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Development of a 2-Aza-Cope-[3+2] Dipolar Cycloaddition Strategy for the Synthesis of Quaternary Proline Scaffolds

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Abstract

A one-pot multicomponent procedure for the synthesis of highly functionalized pyrrolidine rings through a domino 2-aza-Cope-[3+2] dipolar cycloaddition sequence has been demonstrated. This protocol was found to be both high yielding and stereoselective for the *endo*-cycloadduct.

The pyrrolidine ring represents a prevalent scaffold for many compounds of pharmaceutical interest as well as a structural element common to the *Amaryllidaceae* and *Erythrina* alkaloids.¹ The development of mild, efficient, and operationally simple methods for their construction continues to warrant interest. As chemical synthesis places an ever-increasing emphasis on concise molecular assembly, processes that rapidly assemble complex structures in a stereocontrolled fashion are highly desirable. Toward these ends, multicomponent reactions have played an important role.² The orchestration of two or more distinct chemical events involving multiple components permits a magnification of structural complexity in a minimal number of synthetic steps.³ In the context of heterocyclic chemistry, strategic extensions of the 2-aza-Cope rearrangement could potentially meet these criteria. Specifically, the merging of the 2-aza-Cope rearrangement with a [3+2] dipolar cycloaddition reaction could provide new and more concise routes to a variety of pyrrolidine-containing targets.

The 2-aza-Cope rearrangement affords imine or iminium products which could in principle be used directly for additional carbon-carbon bond forming events. A classic example of this strategy is well illustrated by Overman's aza-Cope-Mannich reaction (Scheme 1).⁴ In this powerful variant, a charge-accelerated cationic 2-aza-Cope rearrangement affords an iminium ion having an enol moiety correctly positioned for Mannich cyclization. The utility of this process has been amply demonstrated by Overman⁵ and others⁶ in many elegant total syntheses. Bennett and others have used a 2-aza-Cope-iminium ion solvolysis protocol to prepare allylglycine derivatives.⁷

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. X-ray crystallographic information for 2-allyl proline **4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Inspired by these advancements, we took interest in developing conceptually new unions of the 2-aza-Cope rearrangement with other carbon-carbon bond forming reactions. We first envisioned that the 2-aza-Cope rearrangement could be used to prepare azomethine ylide precursors for direct use in [3+2] dipolar cycloadditions. Such a strategy would capitalize on the considerable bond-reorganization properties of the Cope rearrangement as well as the diversity and facility of azomethine ylide cycloaddition. Condensation of a homoallylic amine with a glyoxylate ester would provide imine **I** (Scheme 1) which, after thermodynamically driven 2-aza-Cope rearrangement, would afford imine **II**. The addition of a metal/amine base pair would result in the formation of a metallated azomethine ylide for subsequent [3+2] dipolar cycloaddition with a wide range of dipolarophiles.⁸

Central to our plans was the need for stereocontrol. Cycloaddition could potentially generate up to four stereogenic centers – at least one quaternary – within the proline cycloadduct. Predictions as to which stereoisomers will dominate would require analyses of both azomethine ylide geometry as well as *endo* vs. *exo* approach of the dipolarophile. Cognizant that imines bearing electron-withdrawing groups (e.g. **II**) lead to metallated azomethine ylides with rigid geometries,⁹ more accurate predictions regarding the stereochemical outcome should be possible. As a result, the 2-aza-Cope-[3+2] dipolar cycloaddition sequence should stereoselectively generate functionalized proline scaffolds bearing a quaternary center.

Our survey of substrates centered on homoallyl amines **1a-e** (Figure 1),¹⁰ ethyl glyoxylate (**2**) as the aldehyde component, and dipolarophiles **3a-c**. For our initial optimization studies, homoallylic primary amine **1a**, ethyl glyoxylate (**2**), and *N*-phenyl maleimide (**3a**) were selected, and each step of the process was monitored via ¹H NMR analysis of sequential aliquots. Condensation of **1a** and **2** was rapid (15 min) at rt in toluene (concentration 0.33 M) to afford an imine product of type **I** (Scheme 1).¹¹ Bringing the mixture to reflux for 2 h effected clean 2-aza-Cope rearrangement, determined to be complete and quantitative by ¹H NMR, to furnish a new imine of type **II**. When the dipolarophile (1.5 equiv), AgOAc (1.5 equiv) and Et₃N (2.0 equiv) were added to the reaction mixture and stirred at rt, azomethine ylide formation and [3+2] dipolar cycloaddition occurred within 6 h to provide 2-allyl proline **4a** (entry 1, Table 1) in 84% yield. Stereochemical analysis of **4a** by 1-D NOE enhancement experiments revealed that the cycloaddition exhibited *endo*-selectivity as evidenced from through-space coupling of the protons indicated below (Figure 2), which was unambiguously confirmed via X-ray crystallographic analysis.

