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Synthesis of 2-(4-aminophenyl)-4-triazolylmethyl-1,3-dioxolanes - intermediates of biologically active compounds

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Abstract

Optimal methods for the synthesis of 2-(4-aminophenyl)-4-triazolmethyl-1,3-dioxolanes – the intermediates used in the synthesis of biologically active substances: fungicides, antimycotic agents, antibacterial agents and plant growth regulators have been studied. Five alternative methods for the synthesis of 2-(4-aminophenyl)-4-triazolylmethyl-1,3-dioxolanes by means of the reduction of 2-(4-nitrophenyl)-4-triazolmethyl-1,3-dioxolanes have been studied: using hydrazine, sodium dithionite, hydrogen under the catalysis of the palladium supported on activated carbon, as well as in an autoclave under the catalysis of Raney nickel or palladium. The best results have been shown by a method for molecular hydrogen reduction in an autoclave. A number of 2-(4-aminophenyl)-4-triazolylmethyl-1,3-dioxolane derivatives with a growth-regulatory and fungicidal activity have been obtained.

Keywords: triazole, 1,3-dioxolane, biologically active substances, fungicides, growth regulators, antibacterial drugs

INTRODUCTION

At present, a significant share of the market of fungicides and antimycotic agents account for triazole derivatives, which are characterized by high efficiency and low toxicity. Among the systemic fungicides used, an important role is played by dioxolane-containing drugs: propiconazole, difenoconazole, ketoconazole. In turn, among 1,3-dioxolane derivatives, furolan and other 1,3-dioxolane derivatives have a growth-regulatory activity [1-2].

According to the patents [3,4], alkylamide compounds and the alkyl (benzyl) urea of 2-(4-aminophenyl)-1,3-dioxolanes have herbicidal properties. At the same time, dioxolanes containing the azolylmethyl fragment also exert growth-regulatory properties [5]. Among the 2,2-disubstituted 4-azolylmethyl-1,3-dioxolanes synthesized and studied earlier, substances with a high fungicidal activity, namely substituted 2-phenyl-1,3-dschioxolanes having a bulky lipophilic substituent at the *para* position, have been found [6-9].

It is also known that substituted 4-aminomethyl-1,3-dioxolanes show a wide range of activities: antimycotic [10,11], mucolytic [12], antiarrhythmic [13], anticholinergic [14-22], analgetic [23-27], anti-hypertensive [28].

We assumed that when the fragments of triazole, 1,3-dioxolane, and the aromatic nucleus substituted at the para position with bulky substituents (aryl urea, amide, etc.) are combined in one molecule, such compounds will have a different types of biological activity.

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz). IR spectra were recorded on a Specord M-80 instrument (thin films for liquids and Nujol for solids)/ The course of the reaction was monitored and the purity of the compounds was checked by TLC (Sorbfil A-UF). Substituted ketones were prepared according to a known procedure.

Substituted 2-(4-nitrophenyl)-4-chloromethyl-1,3-dioxolane (general procedure).

A mixture of substituted 4-nitrobenzophenone or 4-nitroalkanophenone 22.1 g (0.2 mol), 3-chloropropane-1,2-diol and 0.96 g (0.005 mol) p-toluenesulfonic acid monohydrate was refluxed in benzene for ~24 h with azeotropic removal of water. The reaction mixture was neutralized with 2% NaOH (200 mL) and washed with water (200 mL), the solvent was removed in vacuo.

Substituted 2-phenyl-2-(4-nitrophenyl)-4-triazolmethyl-1,3-dioxolane (general procedure).

A mixture of a substituted 2-(4-nitrophenyl)-4-chloromethyl-1,3-dioxolane (0.06 mol) and a sodium salt of 1,2,4-triazole was refluxed in DMF (100 mL) for 16-20 h, filtered, and evaporated. The residue was chromatographed on silica gel in acetone-hexane with a concentration gradient of acetone from 10 to 40%, the solvent was removed in vacuo.

VARIOUS METHODS OF REDUCTION OF NITRODERIVATIVES (A-E).

