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SELECTIVE RECYCLIZATION OF 2-AROYLMETHYL-1H-BENZIMIDAZOLE HYDRAZONES BY CONDENSATION WITH DIMETHYLFORMAMIDE

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2-Aroylmethyl-1H-benzimidazole hydrazones are converted to 1-[pyrazol-3(5)-yl]benzimidazoles by refluxing in dimethylformamide in the presence of trifluoroacetic acid. The same products are obtained by refluxing 2-aroylmethyl-1H-benzimidazoles with hydrazine hydrochloride in dimethylformamide. Electron donor substituents in the para position of the aryl fragment of the starting compounds do not favor the reaction.

Keywords: benzimidazoles, hydrazones, pyrazoles, condensation, recyclization, selectivity.

As is known [1], recyclization can lead to the preparation of functionalized heterocycles which are only obtainable with difficulty by other synthetic methods. *Via* a study of previously used conditions involving the potential rebuilding of a benzimidazole ring to give pyrazole compounds, we have reported the following sequence of reactions. Treatment of 2-methylbenzimidazole (**1**) with benzoyl chloride (**2a**) gave the product of C-, N-, and O-tribenzoylation **3a** which gives 2-phenacylbenzimidazole (**4a**) upon morpholinolysis [2]. Compound **4a** reacts with hydrazines to form the moderately stable hydrazones; recyclization of the latter could be achieved only by carrying out the reaction under acylation conditions [3-5]. Hence the reaction of hydrazone **5a** to the (*o*-aminophenylamino)pyrazole **6a** occurs, as we have already reported [6], in refluxing dimethylformamide (DMF) in the presence of benzoic acid and is accompanied by condensation with the solvent to form the N-pyrazolylbenzimidazole **7a**. In our work we now report the preparative potential of this reaction and we investigate the effect of substituents on its course.

Synthesis of the novel starting materials (the hydrazones **5b-d**) occurs, as we have shown, quite efficiently using the three stage scheme referred to with the use of the aroyl chlorides **2b-d** and hydrazine hydrate to give the compounds **3b-d** and **4b-d** in the intermediate stages.

We have found that the reaction studied occurs more readily when benzoic acid is exchanged for trifluoroacetic acid. Thus the reaction of compound **5a** in the presence of trifluoroacetic acid is completed after 3 h in 91% yield (with benzoic acid after 7 h and in 88% yield). Under the same conditions the hydrazones **5b,c** give the N-pyrazolylbenzimidazoles **7b,c** after 1 and 2 h in 87 and 80% yields respectively.

An increase in the reaction times for the hydrazones **5b,c**, respectively to 4 and 6 h, leads to a lowering of the yields to 80 and 64%. Appreciable difficulties are observed when converting the methoxy-substituted hydrazone **5d**; judging by its disappearance from the reaction mixture (TLC method) the reaction is completed after 10 h but the yield of the final product **7d** is 35%. The compounds **7a-d** were obtained in lower yields by refluxing the 2-aroylmethylbenzimidazoles **4a-d** with hydrazine hydrochloride in DMF.

