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

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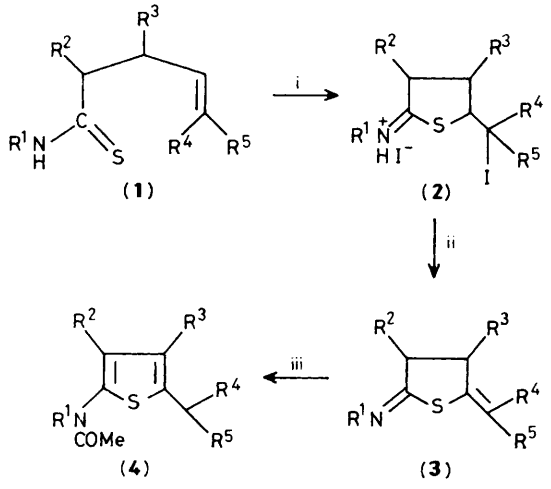
Iodine-induced cyclization of γ,δ-unsaturated secondary thioamides proceeds regio- and chemo-selectively, providing, after elaboration, 2-aminothiophenes.

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 iodoiminothiolactonization to give the iminothiolactones (**2a**—**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 CH_2Cl_2, *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, CH_2Ph), 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]



Scheme 1. *Reagents:* i, I_2; 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.

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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.