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RECYCLIZATION ON INTERACTION OF ARYLHYDRAZONES OF 2-AROYLMETHYL-1H-BENZIMIDAZOLES WITH ETHYL ISOTHIOCYANATE

B. Dzvinchuk and M. O. Lozinskii

Ethyl isothiocyanate reacts with arylhydrazones of 2-aroylmethyl-1H-benzimidazoles initiating recyclization with the formation of the previously unknown1-(1,3-diaryl-1H-pyrazol-5-yl)-1,3-dihydro-2H-benzimidazole-2-thiones.

Keywords: benzimidazoles, hydrazones, isothiocyanates, pyrazoles, recyclization, cyclocondensation.

Recyclizations are unique as a possibility for obtaining functionalized compounds but often have narrow preparative limits, since they are extremely sensitive to the stability of the initial rings and the effect of substituents [1-6]. For example, phenylhydrazones of 2-aroylmethyl-1H-benzimidazoles **1a-f** are not inclined to remake the heterocyclic ring on acid catalysis, but undergo Fischer indolization [7]. However compounds of type **1** (and of the related type **2**) are readily recyclized under the conditions of an acylation reaction, by the action of aroyl chlorides or anhydrides of carboxylic acids they give 5-(2-acylaminoanilino)-1,3-diarylpyrazoles [8-10]. According to our hypothesis and with data of quantum-chemical calculations [11], such a conversion is possibly caused by the direction of the acylation reaction to the benzimidazole nitrogen atom of the initial compounds, with the intermediate formation of the corresponding highly reactive acylbenzimidazolium derivative, which spontaneously undergoes rearrangement as a result of intramolecular nucleophilic attack at its position 2 of the hydrazone amino group. Initiation of an analogous recyclization by weak electrophiles of the isothiocyanate type remains unknown and was studied in the present work for this reason.

We started from two series of compounds, the phenylhydrazones of 2-aroylmethylbenzimidazoles **1a-f** and arylhydrazones of 2-phenacylbenzimidazole **2a-c**. We used ethyl isothiocyanate as the second component of the reaction.

It was found that the reactants interact at a molar ratio of 1:2 on boiling in pyridine. The isothiocyanate is probably added at the benzimidazole nitrogen atom with the intermediate formation of benzimidazolium derivatives **3, 4**, the recyclization of which may proceed further through spiranes of structure **5, 6**. However it does not stop at the stage of forming 5-(2-thioureidoanilino)pyrazoles **7, 8**. Under the reaction conditions one further cyclocondensation readily occurs, which leads to the previously unknown 1-(1,3-diaryl-1H-pyrazol-5-yl)-1,3-dihydro-2H-benzimidazole-2-thiones **9a-f** and **10a-c**.

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02660; e-mail: Rostov@bpci.kiev.ua. Translated from Khimii Geterotsiklicheskikh Soedinenii, No. 4, pp. 522-527, April, 2006. Original article submitted May 13, 2005.

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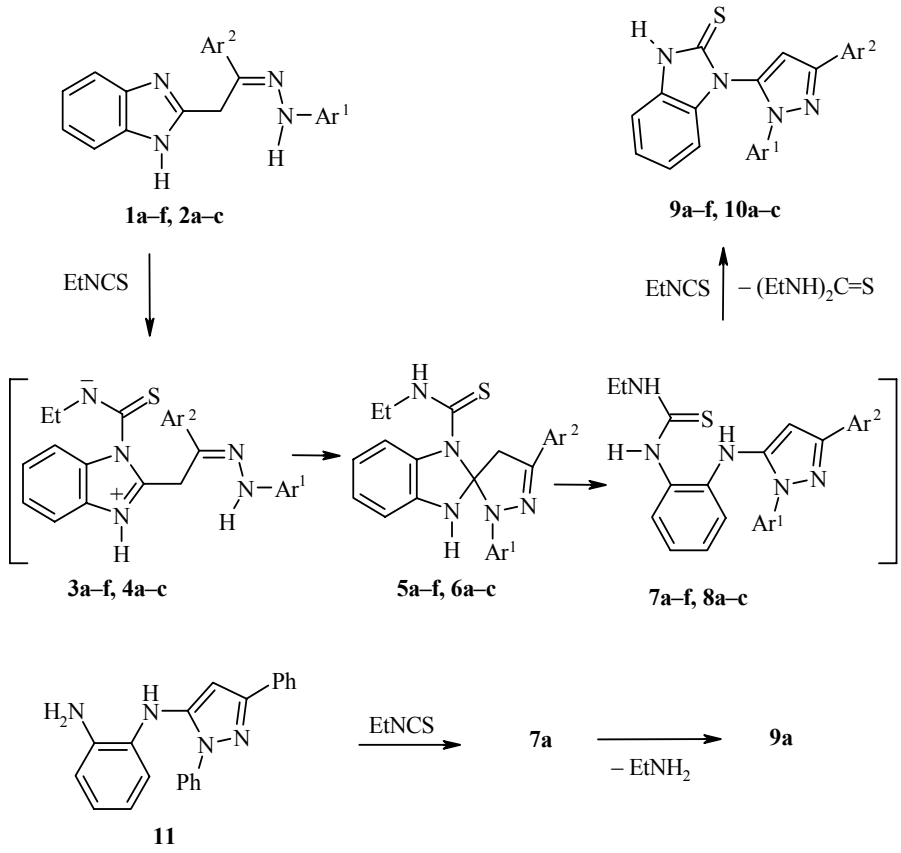

