# A New Entry to Azomethine Ylides from Allylic Amines and Glyoxals: Shifting the Reliance on Amino Ester Precursors

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S Supporting Information

ABSTRACT: The first examples of azomethine ylides derived from allylic amine and glyoxal precursors are reported. The condensation of primary allylic and α-aryl amines with glyoxylates or α-aryl glyoxals affords conjugated azomethine ylides that undergo facile [3 + 2] cycloaddition, providing 5-alkenyl pyrrolidine cycloadducts that cannot be accessed through the classical use of amino esters as ylide precursors.
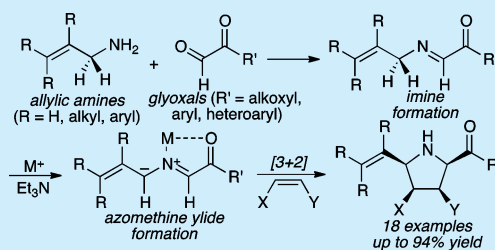
The early reports by Grigg[1] and Hamelin[2] on the generation of ester-stabilized azomethine ylides by thermal 1,2-prototropy of α-iminoesters was a notable advance in heterocyclic chemistry, as access to a variety of pyrrolidines became available through 1,3-dipolar cycloaddition. Later, Grigg's important discovery of metalated azomethine ylides[3] derived from aryl aldehydes and α-amino esters enabled cycloadditions to occur at lower temperatures with enhanced regio- and stereocontrol.[4] Steady progress has been made in the area since, including catalytic metal/base systems,[5] stereo-induction by chiral auxiliaries,[6] and many asymmetric processes via chiral Lewis acid complexes[7] or organocatalysis.[8]

Despite these advances, a commonly overlooked drawback is the almost exclusive reliance on α-amino esters as azomethine ylide precursors. Instances remain in which the condensation of a primary amino ester and an aliphatic aldehyde will not produce the desired azomethine ylide. The condensation of amino ester **2** (Scheme 1) with an aliphatic, α,β-unsaturated aldehyde such as acrolein (**1**) could, in principle, yield a useful, vinyl azomethine ylide (**4**) for the preparation of synthetically versatile 5-alkenyl proline scaffolds (**6**). Such scaffolds have been used for the synthesis of Pro-Pro dipeptide mimics,[9] novel pyrrolidine-derived influenza neuraminidase inhibitors,[10] analogues of the immunomodulatory macrolide ascomycin,[11] and peptidomimetics for the endocrine hormone thyroliberin.[12] However, direct 1,2-addition of the amine onto acrolein is complicated by competing 1,4-conjugate addition (cf. **7** and **8**). Indeed, the synthesis of aldimines from primary amines and acrolein are generally not successful,[13] primarily attributable to 1,4-additions and oligomerization upon exposure to protic or Lewis acids.[14] Further, any acrolein present in the reaction mixture could also compete as a dipolarophile (cf. **9**).[15] Though desirable in some cases, it does not permit the general diversity achievable by varying the dipolarophile. For these reasons, examples of azomethine ylides derived from amino esters and aliphatic, α,β-unsaturated aldehydes are not widespread,[16] attributable to the difficulty of their preparation. A synthetic

route circumventing these difficulties would therefore be desirable.

