

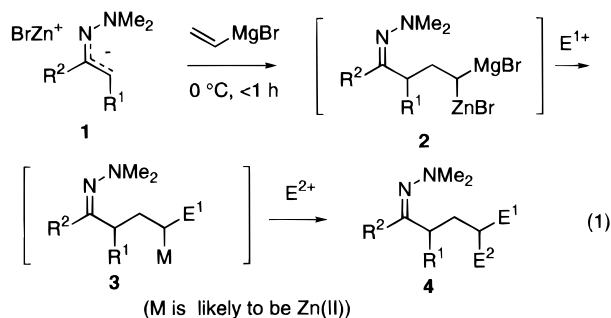
Addition of Zincated Hydrazone to Vinyl Grignard Reagent. Ketone Synthesis by One-Pot Assembly of Four Components

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Electrophilic functionalization reactions of enolate anions occupy the central position in organic chemistry. We report a novel use of vinylmagnesium bromide as an “electrophile” toward an α -anion of a ketone hydrazone.¹ The coupling of a zincated hydrazone **1** with the vinyl Grignard reagent takes place at 0 °C generally within 1 h to generate a dimetallated hydrazone intermediate **2** in a nearly quantitative yield (eq 1). The



intermediate **2** represents a new class of functional organometallic reagent, providing a novel synthetic route to ketone derivatives **4** through two- to four-component coupling of hydrazone, vinyl Grignard reagent, and electrophiles. It may be noted that *N,N*-dimethylhydrazones can be readily synthesized from and converted back to the corresponding ketones.¹

The experimental protocol is easy to perform, and allows quick assembly of equimolar amounts of the hydrazone, the Grignard reagent, and electrophiles: The *N,N*-dimethylhydrazone of 1,5-diphenyl-3-pentanone ($R^1 = \text{PhCH}_2$, $R^2 = \text{PhCH}_2\text{-CH}_2$; 2.80 g, 10.0 mmol) in ether (10 mL) was treated at 0 °C first with *t*-BuLi (10.0 mmol in pentane, 4 h)² and then with ZnBr_2 (10.0 mmol, 0.33 M in ether, 1 h).³ To the pale yellow suspension of the zincated hydrazone was added vinylmagnesium bromide (10.0 mmol, 0.98 M in THF) at 0 °C. After 1 h, the reaction mixture was poured in an ice/water mixture, extracted with ether, and washed with 30% potassium sodium tartarate. Chromatographic purification of the crude product on silica gel⁴ afforded the ethylated hydrazone **4** ($E^1 = E^2 = \text{H}$, 2.86 g, 93% yield; Table 1, entry 1) together with the starting hydrazone (7%). Quenching the reaction with D_2O resulted in exclusive dideuteration on the terminal methyl group (**4**, $E^1 = E^2 = \text{D}$; entry 1). Alternatively, quenching of the reaction with a mixture of $(\text{MeS})_2$ (1.04 g, 11.0 mmol) and allyl bromide (6.05 g, 50.0 mmol)⁵ followed by stirring for 40 h at 25 °C afforded a four-component coupling product (**4**, $E^1 = \text{MeS}$, $E^2 = \text{CH}_2\text{-CHCH}_2$; 2.64 g, 67% isolated yield obtained as a mixture of

diastereomers and oxime stereoisomers; 84% yield on a smaller scale, Table 1, entry 11).

There were a number of experimental parameters to be considered for the initial coupling reaction leading to **2**. The hydrazone anion bearing a lithium counteranion was found to be unreactive toward vinylmagnesium bromide (recovery of the hydrazone), and that with ClZn(II) cation suffered from low solubility. The $\text{Et}_2\text{O/THF/pentane}$ (4:1:1) mixed solvent system was found to be superior to each solvent by itself or 1,2-dimethoxyethane. Substituted vinyl Grignard reagents (such as 2-phenylethenylmagnesium bromide) have so far been found to react very sluggishly with the hydrazone anions. *N,N*-Diphenylhydrazone failed to take part in the present reaction.

