Highly Regioselective Alkylation at the More Hindered α-Site of Unsymmetrical Ketones by Use of Their Potassium Enolates. A Comparative Study with Lithium Enolates

Yannick Quesnel, Laure Bidois-Sery, Jean-Marie Poirier† and Lucette Duhamel*

Université de Rouen, UPRES-A 6014, IRCOF, F-76821 Mont Saint Aignan, Cedex (France)

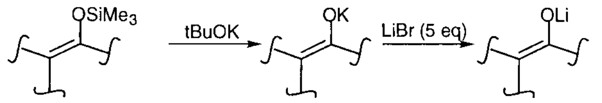
Fax 02 35 52 24 11; Lucette.Duhamel@univ-rouen.fr

† Deceased on May 7, 1997

Received 19 November 1997

Abstract: Alkylation of regioisomeric potassium enolates **4** and **6** obtained from corresponding silyl enol ethers **2** and **3** occurs at the most substituted site affording ketones **8**. Alkylation of corresponding lithium enolates **5** and **7** occurs at the expected site affording ketones **8** or **9**. As an application the one pot synthesis of spiroketones **13** from silyl enol ethers **12** is described.

Alkylation of enolates is a very useful reaction to form carbon-carbon bonds.[1] It is well-known that starting from an unsymmetrical ketone such as 2-methylcyclopentanone **1a** or 2-methylcyclohexanone **1b**, the regioselectivity of the alkylation, in non equilibrating conditions, is directly controlled by the structure of the starting enolate.[2-10] Thus, intensive efforts have been made to generate either the less substituted enolate or the more substituted one.[2-15] Lithium enolates have been intensively studied whereas only comparatively few papers concern potassium enolates. This is due to a lack of convenient methods for regioselective and stereoselective preparation of potassium enolates[6,14] in contrast to their lithium counterparts.[2-4,10-13] We have reported that regiocontrolled and stereocontrolled potassium enolates could be prepared by treating corresponding silyl enol ethers with potassium *tert*-butoxide; a metal exchange using five equivalents of lithium bromide led to the corresponding lithium enolates (Scheme 1).[14]



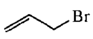
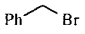
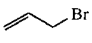
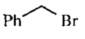
Scheme 1

In this paper we report a comparative study of the reactions of potassium and lithium enolates obtained in these conditions toward alkylhalides.

Starting from 2-methylcyclopentanone **1a** and 2-methylcyclohexanone **1b**, we prepared the tetra- and tri-substituted trimethylsilyl enol ethers **2** and **3**,[16] their corresponding potassium enolates **4** and **6**, and lithium enolates **5** and **7** according to previous procedures (Schemes 1, 2).[14,15] In all cases, control experiments using their condensation with acetyl chloride have shown that the structure of the initial silyl enol ethers was retained.

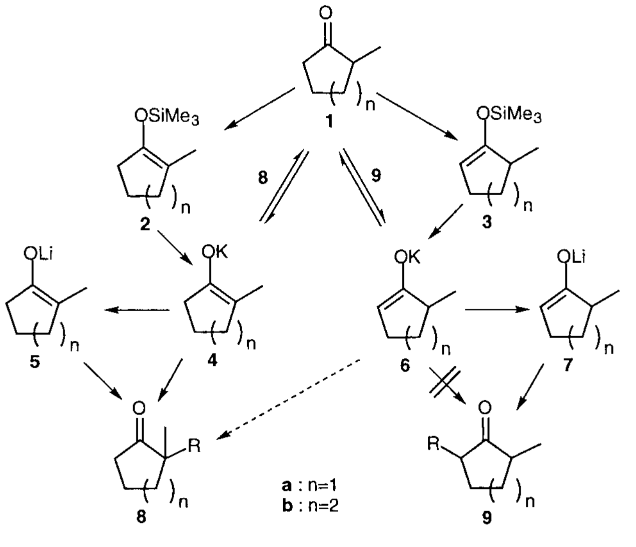
We studied the alkylation of these eight enolates with allylbromide and benzylbromide in THF (-78°C, 1h for K enolates, -15°C, 15h for Li enolates) (Table 1, runs 1-16).[17] The composition of the crude product was determined by ^{1}H NMR and the major alkylated ketones were isolated. As shown in Table 1, lithium enolates **5** and **7** led

