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Synthesis of condensed heterocycles via cyclopropylimine rearrangement of cyclopropylazoles

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ABSTRACT

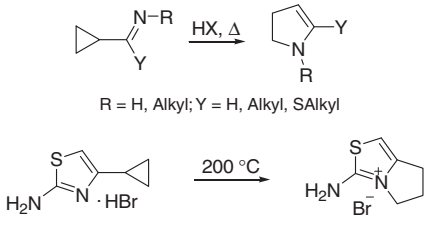
Thermal cyclopropylimine rearrangement of cyclopropylazoles into condensed heterocycles and factors affecting the regioselectivity and conversion are reported. A method of conducting the reaction in the absence of solvents is developed. A series of 2-cyclopropylazoles, including novel examples, is synthesized and their transformations into the corresponding condensed heterocyclic compounds (2,3-dihydro-1*H*-pyrroles and 6,7-dihydro-5*H*-pyrrolo[2,1-*b*]thiazolium salts) are studied.

It has been reported[1] that protonated *C*-cyclopropylimines and the related compounds undergo thermal rearrangement to form five-membered azaheterocyclic compounds. General methods for the synthesis of various alkaloids based on this reaction,[2–7] and a possible mechanism, have been proposed.[2,8,9] The suggested mechanism involves protonation of the imine nitrogen atom, nucleophilic attack of the counterion forming a ring-opened product, and intramolecular alkylation with ring closure. In some cases the rearrangement can also proceed via a different mechanism without the need for a nucleophilic counterion.[9–12] To date, the rearrangement (Scheme 1) has been studied in detail for acyclic derivatives of cyclopropylimines[2,8,9] and cyclopropylthiomethylimidates[13,14] only. To the best of our knowledge, only one example of the rearrangement of a heterocyclic compound has been reported.[15]

We found that α-cyclopropyl-substituted azole hydrohalogenides which contain a cyclopropyliminium fragment undergo ring-opening rearrangement to form condensed pyrrolinium halides or pyrrolines depending on the nature of the starting azole (Scheme 2). This reaction is quite general and some of the heterocyclic compounds obtained are useful synthons for the preparation of both new and known biologically active compounds. For example, pyrrolo[1,2-*a*]imidazoles containing a condensed benzoquinone fragment exhibit pronounced antitumor activity.[16]

The factors affecting the regioselectivity and conversion were studied systematically for 2-cyclopropyl-1*H*-benzimidazole (**1**).[17] The reactions were carried out by heating hydrohalogenides **1a–c** in various solvents or without any solvent; neutral benzimidazoles **1** as well as mixtures with ammonium halides were used (Scheme 3, Table 1).[18] The conversion of compounds **1** into the previously described 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole salts[19] was evident from ^{1}H NMR spectra.

It was found that the reaction rate increases in the transition from hydrochlorides to hydroiodides in all cases. Therefore, the use of iodides is attractive even though they are less readily available. The conversion depends essentially on the temperature and the solvent. For instance, the conversion of highly reactive hydroiodide **1c** in xylene (140 °C, 2.5 h) was just 6% while hydrochloride **1a**, in decalin at 190 °C, rearranged almost completely in the same



Scheme 1.

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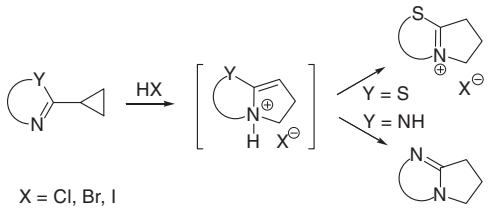
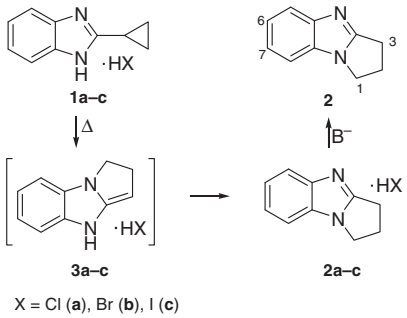


Scheme 2.



