Condensation reactions of vinyl and ethyl derivatives of 2-amino- and 2-formylimidazoles

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New Schiff bases of 1-vinyl- and 1-ethyl-substituted imidazoles and benzimidazoles were synthesized. The condensation reactions of 2-amino- and 2-formylimidazoles with 2-aminobenzimidazoles are virtually independent of the nature of the substituent ($CH=CH_2$ or Et) at position 1 of the heterocycle. The structures of the azomethines synthesized were established by ^{1}H NMR and IR spectroscopy.

Key words: 1-vinylimidazoles, 1-ethylimidazoles, Schiff base, intra- and intermolecular hydrogen bonds, IR spectra, ^{1}H NMR spectra.

Previously, as part of continuing studies of the structures and properties of functional derivatives of vinylimidazoles[1,2] and their complex compounds,[3,4] we have synthesized for the first time polydentate ligand systems, *viz.*, Schiff bases of the 1-vinyl-substituted imidazole and benzimidazole series,[5] which can be successfully used for preparing polycoordinate chelate structures.[6] However, we failed to isolate azomethine based on 2-formyl-1-vinylbenzimidazole (**1**) and unsubstituted 2-aminobenzimidazole (**2**) under the conditions used in our studies.

In this work, we investigated the possibilities of the synthesis of 2-(1-vinylbenzimidazol-2-yl)methyleneaminobenzimidazole (**3**) and new Schiff bases of a number of 1-ethyl derivatives of 2-amino- and 2-formylimidazoles with the aim of elucidating the effect of the nature of the substituents ($CH_2=CH$ and Et) in the heterocycle on the ability of these compounds to form azomethines. The direction of the condensation reaction and the structural features of the synthesized compounds were studied by ^{1}H NMR and IR spectroscopy.

Results and Discussion

When studying the reaction of 2-formyl-1-vinylbenzimidazole (**1**) with 2-aminobenzimidazole (**2**), we found that the formation of azomethine **3** was a highly reversible reaction (Scheme 1), unlike the condensation reported previously,[5] which gave structurally similar Schiff bases. We synthesized 2-(1-vinylbenzimidazol-2-yl)methyleneaminobenzimidazole (**3**) in an anhydrous solvent in a wide acidity range of the medium, namely, under conditions of acid (HCl and AcOH) and basic hydrolysis (KOH, K_2CO_3, and pyridine) and under conditions of uncatalyzed addition. A change in the reaction temperature from 20 to 80 °C, the use of MeOH, EtOH, benzene, and DMF as solvents, or fusion of the initial components at 160—170 °C did not afford azomethine **3** as the major reaction product. Owing to a substantial shift of the reaction toward the aldehyde and amine components, we isolated a mixture, which was difficult to separate. According to the IR spectral data, the mixture contained the condensation product and the

Scheme 1

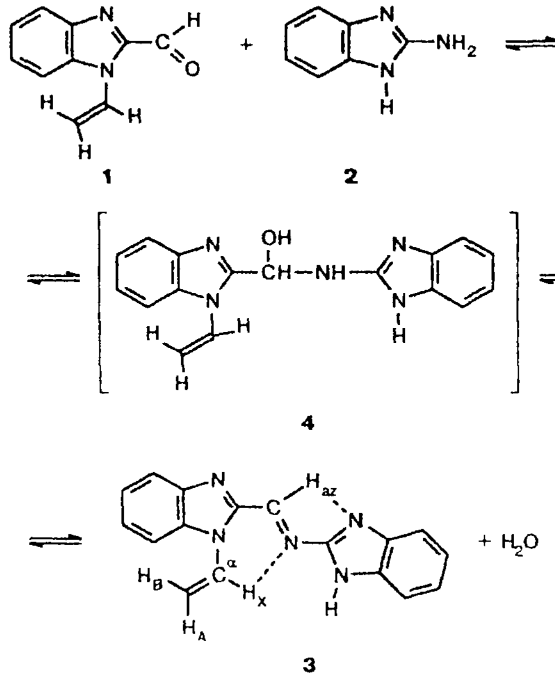

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Table 1. Parameters of the ^1H NMR spectra of compounds **1**, **3**, and **5**

Compound	δ							
	H_A	H_B	H_X	$H_{A'}$	$H_{B'}$	$H_{X'}$	H_{az}	HCHO
1	5.44	5.74	7.71	—	—	—	—	10.05
3	5.48	5.78	8.11	—	—	—	9.46	
5	5.45	5.67	7.87	5.21	5.64	7.49	9.62	

initial reagents. As a result, we have established that the equilibrium of the condensation under study was substantially shifted toward the right if the reaction was carried out with an excess of compound **1** in dioxane under a dry argon atmosphere at room temperature, the stages of the synthesis and isolation of the products being performed at different acidities of the medium. Under the reaction conditions used, azomethine **3** was obtained in 87% yield. It was found that compound **3** is highly sensitive to moisture, which is confirmed by ^1H NMR spectroscopy.

