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SHORT COMMUNICATIONS

Reactions of 2-Thienylmethylidene-6-(2-halophenylmethylidene) cyclohexanones with Hydrazine Hydrate: Regiodirection and the Ratio of Formed *trans*-Hexahydroindazoles

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Cross-conjugated diylidenecyclanones (dienones) are extensily used in designing fused heterocyclic systems, in particular, those of practical importance [1].

We formerly established that the reaction with the hydrazine hydrate of dienones containing a cyclohexane ring and terminal thienyl and aryl substituents yielded mixtures of regioisomeric *trans*-hexahydro-2*H*-indazoles with overwhelming predominance of the thienylmethylene-containing isomers notwithstanding the electronic effect and the position of substituents in the aromatic ring (4-OMe, 3-NO_2) [2].

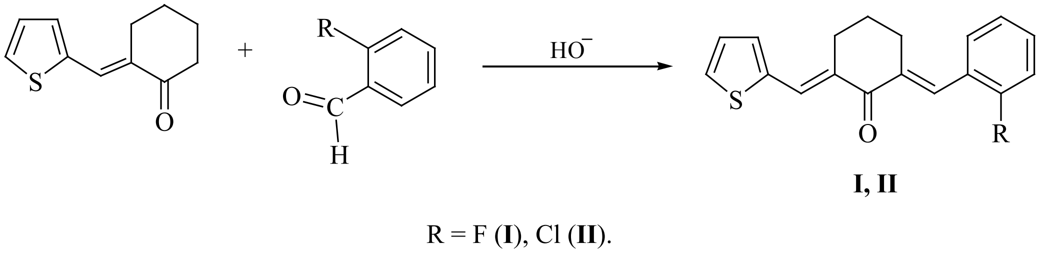
In extension of the previous research we report here new data on the study of regiodirection of the reactions with hydrazine of the thienylaryl-containing dienone analogs with a fluorine or chlorine atom in the *ortho*-position of the benzene ring.

Dienones **I** and **II** were prepared for the first time in 58–65% yield by procedure [3] involving the crotonic condensation of 2-(2-thienylmethylene)cyclohexanone with 2-fluoro(chloro)benzaldehydes under the base catalysis. From the data of the IR spectra ($\nu_{C=O}$ 1662–1645, $\nu_{C=C}$ 1600–1543, $\delta_{C=CH}$ 968–984 cm^{-1}) and the position of the chemical shift of vinyl protons in the ^{1}H NMR spectrum (7.96–8.04 ppm) we concluded by the analogy with our previously obtained data [4] that the products possessed *E,E*-configuration.

The special feature of their reactions with hydrazine hydrate is the formation of regioisomeric 7-(2-thienylmethylene)-3-(2-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (**IIIa**), 3-(2-thienyl)-7-(2-fluorophenylmethylene)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (**IIIb**) and their *ortho*-chlorophenyl-containing analogs **IVa, IVb** in the overall preparative yield 63–68% resulting from the equally probable attack of the nucleophile on the reaction centers β and β'.

According to the data of ^{1}H NMR spectra (by comparison of the integral intensity of the peaks of protons H^3) the ratio of regioisomers a:b was 1:1. In the spectra of the regioisomeric mixtures the signal of the proton H^3 appears as two doublets of equal intensity at 4.85,

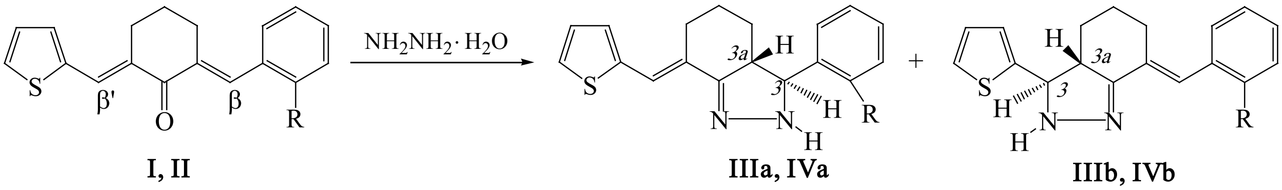
Scheme 1.



I, II

R = F (**I**), Cl (**II**).

Scheme 2.



