Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2133-2136, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00265-7

Stereoselective Cyclopropanation of Enones with Ethyl Dimethylsulfonium Acetate Bromide in the Presence of DBU

Iván Collado, Carmen Domínguez, Jesús Ezquerra, Concepción Pedregal*

Centro de Investigación Lilly, S. A. Paraje de la Cruz s/n. 28130 Valdeolmos, Madrid, Spain.

James A. Monn*

Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285.

Abstract: The cyclopropanation reaction of α, β-unsaturated ketones **1a-c** with ethyl (dimethyl sulfuranylidene) acetate (EDSA), generated *in situ* from the corresponding sulfonium bromide salt and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in toluene, leads exclusively to the *exo* adduct **2a-c** (d.e.=100%). Acyclic enones **1d-g**, give mainly the "trans" cyclopropanes **4d-g** with a high degree of stereocontrol (d.e.≥80%). Changing the solvent to $CHCl_3$ affords a 2:1 mixture of "trans" and "cis" cyclopropanes **4d-g** and **5d-g** respectively. The "cis" isomers **5d-g** can be epimerizated to the alternative "trans" isomers **6d-g** under basic conditions. © 1997 Elsevier Science Ltd.

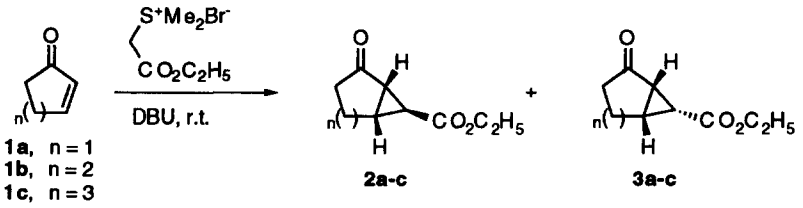
The occurrence of the cyclopropyl subunit in natural and synthetic products has led to the development of many methods for cyclopropanation reactions.[1, 2] While the cyclopropanation of olefins can be achieved *via* carbene insertion through a Simmons-Smith reaction,[3] the cyclopropanation of activated-electron deficient alkenes must proceed through a Michael type addition reaction of various sulfur[2, 4] or phosphorus ylides.[5] Though there are several stereoselective methods for the cyclopropanation of non-polarized olefins,[6] there are few reports of stereoselective cyclopropanation of enones.[7]

Ethyl (dimethyl sulfuranylidene) acetate (EDSA), has been described by Payne.[8] This sulfur ylide reacts with α, β-unsaturated esters, ketones, aldehydes and nitriles to readily afford the corresponding cyclopropanated products as mixtures of diastereomers depending on the substrate. The effect of solvent polarity on the steroselectivity of cyclopropanation of acrolein and methacrolein with the same reagent has been reported by DeLuca,[9] However, the stereochemical outcome for this reaction has never been studied with 3-substituted Michael acceptors.

In this communication, we report that the cyclopropanation of cyclic enones (Scheme 1) and 3-substituted acyclic enones (Scheme 2) with EDSA generated *in situ* by the treatment of ethyl dimethylsulfonium acetate bromide with DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) proceeds smoothly and with a high degree of stereoselectivity.[10]

Table 1 reports the results of the cyclopropanation reactions for several cyclic enones. Payne[8] has described that the cyclopropanation of cyclohexenone (**1b**) with EDSA (preformed from the sulfonium bromide salt by treatment with saturated K_2CO_3 / 12.5 N NaOH solution) in benzene, gives rise to a 2:1

mixture of *exo* **2b** and *endo* **3b** adducts. Furthermore, under the same reaction conditions, we have shown that cyclopentenone (**1a**) in toluene, produces an equimolecular mixture of both **2a** and **3a** in a 70% overall yield.



Scheme 1

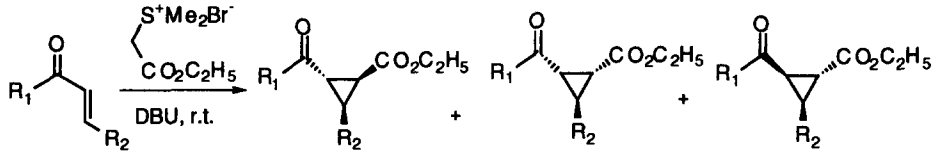
When the reaction was carried out on cycloalkenones **1a-c** (Scheme 1), using ylide generated *in situ* with DBU,[11] in toluene, the *exo* adducts **2a-c** were exclusively obtained (Table 1).[12] The stereochemistry of diastereomers **2a-c** was established on the basis of nOe experiments and coupling constants. To rule out any influence of the basic reaction medium in the stereochemical outcome, adducts **2a** and **3a** were subjected to the DBU reaction conditions without any epimerization.

