Elaboration of the Oxazepine Ring System via CuI/L-Proline-Catalyzed Intramolecular Aryl Amination

Lei Guo,[a,1] Ben Li,[b,1] Wenlong Huang,[a] Gang Pei,[b] Dawei Ma*[c]

[a] Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. of China

[b] Shanghai Institute of Biological Chemistry & Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 319 Yueyang Lu, Shanghai 200031, P. R. of China

[c] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: madw@mail.sioc.ac.cn

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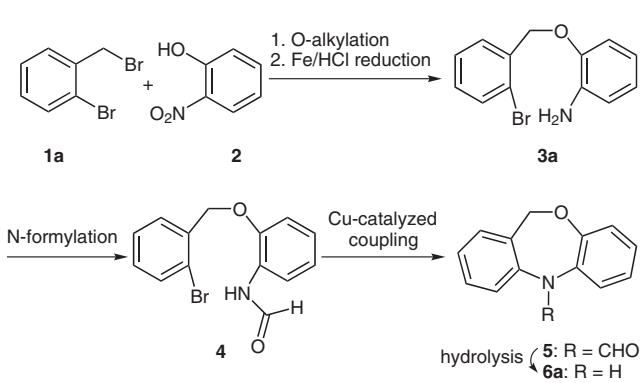
Abstract: A two-step approach for assembling oxazepines is described, which started from 2-aminophenols and substituted 2-bromobenzyl bromides and used CuI/L-proline-catalyzed coupling reaction as the key step.

Key words: cross-coupling, aryl bromide, ethers, oxazepines

The oxazepine moiety has been found in many pharmaceutically important compounds.[2,3] The typical method for elaboration of this tricyclic system is based on a five-step route as depicted in Scheme 1.[3] The key step is a copper-catalyzed intramolecular coupling of amide **4** to the corresponding cyclization product **5**. Obviously, if a metal-catalyzed intramolecular aryl amination of **3a** to **6a** worked well, the formation and saponification steps would be avoided. Recently, Rogers and co-workers reported that this goal could be reached by employing $Pd(dba)_2/P(t\text{-}Bu)_3$ as a catalytic system (Scheme 2).[4] Herein, we wish to describe that an inexpensive CuI/L-proline catalytic system can be used for the same transformation,[5,6] thereby giving a practical approach to assess substituted oxazepines.[7]

As shown in Scheme 3, we started our attempts by modification of the preparation of cyclization precursors. We found that etherification by directly using 2-aminophenol



Scheme 1

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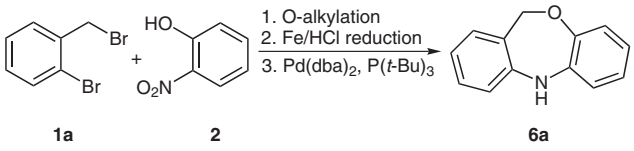
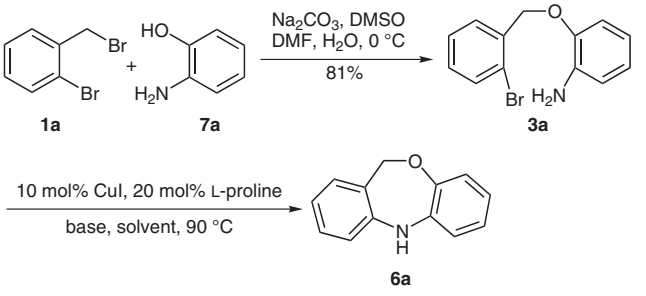


Scheme 2

could proceed smoothly in a mixed solvent at 0 °C to afford **3a** in 81% yield.[8] This success allows further shortening of the previous five-step procedure to two steps because reduction of nitro group was omitted. Next, we explored the possible reaction conditions for CuI/L-proline-catalyzed cyclization. Initially, our standard conditions for aryl amination[5] were used (Table 1, entry 1), and it was found that after 60 hours only 30% desired product was isolated. Changing solvents to DMF, toluene, and dioxane gave worse results (entries 2–4). However, switching base to triethylamine provided a better yield (entry 7), although K_2CO_3 and K_3PO_4 still gave poor yields of the product (entries 5 and 6). Further attempts revealed that DABCO was a better base for this reaction, providing **3a** in 58% yield after 48 hours (entry 8). The best yield was obtained by using DMSO–water as a mixed solvent (entry 9). Adding L-proline was essential for coupling because no product was isolated if it was absent (entry 10).