The scope of the 2-aza-Cope-[3+2] dipolar cycloaddition was next extended to other homoallyl amine substrates (Table 1). For all cases, only the *endo* cycloadducts were detected by ¹H NMR analysis of the reaction mixtures. Each product (**4a-e**) displayed NOE enhancements consistent with the stereoisomer expected to result from cycloaddition of a W-shaped azomethine ylide through *endo* approach of the dipolarophile, as drawn in Scheme 1. The only other compounds observed in the reaction mixtures were variable amounts of unreacted imine after 2-aza-Cope rearrangement. The overall yields were generally good and, as anticipated, appeared to be dependent on the electronic characteristics of the aromatic moiety. Electron deficient *p*-trifluoromethylbenzyl amine **1c** gave a higher yield (97%) than electron rich *p*-methoxybenzyl amine **1b** (70% yield), likely attributable to increased acidity and therefore more facile azomethine ylide formation in the case of substrates bearing electron-withdrawing groups. Gratifyingly, 3-pyridinyl amine **1d** also underwent the transformation in good yield (87%). Overall, furanylamine **1e** was the only difficult substrate as the 2-aza-Cope rearrangement required an additional hour and the resultant imine did not readily undergo either azomethine ylide formation or [3+2] dipolar cycloaddition even after 14 h of stirring at rt (entry 5, Table 1).

We also investigated the reactivities of two other dipolarophiles, dimethyl maleate (**3b**) and dimethyl fumarate (**3c**, Table 2). For each homoallylamine substrate (**1a-e**) explored, the overall yields were good and were generally found to parallel those observed with *N*-phenyl maleimide (**3a**), with yields somewhat better for reactions with fumarate **3c** (entries 6–10, Table 2) than maleate **3b** (entries 1–5). The relative stereochemistries of the isolated 2-allyl prolines **4f-o** once again proved to be those consistent with [3+2] dipolar cycloaddition via an *endo* transition state maleate with a W-shaped azomethine ylide.

In summary, we demonstrate here the first examples of a one-pot domino 2-aza-Cope-[3+2] dipolar cycloaddition for the synthesis of functionalized 2-allyl proline derivatives. The resultant allyl and ester moieties provide convenient points for additional structural elaboration. Importantly, the multicomponent nature of the protocol is evident as a wide variety of amine, glyoxylic ester, and dipolarophile components could potentially be used. The reaction stereoselectively generates four new chiral centers and one quaternary carbon with a high degree of functionalization around a pyrrolidine ring and we anticipate applying this strategy towards the synthesis of alkaloid natural products. Our route to azomethine ylide precursors via the 2-aza-Cope rearrangement is complementary to the condensation of aldehydes with allylglycine derivatives and may afford azomethine ylides not accessible by other means. The transition to non-benzylic homoallylic amine components, monoactivated dipolarophiles, and catalytic asymmetric variants¹² are all important avenues currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- (1). For reviews of these alkaloid classes, see: (a) Lewis JR. *Nat. Prod. Rep.* 1993; 10:291–299. (b) Martin, SF. *The Alkaloids*. Brossi, A., editor. Vol. 30. Academic Press; New York: 1987. p. 252 (c) Tsuda, Y.; Sano, T. *The Alkaloids*. Cordell, GA., editor. Vol. 48. Academic Press; New York: 1996. p. 239 For selected syntheses, see: (d) Jin J, Weinreb SM. *J. Am. Chem. Soc.* 1997; 119:2050–2051. (e) Overman LE, Shim J. J. *Org. Chem.* 1993; 58:4662–4672. (f) Ishizaki M, Hoshino O, Iitaka Y. *Tetrahedron Lett.* 1991; 32:7079–7082. (g) Pansare SV, Lingampally R, Kirby RL. *Org. Lett.* 2010; 12:556–559. [PubMed: 20055457] (h) Jones MT, Schwartz BD, Willis AC, Banwell M.G. *Org. Lett.* 2009; 11:3506–3509. [PubMed: 19591492] (i) Yamada K, Yamashita M, Sumiyoshi T, Nishimura K, Tomioka K. *Org. Lett.* 2009; 11:1631–1633. [PubMed: 19243131]
- (2). (a) Dömling A. *Chem. Rev.* 2006; 106:17–89. [PubMed: 16402771] (b) Dömling A, Ugi I. *Angew. Chem. Int. Ed.* 2000; 39:3168–3210.
- (3). (a) Parsons JP, Penkett CS, Shell AJ. *Chem. Rev.* 1996; 96:195–206. [PubMed: 11848750] (b) Tietze LF. *Chem. Rev.* 1996; 96:115–136. [PubMed: 11848746]
- (4). For a recent perspective, see: Overman LE. *Tetrahedron.* 2009; 65:6432–6446. [PubMed: 20640042] For earlier accounts, see: (a) Overman LE. *Acc. Chem. Res.* 1992; 25:352–359. (b) Jacobsen EJ, Levin J, Overman LE. *J. Am. Chem. Soc.* 1988; 110:4329–4336.

