ORGANIC LETTERS

2006
Vol. 8, No. 13
2735−2737

Alkali Metal Counterion Control of Enolate Protonation Stereoselectivity

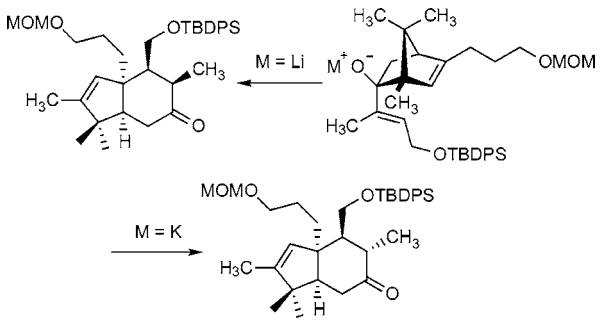
Yang Hu, Raynauld L. Bishop, Andreas Luxenburger, Shuzhi Dong, and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

Received March 29, 2006

ABSTRACT



Generation of the lithium salt of the norbornenol shown (M = H) followed by quenching with aqueous NH_4Cl solution gives predominantly the *β*-epimeric ketone 6. Similar production of the potassium alkoxide leads instead to the α-epimer (99:1). These results reveal the potential importance of alkali metal counterions as stereocontrol elements.

The capacity to adjust conditions for the regioselective deprotonation of unsymmetrical ketones has contributed greatly to advances in synthetic organic chemistry.[1] When kinetic control applies, the product composition is governed by the relative rates of two possible proton abstraction options. Such conditions customarily favor the less-substituted species. On the other hand, if equilibration is capable of operation, thermodynamic control gains importance, with the result that the more substituted enolate is now dominant. When structural features are suitable, stereoisomeric enolates can also result, and control of this type of stereoselectivity is possible to some degree.[2]

Many investigations spawned by the preceding considerations have also led to recognition of important consequences associated with the alkali metal counterion. Thus, lithium enolates are recognized to equilibrate very slowly or not at all with their regioisomers.[3] In contrast, when a small amount of excess ketone is present, potassium enolates experience rapid exchange.[4] This distinctive kinetic difference has been attributed to the increased covalent nature of the oxygen−lithium bond relative to that of the oxygen−potassium counterpart. The much tighter RO^-Li^+ ion pair is presumably less conducive to proton abstraction.

The control by alkali metal counterions of the stereoselectivity of enolate *alkylation* has rarely been encountered and continues to be regarded as a surprising and remarkable phenomenon.[5] To our knowledge, no interdependence between lithium and potassium enolates and the stereochemical control of their *protonation* has yet been documented. The pursuit of such an investigation requires that the identical enolate anion save for the counterion be amenable to generation upon treatment with different bases. The anionically promoted oxy-Cope rearrangement is an important

(1) (a) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*, 3rd ed.; Plenum Press: New York, 1990; pp 209−211.

(2) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

(3) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.

(4) (a) Caine, D. *J. Org. Chem.* **1964**, *29*, 1868. (b) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965.

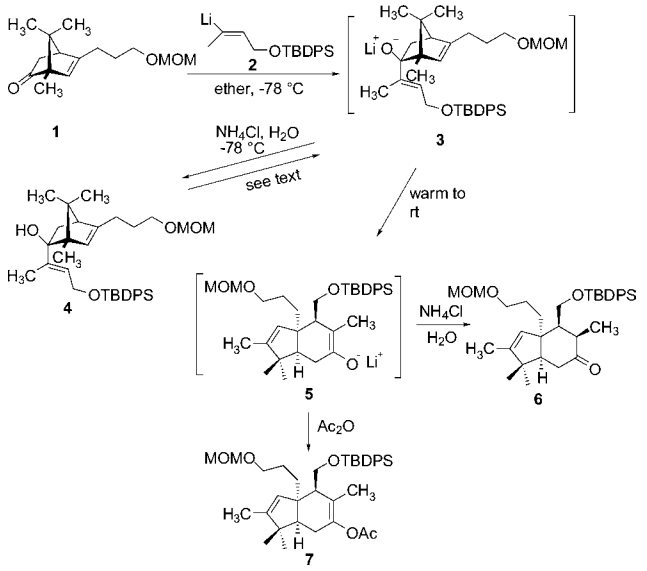
(5) (a) Stork, G.; Gardner, J. O.; Boeckman, R. K., Jr.; Parker, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 2014. (b) Stork, G.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2016.

10.1021/ol060761s CCC: $33.50
Published on Web 05/25/2006

transformation meeting these specifications.[6,7] The locus of the double bonds in the dienol reactants determines their position in the product, and the particular transition state during the [3,3] sigmatropic shift is stereochemically relevant.

The controlling features to be described here were uncovered in the course of a projected total synthesis of the limonoid diterpene known as dumsin.[8] According to the plan, one of the focal points involved 1,2-addition of the vinyllithium reagent **2** to norbornenone **1** (Scheme 1). At

Scheme 1. Formation and Stereoselective Protonation of Lithium Enolate **5**



−78 °C in ether, nucleophilic capture proceeds from the less sterically congested endo surface to generate lithium alkoxide **3**. Although carbinol **4** produced in this way can be conveniently isolated after quenching at low temperature and deprotonated on its own (as **4** to **3**), we soon recognized that the substantial strain in **3** is adequate to allow direct conversion to **5** to materialize simply upon warming to room temperature.