Scheme 3.

Table 1
Conversions of 2-cyclopropyl-1*H*-benzimidazoles **1** into compounds **2** under various conditions[18]

Solvent	*T* (°C)	Time (min)	Conversion[a] of **1** (%)		
			1a	**1b**	**1c**
Xylene[b]	140	150	—	—	6
Decalin[c]	150	150	0	5	—
Decalin[c]	190	150	96	100	100
Cyclohexanone[c]	150	60	25	65	80
DMF[b]	150	60	5	20	65
No solvent	200	10	55	95	100
No solvent[d]	200	10	15	100	100

[a] Conversion determined by ^{1}H NMR spectroscopy. The reaction gives only one product, hence its yield is presumed to be equal to the conversion.
[b] The residue was analyzed after solvent removal by evaporation.
[c] The residue was analyzed after an aqueous extraction and evaporation of the water phase.
[d] Thermolysis of **1** was carried out in the presence of 1.2 equiv of NH_4X [X = Cl (**a**), Br (**b**), I (**c**)].

amount of time. Polar solvents accelerate the rearrangement, for example, the conversion of hydrobromide **1b** in decalin (150 °C, 2.5 h) was about 5%, but in cyclohexanone (150 °C, 1 h) the conversion reached 65% in 60 min.

It should be noted that the reaction can be carried out with melted salts without any evident loss of yield and with a decrease in reaction time. For example, hydrobromide **1** completely rearranged at 200 °C in just 10 min. The only limiting factor in this case is the melting point of the hydrohalogenide since the reaction proceeds only in a melt. This can be considered a green process. Iminocyclopropane–pyrroline rearrangement can be carried out by melting the starting benzimidazole **1** with ammonium halogenides (Table 1). This method is useful for the rearrangement of azoles which do not form hydrohalogenides due to their low basicity. The salts **2a–c** can be easily transformed into the free base **2** upon treatment with aqueous alkali followed by extraction with ethyl acetate.

An important feature of the iminocyclopropane–pyrroline rearrangement is the restoration of the heteroaromatic imidazole ring, thus the anticipated intermediate **3** easily transforms into the more stable structure **2**.

We have further studied this rearrangement with a series of substituted cyclopropylbenzimidazoles **4a–d**. The starting 5-methoxy- and 5-methyl-2-cyclopropyl-1*H*-benzimidazoles **4a**[20] and **4b**[21] were obtained by reaction of the corresponding phenylenediamines with cyclopropanecarboxylic acid iminoester, in yields of 65% and 70%, respectively. 5-Nitro-2-cyclopropylbenzimidazole (**4c**) was synthesized according to a known procedure.[22] 2-Cyclopropyl-5,6-dinitro-1*H*-benzimidazole (**4d**) was prepared by nitration of **1** with a mixture of nitric and sulfuric acids in a yield of 87%.[23]

In order to transform cyclopropylbenzimidazoles **4a–d** into 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazoles **5** and **6**, we chose a method[24] which involved melting a mixture of **4** with ammonium iodide at 150 °C with no solvent, (Scheme 4, Table 2), since compounds **4c** and **4d** contain electron-withdrawing groups making them less basic and unable to form hydrohalogenides.

Electron-withdrawing groups, such as the nitro group, decrease the reaction time while electron-donating groups, such as methyl or methoxy, essentially increase the time. For instance, the conversion of **4a** (melt with ammonium iodide) after 1 h was 28% while **4c** was converted quantitatively. Thus, the more positive the charge on the reaction center, the easier the rearrangement proceeds.