Method A

61.75 g (0.355 mol) of sodium dithionite were added in portions to a solution of 21.65 g (0.059 mol) of 2-(4-nitrophenyl)-2-(4-methylphenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane in 60 ml of ethanol, 80 ml of water and 57 ml of 25% NH4OH, which was followed by an increase in temperature to 55-60 °C. The reaction mixture was heated at 70 °C and stirred for 4 hours (TLC control). It was cooled, extracted with chloroform (3x100 ml), washed with water to remove acid, dried over anhydrous magnesium sulfate, evaporated using RFE solvents, 16.93 g of crude product were derived in the form of a viscous orange mass. It was purified by means of flash chromatography 4.9 g (25%) of 2-(4-aminophenyl)-2-(4-methylphenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived as yellow crystals with a melting point of 82-83 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, *J* / Hz): 2.36 (s, 3H, CH_3); 3.75 (mpl, 2H, NH_2); 3.90-4.16 (m, 2H, CH_2O); 4.26-4.41 (m, 2H, CH_2N); 4.57 (q, 1H, CHO, ^3J = 5.4); 6.60 (d, 2H, $C^{3.5}H$ $C_6H_4NH_2$, ^3J = 8.6); 7.12-7.27 (m, 2H, $C^{2.6}H$ $C_6H_4NH_2$); 7.29-7.38 (m, 3H, PhMe); 7.40 7.55 (m, 2H, PhMe); 7.94 (s, 1H C^3H triaz.); 8.11 (s, 1H, C^5H, triaz.). IR (vaseline oil, ν/cm^{-1}): 3449 (NH_2), 1279 (β CH triaz.); 1245, 1188, 1085 (COCOC).

Method B

A suspension of 0.25 g of Raney nickel in ethyl alcohol (5% of the weight of the nitro compound) was added in small portions to a solution of 5.0 g (0.017 mol) of 2-methyl-2-(4-nitrophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane and 2.16 g (0.043 mol) of hydrazine hydrate in 50 ml of ethanol heated to 30-40 °C. After the completion of the reaction (TLC), the cooled mixture was filtered off from nickel, the organic phase was extracted with chloroform, washed with water, dried over anhydrous magnesium sulfate, chloroform was distilled off using a rotary evaporator. 3.50 g (79%) of crude 2-(4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived in the form of a dark yellow viscous mass (a mixture of the desired product and its diazo compound). The crude product was converted to oxalate with 1.46 g (0.0134 mol) of oxalic acid in 60 ml of acetone, the precipitated crystals were washed with 50 ml of hexane, dried and converted to a free base by dissolving the oxalate in 80 ml of a 5% KOH solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, the solvent was evaporated. The residue was purified using flash chromatography, 3.0 g (48%) of 2-(4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived as cream crystals with a melting point of 80-81 °C. NMR ^{1}H spectrum ($CDCl_3$, δ, ppm, *J* / Hz): 1.58 (s, 3H, CH_3); 3.62 (dd, 0.21H, CH_2O, ^3J = 6.6, ^2J = 8.8); 3.74-3.90 (m, 3.58H, CH_2O + NH_2); 4.09 (dd, 0.21 H, CH_2O diox.); 4.26-4.41 (m, 3H, CH_2N + CHO); 6.62 (d, 2H, $C^{3.5}H$ $C_6H_4NH_2$, ^3J = 8.6); 7.18 (d, 2H, $C^{2.6}H$ $C_6H_4NH_2$); 7.92 (s, 0.21H C^3H triaz.); 7.94 (s, 0.79H C^3H triaz.); 8.15 (s, 0.21H C^5H triaz.); 8.24 (s, 0.79H C^5H triaz.). IR (vaseline oil, ν/cm^{-1}): 3414 (NH), 1270 (β CH triaz); 1245, 1170, 1085 (COCOC).