Table 1[13]

Substrate	Solvent	Time (hours)	Yield (%)[a]	d.e.[b] (%)
1a	$C_6H_5CH_3$	96	66 (**2a**)	100
1b	$C_6H_5CH_3$	96	55 (**2b**)	100
1c	$C_6H_5CH_3$	96	70 (**2c**)	100

[a] Isolated yield. Products in brackets. [b] The diastereomeric excess was determined by ^{1}H-NMR analysis of the crude mixtures.

When this cyclopropanation method was applied to acyclic enones **1d-g** (Scheme 2), the stereochemical outcome was dependant on the reaction conditions used (Table 2). It should be noted that this reaction creates *three contiguous stereogenic centres.*



1d, R_1= CH_3, R_2 = CH_3
1e, R_1= CH_3, R_2 = C_5H_{11}
1f, R_1= $PhCH_2CH_2$, R_2 = CH_3
1g, R_1= $PhCH_2CH_2$, R_2 = C_5H_{11}

Scheme 2

Surprisingly, the reaction of enones **1d-g** with 1.5 equiv. of sulfonium salt in toluene for 48 h., gave rise to **4d-g** (d.e.≥80%) as the major diastereomers in excellent isolated yields. The use of 1 equiv. of sulfonium salt resulted in lower yield and longer reaction times (see entries 1 and 2).

Table 2[13]

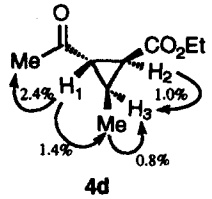
Entry	Substrate	Solvent	Time (hours)	Isolated Yield (%)[a]
1	**1d**	$C_6H_5CH_3$[b]	96	50 (**4d**)
2	**1d**	$C_6H_5CH_3$	48	89 (**4d**)
3	**1d**	$CHCl_3$[b]	18	63 (**4d**)/32 (**5d**)
4	**1e**	$C_6H_5CH_3$	48	84(**4e**)
5	**1e**	$CHCl_3$	48	60 (**4e**)/31 (**5e**)
6	**1f**	$C_6H_5CH_3$	48	90 (**4f**)
7	**1f**	$CHCl_3$	48	67 (**4f**)/26 (**5f**)
8	**1g**	$C_6H_5CH_3$	48	85 (**4g**)
9	**1g**	$CHCl_3$	48	55 (**4g**)/27 (**5g**)

[a] Products in brackets. [b] 1.0 equiv of ylide salt.

In order to identify the minor diastereomers obtained in this cyclopropanation, enones **1d-g** were cyclopropanated using 1.5 equiv. of sulfonium salt and DBU in chloroform. The change of solvent polarity significantly affected the diastereoselectivity of the cyclopropanation, since mixtures of **4d-g** and **5d-g** were obtained in an aproximately 2:1 ratio (entries 3, 5, 7 and 9) together with variable amounts (² 10%) of the corresponding isomers **6d-g** depending on the substrate. Fortunately, both **4d-g** and **5d-g** were easily separated by flash chromatography.

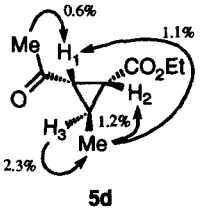
When **4d** was subjected to the cyclopropanation reaction conditions with 0.5 equiv. of the sulfonium salt and DBU no epimerization was observed after 10 days either in chloroform or toluene. However, when the same experiment was carried out with **5d** a 2:1 ratio mixture of **5d** and **6d** was obtained. On the other hand, **5d** was completely transformed into **6d** by treatment with one equivalent of NaOEt in EtOH in only 4 hours. These results suggest that the small amount of isomers **6d-g** present in the crude reaction mixtures can arise from ketones **5d-g** by epimerization under the reaction conditions.

The stereochemical assignment of cyclopropanes **4**, **5** and **6** was done on the basis of nOe experiments on **4d**, **5d** and **6d** (**figure 1**) and coupling constants.



