

**Paramagnetic products formed in the reactions
of organometallic compounds. X.*
Stabilization of intermediate keto products
of salicylic acids by means of nickel**

^aL. MALÍK, ^aA. STAŠKO, ^aA. TKÁČ, and ^bV. ADAMČÍK

^a*Institute of Chemical Physics, Department of Physical Chemistry,
Slovak Technical University, 880 37 Bratislava*

^b*Department of Physical Chemistry, Slovak Technical University,
880 37 Bratislava*

Received 6 June 1978

Accepted for publication 29 August 1978

Dedicated to Professor V. Kellö on his 60th birthday

In the reactions of salicylic acids with Grignard reagents the transition metals increase the yield of keto products. Thus, 3,5-diisopropylsalicylic acid with *n*-butyl magnesium bromide in the presence of nickel forms 2-hydroxy-3,5-diisopropylphenyl *n*-butyl ketone, whereas, in the absence of nickel 2-hydroxy-3,5-diisopropylphenyl di-*n*-butyl carbinol is obtained. The stabilization of keto products in the form of their ketyl radicals was verified in e.s.r. study.

Переходные металлы повышают выход кето продуктов при реакции салициловых кислот с реактивами Гриньяра. В частности, 3,5-диизопропилсалициловая кислота образует с *n*-бутилмагnezий бромидом 2-гидрокси-3,5-диизопропилфенил *n*-бутил кетон, хотя в отсутствие никеля образуется 2-гидрокси-3,5-диизопропилфенил ди-*n*-бутил карбинол. Стабилизация кето продуктов в виде их кетильных радикалов была подтверждена изучением спектров ЭПР.

Usually, the expected reduction products in the reactions of carboxylic acids with Grignard reagents are tertiary alcohols. Investigating the reaction of nickel(II) diisopropylsalicylate [Ni(DIPS)₂] with Grignard reagents (RMgX), high concentrations of ketyl radicals were observed [1—3]. In order to elucidate the role of nickel in such systems, the reaction of 3,5-diisopropylsalicylic acid (HDIPS) with *n*-BuMgBr in the presence of nickel salts is studied and described in this paper.

* For Part IX see Ref. [1].

Experimental

HDIPS and its nickel salts were prepared according to [4, 5], *n*-BuMgBr was obtained in the reaction of *n*-BuBr and magnesium following the standard procedure and finally, water-free NiCl₂ was prepared from its hydrate as described in [6]. The reaction of HDIPS or its nickel salt with *n*-BuMgBr proceeded under argon atmosphere at 20°C. To 5 mdm³ of 0.5 M-Ni(DIPS)₂ in hexane 5 mdm³ of 2.0 M-*n*-BuMgBr in diethyl ether were added slowly, in about 10 min, and mixed continually. After staying overnight the reaction mixture was hydrolyzed with ice and HCl, the ethereal layer separated and the water layer extracted with ether. The joined ethereal extracts were washed with NaHCO₃ solution and dried over MgSO₄. After removal of ether the reaction products were separated on silica gel column Firma Serva 50—100 microns (separation on an Al₂O₃ column, neutral, Firma Reanal, without activation, led to consequent reactions). The extraction with cyclohexane—chloroform at various, successively changed ratios was finished with methanol in order to obtain the strongly adsorbed products. Infrared measurements were carried out on Spectrometer UR-10, ¹H-n.m.r. on Tesla Spectrometer BS 487, and e.s.r. studies as described in the previous paper [1].

Results

In the reaction of HDIPS with *n*-BuMgBr white crystals precipitate; according to our qualitative analysis we assume a similar composition as described by *Huston and Bailey* [7] in the reaction of aliphatic carboxylic acids with Grignard reagents. The authors identified the crystals as MgBrOH·2MgBr₂·4Et₂O. In our analysis of the hydrolyzed products, employing a liquid chromatograph, eight compounds were observed. In their separation by means of column chromatography, besides HDIPS, following major products were isolated and identified: 2-hydroxy-3,5-diisopropylphenyl *n*-butyl ketone and 2-hydroxy-3,5-diisopropylphenyl di-*n*-butyl carbinol.

