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Oxovanadium(V)-Induced Vicinal Dialkylation of Cyclic Enones with Organozinc Compounds

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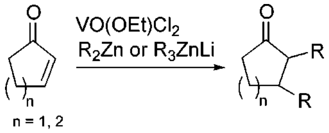
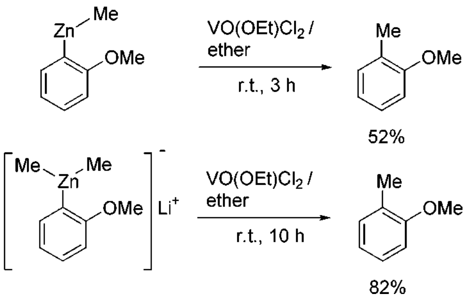
ABSTRACT



Oxovanadium(V) compounds induce nucleophilic α,*β*-vicinal dialkylation of cyclic α,*β*-enones with dialkylzinc reagents. Alkylzinc enolates generated from cyclic enones and lithium trialkylzincates were also oxidized by VO(OEt)Cl$_2$, giving 2,3-dialkylcycloalkanones.

Oxidative transformation of main-group organometallics has been expected to develop a new type of carbon−carbon bond-forming reaction.[1,2] Recently, we reported that oxovanadium(V) compounds induce a selective ligand coupling of two ligands on some organometallic compounds such as organoaluminum,[3] boron,[4] zirconium,[5] and zinc compounds.[6] As for the organozinc compound, arylalkylzinc or aryldialkylzincate is oxidized by VO(OEt)Cl$_2$, providing a ligand coupling product selectively (Scheme 1).[6]

Scheme 1



On the other hand, dialkylzinc reagent (R$_2$Zn) is recognized as a mild nucleophile, and highly selective reactions have been developed by a combination of an additional promoter such as a Lewis acid catalyst.[7] It is known that 1,4-addition of dialkylzinc to an α,*β*-unsaturated carbonyl compound also requires promotion by a Lewis acid. Judging from the characteristic features of oxovanadium(V) compounds as a Lewis acid and one-electron oxidant, they are expected to induce a novel nucleophilic vicinal dialkylation

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[1] For chemical redox reagents of organometallic chemistry, see: Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877 and references therein.

[2] For copper-induced oxidative ligand coupling reactions of organoborons and organozincs, see: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1977**, *99*, 5652. (b) Iyoda, M.; Kabir, S. M. H.; Vorasingha, A.; Kuwatani, Y.; Yosihda, M. *Tetrahedron Lett.* **1998**, *39*, 5393. For oxidative transformation of d^0 organometallics, see: (c) Jordan, R. F.; LaPointe, R. E.; Bajgur, C. S.; Echols, S. F.; Willet, R. *J. Am. Chem. Soc.* **1987**, *109*, 4111. (d) Borkowsky, S. L.; Baenziger, N. C.; Jordan, R. F. *Organometallics* **1993**, *12*, 486. (e) Burk, M. J.; Tumas, W.; Ward, M. D.; Wheeler, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 6133. (f) Sato, M.; Mogi, E.; Kumakura, S. *Organometallics* **1995**, *14*, 3157. (g) Hayashi, Y.; Osawa, M.; Wakatsuki, Y. *J. Organomet. Chem.* **1997**, *542*, 241.

[3] Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Am. Chem. Soc.* **1998**, *120*, 5124.

[4] Ishikawa, T.; Nonaka, S.; Ogawa, A.; Hirao, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1209.

[5] Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Organomet. Chem.* **1999**, *575*, 76.

[6] Hirao, T.; Takada, T.; Ogawa, A. *J. Org. Chem.* **2000**, *65*, 1511.

[7] For organozinc mediated reactions, see: (a) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275 and references therein. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117 and references therein.

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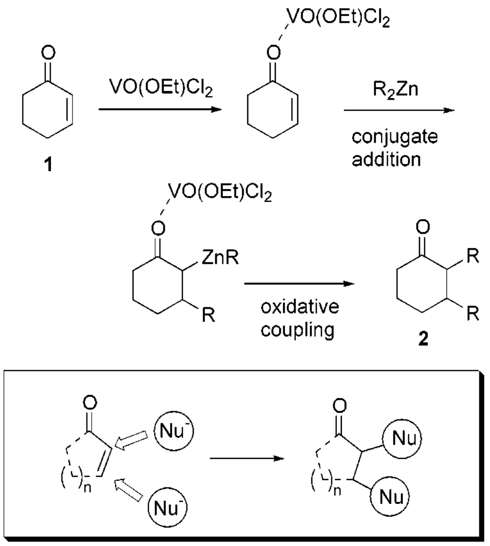
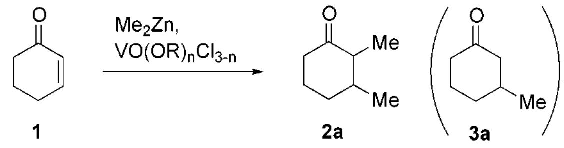
at both the β- and α-positions of an α,β-unsaturated carbonyl compound with a dialkylzinc reagent (Scheme 2). That is, the oxovanadium (V) compound might promote 1,4-addition of R_2Zn to enone **1**, and the resulting zinc enolate is immediately oxidized by the adjacent oxovanadium(V) species, giving the corresponding vicinally dialkylated compound **2**.

