# Convenient Synthesis of 2-Phenylcyclopropenone Acetals

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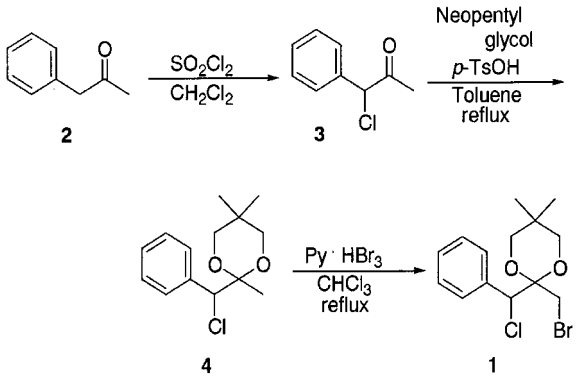
2-Phenylcyclopropenone acetals are key intermediates for some biologically active compounds containing a cyclopropenone moiety, e.g., antimicrobial penitricin derivatives[1] or cysteine proteinase inhibitors.[2] They were prepared by treatment of α,α′-dihaloketone acetals with potassium amide[3] or sodium amide[4] in liquid ammonia. In these methods, an unusual experiment is need for the use of liquid ammonia, and the disposal of corrosive and basic liquid ammonia must be accompanied with neutralization. Therefore we studied more convenient method to prepare 2-phenylcyclopropenone acetals.

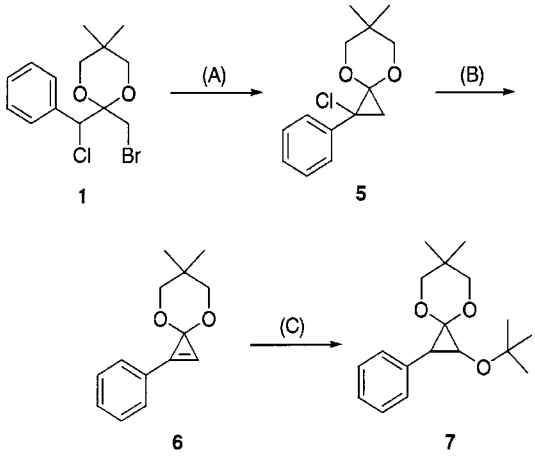
As the starting compound we chose 2-bromomethyl-2-(chlorophenylmethyl)-5,5-dimethyl-1,3-dioxane **1**, which was prepared easily from phenylacetone[5] in three steps as shown in Scheme 1. Thus phenylacetone **2** was chlorinated at its benzylic position by treatment with a slight excess of sulfuryl chloride in dichloromethane, and the obtained α-chloroketone **3** was converted to the corresponding acetal by the usual azeotropic method in refluxing toluene. Then the chlorinated acetal **4** was brominated by pyridinium hydrobromide perbromide in refluxing chloroform[6] to afford the compound **1** in 66% overall yield.

To clarify the reactivity of the acetal **1**, it was treated with various strong bases. The attempted reaction with DBU, sodium amide, sodium hydride, sodium methoxide, or sodium isopropoxide in THF did not proceed at all.[7] *n*-Butyllithium in the presence of TMEDA in THF or sodium hydride in DMF gave a complex mixture. On the other hand, treatment of **1** with potassium *tert*-butoxide (2 equiv) in THF looked encouraging. The resulting mixture contained cyclopropenone acetal **6** accompanied by 2-*tert*-butoxy-3-phenylcyclopropanone acetal **7**[8] and

**Scheme 1**




**Scheme 2**




the starting material **1**. The reaction process can be explained as follows. First, deprotonation of benzylic position followed by intramolecular cyclization yielded the intermediate **5**,[9] and then the dehydrochlorination occurred to give the desired compound **6** (Scheme 2). Further addition of potassium *tert*-butoxide to the olefin moiety in compound **6** led to the adduct **7**.[10]

There seemed to contain three different types of reaction in this process, i.e., cyclization (A), elimination (B), and addition (C). Therefore, we had confidence to be able to control these reactions more selectively. The investigation of solvents and additives gave interesting results, which are summarized in Table 1. As described above, THF afforded a mixture of **6**, **7**, and **1** (entry 1), which indicates that the elimination step (B) is the fastest. However, 1-methyl-2-pyrrolidinone (NMP) or 1,3-dimethyl-2-imidazolidinone (DMI) gave mainly **5** and **6** (entries 4 and 5), which implies the cyclization step (A) is the fastest. On the contrary, the reaction in 2-methyl-2-propanol did not proceed at all (entry 3). The use of an excess base afforded the adduct **7** exclusively (entry 2).

