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Synthesis and Reactivity of Unsymmetrical Azomethine Imines Formed Using Alkene Aminocarbonylation

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ABSTRACT

Complex cyclic azomethine imines possessing a β-aminocarbonyl motif can be accessed readily from simple alkenes and hydrazones. This alkene aminocarbonylation approach allows formation of ketone-derived azomethine imines of unprecedented complexity. Since unsymmetrical hydrazones are used, two stereoisomers are formed: the reactivity of chiral derivatives is explored in both intra- and intermolecular systems.

Azomethine imines are valuable intermediates in synthetic organic chemistry.[1] In addition to being useful 1,3-dipoles in cycloadditions and rearrangements, azomethine imines are versatile electrophiles.[2] Several stereoselective reactions have recently emerged, providing access to both enantioenriched azomethine imines via kinetic resolution and to useful adducts via asymmetric synthesis.[2c−i,3] Most of these recent developments have featured cyclic dipoles accessed from aldehydes and pyrazolidinones,[4] likely due to their convenient preparation and to the bioactivity of the products formed.[2b] However, the condensation approach used to access such azomethine imines is challenging with ketones, and consequently the reactivity of these derivatives has rarely been studied.[1] Herein, we report a simple route to such azomethine imines using an alkene aminocarbonylation approach and perform stereoselective reactions using these complex derivatives.

Recently, we reported an alkene aminocarbonylation reactivity in which symmetrical hydrazones react with alkenes upon heating to afford azomethine imines possessing a β-aminocarbonyl motif.[5] This study focused on the reactivity of a fluorenone-derived hydrazone, which allows high reactivity with several alkene classes and subsequent

(1) For reviews, see: (a) Struckwisch, C. G. *Synthesis* **1973**, 469. (b) Rodina, L. L.; Kolberg, A.; Schulze, B. *Heterocycles* **1998**, *49*, 587. (c) Schantl, J. G. in *Science of Synthesis*; Padwa, A.; Bellus, D., Eds.; Thieme Verlag: Stuttgart, 2004; Vol. 27, pp731−824.

(2) For a review on cycloadditions, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. For recent examples, see: (b) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (c) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642. (d) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (e) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (f) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (g) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (h) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (i) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654.

(3) For recent examples, see: (a) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (b) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (c) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (d) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (e) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (f) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076.

(4) Godteredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1955**, *9*, 1498Usually an aldehyde (or a derivative): see reviews in ref 1.

(5) (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. See also: (b) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. (c) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1982**, 766.

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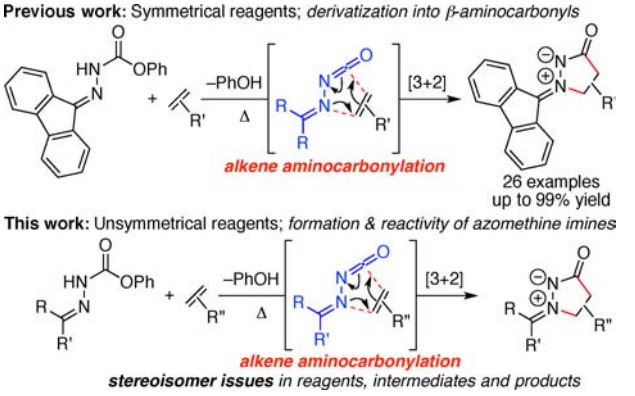
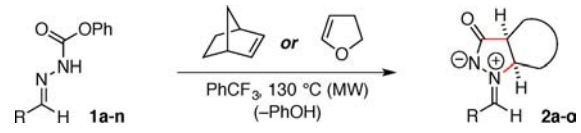
derivatization of the crystalline azomethine imines adducts into β-amino amides, esters, and acids. Since only one unsymmetrical hydrazone was used, the applicability of this approach to access complex azomethine imines via unsymmetrical imino isocyanates was not established. We thus performed a systematic study of the alkene aminocarbonylation reactivity with both aldehydes and unsymmetrical ketones.

