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Synthesis of 3,5-Disubstituted Pyrazole Derivatives with a Carbamate Function

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Abstract—One-pot reaction of 1,3-dipolar cycloaddition of aryldiazamethanes generated *in situ* from the sodium salts of tosylhydrazones of benzaldehyde, *p*-nitro-, *p*-methoxy-, and 3,4-dimethoxybenzaldehyde to propargyl-N-phenyl carbamate under heating led to the formation of 3,5-disubstituted pyrazoles in good yield and high regioselectivity.

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Pyrazole derivatives attract great interest for these compounds are widely used as drugs, dyes, anesthetics, and agricultural chemicals [1, 2]. They are endowed with bacteriostatic, bactericidal, insecticide, fungicide, sedative, antitumor, and psycho-pharmacological action. Pyrazoles are also used as antioxidant additives to fuels [3].

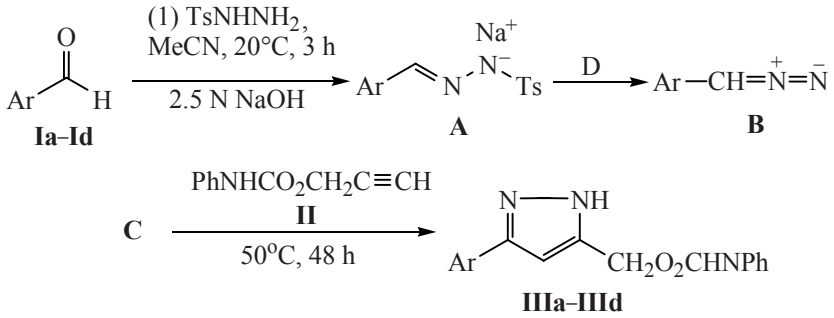
The most important preparation methods of this class heterocycles are hydrazines reaction with β-difunctional compounds [4] and 1,3-dipolar cycloaddition of diazo compounds to a triple bond 5].

Recently a convenient one-pot method of pyrazoles preparation was developed consisting in the 1,3-dipolar cycloaddition of aryldiazomethanes generated from stable sodium salts of tosylhydrazones in situ [6]. An obvious advantage of this method is avoiding the stage of isolation of toxic and potentially explosive diazo compounds. However the synthetic opportunities and the application limits of this method of pyrazoles synthesis were poorly understood.

We investigated the 1,3-dipolar cycloaddition to propargyl-*N*-phenyl carbamate of aryldiazomethanes generated in the course of the reaction from sodium salts of tosylhydrazones obtained from appropriate aromatic aldehydes .

The cycloaddition of aryldiazomethanes obtained from the sodium salts of tosylhydrazones of benzaldehyde, 4-methoxy-, 3,4-dimethoxy-, and 4-nitrobenzaldehyde occurred regioselectively to the terminal triple bond of dipolarophile **II** affording 3,5-disubstituted pyrazoles **IIIa–IIId** in 22–70% yield (see the scheme).

Scheme.



Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**), 4-$NO_2C_6H_4$ (**d**).

The structure of 3-aryl-5-phenylaminocarbonyloxymethyl-1*H*-pyrazoles **IIIa–IIId** was confirmed by IR and ^{1}H NMR spectra.

In the ^{1}H NMR spectra of pyrazoles **IIIa–IIId** the signal of proton H^4 appeared in the region 6.48–6.53 ppm in agreement with the published data [7, 8].

The highest yield was obtained from benzaldehyde (**Ia**). The preparation of pyrazoles **IIIb–IIId** was attended with the formation of intractable tar considerably reducing the yield of the target products.

The high stereoselectivity of the cycloaddition of aryldiazomethanes is controlled by HUMO of the diazo compound when react the terminal atoms with a large orbital factor [9].

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker DRX 500 (500.13 MHz) in DMSO-d_6, internal reference TMS. IR spectra were recorded on a spectrophotometer Specord M82 from pellets with KBr. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates. Tosylhydrazine was obtained by procedure [10], mp 104–107°C.

