## Stereoselective Synthesis of Cyclopropyl Ketones using Phase-Transfer Catalysis

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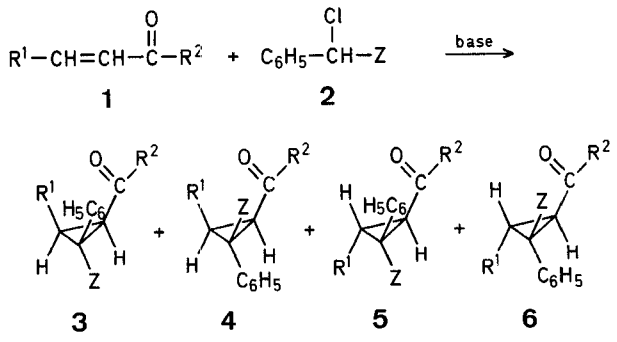
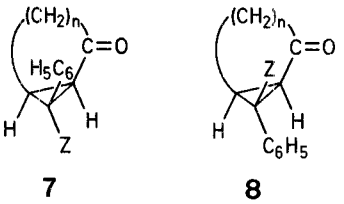
The synthesis of epoxynitriles by reaction of phenylchloroacetonitrile and benzaldehyde in basic medium is highly stereoselective when carried out under phase-transfer conditions[1,2] or in hexamethylphosphoric triamide[3]. We have shown[4] that also the stereoselectivity of the formation of cyclopropane-1,2-dicarboxylic esters from *t*-butyl chloroacetate or *t*-butyl phenylchloroacetate, respectively, and *t*-butyl acrylate is the same under phase-transfer conditions and in dimethylformamide. These results were interpreted by the assumption of a comparable reactivity of the anions associated with tetraalkylammonium cation or with a solvated alkali-metal cation in dipolar aprotic solvents. We have now utilized these observations to extend the above reaction type to the stereospecific synthesis of *cis*-2-phenylcyclopropyl ketones (**3**) and their cyclic analogs (**7**) from open-chain 1-alkenyl ketones (**1**, $R^1=C_6H_5$, $R^2=CH_3$, $C_6H_5$) or 2-cycloalkenones [**1**, $R^1-R^2=-(CH_2)_n-$], respectively, and alkyl phenylchloroacetates (**2**, Z = $COOR_3$) or phenylchloroacetonitrile (**2**, Z = CN).




It was earlier noticed[5] that in tetrahydrofuran/HMPT (1/1) at −80°C methyl phenylchloroacetate (**2**, Z = $COOCH_3$) and phenylchloroacetonitrile (**2**, Z = CN) react stereospecifically with 1-alkenyl ketones such as benzylidenacetone (**1**, $R^1=C_6H_5$, $R^2=CH_3$) or benzylidenacetophenone (**1**, $R^1=R^2=C_6H_5$) to give *cis*-2-phenylcyclopropyl ketones (**3**).

In order to avoid working at low temperatures and the use of expensive solvents, we have now investigated the reaction of the above-mentioned ketones **1** and of 2-cyclohexenone and 2-cyclopentenone with isopropyl and *t*-butyl phenylchloroacetates (**2**, Z = $COOC_3H_7$-*i*, $COOC_4H_9$-*t*) under catalytic phase-transfer conditions at room temperature (methyl esters were not used because of their ease of hydrolysis under the conditions employed). We found, that the reactions of the open-chain 1-alkenyl ketones **1** with *t*-butyl and isopropyl phenylchloroacetate proceed stereospecifically to afford exclusively the *cis*-2-phenylcyclopropyl ketones **3**; the other possible isomers **4**, **5**, and **6** were not observed.

The reaction of 2-cyclohexenone [**1**, $R^1-R^2=-(CH_2)_3-$] with *t*-butyl or isopropyl phenylchloroacetate likewise affords exclusively the bicyclic *cis*-phenyl product **7** (n = 3) whereas with 2-cyclopentenone [**1**, $R^1-R^2=-(CH_2)_2-$] a 67:33 mixture of products **7** and **8** (n = 2) is obtained.




