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Synthesis of Highly Functionalized Pyrrolidines via a Mild One-Pot, Three-Component 1,3-Dipolar Cycloaddition Process

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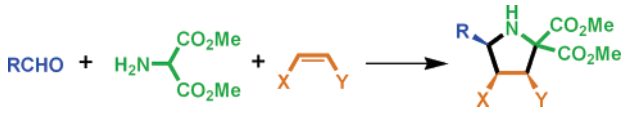
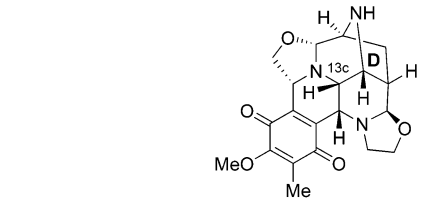
Received September 14, 2005



A simple and efficient one-pot, three-component synthesis of highly functionalized pyrrolidines via cascade imine → azomethine ylide → 1,3-dipolar cycloadditions is reported. Admixing a variety of aldehydes, dimethyl 2-aminomalonate, and electron deficient alkenes in THF leads to the clean production of pyrrolidines in good to excellent yields. The mild reaction conditions enabled the generation of previously inaccessible azomethine ylides from enolizable aldehydes. Endo selectivity was exclusive with *N*-phenyl maleimide and maleic anhydride. Good chemo-, regio-, and stereoselectivities were observed with methyl acrylate, though catalysis by Ag(I) was necessary with this dipolarophile.

The reaction sequence consisting of aldehyde + amine → imine → azomethine ylide + dipolarophile → pyrrolidine first reported by Grigg,[1] and then by Joucla and Hamelin,[2] as well as its metalated variants[3] has become a favored method for the assembly of functionalized pyrrolidines. Recently, examples of catalytic asymmetric cascade [3+2] cycloadditions of azomethine ylides have also been reported.[4] However, the generality of the existing cascade azomethine ylide generation/cycloaddition technology breaks down in certain instances where enolizable aldehydes are used, limiting the full exploitation of this powerful synthetic technology. We recently encountered such a case when the [3+2] cycloaddition of an azomethine ylide derived from glycine methyl ester failed to react cleanly with a tethered acrylamide dipolarophile. The substitution of dimethyl 2-aminomalonate as the amine component provided a solution to this problem providing a synthetic entry to the D-ring core + C-13c of bioxalomycin β1 (Figure 1). In fact, it was not even necessary to preform the imine: a very efficient and selective *intramolecular* [3+2] cycloaddition reaction occurred upon simply mixing the aldehyde-tethered dipolarophile **1** with aminoester **2** in reagent grade THF.[5] While the focus of this study was on α-diastereocontrol during the azomethine ylide cycloaddition, we were intrigued by the operational simplicity and cleanliness of the overall reaction. This in turn prompted us to examine the scope of the one-pot aldehyde + amine + dipolarophile → pyrrolidine cascade, using **2** as the amine component.

While the use of dialkyl 2-aminomalonate and related species in imine → azomethine ylide + dipolarophile → pyrrolidine cascade reactions has been known for some time,[2,6] the examples cited were limited to imines prepared from nonenolizable aryl aldehydes. In 1988, Husinec reported a series of aldehyde + amine + dipolarophile → pyrrolidine cascade reactions between (nonenolizable) formaldehyde and activated dipolarophiles.[7] Heathcock used a related one-pot *intramolecular* [3+2] cycloaddition sequence using a dipolarophile-tethered 2-aminomalonate derivative and formaldehyde in his synthetic approach to sarain A.[8] His group also reinvestigated Husinec's *intermolecular* [3+2] cycloadditions and found that the regioselectivity of these cycloadditions was low with monosubstituted dipolarophiles.[9] These reactions with paraformaldehyde were generally conducted in refluxing toluene. We now report a mild and general one-pot, three-component synthesis of highly functionalized pyrrolidines using dimethyl 2-aminomalonate (**2**) as the amine component. Of particular significance is the successful incorporation of enolizable aldehydes into the cascade [3+2] cycloaddition sequence.



bioxalomycin β1

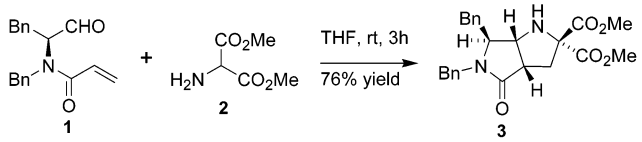


FIGURE 1. Inspiration for the current study.

