Cascade condensation, cyclization, intermolecular dipolar cycloaddition by multi-component coupling and application to a synthesis of (±)-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.

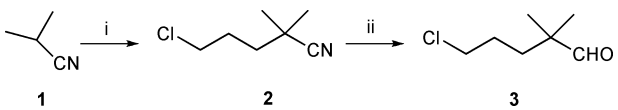
Introduction

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 amino-acids 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 (±)-crispine A.

Preparation of various halo-aldehydes

For the generation of azomethine ylides, we used a variety of halo-aldehydes which were prepared from simple starting materials. The aldehyde **3**, which had been prepared by Pearson and co-workers 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, CH_2Cl_2, –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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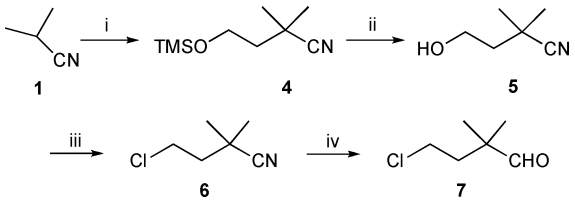
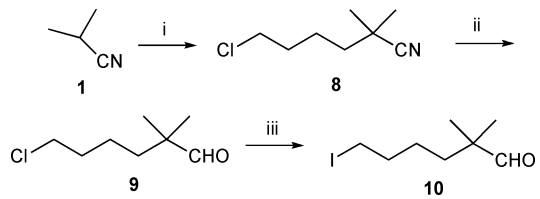
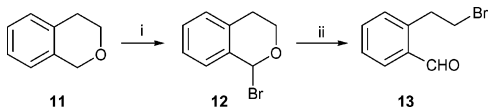
† Electronic supplementary information (ESI) available: CIF and ORTEP diagram of the compounds **27a**, **32** and **38a**. Detailed experimental procedures and characterisation data. Copies of ^{1}H and ^{13}C NMR spectra of crispine A. CCDC reference numbers 714109, 714110 and 714111. For ESI and crystallographic 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, PPh_3, THF, rt, 4 h, 81%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, then HCl, 56%.



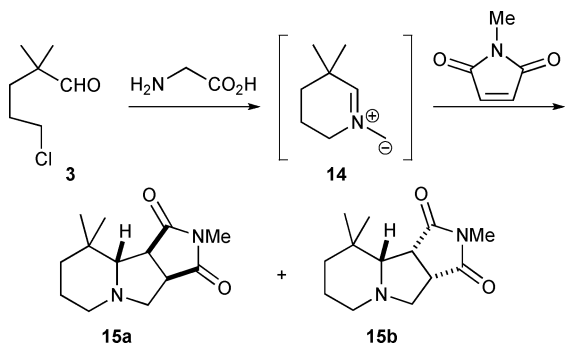
Scheme 3 Preparation of aldehyde **10**. *Reagents and conditions:* i, LDA, THF, −78 °C, 1-bromo-4-chlorobutane, 1 h, 86%; ii, DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, HCl, 80%; iii, NaI, acetone, 12 h, reflux, 99%.



Scheme 4 Preparation of bromo aldehyde **13**. *Reagents and conditions:* i, Br_2, CH_2Cl_2, 2 h, 45 °C; ii, HBr (45%), 100 °C, 0.5 h, 80% (two steps).

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 amino-acid 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**.

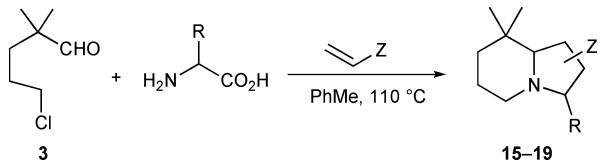


Scheme 5 Cycloaddition of aldehyde **3** with glycine.

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

Entry	R	Z	Product	Yield (%)	dr
1	H		**15**	70	1 : 1
2	H		**16**	63	1 : 1
3	H		**17**	63	1 : 1
4	Me		**18**	52	1.3 : 1
5	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.

