

LETTERS TO THE EDITOR

Synthesis of *N*-Tosyl-5-methyl-3-methylidene-2-ethylindole

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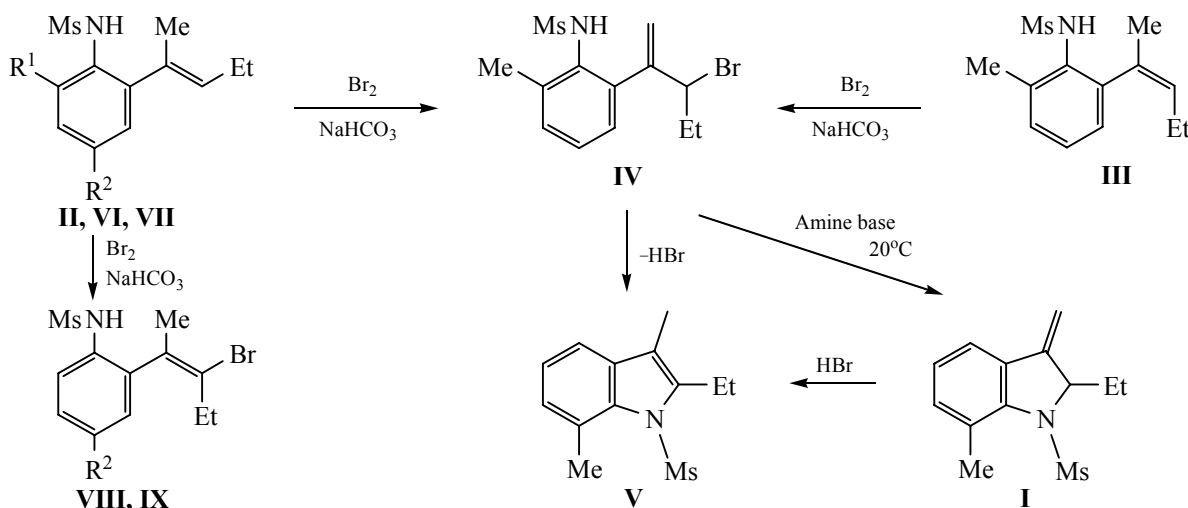
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The 3-methylideneindole derivatives are convenient starting materials for obtaining some heterocyclic compounds with biological activity [1–3]. Therefore these structure attract high interest of synthetic chemists. Such structures can be obtained via the palladium-catalyzed heterofusion reaction of *ortho*-haloanilines with 1,2-octadiene [4], cyclization of *N*-tosyl-2-(1-propen-2-yl)aniline into *N*-tosyl-3-methylideneindole [5], of organotin precursors into a mixture of *N*-acetyl-3-methylideneindole and 3-methylindole [6], respectively. Several 3-methylideneindole derivatives, including *N*-Ac-, *N*-Bz-, *N*-Boc- and *N*-Cbz-2-ethyl-3-methylideneindole as a mixture with the 3-methyl-substituted analog, *N*-tosylates of 4-, 5-, 6-methoxy-, 4-, 5-, 6-chloro-, and 4-methyl-3-methylidene-2-ethylindoles were obtained via the olefins metathesis reactions catalyzed by ruthenium complexes [2, 7, 8] (Grubbs catalyst of the II second generation [9]).

Scholl et al. also obtained 3-methylidene-2-propyl-, 3-methylidene-2-(2-methoxycarbethyl-1)-, and 3-methylidene-2-(3-methoxycarbpropyl-1)indoles mixed with the acyclic structures. At the same time, the *ortho*-methyl- or *ortho*-methoxy-substituted analog could not be synthesized in this way [7]. The palladium-catalyzed heterocyclization of 2-chloro-(α -aminomethyl)styrene can also be used to obtain the unsubstituted 3-methylideneindole [9]. The *N*-benzyl-containing 3-methylideneindole had previously been obtained via the dehydroiodination of the corresponding *N*-benzyl-3-iodomethylindole at heating with DBU [11]. The research in this area is still actual.

