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SYNTHESIS AND FUNCTIONALIZATION OF THE 3-(1,3,4-OXADIAZOL-2-YL)-1H-INDOLES

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A modified method is proposed for the preparative synthesis of 3-(1,3,4-oxadiazol-2-yl)-1H-indoles in high yield. We are the first to demonstrate the functionalization of this heterocyclic system by alkylation. In particular, syntheses are reported for [3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic acids and their amide derivatives.

Keywords: 3-(1,3,4-oxadiazol-2-yl)-1H-indoles, [3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic acids, orthoesters, amide library, intramolecular cyclization.

Compounds containing an indole fragment have a broad spectrum of biological activity. This is also characteristic for indoles containing heterocyclic substituents at C-3. In particular, such compounds include fungicides [1], compounds serving as models of recognition segments on brain cell membranes [2], and a whole series of enzyme inhibitors [3-6]. Hence, the synthesis of new indole derivatives and the study of their biological activity have found considerable present interest.

In this study, we investigated previously unreported amides of [3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic acids, which hold potential biological activity.

The key compounds in our work were 3-(1,3,4-oxadiazol-2-yl)-1H-indoles **1**. Although several methods have been reported for the synthesis of such compounds [7-9], none of these methods are suitable for preparative synthesis for a number of reasons. In particular, the approach of Kelarev and Shvekhgeimer [7] for the synthesis of **1a** using triethyl orthoformate **2a** gave good results for charges of hydrazide **3** of about 1 g. In attempts to scale up this procedure, considerable amounts of side-product **4** as well as products **5** and **6** were formed. The two-step procedure of Monge et al. [8] involves the acylation of hydrazide **3** with subsequent cyclization of the corresponding acyl derivatives with $POCl_3$. However, product **1a** obtained by this method requires further purification. The relative low yield of desired product **1b** is a drawback to the method described by Karakhanov et al. [9].

The basis of our method is a procedure described by Kelarev [7]. Indole **5** was the only product if the mixture of hydrazide **3** and orthoester **2** was not heated at reflux, as described by Kelarev [7], but rather maintained at about 90°C with rapid stirring. Indoles **5** are obtained as mixtures of *E*- and *Z*-isomers, which were not isolated as pure compounds. Table 1 gives the ^{1}H NMR spectral data for indoles **5** from the spectra of the mixtures and the isomer ratio in the mixtures.

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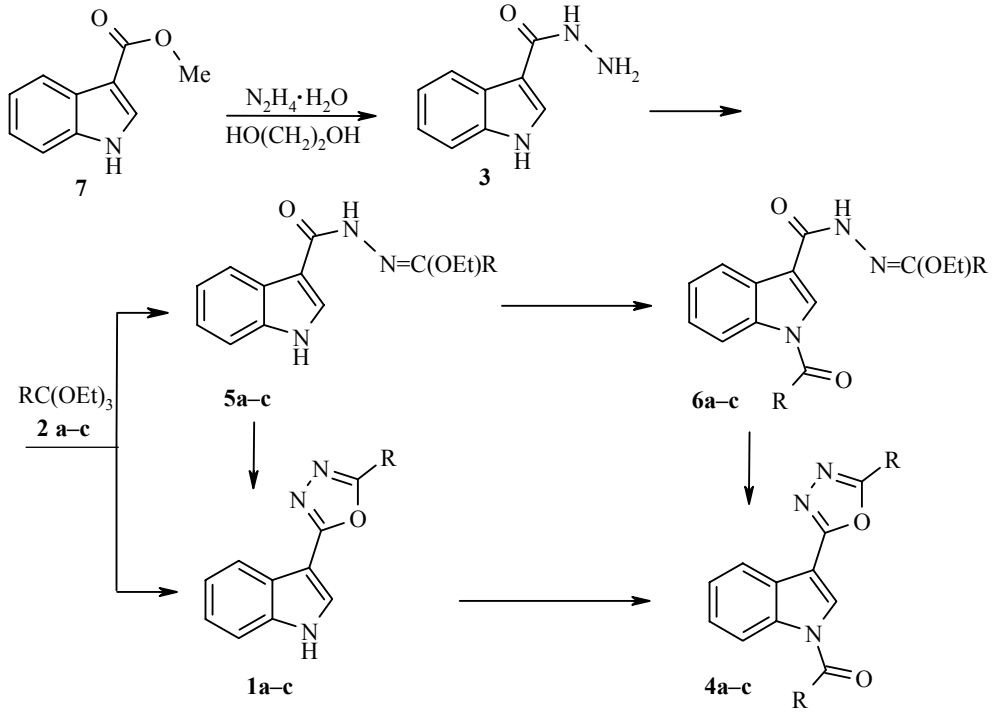
TABLE 1. ^{1}H NMR Spectra and Ratio* of Indoles **5a-c**