The identification of products obtained in the reaction mixtures at various conditions is mainly based on the ¹H-n.m.r. spectroscopy. Table 1 (a) shows the chemical shifts observed in ¹H-n.m.r. spectrum of HDIPS and assigned to its individual protons. An open question appeared to be the assignment of the methine protons belonging to isopropyl groups (3.29 and 2.76 p.p.m.) not assigned as yet. Therefore, 2-hydroxy-3,5-diisopropylbenzyl alcohol was prepared in the reaction of HDIPS with LiAlH₄. The chemical shifts found in its ¹H-n.m.r. spectrum are given in Table 1 (d). The difference in the chemical shifts between the methine protons (3.15 and 2.65 p.p.m.) remained practically unchanged. This suggests that the given difference originates in the hydroxy group placed in the position 2 and not in the carbonyl group in position 1. As the influence of the hydroxy group on the similarly substituted phenols is known [8], its shielding effect for the α protons

Table 1

Assignment of chemical shifts observed in ^1H -n.m.r. spectra of the investigated compounds

Compound	Chemical shifts (p.p.m.)									
	H(4)	H(6)	CH(3)	CH(5)	CH ₃	OH(2)	OH	CH ₂ (α)	CH ₃ (R)	H(ald)
3,5-Diisopropyl-salicylic acid (a)	7.16	7.52	3.29	2.76	1.18	10.4	11.8			
2-Hydroxy-3,5-diisopropylphenyl <i>n</i> -butyl ketone (b)	7.10	7.30	3.29	2.76	1.18	12.50		2.90	0.90	
2-Hydroxy-3,5-diisopropylphenyl di- <i>n</i> -butyl carbinol (c)	6.74	6.38	3.20	2.68	1.11	8.9		1.68	0.85	
2-Hydroxy-3,5-diisopropylbenzyl alcohol (d)	6.82	6.48	3.15	2.65	1.10	7.2		4.46		
Salicylic aldehyde (e)						10.92				9.85
Methyl 3,5-di- <i>tert</i> -butyl salicylate (f)	7.33	7.61				11.23				

in *para* position is considerably higher than in *ortho* position, therefore, the chemical shift 3.29 p.p.m. was assigned to the proton in position 3.

The identification of 2-hydroxy-3,5-diisopropylphenyl *n*-butyl ketone is based on the analysis of its ^1H -n.m.r., mass, and infrared spectra. The chemical shifts found in its ^1H -n.m.r. spectrum are given in Table 1 (b). Characteristic feature of ^1H -n.m.r. spectrum is the high value (12.50 p.p.m.) for chemical shift of OH proton caused by strong intramolecular bond with keto group. This confirms the infrared spectrum showing a broad valence band for OH vibration. The mass spectrum indicates the corresponding molecular weight and the expected fragments in accord with the proposed structure.

Similarly, as in the previous case, followed the identification of 2-hydroxy-3,5-diisopropylphenyl di-*n*-butyl carbinol. The data of its ^1H -n.m.r. spectrum are given in Table 1 (c). A relatively high value for chemical shift of OH proton (8.9 p.p.m.) implies the formation of its strong intramolecular bond. The infrared and mass spectra are in accord with the proposed structure.

In the column chromatography on silica gel the first fraction contains small quantities of familiar minor products; their further separation was not successful. The infrared spectra indicate structures with the hydroxy and the reduced carbonyl group. Also small quantities of 2-hydroxy-3,5-diisopropylphenyl *n*-butyl ketone are obvious from ^1H -n.m.r. spectrum in Fig. 1 showing the characteristic band at 12.50 p.p.m.

The upper part of Fig. 1 represents the spectrum after deuteration with D_2O . We assume the presence of *cis* and *trans* isomers of 1-(2-hydroxy-3,5-diisopropyl)-phenyl nonene-5 which is formed in the dehydration of the corresponding tertiary alcohol. The multiplets with 5.35 p.p.m. are assigned to the =CH proton, the bands between 5.20—4.81 p.p.m. to the OH protons, and the multiplet with 2.18 p.p.m. to the CH_2 protons placed in the α position to the double bond of the two isomers.

The products of pinacol type are expected in such reactions but were not found in the reaction mixture.

