Cascade condensation, cyclization, intermolecular dipolar cycloaddition by multi-component coupling and application to a synthesis of (\pm)-crispine A⁺

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A general approach for the synthesis of various nitrogen-containing heterocyclic compounds is described using an intermolecular dipolar cycloaddition reaction of azomethine ylides and nitrones. Stabilized and non-stabilized azomethine ylide dipoles or the related nitrones were generated by condensation of 4-, 5- or 6-halo-aldehydes with a readily available amino-acid, amino-ester or hydroxylamine to give an imine followed by cyclization and either decarboxylation or loss of a proton. After intermolecular cycloaddition with an activated dipolarophile, bicyclic or polycyclic (if the ylide dipole and/or dipolarophile contain a ring) amines were produced. A short synthesis of the alkaloid (±)-crispine A was achieved based on this tandem/domino 3-component coupling chemistry.

Introduction

Nitrogenous heterocycles are widely distributed among naturally occurring bioactive molecules. A great many alkaloids contain 5-membered cyclic amines. These include monocyclic compounds such as pyrrolidines and pyrroles, bicyclic compounds such as indolizidines and pyrrolizidines, and many polycyclic compounds (for example, a wide range of indole-containing alkaloids).¹ Due to their widespread occurrence and broad range of biological activity, there has been extensive interest in the synthesis of these types of heterocyclic compounds. Among various reported procedures for the synthesis of 5-membered cyclic amines, the cycloaddition reaction of azomethine ylides has proved a very useful method.²

Azomethine ylides can be generated by several methods,³ including the condensation of an aldehyde and a secondary amine followed by deprotonation or decarboxylation.⁴ A recent report from Pearson and co-workers demonstrated that azomethine ylides could be generated from aldehydes bearing a halogen at a suitable distance for intramolecular N-alkylation of the intermediate imine.⁵ Destannylation or desilylation then provided the desired azomethine ylide and intermolecular cycloaddition led to bicyclic and tricyclic products. We have used simple aminoacids and esters to prepare azomethine ylides for intramolecular cycloaddition reactions.⁶ Recently we found that this approach was successful for intermolecular cycloaddition.⁷ In this paper we describe in full our results on this chemistry, which involves cyclization followed by in situ intermolecular dipolar cycloaddition. This cascade chemistry provides a convenient method to prepare functionalized indolizidines and pyrrolizidines. In addition, we

demonstrate here the use of this methodology in the total synthesis of the alkaloid (\pm) -crispine A.

Preparation of various halo-aldehydes

For the generation of azomethine ylides, we used a variety of haloaldehydes which were prepared from simple starting materials. The aldehyde **3**, which had been prepared by Pearson and coworkers using an alkylation of a metalloenamine,⁵ was prepared by a different route starting from isobutyronitrile (**1**) as depicted in Scheme 1. Alkylation of isobutyronitrile using LDA and 1-bromo-3-chloropropane gave the nitrile **2** in good yield. The nitrile group was then reduced to the aldehyde **3** using DIBAL-H.



Scheme 1 Preparation of aldehyde 3. *Reagents and conditions:* i, LDA, THF, -78 °C, 1-bromo-3-chloropropane, 1 h, 86%; ii, DIBAL-H, CH₂Cl₂, -78 °C, 1.5 h, then HCl, 88%.

The homologous aldehyde 7 was prepared from isobutyronitrile following a similar sequence of reactions (Scheme 2). Isobutyronitrile was treated with LDA and 1-bromoethyl trimethylsilyl ether to obtain nitrile 4 in high yield. The silyl ether was deprotected using aqueous HCl to afford nitrile 5 and this was treated with triphenylphosphine and N-chlorosuccinimide to give nitrile 6. Reduction of nitrile 6 with DIBAL-H gave the desired aldehyde 7.

In the same way as the aldehyde **3**, the aldehyde **10** was prepared as shown in Scheme 3. Conversion of the chloride **9** to the iodide **10** was accomplished using NaI in acetone.

Another substrate investigated for this chemistry was the aromatic aldehyde 13, which was prepared from isochroman (11) in one pot.⁸ Isochroman was heated under reflux with bromine in CH_2Cl_2 to give the intermediate bromide 12 which was not isolated. The solvent was evaporated and the mixture was heated with aqueous HBr (45%) to obtain the desired bromo-aldehyde 13 in good yield (Scheme 4).

