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Copper-Catalyzed Intramolecular *N*-Vinylation of Sulfonamides: General and Efficient Synthesis of Heterocyclic Enamines and Macrolactams

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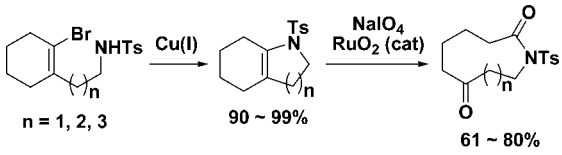

With the catalysis of CuI/*N*,*N*′-dimethylethylenediamine, intramolecular C−N coupling between sulfonamides and vinyl halides was successfully implemented, leading to the efficient synthesis of 5-, 6-, 7-, and even 8-membered heterocyclic enamines in both *exo* and *endo* modes. The bicyclic enamines thus formed provided a convenient entry to the corresponding 9- to 12-membered lactams by oxidative C═C bond cleavage.

Enamines are important synthetic intermediates.[1] Heterocyclic enamines, in particular, are powerful and versatile intermediates in the preparation of natural products and fused heterocyclic compounds.[2] The syntheses of heterocyclic enamines have been studied mainly with the use of *N*-heterocycles as the starting materials.[2] Methods by constructing a *N*-heterocyclic ring moiety are few[3−6] and dominated by dehydrative condensations where the selectivity has to be determined by thermodynamic factors.[3] The nondehydrative methods include the intramolecular addition of vinyl radicals to azomethine nitrogens,[4] the lanthanide-catalyzed intramolecular hydroamination of alkynes,[5] and the copper-catalyzed 1,2-double amination of 1-halo-1-alkynes recently reported by Urabe et al.[6] It is therefore highly desirable to develop efficient and general methods for the synthesis of heterocyclic enamines. Herein we report that 5-, 6-, 7-, and even 8-membered heterocyclic enamines in either *exo* or *endo* type can be conveniently and efficiently synthesized by copper-catalyzed intramolecular C−N coupling between sulfonamides and alkenyl halides.

The formation of aromatic C−N bonds via copper-catalyzed Ullmann coupling between aryl halides and N-centered nucleophiles has received considerable attention in the past few years.[7] The high stability and low costs of the copper catalysts enable these transformations to be a useful complement to the more extensively studied palladium-catalyzed processes.[8] By the appropriate choice of copper source, ligand, base, and solvent, these reactions have been developed to include a wide range of substrates under mild conditions. This methodology was successfully extended to the vinylic C−N bond formation and found important application in natural product synthesis.[9] We recently reported that, with the catalysis of CuI/*N*,*N*′-dimethylethylenediamine (DMEDA), *N*-(3-chloro-1-phenylbut-3-enyl)toluenesulfonamide **1** underwent efficient C−N coupling via a 4-*exo* ring closure to afford 2-alkylideneazetidine **2**, which could be readily converted to the corresponding β-lactam **3** by oxidation with O_3 (Scheme 1).[10] Our interest in Cu(I)-catalyzed intramolecular vinylation[10,11] urged us to extend this methodology to the formation of heterocyclic enamines of various sizes.

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SCHEME 1

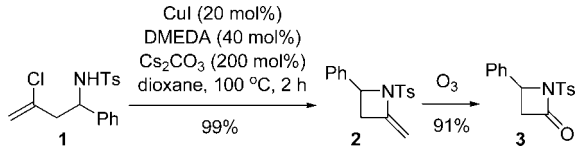

TABLE 1. Intramolecular *N*-Vinylation via *Exo* Modes

entry[a]	substrate	CuI (mol%)	temp / time (°C / h)[b]	product	yield (%)[c]
	X, NHTs			NTs	
1	**4a** (X = Cl)	20	100 / 4	**5a**	99
2	**4b** (X = Br)	10	68 / 2	**5a**	99
3	**4c** (X = I)	20	20 / 24	**5a**	92
4	Cl, NHMs, **4d**	20	100 / 4	NMs, **5d**	99
5	Cl, NHTs, **4e**	20	100 / 4	NTs, **5e**	99
6	Cl, NHTs, **4f**	20	100 / 4	NTs, **5f**	99
	X, NHTs			NTs	
7	**4g** (X = Cl)	20	100 / 144	**5g**	19
8	**4h** (X = Br)	10	68 / 8	**5g**	99
9	Br, O, NHTs, **4i**	10	68 / 8	NTs, O, **5i**	99
10	NHTs, O, Br, **4j**	50	68 / 12	NTs, O, **5j**	66

[a] Conditions: **4** (0.3 mmol), CuI/DMEDA = 1:2, solvent (10 mL), reflux. [b] 68, 100 and 153 °C refer to the refluxing temperatures of THF, dioxane, and DMF, respectively. [c] Isolated yield based on **4**.