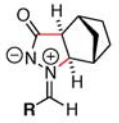
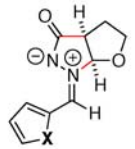
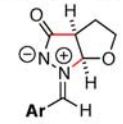


The alkene aminocarbonylation reaction of aldehyde-derived hydrazones is particularly challenging, as the azomethine imine adducts can further react in a [3 + 2] cycloaddition with the alkene present.[6] For example, the use of more forcing conditions or more stable hydrazones (e.g., O-*t*-Bu rather than OPh) initially led to such double addition products. Fortunately, the use of more reactive hydrazones (e.g., OPh as leaving group) improved the aminocarbonylation reactivity and under optimized conditions aldehyde-derived hydrazones provide the desired azomethine imines in modest to good yields (Table 1). This reactivity is applicable to form various aromatic (entries 3−8, 12−15) and heteroaromatic dipoles (entries 1−2, 9−11). In all cases, only one stereoisomer was observed. This reactivity proved superior with reactive alkenes such as norbornene (entries 1−8) and dihydrofuran (entries 8−15). Exploratory trials with aliphatic aldehydes and less reactive alkenes also allowed dipole formation, but typically in lower yields.

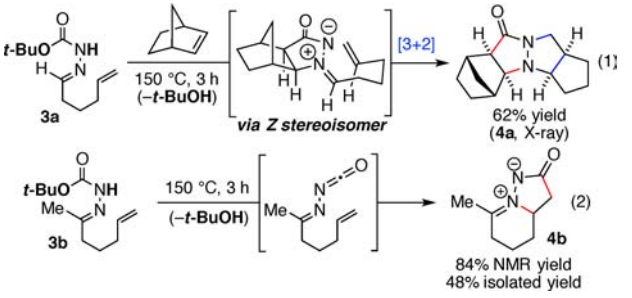
Nevertheless, hydrazones derived from aliphatic aldehydes can be effective when the azomethine imine can perform a subsequent [3 + 2] cycloaddition (eq 1). The preference for an intermolecular over an intramolecular aminocarbonylation event in eq 1 is noteworthy. In contrast to **3a**,[7] methylketone **3b** performed an intramolecular aminocarbonylation in the absence of norbornene (eq 2). The stereochemical outcome of eq 1 also suggests that isomerization occurred under the reaction conditions, since product **4a** can only be formed from the *Z* isomer of the azomethine imine. Thus, isomerization must occur under the reaction conditions since hydrazone **3a** is present mostly as the *E* stereoisomer (*E*:*Z* ratio = 3.6:1).

Table 1. Scope of Alkene Aminocarbonylation Using Aldehyde-Derived Hydrazones[a]



entry	product[b]	equiv of alkene	time (h)	yield (%)
				
1	**R** = 2-furyl, **2a**	2	1.5	53
2	**R** = 2-thiophenyl,**2b**	1.2	1.5	46
3	**R** = C_6H_5, **2c**	5	3	51[c]
4	**R** = 2-$MeOC_6H_4$, **2d**	2	3	34
5	**R** = 3-$MeOC_6H_4$, **2e**	2	3	36
6	**R** = 2-ClC_6H_4, **2f**	5	1	46[d,e]
7	**R** = 2-BrC_6H_4, **2g**	5	1	43[d,f]
8	**R** = 1-naphthyl, **2h**	5	3	36
				
9	**X** = O, **2i**	2	1	82
10	**X** = S, **2j**	1.5	1.5	90
11	**X** = NMe, **2k**	2	1	45[d]
				
12	**Ar** = 2-$MeOC_6H_4$, **2l**	2	1.5	65
13	**Ar** = 3-$MeOC_6H_4$, **2m**	2	1.5	60[d]
14	**Ar** = 4-$MeOC_6H_4$, **2n**	2	1.5	61
15	**Ar** = 1-naphthyl, **2o**	2	1	37[d]

[a] Conditions: hydrazone (1 equiv), alkene (1.2−10 equiv, see above) in $PhCF_3$ (0.05 M) heated in a sealed vial (microwave reactor, 130 °C, 1−3 h). Typical scale: 0.2 mmol of **1a**−**n**. [b] The identity of the major stereoisomer was secured by NOE experiments on **2a**. Stereochemistry of other dipoles was assigned by analogy. [c] 120 °C. [d] NMR yield. [e] 150 °C. [f] 140 °C.