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^bAstraZeneca, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG † Electronic supplementary information (ESI) available: CIF and ORTEP diagram of the compounds **27a**, **32** and **38a**. Detailed experimental procedures and characterisation data. Copies of ¹H and ¹³C NMR spectra of crispine A. CCDC reference numbers 714109, 714110 and 714111. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b822743h



Scheme 2 Preparation of aldehyde 7. *Reagents and conditions:* i, LDA, THF, -78 °C, 1-bromoethyl trimethylsilyl ether, 1.5 h, 98%; ii, 2 M HCl, rt, 1 h, 86%; iii, NCS, PPh₃, THF, rt, 4 h, 81%; iv, DIBAL-H, CH₂Cl₂, -78 °C, 1.5 h, then HCl, 56%.





Cascade condensation-cyclization-cycloaddition

The aldehyde **3** was heated with glycine and *N*-methylmaleimide to give the products **15a** and **15b** (diastereomer ratio, dr 1 : 1) (Scheme 5, Table 1). Best yields were obtained with an excess (four equivalents) of glycine and 1.5 equivalents of *N*-methylmaleimide with respect to the aldehyde and by heating in toluene for 24 h. The reaction is thought to proceed by condensation of the aminoacid with the aldehyde then intramolecular *N*-alkylation and decarboxylation to generate the nonstabilized azomethine ylide **14**. This ylide can undergo dipolar cycloaddition to afford the tricyclic products **15a** and **15b**.



Scheme 5 Cycloaddition of aldehyde 3 with glycine.

A variety of dipolarophiles proved effective together with glycine or alanine to produce the cycloadducts **15–19** in good yields under these reaction conditions (Scheme 6, Table 1). Reaction with alanine (entries 4 and 5) afforded only two isomers of

Table 1	Cycloaddition of aldehyde 3 via nonstabilized ylides
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Entry	R	∕∕∼z	Product	Yield (%)	dr
1	Н	O NMe	15	70	1:1
2	Н	O ₹NPh O	16	63	1:1
3	Н	CO ₂ Me CO ₂ Me	17	63	1:1
4	Me	O NMe O	18	52	1.3 : 1
5	Me	CO ₂ Me CO ₂ Me	19	51	1.2 : 1



Scheme 6 Cycloaddition of 3 using glycine and alanine.

cycloadducts **18** and **19**. The stereochemistry of compounds **18a** and **18b** (see Fig. 1) was established from 2D COSY and NOESY as the 2,5-*trans* disubstituted pyrrolidines, indicating that there was a preference for cycloaddition through the S-shaped ylide. The stereochemistry of the compounds **19a** and **19b** was assumed based on the expected preference for cycloaddition through the same ylide.



Heating the aldehyde **3** with glycine ethyl ester generates the ester-stabilised azomethine ylide which was trapped with various dipolarophiles (Scheme 7, Table 2). Optimum reaction

 Table 2
 Cycloaddition of aldehyde 3 via an ester-stabilized ylide

Entry	∕∕∼z	Product	Yield (%)	dr
1	O (NMe O	20	94	2.2:2:1
2	CO₂Me CO₂Me	21	74	2.5 : 1 : 1
3	MeO ₂ C- _ CO ₂ Me	22	45ª	1:0
" Yield for reaction at room temp.				

conditions were the addition of 1.5 equivalents of glycine ethyl ester hydrochloride salt with respect to aldehyde 3. On heating with *N*-methylmaleimide, three isomers of compound 20 were obtained (Fig. 2). The major isomer was separated by column chromatography and X-ray crystallographic study showed the relative stereochemistry as 20a. This must be formed from the S-shaped ylide and *endo* addition of *N*-methylmaleimide.



Scheme 7 Cycloaddition of aldehyde 3 using glycine ethyl ester.



Fig. 2 Cycloadducts 20-22.

Compound 22 was isolated as a single isomer (stereochemistry verified by NOESY). In this case, the best results were obtained when generation of the azomethine ylide was carried out at 60 $^{\circ}$ C for 2 h by mixing the aldehyde with glycine ethyl ester followed by cooling to room temperature for the cycloaddition reaction with dimethyl acetylene dicarboxylate (DMAD).

