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X=Y–ZH compounds as potential 1,3-dipoles. Part 65: atom economic cascade synthesis of highly functionalized pyrimidinylpyrrolidines☆

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ABSTRACT

The results of the reaction of aminomethyl heterocycles and 4,6-dimethyl-2-formylpyrimidine and of activated secondary amines with different aryl/heteroaryl or aliphatic aldehydes and *N*-methylmaleimide or maleimide are described. In the former case the reactions gave single diastereomers via *endo*-transition states whilst the latter gave a mixture of diastereomers, which are believed to arise from *anti*-dipoles via *endo*/*exo* transition states. The stereochemistry of the cycloadducts was determined by ^{1}H NMR and confirmed by X-ray crystallography.

1. Introduction

The pyrimidinyl nucleus occurs widely in both aromatic (e.g., thiamine pyrophosphate) and non-aromatic form (e.g., cytosine, thymine, uracil and barbiturates) and as part of a wide variety of purine derivatives (e.g., adenine and guanine). The nucleus features in an extraordinary, and growing, array of pharmaceuticals and agrochemicals (Fig. 1).[2–6] In the field of crop protection, pyrimidine derivatives span pesticidal nucleosides with a pyrimidine or purine nucleobase,[7] herbicides and fungicides.[8] Although a variety of methods for the synthesis of pyrimidinylpyrrolidines have been developed, the use of azomethine ylide cycloaddition reactions has attracted little attention.[9] These processes are attractive because a variety of strategies and catalysts are available. Furthermore there are a substantial number of bioactive synthetic and natural products containing pyrrolidine motifs.[10] The cycloaddition reactions may be carried out as two component processes with preformed imines, or as three-component cascade processes with an aldehyde, a primary or secondary amine and a dipolarophile. The latter strategy is highly atom economic (water is the only by-product), and high density functionality occupying all five positions of the pyrrolidine ring can be easily introduced.

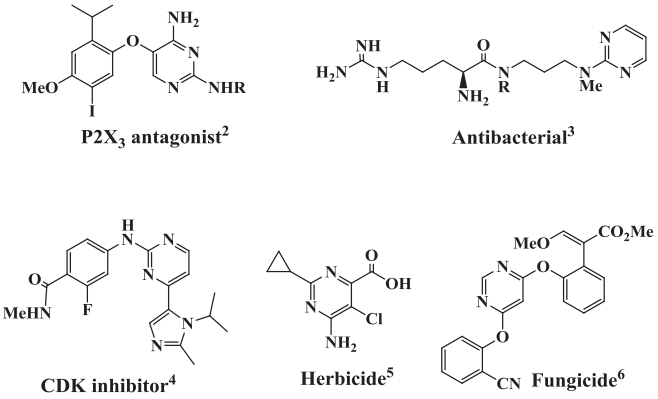

Fig. 1. Bioactive pyrimidines.

The reactions are catalyzed by a wide variety of Bronsted and Lewis acids including main group and transition metal salts and display excellent *endo*-selectivity.[11] This paper is concerned with the three component strategy.

2. Three-component cascade processes of primary amines

The concept of a thermal formal 1,2-prototropy in X=Y–ZH substrates generating 1,3-dipoles (Scheme 1) was introduced by us

☆ See Ref. 1.

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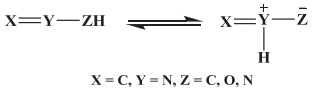
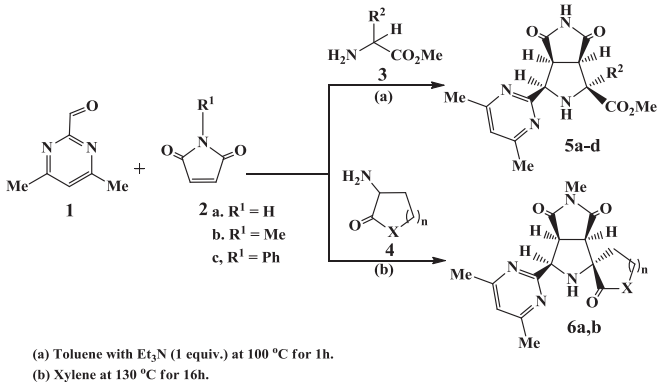


Scheme 1.