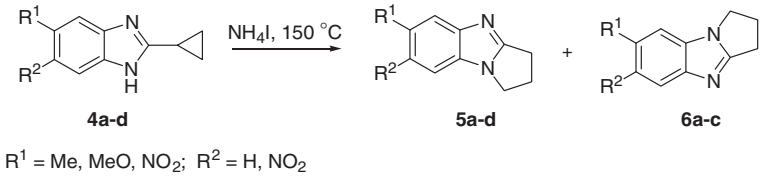
In the case of asymmetrically substituted benzimidazoles **4a–c** the reaction leads to a mixture of two isomers. There is a small prevalence of isomers **5a**,**b** containing the donating groups, while the formation of **6c** is preferred in the case of the nitro derivative. This can be explained by the difference in the electronic effects of the substituents on the nitrogen atoms of the imidazole ring. In the case of compounds **4a**,**b**, cyclization mainly occurs at the nitrogen atom which is *para* relative to the donating groups, and for the nitro derivative, at the *meta* position. Identification of the isomers was based on the spin constants in the ^{1}H NMR spectra and on NOESY experiments.

In most cases when describing the transformations of cyclopropylimine derivatives into pyrrolines, reports do not draw analogy with the vinylcyclopropane–cyclopentene rearrangement[25] and the process is considered as bimolecular.

We have found that in the presence of effective electron-withdrawing groups, as with the dinitro derivative **4d**, the rearrangement can proceed without the need for a nucleophilic counterion by simply melting the starting material (~200 °C). Apparently, the presence of the electron-withdrawing groups creates a sufficient positive charge at the reaction center, and the intermediate in this case is neutral, as in the case of the vinylcyclopropane–cyclopentene and azocyclopropane–pyrazoline rearrangements. However, the yield of the desired product **5d** was lower (40%) than, for example, in the case of melting the reagent with ammonium iodide (Table 2), where the degree of side transformations was extremely low.

Further, we have synthesized and studied the transformations of other cyclopropylazoles, in particular 2-cyclopropylbenzothiazole **7** and 2-cyclopropylbenzoxazole **8** hydrobromides. The benzoxazole **8** was synthesized according to a known procedure,[26] and compound **7** was prepared from 2-aminothiophenol and cyclopropanecarboxylic acid chloride in a yield of 70%. It should be noted that the cyclization of thioamide **9** proceeds in the presence of PPA at 180 °C. In spite of these harsh conditions the 2-cyclopropylbenzothiazole does not rearrange, whereas the transformation of hydrobromide **7** was complete in less than 30 min as a melt at 150 °C,[27] to give the previously described 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*]thiazol-9-ium bromide (**10**)[28] in a yield of 72% (Scheme 5). Thus, hydrobromide **7** is more reactive than 2-cyclopropylbenzimidazole hydrobromide **1b**, which rearranges under these conditions only by 5%.

In contrast to benzothiazole **7**, the rearrangement of benzoxazole **8** proceeds differently. Instead of the expected condensed heterocycle **11** the only reaction product was pyrrolidin-2-one **12**,

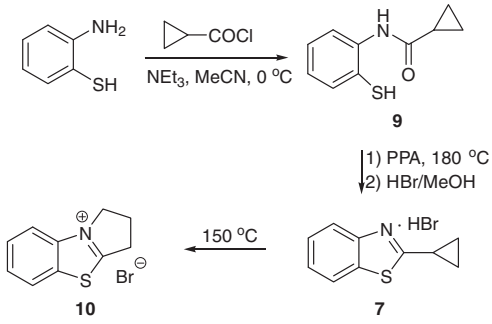


Scheme 4.

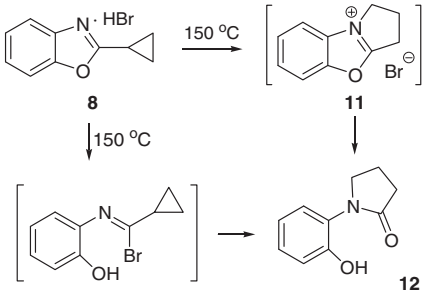
Table 2
Cyclopropylimine rearrangement of substituted 2-cyclopropyl-1*H*-benzimidazoles **4a–d** into compounds **5a–d** and **6a–c** in the presence of ammonium iodide at 150 °C[24]

Compound	R^1	R^2	Time (h)	Yield (%)	Ratio **5**:**6**[a]
4a	MeO	H	6	76	60:40
4b	Me	H	2.5	55	56:44
4c	NO_2	H	0.7	58	45:55
4d	NO_2	NO_2	1	83	—

[a] The ratio was determined from the NMR spectra of the reaction mixtures and did not change considerably after purification.



