

Novel Synthesis of 2-Aminothiophenes via Iodoiminolactonization of γ,δ -Unsaturated Secondary Thioamides

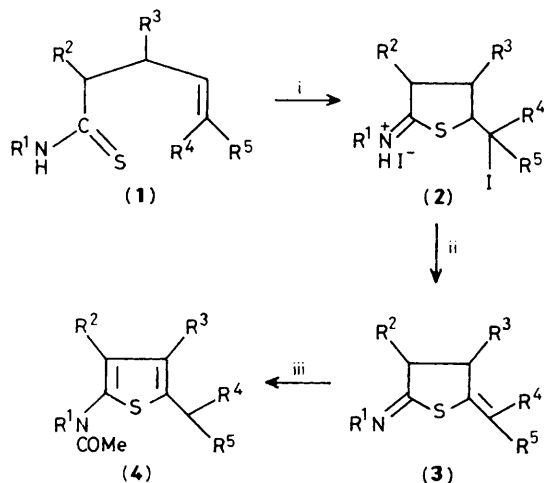
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Iodine-induced cyclization of γ,δ -unsaturated secondary thioamides proceeds regio- and chemo-selectively, providing, after elaboration, 2-aminothiophenes.

Much attention is focused on electrophilic olefin cyclization processes that form carbon-heteroatom bonds as well as carbon-carbon bonds.¹ Although among them halogenolactonization is a well established important synthetic tool,² the analogous thiolactonization using a thioamide group has been less investigated.³ Because of its versatility, the thioamide group has increasingly been recognized as a useful synthon.⁴ In continuation of our studies using thioamides as synthetic intermediates for heterocycles,⁵ we now report a novel one-pot synthesis of 2-aminothiophenes by iodine-induced intramolecular S-C bond formation with γ,δ -unsaturated secondary thioamides followed by dehydroiodination and *N*-acetylation.

The readily available γ,δ -unsaturated secondary thioamides (**1a-h**)[†] with iodine in tetrahydrofuran (THF) underwent the iodoiminolactonization to give the iminothiolactones (**2a**



Scheme 1. Reagents: i, I₂; ii, DBU; iii, MeCOCl, DBU, DMAP (cat.).

Table 1. Preparation of 2-aminothiophenes (**4a-h**).

Substrate	R ¹	R ²	R ³	R ⁴	R ⁵	Product (yield, ^a %)
(1a)	PhCH ₂	H	H	H	H	(4a) 57
(1b)	Ph	H	H	H	H	(4b) 53
(1c)	PhCH ₂	H	H	H	Me	(4c) 25 ^b
(1d)	PhCH ₂	H	H	H	Ph	(4d) 50 ^c
(1e)	PhCH ₂	H	H	Me	Me	(4e) 47
(1f)	PhCH ₂	H	Me	H	H	(4f) 49
(1g)	Ph	Me	H	H	H	(4g) 54
(1h)	PhCH ₂	Me	Me	H	H	(4h) 37

^a Overall yield from (1). ^b (1c) was recovered in 17% yield. ^c (1d) was recovered in 24% yield.

[†] Compounds (**1a-h**) were prepared by allylation of dianions generated from secondary thioamides or thio-Claisen rearrangement of *S*-allylthioimidates.

—h), which without isolation were converted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equiv.) in the same flask into the *exo*-olefins (**3a-h**).[‡] After THF as a solvent was replaced by CH₂Cl₂, *N*-acetylation of (**3a-h**) with acetyl chloride in the presence of DBU as a base and 4-dimethylaminopyridine (DMAP) as a catalyst followed by spontaneous aromatization gave (chromatography: silica; ethyl acetate-hexane) the 2-aminothiophenes (**4a-h**) (Table 1). No trace of other compounds such as nitrogen-heterocycles was isolated. Accordingly, it was found that this iodine-induced cyclization proceeded regio- (*5-exo*-trigonal process)⁶ and chemo-selectively (sulphur-carbon bond formation).[§] The structures assigned were confirmed by spectral data;[¶] e.g. (**4a**), m.p. 85–88 °C; ν 1645 cm⁻¹ (C=O); δ_{H} (270 MHz) 2.03 (s, 3H, COMe), 2.36 (d, *J* 1.1 Hz, 3H, Me), 4.80 (s, 2H, CH₂Ph), 6.34 (d, *J* 3.3 Hz, 1H, C-3-H), 6.46 (m, 1H, C-4-H); *m/z* 245 (*M*⁺).

This method should be applicable to the synthesis of polyfunctionalized 2-aminothiophenes using a variety of accessible unsaturated secondary thioamides. In addition, the intermediates (**2**) and (**3**) may be used for further elaboration.⁷

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[‡] At this stage, it was possible to isolate compounds (**3**).

[§] Amidoselenation using γ,δ -unsaturated secondary amides was not so regio- and chemo-selective: A. Toshimitsu, K. Terao, and S. Uemura, *Tetrahedron Lett.*, 1984, **25**, 5917; *J. Chem. Soc., Chem. Commun.*, 1986, 530.

[¶] All new compounds had satisfactory combustion or high resolution mass spectral.