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Synthesis of Substituted Pyrroles from an Alkyne, an Imine and Carbon Monoxide via an Organotitanium Intermediate

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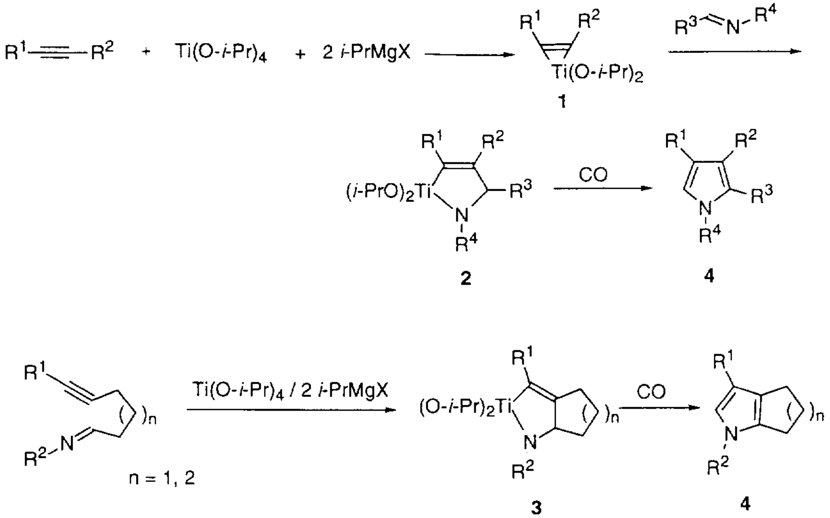
Abstract: *Azatitanacyclopentene complexes **2** react with carbon monoxide under atmospheric pressure to afford pyrroles in good to excellent yields, thus providing a convenient and general method for synthesis of substituted pyrroles from an alkyne, an imine and carbon monoxide.* Copyright © 1996 Elsevier Science Ltd

In 1989, Buchwald and co-workers reported on the synthesis of substituted pyrroles using zirconocene complexes of imines which can be readily prepared from zirconocene dichloride and primary amines.[1] Thus, the reaction of the zirconium-imine complexes with alkynes furnished azazirconacyclopentenes which, in turn, reacted with carbon monoxide (CO) to afford pyrroles after aqueous workup. Their work opened up a convenient way to synthesize pyrroles from a primary amine, an alkyne and carbon monoxide in a one-flask operation. However, high-pressure carbon monoxide was required to accomplish the reaction; the reaction was best performed at a pressure of 1500 psi of carbon monoxide.

We have recently reported that titanium-acetylene complexes **1**[2] generated *in situ* from acetylenes, Ti(O-*i*-Pr)$_4$ and *i*-PrMgX (X = Cl or Br) react with imines to afford azatitanacyclopentenes **2**.[3] We have also reported on the synthesis of bicyclic azatitanacyclopentenes **3** from unsaturated imines, Ti(O-*i*-Pr)$_4$ and *i*-PrMgX.[4] In this communication we report that these complexes **2** and **3** react with carbon monoxide *under atmospheric pressure* to provide the corresponding pyrroles **4** , thus providing a new, efficient entry to a variety of substituted pyrroles from an alkyne, an imine and carbon monoxide (Scheme 1).[5]

When **2b** (**2**; $R^1 = SiMe_3$, $R^2 = C_6H_{13}$, $R^3 = Ph$, $R^4 = C_3H_7$) in ether was carbonylated under atmospheric pressure of CO at room temperature for 24 h, N-propyl-2-phenyl-3-hexyl-4-trimethylsilylpyrrole (**4b**) was isolated in 71% yield after usual workup and chromatography. No deuterium incorporation resulted in the reaction of **2b** with CO and the following treatment with D_2O. These results prompted us to propose the mechanistic rationale shown in Scheme 2 to account for the formation of pyrroles. Insertion of CO into the Ti-C bond of **2** would produce the metallacycle **5**.

Scheme 1



Migration of the nitrogen atom from titanium to the acyl carbon would produce the titanium complex **6**. Intermediate **6** may undergo prototropic rearrangement induced by the *i*-PrO anion (generated by the reaction of Ti(O-*i*-Pr)$_4$ with *i*-PrMgCl) to give **7** which affords pyrrole **4** by alcoholysis with *i*-PrOH produced *in situ.*[6]