Assignment		Chemical shifts, δ, ppm					
		Z-**5a**	*E*-**5a**	*Z*-**5b**	*E*-**5b**	*Z*-**5c**	*E*-**5c**
1H	H-1	11.65	11.55	11.67	11.54	11.72	11.58
1H	NH (am)	9.55	10.45	9.60	10.47	9.55	10.45
1H	H-2	8.04	8.38	8.02	8.40	8.04	8.41
4H	Ar	7.14-8.12	7.14-8.12	7.18-8.15	7.18-8.15	7.19-8.10	7.19-8.10
2H	OCH_2	4.16	4.18	4.17	4.19	4.16	4.18
3H	CH_3	1.29	1.32	1.28	1.33	1.31	1.36
1H	(R)	6.93	8.23	—	—	—	—
2H	CH_2 (R)	—	—	—	—	2.88	3.07
3H	CH_3 (R)	—	—	2.42	2.73	1.30	1.37

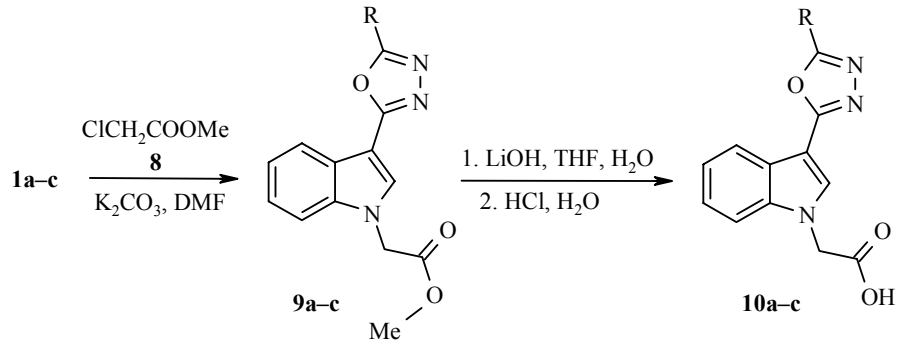
* Content in mixture: *Z*-**5a** **:** *E*-**5a** = 44:56; *Z*-**5b** **:** *E*-**5b** = 41 : 59; *Z*-**5c** **:** *E*-**5c** = 48 : 52.

Indoles **5** are clearly intermediates in the synthesis of indoles **1**. The cyclization of these indoles requires heating at about 130-140°C but competing reactions begin to take place at this temperature in a medium of orthoesters **2a-c**, which significantly lowers the yield of the desired products **1**. The intramolecular cyclization of previously isolated indoles **5** to give indoles **1** proved possible at 90°C in DMF. The reaction proceeds in quantitative yield. The melting point found for indole **1b** differs significantly from the value given by Kelarev [7].



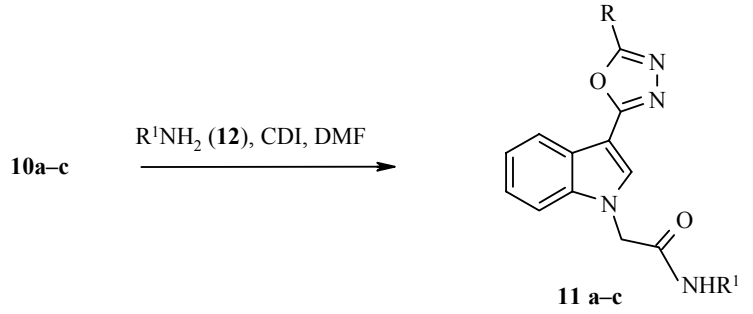
a R = H, **b** R = Me, **c** R = Et

The methods described for the preparation of N-alkyl derivatives of 3-(1,3,4-oxadiazol-2-yl)-1H-indoles [10-12] involve the alkylation of the indole system in the initial steps of a synthetic sequence. We have demonstrated the feasibility of alkylating 3-(1,3,4-oxadiazol-2-yl)-1H-indoles using methyl chloroacetate **8** in high yield. The structure of the N-alkylated esters **9** was indicated by NMR spectroscopy and LC/MS.



