Pergamon

Tetrahedron Letters 43 (2002) 5871–5873

TETRAHEDRON LETTERS

Stereocontrolled synthesis of [3.1.0]bicyclohexanones by cyclopropanation of enones with benzylidene sulfuranes

Alain Krief,[a,*] Dominique Swinnen[b] and Denis Billen[a,c]

[a]*Laboratoire de Chimie Organique de Synthèse, 61 rue de Bruxelles, Namur B-5000, Belgium*
[b]*Serono Pharmaceutical Research Institute, 14 chemin des Aulx, Plan-Les-Ouates, Geneva CH-1228, Switzerland*
[c]*Fond pour la Recherche Scientifique dans l'Industrie et l'Agriculture (F.R.I.A.), 5 rue d'Egmont, Bruxelles B-1000, Belgium*

Received 2 April 2002; accepted 29 May 2002

Abstract—Bicyclo[3.1.0]hexanones bearing an aryl group on the cyclopropane ring are stereoselectively prepared on reaction of the corresponding benzylidene sulfuranes with cyclopentenones. The synthesis of compounds bearing geminal phenyl and methyl groups on the cyclopropane ring proves to be possible because the corresponding sulfonium salt, inaccessible until now, is now available. © 2002 Elsevier Science Ltd. All rights reserved.

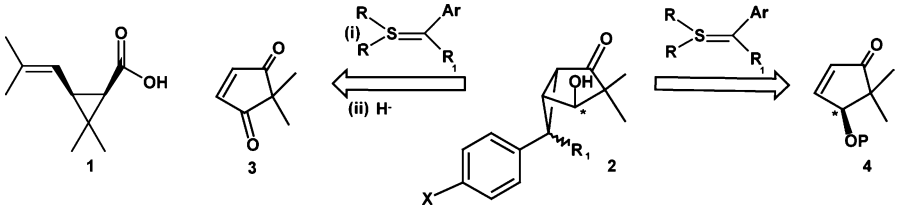
In the course of a work directed toward the enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid **1**, using tailor-made antibodies,[1] we needed stereoisomerically pure bicyclo[3.1.0]hexane derivatives **2** geminally substituted on the cyclopropane ring by an aryl group and an hydrogen or a methyl group (Scheme 1).

Although these could be prepared[2] by cyclopropanation of enones **3** and **4** with suitable substituted sulfuranes, it was known that diphenylsulfonium salts[3] could neither be prepared from diphenyl sulfide and 1-aryl ethane bearing a leaving group at the C_1 position nor from benzyl diphenylsulfonium salts by sequential metalation–methylation reactions.[3,4]

The first experiments have been carried out with diphenylsulfonium tetrafluoroborate salts (1.2 equiv.) derived from primary benzyl halides (Ar: Ph, *p*-NO_2-Ph) on sequential reaction (i) with LDA (1.2 equiv., DME, −78°C, 0.5 h)[4] in the presence of dichloromethane (DCM, 1.2 equiv.) and (ii) the enones **3** or **4** (**4a**: P = Ac, **4b**: P = TBDMS, 1 equiv., −78°C, 1 h; 20°C, 1 h). The reaction proceeds quite efficiently and allows the production of the bicyclic derivatives **2** and **5** in good yields (Scheme 2, Table 1).

The *syn*/*anti*-ratio of stereoisomer is highly dependant on the nature of both the enone and the ylide (Table 1), whereas extremely high stereocontrol leading to the *exo*-epimer, is all the time observed. Although this might result from steric interactions between the 4-substituent on **4** and the bulky benzylidene diphenylsulfuranes, we have to recall that ethylidene diphenylsulfurane provided mainly the *endo*-stereoisomer from the silyloxy derivative **4b**.[2a,†]

Otherwise it is interesting to note the extremely high but divergent stereocontrol especially achieved with

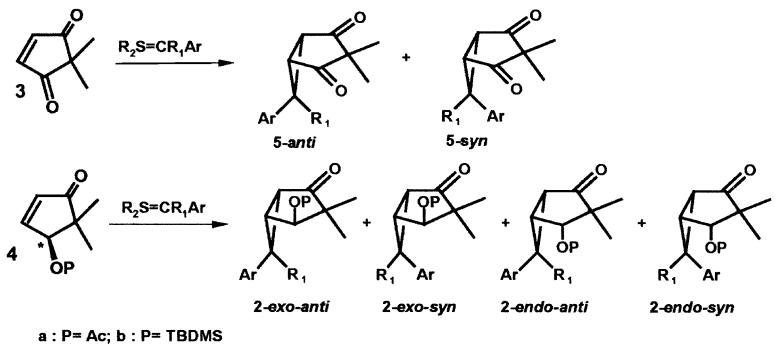


Scheme 1.

* Corresponding author. Tel.: +32 81 724539; fax: +32 81 724536; e-mail: alain.krief@fundp.ac.be

† The *exo*-stereoisomer is nevertheless produced from ethylidenediphenylsulfurane and **4a** bearing an acetoxy group.

PII: S0040-4039(02)01017-1



Scheme 2.

p-nitrophenyl derivatives on the enedione **3** and the γ-silyloxy enone **4b** (Table 1, entries b and f) and which contrasts with the poor stereoselectivity provided by the related γ-acetoxy derivative **4a** (Table 1, compare entry d with entries b and f).

The next objective was the synthesis of geminally arylmethyl substituted cyclopropane derivatives and therefore the synthesis of the corresponding sulfonium salts. The latter have finally been successfully prepared, in almost quantitative yields, from 1-bromo-1-phenyl ethane and its phenyl-substituted analogues (*p*-Me-, *p*-NO_2- and *p*-Cl-Ph) using the more nucleophilic tetrahydrothiophene (THT)[5] rather than diphenyl sulfide (1.1 equiv. ArCH(Me)X, 2 equiv. THT, 1 equiv. $AgBF_4$, acetone, 0°C, 4 h). The same procedure also allows the synthesis of lower homologues from bromomethyl benzene and its *p*-substituted phenyl derivatives (Scheme 3).

