Synthesis of 5-Hydroxy- and 5-Amino-1-tosyl-5-phenyl-3-(2-arylvinyl)-4,5-dihydropyrazoles

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Abstract: The reaction of β-arylacryloyloxiranes with tosylhydrazine leads to unexpected 5-hydroxysubstituted Δ^2-pyrazolines. A series of 3-styryl substituted pyrazoles and 5-amino-Δ^2-pyrazolines were synthesized from the 5-hydroxy-Δ^2-pyrazolines. The mechanism of this process has been proposed based on current and previous results.

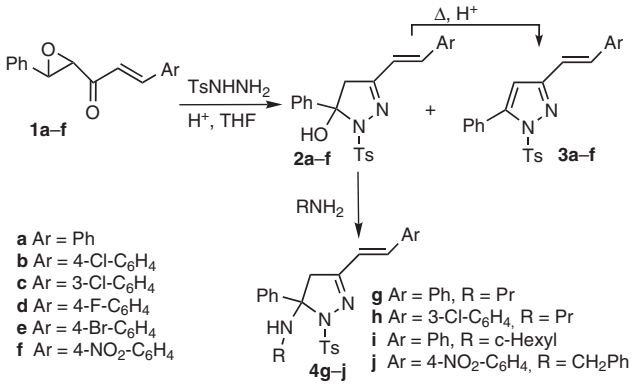
Key words: epoxy enones, hydrazones, rearrangements

The reaction of hydrazine and its derivatives with α,β-unsaturated ketones and α,β-epoxy ketones is one of the preparative methods for the synthesis of pyrazolines and pyrazoles. Pyrazolines are typical products of these reactions, when α,β-unsaturated ketones are used, and 4-hydroxy pyrazolines in the case where α,β-epoxy ketones are applied.[1] Combination of the functionalities of the β-arylacryloyloxiranes allowed evaluation of the reactivity of the carbonyl group, oxirane ring and conjugated double bond to nucleophilic reagents such as hydrazine.

Earlier, we found that the reaction of β-arylacryloyloxiranes with hydrazine gives the oxiranylpyrazoline intermediates, stable enough for isolation. However, in solution these compounds undergo further intramolecular oxidative–reductive transformation to β-hydroxyalkylpyrazoles.[2] These data indicate that hydrazine reacts preferentially with the conjugated double bond of β-arylacryloyloxiranes. Reaction of phenylhydrazine with β-arylacryloyloxiranes in proton solvents gives β-arylvinylpyrazoles, which shows participation of the oxirane ring in the cyclization process.[3]

In this paper, the reaction of β-arylacryloyloxiranes with tosylhydrazine is reported. Pyrazoles and pyrazolines with aromatic substituents are interesting as potential bioreceptor ligands.[4]

Although 4-hydroxypyrazolines are the typical products of the reaction of α,β-epoxy ketones with tosylhydrazine[5] and other hydrazines,[1] we found that the reaction of 3-aryl-1-(3-phenyloxiran-2-yl)-prop-2-en-1-ones (**1a–f**) with tosylhydrazine under acid catalysis leads to formation of 3-(2-arylvinyl)-5-hydroxy-5-phenyl-1-tosyl-2-pyrazolines (**2a–f**) with 58–83% yield (Scheme 1). Additionally, 3-(2-arylvinyl)-5-phenyl-1-tosyl-1*H*-pyrazoles (**3a–f**) were isolated with 7–21% yield by chromatography after crystallization of the major products.[6]



Scheme 1

The structures of 5-hydroxy-3-styrylpyrazolines (**2a–f**) were determined by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.[7] Thus, the hydroxyl, azomethine and vinyl group absorptions were observed in IR spectra, but there was no presence of the carbonyl band.

