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SYNTHESIS AND ELABORATION OF HETEROCYCLES VIA IODOCYCLISATION OF UNSATURATED THIOUREAS

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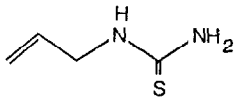
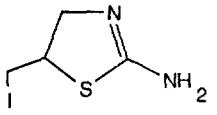
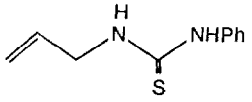
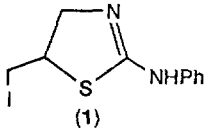
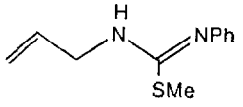
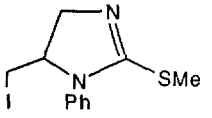
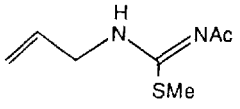
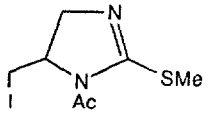
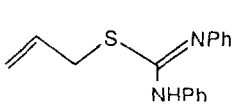
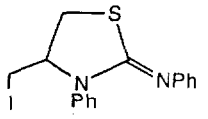
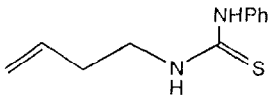
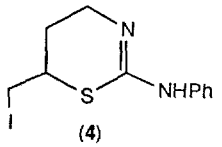
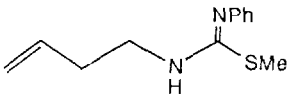
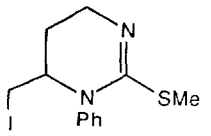
Abstract. Iodocyclisation of N-allyl or S-allyl thioureas leads efficiently to dihydrothiazoles, and dihydroimidazoles and homologous thioureas afford dihydrothiazines. The products are readily elaborated to give unusual heterocyclic systems.

Electrophilic additions to functionalised alkenes leading to heterocyclic skeletons via a cyclisation of the remote functional group of the alkene[1] are widely used in synthesis. Many electrophiles have been studied, but iodocyclisation is particularly well developed because of the mild conditions of cyclisation and the ease of subsequent elaboration[2]. The earlier interest in iodolactonisation[3] and iodoetherification[4] has been recently extended to iodolactamisation[5] with examples of participation of nitrogen from a variety of neighbouring functional groups. Participation of a neighbouring sulphur to give sulphur heterocycles is known in mercaptans[6] and in thioamides[7,8]. In the case of allylic ureas[9] halocyclisation can occur either with oxygen participation to afford dihydrooxazoles, or with nitrogen participation to afford dihydroimidazoles. Similar products are obtained from allylic ureas[10] with organoselenium induced cyclisation. However few investigations have been made of the behaviour of thioureas. The early literature[11] describes the halogenation of allylthioureas, but even a more modern study[12] of the halogenation of a thiourea is tentative in assignment of a dihydrothiazole structure to the product. In this paper we report the iodocyclisation of a number of allylic- and homoallylic thioureas. This procedure in combination with subsequent transformations of the iodide products permits the synthesis of many interesting heterocyclic systems.

The required allylic and homoallylic thioureas were readily prepared by standard procedures[13]. Iodination of the thioureas afforded the products shown in Table 1. The formation of the five-membered ring dihydrothiazoles and dihydroimidazoles from allylic thioureas rather than the six-membered dihydrothiazines and tetrahydropyrimidines, was established by ^{13}C. n.m.r. spectroscopy. In those cases offering the choice of formation of a heterocycle by sulphur participation, or by nitrogen participation the former was observed. Similar results have been obtained with thioamides[8]. Homoallylic thioureas in an analogous manner give dihydrothiazines and tetrahydropyrimidines.