Our research program is centered on new methodologies for the formation of structurally advanced azomethine ylide systems. We previously described a method for the synthesis of azomethine ylides through the 2-aza-Cope rearrangement of imines derived from homoallylic amines and glyoxylate esters, which after [3 + 2] dipolar cycloaddition afforded multi-substituted 2-allylpyrrolidine products.[17] Drawing on this work, we now report a method for ylide formation that circumvents the reliance on α-amino esters as ylide precursors, thereby providing access to new azomethine ylide systems unattainable by classical methods (Scheme 2). It should be synthetically feasible to condense an allylic amine (**10**) onto a α-dicarbonyl compound such as a glyoxylate ester (**11**). The enhanced electrophilicity of the aldehyde function would promote rapid imine formation (**13**), thereby satisfying the first criterion for azomethine ylide formation. Although glyoxylimine **13** is isolable,[18] a deprotonation event must occur at its allylic carbon to generate the desired, ester-stabilized azomethine ylide. Unfortunately, the pK_a of the allylic protons, though not unreasonably high, are beyond the reach of most organic bases. However, if a catalytic, coordinating metal is present to establish a chelate between the ester and imine moieties, the acidity of the allylic protons may be reduced to an extent that would permit deprotonation. A mild amine base would therefore allow the formation of an azomethine ylide (**4**) *identical to that seemingly unattainable from acrolein.* Dipolar cycloaddition with a dipolarophile (**5**) would afford pyrrolidine scaffolds (**6**) bearing an alkenyl moiety for further structural advancement.

Control experiments attempting to obtain ylide **4** through classical methods (i.e., Scheme 1) confirmed that the reaction of glycine methyl ester (**2**) with acrolein (**1**), silver acetate,

Scheme 1. Competing Processes with the Use of α-Amino Esters and α,β-Unsaturated Aldehydes toward Azomethine Ylides
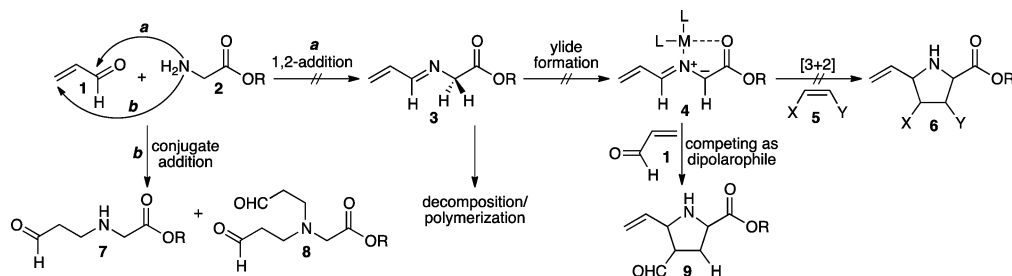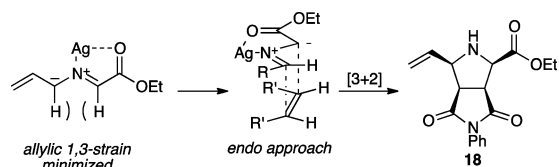

Scheme 2. A Conceptually Different Strategy for Azomethine Ylide Formation
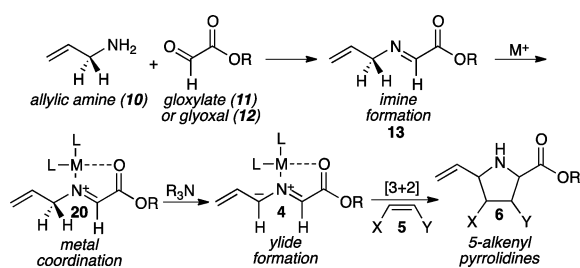
**Table 1. Optimization of Reaction Conditions for Cycloadduct Formation**[a]
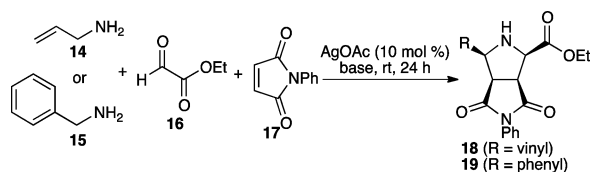
entry	amine	base	14/15: 16:17	solvent	product	yield (%)
1	14	Et$_3$N	1:1:1	PhMe	18	50
2	15	Et$_3$N	1:1:1	PhMe	19	60
3	14	DBU	1:1:1	PhMe	18	10
4	15	DBU	1:1:1	PhMe	19	23
5	15	Et$_3$N	1:1:1	THF	19	36
6	15	Et$_3$N	1:1:1	CH$_2$Cl$_2$	19	42
7	15	Et$_3$N	1:1:1	MeCN	19	47
8	14	Et$_3$N	2:2:1	MeCN	18	84
9	15	Et$_3$N	2:2:1	MeCN	19	86

