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Free Radical-Mediated Vinyl Amination: Access to *N,N*-Dialkyl Enamines and Their β-Stannyl and β-Thio Derivatives

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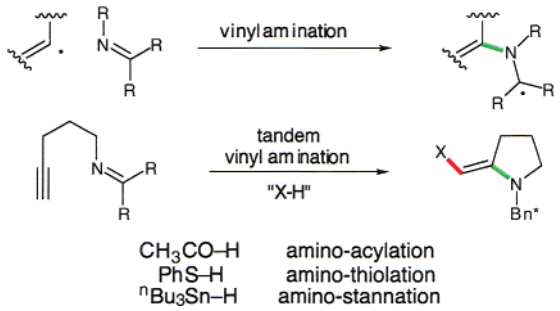
ABSTRACT



The first examples of free radical-mediated vinyl amination are described by nonconventional vinyl radical addition to azomethine nitrogen. This new vinyl amination protocol is mild and provides convenient synthetic access to nonstabilized *N,N*-dialkyl enamines and tandem bond-forming processes.

In contrast to the growing number of methods that form aryl−nitrogen bonds, almost exclusively from aryl halides or triflates and an amine,[1−3a,b] the analogous vinyl amination process has evolved at a relatively slow pace.[3] This is despite the fact that enamines occupy a prominent place as intermediates in organic synthesis,[4] target-oriented synthesis,[5] and as monomers for polymerization.[6] Metal-mediated and thermal vinyl−nitrogen bond-forming processes have been reported to form both resonance-stabilized (*N*-acyl or *N*-aryl)[1d,3] and highly nucleophilic enamines (*N*-alkyl).[7] Approaches to the latter must contend with the high degree of *N,N*-dialkyl enamine nucleophilicity[8] and the attendant potential for single-electron transfer. As a result, methods for their formation are few in number and dominated by dehydrative protocols where selectivity, when an issue, is determined by thermodynamic considerations.[9] Alkyne hydroamination is

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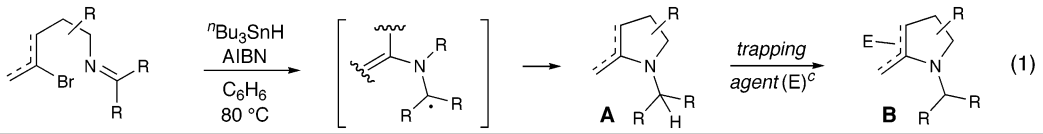
Table 1. Enamine Synthesis by Free Radical-Mediated Vinyl Amination of Vinyl Bromides[a]



entry	ketimine	intermediate enamine[b] (**A**)	isolated product (**B**)	overall yield[c]/*steps*
1	*Z*:*E* = 4:1 **1**	**9a**	**9b**	68/*2*
2	*Z*:*E* = 1:1 **2**	**10a**	**10b**	54/*2*
3	*cis*-**3**	*cis*-**11a**	*cis*-**11b**	64/*2*
4	*trans*-**3**	*trans*-**11a**	*trans*-**11b**	57/*2*
5	*Z*:*E* = 4:1 **4**	**12a**	**12b**	34[d]/*3*
6	**5**	**12a**	**12b**	36[d]/*3*
7	**6**	**13a**	**13b**	31[e]/*3*
8	R=CH_3 (**7**)	**14**	**14**	64/*2*
9	R=Ph (**8**)	**15**	**15**	53/*2*

[a] See Supporting Information for individual experimental details. [b] Observed by ^{1}H NMR. [c] Isolated yields from amine (2−3 steps depending on substrate) after trapping with PhCOCl (**9a**−**12a**), maleimide (**13a**), or no trapping agent (**14** and **15**). [d] Enamine **12a** is volatile. [e] A single diastereomer was observed and isolated after trapping.

presently the most promising entry to nucleophilic enamines, yet functional group tolerance remains a substantial issue with lanthanide-based catalysts,[10] as well as with methods requiring oxidative[11] or basic conditions.[12] This Letter describes our discovery that the addition of vinyl radicals to the nitrogen of an azomethine provides a pH-neutral method for directed, regioselective enamine formation. Furthermore, the vinyl radical intermediate may be formed either directly or as part of a tandem series of bond-forming events.

Departing from the conventional approaches that activate an N−H σ-bond toward coupling, we recently investigated the scope of aryl radical additions to the nitrogen of azomethines.[13−15] However, it was unclear whether nucleophilic enamines could be produced using this protocol since

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(11) Leonard, N. J.; Cook, A. G. *J. Am. Chem. Soc.* **1959**, *81*, 5627−5631.

(12) Dimethyl titanocene: (a) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393−2396. (b) Pyrolysis of cyclopropyl ketimines: Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174−1187; Stevens, R. V.; Ellis, M. C.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5576−5579 and 5580−5583. (c) Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383.