Scheme 5.



Scheme 6.

which was identified by comparing its ^{1}H NMR spectrum with that previously described.[26] The reaction was carried out by heating hydrobromide **8** for 30 min at 150 °C. Despite preliminary drying of the starting hydrobromide under vacuum and carrying out the reaction under an inert atmosphere, the sample probably contained sufficient water for the formation of compound **12** which can form via two different pathways. Oxazole ring-opening can take place after rearrangement of compound **8** into compound **11**. On the other hand, the unstable oxazole can undergo ring-opening first followed by rearrangement of the resulting bromocyclopropylimine and hydrolysis (Scheme 6).

In conclusion, a simple and environmentally friendly method for the synthesis of condensed azoles has been developed. This method is useful for the synthesis of benzopyrroloimidazoles and benzopyrrolothiazolium salts.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.096.

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18. *The rearrangement of 2-cyclopropylbenzimidazole* (**1**) *into 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole* (**2**): hydrohalogenide **1a–c** (0.5 mmol), either in 2 ml of solvent or without any solvent in a melt, as well as a mixture of neutral benzimidazole with an ammonium halide (0.6 mmol), was heated at the temperature and for the time indicated in Table 1. After cooling to room temperature the solvent (xylene or DMF) was removed in vacuo, or in other cases, the mixture was initially treated with H_2O and the aqueous phase evaporated in vacuum. The residue was analyzed by ^{1}H NMR spectroscopy ($CDCl_3$) to determine the conversion (see Table 1).
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(d, ^4J = 2.6 Hz, 1H, H-4), 7.28 (d, ^3J = 8.8 Hz, 1H, H-7), 12.00 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4 ($2CH_2$) 8.6 (CH), 54.8 (OCH_3), 97.0 (C-4), 109.1 (C-6), 113.7 (C-7), 132.9 (C-3a), 138.4 (C-7a), 154.5 (C-5), 155.9 (C-2).