Scheme 3

After the optimized reaction conditions were obtained,[9] we explored the scope and limitations of this method by varying the bromides and phenols. As shown in Table 2, all examined substrates gave good yields in the etherification step. However, the yields of the intramolecular coupling step were found to be highly dependent on the

Table 1 CuI-Catalyzed Intramolecular Aryl Amination of **3a** under Various Conditions[a]

Entry	Base	Solvent	Time (h)	Yield (%)[c]
1	Na_2CO_3	DMSO	60	30
2	Na_2CO_3	DMF	60	12
3	Na_2CO_3	toluene	60	8
4	Na_2CO_3	dioxane	60	0
5	K_2CO_3	DMSO	60	20
6	K_3PO_4	DMSO	60	0
7	Et_3N	DMSO	72	65[b]
8	DABCO·$6H_2O$	DMSO	48	58[b]
9	DABCO·$6H_2O$	DMSO–H_2O	48	78[b,d]
10	DABCO·$6H_2O$	DMSO–H_2O	48	0[b,d,e]

[a] Reaction conditions: **3a** (0.5 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), base (2 mmol), DMSO (4 mL), 90 °C.
[b] 5 mmol of base was added.
[c] Isolated yield.
[d] 1 mL of water was added.
[e] Without addition of L-proline.

electronic nature of the reactants. The 2-bromo-5-methoxybenzyl bromide derived ether gave only 35% yield of the desired product **6b** after 48 hours (entry 1), while the 2-bromo-5-(*tert*-butoxycarbonyl)benzyl bromide derived ether delivered the coupling product **6c**[10] in 80% yield after 24 hours (entry 2). These results indicated that an additional electron-withdrawing group in the aryl bromide part was favorable for the coupling reaction, which was consistent with our previous observation for intermolecular aryl amination.[5] The orientation of the electron-withdrawing group in the aryl bromide part also influenced the coupling process, as evident from that the 2-bromo-3-(*tert*-butoxycarbonyl)benzyl bromide derived ether showed good conversion in 24 hours (entry 3), while the 2-bromo-4-acylbenzyl bromide derived ether required 48 hours to provide the satisfactory conversion (entry 4). From naphthalene-embodied bromide **1f**, tetracyclic compound **6f**[11] was obtained in 61% overall yield (entry 5).

We then checked the influence of electronic properties in 2-aminophenol part to the coupling process. It was found that introduction of an additional electron-donating group could facilitate this reaction, because 4-chloro-2-aminophenol derived ether gave low conversion (entry 6), while 4-methyl-2-aminophenol derived ether provided the desired product **6h**[12] in good yield (entry 7). The orientation of the electron-donating group in 2-aminophenol also played an important role for promoting the reaction, as an excellent coupling yield observed in a shorter reaction time when 3-methyl-2-aminophenol derived ether was employed (compare entries 7–9). This phenomenon was easily understandable because the additional electron-donating groups could enhance the nucleophilicity of the amine.

Table 2 Assembly of Oxazepines via Etherification and Subsequent CuI/L-Proline-Catalyzed Coupling of 2-Aminophenols and Substituted 2-Bromobenzyl Bromides[a]

