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One-Pot Synthesis of Pyrroles through Carbometalation Reaction of Zincated Hydrazone with Vinylstannane

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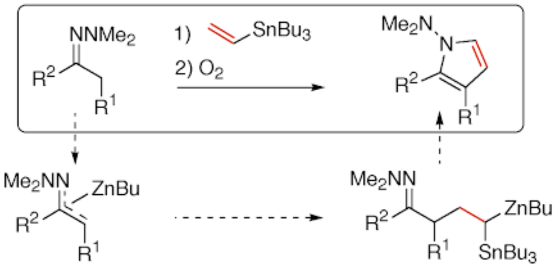
ABSTRACT

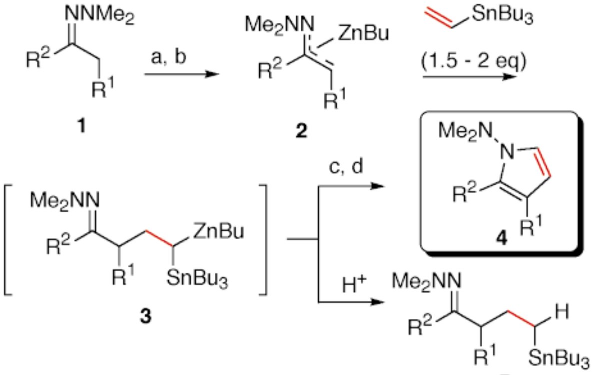


A new one-pot synthesis of pyrrole derivatives from ketone hydrazone has been developed by aerobic oxidation of functionalized *gem*-Zn/Sn dimetallic species, which are prepared by the carbometalation reaction of zincated hydrazone with vinylstannane.

Pyrroles represent a major class of heterocycles, and their importance in organic chemistry has resulted in continuing evolution of new synthetic methods.[1] We report herein a straightforward one-pot synthesis of 1-(dimethylamino)-1*H*-pyrroles through [3 + 2] coupling of a ketone hydrazone and a vinylstannane (Scheme 1). The keys to the development of this process are the carbometalation reaction of zincated hydrazone **2** with a vinylstannane and efficient aerobic oxidation of the resulting functionalized *gem*-Zn/Sn dimetallic species **3** under mild reaction conditions.

Pursuing our long-standing interest in the chemistry of functionalized organometallics,[2] especially zinc reagents,[3] we recently reported synthetic routes to γ-zincated and γ-zincated-γ-metalated carbonyl derivatives through high-yield addition of a zinc enolate of ester, amide,[4] or hydrazone (e.g., **2**) to a simple olefin (e.g., ethylene)[5] and a vinylmetal compound,[6] respectively. The reactions represented the first

Scheme 1. Carbozincation Reaction of Zincated Hydrazone with Vinylstannane and Subsequent Aerobic Oxidation[a]



[a] (a) *t*-BuLi; (b) BuZnI; (c) ZnCl$_2$ (1 equiv); (d) O$_2$, −45 to 25 °C, 2−20 h.

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(1) (a) Patterson, J. M. *Synthesis* **1976**, 281−304. (b) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193−1232. (c) Enders, D.; Maassen, R.; Han, S.-H. *Liebigs Ann.* **1996**, 1565−1574.

(2) Metal homoenolates, Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Chapter 1.14. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360−7361. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651−652.

(3) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−3370. Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066.

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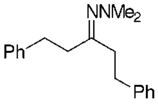
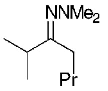
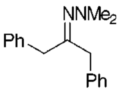
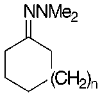
set of novel examples of counterintuitive addition of enolate anions to simple olefins. With these results in hand, we conjectured about the use of the γ-zincated hydrazone species for further synthetic elaboration and found that the aerobic oxidation of *gem*-Zn/Sn dimetallic species **3** affords the pyrrole derivatives **4** with high efficiency.[7]

The synthesis starts with the zincated hydrazone **2**, which can be generated from the corresponding hydrazone **1** as previously reported[5,6] or by a simplified new procedure (treatment of a lithiated hydrazone with BuZnI, Scheme 1). We found that the use of the BuZn countercation (equally useful are MeZn and *t*-BuZn) is mandatory, as hydrazone anions with a ZnBr or Li countercation were inert to tributylvinylstannane. Zincated hydrazone **2** added smoothly at 30 °C to give dimetallic adduct **3**, which, upon hydrolysis, afforded the corresponding γ-stannylhydrazone **5** in good yield (column 3 in Table 1). Dimetallic species **3** was found to be perfectly stable at room temperature for a few days under nitrogen. The vinylstannane reacted smoothly also with hydrazone **1c** (entry 3), which does react with vinylmagnesium bromide.[5,6] The zincated hydrazones derived from a cyclic ketone also react with the vinylstannane to afford **3** (entries 4−6).


