Thermal rearrangement of an *N*-hydroxyimidazole thiocarbamoyl derivative as a simple entry into the 4-thioimidazole motif

Luís F. V. Pinto, Gonçalo C. Justino, Abel J. S. C. Vieira, Sundaresan Prabhakar,* and Ana M. Lobo*

Chemistry Department, REQUIMTE/CQFB, Faculty of Sciences and Technology, New University of Lisbon, and SINTOR-UNINOVA, 2829-516 Monte de Caparica, Portugal
E-mail: aml@fct.unl.pt

Dedicated to Professor António M. d'A. Rocha Gonsalves on the occasion of his 70th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.503

Abstract
A thermal rearrangement of a thio-ester derivative of *N*-hydroxyimidazole gives rise, in a clean reaction, to the corresponding 4- and 2-thiol ester derivatives in a 1 : 1 ratio.

Keywords: Sigmatropic rearrangements, 4-thioimidazole, thiocarbamoylation

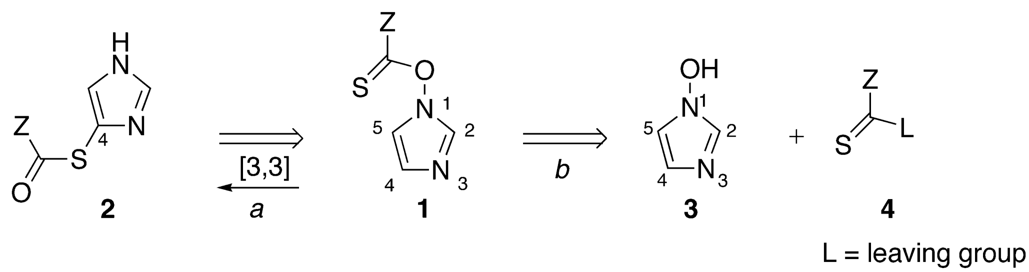
Introduction

Imidazole is a heterocycle which appears often in natural products of great importance, such as peptides, amino acids and alkaloids.[1] Its role in general acid-base catalysis has secured it an undisputed prominence among commonly encountered heterocycles, and explains its crucial action in the mechanism of enzymes.[2] Often the imidazole ring has suffered further metabolism and may appear substituted with heteroatoms, but to this date there is no simple direct way to introduce a sulfur into position 4 of such a heterocycle.[3]

In connection with the need to introduce a sulfur, we sought to use a thermally induced rearrangement as was earlier disclosed by us for ene-hydroxylamine derivatives.[4,5] The sulfur atom is, in this strategy, part of a reactive thiocarbonyl, a functional group which can modulate molecular reactivity, and has found ample use in synthesis.[6] We report here our results on a formal sigmatropic rearrangement to achieve this goal.

