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REACTION OF 4,5-DIHYDROXY-2-IMIDAZOLIDINONES WITH ARYLSULFINIC ACIDS. SYNTHESIS OF 4-ARYLSULFONYL-2-IMIDAZOLINONES

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The reaction of 4,5-dihydroxy-2-imidazolidinones with arylsulfinic acids in water upon heating leads to 4-arylsulfonyl-2-imidazolinones. The formation of such compounds was found to proceed through the loss of a water molecule or sulfinic acid from intermediate 4-hydroxy-5-arylsulfonyl-2-imidazolidinones and 4,5-di(arylsulfonyl)-2-imidazolidinones. 4-Arylsulfonyl-2-imidazolinones are also formed upon heating glyoxal, urea, and arylsulfinic acids in water.

In previous work [1], we showed that 4,5-dihydroxy-2-imidazolidinone reacts with *p*-toluenesulfinic acid in water at room temperature to give 4-hydroxy-5-(*p*-tolylsulfonyl)-2-imidazolidinone and, then, 4,5-di(*p*-tolylsulfonyl)-2-imidazolidinone. These compounds contain a tolylsulfonyl group in the α-position relative to the nitrogen atom, which, as already established for hexahydro-2-pyrimidinones and hexahydro-2-pyrimidinethiones [2, 3], is a facile leaving group in nucleophilic substitution reactions. Such compounds apparently may be used as starting reagents for the introduction of various groups at $C_{(4)}$ and $C_{(5)}$ of the imidazole ring. Thus, we undertook the synthesis of various arylsulfonyl-2-imidazolidinones and studied their reactions with nucleophilic reagents.

We have shown that 4,5-dihydroxy-2-imidazolidinones (IIa and IIb), formed upon the reaction of glyoxal with urea (Ia) or 1,3-dimethylurea (Ib), readily react with *p*-toluenesulfinic acid (IIIa) in water at room temperature to give the products of the replacement of one hydroxyl group, namely, the corresponding 4-hydroxy-5-(*p*-tolylsulfonyl)-2-imidazolidinones (IVa and IVc) in 91-93% yield (as a rule, with excess II). 4-Hydroxy-5-phenylsulfonyl-2-imidazolidinone (IVb) was formed by an analogous procedure in 88% yield from imidazolidinone IIa and benzenesulfinic acid (IIIb) in 88% yield. We should note that IVa-IVc are obtained stereospecifically as the *trans* diastereomers.

The reaction of dihydroxyimidazolidinones IIa and IIb with two molar equivalents of acid IIIa in water at room temperature involves the gradual transformation of the initial monosubstitution products IVa and IVc into the disubstitution products, namely, 4,5-di(*p*-tolylsulfonyl)-2-imidazolidinones (Va and Vc). The rate of formation of disulfones Va and Vc is much lower than the rate of formation of monosulfones IVa and IVc. This behavior may be attributed to the low solubility of these monosulfones in the reaction medium. For example, Va is formed in 86% yield in the reaction of imidazolidinone IIa and sulfinic acid IIIa in 18 days. On the other hand, the reaction between IIb and IIIa proceeds through a more complicated scheme and a 55:45 mixture of disubstitution product Vc and 1,3-dimethyl-4-(*p*-tolylsulfonyl)-2-imidazolinone (VIc) is formed after 14 days. The reaction of dihydroxyimidazolidinone IIa and IIb with benzenesulfinic acid IIIb proceeds more rapidly than with *p*-toluenesulfinic acid. However, a 77:23 mixture of disubstitution product Vb and 2-imidazolinone (VIb) is formed after 19 h reaction and a 55:45 mixture of disubstitution product Vd and 2-imidazolinone (VId) is formed after three days reaction. The amount of 2-imidazolinones VIb-VId increases with increasing reaction time and increasing temperature. Thus, the ratio of products Vb and VIb reaches 52:48 in the reaction of IIa and IIIb at room temperature after nine days. We also note that disulfones Va-Vc are obtained in these reactions with complete stereospecificity as the *trans* diastereomers.

