Ylide Reactions in the Solid State: a Simple Procedure for the Synthesis of Cyclopropanes, Oxiranes and Aziridines

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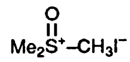
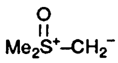
Treatment of chalcones, cyclohexanones and imines with trimethyloxosulfonium or trimethylsulfonium iodide and KOH in the solid state give cyclopropanones, oxiranes and aziridines, respectively, in good yields. Solid-state methylene transfer also occurs enantioselectively when an optically active sulfoximine and/or an optically active host compound is used.

Methylene transfer from ylides to electrophilic unsaturated linkages, C=C, C=O and C=N, are useful for the synthesis of cyclopropanes, oxiranes and aziridines, respectively.[1] Dimethyloxosulfoniumylmethanide **2** and dimethylsulfoniumylmethanide **4**, generated from trimethyloxosulfonium **1** and trimethylsulfonium iodide **3**, respectively, on treatment with base, have been reported as sources of active methylene.[1]



$Me_2\overset{O}{\overset{\|}{S}}{}^+\text{–}CH_3I^-$

1



$Me_2\overset{O}{\overset{\|}{S}}{}^+\text{–}CH_2^-$

2

$Me_2S^+\text{–}CH_3I^-$

3

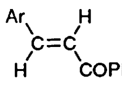
$Me_2S^+\text{–}CH_2^-$

4

However, the experimental procedure for the ylide generation is complicated.[1] Heating **1** under reflux with NaH in THF and stirring **3** with BuLi at 0 °C in THF gives THF solutions of **2** and **4**, respectively, which on treatment with the reactant under nitrogen at 50–55 °C give the methylene transfer product. Recently, an improved procedure for methylene transfer has been reported.[2] For example, to a vigorously stirred suspension of trimethylsulfonium methanesulfonate in dry CH_2Cl_2 containing dried finely powdered KOH, was added freshly distilled methacrolein over 5 h at room temperature. After work-up, 3,4-epoxy-2-methylbut-1-ene was obtained in 40% yield.[2] However, this method still requires dry CH_2Cl_2 as solvent, and the methylene transfer occurs in solution. Furthermore, this method may not be suitable for CH_2Cl_2-insoluble compounds.

We have developed a very simple methylene transfer procedure which can be carried out at room temperature under atmospheric conditions in the absence of solvent. When a mixture of powdered **1** or **3**, KOH, and reactant was left for several hours, the methylene transfer product was obtained. In cases where the production of stereoisomers is possible, a selective reaction occurred in the solid state. Enantioselective solid-state methylene transfer reactions are also reported. This communication is of value not only because it reports a new synthetic procedure but also because it details a new, efficient solid-state methylene transfer reaction.

The procedure for the synthesis of cyclopropane **6a** from chalcone **5a** using KOH as base is given in the Experimental section. It has been reported that when the reaction is carried out in dimethyl sulfoxide (DMSO) under nitrogen using NaH as base for 16 h, **6** is obtained in 86–88% yield.[1] Application of the same methylene transfer reaction in the solid state to various chalcone derivatives (**5b–e**), gave the corresponding cyclopropane derivatives **6b–e** in the yields shown in Table 1.



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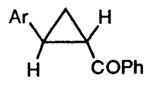
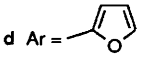
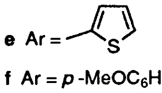


6

a Ar = Ph
b Ar = *m*-ClC$_6$H$_4$
c Ar = *p*-PhC$_6$H$_4$



d Ar =



e Ar =

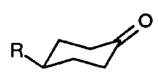
f Ar = *p*-MeOC$_6$H$_4$

Table 1 Yield of cyclopropane **6** from the reaction of **5** with **1** and KOH at room temperature for 3 h in the solid state

Chalcone **5**	Yield (%) of **6**
a	79
b	91
c[a]	79
d	82
e	81

[a] Reaction was carried out at 60 °C.

Treatment of 4-alkylcyclohexanone **7** with **1** or **3** in the solid state gave mainly *trans*-oxiranes **8** produced by methylene insertion from the *anti* direction of the alkyl group (Table 2). For example, a mixture of 4-*tert*-butylcyclohexanone **7a** (0.5 g), **1** (1.1 g) and KOH (0.36 g) after 3 h at room temperature gave, upon work-up and distillation *in vacuo*, the *trans*-isomer **8a** as a colourless oil (0.45 g, 83% yield). Although the spectral data of **8a** are comparable to those reported, gas chromatography showed that the product is composed of **8a** and the *cis*-isomer **9a** in a 97:3 ratio. In all other cases of methylene insertion, the oxiranes formed are contaminated with 3–9% of the *cis*-isomers. Solid-state methylene insertions using reagent **3** gave the *cis*-isomer as the major product (Table 2).



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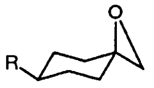
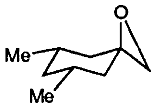


8

9

a R = Bu^t
b R = Me
c R = Et
d R = Ph

10



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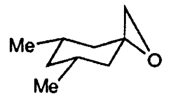


12

Treatment of *cis*-3,5-dimethylcyclohexanone **10** with **1** and KOH at room temperature in the solid state gave **11** and **12** in a 97:3 ratio in 77% yield. Similar treatment of **10** with **3** and KOH at 65 °C gave **11** and **12** in a 68:32 ratio in 81% yield.