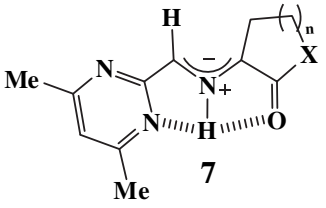
and subsequently shown to be viable for generating azomethine ylides, nitrones and azomethine imines.[12]

In the current investigation we initially employed the pyrimidine aldehyde **1** and the dipolarophiles maleimide **2a** or *N*-methylmaleimide **2b** with acyclic **3** and cyclic **4** amino esters (Scheme 2). In all cases the reaction occurred smoothly (toluene, 100 °C, oil bath) and in good yield via *endo*-transition states with precipitation of the cycloadduct from the hot toluene solution (Table 1) in the case of **5a**–**d** (Table 1, entries 1–4). Formation of spirocyclic cycloadducts **6a**,**b** (Table 1, entries 5 and 6) required more forcing conditions (xylene, 130 °C).



Scheme 2.

The proton NMR spectra (DMSO-d_6) of **5a**–**c** showed a singlet for the maleimide NH proton at δ 11.14–11.16 ppm and doublet for the pyrrolidine NH proton at δ 3.68–3.38 ppm. The corresponding signals for **5d** in $CDCl_3$ occurred at δ 8.29 and 4.14 ppm. The stereochemistry of **6a**,**b**, which was determined by NOE studies (see Experimental section), implicates the 1,3-dipoles **7**.



The reaction of **1** and **2c** with prolinamide **8** under analogous conditions afforded the tricyclic cycloadduct **10** in 89% yield via azomethine ylide **9** (Scheme 3). The stereochemistry of **10** was established by an X-ray crystal structure (Fig. 2). The high yield of **10** suggests that a series of prolinamide peptides would react similarly. The proton NMR spectrum of **10** (DMSO-d_6) clearly shows restricted rotation about the amide bond showing two signals for the NH_2 at δ 7.63 (J=2.3 Hz) and 7.32 (J=2.3 Hz).

A further small series of three-component cascades were studied in which the amino ester component of Scheme 2 was replaced by 2-aminomethyl heteroaromatic compounds **11a**,**b** and **12**.

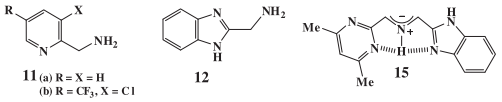
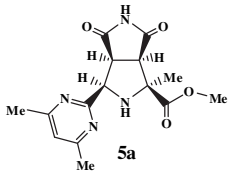
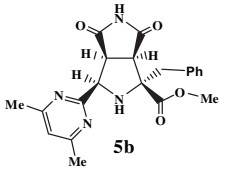
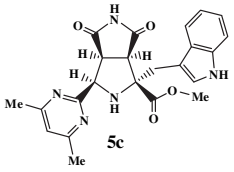
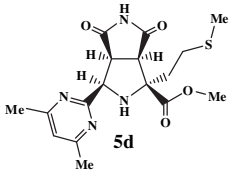
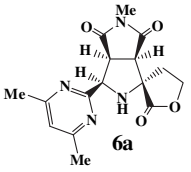
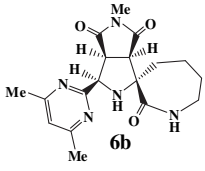
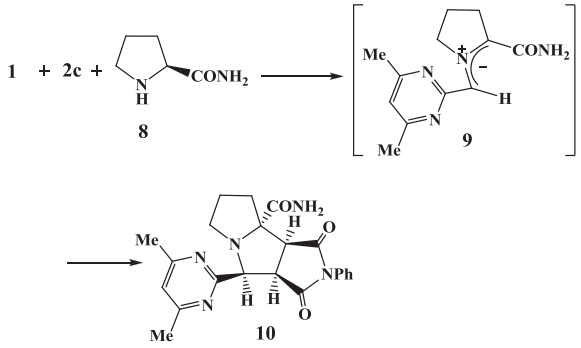


Table 1
Three-component cycloaddition cascades of **1** and **2** with **3** and **4**[a]

Entry	Amine ester HCl	Cycloadduct	Yield[b] (%)
1	Alanine	 **5a**	66
2	Phenylalanine	 **5b**	83
3	Tryptophan	 **5c**	74
4	Methionine	 **5d**	64[c]
5	**4a**	 **6a**	62[d]
6	**4b**	 **6b**	75[d]

[a] Conditions: **1** (1 mmol), amine ester hydrochloride (1 mmol), maleimide (1 mmol) and Et_3N (1 mmol) in toluene (7 mL) at 100 °C (oil bath) for 1 h.
[b] Isolated yield.
[c] Reaction (2 h).
[d] Xylene 16 h, 130 °C (oil bath), no Et_3N added.



Scheme 3.