ORGANIC LETTERS

2012
Vol. 14, No. 23
6092–6095

Formation of Carbon–Carbon Bonds Using Aminal Radicals

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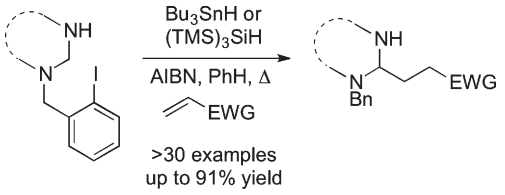
Received October 30, 2012

ABSTRACT



Aminal radicals were generated by radical translocation processes. For the first time, it is shown that they participate in carbon–carbon bond forming reactions. Either stannane or silane hydrogen atom donors are suitable for the reaction. More than 30 substrate combinations are reported, and chemical yields are as high as 91%.

Nitrogenous molecules are ubiquitous in Nature. Pharmaceuticals, molecular catalysts, and secondary metabolites often contain nitrogen. As a result, nitrogenous molecules, such as alkaloids, make compelling targets for synthesis. However, alkaloid synthesis is inherently complicated by the nitrogen atom.[1] The Lewis basic lone pair found on amines, the presence of weakly acidic N–H hydrogens, and the readiness of amines to quaternize often lead to undesired reactivity. These factors conspire against the synthetic chemist.

Traditional strategies used to circumvent the Lewis acid–base reactivity of nitrogen include: using protecting groups,[2] installing nitrogen at the end of a synthesis,[3] or packaging the nitrogen in a less reactive functional group (e.g., as a nitrile[4] or nitro[5] group). Such strategies have enjoyed widespread success in synthesis. However, a conceptually different approach to avoid the acid–base properties of nitrogen is to use single electron processes

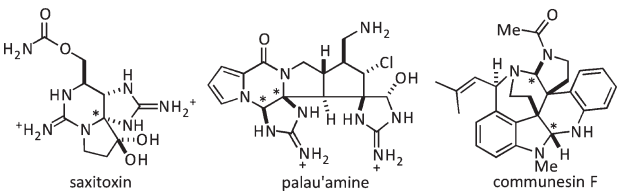


Figure 1. Selected nitrogen-rich alkaloids; aminals indicated by *.

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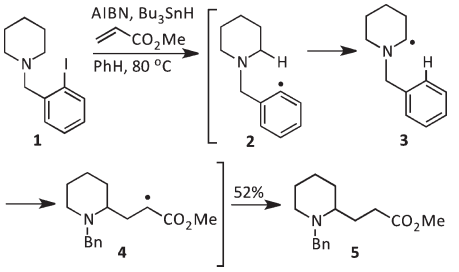
(2) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th Ed. WILEY, Hoboken, NJ, 2007, pp 696–926.
(3) For example: (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420. (b) Ge, H. M.; Zhang, L.–D.; Tan, R. X.; Yao, Z.–J. *J. Am. Chem. Soc.* **2012**, *134*, 12323–12325.
(4) Tennant, G. in *Comp. Org. Synth.*, Vol. 2 (Eds: Barton, D.; Oates, W. D.), Pergamon Press, Oxford, 1979, pp 383–590.
(5) Ono, N. *The Nitro Group in Organic Synthesis*, WILEY-VCH, New York, 2001.
(6) For selected recent examples of radical reactions as key steps in alkaloid synthesis, see: (a) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693. (b) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725–3728. (c) Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 10376–10378. (d) Palframan, M. J.; Parsons, A. F.; Johnson, P. *Tetrahedron Lett.* **2011**, *52*, 1154–1156.
(7) For review, see: (a) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594. (b) Heasley, B. *Eur. J. Org. Chem.* **2009**, 1477–1489. (c) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447–457.
(8) (a) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 20172–20174. (b) Iwamoto, O.; Shinohara, R.; Nagasawa, K. *Chem. Asian J.* **2009**, *4*, 277–285. (c) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964–9975. (d) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594–5598. (e) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818–2819. (f) Jessen, H. J.; Gademann, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2972–2974. (g) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098. (h) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228. (i) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795. (j) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000.

