Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4495-4498, 1996

0040-4039/96 $15.00 + 0.00

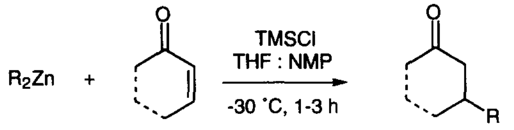
PII: S0040-4039(96)00915-X

Uncatalyzed Conjugate Additions of Diorganozincs in N-Methylpyrrolidinone

Ch. Kishan Reddy, A. Devasagayaraj and P. Knochel*
Fachbereich Chemie der Philipps-Universität Marburg
D - 35032 Marburg, Germany

Abstract: Diorganozincs efficiently add to enones, unsaturated nitriles and nitroolefins in a mixture of THF and NMP furnishing the corresponding Michael adducts in good to excellent yields. Copyright © 1996 Elsevier Science Ltd

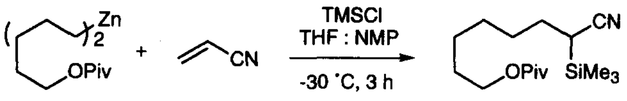
The conjugate addition of organometallics to enones is an important synthetic transformation.[1] Organocuprates used as stoichiometric reagents have proven to be very efficient,[1,2] however alternative procedures involving the use of catalytic amounts of copper salts and stoichiometric amounts of a magnesium[2,3] zinc[4] or aluminium reagent[5] have been developed. The performance of copper free 1,4-addition reactions of organometallics is especially interesting and Rieke has recently shown that *secondary* and *tertiary* alkylzinc halides were reactive enough to add to enones in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv).[6] Herein, we wish to report a method allowing the addition of primary and secondary diorganozincs to enones as well as to related Michael acceptors. Whereas primary diorganozincs[7] do not add to enones like cyclohexenone in THF, we have found that a smooth addition reaction of R_2Zn (**1**) to enones **2** occurs by using N-methylpyrrolidinone (NMP) as cosolvent. It furnishes the 1,4-addition products **3** in 72-83 % isolated yield (eq 1 and Table 1). Thus the reaction of $Pent_2Zn$ (1 equiv) with cyclohexenone **2a** (1 equiv) in a THF: NMP (1:1) mixture in the presence of chlorotrimethylsilane[8] (TMSCl; 1.0 equiv) at -30 °C affords within 1 h of reaction time, 3-pentylcyclohexanone (**3a**; entry 1 of Table 1) in 83 % isolated yield. More complex zinc reagents like dimyrtanylzinc **1e**[9] (entries 5 and 8) or functionalized diorganozincs (entries 2, 3, 7 and 10) add to cyclohexenone with similar yields.



(1)

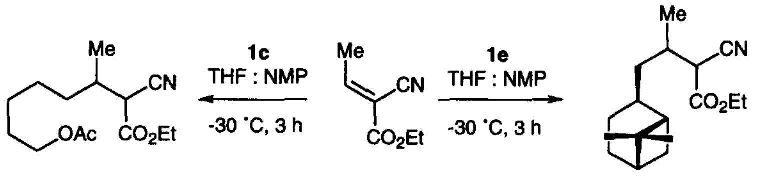
1 **2** **3** : 72-83 %

Additions to cyclopentenone **2b** or an acyclic ketone like 3-penten-2-one (**2c**) proceed as well. However, the addition to β-disubstituted enones is not possible and the addition of alkylzinc iodides instead of dialkylzincs[9] is significantly slower and affords the conjugate addition products only in the presence of bromotrimethylsilane[10] (1.0 equiv) in moderate yield (entries 3 and 4 of Table 1).