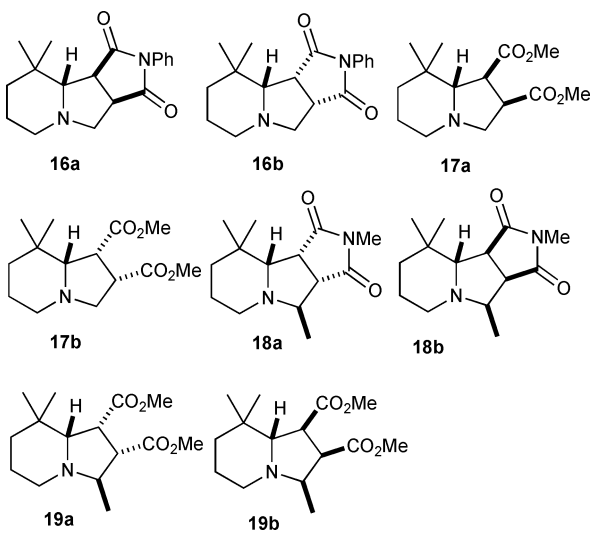


Fig. 1 Cycloadducts **16–19**.

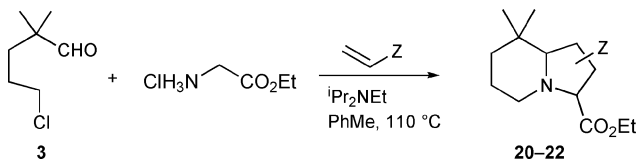
Heating the aldehyde **3** with glycine ethyl ester generates the ester-stabilised azomethine ylide which was trapped with various dipolarophiles (Scheme 7, Table 2). Optimum reaction

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

Entry	Z	Product	Yield (%)	dr
1		**20**	94	2.2 : 2 : 1
2		**21**	74	2.5 : 1 : 1
3	$MeO_2C{\equiv}CO_2Me$	**22**	45[a]	1 : 0

[a] 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.

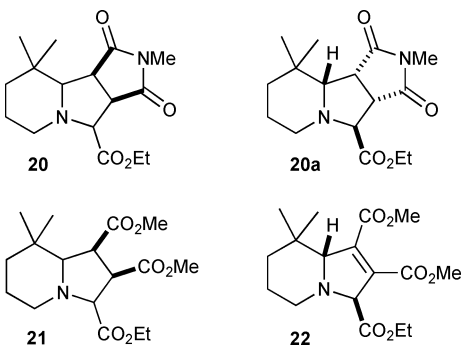
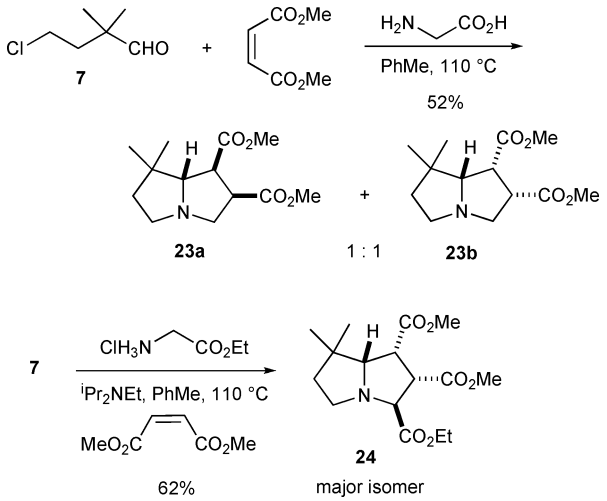


Fig. 2 Cycloadducts **20–22**.

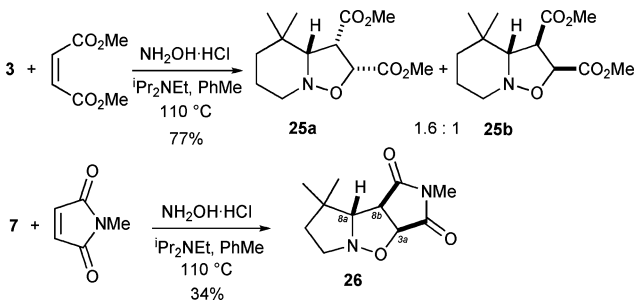
Compound **22** was isolated as a single isomer (stereochemistry verified by NOESY). In this case, the best results were obtained when generation of the azomethine ylide was carried out at 60 °C for 2 h by mixing the aldehyde with glycine ethyl ester followed by cooling to room temperature for the cycloaddition 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 ^{1}H NMR NOESY and COSY analysis.



