Synthesis of Tetra- and Penta-Substituted Pyrrole Derivatives from Azazirconacyclopentene and Acyl Halide in the Presence of CuCl

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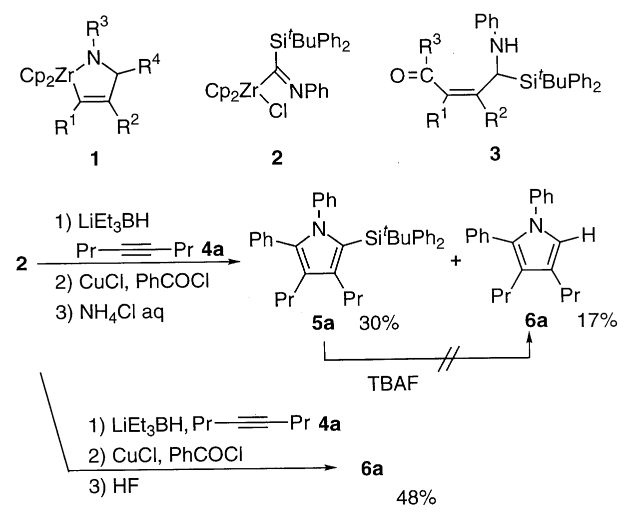
Tetra- and penta-substituted pyrrole derivatives **5** and **6** were synthesized from acyl halide and azazirconacyclopentene **1**, prepared from iminosilaacyl complex **2** and alkyne **4** in the presence of $LiEt_3BH$, by transmetalation of zirconium to copper by a one-pot reaction.

Azazirconacyclopentene **1**, prepared by insertion of alkyne **4** into azazirconacyclopropane, is useful in synthetic organic chemistry.[1,2] Using transmetalation of azazirconacyclopentene **1** to other metals, new carbon-carbon bond was formed.[2c]

Previously, we reported the synthesis of azazirconacyclopentene **1** from iminosilaacyl complex **2**, and alkyne **4** in the presence of $LiEt_3BH$ *via* azazirconacyclopropane.[2a] From this azazirconacyclopentene **1**, a carbon-carbon bond was formed using transmetalation of **1** into copper complex followed by treatment with alkyl halide .[2c]

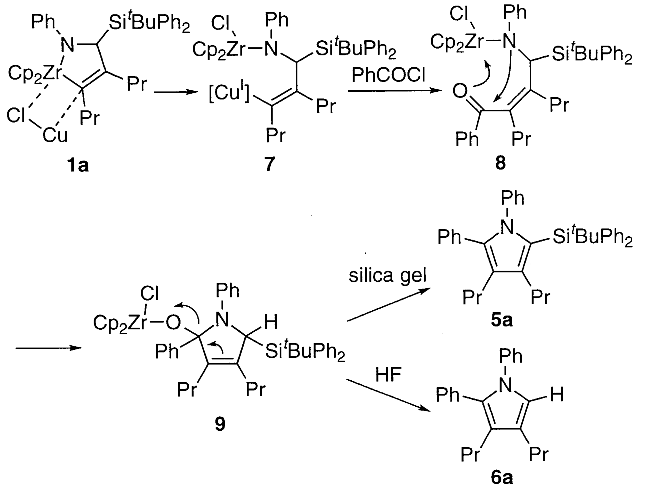
It was expected that the reaction of **1** with acyl halide in the presence of copper complex to give α,β-unsaturated ketone **3**. However, we obtained pyrrole derivatives. Here we report the synthesis of tetra- and penta-substituted pyrrole derivatives **5** and **6** from azazirconacyclopentene **1** and acyl halides.



Scheme 1.

To an ethereal solution of iminosilaacyl complex **2** (1 equiv.), prepared from silylzirconium complex and phenyl isonitrile, and 4-octyne **4a** (2 equiv.) was added a solution of $LiEt_3BH$ (2 equiv.) and the solution was stirred at room temperature for 14 h. The solution was then added to an ethereal solution of benzoyl chloride (2 equiv.) and CuCl (2 equiv.), and the solution was stirred overnight. After the usual workup, pyrrole derivatives **5a** and **6a** were obtained[4] in yields of 30% and 17%, respectively. In order to determine the structure of these derivatives, **5a** was treated with Bu_4NF, but the starting material was recovered unchanged. This means that the desilylation would occur during purification. As it was thought that the crude product changed into the pyrrole derivatives during silica gel column chromatography, to an ether solution of the reaction mixture was added silica gel and the solution was stirred at room temperature for 30 min. The penta-substituted pyrrole derivative **5a** was obtained in 59% yield as a sole product after usual workup (Table1, run 1).[5]

