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Synthesis and Some Transformations of 7-(Fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazole

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Abstract—*N*-Methylation of 5-nitro-1*H*-indazole in a KOH–DMSO system resulted in a mixture of 1-methyl-5(6)-nitroindazoles in a ratio of 1 : 2. Reduction of the isomers with tin in concentrated hydrochloric acid afforded pure 1-methyl-1*H*-indazole-6-amine. Condensation of the latter with furoyl chloride in 2-propanol yielded *N*-(1-methylindazol-6-yl)furan-2-carboxamide, treatment of which with an excess of P_2S_5 in anhydrous pyridine gave the corresponding carbothioamide. 7-(Fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazole was synthesized by Jacobson oxidation of *N*-(1-methylindazol-6-yl) furan-2-carbothioamide with potassium ferricyanide in an alkaline medium. Some transformations of 7-(fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*][1,3]-benzothiazole such as formylation and acylation were performed.

Keywords: 5-nitroindazole, oxidation, 1-methyl-1*H*-5(6)-nitroindazole, potassium ferricyanide, electrophilic substitution reactions, formylation, acylation

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Among the fields of heterocyclic chemistry, chemistry of bihetaryl compounds consisting of two hetero-aromatic fragments connected by a single bond has attracted considerable attention. These compounds are used as pharmaceuticals and pesticides. The mutual influence of heterocyclic fragments in bihetaryls both in terms of their structure and reactivity is an interesting and still insufficiently studied problem.

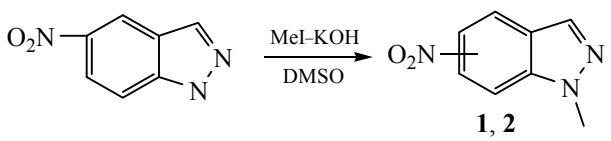
There is practically no information on the preparation and reactivity of thiazoles containing the furan fragment annelated with the indazole ring. At the same time, bisheterocyclic compounds of this type are of interest as potential biologically active substances [1, 2] and organic phosphors [3]. In this regard, of interest is to develop or select a convenient method of annelation of 2-(fur-2-yl)thiazole fragment to 1-methyl-1*H*-indazole. To this end, we tried to apply the Jacobson method of obtaining benzothiazoles [4] by cyclization of benzene thioamides in aqueous alkali medium in the presence of potassium ferricyanide.

Methylation of commercial 5-nitro-1*H*-indazole was successfully carried out in a KOH–DMSO system using an equivalent amount of methyl iodide. The yield of target compound was close to quantitative. Like the previously studied unsymmetrical heterocyclic systems [5], due to fast annular tautomerism of 1-methyl-1*H*-indazole a mixture of two *N*-methyl derivatives 5-nitro-1-methyl-1*H*- (**1**) and 6-nitro-1-methyl-1*H*-indazoles (**2**) were obtained in a 1 : 2 ratio (Scheme 1). It should be noted that the annulation of the thiazole ring to non-alkylated indazole did not proceed.

Unfortunately, nitro compounds **1** and **2** could not be separated due to a slight difference in their chromatographic mobility, however, each of the isomers in the mixture is easily identified by the ^{1}H NMR spectroscopy data (Tables 1, 2).

When compounds **1** and **2** were reduced with tin in concentrated hydrochloric acid followed by decomposition of the tin salt with KOH in 2-propanol, a mixture of 5(6)-amines was obtained, upon recrystallization of which from 2-propanol one pure isomer was unexpectedly isolated in 49% yield (Scheme 2).

Scheme 1.



1, **2**

Table 1. Melting points, elemental analysis data and yields of compounds **1**–**10**[a]

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
1+2	89	126–127	53.98	3.73	23.79	$C_8H_7N_3O_2$	54.24	3.98	23.72
3	49	117–118	65.47	6.23	28.39	$C_8H_9N_3$	65.29	6.16	28.55
4	78	176–177	64.93	4.47	17.19	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42
5	72	154–155	60.73	4.49	16.17	$C_{13}H_{11}N_3OS$	60.68	4.31	16.33
6	32	174–175	61.37	3.39	16.55	$C_{13}H_9N_3OS$	61.16	3.55	16.46
7	67	190–191	59.17	2.98	15.09	$C_{14}H_9N_3O_2S$	59.35	3.20	14.83
8	29	153–154	60.73	3.59	13.87	$C_{15}H_{11}N_3O_2S$	60.59	3.73	14.13
9	11	233–234	59.91	4.12	12.17	$C_{17}H_{13}N_3O_3S$	60.17	3.86	12.38
10	68	239–240	67.11	3.49	11.73	$C_{20}H_{13}N_3O_2S$	66.84	3.65	11.69