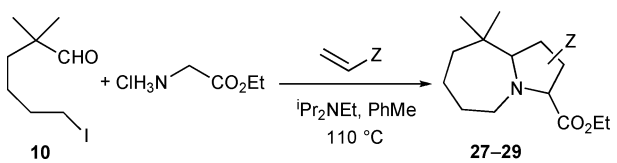
Scheme 8 Synthesis of pyrrolizidine derivatives.

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 ^{i}Pr$_2$NEt (Scheme 9). Two diastereoisomers of compound **25** were separated by column chromatography and from ^{1}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}H NMR spectrum, there was a singlet at δ3.38 for C8a indicating an *anti* relationship between it and the proton at C8b, which appeared as a doublet at δ3.56 (*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.

Table 3 Synthesis of compound **27–29**

Entry	Z	Product	Yield (%)	dr
1		**27**	65	3 : 1.7 : 1
2		**28**	46	5.8 : 1.7 : 1
3		**29**	45	ND

[a]ND = not determined.

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.

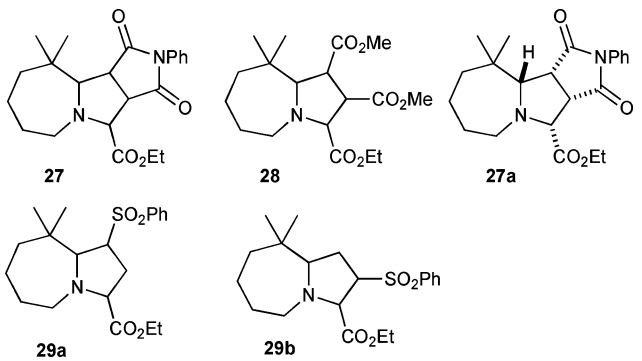
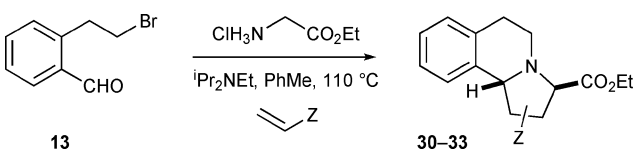


Fig. 3 Cycloadducts **27–29**.

The products from the reactions described above contain a gem-dimethyl 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 compound **30–33**

Entry	Z	Product	Yield (%)	dr
1		**30**	78	1 : 1
2		**31**	83	1 : 1
3		**32**	75	1 : 0
4		**33**	72	ND

[a]ND = not determined.

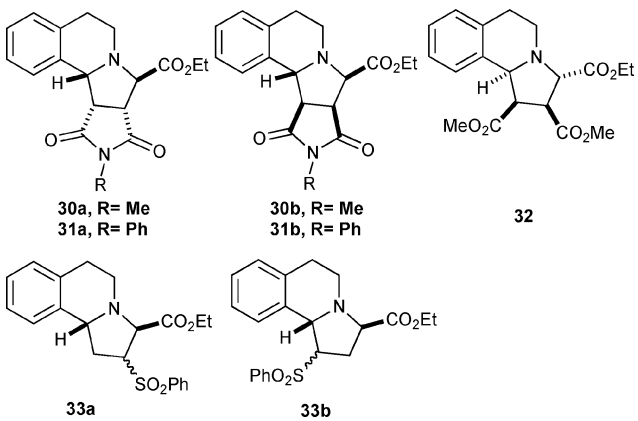
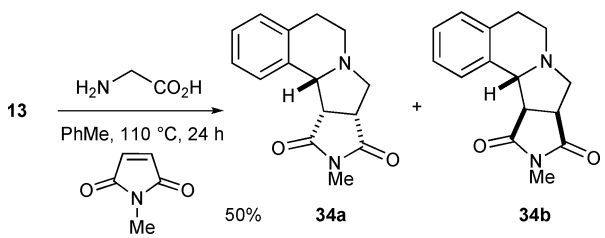


Fig. 4 Cycloadducts **30–33**.

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

this methodology to the synthesis of the pyrrolidinoisoquinoline alkaloid crispine A (Fig. 5).

