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Synthesis of 2,5-Diaryl-1,3-oxazoles Containing a Carbamate Group

A. V. Velikorodov,* E. A. Shustova, and S. B. Nosachev

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

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Abstract—Acetophenones containing a methoxycarbonylamino group in position *2*, *3*, or *4* of the aromatic ring reacted with phenylglycine in the presence of 2 equiv of iodine and 0.5 equiv of sulfanilic acid in DMSO at 100°C for 6 h to give methyl [2(3,4)-(2-phenyl-1,3-oxazol-5-yl)phenyl]carbamates. The reaction was presumed to involve intermediate formation of methyl [(iodoacetyl)phenyl]carbamate. This was confirmed by the isolation of methyl [2-(iodoacetyl)phenyl]carbamate in the reaction of methyl (2-acetylphenyl)carbamate with iodine in glacial acetic acid and its subsequent transformation to methyl [2-(2-phenyl-1,3-oxazol-5-yl)-phenyl]carbamate.

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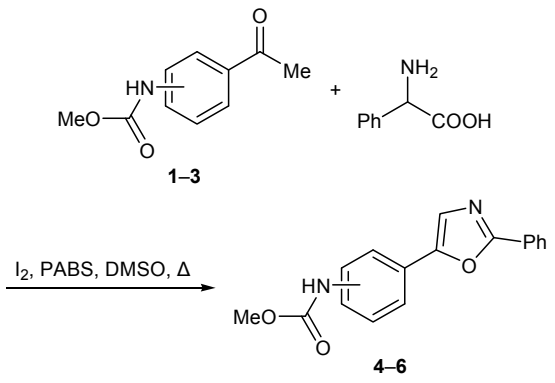
1,3-Oxazoles constitute a class of heterocycles that attract interest [1, 2] since 1,3-oxazole ring is a structural fragment of a number of natural compounds, pharmaceuticals, and other biologically active compounds [3–5]. Diazonamide and phorboxazole are biologically active natural compounds containing an oxazole ring, which exhibit anticarcinogenic activity [6, 7]. Furthermore, corrosion inhibitors [8], fluorescent dyes [9], and chiral ligands widely used in asymmetric synthesis [10, 11] were found among 1,3-oxazole derivatives.

In the series of functionally substituted 1,3-oxazoles, of particular interest are 2,5-disubstituted derivatives which can be obtained by intramolecular oxidative cyclization of *N*-styrylbenzamides by the action of $PhI(OTf)_2$ generated *in situ* [12], ring expansion of ketoaziridines in the presence of *N*,*N*′-dicyclohexylcarbodiimide and iodine in boiling acetonitrile [13], mild one-pot synthesis from styrenes and benzylamines in the presence of *t*-BuOOH–I_2 [14], iodine-catalyzed tandem oxidative cyclization of condensation products of various aromatic aldehydes and 2-amino-1-phenylethanone hydrochloride [15], and by reaction of primary aromatic amides with 2,3-dibromopropene in DMSO in the presence of Cs_2CO_3 [16].

Hu et al. [17] recently proposed a procedure for the synthesis of 2,5-disubstituted 1,3-oxazoles from aryl ketones and 2-amino-2-arylacetic acids in DMSO in the presence of iodine and sulfanilic acid (PABS). With the goal of estimating the scope of this method, we studied analogous reactions of methyl (acetylphenyl)-carbamates **1**–**3** with phenylglycine. The optimal conditions included the use of 2 equiv of iodine and 0.5 equiv of sulfanilic acid, temperature 100°C, and reaction time 6 h.

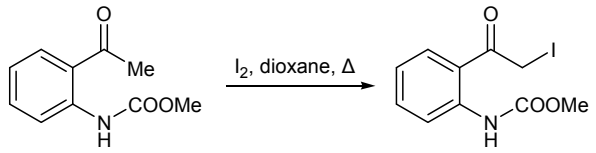
On the basis of IR, ^{1}H NMR, and mass spectral data, the isolated products were identified as methyl [2(3,4)-(2-phenyl-1,3-oxazol-5-yl)phenyl]carbamates **4**–**6**; their yields were 75–85% (Scheme 1). The ^{1}H NMR spectra of **4**–**6** contained signals from protons of the methoxy and NH groups, aromatic proton signals, and a one-proton singlet at δ 7.49–7.80 ppm which was assigned to 4-H of the oxazole ring [17].

Scheme 1.