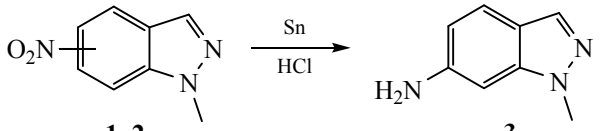
[a] The results of elemental analysis for the content of C, H and N correspond to the calculated values within ±0.34%.

Table 2. The IR and ^{1}H NMR spectral data for compounds **1**–**10**

Comp. no.	ν, cm^{-1}	δ, ppm (*J*, Hz)
1	1540 [$\nu_{as}(NO_2)$]	4.11 s (3H, NCH_3), 7.83 d (1H, H^7_{Ar}, *J* = 9.0), 8.21 d (1H, H^6_{Ar}, *J* = 9.0), 8.36 s (1H, $H^3_{pyrazole}$), 8.80 s (1H, H^4_{Ar})
2	1382 [$\nu_s(NO_2)$] 1540 [$\nu_{as}(NO_2)$],	4.23 s (3H, NCH_3), 7.74 d (1H, H^4_{Ar}, *J* = 9.0), 7.98 s (1H, H^7_{Ar}), 8.74 s (1H, $H^3_{pyrazole}$), 8.85 d (1H, H^5_{Ar}, *J* = 9.0)
3	1382 [$\nu_s(NO_2)$] 3376 [$\nu_{as}(NH_2)$],	3.69 s (3H, NCH_3), 6.59 s (2H, NH_2), 6.77 s (1H, H^7_{Ar}), 6.86 d (1H, H^5_{Ar}, *J* = 8.4), 7.38 d (1H, H^4_{Ar}, *J* = 8.4), 8.08 s (1H, $H^3_{pyrazole}$)
4	3203 [$\nu_s(NH_2)$]	4.07 s (3H, NCH_3), 6.69–6.70 m (1H, H^4_{furan}), 7.32 d (1H, H^3_{furan}, *J* = 3.6), 7.49 d (1H, H^5_{Ar}, *J* = 9.0), 7.65 s (1H, H^7_{Ar}), 7.77 d (1H, H^4_{Ar}, *J* = 9.0), 7.92 d (1H, H^5_{furan}, *J* = 1.2), 8.10 s (1H, $H^3_{pyrazole}$), 10.01 s (1H, NH)
5	1689 (C=O), 3263 (NH)	4.09 s (3H, NCH_3), 6.69–6.70 m (1H, H^4_{furan}), 7.38 d (1H, H^3_{furan}, *J* = 3.0), 7.49 d (1H, H^4_{Ar}, *J* = 9.0), 7.68 s (1H, H^7_{Ar}), 7.82 d (1H, H^4_{Ar}, *J* = 9.0), 7.99 d (1H, H^5_{furan}, *J* = 1.2), 8.13 s (1H, $H^3_{pyrazole}$), 11.52 s (1H, NH)
6	1235 (C=S), 3360 (NH)	4.14 s (3H, NCH_3), 6.76–6.78 m (1H, H^4_{furan}), 7.30 d (1H, H^3_{furan}, *J* = 3.3), 7.82 d (1H, H^4_{Ar}, *J* = 9.0), 7.99 d (1H, H^5_{furan}, *J* = 0.9), 8.01 d (1H, H^5_{Ar}, *J* = 9.0), 8.37 s (1H, $H^3_{pyrazole}$)
7	1658 s (C=O)	4.09 s (3H, NCH_3), 7.48 d (1H, H^5_{Ar}, *J* = 9.0), 7.54 d (1H, H^4_{furan}, *J* = 3.6), 7.68 d (1H, H^3_{furan}, *J* = 3.6), 7.69 d (1H, H^4_{Ar}, *J* = 9.0), 8.13 s (1H, $H^3_{pyrazole}$), 9.76 s (1H, CHO)
8	1678 s (C=O) 1639 s (C=O),	2.70 s (3H, CH_3), 4.10 s (3H, NCH_3), 7.46 d (1H, H^3_{furan}, *J* = 3.6), 7.58 d (1H, H^4_{furan}, *J* = 3.6), 7.86 d (1H, H^4_{Ar}, *J* = 8.9), 8.06 d (1H, H^5_{Ar}, *J* = 9.0), 8.29 s (1H, $H^3_{pyrazole}$)
9	1675 s (C=O)	2.49 s (3H, CH_3), 4.12 s (3H, NCH_3), 6.22 d (1H, H_α, *J* = 1.4), 6.80 d (1H, H_β, *J* = 2.2), 7.48 d (1H, H^3_{furan}, *J* = 3.6), 7.60 d (1H, H^4_{furan}, *J* = 3.6), 7.89 d (1H, H^4_{Ar}, *J* = 8.9), 8.09 d (1H, H^5_{Ar}, *J* = 9.0), 8.30 s (1H, $H^3_{pyrazole}$)
10	1685 s (C=O)	4.11 s (3H, NCH_3), 7.42 d (1H, H^3_{furan}, *J* = 3.8), 7.56 d (1H, H^4_{furan}, *J* = 3.8), 7.60 t (3H, $H^{3,4,5}_{Ar}$, *J* = 7.8), 7.84 d (1H, H^4_{Ar}, *J* = 9.0), 8.01 d (1H, H^5_{Ar}, *J* = 9.0), 8.14 d (1H, $H^{2,6}_{Ar}$, *J* = 7.8), 8.30 s (1H, $H^3_{pyrazole}$)

