A Regiospecific Rearrangement of 4(5)-Substituted 2-Phenacylthio-1*H*-imidazoles to 4-Substituted 2-Mercapto-1-phenacyl-1*H*-imidazoles

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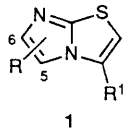
4(5)-Substituted 2-phenacylthio-1*H*-imidazoles thermally rearrange to give 4-substituted 2-mercapto-1-phenacyl-1*H*-imidazoles

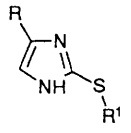
During the course of our search for a potential immunomodulator, we became interested in bicyclic structures such as **1**. The preparation of **1a** by exposing ethyl 2-phenacylthio-1*H*-imidazole-4(5)-carboxylate **2a** to concentrated sulphuric acid has been described.[1] Depending on the mode of cyclisation, the reaction can, in principle, lead to two possible isomeric products. These authors claimed to have isolated only one isomer and assigned a probable structure **1a** to it as the 5-isomer. The reaction, in our hands, also produced one isomer in good yield (83%). The structure **1b**, however, has been assigned to it on the basis of spectroscopic evidence. In a NOE study, irradiation of the imidazole proton (δ_H 8.27) results in an enhancement of the *ortho* protons of the phenyl ring confirming the structure as the 6-isomer.

To see whether a different cyclisation procedure would result in one or both the isomers, **2a** was subjected to refluxing toluene in the presence of a catalytic amount of toluene-*p*-sulphonic acid (TPSA) for 24 h. No evidence for any cyclised material was found. A crystalline solid, isolated in 35% yield after work-up, was found to be ethyl 2-mercapto-1-phenacyl-1*H*-imidazole-4-carboxylate **5a** [m.p. 233–235 °C (THF–hexane)]. The chemical shift δ_C 52 for the methylene carbon shows that the substitution is on N rather than on S. Mutual NOE enhancement between the imidazole proton and methylene protons shows their close proximity. A long range coupling $^3J_{CH}$ 4 Hz observed for the imidazole C-5 (δ_C 125) also supports this structure. Final confirmation was derived from X-ray diffraction studies on a single crystal.



1

	R	R^1	M.p. (°C)
a	5-CO_2Et	Ph	160–160.5 (lit.[1])
b	6-CO_2Et	Ph	162–163 (from EtOH)

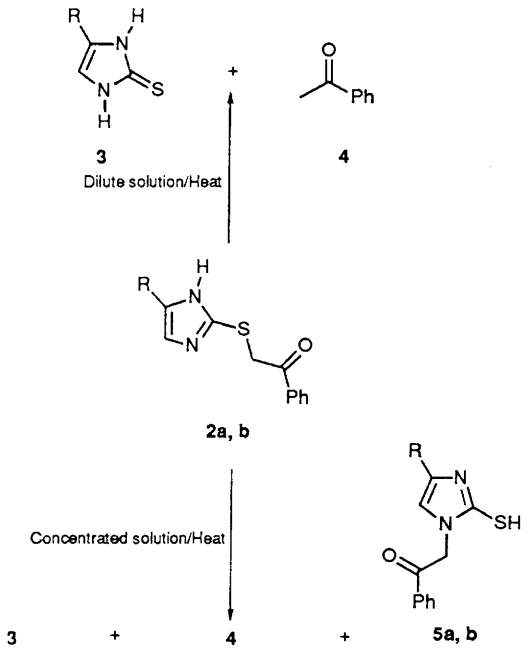


2*

	R	R^1	M.p. (°C)
a	CO_2Et	Phenacyl	128–130 (from EtOH)
b	Ph	Phenacyl	121–123 (from EtOH)
c	CO_2Et	Phenylethyl	136–137 (from EtOAc)

* Compounds **2a–c** were prepared by alkylation of the thiolate anion of the respective thione **3** with phenacyl bromide or phenylethyl bromide. Compound **2a** is reported in the literature[1] as having a m.p. 127.5–128 °C. All structures were supported by spectroscopic data ($\delta_C \sim 40$ for the methylene carbon shows that the substitution is on S for compounds **2a–c**).

