

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

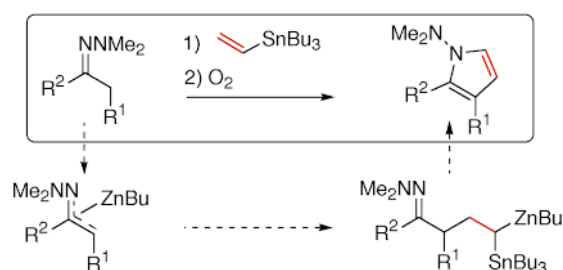
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ABSTRACT

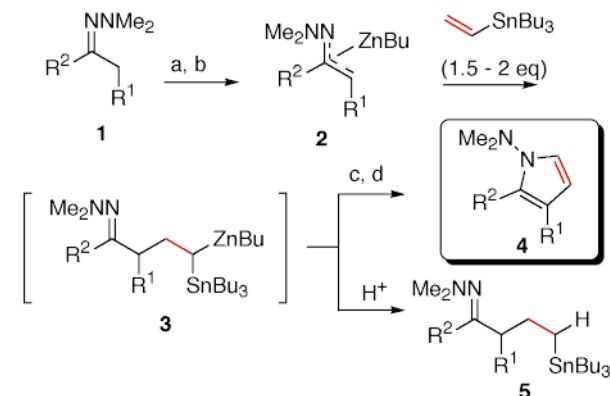


A new one-pot synthesis of pyrrole derivatives from ketone hydrazone has been developed by aerobic oxidation of functionalized *gem*-Zn/Sn dimetallic species, which are prepared by the carbometalation reaction of zincated hydrazone with vinylstannane.

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

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



^a (a) *t*-BuLi; (b) BuZnI; (c) ZnCl₂ (1 equiv); (d) O₂, -45 to 25 °C, 2–20 h.

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

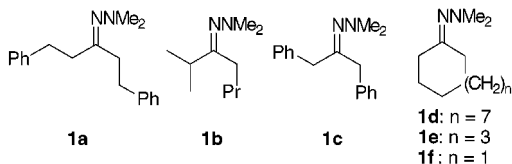
(1) (a) Patterson, J. M. *Synthesis* **1976**, 281–304. (b) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193–1232. (c) Enders, D.; Maassen, R.; Han, S.-H. *Liebigs Ann.* **1996**, 1565–1574.

(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 I.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.

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 counteranion (equally useful are MeZn and *t*-BuZn) is mandatory, as hydrazone anions with a ZnBr or Li counteranion 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 not 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).

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 vinyl-

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).

(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 carbocationization 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 ZnCl₂ (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.

stannane.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

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 ZnCl₂ 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

(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

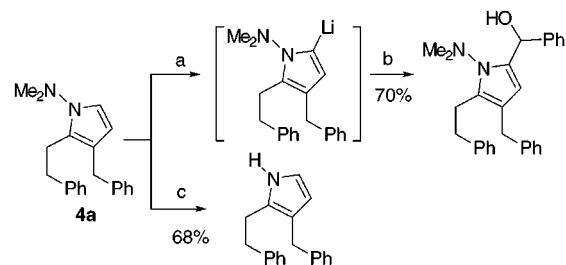
The 1-(dimethylamino)-1*H*-pyrrole products serve as useful intermediates for further synthetic elaboration. Thus, as shown in Scheme 2, the *N,N*-dimethylamino group acts as a directing group for lithiation¹³ and can be removed under Birch conditions to afford the corresponding pyrrole.^{1c}

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

(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.

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), NH₃, –78 to 20 °C, 3 h, 0.8 to 1.1 MPa.

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.

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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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