of 2-halotrifluoroacetanilides with L-proline or pipecolinic acid in DMSO at 90–110 °C followed by in situ hydrolysis at 100 °C afforded tetrahydropyrrolo[1,2-*a*]quinoxalines or tetrahydropyrido[1,2-*a*]quinoxalines.

Key words: catalysis, coupling, heterocycle, quinoxaline, one-pot process

Tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[1,2-*a*]quinoxalines and their derivatives have often been used for developing pharmaceutical agents.[1] Antitumor agent **1** (Figure 1),[2] vascular smooth muscle relaxant **2**,[3] antitrypanosomal compound **3**,[4] and PARP-1 inhibitor **4**[5] are some successful examples.

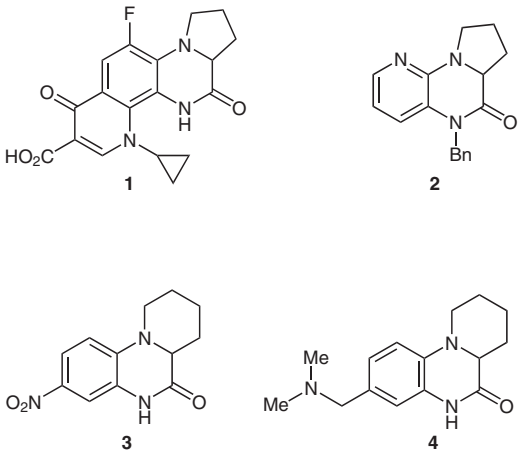

Figure 1 Some bioactive tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[1,2-a]quinoxalines

The most typical approach for construction of these two classes of heterocycles is dependent on employing *o*-nitrohalobenzenes as the starting materials.[6] After nucleophilic aromatic substitution of these aryl halides with proline and pipecolinic acid, reduction of the nitro group and subsequent condensative cyclization produced the corresponding tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[1,2-*a*]quinoxalines. A significant drawback of this procedure is that only *o*-nitrohalobenzenes bearing electron-donating groups are suitable substrates. Recently, Tanimori and co-workers reported that CuI-catalyzed coupling reaction of *o*-bromoanilines with racemic amino acids followed by condensative cyclization gave tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[1,2-*a*]quinoxalines.[1a] In this case the coupling reaction was conducted at 125 °C, which might lead to racemization of the amino acid moiety if enantiopure amino acids were utilized. We revealed that the *ortho*-substitution effect caused by $NHCOCF_3$ could facilitate some Ullmann-type coupling reactions at relatively low reaction temperatures.[7] As an extension of this work, we investigated the coupling reaction of 2′-halotrifluoroacetanilides with L-proline.[8] We envisaged that if this reaction proceeded under milder conditions, enantiopure pyrrolo[1,2-*a*]quinoxalines could be obtained upon hydrolysis of the amide part in the coupling products and subsequent intramolecular condensation as indicated in Scheme 1.

With the above idea in mind, we selected the reaction of 2-iodotrifluoroacetanilide with L-proline as a model to explore the optimized coupling conditions. It was found that under the catalysis of 10 mol% CuI and K_2CO_3, this reaction took place at 60 °C in DMSO. However, only 50% yield of the coupling product was obtained mainly because of incomplete conversion. The complete conversion and excellent coupling yield (95%) was only seen when the reaction temperature was raised to 90 °C. We next explored the optimized conditions for one-pot conversion of the coupling products to pyrrolo[1,2-*a*]quinoxalines. After some experiments, we were pleased to find that adding water to the coupling reaction mixture followed by heating at 100 °C provided the desired product **8a** in good yield with little racemization (Table 1, entry 1). When less reactive bromotrifluoroacetanilide was used, the coupling reaction required a higher temperature (110 °C) and using Cs_2CO_3 as the base to complete. In this case **8a** was isolated in 76% yield and 90% ee after hydrolysis (entry 2). Based on these results, we next attempted to synthesize substituted tetrahydropyrrolo[1,2-*a*]quinoxalines using functionalized 2′-halotrifluoroacetanilides. To our delight, both electron-rich and electron-deficient 2′-halotrifluoroacetanilides were found compatible for this process, affording the corresponding products **8b–j**. In most cases,

