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Synthesis of New Spiro Compounds Containing a Carbamate Group

A. V. Velikorodov, O. Yu. Poddubnyi, A. K. Kuanchalieva, and O. O. Krivosheev

Astrakhan State University, pl. Shaumyana 1, Astrakhan, 414000 Russia
e-mail: avelikorodov@mail.ru

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Abstract—1,3-Dipolar cycloaddition to methyl 4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-1-oxoethyl]-phenylcarbamate of diazomethane in chloroform–diethyl ether and of 3,4-dimethoxybenzonitrile oxide generated from the corresponding aldehyde oxime by the action of *N*-chlorobenzenesulfonamide sodium salt (Chloramine B) in boiling ethanol gave, respectively, methyl 4-(2-oxo-1′,5′-dihydro-1*H*-spiro[indole-3,4′-pyrazol]-3′-ylcarbonyl)phenylcarbamate and methyl 4-[3′-(3,4-dimethoxyphenyl)-2-oxo-1*H*,4′*H*-spiro[indole-3,5′-isoxazol]-4′-ylcarbonyl]phenylcarbamate. The condensation of methyl 4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-1-oxoethyl]phenylcarbamate with hydrazine hydrate in ethanol afforded methyl 4-(2-oxo-1,2,2′,4′-tetrahydrospiro[indole-3,3′-pyrazol]-5′-yl)phenylcarbamate.

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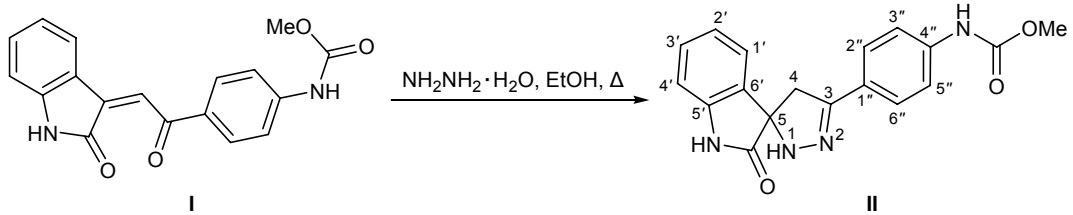
Unsaturated ketones are widely used in the synthesis of various heterocyclic compounds [1]. With a view to obtain new biologically active compounds possessing a carbamate functionality in the present work we examined reactions of methyl 4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)-1-oxoethyl]phenylcarbamate (**I**) with diazomethane, 3,4-dimethoxybenzonitrile oxide, and hydrazine hydrate. Compound **I** was prepared by the Knoevenagel condensation of indole-2,3-dione with methyl (4-acetylphenyl)carbamate in the presence of diethylamine in anhydrous ethanol, followed by dehydration of the condensation product on heating in glacial acetic acid in the presence of concentrated hydrochloric acid.

cis Isomers of chalcones are generally less stable than their *trans* isomers, and they readily undergo isomerization, e.g., by the action of nucleophiles [2, 3]. Unlike α,β-unsaturated aldehydes, *s-cis* conformer of chalcones predominates, and the energy barrier to the conformational isomerization *s-cis* → *s-trans* is 20–40 kJ/mol [4].

