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A General Route to Cyclic Amidines and Isothioureas Based on Formal Aza Diels Alder Reactions of Aminoheterocycles

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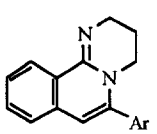
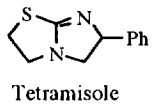
Abstract: 2-Aminobenzothiazoles, 2-aminopyrazine, 1-aminoisoquinoline and 2-aminonaphthyridines all undergo reaction with formaldehyde and electron rich alkenes such as styrenes, cyclopentadiene, cyclohexadiene and indene to give cyclic amidines, or in the case of the benzothiazoles cyclic isothioureas. The relationship of the diverse series of skeletons, which are easily prepared, to compounds of known biological activity is emphasized.

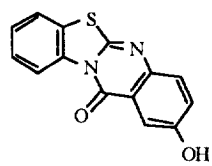
The successful synthesis of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines, described[1] in the preceding paper, by regioselective reaction of electron rich alkenes and formaldehyde with 2-aminopyridines, suggests that similar reaction with other nitrogen and sulfur heterocycles might open a general route to novel cyclic amidines and isothioureas respectively. Although the biological activity of cyclic amidines has long attracted interest[2], recently there have been renewed synthetic studies[3] driven by the many biological roles of amidines[4], including their potential as agonists in the treatment of Alzheimer's disease, their clinical use in anti-cancer therapy and the ability of pyrimido[2,1-*a*]isoquinolines to antagonize platelet activating factor. Similarly, although the biological activity of cyclic isothioureas such as the widely used anthelmintic tetramisole[5], an imidazo [2,1-*b*] thiazole now also used in treatment of cancers[6], and pyrimido[2,1-*b*]benzothiazoles[7], had stimulated further synthetic studies[8], recent findings have provided a new urgency in the development of routes to cyclic isothioureas. Nitric oxide[9] has been linked with pathological states such as septic shock and chronic inflammation. The selective inhibition of neuronal nitric oxide synthase[10] could be a powerful tool in the treatment of strokes and some neurodegenerative diseases and it has recently been found that isothioureas[11], including cyclic isothioureas[12] such as aminothiazoles and aminothiazolines, are the most potent known inhibitors of the nitric oxide synthases. The need to develop new routes both to novel amidine and isothiourea skeletons prompts us to communicate a generalisation of aza Diels Alder type additions with diverse aminoheterocycles.



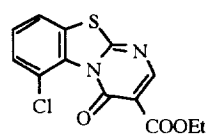
A pyrimido[2,1-*a*]isoquinoline antagonizes platelet activating factor



Tetramisole
Anthelmintic and as levamisole clinically used anti-cancer agent



OH
Pyrimido[2,1-*b*]benzothiazoles
Cytotoxic Agonist for benzodiazepine receptor



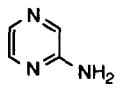
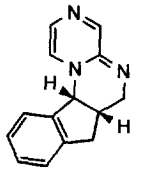
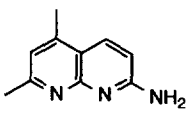
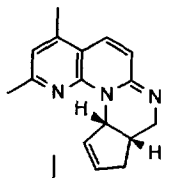
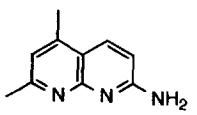
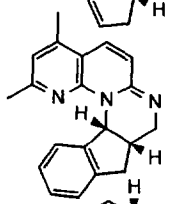
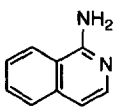
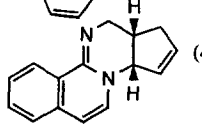
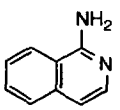
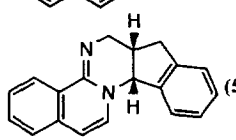
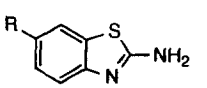
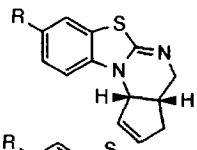
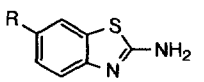
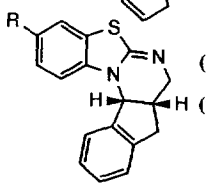
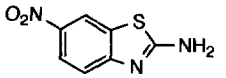
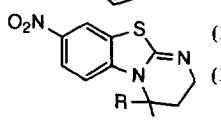
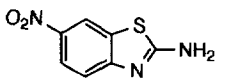
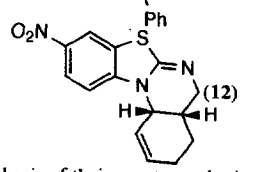
Grieco and Bahsas[13] have shown the potential for creation of cyclic systems based on the addition of the electron rich cyclopentadiene to imines, generated *in situ* by reaction of formaldehyde with anilines. We have

