# Unusual Course in a Grignard Reaction of a Mesyl Substituted Ketonic Bicyclo[2.2.1]heptane Compound

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*The Grignard reaction of 2-bromomagnesium ethanol-TBDMS-ether **3** with the ketone: ((1S,2S,4S,7R)-2-Chloro-5-oxobicyclo[2.2.1]heptan-7-yl)methyl methanesulfonate, **5**, gave no addition to the ketone group. Instead, the basicity of organomagnesium compound **3** induce a dehydrochlorination followed by substitution of the mesyl group with bromide to the tricyclic compound **9**. The intermediate bromide **8**, resulted from substitution of the mesyl group of the starting compound **5**, was also isolated. The oximes, acetylated oximes and 2,4-dinitrophenyl-hydrazone of compound **9** were also synthesized to characterize the final product.*

*Keywords: Grignard reaction, organomagnesium compound, mesyl group, oximes*

Nucleoside analogues play now an important role as drugs especially in the treatment of cancer and viral infection deseases [1] and the research in this direction is growing up continuously. The problem with nucleosides is the fact that in time, the resistence of viruses [2a-b] to the drugs becomes an important fact and also must not be neglected the side effects of associated with their use, especially their toxicity [2c-d]. Many efforts were done for discovering new compounds with more specified therapeutic profile and lower side effects. These take into account the changes on the base or on the sugar moiety or boths.

In these efforts, we realized the syntheses of new nucleoside analogues by changing the usual sugar moiety with an oxabicyclo[3.3.0]octane fragment, [3a-b] a bicyclo[2.1.0]heptane fragment, [3c] on even some $O^2$,$O^4$-bis-substituted-pyrimidine analogues, [3d].

Acyclic nucleoside play an important role especially as antiviral drugs, like the known acyclovir, [4] ganciclovir, [5] and other numerous analogues, especially prodrugs (famciclovir, alaciclovir), phosphates and phosphonates [6].

We wanted to obtain nucleoside analogues with an elongated chain in the 5-position, $CH_2CH_2$-OH instead a $CH_2$-OH group on the bicyclo[2.1.0]heptane fragment.

Studies for synthesis of a longer chain in position 5 were presented in the literature with a $CH_2CH_2$-OH group [7] a $(EtO)_2P(O)$-$CH_2CH_2$ group [8] a $(HO)_2P(O)$-$CH_2OCH_2$-group [9] etc.

In our case, introduction of this group was intended to be realized by a Grignard reaction of a ketone group with the corresponding organomagnesium derivative.

## Experimental part

Melting points (uncorrected) were determined in open capillary on an OptiMelt melting point apparatus. Progress of the reaction was monitored by TLC on Merck silica gel 60 or $60F_{254}$ plates (Merck) eluted with the solvent system presented for each compound. Spots were developed with 2,4-dinitrophenylhydrazine reagent. IR spectra were recorded on a FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequences are expressed in $cm^{-1}$, with the following abreviations: w = weak, m = medium, s = strong, v = very, br = broad. Silicagel flash column purified fractions were injected into a Trace GC Ultra gas cromatograph (Thermo) with column TR 5 MS (30 m, .25 mm i.d., 0.25 μm film).

Program temperature was set as follows: start 50°C, ramping with 20°C/ min until 250°C, then 3 min isotherm. Total analyses time 13 min. As detector was used Polaris Q ion trap mass spectrometer (Thermo) set up in full scan mode in the range 50-350 m/z. Retention time 9.82 min for **9** and 10.88 min for **8**. $^1$H- and $^{13}$C-NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for $^1$H and 75 MHz for $^{13}$C) in $CDCl_3$, chemical shifts are given in ppm relative to TMS as internal standard. Complementary 2D-NMR spectra: COSY, HETCOR, were registred for each compound to correctly assign the signals for each proton and carbon atom in the molecules.

The numbering of the atoms in compounds is presented in schemes.

### Synthesis of 2-bromoethyl-1-tert-butyldimethylsilyl ether, 3

To solution of freshly distilled 2-bromoethanol (83g, 0.664 M) and imidazole (90.44g, 1.328 M) in dichlorometane (250mL), cooled on an ice-water bath, *tert*-butyldimethyl-silyl chloride (110.1g, 0.7304M) dissolved in dichloro-methane (150mL) was added dropwise under stirring, then the solution was stirred at r.t. over weekend. The reaction mixture was poured on a mixture of $NaHCO_3$ (50g), water (250 mL) and crushed ice (250g), stirred one more hour, organic phase separated and washed with sat. $NaHCO_3$ soln., [The aqueous phases were extracted with dichloromethane (150 mL)], dried ($Na_2SO_4$), filtered, concentrated and coevaporated with toluene, resulting 153.2g (96.5%) product as oil. IR: 2955vs, 2931vs, 2886s, 2857vs, 1469m, 1288s, 1123m, 1092s, 1022w, 1006w,

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943w, 891w, 834vs, 775vs, 673w, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.86(t, 2H, $CH_2O$, 6.4), 3.37(t, 2H, $CH_2Br$, 6.4), 0.88(s, 9H, $C\underline{H}_3C$), 0.06(s, 6H, $C\underline{H}_3Si$), $^{13}$CNMR ($CDCl_3$, δ ppm): 63.65($\underline{C}H_2O$), 33.44($CH_2Br$), 25.97($\underline{C}H_3C$), 18.47($\underline{C}CH_3$), -5.13($\underline{C}H_3Si$).