1, **9, 10 a** R = H, **b** R = Me, **c** R = Et

Esters **9a-c** are converted in high yield under mild conditions into the corresponding acids **10a-c**. The hydrolysis was carried out in THF-water with lithium hydroxide as the base. A library of amides **11** was obtained from acids **10a-c** by means of liquid-phase parallel combinatorial synthesis using both primary and secondary aliphatic, aromatic, and heterocyclic amines. Representative amides **11** are given in the Experimental.



11 a R = H, R^1 = 2-Bu, **b** R = Me, R^1 = cyclopentyl, **c** R = Et; R^1 = 2-furylmethyl,
CDI – carbonyldiimidazole

Our studies have led to better methods for preparing 3-(1,3,4-oxadiazol-2-yl)-1H-indoles **1**. Feasibility was demonstrated for functionalization of indoles **1** by means of alkylation and a whole series of previously unreported derivatives **1c, 9a-c,** and **10a-c** was obtained. A library of amides **11** with potential biological activity was obtained by methods of classical organic chemistry under conditions of parallel combinatorial synthesis.

EXPERIMENTAL

The melting points were obtained on a Buchi B-520 instrument. The NMR spectra were taken on a Bruker DPX-400 spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The LC/MS spectra were obtained using the Shimadzu Analytical 10Avp system with a Gilson 215 autosampler, Sedex 75 ELSD (evaporating light scattering detector), and PE SCIEX API 150 mass spectrometer.

3-(1,3,4-Oxadiazol-2-yl)-1H-indoles 1a-c (General Method). Hydrazide (0.5 mol) of 1H-indole-3-carboxylic acid (**3**) was suspended in triethyl orthoformate **2a** (or triethyl orthoacetate **2b** or triethyl orthopropionate **2c**) (4 mol). The heterogeneous reaction mixture was maintained with rapid stirring at 90°C for 5-7 h and cooled. Product **5** was filtered off and washed with cold ethanol and hexane. Isolated product **5** was used in the next step without further purification.

The suspension of compound **5** in DMF (150 ml) was stirred at 90° C for 3-4 h (monitored by TLC EtOH:$CHCl_3$ 5:95). The reaction mixture was cooled then diluted with water. Precipitate was collected with filtration and washed with water, cold ethanol, and hexane. Compounds **1a-c** were used for the following steps without further purification.

3-(1,3,4-Oxadiazol-2-yl)-1H-indole (1a) was obtained in 98% yield, mp 193-195°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 7.20-7.30 (2H, m, arom); 7.52-7.57 (1H, m, arom); 8.09-8.14 (1H, m, arom); 8.17 (1H, s, H-2); 9.15 (1H, s, CH oxadiazole); 11.96 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 186.21 $[M+H]^+$. Found, %: C 64.90; H 3.84; N 22.69. $C_{10}H_7N_3O$. Calculated, %: C 64.86; H 3.81; N 22.69.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)-1H-indole (1b) was obtained in 98% yield; mp 235-237°C (ethanol–DMF) (138-139°C [7]). ^{1}H NMR spectrum, δ, ppm: 2.56 (3H, s, CH_3); 7.19-7.29 (2H, m, arom); 7.50-7.56 (1H, m, arom); 8.05-8.15 (2H, s+m, arom + H-2); 11.93 (1H, br. s, NH). Mass spectrum, *m/z*: 200.22 $[M+H]^+$. Found, %: C 66.35; H 4.54; N 21.19. $C_{11}H_9N_3O$. Calculated, %: C 66.32; H 4.55; N 21.09.

3-(5-Ethyl-1,3,4-oxadiazol-2-yl)-1H-indole (1c) was obtained in 95% yield; mp 207-209°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.5, CH_3); 2.92 (2H, q, *J* = 7.5, CH_2); 7.19-7.29 (2H, m, arom); 7.50-7.55 (1H, m, arom); 8.07-8.10 (1H, m, arom); 8.11 (1H, s, H-2); 11.95 (1H, s, NH). Mass spectrum, *m/z*: 214.29 $[M+H]^+$. Found, %: C 65.62; H 5.18; N 19.79. $C_{12}H_{11}N_3O$. Calculated, %: C 65.59; H 5.20; N 19.71.