[a]Conditions for entries 1−7: amine **14** or **15** (1.0 equiv), **16** (1.0 equiv), **17** (1.0 equiv), Et$_3$N or DBU (1.0 equiv), AgOAc (0.1 equiv), solvent, rt, 24 h. Conditions for entries 8−9: amine **14** or **15** (2.0 equiv), **16** (2.0 equiv), **19** (1.0 equiv), Et$_3$N (2.0 equiv), AgOAc (0.1 equiv), MeCN, rt, 24 h.

Scheme 3. Origins of Stereoselectivity

Table 2. Substrate Survey of the Allylic Amine Component[a]
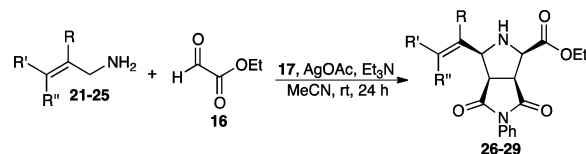
entry	amine	product	yield (%)
1	**21**	**26**	70
2	**22**	**27**	66
3	**23**	**28**	64
4	**24**	**29**	81
5	**25**	**29**	80

[a]Reaction conditions: amine **21−25** (2 equiv), **16** (2 equiv), Et$_3$N (2 equiv for **21−24**), MeCN, 30 min; then **17** (1 equiv), AgOAc (0.1 equiv), Et$_3$N (2 equiv), rt, 24 h.

triethylamine, and phenyl maleimide led to no detectable cycloadduct (**6**) and only a complex mixture. Therefore, the feasibility of reaching ylide **4** through the logic outlined in Scheme 2 was investigated. For our initial optimization studies, allylamine (**14**), ethyl glyoxylate (**16**), and phenyl maleimide (**17**) were selected as substrates. Control experiments revealed

that clean glyoxylimine formation between **14** and **16** was achieved within 10 min. Encouragingly, stirring a 1:1:1 mixture of **14**, **16**, and **17** in PhCH$_3$ with Et$_3$N (2 equiv) and catalytic AgOAc (10 mol %) effected azomethine ylide formation and cycloaddition within 24 h at rt, delivering 5-vinyl pyrrolidine **18** (Table 1, entry 1) in 50% yield as one diastereomer. Benzylamine (**15**, Table 1, entry 2) was also investigated on the basis that the benzylic proton of its glyoxylimine would be sufficiently acidic through catalysis.[19] Prior to our work, azomethine ylides were generated via the imines of secondary benzylic amines and glyoxylates under only thermal, protropic conditions.[20]

Table 3. Surveying the Dicarbonyl Substrate: Phenyl Glyoxal[a]

entry	amine	product	yield (%)
1	**14**	**31**	86
2	**15**	**32**	65
3	**21**	**33**	72
4	**22**	**34**	74
5	**23**	**35**	82
6	**25**	**36**	67

[a]Reaction conditions: amine **14**, **15**, **21–23**, **25** (2 equiv), **30** (2 equiv), Et$_3$N (2 equiv for **21–23**), MeCN, 30 min; **17** (1 equiv), AgOAc (0.1 equiv), Et$_3$N (2 equiv), rt, 24 h.

Table 4. Surveying the Dicarbonyl Substrate: Indole Glyoxal[a]

entry	amine	product	yield (%)
1[b]	**14**	**38**	84
2[b]	**15**	**39**	75
3[c]	**21**	**40**	92
4[c]	**22**	**41**	93
5[c]	**23**	**42**	94
6[c]	**25**	**43**	62

[a]Reaction conditions: amine **14**, **15**, **21–23**, **25** (2 equiv), **37** (2 equiv), Et$_3$N (2 equiv for **21–23**), 30 min; **17** (1 equiv), AgOAc (0.1 equiv), Et$_3$N (2 equiv), rt, 24 h. [b]In THF. [c]In MeCN.