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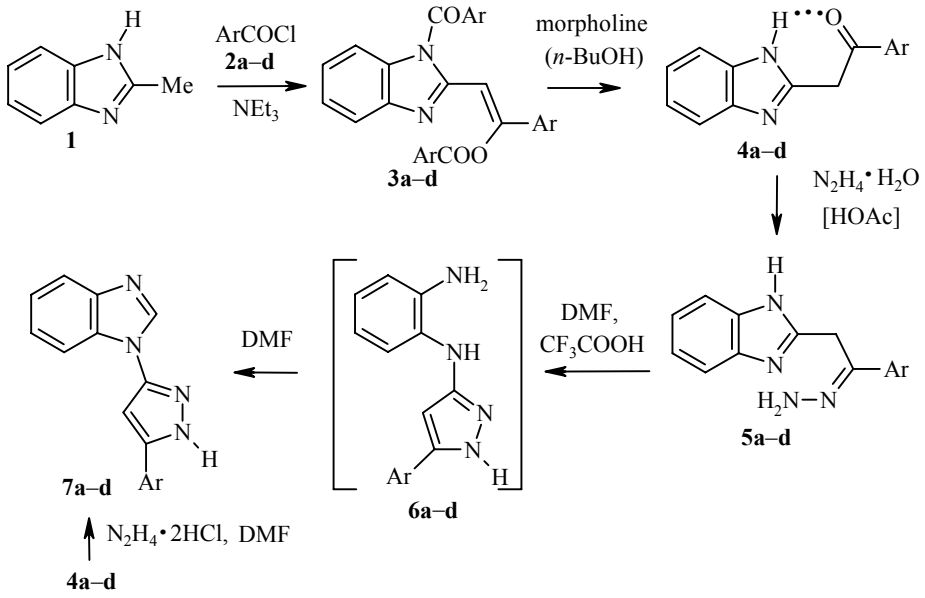
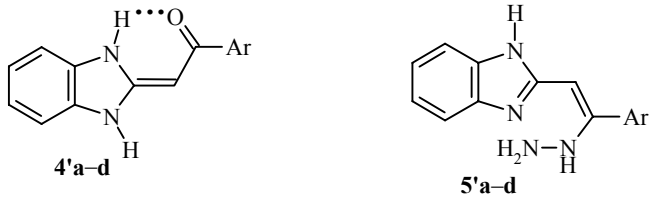


2-7 a Ar = Ph, **b** 4-$O_2NC_6H_4$, **c** 4-ClC_6H_4, **d** 4-$CH_3OC_6H_4$

The synthesized compounds **4b-d** and **7b-d** are stable, crystalline materials and the hydrazones **5b-d** darken upon prolonged standing at 20-25°C. Compound **4b** has a dark red coloration, compounds **4c,d**, **5b** and **7b** are yellowish, and the rest are colorless. Compounds **4b-d** give a green coloration with a methanol solution of ferric chloride.

Several characteristics are given for the novel compounds **4b-d**, **5b-d**, and **7b-d** in Table 1 and their structures were confirmed through their ^{1}H NMR spectra (Table 2). From these spectra it is apparent that compounds **4b-d** exist in solution in equilibrium with the enamino ketone forms **4'b-d**. The signals for the methylene group protons are seen at 4.61-4.79 and the methine protons of the ketovinyl fragment at 6.02-6.15 ppm.

The enamino-keto form contents are decreased according to a decrease in the electron-acceptor properties of the aryl substituent and amount to 96, 88, and 48% respectively. For compound **4a**, as previously found [2], the tautomer **4'a** content is 79%.



a Ar = Ph, **b** 4-$O_2NC_6H_4$, **c** 4-ClC_6H_4, **d** 4-$CH_3OC_6H_4$

For the hydrazones **5b,c**, like **5a** [6], the tendency to tautomerize is not observed. Evidently, their structure is stabilized by an energetically favored system of conjugation in which there is the possibility of transferring the electronic effect from the hydrazone amino group donor to the aryl fragment acceptor. The spectrum of the methoxy-substituted hydrazone **5d** shows the presence of 20% of the enhydrazine form **5'd**. The methylene group protons absorb at 4.20 ppm and the methine proton of the vinyl fragment at 4.72 ppm. The relative stability of tautomer **5'd** is evidently due to the formation of an energetically favored conjugative system in which transfer of the electronic effect to the heterocyclic acceptor from the hydrazine fragment is supplemented by the electron donor effect of the methoxy group.