Table 1 . Alkylation of enolates **4-7**

					Crude alkylation product[a]				Isolated yield[b]	
	n	**2/3**	M	RX	**1**	**8**	**9**	**10**[c]	**8**%	**9**% (*cis/trans*)[a]
1	1	95/5	Li		8	88	<2	<2	71	55 (69/31)
2		1/99	Li		18	17	63	<2	13	
3		95/5	K		10	86	<2	<2	72	
4		1/99	K		14	82	<2	<2	70	
5	1	95/5	Li		21	75	<2	<2	68	45 (58/42)
6		1/99	Li		30	15	53	<2	12	
7		95/5	K		10	86	<2	<2	72	
8		1/99	K		13	79	6	<2	79	
9	2	95/5	Li		19	79	<2	<2	71	65 (58/42)
10		1/99	Li		18	<2	78	<2		
11		95/5	K		22	69	7	<2	51	
12		1/99	K		16	82	<2	<2	70	
13	2	95/5	Li		36	60	<2	<2	53	67 (59/41)
14		1/99	Li		21	<2	75	<2		
15		95/5	K		23	73	<2	<2	53	
16		1/99	K		16	78	4	<2	60	
17	1	95/5	K	MeI	16[d]	67[d] (58)[e]	2[d]	13[d,f]		
18		1/99	K		16[d]	68[d] (55)[e]	1[d]	13[d,f]		
19		50/50	K		15[d]	69[d] (60)[e]	1[d]	13[d,f]		

a) Determined by ^{1}H NMR, unless otherwise stated.
b) After chromatography on silica gel.
c) See note 18.
d) Determined by GC (surface ratio).
e) Determined by GC, using propylbenzene as internal standard.
f) Tetramethylcyclopentanone (2%) was detected by GC.

predominantly to the expected monoalkylated ketones **8** and **9**, respectively. Surprisingly, starting from potassium enolates **4** and **6**, the 2,2-disubstituted ketones **8** were obtained independently from structure **4** or **6** as the starting enolates (Scheme 2); the regioisomeric disubstituted ketone **9** was detected as a very minor by-product, in addition to the minor dialkylation product **10**.[18] The predominant ketones **8** or **9** were purified by chromatography on silica gel and isolated from the crude material without contamination with other ketones (Scheme 2).

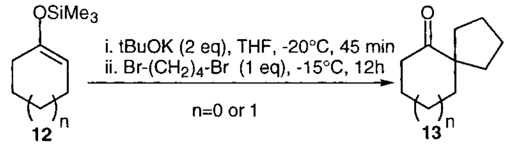


Scheme 2

Methylation of potassium enolates **4a** and **6a** using methyliodide (THF, -75°C, 2h) confirms the preceding results (Table 1, runs 17-19): the composition of the crude product was the same, whatever the structure of the starting silyl enol ethers **2a**, **3a** and 2,2-dimethylcyclopentanone was the main methylation product.[19]

These results can be explained by the known propensity of potassium enolates to equilibrate.[7,15] The equilibration **6** ↔ **4** occurs via the ketone **1** and can be initiated by a catalytic amount of a ketonic compound (ketone **8** or **9**). The alkylation reaction takes place on the most nucleophilic tetrasubstituted potassium enolate **4** (Scheme 2).[20] With lithium enolates, the tightness of the oxygen-metal bond is generally sufficient to prevent proton transfer. [2,21]

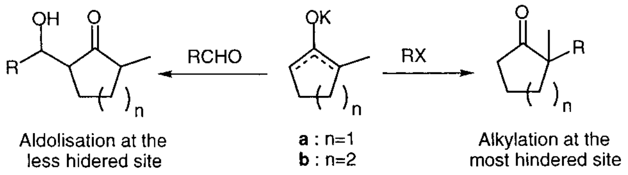
We used the above property to prepare in one pot, spiroketones **13** from silyl enol ethers **12** by dialkylation of their potassium enolates with 1,4-dibromobutane (Scheme 3). This one pot procedure afforded ketones **13** with a 78% yield which compares favorably with those reported in the literature.[22]



Scheme 3

In connection with these results, the regioselective alkylation at the more hindered α–site of the unsymmetrical ketones has been recently reported using another methodology : alkylation of the tetrasubstituted lithium enolates generated by the combined use of aluminium tris(2,6-diphenylphenoxide) and LDA.[10]

Lastly, the complementary results obtained from the aldolisation[15] and the alkylation of potassium enolates must be noted. The aldolisation occurs on the less substituted site, the alkylation on the most substituted one, whatever the starting potassium enolate (Scheme 4). Concerning aldolisation all reactions are equilibrated and the result reflects the relative stability of the potassium aldolates. The formation of alkylated ketones **8** or **9** is obviously non reversible and the alkylation takes place with the most nucleophilic tetrasubstituted enolate.