As summarized in Table 1, the present coupling reaction⁶ has a considerable scope as to the structure of the ketone substrate.⁷ The coupling of equimolar amounts of a hydrazone and the vinyl anions was achieved at 0 °C, and the reaction mixture was quenched either with excess water (entries 1–4) or with 1.1 equiv of benzaldehyde (entries 5–7). Cyclic and acyclic ketone hydrazones reacted equally well (entries 1–3). Deprotonation of an unsymmetrical ketone hydrazone (entry 4) took place at a less hindered side, and the subsequent reaction with the vinyl Grignard reagent took place with retention of this regiochemistry. The reaction with benzaldehyde⁸ (entries 5–7) afforded benzylidenated products through a two-stage reaction, formation of **3** ($E^1 = \text{PhCHOMgBr}$) followed by 1,2-elimination of BrMgOZnBr . The stereochemistry of the resulting olefinic bond was mainly *trans* and varied in each run (67:33 to 84:16). The formation of benzyl alcohol (16%) accounts for the lower yield in the benzaldehyde trapping (entry 5) than in water trapping (entry 1). The nature of this side reaction is yet to be elucidated.

The nucleophilic chemistry of the novel dimetallated hydrazone **2** was examined for the case of 1,5-diphenyl-3-pentanone (entries 8–11). The reaction of **2** with allyl bromide was promoted particularly cleanly with a Cu(I) salt⁹ to afford the corresponding double trapping products in 78% isolated yield (entry 8).¹⁰ Trapping of **2** with two different electrophiles can also be achieved. Reaction of **2** first with *tert*-butyl alcohol to protonate one of the two anionic sites followed by Me_3SiCl -accelerated conjugate addition of the resulting zinc species **3**¹¹ afforded an enol silyl ether in 33% yield (entry 9, no conjugate addition in the absence Me_3SiCl),¹² and reaction of **2** first with *tert*-butyl alcohol followed by trapping with allyl bromide afforded a mono-allylated product in 82% yield (entry 10). Treatment of **2** with a mixture of $(\text{MeS})_2$ and allyl bromide afforded a sulfide product in 84% yield (vide infra, entry 11), indicating that the double trapping of the dimetallic species **2** took place in nearly quantitative yields.

Though the mechanism of the present reaction is still open to questions, several points may be noted. First, the structure of the starting zincated hydrazone is uncertain. The only relevant information available now is for the lithio hydrazones, which have either an aza- π -allylic metal or a metal aza-enolate structure.¹³ Second, the reaction does not take place (maximum

(6) Enolates derived from ketone, ester, and amide have so far been found unreactive to vinylmagnesium bromide.

(7) The products in Table 1 consisted largely of one isomer (stereochemistry not assigned), which in some cases afforded a stereoisomeric mixture upon standing (cf. ref 1b).

(8) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 27, 1039–1042.

(9) Cf.: Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, 29, 5155–5156. Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, 58, 5121–5129 and references therein.

(10) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 27, 4427–4430.

(11) Nakamura, E.; Kuwajima, J. *Am. Chem. Soc.* **1984**, 106, 3368–3370.

(12) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 27, 4431–4434.

(1) Cf.: (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, 93, 5938–5939. (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6. (c) Bergbreiter, D. E.; Momongan, M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 503–526.

(2) We have so far not been able to obtain synthetically useful levels of yield and stereoselectivity with Enders' chiral SAMP/RAMP hydrazones (Enders, D. *Asymmetric Synthesis*; Morrison, J. M., Ed.; Academic Press: New York, 1984; Vol. 3, pp 275–339).

(3) Cf.; Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, 62, 792–793.

(4) To avoid hydrolysis of the hydrazone, silica gel packed in a column was treated first with *N,N*-dimethylaniline (2 mL for 10 g of silica gel) and washed thoroughly with EtOAc before use.

