

Donald E. Bergstrom* and P. Anantha Reddy

Department of Chemistry, University of North Dakota,
Grand Forks, North Dakota 58202

Received October 20, 1982

Synthesis of a naturally occurring irregular isoprenoid benzofuran, furoventalene (**3**), has been achieved in high yield *via* the nickel catalyzed coupling of 4-methyl-3-penten-1-ylmagnesium bromide (**1**) with 3-methyl-6-chlorobenzofuran (**2**).

J. Heterocyclic Chem., **20**, 469 (1983).

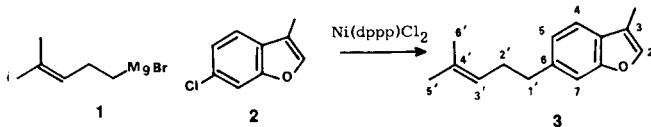
The structure of the marine benzofuran, furoventalene (**3**) isolated from the sea fan, *Gorgonia ventalina*, was determined by Weinheimer and Washecheck in 1969 (1). To confirm the structure by synthesis, 6-bromo-3-methylbenzofuran was transformed to **3** in five steps *via* a sequence that introduced the double bond non-regioselectively (1). A more recent synthesis, although regioselective, required eight steps and gave an overall yield of only 3% (2).

The key step is a reaction that allows Grignard reagents to be coupled to heterocyclic compounds at the position of a chlorine substituent. A catalyst introduced by Kumada (3), dichloro[1,3-bis(diphenylphosphine)propane]nickel(II) [Ni(dppp)Cl₂] is particularly effective for this coupling reaction.

The two halves were synthesized by conventional procedures. Grignard reagent **1** is derived from 5-bromo-2-methyl-2-pentene, which is readily synthesized in two steps from cyclopropylmethyl ketone (4).

3-Methyl-6-chlorobenzofuran (**2**) is obtained from 3-chlorophenol in an overall yield of 28%. The sequence proceeds *via* acetylation and Fries rearrangement to give 2-acetyl-5-chlorophenol (5), which on reaction with ethyl chloroacetate in the presence of potassium carbonate in refluxing acetone gave 2-(ethoxycarbonylmethoxy)-4-chloroacetophenone (6). The ester was hydrolyzed in aqueous sodium hydroxide and the resulting phenoxyacetic acid transformed to **3** by heating with fused sodium acetate in acetic anhydride.

When Grignard reagent **1** and 3-methyl-6-chlorobenzofuran (**2**) were combined in the presence of a catalytic quantity of Ni(dppp)Cl₂ furoventalene (**3**) was formed in virtually quantitative yield.



EXPERIMENTAL

The ¹H and ¹³C nmr spectra were obtained on a Jeol FX 60 60 MHz FT NMR spectrometer operating at 60 and 15.03 MHz, respectively. Ultraviolet spectra were taken on a Cary 14 spectrophotometer and infrared spectra on a Nicolett MX-S spectrophotometer.

To a solution of the Grignard reagent **1**, (prepared from 5-bromo-2-methyl-2-pentene (4.08 g) and magnesium (0.6 g) in diethyl ether (100 ml), was added (5 minutes) a mixture of Ni(dppp)Cl₂ (25 mg) and 3-methyl-6-chlorobenzofuran (0.415 g, 2.5 mmoles) in ether (30 ml) at 0° under a nitrogen atmosphere. After 10 minutes the brown reaction mixture was allowed to warm to room temperature and stirred overnight. Excess Grignard reagent was decomposed with saturated aqueous ammonium chloride (20 ml) and the product isolated from the ether layer by extraction to yield after removal of the solvent *in vacuo* 0.530 g of **3**. The ¹H nmr, uv and ir data were identical to that reported in the literature (1,2). The structure was further confirmed by ¹³C nmr.

Table

Furoventalene ¹³C NMR Assignments
(δ values relative to TMS)

C-2	140.80	C-5	118.77	C-2'	30.34
C-3	115.22	C-6	138.91	C-3'	123.64
C-3Me	7.80	C-7	110.84	C-4'	132.03
C-3a	126.76	C-7a	155.68	C-5'	25.53
C-4	122.99	C-1'	36.19	C-6'	17.59

Acknowledgment.

This work was supported by Grant No. CA 30050 awarded by the National Cancer Institute, which we gratefully acknowledge.

REFERENCES AND NOTES

- (1) A. J. Weinheimer and P. H. Washecheck, *Tetrahedron Letters*, 3315 (1969).
- (2) F. Kido, Y. Noda, T. Maruyama, C. Kabuto, and A. Yoshikoshi, *J. Org. Chem.*, **46**, 4264 (1981).
- (3) M. Kumada, K. Tamao, and K. Sumitani, *Org. Synth.*, **58**, 127 (1973).
- (4) F. Medina and A. Manjarrez, *Tetrahedron*, **20**, 1807 (1964).
- (5) K. A. Thakar, *J. Indian Chem. Soc.*, **40**, 539 (1963).
- (6) R. Royer and L. Rene, *Bull. Soc. Chim. France*, 3601 (1970).