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THE SYNTHESIS OF ALLYLIC SPIRODIOLS USING ORGANOCERIUM REAGENTS

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ABSTRACT. The organocerium reagents were successfully used to perform the 1,2-addition reactions to carbonyl groups of the α,β-unsaturated spirodiketones. Thus, using phenylcerium (II) chloride and thienylcerium (II) chloride, we have prepared the allylic diols 1,6-dithienylspiro[4,4]nona-2,7-diene-1,6-diol (**3**) and 1,6-diphenylspiro[4,4]nona-2,7-diene-1,6-diol (**4**) in yield 85% and 45% respectively. In addition, we have obtained 6-hydroxy-6-phenylspiro[4,4]nona-2,7-dien-1-one (**5**) in 25% yield.

INTRODUCTION

The stereochemical features and chiroptical properties of substituted spirane systems have been the focus of several studies. In this context, successful chiral resolutions of those systems have been reported[1-6]. The use of the rigid framework of spiranes for stereocontrol of pharmacophoric groups in bioorganic molecules, or the use of appropriately substituted spiranes as chiral auxiliaries, have received little attention. The enantiomers of *cis/cis*-spiro[4,4]nonan-1,6-diols, however, have been investigated for their ability to induce stereoselectivity in metal hydride reductions of phenyl alkyl ketones[7], and in the hydroformilation of styrene[8]. Simple symmetrical systems such as the spiro[4,4]nonane system have been studied in connection with their C_2-symmetry and chiroptical properties[1,3,6,9].

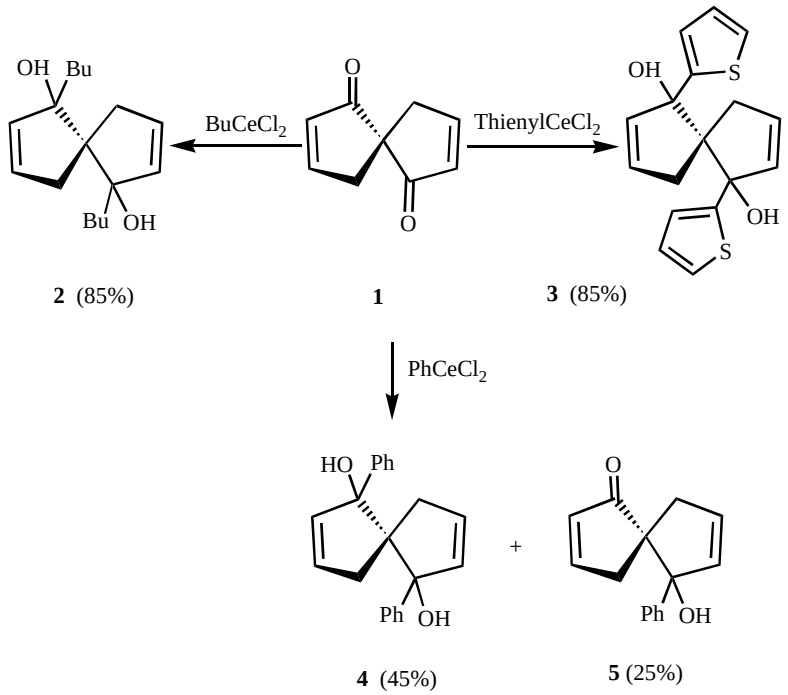
RESULTS AND DISCUSSIONS

We have initiated work on the preparation and palladium mediated transformations of cyclospiranes. In a previous paper[10], we reported results from studies on substitutions and stereoselectivities in reactions in the spiro[4,4]nona-2,7-diene-1,6-dione[11]. We have extended our investigations on the substitutions in the same spirane, being primarily interested in substitutions next to the spirocenter, in the α,α'-positions. This is a difficult task, due to the stereohindrance created by the spirocenter.