The examples so far make use of the aldehyde **3** and lead to the indolizidine ring system. For the synthesis of the pyrrolizidine moiety we prepared the azomethine ylide from the aldehyde **7**. Successful condensation, cyclization then cycloaddition was achieved with nonstabilized and stabilized azomethine ylides (Scheme 8). Several dipolarophiles can be used,⁷ although Scheme 8 illustrates only the formation of compounds **23** and **24** by use of dimethyl maleate. Compound **24** was a mixture of three diastereomers (dr 15:2:1) of which the major isomer was separable. This is shown in Scheme 8 and the stereochemistry was determined from ¹H NMR NOESY and COSY analysis.



Scheme 8 Synthesis of pyrrolizidine derivatives.

In a similar way, nitrones were generated by condensation of the aldehydes **3** and **7** with hydroxylamine hydrochloride salt in the presence of the base ${}^{1}\text{Pr}_{2}\text{NEt}$ (Scheme 9). Two diastereoisomers of compound **25** were separated by column chromatography and from ${}^{1}\text{H}$ NMR NOESY and COSY analysis, we were able to determine their structures. From aldehyde **7**, only one isomer of compound **26** was obtained from the reaction mixture. In the ${}^{1}\text{H}$ NMR spectrum, there was a singlet at $\delta 3.38$ for C8a indicating an *anti* relationship between it and the proton at C8b, which appeared as a doublet at $\delta 3.56$ (*J* 7 Hz).



Scheme 9 Cycloaddition reactions from nitrone ylides.

Using the longer chain analogue 9, cycloaddition was unsuccessful using glycine or glycine ethyl ester and *N*-phenylmaleimide. However, conversion to the iodide 10 allowed the desired cyclization–cycloaddition, but only with the stabilized azomethine ylide generated using glycine ethyl ester (Scheme 10). In this case a few dipolarophiles were screened and the results are shown in Table 3.



Scheme 10 Cycloaddition of aldehyde 10 via an ester-stabilized ylide.

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Entry	∕∕∼z	Product	Yield (%)	dr
1	O ≪NPh O	27	65	3:1.7:1
2	€ CO₂Me	28	46	5.8 : 1.7 : 1
3	SO ₂ Ph	29	45	ND
$^{a}ND = not determined.$				

Table 3Synthesis of compound 27–29

Three diastereoisomers of compounds 27 and 28 were obtained
(Fig. 3). A minor isomer of 27 was separated and the structure was
determined by X-ray crystallographic analysis (27a). This would
have arisen from the W-shaped ylide. We assume that the major
isomers of compounds 27 and 28 arise from the S-shaped ylide.
For compound 29, four isomers were produced but these were
inseparable and the ratio could not be determined. However, these
are likely to be the endo and exo isomers of each regioisomer (29a
and 29b) formed from the S-shaped ylide.



Fig. 3 Cycloadducts 27-29.

The products from the reactions described above contain a gemdimethyl group to block enolisation. We wanted to illustrate the potential of this condensation–cyclization–intermolecular dipolar cycloaddition reaction with other aldehyde substrates. Therefore, we prepared the aromatic aldehyde **13** and were pleased to find that it reacts cleanly with glycine ethyl ester to generate a stabilized azomethine ylide which undergoes cycloaddition with various dipolarophiles in high yields (Scheme 11, Table 4).



Scheme 11 Cycloaddition of aldehyde 13 via an ester-stabilized ylide.

Cycloaddition with *N*-methyl- or *N*-phenylmaleimide was efficient and gave only two diastereoisomers **30** and **31** (dr of each 1 : 1) (Fig. 4), which were assigned in comparison with the literature.⁹ These must arise from the S-shaped ylide with *endo* and *exo* approach of the dipolarophile. A slight preference

Table 4 Synthesis of	of compound 30-33
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Entry	∕∕z	Product	Yield (%)	dr
1	O NMe	30	78	1:1
2	O ↓ NPh O	31	83	1:1
3	CO ₂ Me CO ₂ Me	32	75	1:0
4	SO ₂ Ph	33	72	ND

^aND = not determined.



Fig. 4 Cycloadducts 30–33.

for isomer **30a** (ratio 2:1) was found when azomethine ylide formation was carried out in toluene at room temperature for 12 h prior to addition of *N*-methylmaleimide. Using dimethyl maleate, compound **32** was obtained as a single diastereoisomer and the relative stereochemistry was determined using X-ray crystallographic analysis. Compound **33** was isolated as a mixture of four inseparable isomers.

The aldehyde 13 was found to react with glycine and N-methylmaleimide to give a mixture of the diastereoisomers 34a and 34b in a 1 : 1 ratio (Scheme 12). These isomers could be separated by column chromatography.