**Synthesis of ((1S,2S,4S,7R)-2-Chloro-5-oxabicyclo [2.2.1]heptan-7-yl)methyl methanesulfonate, 5**

To a solution of 34.9 g (0.2 M) compound **4** in 150 mL $CH_2Cl_2$ and 70 mL pyridine, cooled on an ice-water bath, 23.2 mL (34.37 g, 0.3 M) methansulfonyl chloride was added dropwise, then the reaction mixture was stirred overnight, monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\,4}$ = 0.30, $R_{f\,5}$ = 0.41). The reaction mixture was poured on a mixture of 20 g $NaHCO_3$ in 150 mL water and 100 g crushed ice, stirred for one hour, phases separated, organic phase washed with 100 mL sat. soln. $NaHCO_3$, dried ($Na_2SO_4$) concentrated and product crystallized from ethyl acetate-hexane. Resulted 43.5 g (95.5%) **5**, m.p. = 76.7-78.7°C, $[\alpha]_D^{20}$ = -30.35°(1% in THF), IR: 1742vs, 1473w, 1405w, 1355s, 1329m, 1275w, 1179w, 1161s, 1117w, 997w, 978w, 961m, 946s, 925w, 897w, 829m, 783m, 720w, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 4.69(dd, 1H, H-8, 9.1, 10.7); 4.55(dd, 1H, H-8, 6.3, 10.7); 4.12(ddd, 1H, H-2, 1.1, 4.9, 7.1); 3.07(s, 3H, $CH_3$); 2.94(d, 1H, H-1, 4.9); 2.84(m, 1H, H-4); 2.54(dd, 1H, H-7, 6.3, 9.1); 2.41(ddd,1H, H-3, 1.1, 7.4, 15.1); 2.35(dd,1H, H-3, 4.4, 15.1); 2.32(ddd, 1H, H-6, 1.1, 4.9, 18.4); 2.00(d, 1H, H-6, 18.4), $^{13}$C-NMR ($CDCl_3$, δ ppm): 211.31(C-5); 66.83(C-8); 57.43(C-2); 52.26(C-4); 48.03(C-7); 46.90(C-1); 45.28(C-6); 37.62($CH_3S$); 34.24(C-3),

**Synthesis of 5-(bromomethyl)tricyclo[2.2.1.0$^{2,6}$]heptan-3-one, 9**

*a) Synthesis of organomagnesium compound **3***

In a 250 mL round bottom flask under argon 1.01 atomg (41.5 mM) magnesium, 10 mL THF and an iodine crystal were added, then 5 mL of a solution of 9.93 g (41.51 mM) $BrCH_2CH_2OTBDMS$ (**3**) in 25 mL THF was added and the reaction was initialized by warming the reaction mixture to 60°C. The remaining of the bromide solution was then added at reflux in 110 min. There remains very small unreacted magnesium erodated pieces and the solution was refluxed for two hours. The solution was cooled to room temperature, then on ice-water bath to 5°C.

*b) Grignard reaction of organomagnesium compound **3** with compound **5***

A solution of 10.49 g (41.51 mM) compound **5** in 20 mL THF was dropwise (~45 min.) added to the cooled organomagnesium compound **3** (the vessels were washed with 10 mL THF), then the reaction mixture stirred at room temperature for ten days monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\,5}$ = 0.42, $R_{f\,7}$ = 0.30, $R_{f\,9}$ = 0.63, $R_{f\,8}$ = 0.68). The formation of a dehydrochlorinated compound **7** was observed from the first hours, by comparison with a standard synthesized compound [10], which looks to be the intermediate in the synthesis of compound **9**. Unreacted initial compound **5** and also the intermediate **7** are present in the reaction mixture and 15 mL of a organomagnesium solution, prepared as above, was added and refluxed for 3 h, then overnight at room temperature. Another 10 mL organomagnesium solution was added and stirred for 7 days at r.t., then the reaction was quenched by pouring in 75 mL cooled satd. soln. $NH_4Cl$ in 15 min. The stirring was continued until a clear solution resulted, phases separated, organic phase washed with 50 mL satd. soln. $NH_4Cl$ and concentrated under reduced pressure. (The aqueous phases were extracted with 2x60 mL THF). The crude product (13.6 g) was purified by pressure chromatography, resulting 7.7 g (92.27%) of pure compound **9** as oil, $[\alpha]_D$ = -58.55Ú(1% in THF), $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.35(dd, 1H, H-8, 8.0, 10.2); 3.28(dd, 1H, H-8, 8.0, 10.2); 2.63(tt, 1H, H-7, 1.4, 8.0); 2.23(tt, 1H, H-6, 1.4, 5.5); 2.18(dt, 1H, H-1, 1.4, 5.0); 2.05(m, 1H, H-4); 1.97(dt, 1H, H-3, 1.4, 11.5); 1.88(dt, 1H, H-3, 1.4, 11.5); 1.55(br t, 1H, H-2, 5.5), $^{13}$C-NMR ($CDCl_3$, δ ppm): 210.80(C-5); 44.94(C-7); 42.27(C-4); 31.55(C-8); 27.51(C-3); 24.15(C-6); 21.87(C-2); 19.68(C-1), Mwt. 201.06, GC-MS 70 eV, (m/z, % abundance), 200/202 (22.4/20.7) $M^{+\cdot}$, 121 (20.6 $[M\text{-}Br]^+$, 93 (63.5), 91 (100, BP), 79 (54.7), 77 (72.3) typical fragments from bicyclonorbornane system.

