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Syntheses with 2-Furylmagnesium Bromides. I. Synthesis of Rosefuran and Sesquirosefuran*

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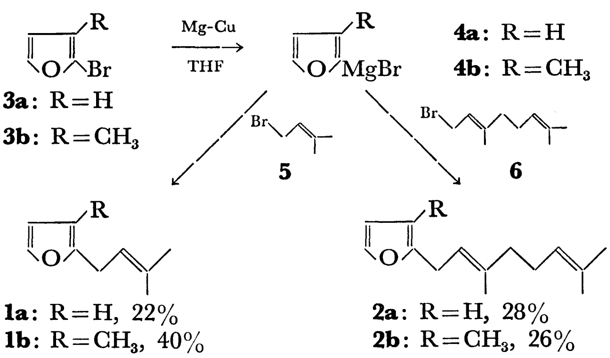
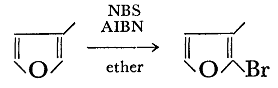
Synopsis. The preparation and reactions of 2-furylmagnesium bromide and 3-methyl-2-furylmagnesium bromide (**4b**) have been studied. Activated 90% magnesium–copper alloy was used to prepare the Grignard reagents. The reaction of 1-bromo-3-methyl-2-butene with **4b** gave rosefuran in a 40% yield; that of geranyl bromide with **4b** gave sesquirosefuran in a 26% yield.

Furylmetal compounds such as 2-furyllithium1,2) and di-2-furylmercury(II)1–3) are widely used for introducing 2-furyl moiety of natural products, *i.e.* rosefuran (**1b**), a trace component of Bulgarian rose oil (*Rosa damascene* Mill.),1) and sesquirosefuran (**2b**), a constituent isolated from the oil of the leaves of *Actinodaphne longifolia* (Blume) Nakai.4) The scheme of synthesis with 2-furylmagnesium derivatives has not been studied before. It seems worth while to devise a synthetic route leading to these natural products in which innoxious Grignard reagents are used in place of organomercury compounds. We have studied the preparation and reaction of 2-furylmagnesium bromides, and wish to report a new synthesis of compounds **1b** and **2b** by the reaction of 3-methyl-2-furylmagnesium bromide (**4b**) with 1-bromo-3-methyl-2-butene (**5**)6) for the former, and geranyl bromide (**6**)2) for the latter.



3a: R=H
3b: R=CH$_3$
4a: R=H
4b: R=CH$_3$
5
6
1a: R=H, 22%
1b: R=CH$_3$, 40%
2a: R=H, 28%
2b: R=CH$_3$, 26%

Few studies have been carried out on the reaction of 2-furylmagnesium compounds, except for the first work on the preparation of 2-furylmagnesium bromide (**4a**),5) which was transformed into furoic acid by the action of carbon dioxide solely for the sake of confirming its formation. We have thus carried out the synthesis of 2-(3-methyl-2-butenyl)furan (**1a**)7) and 2-geranylfuran (**2a**). The solution of 2-furylmagnesium bromide was prepared by reacting 2-bromofuran (**3a**)8) with an activated magnesium–copper alloy (90 : 10) in THF, at room temperature for 3.5 h. Conversion of **3a** into the Grignard reagent was confirmed by a test with Michler's ketone.9) Since the 12.75% Cu–Mg alloy recommended by Shepard *et al.*5) was not available, we used the powder alloy obtained from a mixture of 90 parts of magnesium powder and 10 parts of copper powder by heating to red-hot under nitrogen. For each reaction, the alloy was reactivated by heating with half its weight of iodine at 50 °C. The reaction of the Grignard reagent **4a** with the bromide **5** gave furan **1a** in a 22% yield and that with bromide **6** gave furan **2a** in a 28% yield. The structures of these products were confirmed by spectral data (IR, NMR, and MS).



3b

The solution of Grignard reagent **4b** was prepared from 2-bromo-3-methylfuran (**3b**) in a way similar to that for the formation of **4a**. Bromofuran **3b** was obtained in a 56% yield by the action of *N*-bromosuccinimide (NBS) on 3-methylfuran by means of the procedure of Prugh *et al.*8) The reaction of **4b** with compound **5**, gave furan **1b** in a 40% yield and that with compound **6** gave furan **2b** in a 26% yield. The spectral data (IR, NMR, and MS) of these synthetic furans were identical with those reported.1,4) Although the yields are small as compared with those of the Friedel-Crafts-type alkenylation of furan,7) the present route has a merit for the synthesis of 2,3-disubstituted furans, since it affords no other disubstituted isomers.