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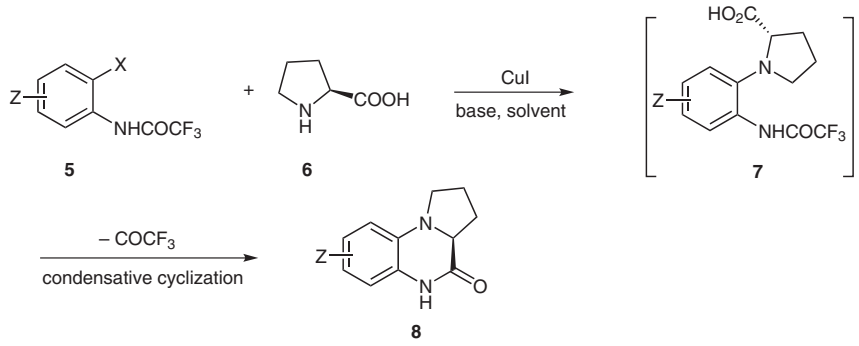
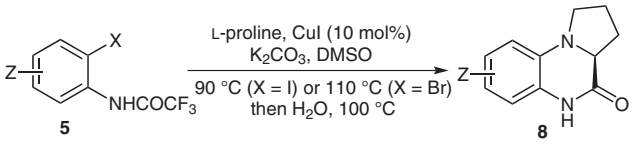


Scheme 1 One-pot coupling–hydrolysis–condensation approach to enantiopure tetrahydropyrrolo[1,2-*a*]quinoxaline

slight racemization occurred with the products having ee values ranging from 91% to 99%. When 4′-acyl-2′-iodotrifluoroacetanilide was used, **8f** was isolated with 70% ee (entry 9), presumably because of the strong electron-withdrawing effect of the acyl group.

Table 1 Synthesis of Tetrahydropyrrolo[1,2-*a*]quinoxalines **8** via a CuI-Catalyzed One-Pot Process[a]



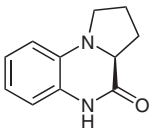
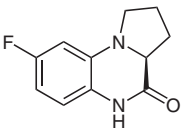
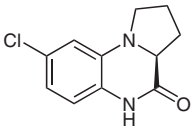
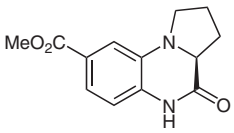
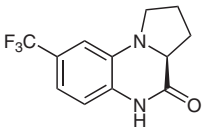
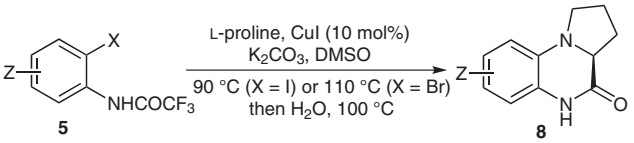
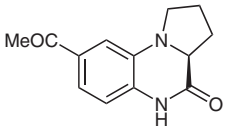
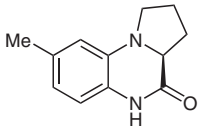
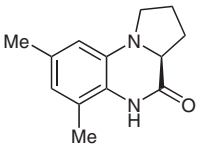
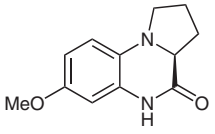
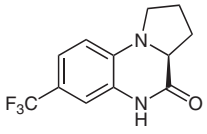
Entry	X	Time (h)[b]	Product	Yield (%)[c]	ee (%)
1	I	15		78	97
2[d]	Br	10		76	90
			8a		
3	I	17		78	95
4[d]	Br	10		72	95
			8b		
5	I	18		77	91
6[d]	Br	12		76	94
			8c		
7	I	17		85	91
			8d		
8	I	24		83	95
			8e		

Table 1 Synthesis of Tetrahydropyrrolo[1,2-*a*]quinoxalines **8** via a CuI-Catalyzed One-Pot Process[a] (continued)

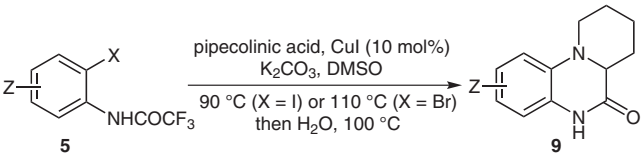


Entry	X	Time (h)[b]	Product	Yield (%)[c]	ee (%)
9[e]	I	17		75	70
			8f		
10	I	13		74	95
11[d]	Br	10		72	96
			8g		
12	I	10		60	99
			8h		
13	I	6		30[f]	97
			8i		
14[d]	Br	14		70	94
			8j		

[a] Reaction conditions: 2-iodotrifluoroacetanilide (0.5 mmol), L-proline (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (1 mmol), DMSO (4 mL), 90 °C (for bromide, 110 °C), then H_2O (3 mL) was added and the mixture was heated to 100 °C.
[b] For coupling step.
[c] Isolated yield.
[d] Cs_2CO_3 was used.
[e] Amount of CuI used: 20 mol%.
[f] Deiodination product was isolated in about 35% yield.