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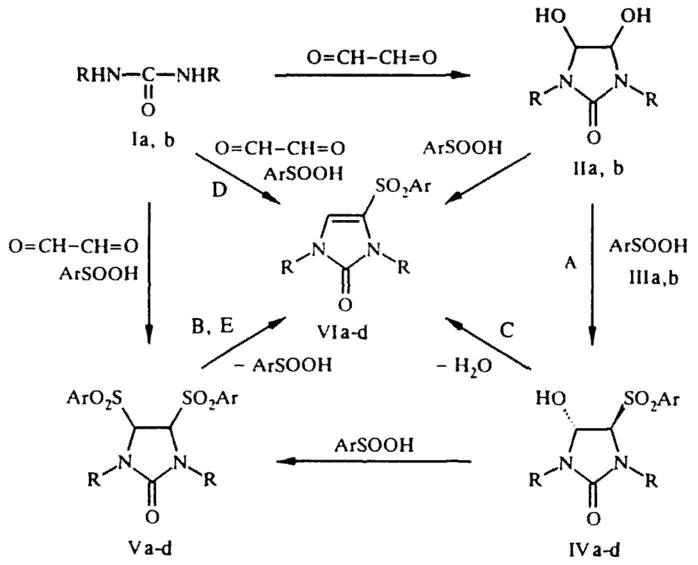

I, II a R = H, b R = Me. III a Ar = 4-MeC$_6$H$_4$, b Ar = Ph. IV—VI a R = H, Ar = 4-MeC$_6$H$_4$; b R = H, Ar = Ph; c R = Me, Ar = 4-MeC$_6$H$_4$; d R = Me, Ar = Ph

In order to simplify the synthesis of Va and Vb, we combined the procedure for obtained dihydroxy-2-imidazolidinone IIa and its reaction with sulfinic acids IIIa and IIIb in a single reaction apparatus. Thus, we obtained Va and Vb upon the reaction of urea, glyoxal, and acids IIIa and IIIb taken in 1:1:2 mole ratio in water. However, in both cases, the corresponding 4-arylsulfonyl-2-imidazolinones VIa and VIb (Va:VIa = 51:49, Vb:VIb = 70:30) are formed as side products.

The reaction of dihydroxyimidazolidinones IIa and IIb with *p*-toluenesulfinic acid IIIa in water upon heating on a steam bath for 30-45 min gives *p*-tolylsulfonylimidazolinones VIa and VIc as the sole products in 89-100% yield. Analogously, heating IIa and IIb with benzenesulfinic acid IIIb in water gives phenylsulfonyl-2-imidazolinones VIb and VId in 54-91% yield. Products VIa-VId are probably formed upon the loss of a water molecule or sulfinic acid from intermediate imidazolidinones IVa-IVd or Va-Vd (see above). Indeed, IVa-IVc and Va-Vd are readily converted into imidazolinones VIa-VId upon brief heating in water or organic solvents (see Experimental section). This feature hinders purification of IVa-IVc and Vb-Vd by recrystallization.

Arylsulfonyl-2-imidazolinones VIa and VIb may be readily obtained in yields of about 85% also upon heating urea, glyoxal, and the corresponding arylsulfinic acid III in water on a steam bath for 1 h.

The feasibility of the nucleophilic substitution of the arylsulfonyl groups was studied in the reaction of di(tolylsulfonyl)-2-imidazolidinone Va with sodium ethyl malonate. However, imidazolinone VIa was obtained in 86% yield in the reaction of these compounds in acetonitrile at room temperature for 4 h instead of the expected disubstitution product, 4,5-bis[di(ethoxycarbonyl)methyl]-2-imidazolidinone [1]. This reaction pathway is probably related to the observed tendency of disulfones V to undergo elimination of a sulfinic acid molecule.

The structures of IVb, IVc, Vb-Vd, and VIa-VId were supported by PMR and IR spectroscopy.

