Tetrahedron Letters 52 (2011) 777–780

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New strategy for the synthesis of *N*-aryl pyrroles: Cu-catalyzed C–N cross-coupling reaction of *trans*-4-hydroxy-L-proline with aryl halides

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ARTICLE INFO

Article history:
Received 21 September 2010
Revised 2 December 2010
Accepted 4 December 2010
Available online 9 December 2010

Keywords:
Aryl halides
trans-4-Hydroxy-L-proline
N-Aryl pyrroles
Cross-coupling
Copper iodide

ABSTRACT

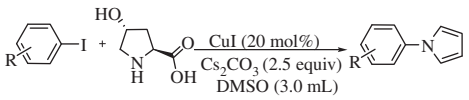
trans-4-Hydroxy-L-proline is used for the first time as an effective nucleophilic coupling partner with aryl halides mediated by copper iodide with Cs_2CO_3 as the base and DMSO as the solvent. Utilizing this protocol cross-coupling of *trans*-4-hydroxy-L-proline with a wide variety of substituted aryl halides to produce *N*-aryl pyrroles in moderate to good yields.

Pyrroles are an important class of organic compounds found in many natural products and bioactive molecules.[1] These compounds exhibit remarkable activities such as antitumor, immunosuppressant, anti HIV, anti inflammatory, antioxidant etc.[2] They have also been widely used in material science and molecular recognition studies.[3]

In view of their significance, several useful strategies have been developed for construction of the pyrrole moiety.[4–6] Conventional, protocols for their preparation include the cyclocondensation of primary amines with 1,4-dicarbonyl compounds[5] (Pall–Knorr reaction) or 2,5-dimethoxy tetrahydrofuran[7] and transition metal catalyzed coupling of aryl halides with pyrroles.[8] Despite these huge developments, the transition metal catalyzed cross-coupling reaction is considered to be the most attractive method for the synthesis of pyrroles. Recently Che and co-workers reported ligand-free CuCl-catalyzed C–N bond formation in 40% $^{n}Bu_4N^{+}OH^{-}$ aqueous solution.[9] In these reactions, the coupling between pyrroles and aryl halides is commonly involved. Since pyrrole is not a biomass resource, we have explored *trans*-4-hydroxy-L-proline (obtained from collagen[10]) as a sustainable replacement of pyrrole for synthesizing *N*-arylpyrroles.

Our recent report on β-CD catalyzed synthesis of pyrrole-substituted indolinones by using *trans*-4-hydroxy-L-proline[6c] prompted us to attempt *trans*-4-hydroxy-L-proline as a nucleophilic coupling partner in Cu catalyzed C–N cross-coupling reaction. In the course of our continuing investigations in the field of cross-coupling reactions,[11] we report, herein, a new approach for the synthesis of *N*-aryl pyrroles via C–N cross coupling of *trans*-4-hydroxy-L-proline with aryl halides catalyzed by CuI/Cs_2CO_3/DMSO at 110 °C for 24 h via an one-pot procedure (Scheme 1). To the best of our knowledge, this is the first protocol explored for the synthesis of *N*-aryl pyrroles *via* C–N cross-coupling of *trans*-4-hydroxy-L-proline with aryl halides.

Initially the reaction between *trans*-4-hydroxy-L-proline with iodo benzene was selected as a model reaction for optimizing the reaction conditions, such as various copper sources, bases, solvents, and temperature (Table 1). First, several copper catalysts were screened (Table 1, entries 1 and 10–14), and CuI was proven to be preeminent for this tandem reaction (Table 1, entry 5). Among various bases screened, KOH and Cs_2CO_3 provided the *N*-aryl pyrrole in moderate to excellent yields (Table 1, entries 3 and 5). Other bases such as NaOMe and K_3PO_4 gave lesser amount of the desired product (Table 1, entries 4 and 6). Among the solvents, DMSO yielded the best results whereas PEG gave the products in moderate yields (Table 1, entry 8) while solvents like toluene, water, and DMF were ineffective (Table 1, entries, 6, 7, and 9). The coupling reaction did not occur in the absence of catalyst (Table 1, entry 15) as well as the base (Table 1, entry 16). When



Scheme 1. CuI catalyzed synthesis of *N*-aryl pyrroles.