During column chromatography purification, a fraction of 1.32g of compound **10** was isolated as oil, IR: 2954vs, 2931vs, 2888s,2858vs, 1470m, 1253s, 1091s, 1006w, 939w, 832vs, 772vs, 662w, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.62(m, 4H, 2H-1, 2H-4), 1.56(m, 4H, 2H-2, 2H-3), 0.89, 0.88, 0.85(3s, 18H, $C\underline{H}_3C$), 0.36, -0.10(2s, 12H, $C\underline{H}_3Si$), $^{13}$C-NMR ($CDCl_3$ δ ppm): 63.28(2C, $CH_2O$, C-1, C-4), 29.12(2C, C-2, C-3), 26.12, 25.85 $\underline{C}H_3C$), 18.51($CH_3\underline{C}$), -2.80, -5.12($\underline{C}H_3Si$), MS: 318 (fragments: 303; 304[M-15], 261[M-57], etc.)

**Isolation of (1S,4S,5S,7R)-7-(bromomethyl)-5-chlorobicyclo[2.2.1]heptan-2-one as intermediate in Grignard reaction, 8**

A solution of 2 mM compound **5** in 5 mL THF was added to a solution of 4 mL organomagnesium compound **3** diluted with 5 mL THF and stirred over weekend at r.t.. After work-up as above, the crude product was purified by pressure chromatography, resulting a pure fraction (69.2 mg) of compound **8** as oil, IR: 2970m, 2925m, 1737vs, 1453m, 1437m, 1407w, 1315m, 1277w, 1250m, 1218m, 1126m, 1071m, 981w, 952w, 869m, 740m, 726w, 631m, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 4.08(dt, 1H, H-2, 1.1, 6.3), 3.83(dd, 1H, H-8, 8.1, 10.7); 3.76(dd, 1H, H-8, 7.1, 10.7); 2.94(dd, 1H, H-1, 1.4, 4.9); 2.83(m, 1H, H-4); 2.57(tl, 1H, H-7, 8.1); 2.36(m, 2H, H-3); 2.31(ddd, 1H, H-6, 1.4, 4.9, 18.4); 1.99(dd, 1H, H-6, 1.1, 18.4), $^{13}$C-NMR ($CDCl_3$, δ ppm): 211.89(C-5); 57.39(C-2); 54.20(C-4); 51.70(C-7); 48.22(C-1); 46.16(C-6); 34.24(C-3), 30.00($CH_2$, C-8), Mw: 237.52, GC-MS 70 eV, (m/z, % abundance), 236/238/240 (2.0/3.3/0.5) $M^{+\cdot}$, 200/202 (10.2/10.5) $[M\text{-}Cl]^{+\cdot}$, 121 (47.8) $[M\text{-}Br\text{-}Cl]^{+\cdot}$, 93 (100, BP), 91 (73.4), 79 (68.4), 77 (54.9) typical fragments from bicyclonorbornane system.

**Synthesis of oximes of compound 9: (Z)-5-(bromomethyl)tricyclo[2.2.1.02,6]heptan-3-one oxime, (major oxime) 11, and (E)-5-(bromomethyl) tricyclo[2.2.1.02,6]heptan-3-one oxime (minor oxime) 12**

To a solution of compound **9** (230 mg, 1.14 mM) in 4 mL methanol, anhydrous sodium acetate (123 mg, 1.50 mmoles) was added, the solution stirred a few minutes to become clear, then hydroxylamine hydrochloride (1.49 mM, 103.5 mg) was added and stirred at r.t., monitoring the reaction by TLC (silicagel, ethyl acetate, hexane-acetic acid, 5 : 4 : 1, $R_{f\,tin}$ = 0.60, $R_{f\,oxime\,11}$ = 0.53, $R_{f\,oxime\,12}$ = 0.47; the oximes were formed in a ratio of ~3:1, less polar/more polar oxime). Methanol was distilled at low pressure, water (3 mL was added, but the oxime didn't crystallized. The oximes were extracted with $CH_2Cl_2$ (2x15 mL), and purified by pressure chromatography (hexane-ethyl acetate, 5 : 1.5), resulting a pure fraction of less polar oxime **11** (130 mg) as oil, $[\alpha]_D$ = +24.07° (1% in THF), IR: 3240 vs, 3148vs,

2953s, 2908s, 2880s, 1704m, 1466m, 1433m, 1294m, 1270m, 1247m, 1227m, 1212m, 1179w, 967m, 930s, 910s, 891m, 853m, 839s, 794s, 775m, 681m, 611m, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.61(s, OH); 3.31(dd, 1H, H-8, 7.1, 10.2); 3.21(dd, 1H, H-8, 8.5, 10.2); 2.45(m, 1H, H-7, 8.5); 2.41(m, 1H, H-4); 2.34(dt, 1H, H-1, 0.8, 5.5); 1.91-1.89($m_{dd}$, 2H, H-6, H-2, 1.1, 5.5); 1.73(sl, 2H, H-3), $^{13}$C-NMR ($CDCl_3$ δ ppm): 166.09(C-5); 47.64C-7); 37.59(C-4); 31.73(C-8); 29.51(C-3); 22.06(C-6); 17.33(C-2); 14.90(C-1).