- (5). For selected examples, see: (a) Martin CL, Overman LE, Rohde JM. *J. Am. Chem. Soc.* 2008; 130:7568–7569. [PubMed: 18491907] (b) Dunn TB, Ellis JM, Kofink CC, Manning JR, Overman LE. *Org. Lett.* 2009; 11:5658–5661. [PubMed: 19904991] (c) Knight SD, Overman LE, Pairaudeau G. *J. Am. Chem. Soc.* 1995; 117:5776–5788.
- (6). (a) Brummond KM, Hong S. *J. Org. Chem.* 2005; 70:907–916. [PubMed: 15675848] (b) Agami C, Cases M, Couty F. *J. Org. Chem.* 1994; 59:7937–7940.
- (7). (a) Bennett DJ, Hamilton NM. *Tetrahedron Lett.* 2000; 41:7961–7964. (b) Agami C, Couty F, Lin J, Mikeaeloff A, Poursoulis M. *Tetrahedron.* 1993; 49:7239–7250.
- (8). (a) Pandey G, Banerjee P, Gadre SR. *Chem. Rev.* 2006; 106:4484–4517. [PubMed: 17091927] (b) Coldham I, Hufton R. *Chem. Rev.* 2005; 105:2765–2809. [PubMed: 16011324] (c) Najera C, Sansano JM. *Curr. Org. Chem.* 2003; 7:1105–1150.
- (9). (a) Grigg, R.; Sridharan, V. *Advances in Cycloaddition*. Curran, DP., editor. Vol. 3. JAI Press; London: 1993. p. 161 (b) Grigg R, Montgomery J, Somasunderam A. *Tetrahedron.* 1992; 48:10431–10442. (c) Grigg R, Gunaratne HQN. *Chem. Commun.* 1982:384–386. (d) Grigg R, Kemp J, Malone J, Tangthongkum A. *Chem. Commun.* 1980:648–650.
- (10). Preparation of **1a**, **1b**, and **1e**: (a) Hart DJ, Kanai K, Thomas DG, Yang TK. *J. Org. Chem.* 1983; 48:289–294. Preparation of **1d**: (b) McCoy CP, Morrow RJ, Edwards CR, Jones DS, Gorman SP. *Bioconjugate Chem.* 2007; 18:209–215. (c) Felpin FX, Girard S, Vo-Thanh G, Robins RJ, Villiéras J, Lebreton J. *J. Org. Chem.* 2001; 66:6305–6312. [PubMed: 11559179] For the preparation of **1c**, see Supporting Info.
- (11). We found it convenient to conduct the reactions in the presence of 4 Å molecular sieves, thereby reducing the possibility of by-product formation from competing processes with water.
- (12). (a) Longmire JM, Wang B, Zhang X. *J. Am. Chem. Soc.* 2002; 124:13400–13401. [PubMed: 12418889] (b) Chen C, Li X, Schreiber SL. *J. Am. Chem. Soc.* 2003; 125:10174–10175. [PubMed: 12926931] (c) Zeng W, Zhou YG. *Org. Lett.* 2005; 7:5055–5058. [PubMed: 16235956]

Figure 1.
Survey of amine, aldehyde, and alkene components.

Figure 2.
NOE enhancements and X-ray crystal structure of **4a**.

Overman: 2-Aza-Cope-Mannich Cyclization **Bennett: 2-Aza-Cope-Iminium Hydrolysis** **This work: 2-Aza-Cope-[3+2] Dipolar Cycloaddition**

Scheme 1.
Applications of the 2-Aza-Cope Rearrangement.

Table 1

Exploring the Substrate Scope of the 2-Aza-Cope-[3+2] Dipolar Cycloaddition: Homoallylamine **1a-e** and Maleimide **3a**^a

entry	amine	product	yield ^b
1	1a		84%
2	1b		70%
3	1c		97%
4	1d		87%
5	1e		36%

^a Reaction conditions: homoallylic amine **1a-e** (1.0 mmol), ethyl glyoxylate (**2**, 1.0 mmol), 4 Å MS, toluene (3 mL), reflux, 2-3 h; then add *N*-phenyl maleimide (**3a**, 1.5 mmol), AgOAc (1.5 mmol), Et₃N (2.0 mmol), rt, 6 h.

^b Isolated yields after flash column chromatography on silica gel or recrystallization.

Table 2

Extending the Substrate Scope of the 2-Aza-Cope-[3+2] Dipolar Cycloaddition with Dimethyl Maleate and Dimethyl Fumarate^a

entry	amine	dipolarophile	product	yield ^b
1	1a	3b	4f	69%
2	1b	3b	4g	50%
3	1c	3b	4h	71%
4	1d	3b	4i	86%
5	1e	3b	4j	29%
6	1a	3c	4k	97%

entry	amine	dipolarophile	product	yield ^b
7	1b	3c	4l	75%
8	1c	3c	4m	87%
9	1d	3c	4n	70%
10	1e	3c	4o	52%

^aReaction conditions: homoallylic amine **1a-e** (1.0 mmol), ethyl glyoxylate (**2**, 1.0 mmol), 4 Å MS, toluene (3 mL), reflux, 2-3 h; then add **3b** or **3c** (1.5 mmol), AgOAc (1.5 mmol), Et₃N (2.0 mmol), rt, 6 h.

^bIsolated yields after flash column chromatography on silica gel or recrystallization.