1, 3, 5, 7, 9 Ar^1 = Ph; **a** Ar^2 = Ph, **b** Ar^2 = 4-$MeOC_6H_4$, **c** Ar^2 = 4-BrC_6H_4, **d** Ar^2 = 4-ClC_6H_4, **e** Ar^2 = 4-$O_2NC_6H_4$, **f** Ar^2 = 2-thienyl;
2, 4, 6, 8, 10 Ar^2 = Ph, **a** Ar^1 = 4-MeC_6H_4, **b** Ar^1 = 4-FC_6H_4, **c** Ar^1 = 3-ClC_6H_4

The last stage of the conversion is an intramolecular transamination and is accompanied by the elimination of ethylamine, which reacts with the initial isothiocyanate with the formation of N,N'-diethylthiourea. For this reason it is necessary to use more than 2 equiv. of ethyl isothiocyanate to achieve complete conversion. We note that N,N'-diethylthiourea possesses an enhanced solubility and does not interfere with the isolation of the desired products. It is also possible to use other isothiocyanates in the reaction but this is not always acceptable. We have found that the interaction of the phenylhydrazone of 2-phenacylbenzimidazole **1a** with phenyl isothiocyanate also gives compound **9a** highly selectively, but the isolation of **9a** from the reaction mixture in high yield and in a pure state is problematical, since the relatively poorly soluble N,N'-diphenylthiourea is the second product.

In the majority of the examples the reaction with ethyl isothiocyanate was totally complete after 2 h. But the time for conversion of halo-substituted compounds **1c,d** was extended to 4 h. Reaction of the phenylhydrazone of 4-nitrophenacylbenzimidazole **1e** and the 3-chlorophenylhydrazone of 2-phenacyl-benzimidazole **2c** was not fully complete after 12 h and was complicated by side reactions, which nonetheless did not impede isolation of the desired products. Attempts by us to carry out the corresponding conversion of a 4-nitrophenylhydrazone of type **2** were not at all successful. It is evident that an increase in electron-withdrawing properties of any of the other aryl substituents in the initial hydrazones was not conducive to the initiation of recyclization with isothiocyanate. This regularity is in agreement with the mechanism presented for the reaction. Structural factors reducing the nucleophilicity of the hydrazone amino group hamper the formation of spiranes of types **5** and **6** needed for the desired transformation.

It is noteworthy that initiation of recyclization with acid chlorides and anhydrides of carboxylic acids occurs under milder conditions (20 or 100°C), more quickly (1 or 2 h), and more efficiently (4-nitrobenzoyl chloride may recyclize the 4-nitrophenylhydrazone [8] mentioned, and trifluoroacetic anhydride even the corresponding benzoylhydrazone [12]).

Compound **9a** was also synthesized by an independent method from 5-(2-aminoanilino)pyrazole **11**. In this case the process may be carried out using only 1 equiv. ethyl isothiocyanate. On boiling in 2-propanol the reaction stops at the stage of forming the thiourea derivative **7a**, which is then cyclized on boiling in pyridine with the elimination of ethylamine. Such a pathway for the synthesis of compound **9a** is acceptable confirmation of its structure, but has no particular preparative value. This is due to the initial compound **11** being less available than phenylhydrazone **1a** (it is synthesized in two stages from phenylhydrazone **1a** [10]).

