Tetrahedron Letters, Vol. 34, No. 46, pp. 7395-7398, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

α-Methylation of Ketones via Manganese-Enolates: Absence of Undesired Polyalkylation

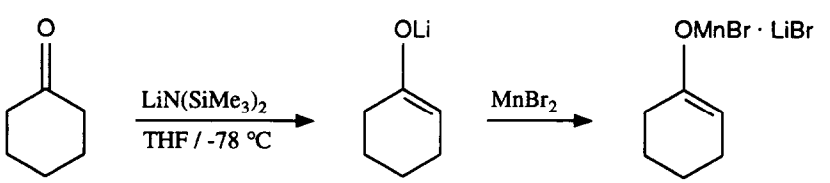
Manfred T. Reetz* and Helmut Haning

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany

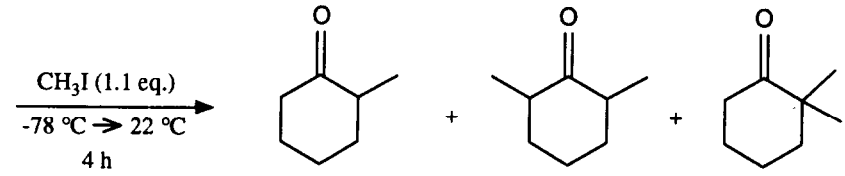
Summary: *The transmetalation of ketone lithium-enolates using $MnBr_2$ generates manganese-enolates which react with CH_3I to provide α-methylated ketones with essentially no undesired polyalkylated byproducts.*

The α-alkylation of ketones via their enolates is one of the standard reactions in organic synthesis.[1] Two complementary methods are available for the introduction of primary and tertiary alkyl groups, respectively: 1) Lithiumenolates are reacted with CH_3I or other S_N2-active alkylating agents[1,2], and 2) enolsilanes are allowed to interact with S_N1-active alkylhalides (e. g., R_3CCl) in the presence of Lewis acids such as $TiCl_4$.[3] Whereas the latter process provides mono-alkylated ketones[3], the former reaction is often accompanied by the undesired formation of polyalkylated products (10 - 30%).[1,2] In order to solve the longstanding problem of polyalkylation, a number of methods has been developed, generally involving at least two synthetic steps.[1-4] For example, a classical and reliable procedure involves introduction of an activating ester moiety at the α-carbonyl position via Claisen condensation, mono-alkylation of the 1,3-dicarbonyl compound and removal of the ester function via decarboxylation.[1] Recently, several attractive new strategies have been proposed, including the reaction of Li-enolates with Me_2Zn followed by RI.[5] Furthermore, enolsilanes have been alkylated with RI/NBu_4F[6], with $ROTf/CH_3Al(OAr)_2$[7] or with RI/CF_3CO_2Ag[8]. In most cases an excess of primary alkylating agent is necessary. We now report that manganese enolates react with the equivalent amount of CH_3I to provide the α-methylated products which are essentially free of undesired polyalkylated byproducts.

Upon transmetalating the Li-enolate **(2)** (prepared by deprotonating cyclohexanone **(1)** with $LiN(SiMe_3)_2$) with $MnBr_2$, a manganese enolate **(3)** of unknown structure or aggregation state is generated which reacts with CH_3I (1.1 equiv.) to form 76% of 2-methylcyclohexanone **(4)** together with traces of dimethylated products **(5)** and **(6)**, the rest being small amounts of **(1)** and aldol condensation byproducts (as monitored by GC). No tri-methylated products could be detected.



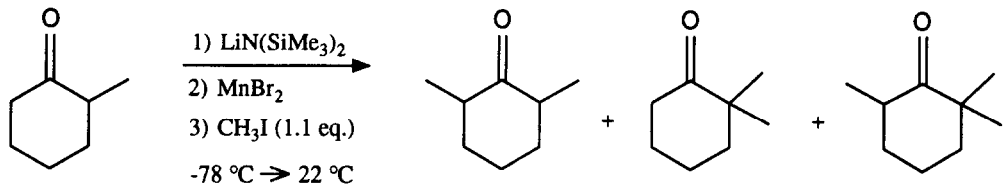
(1) **(2)** **(3)**

(3) 