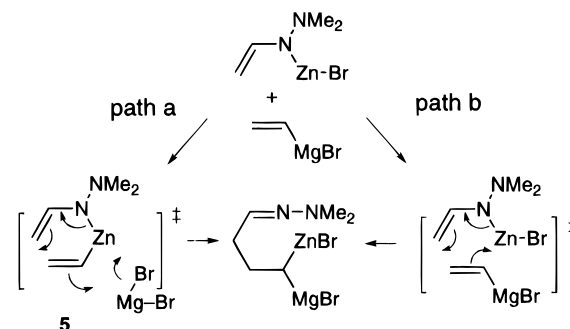
(5) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 27, 1043–1046.

Table 1. Two- to Four-Component Coupling Synthesis of Hydrazones^a

entry	hydrazone or electrophiles	product	% yield ^b
H₂O (D₂O) quench			
1			93
2			85
3			74
4			74
benzaldehyde quench			
5			67
6			83
7			76
quenching with two electrophiles (starting with 1,5-diphenyl-3-pentanone hydrazone)			
	E¹	E²	
8	CH ₂ CHCH ₂ Br (3 eq) CuCN (1 eq) -70-0 °C, 1 h	"	 78
9	<i>t</i> -BuOH (1 eq) -70-40 °C 1 h	CH ₃ COCHCH ₂ (2 eq) CuCN (1 eq) Me ₂ SiCl HMPA, -70 °C, 1 h	 33
10	<i>t</i> -BuOH (1 eq) -70-40 °C 1 h	CH ₂ CHCH ₂ Br (2 eq) CuCN (1 eq) -70 °C, 1 h	 82
11	MeSSMe (1.1 eq) 0-rt, 1.5 h	CH ₂ CHCH ₂ Br (5 eq) rt, 15 h	 84 ^d

^a The reactions were carried out as described in the text. The time required for completion of the initial coupling reaction was 1 h at 0 °C for all reactions but in entry 4 (4 h). ^b Yields based on pure isolated product. ^c The cis/trans ratio changed slightly during the reaction course. ^d Out of four possible stereoisomers, three were identified and isolated (in a 44:29:27 ratio).

yield of 7%) when the ZnBr complex **1** was treated with 1 equiv of BuLi (supposedly generating a BuZn(II) counteranion) before treatment with the vinylmagnesium bromide. This observation is contrary to the importance of a hydrazone anion bearing a

Scheme 1

BuZn(II) cation in the carbometalation of cyclopropene.^{3,14} A neutral Zn(II) intermediate such as **5** bearing both a vinyl group and a hydrazone moiety may thus be essential for the reaction.¹⁵ We may therefore speculate that the reaction involves a metallaza-Claisen rearrangement (path a, Scheme 1)¹⁶ rather than carbometalation of the vinyl Grignard reagent (path b).¹⁷ However, this mechanism still does explain why such an apparently counter thermodynamic reaction takes place so readily.

We have discovered a new possibility in the carbon chain elongation reaction of carbonyl compounds. The dimetallic hydrazone **2** generated by two-carbon homologation of a ketone hydrazone may be viewed as a "bishomoenolate" species and will be complementary to the chemistry of homoenolate species.^{8,18,19} The present reaction has a potential value as a quick method to construct a library of various ketone derivatives, and this aspect will be the subject of further studies.

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Supporting Information Available: Experimental details (17 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Duyne, G. V. *J. Am. Chem. Soc.* **1984**, *106*, 4865–4869. Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078–2082. Enders, D.; Bachstader, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1522–1524.

(14) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867–5868. Nakamura, E. *Pure Appl. Chem.* **1996**, *68*, 123–130.

(15) Possible participation of an ate complex bearing a hydrazone anion, a vinyl group and a butyl group may also be discounted.

(16) Cf.: Gaudemar, M. C. *R. Acad. Sci. Paris, Ser. C* **1971**, *273*, 1669. Frangin, Y.; Gaudemar, M. C. *R. Acad. Sci. Paris, Ser. C* **1974**, *278*, 885. Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241–3267, ref 8, and references cited therein.

(17) Theory predicts that an electron-rich olefin may be kinetically more reactive in a certain carbometalation reaction: Nakamura, E.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686–6692.

(18) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360–7361. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651–652. Kuwajima, I.; Nakamura, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 441–454.

(19) (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 2329–2332. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559–5562.