Methylene insertion to imines in the solid state occurred

Table 2 Yields of oxiranes **8** and **9** from the reaction of **7** with **1** or **3** and KOH at room temperature for 3 h in the solid state

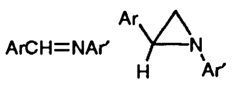
	1		**3**	
Cyclohexanone **7**	Yield of **8** + **9** (%)	Ratio[a] **8**:**9**	Yield of **8** + **9** (%)	Ratio[a] **8**:**9**
a	83	97:3	80	32:68
b	33	91:9	71	41:55
c	75	92:8	77	46:54
d	82	97:3	87	41:59

[a] The ratio of **8**:**9** was determined by gas chromatography.

Table 3 Yields of aziridine **14** from the reaction of **13** with **1** and KOH at 50 °C for 3 h in the solid state

Imine **13**	Yield (%) of **14**
a	56
b	34
c	38
d	36

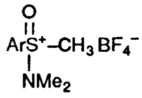
at a relatively high temperature. The procedure for the synthesis of **14** from **13** is given in the Experimental section and the yields are shown in Table 3. The yields were comparable to those obtained by the reaction in solution.[1]



13 **14**

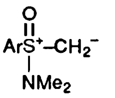
a Ar = Ar′ = Ph
b Ar = Ph, Ar′ = p-MeOC$_6$H$_4$
c Ar = p-ClC$_6$H$_4$, Ar′ = p-MeOC$_6$H$_4$
d Ar = p-MeC$_6$H$_4$, Ar′ = p-MeOC$_6$H$_4$

Enantioselective methylene transfer reactions using optically active oxosulfonium ylides have been reported.[3,4] For example, reactions of olefins, aldehydes and ketones with the optically active oxosulfonium salt **15** in the presence of NaH gave the corresponding methylene insertion product in relatively low optical purity, 10–35% e.e. We also found that the enantioselective methylene transfer occurs in the solid state reaction. Treatment of chalcone **5a** with (+)-*S*-methyl-*S*-phenyl-*N*-(*p*-tolyl)sulfoximide **17** and KOH in the solid state at 70 °C gave optically active **6a** of 14% e.e. in 19% yield. When the reaction was carried out using Bu^{t}OK at room temperature, (+)-**6a** of 24% e.e. was obtained in 94% yield. Sulfoximide **17** can be prepared easily by the treatment of (+)-methyl phenylsulfoxide[5] with NaN$_3$–Cu.



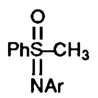
$\mathrm{Ar}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NMe_2}{|}}{S^+}}\!-\!CH_3\,BF_4^-$

15



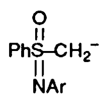
$\mathrm{Ar}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NMe_2}{|}}{S^+}}\!-\!CH_2^-$

16



$\mathrm{Ph}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NAr}{\|}}{S}}\!-\!CH_3$

17

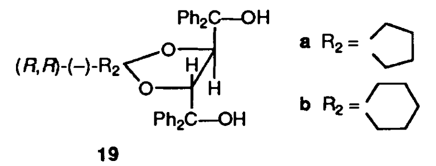


$\mathrm{Ph}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NAr}{\|}}{S}}\!-\!CH_2^-$

18

a Ar = Ph
b Ar = p-MeC$_6$H$_4$

Ar = p-MeC$_6$H$_4$SO$_3$



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Since the enantioselectivity of the methylene transfer from **18** to **5a** is low, the reaction was carried out in an inclusion crystal of the chalcone with the optically active host compound **19**. Treatment of 1:1 inclusion complexes of **5e** and (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane **19a**,[6] and of **5f** and (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane **19b**[6] with **1** and KOH in the presence of the phase transfer reagent, tetrabutylammonium iodide, gave **6e** of 9% e.e. in 81% yield and **6f** of 5% e.e. in 78% yield, respectively. Although the chemical yields are high, the optical yields are low. Treatment of the 1:1 inclusion complex of **5e** and **19a**[6] with the chiral ylide **18** derived from **17** using Bu^{t}OK as the base at room temperature gave **6e** of 24% e.e. in 11% yield. Although the optical yields are still not high, it is interesting to note that methylene transfer occurs efficiently and even enantioselectively in the solid state.

Experimental

Synthesis of rac-trans-1-*Benzoyl-2-phenylcyclopropane* **6a**.—A mixture of powdered chalcone **5a** (0.5 g), compound **1** (1.1 g) and KOH (1.5 g) was kept at room temperature for 3 h, after which the reaction mixture was washed with water and the residual crude product was taken up in diethyl ether. The ethereal solution was dried over Na$_2$SO$_4$ and then evaporated leaving the crude product, which was purified by column chromatography on silica gel using toluene as the eluent to give the title compound **6a** as colourless needles (0.42 g, 79%, m.p. 45–50 °C (lit.,[1] m.p. 45.5–50 °C). Spectral data were identical with those reported.[1]

Synthesis of Aziridines **14** *from* N-*Benzylideneanilines* **13**.—1,2-*Diphenylaziridine* **14a**. A mixture of powdered *N*-benzylideneaniline **13a** (2 g), compound **1** (3.6 g) and KOH (1.8 g) was kept at 50 °C for 3 h after which it was washed with water. The residual crude product was taken up in diethyl ether and the ethereal solution was worked up to give aziridine **14a** as pale yellow crystals (1.2 g, 56%), m.p. 38–39 °C (lit.,[1] 38–39.5 °C). The spectral data of **14a** were identical with those of an authentic sample.[3]

By the same procedure, imines **13b–d** gave the corresponding aziridines **14b–d** in the yields shown in Table 3.

Acknowledgements

We thank the Ministry of Education, Science and Culture, Japan, for a grant-in-aid for Developmental Scientific Research, No. 05554020.

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Paper 4/03167I
Received 27*th May* 1994
Accepted 2*nd August* 1994