In all cases, minor amounts of phenylchloroacetic acid could be isolated from the aqueous-alkaline phase upon acidification. This fact shows that ester hydrolysis competes with cyclopropane formation even in the case of the *t*-butyl ester and thereby lowers the yields of the cyclopropane derivatives. In this context it should be mentioned that rather poor yields of cyclopropane derivatives were also obtained from the reaction of 2-alkenals with dialkyl bromomalonates under phase-transfer conditions[6].

Of the four $\alpha,\beta$-unsaturated ketones **1** investigated, only benzylidenacetophenone ($R^1=R^2=C_6H_5$) reacts with phenylchloroacetonitrile (**2**, Z = CN) to give a cyclopropyl ketone (**3e**) whereas in the other cases the starting ketones **1** are recovered while conversion products of phenylchloroacetonitrile are formed.

For comparison, we performed the reactions of ketones **1** with *t*-butyl and isopropyl phenylchloroacetate (**2**, Z = $COOC_4H_9$-*t*, $COOC_3H_7$-*i*) in HMPT and tetrahydrofuran/HMPT (1/1) at room temperature and in tetra-

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**Table 1.** Cyclopropyl Ketones (**3**) and 2-Oxobicyclo[m.1.0]alkanes (**7**, **8**) prepared using Phase-Transfer Catalysis

| $R^1$ | $R^2$ | Z | Reaction time [h] | Product | Yield [%] | | m.p. | Molecular formula[b] |
|---|---|---|---|---|---|---|---|---|
| | | | | | Crude product[a] | Crystallized product | | |
| $C_6H_5$ | $CH_3$ | $COOC_4H_9$-*t* | 2 | **3a** | 60 | 35 | 86–87°C (hexane/ethanol) | $C_{22}H_{24}O_3$ (336.4) |
| $C_6H_5$ | $CH_3$ | $COOC_3H_7$-*i* | 1.5 | **3b** | 60 | 30 | 77–78°C (hexane/ethanol) | $C_{21}H_{22}O_3$ (322.4) |
| $C_6H_5$ | $C_6H_5$ | $COOC_4H_9$-*t* | 2 | **3c** | 60 | 40 | 108°C (hexane/ether) | $C_{27}H_{25}O_2$ (398.5) |
| $C_6H_5$ | $C_6H_5$ | $COOC_3H_7$-*i* | 2 | **3d** | 60 | 40 | 118–119°C (hexane/ethanol) | $C_{26}H_{24}O_3$ (384.5) |
| $C_6H_5$ | $C_6H_5$ | CN | 1 | **3e** | 25 | 10 | 169–170°C (hexane/ethanol) | $C_{23}H_{17}NO$ (323.4) |
| $(CH_2)_3$ | | $COOC_4H_9$-*t* | 2 | **7a** | 60 | 40 | 86–87°C (hexane/ethanol) | $C_{18}H_{22}O_3$ (286.4) |
| $(CH_2)_3$ | | $COOC_3H_7$-*i* | 2 | **7b** | 60 | 40 | 59–60°C (hexane/ethanol) | $C_{17}H_{20}O_3$ (272.3) |
| $CH_2$ | $CH_2$ | $COOC_4H_9$-*t* | 2 | **7c** (67%)[c] + **8c** (33%)[c] | 60 | 50 | 65–66°C (hexane) 82–83°C (hexane) | $C_{16}H_{18}O_3$ (258.3) $C_{16}H_{18}O_3$ (258.3) |

[a] Determined by $^1$H-N.M.R. analysis of crude product mixture for compounds **3** and by weighing the residue obtained from the first evaporation for products **7** and **8**.

[b] The microanalyses (except for **3e**) were in good accordance with the calculated values: C, ±0.26; H, ±0.20; O, ±0.27. Compound **3e**: C, −0.72; H, −0.07; N, −0.03; O, −0.07. The analyses were carried out by the "Centre de Microanalyse du CNRS", Gif sur Yvette.

[c] The isomers were isolated by column chromatography on silica gel using hexane/ether (80/20) as eluent and were then recrystallized from hexane.

