A Novel Synthesis of Isoindoline and Isoquinoline Using Chromium Carbene Complex

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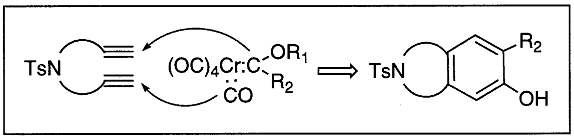
The reaction of diyne **1** which has nitrogen in a tether with chromium carbene complex **2** afforded isoindoline **4** in good yield. In this reaction, the two carbene carbons (carbene carbon of chromium carbene complex and carbon monoxide) reacted with the two alkynes, respectively, to form an aromatic ring, that is, [2+2+1+1] cocyclization. Using this procedure, isoquinoline derivatives, **6a**, **7a**, and **9a**, were synthesized.

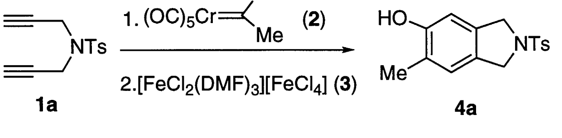
Cyclizations of diene, enyne, and diyne using transition metals are quite interesting. For that purpose, various transition metal complexes can be used. Previously, the enyne cyclization using chromium carbene complex was reported by our group.[1] Now we want to report the diyne cyclization using chromium carbene complex. In the diyne cyclization, two alkyne annulation[2] occurred, and a heterocycle fused aromatic ring was obtained by [2+2+1+1] cocyclization.

Scheme 1.



An CH_3CN solution (130mM) of **1a** and chromium carbene complex **2** was warmed at 70 °C for 1 h followed by treatment with $[FeCl_2(DMF)_3][FeCl_4]$[3] (**3**) to give isoindoline **4a** in 17% yield. The yield was improved to 59% when THF was used as the solvent and the reaction was carried out in a sealed tube (Table 1, run 3). By decreasing the concentration (6 mM), the yield of the desired product **4a** was increased (runs 4-5), because oligomerization and polymerization could be avoided. The addition of the ligands affected the yield of **4a**, and the usage of PPh_3[2c] or $P(OPh)_3$ increased the yield of the desired product, but DMAP (dimethylamino-pyridine) or PBu_3 was not a good ligand (runs 8-11).

Scheme 2.



The reaction of diyne **1b** having a methyl group on one of the two alkynes with chromium carbene complex **2** proceeded smoothly to produce isoindoline **4b** in 71% yield as a sole product. The various isoindolines having three substituents on the aromatic ring, **4c** and **4d**, were obtained in good yields. The stereochemistry of these products, **4b**, **4c**, and **4d**, respectively, was determined by NOE experiments as shown in Scheme 3. It means that chromium carbene complex **2** reacted firstly with the unsubstituted alkyne to afford chromium carbene complex **II**, because of steric demand. However, diyne **1e** which has an electron withdrawing group on the alkyne gave **4e** in 16% yield.

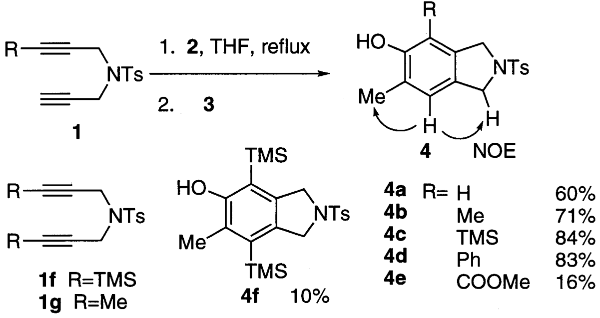
Table 1. Reaction of Chromium Carbene Complex with **1a**

Run	Solvent	Temp.(°C)	Time (h)	Conc.(mM)	Additive	Yield (%)
1	CH_3CN	70	1	130	—	17
2	Benzene	70	4	130	—	31
3	THF	reflux	3	130	—	59[a]
4	THF	reflux	3	130	—	40
5	THF	reflux	2	13	—	56
6	THF	reflux	1	6	—	57 (60)[b]
7	THF	reflux	1	6	PPh_3[c]	71[b]
8	THF	reflux	1	6	—[d]	74
9	THF	reflux	1	6	DMAP[c]	19[b]
10	THF	reflux	1	6	$P(OC_6H_5)_3$[c]	71[b]
11	THF	reflux	1.5	6	PBu_3[c]	27[b]