N-(4-Chloropent-4-enyl)toluenesulfonamide (**4a**) was thus synthesized.[12] Our previous optimized conditions (20 mol % CuI, 40 mol % DMEDA, 200 mol % cesium carbonate, dioxane, reflux)[10] were directly applied. We were delighted to find that the starting material **4a** was all consumed within 4 h and the expected coupling product **5a** via a 5-*exo* ring closure was obtained in quantitative yield. Thus, a number of substrates of typical structures, which were readily prepared according to the literature procedures,[12] were tested and the results are summarized in Table 1. The iodide **4c** had the highest reactivity and its reaction took place even at room temperature (entry 3, Table 1). The vinyl bromide **4b** showed a higher reactivity than its chloro analogue **4a** (entry 2, Table 1). Methanesulfonamide **4d** had a similar behavior as toluenesulfonamide **4a**. With methyl or *gem*-dimethyl substitution (**4e** and **4f**), the expected cyclization products were also obtained quantitatively. The easy formation of **5a** and **5d**−**f** implied that the 5-*exo* ring closure is of comparable rate to the corresponding 4-*exo* ring closure,[10] which will be further discussed later.

TABLE 2. Intramolecular *N*-Vinylation via *Endo* Modes

entry[a]	substrate	CuI (mol%)	temp / time (°C / h)[b]	product	yield (%)[c]
1	Br, NHTs, **6a**	10	68 / 2	Ts, N, **7a**	99
2	Br, NHTs, **6b**	10	68 / 24	Ts, N, **7b**	NR[d]
3		30	100 / 3		91
4	Br, NHTs, **6c**	10	68 / 3	Ts, N, **7c**	99
5	Br, NHTs, **6d**	10	100 / 24	Ts, N, **7d**	NR[d]
6		40	100 / 3		96
7	Br, O, NHTs, **6e**	10	100 / 3	Ts, N, O, **7e**	90
8	Br, O, TsHN, **6f**	100	100 / 5	Ts, N, O, **7f**	22
9		20	153 / 48		62

[a] Conditions: **4** (0.3 mmol), CuI/DMEDA = 1:2, solvent (10 mL), reflux. [b] 68, 100 and 153 °C refer to the refluxing temperatures of THF, dioxane, and DMF, respectively. [c] Isolated yield based on **6**. [d] No reaction.

We then extended the strategy to the C−N bond formation via a 6-*exo* or 7-*exo* mode of cyclization. The prolonged reaction of **4g** in refluxing dioxane gave the expected enamine **5g** in only 19% yield while a large portion of the substrate **4g** was recovered (entry 7, Table 1). However, the cyclization of the bromo analogue **4h** proceeded smoothly in refluxing THF leading to the quantitative formation of **5g**. Substrate **4i** behaved similarly to **4h**. The 7-*exo* cyclization of **4j** was also successful, although a larger amount of the catalyst CuI was required and the product yield was lower (entry 10, Table 1). In all cases screened, the enamines **5** with an exocyclic double bond were obtained without isomerization, indicating the mildness of the copper-catalyzed method. The results in Table 1 also showed that the rate of cyclization follows the order of 4-*exo* ≈ 5-*exo* > 6-*exo* > 7-*exo*.