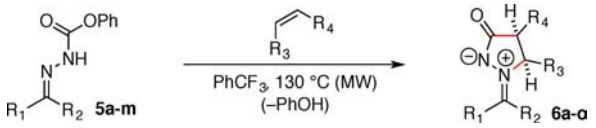
We then surveyed the use of hydrazones derived from unsymmetrical ketones to form complex azomethine imines (Table 2). To allow comparison, the reactivity was surveyed using norbornene as the substrate and using hydrazones prone to formation of the imino isocyanate

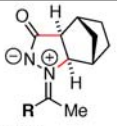
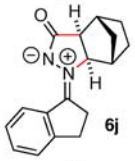
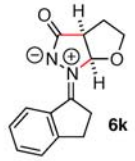
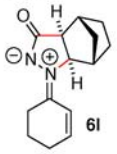
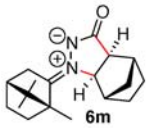
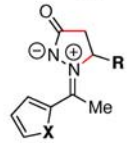
(6) Such "criss-cross" reactivity has been observed with azines. For examples, see: (a) Burger, K.; Thenn, W.; Gieren, A. *Angew. Chem., Int. Ed.* **1974**, *13*, 474. (b) Burger, K.; Thenn, W.; Rauh, R.; Schickaneder, H.; Gieren, A. *Chem. Ber* **1975**, *108*, 1460.

(7) Heating in the absence of C_7H_{10} did not afford the desired dipole, but a 35% unoptimized yield of a dimer in which the dipole reacted in a [3 + 2] with an equivalent of the imino isocyanate.

(OPh as leaving group). We observed two differences using these reagents: (1) stereoisomeric mixtures were typically obtained; (2) higher yields were isolated suggesting that the [3 + 2] cycloaddition side reaction is more difficult with these more hindered dipoles.[5a]

Table 2. Scope of Alkene Aminocarbonylation Using Ketone-Derived Hydrazones[a]



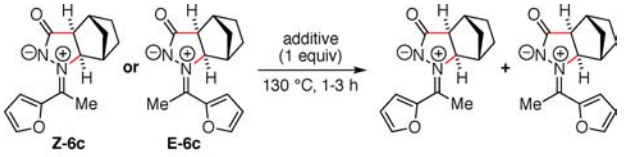
entry	product 6	yield (%)	isomer ratio[b]
			
1	**R** = Ph, **6a**	68	2:1
2	**R** = 4-EtC_6H_4, **6b**	64	2:1
3	**R** = 2-furyl, **6c**	92[b]	3:1
4	**R** = 2-thiophenyl, **6d**	82	>20:1
5	**R** = 2-pyridinyl, **6e**	58	2:1
6	**R** = (*E*)-2-styrenyl, **6f**	51	2:1
7	**R** =cyclopropyl, **6g**	66	2:1
8	**R** = *t*-Bu, **6h**	82	>20:1
9	**R** = 2-indolyl, **6i**	70	2:1
			
10	**6j**	80	3:1
			
11[c]	**6k**	50	6:1
			
12	**6l**	81	3:1
			
13[d]	**6m**	80	40:35:19:6
			
14	**R** = Ph, **X** = S, **6n**	46	>20:1
15[c]	**R** = ferrocenyl, **X** = S, **6o**	53	>20:1
16	**R** = *n*-Bu, **X** = O, **6p**	36	3:1

[a] Conditions: hydrazone (1 equiv), alkene (10 equiv) in $PhCF_3$ (0.05 M) heated in a sealed vial (microwave reactor, 130 °C, 1–3 h). Typical scale: 0.2 mmol of **5a**–**m**. [b] The identity of the major stereoisomer was secured by NOE experiments on **6c**, **6f**, **6l**, and **6k** and by X-ray crystallographic analysis of **6c**. Stereochemistry of other dipoles was assigned by analogy. [c] 5 equiv of norbornene was used. [d] O-*t*-Bu substituted hydrazone was used at 150 °C.

As shown in Table 2 the aminocarbonylation reactivity occurs with a variety of unsymmetrical ketones. Both acyclic (entries 1–9) and cyclic hydrazones (entries 10–13) react efficiently, and alkyl (entries 7–8), aryl (entries 1–2), heteroaryl (entries 3–5, 9), and alkenyl (entries 6 and 12) substituents are tolerated. This reactivity is not limited to norbornene: encouraging reactivity using other alkene classes also provided the desired azomethine imines under similar conditions (entries 11, 14–16). Several dipoles shown in this table were targeted to show the complementary of this reactivity with the condensation of ketones and pyrazolidinones,[4] which would be challenging on hindered ketones (entries 7 and 13) or could result in 1,4-addition with enones (entries 6 and 12). To demonstrate the robustness of this methodology, entry 3 was also performed on a 5-g scale: a 94% yield was obtained and the two stereoisomeric dipoles were separated using silica gel chromatography. The ability to separate these stereoisomers allowed us to study their interconversion and reactivity.