The possible reaction course for the formation of pyrrole is shown in Scheme 2. Transmetalation of zirconium into copper occurs to give complex **7**, which reacts with benzoyl chloride to give **8**. Then, zirconium of **8** migrates from nitrogen to oxygen to give nitrogen anion, which attacks the carbonyl carbon to give pyrrolidine derivative **9**. Treatment of **9** with silica gel should give pyrrole derivative **5a**. If fluoride anion attacks the silyl group of complex **9**, desilylated pyrrole would be formed. As expected, the crude product was treated with HF to give tetra-substituted pyrrole **6a** in 48% yield as a sole product.



Scheme 2. Possible Reaction Mechanism

In a similar manner, various penta-substituted and tetra-substituted pyrrole derivatives **5** and **6** were obtained in good to moderate yields (Table 1). When trimethylsilylpropyne was used as alkyne, the trimethylsilyl group was removed to give **14**. The use of acetyl chloride as acyl halide did not give the desired pyrrole derivative.

When cinnamoyl chloride was used as acyl halide, tetra-substituted benzene derivative **11** was obtained in 24% yield. In this case, a carbon-carbon bond forming reaction occurs to give **12**, whose silyl group migrates from carbon to oxygen. Then, cyclization followed by deamination occurs to give **11** *via* **13**.

A catalytic amount of CuCl was effective for this reaction and

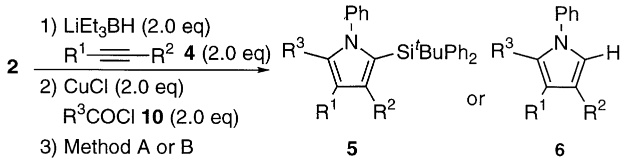
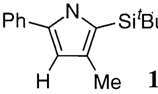


Table 1. Synthesis of Pyrrole Derivative from **2** and alkyne **4**

						Yield/%	
run	R^1	R^2	R^3COCl		Method	**5**	**6**
1	Pr	Pr	PhCOCl	**10a**	A	59	
2	Pr	Pr	PhCOCl	**10a**	B		48
3	Et	Et	PhCOCl	**10a**	A	48	
4	TMS	Me	PhCOCl	**10a**	A	37[a)]	
5	Pr	Pr	4-Me-C_6H_4COCl	**10b**	A	59	
6	Pr	Pr	4-Me-C_6H_4COCl	**10b**	B		62
7	Pr	Pr	4-MeO-C_6H_4COCl	**10c**	A	51	
8	Pr	Pr	4-MeO-C_6H_4COCl	**10c**	B		37
9	Pr	Pr	4-$MeOCOC_6H_4COCl$	**10d**	A	43	
10	Pr	Pr	4-$MeOCOC_6H_4COCl$	**10d**	B		26
11	Pr	Pr	4-Cl-C_6H_4COCl	**10e**	A	63	
12	Pr	Pr	4-Cl-C_6H_4COCl	**10e**	B		26
13	Pr	Pr	2-Furoyl chloride	**10f**	A	23	
14	Pr	Pr	${}^tBuCOCl$	**10g**	A	22	

Method A ; Crude product was treated with silica gel.
Method B ; Crude product was treated with HF.
a) Desilylated product **14** was obtained.



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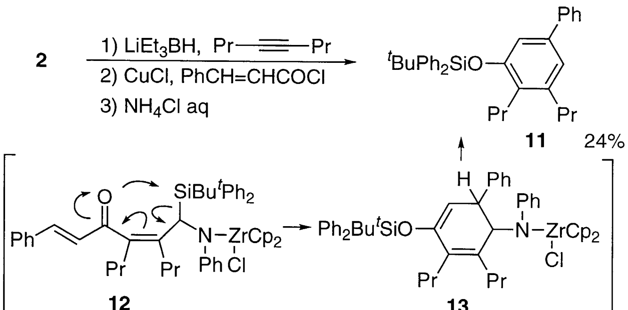
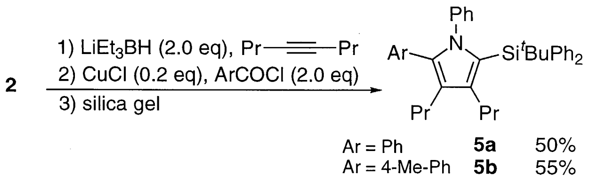


Scheme 3.