10.1021/ol3029912
Published on Web 11/29/2012

(i.e., radical reactions) to build the C–C bonds of alkaloid molecular architectures.[6]

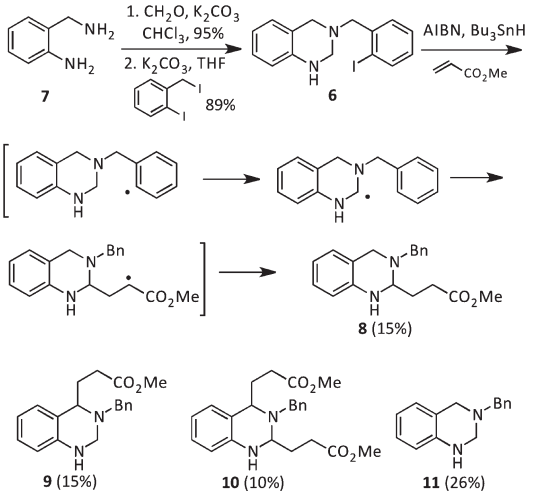
Figure 1 shows a selection of alkaloids that has attracted considerable interest from the synthetic community.[7,8] Although more than half of the 55 carbons depicted in Figure 1 bear heteroatoms, only five are disubstituted with nitrogen (i.e., diamino or aminal carbons). Harnessing reactivity specific to the aminal carbon in the presence of heteroatom-bearing carbons could be useful in alkaloid synthesis. Toward this end, we envisioned creating an aminal radical intermediate that could be used in the formation of C–C bonds. We expected such a radical would be unreactive toward acidic N–H bonds and Lewis basic lone pairs,[9] and it would be well suited to forging C–C bonds in nitrogen-rich molecular architectures. Aminal radicals have been generated, and their spectral and physical properties have been studied.[10] However, to the best of our knowledge, they have not been used in synthesis.[11] Herein, we describe bond-forming reactions of aminal radicals for the first time.

Scheme 1. Radical Translocation



Carbon-centered radicals bearing one nitrogen (α-amino radicals) are well-known.[12] A convenient method for their generation is by radical translocation (Scheme 1). For example, homolytic cleavage of a C–I bond in **1** generates intermediate **2**, which undergoes hydrogen-atom transfer to generate stabilized α-amino radical **3**.[13] The stability provided by the neighboring nitrogen atom is 11 kcal/mol.[14] Addition to a radical acceptor such as methyl acrylate leads to **4**, which receives a hydrogen atom from Bu_3SnH to form the product (**5**). Use of iodobenzyl to initiate radical translocation results in a benzyl-protected amine product.

Scheme 2. Initial Investigations of Aminal Radical Reactivity



Computational methods estimate the stabilization of an aminal radical to be approximately 2 kcal/mol relative to the α-amino radical.[14] Thus, it should be possible to selectively form an aminal radical in the presence of other nitrogen-bearing carbons. The first substrate chosen to evaluate this hypothesis was aminal **6**, prepared in two steps from diamine **7** (Scheme 2).

Reaction of aminal **6** with methyl acrylate as a radical acceptor led to the formation of the desired addition product **8**, presumably via the route shown. Unreacted starting material, isomer **9**, overaddition product **10**, and the product of deiodination (**11**) were present in the reaction mixture. Attempts to improve the yield of **8** by adjusting reagent stoichiometry, concentration, or the hydrogen-atom source were unsuccessful. We suspect that competitive formation of **9** is the result of the additional stabilization at the benzylic position (*vide infra*).

We next prepared substrate **12** in order to block reactivity at the benzylic position and simplify the product mixture (Table 1, entry 1). Substrate **12** is prepared in two steps and 70% overall yield from inexpensive anthranilamide. Gratifyingly, **12** showed cleaner reactivity giving 61% yield of the desired products (49% yield of **13**, accompanied by 12% of the corresponding lactam **14**). The increased yield may be partially attributable to the capto-dative effect: one nitrogen is relatively electron poor, and one nitrogen is relatively electron rich.[15]

Thiols are used as polarity-reversal catalysts in radical reactions and may assist in hydrogen atom transfer events,[16] and the addition of BnSH increased reaction yields (entry 2). Further increasing the stoichiometry of the thiol had little effect on the overall yield (entry 3), but **13** was formed as the

(9) N–H bonds, O–H bonds, and lone pairs are known to be spectators in radical reactions. For example, see: (a) Urry, W. H.; Juveland, O. O.; Stacey, F. W. *J. Am. Chem. Soc.* **1952**, *74*, 6155. (b) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1986**, *51*, 4905–4910. (c) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200–9201.