	(4)	(5)	(6)
	76%	0.8%	0.4%
DMPU as additive:	94%	1.7%	0.8%

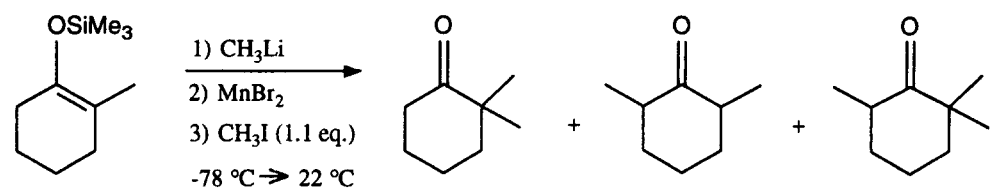
In the presence of 3 eq. of 1,3-dimethyl-2-oxohexahydropyrimidine (DMPU) conversion to **(4)** is higher (94%), the mono- to dimethylation ratio being 97 : 3. At room temperature the latter reaction is similar (95% **(4)**; **(4)** : **(5+6)** = 98 : 2).

Using the same method, 2-methylcyclohexanone **(4)** was transformed into ketones **(5)** and **(6)**, the ratio of mono- to dialkylation being 99 : 1. Again, no sign of trimethylation (i. e., no tetra-methylcyclohexanone) was observed. Regioselectivity is high ((**5**) : (**6**) = 95 : 5) and reflects the regioselectivity in the deprotonation step. In all cases ketone **(5)** is formed as a mixture of diastereomers (60 : 40).

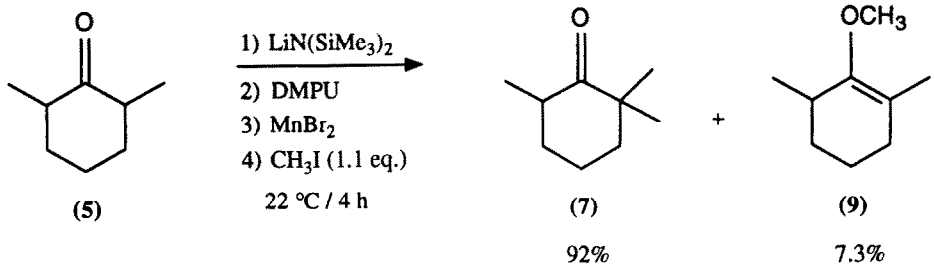


(4)	(5)	(6)	(7)
	89%	5%	1%

Upon generating the "thermodynamic" enolate corresponding to the enolsilane **(8)**, essentially complete mono-methylation was realized once again (mono- to dialkylation = 99 : 1). Furthermore, regioselectivity turned out to be excellent (99%). The methylation can also be performed at room temperature, the results being essentially the same. Ketone **(5)** was smoothly methylated to form **(7)** with no signs of dialkylation. The only side-product is the O-methylated compound **(9)** (7.3%) and starting ketone **(5)** (0.7%).



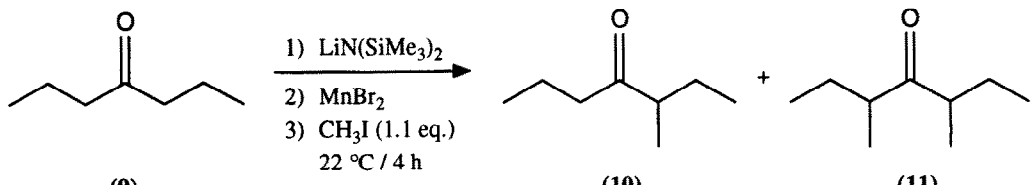
(8)	(6)	(5)	(7)
	77%	1%	0.9%



(5) (7) (9)

92% 7.3%

Finally, 4-heptanone (**9**) was smoothly mono-methylated, DMPU not being necessary:

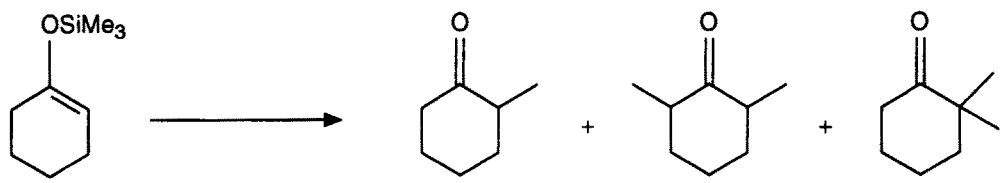


(9) (10) (11)

95% 0.5%

The synthetic protocol described herein has some limitations. For example, alkylations with n-alkyl iodides such as n-BuI do not work as well. It is also worth mentioning that the use of lithium diisopropylamide (LDA) in place of $LiN(SiMe_3)_2$ results in lower yields and more undesired polyalkylation.