The structures of the obtained compounds were confirmed by elemental analysis (Table 1) and by spectral investigations. According to data of ^{1}H NMR spectra (Table 2) and IR spectra product **9a**, compounds of types **9** and **10** exist completely in the thione form in solution and in the crystalline state.

The recyclization of arylhydrazones of 2-acylmethyl-1H-benzimidazoles may therefore be initiated by isothiocyanates, although not so effectively as by acid chlorides or anhydrides of carboxylic acids. Nonetheless the reaction with isothiocyanate is sufficiently attractive as a preparatively convenient method for the synthesis of a series of 1-(1,3-diaryl-1H-pyrazol-5-yl)-1,3-dihydro-2H-benzimidazole-2-thiones.

EXPERIMENTAL

A check on the progress of reactions and the purity of the synthesized compounds was carried out by TLC on Silufol UV 254 plates in the solvent system benzene–ethanol, 9:1, with visualization in UV light. The ^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer in DMSO-d_6, internal standard

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
7a	$C_{24}H_{23}N_5S$	69.64 / 69.71	5.78 / 5.61	17.08 / 16.93	158-159	93
9a	$C_{22}H_{16}N_4S$*	71.67 / 71.72	4.58 / 4.38	15.34 / 15.21	232-233.5	93
9b	$C_{23}H_{18}N_4OS$	69.25 / 69.33	4.71 / 4.55	13.97 / 14.06	198-199.5	94
9c	$C_{22}H_{15}BrN_4S$	58.94 / 59.07	3.43 / 3.38	12.48 / 12.52	212-213.5	97
9d	$C_{22}H_{15}ClN_4S$	65.41 / 65.58	3.88 / 3.75	13.87 / 13.91	202-203.5	79
9e	$C_{22}H_{15}N_5O_2S$	63.87 / 63.91	3.78 / 3.66	16.83 / 16.94	289-290.5	52
9f	$C_{20}H_{14}N_4S_2$	64.03 / 64.15	3.86 / 3.77	15.07 / 14.96	195-196.5	83
10a	$C_{23}H_{18}N_4S$	72.11 / 72.23	4.85 / 4.74	14.78 / 14.65	239-240.5	88
10b	$C_{22}H_{15}FN_4S$	68.26 / 68.38	4.05 / 3.91	14.64 / 14.50	238.5-240	84
10c	$C_{22}H_{15}ClN_4S$	65.44 / 65.58	3.83 / 3.75	13.98 / 13.91	207.5-209	59