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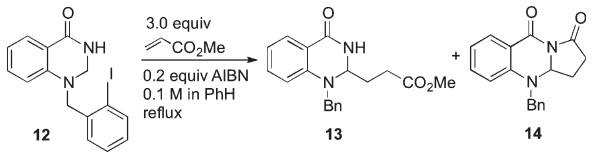
(15) Leroy, G.; Dewispelaere, J.–P.; Benkadour, H.; Riffi Temsamani, D.; Wilante, C. *Bull. Soc. Chim. Belg.* **1994**, *103*, 367–378.

(16) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

Table 1. Reactivity of Aminal **12**



entry	R–H	additive	combined yield (**13**:**14**)
1	2 equiv of Bu_3SnH	none	61% (80:20)
2[a]	2 equiv of Bu_3SnH	0.1 equiv of BnSH	86% (30:70)
3	2 equiv of Bu_3SnH	0.9 equiv of BnSH	75% (100:0)
4	none	0.9 equiv of BnSH	0%
5[b]	2 equiv of Bu_3SnH	0.9 equiv of BnSH	18% (100:0)
6	2 equiv of $(TMS)_3SiH$	none	48% (48:52)
7[a]	2 equiv of $(TMS)_3SiH$	0.1 equiv of BnSH	91% (77:23)
8	2 equiv of $(TMS)_3SiH$	0.9 equiv of BnSH	89% (81:19)

[a] 5 equiv of methyl acrylate used. [b] AIBN was omitted from the reaction mixture.

sole product. No product formation occurs in the absence of stannane (entry 4), suggesting the thiol is not the terminal hydrogen atom donor. We also performed a control experiment by omitting the AIBN and observed only modest product formation (entry 5). We speculate that in hot benzene some homolytic cleavage of the C–I bond may occur. The aminal radical reaction is also successful using $(TMS)_3SiH$ as a hydrogen atom donor (entry 6). The yield of the reaction is improved by adding BnSH (entries 7 and 8).

The aminal radical reaction was examined with various aminals and radical acceptors. The aminals were made by condensing the corresponding amino amide with formalin (see Supporting Information). Use of acrylonitrile, *tert*-butyl acrylate, and acrolein as radical acceptors in the reaction with **12** results in good yields of the addition products **15**, **16**, and **17**, respectively (Figure 2). Use of Bu_3SnH as a hydrogen atom source gives superior yields compared with $(TMS)_3SiH$. However, use of the silane often gives synthetically useful yields without the use of heavy metals, and we report yields with both reagents. Attachment of the iodobenzyl group at the amide nitrogen also resulted in productive reactions with methyl acrylate, acrylonitrile, or *tert*-butyl acrylate to give products **18**, **19**, and **20**, respectively.

Aliphatic six-membered ring aminals participated in the reaction, provided one nitrogen bears an electron-withdrawing group. The acetamide-derived aminal added to methyl acrylate to give **21** in good yield. We found that trifluoroacetamides also participate in the reaction giving **22**. Note that the aminal radical is generated in the presence of the amino-substituted carbon. In these cases, products derived from formation of the α-amino radicals are not observed. It appears that, in the absence of benzylic stabilization (vis-à-vis with substrate **6**), aminal radicals selectively form in the presence of amino-substituted carbons. Substrates that lacked electron-withdrawing carbonyl