Earlier we developed a synthesis of *ortho*-methyl-3-methylideneindole **I** by the reaction of mesylates **II** and **III** with Br₂. This reaction occurs through the formation of a relatively stable allyl halide **IV** [12]. In

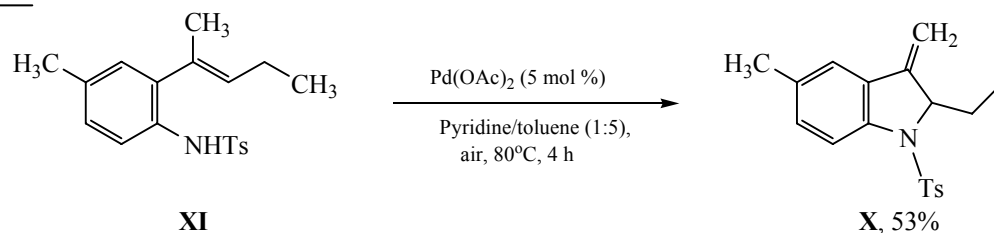


II, R¹ = Me, R² = H; **VI**, R¹ = R² = H; **VII**, R¹ = H, R² = Me; **VIII**, R² = H; **IX**, R² = Me.

the presence of NH_3 or Et_2NH bromide **IV** easily transforms into the indoline **I** containing an *exo*-methylidene group. In the absence of amine compound **IV** underwent spontaneous cyclization into indole **V** in a quantitative yield. The treatment of **I** with HBr solution also results in indole **V**.

But this method has some limitations, since it was not possible to synthesize a similar 3-methylidene-indole from the aniline derivative **VI** or *p*-toluidine **VII**. Unlike sulfonyltoluidines **II** and **III**, the reaction of methanesulfonylanilines **VI** or **VII** with Br_2 gives rise only to vinyl bromides **VIII** or **IX** [12].

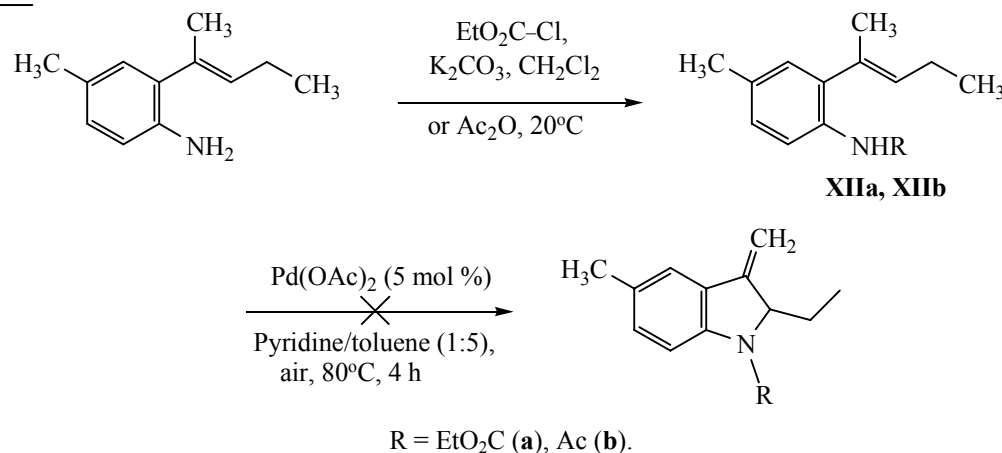
In this work we present the approaches to the synthesis of 3-methylideneindole starting from some alkenylanilines. We found that an analog of **I** with a *para*-positioned methyl group, 2-ethyl-5-methyl-3-methylene-1-[(4-methylphenyl)sulfonyl]indoline **X**, can be obtained via the oxidative cyclization of *N*-tosylate **XI** [12] in the presence of palladium acetate. One of the possible transformations of 3-methylideneindole is obtaining 3-oxoindoles, the application scope of which is quite diverse, including using them as starting materials for the preparation of compounds with photochrome properties [13].