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(5) Research Approval No: Kanagawa 3604.

(6) Reflux in $CHCl_3$ is necessary to avoid the decomposition of the acetal moiety. The reaction mixture became acidic due to the generated hydrogen bromide, which can be removed immediately by refluxing.

(7) All reactions were performed below 30 °C because of the instability of the product **6**.

(8) It was reported that treatment of 1-bromo-3-chloro-2,2-dimethoxypropane with 3 equiv of potassium *tert*-butoxide in DMSO gave 1,1-dimethoxy-2-*tert*-butoxycyclopropane in 50% yield: see ref 3a. However, any reaction did not proceed in the reaction of it with *t*-BuOK in THF.

(9) Treatment of the isolated intermediate **5** with 1 equiv of potassium *tert*-butoxide in THF afforded the cyclopropenone acetal **6** in 79% isolated yield, and treatment of **5** with 1.5 equiv of *t*-BuOK in THF gave the adduct **7** in 92% isolated yield.

(10) Reaction of the cyclopropenone acetal **6** with 1 equiv of potassium *tert*-butoxide in THF afforded the adduct **7** in excellent yield.

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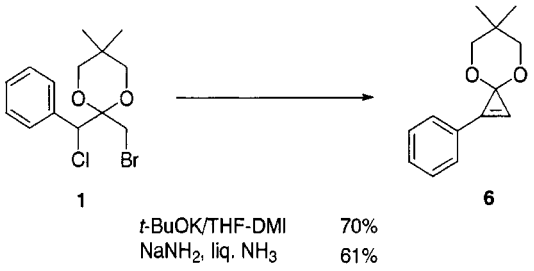
**Table 1. Investigation of Reaction Conditions[a]**

| entry | solvent | equiv of *t*-BuOK | additive (equiv) | reaction condition | product ratio, %[b] 1 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| 1 | THF | 2.0 | none | rt, 3 h | 32 | 0 | 36 | 32 |
| 2 | THF | 2.6 | none | rt, 5 h | 0 | 0 | 0 | 100 |
| 3 | *t*-BuOH | 2.0 | none | rt, 15 h | 100 | 0 | 0 | 0 |
| 4 | NMP[c] | 2.0 | none | rt, 3 h | 0 | 22 | 66 | 12 |
| 5 | DMI | 2.0 | none | rt, 3 h | 0 | 23 | 72 | 5 |
| 6 | THF | 2.0 | DMI (1.0) | rt, 1 h | 8 | 0 | 88 | 4 |
| 7 | THF | 2.0 | DMF (3.0) | rt, 1 h | 15 | 0 | 72 | 13 |
| 8 | THF | 2.0 | TMEDA (3.0) | rt, 3 h | 21 | 0 | 40 | 39 |
| 9 | THF−DMI | 2.0 | none | rt, 5 h | 0 | 11 | 86 | 3 |

[a] All reactions were performed in 0.30 mmol scale. [b] Determined by $^1$H NMR. [c] Reaction mixture became red quickly.

**Scheme 3**




The effect of additives was also examined, and 1 equiv of DMI in THF gave a satisfactory result (entry 6), but no satisfactory result was obtained by the use of DMF or TMEDA (entries 7 and 8). Alternatively, a 1:1 mixture of THF and DMI also gave an excellent result (entry 9).

Next we confirmed the isolated yield. The dihalide **1** was treated with 2 equiv of potassium *tert*-butoxide in THF and DMI (1:1), and the crude product was purified by column chromatography to afford the desired cyclopropenone acetal **6** in 70% yield (Scheme 3), which is comparable to the isolated yield 61% by treatment of **1** with sodium amide in liquid ammonia. Alternatively, the recrystallization of the crude product from *n*-heptane gave the pure product in 40% yield.

