ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 2, pp. 270–272. © Pleiades Publishing, Ltd., 2009.
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Approach to the Synthesis of 1*H*-2-Azaphenalene Derivatives

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Received February 1, 2008

Abstract—By the Hartree–Fock method in the basis 6-31G(d) with complete geometry optimization the charge value on the carbon atom of carbenium ion was shown to be decisive in Ritter reaction with nitriles. It was established that the attack on the *peri*-position of the naphthalene system to form 1*H*-2-azaphenalene derivatives was possible only for tetralin derivatives. From the naphthalene only benzo[f]isoquinoline derivatives were formed.

DOI: 10.1134/S1070428009020201

We showed formerly that 3-methyl-2-(1-naphthyl)-butan-2-ol and nitriles underwent cyclization in sulfuric acid exclusively at the position *2* of the naphthalene ring [1]. Yet the Ritter reaction at the *peri*-position of the naphthalene system with the formation of 1*H*-2-azaphenalene derivatives was not documented. This is due in particular to the fact that these monoazaheterocyclic systems are poorly explored. For instance, the popular monograph [2] dealing with the heterocyclic compounds does not mention 2-azaphenalene derivatives at all. Some examples are published in current magazines [3], but the 2-azaphenalene derivatives are mentioned only as side products.

We established that the reaction of acetonitrile with dimethyl-α-naphthylcarbinol in the concn. sulfuric acid did not lead to the formation of the target product. Evidently the arising carbenium ion possessed too low energy and was incapable to attack the nitrogen atom of the cyano group; therefore no nitrilium ion formed that otherwise would have been stabilized by an attack on the *peri*-position of the ring.

To demonstrate the governing influence of the carbenium ion character on the direction of the reaction with nitriles we brought into Ritter reaction 3-methyl-2-(1-naphthyl)butan-2-ol (**I**). According to the above, the α-naphthyl-containing carbenium ion **A** formed in the first stage of the reaction should not react with the cyano group, whereas its equilibrium carbenium ion **B** unstabilized with an aryl moiety should easily lead to the corresponding benzo[*f*]isoquinoline derivative.

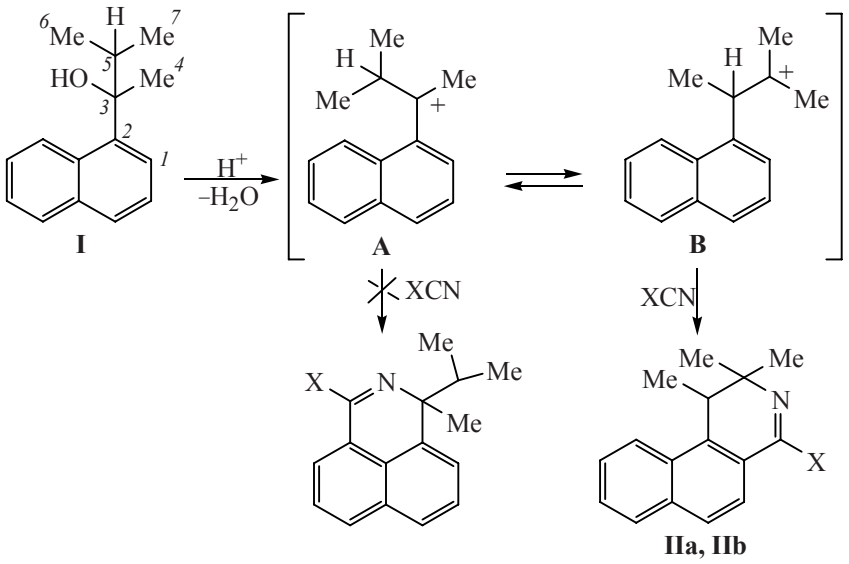
The results of ab initio calculations of these cations by the Hartree–Fock method in the basis 6-31G(d) with the complete geometry optimization were consistent with the above considerations (the calculations were carried out along the software GAUSSIAN 94 W [4]). In keeping with the calculations cation **A** is more stable than cation **B** by 11.34 kcal mol^{-1}, therefore the former is less capable to attack the nitrile and to form the nitrilium ion.

Besides, according to the calculation, in cation **A** the dihedral angle $C^1C^2C^3C^5$ equals 151.9°. Consequently, the $C^3\cdots C^5$ bond in this cation deviated from the plane of the aromatic rings by 28.1°, and atom C^3 proved to be additionally sterically hindered.