(2)

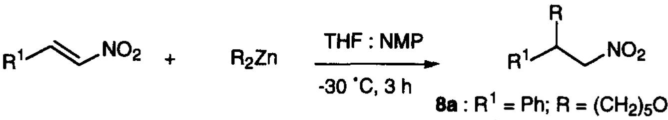
1f **4** : 82 %



(3)

6 : 84 % **5** **7** : 78 %

Interestingly, the amount of NMP used for these reactions can be considerably reduced and the addition of $Pent_2Zn$ to cyclohexenone in the presence of only one equivalent of NMP affords **2a** in 84 % yield. Another polar solvent like DMSO is not suited for promoting these Michael additions and provide low yields of the 1,4-addition product. Remarkably, this procedure can be extended to other Michael acceptors and the reaction of $(PivO(CH_2)_5)_2Zn$ (**1f**) with acrylonitrile in the presence of TMSCl provides the conjugate addition product **4** with incorporation of the TMS moiety at the α position in 82 % yield (eq 2).



(4)

8a : R^1 = Ph; R = $(CH_2)_5OAc$: 84 %
8b : R^1 = Hex; R = $(CH_2)_5OAc$: 85 %
8c : R^1 = Hex; R = Pent : 89 %
8d : R^1 = Hex; R = *c*-Hex : 83 %

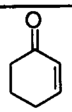
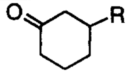
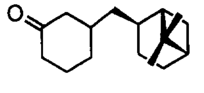
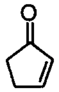
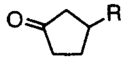
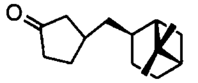
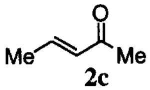
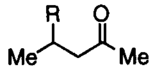
The substituted nitrile **5** adds the zinc reagents **1c** and **1e** giving the adducts **6** and **7** in respectively 84 % and 78 % yield (eq 3). The reaction of diorganozincs with aryl substituted nitroolefins can be complicated by an ipso-substitution of the nitro group in solvents like ether or THF.[11] By using a THF:NMP mixture, a smooth addition reaction occurs under mild conditions furnishing the expected nitroalkanes **8a-d** in 83-89 % isolated yield (eq 4). The origin of the reaction rate increase in NMP is not clear but may result from the ionization of the diorganozinc providing a more reactive organometallic system: $RZn(NMP)^+ R_3Zn^-$.[12]

In summary, we have shown that diorganozincs add efficiently to a range of Michael acceptors [13] in a solvent mixture of THF and NMP. Studies of the scope of this reaction, its mechanism and applications in asymmetric synthesis using chiral NMP derivatives are currently underway in our laboratory.

Acknowledgments:

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (SFB 260). A. D. and C. K. R. thank the Alexander-von-Humboldt-Stiftung for a fellowship. We thank also the BASF AG, Witco GmbH, Schering AG, Bayer AG, Sipsy, Chemetall GmbH and Chiroscience for the generous support and the gift of chemicals.

Table 1. 1,4-Addition Products **3a-k** obtained by the Reaction of Diorganozincs **1a-e** to Enones **2a-c** in NMP (-30 °C, 1-3 h).

entry	enone	R_2Zn	product	yield (%)[a]
1		**1a** : R = Pent	 **3a** : R = Pent	83
2	**2a**	**1b** : R = PivO$(CH_2)_3$	**3b** : R = $(CH_2)_3$OPiv	72
3	**2a**	**1c** : R = AcO$(CH_2)_5$	**3c** : R = $(CH_2)_5$OAc	74[b]
4	**2a**	**1d** : R = *c*-Hex	**3d** : R = *c*-Hex	82 (51)[c]
5	**2a**	**1e** : R = Myrt	 **3e**	78
6		**1d** : R = *c*-Hex	 **3f** : R = *c*-Hex	82
7	**2b**	**1c** : R = $(CH_2)_5$OAc	**3g** : R = $(CH_2)_5$OAc	83
8	**2b**	**1e** : R = Myrt	 **3h**	79
9	 **2c**	**1a** : R = Pent	 **3i** : R = Pent	81
10		**1c** : R = $(CH_2)_5$OAc	**3j** : R = $(CH_2)_5$OAc	82
11		**1d** : R = *c*-Hex	**3k** : R = *c*-Hex	82

[a] Isolated yield of analytically pure products. [b] By using the corresponding alkylzinc iodide, a yield of 20 % is obtained in the presence of TMSCl and 45 % in the presence of TMSBr. [c] Yield obtained by using *c*-HexZnI (1.0 equiv) and TMSBr (1.0 equiv).