Scheme 4

In conclusion alkylation of unsymmetrical ketones *via* their potassium enolates obtained from silyl enol ethers occurs at the more substituted α-site whatever the regioisomeric structure of the starting silyl enol ethers, due to the equilibration as the alkylation starts. The proposed method is very convenient for preparative purposes. Only the alkylated ketone **8** has been obtained starting from a mixture of silyl enol ethers **2** and **3**.

Acknowledgment

We thank the Ministère de la Recherche et de la Technologie for a grant (Y.Q.) and Rhône Poulenc Industrialisation for a financial support (L.B.S).

References and notes

(1) House, H.O. *Modern Synthetic Reactions*; Benjamin W.A.; Menlo Park: California, 2nd ed., **1972**, 492-570. d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979-2990. Heathcock, C.H. *Asymmetric Synthesis* vol. 3, Morisson, J.P. Ed Academic Press: New York, **1984**, 1-110. Larock, R.C. *Comprehensive Organic Transformation;* V.C.H. Publishers: New-York, **1989**, p 737-784.

(2) Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.*; **1968**, *90*, 4462-4465.

(3) Patterson, J.W.; Jr. Fried J.H. *J. Org. Chem.* **1974**, *39*, 2506-2509.

(4) Binkley, E.S.; Heathcock C.H. *J. Org. Chem.* **1975**, *40*, 2156-2160.

(5) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257-3258. Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223-1225. Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831-6833.

(6) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R.A. *J. Org. Chem.* **1982**, *47*, 3188-3190. Negishi, E.; Luo, F.T. *J. Org. Chem.* **1983**, *48*, 2427-2430.

(7) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341-1344.

(8) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598-1608.

(9) Reetz, M.T.; Haning, H. *Tetrahedron Lett.* **1993**, *34*, 7395-7398. Bates, R.B.; Taylor, S.R. *J. Org. Chem.* **1993**, *58*, 4469-4470. Cahiez G.; Figadère, B.;. Cléry P *Tetrahedron Lett.* **1994**, *35*, 3065-3068. Cahiez, G.; Chau, K.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3069-3072.

(10) Saito, S.; Ito, M.; Yamamoto H. *J. Am. Chem. Soc.* **1997**, *119*, 611-612.

(11) Stork, G.; Rosen, P.; Goldman, N.L. *J. Am. Chem. Soc.* **1961**, *83*, 2965-2966. Weiss, M.J.; Schaub, R.E; Poletto, J.F.; Jr Allen, G.R.; Coscia, C.J. *Chemistry and Industry* **1963**, 118-119.

(12) House, H.O.; Trost, B.M. *J. Org. Chem.* **1965**, *30*, 1341-1348 and 2502-2509.

(13) Stork, G.; Uyeo, S.; Wakamatsu T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945-4947. Posner, G.H. *Org. React*, Wiley: New York, **1972**, *19*, 1-113. Borowitz, I.J.; Casper, E.W.R.; Crouch, R.K.; Yee, K.C. *J. Org. Chem.* **1972**, *37*, 3873-3878. Lee, S.H.; Hulce, M. *Synlett* **1992**, 485-488.

(14) Duhamel, P.; Cahard, D.; Poirier, J.M. *J. Chem. Soc. Perkin Trans. I* **1993**, *21*, 2509-2511.

(15) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.M. *J. Org. Chem.* **1996**, *61*, 2232-2235.

(16) Cazeau, P.; Moulines, F.; Laporte, O.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9-C13. Cazeau, P; Duboudin, F.; Moulines, F.; Babot O.; Dunoguès J.*Tetrahedron* **1987**, *43*, 2075-2088.House, H.O. *Rec. Chem. Prog.* **1967**, *28,* 98-120. House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem*. **1969**, *34*, 2324-2336.

(17) Prior to use, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and stored under argon. Potassium *tert*-butoxide was purchased from Aldrich and sublimed prior to use. Lithium bromide was dried by heating under reduced pressure.

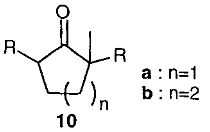
General procedure for alkylation of potassium enolates 4 and 6. To a solution of silyl enol ether **2** or **3** (5 mmol) in THF (10 mL) under argon was added at -15°C a solution of potassium *tert*-butoxide (5 mmol) in THF (5mL) and then stirred for 45 min. After cooling to -78°C, alkyl halide (5mmol) in THF (5mL) was added and stirred for 1 hour at this temperature. The mixture was quenched with water (10mL) at -78°C and extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The ratio of regioisomers was determined by ^{1}H NMR analysis of the crude mixture (Bruker A. C. Spectrometer 200 MHz in chloroform-*d*). The alkylated ketones **8** were isolated by flash chromatography on silica gel (petroleum ether:ether = 98:2) (see table 1).