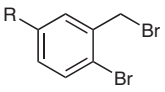
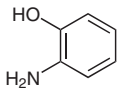
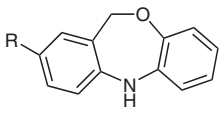
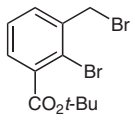
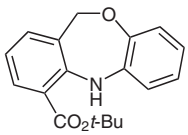
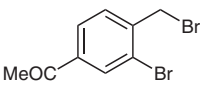
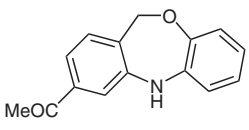
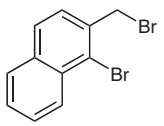
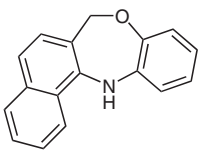
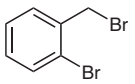
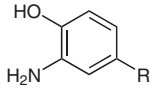
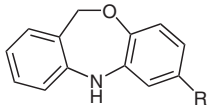
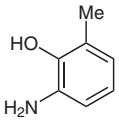
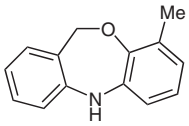
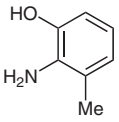
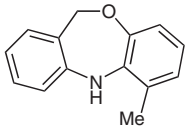
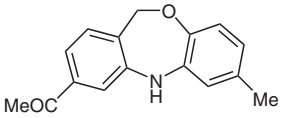
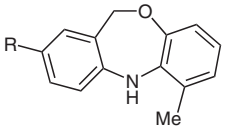
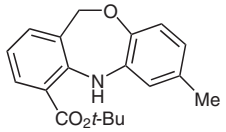
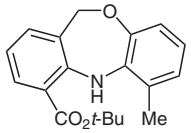
Entry	Bromide	2-Aminophenol	Product	Time (h)[b]	Yield (%)[c] of etherification/coupling
1	 **1b**: R = OMe	 **7a**	 **6b**: R = OMe	48	84/35[d]
2	**1c**: R = CO_2t-Bu		**6c**: R = CO_2t-Bu	24	80/80
3	 **1d**		 **6d**	24	70/81
4	 **1e**		 **6e**	48	65/63
5	 **1f**		 **6f**	48	82/75

Table 2 Assembly of Oxazepines via Etherification and Subsequent CuI/L-Proline-Catalyzed Coupling of 2-Aminophenols and Substituted 2-Bromobenzyl Bromides[a] (continued)

Entry	Bromide	2-Aminophenol	Product	Time (h)[b]	Yield (%)[c] of etherification/coupling
6	 **1a**	 **7b**: R = Cl	 **6g**: R = Cl	72	83/40[d]
7		**7c**: R = Me	**6h**: R = Me	72	68/73
8		 **7d**	 **6i**	72	72/66
9		 **7e**	 **6j**	24	75/93
10	**1e**	**7c**	 **6k**	48	88/63
11	**1c**	**7e**	 **6l**: R = CO_2t-Bu	24	78/92
12	**1b**	**7e**	**6m**: R = OMe	24	75/90
13	**1e**	**7c**	 **6n**	24	77/65
14	**1e**	**7e**	 **6o**	24	74/71

[a] Reaction conditions: Etherification step: 2-aminophenol (21 mmol), substituted 2-bromobenzyl bromide (10 mmol), Na_2CO_3 (40 mmol), DMF (20 mL), DMSO (20 mL), H_2O (2 mL), 0 °C. Coupling step: etherification product (0.5 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), DABCO·$6H_2O$ (5 mmol), DMSO (4 mL), H_2O (1 mL), 90 °C.
[b] For coupling step.
[c] Isolated yield.
[d] About 20% coupling precursor was recovered.

Starting from substituted 2-bromobenzyl bromides and 2-aminophenols, several disubstituted oxazepines were assembled (entries 10–14). Noteworthy was that an ether derived from 2-bromo-5-methoxybenzyl bromide and 3-methyl-2-aminophenol produced **6m**[13] in 90% yield (entry 12), indicating that the more reactive amine could overcome the poor conversion problem caused by the electron-rich aryl bromide (compare entries 1 and 12).

In conclusion, we have developed a two-step approach for the assembly of substituted oxazepines. Some functional groups like ester, ketone, methoxy, and chloride could be introduced at the different positions of the oxazepine ring system by choosing suitable substrates. The cheap catalyt-

ic system and easy operation in this method are remarkable. Thus, it may find applications in elaboration of designed biological molecules.