Several other transmetalating agents were tested ($Mn(OC(O)tBu)_2$, $Fe(acac)_2$, and CuBr · 2 LiBr), but they all turned out to be considerably less efficient, as shown by the reaction of the metal enolate corresponding to enolsilane (**12**). Relevant is Posner's observation that the Li-enolate derived from 3-methyl-3-phenylcyclopentanone can be transmetalated with CuCN and reacted with a five-fold excess of CH_3I in the presence of HMPA to form mainly mono-methylated product (5% undesired dimethylation).[9]



(12) (4) (5) (6)

1) CH_3Li 2) CH_3I (1.1 eq.) -78 °C → 22 °C / 3 h	66%	7%	8%
1) CH_3Li 2) CuBr · 2 LiBr 3) CH_3I (1.1 eq.) -78 °C → 22 °C / 3 h	75%	5%	7%

In conclusion, we have shown that the transmetalation of Li-enolates derived from simple ketones leads to manganese analogs which react fairly cleanly with CH_3I to provide α-methylated ketones. Cahiez

has discovered similar effects upon deprotonating ketones with $Mn[NR(Ar)]_2$ and reacting the corresponding Mn-enolates with CH_3I.[10] Apparently, the rate of trans-protonation between alkylated products and initial manganese enolates is slow with respect to alkylation, so that undesired polyalkylation cannot easily compete. The alkylation of Mn-enolates expands the scope of organomanganese reagents in organic synthesis.[11]

Typical Procedure: A ketone (3 mmol) is added to a solution of 3.05 mmol LiHMDS in 8 ml of dry THF under argon at -78 °C. The solution is stirred for 40 minutes at this temperature. After warming to room temperature, 9 mmol (1.09 ml) DMPU are added and the mixture stirred for 10 minutes. The enolate-solution is cannulated to 3 mmol (645 mg) anhydrous $MnBr_2$ and stirred until a clear reddish-brown solution is obtained (10 - 15 min). Then 3.3 mmol (205 µl) methyl iodide are added via a syringe. After 4 h the reaction is quenched with sat. NH_4Cl, diluted with 50 ml ether, extracted with sat. aq. EDTA solution, sat. $NaHCO_3$ and water and dried over $MgSO_4$. The solution is subjected to GC analysis.

Acknowledgement

This work was supported by the DFG (Leibniz-Programm). H. Haning thanks the Schering AG for a predoctoral stipend. We thank F. Sagheb for GC analyses.

References and Notes

1 (a) House, H. *Modern Synthetic Reactions*, 2nd ed., Benjamin, W. A. Menlo Park 1972. (b) Caine, D. *Carbon-Carbon Bond Formation* (Augustine, R. L., ed.), Marcel Dekker, N. Y. 1979, Vol. 1, p. 85 ff. (c) Caine, D. in *Comprehensive Organic Synthesis* (Trost, B. M., ed.), Pergamon Press, Oxford 1991, Vol. III.

2 (a) Tardella, P. A. *Tetrahedron Lett.* **1969**, 1117. (b) Liotta, C. L.; Caruso, T. C. *Tetrahedron Lett.* **26** (1985) 1599. (c) Haynes, R. K.; Lambert, D. E.; Schober, P. A.; Turner, S. G. *Aust. J. Chem.* **40** (1987) 1211.

3 Review of α-alkylation of carbonyl compounds via their enolsilanes using S_N1-active alkyl halides in the presence of Lewis acids: (a) Reetz, M. T. *Angew. Chem.* **94** (1982) 97; *Angew. Chem. Int. Ed. Engl.* **21** (1982) 96. See also (b) Reetz, M. T.; Chatziiosifidis, J.; Hübner, F.; Heimbach, H. *Org. Synth.* **62** (1984) 95.

4 d'Angelo, J. *Tetrahedron* **32** (1976) 2979.

5 Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **54** (1989) 1785.

6 Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **104** (1982) 1025.

7 Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **114** (1992) 4422.

8 Jefford, C. W.; Sledeski, A. W.; Lelandais, P.; Boukouvalas, J. *Tetrahedron Lett.* **33** (1992) 1855.

9 Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **101** (1979) 934.

10 Cahiez, G. personal communication 1993.

11 Reviews of organomanganese reagents: (a) Cahiez, G.; Normant, J. F. *Modern Synthetic Methods* (Scheffold, R. ed.), Wiley, N. Y. 1983, Vol. III, p. 173. (b) Kasatkin, A. N.; Tsypyshev, O. Y.; Romanova, T. Y.; Tolstikov, G. A. *Russ. Chem. Rev.* **61** (1992) 537. See also (c) Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **33** (1992) 6963.

(Received in Germany 4 September 1993; accepted 14 September 1993)