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Unexpected opening of benzimidazole derivatives during 1,3-dipolar cycloaddition

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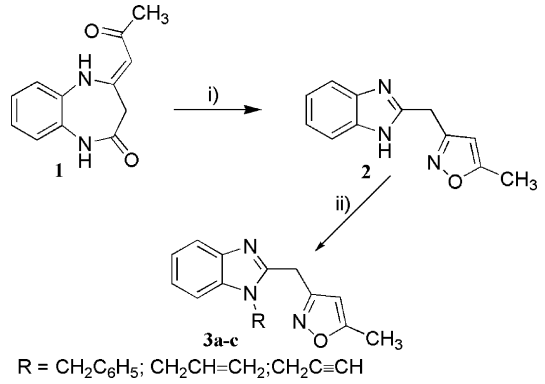
Abstract—Hydroxylamine hydrochloride adds via a Michael reaction on the acetonylidene moiety of (4*Z*)-(2-oxopropylidene)-1,2,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one, leading only to 2-[(5-methyl-isoxazol-3-yl)]methyl]benzimidazoles. This report describes the difference of reactivity of *C*-phenyl-*N*-phenyl formohydrazonoyl chloride with benzimidazole. For the N-substituted benzimidazole, an unexpected opening of the azole ring occurs, which was confirmed by single crystal X-ray diffraction analysis.

Benzimidazole derivatives are compounds that have received much attention because of their applications in several areas. They are used as antibacterial,[1] anticancer,[2,3] and antiulcer agents.[4,5] They also have herbicidal, insecticidal and complexing properties.[6–8] Our investigations in the field of heterocyclic compounds led us to develop a new method for the synthesis of different 2-substituted benzimidazoles.[9–13] Thus, when hydroxylamine hydrochloride was reacted with (4*Z*)-(2-oxopropylidene)-1,2,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one, in ethanol, 2-[(5-methyl-isoxazol-3-yl)]methyl]benzimidazole **2** was obtained exclusively.[14]

Substitution of the nitrogen atom of **2** under solid–liquid phase transfer catalytic conditions led, with benzyl chloride, allyl bromide and propargyl bromide, to benzimidazoles **3a**–**c** (Scheme 1).[15]

In order to obtain tricyclic compounds which are expected to show interesting pharmacological properties, dipolar-1,3 cycloaddition reactions with these benzimidazoles were studied. Diphenylnitrilimine **4**, used in this study, was generated in situ by the reaction of *C*-phenyl-*N*-phenylformohydrazonoyl chloride with triethylamine using a method described in the literature.[16]



Scheme 1. Reagents and conditions: (i) NH_2OH, HCl, ethanol, reflux; (ii) K_2CO_3, DMF, RX, TBAB.

The reactivity of the non-substituted benzimidazole **2** and of the N-substituted compounds **3a**–**c** towards hydrazonoyl chloride **4** is reported in this letter.

Keywords: Benzimidazole; Diphenylnitrilimine; 1,3-Dipolar cycloaddition.
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Moreover, an interesting cleavage reaction of the azolic ring occurs in the case of compounds **3a–c**, which was confirmed in the case of compound **6a** by X-ray analysis.

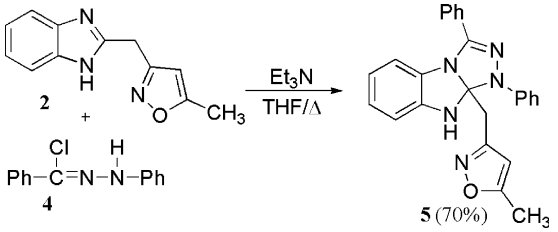
The reaction of *C*-phenyl-*N*-phenylformohydrazonoyl chloride with 2-[(5-methylisoxazol-3-yl)methyl]benzimidazole **2**, under reflux, in tetrahydrofuran in the presence of triethylamine afforded a product, which gave analytical data consistent with triazolo benzimidazole **5**[17] (Scheme 2).

The mass spectrum ($m/z = 407$) and elemental analysis were in accord with the molecular formula $C_{25}H_{21}N_5O$. The ^1H NMR spectrum exhibited the characteristic signals of benzimidazole and isoxazole groups and the protons assignable to the methylene group appeared as an AB system. The AB system is observed both at room temperature and at 110 °C, as expected for a methylene linked to a chiral carbon atom.

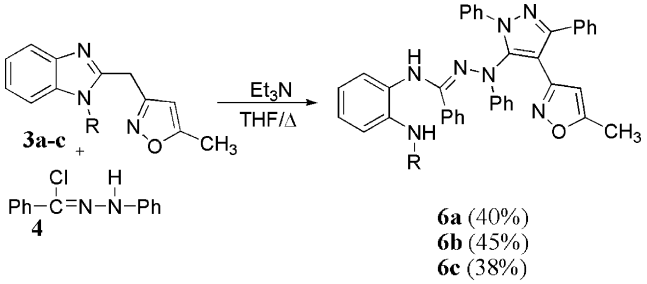
When the substituted benzimidazoles **3a–c** were reacted under the same conditions, a quite different result was obtained (Scheme 3).