The composition and structure of compound **X** was proved by the elemental analysis and spectral data. In the ^1H NMR spectrum of compound **X** a methyl group of CH_3CH_2 fragment is represented as a triplet at 0.88 ppm (J 7.5 Hz). The methylene protons of this fragment are magnetically non-equivalent, as evidenced by the nature of their splitting. Thus, the proton $\text{H}^{1\text{A}}$ appears as a doublet of doublets of quartets at 1.80 ppm (J_1 4.0, J_1 7.5, J_{gem} 14.0 Hz). A doublet of doublets of quartets at 2.15 ppm (J_1 5.3, J_1 7.5, J_{gem} 14.0 Hz) belongs to the proton $\text{H}^{1\text{B}}$. These protons differ in the coupling constants with the H^2 proton of indole ring. The latter appears at δ 4.58 ppm as a complex multiplet due to the long-range coupling constants (J 2.0 Hz). The coupling constants of the protons of terminal double bond, observed at 4.84 and

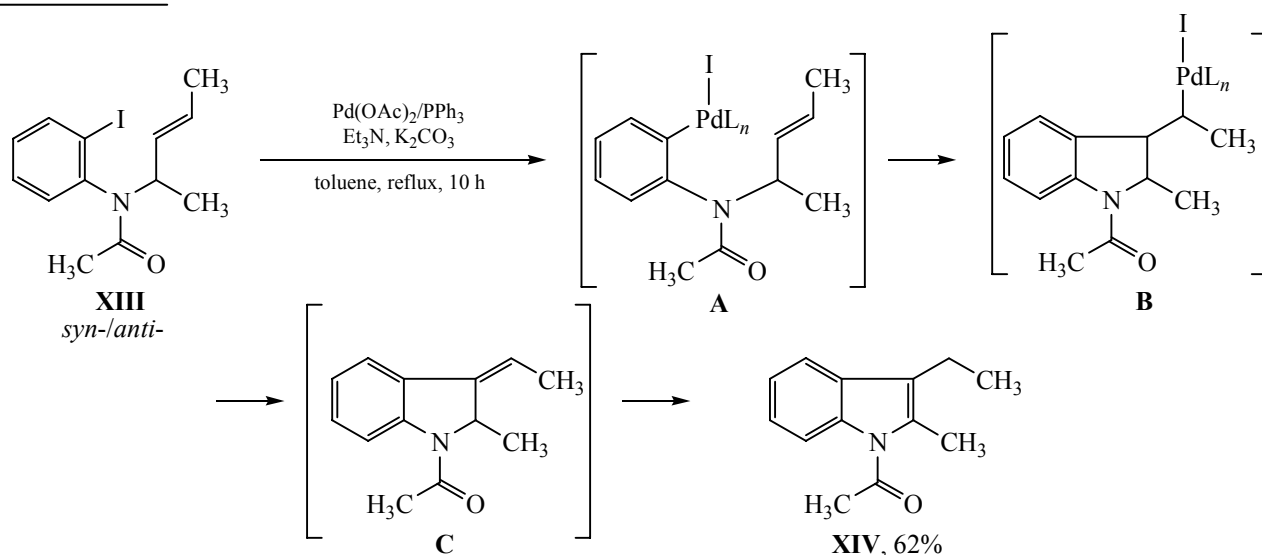
5.34 ppm, are small (2.0 Hz) and consistent with the literature data. The location of the methyl protons of aromatic fragments (δ 2.32 and 2.34 ppm) corresponds to the calculated values. The aromatic protons of tosyl groups are represented as the doublets at 7.15 and 7.54 ppm (J 8.2 Hz). The protons *ortho*-positioned relative to the sulfonyl group have a small long-range spin-spin coupling constant. The aromatic ring protons appear at 7.08 (H^7 , d, d, J_1 2.0, J_2 8.0 Hz), 7.11 (H^4), and 7.64 ppm (H^6 , d, J 8.0 Hz).

