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A new route to 1,4-disubstituted 5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-ones†

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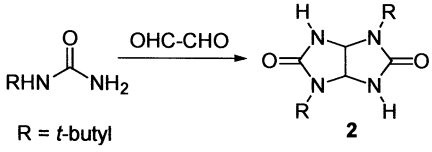
Abstract—1,4-Disubstituted 5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-ones were prepared by one-pot criss-cross cycloaddition reactions of 1,4-disubstituted 1,4-diazabuta-1,3-dienes with HNCS and HNCO generated in situ from potassium salts by acetic acid. © 2002 Elsevier Science Ltd. All rights reserved.

Structures with carbamide fragments have a broad spectrum of biological activity. For example, 1,3,4,6-tetramethylperhydroimidazo[4,5-*d*]imidazol-2,5-dione was successfully used as a day-time tranquilizer and was introduced into medical practice in 1979 under the name Mebicar.[1]

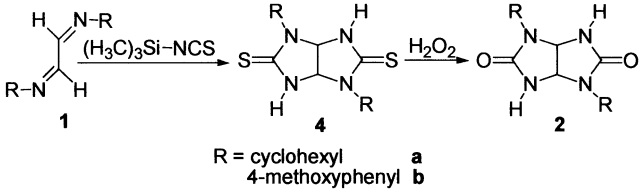
Symmetrical compounds with this skeleton (**2** or **4**) were prepared either by a condensation of *N*-substituted ureas with glyoxal under acidic catalysis or by a criss-cross addition on **1**.

For example, *N*-(*t*-butyl)urea with glyoxal and HCl catalyst forms **2** in a 62% yield[2] (Scheme 1).

Reactions of 1,4-diazabuta-1,3-dienes **1** are rare in the literature. Thus, Sakamoto et al.[3] described the reaction of 1,1′-biisoquinolines with aryl and benzoyl isocyanates. Takahashi[4] described the reaction of trimethylsilylisothiocyanate with symmetrical 1,4-diazabuta-1,3-dienes derived from aromatic and aliphatic amines (Scheme 2). The criss-cross addition on **1a** in THF with trimethylsilylisothiocyanate affords 1,4-dicyclohexylperhydroimidazo [4,5-*d*]imidazol-2,5-dithione **4a** in 53% yield, and its oxidation with 30% H_2O_2 gave **2a** in 75% yield.[4] Reaction of **1b** with trimethylsilylisothiocyanate (dioxane, 3 h) afforded **4b** (24%) at room temperature.[4]



Scheme 1.



Scheme 2.

On the other hand, criss-cross cycloadditions on 2,3-diazabuta-1,3-dienes are well documented. In 1917 Bailey and Moore[5] described the reaction between some aromatic aldazines and thiocyanic acid or cyanic acid in acetic acid. The reaction was carried out by a slow addition of potassium thiocyanate or cyanate into a solution of the aldazine in acetic acid. Similarly Schantl et al.[6] prepared criss-cross products from various aliphatic ketazines by a slow addition of an acetic acid solution of the ketazine into aqueous potassium cyanate. The molar ratio of acetic acid and cyanate was 1:1, in slight excess over the azine. Such a modification was used in order to avoid exposure of the already formed criss-cross adduct to an acidic environment which would cause its decomposition.

Keywords: criss-cross; cycloaddition; glyoxalimine; 1,4-diazabuta-1,3-diene; 5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-one.

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† Dedicated to Professor Jaroslav Jonas on the occasion of his 65th birthday.

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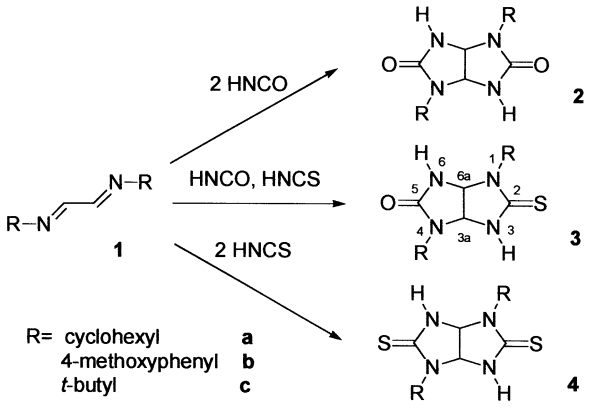
In our communication we would like to report a new and quick method for the preparation of mixed derivatives, 5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-ones **3**, substituted at positions 1 and 4 (Scheme 3). To the best of our knowledge, this is the only method for the synthesis of these substances.