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23. *2-Cyclopropyl-5,6-dinitro-1H-benzimidazole* (**4d**): 2-cyclopropyl-1*H*-benzimid azole **1** (1.00 g, 5.0 mmol) was added to a mixture of 57% HNO_3 (2 ml) and concentrated H_2SO_4 (10 ml) at 10–15 °C and the mixture was stirred for 1 h and then heated to 70–80 °C and treated with further 57% HNO_3 (2 ml). The mixture was stirred for 30 min, cooled to room temperature, and poured into ice water (100 ml). The resulting precipitate was filtered and dried in air to give **4d**: 87% yield; light yellow crystals; IR (KBr): ν 3604, 3044, 2928, 1632, 1544, 820; EI-MS, m/z: 248 (M^+, 90), 156 (M^+-2NO_2, 100), 130 (25). Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.23; H, 3.30; N, 22.65. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.14–1.34 (m, 4H, $2CH_2$), 2.23–2.38 (m, 1H, CH), 8.31 (s, 2H, 2CH), 9.43 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.1 (CH) 10.3 ($2CH_2$), 111.4 (2CH), 137.7 and 138.0 (2 × 2C), 164.8 (C=N).
24. *General procedure for the rearrangement of substituted 2-cyclopropylbenzimida zoles* (**4a**–**d**) *into substituted 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazoles* (**5** and **6**): compound **4a**–**d** (5.3 mmol) was ground with NH_4I (6.4 mmol) and then heated at 150 °C for the time indicated in Table 2. After cooling to room temperature, the mixture was treated with a solution of NaOH (16 mmol) in H_2O (20 ml) in the case of compounds **4a**,**b**, or the mixture was treated with H_2O (20 ml) in the case of nitrocompounds **4c**,**d**, and the aqueous phase was extracted with EtOAc (2 × 20 ml). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The residue was crystallized from a mixture of toluene and acetonitrile (9:1) to give a regioisomeric mixture of **5a**–**c** and **6a**–**c** or pure compound **5d** (see Table 2).
*6-Methoxy- (**5a**) and 7-methoxy-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imida zoles* (**6a**) (60:40): light-brown crystals; IR (KBr): ν 2928, 2832, 1628, 1484; EI-MS, m/z: 188 (M^+, 67), 173 (M^+-CH_3, 100), 145 (26); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64–2.74 (m, both isomers, 4H, CH_2), 2.98 (t, ^3J = 6.6 Hz, 1.6H, CH_2 for **6a**), 3.01 (t, ^3J = 7.1 Hz, 2.4H, CH_2 for **5a**), 3.85 (s, 2.4H, OCH_3 for **5a**), 3.87 (s, 3.6H, OCH_3 for **6a**), 4.13 (t, ^3J = 7.0 Hz, 1.6H, NCH_2 for **6a**), 4.14 (t, ^3J = 6.9 Hz, 2.4H, NCH_2 for **5a**), 6.85–6.90 (dd, ^3J = 8.7, ^4J = 2.4 Hz, 2H, both isomers), 7.10 (d, ^4J = 2.4 Hz, 0.8H, for **6a**), 7.17 (d, ^4J = 2.4 Hz, 1.2H, for **5a**), 7.42 (d, J = 8.7 Hz, 1.2H, for **5a**), 7.49 (d, J = 8.7 Hz, 0.8H, for **6a**); ^{13}C NMR (75 MHz, DMSO-d_6) δ for **5a**: 22.6 (C-2), 25.1 (C-3), 42.1 (C-1), 54.9 (OCH_3), 101.3 (C-5), 109.5 (C-7), 109.8 (C-8), 126.3 (C-8a), 148.5 (C-4a), 154.5 (C-6), 160.9 (C=N); for **6a**: 22.3 (C-2), 25.2 (C-3), 41.8 (C-1), 55.0 (OCH_3), 93.5 (C-8), 109.7 (C-6), 118.3 (C-5), 132.2 (C-8a), 141.9 (C-4a), 154.6 (C-6), 159.6 (C=N).
6,7-Dinitro-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (**5d**): light yellow crystals, mp 256–258 °C; IR (KBr): ν 3768, 3028, 2956, 1620, 1544, 1528; EI-MS, m/z: 248 (M^+, 100), 218 (16), 172 (6). Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.50; H, 3.37; N, 22.44. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.69 (quin, ^3J = 7.5 Hz, 2H, CH_2), 3.10 (t, ^3J = 7.5 Hz, 2H, CH_2), 4.28 (t, ^3J = 7.5 Hz, 2H, NCH_2), 8.37 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.0 (C-2), 25.1 (C-3), 43.6 (C-1), 108.7 and 115.5 (C-5, C-8), 132.6 and 136.7 (C-6, C-7), 137.5 (C-4a), 148.3 (C-8a), 168.8 (C=N).
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27. *2,3-Dihydro-1H-benzo[d]pyrrolo[2,1-b]thiazol-9-ylium bromide* (**10**): concentrated hydrobromic acid (3.7 ml) was added to a suspension of 2-cyclopropylben zothiazole (5.40 g, 31 mmol) in a mixture of H_2O (20 ml) and MeOH (10 ml). The mixture was stirred for 1 h and evaporated. The residue (compound **7**) was heated at 150 °C for 30 min and allowed to cool to room temperature. The mixture was dissolved in 2-propanol (50 ml), filtered, concentrated, and crystallized from 2-propanol to give the known[28] product **10** in 72% yield.
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