We could not obtain pure the more polar oxime by column chromatography purification, because it looks that this oxime isomerizes to the lower polar oxime. In $^{13}$C-NMR the signals of the carbon atoms of the more polar oxime are readily distinguished, but they are not so different from that of the lower polar oxime: $^{13}$C-NMR ($CDCl_3$ δ ppm): 166.20(C-5); 47.16(C-7); 33.24(C-4); 31.70(C-8); 29.14(C-3); 21.61(C-6); 16.93(C-2); 14.88(C-1).

**Synthesis of acetylated oximes of compound 9: (Z)-5-(bromomethyl)tricyclo[2.2.1.02,6]heptan-3-one O-acetyl oxime (*major*), 13, and (E)-5-(bromomethyl) tricyclo[2.2.1.02,6]heptan-3-one O-acetyl oxime (*minor*), 14.**

The crude oximes mixture obtained in a separate synthesis on 1.14 mM, as in example 3.5., was dissolved in 3 mL pyridine, the solution cooled on an ice-water bath and acetylated with 1 mL acetic anhydride under stirring overnight, monitoring the reaction by TLC (hexane-ethyl acetate-acetic acid, 5:1:0.1, $R_{f\ in}$ =0.18, $R_{f\ in}$ =0.26). The acetylated oximes were no more distinguished in TLC, appearing as a single spot on the chromatography plate. The reaction mixture was poured under stirring on crushed ice, stirred until there is no more ice, acetylated oximes extracted with 3x20 mL $CH_2Cl_2$, organic phases washed with 15 mL sat. sol. $NaHCO_3$, dried (anh. $Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by pressure chromatography (silicagel, eluent: hexane-ethyl acetate, 10:3), resulting 247 mg (91.76%) pure inseparable mixture of acetylated oximes as oil, $[\alpha]_D$ = + 27.08°(1% in THF), IR: 2960w, 2924w, 1755vs, 1681m, 1434w, 1365m, 1297w, 1270w, 1207s, 1175s, 1002m, 918m, 889w, 852w, 835m, 813w, 798w, $^1$H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.80(dd, 1H, H-8, 8.5, 10.7), 3.73(dd, 1H, H-8, 6.9, 10.7), minor oxime, 3.31(dd, 1H, H-8, 7.7, 10.3), 3.22(dd, 1H, H-8, 8.5, 10.3), major oxime, 2.64(br.s, 1H, H-4), 2.54(br t, 1H, H-7, 7.7), 2.33(t, 1H, H-6, 5.5), 2.15(s, $CH_3CO$, major oxime), 2.14(s, $CH_3CO$, minor oxime), 2.02(dl, 2H, H-2, H-6, 5.2), 1.85(d, 1H, H-3, 11.5); 1.80(d, 1H, H-3, 11.5), $^{13}$C-NMR ($CDCl_3$, δ ppm)(signals only for major oxime): 173.07(COO), 169.10(C-5), 47.57(C-7), 38.15(C-4), 30.90(C-8), 29.66(C-3), 23.12(C-6), 19.63, 19.51($CH_3$), 18.55(C-2), 16.66(C-1).

**Synthesis of 2,4-dinitrophenylhydrazone from compound 9: (Z)-1-(5-(bromomethyl)tricyclo [2.2.1.02,6]heptan-3-ylidene)-2-(2,4-dinitrophenyl) hydrazine, 15**

To a solution of compound **9** (191 mg, 0.95 mM) in 3 mL EtOH an equivalent 0.25M solution of 2,4-dinitrophenylhydrazine in $H_3PO_4$-EtOH (as presented in Vogel[12]) was added dropwise under stirring, the precipitated hydrazone was filtered, washed on filter with 3x2 mL EtOH and recristallized from ethyl acetate. The pure hydrazone (fraction 1, 153.5 mg) has m.p. 179.6-181.3°C, $[\alpha]_D$ = +114.55°(1% in THF), $^1$H-NMR ($C_6D_6$, δ ppm, *J* Hz): 10.63(NH), 8.84(d, 1H, H-3'', 2.5), 7.79(dd, 1H, H-5'', 2.5, 9.6), 7.42(d, 1H, H-6'', 9.6), 2.61(dd, 1H, H-8, 8.0, 10.1), 2.54(dd, 1H, H-8, 8.2, 10.1), 2.14(brt, 1H, H-4, 1.4), 1.97(dd, 1H, H-7, 8.0, 8.2), 1.27(dt, 1H, H-6, 1.1, 5.2), 1.22(tt, 1H, H-1, 1.1, 5.2), 1.17(dt, 1H, H-3, 1.4, 11.7), 1.12(dt, 1H, H-2, 1.1, 5.0), $^{13}$C-NMR ($C_6D_6$, δ ppm): 166.61(C-5), 145.76(C-1''), 138.39(C-4''), 130.20(C-5''), 124.10(C-6''), 115.98(C-3''), 48.08(C-7), 39.89(C-4), 31.60(C-8), 29.63(C-3), 23.96(C-6), 19.36 (C-2) 15.86(C-1): $^1$H-NMR ($CDCl_3$, δppm *J* Hz): 11.12(NH), 9.12(d, 1H, H-3'', 2.5), 8.28(dd, 1H, H-5'', 2.5, 9.6), 7.85(d, 1H, H-6'', 9.6), 3.38(dd, 1H, H-8, 7.7, 10.1), 2.54(dd, 1H, H-8, 8.2, 10.1), 2.57(m, 1H, H-4), 2.54($m_{dd}$, 1H, H-7, 8.2), 2.15-2.10(m, 3H, H-1,2,6), 1.86(brs, 2H, H-3), $^{13}$C-NMR ($CDCl_3$, δ ppm): 167.51(C-5), 145.56(C-1''), 137.54(C-4''), 130.08(C-5''), 123.73(C-6''), 116.14(C-3''), 47.54(C-7), 39.36(C-4), 31.07(C-8), 29.44(C-3), 23.78(C-6), 19.22(C-2), 15.74(C-1).