TABLE 1. Characteristics for the Synthesized Compounds **4b-d**, **5b-d**, and **7b-d**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
4b	$C_{15}H_{11}N_3O_3$	64.18 / 64.05	3.81 / 3.94	14.98 / 14.94	296-297	69*[2]
4c	$C_{15}H_{11}ClN_2O$	66.64 / 66.55	4.06 / 4.10	10.22 / 10.35	226-228	85*[2]
4d	$C_{16}H_{14}N_2O_2$	72.31 / 72.16	5.18 / 5.30	10.60 / 10.52	208-209	82*[2]
5b	$C_{15}H_{13}N_5O_2$	59.88 / 61.01	4.49 / 4.44	23.66 / 23.72	187-189*[3]	88
5c	$C_{15}H_{13}ClN_4$	63.11 / 63.27	4.63 / 4.60	19.61 / 19.68	173-174	86
5d	$C_{16}H_{14}N_4O$	69.23 / 69.05	5.19 / 5.07	20.22 / 20.13	206-208	90
7b	$C_{16}H_{11}N_5O_2$	62.76 / 62.94	3.43 / 3.63	22.73 / 22.94	342.5-344	87*[4]
7c	$C_{16}H_{11}ClN_4$	65.35 / 65.20	3.59 / 3.76	18.86 / 19.01	250-51*[3]	80*[4]
7d	$C_{17}H_{14}N_4O$	70.51 / 70.33	4.69 / 4.86	19.20 / 19.30	201-202	35*[4]

* Compounds were crystallized from a mixture of BuOH–DMF, 2:1 (**4b,c**), BuOH (**4d, 5b-d**), DMF (**7b**), aqueous DMF, 1:4 (**7c**), and MeCN–DMF (**7d**).

*[2] Calculated from 2-methylbenzimidazole (**1**).

*[3] With decomposition.

*[4] Using method B the yields were, %: 66 (**7b**), 55 (**7c**), 35 (**7d**).

In the pyrazolylbenzimidazoles **7b-d** the pyrazole ring 4-H proton appears at 7.15-7.72 ppm and the benzimidazole ring 5-, 6-H protons as a narrow multiplet at 7.31-7.44 ppm (the 4-H and 7-H protons are observed separately at 7.79-7.81 and 8.11-8.12 ppm respectively) and this is in agreement with data for 1-arylbenzimidazoles [7].

The 2-H protons of the benzimidazole ring in compounds **7a-d** appear at virtually the same position at 8.75-8.76 ppm and this may be due to the absence of efficient conjugation between the aryl substituents and the benzimidazole ring. The signal for the proton at position 1 of the pyrazole ring (NH) is found at 13.41-13.93 ppm and this is lost on addition of D_2O.

We have observed trends in the investigated reaction. According to the yields, all of the substituents investigated hinder its course. However, the products **7b,c**, which contain electron acceptor substituents, can be obtained in preparatively acceptable yields. Lowering of the yields of these compounds, as mentioned already, increases with an increase in reaction time and is very likely due to concurrent processes (e.g. oxidation and substitution) involving the substituents themselves. The electron donor methoxy group is the only one which differs markedly. Hence the pattern is , in our view, readily explicable.

Representation of the reaction is complex. It can be separated into two basic processes, i.e. recyclization and condensation with DMF. We consider that the effect of the substituent on each or these processes separately does not touch upon the question of the limiting stage.

The ease of the recyclization reaction depends upon the nucleophilicity of the hydrazone amino group and the electrophilicity of the $C_{(2)}$ atom of the heterocycle in the starting compounds **5a-d**. One should bear in mind a number of circumstances. Firstly, the electron effect of the substituent can be distributed at both reaction centers since, in the reaction conditions, all of the starting hydrazones can cross to the enhydrazine forms **5'a-d**.

TABLE 2. ^{1}H NMR Spectra of Compounds **4b-d**, **5b-d**, **7b-d** and their Tautomeric Forms **4'b-d, 5'd**

