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Synthesis of 1,5-Dihydro-2*H*-pyrrol-2-ones from an Alkyne, an Imine and Carbon Dioxide *via* an Organotitanium Intermediate

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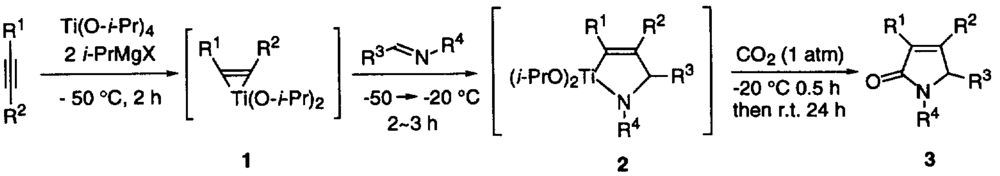
Abstract: *Azatitanacyclopentene complexes 2 react with carbon dioxide under atmospheric pressure to afford 1,5-dihydro-2H-pyrrol-2-ones, thus providing a one-pot procedure for synthesizing a variety of 1,5-dihydro-2H-pyrrol-2-ones from an alkyne, an imine and carbon dioxide under mild conditions.*

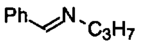
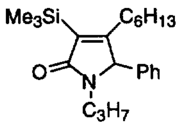
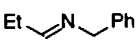
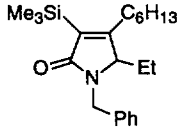
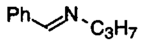
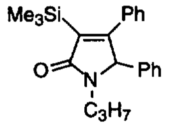
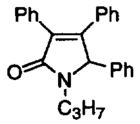
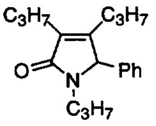
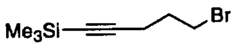
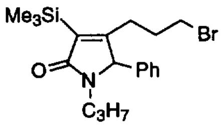
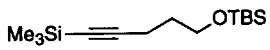
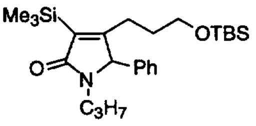
The use of transition metals for the preparation of heterocyclic compounds has increased in recent years due in part to the fact that organometallic transformations can be selective and efficient processes.[1] In this communication we report a new method for synthesizing substituted 1,5-dihydro-2*H*-pyrrol-2-ones (3-pyrrolin-2-ones) from an alkyne, an imine and carbon dioxide (CO_2) *via* an organotitanium intermediate.

Recently, we have reported that titanium-alkyne complexes (η^2-alkyne)Ti(O-*i*-Pr)$_2$ (**1**) can be readily prepared from alkynes and Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgX reagent.[2] In the course of our studies for utilizing **1** in organic synthesis, we have observed that they react with imines to give azatitanacyclopentene complexes **2**,[3,4] and which, in turn, react with carbon monoxide (CO) to provide pyrroles.[5] The production of pyrroles can be explained by assuming insertion of CO into the titanium-carbon bond of **2** which was followed by migration of the nitrogen atom from titanium to the acyl carbon. Precedents for insertion of carbon dioxide (CO_2) into a titanium-carbon bond[6] prompted us to investigate the reaction of **2** with CO_2 which we anticipated would afford 3-pyrrolin-2-ones **3**.

When the compound **2**, generated *in situ* in ether, was exposed to atmospheric pressure of CO_2 (from cylinder through calcium chloride) at -20 °C to room temperature for 0.5 h and then for 24 h at room temperature, 3-pyrrolin-2-one **3** was obtained, as expected, in moderate to excellent yield after usual workup and column chromatography on silica gel. The results are summarized in Table 1.[7] It should be noted that the entire reaction sequence was performed in a one-flask operation starting from an alkyne starting material. As can be seen from Table 1, an efficient and general synthetic method for synthesizing a variety of 3-pyrrolin-2-ones **3** from readily available alkynes, imines and CO_2 has been developed. That the reaction sequence will tolerate some functional groups is demonstrated by entries 6 and 7. Thus, the reaction allows the preparation of 1,5-dihydro-2*H*-pyrrol-2-ones containing bromo and siloxy substituents.

