Tetrahedron Letters, Vol. 34, No. 46, pp. 7405-7408, 1993
Printed in Great Britain

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

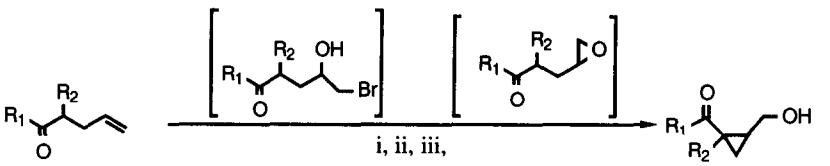
# A Simple One-Pot Preparation Of (Z)-Cyclopropanes from γ,δ-Ketoalkenes using KOH/DMSO Intramolecular Alkylation Conditions.

**Luc Dechoux, Maurice Ebel, Louis Jung, Jean Francois Stambach***

Laboratoire de Chimie Thérapeutique, Université Louis Pasteur, Faculté de Pharmacie,
74 Route du Rhin, 67401 Illkirch Cedex, France. *Fax: 88 66 01 90

***Abstract:*** *Sequential treatment of γ,δ-ketoalkenes with aqueous NBS in DMSO and KOH as solid provides (Z)-cyclopropanes in good overall yields with a diastereoselective excess >99%.*

Solid KOH in dimethyl sulfoxide (DMSO) is a very strong base with pKa value of 27 or even higher[1]. On the other hand, the nucleophilicity of this reagent is low due to the low solubility of KOH in DMSO. Therefore, the mixture is especially useful as a base for the alkylation reaction of ketones[2].
Here we wish to report a one-pot approach to α-keto-α'-hydroxymethyl cyclopropanes from γ,δ-ketoalkenes via intramolecular displacement of γ,δ-ketooxiranes (scheme 1).



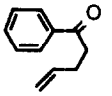
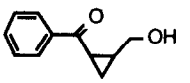
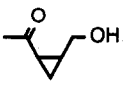
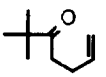
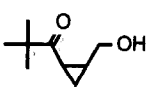
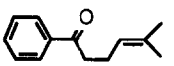
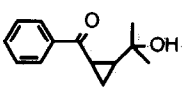
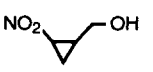
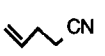
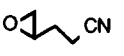
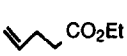
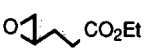
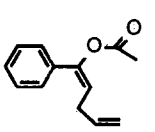
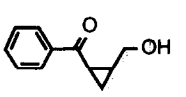
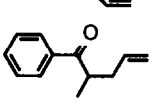
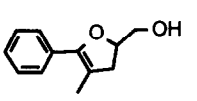
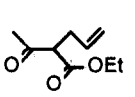
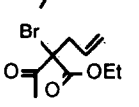
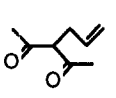
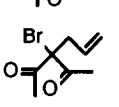
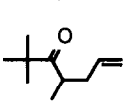
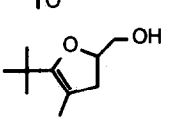
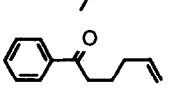
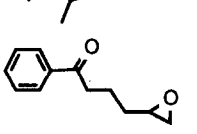

i, NBS-$H_2O$/DMSO. ii, solid KOH . iii, AcOH

**Scheme 1**

Intramolecular nucleophilic substitution at a remote center by a stabilized carbanion is a method that has been extensively utilized for cyclopropane ring formation. Halogenides[3], sulfonic esters[4], and epoxidic oxygens[5] have most often been used as the leaving group, while the carbanion could be stabilized by a carbonyl[6], nitrile[7], carboxylate[8], sulfone[9], dithiane,[10] double bond[11] or phosphorane[12]. When the electron withdrawing group is a carbonyl, some ambiguity may result from the presence of two nucleophilic sites which could displace intramolecularly the epoxide leading respectively to dihydrofurans (O-alkylation) or to cyclopropanes (C-alkylation)[13].

This communication gives a detailed account of our investigation regarding the KOH-DMSO induced reaction of γ,δ-ketoepoxides as applied to the studies of regio and stereochemical control.