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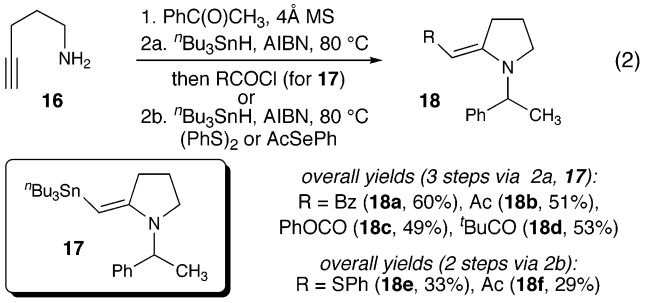
(14) For prior related work, see: (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (b) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149. (c) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (d) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. Review: (e) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496.

the corresponding vinyl radicals possess a greater degree of conformational and configurational freedom (eq 1).[16] When vinyl bromide **1** was treated with $^{n}Bu_3SnH$ and AIBN in refluxing benzene, enamine **9a** was formed and trapped as its benzoylated adduct in 68% yield (two steps from the imine); the product of direct reduction was not observed in the ^1H NMR spectrum of the reaction mixture. Terminal vinyl bromide **2** was cyclized to enamine **10a** and isolated as its benzoylated adduct in good overall yield (54%, 2 steps). Ketimines possessing additional conformational constraints readily cyclized to a variety of heterocyclic products as well. Indolizidine enamines **11a** were accessed from vinyl bromides **3**, giving rise to their respective benzoylated derivatives in 64% and 57% yield (entries 3 and 4).

Even vinyl bromides with increased conformational mobility (**4** and **5**) readily cyclized to provide enamine **12** in both cases. The lower overall yields of 34% and 36% after benzoylation (3 steps from amine) most likely reflect a combination of the volatility of the enamine and the use of boiling benzene since direct analysis of the reaction when performed in C_6D_6 revealed clean product formation. The cyclization of **4** provided the exocyclic enamine isomer as the first observable enamine in this transformation, presumably resulting from thermal isomerization of the endocyclic enamine.[11,17]

A rapid [1,5]-hydrogen shift followed enamine formation from **6** to give isoindole **13a**. This intermediate was observed by ^1H NMR spectroscopy and fully characterized as its crystalline, diastereomerically pure maleimide cycloadduct. Ketimines **7** and **8** cyclized to indoles **14** and **15** with comparable ease, demonstrating that competitive direct reduction of the azomethine by stannane is not problematic.[18]

Scheme 1. Free Radical-Mediated Tandem Addition/Vinyl Amination (eq 2)



An advantage to the use of vinyl radicals as a strategy for amination is the potential for development of carbon−carbon bond-forming reactions as part of a reaction cascade.[19] Furthermore, vinyl radicals might also be produced by the addition of heteroatom-centered radicals to alkyne π-bonds. Hence, aminostannation was achieved by addition of a stannyl radical to the ketimine derived from alkyne **16** in a highly regio- and stereoselective conversion to β-stannylenamine **17** (eq 2).[20−22] Not unexpectedly, enamine **17** acylated at low temperature without the use of additives.[23] A variety of acid chlorides varying in oxidation state and steric hindrance furnished vinylogous amides and carbamates **18a**−**d** with comparable ease.[24] Throughout both amination and acylation, a single olefin stereoisomer is observed spectroscopically.[25] Overall yields ranged from 49 to 60% (three steps) for the aminostannation sequence. Although less efficient due to the propensity for thiyl and acyl radicals to dimerize, both alkyne aminothiolation and aminoacylation could be similarly effected. Aminothiolation of the intermediate iminoalkyne provided β-arylthioenamine **18e** in 33% yield (two steps) with diphenyl disulfide as the thiyl radical precursor (eq 2).[26] Similarly, phenylselenoacetate and tributylstannane gave the product of aminoacylation (**18f**) in 29% yield (two steps).

In summary, vinylic free radicals add efficiently to the nitrogen of an azomethine under conditions sufficiently mild for regioselective production of even nonstabilized (*N*,*N*-dialkyl) enamines. These kinetically controlled transformations constitute a reductive, nondehydrative method for enamine formation. As a synthetic method, carbon radical additions to the nitrogen of an azomethine are presently unique in their ability to transcend aryl and vinyl amination, as well as their tandem variants.

Acknowledgment. This work was supported by NIGMS (GM-63577-01). E.N.P., B.M.N., and A.L.W. were supported

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(22) Vinyl stannanes have been used extensively in target-oriented synthesis. Review: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Organic Reactions*; Wiley: New York, 1997; Vol. 50, Chapter 1.

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

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