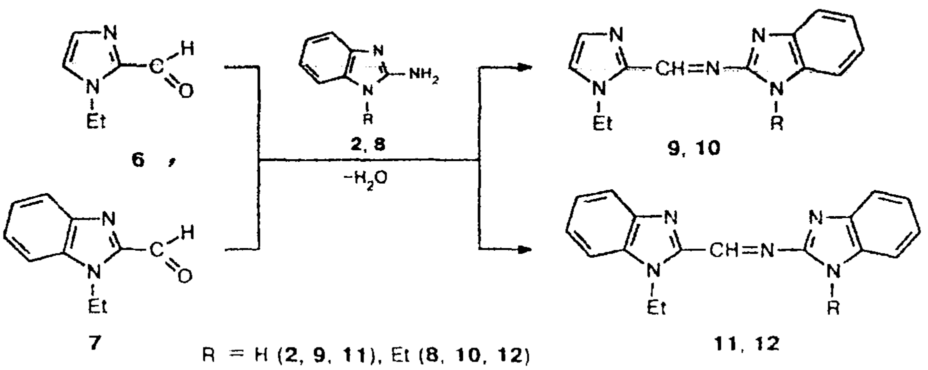
The ^1H NMR spectrum of the freshly prepared condensation product **3** in DMSO-d_6 has low-intensity signals for the protons of the initial 2-formyl-1-vinylbenzimidazole[4] along with signals for the protons of the vinyl and azomethine groups. The presence of the initial compound is most probably associated with the presence of water in the deuterated solvent (Table 1). After storage of base **3** for 5 days, the intensities of signals for the protons belonging to aldehyde **1** observed in the ^1H NMR spectrum increased and the ratio of compounds **1** : **3** (judging from the integral intensities of the signals) was 1 : 4, while the analogous ratio in the initial sample was 1 : 10.

Therefore, the data of ^1H NMR spectroscopy confirm that azomethine **3** readily undergoes hydrolysis in neutral media to the starting components **1** and **2**, unlike structurally similar Schiff bases synthesized by us previously.[5]

In the conditions under study, we failed to detect the formation of an intermediate, *viz.*, carbinolamine **4**, by ^1H NMR spectroscopy. The formation of this intermediate should be accompanied by the appearance of a characteristic signal of the CHOH group in the region of 6.2—6.3 ppm.[2] Previously,[5] the characteristic features of the spatial molecular structures of a series of functional derivatives of 1-vinylimidazoles and the effect of intramolecular interactions on the values of chemical shifts in the ^1H NMR spectra were analyzed in detail. A comparison of the positions of the signals for the protons of the vinyl and azomethine groups in the spectrum of base **3** and the corresponding signals for the protons of 1-vinyl-2-(1-vinylbenzimidazol-2-yl)methyleneaminobenzimidazole (**5**)[5] demonstrated that the low-field arrangement of the chemical shifts for the H_X and H_{az} protons (see Table 1) is retained. This is indicative of the presence of an intramolecular specific C—H...N interaction of the weak-hydrogen-bond type with the participation of the "pyridine" (N(3)) and "azomethine" nitrogen atoms.[5] Consequently, azomethine **3** has predominantly cisoid orientations of the azomethine and vinyl groups and exists as the *E*-isomer. In addition, for a C—H_{az}...N interaction to occur in molecule **3**, the labile proton of the NH group must be localized primarily on the N(1) atom.

The rate of formation of azomethines is determined to a large extent by the basicity of the initial amines and aldehydes.[7] In this connection, we studied the reactions of 2-amino- and 2-formylimidazole derivatives, in which the CH_2=CH substituent at position 1 of the heterocycle is replaced by a stronger electron-donating Et group. We performed condensation with the use of 1-ethyl-2-formylimidazole (**6**), 1-ethyl-2-formylbenzimidazole (**7**), 2-amino-1-ethylbenzimidazole (**8**), and unsubstituted 2-aminobenzimidazole (**2**). Uncatalyzed condensation of aldehyde **6** with amines **2** and **8** in ethanol or dioxane afforded the corresponding azomethines **9** and **10**. However, their yields were only 37 and 40%, respectively. Heating of the reaction mixture to 70 °C or the use of KOH or AcOH as a catalyst did not promote addition. Azomethines **9** and **10** can be obtained in high yields (81 and 90%, respectively) by fusing the initial reagents at 95—100 °C with simultaneous removal of water that formed from the reaction mixture.

