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Regioselective Monoalkylation of Ketones with Allylic Nitro Compounds

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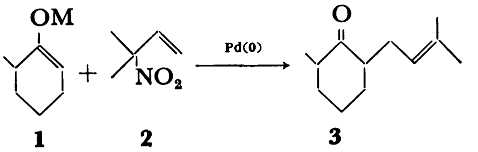
Synopsis. Lithium enolates from 2-methylcyclohexanone and *p*-methylacetophenone react with allylic nitro compounds in the presence of triethylborane (2 equiv) and Pd(PPh$_3$)$_4$ (5 mol%) to give monoallylated compounds regioselectively.

Palladium-catalyzed allylic alkylations are extremely useful synthetic reactions, with allylic acetates being among the most commonly used allylic compounds.[1] Recently, allylic nitro compounds have been demonstrated to react with stabilized nucleophiles such as carbanions from active methylene compounds, amines or sulfinate ions in a similar way.[2,3] In this paper we wish to report the allylic alkylation of allylic nitro compounds with the less stabilized nucleophiles such as enolates from ketones, which will expand the scope of the allylic alkylation.

The reaction of various enolates (**1**) from 2-methylcyclohexanone with 3-methyl-3-nitro-1-butene (**2**) was carried out under the conditions summarized in Table 1. The results are also summarized in this table.



(1)

1 **2** **3**

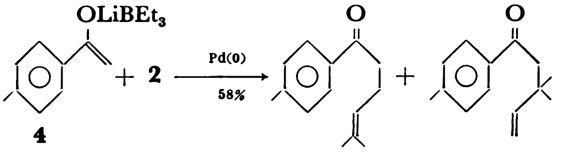
M = Li, Li + 2BEt$_3$, ZnCl, MgCl, CdCl, SnBu$_3$, SiMe$_3$

The reaction of the lithium enolate with **2** did not give the allylated compound (**3**) in good yield even if a catalytic system [bis(dibenzylideneacetonato)palladium+1, 2-bis(diphenylphosphino)ethane, Pd(dba)$_2$-dppe] which allowed the alkylation of allylic acetates with lithium enolates[4] was used. However conversion of the counter cation from lithium to boron or zinc enhanced the reactivity of the present reaction.[5] Thus, 6-methyl-2-prenylcyclohexanone (**3**) was prepared in 62% or 45% yield by the reaction with the boron or zinc enolate, respectively, where the regiochemistry of the enolate was preserved and the nucleophile attacked at the less hindered site predominantly.[6] Although enol stannates are reported to be reactive to palladium-catalyzed reaction of allylic acetates,[7] they are inert to **2**.[8] *p*-Methylacetophenone (**4**) was also monoalkylated to give **5** and **5′** in the similar way. (Eq. 2).

Table 1. Reaction of metal 6-methylcyclohexenolates with **2**

M	Catalyst[a)]	Yield of **3** %[b)]
Li	A	11
Li	B	24
Li+2BEt$_3$	A	70 (62)[c)]
Li+2BEt$_3$	None	0
ZnCl	A	52 (45)[c)]
MgCl	A	0
CdCl	A	3
SnBu$_3$	A	0
SiMe$_3$	A	0

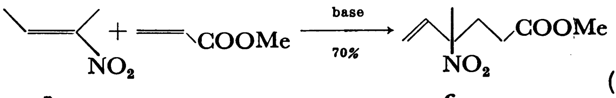
a) A: Pd(PPh$_3$)$_4$ (5 mol%) B: Pd(dba)$_2$+dppe (3 mol%). b) Yields were determined by GLC. c) Isolated yields.
All reactions were carried out at room temperature for 20 h in dry THF.



(2)

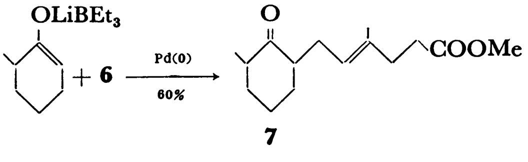
5 (90 : 10) **5′**

Although compounds **3** and **5** can be prepared by the reaction of the corresponding acetate, the use of allylic nitro compounds as allylic electrophiles has also its own merits over the conventional alkylating agents. Allylic nitro compounds can be prepared by different methods from those for preparation of other alkylating agents.[2,3] Furthermore, electrophiles can be introduced regioselectively at the α-position of the nitro compounds. For example, 2-nitro-2-butene (**5**) was readily converted into allylic nitro compound (**6**) by very simple procedures as shown in Eq. 3, where the isomerization of **5** and the Michael addition of the resultant allylic nitro compound to methyl acrylate took place simultaneously. Alkylation of **1** with **6** gave the monoalkylated product, **7**, in good yield.[9]