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doi:10.1016/j.tetlet.2010.12.016

Table 1
Screening of copper-catalyzed cross-coupling of aryl iodide with *trans*-4-hydroxy-L-proline[a]

Entry	Catalyst	Solvent	Base	T (°C)	Yield[b] (%)
1	CuI	DMSO	KOH	rt	0
2	CuI	DMSO	KOH	80	20
3	CuI	DMSO	KOH	110	46
4	CuI	DMSO	NaOMe	110	10
5	CuI	DMSO	Cs_2CO_3	110	94
6	CuI	Toluene	K_3PO_4	110	10
7	CuI	H_2O	Cs_2CO_3	110	Trace
8	CuI	PEG	Cs_2CO_3	110	60
9	CuI	DMF	Cs_2CO_3	110	20
10	CuO	DMSO	Cs_2CO_3	110	73
11	Cu_2O	DMSO	Cs_2CO_3	110	75
12	$CuCl_2{\cdot}2H_2O$	DMSO	Cs_2CO_3	110	85
13	$CuSO_4{\cdot}5H_2O$	DMSO	Cs_2CO_3	110	69
14	$Cu(OAc)_2{\cdot}H_2O$	DMSO	Cs_2CO_3	110	81
15	—	DMSO	Cs_2CO_3	110	0[c]
16	CuI	DMSO	—	110	0[d]

[a] Reaction conditions: iodobenzene (1.0 mmol), *trans*-4-hydroxy-L-proline (2.0 mmol), catalyst (20 mol %), base (2.5 equiv), solvent (3.0 mL), 24 h.
[b] Isolated yield.
[c] In the absence of catalyst.
[d] In the absence of base.

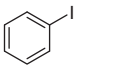
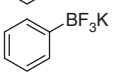
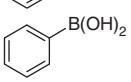
the reaction was conducted at room temperature and at 80 °C, the yields observed were very low (Table 1, entries 1 and 2). The ideal temperature for the reaction was found to be 110 °C.

We have also made a study of C–N cross coupling with various electrophiles under these conditions. Among these electrophiles iodo benzene yielded the best results whereas other electrophiles were ineffective (Table 2).

To explore the scope of this novel transformation, we examined the cross-coupling of various substituted iodo benzenes with *trans*-4-hydroxy-L-proline (Table 3).[12] In general, all the reactions were very clean, and the *N*-aryl pyrroles were obtained in high yields under the optimized conditions. The results have shown that substitution played a major role in governing the reactivity of the substrate.

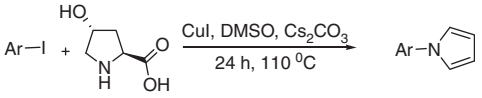
This protocol efficiently coupled iodo benzenes having electron donating groups (e.g., Me, Et, ^{t}Bu and OMe) with *trans*-4-hydroxy-L-proline to produce the corresponding products in excellent yields (Table 3, entries 2 and 4–7), whereas in the presence of electron withdrawing group (NO_2) a slight decrease in the yield of the *N*-aryl pyrroles (Table 3, entries 15–17) was observed. However, when sterically demanding ortho substituent is present in the aryl iodide, the corresponding *N*-aryl pyrroles were obtained in lower yields as compared to *meta* and *para* substituents (Table 3, entries 6–8 and 15–17) on the ring. Unfortunately, all attempts to couple 2-iodo 1,3-dimethyl benzene with *trans*-4-hydroxy-L-proline have failed (Table 3, entry 3). The reactivity of the iodo benzene moiety was confirmed by the chemoselective results obtained from the benzene substituted with mixed halides. The cross-coupling