In cation **B** the dihedral angle $C^1C^2C^3C^5$ amounts to 109.5°, and thus the $C^3\cdots C^5$ bond deviated from the plane of the aromatic rings by 70.5°, and C^5 proved to by quite accessible for the reaction with the nitrile.

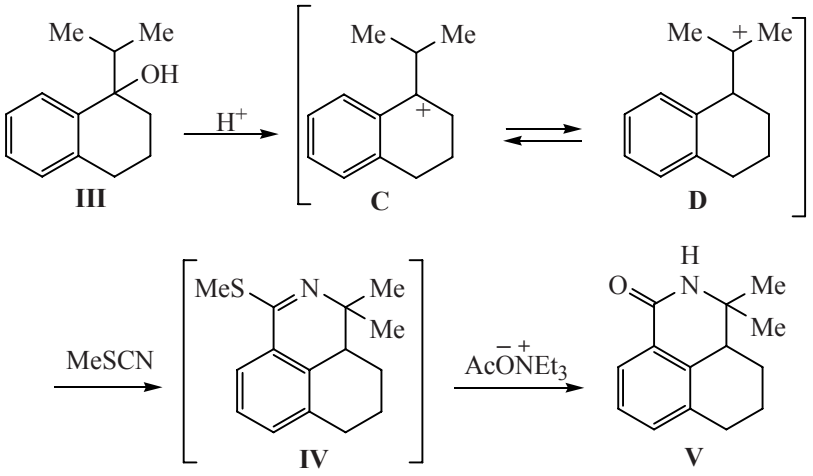
Actually, we isolated from the reaction of carbinol **I** with acetonitrile and methyl thiocyanate 1-substituted 1,2,2-trimethyl-1,2-dihydrobenzo[*f*]isoquinolines **IIa** and **IIb** in good yield (Scheme 1). In the ^{1}H NMR spectra of isoquinoline **IIa** derivatives appeared a quartet signal from the aliphatic proton CH, a doublet from the protons of the methyl group in the position *1* of the ring , and two singlets from the protons of the *gem*-dimethyl group. The study of computer models revealed that the protons of the methyl group in the position *1* and the hydrogen atom in the position *10* at a coplanar location coincided, therefore these atomic groups suffered repulsion and consequently the methyl group was deviated from the

Scheme 1.



X = CH_3 (**a**), SCH_3 (**b**).

Scheme 2.



plane by an angle of 92.6°, and as a result the dihydropyridine ring existed in the *semiboat* form. Naturally, therewith the methyl groups in the position *3* deviated from the plane of the ring by the angles of –71.3 and 168.5 deg, and this fact is reflected in the ^{1}H NMR spectra.

Whereas the above data showed that the carbenium ion stabilized by the α-naphthyl substituent was incapable to attack the cyano group and form the nitrilium ion followed by the attack on the free *ortho*-position, we carried out a reaction of 1-isopropyl-1,2,3,4-tetrahydro-1-naphthol (**III**) with methyl thiocyanate. The stabilized carbenium ion **C** formed primarily from this alcohol under Ritter reaction conditions existed in an equilibrium with the carbenium ion **D** unstabilized with aryl substituent. The reactivity of the latter was sufficient for the successful formation of substituted 1*H*-2-azaphenalene **IV** (Scheme 2).

These data are well consistent with ab initio calculations of **C** and **D** cations by the RHF/6-31G(d) with the complete geometry optimization. According to the calculations cation **C** is by 16.79 kcal mol^{-1} more stable than cation **D**.

The choice of methyl thiocyanate for the nitrile component was not only due to the highest yields of 3,4-dihydroisoquinoline derivatives obtained with it among all tested compounds (up to 94% [5]) but also to its ready conversion into a well crystallized lactam **V** [6].

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Bruker AM 300 at operating frequency 300 MHz from solutions in DMSO-d_6, internal reference Me_4Si. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent chloroform–acetone, 9:1, development with 0.5% chloranil solution in toluene.