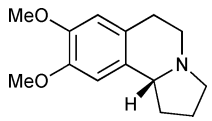
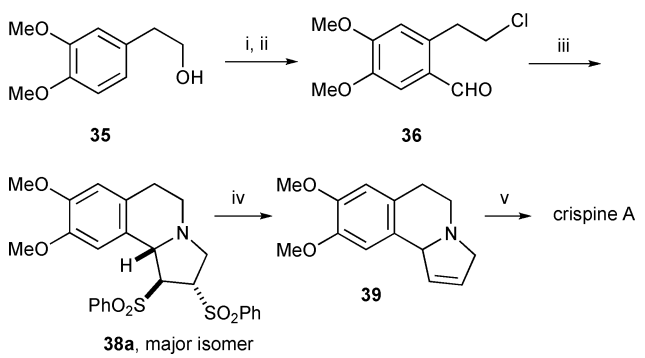


Fig. 5 (+)-Crispine A.

(+)-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 (±)-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. Elimination[12] 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 (±)-crispine A. *Reagents and conditions:* i, $CH(OEt)_3$, $BF_3{\cdot}OEt_2$, r.t., 2.5 h, 45%; ii, CH_3COCl, heat, 3.5 h, 70%; iii, glycine, (*E*)-$PhSO_2CH{=}CHSO_2Ph$ **37**, PhMe, 110 °C, 24 h, 70%; iv, Na-Hg, Na_2HPO_4, CH_3OH, 0 °C, 2 h, 55%; v, H_2, 10% Pd-C, CH_3OH, 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 (±)-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.†

(1*SR*,2*SR*,10*bSR*)-8,9-Dimethoxy-1,2-bis(phenylsulfonyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline 38a. The aldehyde **36**[8] (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_f 0.20 [petrol–EtOAc (3 : 2)]; ν_{max}/cm^{-1} 2935, 1510, 1445, 1305, 1145; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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. $C_{26}H_{28}NO_6S_2$ 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. Na_2HPO_4 (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 $CHCl_3$ (2 × 25 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and was dried ($MgSO_4$). The solvent was evaporated and the mixture was purified by column chromatography, eluting with MeOH–CH_2Cl_2 (3 : 97), to give the alkene **39** (110 mg, 55%) as an oil; R_f 0.39 [MeOH–CH_2Cl_2 (3 : 97)]; ν_{max}/cm^{-1} 2930, 2830, 1610, 1510, 1465; ^1H NMR ($CDCl_3$, 400 MHz) $\delta = 6.59$ (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); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 147.6, 147.1, 131.7, 129.1, 127.4, 126.4, 111.7, 108.7, 65.9, 57.5, 55.9, 55.8, 46.0, 23.7$; HRMS (ES) Found: MH^+ (ES), 232.1329. $C_{14}H_{18}NO_2$ 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–CH_2Cl_2 (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_f 0.18 [MeOH–CH_2Cl_2 (5 : 95)]; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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. $C_{14}H_{20}NO_2$ requires MH^+, 234.1494; spectroscopic data consistent with the literature.[11]

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Notes and references

1 See, for example (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (*b*) J. R. Liddell, *Nat. Prod. Rep.*, 2002, **19**, 773; (*c*) K. Higuchi and T. Kawasaki, *Nat. Prod. Rep.*, 2007, **24**, 843; (*d*) G. Lesma, A. Colombo, A. Sacchetti and A. Silvani, *J. Org. Chem.*, 2009, **74**, 590; (*e*) T. Ritthiwigrom and S. G. Pyne, *Org. Lett.*, 2008, **10**, 2769; (*f*) T. Machan, A. S. Davis, B. Liawruangrath and S. G. Pyne, *Tetrahedron*, 2008, **64**, 2725; (*g*) T. J. Donohoe, R. E. Thomas, M. D. Cheeseman, C. L. Rigby, G. Bhalay and I. D. Linney, *Org. Lett.*, 2008, **10**, 3615; (*h*) T. Sengoku, Y. Satoh, M. Oshima, M. Takahashi and H. Yoda, *Tetrahedron*, 2008, **64**, 8052; (*i*) Y. Matsuda, M. Kitajima and H. Takayama, *Org. Lett.*, 2008, **10**, 125; (*j*) R. G. Vaswani and A. R. Chamberlin, *J. Org. Chem.*, 2008, **73**, 1661; (*k*) C. Alegret and A. Riera, *J. Org. Chem.*, 2008, **73**, 8661; (*l*) P. Liu, S. Hong and S. M. Weinreb, *J. Am. Chem. Soc.*, 2008, **130**, 7562.

