JOC*Note*

A One-Pot Coupling/Hydrolysis/Condensation Process to Pyrrolo[1,2-*a*]quinoxaline

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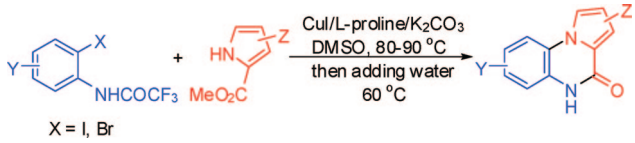

CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with pyrrole-2-carboxylate esters in DMSO at 80−90 °C followed by in situ hydrolysis at 60 °C afforded pyrrolo[1,2-*a*]quinoxalines. Indole-2-carboxylate esters underwent the same process smoothly to provide the corresponding tetracyclic products.

The pyrrolo[1,2-*a*]quinoxaline moiety has been found in many pharmaceutically important molecules, including antipsychotic agent **1**,[1] anti-HIV agent **2**,[2] adenosine A_3 receptor modulator **3**,[3] and antitumor agent **4**[4] (Figure 1). In addition, pyrrolo[1,2-*a*]quinoxaline compounds have served as key intermediates for the assembly of several heterocycles that displayed a wide range of biological activities.[5]

The common method for the construction of pyrrolo[1,2-*a*]quinoxalines starts from 2-nitroanilines and proceeds in three steps (pyrrole ring formation, nitro group reduction, and cyclization with triphosgene).[5] This approach suffers from inconvenient operation and a limited number of suitable substrates for diverse synthesis. Recently, Beccalli and coworkers described a Pd-catalyzed intramolecular C−N bond formation strategy to assemble these tricyclic compounds from 2-haloanilines and pyrrole-2-carboxylic acids.[6] However, preliminary methylation of the commercially available 2-haloanilines is required. This additional manipulation limits the scope of application of this method.

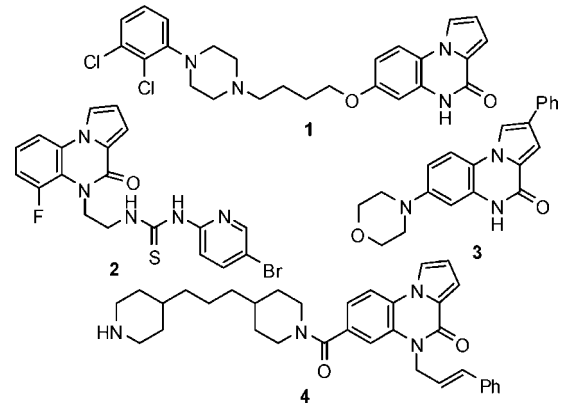

FIGURE 1. Structures of some pharmaceutically important pyrrolo[1,2-*a*]quinoxalines.

We recently revealed that there exists an ortho-substitution effect caused by NHCOR groups in some CuI/amino acid-catalyzed Ullmann-type coupling reactions.[7] On the basis of this discovery we have developed new cascade processes for the assembly of benzimidazoles,[7c] 1,3-dihydrobenzimidazol-2-ones,[8] and indoles.[7d,9] In connection with these investigations, we envisioned that the coupling reaction of pyrrole-2-carboxylate esters **6** with 2-halotrifluoroacetanilides **5** would proceed smoothly to deliver the coupling products **7**,[10,11] which upon liberation of the amine group by hydrolysis and subsequent intramolecular condensation would provide pyrrolo[1,2-*a*]quinoxaline compounds (Scheme 1).