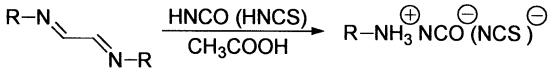


Scheme 3.

We attempted to synthesize these products by criss-cross cycloaddition of HNCS and HNCO with 1,4-disubstituted 1,4-diazabuta-1,3-dienes **1**. The diazabutadienes **1a–c** were prepared from glyoxal and the corresponding amines.[7]

When we tried to prepare criss-cross adducts from simple aliphatic or aromatic 1,4-diazabuta-1,3-dienes **1** and HNCS or HNCO according to Bailey's[5] or Shantl's[6] method, only traces of the desired products were obtained. In some cases, the major isolated product was the corresponding salt of the amine due to the instability of substituted 1,4-diazabuta-1,3-dienes **1** in acid (Scheme 4).

Slow addition of the substituted 1,4-diazabuta-1,3-diene **1** into potassium isocyanate dissolved in carefully dried acetic acid, improved the procedure. Due to the large difference in reactivity between HNCS and HNCO, we were able to obtain mixed cycloadducts **3** (Scheme 3) in a one-pot procedure, when substituted 1,4-diazabuta-1,3-dienes **1** were added to a mixture of both acids. We examined the influence of concentration, as well as



Scheme 4.

Table 1. Effect of reactant concentration ratio upon composition of the reaction mixture after reaction of **1a** with HNCO and HNCS

1a starting concentration $c=0.1$ mol/l (ambient temperature), 1 h					
c_{KNCS} (mol/l)	c_{KNCO} (mol/l)	**2a** (mol%)	**3a** (mol%)	**4a** (mol%)	Overall yield [%]
0.10	0.10	2	56	42	47
0.10	0.15	3	65	32	42[a]
0.10	0.21	3	81	16	56
0.10	0.40	7	82	11	52

[a] 30 min.

Table 2. Effect of temperature upon composition of the reaction mixture after reaction of **1a** with HCNO and HCNS

1a starting concentration $c=0.1$ mol/l ($c_{KNCS}=0.1$ mol/l, $c_{KNCO}=0.2$ mol/l), 1 h				
Temperature (°C)	**2a** (mol%)	**3a** (mol%)	**4a** (mol%)	Overall yield (%)
15	3	63	33	45
30	4	70	26	49
45	3	71	26	47

Table 3. Composition of reaction mixtures after reaction of **1a–c** with mixtures of acids in ratio $c_{HNCO}/c_{HNCS}=2$, (reaction time 1 h)

	R	**2** (mol%)	**3** (mol%)	**4** (mol%)	Overall yield (%)
1a	Cyclohexyl	3	71	26	47
1a	Cyclohexyl[a]	3	84	13	60
1b	4-Methoxyphenyl	0	96	4	43
1c	*t*-Butyl[b]	0	76	24	54

[a] 30 min, $c_{KNCO}=0.25$ mol/l, $c_{KNCS}=0.25$ mol/l, $c_{diene}=0.125$ mol/l.
[b] Vigorous agitation.

temperature, upon the composition of the reaction mixture from **1a** with the mixture of HCNO and HCNS. Results are summarized in Tables 1 and 2.

Based on the results shown in Table 1, the ratio of concentrations $c_{HNCO}/c_{HNCS}=2$ was used for further experiments.

The major products under these conditions were mixed criss-cross cycloadducts **3**, which were separated, for analysis, on a silica gel column (CH_2Cl_2/acetone 5:1) and characterized.[8] Compositions of final mixtures were analyzed by ^{1}H NMR spectra and the results are presented in Table 3.

