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Copper-catalyzed one-pot N-alkenylation and N-alkylation of amides: an efficient synthesis of substituted 2,3-dihydropyrroles

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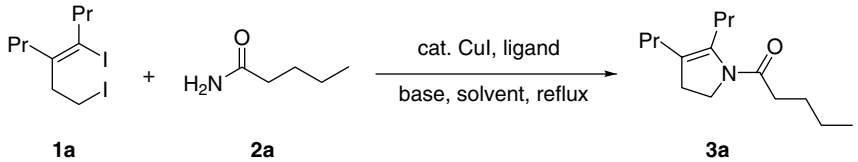
Abstract—A novel copper-catalyzed synthesis of substituted 2,3-dihydropyrroles via one-pot N-alkenylation and N-alkylation of amides with 1,4-diiodobut-1-ene derivatives has been developed. The reactions proceed in good to high yields using CuI as the catalyst, K_2CO_3 as the base, and *rac-trans-N,N′*-dimethylcyclohexane-1,2-diamine as the ligand.

Pyrrole or dihydropyrrole derivatives exhibit a variety of biological and medical properties.[1–3] Much efforts of synthetic chemists have been directed to the syntheses of this class of heterocycles.[4] Among them, the development of transition-metal-catalyzed C–N bond formation has received considerable attention. The key step for the synthesis of pyrrole derivatives mediated by transition metals is the construction of C–N bond either by N-alkenylation or by N-alkylation. A number of pioneering works have been reported concerning the C–N bond forming reaction using palladium.[5] In the past few years, copper-catalyzed aryl C–X bond (X = N, O, S, etc.) formation through coupling between aryl halides and heterocentered nucleophiles has provided an excellent complement to the palladium-catalyzed reactions.[6] More recently, this methodology has been successfully extended to the coupling reactions using allenyl halides,[6g] vinyl halides,[7] and iodoamides.[6h] Reports on N-alkenylation of amides have appeared in the literature.[6g,7,8] On the other hand, N-alkylation between amides or amines and alkyl halides is well documented.[9] Recently, we reported a copper-catalyzed double N-alkenylation of amides, which provided an efficient route for the synthesis of di- or trisubstituted N-acylpyrroles.[10] During the course of our studies on the copper-catalyzed C–N bond forming reactions, we envisaged that the dihydropyrrole derivatives could be accessed by the combination of N-alkylation and N-alkenylation starting from amides and 1,4-dihalobut-1-ene derivatives. This straightforward approach has not been explored previously, to the best of our knowledge. Herein we describe a novel synthesis of dihydropyrroles via copper-catalyzed N-heterocyclization between amides and 1,4-diiodobut-1-enes.

The requisite 1,4-diiodobut-1-ene derivatives **1** were conveniently synthesized through iodination of zirconacyclopentenes according to the reported procedure.[11] We started our investigation with (*Z*)-3-propyl-1,4-diiodohept-3-ene (**1a**). The reaction of **1a** with valeramide



1a **2a** **3a** (1)

Keywords: Copper catalyst; N-Alkenylation; N-Alkylation; Amides; Dihydropyrroles.
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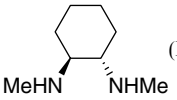
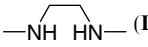
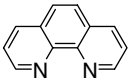
Table 1. Optimization of reaction conditions for the formation of **3a**

Entry	Ligand/mol %	CuX/mol %	Base (2 equiv)	Yield[a] (%)
1	 (**L1**)/10	Cu I/10	Cs_2CO_3	27[b]
2	**L1**/20	Cu I/20	Cs_2CO_3	53[c]
3	**L1**/20	Cu I/20	K_2CO_3	80
4	**L1**/10	Cu I/10	K_2CO_3	55
5	**L1**/10	Cu I/10	K_2CO_3	35[d]
6	None	Cu I/20	K_2CO_3	49
7	**L1**/20	Cu I/20	$NaHCO_3$	0
8	**L1**/20	Cu I/20	Triethylamine	4
9	**L1**/20	Cu CN/20	K_2CO_3	68
10	**L1**/20	Cu Cl/20	K_2CO_3	57
11	**L1**/20	Cu Br/20	K_2CO_3	48
12	L-Proline (**L2**)/20	Cu I/20	K_2CO_3	0
13	 (**L3**)/20	Cu I/20	K_2CO_3	63
14	 (**L4**)/20	Cu I/20	K_2CO_3	61

[a] Yields were determined by GC after hydrolysis. All these reactions were done for 48 h. Unless noted, all the reactions were carried out in toluene.
[b] (*Z*)-4-Iodo-5-vinyloct-4-ene(**4**) was obtained in 53% yield.
[c] **4** was obtained in 38% yield.
[d] 1,4-Dioxane was used as solvent.