The electronic nature of the substituted 2-halotrifluoroacetanilides also had a significant influence on the rate of the coupling step. In case of 4′-acyl-2′-iodotrifluoroacetanilide, increasing the catalytic loading was required to complete the conversion (entry 9). This phenomenon indicated that electron-rich aryl halides are more reactive than electron-deficient ones, which is consistent with that observed in other coupling reactions.[7] In the case of 5′-methoxy-2′-iodotrifluoroacetanilide, although coupling reaction proceeded quite fast, low yield was observed mainly because severe deiodination occurred (entry 13).

Table 2 Synthesis of Tetrahydropyrido[1,2-*a*]quinoxalines **9** via a CuI-Catalyzed One-Pot Process[a]



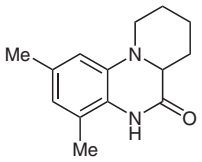
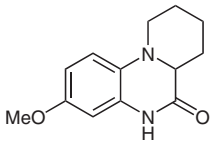
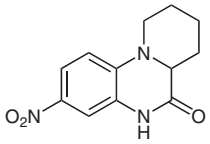
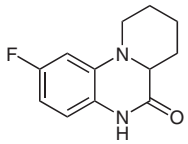
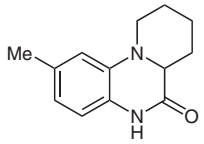
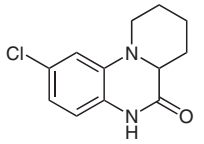
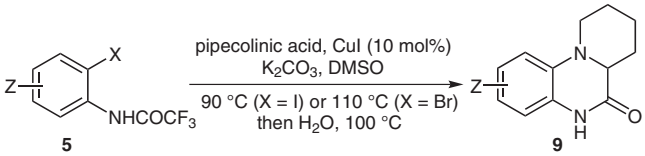
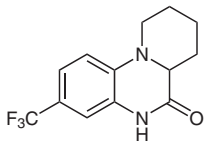
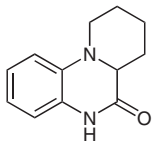
Entry	X	Time (h)	Product	Yield (%)[b]
1	I	13	 **9a**	78
2	I	13	 **9b**	86
3	I	12	 **9c**	84
4[c]	Br	12	 **9d**	75
5[c]	Br	12	 **9e**	92
6[c]	Br	12	 **9f**	60

Table 2 Synthesis of Tetrahydropyrido[1,2-*a*]quinoxalines **9** via a CuI-Catalyzed One-Pot Process[a] (continued)



Entry	X	Time (h)	Product	Yield (%)[b]
7[c]	Br	12	 **9g**	70
8[c]	Br	11	 **9h**	90
9[c]	Cl	43		40

[a] Reaction conditions: 2-halotrifluoroacetanilide (0.5 mmol), pipecolinic acid (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (1 mmol), DMSO (4 mL), 90 °C (for bromides and chloride, 110 °C), then H_2O (3 mL) was added and the mixture was heated to 100 °C.
[b] Isolated yield.
[c] Cs_2CO_3 was used as the base.

By switching the coupling partner from L-proline to pipecolinic acid, we were able to obtain tetrahydropyrido[1,2-*a*]quinoxalines with good to excellent yields (Table 2). Interestingly, when 5-methoxy-2-iodotrifluoroacetanilide was used, tricyclic product **9b** was isolated in a good yield, indicating that pipecolinic acid is more reactive than L-proline as a coupling partner in this case (compare entry 2 with entry 13 of Table 1). 2-Chlorotrifluoroacetanilide was also compatible with these reaction conditions, giving **9h** in a moderate yield (entry 9).

In conclusion, we have developed a new method for assembling tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[1,2-*a*]quinoxalines,[9] which relied on a one-pot amination–hydrolysis–condensation process of 2-halotrifluoroacetanilides with L-proline and pipecolinic acid. A considerable number of functional groups such as halo, nitro, ester and keto groups are tolerated under these reaction conditions, thereby allowing diverse synthesis of these heterocycles.[10]

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

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(9) **General Procedure for the Synthesis of Quinoxaline Derivatives**: A Schlenk tube was charged with 2-iodotrifluoroacetanilide (0.5 mmol), CuI (10 mg, 0.02 mmol), L-proline (or pipecolinic acid) (1.5 mmol), and K_2CO_3 (1.0 mmol) (for bromide, Cs_2CO_3 was used). The tube was evacuated and backfilled with argon. DMSO (4 mL) was added into the tube. The reaction mixture was stirred at 90 °C (for bromide, 110 °C) for 10–24 h. Then H_2O (3 mL) was added and the reaction mixture was stirred at 100 °C for 8–12 h. After the reaction mixture was cooled, sat. NH_4Cl (10 mL) solution was added. The mixture was extracted with EtOAc and the organic layer was washed with H_2O, brine and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel (eluting with 6:1 → 4:1 PE–EtOAc) to provide the desired product.

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