Scheme 2



To accomplish this kind of vicinal alkylation, first, the reaction of 2-cyclohexenone (**1**) with dimethylzinc in THF was investigated (Table 1). Dimethylzinc was inert to **1** without an oxovanadium(V) complex (entry 1), whereas VO(OPr^i)$_3$ activated only the 1,4-addition process to give 3-methylcyclohexanone (**3a**) in 34% yield (entry 2). Use of VO(OEt)Cl_2, a more efficient Lewis acid and oxidant than VO(OPr^i)$_3$,[8] led to the formation of 2,3-dimethylcyclohexanone (**2a**) in 26% yield as a diastereomeric mixture.[9] This result encouraged us to examine the precise reaction conditions. When the reaction was carried out at −78 °C for 4 h and then at −30 °C for 6 h, the yield of **2a** was increased to 60% (entry 4). Next, the substituent of oraganovanadium(V) compounds was screened to find that the stronger Lewis acid and oxidant gave the better results. Accordingly, the yield of **2a** decreased in the order VO(OEt)Cl_2 > VO(OPr^i)Cl_2 > VO(OPr^i)$_2$Cl to 60%, 56%, and 20%, respectively (entries 4−6).[8] Finally, the yield of **2a** was improved to 78% when 2 molar equiv of dimethylzinc and 2 molar equiv of VO(OEt)Cl_2 were employed at −78 °C for 20 h (entry 7).[10] When the solvent was replaced with ether or dichloromethane, the yield of **2a** decreased (entries 8 and 9).

Table 1. Vicinal Dimethytlation of **1** with Dimethylzinc[a]

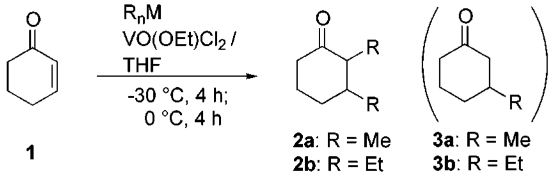


entry	oxovanadium(V) (equiv)	solvent	conditions °C, h	yield / %[b] of **2a** (*trans*/*cis*)
1	—	THF	0, 6	no reaction
2	VO(OPr^i)$_3$ (1.5)	THF	0, 6	0, **3a**, 34%
3	VO(OEt)Cl_2 (1.5)	THF	0, 6	26 (53 / 47)
4	VO(OEt)Cl_2 (1.5)	THF	-78, 4 and -30, 6	60 (58 / 42)
5	VO(OPr^i)Cl_2 (1.5)	THF	-78, 4 and -30, 6	56 (54 / 46)
6	VO(OPr^i)$_2$Cl (1.5)	THF	-78, 4 and -30, 6	20 (50 / 50)
7	VO(OEt)Cl_2 (2.0)	THF	-78, 20	78 (62 / 38)
8	VO(OEt)Cl_2 (2.0)	Et_2O	-78, 20	34 (57 / 43)
9	VO(OEt)Cl_2 (2.0)	CH_2Cl_2	-78, 20	52 (54 / 46)

[a] 1.3 equiv of Me_2Zn in entries 1-6 and 2.0 equiv in entries 7-9 were used. [b] Determined by ^{1}H NMR.

The same dialkylation takes place with diethylzinc as shown in Table 2. Furthermore, this method could be applied to trialkylaluminum (R_3Al)[3] and trialkylborane (R_3B)[4] compounds. Diethylation of **1** with diethylzinc, triethylalminum,

Table 2. Dialkylation of **1** with Organometallic Reagent[a]



entry	R_nM	yield / %[b]	
		2 (*trans*/*cis*)	**3**
1	Et_2Zn	74[c] (77 / 23)	10
2	Et_3Al	84[d] (74 / 26)	—
3[e]	Et_3B	50 (68 / 32)	8
4	Me_2CuLi	—	quant

[a] Me_2CuLi was prepared from CuI and 2.0 equiv of MeLi *in situ*. [b] Determined by GC analysis. [c] Isolated yield was 72%. [d] Isolated yield was 75%. [e] **1** (18%) was recovered.

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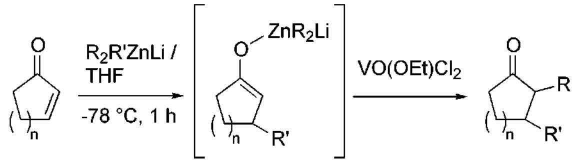
(8) The order of the reactivity of oxovanadium(V) reagents is as follows: VO(OR)Cl_2−AgOTf or Me_3SiOTf > VO(OR)Cl_2 > VO(OR)$_2$Cl > VO(OR)$_3$. Hirao, T.; Mori, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn*. **1989**, *62*, 2399. Hirao, T.; Mori, M.; Ohshiro, Y. *J. Org. Chem*. **1990**, *55*, 358. Hirao, T.; Mori, M.; Ohshiro, Y. *Chem. Lett*. **1991**, 783.