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References and Notes

(1) These authors contributed equally to this paper.
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(8) **Typical Procedure for Etherification**
To a flask containing 2-aminophenol (21 mmol) and Na_2CO_3 (40 mmol) was added DMF (20 mL), DMSO (20 mL), and H_2O (2 mL). At 0 °C a solution of 2-bromobenzyl bromide (10 mmol) in DMF (5 mL) was added dropwise. After the mixture was stirred for about 4 h, it was filtered. The filtrate was partitioned between EtOAc and H_2O. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residual oil was loaded on a silica gel column and eluted with 1:10 EtOAc–PE to afford the etherification product.
(9) **Typical Procedure for Coupling**
A Schlenk tube was charged with the above ether (0.5 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), and DABCO·$6H_2O$ (5.0 mmol), evacuated, and backfilled with Ar. Then, DMSO (4 mL) and H_2O (1 mL) were added. The reaction mixture was heated at 90 °C until the starting material disappeared (monitored by TLC). The cooled mixture was partitioned between EtOAc and H_2O. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel to provide the coupling product.
(10) **Selected Data for 6c**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 1.8, 8.1 Hz, 1 H), 7.69 (d, *J* = 2.1 Hz, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.99 (dd, *J* = 1.5, 7.8 Hz, 1 H), 6.74 (td, *J* = 1.8, 7.8 Hz, 1 H), 6.59 (td, *J* = 1.2, 8.1 Hz, 1 H), 6.46 (dd, *J* = 1.8, 8.1 Hz, 1 H), 4.31 (s, 2 H), 3.84 (s, 1 H), 1.48 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 161.2, 114.3, 138.6, 130.8, 130.4, 129.6, 127.4, 124.4, 121.8, 120.3, 119.4, 118.7, 80.8, 47.1, 28.1. ESI-MS: *m/z* = 298.1 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$: 298.1438; found: 298.1432.
(11) **Selected Data for 6f**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.1 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H), 7.40–7.53 (m, 3 H), 7.31 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.18 (d, *J* = 8.1 Hz, 1 H), 6.82 (td, *J* = 1.2, 7.2 Hz, 1 H), 6.69 (td, *J* = 1.5, 7.8 Hz, 1 H), 6.51 (dd, *J* = 1.2, 7.8 Hz, 1 H), 4.52 (s, 2 H), 3.75 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 144.6, 139.2, 134.2, 127.6, 127.1, 126.6, 126.2, 126.1, 125.8, 124.4, 123.6, 122.0, 121.8, 119.2, 118.8, 46.9. ESI-MS: *m/z* = 248.1 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{14}NO$ $[M + H]^+$: 248.1070; found: 248.1068.
(12) **Selected Data for 6h**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05–7.18 (m, 3 H), 6.97–6.99 (m, 1 H), 7.00 (d, *J* = 8.1, 1 H), 6.39 (dd, *J* = 1.5, 8.1 Hz, 1 H), 6.27 (d, *J* = 1.2 Hz, 1 H), 4.35 (s, 2 H), 3.56 (s, 1 H), 2.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 142.9, 138.2, 133.9, 131.7, 128.9, 128.0, 124.1, 121.7, 120.4, 119.9, 118.9, 46.8, 20.5. ESI-MS: *m/z* = 212.0 $[M + H]^+$.
(13) **Selected Data for 6m**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 4.2, 5.1 Hz, 1 H), 6.91 (d, *J* = 4.2 Hz, 1 H), 6.59–6.70 (m, 3 H), 6.53 (t, *J* = 7.8 Hz, 1 H), 4.45 (s, 2 H), 3.68 (s, 3 H), 1.99 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 152.4, 145.0, 136.6, 133.1, 125.9, 125.3, 120.9, 119.7, 118.0, 113.2, 113.1, 55.6, 46.3, 17.7. ESI-MS: *m/z* = 242.0 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{15}H_{16}NO_2$ $[M + H]^+$: 242.1179; found: 242.1176.