To elucidate the role of nickel in the reaction of HDIPS with *n*-BuMgBr following experiments are compared:

a) HDIPS + *n*-BuMgBr

b) HDIPS + $NiCl_2$ + *n*-BuMgBr (HDIPS : Ni = 10 : 1)

c) $Ni(DIPS)_2$ + *n*-BuMgBr

The ethereal solutions obtained after hydrolysis were analyzed and their 1H -n.m.r. spectra are shown in Fig. 3. Generally, a considerable amount of unreacted HDIPS remains in the reaction mixture. In the presence of nickel (experiment *b*, *c*) new bands appeared at 12.6, 11.4, 9.7 p.p.m. (observable only in experiment *c*), and 7.35 p.p.m. The band having chemical shift 12.6 p.p.m. belongs to the phenoxy group and the band with 7.35 p.p.m. to the proton in position 6 of 2-hydroxy-3,5-diisopropylphenyl *n*-butyl ketone. On shaking the sample with D_2O the bands

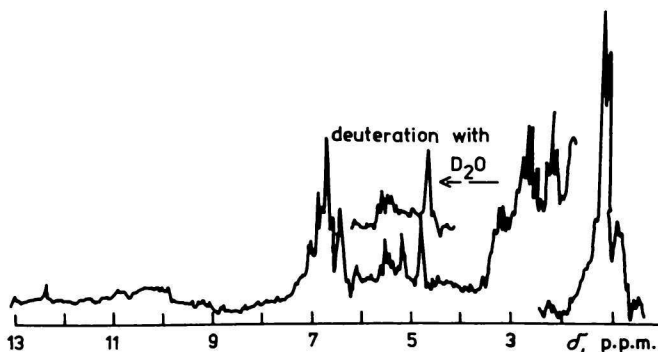


Fig. 1. 1H -N.m.r. spectrum of the first chromatographic fraction of the products formed in the reaction of $Ni(DIPS)_2$ with *n*-BuMgBr.

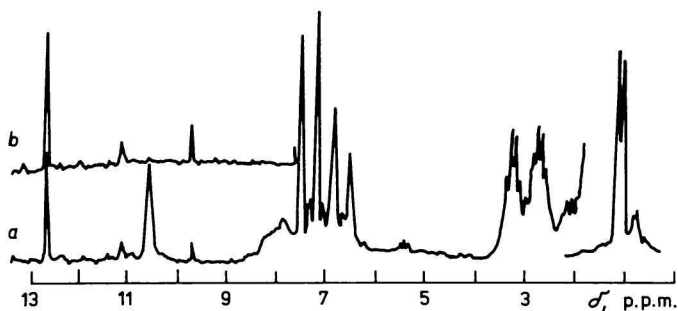


Fig. 2. $^1\text{H-N.m.r.}$ spectra of the products obtained in the reaction of Ni(DIPS)_2 with $n\text{-BuMgBr}$ measured in CCl_4 solvent.

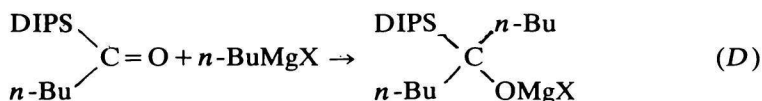
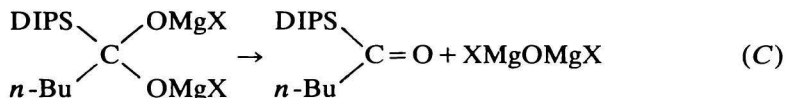
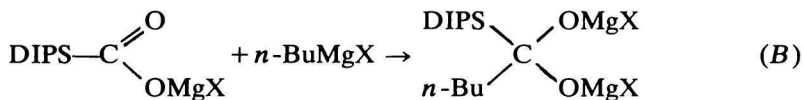
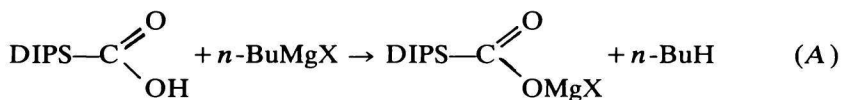
a) Original spectrum; b) after CH_3OH addition.

at 12.6 and 11.4 p.p.m. disappeared, whereas the band at 9.7 p.p.m. remained unchanged and indicated aldehydic proton. The products obtained in experiment *c* were transferred into CCl_4 solvent and then methanol was added. The lower part of Fig. 2 shows the original spectrum and the upper part after methanol addition. On the addition of methanol the band at 10.5 p.p.m. and the bands in the region over 8 p.p.m. disappeared, whereas the bands at 11.0 and 12.5 p.p.m. remained unchanged. This suggests that the bands with 11 and 12.5 p.p.m. belong to the OH protons which participate in a strong intramolecular bond.