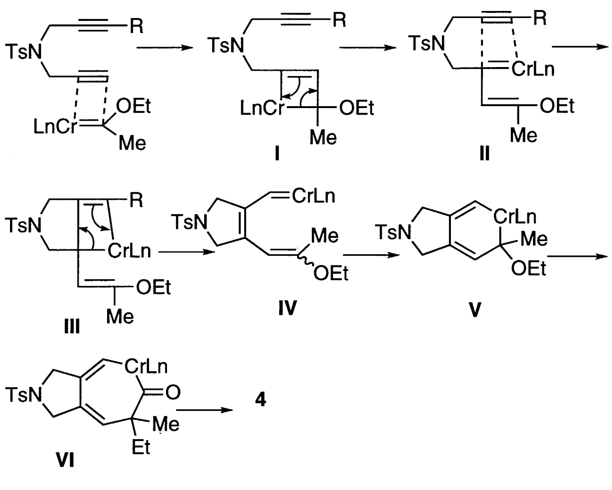
[a] in a sealed tube. [b] **2**; 2 equiv. [c] Ligand; 4 equiv.
[d] The solution of **2** and PPh_3 (4 equiv.) in benzene and hexane (1/1) was refluxed for 15 h and then solvent was removed. To the residue was added **1a** in THF and the solution was refluxed for 1h.

The reaction of disubstituted diyne **1f** with **2** afforded only 10% of cyclized product **4f**, and two alkyne annulation did not occur in the case of diyne **1g**.

Scheme 3.

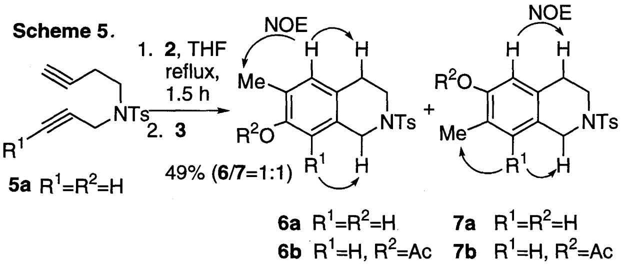


Scheme 4. Possible Reaction Course



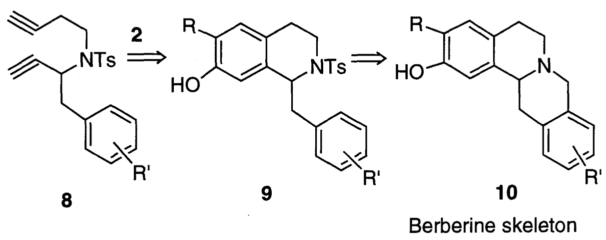
Subsequently, isoquinoline was synthesized using two alkyne annulation. The reaction of **5a** with chromium carbene complex **2** in a similar manner followed by treatment with **3** gave isoquinoline **6a** and **7a** in 49% yield in a ratio of 1 to 1 as an inseparable mixture.[4] Acetylation of a mixture of **6a** and **7a** afforded a separable mixture of **6b** and **7b**. The respective structures of **6b** and **7b** were determined by NOE experiments as shown in Scheme 5.

Scheme 5.

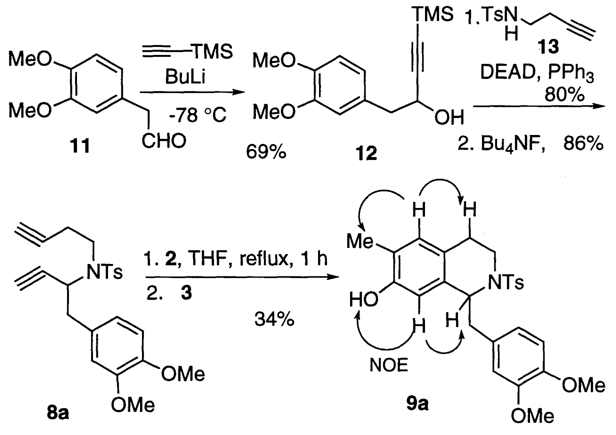


On the basis of these results, it was tried to synthesize berberine skeleton by use of two alkyne annulation. Our plan for the synthesis of berberine skeleton is shown in Scheme 6. The starting material **8a** was prepared from 3,4-dimethoxyphenyl acetaldehyde **11**. The reaction of **11** with lithium TMS acetylide afforded alcohol **12** in 69% yield. Condensation of **12** with tosylamide **13** using the Mitsunobu reaction[5] followed by treatment with Bu_4NF gave diyne **8a** in good yield. When a THF solution of diyne **8a** (6 mM) and chromium carbene complex **2** was refluxed for 1 h followed by treatment with **3**, it afforded isoquinoline **9a** in 34% yield as a sole product, whose stereochemistry was determined by NOE experiments.

Scheme 6.



Scheme 7.



Isoquinoline **9a** could easily be converted into papaverine analogue or berberine skeleton.

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References and Notes

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3 S. Tobinaga and E. Kotani, *J. Am. Chem. Soc.*, **94**, 309 (1972).

4 In the isoquinoline synthesis, the diyne having substituents on the one of alkyne decreased the yield of the desired product (R^1=Me, 17%; R^1=TMS, 10%; R^1=Ph, 9%).

5 The Mitsunobu Reaction: D. L. Hughes, *Organic Reactions*, **42**, 335 (1992).