Following the rapid introduction of saturated NH_4Cl solution, **6** was isolated as the major rearrangement product in 78% yield. In a follow-up experiment, the norbornenol **4** dissolved in anhydrous THF was treated with an equivalent of *tert*-butyllithium in pentane at −78 °C. The processing of this reaction mixture in a parallel manner furnished a two-component mixture of ketones dominated by the β-isomer (**6**/**9** = 5:1, Table 1, runs 1 and 2).[9] Continued dominance of the product ratio by **6** was seen when recourse was made to approximately equimolar levels of lithium hexamethyldisilazide in THF (run 3).

(6) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609. (c) Paquette, L. A. *Synlett* **1990**, 67. (d) Paquette, L. A. *Chem Soc. Rev.* **1995**, 9.

(7) (a) Wilson, S. R. *Org. React.* **1993**, *43*, 93. (b) Hill, R. K. In *Compressive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.1.

(8) Paquette, L. A.; Hong, F.-T. *J. Org Chem.* **2003**, *68*, 6905.

(9) The α/β nomenclature is adapted from the field of steroid chemistry.

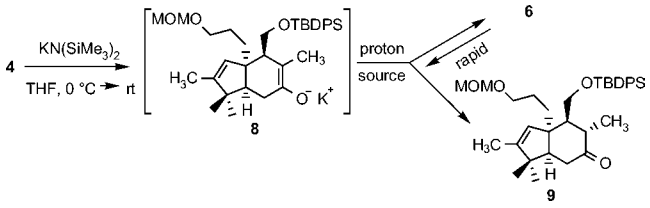
Table 1. Prototypical Deprotonation Studies Involving **4** as the Reactant

run	quantity of **4**	base	amount of base	ratio **6**/**9**	yield, %
		A. Direct Quench[a]			
1	96 mg (0.17 mmol)	*tert*-BuLi[b] (1 M in pentane)	0.19 mmol (1.1 equiv)	5:1	60
2	95 mg (0.17 mmol)	*tert*-BuLi[b] (1 M in pentane)	0.18 mmol (1.05 equiv)	5:1	69
3	50 mg (0.09 mmol)	LiHMDS[c] (1 M in THF)	0.10 mmol (1.1 equiv)	8:1	58
4	85 mg (0.15 mmol)	NaHMDS[c] (1 M in THF)	0.32 mmol (2.1 equiv)	8:1	60
5	116 mg (0.21 mmol)	KHMDS[c] (0.66 M in toluene)	0.23 mmol (1.1 equiv)	1:99	49
6	100 mg (0.18 mmol)	KHMDS[c] (0.66 M in toluene)	0.16 mmol (0.9 equiv)	1:99	44
		B. Inverse Quench[d]			
7	30 mg (0.05 mmol)	*tert*-BuLi[b] (1.7 M in pentane)	0.08 mmol (1.5 equiv)	5:1	66
8	310 mg (0.56 mmol)	KHMDS[c] (0.5 M in toluene)	0.72 mmol (1.3 equiv)	1:99	40
		C. Homogeneous Quench[e]			
9	30 mg (0.05 mmol)	KHMDS[c] (0.5 M in toluene)	0.06 mmol (1.2 equiv)	1:99	44

[a] The enolate solution is cooled to −78 °C at which point aqueous NH_4Cl solution is introduced. [b] Reaction conducted in THF at −78 °C to room temperature. [c] Reaction conducted in THF at 0 °C to room temperature. [d] The cold (−78 °C) enolate anion solution is transferred to the solution of NH_4Cl via cannula. [e] The enolate anion solution was cooled to −78 °C, and a solution of acetic acid in THF was introduced. The mixture was allowed to warm to room temperature, diluted with ether, and washed successively with $NaHCO_3$ and NaCl solutions.

The noteworthy level of stereocontrol found to be operative during the protonation of $Li^+\mathbf{5}^-$ and $Na^+\mathbf{5}^-$ (run 4) prompted comparable scrutiny of the response of the related potassium enolate **8**. This species was generated by proton abstraction from **4** with approximately a molar equivalent of potassium hexamethyldisilazide in THF at a temperature (0 °C) sufficiently elevated to promote rapid and irreversible oxyanionic Cope rearrangement (Scheme 2, runs 5 and 6).