References and Notes.

(1) Kozlowski, J. A. in *Comprehensive Organic Synthesis*, Ed. Trost, B. M.; Fleming, I.; Semmelhack, M. F. Vol. 4, p. 169-198.

(2) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Lipshutz, B. H. *Synlett* **1990**, 119. (c) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(3) (a) Cahiez, G.; Alami, M. *Tetrahedron* **1989**,*45*, 4163. (b) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541. (c) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1990**, *31*, 7423. (d) Reetz, M. T.; Kindler, A. *J. Chem. Soc., Chem. Commun.* **1994**, 2509. (e) Reetz, M. T.; Kindler, A. *J. Organomet. Chem.* **1995**, *502*, C5.

(4) (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 351. (c) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126. A Ni(II)-catalyzed Michael addition has also been developed: (d) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. J. *Org. Chem.* **1988**, *53*, 4149. (e) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S.

Chem. Lett. **1988**, 1571. (f) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205. (g) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron: Asymm.* **1992**, *3*, 581. (h) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, 297,

(5) (a) Westermann, J.; Nickisch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1368. (b) Maruoka, K.; Shimada, I.; Akakura, M.; Yamamoto, H. *Synlett* **1994**, 847. (c) Pecuniso, A.; Menicagli, R. *J. Org. Chem.* **1989**, *54*, 2391. (d) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* **1994**, 679.

(6) Hanson, M. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 10775.

(7) For the preparation and the reactivity of diorganozincs, see: (a) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P. *Synlett* **1995**, 393.

(8) (a) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (b) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(9) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410.

(10) Iodotrimethylsilane activated additions of organocopper reagents to enoates have been reported: (a) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055. (b) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535.

(11) Seebach, D.; Schäfer, H.; Schmidt, B., Schreiber, M. *Angew. Chem, Ind. Ed. Engl.* **1992**, *31*, 1587.

(12) Fabicon, R. M.; Pajerski, A. D.; Richey, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 9333.

(13) **Typical procedure : Preparation of 3-Myrtanylcyclopentanone (3 h).**

A 25 mL two-necked flask was charged with β-pinene (1.36 g, 10 mmol) and diethylborane (2.0 g, 10 mmol) in ether, was added at 0 °C. The resulting solution was stirred for 15 min, was allowed to warm to rt and was further stirred for 1 h. It was then cooled to 0 °C and the solvents were removed by applying high vacuum (0.1 mmHg) for 15 min at 0 °C, and for 30 min at rt. The reaction mixture was cooled to 0 °C and Et_2Zn (2 mL, 20 mmol) was added. The reaction mixture was stirred for 10 min at 0 °C and for 20 min at rt. It was again cooled to 0 °C and the solvents were removed as described above. The resulting zinc reagent (**1e**) was diluted in THF (3 mL) and was ready to use.

A 50 mL three-necked flask was charged with THF (2 mL) and NMP (3 mL) and was cooled to -30 °C. 2-Cyclopenten-1-one (410 mg, 5 mmol) and TMSCl (500 mg, 5 mmol) were added followed by *bis*(myrtanyl)zinc (**1e**) (3 mL of the above prepared solution, 5 mmol). The resulting reaction mixture was stirred for 3 h at -30 °C and was poured into an aqueous 10 % HCl solution (20 mL) in THF (20 mL), stirred for 15 min and was worked up as usually. After evaporation of the solvents, the crude residue was purified by flash chromatography (hexane:ether = 95:5) providing 3-myrtanylcyclopentanone (**3h**; 869 mg, 79 %) as a colorless oil.

(*Received in Germany* 30 *April* 1996; *accepted* 9 *May* 1996)