R = F (**I, III**), Cl (**II, IV**).

5.08 (**IIIa, IVa**) and 4.72 ppm (**IIIb, IVb**), H^{3a}, at 2.82, 2.99 ppm (**IIIa, IVa**) and 3.14, 3.15 ppm (**IIIb, IVb**), and the position of the signals of protons H^3 and H^{3a} indicates their *trans*-location (analogously to [2]).

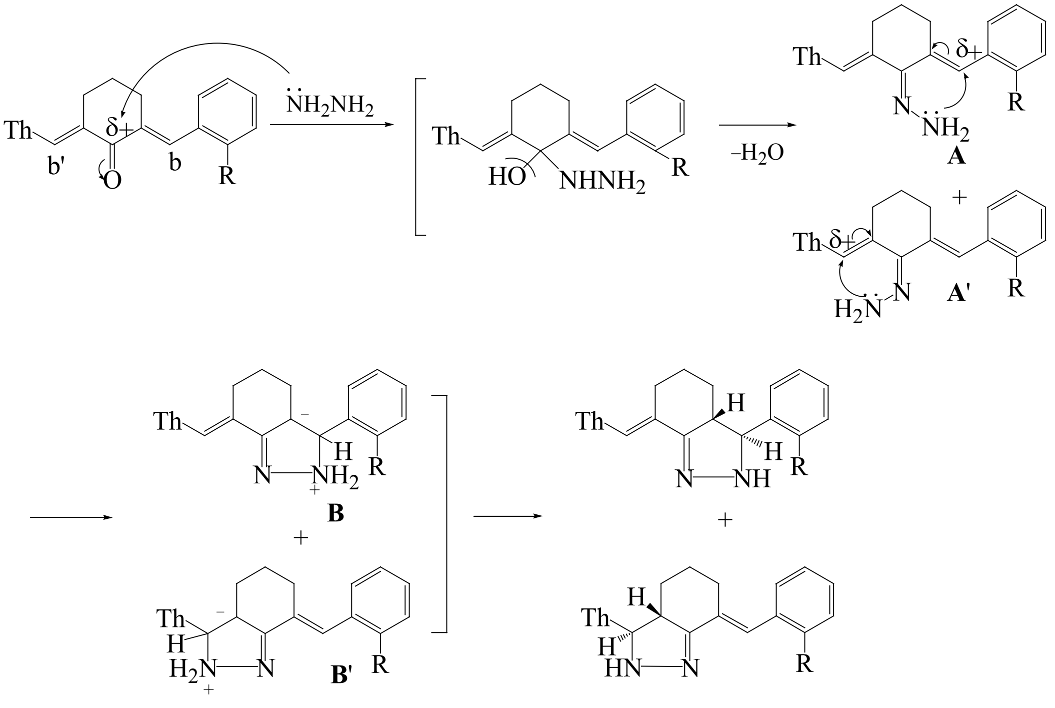
The presumable pathway of the formation of the hexahydroindazoles involves the primary formation of hydrazones **A** and **A'** followed by the addition of the amino group to the exocyclic double bonds giving bipolar ions **B** and **B'** that are stabilized by the NH–C 1,3-intramolecular proton transfer.

Thus the introduction into the *ortho*-position of the phenyl ring of the dienone of a fluorine or a chlorine atom resulted in the activation of the reaction center β' apparently due to the *ortho*-effect, steric and electronic influence of the halogen atom in the *ortho*-position hindering the nucleophilic attack on the β-carbon atom.

The data obtained are the first example of the equally probable azacyclization of unsymmetrical dienones with hydrazine that is possible in the presence of the comparable in activity reaction centers β and β'.

2-(2-Thienylmethylene)-6-(2-fluorobenzylidene) cyclohexanone (I). To a mixture of 1 g (5.2 mmol) of 2-(2-thienylmethylene)cyclohexanone, 0.66 g (5.3 mmol) of *o*-fluorobenzaldehyde, and 20 ml of 2-propanol was added dropwise while stirring 5 ml of 20% solution of sodium hydroxide. The precipitated yellow crystals were washed with a large amount of water and recrystallized from 2-propanol. Yield 0.97 g (65%), mp 97–99°C. IR spectrum, ν, cm^{-1}: 1662 (C=O), 1543 (C=C), 753–700 [CS(Th)]. ^{1}H NMR spectrum, δ, ppm: 1.62−1.99 m (2H, H^4), 2.88–2.94 m (4H, $H^{3,5}$), 8.01 s (1H, =CHTh), 7.96 s (1H, =CHAr), 7.07–7.24 m (4H, Ar), 7.29–7.51 m (3H,

Scheme 3.