With this idea in mind, we first attempted the CuI/L-proline-catalyzed coupling of 2-iodotrifluoroacetanilide **5a** and pyrrole-2-carboxylate methyl ester **6a**. As expected, this reaction worked well in DMSO at 80 °C to afford coupling product **7a** in 96% yield (Scheme 2). Under the same conditions the coupling of 2-iodoacetanilide **10** with **6a** gave only 10% yield of product **12**, while 2-iodoanisole **11** gave no coupled product at all. These results indicated that an ortho-substitution effect directed by NHCOR groups also exists for the present coupling reaction, and that $NHCOCF_3$ has a significantly better accelerating ability than $NHCOCH_3$, which is consistent with our previous observations.[7a] Further evidence was provided by the fact that

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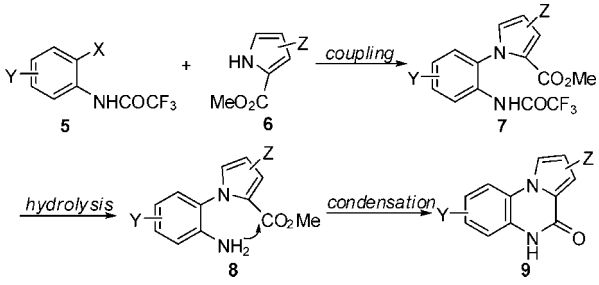
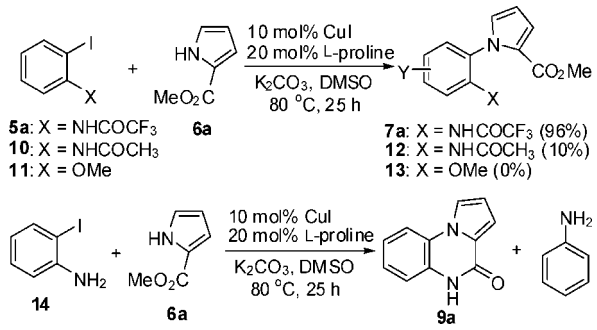
SCHEME 1. Coupling/Hydrolysis/Condensation Approach to Pyrrolo[1,2-*a*]quinoxaline



SCHEME 2. CuI/L-Proline-Catalyzed Couplings of Ortho-Substituted Iodobenzenes with Pyrrole-2-carboxylate Methyl Ester



coupling of 2-iodoaniline **14** with **6a** furnished the coupling/condensative cyclization product **9a** in only 25% yield, together with 61% of recovered **14** and 8% of aniline (dehalogenation product).

For the coupling of 2-iodoaniline **14** with **6a**, exclusive isolation of **9a** indicated that the intramolecular condensative cyclization was much faster than the coupling, which implied that a one-pot process for the assembly of pyrrolo[1,2-*a*]quinoxalines could be developed if the trifluoroacetyl group was selectively removed after coupling of **5** and **6**. Consequently, the conditions for the deprotection step were closely investigated. After careful experimentation, we were pleased to find that the addition of water to the coupling reaction mixture followed by heating to 60 °C could provide the cyclization product **9a** in excellent yield (Table 1, entry 1). These conditions were then examined for a variety of 2-halotrifluoroacetanilides and pyrrole-2-carboxylate esters. The electronic properties of pyrrole-2-carboxylate esters obviously had little influence on this process, as is evident from the fact that both electron-rich and electron-deficient pyrrole-2-carboxylate esters afforded good yields of tricyclic products (entries 2−5). However, only electron-rich 2-iodotrifluoroacetanilides gave rise to the desired products in excellent yields (Table 1, entries 6 and 7), while electron-deficient 2-iodotrifluoroacetanilides gave good to moderate yields (Table 1, entries 8, 9, and 17). In the latter case, the problem should result from the sluggish coupling reaction, demonstrating that electron-deficient 2-halotrifluoroacetanilides are less reactive than electronic-rich ones. These phenomena have also been observed in our previous studies,[7a,b] although the reason is not fully clear yet.

Disubstituted pyrrolo[1,2-*a*]quinoxalines **9j**−***l*** could be elaborated from the corresponding substituted coupling partners in good yields (Table 1, entries 10−12). Starting from **9*l***, some new analogues of antitumor agent **4** could be prepared.

2-Bromotrifluoroacetanilides also worked well in our process, although slightly higher reaction temperatures were required during the coupling step (Table 1, entries 13−16). Noteworthy is that pyrido-fused heterocycles **9o** and **9p** (Table 1, entries 15 and 16) were obtained from *N*-(2,6-dibromopyridin-3-yl)-2,2,2-trifluoroacetamide **5i**. The exclusive isolation of one isomer in these two reactions illustrated that the coupling only occurred at the ortho-position of the amide group. This result gave additional evidence for the proposed ortho-substitution effect in the coupling step. The bromide moiety in **9o** and **9p** allows further coupling manipulations for the elaboration of more diverse compounds, e.g., amination of **9o** would afford analogues of adenosine A_3 receptor modulator **3**.