**Table 1**

| Entry | Ketoalkenes | Products | *cis/trans* [a] | Yield %[b] |
|---|---|---|---|---|
| 1 |  |  | > 99: 1 | 92 |
| 2 |  |  | > 99: 1 | 87 |
| 3 |  |  | > 99: 1 | 94 |
| 4 |  |  | > 99: 1 | 97 |
| 5 |  |  | > 99: 1 | 65 |
| 6 |  |  | | 98 |
| 7 |  |  | | 97 |
| 8 |  |  | >99: 1 | 76 |
| 9 |  |  | | 67 |
| 10 |  |  | | 79 |
| 11 |  |  | | 84 |
| 12 |  |  | | 49 |
| 13 |  |  | | 96 |

[a] The configuration of cyclopropanes was determined by $^1$H NMR; the *cis/trans* ratio was based on the integration of $^1$H NMR signals. [b] Based on isolated chromatographically homogeneous material.

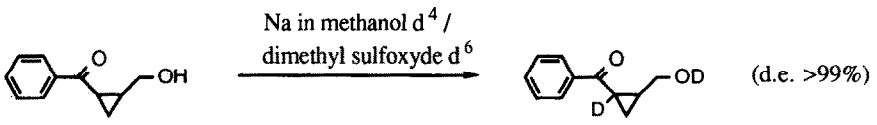
Some representative condensations are summarized in table 1. The reactions were monitored by $^1H$ NMR; the reaction proceeds as depicted on scheme 1 by the regioselective formation of the Markovnikov halohydrin, consequent epoxide formation is then followed by intramolecular oxirane displacement. Utilizing the standard procedure, γ,δ-ketoalkenes bearing two hydrogens on the α–keto position experienced exclusive C-alkylation leading to (Z)-cyclopropane products with diastereoexcess >99% (entries 1-4)[14,15]. No cyclobutane resulting from a 4-endo mode cyclization was formed.

When ambident carbon nucleophiles were present such as in entry 2, the proton under thermodynamic control was regioselectively abstracted, leading to cyclopropanes. No cyclopentanones or dihydrofurans could be observed. Moreover hindered alkenes, such as in entry 4, were also suitable substrates[17].

Even the acylenol (entry 8) experienced C-alkylation under the same stereocontrol as ketone substrates. γ,δ-Ketoalkenes, bearing electron-donating substituents at the α-position, experienced exclusive O-alkylation under KOH induced displacement conditions, leading to dihyhrofuran products (entries 9 and 12). With electron-withdrawing substituents, such as 1,3-ketoester or 1,3-diketo examples in entries 10 and 11 respectively, α–brominated products were formed.

Attempts to obtain cyclobutanes or dihydropyrans under our conditions were unsuccessful (entry 13). The study was extended to other electron-withdrawing substituents (EWG=CN, $NO_2$, $CO_2R$); the γ,δ-nitriloalkene (entry 6), γ,δ-carboxyalkene (entry 7) did not experience intramolecular KOH displacement, the reaction was stopped at the oxirane step. The γ,δ-nitroalkene led in these conditions to the C-alkylated product. Here only cyclopropane was recovered. No 2-isoxazolin-2-oxide that might have resulted from O-alkylation was found in the crude mixture.

In conclusion, the one-pot procedure preparation via base-induced displacement of γ,δ-ketoepoxides gave evidence of building (Z)-cyclopropane rings. Nevertheless, in some cases, dihydrofurans were instead obtained with complete regioselectivity. Electronic rather than steric factors seem to govern the regiocontrol. A greater charge delocalization promotes O-alkylation. The stereocontrol towards cyclopropanes may result from a tight six membered chair like transition state, in which participate the potassium atom which chelates the two oxygen atoms of the ketone and oxirane functions. The high stereocontrol of the reaction suggest that the configurations of (Z)-cyclopropanes are stable under basic conditions. The below scheme showes that the reaction of cyclopropane **1** with metal alkoxides in dipolar protic solvents occurs with a high degree of retention. The cyclopropyl ring must, therefore provide an energy barrier to the inversion or delocalization of the carbanion[18].




**1**

**Scheme 2**

In a typical experiment, to a stirred mixture of γ,δ-ketoalkene (1.0 mmole) in 5 ml wet DMSO (1% $H_2O$) *N*-bromosuccinimide (1.1 mmole) was added as solid over a period of 30 sec in an ice bath. After five minutes 0.25g of KOH as solid (5 mmoles) was added. The reaction was filtered off 15 hrs later, neutralized with a 1 M acetic acid solution and extracted twice with $CH_2Cl_2$. The organic layers were washed twice with a saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated on vacuum. The residual oil was purified by $SiO_2$ column chromatography to afford (*Z*)-cyclopropanes in entries 1,2,3,4,5,8, dihydrofurans in entries 9 and 12, oxiranes in entries 6,7,13, bromoketones in entries 10,11. All products have the expected $^1H$ and $^{13}C$ NMR spectrums.

