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Cyclization Reactions of Homopropargyl Azide Derivatives Catalyzed by $PtCl_4$ in Ethanol Solution: Synthesis of Functionalized Pyrrole Derivatives

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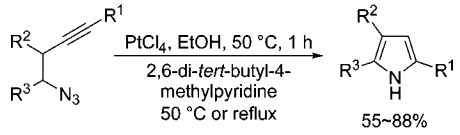
ABSTRACT



$PtCl_4$-catalyzed cyclization reactions of homopropargyl azide derivatives to pyrrole rings were investigated. Using ethanol as solvent with 2,6-di-*tert*-butyl-4-methylpyridine as the base was found to be the best set of conditions for effecting this ring-closing reaction. These reaction conditions can be applied to the preparation of functionalized pyrrole derivatives, with no effect on the functional groups.

Carbon−nitrogen bond formation reactions are an important tool in the synthesis of biologically active heterocyclic substances.[1] In our efforts directed toward the development of new synthetic methods for obtaining heterocyclic compounds, we had previously reported effective methods for the synthesis of substituted indole derivatives, catalyzed by Cu(II) salts[2] or $Pd(PPh_3)_4$−methyl propiolate complex.[3] Intermolecular nucleophilic addition reactions of the nitrogen atom to the alkyne moiety, that do not conjugate to the sp^2- or sp-hybridized carbon, tend to be difficult, apparently due to the low reactivity of the alkyne group. Until now, cyclization reactions, which involve the formation of carbon−nitrogen bonds, catalyzed by early transition metal or organolanthanoide complexes have been well investigated.[1,4] In addition, examples for the same type reactions catalyzed by late transition metal complex, which contain, e.g., Pd, Au, Ag, Cu, and Ru, also have been reported.[1,5] In spite of the powerful catalytic properties of Cu(II) salts[2] and Pd-$(PPh_3)_4$−methyl propiolate complex,[3] the cyclization reactions of **1** to **2** could not be effected, and starting material was recovered quantitatively (Scheme 1). After several attempts, we found that the cyclization reaction of **1** was

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(1) (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (b) Hosokawa, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; de Meijere, A., associate Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 2, pp 2211−2244. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.

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(5) (a) Esseveldt, B. C. J. v.; Vervoort, P. W. H.; Delft, F. L. v.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791−1795. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963. (c) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366−12367.

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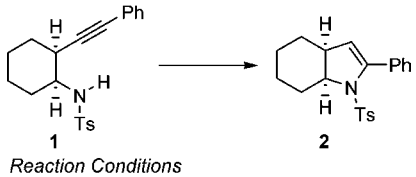
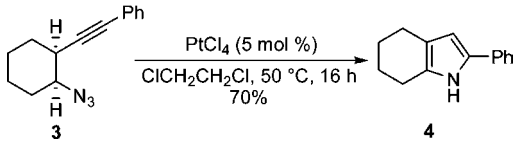
Scheme 1. Cyclization Reactions of the Tosylamide **1** System



catalyzed by platinum catalyst, recently reported to be an activator of π-bonds (Scheme 1).[6,7]

Disappointingly, it was found that the $PtCl_4$-catalyzed cyclization reaction can only be applied to a limited number of substrates, due to the instability of the enamine moiety of the products. However, in the process of surveying new substrates and catalyst systems, we unexpectedly found that homopropargyl azide derivatives could be converted to pyrrole rings in the presence of catalytic amounts of $PtCl_4$, in 70% yield (Scheme 2). While we were working on

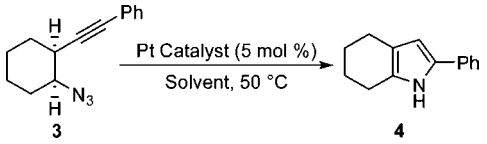
Scheme 2. $PtCl_4$-Catalyzed Cyclization Reaction of Homopropargyl Azide Derivatives



optimizing our reaction conditions, Toste's research group published a paper describing nearly identical reactions, including the conversion of homopropargyl azide derivatives to substituted pyrroles in the presence of catalytic amounts of $(dppm)Au_2Cl_2$ and $AgSbF_6$ in dichloromethane under mild conditions.[8] Toste's group proposed a reaction mechanism in which gold(I) induces activation of the alkyne toward nucleophilic addition of the proximal nitrogen atom of the azide. Herein, we describe a simpler catalytic system for efficient pyrroles synthesis as Toste's reaction.[9]