Scheme 2

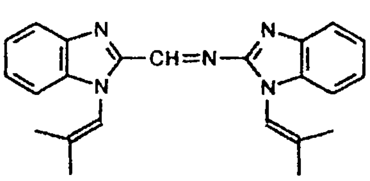


We failed to prepare azomethines by fusing amines **2** and **8** with benzimidazole-2-carbaldehyde **7**; instead, we obtained a mixture of azomethine, the initial compounds, and products of their resinification, which were difficult to separate. At the same time, azomethines **11** and **12** were obtained in good yields (70 and 75%, respectively) in dioxane or ethanol at 70 °C.

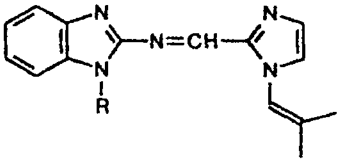
Azomethines **3** and **9—12** are bright-yellow crystalline compounds, which are readily soluble in acetone, acetonitrile, benzene, and dioxane and insoluble in water and diethyl ether. Compound **11**, like its analog **3**, was hydrolyzed in neutral media to the starting amine **2** and aldehyde **7**.

Therefore, the course of condensation of 2-amino- and 2-formylimidazoles is virtually independent of the character of the substituent ($CH=CH_2$ or Et) at position 1 of the heterocycle. This is apparently associated with the fact that the molecules under consideration contain two nucleophilic centers (the N(3) atom of the ring and the NH_2 group), which compete for electrons, as well as with the inductive effect of the substituents at positions 1 and 2 of the heterocycle on the basic properties of the "pyridine" nitrogen atom N(3).[4,8]

It was difficult to interpret the IR spectra of azomethine **3** as well as those of the Schiff bases of the 1-vinylimidazole series synthesized previously,[5] due to possible overlap of absorption bands of the azomethine and vinyl groups and the benzimidazole ring in the 1600—1700 cm^{-1} region. A comparative analysis of the IR spectra of these azomethines and compounds **9—12** made it possible to establish the position of the stretching absorption band of the —N=CH— group. Generally, ν(N=CH) stretching vibrations of the azomethine bond in anils of the heterocyclic and aromatic series are manifested at 1610—1630 cm^{-1} [9,10] and ν($CH=CH_2$) absorption bands of the vinyl group in 1-vinylimidazoles are observed at 1630—1650 cm^{-1}.[3,4] We found that a very intense band observed in the IR spectra of 1-ethyl derivatives of bases **9** and **10** at 1598—1602 cm^{-1}, which overlaps with a low-intensity stretching absorption band of the benzimidazole ring, corresponds to the ν(N=CH) vibration.[11] The spectra of azomethines **11** and **12** have a doublet with maxima at 1600 and 1620 cm^{-1} corresponding to vibrations of the —CH=N— bond and to stretching vibrations of two benzimidazole rings. The IR spectra of the corresponding 1-vinyl derivatives of azomethine **3** as well as those of 1-vinyl-2-(1-vinylbenzimidazol-2-yl)methyleneaminobenzimidazole (**5**), 2-(1-vinylimidazol-2-yl)methyleneaminobenzimidazole (**13**), and 1-vinyl-2-(1-vinylimidazol-2-yl)methyleneaminobenzimidazole (**14**) prepared by us previously[5] have a band at 1630 cm^{-1} corresponding to stretching vibrations of the $CH=CH_2$ group in addition to bands corresponding to stretching vibrations of the —CH=N— group and the benzimidazole rings, which are manifested analogously to those in the spectra of 1-ethyl-substituted compounds **9—12**.