## Results and discussions

*Chemistry*

The organomagnesium reagent was obtained starting from 2-bromo-ethanol **1** which, for Grignard reaction was first protected with a TBDMS group, then reacted with magnesium in THF as solvent, in usual way, resulting the compounds **3** .


Scheme 1. Synthesis of organomagnesium reagent **3**

The starting ketone **4** for Grignard reaction must be protected at the hydroxyl group. This can not be realized with an ester protecting group because this react also with the organomagnesium reagent. Also, a TBDMS-ether is not recommended, because in the final product there is no differentiation between the two primary alcohol groups. So we chose to use a mesyl group, taking into account the next alkylation reaction of a purine or pyrimidine base at the C-8 carbon atom of the bicyclo[2.1.0]heptane fragment, mesyl group being a well recognized good leaving group.

The reaction was realized at room temperature in an inert atmosphere and we observed (TLC) from the first hours that instead of the desired compound **6**, three compounds active to 2,4-dinitrophenylhydrazine reagent (specific for ketone and aldehyde group) resulted:

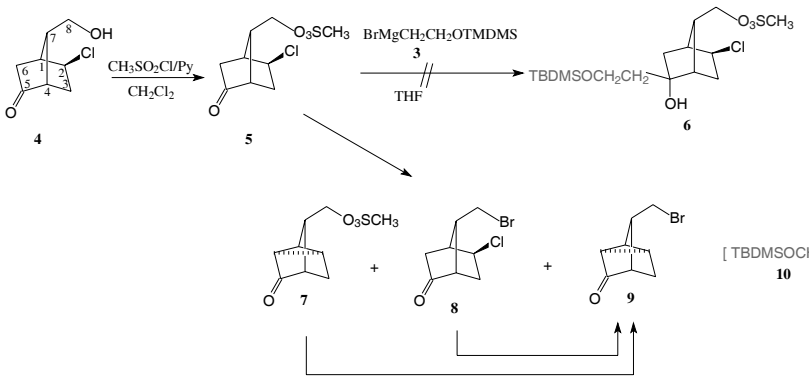
-the red-orange compound **7**, identical with a standard synthesized separatelly, [10] which means that due to the basicity of the organomagnesium reagent **3** the compound **5** was dehydrohalogenated in the reaction with the formation of a cyclopropyl ring.

-the orange compound **8**, in which the mesyl group was substituted with bromine and

-the red-orange compound **9**, in which the mesyl group was substituted with bromine and in the same time took place the dehydrohalogenation reaction with the formation of the cyclopropyl ring (scheme 2).

A secondary byproduct **10** was also isolated, which resulted from a disproportionation (Wurtz) reaction of organomagnesium reagent **3** or by its reaction with alkyl bromide **2** [11].

The ratio between the compounds **8** and **9** was growing up in time with the final formation of only the compound **9**,



Scheme 2. Grignard reaction of organomagnesium compound **3** with ketonic compound **5**

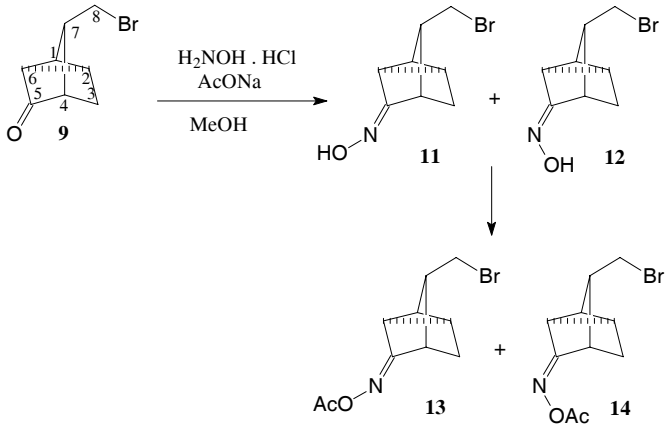
which means that though the compound **8** is formed concomitant with compound **9**, it is not accumulated during time, but it is dehydrochlorinated to **9**. The reaction was slowly at room temperature and also supplementary Grignard reagent was used to complete the reaction.

Using 1.06 equivalents of organomagnesium compound **3**, 15 min. stirring at r.t. and a heating period of only 10 min. at 60°C, about half of the starting compound **5** was quickly dehydroclorinated to compound **7** (fig. 1., *b*.). After another 60 min heating, the ratio of **5**/**7** was grown up to about 1:2 (fig. 1. *c*) and the brominated compound **9** begin to be formed. It is observed that continuing with 40 min heating and 96 h stirring at r.t. (another 1.27 mM organomagnesium compound **3** was added after 16h at r.t.), the brominated compound **9** is formed together with a minor quantity of the brominated compound **8** in which the dehydrochlorination reaction did not took place (fig. 2. h).