Properly tuned multicomponent reactions (MCRs) offer a powerful and efficient means for assembling complex molecular structures.[10] Optimal MCRs are tolerant of

(1) Grigg, R.; Kemp, G.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109.
(2) Joucla, M. H.; Hamelin, J. *Tetrahedron Lett.* **1978**, 2885.
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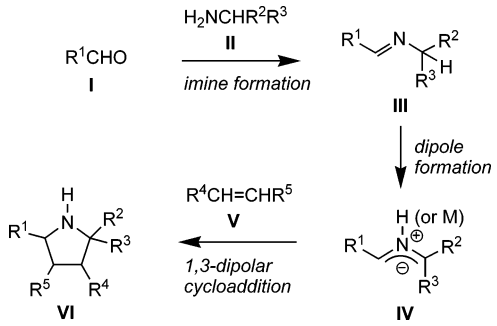
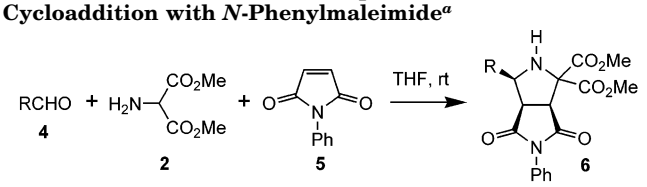
10.1021/jo051926y CCC: $30.25
Published on Web 11/22/2005

SCHEME 1. Aldehyde → Imine → Dipole → Cycloadduct Reaction Cascade



structural diversity yet selective, atom-economical, and convergent. In the context of developing a one-pot, aldehyde + amine + dipolarophile → pyrrolidine 3-CR, the following requirements must be met (Scheme 1). First, the aldehyde **I** must cleanly and quickly condense with the amine component **II** to give the intermediate imine **III**. Enolizable aldehydes and their imines must resist tautomerization to the corresponding enol and enamine, respectively. The amine component must not react in a nucleophilic sense with activated dipolarophiles. Second, the reaction conditions must generate a steady state of the reactive azomethine ylide **IV** from the imine **III** without any unwanted ancillary reactivity during the net tautomerization process. Third, the azomethine ylide **IV** must be efficiently trapped by the alkene dipolarophile **V** to afford the requisite pyrrolidine **VI**. Competitive heterocycloaddition to either the aldehyde (oxazolidine formation) or imine (imidazolidine formation) must be minimized. In addition to the examples cited above, a number of 3-CR approaches to pyrrolidines based on azomethine ylide cycloadditions have been reported over the years.[11–17] However, lower yields were generally obtained with aliphatic aldehydes.

TABLE 1. One-Pot, Three-Component [3+2] Cycloaddition with *N*-Phenylmaleimide[a]



entry	aldehyde	reaction time	product & yield
1	PhCHO **4a**	3.5 h	**6a** (100%)
2	Ph–CH=CH–CHO **4b**	5 h	**6b** (100%)
3	*i*-PrCHO **4c**	1 h	**6c** (90%)
4	$Ph(CH_2)_2CHO$ **4d**	1 h	**6d** (100%)
5	$Me(CH_2)_3CHO$ **4e**	3 h	**6e** (83%)
6[b]	MeCHO **4f**	5 h	**6f** (100%)
7	$BocHNCH_2CHO$ **4g**	3 h	**6g** (50%)

[a] Reaction conditions A: aldehyde **4** (1 equiv), dimethyl 2-aminomalonate (**2**, 2 equiv), and *N*-phenylmaleimide (**5**, 2 equiv) were combined in THF (2.5 mL per mol of **4**) and the mixture was stirred at room temperature for the indicated time. [b] Reaction conditions B: aldehyde **4** (4 equiv-VOLATILE), amine **2** (1 equiv), and dipolarophile **7** (1 equiv) were combined in THF (1.25 mL per mmol of **2**) and the mixture was stirred at room temperature for the indicated time. The reactions were concentrated and the products **6** purified by flash chromatography.