A very good approach for preparation of α,α'-substituted spiranes was to use organo-cerium reagents. It is known that using organolitium reagents and cerium (III) halides we can prepare organocerium reagents.[12] The last ones have been found to be extremely useful in organic synthesis, reacting with α,β-unsaturated carbonyl compounds to give 1,2-addition products (allylic alcohols) in good to high yields.

We used initially a simple organolithium compound, BuLi, to find the reaction conditions for preparation of $BuCeCl_2$ and for the 1,2-addition to the spiro[4,4]nona-2,7-diene-1,6-dione (**1**) (Scheme 1). The first step was to carefully dry $CeCl_3$ heptahydrate, and then to prepare the organocerium reagent. The reaction of $BuCeCl_2$ with the spirodiketone (**1**) took place in 1 h and we obtained, after purification, 85% of 1,6-dibutyl-spiro[4,4]nona-2,7-diene-1,6-diol (**2**). The structural assignment of the signals of the product was made using the ^1H and ^{13}C NMR spectra.

Scheme 1:



2 (85%) **1** **3** (85%)

4 (45%) **5** (25%)

Our goal was to introduce in the α,α'-positions thienyl and phenyl substituents. Our target molecules were 1,6-bis(thienyl)-spiro[4,4]nona-2,7-diene-1,6-diol (**3**) and 1,6-diphenyl-spiro[4,4]nona-2,7-diene-1,6-diol (**4**) (Scheme 1). Following the same procedure and reactions conditions similar with the ones we used for our test reaction, we have obtained the products **3** and **4** in yield 85% and 45% respectively. In the case of phenylceriumchloride we have obtained also 25% of the mono-addition product: 6-hydroxy-6-phenylspiro[4,4]nona-2,7-dien-1-one (**5**). This result showed that the reaction with phenylceriumchloride occures slower and the stereohindrance at the α-carbon is bigger, when we have already introduced a phenyl substituent. The correct assignment of the signals of the products was made using ^1H and ^{13}C NMR spectroscopy. We have also used IR, elemental analysis and HRMS, and they were all in accordance with the structures presented for the products **2-5**.

CONCLUSIONS

We have successfully used organocerium derivatives to perform the 1,2-addition to the carbonyl groups from the α,β-unsaturated spirodiketones. The procedure was relatively simple and the reactions time was short. The new products 1,6-bis(thienyl)-spiro[4,4]nona-2,7-diene-1,6-diol (**3**) and 1,6-diphenyl-spiro[4,4]nona-2,7-diene-1,6-diol (**4**) were obtained in in yield 85% and 45% respectively. In addition, we have obtained 6-hydroxy-6-phenylspiro[4,4]nona-2,7-dien-1-one (**5**) in 25% yield. The structures of all the products were in accordance with the NMR, IR and HRMS spectra.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz with Bruker DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 50 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77.00 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.).

General procedure for preparation of organocerium reagents: Cerium (III) chloride heptahydrate (*ca*. 20 g) was placed in a round-bottomed flask connected to a dry ice-trap. The flask was evacuated and heated to 100 °C for 2 h. The resulting opaque solid was then heated *in vacuo,* at 140 °C for 4-5 h. While the flask was still hot, argon gas was introduced, after which the flask was cooled in an ice bath. THF (10 ml / g $CeCl_3$) was added with vigorous stirring. The ice bath was removed and the suspension was stirred well for 2 h or more (o.n.) under argon at room temperature. The flask was cooled to -78 °C and an organolithium compound (1.5 eqv.) was added with a syringe. Stirring for 0.5-2 h at the same temperature, or a somewhat higher temperature (-40 to -20 °C), results in the formation of a yellow or red suspension, which was ready for use.