Optimization of the Pt-catalyzed reactions began with the selection of the solvent. The long reaction time (16 h) necessary in 1,2-dichloroethane was presumed to be due to low solubility of $PtCl_4$ (Table 1, entry 1). This problem was

Table 1. Cyclization Reactions Catalyzed by $PtCl_4$ or $PtCl_2$



entry	Pt catalyst	solvent	time (h)	yield (%)
1	$PtCl_4$	$ClCH_2CH_2Cl$	16	70
2	$PtCl_4$	EtOH	9	65
3[b]	$PtCl_4$	EtOH	1	79
4	$PtCl_4$	*tert*-BuOH	24	2 (58)[a]
5	$PtCl_2$	$ClCH_2CH_2Cl$	24	10 (76)[a]
6	$PtCl_2$	EtOH	24	21 (67)[a]
7[b]	$PtCl_2$	EtOH	24	40 (48)[a]

[a] The numbers in parentheses are yields of recovered **3**. [b] The reactions were started after stirring the platinum catalyst in ethanol for 1 h at 50 °C.

resolved by changing the solvent to ethanol (Table 1, entry 2). Surprisingly, the reaction rate was much improved by stirring the solution of $PtCl_4$ in ethanol for 1 h at 50 °C before adding the substrate (Table 1, entry 2 vs 3). The requirement of the induction period for obtaining higher catalytic activities suggested the possibility that initially added $PtCl_4$ is transformed to other active species.

In 1974, Hass and Hauthal reported that ethanol was oxidized by $PtCl_4$ to produce $PtCl_2$, acetaldehyde, and hydrogen chloride.[10] Noting from our results that *tert*-butanol was not an effective solvent (Table 1, entry 4), we speculated that perhaps the active species in ethanol is $PtCl_2$, which could be generated in situ. However, when the reaction was performed in the presence of commercially available $PtCl_2$, completely different results were obtained than from the reaction with $PtCl_4$. Namely, the reaction rates were much slower in either dichloroethane or ethanol, and the rates could not be improved, even with an induction period (as in entry 3). Furthermore, the reaction did not proceed to completion even after 24 h (Table 1, entries 5, 6, and 7). From these results, it is obvious that $PtCl_4$ in ethanol is being converted into a species other than $PtCl_2$. However, the true active species cannot be identified at the present time. On the other hand, since it is difficult to imagine that Pt(IV) could be reduced to Pt(II) in dichloroethane, the structure of the catalyst may vary depending upon the solvent used.

(6) Pt(II) catalyst: (a) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423−15430. (b) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023−5026. (c) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244−8245. (d) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022−15023. (e) Fürstner, A.; Davies, P. W., *J. Am. Chem. Soc.* **2005**, *127*, 15024−15025. (f) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307−5310.

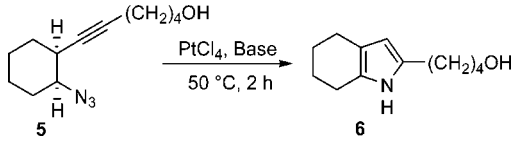
(7) Pt(IV) catalyst: (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. (b) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053−4055. (c) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859−8868.

(8) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260−11261.

(9) For recent examples on the pyrrole synthesis, see: (a) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260−9266. (b) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835−838. (c) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151−2153. (d) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525−4529 and references cited therein. (e) Freifeld, I.; Shojaei, H.; Langer, P. *J. Org. Chem.* **2006**, *71*, 4965−4968. (f) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050−12051. (g) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046−12047.