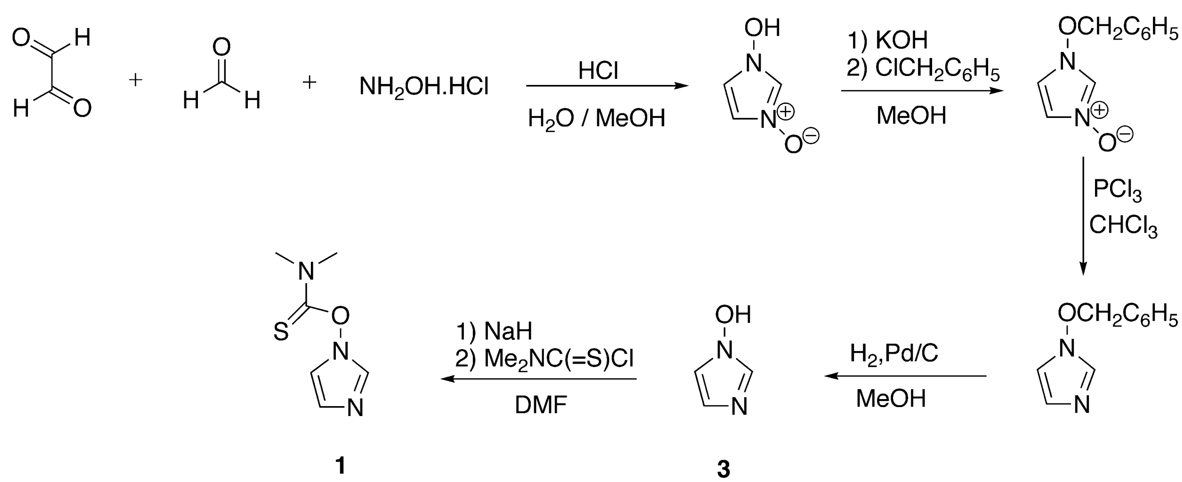
Results and Discussion

The substrate selected, the imidazole thiocarbonyl derivative **1**, could, in principle through a [3,3]-sigmatropic rearrangement, deliver the sulfur to C-4 of the heterocycle to give rise to **2** (Scheme 1, *a*). By a simple retrosynthesis access to **1** was reduced to the synthesis of *N*-hydroxyimidazole (**3**), since there are compounds of type **4** commercially available (Scheme 1, *b*).



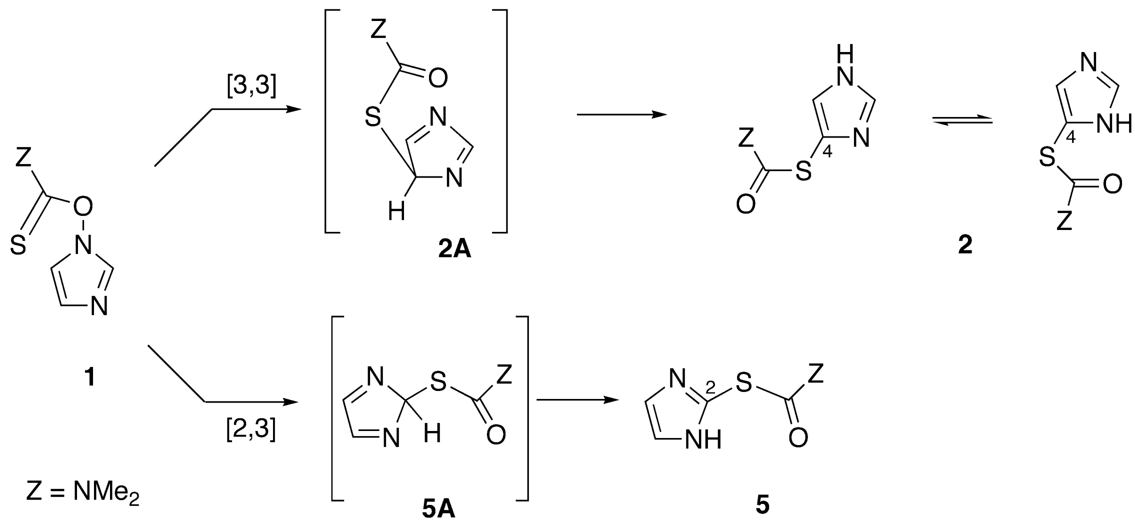
Scheme 1. Retrosynthetic analysis for **2** involving a [3,3]-sigmatropic rearrangement.

The actual synthesis of compound **1** (Z = NMe_2) is shown in Scheme 2, where for the steps leading to **3** literature procedures were used.[7,8] The appropriate thiocarbamoyl chloride was then reacted with compound **3** to afford target **1** in 88% yield as a low melting yellow solid.



Scheme 2. Synthesis of **1**.

The rearrangement of **1** was initially conducted in a 0.09 M solution in chlorobenzene at 140 °C and found by TLC and ^{1}H NMR monitoring to be completed within one hour, leading only to two products, namely the expected compound **2** and another compound **5** in ratio of 1 : 1 (Scheme 3).



Scheme 3. Thermal rearrangement of compound **1** to give the isomers **2** and **5**.

Mass spectrometry of **2** and **5** showed that both products were isomeric with the starting material, with an M^+ consistent with the molecular formula $C_6H_9N_3OS$. While the IR showed the presence in both of carbonyl stretching at 1667 (for **2**) and 1681 cm^{-1} (for **5**), the ^{1}H-NMR showed that while the thio group had moved to the expected position 4 in **2** (absence of the proton at carbon-4), in compound **5** the same group had occupied the position at carbon-2 (absence of the proton at carbon-2).