The reaction is likely to involve intermediate formation of the corresponding iodoacetyl derivatives. This was confirmed by the isolation of methyl [2-(iodoacetyl)phenyl]carbamate (**7**) in the reaction of methyl (2-acetylphenyl)carbamate (**3**) with iodine on heating in glacial acetic acid (Scheme 2). As expected, carbamate **7** reacted with phenylglycine in the presence of 1 equiv of iodine and 0.5 equiv of sulfanlic acid to give 76% of methyl [2-(2-phenyl-1,3-oxazol-5-yl)phenyl]carbamate (**6**).

Scheme 2.



3 **7**

It is known that iodoacetophenones are oxidized to arylglyoxals **A** by the action of DMSO [18]. The condensation of intermediate **A** with phenylglycine yields Schiff base **B** which isomerizes to intermediate **C** through [1,5]-H shift. Presumably, sulfanilic acid accelerates the reaction via coordination to the imino nitrogen atom, which increases the electrophilicity of the C^1 atom in **C** thus favoring ring closure with formation of intermediate **D**. The latter undergoes oxidative decarboxylation with iodine to afford final methyl [2(3,4)-(2-phenyl-1,3-oxazol-5-yl)phenyl]-carbamates **4**–**6** (Scheme 3).

EXPERIMENTAL

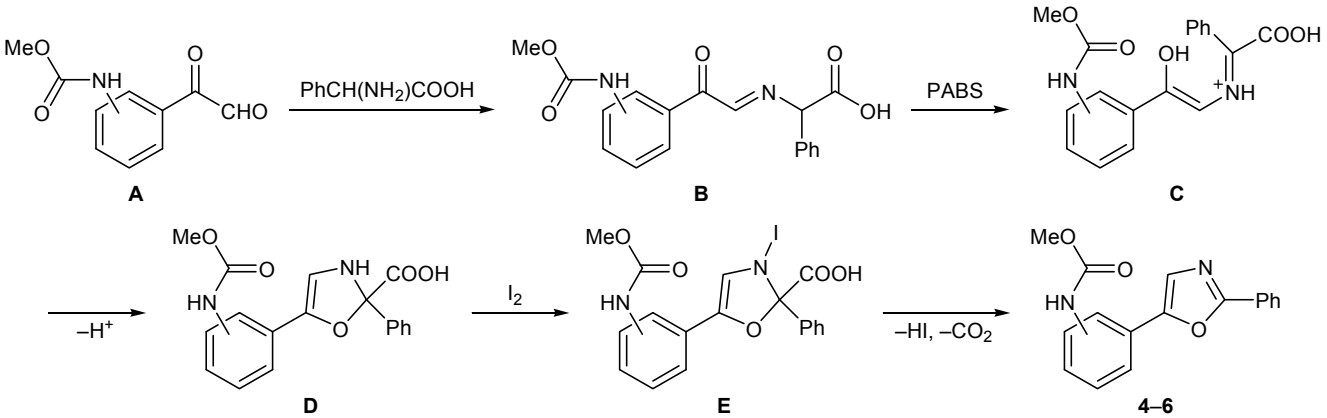
The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The IR spectra (4000–400 cm^{-1}) were measured on an InfraLUM FT-02 spectrometer with Fourier transform from KBr discs or thin films. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS 50 instrument. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

Methyl [4-(2-phenyl-1,3-oxazol-5-yl)phenyl]-carbamate (4). A mixture of 0.07 g (0.38 mmol) of methyl (4-acetylphenyl)carbamate (**1**), 0.057 g (0.38 mmol) of phenylglycine, 0.19 g (0.76 mmol) of iodine, and 0.03 g (0.19 mmol) of sulfanilic acid in 2 mL of DMSO was stirred for 6 h at 100°C. The mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with brine (5 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on activated silica gel (100–400 μm) using ethyl acetate–petroleum ether (1 : 1) as eluent. Yield 0.08 g (75%), off-white crystals, mp 115–117°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1710 (C=O), 1610, 1575, 1565 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 6.93 d (2H, H$_{arom}$, J = 8.6 Hz), 7.22 d (2H, H$_{arom}$, J = 8.6 Hz), 7.37–7.45 m (3H, H$_{arom}$), 7.49 s (1H, 4-H), 8.11 d (2H, H$_{arom}$, J = 7.9 Hz), 9.79 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 295 (1.5) $[M + 1]^+$, 294 (7.7) $[M]^+$, 281 (3), 262 (3), 193 (40), 179 (7.7), 178 (100), 162 (1.5), 146 (37), 135 (3), 118 (3), 106 (4.6), 91 (9), 77 (9). Found, %: C 69.14; H 4.55; N 9.44. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.39; H 4.76; N 9.52.