Compound	^{1}H NMR spectrum, δ, ppm, *J* (Hz)
4b*	4.79 (2H, s, CH_2CO); 8.17-8.36 (4H, m, *p*-C_6H_4)*[2]
4'b	6.15 (1H, s, CHCO); 7.18-7.74 (4H, m, *o*-C_6H_4); 8.10-8.32 (4H, m, *p*-C_6H_4); 12.43 (1H, s, NH)
4c*	4.70 (2H, s, CH_2CO); 7.50-8.03 (4H, m, *p*-C_6H_4)*[2]
4'c	6.05 (1H, s, CHCO); 7.63-8.12 (4H, m, *p*-C_6H_4); 7.15-7.59 (4H, m, *o*-C_6H_4); 12.29 (1H, s, NH)
4d*	3.82 (3H, s, OCH_3); 4.61 (2H, s, CH_2CO); 7.07-8.09 (4H, m, *p*-C_6H_4); 7.13-7.53 (4H, m, *o*-C_6H_4); 12.36 (1H, s, NH)
4'd	3.86 (3H, s, OCH_3); 6.02 (1H, s, CHCO); 7.00-7.84 (4H, m, *p*-C_6H_4); 12.21 (1H, s, NH)*[2]
5b	4.29 (2H, s, CH_2); 7.12-7.49 (4H, m, *o*-C_6H_4); 7.69 (2H, s, NH_2); 7.96-8.19 (4H, m, *p*-C_6H_4); 12.37 (1H, s, NH)
5c	4.22 (2H, s, CH_2); 7.12-7.52 (4H, m, *o*-C_6H_4); 7.20 (2H, br. s, NH_2); 7.36-7.79 (4H, m, *p*-C_6H_4); 12.37 (1H, br. s, NH)
5d*[3]	3.75 (3H, s, CH_3); 4.20 (2H, s, CH_2); 6.87-7.23 (4H, m, *p*-C_6H_4); 6.96 (2H, br. s, NH_2); 7.12-7.50 (4H, m, *o*-C_6H_4); 12.38 (1H, br. s, NH)
5'd	4.72 (2H, s, CH); 6.92-7.94 (4H, m, *p*-C_6H_4)*[2]
7b	7.32-7.44 (2H, m, 5-, 6-H); 7.52 (1H, s, 4'-H); 7.79 (1H, d, *J* = 8, 4-H); 8.11 (1H, d, *J* = 8, 7-H); 8.12-8.43 (4H, m, *p*-C_6H_4); 8.76 (1H, s, 2-H); 13.93 (1H, s, NH)
7c	7.30 (1H, s, 4'-H); 7.31-7.44 (2H, m, 5-, 6-H); 7.61-7.91 (4H, m, *p*-C_6H_4); 7.79 (1H, d, *J* = 8, 4-H); 8.11 (1H, d, *J* = 8, 7-H); 8.75 (1H, s, 2-H); 13.63 (1H, s, NH)
7d	3.83 (3H, s, CH_3); 7.09-7.82 (4H, m, *p*-C_6H_4); 7.15 (1H, s, 4'-H); 7.31-7.43 (2H, m, 5-, 6-H); 7.79 (1H, d, *J* = 7, 4-H); 8.12 (1H, d, *J* = 8, 7-H); 8.75 (1H, s, 2-H); 13.41 (1H, s, NH)

* Tautomeric ratio of **4** and **4'** 4:96 (**b**), 12:88 (**c**), 52:48 (**d**).
*[2] Remaining signals obscured by the signals of the tautomer.
*[3] Tautomeric ratio of **5d** and **5'd** 80:20.

Secondly, the transfer from the hydrazone form to the enhydrazine leads to an increase in the nucleophilicity of the amino group in compounds with electron-acceptor substituents and, on the other hand, to its lowering with the methoxy-substituted compound. Thirdly, in the hydrazone form the effect of the substituent on the electrophilic center is insignificant but shows up in the nucleophile (an electron acceptor lowering its reactivity and a methoxy group increasing it). Fourthly, and contrariwise, in the enhydrazine form the effect of the substituent on the nucleophilic center is insignificant but shows up in the electrophile (an electron acceptor increases its activity and a methoxy group lowers it). Correlation of such complex electronic effects with experimental data obtained is possible if one infers that the tendency of the hydrazones discussed towards recyclization is determined by the reactivity of the electrophilic center. It follows from this that: 1) the recyclization of compounds with electron acceptor substituents is highly favored in the enhydrazine form; 2) for recyclization of compound **5a** in the enhydrazine form a long reaction time is necessary; and 3) the tendency of the methoxy-substituted compound **5d** to recyclize is distinctly weak, particularly in the enhydrazine form.

