Synthesis of Novel Functionalized Hydroxyiminoimines by Direct Nitrosation of β-Thio-β-amino-α,β-unsaturated Ketones and Their Further Transformations: New General Syntheses for Imidazole, Quinoxaline, and Thiazole Derivatives

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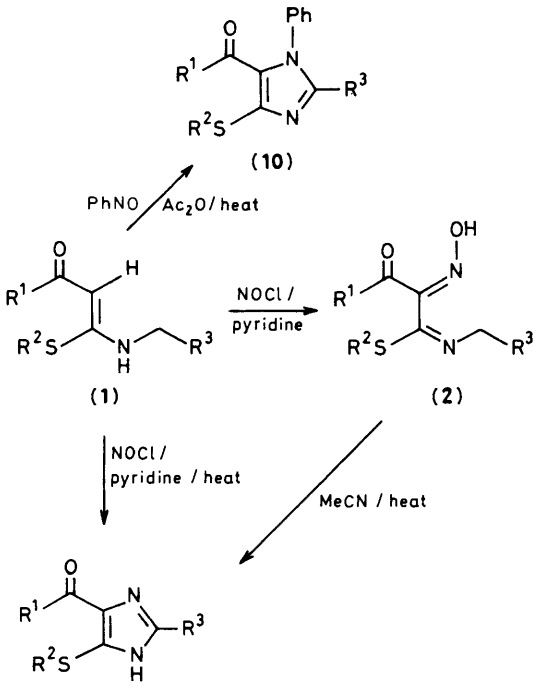
New general methods for the synthesis of imidazole (**3**), (**10**), quinoxaline (**6**), and thiazole (**9**) derivatives have been developed from the corresponding novel functionalized 1,2-hydroxyiminoimines (**2**), (**5**), and (**8**) obtained by direct nitrosation of β-thio-β-amino-α,β-unsaturated ketones with nitrosyl chloride.

There has been considerable interest in recent years in the synthesis of purines[1,2] and alloxazines[3] *via* the condensation cyclization of 6-amino-5-nitrosopyrimidine derivatives. However, similar synthetic operations based on open-chain nitrosoenamines/enaminones (or hydroxyiminoimines) to give imidazole[4] or quinoxaline[5] derivatives have not been investigated. The only related reference reported in the literature involves the synthesis of 4-acetyl-2-aryl-5-methyl imidazoles from 3-hydroxyiminopentane-2,4-diones and benzylamines.[6] The scant literature on such transformations is primarily due to the lack of appropriate open-chain nitrosoenamine/enaminone (or hydroxyiminoimine) precursors. Despite the report of the preparation of 1,2-hydroxyiminoimine derivatives by condensation of α-hydroxyiminoketones with appropriate amines,[6,7] the alternative general approach to these precursors, electrophilic nitrosation of open-chain or cyclic enamines[8] or enaminones,[8] has not been reported. We now report a direct general method for the synthesis of novel functionalized hydroxyiminoimines, by reaction of readily available β-thio-β-amino-α,β-unsaturated ketones[9] with nitrosyl chloride, and their further transformations to imidazole, quinoxaline, and thiazole derivatives.

In a typical experiment (Method A), a mixture of (**1a**) (0.01 mol), nitrosyl chloride (0.012 mol in 30 ml of diethyl ether), and pyridine (2 ml) was stirred at 0—5 °C (10 min). The corresponding hydroxyiminoimine (**2a**) was obtained in 80% yield, m.p. 140—141 °C.† Subsequently (**2a**) underwent a facile cyclodehydration on refluxing in acetonitrile (25 ml, 3 h) to yield the corresponding 4-benzoyl-5-methylthio-2-phenylimidazole (**3a**), (78%) as light yellow needles (AcOH), m.p. 215 °C, *m/z* 294 (100%, M^+); i.r. (KBr): 3240 (NH) and 1600 (conjugated CO) cm^{-1}; ^1H n.m.r. [$(CD_3)_2SO$]: δ 2.55 (s, 3H, SCH_3), 7.45 (m, 6H, Ar), 7.88 (m, 2H, Ar), 8.15 (m, 2H,



a; R^1 = Ph, R^2 = Me, R^3 = Ph
b; R^1 = Me, R^2 = Me, R^3 = Ph
c; R^1 = Ph, R^2 = Me, R^3 = H
d; R^1 = Ph, R^2 = Me, R^3 = Me
e; R^1 = Ph, R^2 = Et, R^3 = Ph
f; R^1 = Ph, R^2 = $PhCH_2$, R^3 = Ph
g; R^1 = Ph, R^2 = Me, R^3 = CO_2Et

