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The Use of Zinc/Silver Couple in the Cyclocoupling Reaction of Polybromo Ketones and Furan

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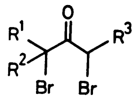
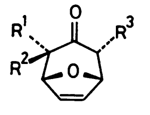
Synopsis. The title 3+4→7 reaction, followed by Zn/Cu couple reduction in methanol, affords 8-oxabicyclo-[3.2.1]oct-6-en-3-ones in satisfactory yields.

During the course of our recent project on *C*-nucleoside synthesis,[1] the need arose for the large-scale preparation of the oxabicyclic product **5** by the reductive cyclocoupling reaction of α,α,α′,α′-tetrabromoacetone (**1**) and furan.[2] Among various reducing agents, Zn/Ag couple[3] was found to be an effective reagent for such purpose. Thus reaction of **1** and furan in THF with the aid of Zn/Ag couple and subsequent treatment of the product with Zn/Cu couple[5] in methanol gave rise to **5** in 55% yield. The yield of the present 3+4 cyclocoupling reaction was not as high as that of the iron carbonyl promoted reaction[4] but these reaction conditions may be suitable for the medium- to large-scale synthesis of **5** because of the operational simplicity and from economical point of view. Use of Zn/Cu couple[5] or activated Zn[6] in place of Zn/Ag couple resulted in decrease in product yield.[7] THF was the best among solvents so far examined. Zn/Ag couple could be employed also in the reaction of the polybromo ketones **2**—**4** and furan.





1, $R^1=R^3=Br$; $R^2=H$
2, $R^1=R^3=Br$; $R^2=CH_3$
3, $R^1=R^2=CH_3$; $R^3=Br$
4, $R^1=R^3=CH_3$; $R^2=H$
5, $R^1=R^2=R^3=H$
6, $R^1=CH_3$; $R^2=R^3=H$
7, $R^1=R^2=CH_3$; $R^3=H$
8, $R^1=R^3=CH_3$; $R^2=H$

Experimental

The brominated ketones **1**—**4**[8] and Zn/Cu couple[5] were made by the known methods. Zn/Ag couple was prepared by the Heathcock's procedure using 65 mg of $AgOCOCH_3$ per g of Zn.[3a] Solvent THF was freshly distilled from sodium/benzophenone in a recycling still. All reactions were carried out under argon atmosphere. Filtration was carried out using a Celite 545 pad. Unless otherwise stated, concentration of solutions containing nonvolatile materials was achieved on a rotary evaporator (30—40 mmHg) at room temperature. Drying of organic solutions was performed over anhydrous Na_2SO_4. All melting and boiling points are uncorrected.

8-Oxabicyclo[3.2.1]oct-5-en-3-one (**5**). A mixture of Zn/Ag couple (29.3 g, 0.450 g-atom) and furan (210 ml, 3.00 mol) in dry THF (450 ml) was placed in a 2-litre three-necked flask and cooled at −10 °C. A solution of **1** (112 g, 0.300 mol) in dry THF (200 ml) was added dropwise over a period of 2 h with stirring and then the resulting mixture was allowed to warm up to room temperature and stirred for 12 h. The insoluble materials were removed by filtration and the filtrate was concentrated. The tarry brown residue was chromatographed on a silica gel column (E. Merck, 700 g, 1:20 to 1:5 hexane/ethyl acetate mixture as eluent) to give crude 2α,4α-dibromo-8-oxabicyclo[3.2.1] oct-6-en-3-one[4] as yellowish crystals (55 g). Recrystallization from hexane gave a pure sample melting at 126.5—127 °C. The dibromo adduct was dissolved in saturated NH_4Cl solution in CH_3OH (1.3 litre) and to this was added portionwise Zn/Cu couple (120 g, 1.85 g-atom) over 10 min at room temperature. The suspension was stirred for an additional 1 hr and filtered. The filtrate was divided into four portions and each portion was diluted with water (200 ml) and saturated Na_2H_2edta solution (300 ml). Extraction was then performed with CH_2Cl_2 successively (300 ml and then 200 ml×2). The combined extracts were dried and CH_2Cl_2 was removed by distillation at atmospheric pressure through a 40-cm Vigreux column. Finally the residue was subjected to light suction by an aspirator at room temperature to leave the bicyclic compound **5**, contaminated with a small amount of CH_2Cl_2, as a pale yellow liquid (20.4 g, 95% pure by NMR analysis[4]). Overall yield based on **1** was 55%. Pure crystalline sample of **5**, mp 37—39 °C, was obtained by bulb-to-bulb distillation (50—80 °C/0.01 mmHg).