1,6-Dibutylspiro[4,4]nona-2,7-diene-1,6-diol (2): With the method described above, we have prepared $BuCeCl_2$. To the suspension of this organocerium reagent, cooled at –78 °C, a solution of spirodiketone **1** (0.5 g, 3.37 mmol) in dry THF was added. After 1 h at the same temperature, the reaction was completed (follow TLC). Concentrated aq. ammonium chloride was added to the reaction mixture and the resulting solution was filtered through Celite. The filtrate was extracted with ethyl acetate (2x) and the resulting organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo*, and the product was purified by flash chromatography, using hexane: ethyl acetate, 6 : 1 as eluent. We have obtained 0.75 g (85%) of pure product as a white solid, having m.p. 72 °C (from EtOAc/hexane). Found: C, 77.49; H, 10.84. Calc. for $C_{17}H_{28}O_2$: C, 77.27, H, 10.60. HRMS: *M* 264.2077. Calc. for $C_{17}H_{28}O_2$: 264.2089. ^{1}H NMR (200 MHz): δ 0.9 (t, 6H,

CH_3), 1.25 (m, 6H, CH_2), 1.55 (m, 4H, CH_2), 1.85 (m, 4H, CH_2), 2.75 (d, 2H, CH_2), 3.2 (s, 2H, OH), 5.9 (m, 4H, CH=). ^{13}C NMR δ 14 (CH_2), 24 (CH_2), 27 (CH_2), 38 (CH_2), 42 (CH_2), 61 (C), 88 (CHOH), 133 (CH=), 137 (CH=). IR (film) ν cm^{-1}: 3450 (br.), 3000, 1350. MS(EI): *m/z* 264 (M^+, 6), 246 (100), 228 (10), 203 (26), 189 (60), 161 (62), 133 (29), 117 (26), 105 (25), 91 (34), 85 (28), 57 (39), 41 (32).

1.6-Dithienylspiro[4,4]nona-2,7-diene-1,6-diol (3): The thienyllitium reagent was prepared by adding BuLi (10.11 ml sol 1.6 M in hexane, 16.2 mmol) to a solution of thiophene (1.77 ml, 21.6 mmol) in dry THF (10 ml), cooled to 0 °C. The mixture was allowed to warm up to room temperature and stirred for another 0.5 h. Then, the flask was cooled at -78 °C and the solution containing thienyllitium was added over the $CeCl_3$ suspension in THF, precooled at -78 °C. The resulting mixture, containing the thienylcerium reagent was stirred at this temperature for 1 h, before the spiro[4,4]nona-2,7-diene-1,6-dione (**1**) (1 g, 6.75 mmol) in dry THF (10 ml) was added. The resulting brown mixture was stirred for another hour at -78 °C, when TLC monitoring showed the reaction to be completed. Concentrated aq. ammonium chloride was added to the reaction mixture and the resulting solution was filtered through Celite. The filtrate was extracted with ethyl acetate (2x), the resulting organic layers were dried ($MgSO_4$), the solvent was removed *in vacuo* and the product was purified by flash chromatography, using hexane: ethyl acetate 4 : 1 as eluent. 1.7 g (80%) of an yellow oil was obtained. HRMS: *M* 316.0599. Calc. for $C_{17}H_{16}O_2S_2$: 316.0597. ^{1}H NMR (200 MHz): δ 2.05 (d, 1H, CH_2), 2.3 (d, 1H, CH_2), 2.55 (d, 1H, CH_2), 2.8 (s, 1H, OH), 3.6 (d, 1H, CH_2), 3.8 (s, 1H, OH), 5.8 (m, 2H, CH=), 5.95 (s, 1H, CH=), 6.1 (d, 1H, CH=), 6.2 (m, 1H, CH=), 6.75 (t, 1H, CH=), 6.9 (m, 2H, CH=), 7.05 (d, 1H, CHS), 7.2 (d, 1H, CHS). ^{13}C NMR δ 43 (CH_2), 44 (CH_2), 60 (C), 81 (d, CHOH), 123, 123.5, 124, 125.5, 125.8, 126, 130, 136, 137, 139 (CH=), 153, 154 (CS). IR (film) ν cm^{-1}: 3450, 3000, 2940, 1420. MS(EI): *m/z* 316 (M^+, 3), 299 (20), 298 (100), 280 (18), 247 (6), 187 (91), 172 (21), 153 (28), 147 (25), 111 (65), 97 (9), 77 (9), 45 (9), 39 (16).