In the NMR spectrum of symmetrical molecules **2a** and **4a** there was only one signal for the protons H-3a and H-6a, as a singlet with double intensity, $\delta=5.26$ ppm and $\delta=5.66$ ppm, respectively. In the mixed derivative **3a**, the signals of these protons differ in chemical shift ($\delta=5.40$ ppm, $\delta=5.52$ ppm), and their coupling constant $^3J_{H3a-H6a}=8.9$ Hz suggests a *cis* orientation. The second coupling with the proton at the neighboring nitrogen atom appears for only one of the H-3a and H-6a proton signals.‡ This coupling with $^3J_{H3a-H3}=2$ Hz disappears after addition of D_2O. The stereochemistry of the structure **3a** has been proved by X-ray analysis.[9] The crystal packing of **3a** is shown in Fig. 1.

We propose that the substituted 1,4-diazabuta-1,3-dienes **1** react with the more reactive species in the reaction mixture i.e. thiocyanic acid, forming an intermediate (1+1 adduct), which then reacts with cyanic acid present in excess. Under properly chosen conditions product **3** predominates and the reaction represents a facile method for the preparation of such a mixed product.

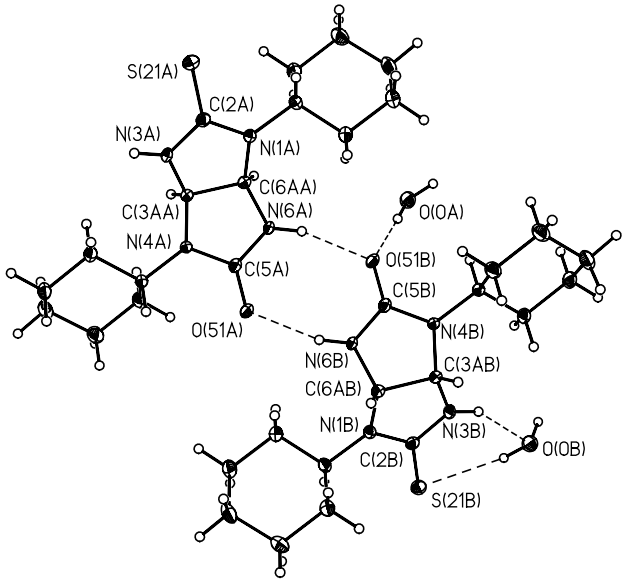


Figure 1. Crystal packing of compound **3a**.

‡ ^{1}H NMR (300 MHz) Bruker Avance in DMSO-d_6, at 600 MHz in CD_3COCD_3 both couplings are visible.