Methyl [3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-yl] Acetates 9a-c (General Method). Anhydrous potassium carbonate (0.24 mol) and methyl chloroacetate **8** (0.22 mol) were added to a solution of indole **1** (0.2 mol) in distilled DMF (120 ml). The reaction mixture was stirred vigorously for 3-4 h at 70°C with monitoring by thin-layer chromatography using Silufol UV-254 plates and 5% ethanol in chloroform as the eluent. Then, the mixture was cooled and poured into cold water. The precipitate formed was filtered off and washed with water and hexane. The resultant esters **9** were used in subsequent transformation without further purification.

Methyl [3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-yl] Acetate (9a) was obtained in 91% yield; mp 108-110°C (acetonitrile). ^{1}H NMR spectrum, δ, ppm: 3.71 (3H, s, OCH_3); 5.32 (2H, s, CH_2); 7.26-7.36 (2H, m, arom); 7.57-7.62 (1H, m, arom); 8.10-8.15 (1H, m, arom); 8.25 (1H, s, H-2); 9.20 (1H, s, oxadiazole). Mass spectrum, *m/z*: 258.26 $[M+H]^+$. Found, %: C 60.95; H 4.40; N 16.29. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

Methyl [3-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-yl] Acetate (9b) was obtained in 88% yield; mp 128-130°C (acetonitrile). ^{1}H NMR spectrum, δ, ppm: 2.57 (3H, s, CH_3); 3.71 (3H, s, OCH_3); 5.29 (2H, s, CH_2); 7.25-7.35 (2H, m, arom); 7.55-7.60 (1H, m, arom); 8.09-8.14 (1H, m, arom); 8.16 (1H, s, H-2). Mass spectrum, *m/z*: 272.33 $[M+H]^+$. Found, %: C 62.09; H 4.93; N 15.56. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.99; H 4.83; N 15.49.

Methyl [3-(5-ethyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-yl] Acetate (9c) was obtained in 92% yield; mp 97-99°C (isooctane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 2.93 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 3.70 (3H, s, OCH_3); 5.30 (2H, s, CH_2); 7.25-7.35 (2H, m, arom); 7.55-7.61 (1H, m, arom); 8.09-8.14 (1H, m, arom); 8.18 (1H, s, H-2). Mass spectrum, *m/z*: 286.31 $[M+H]^+$. Found, %: C 63.21; H 5.41; N 14.69. $C_{15}H_{15}N_3O_3$. Calculated, %: C 63.15; H 5.30; N 14.73.

[3-(1,3,4-Oxadiazol-2-yl)-1H-indol-1-yl]acetic Acids 10a-c (General Method). Lithium hydroxide (0.17 mol) dissolved in water (15 ml) was added to a solution of corresponding ester **9** (0.15 mol) in THF (150 ml). The reaction mixture was stirred at room temperature for 2-4 h with monitoring by thin-layer chromatography on Silufol UV-254 plates and 5% ethanol in chloroform as the eluent. Then, concentrated hydrochloric acid was added dropwise to bring the reaction mixture to pH 2-3. The precipitate formed was filtered off, washed with water, cold ethanol, and hexane, and dried in the air. The product may be used in subsequent transformations without further purification.

[3-(1,3,4-Oxadiazol-2-yl)-1H-indol-1-yl]acetic Acid (10a) was obtained in 90% yield; mp 211-213°C (ethanol-DMF); ^{1}H NMR spectrum, δ, ppm: 5.19 (2H, s, CH_2); 7.25-7.35 (2H, m, arom); 7.55-7.61 (1H, m, arom); 8.10-8.16 (1H, m, arom); 8.24 (1H, s, H-2); 9.19 (1H, s, oxadiazole); 13.20 (1H, br. s, $CO_2\underline{H}$). Mass spectrum, *m/z*: 244.24 $[M+H]^+$. Found, %: C 59.34; H 3.75; N 17.31. $C_{12}H_9N_3O_3$. Calculated, %: C 59.26; H 3.73; N 17.28.