5



13, 14

R = H (**13**), $CH=CH_2$ (**14**)

The IR spectra of azomethines **3**, **9**, **11**, and **13**, in which the amine fragment contains the free NH group in the heterocycle, have broad structured bands due to ν(NH...N) absorption of intermolecular hydrogen bonds. For compounds **9** and **13**, these bands are observed in the 2600—3200 cm^{-1} region, while for derivatives **11** and **3** these bands occur in the 2900—3400 cm^{-1} region. The ν(NH...H) absorption bands in the spectra of these compounds are shifted to the long-wavelength region, while the position of the ν(CH=N) band remains unchanged, which suggests that intermolecular hydrogen bonds are formed with the participation of the imidazole N(3) atom in the case of bases **9** and **13** and with the involvement of the less basic benzimidazole N(3) atom in compounds **11** and **3**.[11]

Experimental

The ^1H NMR spectra (in DMSO-d_6) were recorded on a Bruker DPX-250 instrument (250 MHz, HMDS as the internal standard). The IR spectra were measured on a Specord UR-75 spectrophotometer in KBr pellets or as Nujol mulls. Compounds were synthesized with the use of anhydrous solvents. All operations were carried out under atmospheric pressure (706—725 Torr); under these conditions, the b.p. of dioxane is 94—98 °C.

1-Vinyl derivatives of azomethines **5**, **13**, and **14**, 2-formyl-1-vinylimidazole (**15**), benzimidazole (**1**), and 2-amino-1-vinylbenzimidazole (**16**) were synthesized according to procedures reported previously.[1,2,5]

Ethyl derivatives of imidazoles (6—8) were prepared by hydrogenation of the corresponding 1-vinyl analogs **15**, **1**, and **16** in the presence of Raney nickel (10%) in ethanol in an autoclave at a hydrogen pressure of 30 atm at 50—55 °C for 24 h. The melting point of amine **8** corresponded to the published data.[12]

2-(1-Vinylbenzimidazol-2-yl)methyleneaminobenzimidazole (3). A solution of amine **2** (1.3 g, 9.7 mmol) in dioxane (30 mL) was added dropwise with stirring to a solution of aldehyde **1** (2.017 g, 11.6 mmol) in dioxane (20 mL) at 25 °C for 2 h. The reaction mixture was stirred at 25 °C and

Table 2. Yields, melting or boiling points, and data of elemental analysis for compounds **3** and **6—12**

Compound	Yield (%)	M.p./°C [b.p./°C] (*p*/Torr)	Found / Calculated (%)			Molecular formula
			C	H	N	
3	87	164—166	71.36 71.08	4.31 4.53	24.63 24.39	$C_{17}H_{13}N_5$
6	93	[76—77] (4)	58.27 58.06	6.39 6.45	22.71 22.58	$C_6H_8N_2O$
7	95	46—48	69.03 68.97	5.69 5.75	16.05 16.09	$C_{10}H_{10}N_2O$
8	90	157—158	67.17 67.08	6.93 6.83	26.11 26.09	$C_9H_{11}N_3$
9	81	241—243	65.09 65.27	5.59 5.44	29.16 29.29	$C_{13}H_{13}N_5$
10	90	134—135	67.37 67.42	6.21 6.37	26.32 26.22	$C_{15}H_{17}N_5$
11	70	150—152	70.21 70.59	5.32 5.19	24.42 24.22	$C_{17}H_{15}N_5$
12	75	147—149	71.87 71.92	6.08 5.99	22.27 22.08	$C_{19}H_{19}N_5$

pH 6—8 for 10 h (pH was determined using a universal indicator paper). Then the turbid solution was filtered through a Schott funnel. Two drops of glacial AcOH (pH 4—5) were added to the filtrate and the solvents were completely distilled off at 50—55 °C and at a pressure of 10—15 Torr. The bright-yellow residue was dried at 50—60 °C and at a pressure of 5—7 Torr for 30 min and dissolved in benzene (15 mL). The resulting solution was added dropwise to diethyl ether through a filter. The bright-yellow precipitate that formed was filtered off and dried. Azomethine **3** was obtained in a yield of 2.4 g.

2-(1-Ethylimidazol-2-yl)methyleneaminobenzimidazole (9). A mixture of aldehyde **6** (0.74 g, 6.0 mmol) and amine **2** (0.67 g, 5.0 mmol) was heated at 100 °C for 1 h with simultaneous distillation of water that formed into a cooled trap at a pressure of 10—15 Torr. The resulting yellow mixture was triturated with dioxane (8 mL). The bright-yellow precipitate that formed was filtered off and dried. Azomethine **9** was obtained in a yield of 1.1 g.

1-Ethyl-2-(1-ethylimidazol-2-yl)methyleneaminobenzimidazole (10) was prepared analogously to azomethine **9** from a mixture of aldehyde **6** (0.74 g, 6.0 mmol) and amine **8** (0.81 g, 5.0 mmol). The brown-yellow solid mixture was ground, dissolved in dioxane (5 mL), and poured into water through a Schott funnel. The yellow precipitate that formed was filtered off and dried. Azomethine **10** was obtained in a yield of 1.43 g.