As indicated above, there are very few examples of unsymmetrical azomethine imines in the literature.[8] Seeking to determine if the isomeric mixtures obtained in Table 2 were the result of thermodynamic equilibration or were dependent on the stereoisomeric ratio of the imino isocyanate, we subjected each stereoisomer to the reaction conditions (heating in the presence of the leaving group released under the reaction conditions, Scheme 1).

Scheme 1. Equilibration Studies on *Z* and *E* Azomethine Imines

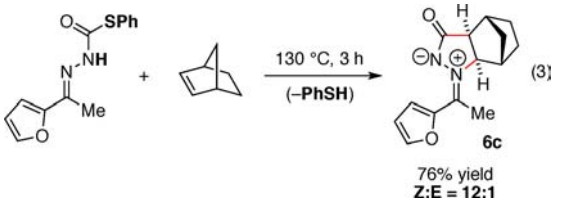


substrate	*additive*	*Z:E ratio*
Z-6c	*none*	*2.5:1*
Z-6c	*PhOH*	*3.2:1*
Z-6c	*PhSH*	*>25:1*
E-6c	*none*	*2.5:1*
E-6c	*PhOH*	*2.5:1*
E-6c	*PhSH*	*8.3:1*

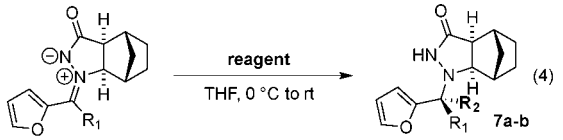
The results in Scheme 1 show the importance of the leaving group (released during iminoisocyanate formation) on the stereochemical outcome of the reactions. Encouragingly, the use of thiophenol as an additive favored the Z stereoisomer. In contrast, the absence of an additive or the presence of phenol appeared to induce an equilibrium toward a ca. 3:1 stereoisomeric mixture (likely due to the increased ability of ***E*-6c** to engage in hydrogen bonding due to the anti orientation of the electron-rich furan ring system relative to the Lewis basic part of the dipole[9]).

(8) (a) Taylor, E. C.; Haley, N. F.; Clemens, R. *J. Am. Chem. Soc.* **1981**, *103*, 7743. (b) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567. (c) Tomaschewski, G.; Geissler, G.; Schauer, G. *J. Prakt. Chem.* **1980**, *322*, 623. (d) Panfil, I.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199. See reference 8c.

Importantly, these results clearly highlight the importance of additives under the reaction conditions and provide the opportunity to access unsymmetrical azomethine imines with high stereocontrol, as illustrated by the use of a modified aminocarbonylation reagent (eq 3).



Conditions allowing for high stereocontrol during the formation of unsymmetrical azomethine imines allow the use of these complex dipoles in stereoselective synthesis. We thus explored nucleophilic additions to aldehyde and ketone-derived azomethine imines (**2c** and **6c** respectively, eq 4) and were pleased to observe high diastereoselectivities for the formation of adducts **7a** and **7b**.[10]



substrate	*reagent*	*yield, dr*	*major product*
R^1 = H (**2c**)	vinyl-MgBr	74%, 14:1 *dr*	R_1 = H,R_2 = C_2H_3 (**7a**)
R^1 = Me (**6c**)	K-Selectride	72%, >25:1 *dr*	R_1 = Me,R_2 = H (**7b**)

(9) In the crystal structure of **Z-6c** the furyl ring system is conjugated with the azomethine imine. Similarly, in **E-6c** the furyl ring system could be conjugated to increase the electron density of the amide portion of the dipole, thus increasing its ability to act as H-bond acceptor relative to **Z-6c**. Arguably, such H-bonding would result in increased stabilization of a dipole that should otherwise be quite disfavored sterically. Additional experiments to probe the generality of this observation and to provide additional insight on the effect of additives will be reported in due course.

In summary, we have shown that a variety of unsymmetrical hydrazones react with alkenes to form complex azomethine imines. Intra- and intermolecular variants of this reactivity were reported. This alkene aminocarbonylation reactivity provides a versatile approach to complex dipoles, and conditions allowing for equilibration and high stereocontrol in the synthesis of unsymmetrical azomethine imines were identified. Further development and applications of this reactivity in target oriented synthesis will be reported in due course.

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Supporting Information Available. Complete experimental procedures, characterization data, X-ray crystal structures (**4a**, **6c**), and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) For precedence on a diastereoselective addition to an aldehyde-derived azomethine imine see ref 3a.

The authors declare no competing financial interest.