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The development of carbon–carbon bond forming reactions of aminal radicals

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ABSTRACT

Aminal radicals were generated and used in synthetic reactions for the first time. Aminal radicals are formed from aminals by radical translocation using AIBN and a stoichiometric hydrogen atom donor, or by SmI_2 reduction of *N*-acyl amidines or amidinium ions in the presence of a proton source. Aminal radicals were found to participate in inter- and intramolecular C–C bond forming reactions with electron deficient alkenes. Chemical yields were as high as 99%.

1. Introduction

Many biologically active molecules, including pharmaceuticals, contain one or more nitrogen atoms. As a result, nitrogen-rich compounds, such as alkaloids and pharmaceuticals, make compelling synthetic targets.[1] However, the complex reactivity of nitrogen can be problematic in synthesis. The ability to quaternize, the Lewis basic lone pair, and the weakly acidic N–H protons found in nitrogen-containing molecules often give rise to undesired reactivity.

In order to mask the complex Lewis acid–base reactivity of nitrogen, synthetic chemists often resort to the use of protective groups.[2] Other strategies, which have proven successful for the synthesis of nitrogen-containing structures include opting to install nitrogen late in the synthesis[3] or in the form of a less reactive functional group (e.g., as a nitro[4] or nitrile[5] group). An alternative means to circumvent the pitfalls of alkaloid synthesis is the use of single electron reactivity (i.e., free radical reactions). Free radicals are known to tolerate heteroatom lone pairs, and N–H bonds are resistive to homolytic cleavage.[6] As a result, free radical reactions have been used successfully for key C–C bond forming reactions in the synthesis of complex alkaloids (e.g., Scheme 1, Eq. 1).[7]

The addition of carbon-centered radicals bearing heteroatoms to C–C multiple bonds has been known for over 50 years.[8] α-Aminoalkyl radicals, such as **1** (Scheme 1), gain stability from the electron lone pair on the adjacent nitrogen atom and react with alkenes to give products of C–C bond formation.[9] This reactivity has proven useful for the synthesis of heterocycles as well as in the total synthesis of alkaloids.[10] Carbon-centered radicals bearing two adjacent heteroatoms, such as acetal radical **2**, are also known to undergo C–C bond forming reactions with alkenes (Scheme 1, Eq. 2). Additionally, *N*,*S*- and *N*,*O*-acetal radicals (**3**) have been presumed as intermediates in C–C bond forming reactions (Scheme 1, Eq. 3).[11]

Carbon-centered radicals bearing two adjacent nitrogen atoms (i.e., aminal radicals) have been implicated as intermediates in the free radical and radiative damage of DNA nucleotide bases,[12] they have been experimentally generated and studied spectroscopically,[13] and long-lived aminal radicals have been isolated.[14] Applications of aminal radicals include their use as photochromic dyes[15] and as tools for mechanistic investigations.[16] Although there are reports of fragmentation,[17] protonation,[18] and dimerization reactions of aminal radicals, there had been no reports of their synthetic utility prior to recent work from our laboratory.[19]

Having considered the known reactivity of acetal and α-aminoalkyl radicals, the creation of a new reaction was envisioned wherein an aminal radical would undergo addition to an alkene to give the product of C–C bond formation. Computational studies indicated that aminal radicals are 1–2 kcal/mol more stable than analogous α-aminoalkyl radicals.[20] This suggested that it would be possible to selectively generate aminal radicals in the presence of carbon atoms bearing a single nitrogen atom. Based on these considerations, we postulated that aminal radical intermediates would be well suited for the construction of the carbon framework in