This rearrangement also proceeds in the absence of TPSA, but at a relatively slow rate, as determined by isolated yields, which were typically $<15\%$. The yield of **5a** was, however, improved, when **2a** was heated in boiling *p*-xylene (b.p. 138–



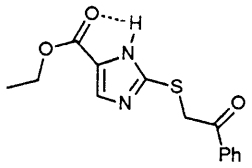
Scheme 1

140 °C) for 48 h (yield: 38% by HPLC, 31% isolated) supporting the thermal nature of the rearrangement.

The transformation of 1-methyl-2-methylthiobenzimidazole or 2-allylthio-1-methylbenzimidazole to 1,3-dimethylbenzimidazole-2-thione and 3-allyl-1-methylbenzimidazole-2-thione, respectively, has been reported[2] as a Claisen type rearrangement. The migration of the allyl group was found to be much faster than the methyl group. However, when **2c**, bearing a 2-phenylethylthio group, was subjected to refluxing toluene or *p*-xylene with or without TPSA for an extended period (105 h), no rearrangement was observed. On the other hand, **2b** when heated in boiling *p*-xylene for 48 h largely decomposed, only a minute amount of the rearranged product **5b** (R = Ph) being isolated. The structure was derived from spectroscopic evidence: δ_C 52.7 (CH_2 – N). Mutual NOE enhancement between imidazole 5-H and methylene protons also supports the structure.

It would appear that there is a marked difference in the electronegativity of the substrate in the previously reported rearrangement[2] and the present example. It is also reported[3] from related studies of SR⇌NR equilibria of a series of 1-alkyl-2-alkylthioimidazoles that the basicity of the substrate is important. In these studies it was found that a catalyst, *viz.* methyl iodide, which forms an imidazolium ion, is necessary for the rearrangement. Although an electron-withdrawing ester or phenyl group lowers the basicity,[4] in fact, **2a** is amphoteric and forms salts with dilute HCl or NaOH. It seems, therefore, that the electron deficient imidazole ring or, perhaps its protonated form, can render the C–S bond vulnerable to cleavage which is further assisted by the phenacyl group. This is supported by the evidence that a significant amount of acetophenone **4**, detected by HPLC, and imidazolethione[5] **3**, measured by GLC, is present in the reaction mixture. A diminishing yield of the rearranged material with increasing dilution was also observed, while the proportions of the cleavage products remained approximately the same in all cases. This indicates that a unimolecular fission of **2** to give **3** and **4** is occurring, which competes in relatively concentrated solution in an intermolecular reaction to yield the rearranged products **5a,b**.

A homolytic mechanism might have reasonably explained



Proposed hydrogen bonding between groups on **2a** as an explanation for the observed regiospecificity of the rearrangement to give **5a**

these observations, but no marked diminution of yield was apparent when a free-radical inhibitor, 2,6-di-t-butylphenol[6] was included in the solution containing **2a** (**5a** was isolated in 27% yield); furthermore, by-products of homolysis, such as 2,2′-dimethylbibenzyl, were not observed when the process was repeated in *o*-xylene (b.p. 143–145 °C). The involvement of solvent in the formation of **3** and **4** with concomitant rearrangement has not been demonstrated. Possible further reactions of the cleavage products with **2a,b** to give **5a,b** were also discounted, *i.e.* the yield of the rearrangement when performed in the presence of added **4** was not markedly improved (38% isolated yield), the yield was also not significantly improved when **3** was included in another reaction (35% isolated yield). Attack on **2a,b** by a phenacyl ion is an alternative possibility in explaning how the rearrangement might proceed in concentrated solution, but when phenacyl bromide was added to a solution of **2a** and heated under reflux for 24 h and the reaction mixture was subsequently worked up, the yield of **5a** was actually lower than previous experiments (15% isolated yield). When considering these results it can be seen that no satisfactory explanation can be found for the formation of **3**, **4** and particularly **5a,b** in this reaction. The regiospecificity may be a result of hydrogen bonding of the proximal NH with the C=O of the ester group of **2a** rendering the NH group unavailable for substitution; the association of these two groups may also exert a blocking effect on the approach of an attacking species. All new compounds gave satisfactory spectroscopic data and elemental analysis (±0.4% of theoretical values) excepting **5b**, where high resolution MS gave a molecular ion consistent with the formula for this compound (Found: *m/z* 294.0843 ± 5.5 ppm. $C_{17}H_{14}N_2OS$ requires *m/z* 294.0827).

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