The given data confirm the formation of keto products. In accord with the chemical shifts presented in Table 1, the bands at 12.5 (12.6 p.p.m. in Et_2O solution) and 7.30 p.p.m. (7.35 p.p.m. in Et_2O solution) and their corresponding changes after deuteration indicate the formation of ketone and, similarly, the bands at 11.4 and 9.7 p.p.m. the formation of aldehyde. With concentration increase of nickel in experiments *a*, *b*, *c* the yield of keto products is increasing.

Discussion

Generally, Grignard reagents in their reactions are added to ketones under the formation of the corresponding tertiary alcohols [9]. In accord with this generalization, in experiment *a*, *i.e.* in the absence of nickel (Fig. 2*a*), keto products were not found and the following scheme should be expected in the reaction of HDIPS (in the scheme HDIPS is reformulated as DIPSCOOH) with $n\text{-BuMgX}$



Reaction *D* proceeds probably much quicker than the previous reaction steps, therefore, the commonly obtained products are the corresponding tertiary alcohols also at the low ratios of Grignard reagents to acids. To prepare ketones in this way successfully, it is necessary to eliminate reaction *D* or to lower its reaction rate. In order to succeed in this, following two possibilities had been explored effectively: the employment of basic solvents and the lowering of the reaction temperature. *Fauvarque* and coworkers [10] obtained a good yield of ketone in the reaction of benzoyl chloride with Grignard reagents employing hexamethylphosphortriamide as solvent. *Percival* and coworkers [11] yielded 72% of hexanone in the reaction of acetyl chloride with *n*-BuMgBr at low temperature adding FeCl₃ into the reaction mixture.

Only very few studies on the influence of transition metals in similar systems as described by *Percival* have been undertaken, and nickel was not employed so far. In our experiments also the influence of Cu, Mn, Fe, Co was investigated. From the applied metals nickel showed to be the most effective in the stabilization of the obtained products in the form of their ketyl radicals. This stabilization was confirmed in e.s.r. studies.

Fig. 4 shows the experimental and simulated spectra obtained in the reaction of HDIPS with *n*-BuMgBr. The splitting constants found by simulation are in good agreement with the proposed structure of *n*-butyl 1-[2-(oxido-anion)-3,5-diisopropyl]phenyl ketyl radical. The assignment of its splitting constants is based on our systematical studies of similar structures described previously [1].

For the role of nickel in such reactions two explanations may be taken into account. The first one would propose the acid properties of nickel and consequently a rapid acceleration of reaction *A* compared to the rate of reaction *D*. So it came to the accumulation of the keto products in the reaction mixture. In the second

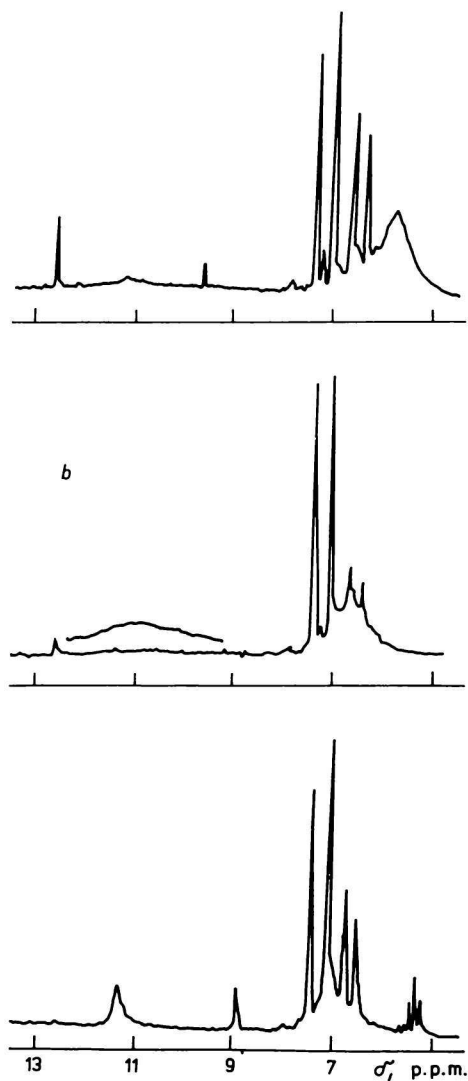


Fig. 3. $^1\text{H-N.m.r.}$ spectrum of the reaction products.

a) HDIPS + $n\text{-BuMgBr}$; b) HDIPS + NiCl_2 + $n\text{-BuMgBr}$; c) $\text{Ni}(\text{DIPS})_2$ + $n\text{-BuMgBr}$.