(3)

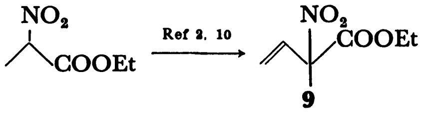
5 **6**



(4)

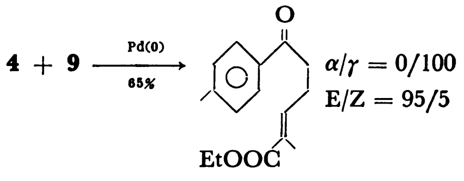
7

Introduction of a vinyl group to nitroalkanes also provides a useful method for the preparation of allylic nitro compounds.[2] Ethyl 2-methyl-2-nitro-3-butenoate (**9**) was prepared by this procedure. Alkylation of **4** with **9** gave the monoalkylated compound, **10**, in 65% yield with high regio-and stereoselectivity. The products **5** and **10** are good precursors of terpenoids such as curcumene and dehydrolancenol, respectively.



(5)

9



$\alpha/\gamma = 0/100$ (6)

E/Z = 95/5

10

Experimental

Preparation of Allylic Nitro Compounds. Allylic nitro compounds, **2**[9] and **9** were prepared by the Michael addition of the corresponding nitro compounds to phenyl vinyl sulfoxide and the subsequent termolysis.[2,10] **9**: IR (neat) 1340, 1540, 1730 cm^{-1}, NMR ($CDCl_3$) δ 1.36 (3H, t, J=8 Hz), 1.84 (3H, s), 4.22 (2H, q, J=8 Hz), 5.30 (1H, d, J=10 Hz), 6.28 (1H, dd, J=10 and 17 Hz). 4-Methyl-4-nitro-5-hexenoate (**6**) was prepared as follows: A solution of 2-nitro-2-butene (**5**, 1.01 g, 10 mmol), methyl acrylate (1.03 g, 12 mmol) and tetramethylguanidine (0.233 g, 2 mmol) in 10 ml of acetonitrile was kept at room temperature for 24 h. The reaction mixture was poured into water and extracted with diethyl ether. The usual work-up followed by distillation with Kugelrohr gave **6**, 1.31 g (70%), bp 150 °C/1 mmHg (1 mmHg=133.322 Pa). IR (neat) 1370, 1535, 1720 cm^{-1}, NMR ($CDCl_3$) δ 1.64 (3H, s), 2.26 (4H, m), 3.60 (3H, s), 5.20 (1H, d, J=17 Hz), 5.24 (1H, d, J=10 Hz), 6.12 (1H, dd, J=17 and 10 Hz). Found: C, 51.28; H, 6.99; N, 7.48. Calcd for $C_8H_{13}NO_4$: C, 51.32; H, 6.94; N, 7.48.

Reaction of 2-Methylcyclohexanone with **2**. *Preparation of 3*: The lithium enolate of 2-methylcyclohexanone was prepared according to the literature[5] by using *n*-BuLi (1.6 M (1 M=1 mol dm^{-3}) in hexane, 0.683 ml, 1.1 mmol), diisopropylamine (0.11 g, 1.1 mmol) and THF (3 ml). Triethylborane (1 M in hexane, 2 ml) was added to the lithium enolate at −75 °C and stirred for 35 min at this temperature. To the above solution was added a solution of **2** (0.115 g, 1 mmol) and $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) in THF (1 ml). The reaction mixture was warmed to room temperature and stirred for 20 h, then worked up in the usual way after destroying Et_3B by adding 3 M NaOH (1 ml) and H_2O_2 (30%, 0.5 ml). Pure **3** was isolated by column chromatography (silica gel/benzene–hexane), 0.11 g (62%). IR (neat) 1700 cm^{-1}, NMR ($CDCl_3$) δ 0.98, 1.05 (3H, d, J=7 Hz), 1.2—1.6 (10H, m), 1.60 (3H, s), 1.68 (3H, s), 4.9—5.2 (m, 1H). The ratio of **3**/other isomers was determined by GLC to be 98/2. The spectral data were in good agreement with those of the literature.[5] Other metal enolates were preapard according to the literature[5] and the reaction of them with **2** was carried out in the same way. The yield of **3** was determined by GLC or isolation of pure product. Following compounds were prepared by this procedure.