The results of our initial survey of the aldehyde **4** (variable) + dimethyl 2-aminomalonate (**2**) + *N*-phenyl-

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(7) Husinec, S.; Savic, V.; Porter, A. E. A. *Tetrahedron Lett.* **1988**, *29*, 6649.
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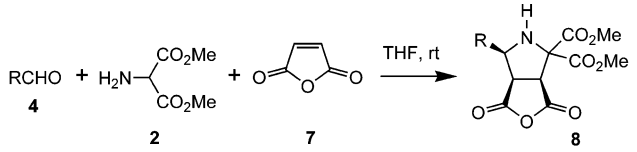
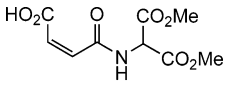
TABLE 2. One-Pot, Three-Component [3+2] Cycloaddition with Maleic Anhydride[a]



entry	aldehyde	reaction time	product & yield
1	Ph–CHO **4b**	1 h	**8b** (58%)
2	*i*-PrCHO **4c**	1 h	**8c** (64%)
3	$Ph(CH_2)_2CHO$ **4d**	1 h	**8d** (100%)
4	$Me(CH_2)_3CHO$ **4e**	1 h	**8e** (96%)
5	MeCHO **4f**	1 h	**8f** (92%)

[a] Reaction conditions B: see Table 1 for details. The reaction mixtures were concentrated, then quickly filtered through a short plug of silica gel to remove the maleamic acid byproduct **9**.



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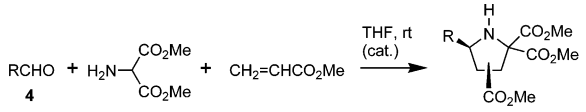
maleimide (**5**) → pyrrolidine cascade are compiled in Table 1. This reactive dipolarophile easily fulfills the third chemoselectivity requirement, effectively trapping the azomethine ylide as soon as it forms. The weakly nucleophilic amine **2** either does not add to *N*-phenylmaleimide fast enough to compete with the desired cascade or its conjugate addition product undergoes spontaneous β-elimination to recycle the components in situ. The one-pot reaction cascade proceeds quickly and cleanly with benzaldehyde (**4a**) and cinnamaldehyde (**4b**) to give the pyrrolidines **6a** and **6b**, respectively, in quantitative yield (entries 1 and 2). More interestingly, a series of enolizable aldehydes (isobutryaldehyde (**4c**), dihydrocinnamaldehyde (**4d**), valeraldehyde (**4e**), acetaldehyde (**4f**), and *N*-Boc-glycinal (**4g**)) were found to participate in the one-pot cascade process equally well (entries 3−7). The successes with **4f** and **4g** are particularly noteworthy. Tsuge had documented the propensity of acetaldehyde to condense with itself prior to azomethine ylide formation under thermal conditions.[17] Grigg had stated that he was unable to form an imine from the combination of aldehyde **4g** and phenylalanine methyl ester.[18] The 5-*endo* assignments for the cycloadducts in Table 1 are based on selected *J*-coupling and/or NOE data (Supporting Information).

Table 2 illustrates the one-pot, three-component [3+2] cycloaddition process with maleic anhydride (**7**) as the

TABLE 3. One-Pot, Three-Component [3+2] Cycloaddition with Methyl Acrylate



entry	aldehyde	reaction time	products & yields
1[a]	PhCHO **4a**	12 h	**11a** (95%) **12a** (5%)
2[a]	Ph–CHO **4b**	1 h	**11b** (90%) **12b** (9%)
3[b,c]	$Ph(CH_2)_2CHO$ **4d**	4 h	**11d** (73%) **12d** (12%)
4[b,c]	$Me(CH_2)_3CHO$ **4e**	4 h	**11e** (61%) **12e** (17%)
5[b]	$BocHNCH_2CHO$ **4g**	6 h	**11g** (48%)

[a] Reaction conditions A. [b] Reaction conditions C: aldehyde **4** (1 equiv), amine **2** (2 equiv), and catalyst (10 mol % of AgOAc + 20 mol % of Ph_3P) were conbined in methyl acrylate (**10**, 20 equiv) and the mixture was stirred at room temperature for the indicated time. After aqueous workup and concentration, the products **11** and **12** were purified by flash chromatography. [c] Minor amounts of the trans isomers corresponding to **11** (7−10%) as well as oxazolidines (~5%) were also formed.