shown that these reactions, which might be considered to be single step aza-Diels Alder reactions, proceed[14] by a multi-step pathway, and we have reported the construction of a variety of heterocyclic systems based on the use of 2-aminopyridines[1], aminotetralones and aminoindanones[15], and aminoanthraquinones[16]. A key aspect of these additions is the choice of amine: the most satisfactory additions are observed with amines which on the one hand give relatively electrophilic imines to permit reaction with the alkene, yet on the other hand are sufficiently nucleophilic to permit the final cyclisation to give tetrahydroquinolines in the case of anilines and dihydropyridopyrimidines in the case of 2-aminopyridines.The electron rich aminonaphthalenes and the electron poor 3- and 4-aminopyridines for different reasons do not give adducts in acceptable yields. Thus in extending our synthetic strategy to provide a general route to cyclic amidines and cyclic isothioureas we were concerned with the possibility of inefficient reaction of the amine partners. Gratifyingly, as shown in the Table, the cycloaddition protocol can be extended to the creation of many novel polycyclic skeletons. Reactions were carried out in acetonitrile at reflux in the presence of trifluoroacetic acid and the appropriate alkene, and products were isolated following chromatography. By illustration with five different alkenes we consider that a wide variety of alkenes may be used in these additions. The reaction of 2-aminopyrazine with indene affords a single adduct (**1**). The structure (**1**), characterized by the cis ring junction (J 6.2Hz), could be assigned by analogy with adducts of 2-aminopyridine[1] (J 6Hz), where X-ray evidence established the structures. Hence reaction proceeds by formation of an imine at the primary amine site, with the anticipated regioselective addition to indene, and the final cyclisation affording a single amidine. Similar modes of addition with a more complex naphthyridine and 1-aminoisoquinoline were observed. Spectroscopic evidence (J_{cis} 5.8Hz) was used to assign structures to the amidines (**2**) and (**3**). Similarly the steroidal amidines (**4**) and (**5**) were easily isolated and characterized. In each case formaldehyde leads to product formation by reaction at the primary amino centre. We find no evidence for product formation by reaction of formaldehyde at a nuclear nitrogen site. In view of the interest in anti-fungal azasteroids, the creation of the steroidal skeletons in a single step suggests an interest in this effective route to 7,11-diazasteroids. In contrast to these successful additions we find that under similar reaction conditions products are not obtained from 2-aminopyrimidine or a 4-aminoquinazoline. These contrasting results emphasize the delicate balance controlling the multi-step process of adduct formation.

Reaction with 2-aminobenzothiazoles gave the adducts (**6-12**). Cyclopentadiene with 2-aminobenzothiazole gave an adduct, which by spectroscopic data (J_{cis} 6Hz) could be assigned the structure (**6**). With cyclopentadiene, indene, styrene, α-methylstyrene and cyclohexadiene as partners the adducts (**7-12**) were obtained. The pyrimido[2,1-*a*]benzothiazole structures were easily assigned by spectroscopic comparison with the adduct (**6**) and the adducts reported in the previous paper[1]. Formaldehyde might react with 2-aminobenzothiazoles at sites other than the primary amine. The difficulty in recognising the regiochemical outcome in creation of pyrimido[2,1-*a*]benzothiazoles by reaction of esters of acetylenedicarboxylic acid and related unsaturated esters with 2-aminobenzothiazole has been emphasized[17]. Our studies establish routes to

TABLE

Synthesis of Cyclic Amidines by Reaction of Amines with Formaldehyde and Alkenes

Substrates		Products		(Yields %)[a]
	Indene		(1)	44
	Cyclopentadiene		(2)	34
	Indene		(3)	48
	Cyclopentadiene		(4)	24
	Indene		(5)	84
	Cyclopentadiene		(6) R = H (7) R = NO_2	88 72
	Indene		(8) R = H (9) R = NO_2	90 72
	Styrene α-Methylstyrene		(10) R = H (11) R = Me	48 64
	Cyclohexadiene		(12)	63

a) All new compounds were fully characterised on the basis of their spectra and microanalytical data.

five different amidine skeletons and to four new isothiourea skeletons and in each case the regiochemical outcome is unambiguous. The potential of a general elaboration of aminoheterocycles to give skeletons of interest in medicinal chemistry is established. Both polycyclic amidines and isothioureas are available via a simple one pot, but multi-step procedure.

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