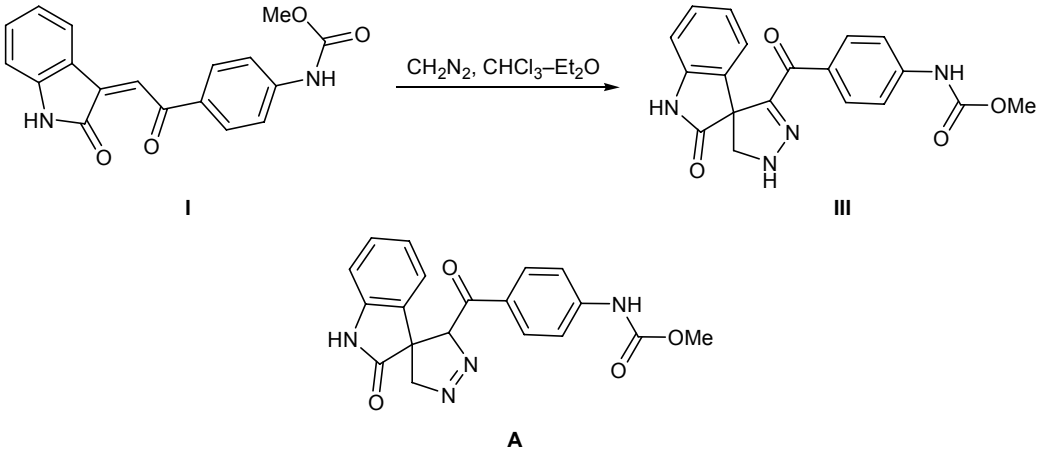
Condensations of chalcones with various 1,2-binucleophiles (such as hydrazine and hydroxylamine derivatives) underlie an important synthetic approach to five-membered heterocyclic compounds [5–9]. The condensation of compound **I** with hydrazine hydrate was carried out by heating equimolar amounts of the reactants in boiling anhydrous ethanol over a period of 1 h. The product structure was determined on the basis of its IR and ^{1}H and ^{13}C NMR spectra; it was identified as methyl 4-(2-oxo-1,2,2′,4′-tetrahydrospiro[indole-3,3′-pyrazol]-5′-yl)phenylcarbamate (**II**) (Scheme 1). The yield of **II** was 93%. The ^{1}H NMR spectrum of **II**, apart from other signals, contained two doublets belonging to two diastereotopic methylene protons 4-H$_A$ and 4-H$_B$ (δ 3.65 and 4.03 ppm, respectively). In the ^{13}C NMR spectrum of **II** we observed a signal from the pyrazole C=N carbon atom at δ_C 153.80 ppm, and the

Scheme 1.



I II

Scheme 2.



signal at δ_C 68.96 ppm was assigned to the spiro carbon atom, in keeping with published data [10]. Spiro compound **II** displayed a strong molecular ion peak in the mass spectrum (*m*/*z* 336). Obviously, the first step in the reaction of **I** with hydrazine is condensation at the chalcone carbonyl group, and the second step is intramolecular cyclization via addition of the second nucleophilic center at the C=C bond [11].

Chalcones having a strongly polarized double C=C bond are capable of participating in 1,3-dipolar cycloaddition reactions. Reactions of various chalcone derivatives with diazomethane were studied previously [12–17], but the available data concerning the product structure still remain contradictory [18, 19].

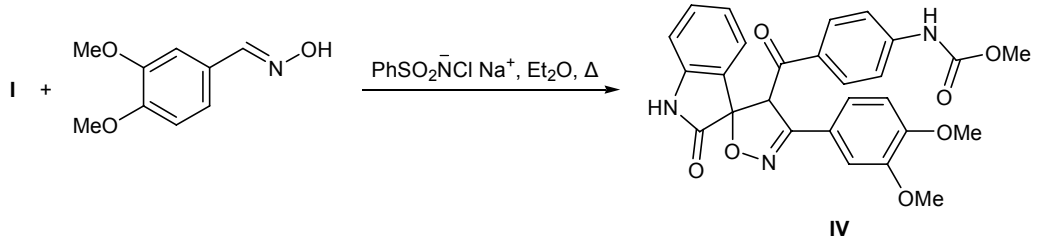
We examined the reaction of compound **I** with diazomethane in chloroform–diethyl ether, and the product structure was studied by IR and ^{1}H and ^{13}C NMR spectroscopy. The results showed that 1,3-dipolar cycloaddition of diazomethane to compound **I** leads to the formation of methyl 4-(2-oxo-1′,5′-dihydro-1*H*-spiro[indole-3,4′-pyrazol]-3′-ylcarbonyl)phenylcarbamate (**III**) (Scheme 2). In the ^{13}C NMR spectrum of **III**, the spiro carbon atom ($C^{4'}$) resonated at δ_C 81.10 ppm), and the signal from the sp^3-hybridized C^5 atom in the pyrazole ring appeared at δ_C 45.22 ppm. Presumably, the process involves intermediate formation of spiro-fused pyrazole **A** which undergoes tautomerization into compound **III**.