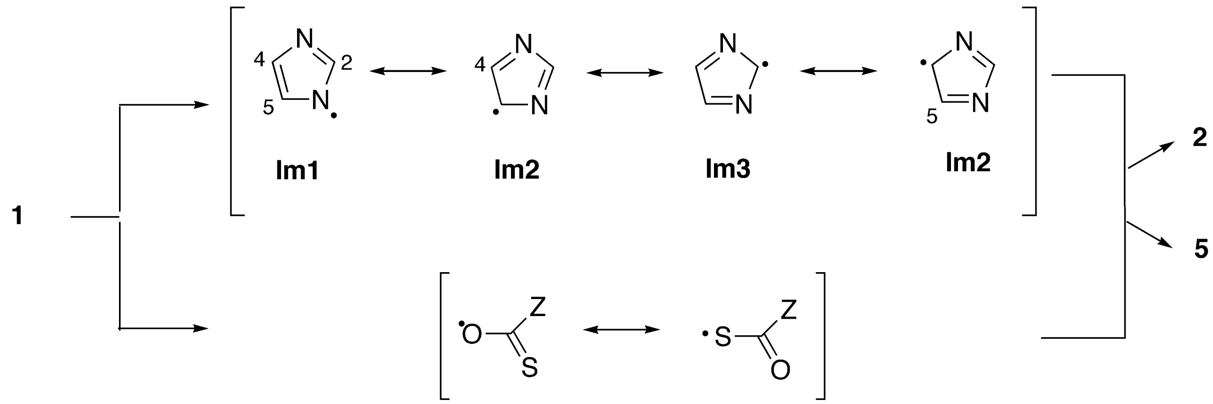
Reactions in other solvents were also assessed and the results are collected in the Table 1. The ratio of products remained close to 1:1 (Table 1, *cf.* entries 1 to 4), except for the reaction conducted in benzene where the yield of compound **5** dropped 13% in relation to that of **2** in a slow reaction over six days (entry 5).

Table 1. Thermal rearrangement of compound **1** giviing compounds **2** and **5**

Entry	Solvent[a]	Temperature [°C]	Time	Yield **2** [%][b]	Yield **5** [%][b]	*Ratio* **2 : 5**
1	Diphenyl ether	265	3 min	50	50	1 : 1
2	*o*-Dichlorobenzene	180	30 min	50	50	1 : 1
3	Chlorobenzene	140	60 min	50	47	1.06 : 1
4	Toluene	110	24 h	45	43	1.05 : 1
5	Benzene	80	6 d	47	34	1.38 : 1

[a] Solutions 0.09 *M*. [b] Isolated yields.

A possible mechanism is presented in Scheme 3. While compound **2** appears to result from a straighforward [3,3]-sigmatropic rearrangement *via* **2A**, compound **5** could result from a [2,3]-sigmatropic rearrangement through an intermediate **5A**.[9] The intermediacy of a possible radical pathway cannot be ruled out. If radicals are indeed involved, the fact that two canonical equivalent forms are possible for **Im2** (Scheme 4) would favour formation of **2**, whereas preferential formation of **5** would be expected on account of spin densities alone. The observed 1:1 ratio of products could then imply that both effects cancel each other.



Scheme 4. Possible radicals involved in the reaction pathway for compounds **2** and **5**.

The calculated spin density of the imidazoyl radical, using 6-311++G(3df,3pd), (*cf.* Experimental – General Procedures) at carbon-4 (and -5) is 0.35, while at carbon-2 this value increases to 0.50, giving a ratio of spin densities at C-4 (**Im2)**/C-2 (**Im3)** of 1.4:1. Inspection of earlier literature shows a similar trend,[10] and Solé's calculations of the spin density of a π-type imidazoyl radical at C-4 (and C-5) found a value of 0.0952, while at C-2 the value increased to 0.1607,[11] resulting in a similar ratio of 1.2:1, closer to the ratio of products found. Of course if radicals are indeed involved they would have to be associated within a tight radical pair, since no dimeric products were detected.