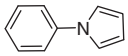
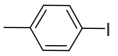
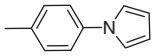
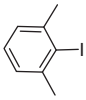
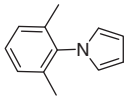
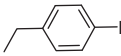
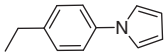
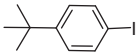
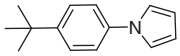
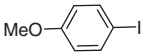
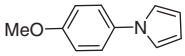
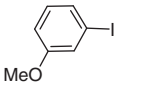
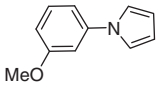
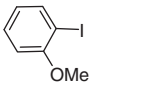
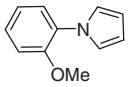
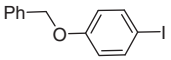
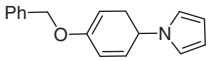
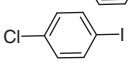
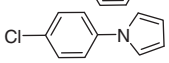
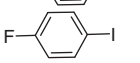
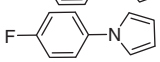
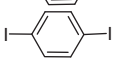
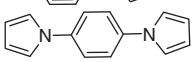
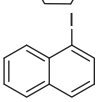
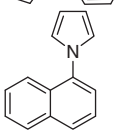
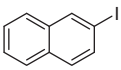
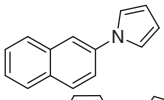
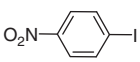
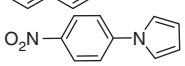
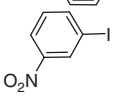
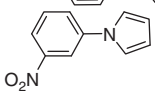
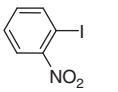
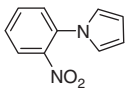
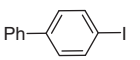
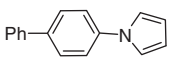
Table 2
Cu catalyzed C–N cross-coupling of *trans*-4-hydroxy-L-proline with different electrophiles[a]

Entry	Electrophiles	Yields[b] (%)
1		94
2		0
3		Trace

[a] Reaction conditions: electrophile (1.0 mmol), *trans*-4-hydroxy-L-proline (2.0 mmol) CuI (20 mol %), Cs_2CO_3 (2.5 equiv), DMSO (3.0 mL), 110 °C, 17 h.
[b] Isolated yield.

Table 3
N-Aryl pyrroles synthesis from various aryl iodides[a]



Entry	Aryl halide	Product	Yield[b] (%)
1			94 93[c]
2			86
3			0
4			89
5			84
6			92
7			89
8			70
9			89
10			86
11			84
12			81[d]
13			84
14			90
15			78
16			70
17			61
18			84
19			72
20			69

[a] Reaction conditions: aryl iodide (1.0 mmol), CuI (20 mol %), DMSO (3.0 mL), Cs_2CO_3 (2.5 equiv), *trans*-4-hydroxy-L-proline (2.0 equiv) 110 °C.
[b] Isolated yield.
[c] No difference in the yield was observed when 4-hydroxy proline was used.
[d] *trans*-4-Hydroxy-L-proline (4.0 equiv).

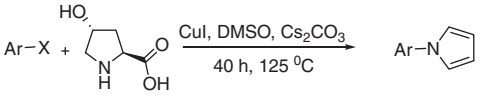
reaction takes place only on the carbon atom with the iodo substituent in the presence of fluoro and chloro (Table 3, entries 10 and 11). Utilizing these conditions, various hetero aromatic iodides were reacted with *trans*-4-hydroxy-L-proline to give the corresponding *N*-aryl pyrroles in encouraging yields (Table 3, entries 19 and 20).