Experimental

Elemental analysis was carried out by Mr. Eiichiro Amano. Analytical determinations by GLPC were performed on a Hitachi Model K-53 gas chromatograph fitted with the following columns (3 mm o.d. × 1 m): A, 10% Apiezon Grease L on Chromosorb W; B, 10% poly(neopentyl succinate) on Chromosorb W; C, 10% SE-30 on Chromosorb W. Mass spectra were obtained with a Hitachi Model RMS-4 mass spectrometer. ^{1}H NMR spectra were taken at 60 MHz on a Hitachi Model R-24 apparatus. ^{13}C NMR spectra were obtained with a JEOL Model JNM-FX-100 spectrometer. Thin layer chromatograms were prepared with Merck Kieselgel 60 PF$_{254}$ (E. Merck AG, Darmstadt). Compounds **3a**,8) **5**,6) **6**,2) and 3-methylfuran10) were prepared according to reported methods.

Preparation of a 90% Mg–Cu Alloy. A small glass tube (15 mm i.d. × 15 cm) was charged with a mixture consisting of 1.8 g of magnesium powder and 0.2 g of copper powder. After the air in the tube was sufficiently replaced by nitrogen, the mixed metal powder was heated to red-hot with a colorless flame for 20 min under nitrogen. After being cooled, the lump of alloy was crushed in a mortar, and stored in a small rubber-stoppered bottle.

*2-(3-Methyl-2-butenyl)furan (**1a**).*7) A mixture of 0.21 g of 90% Mg–Cu alloy and 0.1 g of iodine was heated for 1 h at 50 °C under nitrogen. To the resulting mixture was added

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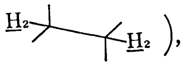
slowly a solution of 2-bromofuran (0.73 g, 5.0 mmol) in 2 ml of THF, over a period of 20 min. Stirring was continued for 3 h at room temperature. After the formation of the Grignard reagent **4a** in the solution had been confirmed by a test with Michler's ketone,[9] it was added dropwise to a boiling solution of 1-bromo-3-methyl-2-butene (**5**) (0.74 g, 5.0 mmol) in 2 ml of THF over a period of 1 h under nitrogen. The mixture was refluxed for 1 h, and then allowed to stand at room temperature for 12 h. It was neutralized with dilute H_2SO_4, extracted with ether, and dried over $MgSO_4$. Distillation of the residue obtained after removal of the solvent gave 147 mg (22%) of **1a**: IR (neat) 1670, 1595, 1563, 1508, 1093, 1012, and 736 cm^{-1}; NMR ($CDCl_3$) δ 1.64 $\left(\mathrm{s,\ 6H,}\ =\!\langle{}^{\mathrm{CH_3}}_{\mathrm{C\underline{H}_3}}\right)$, 3.29 (d, J=7 Hz, 2H, $-\mathrm{C\underline{H}_2}-$), 5.28 $\left(\mathrm{t,}\ J=7\ \mathrm{Hz,\ 1H,}\ \rangle\!=\!\langle_{\underline{\mathrm{H}}}\right)$, 5.90 (m, 1H, β'-H of furan), 6.20 (m, 1H, β-H of furan), and 7.24 ppm (m, 1H, α-H of furan).

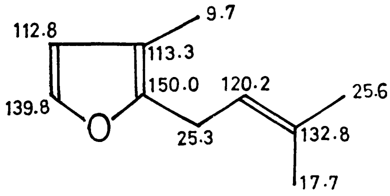
*2-Geranylfuran (**2a**).* A solution of **4a** prepared from 1.1 g (7.5 mmol) of **3a** in 3 ml of THF and 0.33 g of Mg–Cu alloy was reacted with a solution of geranyl bromide (**6**) (1.63 g, 7.5 mmol) in the same way as in the foregoing experiment of **1a**. A crude product (700 mg, 28%) with a 62% purity by GLPC was obtained by distillation: bp (bath temperature) 100—120 °C (2 Torr). It was purified by preparative TLC (silica gel, hexane, R_f=0.3) and analyzed: IR (neat) 1596, 1503, 1007, 798, and 728 cm^{-1}; NMR (CCl_4) δ 1.59 $\left(\mathrm{s,\ 3H,}\ /\!=\!\langle_{\mathrm{C\underline{H}_3}}\right)$, 1.67 $\left(\mathrm{s,\ 6H,}\ =\!\langle{}^{\mathrm{CH_3}}_{\mathrm{C\underline{H}_3}}\right)$, 2.0 (br, s, 4H, ), 3.27 (d, J=8 Hz, 2H, $-\mathrm{C\underline{H}_2}-$), 5.04 $\left(\mathrm{br,\ m,\ 1H,}\ {}^{\underline{\mathrm{H}}}\rangle\!=\!\langle{}^{\mathrm{CH_3}}_{\mathrm{CH_3}}\right)$, 5.29 $\left(\mathrm{t,}\ J=8\ \mathrm{Hz,\ 1H,}\ {}^{\underline{\mathrm{H}}}\rangle\!=\!\langle_{\mathrm{CH_3}}\right)$, 5.80 (m, 1H, β'-H of furan), 6.12 (t, 1H, β-H of furan), and 7.18 ppm (m, 1H, α-H of furan); MS (70 eV) *m/e* (rel intensity) 204 (1, M^+), 162 (3), 123 (18), 81 (47), 67 (100).