Experimental Section

General Procedures. Melting points were determined with a Reichert Thermovar hot-stage microscope and are uncorrected. Chromatography was performed using E. Merck silica gel 60 (70-230 mesh). Preparative thin-layer chromatography (PTLC) was performed on plates precoated with silica gel GF_{254} (0.5 mm). Infrared spectra (IR) were recorded with a Fourier Perkin-Elmer 157G and 683 infrared spectrometers and the frequencies reported in cm^{-1}. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained with a Bruker ARX 400. Chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectra were obtained on a mass spectrometer GC-TOF Micromass GTC. All solvents were purified by standard methods.

Calculations were performed with the Gaussian 03 software[12] at the DFT level using the hybrid functional B3LYP[13] and the 6-311++G(3df,3pd) basis set.[14] Full geometry optimization was performed for all species in the gas phase, and the optimized geometries were used for the calculations.

Thiocarbamoylation of *N*-hydroxy-imidazole to afford thiocarbamoyl imidazole 1

To a stirred solution of *N*-hydroxyimidazole (**3**) (20 mg, 0.24 mmol) in dry DMF (2 mL) was added NaH (60% mineral oil dispersion) (10 mg, 0.24 mmol). After the liberation of H_2 ceased (10 m), *N*,*N*-dimethylthiocarbamoyl chloride (30 mg, 0.24 mmol) in DMF (0.5 mL) was added dropwise, and the reaction allowed to proceed for a further 10 min. The reaction was stopped by adding H_2O (2 mL) and extracting the mixture with AcOEt (5 x 2 mL), separating and drying the organic phase with Na_2SO_4 and evaporating the solvent under vacuum. The solid residue obtained was purified by column chromatography (SiO_2, EtOAc) to yield the *title compound* **1**, as a yellow solid, 35 mg (88%); mp 43–45 ºC (Et_2O); IR (neat) ν: 3115, 2926, 2854, 1556, 1400 1281, 1259, 1176, 1066 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H: 7.56 (s, 1H), 7.02 (s, 2H), 3.43 (s, 3H), 3.34 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ_C: 186.7 (C=S), 132.7, 125.0, 117.2, 44.9, 38.8; MS (FI): *m/z* = 172 ($[M+H]^+$, 100), 72 (C_3H_6NO, 70). Calcd for $C_6H_9N_3OS$: C, 42.09; H, 5.30; N, 24.54; S, 18.73% Found: C, 42.09; H, 5.19; N, 24.73; S, 18.69%

Thermal rearrangement of imidazole (1). In a round bottom flask a solution of **1** (30 mg, 0.18 mmol) in chlorobenzene (2 mL) was heated to reflux until disappearance of the starting material (60 min), by ^{1}H-NMR and TLC monitoring (AcOEt/MeOH, 4:1). The solvent was then evaporated and the residue purified by preparative thin layer chromatography to yield compounds **2** and **5**. Results with other solvents followed an identical protocol (Table).

4-Thiol-imidazole derivative (**2**)**.** Yield: 15.0 mg (50%); colourless solid; Rf 0.19 (AcOEt/MeOH, 8:1); mp 121-123 ºC (AcOEt); IR (neat) ν: 3119, 2994, 2921, 1667 (C=O), 1487, 1406, 1367, 1258, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ_H: 9.46 (s, 1H, NH), 7.52 (s, 1H), 7.12 (s, 1H), 3.08 (s, 3H, CH_3), 2.99 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ_C: 167.7 (C=O), 137.3, 125.6, 123.3, 37.0; MS (FI): *m/z* = 171 (M^+, 100), 72 (C_3H_6NO, 70); HRMS: *m/z* = 171.046998 (M^+), calcd for $C_6H_9N_3OS$ 171.046634.

2-Thiol-imidazole derivative (**5**)**.** Yield: 14.1 mg (47%); white-brownish solid; Rf 0.33 (AcOEt/MeOH, 8:1); mp 133-135 ºC (AcOEt); IR (neat) ν: 3116, 2998, 2924, 2854, 1681 (C=O), 1550, 1425, 1366, 1257, 1092 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ_H: 9.46 (s, 1H, NH), 7.13 (s, 2H), 3.05 (s, 3H, CH_3), 3.03 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ_C: 165.0 (C=O), 134.0, 124.2, 37.0; MS (FI): *m/z* = 172 (M^++H, 100), 72 (C_3H_6NO, 70); HRMS: *m/z* = 171.046634 (M^+), calcd for $C_6H_9N_3OS$ 171.046677.