3-Aryl-5-phenylaminocarbonyloxymethyl-1*H*-pyrazoles IIIa–IIId. To a solution of 0.28 g (1.5 mmol) of tosylhydrazine in 15 ml of acetonitrile was added 1.5 mmol of aldehyde **Ia–Id**, the mixture was stirred for 3 h at room temperature, 1.5 mmol of 5 N solution of sodium hydroxide was added, and the stirring at the same temperature continued for 20 min more. To the obtained sodium salt of tosylhydrazone was added 1.3 g (7.5 mmol) of propargyl-N-phenyl carbamate (**II**), the mixture was stirred at 50°C for 48 h. The volatile substances were removed in a vacuum, the residue was dissolved in 70 ml of a mixture water–ethyl acetate, 1 : 1. The organic layer was separated, dried with magnesium sulfate, the solvent was removed, the residue was subjected to column chromatography on neutral aluminum oxide, eluent ethyl acetate.

3-Phenyl-5-phenylaminocarbonyloxymethyl-1*H*-pyrazole (IIIa). Yield 1.5 g (70%), colorless crystals, mp 94–95°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 1720 (C=O), 1605, 1520, 1500 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 5.35 s (2H, OCH$_2$), 6.51 s (1H, H^4), 7.37–7.02 m (10H$_{arom}$), 9.54 s (1H, NH), 9.79 s (1H, NH). Found, %: C 69.47; H 5.34; N 14.07. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.63; H 5.12; N 14.33.

[3-(4-Methoxyphenyl)-1*H*-pyrazol-5-yl]methyl *N*-phenylcarbamate (IIIb). Yield 1.3 g (54%), colorless crystals, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3360 (NH), 1720 (C=O), 1600, 1520, 1500 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 4.15 s (3H, OCH$_3$), 5.35 s (2H, OCH$_2$), 6.50 s (1H, H^4), 6.91 d (2H$_{arom}$, *J* 8.5 Hz), 7.36–7.02 m (5H$_{arom}$), 7.76 d (2H$_{arom}$, *J* 8.5 Hz), 9.56 s (1H, NH), 9.79 s (1H, NH). Found, %: C 66.64; H 4.96; N 13.07. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.87; H 5.26; N 13.00.

[3-(3,4-Dimethoxyphenyl)-1*H*-pyrazol-5-yl]-methyl *N*-phenylcarbamate (IIIc). Yield 1.3 g (51%), colorless crystals, mp 79–81°C. IR spectrum, ν, cm^{-1}: 3365 (NH), 1720 (C=O), 1610, 1525, 1500 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.81 s (3H, OCH$_3$), 3.92 s (3H, OCH$_3$), 5.37 s (2H, OCH$_2$), 6.48 s (1H, H^4), 6.95 d (1H$_{arom}$, *J* 8.5 Hz), 7.36–7.02 m (6H$_{arom}$), 7.86 d (1H$_{arom}$, *J* 8.5 Hz), 9.54 s (1H, NH), 9.79 s (1H, NH). Found, %: C 64.63; H 5.12; N 12.05. $C_{19}H_{19}N_3O_4$. Calculated, %: C 64.59; H 5.38; N 11.90.

[3-(4-Nitrophenyl)-1*H*-pyrazol-5-yl]methyl *N*-phenylcarbamate (IIId). Yield 0.55 g (22%), light yellow crystals, mp 159–160°C. IR spectrum, ν, cm^{-1}: 3360 (NH), 1725 (C=O), 1605, 1520, 1500 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 5.37 s (2H, OCH$_2$), 6.53 s (1H, H^4), 7.37–7.02 m (5H$_{arom}$), 7.81 d (2H$_{arom}$, *J* 8.6 Hz), 8.38 d (2H$_{arom}$, *J* 8.6 Hz), 9.55 s (1H, NH), 9.79 s (1H, NH). Found, %: C 60.23; H 3.97; N 16.61. $C_{17}H_{14}N_4O_4$. Calculated, %: C 60.36; H 4.14; N 16.57.

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