1a

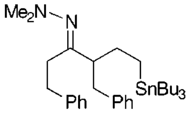
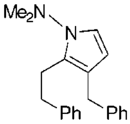
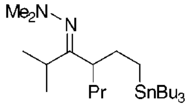
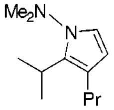
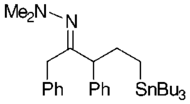
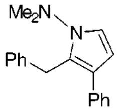
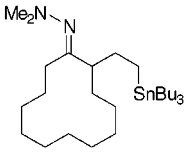
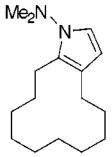
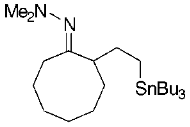
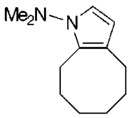
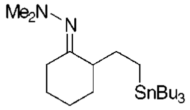
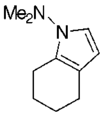

1b


1c


1d: n = 7
1e: n = 3
1f: n = 1

The reaction took place in such a manner that it gives exclusively a *gem*-Zn/Sn dimetallic product rather than a vicinal dimetallic one.[9] In no cases could we find the occurrence of a tin−zinc exchange reaction on the vinylstannane.[10] For all the products of the present reaction, the stereochemistry of the dimethylamino moiety of hydrazone in **5** was *anti* to the 2-stannylethyl side chain.[11]

Table 1. One-Pot Synthesis of 1-(Dimethylamino)-1*H*-pyrroles via *gem*-Zn/Sn Dimetallic Species[a]

entry	hydrazone (**1**)	hydrolysis product (**5**)	yield[b] (%)	(amino)pyrrole (**4**)		yield[b] (%)
1	**1a**		82		**4a**	63
2	**1b**		66[c] 76[d]		**4b**	77
3	**1c**		69		**4c**	53
4	**1d**		55		**4d**	67
5	**1e**		52		**4e**	50
6	**1f**		45		**4f**	29

[a] The reactions were carried out according to the experimental procedure described in the footnote 8 and the Supporting Information. Excess vinylstannane (1.5−2.0 equiv) was used. [b] Isolated yield based on hydrazone **1**. [c] Carbozincation was carried out using BuZnI. See footnote 8. [d] Carbozincation was carried out as previously reported (refs 5 and 6).

Exposure of adduct **3** in situ to oxygen at −45 °C and aging of the mixture under nitrogen at 0 °C to room temperature for several hours afforded directly 2,3-disubstituted 1-(dimethylamino)-1*H*-pyrrole **4**. Optimization of the cyclization conditions necessitated considerable experimentation, which revealed that removal of the butyl group from **3** by addition of 1 equiv of $ZnCl_2$ prior to aerobic oxidation was necessary. The results of one-pot synthesis of 1-(dimethylamino)-1*H*-pyrroles are shown in Table 1. It is rather remarkable that in situ transformation involving quite a

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(4) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792−793.

(5) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493. Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157−2160.

(6) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5458. Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099−7102.

(7) Although tributylvinylsilane and triphenylvinylsilane also react with the zincated hydrazone as reported previously,[6] the rate of carbozincation reaction is considerably slower than that of vinylstannanes. In addition, the oxidative conversion of the resulting *gem*-Zn/Si dimetallic product to pyrrole was much less effective than the *gem*-Zn/Sn dimetallics. For a prior work on the oxygen oxidation of zinc−tin organometallics, see: Knochel, P.; Xiao, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29*, 6697−6700.