The proton spectrum of **6a**[17] in $CDCl_3$ showed a singlet at $\delta = 2.16$ ppm, which was assigned to the protons of the isoxazolic methyl group and a signal at $\delta =$ 4.34 ppm due to the methylenic protons of the benzylic group. A singlet at $\delta = 5.72$ ppm was also observed, corresponding to the isoxazolic proton. Moreover, it was interesting to note that:

(a) No signal was observed for the protons of the methylene group in position 2 of the benzimidazole.
(b) A large excess of aromatic protons incompatible with a single cycloaddition reaction were also observed.



Scheme 2.



Scheme 3.

The ^{13}C NMR spectrum confirmed the lack of a methylene group linked at the 2 position of the benzimidazole. Also, no signal assignable to one or two quaternary carbon atoms, which may result from a dipolar addition on the carbon–nitrogen or carbon–carbon double bond of the bis-heterocyclic system, was observed.

Mass spectrometric analysis was performed by chemical ionization with the presence of a pseudo-molecular ion MH^+ ($m/z = 692$) proving that two molecules of the dipole **4** were involved in the reaction process.

The structure of compound **6a** was determined by X-ray diffraction analysis,[18] which confirmed the spectral characterization (^1H NMR and ^{13}C, IR and mass spectrometry).

An ORTEP representation of **6a** along with the numbering scheme is shown in Figure 1. This study indicated that cleavage of the benzimidazole ring had occurred and that two molecules of the dipole were involved in the reaction. In compound **6a** these appear in acyclic form in the C(45), N(5), N(4) moiety and as part of the pyrazolic ring in N(3), N(2) and C(33).

Considering these results, a reaction mechanism can be advanced to account for the formation of compounds **6a–c**. In the first step, [2+3] cycloaddition of the dipole on the benzimidazole imine double bond leads to a tricyclic intermediate **A** bearing a triazoline moiety which structure is similar to **5**. The rearrangement of intermediate **A** into the highly conjugated intermediate **B** by cleavage of the N1–C2 bond of the benzimidazole can then occur. Next, a second cycloaddition reaction of the dipole to the exocyclic bond of **B** can take place leading to a spiro intermediate **C**. Finally, opening of the triazoline ring of tetracyclic intermediate **C** leads to **6a–c** (Scheme 4).

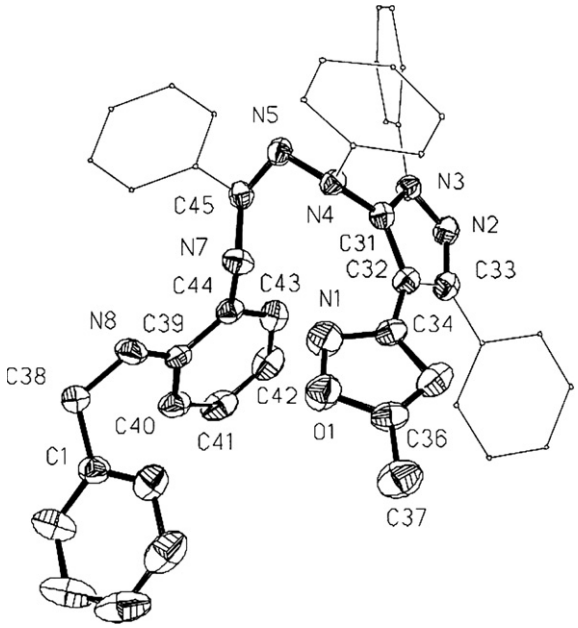
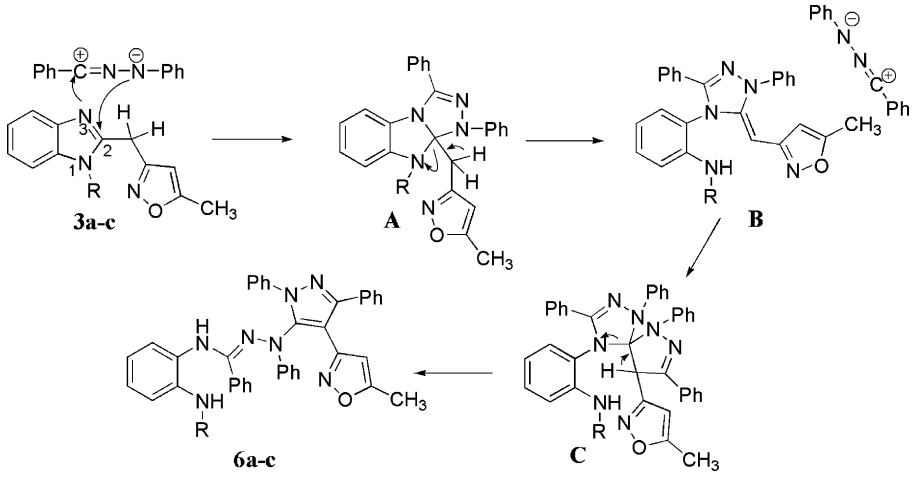


Figure 1. ORTEP representation of **6a**.