Cycloaddition of benzonitrile oxides to α,β-unsaturated ketones was studied fairly poorly. Azizian et al. [20] reported on regioselective cycloaddition of ethoxycarbonylformonitrile oxide to 3-(2-aryl-2-oxoethylidene)indol-2-ones with formation of spiro oxyindoles, the fraction of one regioisomer not exceeding 3%. Highly regioselective cycloaddition of 3,4-dimethoxybenzonitrile oxide (generated from 3,4-dimethoxybenzaldehyde oxime by the action of Chloramine T) to 3[(*E*)-2-oxophenylethylidene]indol-2-one was also described [21].

We performed 1,3-dipolar cycloaddition of 3,4-dimethoxybenzonitrile oxide (generated *in situ* from 3,4-dimethoxybenzaldehyde oxime by the action of *N*-chlorobenzenesulfonamide sodium salt trihydrate) to compound **I** on heating in boiling ethanol over a period of 3 h. The reaction was completely regioselective, and the product was methyl 4-[3′-(3,4-dimethoxyphenyl)-2-oxo-1*H*,4′*H*-spiro[indole-3,5′-isoxazol]-4′-ylcarbonyl]phenylcarbamate (**IV**) which was isolated in 35% yield (Scheme 3).

The structure of compound **IV** was confirmed by the IR, ^{1}H NMR, and mass spectra. The position of signals in the ^{1}H NMR spectrum of **IV** is consistent

Scheme 3.



with the data reported in [20, 21]. Our attempts to perform reactions of compound **I** with oximes having electron-withdrawing substituents, as well as with *p*-methoxybenzaldehyde oxime, were unsuccessful, presumably because of reduced reactivity of the corresponding benzonitrile oxides generated *in situ*.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-500 spectrometer (500.13 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The ^{13}C NMR spectra were measured with complete decoupling from protons on a Bruker DRX 500 spectrometer at 126 MHz from solutions in the same solvent. The IR spectra (4000–400 cm^{-1}) were recorded in KBr on a Specord M82 instrument. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS 50 spectrometer. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates.

Methyl 4-(2-oxo-1,2,2′,4′-tetrahydrospiro[indole-3,3′-pyrazol]-5′-yl)phenylcarbamate (II). A mixture of 3.22 g (10 mmol) of compound **I** and 0.356 g (11 mmol) of 99% hydrazine hydrate in 20 ml of anhydrous ethanol was heated for 1 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed on a filter with 10 ml of cold anhydrous ethanol and 5 ml of diethyl ether, and recrystallized from dioxane. Yield 3.2 g (95%), colorless crystals, mp 255–257°C. IR spectrum, ν, cm^{-1}: 3340–3400 (NH); 1740, 1680 (C=O); 1620, 1580, 1565 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.65 d (4-H$_A$, J = 11.0 Hz), 3.71 s (3H, OMe), 4.03 d (4-H$_B$, J = 11.0 Hz), 7.03–7.17 m (3H, H$_{arom}$), 7.24 d (2H, H$_{arom}$, J = 8.2 Hz), 7.42 d (1H, H$_{arom}$, J = 7.6 Hz), 7.93 d (2H, H$_{arom}$, J = 8.2 Hz), 8.820 s (1H, NH, pyrazole), 9.54 br.s (1H, NHCO), 10.72 br.s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 43.75 (C^4), 51.60 (OMe), 68.96 (C^5), 109.50 (C$^{5'}$), 117.84 (C$^{3''}$, C$^{5''}$), 122.05 (C$^{3'}$), 123.50 (C$^{2'}$), 126.27 (C$^{4'}$), 126.74 (C$^{1''}$), 128.97 (C$^{1'}$), 132.24 (C$^{2''}$, C$^{6''}$), 139.24 (C$^{4''}$), 141.36 (C$^{6'}$), 147.23 (**C**O$_2$Me), 153.80 (C=N), 178.61 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 336 (66.7) $[M]^+$, 308 (100) $[M - N_2]^+$, 276 (51.9), 247 (51.5), 204 (18.5), 192 (7.4), 178 (7.8), 157 (14.8), 146 (22.2), 130 (31.0), 117 (19.3), 104 (16.7), 90 (22.2), 77 (23.7). Found, %: C 64.09; H 4.77; N 16.48. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.29; H 4.76; N 16.67.

