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HYDRAZINOLYTIC RECYCLIZATION OF (*Z*)-3-ACETYL-2-METHYL-2,3-DIHYDRO-1,4-BENZODIOXIN-2-OL

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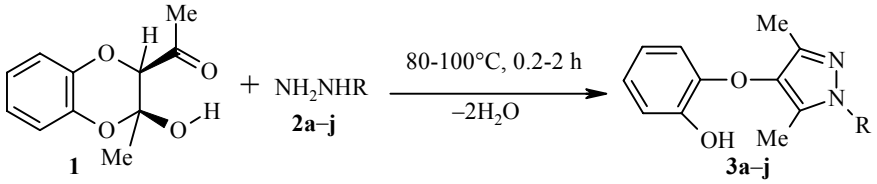
A convenient preparative method has been developed for obtaining previously unknown 4-(o-hydroxyphenoxy) substituted pyrazoles by the reaction of (Z)-3-acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol with hydrazine.

Keywords: 1,4-benzodioxins, hydrazines, pyrazoles, recyclization.

One of the general methods of constructing the pyrazole ring is based on linking hydrazines at both nucleophilic centers (nitrogen atoms) with a three carbon 1,3-dielectrophilic chain [1]. 3-Acyl substituted heterocycles are also 1,3-dielectrophiles (one of the reaction centers is position 2 of the ring and the second is the carbonyl group), which may form a pyrazole ring as a result of hydrazinolytic recyclization of the starting material [2]. For example, pyrazoles substituted at position 4 with *o*-hydroxy, *o*-mercapto, or *o*-aminophenyl groups are obtained from 3-acyl substituted benzofurans [3-5], benzothiophenes [6], or indoles [7] respectively. As is evident from these examples the nature of the substituent in the pyrazole ring is determined by the nature of the initial heterocycle. With the aim of extending the range of functionalized substituents being introduced into the pyrazole ring, we have studied for the first time the hydrazinolytic recyclization of (*Z*)-3-acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol (**1**). This compound is also a 1,3-dielectrophile in which one of the reaction centers, the hemiketal carbon atom, is found in a heterocycle.

We found that compound **1** reacted with hydrazines **2a-j** with the formation of pyrazoles **3a-j** substituted in position 4 with an *o*-hydroxyphenoxy group.



2, 3 a R = H, **b** R = Et, **c** R = Ph, **d** R = 2-$HO_2CC_6H_4$, **e** R = 4-$HO_2CC_6H_4$, **f** R = 4- $O_2NC_6H_4$, **g** R = 2,4,6-$Cl_3C_6H_2$, **h** R = 2-naphthyl, **i** R = 2-pyridyl, **j** R = 2-benzothiazolyl

The reconstruction of the initial heterocycle into a pyrazole occurs under relatively mild conditions with a high degree of selectivity. The process is effected on boiling in aqueous acetic acid (1:1) with hydrazine bases or in acetonitrile with their hydrochlorides. The recyclization has satisfactorily wide preparative limits since in

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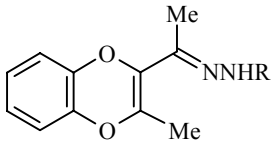
addition to pyrazole **3a** unsubstituted at the nitrogen atom the N-ethyl, aryl, and heteryl derivatives were obtained. The reaction time depends on the reactivity of the hydrazine used and is 0.2-2 h. The yields of products were 60-93%. Preparatively acceptable yields were obtained even with the 2- and 4-carboxy-, 4-nitro-, and 2,4,6-trichlorophenyl-substituted hydrazines **2d-g**, in which the nucleophilicity of one of the nitrogen atoms is significantly reduced.

The synthesized pyrazoles are stable crystalline substances soluble in aqueous alkaline solution. Compounds **3a-e,g-j** were colorless, their nitrophenyl analog **3f** had an orange color. Pyrazoles **3h,i** are inclined to form fairly stable crystallosolvates. To obtain them in the pure state it is necessary to dry them at increased temperature and reduced pressure after crystallization. Certain physicochemical characteristics of compounds **3a-j** and data of elemental analysis are given in Table 1.