The above reactions dealt with the intramolecular C−N coupling via *exo* modes of cyclization. We then applied this methodology further to the cyclization via *endo* modes. To facilitate the *endo* cyclization, the vinylic halogen atom and the nitrogen-containing alkyl chain have to be in a (*Z*)-configuration. To avoid the possible contamination of the (*E*)-isomers, 2-substituted 1-bromocyclohexenes **6a**−**f** were chosen as the model substrates. These compounds were easily prepared from the readily available 1-bromo-2-bromomethylcyclohexene via conventional methods. The results are presented in Table 2. Sulfonamide **6a** underwent smooth cyclization in refluxing THF to afford the product **7a** quantitatively (entry 1, Table 2). This

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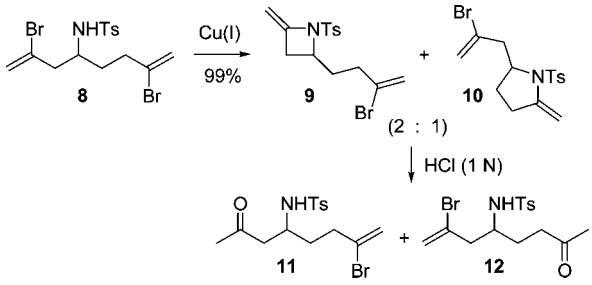
SCHEME 2

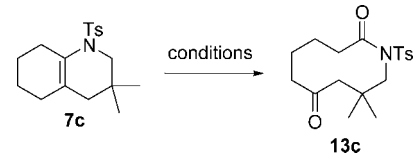


suggests that the 5-*endo* cyclization is of comparable rate to the 5-*exo* cyclization of **4b**. The 6-*endo* cyclization of **6b** was also successful, although it had to be conducted at a higher temperature (dioxane, reflux). The *gem*-dimethyl substitution in **6c** significantly facilitated the 6-*endo* cyclization (entries 2−4, Table 2). The 7-*endo* cyclization also turned out to be an efficient process as evidenced by the high yield generation of **7d** and **7e** (entries 6 and 7, Table 2). Furthermore, 8-*endo* cyclization was also possible (entries 8 and 9, Table 2). While the reaction of **6f** was sluggish in refluxing dioxane, a good yield of the 8-*endo* cyclization product **7f** could be achieved by simply raising the reaction temperature. The above results also indicated that the relative rate of cyclization follows the order of 5-*exo* ≈ 5-*endo* > 6-*endo* > 7-*endo* > 8-*endo*.

The results in Tables 1 and 2 clearly demonstrate that the intramolecular *N*-vinylation of sulfonamides with vinyl halides provides a convenient and general entry to heterocyclic enamines. In addition, the smaller the ring size, the easier the cyclization. We recently reported that the uncommon 4-*exo* ring closure is in fact fundamentally preferred in the intramolecular *O*-vinylation of alcohols.[11e] It is certainly of interest to see if this is also the case in the above *N*-vinylation. Thus, dibromide **8** was synthesized and subjected to the above C−N coupling conditions (THF, reflux, 2 h). ^{1}H NMR of the crude products indicated that the ratio of **9** (4-*exo*) to **10** (5-*exo*) was about 2:1 in favor of the 4-*exo* ring closure (Scheme 2). Since the enamines **9** and **10** were not very stable and difficult to separate by column chromatography on basic alumina, they were converted to the corresponding ketones **11** and **12** via hydrolysis in acidic conditions, which were then separated and characterized. The ratio of **11** to **12** (ca. 2:1) further confirmed our NMR analysis. Although the selectivity is not high, the 4-*exo* cyclization is still the most favored process. This phenomenon, in combination with our previous finding in *O*-vinylation,[11e] reveals the unique property of Cu(I) in cross-coupling reactions.

The bicyclic enamines **7** are unable to be produced by hydroamination of alkynes. The easy preparations of **7** via copper catalysis should expand the synthetic application of heterocyclic enamines. For example, the oxidative C=C bond cleavage of **7** could provide a facile entry to macrolactams, which are an important class of compounds not easily accessed by other methods. As an extension, the oxidation of **7** was also investigated here (Table 3). Ozonolysis of **7c** followed by treatment of PPh_3 failed to give any expected product.[13] Changing PPh_3 to thiourea[14] did not help. We then tried the oxidation with sodium periodate in aqueous methanol.[15] No reaction occurred even with the catalysis of ruthenium dioxide.