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8. Melting points were measured on a Boetius Rapido PHMK 73/2106 (Wägetechnik) instrument. TLC was carried out on Silufol (Kavalier); detection was made by Fluotes Universal (Quazlampen, Hanau) or in I_2 vapors. NMR spectra were recorded on Bruker Avance 300.
1,4-Dicyclohexyl-5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-one (3a)
Mp 290–292°C. ^{1}H NMR (300 MHz, DMSO-d_6): 1.16–1.80 (m, 20H), 3.38–3.45 (m, 1H), 4.11–4.19 (m, 1H), 5.40 (d, 1H, $J=8.9$ Hz), 5.52 (dd, 1H, $J=8.9$ Hz, $J=2.0$ Hz), 7.54 (s, 1H, CO-N**H**), 8.94 (s, 1H, CS-N**H**). ^{13}C NMR (75.5 MHz, DMSO-d_6): 24.7, 25.3, 28.6, 28.9, 30.8, 31.1, 51.2, 54.3, 67.5, 67.6 (O=C-N-**C**H-CH-N-C=S), 67.6 (O=C-N-CH-**C**H-N-C=S), 158.3 (**C**=O), 181.0 (**C**=S). MS (70 eV) *m*/*z* (%): 325 (5), 323 (20), $[M]^+$ 322 (8), 167 (9), 166 (100), 157 (16), 98 (63), 84 (75).
1,4-Di(4-methoxyphenyl)-5-thioxoperhydroimidazo[4,5-*d*]-imidazol-2-one (3b)
Mp 290–291°C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): 3.76 (s, 3H, OC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 5.96 (d, 1H, $J=8.3$ Hz, O=C-N-C**H**-CH-N-C=S), 6.04 (d, 1H, $J=8.3$ Hz, O=C-N-CH-C**H**-N-C=S), 6.93 (2H, d, $J=8.6$ Hz, Ar**H**), 6.98 (2H, d, $J=8.6$ Hz, Ar**H**), 7.32 (2H, d, $J=8.6$ Hz, Ar**H**), 7.45 (2H, d, $J=8.6$ Hz, Ar**H**), 8.20 (s, 1H, CO-N**H**), 9.72 (s, 1H, CS-N**H**). ^{13}C NMR (75.5 MHz, DMSO-d_6): 55.3 (Ar-O**C**H$_3$), 55.3 (Ar-O**C**H$_3$), 69.5 (O=C-N-**C**H-CH-N-C=S), 72.0 (O=C-N-CH-**C**H-N-C=S), 115.0 (Ar), 115.0 (Ar), 122.4 (Ar), 128.9 (Ar), 130.5 (Ar-N), 130.6 (Ar-N), 155.9 (Ar-O), 156.6 (Ar-O), 158.1 (**C**=O), 182.0 (**C**=S). MS (70 eV) *m*/*z* (%): 372 (8), 371 (21), 370 $[M]^+$ (99), 311 (17), 267 (18), 253 (20), 222 (25), 221 (37), 205 (31), 190 (31), 165 (49), 150 (45), 149 (94), 134 (100).
1,4-Di(*t*-butyl)-5-thioxoperhydroimidazo[4,5-*d*]imidazol-2-one (3c)
Mp 259–260°C. ^{1}H NMR (300 MHz, DMSO-d_6): 1.33 (s, 9H, C-C**H**$_3$), 1.56 (s, 9H, C-C**H**$_3$), 5.42 (d, 1H, $J=8.3$ Hz, O=C-N-C**H**-CH-N-C=S), 5.57 (dd, 1H, $J=8.3$ Hz, $J=2.0$ Hz, O=C-N-CH-C**H**-N-C=S), 7.50 (s, 1H, O=C-N**H**), 8.86 (s, 1H, S=C-N**H**). ^{13}C NMR (75.5 MHz, DMSO-d_6): 28.0 (O=C-N-C(**C**H$_3$)$_3$), 28.3 (S=C-N-C(**C**H$_3$)$_3$), 52.3 (O=C-N-**C**(CH$_3$)$_3$), 55.6 (S=C-N-**C**(CH$_3$)$_3$), 68.2 (O=C-N-**C**H-CH-N-C=S), 69.4 (O=C-N-CH-**C**H-N-C=S), 158.8 (**C**=O), 182.0

(**C**=S). MS (70 eV) *m*/*z* (%): 273 (4), 272 (14), $[M]^+$ 270 (100), 213 (10), 199 (42), 157 (25), 140 (42), 125 (36), 116 (28), 100 (25).

9. The X-ray data of **3a** were collected on a KUMA KM-4 CCD kappa-axis diffractometer using a graphite monochromatized Mo–Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (Sheldrick, G. M. *SHELX-97 program package*; University of Göttingen, 1997; Sheldrick, G. M. *SHELXTL V 5.1*; Bruker AXS GmbH.) Non-hydrogen atoms were refined anisotropically while hydrogen atoms were inserted in calculated positions and isotropically refined assuming a 'ride-on' model. Data are deposited in Cambridge Crystallographic Data Centre as supplementary publication number CCDC 179213.
The crystal structure is composed of **3a** molecules and water which are bound into a two dimensional network by a system of four types of hydrogen bonds: N(6)–H···O(51)= C(5) (2.876 Å) between two enantiomers of the molecules of **3a** forming dimers. These dimers are further connected by hydrogen bonds of water molecules through N(3)–H···O (2.868 Å), O–H···O(51)=C (2.755 Å), and O–H···S(21) (3.263 Å).