The structure of pyrazoles **3a-j** was confirmed by data of ^{1}H NMR spectra, which are given in Table 2. The chemical shifts of the singlet signal of the phenolic hydroxyl proton (disappearing on addition of D_2O), and also of the multiplet signals of the aromatic protons of the *o*-hydroxyphenoxy group were practically identical for the whole series. They depended little on the nature of the substituent R, since the *o*-hydroxyphenyl fragment is separated from it and is not linked to it by a conjugation chain. The methyl groups of pyrazole **3a** unsubstituted at the nitrogen atom were chemically equivalent, which is in agreement with the tautomerism known for pyrazoles [8], caused by the rapid migration of proton between the two ring nitrogen atoms. The isomeric structure of hydrazones of type **4a-j** for the compounds synthesized may therefore be excluded.



4a–j

TABLE 1. Physicochemical Characteristics of the Synthesized Pyrazoles **3a-j**

Compound	Empirical formula	Found, % / Calculated, %			Reaction time, h	mp, °C*	Yield, %
		C	H	N			
3a	$C_{11}H_{12}N_2O_2$	64.52 / 64.69	5.85 / 5.92	13.85 / 13.72	0.2	188.5-190.5	93
3b	$C_{13}H_{16}N_2O_2$	67.45 / 67.22	6.89 / 6.94	12.20 / 12.06	0.4	153-154	81
3c	$C_{17}H_{16}N_2O_2$	72.89 / 72.84	5.87 / 5.75	10.11 / 9.99	1.5	162-163	85
3d	$C_{18}H_{16}N_2O_4$	66.51 / 66.66	5.19 / 4.97	8.67 / 8.64	2	178-180	60
3e	$C_{18}H_{16}N_2O_4$	66.48 / 66.66	4.91 / 4.97	8.49 / 8.64	2	220-221.5	65
3f	$C_{17}H_{15}N_3O_4$	62.63 / 62.76	4.58 / 4.65	12.85 / 12.92	2	153.5-155	69
3g	$C_{17}H_{13}Cl_3N_2O_2$	53.37 / 53.22	3.61 / 3.42	7.22 / 7.30	2	149-150.5	85
3h	$C_{21}H_{18}N_2O_2$	76.20 / 76.34	5.61 / 5.49	8.63 / 8.48	2	139-143	83
3i	$C_{16}H_{15}N_3O_2$	68.42 / 68.31	5.50 / 5.37	15.07 / 14.94	2	123.5-125	80
3j	$C_{18}H_{15}N_3O_2S$	64.15 / 64.08	4.59 / 4.48	12.63 / 12.46	2	172-173.5	85

* Crystallized from acetic acid–water, 1:1 (**a,b,f**), 2-propanol (**c**), and acetonitrile (**d,e,g-j**).