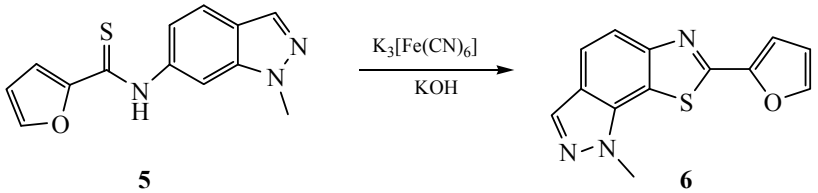
Apparently, the second isomer was too soluble in alcohol and therefore was lost. According to ^{1}H NMR data, 1-methyl-1*H*-indazole-6-amine **3** was isolated. In the ^{1}H NMR spectrum, the singlet signal of the H^7 proton of the aromatic ring was registered in a rather strong field at 6.81 ppm because of the effect of two electron donating groups NH_2 and NCH_3, while the analogous singlet of the H^4 proton deshielded by a

Scheme 2.



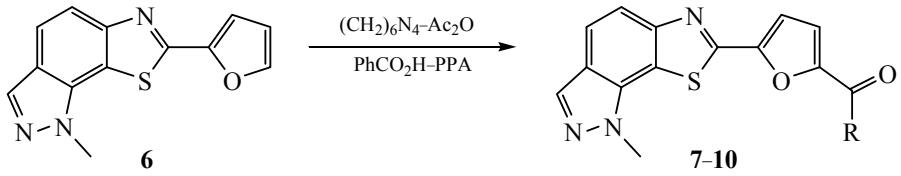
1, **2** **3**

Scheme 3.



5 **6**

Scheme 4.



6 **7**–**10**

R = H (**7**), Me (**8**), CH_2COMe (**9**), Ph (**10**).

pyridine nitrogen atom in the 5-amino derivative would be detected in a weaker field (Table 2).

Condensation of amine **3** with 2-furoyl chloride in 2-propanol gave *N*-(1-methyl-1*H*-indazol-6-yl)furan-2-carboxamide **4** in 78% yield, which when heated in anhydrous pyridine with an excess of phosphorus pentasulfide in 72% yield afforded 6-carbothioamide **5** (Scheme 3). Subsequent oxidation of compound **5** with a 20% aqueous solution of $K_3[Fe(CN)_6]$ furnished 7-(fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazole **6** with a yield of 32%.

In the ^{1}H NMR spectrum of compound **6**, the signals of the aromatic ring were registered not as singlets, which would confirm the 5,6-annelation of the thiazole ring to indazole, but as doublets of the H^4 and H^5 protons at 7.82 and 8.01 ppm with characteristic spin-spin coupling constant of 9.3 Hz. The assignment of the signals was made on the basis of the proton H^5 deshielding by the pyridine nitrogen of the thiazole ring. In addition, in the NMR spectrum of compound **6**, the singlet signal of the *N*-methyl group was observed at 4.14 ppm. Obviously, the upfield shift of the latter is due to the fact that it is more influenced by the thiazole ring.