[3-(5-Methyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic Acid (10b) was obtained in 95% yield; mp 229-231°C (ethanol-DMF). ^{1}H NMR spectrum, δ, ppm: 2.57 (3H, s, CH_3); 5.17 (2H, s, CH_2); 7.24-7.34 (2H, m, arom); 7.54-7.59 (1H, m, arom); 8.08-8.13 (1H, m, arom); 8.16 (1H, s, H-2); 13.22 (1H, br. s, $CO_2\underline{H}$). Mass spectrum, *m/z*: 258.30 $[M+H]^+$. Found, %: C 60.65; H 4.33; N 16.36. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

[3-(5-Ethyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic Acid (10c) was obtained in 84% yield; mp 194-196°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 2.93 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 5.17 (2H, s, CH_2); 7.24-7.34 (2H, m, arom); 7.53-7.59 (1H, m, arom); 8.07-8.13 (1H, m, arom); 8.17 (1H, s, H-2); 13.11 (1H, br. s, CO_2H). Mass spectrum, *m/z*: 272.28 $[M+H]^+$. Found, %: C 62.11; H 4.90; N 15.53. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.99; H 4.83; N 15.49.

Amides of [3-(5-ethyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-yl]acetic acids 11a-c (General Method). Carbonyldiimidazole (1.4 mmol) was added to a solution of corresponding acid **10** (1.2 mmol) in distilled DMF (5 ml) and the reaction mixture was stirred for 2 h at 80°C. Then, corresponding amine **12** (1.3 mmol) and stirred for an additional 3 h under the same conditions. After cooling, the reaction mixture was poured into 3% aqueous sodium bicarbonate. The precipitate formed was filtered off and the oily products were extracted with ethyl acetate. When necessary, the products were purified by crystallization from isooctane or acetonitrile or by chromatography on a column packed with silica gel 40/60 using 3:1 hexane–ethyl acetate as the eluent. In particular, amides **11a-11c** were obtained as oils.

N-(1-Methylpropyl)-3-(1,3,4-oxadiazol-2-yl)-1H-indol-1-ylacetamide (11a) was obtained in 63% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.3, CH_3); 1.09 (3H, d, *J* = 6.8, CH_3); 1.39-1.50 (2H, qd, *J* = 7.3, *J* = 6.8, CH_2); 3.64-3.76 (1H, m, CH); 4.91 (2H, s, CH_2CO); 7.22-7.32 (2H, m, arom); 7.43-7.50 (1H, m, arom); 8.06-8.17 (3H, m, arom+H-2+NH); 9.09 (1H, s, H-oxadiazole). Mass spectrum, *m/z*: 299.39 $[M+H]^+$. Found, %: C 64.45; H 6.19; N 18.83. $C_{16}H_{18}N_4O_2$. Calculated, %: C 64.41; H 6.08; N 18.78.

N-Cyclopentyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indol-1-ylacetamide (11b) was obtained in 78% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39-1.93 (8H, m, $(CH_2)_4$); 2.58 (3H, s, 5-CH_3); 3.96-4.09 (1H, m, CH); 4.87 (2H, s, CH_2); 7.20-7.31 (2H, m, arom); 7.42-7.49 (1H, m, arom); 8.02-8.05 (1H, m, arom); 8.13 (1H, s, H-2); 8.25 (1H, d, *J* = 5.6, NH). Mass spectrum, *m/z*: 325.44 $[M+H]^+$. Found, %: C 66.75; H 6.29; H 17.38. $C_{18}H_{20}N_4O_2$. Calculated, %: C 66.65; H 6.21; N 17.27.

3-(5-Ethyl-1,3,4-oxadiazol-2-yl)-N-(2-furanylmethyl)-1H-indol-1-ylacetamide (11c) was obtained in 74% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 7.5, CH_3); 2.94 (2H, q, *J* = 7.5, CH_2); 4.32 (2H, d, *J* = 5.5, $C\underline{H}_2NH$); 4.98 (2H, s, CH_2CO); 6.25 (1H, d, *J* = 3.0, H-3'); 6.27 (1H, dd, *J* = 3.0, *J* = 2.2, H-4'); 7.21-7.31 (2H, m, arom); 7.43-7.49 (1H, m, arom); 7.53 (1H, d, *J* = 2.2, H-5'); 8.07-8.13 (2H, m, arom + H-2); 8.73 (1H, t, *J* = 5.5, NH). Mass spectrum, *m/z*: 351.49 $[M+H]^+$. Found, %: C 65.22; H 5.24; N 16.05. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13; H 5.18; N 15.99.

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