Scheme 4.

A Zn complex was prepared by the equimolar addition of $ZnCl_2$ to an acetonitrile solution of **6a**. A pseudo-molecular ion $[M,ZnCl]^+$ was observed at ($m/z = 790$, 55%) with the protonated molecular ion at ($m/z = 692$, 100%).

The addition of diphenylnitrilimine to N-substituted benzimidazoles leads unexpectedly to N,N′-disubstituted *o*-phenylenediamine after opening of the azolic ring. This reaction involved two nitrilimine moieties. A study of the complexing properties of compounds **6a**–**c** is in progress.

Acknowledgement

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14. Synthesis of 2-[(methyl-isoxazol-3-yl)methyl]benzimidazole **2**. A mixture of (4*Z*)-(2-oxopropylidene)-1,2,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (10 mmol) and hydroxylamine hydrochloride (10 mmol) in ethanol (40 mL) was refluxed for a period of 2 h. After neutralization with $NaHCO_3$, the solid formed was filtered, dried and recrystallized from ethyl acetate to afford **2** as a colorless solid (70%, mp 188–189 °C ethyl acetate). ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.36 (s, 3H), 4.26 (s, 2H), 6.23 (s, 1H), 7.00–7.60 (m, 4H). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20. Found: C, 67.10; H, 5.40.
15. Synthesis of 1-alkyl-2-[(methyl-isoxazol-3-yl)methyl] benzimidazoles **3a**–**c**. K_2CO_3 (1.39 g, 10 mmol) and tetrabutylammonium bromide (0.154 g, 0.5 mmol) were added to a mixture of **2** (1.06 g, 5 mmol) and alkyl halide (10 mmol) in tetrahydrofuran (60 mL). The resulting mixture was refluxed for 24 h. After cooling to room temperature, filtration and removal of the solvent, the residue was purified by chromatography on silica gel to give **3a**–**c**. Data for **3a**, solid (65%, mp 111–112 °C hexane). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 4.20 (s, 2H), 5.30 (s, 2H), 5.90 (s, 1H), 7.00–7.76 (m, 9H).
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17. General procedure for the synthesis of **5** and **6a**–**c**: To a solution of *C*-phenyl-*N*-phenylformohydrazonoyl chloride (1.19 g, 5.2 mmol) and 2-[(methyl-isoxazol-3-yl)methyl]-benzimidazole **2** (1.06 g, 5 mmol) in tetrahydrofuran (50 mL) was added triethylamine (3 mL) at room temperature. The reaction mixture was refluxed for 24 h. After cooling, triethylammonium chloride was removed by filtration and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (eluent: ethyl acetate/hexane, 2/8). Compound **5** was obtained as a solid (1.4 g, 70%, mp 190–191 °C ethanol). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 3.95 (q, 2H, $^3J = 16.5$ Hz), 5.82 (s, 1H), 6.90–7.90 (m, 14H). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 12.14, 25.90, 102.0, 129.0, 133.9, 142.9, 150.5, 158.8, 170.0. MS (EI) *m*/*z*: 407 (M^+, 41%), 311 (61%), 194 (30%), 91 (100%). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19. Found: C, 73.20; H, 4.90.

Compound **6a** was obtained as a solid (1.6 g, 40%, mp 152–154 °C ethanol), ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 4.34 (s, 2H), 5.72 (s, 1H), 6.25–7.90 (m, 31H). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 12.17, 47.60, 102.60, 162.90, 168.90. MS (DCI, NH_3) m/z: 692 (MH^+, 60%), 393 (90%), 302 (100%).

18. Crystallographic data for **6a**: ($C_{45}H_{37}N_7O$, $M = 691.82$), monoclinic, $P2_1/c$, $Z = 4$, $a = 14.390(2)$ Å, $b = 14.437(1)$ Å, $c = 18.703(3)$ Å, $\beta = 108.64(2)°$, $V = 3681.7(8)$ Å^3, $\rho_{calcd} = 1.248$ g cm^{-3}, $F(0\,0\,0) = 1456$, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $\mu(MoK_\alpha) = 0.077$ mm^{-1}, a total of 21,257 reflections (5074 independent, $R_{int} = 0.0393$), on a STOE-IPDS diffractometer at 273 K. The structure was refined on F to $R = 0.0438$, $R_w = 0.1211$ (487 reflections with $I > 2c(I)$). CCDC 164805 contains the supplementary crystallographic data for this letter.