Method C

A suspension of carbon-based palladium in 30 ml of absolute methanol (possible ignition!) was added to a solution of 21.6 g (0.075 mol) of 2 methyl-2-(4-nitrophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane in 150 ml of absolute methanol, and then 12 g (0.375 mol) of sodium boron hydride were poured in small portions at such a rate that methanol slightly boiled. After the completion of the reaction (TLC control), the reaction mass was cooled, poured out with stirring in 100 ml of water, stirred for 15 minutes, the product was extracted with 200 ml of ethyl acetate, dried over anhydrous magnesium sulfate and filtered through a silica gel layer (35/70) (TLC control), another 150 ml of ethyl acetate were filtered, combined, evaporated using RFE, the residue was dissolved in 50 ml of acetone and mixed with a solution of 9 g (0.071 mol) of oxalic acid monohydrate in 70 ml of acetone. The precipitated oxalate was filtered off, washed with 100 ml of acetone, 200 ml of pentane and air-dried. The oxalate was dissolved in 300 ml of a 5% solution of KOH, extracted with methylene chloride (2x100 ml), washed with water to remove acid, dried over anhydrous magnesium sulfate, the solvent was evaporated using RFE. 3.5 g (18%) of 2 methyl-2-(4-nitrophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived.

Method D

A solution of 5.0 g (0.017 mol) of 2-methyl-2-(4-nitrophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane in 100 ml of a mixture of methanol-THF (1:1) and 0.5 g of the palladium supported on activated carbon was added in a shaking autoclave. It was hydrogenated at room temperature and with the initial hydrogen pressure of 4 atmg for about 16 hours, after which the catalyst was filtered off and the solvent was evaporated using a rotary evaporator and vacuum-processed in a fine vacuum. 4.11 g (93%) of 2-(4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived.

Method E

A solution of 5.0 g (0.017 mol) of 2-methyl-2-(4-nitrophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane in 100 ml of a mixture of methanol-THF (1:1) and 0.5 g of skeletal Raney nickel was added in a shaking autoclave. It was hydrogenated at room temperature and with the initial hydrogen pressure of 4.5 atmg (until 0.4 l of hydrogen was absorbed) for about 30 minutes. The catalyst was filtered off, the solvent was evaporated using a rotary evaporator and vacuum-processed in a fine vacuum. 3.85 g (87%) of 2-(4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane were derived as yellow crystals.

RESULTS AND DISCUSSION

To synthesize the desired derivatives, the corresponding 2-(4-aminophenyl)-4-azolylmethyl-1,3-dioxolanes (amines) were synthesized by reducing the corresponding aromatic nitro derivatives, which had been derived as shown in diagram 1. Table 1 provides the yields and physico-chemical characteristics of the corresponding nitro derivatives.

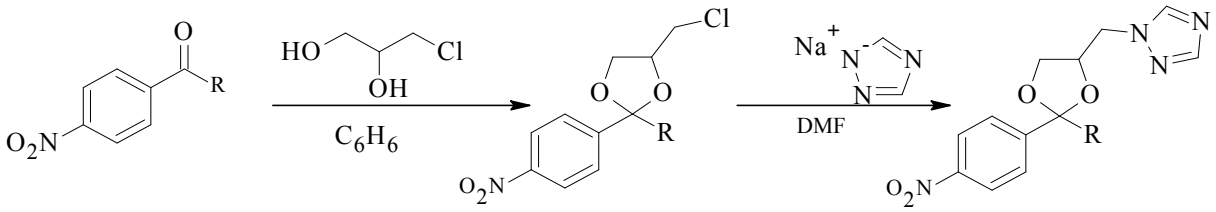

Diagram 1

Table 1. Yields and physico-chemical properties of 2-(4-nitrophenyl)-4-triazolylmethyl-1,3-dioxolanes

№	R	**a:** X = Cl		**b:** X = 1,2,4-triazole	
		β, %	Tm, °C	β, %	Tm, °C
1	CH_3	89	87-88	78	91-92
2	C_6H_6	95	Semicrystalline	83	138-139*
3	4-$CH_3C_6H_6$	92	Semicrystalline	88	161-162*