In the most studied products of halocyclisation, halolactones, the emphasis on further elaboration has been reductive removal of the halogen functionality. The review by Dowle and Davies[2] reports few examples of elaboration by either elimination or substitution pathways. Subsequently not only have elimination reactions of the products of halolactonisation[14] been reported but the methodology has been extended to the preparation of enamides, and of thiophenes and other vinyl sulphides from iodolactams[5], and iminothiolactones[8] respectively. It has been noted[15] that the unsaturated lactones should have a rich chemistry by virtue of their behaviour both as electrophiles (carbonyl site) and as nucleophiles (at the double bond), and this has in part been demonstrated[15,16]. In Table 2 are the results of elimination reactions from the products of iodocyclisation of thioureas. The combination of the efficient steps of cyclisation followed by elimination thus permits the conversion of unsaturated thioureas to novel vinyl sulphides (entries 1-4) and enamines (entry 5) having exocyclic unsaturation, or to products having endocyclic unsaturation (entries 6 and 7). The chemistry of these unsaturated products is being studied.

Table 1 Iodocyclisation of Unsaturated Thioureas [a]

Reactant	Product	Yield (%)[b]
		43[c,d]
	 (1)	95
	 (2)	89
		77
	 (3)	91
	 (4)	96
		86

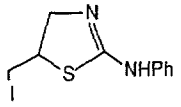
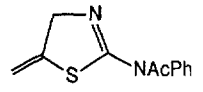
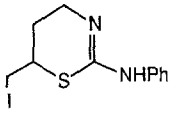
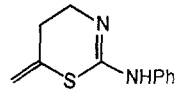
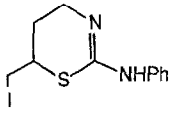
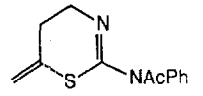
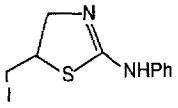
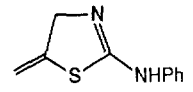
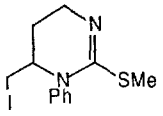
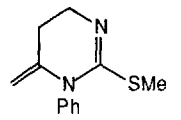
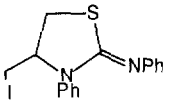
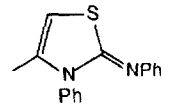
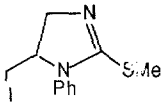
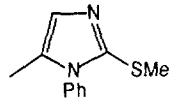
a All reactions were effected in dichloromethane with addition of iodine (1 equivalent).

b Yields of isolated products after work up and chromatography.

c Characterised as the acetyl derivatives.

d Reaction in the presence of pyridine (10 equivalents).

Table 2 Elimination Reactions of Iodinated Products

Entry	Substrate	Conditions	Products	Yield (%)[abc]
1		Ac_2O, Et_3N		97
2		Thf, Et_3N		62
3		Ac_2O, Et_3N		30
4		Et_3N		57
5		DBU		91
6		DBU		76
7		DBU		94

a Yields of isolated products after work up and chromatography.

b Products identified by ^1H and ^{13}C n.m.r. (e.g. for entry 1 vinyl protons at δ 5.0 and 5.2)

c Traces of the more stable endocyclic isomers can also be observed.

Knapp and Levorse[5] have established the ease with which iodolactams, products of iodocyclisation, may undergo substitution with nitrogen, oxygen and carbon nucleophiles. Similarly those products shown in Table 1 are capable of extensive elaboration. Azides are obtained from iodides (**1**) (37%), (**2**) (35%), and (**3**) (50%) by reaction of sodium azide in dimethylformamide. Alcohols are obtained from iodides (**1**) (72%) and (**2**) (84%) by reaction of silver trifluoroacetate in nitromethane/water. Phenylsulphides are prepared from iodides (**1**) (90%), (**2**) (84%), and (**4**) (78%) by reaction of sodium thiophenoxide in dimethylformamide, a phenylsulphone has been obtained from (**2**)(40%) by reaction with the sodium salt of benzenesulphinic acid in dimethylformamide, and finally carbon functionality can be introduced using for example the metal salts of malonate esters.

In view of the accessibility of unsaturated thioureas these results provide a useful extension of the methodology of iodocyclisation. First by participation of either sulphur or nitrogen in the allylic and homoallylic thioureas a variety of heterocyclic skeletons may be prepared, and then the iodo functionality may be developed easily by diverse elimination and substitution reactions.

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