The ^{1}H NMR spectra indicated the presence of the methylene diastereotopic protons at δ = 3.20–3.50 ppm (J = 17.6–17.9 Hz), consistent with 5-hydroxypyrazoline structures.[8,9] The chemical shift of the double bond protons appeared in the range of δ = 6.55–6.66 ppm and 6.92–7.14 ppm (J = 16.4–16.7 Hz). Compared to the initial enones, they are displayed at the higher field as an AB-system. The tosyl group protons are shown in the ^{1}H NMR spectrum as a characteristic singlet at δ = 2.4 ppm (for the methyl group) and AB-system of aromatic protons signals in the low field at the range of δ = 7.22 and 7.68 ppm (J = 8.3 Hz). The ^{1}H NMR spectra of pyrazoles **3a–f** showed analogous pattern of chemical shifts to those of pyrazolines **2a–f** with an exception of the protons at the 4-position. A singlet signal at δ = 6.5 ppm is indicative for the pyrazole.

It is known that 1-acyl-5-hydroxy-2-pyrazolines can react with various amines yielding 1-acyl-5-alkylamino-2-pyrazolines.[10] Thus, pyrazolines **2a**,**c** were subjected to the reactions with primary amines, yielding the corresponding 5-alkylamino-2-pyrazolines (**4g–j**).[11] The structures **4g–j** were confirmed by ^{1}H NMR spectroscopy.[7] Unlike reported 1-phenyl-5-hydroxy-2-pyrazolines[12] which do not undergo dehydration, pyrazoline **2a** produced the corresponding pyrazole **3a** when heated in the presence of hydrochloric acid for 6 hours in THF.[13] These results indicate that the formation of pyrazoles **3a–f** proceeds via dehydration of the 5-hydroxypyrazolines **2a–f**, and not through the competitive 4-hydroxypyrazolines.

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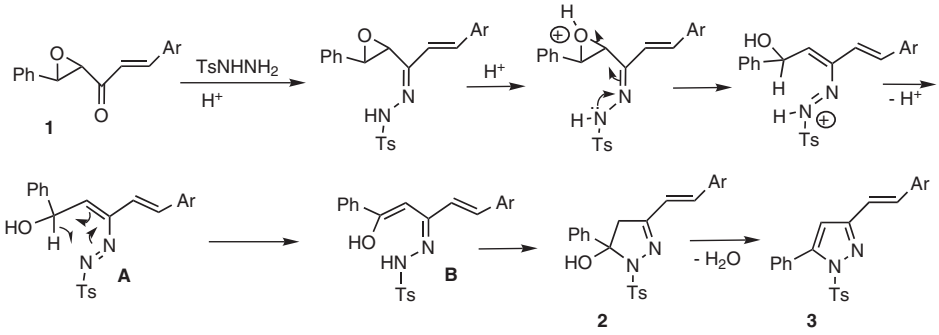

Scheme 2

Formation of pyrazolines **2a–f** proceeded through the oxirane ring-opening at the α-carbon, then probably through the intramolecular rearrangement of azadiene intermediate (**A**). The azadiene **A** is further transformed through a hydride [1,5] sigmatropic shift to 1,3-diketone monohydrazone (**B**, Scheme 2). Intramolecular cyclization leads finally to 5-hydroxypyrazolines **2a–f**.

It has been shown that 1,3-diketone hydrazones form stable 5-hydroxy-2-pyrazolines only if an electron-withdrawing group, i.e. acyl, is at the 1-position, or if a perfluoroalkyl group is present at the 5-position of the pyrazoline ring.[8]

Synthesis of the series of stable 3-(2-arylvinyl)-5-hydroxy-5-phenyl-1-tosyl-2-pyrazolines **2a–f** expands our knowledge about structure-stability dependence of 5-hydroxysubstituted pyrazolines.

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(6) **Typical Procedure:**
Tosylhydrazine (1.02 g, 5.5 mmol) and catalytic amount of the concentrated HCl were added to a solution of 3-aryl-1-(3-phenyloxiran-2-yl)prop-2-en-1-one (**1**, 5 mmol) in 20 mL THF. The reaction was carried out at r.t. for 12–18 h (control by TLC). After evaporation of the solvent in vacuo the residue was diluted with a mixture of Et_2O-benzene (1:3). Further solid pyrazoline **2** was filtered off and purified by recrystallization using EtOH or benzene. The residue mixture was divided on a column and pyrazole **3** and additional pyrazolines **2** were taken.