TABLE 3. Optimization of Conditions for the Oxidation of 7c



entry	conditions	yield (%)[a]
1	O_3, −78 °C; then PPh_3 (2.5 equiv), −78 °C to rt, 4 h	0
2	O_3, −78 °C; then $(NH_2)_2CS$ (1.3 equiv), $NaHCO_3$ (1.0 equiv), −78 °C to rt, 4 h	0
3	$NaIO_4$ (2.0 equiv), MeOH/H_2O, rt, 5 h	NR
4	$RuO_2 \cdot 2H_2O$ (3 mol %), $NaIO_4$ (2.0 equiv), MeOH/H_2O, rt, 5 h	NR
5	$RuO_2 \cdot 2H_2O$ (3 mol %), $NaIO_4$ (2.0 equiv), CCl_4/H_2O, rt, 5 h	37[b]
6	$RuO_2 \cdot 2H_2O$ (3 mol %), $NaIO_4$ (4.0 equiv), CCl_4/H_2O, rt, 5 h	80

[a] Isolated yield based on **7c**. [b] **7c** was recovered in 49% yield.

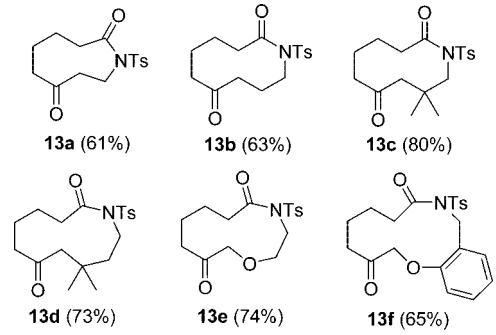


FIGURE 1. Synthesis of macrolactams **13** from cyclic enamines **7**.

However, when the oxidation was performed in CCl_4−H_2O mixture,[16] the ring enlargement product **13c** was obtained in 80% yield.

Thus, bicyclic enamines **7a**−**f** were subjected to the optimized conditions (entry 6, Table 3), respectively. We were glad to find that the expected 9- to 12-membered keto-lactams **13a**−**f** were obtained in satisfactory yields (Figure 1). Therefore, the copper-catalyzed C−N bond formation followed by subsequent oxidation offers a facile route to the synthesis of macrocyclic lactams. This methodology should find important application in natural product synthesis. For example, by further reduction, these keto-amides can be converted to macrocyclic amines, whose skeletons are embedded in a number of natural products such as protopine alkaloids[17] and isohaliclorensin.[18]

In summary, the chemistry detailed above has clearly demonstrated that the Cu(I)-catalyzed intramolecular C−N coupling of sulfonamides with vinyl halides is a highly efficient process, providing a convenient and general entry to heterocyclic enamines of various sizes in both *endo* and *exo* modes. Our investigations have also illustrated that the rate of cyclization decreases when the size of the ring closure increases. This finding allows the rational design of new synthetic strategies based on the vinylic C−N bond formation. As an extension, we have showed that, by oxidation with $NaIO_4$ under the catalysis of RuO_2, the bicyclic enamines thus synthesized offer

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an efficient and easy entry to the corresponding macrocyclic keto-lactams.

Experimental Section

Typical Procedure for the Cu(I)-Catalyzed Intramolecular C−N Coupling. The mixture of *N*-(3-chloro-1-phenylbut-3-en-1-yl)toluenesulfonamide (**4a**, 82 mg, 0.30 mmol), CuI (11 mg, 0.06 mmol), *N*,*N*′-dimethylethylenediamine (13 μL, 0.12 mmol), and Cs_2CO_3 (196 mg, 0.60 mmol) in dioxane (10 mL) was refluxed for 2 h under nitrogen atmosphere. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo and the crude product **5a** was essentially pure. It could be further purified by flash chromatography on basic alumina with hexane/EtOAc (4:1, v:v) as the eluent. Yield 70 mg (99%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.82 (2H, m), 2.33−2.40 (2H, m), 2.43 (3H, s), 3.66 (2H, t, J = 6.6 Hz), 4.24 (lH, s), 5.06 (1H, s), 7.30 (2H, d, J = 8.1 Hz), 7.76 (2H, d, J = 8.1 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5, 22.0, 32.8, 51.5, 90.4, 127.4, 129.4, 134.9, 143.8, 144.5; EIMS *m*/*z* (rel intensity) 237 (M^+, 18), 172 (46), 155 (10), 105 (59), 91 (100), 82 (63), 65 (49), 55 (44). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.34; H, 6.35; N, 5.59.