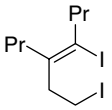
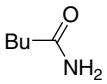
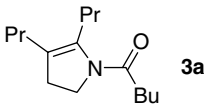
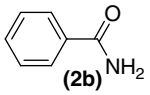
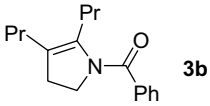
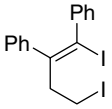
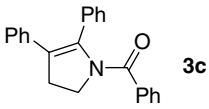
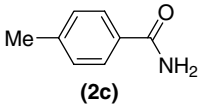
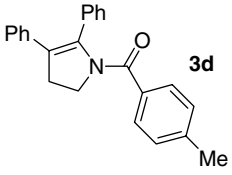
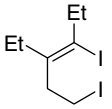
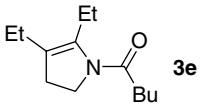
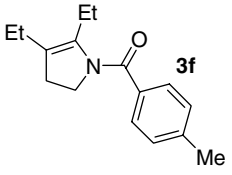
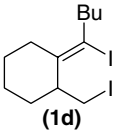
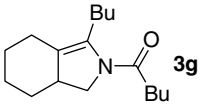
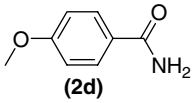
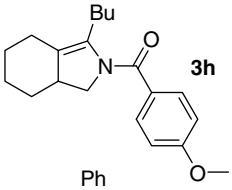
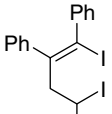
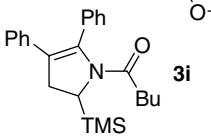
(**2a**) was selected as the prototypical case to optimize the reaction condition (Eq. 1). The results are summarized in Table 1. The original set of reaction conditions used included 10 mol % CuI, 10 mol % *rac-trans-N,N′*-dimethylcyclohexane-1,2-diamine (**L1**), and 2 equiv of Cs_2CO_3 in toluene at reflux. The corresponding dihydropyrrole (**3a**) was produced in only 27% yield (Table 1, entry 1) after 48 h along with 53% of (*Z*)-4-iodo-5-vinyloct-4-ene (**4**).[12] When both CuI and **L1** were increased to 20 mol %, **3a** was obtained in 53% yield with 38% of **4** (Table 1, entry 2). These results indicated the formation of **4** through elimination of HI presumably due to the strong basicity of Cs_2CO_3. As expected, 80% yield of **3a** was generated when a mild base such as K_2CO_3 was used in the reaction, and no formation of **4** was observed (Table 1, entry 3). When the amount of CuI and **L1** was lowered to 10 mol % using K_2CO_3 as the base, the yield of **3a** dropped substantially to 55% with 29% of **1a** remained (Table 1, entry 4). Changing the solvent to 1,4-dioxane, only 35% of **3a** was observed (Table 1, entry 5). Switching to a weaker base such as $NaHCO_3$, or organic base like triethylamine resulted in no coupling reaction or very low yield of the product (Table 1, entries 7 and 8). Other copper salts such as CuCN, and CuCl, CuBr gave the desired compound **3a** in 68%, 57%, and 48% yields, respectively (Table 1, entries 9–11).

It was demonstrated that certain copper ligands play important roles for rate accelerations in the coupling reactions. These ligands are regarded to increase catalyst solubility and stability and to prevent aggregation to the metal. Thus, we carried out ligand screen using 20 mol % of **L2**–**L4**, 20 mol % CuI as the catalyst, and 2 equiv of K_2CO_3 as the base in toluene. Three commercially available ligands, namely, L-proline (**L2**),*N*,*N′*-dimethylethane-1,2-diamine (**L3**), and 1,10-phenanthroline (**L4**) were evaluated for the coupling reaction, and the yields of the corresponding product were 0%, 63%, and 61%, respectively (Table 1, entries 12–14). It was clear that the optimized reaction condition was to use 20 mol % CuI in combination with 20 mol % *rac-trans-N,N′*-dimethylcyclohexane-1,2-diamine (**L1**), and K_2CO_3 as the base in toluene.

Having established an effective catalytic system for the coupling reaction, we explored the scope of the N-alkenylation and N-alkylation reaction under the optimized conditions. This CuI catalyzed one-pot N-heterocyclization reaction was applicable to a variety of amides and diiodides to furnish dihydropyrroles in good to high yields.[13] The representative results are depicted in Table 2. Coupling of **1a** with benzamide **2b** gave the corresponding dihydropyrroles **3b** in 64% yield (Table 2, entry 2). Diphenyl substituted diiodide **1b** reacted with **2b** to produce **3c** in 83% yield (Table 2, entry 3). This reaction is a useful method to synthesize dihydropyrroles with two aryl groups on adjacent positions, which may have interesting biological and pharmacological properties.[2] The coupling of **1b** with 4-methylbenzamide (**2c**) furnished the expected dihydropyrroles in 59% yield (Table 2, entry 4). Reaction of diethyl substituted diiodide **1c** with **2a** afforded **3e** in high yield (Table 2, entry 5). Likewise, the coupling of **1c** with **2c** gave the desired product in 75% yield (Table 2, entry 6).