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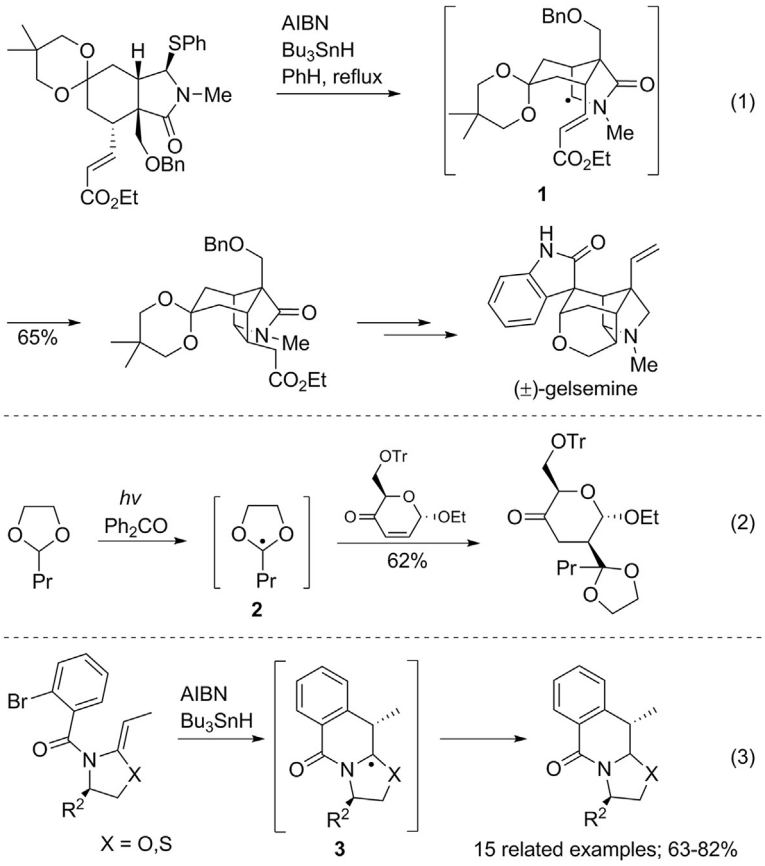

Scheme 1. Selected transformations involving radical intermediates bearing α-heteroatoms.

nitrogen-rich molecules. For example, Fig. 1 shows a selection of biologically active aminal containing natural products, which have attracted the interest of many synthetic chemists.[21] Furthermore, commercial pharmaceuticals quinethazone and metolazone also possess the aminal functional group.

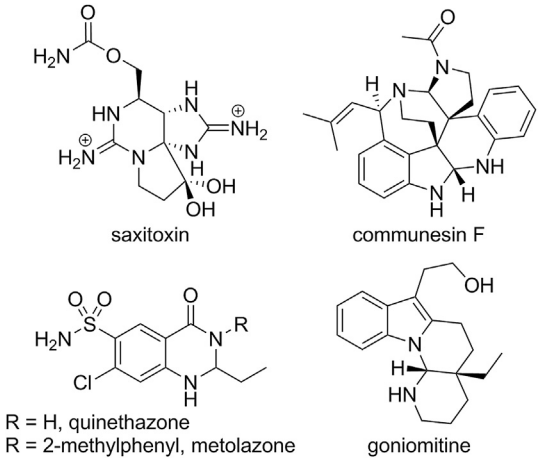

Fig. 1. Selected aminal containing alkaloids and pharmaceuticals.

Herein we give a full account of the development of aminal radical reactivity for use in synthesis. In addition to expanded discussions of the results previously reported, we describe our initial efforts to generate aminal radicals under peroxide initiated conditions, the efforts to optimize translocation reactions of aminals, which do not bear an electron-withdrawing group, a deuterium labeling study on the translocation reactions of aminals, which do not bear an electron-withdrawing group, and applications of the translocation method to acyclic aminals relevant to the synthesis of indole alkaloids.

2. Results and discussion

In 1958, Juveland reported the generation of α-aminoalkyl radical intermediate **4** under peroxide initiated conditions (Scheme 2, Eq. 1).[22] Treatment of piperidine with di-*tert*-butylperoxide in the presence of 1-octene yielded 2-octyl piperidine. Extension of this method to the generation of aminal radicals could involve the treatment of an aminal with di-*tert*-butylperoxide in the presence of a suitable radical acceptor (Scheme 2, Eq. 2). Tetrahydroisoquinazoline (**5**) was chosen because it was easy to prepare, it is chromatographically stable, and it contains a chromophore, which allowed for facile monitoring of reaction progress.

Following Juveland's procedure, **5** was heated in the presence of di-*tert*-butylperoxide and 1-octene in a sealed tube. The reaction produced an intractable mixture of products and none of the desired product **6** was observed. In an effort to affect cleaner reactivity, modified reaction conditions were investigated. Lowering the reaction temperature resulted in no reaction. Performing the reaction neat, tethering the radical acceptor to the substrate, or using activated alkenes as radical acceptors all resulted in the formation of a complex mixture of products.[23]

Based on these results, two plausible explanations were formulated. Either the desired aminal radical **7** was generated, and it was reacting in an unselective manner to give the observed decomposition, or aminal radical **7** had not been generated and the