The presence of the urea fragment in these products is seen in strong IR bands for stretching of the carbonyl group at 1679-1744 cm^{-1}. Furthermore, these spectra show two strong bands related to the arylsulfonyl group or groups at 1294-1328 (ν_{as} SO$_2$) and 1139-1156 cm^{-1} (ν_s SO$_2$) and bands characteristic for the aryl substituent (see Experimental section). Imidazolinones VIa-VId also show a heterocyclic ring C=C band at 1564-1570 cm^{-1}.

Protons 4-H and 5-H in IVb and IVc are seen, respectively, as signals at 5.01-5.18 ppm (doublet) and 4.60-4.73 ppm (singlet for IVc and doublet for IVb). Coupling constant $J_{4,5}$ = 0 Hz indicates *trans* configuration of these compounds. The magnetically equivalent protons 4-H and 5-H of disulfones Vb-Vd are seen as one singlet at 5.13-5.44 ppm. In order to determine the configuration of these compounds, we analyzed the ^{13}C satellites of 4-H and 5-H as described by Gunther [5]. We found $J_{4,5}$ = 0 Hz for disulfones Vb and Vc, indicating their *trans* configuration.

The presence of a singlet for 5-H at 7.07-7.36 ppm is a characteristic feature of the PMR spectra of imidazolinones VIa-VId. Furthermore, broad singlets for the N—H group protons are found in the spectra of VIa and VIb at 10.91-11.12 ppm.

EXPERIMENTAL

The IR spectra were taken on a Shimadzu IR-435 spectrometer for Vaseline mulls. The PMR spectra were taken on a Bruker MSL-200 spectrometer at 200 MHz and Bruker AM-300 spectrometer at 300 MHz for solutions in $CDCl_3$ or DMSO-d_6. The chemical signals were calibrated using the solvent signal relative to TMS ($\delta CHCl_3 = 7.25$, $\delta DMSO = 2.50$ ppm).

Dihydroxy-2-imidazolidinones IIa and IIb were synthesized according to Petersen [4]. Samples of *p*-toluenesulfinic acid IIIa and benzenesulfinic acid IIIb were obtained by the reduction of the corresponding arylsulfonyl chlorides according to a reported procedure [6], dried over P_2O_5, and stored at 0°C.

Satisfactory elemental analysis data could not be obtained for IVa-IVc and Vb-Vd since these compounds are converted into the corresponding 4-arylsulfonyl-2-imidazolinones VIa-VId upon attempts to achieve recrystallization.

***trans*-4-Hydroxy-5-(*p*-tolylsulfonyl)-2-imidazolidinone (IVa)** was obtained in 93.3% yield according to our previous work [1] in the reaction of one equivalent of dihydroxy-2-imidazolidinone IIa with two equivalents of *p*-toluenesulfinic acid in water for 2 h. The spectral indices of this compound were given in our previous work [1].

***trans*-4-Hydroxy-5-phenylsulfonyl-2-imidazolidinone (IVb).** A mixture of 0.526 g (4.45 mmoles) dihydroxy-2-imidazolidinone IIa, 0.316 g (2.22 mmoles) benzenesulfinic acid, and 2 ml water was stirred at room temperature for 3 h and cooled to −5°C. The precipitate was filtered off, thoroughly washed with cold water and hexane, and dried to give 0.471 g (87.5%) IVb. IR spectrum: 3366, 3297 (νN—H, νO—H), 3062 (νC—H_{arom}), 1711 (C=O), 1583 (νC=C), 1294 ($\nu_{as}SO_2$), 1152 (ν_sSO_2), 1076 (νC—O), 749, 712 cm^{-1} (δC—H_{arom}). PMR spectrum in DMSO-d_6: 7.86 (1H, br.s, NH), 7.62-7.92 (5H, m, C_6H_5), 7.49 (1H, br.s, NH), 6.62 (1H, d, $J = 7.1$ Hz, OH), 5.18 (1H, d, $J_{4,5} = 0$ Hz, 4-H), 4.60 ppm (1H, d, $J_{NH,5} = 1.6$ Hz, 5-H).