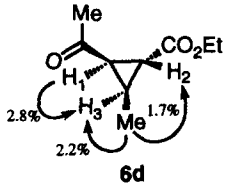
4d

δH_1=2.24 (dd, J_{1-2}=4.5 Hz, J_{1-3}=4.6 Hz)
δH_2=2.46 (dd, J_{2-1}=4.5 Hz, J_{2-3}=9.5 Hz)
δH_3=1.68-1.57 (m)



5d

δH_1=1.31 (dd, J_{1-2}=9.4 Hz, J_{1-3}=6.1 Hz)
δH_2=1.48 (dd, J_{2-1}=9.4 Hz, J_{2-3}=6.1 Hz)
δH_3=1.98-2.07 (m)



6d

δH_1=2.56 (dd, J_{1-2}=4.6 Hz, J_{1-3}=9.4 Hz)
δH_2=2.17 (dd, J_{2-1}=4.6 Hz, J_{2-3}=4.7 Hz)
δH_3=1.96-1.80 (m)

Figure 1

In summary, we have shown that the cyclopropanation reaction of ethyl (dimethyl sulfuranylidene) acetate (EDSA), generated *in situ* from the corresponding sulfonium salt and DBU in toluene, proceeds with high degree of stereocontrol at the newly generated stereogenic centres. The use of $CHCl_3$ as solvent, resulted into an easily separable mixture of diastereomers **4d-g** and **5d-g**. Isomers **6d-g** can be obtained by

direct epimerization of **5d-g** with NaOEt/EtOH. The present methodology allows an efficient access to three different diastereoisomeric cyclopropanes in good chemical yields. Further synthetic applications of this methodology are currently in progress in these laboratories and will be reported on due course.

Acknowledgements: This research was supported by a **CDTI** programme (Plan concertado 94/0036) and the Spanish **FARMA III** programme (Ministerio de Industria y Ministerio de Sanidad).

References and Notes

1 Tsuji, T.; Nishida, S. in "*The Chemistry of Cyclopropyl Group*". Rappoport, Z. Ed.; John Wiley & Sons. **1987**. *part 1*, p 307.

2 Helquist, P. in "*Comprehensive Organic Synthesis*" Pergamon Press: New York, **1991**, vol. 4, pp 968.

3 Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A. Hoines, C. M. *Org. Reactions*, **1973**, *20*, 1.

4 (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) For a review see: Salaün, J. *Chem. Rev.* **1989**, *89*, 1247.

5 Nájera, C.; Chinchilla, R.; García-Granda, S. *Tetrahedron lett.* **1993**, *34*, 5799 and relevant references cited therein.

6 (a) Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58. (b) Kort, U. *Nachr. Chem. Tech. Lab.* **1995**, *43*, 435.

7 (a) In the synthesis of *trans*-substituted chromium cyclopropylmethoxycarbene complexes: Barluenga, J.; Bernard, P. L.; Cocellón, J. M. *Tetrahedron Lett.* **1995**, *36*, 2153. (b) In the cyclopropanation of optically pure α-(*p*-tolylsulfinyl) diphenylacrylate: Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701.

8 Payne, G. B., *J. Org. Chem.* **1967**, *32*, 3351.

9 Curley, R. W.; DeLuca, H. F., *J. Org. Chem.* **1984**, *49*, 1944.

10 With other activated-electron deficient alkenes, such as esters, aldehydes or nitriles, this reaction does not take place.

11 The use of other bases such as triethylamine led to lower diastereoselectivities.

12 (a) Condensation of α-bromocyclohexenone with EDSA in benzene has been reported to produce the *exo* adduct. Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205. (b) During the preparation of this manuscript the synthesis of enantiomerically pure ketone **2a** has been described using the same cyclopropanation procedure in acetonitrile. Moher, E. D. *Tetrahedron lett.* **1996**, *37*, 8637.

13 Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR and C, H, combustion analysis) have been obtained for all compounds reported in this communication. **General Procedure**: A solution of ethyl dimethylsulfonium acetate bromide (61 mmol) and DBU (61 mmol) in the corresponding anhidrous solvent (60 mL) was stirred under inert atmosphere at room temperature for 30 min. To this solution, the corresponding enone (61 mmol) was added and stirring was maintained (see table 1 and 2 for reaction times) until the reaction was completed (monitored by tlc, an excess of ylide must be added for the acyclic enones). The reaction mixture was diluted and washed with 0.5 N HCl solution (2 x 40 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure (due to the low boiling point of **2a**, **4d** and **5d**, the bath temperature should be kept under 25°C). The crude reaction mixture was purified by flash chromatography (using suitable ethyl acetate/hexane mixtures for each case).

(*Received in UK* 7 *March* 1996; *revised* 5 *February* 1997; *accepted* 7 *February* 1997)