In summary, we developed a convenient method to synthesize 2-phenylcyclopropenone acetals, which are the key intermediates for some biologically active compounds containing a cyclopropenone moiety. As this reaction proceeds in THF containing 1 equiv of DMI or in a THF−DMI mixture in good yield and the experimental procedure is very simple in comparison to the previously reported methods,[3,4] it will be useful especially for a small-scale preparation.

## Experimental Section

**General.** All $^1$H NMR spectra taken at 250 MHz were measured on a Bruker AC-250 instrument and are reported in parts per million from internal tetramethylsilane. $^{13}$C NMR spectra taken at 75 MHz were measured on a Bruker ARX-300 instrument and are reported in parts per million. IR spectra were recorded on a JASCO FT/IR-5300 instrument; absorptions are reported in cm$^{-1}$. Most of reagents were purchased from Tokyo Chemical Industry and used without further purification.

**2-Bromomethyl-2-(chlorophenylmethyl)-5,5-dimethyl-1,3-dioxane 1.** Phenylacetone **2** (90.56 g) was dissolved in dichloromethane (500 mL), and sulfuryl chloride (66.0 mL) was added slowly at 0 °C. After stirring at room temperature for 7 h, water (400 mL) was added, and the separated aqueous layer was extracted twice with dichloromethane. Then the combined extracts were washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. Removal of the drying agent and concentration afforded crude α-chloroketone **3** (119.6 g), which was used without purification: $^1$H NMR ($CDCl_3$) 2.23 (s, 3 H), 5.35 (s, 1 H), 7.35−7.47 (m, 5 H).

To a solution of the crude α-chloroketone **3** (119.6 g) in toluene (700 mL) were added neopentyl glycol (105.4 g) and *p*-toluensulfonic acid (2.57 g). Then the mixture was refluxed for 7 h in a Dean−Stark apparatus with continuous removal of separated water. After cooling to room temperature, *n*-hexane (1000 mL) was added, and the resulting solid was removed by filtration and washed with *n*-hexane. The filtrate was washed with diluted $NaHCO_3$ solution, water, and saturated NaCl solution successively and dried over anhydrous $Na_2SO_4$. Removal of the drying agent and concentration afforded crude acetal **4** (174.3 g, containing a small amount of toluene), which was used without purification: $^1$H NMR ($CDCl_3$) 0.80 (s, 3 H), 0.99 (s, 3 H), 1.41 (s, 3 H), 3.48 (dd, $J$ = 11.4 Hz, 1.7 Hz, 1 H), 3.50 (dd, $J$ = 11.7 Hz, 1.7 Hz, 1 H), 3.62 (d, $J$ = 11.4 Hz, 1 H), 3.63 (d, $J$ = 11.7 Hz, 1 H), 4.97 (s, 1 H), 7.20−7.35 (m, 3 H), 7.45−7.55 (m, 2 H).

This crude acetal **4** (174.3 g, containing a small amount of toluene) was dissolved in chloroform (1400 mL), and pyridinium hydrobromide perbromide (230.0 g) was added. After refluxing for 30 min, it was cooled to room temperature, and then water (1000 mL) was added. The aqueous layer was extracted with chloroform, and the combined extracts were washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution successively and dried over anhydrous $Na_2SO_4$. Removal of the drying agent and concentration afforded a crude product, which was recrystallized from *n*-hexane to give the desired compound **1** (148.2 g, 66%): mp 81−82 °C; IR (KBr) 2959, 2868, 1472, 1453, 1426, 1395, 1208, 1129, 1265, 1020, 988, 766, 704; $^1$H NMR ($CDCl_3$) 0.77 (s, 3 H), 0.81 (s, 3H), 3.38−3.65 (m, 5H), 3.94 (d, $J$ = 11.7 Hz, 1H), 5.29 (s, 1H), 7.25−7.40 (m, 3 H), 7.45−7.60 (m, 2 H); $^{13}$C NMR ($CDCl_3$) 21.66, 21.69, 27.21, 29.07, 62.94, 70.44, 70.61, 97.25, 127.20, 127.93, 129.24, 135.94. Anal. Calcd for $C_{14}H_{18}BrClO_2$: C, 50.40; H, 5.44; Br, 23.59; Cl, 10.63. Found: C, 50.30; H, 5.37; Br, 23.71; Cl, 10.34.