***trans*-4-Hydroxy-1,3-dimethyl-5-(*p*-tolylsulfonyl)-2-imidazolidinone (IVc)** was obtained analogously to IVb in 90.5% yield in the reaction of 1.094 g (7.49 mmoles) 2-imidazolidinone IIb with 0.584 g (3.74 mmoles) *p*-tolylsulfonic acid in 10 ml water. IR spectrum: 3252 (νO—H), 3061 (νC—H_{arom}), 1679 (νC=O), 1595 (νC=C), 1318 ($\nu_{as}SO_2$), 1139 (ν_sSO_2), 1054 (νC—O), 814 cm^{-1} (δC—H_{arom}). PMR spectrum in DMSO-d_6: 7.73 (2H, d, $J = 8.1$ Hz, H_{arom}), 7.46 (2H, d, H_{arom}), 6.76 (1H, d, $J = 7.7$ Hz, OH), 5.01 (1H, d, $J_{4,5} = 0$ Hz, 4-H), 4.73 (1H, s, 5-H), 2.81 (3H, s, N—CH_3), 2.41 (3H, s, N—CH_3), 2.40 ppm (3H, s, CH_3 in Ts).

***trans*-4,5-Di(*p*-tolylsulfonyl)-2-imidazolidinone (Va).** A. Product Va was obtained in 85.8% yield according to our procedure [1] by the reaction of one equivalent of dihydroxy-2-imidazolidinone IIa with 2.2 equivalents of *p*-toluenesulfinic acid in water for 18 days. The spectral indices of this product were in accord with reported values [1].

B. A mixture of 0.375 g (6.24 mmoles) urea, 1.940 g (12.42 mmoles) *p*-toluenesulfinic acid, 1.203 g (6.22 mmoles) 30% aqueous glyoxal, and 10 ml water was stirred at room temperature for 33 days, cooled to −5°C, and treated as described for IVb to give 1.385 g of a 51:49 mixture of Va and 2-imidazolinone VIa as indicated by PMR spectroscopy.

***trans*-4,5-Di(phenylsulfonyl)-2-imidazolidinone (Vb).** A. A mixture of 0.202 g (1.71 mmole) dihydroxy- 2-imidazolidinone IIa, 0.538 g (3.78 mmoles) benzenesulfinic acid, and 5 ml water was stirred at room temperature for 19 h and then treated as described for IVb to give 0.383 g of a 77:23 mixture of Vb and 2-imidazolinone VIb as indicated by PMR spectroscopy. IR spectrum of the 77:23 mixture of Vb and VIb: 3363 (νN—H), 3151, 3113 sh, 3082, 3056 (νN—H, νC—H_{arom}), 1702 sh, 1685 (νC=O), 1585, ~1562 sh (νC=C), 1328 ($\nu_{as}SO_2$), 1152 (ν_sSO_2), 756, 719 cm^{-1} (δC—H_{arom}). PMR spectrum of Vb in DMSO-d_6: 8.26 (2H, br.s, 2NH), 7.50-7.99 (10H, m, $2C_6H_5$), 5.13 ppm (2H, s, $J_{4,5} = 0$, $J_{^{13}C\text{-}H} = 162.8$ Hz, 4-H and 5-H).

B. The reaction of 0.281 g (4.68 mmoles) urea, 0.903 g (4.67 mmoles) glyoxal (30% aqueous solution), and 1.330 g (9.35 mmoles) benzenesulfinic acid in 6 ml water for 3.5 h gave 0.958 g of a 70:30 mixture of Vb and 2-imidazolinone VIb as indicated by PMR spectroscopy.

***trans*-1,3-Dimethyl-4,5-di(*p*-tolylsulfonyl)-2-imidazolidinone (Vc).** A mixture of 0.707 g (4.84 mmoles) dihydroxy-2-imidazolidinone IIb, 1.670 g (10.69 mmoles) *p*-toluenesulfinic acid, and 20 ml water was stirred at room temperature for 14 days and then treated as in the case of IVb to give 1.580 g of a 55:45 mixture of Vc and 2-imidazolinone VIc as indicated by PMR spectroscopy. IR spectrum of this mixture of Vc and VIc: 3137, 3085 (νC—H_{arom}), 1744, 1704 (νC=O), 1596, 1568 (νC=C), 1322 ($\nu_{as}SO_2$), 1156 sh, 1139 (ν_sSO_2), 812 cm^{-1} (δC—H_{arom}). PMR spectrum of Vc in DMSO-d_6: 7.39-7.82 (8H, m, H_{arom}), 5.32 (2H, s, $J_{4,5} = 0$, $J_{^{13}C\text{-}H} = 167.4$ Hz, 4-H and 5-H), 2.42 (6H, s, N—CH_3), 2.39 ppm (6H, s, CH_3 in Ts).