2α-Methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**6**). A mixture of Zn/Ag couple (29.3 g, 0.450 g-atom) and furan (210 ml, 3.00 mol) in THF (450 ml) was cooled at −10 °C and to this was added a solution of **2** (116 g, 0.300 mol) in THF (200 ml) in a dropwise manner over 1.5 h. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 17 h, and filtered. The filtrate was concentrated and chromatographed on a column of silica gel (700 g, 1:20 to 1:5 hexane/ethyl acetate) to give 2,4-dibromo-2-methyl-8-oxabicyclo[3.2.1] oct-6-en-3-one as a pale yellow solid (54 g). Mp 78—79 °C (from hexane). This adduct, dissolved in saturated NH_4Cl solution in CH_3OH (1.2 litre), was treated with Zn/Cu couple (120 g, 1.85 g-atom) with stirring at room temperature for 1 h and filtered. The resulting solution was worked up with aqueous Na_2H_2edta and CH_2Cl_2 in the same fashion as described in the preparation of **5**. The combined CH_2Cl_2 solutions were dried and concentrated with a Vigreux column at atmospheric pressure and then with an aspirator (30—40 mmHg, room temperature) to afford **6** (21.9 g, contaminated with 7% of CH_2Cl_2 as determined by NMR[4]). The overall yield was 53% based on **2**. Pure sample of **6** was obtained by bulb-to-bulb distillation (70—100 °C/0.02 mmHg).

2,2-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**7**). To a cooled (−10 °C) mixture of Zn/Ag couple (29.3 g, 0.450 g-atom), furan (210 ml, 3.00 mol), and THF (450 ml) was added a solution of **3** (96.6 g, 0.300 mol) in THF (200 ml) over a period of 1.5 h. The mixture was then stirred at room temperature for 19 h, filtered, and concentrated. The resulting tarry residue was chromatographed (silica gel 700 g, 1 : 20 to 1 : 5 hexane/ethyl acetate) to give 2,2-dimethyl-4α-bromo-8-oxabicyclo[3.2.1]oct-6-en-3-one as crystalline solid (38 g). Mp 95—96 °C (from hexane). The bromide was dissolved in CH_3OH saturated with NH_4Cl (1.4 litre) and treated with Zn/Cu couple (100 g, 1.54 g-atom) at room temperature for 1 h. The reaction mixture was filtered and the filtrate was worked up with aqueous Na_2H_2-edta and CH_2Cl_2 as described above. The combined organic layers were dried and concentrated using a Vigreux column. Subsequent light suction by an aspirator (30—40 mmHg, at room temperature) left **7** of 93% purity (NMR analysis,[4] 22.5 g, 50% overall yield based on **3**), the only impurity being CH_2Cl_2. Its bulb-to-bulb distillation (80—110 °C/0.05 mmHg) afforded pure sample of **7**, mp 46—47 °C.

2α,4α-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (8). A mixture of Zn/Ag couple (19.6 g, 0.300 g-atom), furan (140 ml, 2.00 mol) and THF (300 ml) was stirred at −10 °C, to which a solution of **4** (48.8 g, 0.200 mol) in THF (150 ml) was added dropwise over a period of 1 h. Then the mixture was allowed to warm up to room temperature and stirred for an additional 12 h. The insoluble precipitate was removed by filtration and the filtrate was concentrated. Chromatography of the residue on a silica gel column (500 g, 1:20 to 1:5 hexane/ethyl acetate) afforded **8** as a colorless liquid (24.2 g, 80% yield), identical with authentic sample.[4] No other stereoisomers were formed.

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