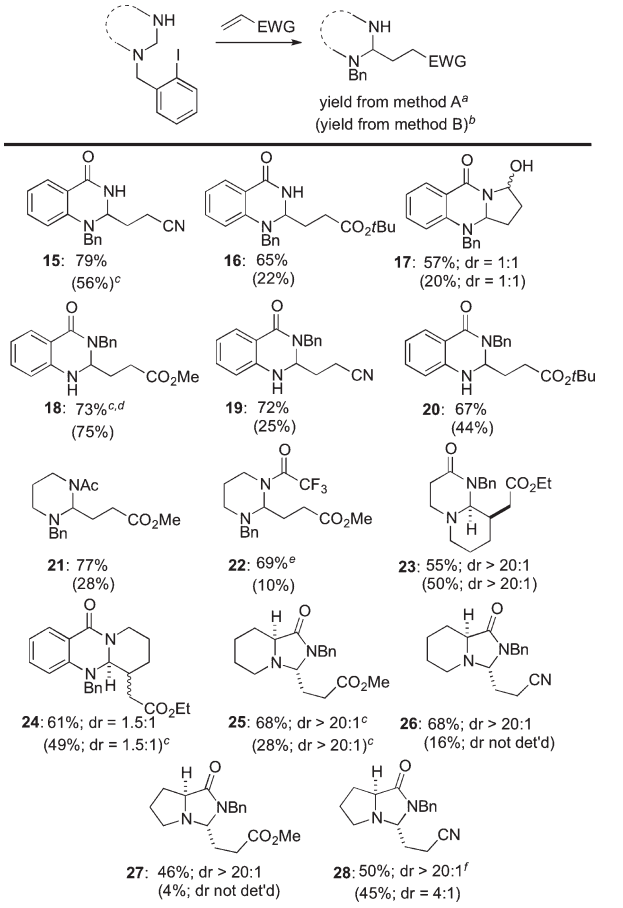


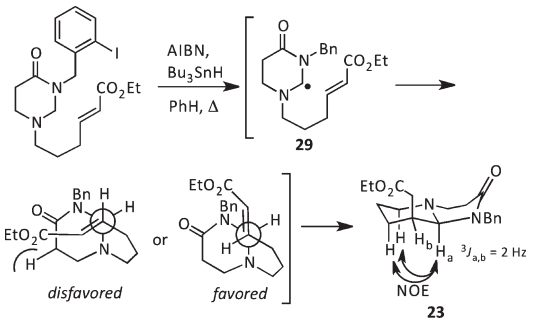
Figure 2. Scope of the aminal radical reaction. [a] Method A: 5.0 equiv of alkene, 2.0 equiv of Bu_3SnH, 0.1 equiv of BnSH, 0.2 equiv of AIBN, 0.10 M PhH, reflux, 3 h. [b] Method B: 5.0 equiv of alkene, 2.0 equiv of $(TMS)_3SiH$, 0.1 equiv of BnSH, 0.2 equiv of AIBN, 0.10 M PhH, reflux, 12 h. [c] 0.9 equiv of BnSH. [d] 3.0 equiv of methyl acrylate. [e] 10 equiv of methyl acrylate. [f] 0.2 equiv of BnSH.

groups did not participate in the reaction; they gave only complex intractible product mixtures.

Intramolecular reactions were possible, and compound **23** was produced as a single diastereomer, whereas **24** was formed as a diastereomeric mixture. Bicyclic five-membered aminals are competent substrates in the reaction. Pipecolic acid derived aminals react with methyl acrylate and acrylonitrile in good yields and selectivities to form **25** and **26**, respectively. Finally, proline-derived aminals undergo diastereoselective reactions giving **27** and **28**, respectively.

The relative stereochemistry of **23** was determined by ^1H NMR methods. First, methyne hydrogen H_a is positioned axial as evidenced by NOESY crosspeaks to the indicated hydrogens (Scheme 3). The small (2 Hz) coupling constant between H_a and H_b suggests H_b is equatorial. The diastereoselectivity in the formation of **23** may be a result of the model shown in Scheme 3. The favored conformation of **29** positions the ester away from the methylene groups on the tetrahydropyrimidone ring. The favored conformation leads to formation of **23**. As the steric size of the

Scheme 3. Plausible Model for Formation of **23**



pyrimidone ring decreases, the selectivity should decrease. This hypothesis is consistent with the observation that **24** is produced as a diastereomeric mixture. The favored diastereomer of the bicyclic aminal products **25**–**28** likely results from addition to the convex face of the bicycle. The relative stereochemistry was confirmed using NOESY methods.

In conclusion, aminal radicals are formed via radical translocation reactions. These carbon-centered radicals react with radical acceptors in C–C bond-forming reactions in good yields with both Bu_3SnH and $(TMS)_3SiH$ as hydrogen atom donors. Aminals can be formed from aromatic or aliphatic diamines, provided that one nitrogen bears an electron-withdrawing carbonyl group. The reactivity of the aminal radical is different from that of the α-amino radical; specifically it can be formed in the presence of amino-substituted carbon atoms. We believe this reactivity will be useful in the synthesis of nitrogen-rich alkaloids, and efforts to apply this chemistry in synthesis are underway in our laboratory.

Acknowledgment. Financial support from Oregon State University is acknowledged. The National Science Foundation (CHE-0722319) and the Murdock Charitable Trust (2005265) are acknowledged for support of the NMR facility.

Supporting Information Available. Experimental procedures, spectroscopic data, depiction of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.