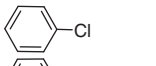
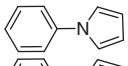
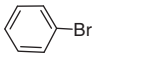
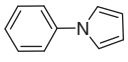
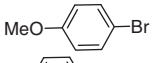
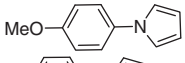
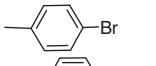
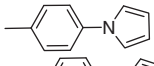
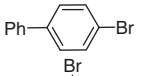
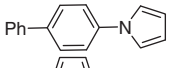
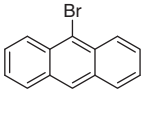
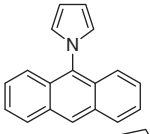
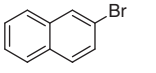
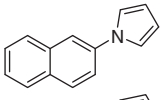
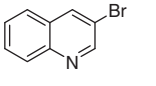
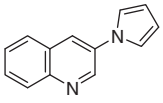
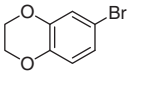
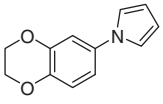
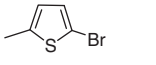
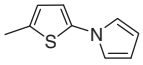
In order to evaluate the scope of the process with respect to the aryl halides, a variety of substituted aryl bromides and chlorides were tested under optimized conditions. In all of the cases the cross-coupling of aryl bromides with *trans*-4-hydroxy proline furnished the corresponding *N*-aryl pyrroles derivatives in moderate to good yields (Table 4).

However, the cross-coupling of various substituted aryl bromides with *trans*-4-L-hydroxy proline required longer reaction times and higher temperatures to get reasonable yields of *N*-aryl pyrrole, whereas shorter reaction times and lower temperatures led to decreased yields (Table 4, entry 2). Poor yields were observed in the coupling of *trans*-4-hydroxy-L-proline with aryl chlorides (Table 4, entry 1). Further more, C–N cross-coupling of heterocyclic bromides, such as quinoline, benzodioxane, and thiophene produced *N*-aryl pyrroles in moderate yields (Table 4, entries 8–10). Iodo benzene was found to be a more reactive substrate than chloro and bromo benzenes.

In conclusion, we have developed for the first time *trans*-4-hydroxy-L-proline as an effective nucleophilic coupling partner in Cu catalyzed C–N cross-coupling reaction with aryl halides to produce *N*-aryl pyrroles in moderate to good yields. The reaction outcome provides a new strategy for constructing *N*-aryl pyrroles from *trans*-4-hydroxy-L-proline. The operational simplicity, inexpensiveness, and ready availability of the metal catalyst should render this protocol attractive both from economic and industrial points of view as compared to the previous methodologies.

Table 4
N-Aryl pyrroles synthesis from various aryl halides[a]



Entry	Aryl halide	Product	Yield[b] (%)
1			15
2			70 48[c] 25[d]
3			64
4			61
5			60
6			57
7			67
8			54
9			51
10			59

[a] Reaction conditions: aryl halides (1.0 mmol), CuI (20 mol %), DMSO (3.0 mL), Cs_2CO_3 (2.5 equiv), *trans*-4-hydroxy-L-proline (2.0 equiv), 125 °C, 40 h.
[b] Isolated yield.
[c] 24 h.
[d] At 110 °C.

Acknowledgments

V.P.R. thanks the CSIR, A.V.K. thanks the UGC, New Delhi, for the award of fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.016.

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12. *General procedure for the synthesis of N-aryl pyrroles*: to a stirred solution of iodo benzene (1.0 mmol) and *trans*-4-hydroxy-L-proline (2.0 equiv) in dry DMSO (3.0 mL) at rt was added CuI (20 mol %) followed by Cs_2CO_3 (2.5 equiv) and heated at 110 °C for 24 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, and

a 1:1 mixture of ethyl acetate/water (20 mL) was added. The combined organic extracts were dried with anhydrous Na_2SO_4. The solvent and volatiles were completely removed under vacuum to give the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to afford the corresponding coupling product. The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopic analyses.

Data of representative examples: *1-phenyl-1H-pyrrole* (Table 3, *entry 1*): white solid; mp 58–61 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 4H), 7.24–7.17 (m, 1H), 7.05 (t, 2H, J = 2.66 Hz), 6.31 (t, 2H, J = 2.66 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.4, 125.3, 120.7, 119.2, 110.3.