(12) Aldehyde + amino acid + dipolarophile: (a) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. J. C. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703. (b) Aly, M. F.; Younes, M. I.; Metwally, S. A. M. *Tetrahedron* **1994**, *50*, 3159.

(13) Aldehyde + dibenzylamine + dipolarophile: Wittland, C.; Arend, M.; Risch, N. *Synthesis* **1996**, 367.

(14) Aldehyde + trimethylsilylbenzylamine + dipolarophile: Torii, S.; Okumoto, H.; Genba, A. *Chem. Lett.* **1996**, 747.

(15) Aldehyde + aminomethylstannane + dipolarophile: Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919.

(16) Imine + diazoester + dipolarophile: (a) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153. (b) Galliford, C. V.; Beenan, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487.

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dipolarophile. In addition to being a reactive dipolarophile, compound **7** provides an additional test by introducing the labile anhydride function into the reaction mixture. In fact, a control experiment showed that amine **2** readily reacts with **7** under the reaction conditions to irreversibly give the corresponding maleamic acid **9**. This problem was readily overcome by employing a 4-fold excess of aldehyde. NMR analysis of the crude reaction mixtures indicated the clean formation of a single cycloadduct **8** in addition to the aforementioned maleamic acid. The cycloadducts **8** were easily separated from this polar byproduct by simple filtration through a short plug of silica gel and the cycloadducts were obtained after removal of the volatiles (entries 2, 4, and 5). Once again, the 5-*endo* stereochemical assignments are based on selected *J*-coupling and/or NOE data (Supporting Information). Prolonged exposure of the cycloadducts to silica gel resulted in lower isolated yields, presumably due to hydrolytic opening of the anhydride moiety. In such cases, the reactivity of the anhydride may be exploited: similar anhydrides have been converted to dimethyl esters by the action of HCl in MeOH.[19] This tactic may be employed with other nucleophiles as well.

The dipolarophile methyl acrylate (**10**) provides a more stringent test of the one-pot, three-component cascade process (Table 3) since it also introduces the issue of [3+2] cycloaddition regioselectivity in addition to the usual *endo*- versus *exo*-cycloaddition considerations. Neither of these problems surfaced with the conjugated aldehydes **4a** and **4b**, which gave excellent yields of the corresponding 2,4,5-trisubstituted *endo*-cycloadducts **11a** and **11b**, respectively (entries 1 and 2). Very minor amounts of the 2,3,5-regioisomers **12a** and **12b** were found in these reactions. However, with aliphatic aldehydes, the overall rate of [3+2] cycloaddition to dipolarophile **10** is apparently slow relative to that of other processes. As a result, competitive siphoning-off of the azomethine ylide via cycloaddition to the starting aldehyde occurs to produce a mixture of *trans*- and *cis*-oxazolidines. The problem could be ameliorated by performing these reactions in methyl acrylate as the solvent and with a soluble Ag(I) catalyst. This modification leads to accelerated [3+2] cycloaddition, providing good yields of the 2,4,5-trisubstituted *endo*-cycloadducts **11d**, **11e**, and **11g**, along with minor regioisomers **12d** and **12e** after flash chromatography (entries 3 and 4). As before, the stereochemical assignments for pyrrolidines **11** and **12** are based on selected *J*-coupling and/or NOE data (Supporting Information). This outcome may be rationalized by a smaller FMO-gap between the metalated ylide and methyl acrylate and/or chelation between these two species.[3c,3f]

In conclusion, a simple and efficient one-pot, three-component synthesis of highly functionalized pyrrolidines via controlled azomethine ylide cycloadditions has been developed. The ability to favor the desired [3+2] cycloaddition cascade over competing pathways (which varied with the dipolarophile component) by rationally adjusting mechanistic parameters was demonstrated. The mild reaction conditions enabled the generation of previously inaccessible azomethine ylides from enolizable aldehydes.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051926Y

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