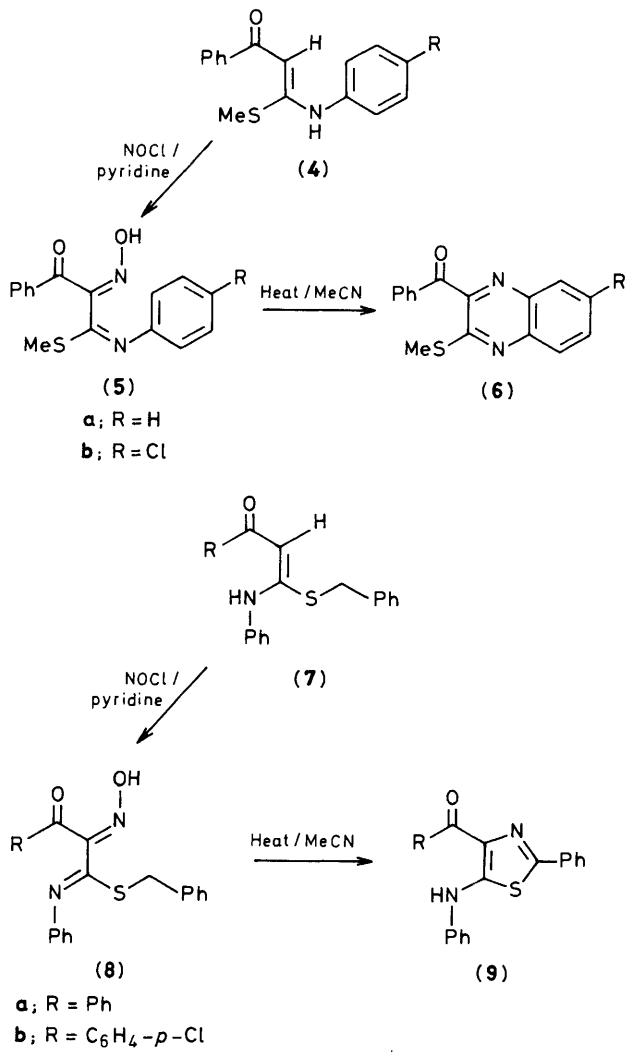
Scheme 1

Table 1. Preparation of the 5-alkylthioimidazoles (**3**), (**10**), the quinoxalines (**6**), and the thiazoles (**9**).

Unsaturated ketone	Product[a]	Yield(%)[b]	M.p./°C
(**1a**)	(**3a**)	78[c]	215
(**1b**)	(**3b**)	58[c]	208—210
(**1c**)	(**3c**)	55[c]	Viscous semisolid
(**1d**)	(**3d**)	60[c]	169—170
(**1e**)	(**3e**)	85[d]	208—209
(**1f**)	(**3f**)	87[d]	227—228
(**1g**)	(**3g**)	55[d]	Viscous liquid
(**1a**)	(**10a**)	85	151—152
(**1b**)	(**10b**)	78	105
(**1c**)	(**10c**)	75	119—120
(**1d**)	(**10d**)	80	129—130
(**4b**)	(**6b**)	67[c]	150
(**7a**)	(**9a**)	55[c]	144—145
(**7b**)	(**9b**)	56[c]	196

[a] Satisfactory spectral and analytical data were obtained for all the products. [b] Yields of pure isolated product. [c] Yields from the corresponding hydroxyiminoimines (Method A). [d] Method B.

† Compound (**2a**) gave a satisfactory elemental analysis; colourless amorphous solid; i.r. (KBr): 3480 (br., OH), 1592 and 1642 (s, C=N) cm^{-1}; λ_{max} (MeOH): 242 (ε 43680) nm; ^1H n.m.r. [CCl_4–$(CD_3)_2SO$] at 90 MHz: δ 2.32 and 2.42 [two singlets (total 3H, 2:1 ratio), *Me*S], 4.38 and 4.55 [two singlets (total 2H, 1:2 ratio), $C_6H_5CH_2$], 6.85—7.55 (m, 8H, Ar), 7.62—8.11 (m, 2H, Ar). The hydroxyiminoimine structure for (**2a**) was assigned on the basis of u.v. spectra and the n.m.r. signal for the benzylic protons which appears as a singlet, while in (**1a**), this signal appears as a doublet (δ 4.45, *J* 6 Hz) owing to coupling with the NH proton (ref. 10). The u.v. and n.m.r. spectra of (**2b—d**), (**5a,b**), and (**8a,b**) show that they exist in the hydroxyiminoimine form, however the appearance of two signals for the MeS and benzylic protons in (**2a**) is probably due to the existence of two geometrical isomers (s-*cis* and s-*trans*); this is under investigation.