General procedure for alkylation of lithium enolates 5 and 7. To a solution of silyl enol ether (5 mmol) in THF (10 mL) under argon was added at -15°C a solution of potassium *tert*-butoxide (5 mmol) in THF (5mL) and then stirred for 45 min. 5 equiv. of LiBr (0.217 g) was added at this temperature and stirring was continued for 20 min. Then alkyl halide (5mmol) in THF (5mL) was added and stirred for 15h at this temperature. The mixture was quenched with water (10mL) at -78°C and extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Ketones were isolated by flash chromatography on silica gel (petroleum ether:ether = 98:2). Ketones **9** (R=allyl, benzyl) were eluted after corresponding ketones **8**. *Cis* and *trans* isomers of **9** were separated, the cis isomers were first eluted. Ketones **8** and **9** were characterized by their ^{1}H and ^{13}C NMR spectra. They were known: R = allyl: **8a**,[23] **8b**,[27] **9a**,[24] **9b**.[28] R = benzyl: **8a**,[25] **8b**,[29] **9a**,[26] **9b**.[29]

Spiro[4,5]nonane 13a : ^{1}H NMR : 1.2-1.65 (6H, m); 1.82 (4H, dd, J=5.9 and 12.5); 2.42 (4H, t, J=5.9).
^{13}C NMR : 23.1, 25.7, 36.1, 39.7, 40.2, 56.9, 213.2.

Spiro[4,5]decane 13b : ^{1}H NMR : 1.2-1.65 (8H, m); 1.73 (4H, dd, J=6.1 and 13.0); 2.31 (4H, t, J=6.1).
^{13}C NMR : 22.7; 25.1; 27.2; 35.3 ; 39.3; 39.8; 56.7; 214.4.
MS (m/z) : 152, 111, 95, 81, 67, 55.

(18)



10

(19) 2,2-Dimethylcyclopentanone was difficult to isolate from the crude product by silica gel chromatography or distillation. For other entries to 2,2-dimethylcyclopentanone from alkali enolates of **1a** see [12] and Bouveault, L.; Locquin, R. *Bull. Soc. Chim. Fr.* **1908**, *3*, 437-441. Haller, A.; Cornubert, R. *Bull. Soc. Chim. Fr.* **1926**, *39*, 1724-1732. In all these references, the polyalkylation was also reported.

(20) The reaction of 2-methylcyclohexanone potassium enolates prepared from ketone **1b** (tBuOK (1 eq.), THF, -20°C, 1h) with benzyl bromide (THF, -78°C, 1h) yielded ketone **8b** (R = benzyl) with a 38% chromatographed yield. The regioisomeric ketone **9b** (R = benzyl) was not detected. A large amount of unreacted ketone **1a** was detected by GC in the crude material.

(21) With onium (TBA, TAS)[5] enolates obtained from silyl enol ethers, the alkylation is reported to maintain the structure of the starting silyl enol ether due to the enhanced nucleophilicity of these naked enolates, compared with lithium enolates.[8] The alkylation conditions are also to be noted : the onium enolates are not preformed but obtained in the presence of the alkylating reagent, thus trapped as soon as they are formed, preventing proton transfer and their equilibration before alkylation.

(22) Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc*. **1954**, *76*, 2753-2757. Krieger, H.; Ruotsalainen, H.; Montin, J. *Chem. Ber*. **1966**, *99*, 3715-3717. Eilerman, R.G.; Willis, B.J. *J. Chem. Soc. Chem. Comm.* **1981**, 30-32. Piers, E.; Lau, C.K.; Nagakura, I. *Can. J. Chem*. **1983**, *61*, 288-297. Fitjer, L.; Schlotmann, W.; Noltemeyer, M. *Tetrahedron Lett.* **1995**, *36*, 4985-4988.

(23) Coates, R. M.; Sowerby, R.L. *J. Am. Chem. Soc.* **1971**, *93*, 1027-1029.

(24) Medarde, M.; Lòpez, J.L.; Morillo, M.A.; Tomé, F.; Adeva, M.; Feliciano, A.S. *Tetrahedron Lett.* **1995**, *44*, 8097-8098.

(25) Jacks, T.E.; Nibbe, H.; Wiemer, D.F. *J. Org. Chem.* **1993**, *58*, 4584-4588.

(26) Cornubert, R.; Borrel, C.H.R. *Bull. Soc. Chim. Fr*. **1930**, *47*, 958-966.

(27) House, H.O.; Manning, D.T.; Melillo, D.G.; Lee, L.F.; Haynes, O.R.; Wilkes, B.E. *J. Org. Chem.* **1976**, *41*, 855-863.

(28) Tsuda, T.: Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421-426.

(29) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085-2088. House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1971**, *36*, 2361-2371.