When a diiodide **1d** fused with a six-membered ring was used, the reaction with **2a** or 4-methoxybenzamide (**2d**) occurred smoothly to produce the desired bicyclic dihydropyrroles in 69% or 59% yield, respectively (Table 2, entries 7 and 8). The coupling of (*E*)-(1,4-diiodo-3,4-

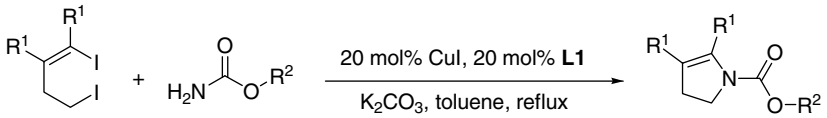
Table 2. Preparation of dihydropyrroles from amides and diiodobutenes

Entry	Diiodide	Amide	Product	Yield[a] (%)
1	 **(1a)**	 **(2a)**	 **3a**	80 (69)
2	(**1a**)	 **(2b)**	 **3b**	64 (46)
3	 **(1b)**	**2b**	 **3c**	83 (65)
4	**1b**	 **(2c)**	 **3d**	59 (47)
5	 **(1c)**	**2a**	 **3e**	84 (70)
6	(**1c**)	**2c**	 **3f**	75 (64)
7	 **(1d)**	**2a**	 **3g**	69 (57)
8	**1d**	 **(2d)**	 **3h**	59 (32)
9	 **(1e)** TMS	**2a**	 **3i**	59 (41)

[a] GC yields. Isolated yields are given in parentheses.

diphenylbut-3-enyl)trimethylsilane (**1e**) with **2a** furnished the expected dihydropyrroles in 59% yield, in which the trimethylsilyl group was well tolerated during the reaction (Table 2, entry 9).

To further expand the scope of the copper-catalyzed N-alkenylation and N-alkylation reaction, carbamates were employed in the reaction with diiodide under the optimized conditions. Treatment of **1a** with ethylcarb-



(2)

3j: R^1 = Pr, R^2 = Et, 63%

3k: R^1 = Ph, R^2 = Benzyl, 38%

amate led to 63% yield of **3j** (Eq. 2). The reaction of **1b** with benzyl carbamate resulted in the formation of **3k** in 38% yield.

In summary, we have developed a copper-catalyzed one-pot N-alkenylation and N-alkylation of amides or carbamates with diiodides. This method provides a facile route for the synthesis of 2,3-dihydropyrrole derivatives. Studies are under way to apply this coupling reaction to the synthesis of biologically active heterocycles in our group.

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13. A typical procedure for the preparation of dihydropyrroles: To a 20 mL Schlenk tube was charged with valeramide (101 mg, 1.0 mmol), CuI (38 mg, 0.2 mmol), and K_2CO_3 (276 mg, 2 mmol). After that, 8 mL of toluene was added, followed by *rac-trans-N,N′*-dimethylcyclohexyldiamine (0.032 mL, 28 mg, 0.2 mmol) and (*Z*)-3-propyl-1,4-diiodohept-3-ene (1.0 mmol). The reaction mixture was heated to 110 °C for 48 h. The reaction was cooled and quenched with aqueous $NaHCO_3$, extracted with ether (3×10 mL), washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purification of the residue with column chromatography on silica gel afforded the corresponding dihydropyrrole derivative **3a** as an orange oil (164 mg, 69%). ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.83 (t, $J = 5.1$ Hz, 3H), 0.84 (t, $J = 6.6$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H), 1.18–1.46 (m, 6H), 1.51–1.61 (m, 2H), 1.98 (t, $J = 7.2$ Hz, 2H), 2.19 (t, $J = 7.5$ Hz, 2H), 2.38 (t, $J = 8.7$ Hz, 2H), 2.52 (t, $J = 6.6$ Hz, 2H), 3.66 (t, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.67, 13.71, 13.73, 21.03, 22.24, 22.35, 26.83, 28.31, 29.11, 30.41, 35.69, 46.89, 120.87, 138.67, 169.22. HRMS for $C_{15}H_{28}NO$ $[M+H]^+$: Calcd 238.2171; found, 238.2165.