Found: C, 82.14; H, 9.76%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

*2-Bromo-3-methylfuran (**3b**).* A 50 ml flask was charged with 5.4 g (34 mmol) of NBS and 0.26 g of AIBN. To the mixture was added a solution of 3-methylfuran[10] in 25 ml of dry ether under nitrogen. The resulting mixture was stirred for 3 h under reflux. It was then filtered, washed with 1% aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$ containing 20 mg of hydroquinone and 0.1 g of $CaCO_3$. After removal of the solvent and subsequent addition of 5 ml of quinoline, the mixture was subjected to fractional distillation under diminished pressure to yield 3.1 g (56%) of **3b**: bp 56—57 °C (60 Torr) [lit,[8] bp 28—30 °C (12 Torr)]; IR (neat) 1495, 1160, 1075, 892, and 736 cm^{-1}; NMR (CCl_4) δ 1.97 (s, 3H, $-\mathrm{C\underline{H}_3}$), 6.18 (d, J=2 Hz, 1H, β-H of furan), and 7.29 ppm (d, J=2 Hz, 1H, α-H of furan).

*2-(3-Methyl-2-butenyl)-3-methylfuran (**1b**). Synthesis of Rosefuran*: A solution of the Grignard reagent **4b** was prepared from 1.21 g (7.5 mmol) of 2-bromo-3-methylfuran (**3b**) dissolved in 4 ml of THF and 0.33 g of 90% Mg–Cu alloy, which was reactivated as usual. It was then added to a boiling solution of **5** (1.11 g, 7.5 mmol) in 3 ml of THF under nitrogen in the course of 45 min. Refluxing was continued for 3 h. It was then cooled and acidified with dilute H_2SO_4. The organic layer was extracted with ether and the ethereal extract was dried over anhydrous $MgSO_4$. After removal of the solvent the residue was distilled to give 512 mg of **1b** (87% purity by GLPC), yield 40%: bp (bath temperature) 80—100 °C (18 Torr) [lit,[1] bp 39—40 °C (1 Torr)]; IR (neat) 1670, 1628, 1512, 1450, 1380, 1158, 1088, 899, 857, and 733 cm^{-1}; NMR ($CDCl_3$) δ 1.70 $\left(\mathrm{d,}\ J=1\ \mathrm{Hz,\ 6H,}\ =\!\langle{}^{\mathrm{CH_3}}_{\mathrm{C\underline{H}_3}}\right)$, 1.94 (s, 3H, ring $-\mathrm{C\underline{H}_3}$), 3.26 (d, J=7 Hz, 2H, $-\mathrm{C\underline{H}_2}-$), 5.23 $\left(\mathrm{t,}\ J=7\ \mathrm{Hz,\ 1H,}\ {}^{\underline{\mathrm{H}}}\rangle\!=\!\langle\right)$, 6.10 (d, J=2 Hz, 1H, β-H of furan), 7.16 (d, J=2 Hz, α-H of furan); MS (70 eV) *m/e* (rel intensity) 150 (79, M^+), 135 (100).

The natural abundance ^{13}C NMR spectrum of **1b** is summarized in the following structure. Off-resonance decoupling was used to support the assignment.



*2-Geranyl-2-methylfuran (**2b**). Synthesis of Sesquirosefuran*: A solution of **4b** prepared from 1.45 g (9.0 mmol) of **3b** and 0.4 g of 90% Mg–Cu alloy was reacted with a solution of **6** (1.96 g, 9.0 mmol) in the same way as in the foregoing experiments. A crude product (909 mg, 26%) with a 56% purity by GLPC was obtained by distillation: bp (bath temperature) 100—120 °C (0.3 Torr). A pure sample was obtained by preparative TLC (silica gel, hexane, R_f= 0.3): IR (neat) 1623, 1560, 1507, 1148, 1079, 886, and 720 cm^{-1}; NMR (CCl_4) δ 1.58 $\left(\mathrm{s,\ 3H,}\ /\!=\!\langle_{\mathrm{C\underline{H}_3}}\right)$, 1.68 $\left(\mathrm{d,}\ J=1\ \mathrm{Hz,\ 6H,}\ =\!\langle{}^{\mathrm{CH_3}}_{\mathrm{C\underline{H}_3}}\right)$, 1.93 (s, 3H, ring $-\mathrm{C\underline{H}_3}$), 2.0 (br, s, 4H, ), 3.21 (d, J=8 Hz, 2H, $-\mathrm{C\underline{H}_2}-$), 5.07 $\left(\mathrm{br,\ m,\ 1H,}\ {}_{\underline{\mathrm{H}}}\rangle\!=\!\langle{}^{\mathrm{CH_3}}_{\mathrm{CH_3}}\right)$, 5.19 $\left(\mathrm{t,}\ J=8\ \mathrm{Hz,\ 1H,}\ {}^{\underline{\mathrm{H}}}\rangle\!=\!\langle_{\mathrm{CH_3}}\right)$, 6.10 (d, J=2 Hz, 1H, β-H of furan), and 7.07 ppm (d, J=2 Hz, 1H, α-H of furan).

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