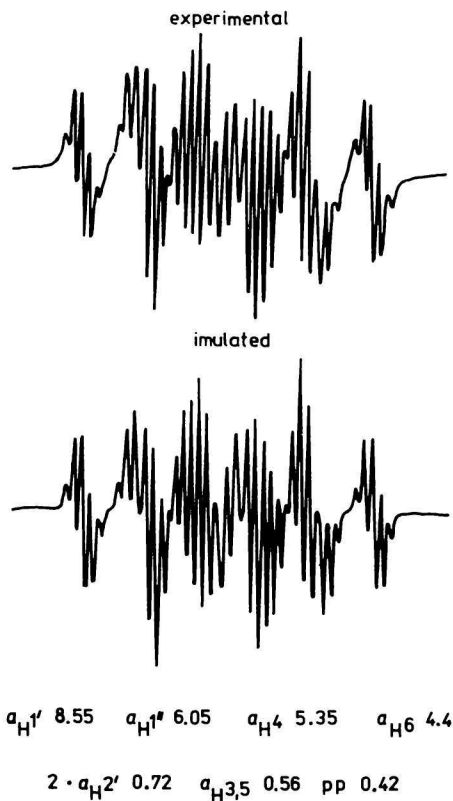
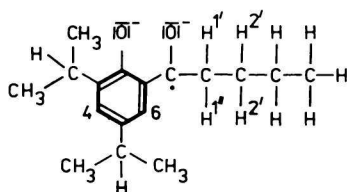


Fig. 4. Experimental and simulated e.s.r. spectrum of ketyl radical observed in the reaction of $\text{Ni}(\text{DIPS})_2$ with $n\text{-BuMgBr}$ (a_{H} are splitting constants and pp peak-to-peak width of simulated spectrum expressed in 0.1 mT).

explanation the stabilization of the obtained keto products in the form of their ketyl radicals is assumed. Now, it is known that the acid properties of nickel are very weak. But also salts with stronger acid properties than nickel, as *e.g.* FeCl_3 , were employed and showed to be less effective than nickel. Therefore, the explanation

proposing the acid catalysis of transition metals in the reaction is not probable. Our experimental data are very well compatible with the assumption that nickel stabilized the keto products in the form of their ketyl radicals, herewith, it eliminates a further addition of Grignard reagents and the formation of tertiary alcohols.

References

1. Staško, A., Malík, L., Tkáč, A., Adamčík, V., and Mafašová, E., *Collect. Czech. Chem. Commun.* **44**, 1731 (1979).
2. Staško, A., Tkáč, A., Malík, L., and Adamčík, V., *J. Organometal. Chem.* **92**, 261 (1975).
3. Staško, A., Malík, L., Tkáč, A., Adamčík, V., and Hronec, M., *Org. Magn. Resonance* **9**, 269 (1977).
4. Desseigne, G., *Bull. Soc. Chim. Fr.* **1948**, 68.
5. Dixon, C., Duck, E. W., and Jenkins, D. K., *Eur. Polym. J.* **8**, 13 (1972).
6. Farady, L., Bencze, L., and Marko, L., *J. Organometal. Chem.* **10**, 505 (1967).
7. Huston, R. C. and Bailey, D. L., *J. Amer. Chem. Soc.* **68**, 1382 (1946).
8. Lindeman, L. P. and Nicksic, S. W., *Anal. Chem.* **36**, 2414 (1964).
9. Cais, M. and Mandelbaum, A., *The Chemistry of the Carbonyl Group*. (Patai, S., Editor.) J. Wiley & Sons, Weinheim, 1966.
10. Fauvarque, J., Ducon, J., and Fauvarque, J. F., *C. R. Acad. Sci. (Paris)* **275**, 511 (1972).
11. Percival, W. C., Wagner, R. B., and Cook, M. C., *J. Amer. Chem. Soc.* **75**, 3731 (1953).

Translated by A. Staško