**Table 2.** Reaction of α,β-Unsaturated Ketones (**1**) with Alkyl Phenylchloroacetates (**2**, Z = $COOR^3$) in HMPT and in Tetrahydrofuran/HMPT

| $R^1$ | $R^2$ | Z | in HMPT at Room Temperature | | | in Tetrahydrofuran/HMPT (2/1) at −80°C | | |
|---|---|---|---|---|---|---|---|---|
| | | | Reaction time [h] | Total Yield [%] | Ratio of Products | Reaction time [h] | Total Yield [%] | Ratio of Products |
| $C_6H_5$ | $CH_3$ | $COOC_4H_9$-*t* | 3 | 50 | **3a/4a** = 35/65 | 6 | 15 | **3a/4a** > 98/2 |
| $C_6H_5$ | $CH_3$ | $COOC_3H_7$-*i* | 3 | 70 | **3b/4b** = 50/50 | | | |
| $C_6H_5$ | $C_6H_5$ | $COOC_4H_9$-*t* | 3 | 45 | **3c/4c** = 60/40 | 6 | 40 | **3c/4c** = 90/10 |
| $C_6H_5$ | $C_6H_5$ | $COOC_3H_7$-*i* | 3 | 90 | **3d/4d** = 50/50 | | | |
| $(CH_2)_3$ | | $COOC_4H_9$-*t* | 3 | 90 | **7a/8a** = 90/10 | | | |
| $CH_2$ | $CH_2$ | $COOC_4H_9$-*t* | 3 | > 98 | **7c/8c** = 65/35 | 6 | 50 | **7c/8c** > 98/2 |

hydrofuran/HMPT (2/1) at −80°C. It was found that in HMPT and in tetrahydrofuran/HMPT the reaction is only poorly stereoselective and affords the isomers **3** and **4** or **7** and **8**, respectively, whereas in tetrahydrofuran/HMPT (2/1) at −80°C the reaction is highly stereoselective in all cases, affording isomers **3** or **7** as the main products (Table 2).

In summary, the present phase-transfer catalytic method provides a convenient means for the synthesis of certain cyclopropane derivatives at room temperature. To obtain comparable results using polar aprotic solvents, the reactions have to be carried out at −80°C under strictly anhydrous conditions.

**Cyclopropyl Ketones 3 and 2-Oxobicyclo[m.1.0]alkanes 7 (m = n + 1 = 3, 4); General Procedure:**

The α,β-unsaturated ketone (**1**; 5 mmol) and isopropyl or *t*-butyl phenylchloroacetate (5 mmol) are dissolved in dichloromethane (25 ml). Tetrabutylammonium bromide (1.62 g, 5 mmol) is dissolved in 50% aqueous sodium hydroxide (10 ml). The two solutions are mixed and the two-phase mixture is stirred at room temperature for 1–2 h (see Table 1). The organic phase is separated, washed with water, dried with sodium sulfate, and evaporated. The residue is taken up in ether (50 ml) and crystalline potassium iodide (1 g) is added with stirring. The precipitated salt is filtered off and washed with ether. The filtrate is dried with sodium sulfate and evaporated. The residual product is recrystallized from hexane/ethanol or hexane (see Table 1).

**1-*cis*-Benzoyl-2-*trans*-cyano-2-*cis*,3-*cis*-diphenylcyclopropane (3e):**

The procedure is the same as that described above except that 2 normal sodium hydroxide solution (25 ml) is used [in the presence of 50% aqueous sodium hydroxide, the side reactions proceed fast and cyclocondensation is not observed].

**Reaction of Ketones 1 with Phenylchloroacetic Esters 2 in HMPT or Tetrahydrofuran/HMPT:**

*At Room Temperature:* Ketone **1** (3 mmol) and alkyl phenylchloroacetate **2** (3 mmol) are dissolved in HMPT (50 ml) or tetrahydrofuran/HMPT (1/1). To this solution, sublimated potassium *t*-butoxide (337 mg, 3 mmol) is added with stirring. After 3 h, ether (100