Using 2 equivalents of organomagnesium compound **3**, in 20 h no mesylated compound **5** remains in the reaction mixture; only dehydrochlorinated compound **7** and the brominated tricyclic compound **9** are present as a proof that the basicity of organomagnesium compound **3** determine predominantly first dehydrochlorination followed by substitution of the 8-OMs group with bromine. After another 76 h stirring at r.t., almost all dehydrochlorinated compound **7** was substituted to the brominated compound **9** (fig. 2. g).

To prove the structure of the compound **9**, we decided to react it with hydroxylamine and 2,4-dinitrophenylhydrazine to obtain the the corresponding oximes (scheme 3) and hydrazones (scheme 4).

In the reaction with hydroxylamine, two oximes were formed, both as oil, in a ratio of about 3/1 (TLC) (determined also by NMR as a ratio of the $CH_3$ protons in acetylated oximes). The crude oximes were separated by pressure chromatography obtaining the lower polar oxime (the



Scheme 3. Synthesis of oximes **11** and **12** from compound **9** and acetyloximes **13** and **14**.

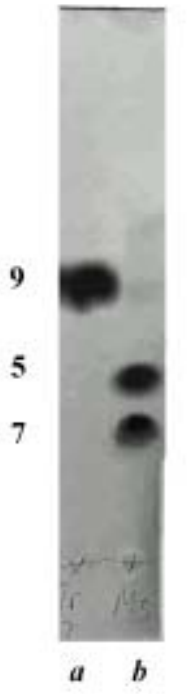


Fig. 1. TLC with ethyl acetate-hexane acetic acid, 5:4:0.1

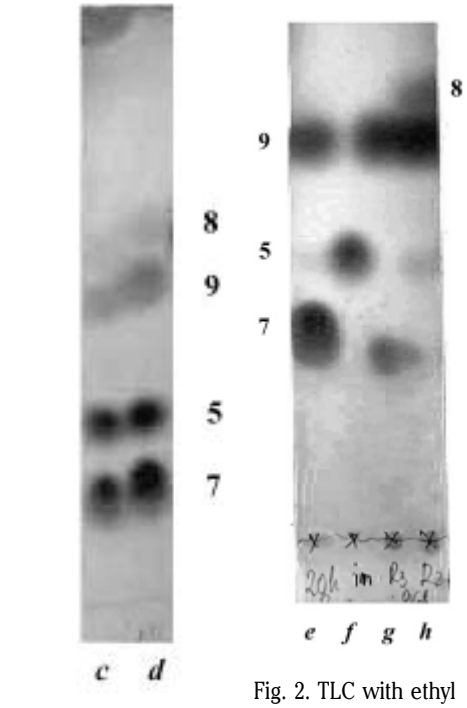
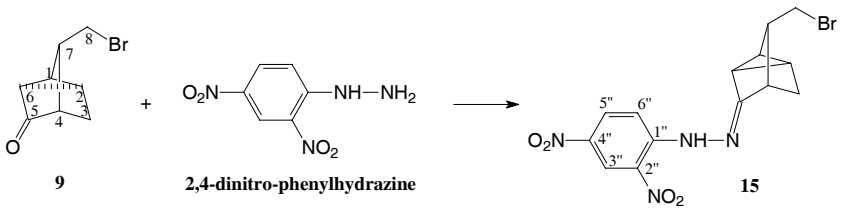


Fig. 2. TLC with ethyl acetate-hexane-acetic acid, 5:4:0.1(eluted twice)

a). Pure product **9**, isolated by pressure chromatography; b). To 2.5 mL (2.12 mM, 1.06 equiv.) solution of organomagnesium compound **3** in THF diluted with 5 mL THF, 505.4 mg (2 mM) mesylated compound **5** were added, stirred 15 min. at r.t. and 10 min. at 60°C; c). The reaction b). was heated further 60 min.; d). The reaction c). was heated further 40 min. and then 16 h at r.t.; h). reaction d) with another 1.5 mL (1.27 mM) organomagnesium compound **3** added, after further 80 h stirring at r.t.; e). To a solution of 253 mg (1mM) mesylated compound **5** in 2.5 mL THF, 2.4 mL (2 mM, 2 equiv.) solution of organo-magnesium compound **3** were added and stirred

major one in the crude reaction mixture) pure as oil, and analysed by IR and NMR. The more polar oxime could not been obtained pure, because it looks to isomerizes on silica gel during purification. A $^{13}$C-NMR spectrum of the more polar oxime could be identified when carbon spectrum was realized on a fraction containing both oximes in ~1:1 ratio, by separating the known signals of lower polar oxime.