**2-Phenylcyclopropenone 2,2-dimethyl-1,3-propanediyl Acetal 6.** To a solution of potassium *tert*-butoxide (672 mg) in DMI (5 mL) was added dihalide **1** (1.0 g) in THF (5 mL) at 0 °C. After stirring for 4 h at 0 °C, water (20 mL) was added, and then the aqueous solution was extracted with *n*-hexane three times. The combined extracts were washed with saturated NaCl solution and dried over anhydrous $Na_2SO_4$. Removal of the drying agent and concentration gave a crude product, which was purified by flush column chromatography (5% ethyl acetate/*n*-hexane) to afford the titled compound (453 mg, 70%): mp 54 °C; IR ($CCl_4$) 3100, 2250, 1960, 1900, 1810, 1720, 1470, 1260; $^1$H NMR ($CDCl_3$) 1.08 (s, 3 H), 1.15 (s, 3 H), 3.75 (s, 4 H), 7.35−7.47 (m, 3 H), 7.60−7.67 (m, 2 H), 7.69 (s, 1 H); $^{13}$C NMR ($CDCl_3$) 21.78, 22.00, 29.95, 77.26, 82.69, 114.12, 125.45, 128.29, 129.13, 129.52, 135.18. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.64; H, 7.54.

**2-Chloro-2-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl Acetal 5.** mp 87 °C; IR (KBr) 2961, 2872, 1473, 1445, 1422, 1364, 1343, 1310, 1258, 1242, 1171, 1088, 1071, 1042, 1020, 984, 953, 916, 735, 700, 658, 648, 617; $^1$H NMR ($CDCl_3$) 0.85 (s, 3 H), 1.15 (s, 3 H), 1.68 (d, $J$ = 8.2 Hz, 1 H), 2.07 (d, $J$ = 8.2 Hz, 1 H), 3.19 (s, 2 H), 3.68 (d, $J$ = 11 Hz, 1 H), 3.84 (d, $J$ = 11 Hz, 1 H), 7.25−7.40 (m, 3 H), 7.45−7.60 (m, 2 H). Anal. Calcd for $C_{14}H_{17}ClO_2$: C, 66.53; H, 6.78; Cl, 14.03. Found: C, 66.17; H, 6.69; Cl, 13.90.

**2-*tert*-Butoxy-3-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl Acetal 7.** mp 75−76 °C; IR (KBr) 2984, 2961, 2868, 1603, 1495, 1474, 1458, 1393, 1366, 1192, 1165, 1123, 1082, 1065, 1049, 897, 883, 696, 630; $^1$H NMR ($CDCl_3$) 0.72 (s, 3 H), 1.20 (s, 3 H), 1.27 (s, 9 H), 2.25 (d, $J$ = 4.9 Hz, 1 H), 3.04 (d, $J$ = 10.8 Hz, 1 H), 3.32 (dd, $J$ = 10.8 Hz, 2.1 Hz, 1 H), 3.62 (d, $J$ = 10.7 Hz, 1 H), 3.66 (d, $J$ = 4.9 Hz, 1 H), 3.72 (dd, $J$ = 10.7 Hz, 2.1 Hz, 1 H), 7.10−7.25 (m, 3 H), 7.25−7.35 (m, 2 H); $^{13}$C NMR ($CDCl_3$) 21.44, 22.25, 27.49, 30.57, 37.91, 61.44, 74.82, 75.15, 90.72, 125.12, 126.22, 127.76, 136.44. Anal. Calcd for $C_{18}H_{26}ClO_3$: C, 74.45; H, 9.02. Found: C, 74.54; H, 9.09.

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