Scheme 12 Cycloaddition of aldehyde 13 using glycine.

With the success in the cyclization-cycloaddition with aromatic aldehyde 13, we turned our attention to the application of



(+)-Crispine A was isolated by Zhao and co-workers in 2002 from the *Carduus crispus* plant.¹⁰ An extract of this plant is used in Chinese folk medicine for treatment of colds, stomach ache and rheumatism. This extract has also been shown to inhibit the growth of some human cancer lines *in vitro* and shows significant cytotoxic activity.¹⁰ There are several reported syntheses of this alkaloid to date.¹¹

For a synthesis of (\pm) -crispine A using the cascade methodology described here, we needed a dipolarophile in which the activating group could be removed after cycloaddition. We anticipated that a benzenesulfonyl group would fulfil this role, since the sulfonyl group would provide the necessary activation for the cascade and should be amenable to reductive cleavage. For the key condensation-cyclization-cycloaddition reaction, we needed the aldehyde 36, which was readily prepared in two steps from the alcohol 35 following the reported procedure (Scheme 13).8 The cascade chemistry was performed with the aldehyde 36, glycine and phenyl vinyl sulfone but gave the desired cycloadduct as mixture of two isomers in poor yield. As a result, we carried out the key step with the more activated bis-sulfone 37 as a dipolarophile. In this case the desired product 38 was obtained in an improved yield (70%) (Scheme 13). This was formed as a mixture of two diastereoisomers and the major isomer (38a) was separated and the structure was confirmed by single crystal X-ray analysis. Elimination¹² of the two benzenesulfonyl groups from compound 38a using Na/Hg in MeOH afforded the alkene 39 in moderate yield. Hydrogenation of alkene 39 using hydrogen and Pd/C gave the desired product (±)-crispine A in good yield. The spectroscopic data for this compound matched those in the literature.¹¹ This sequence of reactions completes the synthesis of the alkaloid crispine A and demonstrates an application



Scheme 13 Synthesis of (\pm)-crispine A. *Reagents and conditions:* i, CH(OEt)₃, BF₃·OEt₂, r.t., 2.5 h, 45%; ii, CH₃COCl, heat, 3.5 h, 70%; iii, glycine, (*E*)-PhSO₂CH=CHSO₂Ph **37**, PhMe, 110 °C, 24 h, 70%; iv, Na-Hg, Na₂HPO₄, CH₃OH, 0 °C, 2 h, 55%; v, H₂, 10% Pd-C, CH₃OH, r.t., 2 h, 80%.

of the cascade condensation-cyclization-intermolecular dipolar cycloaddition chemistry.

Conclusions

We have described the synthesis of various nitrogen-containing heterocycles applying a cascade process involving condensation of various aldehydes and amines followed by *in situ* cyclization then intermolecular cycloaddition all in one pot. Non-enolisable aliphatic and aromatic aldehydes and simple primary amines such as glycine, glycine ethyl ester and hydroxylamine together with activated dipolarophiles were suitable substrates for this three-component coupling chemistry. This strategy was applied successfully to the synthesis of the alkaloid (\pm)-crispine A.

Experimental

General methods

For general experimental details, including information on solvent purifications and the spectrometers used in this research, see previous descriptions.¹³ For procedures and data for compounds **2–10** and **15–34** see the ESI.[†]