Further, we repeated the synthesis of the oximes and acetylated the crude reaction mixture of oximes **11** and **12**, in an idea to suppress the isomerization and to characterize both acetylated oximes **13** and **14**. We obtained the acetylated oximes also as oil, but these were no more separated on TLC and on column chromatography purification. The product fraction separated on column chromatography purification contained the acetylated oximes **13** and **14** in a ratio of ~3:1 (the same as that




Scheme 4. Synthesis of 2,4-dinitrophenylhydrazone **15**

| Compd | Proton and carbon atom number | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| **9** | 2.18(dt, 1.4, 5.0) | 1.55(brt, 5.5) | 1.97(dt, 1.4, 11.5) 1.88(dt, 1.4, 11.5) | 2.05(m) | - | 2.23(tt, 1.4, 5.5) | 2.63(tt, 1.4, 8.0) | 3.35(dd, 8.0, 10.2) 3.28(dd, 8.0, 10.2) |
| | **19.68** | **21.87** | **27.51** | **42.27** | **210.80** | **24.15** | **44.94** | **31.55** |
| **11** Low polar oxime | 2.34(dt, 0.8, 5.5) | 1.91-1.89 (m) | 1.73(sl, 2H) | 2.41(m) | - | 1.89-1.91(m) | 2.45(m, 8.5) | 3.31(dd, 7.1, 10.2) 3.21(dd, 8.5, 10.2) |
| | **14.90** | **17.33** | **29.51** | **37.59** | **166.09** | **22.06** | **47.64** | **31.73** |
| **12** More polar oxime | | | | | | | | |
| | **14.88** | **16.93** | **29.14** | **33.24** | **166.20** | **21.61** | **47.16** | **31.80** |
| Hydrazone **15** $C_6D_6$ | 1.22(tt, 1.1, 5.2) | 1.12(dt, 1.1, 5.0) | 1.17(dt, 1.4, 11.7) 1.04(dt, 1.4, 11.7) | 2.14(br t, 1.4) | - | 1.27(dt, 1.1, 5.2) | 1.97(dd, 8.0, 8.2) | 2.61(dd, 8.0, 11.0) 2.54(dd, 8.2, 11.0) |
| | **15.86** | **19.36** | **29.63** | **39.89** | **166.61** | **23.96** | **48.08** | **31.60** |
| **15** $CDCl_3$ | 2.15-2.10(m, 2H) | | 1.86(br s, 2H) | 2.57(m, 1.4) | - | 2.15-2.10(m) | 2.54(m, 8.0, 8.2) | 3.38(dd, 7.7, 10.1) 2.54(dd, 8.2, 10.1) |
| | **15.74** | **19.22** | **29.44** | **39.36** | **167.51** | **23.78** | **47.54** | **31.07** |

**Table 1**
PROTON AND CARBON SIGNALS FOR ATOMS 1 TO 7 OF COMPOUNDS **9**, **11**, **12** AND **15**

observed by TLC), determined as a ratio of acetyl protons of **13** and **14** in $^1$H-NMR spectrum.

Reaction of compound **9** with 2,4-dinitrophenylhydrazine gave the crystallized hydrazone **15** (scheme 4). On TLC it was not observed the formation of two hydrazones, like in the case of oximes and we suppose that due to steric hindrance the *endo*-hydrazone is favoured.

## $^1$H, $^{13}$C-NMR, MS, elemental analysis and optical rotation

These new compounds were analyzed by MS analysis (for compounds **8** and **9** and 10), optical rotation, IR, $^1$H and $^{13}$C-NMR spectra, presented at the experimental part; the analytical data were in full agreement with the proposed structures.

$^1$H- and $^{13}$C-NMR spectra of compound **9** proved the substitution reaction of 8-OMs group (the 3.07 ppm singlet of $CH_3$ protons and corresponding carbon atom at 37.62 ppm are no more present) with a bromine atom which generate a shielding effect on the vicinal methylene group, protons and carbon atom: 3.35(dd, 1H, H-8, 8.0, 10.2); 3.28(dd, 1H, H-8, 8.0, 10.2); 31.55($CH_2$, C-8) [see for comparison the corresponding signals of compound **5**: 4.69(dd, 1H, H-8, 9.1, 10.7); 4.55(dd, 1H, H-8, 6.3, 10.7); 66.83(C-8)]; the same is observed also for intermediate compound **8**: 3.83(dd, 1H, H-8, 9.1, 10.7); 3.76(dd, 1H, H-8, 7.1, 10.7); 30.00(C-8).

The oxime group of compounds **11** and **12** generate a shielding effect on carbon atoms 1 and 2 of about 4.5 ppm and a smaller effect on C-6 atom, ~ 2 ppm (table 1). The same shielding effect on C-1 atom of ~4 ppm is observed in hydrazine **15**, but smaller on C-2 (~2.5 ppm) and no shielding effect on C-6 atom (table 1).

GS-MS spectrum of compound **9** gave for $M^+$ two values: 200 and 202, corresponding to the two stable isotopes of bromine. Fragmentation profile (see experimental section) gave for the first lower fragment the value 121 (20.6% abundance) corresponding to $[M-Br]^+$.

In the case of compound **8**, the presence in the molecule of two halogen atoms, chlorine and bromine, GS-MS-spectrum gave for $M^+$ three values: 236/238/240 and the fragments $[M-Cl]^+$ with two values due to the two isotopes of chlorine in the fragment: 200/202 (10.2/10.5 % abundence), and $[M-Br-Cl]^+$ with a single value of 121 (47.8% abundance).

MS spectrum of compound **10** was also useful in assigning the molecular mass of the compound, 318 (fragments:261[M-57(*t*-Bu)(~76%abundance), 219(65%), 189(100%), 147(100%), 133(85%)]; this indicate that during Grignard reaction a disproportionation (Wurtz) reaction took place or even in the course of organomagnesium derivative **3** synthesis could take place a reaction of the newly formed reagent and alkyl bromide.