This result indicates the 6,7-annelation of the 2-(fur-2-yl)thiazole fragment to 1-methyl-1*H*-indazole, which is apparently due to the influence of the steric factor on the spatial orientation of the *S*-substituent formed by oxidation with the complex ion.

Further, compound **6** was subjected to medium-strength electrophiles: urotropine in polyphosphoric acid (PPA), acetic anhydride and benzoic acid in PPA (Scheme 4).

Recently, the formyl group was introduced into the furan core of isomeric 1-methyl-2-(2-furyl)-1*H*-benzimidazole [6] by the action of urotropine in PPA. For compound **6**, this method was also successful. The yield of aldehyde **7** was 67%.

Taking into account the deactivating effect of the pyrazolobenzothiazole fragment on the reactivity of the furan ring, acetylation of compound **6** was achieved only by the action of acetic anhydride in the PPA medium at 110–120°C. The reaction proceeded non-selectively and was accompanied by the formation of a by-product, the amount of which increases with increasing temperature, and therefore methyl ketone **8** was obtained in a yield not exceeding 29%. According to ^{1}H NMR data, the by-product separated by column chromatography was diketone **9** formed as a result of the acetylation of the $COCH_3$ group in monoketone **8**. The prochirality of the methylene protons (H_α and H_β) in the acetoacetyl substituent of compound **9** led to a

diastereotopic cleavage of their signals in the form of two doublets at 6.22 and 6.80 ppm. In the IR spectrum of compound **9**, strong double absorption bands of the carbonyl groups of the acetoacetyl fragment were registered in the 1639–1675 cm^{-1} region, confirming the structure of this compound (Table 2).

Acylation of compound **6** with benzoic acid was carried out under the conditions described above, but at a higher temperature (150–160°C). Unlike acetylation, the benzoylation of **6** proceeded smoothly and selectively due to the absence of the activated methyl group in the product obtained. The yield of phenylketone **10** was 68%.

In summary, for the first time 6,7-annelation of 2-(fur-2-yl)thiazole fragment to 1-methyl-1*H*-indazole was successfully carried out. Relative reactivity of the resulting 7-(fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*]-[1,3]benzothiazole in reactions with medium-strength electrophilic reagents was studied.

EXPERIMENTAL

Physico-chemical studies were performed using the equipment of the Center for Collective Use of the Platov South Russian State Polytechnic University.

The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The ^1H NMR spectra were registered on a Varian Unity 300 instrument (300 MHz, DMSO-d_6) relative to internal TMS. The reaction progress was monitored by TLC on plates coated with Al_2O_3 II Brokman activity, evidenced with iodine vapor (eluents – CH_2Cl_2, $CHCl_3$). Elemental analysis was carried out on a Perkin Elmer 2400 analyzer. The melting points were determined by the capillary method on a PTP apparatus.

The physico-chemical and spectral characteristics of the compounds obtained are shown in Tables 1, 2.

1-Methyl-1*H*-5(6)-nitroindazole (1, 2). To a solution of 9.78 g (60 mmol) of 1-methyl-1*H*-indazole in 20 mL of dimethylsulfoxide were successively added 3.53 g (63 mmol) of powdered KOH and 8.52 g (60 mmol) of methyl iodide. The mixture was stirred at room temperature for 3 h, after which it was diluted with 200 mL of water. The precipitate was separated and crystallized from 2-propanol. Yield 9.45 g (mixture of isomers), yellowish crystals.

1-Methyl-1*H*-indazole-6-amine (3). To a mixture of 16 g (0.135 mol) of granular tin and 100 mL of conc. hydrochloric acid was carefully added in portions 8.85 g (0.05 mol) of a mixture of compounds **1** and **2**. The addition of each portion was accompanied by a violent reaction with a strong exothermic effect. At the end of the addition, the clear hot solution was decanted from the tin residues. Upon cooling, formation of a tin amine salt was observed, which was separated, suspended in 200 mL of 2-propanol and subjected to decomposition with solid potassium hydroxide until a slightly alkaline reaction. The $Sn(OH)_2$ precipitate was separated, the filtrate was evaporated to dryness and violet crystals of amine **3** were obtained, which were used without further purification. Yield 3.60 g.