(9) The regiochemistry of dialkylated compounds **2a**−**c** was determined by ^{13}C−^{13}C cosy using the 2D-INADEQUATE technique ($CDCl_3$, 25 °C) and that of **7** was determined by 1D,2D-HOHAHA. The *trans*/*cis* stereochemistry of **2a** and **7** was determined by NOE. The *trans*/*cis* stereochemistry of **2b** and **2c** was determined by J_{CH-CH} coupling constant (for example, major *trans*-**2c**, 7.8 Hz, minor *cis*-**2c**, 4.9 Hz).[12]

and triethylborane proceeded smoothly to afford the 2,3-diethylcyclohexanone **2b** in 74%, 84%, and 50% yields, respectively (Table 2, entries 1−3). In contrast, an organocuprate reagent exhibited no reactivity toward the oxidative coupling at the α-position and gave only conjugate addition product **3a** quantitatively (entry 4).

Contrary to dialkylzinc, lithium trialkylzincate (R_3ZnLi) has enough nucleophilicity for conjugate addition to an α,*β*-unsaturated carbonyl compound without the aid of a Lewis acid.[7] Moreover, the oxovanadium(V)-induced ligand coupling of aryldialkylzincates proceeds more effectively than that of alkylarylzinc compounds as reported.[6] In fact, Me_3ZnLi (1.2 equiv) added to 2-cyclohexenone to afford the zinc enolate, which underwent oxovanadium(V)-induced oxidation, giving **2a** in 78% yield (Table 3, entry 1). This two-step procedure can be applied to various lithium trialkylzincates, affording the corresponding vicinally dialkylated cycloalkanones in good yields (Table 3). Butylzinc enolate **5c** generated from **1** and Bu_3ZnLi was oxidized by $VO(OEt)Cl_2$, giving dibutylcyclohexanone **2c** in 75% yield (entry 2). When Bu_3ZnLi−TMEDA,[11] prepared from a $ZnCl_2$−TMEDA complex and BuLi, was used as a reagent for vicinal alkylation of **1**, **2c** was obtained in 98% yield (entry 3). 2-Cyclopentenone similarly underwent oxidative vicinal alkylation with Bu_3ZnLi−TMEDA to give 2,3-dibutylcyclopentanone (**7**) in 56% yield (entry 4). It is noteworthy that two different alkyl groups can be introduced regioselectively, giving 2-methyl-3-butylcyclohexanone **2d**, when $Me_2BuZnLi$[11] was employed (entry 5).

Table 3. Oxidative Coupling Reaction with Zincate[a]



1: n = 2
4: n = 1

5a: n = 2, R = R' = Me,
5c: n = 2, R = R' = Bu,
5d: n = 2, R = Me, R' = Bu,
6 : n = 1, R = R' = Bu

2a: n = 2, R = R' = Me,
2c: n = 2, R = R' = Bu,
2d: n = 2, R = Me, R' = Bu,
7 : n = 1, R = R' = Bu

entry	substrate	zincate	yield / %[b] (*trans*/*cis*)
1	**1**	Me_3ZnLi	**2a** 78 [72] (54 / 46)
2	**1**	Bu_3ZnLi	**2c** 75 [68] (78 / 22)
3	**1**	Bu_3ZnLi•TMEDA	**2c** 98 [72] (72 / 28)
4	**4**	Bu_3ZnLi•TMEDA	**7** 56 [38] (74 / 26)
5	**1**	$Me_2BuZnLi$	**2d** 60 [51] (71 / 29)

[a] $R_2R'ZnLi$, 1.2 equiv. Reaction conditions for the oxidation with $VO(OEt)Cl_2$; 0 °C - r.t., 20 h in entries 1-2 and 5, -78 °C, 8 h in entries 3-4. [b] Determined by GC. Isolated yields are shown in parentheses.

In summary, a novel nucleophilic vicinal dialkylation at both the α- and *β*-positions of cyclic α,*β*-enones with an organozinc compound is induced by an oxovanadium(V) compound. This method permits selective 1,4-addition and oxidative ligand coupling in a one- or two-step procedure.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Typical procedure for vicinal dialkylation**: To a solution of **1** (1.0 mmol) in THF (2.0 mL) under argon at −78 °C was added Me_2Zn (2.0 mmol, 2.0 mL, 1.0 M in Hexane) followed by $VO(OEt)Cl_2$ (2.0 mmol), and the mixture was stirred for 20 h at −78 °C. Workup gave the desired dialkylated product **2**.

(11) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581.

(12) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141.