We next investigated the applicability of indole-2-carboxylate esters and imidazole-2-carboxylate esters as substrates. As shown in Scheme 3, the coupling reaction of methyl 1*H*-indole-2-carboxylate (**15**) with iodide **5e** and bromide **5k** proceeded smoothly to afford fused tetracyclic compounds **16** in good yields after hydrolysis and subsequent intramolecular condensation. However, the reaction of methyl 1*H*-imidazole-2-carboxylate **17** with iodide **5c** under the same coupling conditions gave only a poor conversion. The reason for this unsatisfactory result is not clear yet.

In conclusion, we have developed a one-pot coupling/hydrolysis/intramolecular condensation process to assemble pyrrolo[1,2-*a*]quinoxalines from pyrrole-2-carboxylate esters. A wide range of these fused heterocycles bearing different functional groups such as ketone, ester, methoxy, bromo, and chloro could be elaborated from suitable substrates, thereby providing a versatile and reliable method for the elaboration of these pharmaceutically important compounds. Indole-2-carboxylate esters were compatible with this process, giving the corresponding fused tetracyclic compounds, while imidazole-2-carboxylate esters gave low yields of the desired coupling products. Further attempts to improve this process are in progress, as well as its application to the synthesis of special target compounds.

Experimental Section

General Procedure for Synthesis of Substituted Pyrrolo[1,2-*a*]quinoxalines. A Schlenk tube was charged with pyrrole-2-carboxylate ester (0.25 mmol), aryl iodide (0.375 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and K_2CO_3 (104 mg, 0.75 mmol), evacuated, and backfilled with argon. After DMSO

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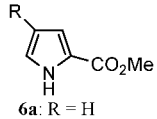
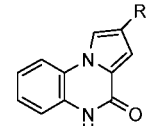
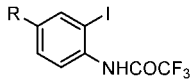
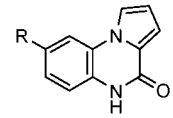
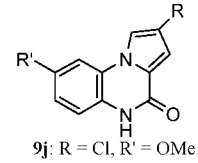
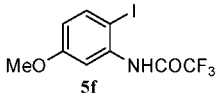
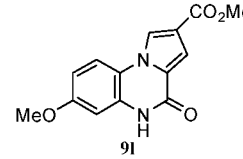
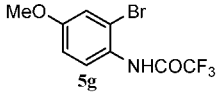
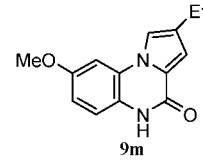
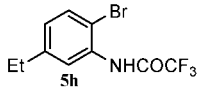
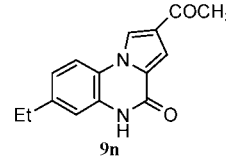
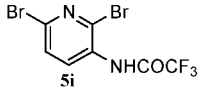
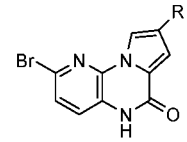
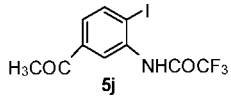
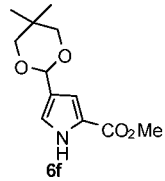
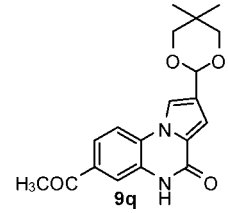
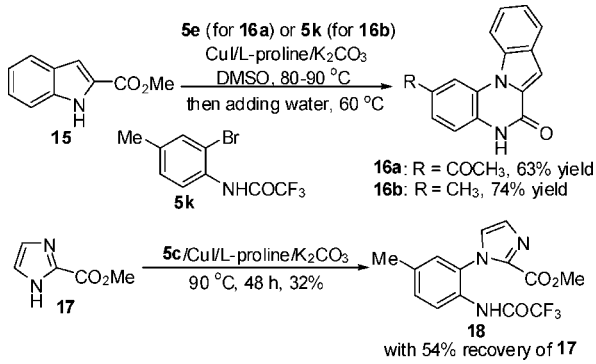
TABLE 1. Synthesis of Pyrrolo[1,2-*a*]quinoxalines via CuI/L-Proline Catalyzed Coupling of 2-Halotrifluoroacetanilides 5 with Pyrrole-2-carboxylate Esters 6[a]