Employing DBU as the base (entries 4 and 5) led to a noticeable decrease in yield through its unfavorable addition reaction with phenyl maleimide. The use of THF or CH$_2$Cl$_2$ as solvents led to slightly decreased yields (entries 5 and 6), while MeCN (entry 7) promoted substrate solubility and a comparable yield to PhCH$_3$. In each case, the high levels of stereocontrol were rationalized through two factors: (1) a conformationally rigid, metal-coordinated W-shaped ylide in which allylic 1,3-strain is minimized and (2) the *endo* approach of the dipolarophile (Scheme 3).

Efforts to account for the mass balance in entries 1–7 revealed that a large portion (up to 43%) of the product was being consumed in a subsequent process: conjugate addition of the pyrrolidine nitrogen onto a second equivalent of phenyl maleimide. To circumvent this problem, it was postulated that increasing the ratio of glyoxylimine to dipolarophile from 1:1 to 2:1 would facilitate consumption of the dipolarophile through cycloaddition before subsequent conjugate addition could occur. Gratifyingly, employing this tactic greatly increased the

yield of the desired cycloadduct for both allyl and benzylamine, providing **18** and **19** in yields of 84% (entry 8) and 86% (entry 9), respectively.

We next investigated the scope of the amine component. In principle, amines bearing substituted π functions other than allyl or benzyl might also serve as azomethine ylide precursors. With the specific goal of studying the chemical reactivity of substituted π and aryl functions within this component, branched allylic systems such as crotyl (**21**, Table 2), isobutenyl (**22**), prenyl (**23**), and cinnamylamine (**24**, **25**) were subjected to our optimized conditions with ethyl glyoxylate as the electrophile. Such π systems were expected to facilitate azomethine ylide formation upon metal coordination in similar fashion to **14**. For convenience, amines **21–24** were used as their hydrochloride salts[21] and liberated in situ prior to condensation with **16**. Each underwent facile azomethine ylide formation and cycloaddition to provide cycloadducts **26–29** in good to excellent yields as one diastereomer (Table 2), whose configuration was determined by 1D-NOE studies as described

in our previous work.[17a] Whether the free base or the HCl-salted amine was used appeared to have no impact on the overall yield (compare entries 4 and 5).

Recognizing the value of accessing pyrrolidines not easily prepared through classical protocols, we viewed our findings as an underdeveloped method for ylide formation and set out to investigate the scope of the electrophile. Based on our success with ethyl glyoxylate, we hypothesized that additional α-dicarbonyl systems such as arylglyoxaldehydes and heteroarylglyoxaldehydes, each bearing functional groups available for both imine condensation and metal coordination, should meet the criteria for azomethine ylide formation and react accordingly. Phenyl glyoxal (**30**, Table 3) was first selected, and gratifyingly, its ability to furnish azomethine ylides upon condensation with amines **14**, **15**, **21–23**, and **25** was successfully demonstrated. Good to excellent yields were obtained for allylic, substituted allylic, α-aryl, and conjugated α-aryl systems, each delivering the corresponding cycloadducts (**31–36**) as one observable diastereomer.

Indole glyoxal (**37**, Table 4) was next investigated as our specific interest in this electrophile centers on its anticipated utility in alkaloid total synthesis.[22] In either MeCN or THF, good to excellent yields were again achieved for all entries.

In summary, we present the first examples of azomethine ylides from allylic amine and glyoxylate or glyoxal precursors, thereby expanding the methods through which these important ylide intermediates may be prepared. It is also important to emphasize that because the corresponding cycloadducts are not readily obtained through the classical method of generating azomethine ylides from α-amino ester precursors, the scope of pyrrolidine scaffolds obtainable through dipolar cycloaddition is also expanded.[23] Efforts toward catalytic, asymmetric variants and applications in alkaloid total synthesis are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Kemp, J.; Sheldrick, G.; Trotter, J.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1978**, 109–111. (b) Thompson, N.; Kemp, J.; Grigg, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, *31*, 2827–2830.