## Conclusions

In the Grignard reaction of mesylated ketone **5** with organomagnesium compound **3** a dehydrochlorination reaction took place with the formation of tricyclic ketone **7**, which gave then a substitution reaction with organomagnesium reagent **3** with formation of bromoalkyl compound **9**. At a smaler extent, the substitution reaction of 8-OMs group of compound **5** with organomagnesium compound **3** has also happened, followed by dehydrochlorination to the same compound **9**. No addition product to the ketone group was formed.

For characterization of the resulted bromoalkyl compound **9**, it was transformed in the corresponding oximes and hydrazone. Two oximes were formed in a ratio of ~ 3:1, the major lower polar oxime being more stable. The acetylated oximes were obtained as oil, only as a mixture in the same ratio of 3:1. The *endo*-2,4-

dinitrophenyl-hydrazone **15** looks to be formed as the only compound, probably due to the steric hindrance of substituted aromatic group.

## References


1. a). BLAGOSKLONNY, M.V., Cell Cycle, 2004, 3:5, 1035-1042, b). GALMARINI, C.M., POPOWYCZ, F., JOSEPH, B.; Current Med. Chem., 2008, 15(11), 1072-1082, c). HERDEWIJN, H. DDT. 1997, 2(6), 235-242. d). DE CLERCQ, E., Clin. Microbiol. Rev. 1997, 10(4), 674-693, e). DE CLERCQ, E., J. Clin. Virol., 2004, 30, 115-133.
2. a). SHIRASAKA, T., KAVLICK, M. F., UENO, T., GAO, W. Y., KOJIMA, E., ALCAIDE, M. L., YARCHOAN, R., MITSUYA, H., CHOKEKIJCHAI, S., ROY, B. M., ARNOL, E., Proc. Natl. Acad. Sci. USA, 1995, 92, 2398-2402. b). CHATIS, P. A., CRUMPACKER, C. S., Antimicrob. Agents Chemother., 1992, 36, 1589-1595, c). PARKER, W. B., CHENG, Y. C., J. NIH Res., 1994, 6, 57-61. d). Martin, J. L., Brown, C. E., Mattews-Davis, N., and Reardon, J. Antimicrob. Agents Chemother., 1994, 38, 2743-2749.
3. a). TĂNASE C., COCU F.G., CĂPROIU M. T., DRĂGHICI C., NEAGOE I., MANDA,G., Rev. Chim. (Bucharest) 2007, **58**, p. 822, b). TĂNASE C., COCU F.G., CĂPROIU M. T., DRĂGHICI C., NEAGOE V.I., MANDA, G., Rev. Roum. Chim. 2011, 56(4), 341-346. c). TĂNASE C., COCU F.G., CĂPROIU M.T., NEAGU M.; MANDA G., Rev. Chim. (Bucharest) 2009, 60, 147-151, e).TĂNASE C., COCU F.G., CĂPROIU M.T., NEAGOE I.V., ENACHE C., NITĂ S., Rev. Chim. (Bucharest) 2010, **61**, no. 10, 929-936.
4. SCHAEFFER H.J.; BEAUCHAMP L.; DE MIRANDA P.; ELION G.B.; BAUER D.J.; COLLINS P., Nature 1978, 272, 583-585.
5. HAMZEH F.H.; LIETMAN P.S. Antimicrob. Agents. Chemother. 1991, 35, 1818-1823, b). Crumpacker C.S. N Engl. J. Med. 1996, 335, 721-729.
6. a). KUKLANOVA M.; KRAYEVSKY A.; PRUSOFF W.; CHENG Y-C. Current Pharmaceutical Design, 2000, 6, 585-598, b). Holy A. Current Protocols in Nucleic Acid Chemistry, UNIT 14.2, Synthesis of acyclic nucleoside phosphonates, John Wiley & Sons, Inc., 2005.
7. JENNY, T.F., HORLACHER, J., PREVISANI, N., BENNER, S. A. Helv. Chim. Acta, 1992, 75, 1944-1954.
8. CHIACCHIO, U., IANNAZZO, D., PIPERNO, A., ROMEO, R., ROMEO, G., RESCIFINA, A., SAGLIMBENI, M., Bioorg. Med. Chem., 2006, 14, 955-959.
9. a). HARDEN, M.R., JARVEST, R. L., Tetrahedron Lett., 1991, 32, 3863, b). HARDEN, M.R., JARVEST, R. L., PARRATT, M. J., J. Chem. Soc. Perkin Trans I, 1992, 2259.
10. *** The synthesis of compound 7 will be presented in a separate paper.
11. a). KHARASCH, M. S., REINMUTH, O. "Grignard Reactions of Nonmetallic Substances," Prentice-Hall. Inc., New York, 1954. b). HAMDOUCHI, C., WALBORSKY, H.H., in Silverman, G.S., Rakita, P.E.(Eds), Handbook of Grignard Reagents, Dekker, New York, 1996, p. 145-218.
12. VOGEL,A.I., Vogel's Textbook of Practical Organic Chemistry, Fifth edition, 1989, by Furniss, B.S., Hannaford, A.J., Smith, P.W.G., Tatchell, a.R., John Wiley Sons, Inc, p. 531-541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