2 (*a*) L. M. Harwood and R. J. Vickers, in '*Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*', eds. A. Padwa, and W. H. Pearson, Wiley, New Jersey, 2003, ch. 3, p. 169; (*b*) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (*c*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; (*d*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887.

3 (*a*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565; (*b*) R. Huisgen, W. Scheer and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 602; (*c*) E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941.

4 (*a*) R. Grigg, J. Kemp, G. Sheldrick and J. Trotter, *J. Chem. Soc., Chem. Commun.*, 1978, 109; (*b*) R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1980, **21**, 2461; (*c*) H. Ardill, R. Grigg, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1988, **44**, 4953.

5 (*a*) W. H. Pearson, P. Stoy and Y. Mi, *J. Org. Chem.*, 2004, **69**, 1919; (*b*) W. H. Pearson, J. E. Kropf, A. L. Choy, I. Y. Lee and J. W. Kampf, *J. Org. Chem.*, 2007, **72**, 4135.

6 (*a*) I. Coldham, K. M. Crapnell, J. D. Moseley and R. Rabot, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1758; (*b*) I. Coldham, K. M. Crapnell, J.-C. Fernàndez, J. D. Moseley and R. Rabot, *J. Org. Chem.*, 2002, **67**, 6181; (*c*) I. Coldham, S. M. Pih and R. Rabot, *Synlett*, 2005, 1743; (*d*) I. Coldham, B. C. Dobson, A. I. Franklin and S. R. Fletcher, *Tetrahedron Lett.*, 2007, **48**, 873; (*e*) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams and N. Oram, *Angew. Chem., Int. Ed.*, 2007, **46**, 6159; (*f*) I. Coldham, B. C. Dobson, S. R. Fletcher and A. I. Franklin, *Eur. J. Org. Chem.*, 2007, 2676; (*g*) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram and N. G. Martin, *J. Org. Chem.*, 2009, DOI: 10.1021/jo8019913.

7 I. Coldham, S. Jana, L. Watson and C. D. Pilgram, *Tetrahedron Lett.*, 2008, **49**, 5408.

8 (*a*) M. Yamato, K. Hashigaki, N. Qais and S. Ishikawa, *Tetrahedron*, 1990, **46**, 5909; (*b*) P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith and A. M. Z. Slawin, *J. Org. Chem.*, 2001, **66**, 6926.

9 H. Ardill, X. L. R. Fontaine, R. Grigg, D. Henderson, J. Montgomery, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1990, **46**, 6449.

10 Q. Zhang, G. Tu, Y. Zhao and T. Cheng, *Tetrahedron*, 2002, **58**, 6795.

11 (*a*) S. M. Allin, S. N. Gaskell, J. M. R. Towler, P. C. B. Page, B. Saha, M. J. McKenzie and W. P. Martin, *J. Org. Chem.*, 2007, **72**, 8972; (*b*) F. D. King, *Tetrahedron*, 2007, **63**, 2053; (*c*) T. Kanemitsu, Y. Yamashita, K. Nagata and T. Itoh, *Heterocycles*, 2007, **74**, 199; (*d*) T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2006, **128**, 9646; (*e*) N. Meyer and T. Opatz, *Eur. J. Org. Chem.*, 2006, 3997; (*f*) J. Szawkalo, A. Zawadzka, K. Wojtasiewicz, A. Leniewski, J. Drabowicz and Z. Czarnocki, *Tetrahedron: Asymmetry*, 2005, **16**, 3619; (*g*) H.-J. Knölker and S. Agarwal, *Tetrahedron Lett.*, 2005, **46**, 1173; (*h*) J. Szawkalo, S. J. Czarnocki, A. Zawadzka, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, Z. Czarnocki and J. Drabowicz, *Tetrahedron: Asymmetry*, 2007, **18**, 406; (*i*) G.-H. Hou, J.-H. Xie, P.-C. Yan and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2009, **131**, 1366.

12 A. López-Pérez, J. Adrio and J. C. Carretero, *J. Am. Chem. Soc.*, 2008, **130**, 10084.

13 I. Coldham, P. O'Brien, J. J. Patel, S. Raimbault, A. J. Sanderson, D. Stead and D. T. E. Whittaker, *Tetrahedron: Asymmetry*, 2007, **18**, 2113.