5: The reaction starting from *p*-methylacetophenone (0.403 g, 3 mmol) gave the mixture of **5** and **5′** (0.35 g, 58%), bp 120—130 °C/1 mmHg. IR (neat) 1700 cm^{-1}, NMR ($CDCl_3$) δ 1.60 (3H, s), 1.64 (3H, s), 2.36 (3H, s), 2.42 (2H, t, J=8 Hz), 2.92 (2H, m), 5.0—5.3 (1H, m), 7.2 (2H, m), 7.8 (2H, m). The regio isomer **5′**; NMR ($CDCl_3$) δ 1.16 (6H, s), 2.36 (3H, s), 2.4 (2H, s), 4.8—5.1 (2H, m), 5.8—6.2 (1H, m), 7.2 (2H, m), 7.8 (2H, m). MS of **5**+**5′**, Found: *m/z* 202.1348. Calcd for $C_{14}H_{18}O$: M, 202.1295.

7: The reaction using 2-methylcyclohexanone (0.336 g, 3 mmol) gave **7**, 0.455 g (60%). IR (neat) 1710, 1720 cm^{-1}, NMR ($CDCl_3$) δ 0.98, 1.04 (3H, d, J=8 Hz), 1.60, 1.64 (3H, s), 1.2—2.6 (14H, m), 3.65, 3.67 (3H, s), 5.0—5.4 (1H, m). This is the mixture of the cis and trans 2,6-isomers whose ratio is about 65/35 by GLC and NMR. Although exact ratio of *E/Z* was not determined, the *E*-isomer was predominant. Found: 252.1712. Calcd for $C_{15}H_{24}O_3$: M, 252.1724.

10: The reaction in 3 mmol scale gave **10**, 0.51 g (65%). IR (neat) 1690, 1710 cm^{-1}, NMR ($CDCl_3$) δ 1.22 (3H, t, J=8 Hz), 1.85 (3H, s), 2.38 (3H, s), 2.46 (2H, q, J=8 Hz), 3.00 (2H, t, J=8 Hz), 4.20 (2H, q, J=8 Hz), 6.82 (1H, t, J=8 Hz), 7.22 (2H, m), 7.80 (2H, m). Found: 260.1423. Calcd for $C_{16}H_{20}O_3$: 260.1411.

The *E/Z* ratio was determined by GLC and NMR to be 95/5.

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3) R. Tamura and L. S. Hegedus, *J. Am. Chem. Soc.*, **104**, 3727 (1982); R. Tamura, K. Hayashi, M. Kakihana, M. Tsuji, and D. Oda, *Chem. Lett.*, **1985**, 229.

4) J. C. Fiaud and J. J. Malleron, *J. Chem. Soc., Chem. Commun.*, **1981**, 1159.

5) E. Negishi and R. A. John, *J. Org. Chem.*, **48**, 4098 (1983), in which similar tendency of the rate enhancement of the reaction with allylic acetates was reported. It is not clear about the structure of the enolate formed by the addition of triethylborane to the lithium enolate, but transmetallation from lithium to boron should occur to some extent.

6) The regiochemistry of the present reaction is affected by mainly two factors, steric and electronic effects. Secondary ketones gave only γ-substitition product as in Eq. 1 and primary ketones gave some amounts of α-substitution product as in Eq 2. This selectivity in the present reaction is higher than that in the reaction with stabilized nucleophiles.[2,3]

7) B. M. Trost and E. Keinan, *Tetrahedron Lett.*, **21**, 2591 (1980).

8) This difference may be due to the difference of catalytic spieces between the reaction of allylic nitro coompounds and allylic acetates. The catalysis in the former reaction involves the nitro group which deactivates the reaction with enol stannates.

9) Allylic alkylation of allylic nitro compounds with enolates of ketones is limited to tretiary nitro compounds. For example, the reaction of **1** with primary or secondary allylic nitro compounds resulted in recovery of 2-methylcyclohexanone.

10) R. Tanikaga, H. Sugihara, K. Tanaka, and A. Kaji, *Synthesis*, **1977**, 299.