1-(4-Ethylphenyl)-1H-pyrrole (Table 3, *entry 4*): white solid; mp 67–70 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, 2H, J = 8.02 Hz), 7.19 (d, 2H, J = 8.02 Hz), 7.008–7.004 (m, 2H), 6.28 (t, 2H, J = 2.26 Hz), 2.64 (q, 2H, J = 7.13 Hz), 1.25 (t, 3H, J = 7.13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 139.0, 128.8, 120.7, 119.1, 110.4, 28.4, 15.8; Anal Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.09; H, 7.57; N, 8.11.

1-(4-(Benzyloxy)phenyl)-1H-pyrrole (Table 3, *entry 9*): white solid; mp 102–105 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.21 (m, 8H), 6.95 (d, 2H, J = 8.30 Hz), 6.91 (q, 2H, J = 2.26 Hz), 6.22 (t, 1H, J = 2.26 Hz), 5.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 136.7, 134.6, 129.4, 128.5, 128.0, 127.4, 122.0, 120.9, 119.5, 115.7, 114.7, 109.8, 70.3; Anal Calcd for $C_{17}H_{15}NO$: C, 81.24; H, 6.06; N, 5.62. Found: C, 81.16; H, 5.98; N, 5.56.

1,4-Di(1H-pyrrol-1-yl)benzene (Table 3, *entry 12*): white solid; mp 234–238 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.41 (m, 4H), 7.00 (t, 4H, J = 2.06 Hz), 6.28 (t, 4H, J = 2.06 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 121.5, 119.2, 110.8; Anal Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.68; H, 5.74; N, 13.39.

1-(5-Methylthiophen-2-yl)-1H-pyrrole (Table 3, *entry 17*): white solid; mp 87–91 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.85 (t, 2H, J = 2.0 Hz), 6.62–6.61 (m, 1H), 6.52–6.51 (m, 1H), 6.19 (t, 2H, J = 2.0 Hz), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 133.9, 123.7, 121.2, 115.7, 110, 15.3; Anal Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58; S, 19.64. Found: C, 66.16; H, 5.48; N, 8.49; S, 19.56.

1-(Thiophen-2-yl)-1H-pyrrole (Table 3, *entry 18*): white solid; mp 75-78 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96–6.82 (m, 5H), 6.22–6.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 126.0, 121.3, 119.1, 115.4, 110.4; Anal Calcd for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.28; H, 4.65; N, 9.31; S, 21.41.

1-(Anthracen-9-yl)-1H-pyrrole (Table 4, *entry 6*): white solid; mp 149–153 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 7.99 (d, 2H, J = 7.76 Hz), 7.54–7.37 (m, 6H), 6.94 (t, 2H, J = 2.26 Hz), 6.44 (t, 2H, J = 2.26 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.4, 131.3, 129.1, 128.0, 127.2, 126.8, 125.6, 125.2, 124.4, 123.3, 108.8; Anal Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.76. Found: C, 88.79; H, 5.31; N, 5.69.

3-(1H-Pyrrol-1-yl) quinoline (Table 4, *entry 8*): white solid; mp 69-74 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.06 (d, 1H, J = 2.64 Hz), 8.11 (d, 1H, J = 8.98 Hz), 8.04–8.02 (m, 1H), 7.82–7.80 (m, 1H), 7.70–7.65 (m, 1H), 7.59–7.54 (m, 1H), 7.17 (t, 2H, J = 2.64 Hz), 6.39 (t, 2H, J = 2.64 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.5, 129.5, 128.9, 127.7, 127.4, 124.6, 119.4, 111.6; Anal Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.28; H, 5.11; N, 14.36.

1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1H-pyrrole (Table 4, *entry 9*): white solid; mp 94–97 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.90 (t, 2H, J = 2.07 Hz), 6.85–6.83 (m, 3H), 6.24 (t, 2H, J = 2.07 Hz), 4.27–4.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 141.5, 134.8, 119.5, 117.7, 113.7, 110.0, 109.9, 64.4, 64.2; Anal Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.55; H, 5.42; N, 6.89.