2-(1-Ethylbenzimidazol-2-yl)methyleneaminobenzimidazole (11). Amine **2** (0.67 g, 5.0 mmol) was added portionwise with stirring to a solution of aldehyde **7** (0.87 g, 5.0 mmol) in dioxane (30 mL). The reaction mixture was refluxed for 5 h. Then the solvents were completely distilled off at 50—55 °C and at a pressure of 10—15 Torr. The dry bright-yellow residue was triturated with a 1 : 10 dioxane—ether mixture (22 mL). The resulting yellow precipitate was filtered off and dried. Azomethine **11** was obtained in a yield of 1.1 g.

1-Ethyl-2-(1-ethylbenzimidazol-2-yl)methyleneaminobenzimidazole (12). A solution of amine **8** (0.81 g, 5.0 mmol) in dioxane (15 mL) was added with stirring to a solution of aldehyde **7** (0.87 g, 5.0 mmol) in dioxane (15 mL). The reaction mixture was refluxed with the use of a Dean—Stark trap for 4 h. The solvents were removed to 20—25 mL and the resulting yellow-brown solution was poured into cold diethyl ether (100 mL). The bright-yellow precipitate that formed was filtered off and dried. Azomethine **12** was obtained in a yield of 1.2 g.

The physicochemical constants, the yields, and the data of elemental analysis of the synthesized compounds are given in Table 2.

References

1. L. V. Baikalova, E. S. Domnina, and A. V. Afonin, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 749 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 588 (Engl. Transl.)].
2. A. V. Afonin, L. V. Baikalova, and E. S. Domnina, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1197 [*Russ. Chem. Bull.*, 1996, **45**, 1137 (Engl. Transl.)].
3. L. V. Baikalova, E. S. Domnina, N. N. Chipanina, L. D. Khamaganova, A. V. Afonin, and G. A. Gavrilova, *Koord. Khim.*, 1997, **23**, 95 [*Russ. J. Coord. Chem.*, 1997, **23** (Engl. Transl.)].
4. L. V. Baikalova, E. S. Domnina, T. V. Kashik, G. A. Gavrilova, V. A. Kukhareva, A. V. Afonin, and T. V. Mamaseva, *Zh. Obshch. Khim.*, 1998, **68**, 842 [*Russ. J. Gen. Chem.*, 1998, **68** (Engl. Transl.)].
5. L. V. Baikalova, A. V. Afonin, and E. S. Domnina, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1857 [*Russ. Chem. Bull.*, 1997, **46**, 1763 (Engl. Transl.)].
6. A. D. Garnovskii, A. L. Nivorozhkin, and V. I. Minkin, *Coord. Chem. Rev.*, 1993, **126**, 1.
7. B. A. Porai-Koshits and A. L. Remizov, *Zh. Obshch. Khim.* [*J. Gen. Chem.*], 1954, **24**, 372 (in Russian).
8. L. V. Baikalova, E. S. Domnina, T. V. Kashik, D. K. Danovich, and A. V. Afonin, *Koord. Khim.*, 1998, **24**, 78 [*Russ. J. Coord. Chem.*, 1998, **24** (Engl. Transl.)].

9. A. D. Garnovskii, B. A. Tertov, V. I. Minkin, M. A. Kazanbiev, F. T. Pozharskii, and O. A. Raevskii, *Zh. Obshch. Khim.*, 1966, **36**, 328 [*J. Gen. Chem. USSR*, 1966, **36** (Engl. Transl.)].
10. A. D. Garnovskii, V. A. Kogan, O. A. Osipov, S. G. Kochin, L. I. Kuznetsova, and G. K. Mitina, *Zh. Obshch. Khim.*, 1971, **41**, 1370 [*J. Gen. Chem. USSR*, 1971, **41** (Engl. Transl.)].
11. *Fizicheskie metody v khimii geterotsiklicheskikh soedinenii* [*Physical Methods in Heterocyclic Chemistry*], Ed. A. R. Katritzky, Khimiya, Moscow—Leningrad, 1966, 660 pp. (in Russian).
12. A. M. Simonov and A. D. Garnovskii, *Zh. Obshch. Khim.*, 1961, **31**, 114 [*J. Gen. Chem. USSR*, 1961, **31** (Engl. Transl.)].

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