* Found, %: S 8.59. Calculated, %: S 8.70.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
7a	1.03 (3H, t, *J* = 7.2, CH_3); 3.43 (2H, m on the water signal, S,H_2); 6.57 (1H, s, pyrazole: H-4); 6.89 (1H, t, *J* = 7.5, $CSNHC_6H_4$: H-4); 6.98 (1H, d, *J* = 7.8, $CSNHC_6H_4$: H-6); 7.12 (1H, t, *J* = 7.8, $CSNHC_6H_4$: H-5); 7.21 (1H, d, *J* = 7.5, $CSNHC_6H_4$: H-3); 7.33-7.50 (7H, m, CPh: H-3,4,5 + NPh: H-3,4, 5 + AlkNHCS); 7.62 (1H, s, NHHet); 7.71 (2H, d, *J* = 7.8, NPh: H-2,6); 7.86 (2H, d, *J* = 7.5, CPh: H-2,6); 8.85 (1H, s, ArNHCS)
9a	6.95 (1H, d, *J* = 7.8, H-4); 7.09-7.15 (1H, m, H-6); 7.19-7.25 (2H, m, H-5,7); 7.31 (1H, m, NPh: H-4); 7.36-7.46 (6H, m, NPh: H-2,3,5,6 + H-4' + CPh: H-4); 7.48-7.53 (2H, m, Ph: H-3,5); 7.99 (2H, d, *J* = 6.9, Ph: H-2,6); 13.29 (1H, s, H-3, subject to deuterium exchange)
9b	3.82 (3H, s, CH_3); 6.93 (1H, d, *J* = 8.4, H-4); 7.06 and 7.91 (2 × 2H, two d, *J* = 8.7, $C_6H_4OCH_3$); 7.10-7.14 (1H, m, H-6); 7.18-7.23 (2H, m, H-5,7); 7.27 (1H, s, H-4'); 7.29-7.31 (1H, m, NPh: H-4); 7.34-7.43 (4H, m, NPh: H-2,3,5,6); 13.25 (1H, s, H-3)
9c	6.95 (1H, d, *J* = 8.1, H-4); 7.09-7.14 (1H, m, H-6); 7.18-7.25 (2H, m, H-5,7); 7.29-7.45 (5H, m, C_6H_5); 7.40 (1H, s, H-4'); 7.56 and 8.00 (2 × 2H, two d, *J* = 8.7, C_6H_4Br); 13.25 (1H, s, H-3)
9d	6.95 (1H, d, *J* = 8.4, H-4); 7.08-7.14 (1H, m, H-6); 7.18-7.24 (2H, m, H-5,7); 7.29-7.45 (5H, m, C_6H_5); 7.40 (1H, s, H-4'); 7.70 and 7.94 (2 × 2H, two d, *J* = 8.4, C_6H_4Br); 13.26 (1H, s, H-3)
9e	7.00 (1H, d, *J* = 7.8, H-4); 7.09-7.15 (1H, m, H-6); 7.22-7.23 (2H, m, H-5,7); 7.33-7.48 (5H, m, C_6H_5); 7.60 (1H, s, H-4'); 8.25 and 8.36 (2 × 2H, two d, *J* = 8.7, $C_6H_4NO_2$); 13.29 (1H, s, H-3)
9f	6.96 (1H, d, *J* = 7.5, H-4); 7.08-7.14 (1H, m, H-6); 7.17-7.19 (1H, m, thienyl: H-4); 7.21-7.22 (2H, m, H-5,7); 7.27 (1H, s, H-4'); 7.30-7.39 (5H, m, NC_6H_5); 7.60 and 7.62 (2 × 1H, two d, *J* = 5.1, thienyl: H-3,5); 13.28 (1H, s, H-3)
10a	2.25 (3H, s, CH_3); 6.93 (1H, d, *J* = 7.8, H-4); 7.09-7.15 (1H, m, H-6); 7.18 and 7.32 (2 × 2H, two d, *J* = 8.1, $CH_3C_6H_4$); 7.21-7.23 (2H, m, H-5,7); 7.34 (1H, s, H-4'); 7.40 (1H, m, Ph: H-4); 7.49 (2H, m, Ph: H-3,5); 7.97 (2H, d, *J* = 6.9, Ph: H-2,6); 13.25 (1H, s, H-3)
10b	7.00 (1H, d, *J* = 7.5, H-4); 7.11-7.16 (1H, m, H-6); 7.23-7.24 (2H, m, H-5,7); 7.26-7.29 (m, FC_6H_4: H-2,6); 7.37 (1H, s, H-4'); 7.41-7.52 (5H, m, FC_6H_4: H-3,5 + Ph: H-3,4,5); 7.97 (2H, d, *J* = 6.9, Ph: H-2,6); 13.29 (1H, s, H-3)
10c	7.01 (1H, d, *J* = 7.5, H-4); 7.12-7.18 (1H, m, H-6); 7.24-7.26 (2H, m, H-5,7); 7.32-7.35 (1H, m, ClC_6H_4: H-5); 7.41-7.45 (3H, m, Ph: H-4 + ClC_6H_4: H-4,6); 7.48-7.54 (3H, m, Ph: H-3,5 + ClC_6H_4: H-2); 7.99 (2H, d, *J* = 6.9, Ph: H-2,6); 13.32 (1H, s, H-3)

was TMS. The IR spectrum of compound **9a** was recorded on a UR 20 instrument in KBr disks. The synthesized compounds of types **9** and **10** were dried for 7 h in a water-jet pump vacuum at 115°C before determining elemental content and spectral investigations.

N-{[2-(1,3-Diphenyl-1H-pyrazol-5-yl)amino]phenyl}-N'-ethylthiourea (7a). A mixture of compound **11** (0.326 g, 1 mmol) and ethyl isothiocyanate (0.109 g, 1.25 mmol) in 2-propanol (2 ml) was boiled for 1 h. Water (2 ml) and acetic acid (0.5 ml) were added. After cooling, the solid was filtered off, washed with 2-propanol, crystallized from a mixture of acetone–water, 3:1, and dried at 80°C for 8 h.