(7) Selected physical and spectroscopic data.
Compound **2a**: yield 77%, mp 169–172 °C (EtOH). IR (KBr): ν_{max} = 3504 (OH), 1600 (C=N), 1364, 1168 (S=O), 960 (HC=) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3 H, s, CH_3), 3.23 (1 H, d, *J* = 17.6 Hz, CH_2), 3.51 (1 H, d, *J* = 17.6 Hz, CH_2), 6.63 (1 ,H d, *J* = 16.4 Hz, CH=), 7.02 (1 H, d, *J* = 16.4 Hz, CH=), 7.23 (2 H, d, *J* = 8.3 Hz, C_6H_4), 7.29–7.50 (10 H, m, arom.), 7.69 (2 H, d, *J* = 8.3 Hz, C_6H_4). MS: *m/z* (%) = 418 (5.4) [M^+], 91 (100).
Compound **2c**: yield 83%, mp 98–100 °C (C_6H_6). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3 H, s, CH_3), 3.21 (1 H, d, *J* = 17.6 Hz, CH_2), 3.49 (1 H, d, *J* = 17.6 Hz, CH_2), 6.55 (1 H, d, *J* = 16.4 Hz, CH=), 7.00 (1 H, d, *J* = 16.4 Hz, CH=), 7.22 (2 H, d, *J* = 8.3 Hz, C_6H_4), 7.25 (5 H, m, C_6H_5), 7.32–7.50 (4 H, m, C_6H_4), 7.68 (2 H, d, *J* = 8.3 Hz, C_6H_4). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 21.61 (CH_3), 50.50 (CH_2), 97.82 (C-OH), 121.91 (CH=), 125.02 (CH=), 125.05, 126.90, 127.96, 128.33, 128.59, 128.94, 129.38, 130.08, 135.15, 137.6, 142.8 (arom.),153.02 (C-3).
Compound **3a**: yield 12%, mp 122–124 °C (EtOH). IR (KBr): ν_{max} = 1383, 1176 (S=O), 970 (HC=) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (3 H, s, CH_3), 6.53 (1 H, s, 4-H), 7.08 (1 H, d, *J* = 16.6 Hz, CH=), 7.16 (1 H, d, *J* = 16.6 Hz, CH=), 7.20 (2 H, d, *J* = 8.2 Hz, arom.), 7.27–7.52 (10 H, m, arom.), 7.56 (2 H, d, *J* = 8.2 Hz, C_6H_4).
Compound **4i**: yield 79%, mp 190–192 °C (MeOH). IR (KBr): ν_{max} = 3385 (NH), 2928, 2856 (CH), 1344, 1160 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–2.25 (10 H, m, C_6H_{11}), 2.38 (3 H, s, CH_3), 2.81 (1 H, m, C_6H_{11}), 3.17 (1 H, d, *J* = 18.0 Hz, CH_2), 3.56 (1 H, d, *J* = 18.0 Hz, CH_2), 6.60 (1 H, d, *J* = 16.4 Hz, CH=), 7.10 (1 H, d, *J* = 16.4 Hz, CH=), 7.12–7.45 (14 H, m, arom.).

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(11) Amine (propyl-, cyclohexyl- or benzylamines) (1 mmol) was added to the colorless solution of the pyrazoline **2** (1 mmol) in 10 mL THF or MeOH (the color of the solution becomes brightly orange). Reaction mixture was left at r.t. for 12 h. After evaporation of the solvent in vacuo, the residue was diluted with a mixture of $CHCl_3$–MeOH. Further solid 5-aminopyrazoline **4** was filtered off or taken as an oil.

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(13) Pyrazoline **2** (1 mmol) was dissolved in 10 mL THF with catalytic amount of the concentrated HCl and left at 50 °C for 6 h. After solvent evaporation in vacuo, the oil was diluted with Et_2O from which pyrazole **3** was crystallized.