Acknowledgements

We thank Fundação para a Ciência e Tecnologia (FC&T, Lisbon, Portugal) for partial financial support (Project POCTI/QUI/36456). One of us (L. F. V. P.) is grateful for the award of a doctoral fellowship from FC&T.

References and Notes

1. Review on imidazole and substituted imidazoles: Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W. Eds.; Elsevier: Oxford, 1996; Vol. 3, p 190.
2. (a) Dugas, H. *Biorganic Chemistry – A Chemical Approach to Enzyme Action*, 3rd Edn.; Springer India: New Delhi, 2003; p 159. (b) Domling, A.; Beck, B.; Herdtwerck, E.; Antuch, W.; Oefner, C.; Yehia, N.; Gracia-Marques, A. *Arkivoc* **2007**, (iii), 99.
3. (a) Zoete, V.; Bailly, B.; Catteau, J.-P.; Bernier, J.-L. *J. Chem. Soc, Perkin Trans 1* **1997**, 2983. (b) Biernaz, C.; Cornwell, M. J. *Tetrahedron* **1993**, *34*, 939. (c) Asinger, F.; Sans, A; Offermanns, H.; Krings, P.; Andree, H. *Justus Liebigs Ann. Chem.* **1971**, *744*, 51. (d) Caille, J. C.; Didierlaurent, S.; Lefrançois, D.; Lelièvre, M. H.; Sury, C.; Aszodi, J. *Synthesis* **1995**, *6*, 635. (e) Spaltenstein, A.; Holler, T. P.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 2977. (f) Zyabrev, V. S.; Kiselev, V. V.; Romanenko, E. O.; Drach, B. S. *Zh. Org. Khim.* **1994**, *5*, 715.
4. (a) Reis, L. V.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1994**, *35*, 2747. (b) Reis, L. V.; Lobo, A. M.; Prabhakar, S.; Duarte, M. P. *Eur. J. Org. Chem.* **2003**, 190. (c) Duarte, M. P.; Mendonça, R. F.; Prabhakar, S.; Lobo, A. M. *Tetrahedron Lett.* **2006**, 1173.
5. Pereira, M. M. A.; Santos, P. P. In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Rappoport, Z.; Liebman, J. F. Eds.; John Wiley: London, 2008; p 343.
6. (a) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (b) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; p 85. (c) Barton, D. H. R.; Parekh, S. I. *Half a Century of Free Radical Chemistry*; Cambridge University Press: Cambridge, 1992. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995; p 188.
7. Laus, G.; Stadlwieser, J.; Klotzer, W. *Synthesis* **1989**, 773.
8. Eriksen, B. L.; Vedso, P.; Morel, S.; Begtrup, M. *J. Org. Chem.* **1998**, *63*, 12.
9. For Claisen and thio-Claisen rearrangements' mechanism, see: (a) Arnaud, R.; Dillet, V.; Pelloux-Léon, N.; Vallée, Y. *J. Chem. Soc, Perkin Trans 2* **1996**, 2065. (b) Arnaud, R.; Vallée, Y. *J. Chem. Soc, Perkin 2* **1997**, 2373. (c) Ganem, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 936. (d) Gajeswki, J. J. *Acc. Chem Res.* **1997**, *30*, 219. (e) Rehbein, J.; Hiersemann, M. In *The Claisen Rearrangement: Methods and Applications*, Hiersemann, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; p 525.

10. Lassmann, G.; Eriksson L. A.; Himo, F.; Lendzian F.; Lubitz, W. *J. Phys. Chem. A* **1999**, *103*, 1283.
11. Bofill, J. M.; Olivella, S.; Solé, A. *J. Am. Chem. Soc.* **1989**, *111*, 7740.
12. Gaussian 03, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.
13. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648 .
14. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.