(2) Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, *19*, 2885–2888.

(3) (a) Barr, D. A.; Grigg, R.; Nimal Gunaratne, H. Q.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557–570.

(b) Thianpatunagul, S.; Sridharan, V.; Grigg, R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1669–1675.

(4) Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727–4730.

(5) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, p 161.

(6) For a review, see: Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517.

(7) For selected, recent examples, see: (a) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893–4896. (b) Wang, M.; Wang, Z.; Shi, Y.-H.; Shi, X.-X.; Fossey, J. S.; Deng, W.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 4897–4900. (c) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272–6276.

(8) Recent reports: (a) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873–9877. (b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653. (c) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170.

(9) Zaminer, J.; Brockmann, C.; Huy, P.; Opitz, R.; Reuter, C.; Beyermann, M.; Freund, C.; Müller, M.; Oschkinat, H.; Kühne, R.; Schmalz, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7111–7115.

(10) Krueger, A. C.; Xu, Y.; Kati, W. M.; Kempf, D. J.; Maring, C. J.; McDaniel, K. F.; Molla, A.; Montgomery, D.; Kohlbrenner, W. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1692–1695.

(11) Bulusu, M.; Waldstätten, P.; Tricotet, T.; Rochais, C.; Steck, A.; Bacher, M. *Tetrahedron Lett.* **2004**, *45*, 5833–5836.

(12) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113–10125.

(13) Kitayama, T.; Hall, H. K. *Macromolecules* **1987**, *20*, 1451–1415.

(14) Hall, H. K. *Makromol. Chem.-M. Symp.* **1992**, *54/55*, 73–81.

(15) Gu, Y. G.; Xu, Y.; Krueger, A. C.; Madigan, D.; Sham, H. L. *Tetrahedron Lett.* **2002**, *43*, 955–957.

(16) For a limited example, see: Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418–2421.

(17) (a) McCormack, M. P.; Shalumova, T.; Tanski, J. M.; Waters, S. P. *Org. Lett.* **2010**, *12*, 3906–3909. (b) McCormack, M. P.; Waters, S. P. *J. Org. Chem.* **2013**, *78*, 1176–1183. (c) Liu, X.; McCormack, M. P.; Waters, S. P. *Org. Lett.* **2012**, *14*, 5574–5577.

(18) (a) De Lamo Marin, S.; Catala, C.; Kumar, S. R.; Valleix, A.; Wagner, A.; Mioskowski, C. *Eur. J. Org. Chem.* **2010**, *21*, 3985–3989. (b) Barluenga, J.; Mateos, C.; Aznar, F.; Valdez, C. *J. Org. Chem.* **2004**, *69*, 7114–7122.

(19) Processes taking advantage of this effect for benzylic amines have only recently emerged: (a) Tian, L.; Hu, X.-Q.; Li, Y.-H.; Xu, P.-F. *Chem. Commun.* **2013**, *9*, 7213–7215. (b) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676–2679.

(20) (a) Ardill, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J. *Tetrahedron* **1990**, *46*, 6449–6466. (b) Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Somasunderam, A. *Tetrahedron* **1993**, *49*, 8679–8690.

(21) Wiecek, M.; Kottke, T.; Ligneau, X.; Schunack, W.; Seifert, R.; Stark, H.; Handzlik, J.; Kiec-Kononowicz, K. *Bioorg. Med. Chem.* **2011**, *19*, 2850–2858.

(22) See, for example, the pyrrolidine-containing indole alkaloid borrecapine: Jossang, A.; Pousset, J. L.; Jacquemin, H.; Cavé, A. *Tetrahedron Lett.* **1977**, *18*, 4317–4318.

(23) To demonstrate the amenability of this process to multigram synthesis, a scaled-up reaction of **14** (60 mmol), **16** (60 mmol), and **17** (30 mmol) delivered 6.13 g (65% yield) of pyrrolidine **18** after purification by column chromatography.