1,2,2,4-Tetramethyl-1,2-dihydrobenzo[*f*]isoquinoline (IIa). A mixture of 21.4 g (0.1 mol) of 3-methyl-2-(1-naphthyl)butan-2-ol (prepared from 1-bromomagnesiumnaphthalene and methyl isopropyl ketone in ether and used without additional purification) and 4.1 g (0.1 mol) of acetonitrile was added dropwise at cooling (0–5°C) while stirring to 50 ml of concn. H_2SO_4. The mixture was stirred for 30 min, diluted with 300 ml of water, and extracted with 50 ml of benzene. The water layer was neutralized with ammonium carbonate till pH 8–9. The separated product was extracted with methyl *tert*-butyl ether, and dried with $MgSO_4$. The solvent was distilled off, the residue was subjected to a vacuum distillation. Yield 7.6 g (32%), bp 130–135°C (5 mm Hg). The product was characterized as salicylate: to a solution of 2.37 g (0.01 mol) of compound **IIa** in 10 ml of anhydrous ethyl ether was added in one portion a solution of 1.38 g (0.01 mol) salicylic acid in 20 ml of ether, the mixture was stired and left standing for 30 min. The separated precipitate was filtered off, washed on the filter with 15 ml of ether, and recrystallized from ethanol, mp 214–215°C. ^{1}H NMR spectrum, δ, ppm: 1.20 s (3H, 2-$Me_{pseudoax}$), 1.31 s (3H, 2-$Me_{pseudoeq}$), 1.54 δ (3H, 1-Me, $J_{4,14}$ 7 Hz), 2.92 s (3H, 4-Me), 3.49 q (1H, H^1, $J_{14,4}$ 7 Hz), 7.28–8.03 m (10H, H_{arom}), 12.14 br.s (1H, OH_{phenol}).

1,2,2-Trimethyl-4-methylthio-1,2-dihydrobenzo-[*f*]isoquinoline (IIb) was similarly obtained from 21.4 g (0.1 mol) of 3-methyl-2-(1-naphthyl)butan-2-ol and 7.3 g (0.1 mol) of methyl thiocyanate. Yield 11.8 g (44%), mp 58–59°C (from hexane). IR spectrum, ν, cm^{-1}: 1620 (C=N), 1595, 1320 (MeS). ^{1}H NMR spectrum, δ, ppm: 1.24 s (3H, 2-$Me_{pseudoax}$), 1.32 s (3H, 2-$Me_{pseudoeq}$), 1.49 d (3H, 1-Me, $J_{4,14}$ 7 Hz), 2.40 s (3H, 4-SMe), 3.43 q (1H, H^1, $J_{14,4}$ 7 Hz), 7.19–8.03 m (5H, H_{arom}), 8.54 d (1H, H^5). Found, %: C 75.99; H 6.90; N 5.27. $C_{17}H_{19}NS$. Calculated, %: C 75.84; H 7.06; N 5.20.

3,3-Dimethyl-2,3,3a,4,5,6-hexahydro-1*H*-benzo-[*d,e*]isoquinolin-1-one (V). A solution of 1.9 g (0.01 mol) of 1-isopropyl-1-tetralol (obtained from 1-tetralone and isopropylmagnesium bromide in anhydrous THF) and 0.73 g (0.01 mol) of methyl thiocyanate in 5 ml of anhydrous benzene was added dropwise at stirring to 10 ml of concn. H_2SO_4. After stirring for 15 min the mixture was poured into 50 ml of water, extracted with 20 ml of benzone, water layer was neutralized till pH 7–8. The separated crude 1,1-dimethyl-3-(methylthio)-7,8,9,9a-tetrahydro-1*H*-benzo[*d,e*]isoquinoline (**IV**) (2.1 g, 85%) was dissolved in 20 ml of 80% acetic acid with 3 drops of triethylamine added, the mixture was heated for 3 h, diluted with 100 ml of water, alkalinized with aqueous ammonia till pH 7–8. The separated precipitate was filtered off, dried in air, and recrystallized from ethyl acetate. Yield 1.72 g (93% calculated with respect to the initial compound **IV**), mp 191–192°C. IR spectrum, ν, cm^{-1}: 3180 br (NH), 1655 (C=O), 1600 (Ar). ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, 3-$Me_{pseudoax}$), 1.30 s (3H, 3-$Me_{pseudoeq}$), 1.67–2.80 m [7H, H^4, $(CH_2)_3$], 7.10–7.27 m (2H, $H^{6,7}$), 7.65 d (1H, H^8). Found, %: C 77.90; H 8.11; N 6.64. $C_{14}H_{17}NO$. Calculated, %: C 78.14; H 7.91; N 6.51.

The study was carried out under a financial support of the collaboration program of the Ural Division and Siberian Division of the Russian Academy of Sciences on the theme "Purposeful synthesis and optimization of properties of biologically active compounds" and of the Russian Foundation for Basic Research (grants nos. 07-03-00001 and 07-03-96012).

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