Typical Procedure for the Synthesis of Macrocyclic Lactams. The mixture of *N*-(3-(2-bromocyclohex-1-enyl)-2,2-dimethyl)-4-methylbenzenesulfonamide (**6c**, 400 mg, 1.0 mmol), CuI (19 mg, 0.10 mmol), *N*,*N*′-dimethylethylenediamine (22 μL, 0.20 mmol), and Cs_2CO_3 (652 mg, 2.0 mmol) in THF (30 mL) was refluxed for 3 h under nitrogen atmosphere. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo and the crude product **7c** (319 mg, ∼1.0 mmol), without further purification, was dissolved in CCl_4 (10 mL). The water (10 mL) solution of $NaIO_4$ (857 mg, 4.0 mmol) was added. $RuO_2 \cdot 2H_2O$ (5 mg, 0.03 mmol) was then added and the mixture was vigorously stirred at rt for 10 h. Isopropanol (10 mL) was then added to quench the reaction. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and then concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel with hexane/EtOAc (1:1, v:v) as the eluent to give the pure **13c** as a white solid. Yield 280 mg (80%); mp 162−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (6H, s), 1.83 (4H, br), 2.35−2.41 (6H, m), 2.41 (3H, s), 3.95 (2H, s), 7.28 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6, 23.7, 24.4, 27.8, 32.6, 36.6, 45.2, 47.1, 53.7, 128.3, 129.4, 136.6, 144.5, 174.6, 213.5; ESI-MS *m*/*z* 374 (M^+ + Na). Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.64; H, 7.25; N, 3.75.

***N*-(7-Bromo-2-oxooct-7-en-4-yl)-4-methylbenzenesulfonamide (11) and *N*-(2-Bromo-7-oxooct-1-en-4-yl)-4-methylbenzenesulfonamide (12).** The mixture of *N*-(2,7-dibromoocta-1,7-dien-4-yl)-4-methylbenzenesulfonamide (**8**, 219 mg, 0.50 mmol), CuI (10 mg, 0.05 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.10 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in THF (15 mL) was refluxed for 2 h under nitrogen atmosphere. The resulting mixture was cooled to room temperature and filtered. Aqueous hydrochloric acid (1 N, 2 mL) was added to the filtrate and the solution was stirred at rt for 1 h. Water (15 mL) was added and mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and then concentrated in vacuo. The resulting crude products were separated by column chromatography on silica gel with hexane/EtOAc (3:1, v:v) as the eluent to give the pure **11** (112 mg, 60% yield) and **12** (56 mg, 30% yield). **11**: colorless oil; IR (film) ν (cm^{-1}) 3281, 1714, 1159, 1093; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−1.80 (2H, m), 2.00 (3H, s), 2.25−2.45 (2H, m), 2.42 (3H, s), 2.47−2.61 (2H, m), 3.40−3.52 (1H, m), 5.33 (1H, s), 5.42 (1H, d, J = 9.3 Hz), 5.45 (1H, s), 7.29 (2H, d, J = 7.8 Hz), 7.72 (2H, d, J = 8.4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5, 30.7, 33.0, 37.9, 47.0, 49.5, 117.6, 127.0, 129.8, 132.9, 138.1, 143.5, 207.5; ESI-MS *m*/*z* 398/396 (M^+ + Na); HRMS calcd for $C_{15}H_{20}BrNO_3SNa$ (M^+ + Na) 396.0245, found 396.0239. **12**: colorless oil; IR (film) ν (cm^{-1}) 3278, 2925, 1714; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48−1.61 (1H, m), 1.79−1.83 (1H, m), 2.10 (3H, s), 2.30−2.64 (7H, m), 3.44−3.56 (1H, m), 4.95 (1H, d, J = 8.7 Hz), 5.34 (1H, s), 5.52 (1H, s), 7.29 (2H, d, J = 7.8 Hz), 7.74 (2H, d, J = 8.4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5, 27.3, 30.0, 39.5, 47.3, 52.1, 120.2, 127.1, 129.0, 129.6, 137.8, 143.4, 208.6; ESI-MS *m*/*z* 398/396 (M^+ + Na); HRMS calcd for $C_{15}H_{20}BrNO_3SNa$ (M^+ + Na) 396.0245, found 396.0239.

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Supporting Information Available: Characterizations of **4**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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