**Table 3.** I.R.- and $^1$H-N.M.R.-Spectral Data of Compounds **3**, **4**, **7**, and **8**

| Compound | I.R. ($CHCl_3$) $\tilde{\nu}_{C=O}$ [$cm^{-1}$] | $^1$H-N.M.R. ($CCl_4$ or $C_6D_6$/TMS, 60 MHz) $\delta$ [ppm] |
|---|---|---|
| **3a** | 1715–1735 | ($CCl_4$) 1.00 [s, 9H, $C(CH_3)_3$]; 2.21 (s, 3H, $CH_3$); 3.66 (s, 2H, cyclopropane-H); 7.30 (s, $10H_{arom}$) |
| **4a** | 1715–1735 | ($CCl_4$) 1.33 [s, 9H, $C(CH_3)_3$]; 2.40 (s, 3H, $CH_3$); 2.91 ($\nu_A$), 3.43 ($\nu_B$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 7.0 (s, $10H_{arom}$) |
| **3b** | 1715–1735 | ($CCl_4$) 0.76 [d of d, 6H, $CH(CH_3)_2$]; 2.16 (s, 3H, $CH_3$); 3.60 (s, 2H, cyclopropane-H); 7.28 (s, $10H_{arom}$) |
| **4b** | 1715–1735 | ($CCl_4$) 1.20 [d of d, 6H, $CH(CH_3)_2$]; 2.43 (s, 3H, $CH_3$); 3.14 ($\nu_B$), 3.56 ($\nu_A$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 7.15 (s, $10H_{arom}$) |
| **3c** | 1690–1720 | ($CCl_4$) 1.00 [s, 9H, $C(CH_3)_3$]; 3.83 ($\nu_B$), 4.26 ($\nu_A$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 7.12–8.25 (m, $15H_{arom}$) |
| **4c** | 1690–1720 | ($CCl_4$) 1.2 [s, 9H, $C(CH_3)_3$]; 3.55 ($\nu_B$), 3.86 ($\nu_A$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 6.91–8.16 (m, $15H_{arom}$) |
| **3d** | 1690–1720 | ($CCl_4$) 0.9 [d of d, 6H, $CH(CH_3)_2$]; 3.96 ($\nu_B$), 4.40 ($\nu_A$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 6.96–8.26 (m, $15H_{arom}$) |
| **4d** | 1690–1720 | ($CCl_4$) 1.00 [d of d, 6H, $CH(CH_3)_2$]; 3.67 ($\nu_A$), 3.73 ($\nu_B$) (AB system, 2H, $J_{AB}=7$ Hz, cyclopropane-H); 6.6–8.3 (m, $15H_{arom}$) |
| **3e** | 1690–2255 ($\nu_{C\equiv N}$) | ($CDCl_3$) 3.98 ($\nu_A$), 4.08 ($\nu_B$), (AB system, 2H, $J_{AB}=7.5$ Hz, cyclopropane-H); 7.28–8.15 (m, $15H_{arom}$) |
| **7a** | 1700–1715 | (benzene-$d_6$) 1.16 [s, 9H, $C(CH_3)_3$]; 2.83 (d, 1H, $J=8$ Hz, cyclopropane-H); 7.26–7.33 (m, $5H_{arom}$) |
| **8a** | 1700–1715 | (pyridine-$d_5$) 1.33 [s, 9H, $C(CH_3)_3$]; 7.26–7.33 (m, $5H_{arom}$) |
| **7b** | 1700–1715 | (benzene-$d_6$) 0.88, 0.98 [d of d, 6H, $CH(CH_3)_2$]; 3.07 (d, 1H, $J=9$ Hz, cyclopropane-H); 4.92 [quin, 1H, $CH(CH_3)_2$]; 7.03–7.33 (m, $5H_{arom}$) |
| **7c** | 1725 | ($CDCl_3$) 1.33 [s, 9H, $C(CH_3)_3$]; 1.50–2.93 (m, 6H); 7.28 (s, $5H_{arom}$) |
| **8c** | 1725 | ($CDCl_3$) 1.40 [s, 9H, $C(CH_3)_3$]; 1.77–2.80 (m, 6H); 7.13–7.43 (m, $5H_{arom}$) |

ml) is added to the stirred mixture followed by the addition of saturated aqueous sodium chloride (20 ml). The organic layer is separated, washed several times with saturated aqueous sodium chloride, dried, and evaporated. $^1$H-N.M.R. analysis of the crude product shows the presence of two isomeric cyclopropyl ketones and the starting materials. The isomeric ketones may be separated by preparative T.L.C. on silica gel using hexane/ether as eluent.

*In Tetrahydrofuran/HMPT (2/1) at −80°C:* The reaction is carried out as described in Ref. [5].

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