***N*-(1-Methyl-1*H*-indazol-6-yl)furan-2-carboxamide (4).** Furoyl chloride (3.20 g, 24.5 mmol) was added to a solution of 3.53 g (24 mmol) of amine **3** in 30 mL of 2-propanol. The mixture was heated at reflux for 2 h, and then poured into 50 mL of water, neutralized with ammonia solution to a slightly alkaline reaction and kept in a refrigerator for 24 h. The precipitate was filtered off and crystallized from 2-propanol. Yield 4.51 g, colorless crystals.

***N*-(1-Methyl-1*H*-benzimidazol-6-yl)furan-2-carbothioamide (5).** Phosphorus pentasulfide (2.66 g, 6 mmol) was added to a solution of 4.34 g (18 mmol) of compound **4** in 15 mL of anhydrous pyridine. The mixture was refluxed for 3 h, then cooled and poured into 100 mL of water. The yellow precipitate was separated and crystallized from aqueous 2-propanol. Yield 3.33 g.

7-(Fur-2-yl)-1-methyl-1*H*-pyrazolo[4,3-*g*][1,3]-benzothiazole (6). To a solution of 3.33 g (12.96 mmol) of compound **5** in 20 mL of 2-propanol were added 10 mL of 1% potassium hydroxide and then 40 mL of a warm aqueous solution of 12.8 g (38.9 mmol) $K_3[Fe(CN)_6]$. The mixture was kept at room temperature overnight, the precipitate was separated and crystallized from aqueous 2-propanol. Yield 1.06 g, colorless crystals.

5-(1-Methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazol-7-yl)furan-2-carbaldehyde (7). A mixture of 0.255 g (1 mmol) of compound **6** and 0.42 g (3 mmol) of urotropine in 5 g of polyphosphoric acid was stirred at 110–120°C for 6 h, then diluted with 10 mL of water and carefully neutralized with an ammonia solution. The separated reaction product was extracted with 10 mL of chloroform and chromatographed on a column (*l* 10 cm, *d* 2.5 cm) filled with alumina, eluting

with chloroform. Compound **7** was crystallized from ethanol. Yield 0.19 g, yellow crystals.

1-[5-(1-Methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazol-7-yl)fur-2-yl]ethanone (8). A mixture of 0.255 g (1 mmol) of compound **6** and 0.31 g (3 mmol) of acetic anhydride in 5 g of polyphosphoric acid was stirred at 110–120°C for 28 h, then diluted with 10 mL of water and neutralized with an ammonia solution. Further isolation of the reaction product was carried out similar to compound **7**. Compound **8** was crystallized from methanol. Yield 0.086 g, colorless crystals.

1-[5-(1-Methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazol-7-yl)fur-2-yl]butane-1,3-dione (9). Compound **9** was isolated by chromatography of the reaction mixture obtained by acetylation of compound **6**. Yield 0.032 g, orange crystals.

[5-(1-Methyl-1*H*-pyrazolo[4,3-*g*][1,3]benzothiazol-7-yl)fur-2-yl]phenylmethanone (10). A mixture of 0.255 g (1 mmol) of compound **6** and 0.37 g (3 mmol) of benzoic acid in 5 g of PPA was stirred for 10 h at 150–160°C. Further isolation of the reaction product was carried out in a manner analogous to compound **7**. Compound **10** was crystallized from methanol. Yield 0.24 g, yellow-orange crystals.

REFERENCES

1. Simonov, A.M., El'chaninov, M.M., Oleinikova, L.Ya., and Kolbacheva, N.G., Invention Certificate no. 599510, 1977; *Bull. Izobret.*, 1983, no. 23.
2. Grebennikov, V.A., El'chaninov, M.M., Nakhratskii, I.I., Simonov, A.M., and Bokaneva, S.A., Invention Certificate no. 1203861, 1985; *Bull. Izobret.*, 1986, no. 28.
3. El'chaninov, M.M and Aleksandrov, A.A., *Russ. J. Gen. Chem*., 2016, vol. 86, no. 5, p. 1204. doi 10.1134/S107036321605039X
4. Jacobson, P., *Ber*., 1886, vol. 19, pp. 1067, 1811.
5. Aleksandrov, A.A., El'chaninov, M.M., and Dedeneva, A.S., *Russ. J. Gen. Chem*., 2012, vol. 82, no. 7, p. 1263. doi 10.1134/S1070363212070134
6. El'chaninov, M.M., Simonov, A.M., and Oleinikova, L.Ya., *Chem. Heterocycl. Compd*., 1983, vol. 19, no. 10, p. 1041. doi 10.1007/BF 00505746