(10) (a) Hass, D.; Hauthal, T. *Z. Chem.* **1975**, *15*, 33−34. (b) Hass, D.; Hauthal, T. *Z. Chem.* **1975**, *15*, 65−66. (c) Labinger, J. A.; Herring, A. M.; Lyon, D. K.; Luinstra, G. A.; Bercaw, J. E. *Organometallics* **1993**, *12*, 895−905.

Table 2. Cyclization Reactions in the Presence of Base[a]



5 6

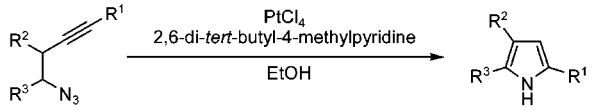
entry	$PtCl_4$ (mol %)	base (mol %)	yield (%)
1	5		50 (17)[b]
2	5	Cs_2CO_3 (20)	0 (68)[b]
3	5	proton-sponge (20)	0 (91)[b]
4	5	2,6-di-*tert*-butyl-4-methylpyridine (20)	43 (44)[b]
5	15	2,6-di-*tert*-butyl-4-methylpyridine (60)	72

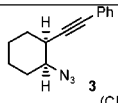
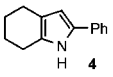
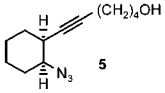
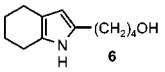
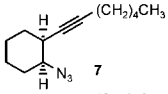
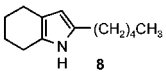
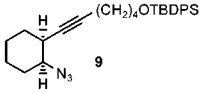
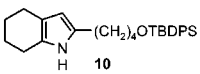
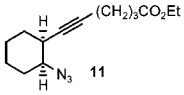
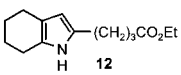
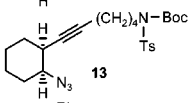
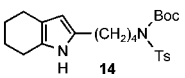
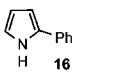
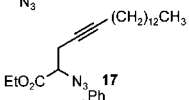
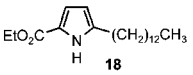
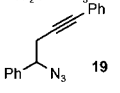
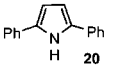
[a] For all entries, **5** and the base were added after the solution of $PtCl_4$ in ethanol was stirring for 1 h at 50 °C. [b] The numbers in parentheses are yields of recovered **5**.

Since pyrroles are π-electron-rich heteroaromatic compounds, it is known that the pyrrole ring may be prone to decomposition even under weakly acidic conditions. In fact, when the reaction was applied to **5**, the pyrrole **6** gradually decomposed over the long course of the reaction time. Because the possibility for generation of hydrogen chloride could not be ruled out, we next ran the reaction in the presence of a variety of bases. The addition of either the inorganic base Cs_2CO_3 or the proton-sponge completely inhibits the reaction (Table 2, entries 2 and 3). On the other hand, in the presence of a bulkier base, such as 2,6-di-*tert*-butyl-4-methylpyridine, the stoichiometry of the reaction was much improved over that obtained in the reaction run in the absence of base [Table 2, entry 1 (**5** + **6** = 67%) vs 4 (**5** + **6** = 87%)], although the reaction rate was slightly suppressed. Finally, the reaction could be run to completion by increasing the amount of both $PtCl_4$ and the base to provide the pyrrole **6** in 72% yield.

Having established the reaction conditions, we next applied it to other substrates with a variety of functional groups, producing the results compiled in Table 3. The reaction conditions have to be modified slightly, depending on the

Table 3. Platinum-Catalyzed Cyclization Reactions[g]



entry	homopropargyl azide	product	T °C	yield (%) (time) under Ar atmospher	yield (%) (time) under aerobic condition
1[a]	 **3**	 **4**	50 °C	88 (4 h)	78 (60 min)
2[b]	 **5**	 **6**	50 °C	72 (120 min)	–
3[b]	 **7**	 **8**	50 °C	55 (90 min)	24 (80 min)
4[b]	 **9**	 **10**	50 °C	65 (60 min)	–
5[b]	 **11**	 **12**	50 °C	64 (60 min)	–
6[c]	 **13**	 **14**	50 °C	69 (30 min)	23 (14)[f] (60 min)
7[d]	 **15**	 **16**	reflux	74 (6 h)	70 (3)[f] (160 min)
8[d]	 **17**	 **18**	reflux	61 (14 h)	–
9[d]	 **19**	 **20**	reflux	57 (82)[e] (50 min)	65 (31)[f] (80 min)