***oxalates**

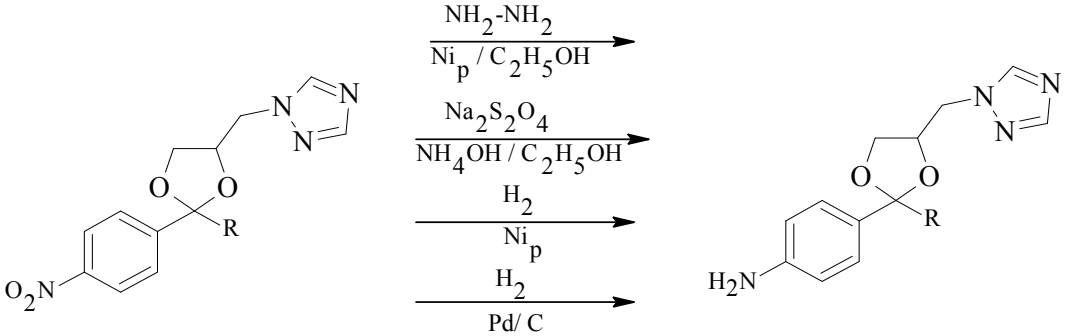

Diagram 2

The only method proposed in the literature [3-5] for the reduction of such compounds - a method using iron powder when boiling with concentrated hydrochloric acid - was not used, as we have previously found that such compounds are hydrolyzed even by weak hydrochloric acid solutions at room temperature.

The nitro derivatives **3b** was reduced by sodium dithionite in a water-ammonia-alcohol medium with a yield of 25%. This low yield is explained by the data of TLC and chromatography-mass spectrometry, the presence, in addition to the desired product, of approximately equal proportions of 4-aminophenyl-4'-methylbenzophenone and triazolylpropanediol derived when hydrolyzing the desired product, and the Schiff base derived from the desired product and 4-aminophenyl-4'-methylbenzophenone.

The attempts to purify the target product using the methods of column and flash chromatography did not lead to positive solutions. The purification of the product using preparative HPLC (the direct phase is water-methanol) was not successful either, since the desired product was completely hydrolyzed during the elution process (according to chromatographic mass spectrometry).

The unsatisfactory yield of the product when reducing with dithionite caused synthesis optimization. Thus, the nitro compound **1b** was reduced in five ways: 1) using sodium dithionite in a water-ammonia-alcohol medium, 2) using hydrazine hydrate in ethanol based on Raney nickel, 3) using the hydrogen disengaged during the reaction of sodium boron hydride with methanol, when catalysed by the palladium supported on activated carbon, 4) using hydrogen in an autoclave, when catalyzed by Raney nickel, 5) using hydrogen in an autoclave, when catalysed by the palladium supported on activated carbon (diagram 2):

In the case of hydrazine hydrate reduction, the product was derived with an acceptable yield, but it was heavily contaminated with a diazo compound (VI). When reduced by sodium dithionite, the yield of the product **1b** increased compared to **3b**, but the composition of by-products did not change. When the nitro compound **1b** was reduced by the hydrogen disengaged during the reaction of sodium boron hydride with methanol at room temperature, the yield of the product was 18%. Such a low yield is caused (when comparing TLC and according to the chromatography-mass spectrometry data) by both the formation of Schiff bases (as in the case of sodium dithionite) and, apparently, the interaction of excess sodium boron hydride with the final compound with the formation of products with an unidentified structure.

The optimal way to reduce the nitro compound **3b** was a method for reduction using molecular hydrogen in an autoclave. The reactions were carried out with the initial hydrogen pressure of 4 atm, at room temperature, the solvent was methanol/THF 1:1. In the case of Raney nickel catalysis, the reaction took about 30 minutes with a yield of 87%, in the case of catalysis with the palladium supported on activated carbon, the yield increased to 93%, but the reaction time increased to 16 hours. In both cases, the products were preparatively pure. The structures of all the synthesized compounds and their purity were determined according to TLC, PMR spectroscopy and chromatography-mass spectrometry.

It is interesting to note that there were two signals with different retention times in the chromatography-mass spectra of the products of nitro compounds reduction, but with identical molecular ions, which probably speaks for the presence of a mixture of optical isomers.

CONCLUSIONS

The optimal way to synthesize corresponding 2-(4-aminophenyl)-4-azolylmethyl-1,3-dioxolanes to reduce the nitro compound was a method for reduction using molecular hydrogen in an autoclave.

The synthesized compounds showed a significant retardant and antibacterial activity.

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