In order to obtain an analog of **X** containing readily leaving *N*-acetyl or *N*-ethoxycarbonyl groups, we tried to carry out the cyclization of compound **XIIa**, **XIIb** under action of Pd(OAc)_2 . Both attempts were unsuccessful. The cyclization product was not formed.



The heating of a mixture of atropisomers *syn*-**XIII** and *anti*-**XIII** [14] in the presence of $\text{Pd}(\text{OAc})_2$ results in 1-acetyl-3-ethyl-2-methyl-1*H*-indole **XIV** in 62% yield after chromatographic purification. We believe

that the formed intermediate **C** is unstable, therefore the exocyclic double bond undergoes migration as a result of a 1,3-H-shift to form the aromatic structure **XIV**, which is more favorable by the energy.



The composition and the structure of resulting indole **XIV** were determined on the basis of the elemental analysis and spectral data. The presence of the ethyl group was proved by the presence in the ^1H NMR spectrum of a triplet signal at 1.10 ppm and a quartet at 2.58 ppm (coupling constant ≈ 7.5 Hz). In addition, there are two singlet signals of two methyl groups at 2.45 and 2.62 ppm. The signals of aromatic protons are shifted downfield.

The IR spectra were recorded on a FT IR Prestige-21 (Shimadzu) spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 instrument operating at 300.13 and 75.45 MHz and Bruker Avance III 500 spectrometer operating at 500.13 and 125.73 MHz, internal reference TMS. The elemental analysis was performed on a CHN Analyzer M-185B. The mass spectra (APCI) were taken on a LCMS-2010EV spectrometer (mobile phase methanol–water, 50:50). The purity of the samples was determined on a Chromos GC-1000 complex using helium as a carrier gas, flame-ionization detector, column of 1 m $\times$ 3 mm, 5% SE 30 on a Chromaton N-AW carrier. TLC analysis was performed using Sorbfil plates (Sorbpolimer, Krasnodar) and detecting with UV irradiation (λ 254 nm) or iodine vapor.

2-Ethyl-5-methyl-3-methylene-1-[(4-methylphenyl)-sulfonyl]indoline (X**).** To a solution of 1.435 g

(4.4 mmol) of tosylamide **XI** in 1 ml of toluene and 0.2 ml of pyridine was added 0.096 g (0.5 mmol) of $\text{Pd}(\text{OAc})_2$. The reaction mixture was heated at 80°C with blowing air through the solution for 5 h, cooled to room temperature, transferred to a column filled with 30 g of silica gel and eluted with benzene to yield 1.34 g of crude product. The latter was recrystallized from ethanol. Yield 0.76 g (53%), white crystals, mp 113–116°C. The spectral characteristics are discussed in the text. Chromatography of the mother liquor on silica gel gave an additional 0.41 g of the starting amide **XI** and the cyclization product **X** in equal ratios.

1-Acetyl-3-ethyl-2,5-dimethyl-1*H*-indole (XIV**).** To a solution of 0.009 g (0.04 mmol) of $\text{Pd}(\text{OAc})_2$, 0.02 g (0.08 mmol) of PPh_3 in 3 ml of toluene was added 0.011 ml (0.12 mmol) of triethylamine, 0.017 g (0.12 mmol) of K_2CO_3 , and 0.14 g (0.04 mmol) of the atropisomers **XIII** mixture. The reaction mixture was refluxed for 10 h, then cooled to room temperature, transferred into a column filled with 3 g of silica gel, and eluted with benzene. Yield 0.05 g (62%), R_f 0.74 (C_6H_6 – EtOAc , 10:1). ^1H NMR spectrum (CDCl_3), δ , ppm: 1.10 t (3H, CH_3 , J 7.5 Hz), 2.45 s (3H, CH_3), 2.58 q (2H, CH_2 , J 7.5 Hz), 2.62 s (3H, CH_3), 7.12–7.16 m (2H_{Ar}), 7.36–7.38 m (1H_{Ar}), 7.85–7.89 m (1H_{Ar}). Mass spectrum, m/z : 202 [$M + \text{H}$] $^+$.

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