(1SR,2SR,10bSR)-8,9-Dimethoxy-1,2-bis(phenylsulfonyl)-1,2, 3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline 38a. The aldehyde 36⁸ (130 mg, 0.57 mmol), glycine (171 mg, 2.28 mmol) and E-1-(2-(phenylsulfonyl)vinylsulfonyl)benzene 37 (193 mg, 0.63 mmol) in toluene (5 mL) were heated under reflux. After 24 h, the mixture was cooled to room temperature, evaporated and purified by column chromatography, eluting with petrol-EtOAc (3:2), to give the amine **38** (205 mg, 70%) as a mixture of two isomers (ratio not determined). The major isomer (38a) (165 mg, 56%) was separated [by column chromatography] as needles; mp 110–112 °C; $R_{\rm f}$ 0.20 [petrol-EtOAc (3 : 2)]; v_{max}/cm^{-1} 2935, 1510, 1445, 1305, 1145; ¹H NMR (CDCl₃, 500 MHz) $\delta = 8.00$ (d, J 8 Hz, 2H), 7.74 (t, J 7.5 Hz, 1H), 7.65 (dd, J 8, 7.5 Hz, 2H), 7.61 (d, J 8 Hz, 2H), 7.55 (t, J 7.5 Hz, 1H), 7.38 (dd, J 8, 7.5 Hz, 2H), 6.51 (s, 1H), 6.44 (s, 1H), 4.54 (d, J 3 Hz, 1H), 4.18–4.14 (m, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.37 (dd, J 10, 5 Hz, 1H), 3.12 (dd, J 10, 7 Hz, 1H), 3.06-3.03 (m, 1H), 2.88 (td, J 12.5, 5 Hz, 1H), 2.76-2.69 (m, 1H), 2.38 (dd, J 16.5, 5 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) $\delta = 147.9$, 147.7, 137.5, 137.4, 134.5, 133.9, 129.7, 129.1, 128.9, 128.7, 126.2, 126.0, 111.4, 108.6, 70.4, 65.1, 62.2, 55.9, 55.8, 51.3, 45.5, 23.9; HRMS (ES) Found: MH⁺ (ES), 514.1379. C₂₆H₂₈NO₆S₂ requires MH+ 514.1358; LRMS m/z (ES) 514 (100%, MH+).

8,9-Dimethoxy-3,5,6,10*b***-tetrahydro-pyrrolo[2,1-***a***]isoquinoline 39.** Na₂HPO₄ (977 mg, 6.88 mmol) and Na-Hg amalgam (2.37 g, 5.15 mmol) were added to the amine **38a** (440 mg, 0.86 mmol) in MeOH (4 mL) at 0 °C. After 2 h, the mixture was filtered, evaporated, diluted with water and extracted with CHCl₃ (2 × 25 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and was dried (MgSO₄). The solvent was evaporated and the mixture was purified by column chromatography, eluting with MeOH–CH₂Cl₂ (3 : 97), to give the alkene **39** (110 mg, 55%) as an oil; R_f 0.39 [MeOH–CH₂Cl₂ (3 : 97)]; v_{max}/cm^{-1} 2930, 2830, 1610, 1510, 1465; ¹H NMR (CDCl₃, 400 MHz) δ = 6.59 (s, 1H), 6.58 (s, 1H), 5.97–5.95 (m, 1H), 5.84–5.82 (m, 1H), 5.08 (br s, 1H), 3.85–3.84 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.68–3.62 (m, 1H), 3.11 (dd, *J* 7.5, 4 Hz, 2H), 2.90–2.83 (m, 1H), 2.45 (dt, *J* 16, 4 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ = 147.6, 147.1, 131.7, 129.1, 127.4, 126.4, 111.7, 108.7, 65.9, 57.5, 55.9, 55.8, 46.0, 23.7; HRMS (ES) Found: MH⁺ (ES), 232.1329. C₁₄H₁₈NO₂ requires MH⁺, 232.1338; LRMS *m*/*z* (ES) 232 (95%, MH⁺).

Crispine A. The alkene 39 (100 mg, 0.43 mmol) was dissolved in MeOH (3 mL) and stirred with Pd/C (~100 mg, 10 wt%) under an atmosphere of hydrogen at room temperature. After 2 h, the mixture was filtered, evaporated and purified by column chromatography on neutral alumina, eluting with MeOH-CH2Cl2 (5:95), to give crispine A (80 mg, 80%) as needles; mp 79-81 °C (lit. gives the following: lit.¹⁰ 87-89 °C, lit.^{11a,b} 88-89 °C, lit.^{11g} 76-78 °C, lit.11i 77-79 °C, other references do not mention m.p.); $R_{\rm f}$ 0.18 [MeOH–CH₂Cl₂ (5 : 95)]; ¹H NMR (CDCl₃, 400 MHz) $\delta = 6.59$ (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.39 (t, J) 8.5 Hz, 1H), 3.19-3.14 (m, 1H), 3.09-2.97 (m, 2H), 2.74-2.50 (m, 3H), 2.34–2.27 (m, 1H), 1.98–1.79 (m, 2H), 1.75–1.65 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) $\delta = 147.2, 147.1, 130.9, 126.2, 111.2,$ 108.7, 62.9, 55.9, 55.8, 53.1, 48.3, 30.4, 28.0, 22.1; HRMS (ES) Found: MH⁺ (ES), 234.1484. C₁₄H₂₀NO₂ requires MH⁺, 234.1494; spectroscopic data consistent with the literature.11

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