(8) **Carbozincation procedure using BuZnI:** To a solution of 2-methylheptan-3-one *N,N*-dimethylhydrazone (**1b**) (0.21 mL, 1.0 mmol) in dry ether was added *t*-BuLi (1.52 M in pentane, 0.66 mL, 1.0 mmol) at −78 °C, and the mixture was stirred at 0 °C for 6.5 h. A solution of BuZnI (1.04 M in THF, 0.96 mL, 1.0 mmol) was added to a suspension of lithiated hydrazone at 0 °C, and the resulting solution was stirred for 1.5 h at that temperature. Tributylvinylstannane (0.58 mL, 2.0 mmol) was added at 0 °C, and the mixture was stirred at 30 °C. After 44 h, a pH-6.9 standard buffer solution was added. Aqueous quenching of the resulting adduct **3b** gave an oil (0.871 g), which was purified on silica gel to obtain the adduct **5b** (0.323 g, 66% yield). **Synthesis of 1-(dimethylamino)-1*H*-pyrrole:** To *gem*-Zn/Sn dimetallic **3b** prepared from hydrazone **1b** (0.4 mmol) was added an ethereal solution of $ZnCl_2$(0.40 mmol) at 0 °C. The reaction mixture was cooled to −45 °C and exposed to a dry oxygen atmosphere for 4.5 h. After removal of excess oxygen by degassing, the reaction mixture was stirred for 13 h at 0 °C and then filtered through a pad of silica gel to afford a crude product as a colorless oil (214 mg). Purification on silica gel afforded the substituted pyrrole **4b** (60 mg, 0.31 mmol) in 77% yield.

(9) For theoretical analysis of regiochemistry of carbometalation, see: Nakamura, E.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686−6692.

(10) Unreacted vinylstannane was recovered quantitatively.

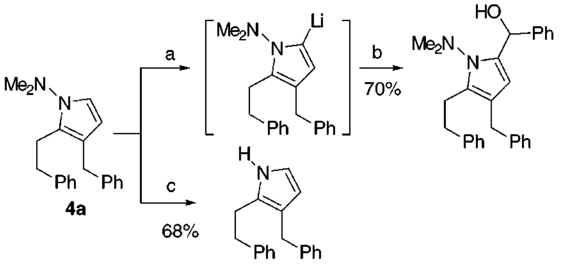
(11) *Syn* stereochemistry of the hydrazone products tentatively assigned in our previous reports (refs 4−6) should be corrected to be *anti*. Note that the starting lithiated hydrazone is in *syn* stereochemistry, and it reacts with an alkyl halide with retention of the *syn* stereochemistry. Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Van Duyne, G. *J. Am. Chem. Soc.* **1984**, *106*, 4865−4869.

number of steps has been achieved in up to 77% overall yield based on the starting hydrazone. Thus, a straight-chain hydrazone, 1,5-diphenylpentan-3-one *N*,*N*-dimethylhydrazone **1a**, was converted first to the dimetallic species **3a** (characterized as **5a** after protonation in 82% yield) and then oxidatively transformed to 3-benzyl-1-(dimethylamino)-2-(2-phenylethyl)-1*H*-pyrrole **4a** in 63% overall yield (entry 1). Regioselective deprotonation of the unsymmetrical hydrazone **1b** in entry 2 followed by the addition and the oxidation reactions afforded exclusively 2-isopropyl-3-propyl-substituted product **4b** in 77% yield. The pyrrole moiety could be fused efficiently to a cyclic hydrazone. The process was applied to the hydrazones of medium and large size ketones in good overall yields (entries 4 and 5). The pyrrole synthesis starting with cyclohexanone hydrazone **1f** was less efficient because of the low conversion of a peroxy intermediate to pyrrole.[12]

The 1-(dimethylamino)-1*H*-pyrrole products serve as useful intermediates for further synthetic elaboration. Thus, as shown in Scheme 2, the *N*,*N*-dimethylamino group acts as a directing group for lithiation[13] and can be removed under Birch conditions to afford the corresponding pyrrole.[1c]

In summary, we have shown that the one-pot pyrrole synthesis from simple hydrazones can be achieved through oxygenation of the *gem*-Zn/Sn dimetallic species generated by the carbometalation reaction. We have also shown that the vinylstannane is a more reactive carbometalation acceptor than terminal alkenes or vinylsilanes.[5,6] The present results have shown, for the first time, that a trialkylstannyl group accelerates olefin carbometalation, and the nature of such acceleration will be the subject of further studies.

Scheme 2. Directed Lithiation of **4a** and Removal of the *N*,*N*-Dimethylamino Group[a]



[a] (a) BuLi, TMEDA, hexane, 25−50 °C; (b) PhCHO (1.5 equiv), 0 °C, 2.5 h; (c) Na (19 equiv), NH_3, −78 to 20 °C, 3 h, 0.8 to 1.1 MPa.

Acknowledgment. This work is supported by a Grant-in-Aid for Scientific Research from Mombusho (No. 09740535).

Supporting Information Available: Detailed experimental procedures for the carbozincation and the aerobic oxidation and spectroscopic and physical data for compounds **4a−f** and **5a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A hydroperoxide, which formed through oxidation of the C−Zn bond of the Zn/Sn dimetallic species and subsequent hydrolysis, was obtained as a byproduct in ca. 20% yield.

(13) Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3861−3763.