Scheme 2

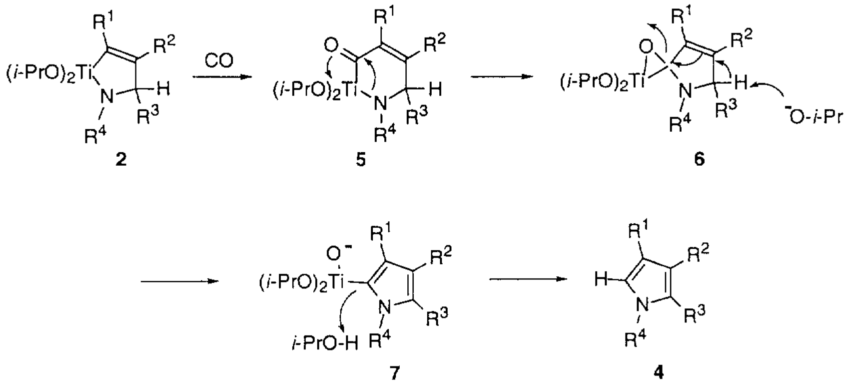
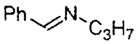
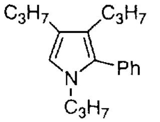
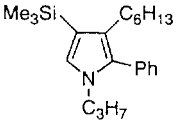
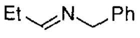
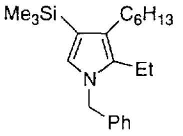
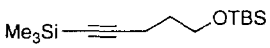
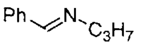
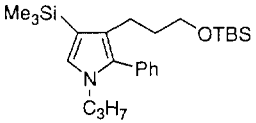
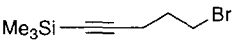
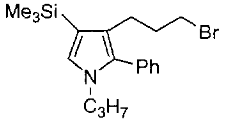
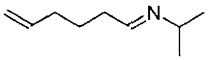
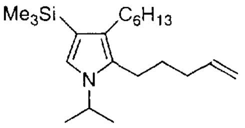
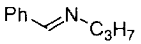
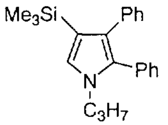
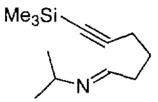
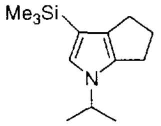
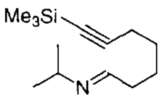
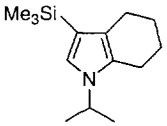


Table 1 summarizes the results of the reaction of a variety of **2** and **3** with carbon monoxide. It should be noted that the entire reaction sequence was performed in a one-flask operation starting from an alkyne starting material.[7] As can be seen, a variety of trisubstituted pyrroles including dihydrocyclopenta- and tetrahydrocyclohexa-[*b*]pyrrole derivatives (entries 8 and 9) can be easily synthesized in good to excellent yields. That the reaction sequence will tolerate a variety of functional

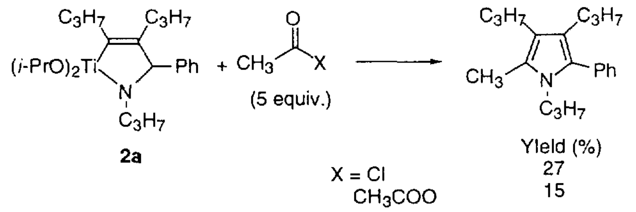
Table 1. One-pot synthesis of substituted pyrroles from an alkyne, an imine and carbon monoxide via **2** or **3**[a]

Entry	Alkyne	Imine	2 or 3	Pyrrole (**4**)	Yield (%)[b]
1	$C_3H_7-\equiv-C_3H_7$		**2a**		61
2	$Me_3Si-\equiv-C_6H_{13}$	"	**2b**		71
3	"		**2c**		74
4			**2d**		64
5		"	**2e**		63
6	$Me_3Si-\equiv-C_6H_{13}$		**2f**		67
7	$Me_3Si-\equiv-Ph$		**2g**		76
8			**3a**		84
9			**3b**		82

[a] The reaction was carried out with reactant ratio of alkyne:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl:imine =1:1.2:2.4:0.8 for entries 1~7 and acetylenic imine:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl = 1:1.2:2.4 for entries 8 and 9, see ref. 7. [b] Isolated yield based on the imine.

groups is demonstrated by entries 4, 5 and 6. Thus, it is possible to prepare pyrroles containing siloxy, bromo and olefinic substituents.[8]

In connection with the present finding, we report next that the complexes **2** also afford pyrroles by a reaction with carboxylic acid derivatives. Thus, as shown in eq. 1, **2a** reacted with an excess (5 equiv) of acetyl chloride or acetic anhydride to afford the corresponding pyrrole. However, since the reaction necessitated an excess amount of the acid derivative and the yield was low, it seems to be of little value from the synthetic point of view.



(1)

In summary, we have developed a convenient and general method for the formation of substituted pyrroles from an alkyne, an imine and carbon monoxide. The reaction is highly practical since the reaction uses nontoxic, commercially available inexpensive metallic reagents (Ti(O-*i*-Pr)$_4$ and *i*-PrMgX), and the reaction procedure is operationally simple.

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6. Similar zirconium intermediates corresponding to **5** and **6** were postulated for the reaction of azazirconacyclopentenes with CO by Buchwald, see: reference 1.
7. The following procedure is typical: To a stirred solution of Ti(O-*i*-Pr)$_4$ (0.239 g, 0.84 mmol) and 1-trimethylsilyl-1-octyne (0.128 g, 0.70 mmol) in ether (6 mL) was added a 1.16 M ethereal solution of *i*-PrMgCl (1.45 mL, 1.68 mmol) at -78 °C. The reaction mixture was warmed to -50 °C over 0.5 h and stirred at the same temperature for 2 h, and then *N*-bezylidene propylamine (0.082 g, 0.56 mmol) was added. The reaction mixture was stirred for 1 h at -50 °C and was gradually warmed to -20 °C over 2 h. Then the solution was exposed to CO with aid of a balloon and allowed to react at room temperature for 24 h. The reaction was terminated by dropwise addition of water (2 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether (10 mL x 3). The combined organic layer was dried on MgSO$_4$ and concentrated to an oil, which was chromatographed on silica gel to afford *N*-propyl-2-phenyl-3-hexyl-4-trimethylsilylpyrrole (0.136 g, 71%).
8. For review on the synthesis of pyrroles, see: Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry;* Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon Press: Mew York, 1984, Vol. 4.

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