1,6-Diphenylspiro[4,4]nona-2,7-diene-1,6-diol (4) was prepared using the procedure described above for compound **3**. 3.2 g (8.6 mmol) of $CeCl_3 \cdot 7H_2O$ were dried, dissolved in THF (30 ml), then phenyllithium (5.37 ml sol 1.6 M in THF, 8.6 mmol) was added. To the $PhCeCl_2$ suspension, cooled at -78 °C, a solution of diketone **1** (424 mg, 2.86 mmol) dissolved in THF (5 ml) was added. The reaction mixture was stirred at the same temperature for 1 h. After work up, the product was purified by flash chromatography, eluting with hexane : EtOAc, 4 : 1. The pure product was a yellow crystalline solid having m.p. 126-128 °C (CH_2Cl_2); yield 392 mg (45%). Found: C, 83.07; H, 6.78. Calc. for $C_{21}H_{20}O_2$: C, 82.89; H, 6.57. HRMS *M*: 304.1482. Calc. for $C_{21}H_{20}O_2$: 304.1485. ^{1}H NMR (200 MHz): δ 1.95 (d, *J* 17 Hz, 2 H, CH_2), 2.50 (d, *J* 17 Hz, 2 H, CH_2), 4.25 (s, 2 H, OH), 5.79-5.85 (m, 2 H, CH=), 5.89-5.96 (m, 2 H, CH=), 7.25-7.45 (m, 8 H, Ph), 7.65 (d, *J* 9 Hz, 2 H, Ph). ^{13}C NMR δ 44.8 (CH_2), 63.0 (C), 90.8 (CHOH), 127.0, 127.6, 129.5, 143.5 (Ph), 133.9, 137.5 (CH=). IR (film) ν cm^{-1}: 3460, 2980, 2900, 1450. MS(EI): *m/z* 304 (M^+, 1), 287 (24), 286 (100), 268 (10), 181 (87), 166 (23), 141 (14), 115 (16), 105 (62), 77 (28).

6-Hydroxy-6-phenylspiro[4,4]nona-2,7-dien-1-one (5) was obtained together with product **4** and the products were separated by flash chromatography. Pale yellow crystalline material with m.p. 120-122 °C ($CDCl_3$); yield 162 mg (25%). Found: C, 79.89; H, 6.34. Calc. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19. HRMS: *M* 226.0988. Calc. for $C_{15}H_{14}O_2$: 226.0993. ^{1}H NMR (200 MHz): δ 2.15-2.28 (doublet of multiplets, 1 H, CH_2), 2.35-2.46 (doublet of multiplets, 2 H, CH_2), 2.89-2.98 (doublet of multiplets, 1 H, CH_2), 4.40 (s, 1 H, OH), 5.91-5.99 (m, 1 H, CH=), 6.10-6.15 (m, 1 H, CH=), 6.19-6.24 (m, 1 H, CH=), 7.22-7.39 (m, 5 H, Ph), 7.46-7.51 (m, 1 H, CH=). ^{13}C NMR δ 42.9 (CH_2), 44.5 (CH_2), 60.0 (C), 89.4 (CPh), 125.7, 127.4, 128.1, 142.5 (Ph), 132.45, 132.48, 137.4, 164.5 (CH=), 213.2 (CO). IR (film) ν cm^{-1}: 3400, 2900, 1680. MS(EI): *m/z* 226 (M^+, 62), 208 (13), 179 (13), 165 (11), 144 (11), 128 (14), 121 (100), 105 (72), 77 (18), 55 (26), 51 (28), 39 (22), 28 (20).

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