1-(1,3-Diphenyl-1H-pyrazol-5-yl)-1,3-dihydro-2H-benzimidazole-2-thione (9a). A. A mixture of compound **1a** (0.326 g, 1 mmol) and ethyl isothiocyanate (0.218 g, 2.5 mmol) in anhydrous pyridine (1 ml) was boiled for 2h. The boiling reaction solution was evaporated to half volume and acetic acid (1 ml) was added. Water was added dropwise to the boiling stirred solution until crystallization began. After cooling, the solid was filtered off and washed with 2-propanol. An analytically pure product was obtained. IR spectrum, ν, cm^{-1}: 685, 700, 1220, 1320, 1370, 1450, 1510, 1580, 1605, 3080, 3120, 3160.

Compounds **9b-d,f** and **10a,b** were obtained analogously from compounds **1b-d,f** and **2a,b**. When obtaining compounds **9c,d** the duration of boiling was 4 h. Compounds **9f** and **10b** were purified by crystallization from a mixture of acetic acid–water, 4:1.

B. A mixture of compound **1a** (0.326 g, 1 mmol) and phenyl isothiocyanate (0.297 g, 2.2 mmol) in anhydrous pyridine (1 ml) was boiled for 2 h. The boiling reaction solution was evaporated to half volume and acetic acid (2 ml) was added. Water was added dropwise to the boiling stirred solution until crystallization began. After cooling, the solid was filtered off, washed with 2-propanol and crystallized from a mixture of acetic acid–water, 4:1. Yield 0.268 g (73%); mp 229-231°C. A mixing test with a sample obtained by method A gave no depression of melting point.

B. A mixture of compound **7a** (0.413 g, 1 mmol) and anhydrous pyridine (1 ml) was boiled for 2 h. The reaction mixture was processed analogously to method A. Product **9a** (0.359 g, 97%) of mp 232-233.5°C was obtained. A mixing test with a sample obtained by method A gave no depression of melting point.

1-[3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-5-yl]-1,3-dihydro-2H-benzimidazole-2-thione (9e). A mixture of compound **1e** (0.371 g, 1 mmol) and ethyl isothiocyanate (0.218 g, 2.5 mmol) in anhydrous pyridine (1 ml) was boiled for 12 h. Further ethyl isothiocyanate (0.096 g, 1.1 mmol) was added twice (after each 4 h) . Acetic acid (2 ml) was added and the mixture boiled with stirring while adding water dropwise until crystallization began. After cooling the solid was filtered off, washed with 2-propanol, and crystallized from a mixture of pyridine–water, 4:1).

Compound **10c** was obtained analogously from compound **2c**, but was isolated from the reaction mixture as when obtaining compound **9a** by method A.

REFERENCES

1. O. P. Shvaika and V. N. Artemov, *Zh. Obshch. Khim.*, **41**, 1788 (1972).
2. H. C. Van der Plas, *Ring Transformation of Heterocycles*, Wiley, New York (1972).
3. N. Vivona, S. Buscemi, V. Frenna, and G. Gusmano, *Adv. Heterocycl. Chem.*, **56**, 49 (1993).
4. E. V. Babaev, *Khim. Geterotsikl. Soedin.*, 1564 (1996).
5. G. Hajos, Z. Riedl, and G. Kollenz., *Eur. J. Org. Chem.*, **18**, 3405 (2001).
6. I. O. Zhuravel', S. M. Kovalenko, V. P. Chernykh, and S. V. Rusanova, *Zh. Org. Farm. Khim.*, **1**, No. 3-4, 21 (2003).
7. I. B. Dzvinchuk and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 206 (2005).
8. I. B. Dzvinchuk, A. V. Vypirailenko, and M. O. Lozinskii, *Zh. Org. Khim.*, **33**, 116 (1997).
9. I. B. Dzvinchuk, A. V. Vypirailenko, M. O. Lozinskii, and A. Ya. Il'chenko, *Zh. Org. Farm. Khim.*, **1**, No. 1-2, 13 (2003).
10. I. B. Dzvinchuk, A. V. Turov, and M. O. Lozinskii, *Zh. Org. Farm. Khim.*, **2**, No. 3 (7), 41 (2004).
11. A. M. Nesterenko, A. Ya. Il'chenko, I. B. Dzvinchuk, and M. O. Lozinskii, *Teor. Exp. Khim.*, **40**, 204 (2004).
12. I. B. Dzvinchuk and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 436 (2003).