TABLE 2. ^{1}H NMR Spectra of Pyrazoles **3a-j**

Compound	Chemical shifts (DMSO-d_6), δ, ppm, *J* (Hz)
3a	1.99 (6H, s, $2CH_3$); 6.51-6.85 (4H, m, C_6H_4); 9.29 (1H, s, OH); 12.18 (1H, br. s, NH)
3b	1.28 (3H, t, $\underline{CH_3}CH_2$, *J* = 7); 1.91 (3H, s, CH_3); 2.05 (3H, s, CH_3); 3.98 (2H, q, $\underline{CH_2}CH_3$, *J* = 7); 6.49-6.85 (4H, m, C_6H_4); 9.28 (1H, s, OH)
3c	2.04 (3H, s, CH_3); 2.19 (3H, s, CH_3); 6.66-6.89 (4H, m, C_6H_4); 7.39-7.56 (5H, m, C_6H_5); 9.42 (1H, s, OH)
3d	1.94 (3H, s, CH_3); 1.98 (3H, s, CH_3); 6.69-6.91 (4H, m, C_6H_4O); 7.53-7.90 (4H, m, C_6H_4C=O); 9.38 (1H, s, OH); 13.06 (1H, br. s, COOH)
3e	2.05 (3H, s, CH_3); 2.29 (3H, s, CH_3); 6.67-6.90 (4H, m, C_6H_4O); 7.74 (2H, d, *m*-protons C_6H_4C=O, *J* = 8.4); 8.06 (2H, d, *o*-protons C_6H_4C=O, *J* = 7); 9.43 (1H, s, OH); 13.11 (1H, br. s, COOH)
3f	2.06 (3H, s, CH_3); 2.33 (3H, s, CH_3); 6.68-6.90 (4H, m, C_6H_4O); 7.91 (2H, d, *m*-protons $C_6H_4NO_2$, *J* = 8.4); 8.34 (2H, d, *o*-protons $C_6H_4NO_2$, *J* = 8.4); 9.43 (1H, s, OH)
3g	1.87 (3H, s, CH_3); 2.03 (3H, s, CH_3); 6.60-6.89 (4H, m, C_6H_4O); 7.99 (2H, s, $C_6H_2Cl_3$); 9.40 (1H, s, OH)
3h	2.08 (3H, s, CH_3); 2.29 (3H, s, CH_3); 6.70-6.91 (4H, m, C_6H_4); 7.59-8.10 (7H, m, $C_{10}H_7$); 9.42 (1H, s, OH)
3i	2.06 (3H, s, CH_3); 2.48 (3H, s, CH_3); 6.60-6.92 (4H, m, C_6H_4); 7.30-8.46 (4H, m, C_5H_4N); 9.42 (1H, s, OH)
3j	2.08 (3H, s, CH_3); 2.61 (3H, s, CH_3); 6.72-6.92 (4H, m, C_6H_4O); 7.37-8.06 (4H, m, NC_6H_4S); 9.46 (1H, s, OH)

As is known [2], many recyclization reactions allow the preparation of functionalized heterocycles the synthesis of which by other methods is extremely complex or generally impossible. The approach developed by us leads to previously unknown pyrazoles capable of further structural modification by simple reactions and simplifies the search for new substances useful in practice.

EXPERIMENTAL

A monitoring on the progress of reactions and the homogeneity of compounds was carried out by TLC (Silufol UV 254, benzene–ethanol, 9:1, visualization in UV light). After crystallization the synthesized compounds were dried for 3 h in a Fischer pistol with a water-jet pump vacuum at 115°C. The ^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer with an operating frequency of 300 MHz (DMSO-d_6, internal standard was TMS). Compound **1** was obtained by the method of [9].

4-(*o*-Hydroxyphenoxy)-3,5-dimethylpyrazoles (3a-j). Compound **1** (3.12 g, 15 mmol) was boiled either with hydrazine **2a,b** (30 mmol), with hydrazine **2c-j** (15 mmol) in aqueous acetic acid (1:1) (15 ml), or with hydrazine hydrochloride **2d,e** (15 mmole) in acetonitrile (10 ml). Reaction times are shown in Table 1. To isolate products **3b-j** the hot reaction mixture was slowly diluted with water (10 ml) with stirring. After cooling, the solid was filtered off, washed with 2-propanol (products **2a,b,h,i** with water), and dried at 110-120°C.

REFERENCES

1. J. Elguero, in A. R. Katritzky, C. W. Rees, and K. T. Potts (editors), *Comprehensive Heterocyclic Chemistry,* Vol. 5, Pergamon, Oxford (1984), p. 167.
2. O. P. Shvaika and V. N. Artemov, *Usp. Khim.*, **41**, 1788 (1972).
3. M. Descamps, F. Binon, and J. Van der Elst, *Bull. Soc. Chim. Belg.*, **73**, 459 (1964).

4. M. Hubert-Habart, K. Takagi, A. Cheutin, and R. Royer, *Bull. Soc. Chem. Fr.*, 1587 (1966).
5. I. B. Dzvinchuk, Yu. A. Okolovskii, and M. O. Lozinskii, *Zh. Org. Khim.*, **30**, 1673 (1994).
6. C. Alberti, *Gazz. Chim. Ital.*, **55**, 245 (1955).
7. C. Alberti, *Gazz. Chim. Ital.*, **47**, 398 (1947); *Chem. Abstr.*, **42**, 2963 (1948).
8. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, Suppl. 1, 34, 41, 48, 269 (1976).
9. I. B. Dzvinchuk and M. O. Lozinskii, *Zh. Org. Khim.*, **25**, 1273 (1989).