Compounds **5** and **6** were synthesized in a similar way.

Methyl [3-(2-phenyl-1,3-oxazol-5-yl)phenyl]-carbamate (5). Yield 0.09 g (85%), yellow crystals, mp 179–181°C. IR spectrum, ν, cm^{-1}: 3335 (NH),

Scheme 3.



A **B** **C** **D** **E** **4–6**

1720 (C=O), 1610, 1570, 1568 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 7.38–7.50 m (3H, H_{arom}), 7.53–7.60 m (3H, H_{arom}), 7.79 s (1H, 4-H), 7.99 s (1H, H_{arom}), 8.12 d (2H, H_{arom}, J = 7.9 Hz), 9.83 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 295 (33.8) $[M + 1]^+$, 294 (100) $[M]^+$, 262 (36), 235 (17), 224 (6.7), 208 (5), 194 (1), 180 (7.7), 165 (5), 146 (1), 135 (1), 116 (5), 106 (4), 91 (2.7), 77 (12). Found, %: C 69.23; H 4.81; N 9.38. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.39; H 4.76; N 9.52.

Methyl [2-(2-phenyl-1,3-oxazol-5-yl)phenyl]carbamate (6). Yield 0.08 g (75%), light yellow oil, n_D^{20} = 1.4600. IR spectrum, ν, cm^{-1}: 3340 (NH), 1715 (C=O), 1610, 1570, 1565 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 7.21 d (1H, H_{arom}, J = 7.9 Hz), 7.32–7.46 m (5H, H_{arom}), 7.73 s (1H, H_{arom}), 7.80 s (1H, 4-H), 8.11 d (2H, H_{arom}, J = 7.8 Hz), 9.81 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 295 (2) $[M + 1]^+$, 294 (5.6) $[M]^+$, 262 (24), 248 (22), 236 (2.8), 223 (59), 208 (11.5), 195 (1), 178 (14), 164 (2.8), 146 (100), 119 (8), 106 (3), 90 (22), 78 (8). Found, %: C 69.30; H 4.65; N 9.28. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.39; H 4.76; N 9.52.

Methyl [2-(2-iodoacetyl)phenyl]carbamate (7). A mixture of 0.193 g (1 mmol) of methyl (2-acetylphenyl)carbamate (**3**) and 0.254 g (1 mmol) of iodine in 5 mL of glacial acetic acid was heated for 7 h at 70°C. The mixture was cooled and poured into 50 mL of ice water, and the precipitate was filtered off, washed with water (50 mL), dried in air, and recrystallized from chloroform. Yield 0.24 g (75%), yellow–brown crystals, mp 82–85°C. IR spectrum, ν, cm^{-1}: 3335 (NH), 1720, 1665 (C=O), 1610, 1568, 1565 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 4.05 s (2H, CH_2I), 7.32 t (1H, H_{arom}, J = 7.8 Hz), 7.62 t (1H, H_{arom}, J = 7.8 Hz), 8.01 d (1H, H_{arom}, J = 7.8 Hz), 8.87 d (1H, H_{arom}, J = 7.8 Hz), 9.85 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 320 (3) $[M + 1]^+$, 319 (20) $[M]^+$, 254 (12), 193 (100), 178 (15), 161 (3), 146 (17), 132 (100), 116 (1.5), 106 (1), 77 (1). Found, %: C 37.58; H 3.04; N 4.18. $C_{10}H_{10}INO_3$. Calculated, %: C 37.62; H 3.14; N 4.39.

Compound **6** was also synthesized by heating a mixture of 0.06 g (0.2 mmol) of compound **7**, 0.03 g (0.2 mmol) of phenylglycine, 0.05 g (0.2 mmol) of iodine, and 0.017 g (0.1 mmol) of sulfanilic acid in 2 mL of DMSO for 5 h at 100°C with stirring. The mixture was then cooled to room temperature and treated as described above in the synthesis of **4**. Yield 0.07 g (76%), light yellow oil, n_D^{20} = 1.4600. Found, %: C 69.02; H 4.64; N 9.39. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.39; H 4.76; N 9.52.

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