Scheme 4.

penta-substituted pyrroles **5a** and **5b** were obtained in moderate yields.

These results indicate that tetra- and penta-substituted pyrrole derivatives are formed by a one-pot reaction following the addition of the acyl group and silylimino group onto two alkyne carbon, respectively.

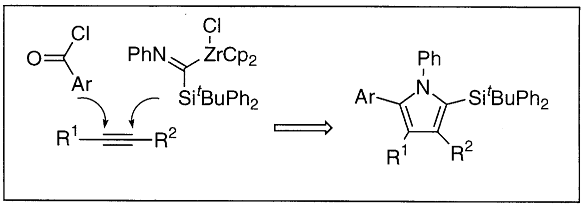


Figure 1. Tetra- and penta-substituted pyrrole synthesis from alkyne

References and Note

1 a) M. Jensenand, T. Livinghouse, *J. Am. Chem. Soc.*, **111**, 4495 (1989); b) H. Ito, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.*, **33**, 4469 (1992); c) S. L. Buchwald, and M. W. Wannamaker, *J. Am. Chem. Soc.*, **111**, 776 (1989); d) R. B. Grossman, W. M. Davis, and S. L. Buchwald, *J. Am. Chem. Soc.*, **113**, 2321 (1991); e) J. M. Davis, R. J. Whitby, and A. Jaxa-Chamiec, *Tetrahedron Lett.*, **33**, 5655 (1992); f) M. C. J. Harris, R. J. Whitby, and J. Blagg, *Tetrahedron Lett.*, **36**, 4289 (1995).

2 a) T. Honda, S-ich.Satoh, and M. Mori, *Organometallics*, **14**, 1548 (1995); b) T. Honda and M. Mori, *J. Org. Chem.*, **61**, 1196 (1996); c) T. Honda and M. Mori, *Organometallics*, **15**, 5464 (1996).

3 Transmetalation of zirconacycle to copper complex: a) T. Takahashi, M. Kotora, K. Kasai, and N. Suzuki, *Organometallics*, **13**, 4183 (1994); b) K. Kasai, M. Kotora, N. Suzuki, and T. Takahashi, *J. Chem. Soc., Chem. Commun.*, **1995**, 109; c) T. Takahashi, M. Kotora, and Z. Xi, *J. Chem. Soc., Chem. Commun.*, **1995**, 361; d) T. Takahashi, R. Hara, Y. Nishihara, and M. Kotora, *J. Am. Chem. Soc.*, **118**, 5154 (1996); e) T. Takahashi, M. Kotora, and Z. Xi, *J. Chem. Soc., Chem. Commun.*, **1995**, 1503; f) T. Takahashi, Z. Xi, M.Kotora, and C. Xi, *Tetrahedron Lett.*, **37**, 7521 (1996); g) B. H. Lipshutz, and M. Segi, *Tetrahedron*, **51**, 4407 (1995); h) P. Wipf, and H. Jahn, *Tetrahedron*, **52**, 12853 (1996).

4 Formations of pyrrole ring using zirconium complex[1c] and titanium complex[4] were reported. Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.*, **43**, 7787 (1996).

5 Typical Peocedure: To a suspension of iminosilacyl complex **2** (50.0 mg, 83.4 μmol) in Et_2O (1.0 mL) was added 4-octyne (25 μL, 170 μmol) and $LiEt_3BH$ (1.0 mol dm^{-1} THF solution, 0.17 mL, 170 μmol) at 0 °C. After stirring at room temperature for 14 h, the solution was added to a solution of CuCl (16.5 mg, 167 μmol) and PhCOCl in Et_2O (0.5 mL)and the whole solution was stirred at room temperature for 24 h. To this solution was added Et_2O (1 mL) and silica gel (Merk silica gel 60, 70~230 mesh ASTM, 500 mg) and the suspension was stirred at room temperature for 30 min. The reaction mixture was filtered and filtrate was washed with sat. NH_4Claq.and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flush column chromatography on silica gel (hexane/Et_3N, 99/1) to give colorless crystals of **5a** (29.8 mg, 59 %).