Table 1. Reaction of enones **3** and **4** with benzylidene diphenylsulfuranes according to Scheme 3

	3 or **4**	Ar	R_1	**2** or **5** (%)	*syn*	*anti*
a	**3**	C_6H_5	H	86	88	12
b	**3**	*p*-NO_2-C_6H_4	H	94	99.5	0.5
c	**4a**	C_6H_5	H	60	50	50
d	**4a**	*p*-NO_2-C_6H_4	H	45	55	45
e	**4b**	C_6H_5	H	91	10	90
f	**4b**	*p*-NO_2-C_6H_4	H	60	0	100

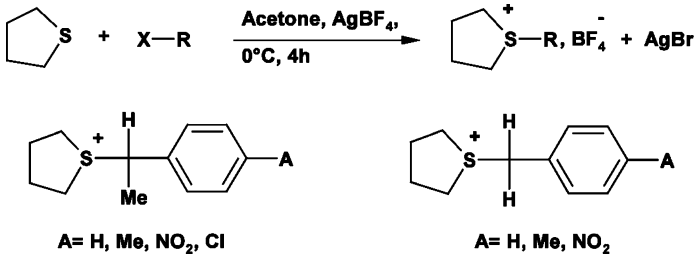
Those latter sulfonium salts, unsubstituted at their benzylic site, led to cyclopropane derivatives on reaction with the enones **3** or **4** under conditions described above for their diphenyl sulfonium analogs (Scheme 3, Table 2, entries a–f). This procedure neither works with the *p*-nitro-phenyl derivative nor with the homologous sulfonium salts bearing a methyl substituent at the benzylic position.

Cyclopropanation of enones **3** and **4** was nevertheless successfully achieved from the sulfonium salt derived from THT and 1-bromo-1-phenyl ethane at the only condition that the whole process is carried out at much

Table 2. Reaction of enones **3** and **4** with the benzylidene sulfuranes derived from THT according to Scheme 2

	3 or **4**	Ar	R_1	Yield (%)	*syn*	*anti*
a	**3**	C_6H_5	H	72	40	60
b	**3**	*p*-Me-C_6H_4	H	69[a]	13	87
c	**4a**	C_6H_5	H	84	50	50
d	**4b**	C_6H_5	H	82	37	63
e	**4a**	*p*-Me-C_6H_4	H	88[b]	50	50
f	**4b**	*p*-Me-C_6H_4	H	87	50	50
g	**3**	C_6H_5	Me	73	63	37
h	**4a**	C_6H_5	Me	73	10	90
i	**4b**	C_6H_5	Me	73	05	95

[a] Polluted by a small percentage of impurities.
[b] Traces (1%) of the *endo*-isomers are observed by ^1H NMR.



Scheme 3. Synthesis of benzylic sulfonium salts derived from tetrahydrothiophene.

‡ It avoids extensive decomposition of the ylide leading to styrene when the reaction is carried out at −78°C (a yellow color appears once the base is introduced to the medium but immediately fades). This might result from the rearrangement of the benzylidene sulfurane or from extensive metalation of the THT moiety followed by an intramolecular β-elimination reaction.[6]

lower temperature (−100°C) with higher amounts of dichloromethane in which the salt is more soluble (Table 2, entries g–i).[‡] Surprisingly enough, this reaction cannot be extended to aryl substituted derivatives including the *p*-methyl substituted one.

Comparison of the stereochemical results presented in Table 2, with those described in Table 1 shows that again the *exo*-stereoisomers are in all cases produced from **4** but the reaction involving sulfur ylides derived from tetrahydrothiophene unsubstituted at the benzylic carbon is generally less *syn*/*anti*-stereoselective (Table 2, entries a–f; compare Table 2, entry a with Table 1, entry a and Table 2, entry d with Table 1, entry e).

However, very high stereocontrol has been unexpectedly observed from enones **4** and sulfonium salts bearing a methyl group at the benzylic carbon (Table 2, entries h and i, compare Table 2, entry h with entry c and entry i with entry d).

References

1. (a) Krief, A.; Letesson, J.-J.; Swinnen, D.; Billen, D. *Synlett* **2001**, 931; (b) Krief, A.; Letesson, J.-J.; Billen, D. *Tetrahedron Lett*., in press.
2. (a) Krief, A.; Swinnen, D. *Tetrahedron Lett*. **1996**, *37*, 7123; (b) Kreiser, W.; Wiggermann, A.; Krief, A.; Swinnen, D. *Tetrahedron Lett*. **1996**, *37*, 7119; (c) Krief, A. *Pestic. Sci*. **1994**, *41*, 237.
3. LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem*. **1971**, *36*, 1126.
4. (a) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett*. **1967**, *24*, 2325; (b) Romo, D.; Meyers, A. I. *J. Org. Chem*. **1992**, *57*, 6265; (c) Zhang, R.; Madaglengoitia, J. S. *J. Org. Chem*. **1999**, *64*, 547.
5. (a) Furstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1997**, *119*, 2944; (b) Hetschko, M.; Gosselck, J. *Chem. Ber*. **1973**, *106*, 996; (c) Forrester, J.; Jones, R. V. H.; Newton, L.; Preston, P. N. *Tetrahedron* **2001**, *57*, 2871.
6. (a) Halazy, S.; Krief, A. *Tetrahedron Lett*. **1979**, 4233; (b) Halazy, S.; Krief, A. *J. Chem. Soc*., *Chem. Commun*. **1979**, 1136.