1,3-Dimethyl-4,5-di(*p*-tolylsulfonyl)-2-imidazolidinone (Vd). A mixture of 0.213 g (1.46 mmole) dihydroxy-2-imidazolidinone IIb, 0.557 g (3.92 mmoles) benzenesulfinic acid, and 5 ml water was stirred at room temperature for 72 h. The precipitate was filtered off, thoroughly washed with cold water and hexane and dried to give 0.396 g of a 55:45 mixture of Vd and 2-imidazolinone VId as indicated by PMR spectroscopy. IR spectrum of this mixture of Vd and VId: 1711 (νC=O), 1584, 1570 (νC=C), 1322 ($\nu_{as}SO_2$), 1148 ($\nu_{s}SO_2$), 748, 717 cm^{-1} (δC—H$_{arom}$). PMR spectrum of Vd in DMSO-d$_6$: 7.56-8.06 (10H, m, C_6H_5), 5.44 (2H, s, 4-H and 5-H), 2.39 ppm (6H, s, N—CH_3).

4-(*p*-Tolylsulfonyl)-2-imidazolinone (VIa). A. A mixture of 0.202 g (1.71 mmole) dihydroxy-2-imidazolidinone IIa, 0.534 g (3.42 mmoles) acid IIIa, and 5 ml water was stirred on a steam bath for 45 min. A crystalline product began to form 5 min after the reaction onset. The reaction mixture was treated as in the case of IVb to give 0.407 g (99.9%) VIa, which was recrystallized from acetonitrile or methanol, mp 282°C (dec.). In the case of the recrystallization from methanol, the sample turns dark brown at 275°C. Found: C, 50.09; H, 4.27; N, 11.50; S, 13.45%. Calculated for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46%. IR spectrum: 3157, 3123 sh (νN—H), 1691 (νC=O), 1594, 1494 (νC=C in Ts), 1570 (νC=C in heterocycle), 1326 ($\nu_{as}SO_2$), 1147 ($\nu_{s}SO_2$), 816 (δC—H$_{arom}$). PMR spectrum in DMSO-d$_6$: 11.10 (1H, br.s, N—H), 10.91 (1H, br.s, N—H), 7.80 (2H, d, J = 7.8 Hz, H$_{arom}$), 7.42 (2H, d, H$_{arom}$), 7.31 (1H, s, 5-H), 2.38 ppm (s, 3H, CH_3).

B. A suspension of 0.305 g (0.77 mmole) 2-imidazolidinone Va in 5 ml acetonitrile was heated at reflux with stirring for 2 h and then subjected to the standard work-up as in the case of IVb to give 0.140 g (76.0%) VIa.

Product VIa was also formed in 98.0% yield upon maintaining 2-imidazolidinone Va in water on a steam bath for 30 min with subsequent cooling of the reaction mixture and filtration.

C. Product IVa was heated at reflux in acetonitrile (see method B). The yield of VIa was 72.5%.

D. A mixture of 0.380 g (6.33 mmoles) urea, 1.975 g (12.64 mmoles) acid IIIa, 1.220 g (6.31 mmoles) 30% aqueous glyoxal, and 10 ml water was stirred on a steam bath for 1 h. The standard work-up gave 1.276 g (85.1%) VIa.