Methyl 4-(2-oxo-1′,5′-dihydro-1*H*-spiro[indole-3,4′-pyrazol]-3′-ylcarbonyl)phenylcarbamate (III). A solution of diazomethane (prepared from 2 g of nitrosomethylurea and 6 ml of 40% potassium hydroxide) in 40 ml of diethyl ether was added to a cold solution of 1.61 g (5 mmol) of compound **I** in 35 ml of chloroform [20]. The mixture was kept for 8 h at 0°C, and the precipitate was filtered off, washed on a filter with diethyl ether (15 ml), dried in air, and purified by column chromatography on silica gel (100–400 μm) using methylene chloride as eluent. Yield 1.7 g (95%), colorless crystals, mp 152–154°C. IR spectrum, ν, cm^{-1}: 3330–3410 (NH); 1720, 1680 (C=O); 1620, 1575, 1560 (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.71 s (3H, OMe), 4.84 d and 4.97 d (1H each, CH$_2$, J = 10.0 Hz), 7.07–7.47 m (6H, H$_{arom}$), 8.31 d (2H, H$_{arom}$, J = 8.5 Hz), 9.54 br.s (1H, NHCO), 10.75 s (1H, NH, pyrazole), 11.53 br.s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 45.22 (C^5), 51.86 (OMe), 81.10 (C^4), 109.57 (C$^{4'}$), 117.55 (C$^{3''}$, C$^{5''}$), 119.95 (C$^{2'}$), 121.29 (C$^{1'}$), 126.38 (C$^{6'}$), 127.39 (C$^{1'}$), 130.10 (C$^{3'}$), 132.51 (C$^{2''}$, C$^{6''}$), 135.70 (C$^{1''}$), 142.29 (C$^{5'}$), 145.25 (C=N), 153.77 (NHCO), 175.35 (C=O), 196.20 (3′-C=O). Found, %: C 62.45; H 4.46; N 15.27. $C_{19}H_{16}N_4O_4$. Calculated, %: C 62.64; H 4.40; N 15.39.

Methyl 4-[3′-(3,4-dimethoxyphenyl)-2-oxo-1*H*,4′*H*-spiro[indole-3,5′-isoxazol]-4′-ylcarbonyl]-phenylcarbamate (IV). A mixture of 1.13 g (3.5 mmol) of compound **I**, 0.63 g (3.5 mmol) of 3,4-dimethoxybenzaldehyde oxime, and 1.2 g (4.5 mmol) of Chloramine **B** trihydrate in 25 ml of ethanol was heated for 3 h under reflux. The precipitate was filtered off, the solvent was distilled off from the filtrate under reduced pressure, the residue was treated with diethyl ether (3×15 ml), the ether solution was washed with a 1 N solution of sodium hydroxide (50 ml) and water (50 ml), and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was recrystallized from methanol to obtain 0.6 g (35%) of spiro compound **IV**. Colorless crystals, mp 199–201°C. IR spectrum, ν, cm^{-1}: 3340–3410 (NH); 1720, 1690 (C=O); 1610, 1575, 1560 (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.70 s (3H, NHCOO**Me**), 3.78 s (3H, OMe), 3.79 s (3H, OMe), 6.21 s (1H, 4-H), 6.73 d (1H, 6‴-H, J = 7.9 Hz), 6.97 s (1H, 2‴-H), 7.12 t (2H, 5′-H, 6′-H, J = 7.4 Hz), 7.32 d (1H, 5″-H, J = 8.6 Hz), 7.42 d (1H, H$_{arom}$, J = 7.6 Hz), 7.44 d (1H, 4′-H, J = 7.6 Hz), 7.66 d (1H, 7′-H, J = 7.8 Hz), 7.95 d (1H, 2″-H, J = 7.9 Hz), 8.06 d (2H, 2″-H, 6″-H, J = 8.6 Hz), 10.03 br.s (1H, NHCO), 10.78 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 501 (3.3) $[M]^+$, 322 (38.3), 294 (100), 262 (30), 234 (24.7),

207 (4.2), 178 (70), 146 (66.7), 116 (28.3), 90 (15.0), 77 (18.3). Found, %: C 64.58; H 4.63; N 8.30. $C_{27}H_{23}N_3O_7$. Calculated, %: C 64.67; H 4.59; N 8.38.

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