entry	2-halotrifluoroacetanilide	pyrrole-2-carboxylate ester	time (h) (coupling/ hydrolytic cyclization)	product	yield (%)[b]
1	**5a**	 **6a**: R = H	25/8	 **9a**: R = H	93
2	**5a**	**6b**: R = Et	21/12	**9b**: R = Et	83
3	**5a**	**6c**: R = Cl	23/11	**9c**: R = Cl	85
4	**5a**	**6d**: R = $COCH_3$	25/11	**9d**: R = $COCH_3$	84
5	**5a**	**6e**: R = CO_2CH_3	35/12	**9e**: R = CO_2CH_3	86
6	 **5b**: R = OMe	**6a**	23/12	 **9f**: R = OMe	97
7	**5c**: R = Me	**6a**	24/9	**9g**: R = Me	93
8	**5d**: R = F	**6a**	40/10	**9h**: R = F	75
9	**5e**: R = $COCH_3$	**6a**	36/15	**9i**: R = $COCH_3$	44
10	**5b**	**6c**	20/15	 **9j**: R = Cl, R' = OMe	84
11	**5c**	**6d**	26/15	**9k**: R = $COCH_3$, R' = Me	88
12	 **5f**	**6e**	29/13	 **9l**	72
13	 **5g**	**6b**	20/12	 **9m**	81
14	 **5h**	**6d**	38/12	 **9n**	89
15	 **5i**	**6e**	13/13	 **9o**: R = CO_2CH_3	77
16		**6b**	15/13	**9p**: R = Et	64
17	 **5j**	 **6f**	36/15	 **9q**	54

[a] Reaction conditions: 2-halotrifluoroacetanilide **5** (0.37 mmol), pyrrole-2-carboxylate ester **6** (0.25 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), K_2CO_3 (0.75 mmol), DMSO (0.5 mL), 80 °C (90 °C for bromides); then adding 1.5 mL of water, 60 °C. [b] Isolated yield.

(0.5 mL) was injected, the reaction mixture was stirred at 80 °C until pyrrole-2-carboxylate ester disappeared monitored by TLC. To the cooled solution was added 1.5 mL of water. The mixture was then heated at 60 °C for 8−15 h. The mixture was cooled to

SCHEME 3. Assembly of Fused Tetracyclic Compounds 16



room temperature and diluted with 150 mL of ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 3:1 to 1:10 petroleum ether/ethyl acetate) to provide the desired product.

Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.15 (dd, J = 2.8, 1.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.27−7.22 (m, 2H), 7.18−7.14 (m, 1H), 6.99 (dd, J = 4.1, 1.4 Hz, 1H), 6.65 (dd, J = 3.7, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.53, 129.04, 126.15, 123.78, 123.11, 123.07, 118.57, 116.99, 115.53, 113.25, 111.89; EI-MS *m*/*z* 184 (M^+), 155, 129; EI-HRMS calcd for $C_{11}H_8N_2O$ (M^+) 184.0637, found 184.0642.

2-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 7.96 (d, J = 1.4 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.27−7.11 (m, 3H), 6.85 (d, J = 1.4 Hz, 1H), 2.58 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.34, 130.61, 128.86, 125.68, 123.46, 123.02, 116.89, 115.86, 115.23, 111.27, 20.26, 15.55; EI-MS *m*/*z* 212 (M^+), 197, 184, 168; EI-HRMS calcd for $C_{13}H_{12}N_2O$ (M^+) 212.0950, found 212.0959.