E. A solution of 0.498 g (3.11 mmoles) ethyl malonate in 6 ml acetonitrile was added dropwise to a mixture of 0.072 g (3.00 mmoles) sodium hydride in 6 ml dry acetonitrile with stirring and cooling in a water bath. A sample of 0.541 g (1.37 mmole) disulfone Va was added to the suspension of sodium ethyl malonate obtained and stirred at room temperature for 4 h. The reaction mixture was evaporated in vacuum. Then, 2.5 ml water was added to the residue and cooled to −5°C. The precipitate was filtered off, washed with cold water, and dried to give 0.282 g (86.3%) VIa.

4-Phenylsulfonyl-2-imidazolinone (VIb). Product VIc was obtained analogously to VIa in 90.6% yield using method A from dihydroxy-2-imidazolidinone IIa and benzenesulfinic acid, in 61.1% yield using method B by heating a 1:1 mixture of Vb and VIb in acetonitrile at reflux (the yield is given relative to pure Vb), in 81.7% yield using method C from IVb, and in 84.7% yield using method D from urea, glyoxal, and benzenesulfinic acid. Product VIb was purified by recrystallization from acetonitrile or methanol, mp 244-246°C (dec., methanol). Found: C, 48.22; H, 3.78; N, 12.33; S, 13.78%. Calculated for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30%. IR spectrum: 3146 sh, 3113 (νN—H), 1690 (νC=O), 1564 (νC=C), 1326 ($\nu_{as}SO_2$), 1147 ($\nu_{s}SO_2$), 753, 715 cm^{-1} (δC—H$_{arom}$). PMR spectrum in DMSO-d$_6$: 11.12 (1H, br.s, NH), 10.94 (1H, br.s, NH), 7.55-7.95 (5H, m, C_6H_5), 7.36 ppm (1H, s, 5-H).

1,3-Dimethyl-4-di(*p*-tolylsulfonyl)-2-imidazolinone (VIc). A mixture of 0.415 g (2.84 mmoles) dihydroxy-2-imidazolidinone IIb, 0.886 g (5.67 mmoles) *p*-toluenesulfinic acid, and 12 ml water was heated with stirring on a steam bath for 30 min. An oily precipitate began to separate 5 min after the reaction onset. The reaction mixture was cooled to 20°C and 7 ml ethanol was added to obtain a homogeneous solution, which was then cooled to −5°C. The precipitate formed was filtered off, thoroughly washed with cold 2:1 water—ethanol and, then, hexane, and dried to give 0.670 g (88.6%) VIc, which was recrystallized from a 10:1 mixture of petroleum ether (70-100°C) and ethanol, mp 151-154°C. Found: C, 53.91; H, 5.41; N, 10.42; S, 11.63%. Calculated for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04%. IR spectrum: 3138, 3084 (νC—H$_{arom}$), 1703 (νC=O), 1594 (νC=C in Ts), 1564 (νC=C in heterocycle), 1324 ($\nu_{as}SO_2$), 1156 ($\nu_{s}SO_2$), 812 cm^{-1} (δC—H$_{arom}$). PMR spectrum in $CDCl_3$: 7.77 (2H, d, J = 8.3 Hz, H$_{arom}$), 7.32 (2H, d, H$_{arom}$), 7.07 (1H, s, 5-H), 3.30 (3H, s, N—CH_3), 3.24 (3H, s, N—CH_3), 2.42 ppm (3H, s, CH_3 in Ts).

1,3-Dimethyl-4-phenylsulfonyl-2-imidazolinone (VId) was obtained in 53.5% yield analogously to VIc upon heating dihydroxy-2-imidazolidinone IIb with benzenesulfinic acid in water, mp 153-256°C (dec., acetonitrile). Found: C, 52.51; H, 4.81; N, 11.02%. Calculated for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10%. IR spectrum: 3136, 3088 (νC—H$_{arom}$), 1704 sh, 1691 (νC=O), 1569 (νC=C), 1321 ($\nu_{as}SO_2$), 1153 ($\nu_{s}SO_2$), 739, 716 cm^{-1} (δC—H$_{arom}$). PMR spectrum in $CDCl_3$: 7.36-7.93 (5H, m, C_6H_5), 7.13 (1H, s, 5-H), 3.32 (3H, s, N—CH_3), 3.23 ppm (3H, s, N—CH_3).

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