Scheme 2

Ar), and 12.85 (NH); λ_{max} (MeOH): 270, 350 (ε 34700, 16800) nm pointing to a β-aminoenone moiety; λ_{max} (MeOH) for (**1a**): 245, 342 (ε 22300, 38000) nm. Similarly the hydroxyiminoimines (**2b—d**) underwent facile cyclodehydration to yield the corresponding 4-acetyl (**3b**), 2-unsubstituted (**3c**), and 2-methyl (**3d**) imidazoles in 55—60% overall yields. Alternatively (**3a**) was obtained directly in one step in 75% yield [m.p. and i.r. and n.m.r. spectra in agreement with (**3a**) obtained by Method A], when a mixture of (**1a**) (0.01 mol) and nitrosyl chloride (0.012 mol in 5 ml of dry diethyl ether) was refluxed in pyridine (25 ml) for 2 h (Method B). Method B thus provides a direct entry to (**3a**) without the need for the isolation of (**2a**). Similarly the corresponding *S*-ethyl (**3e**), *S*-benzyl (**3f**), and 2-ethoxycarbonyl (**3g**) imidazoles were obtained in 55—87% overall yields (Method B). When the unsaturated ketones (**1a—d**) (0.01 mol) were treated with nitrosobenzene (0.03 mol) and acetic anhydride (25 ml) in a sealed tube (200 °C),[11] the corresponding 1-phenylimidazoles (**10a—d**) were obtained in excellent yields (Table 1, Scheme 1).

When a solution of the hydroxyiminoimine (**5a**), m.p. 129—130 °C, derived from the β-arylamino-α,β-unsaturated ketone (**4a**), in acetonitrile (25 ml) was heated in a sealed tube (200 °C), the corresponding 3-benzoyl-2-methylthioquinoxaline (**6a**),‡ m.p. 109 °C was obtained in 65% yield. Similarly the quinoxaline (**6b**) was obtained from (**5b**) in 67% yield. To the best of our knowledge, this is the first report of quinoxaline synthesis from hydroxyiminoimine intermediates.

Interestingly when the hydroxyiminoimines (**8a**) and (**8b**) were subjected to thermal cyclodehydration, the corresponding 5-anilino-2-aryl-4-benzoylthiazoles (**9a**) and (**9b**) were obtained in 55% and 56% yields, respectively (Scheme 2).

The hydroxyimino compounds (**2**), (**5**), and (**8**) available from a wide variety of active methylene ketones and their derivatives, thus constitute an important class of functionalized synthons. The transformations described in this report are only an account of their expedient and versatile applications in the synthesis of a few selected heterocyclic systems. The scope of these reactions and other synthetic applications are being investigated.

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References

1 F. Yoneda and T. Nagamatsu, *J. Chem. Soc., Perkin Trans.* 1, 1976, 1547, and references therein.
2 F. Yoneda and T. Nagamatsu, *Chem. Pharm. Bull. Jpn.*, 1975, **23**, 2001; F. Yoneda and Y. Sakuma, *ibid.*, 1973, **21**, 448, 260.
3 E. C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Am. Chem. Soc.*, 1967, **89**, 3369.
4 For a recent review on imidazoles, see: M. R. Grimmett, 'Advances in Heterocyclic Chemistry,' vol. 27, Academic Press, London and New York, 1980, p. 241.
5 For a review on quinoxaline, see: G. W. H. Cheeseman and E. S. G. Werstiuk, 'Advances in Heterocyclic Chemistry,' vol. 22, Academic Press, London and New York, 1978, p. 367.
6 A. C. Veronese, F. D. Angeli, G. Zanotti, and A. D. Pra, *J. Chem. Soc., Chem. Commun.*, 1977, 443; A. C. Veronese, G. Cavicchioni, G. Servadio, and G. Vecchiati, *J. Heterocycl. Chem.*, 1980, 1723.
7 L. Rügheimer and G. Ritter, *Chem. Ber.*, 1912, **45**, 1332.
8 For recent reviews on enamines and enaminones see: P. W. Hickmott, *Tetrahedron*, 1982, **38**, 1975, 3363; J. F. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277; see also, C. B. Kanner and U. K. Pandit, *Tetrahedron*, 1982, **38**, 3597.
9 For earlier references on the reactions of β-thio-β-amino-α,β-unsaturated ketones with electrophilic compounds see: V. Aggarwal, A. Kumar, H. Ila, and H. Junjappa, *Synthesis*, 1981, 1571; V. Aggarwal, H. Ila, and H. Junjappa, *ibid.*, 1983, 147.
10 G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, 1962, **84**, 2691.
11 E. C. Taylor and F. Yoneda, *J. Org. Chem.*, 1972, **37**, 4464.

‡ No trace of the quinoxaline (**6a**) was obtained by Method B.