[a] $PtCl_4$ (5 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol %) in 0.1 M substrate concentration in ethanol. [b] $PtCl_4$ (15 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (60 mol %) in 0.1 M substrate concentration in ethanol. [c] $PtCl_4$ (5 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol %) in 0.03 M substrate concentration in ethanol. [d] $PtCl_4$ (15 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (60 mol %) in 0.01 M substrate concentration in ethanol. [e] The number in parentheses was the yield of the reaction in 1,2-dichloroethane. [f] The number in parentheses was the yield of the recovered starting material. [g] For all entries, both substrate and base were added after stirring the solution of $PtCl_4$ in ethanol for 1 h at 50 °C.

structure of the substrate, in order to obtain maximum chemical yield. Namely, the substrate bearing the phenylethynyl group is the most reactive and just 5 mol % of $PtCl_4$ and 20 mol % of 2,6-di-*tert*-butyl-4-methylpyridine are enough to afford the product in good yield (Table 3, entry 1). Substrates with an alkyl group substituted on the alkyne terminal (Table 3, entry 3), as well as compounds with silyl ether (Table 3, entry 4), hydroxyl (Table 3, entry 2), and ethoxycarbonyl groups (Table 3, entry 5), gave the corresponding pyrrole rings in reasonable yields under standard reaction conditions (15 mol % of $PtCl_4$ and 60 mol % of 2,6-di-*tert*-butyl-4-methylpyridine, 0.1 M solution of the azide in ethanol). The amino group in the substrate must be protected in order to obstruct complexation between the amino group and $PtCl_4$. In our case, *N*-Boc tosylamide was used as the protecting group; however, partial elimination of the Boc group in the product was observed under standard reaction conditions. This side reaction was avoided by diluting the reaction mixture from 0.1 to 0.03 M solution (Table 3, entry 6).

It is known that terminal alkynes react with organic azides to produce triazole compounds.[11] In our reactions, we observed low yields of the products under standard reaction conditions, presumably due to intermolecular polymerization of the acyclic starting materials. However, diluting the reaction conditions proved effective for such substrates. In these cases, 0.01 M proved to be the best concentration for the substrate, and the corresponding pyrroles **16**, **18**, and **20** were afforded in reasonable yields (Table 3, entries 7, 8, and 9).

Importantly, these reaction conditions can be carried out under aerobic condition for phenyl-substituted pyrrole syntheses (Table 3, entries 1, 7, and 9). For theses substrates, the solvent (ethanol) also can be used without any purification. However, decomposition of the pyrroles during the reactions for the other substrates was observed (Table 3, entries 3 and 6).

One possibility for the mechanism of this cyclization reaction may be the same as that proposed by Toste.[8] However, we observed that the azide group was completely decomposed under the cyclization reaction conditions.[12] Thus, another pathway cannot be ruled out. Clarification of the mechanism, further improvement of the conditions, and applications to the synthesis of biologically active pyrrole-containing compounds are currently underway in our laboratory.

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Supporting Information Available: Experimental detail for the synthesis of the homopropargyl azide derivatives, a general experimental procedure for the cyclization reaction, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The reaction of (4-azidobutyl)benzene in the presence of 15 mol % of $PtCl_4$ and 60 mol % of 2,6-di-*tert*-butyl-4-methylpyridine, which was stirred in EtOH for 1 h at 50 °C before adding the substrate, at 50 °C gave the starting material in 80% yield and the complete decomposition of the starting material was observed in the presence of 100 mol % of $PtCl_4$ and 2,6-di-*tert*-butyl-4-methylpyridine.