Table 1. One-pot synthesis of substituted 1, 5-dihydro-2*H*-pyrrol-2-ones from an alkyne, an imine and carbon dioxide via **2**[a]



Entry	Alkyne	Imine[b]	3-Pyrrolin-2-one (**3**)	Yield (%)[c]
1	$Me_3Si-C\equiv C-C_6H_{13}$			77
2	"			67
3	$Me_3Si-C\equiv C-Ph$			65
4	$Ph-C\equiv C-Ph$	"		56
5	$C_3H_7-C\equiv C-C_3H_7$	"		32
6		"		51
7		"		56

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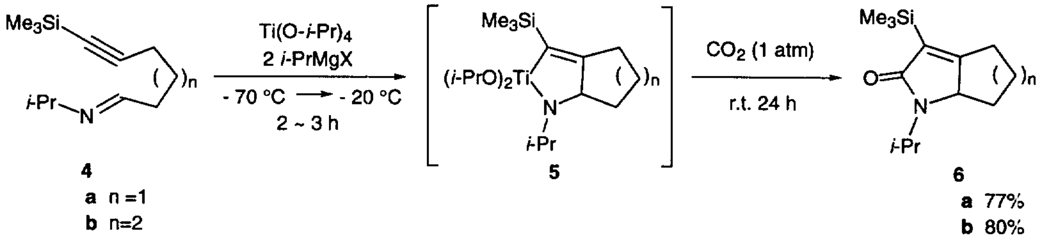
[a] The reaction was carried out with reactant ratio of alkyne:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl:imine =1:1.2:2.4:0.8, see ref. 7. [b] Prepared from the corresponding aldehyde and amine, and used after distillation. [c] Isolated yield based on the imine.

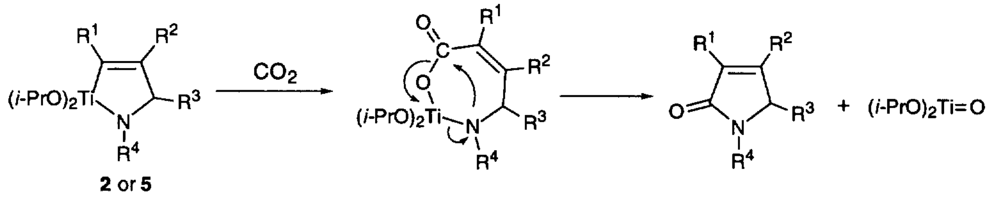
The reaction of unsaturated imines **4** with Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgX reagent has been reported to generate bicyclic azatitanacyclopentenes **5**.[4,8] We have found that **5** also react with CO$_2$. Thus, as shown in Scheme 1, cyclopenta[*b*]-3-pyrrolin-2-one derivative **6a** and indolin-2-one derivative **6b**[9] were obtained in excellent yields, respectively.

Scheme 1



A plausible reaction mechanism which can explain the production of 1,5-dihydro-2*H*-pyrrol-2-ones from **2** or **5** and CO$_2$ is shown in Scheme 2 which involves the insertion of CO$_2$ into the titanium-carbon bond of **2** or **5** and the following lactamization reaction.

Scheme 2



The method for synthesizing a variety of the substituted 1,5-dihydro-2*H*-pyrrol-2-ones developed here represents a significant deviation from the existing methods so far reported.[10] The present method is flexible to access to a variety of substituted 1,5-dihydro-2*H*-pyrrol-2-ones only by changing an alkyne and/or an imine.

In conclusion, we have developed a convenient and general method for the formation of substituted 1,5-dihydro-2*H*-pyrrol-2-ones from an alkyne, an imine and carbon dioxide. 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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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 1 atm of CO$_2$ at -20 °C for 0.5 h 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 over MgSO$_4$ and concentrated to an oil, which was chromatographed on silica gel to afford *N*-propyl-3-trimethylsilyl-4-hexyl-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (**3a**) (0.154 g, 77%).
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