Scheme 2. Generation and Protonation Stereoselectivity Realized with Potassium Enolate **8**



Of direct concern was the proper assessment of the change in reactivity brought on by this seemingly modest structural modification. In fact, the protonolysis of **8** with aqueous NH_4Cl solution gave the α-methyl ketone uniquely without any indication of the coproduction of epimer **6**. This striking demarcation in the partitioning involving **6** and **9** proved to be scale dependent when potassium ions were involved. As long as the quantity of **4** was kept low (100−300 mg), the unidirectional conversion to **9** could be cleanly and repeatedly

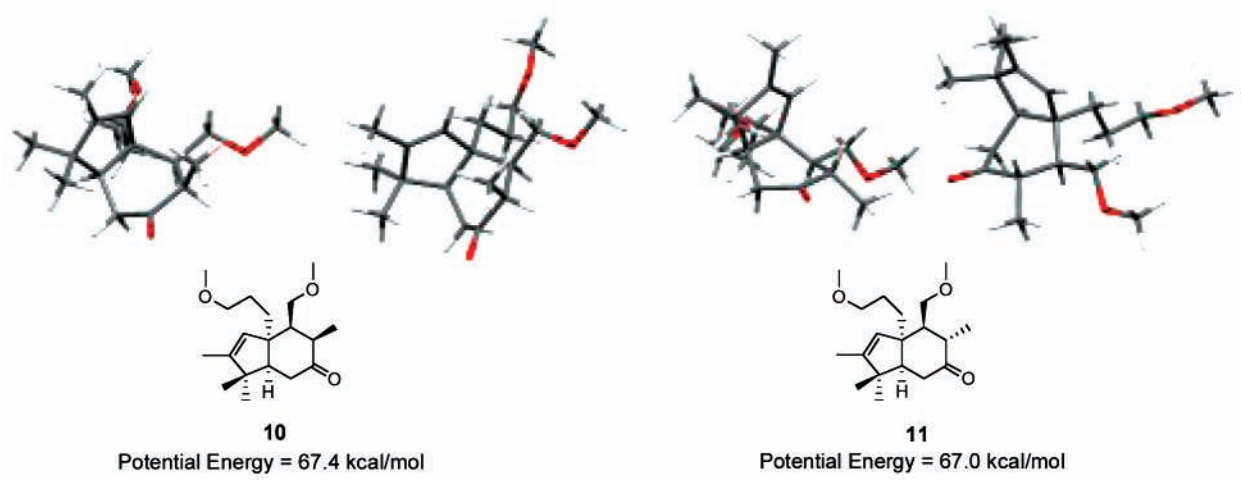


Figure 1. Global minimal energy conformations and steric energies for **10** and **11**.

realized. On the other hand, when samples of **4** on the order of grams were involved and reaction times were not extended, the competitive generation of **6** was made evident. The levels of **6** varied from 5 to 40% depending on the run.

Quenching studies were also carried out by adding the enolate anion to NH_4Cl (inverse quench, runs 7 and 8) and by involving acetic acid dissolved in THF as the proton source (homogeneous quench, e.g., run 9). The involvement of these classical kinetic protonation conditions brought no change in product distributions.

The structural and mechanistic basis advanced for the interrelationships between the nature of the counterion and protonolysis stereoselectivity is as follows. Lithium enolate **5** is considered to be a stable entity with limited reactivity under the conditions specified. Protonation is experienced only upon ultimate quenching with water, with the proton transfer occurring under kinetic control. Alternative treatment of $Li^+\mathbf{5}^-$ solutions generated from either **1** or **4** as in runs 1−3 with acetic anhydride[10] gave enol acetate **7** in high yield. In contrast, all attempts to trap **8** when potassium ions were involved invariably returned only **9** and no **6** or **7**. These data indicate that the more reactive K^+ enolate experiences proton transfer whenever possible, leading rather quickly to the thermodynamic stereoisomer **9**.

The thermodynamic advantage enjoyed by **9** relative to **6** is apparent from two independent directions. First, control experiments involving the admixture of charged **8** with neutral **4** resulted in rapid, wholesale conversion of the latter to **9** (TLC analysis). No comparable equilibration was evident when **5** was the enolate anion involved. Second, MMFFs force field calculations performed on the structurally simplified methyl ethers **10** and **11** provided computational evidence that the α-methyl-oriented isomer **11** is more stable than **10** by 0.4 kcal/mol (Figure 1). A major cause of this energy difference is presumably derived from the nonbonded steric interactions that arise between the axial CH_3 group positioned on the cyclohexane ring and the cyclopentyl methyl substituents in **10**.

In summary, observations have been made that whereas lithium enolate **5** is amenable to kinetically controlled protonolysis with predominant formation of ketone **6** the more reactive potassium salt **8** differs in giving rise instead to **9**. In addition, enol acetate **7** can be readily produced from **5** but not from **8**. This result likely stems from the alternative quenching of **8** by one or more proton sources in advance of the reaction with acetic anhydride. Because **6** is capable of rapid epimerization to **9** in the presence of potassium bases, substantial reversal of stereochemistry is made evident. In light of this profound effect, the specific nature of the alkali metal cation should be given added importance as a possible stereocontrol element in targeted synthesis.

Acknowledgment. Fellowship support by the Alexander von Humboldt Foundation (Feodor Lynen Award to A.L.), the National Cancer Institute (Minority Award to R.L.B.), and the Graduate School of The Ohio State University (Presidential Fellowship to S.D.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and $^1H/^{13}C$ NMR spectral data for **6**, **7**, and **9**. This material is available free of charge via the Internet at http://pubs.asc.org.

OL060761S

(10) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 763−765.