It should also be born in mind that the values of the aromatic indices for the benzimidazole and pyrazole rings are extremely similar (0.050 and 0.055 respectively [8]). Hence the thermodynamic factors do not favor reconstruction of the benzimidazole ring to a pyrazole. This recyclization probably has an equilibrium character; separation of its products without the use of DMF could not be achieved.

DMF reacts with the recyclization products **6a-d** at the amino group of the *o*-phenylenediamine fragment. Its reactivity is typical of an aniline and is virtually independent of the effect of the substituent in the pyrazole ring due to the absence of system conjugation. Of course, DMF can react at both the amino group of

the starting hydrazones **5a-d** and their enhydrazine forms **5a'-d**. The relative contribution of this effect to the overall result depends on the reactivity of the nucleophilic center. As we have shown, it is at a minimum for the nitro-substituted compound **5b** and a maximum for the methoxy-substituted **5d**.

With the effects of these factors in mind we can propose the following. Under the reaction conditions there exists an equilibrium between the hydrazones **5a-d** and the recyclization products **6a-d**. For compounds **5a-c** it is achieved quite rapidly and condensation with DMF occurs principally at the amino group of the recyclization products **6a-c** which also leads to the final compounds **7a-c** in high yields. In these examples DMF plays the role of a reagent selectively binding the more reactive recyclization products with virtually no effect on the starting hydrazones. Formation of the product is thus effected resulting in a shift of the reaction equilibrium towards its formation. Recyclization of the methoxy-substituted hydrazone **5d** occurs slowest. In addition, in this case, the selectivity of the reaction of the recyclization product with DMF is absent. However, here the DMF stabilizes the product and compound **7d** is separated from the reaction mixture thanks to its lowered solubility.

Finally, the role of the aid. Without it, as we have shown [6], the reaction becomes poorly selective. The action of the acid at the DMF reflux temperature is probably a varying one. Evidently protonation of the nitrogen atom of the starting benzimidazole ring, the hydrazone fragment, and the solvent itself can occur. This can enable an increase in the reactivity of the ring electrophile center transferring to the reactive enhydrazine form and finally the product of recyclization with DMF.

Hence 2-aroylmethyl-1H-benzimidazole hydrazones, when refluxed in DMF in the presence of acid, are recyclized to form 1-[pyrazol-3(5)-yl]benzimidazoles. An electron-donor substituent in the *para* position of the aryl fragment does not favor the reaction course.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) instrument using DMSO-d_6 solvent and TMS internal standard. The course of the reaction and the purity of the synthesized compounds was monitored by TLC (Silufol UV-254, benzene–ethanol, 9:1),

Compounds 3b-d, 4b-d, and 5b-d. These were obtained similarly to compounds **3a**, **4a** [5], and **5a** [6]. Compounds **3b-d** were used after separation without purification. Compound **4b** was prepared by refluxing compound **3b** (2 mmol) in a mixture of *n*-butanol (1 ml) and DMF (1 ml) for 0.5 h. The product precipitated on cooling.

1-[Pyrazol-3(5)-yl]benzimidazoles (7a-d). A. The corresponding hydrazone **5a-d** (2 mmol) and trifluoroacetic acid (3 mmol) were refluxed in DMF (2 ml). The reaction times were: 3 h (**a**), 1 h (**b**), 2 h (**c**), and 10 h (**d**). Water was added to the hot solution until crystallization began. After cooling, the precipitate was filtered off, washed with 2-propanol, and recrystallized.

B. The corresponding compound **4a-d** (2 mmol) and hydrazine hydrochloride (3 mmol) were refluxed in DMF (2 ml). The reaction times were: 3 h (**a**), 9 h (**b**), 5 h (**c**), and 4 h (**d**). The reaction mixture was worked up similarly to method A.

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