8-Methoxypyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9f). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 8.19 (dd, J = 2.8, 1.4 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 6.97 (dd, J = 3.7, 1.4 Hz, 1H), 6.88 (dd, J = 8.7, 2.3 Hz, 1H), 6.64 (dd, J = 3.7, 2.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.67, 155.13, 123.93, 123.67, 122.66, 118.79, 117.92, 113.18, 112.97, 111.81, 100.64, 56.39; EI-MS *m*/*z* 214 (M^+), 199, 171, 143; EI-HRMS calcd for $C_{12}H_{10}N_2O_2$ (M^+) 214.0742, found 214.0746.

2-Acetyl-8-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9k). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.04 (s, 1H), 7.28 (d, J = 1.4 Hz, 1H), 7.17−7.11 (m, 2H), 2.48 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.51, 155.38, 132.89, 128.17, 128.07, 127.27, 125.06, 122.36, 121.85, 117.03, 116.25, 110.89, 28.02, 21.08; EI-MS *m*/*z* 240 (M^+), 225, 197, 169, 112; EI-HRMS calcd for $C_{14}H_{12}N_2O_2$ (M^+) 240.0899, found 240.0904.

Methyl 7-Methoxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]-quinoxaline-2-carboxylate (9l). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.68 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 10.1 Hz, 1H), 7.20, (d, J = 1.4 Hz, 1H), 6.80−6.72 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.16, 158.37, 155.38, 130.75, 124.18, 121.60, 118.62, 117.57, 116.63, 111.72, 109.72, 101.43, 56.01, 51.98; EI-MS *m*/*z* 272 (M^+), 257, 241, 229; EI-HRMS calcd for $C_{14}H_{12}N_2O_4$ (M^+) 272.0797, found 272.0796.

2-Ethyl-8-methoxypyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9m). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.01 (d, J = 0.9 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 9.2 Hz, 1H), 6.86−6.81 (m, 2H), 3.79 (s, 3H), 2.57 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.65, 154.95, 130.55, 123.62, 122.47, 117.82, 116.06, 112.66, 111.23, 100.16, 56.35, 20.30, 15.52; EI-MS *m*/*z* 242 (M^+), 227, 212, 199, 184; EI-HRMS calcd for $C_{14}H_{14}N_2O_2$ (M^+) 242.1055, found 242.1058.

2-Acetyl-7-ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (9n). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.82 (d, J = 1.8 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.10−7.05 (m, 2H), 2.61 (q, J = 7.3 Hz, 2H), 2.48 (s, 3H), 1.17 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.54, 155.58, 143.25, 129.58, 128.10, 124.82, 123.04, 121.78, 120.69, 116.17, 115.98, 110.98, 28.29, 28.06, 15.90; EI-MS *m*/*z* 254 (M^+), 239, 226, 211, 196, 183; EI-HRMS calcd for $C_{15}H_{14}N_2O_2$ (M^+) 254.1055, found 254.1048.

Methyl 2-Bromo-6-oxo-5,6-dihydropyrido[3,2-*e*]pyrrolo-[1,2-*a*]-pyrazine-8-carboxylate (9o). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.25 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.70, 154.65, 134.48, 131.30, 128.04, 127.13, 125.42, 125.26, 120.14, 119.84, 112.86, 52.26; EI-MS *m*/*z* 323 (M^+, ^{81}Br), 321 (M^+, ^{79}Br), 292, 290, 262, 234; EI-HRMS calcd for $C_{12}H_8BrN_3O_3$ (M^+, ^{79}Br) 320.9749, found 320.9747.

2-Acetylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (16a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.75 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.60 (t, J = 8.7 Hz, 1H), 7.49 (s, 1H), 7.41−7.34 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.84, 156.41, 134.35, 132.90, 131.93, 129.03, 128.75, 126.57, 125.75, 125.27, 123.73, 123.18, 117.01, 114.99, 114.59, 106.77, 27.15; EI-MS *m*/*z* 276 (M^+), 261, 214, 199, 171; EI-HRMS calcd for $C_{17}H_{12}N_2O_2$ (M^+) 276.0899, found 276.0887.

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Supporting Information Available: Analytical data of compounds **9c**−**e**, **9g**−**j**, **9p**, and **16b**, and the copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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