## References and Notes


**1.** Jolly, W.L., *J. Chem. Educ.* 1967, *44,* 304-306.

**2.** Langhals, E.; Langhals H., *Tetrahedron Lett.* 1990, *32*, 859-862.

**3.** (a) Kleschick, W.A.; Reed, M.W.; Bordner J., *J. Org. Chem.* 1987, *52*, 3168-3169; (b) Henniges, H.; Militzer, H. G.; de Meijere A., *Synlett* 1992, 735-737.

**4.** Bryson, T.R.; Koen J. H.; Roth, G.A., *Synlett* 1992, 723-724.

**5.** (a) Majewski, M.; Snieckus, V., *J. Org.Chem.* 1984, *49*, 2682-2687; (b) Schaumann, E.; Kirschning,A.; Narjes, F., *J. Org. Chem.* 1991, *56*, 717-723.

**6.** Gaoni, Y., *Israel J.Chem.* 1971, *9*, 63-69.

**7.** (a) Stork, G.; Cama, L.D.; Coulson, D.R., *J. Am. Chem. Soc.* 1974, *96*, 5268-5270; ; (b) Lambs, L.; Singh, N.P.; Biellmann, J.F., *J.Org.Chem.* 1992, *57*, 6301-6304.; (c) Lallemand, J.Y.; Onanga, M., *Tetrahedron Lett.* 1975, 585-588.

**8.** (a) Pirrung, M.C.; Dunlap, S.E.; Trinks, U.P., *Helv. Chim. Act.* 1989, *72*, 1301-1310.; (b) Reissig, H.U.; Böhm, I., *J.Am.Chem.Soc.* 1982, *104,* 1735-1736.; (c) Babler, J.H.; Tortorello, A.J., *J. Org. Chem.* 1976, *41*, 885-887.

**9.** (a) Decesare, J.M.; Corbel, B.; Durst, T.; Blount, J.F., *Can.J.Chem.* 1981, *59*, 1415-1424; (b) Gaoni, Y., *Tetrahedron Lett.* 1981, *22*, 4339-4340.; (c) Gaoni, Y., *J.Org.Chem.* 1982, *47*, 2564-2571.

**10.** Krohn, K.; Börner, G., *J.Org.Chem.* 1991, *56*, 6038-6043.

**11.** (a) Beckwith, A.L.J.; Tozer, M.J., *Tetrahedron.Lett.* 1992, *33*, 4975-4978.; (b) Apparu, M.; Barrelle, M., *Tetrahedron* 1978, *34,* 1691-1697.

**12.** Turcant, A.; Le Corre M., *Tetrahedron Lett.* 1977, 789-792.

**13.** (a) Ershov, B.A.; Ermakov, O.A.; Leus, Z.G., *Zh. Org. Khim.* 1969, *5*, 1190-1198. *Chem.Abstr. 71*:101616b (1969); (b) Gaoni, Y., *J.Chem. Soc.(C)* 1968, 2925-2934.

**14.** The *cis /trans* ratios of cyclopropanes in each case were easily calculated by the relative intensities of the methylene protons signals in the $^1H$ RMN spectrum of the crude mixture[16].

**15.** Isomerizations to *trans* products were achieved, with NaH in dipolar aprotic solvents such HMPT or in acidic aprotic conditions ($TFA/CH_2Cl_2$)[17].

**16.** The methylene protons were part of an AA'X system. The δ ppm of the quartet methylene proton is upshielded in the *trans* cyclopropanes, relative to the *cis* isomers.

**17.** The cyclopropane in entry 4, did not isomerize under acidic or basic conditions toward the thermodynamic *trans* isomers.

**18.** (a) Motes, J.M.; Walborsky, H.M., *J.Am.Chem.Soc.* 1970, *92*, 3697-3699.; (b) Walborsky, H.M.; Motes, J.M., *J.Am.Chem.Soc.* 1970, *92*, 2445-2450.


(Received in France 8 July 1993; accepted 13 September 1993)