Th). Found, %: C 72.45; H 5.34. $C_{18}H_{15}FOS$. Calculated, %: C 72.48; H 5.03.

2-(2-Thienylmethylene)-6-(2-chlorobenzylidene)-cyclohexanone (II) was similarly obtained. Yield 58%, mp 83–85°C. IR spectrum, ν, cm^{-1}: 1645 (C=O), 1600 (C=C), 764–721 [CS(Th)]. ^{1}H NMR spectrum, δ, ppm: 1.58–2.01 m (2H, H^4), 2.73–3.06 m (4H, H^{3,5}), 8.04 s (1H, =CHTh), 7.98 s (1H, =CHAr), 7.14–7.52 m (4H, Ar), 7.52–7.62 m (3H, Th). Found, %: C 73.27; H 4.07. $C_{18}H_{15}FOS$. Calculated, %: C 73.10; H 4.35.

7-(2-Thienylmethylene)-3-(2-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (IIIa), 3-(2-thienyl)-7-(2-fluorobenzylidene)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (IIIb). To a boiling solution of 0.5 g (1.7 mmol) of dienone **I** in 30 ml of 2-propanol was added 0.42 ml (8.5 mmol) of hydrazine hydrate. The reaction mixture was boiled for 50 min. The precipitated yellow crystals were washed with a large amount of water. Yield 0.33 g (63%), mp 118–120°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 3105 [CH(Th)], 3022–3074 [CH(Ph)], 721–700 [CS(Th)]. ^{1}H NMR spectrum, δ, ppm: 4.72 d, 4.85 d (1H, H^3, *J* 13.6, 13.6 Hz), 3.15 d, 2.99 d (1H, H^{3a}, *J* 16, 16 Hz), 6.64 s (1H, =CHTh), 1.21–1.63 m (2H, H^4), 1.76–2.15 m (1H, H^5), 2.30–3.07 m (1H, H^6), 7.00–7.54 m (4H, Ar), 7.00–7.54 m (3H, Th), 7.72 s (1H, NH). Found, %: C 70.02; H 5.19; N 9.19. $C_{18}H_{17}FN_2S$. Calculated, %: C 69.68; H 4.84; N 9.03.

7-(2-Thienylmethylene)-3-(2-chlorophenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (IVa), 3-(2-thienyl)-7-(2-chlorobenzylidene)-3,3a,4,5,6,7-hexahydro-2*H*-indazole (IVb) were similarly prepared. Yield 68%, mp 132–134°C. IR spectrum, ν, cm^{-1}: 3352 (NH), 3116 [CH(Th)], 3018–3065 [CH(Ph)], 721–700 [CS(Th)]. ^{1}H NMR spectrum, δ, ppm: 4.72 d, 5.08 d (1H, H^3, *J* 14.0, 13.6 Hz), 3.14 d, 2.82 d (1H, H^{3a}, *J* 12, 12 Hz), 6.97 s (1H, =CHTh), 1.07–1.59 m (2H, H^4), 1.80–2.33 m (1H, H^5), 2.43–2.92 m (1H, H^6), 7.03–7.34 m (4H, Ar), 7.03–7.34 m (3H, Th), 7.41 s (1H, NH). Found, %: C 70.02; H 5.19; N 9.19. $C_{18}H_{17}FN_2S$. Calculated, %: C 69.68; H 4.84; N 9.03.

IR spectra of compounds were recorded on a Fourier spectrophotometer FSM-1201 (from pellets with KBr), ^{1}H NMR spectra, on a spectrometer Varian 400 MHz in $CDCl_3$ (internal reference TMS). The reaction progress was monitored and the purity of the compounds was checked by TLC on Silufol UV-254 plates (eluent hexane–diisopropyl ether–chloroform, 3 : 1 : 1).

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