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BNAH-mediated free radical addition to aromatic imines

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Abstract

Benzyl radical is added regioselectively to the carbon–nitrogen double bond of aromatic imines by UV irradiation ($\lambda > 300$ nm) of a ternary mixture of benzyl bromide/aromatic imines/1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile via a BNAH-mediated photoinduced electron transfer mechanism.

Keywords: photoinduced electron transfer; regioselective free radical addition.

In contrast to extensive studies on free radical addition reactions onto C=C bonds, free radical addition onto C=N bonds has received much less scrutiny until recently.[1] An early example of an intramolecular aryl radical addition onto an imine bond was reported by Takano and co-workers[2] in 1990. Similar aryl radical addition reactions to the C=N bond of imines were reported latter by Takano and co-workers,[3] Warkentin and Tomaszewiski,[4] Leardini and co-workers,[5] and Bowman and co-workers.[6] Recently, Ryu et al.[7] reported vinyl radical addition to aldimines. All of these reactions were accomplished by using tin hydride-mediated radical reaction to generate primary carbon-centered radicals from aryl halides,[3–5] vinyl halides[7] or from phenyl selenides.[6] We wish to report herein an alternative photochemical approach to generate free radicals for radical addition to aromatic imimes. This reaction was mediated by 1-benzyl-1,4-dihydronicotinamide (BNAH, an NADH model molecule). To the best of our knowledge, this is the first photoinduced radical addition reaction to imines.[8]

Aromatic imine **1**, benzyl bromide **2** and BNAH were dissolved in dry acetonitrile and irradiated with a 500-W high pressure mercury lamp in a Pyrex bottle ($\lambda > 300$ nm) under argon atmosphere at ambient temperature. The reaction was monitored by thin layer chromatography. After irradiation, the solvent was removed under reduced pressure and the products were isolated by column chromatography with neutral alumina. The nitrogen-addition product, *tert*-amine **3**, and/or the carbon-addition product, *sec*-amine **4**, were obtained in good yield (Scheme 1). The results are summarized in Table 1.

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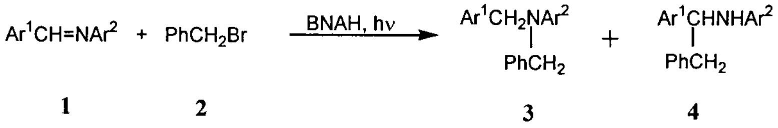


$$Ar^1CH{=}NAr^2 + PhCH_2Br \xrightarrow{BNAH,\ h\nu} Ar^1CH_2N(CH_2Ph)Ar^2 + Ar^1CH(CH_2Ph)NHAr^2$$

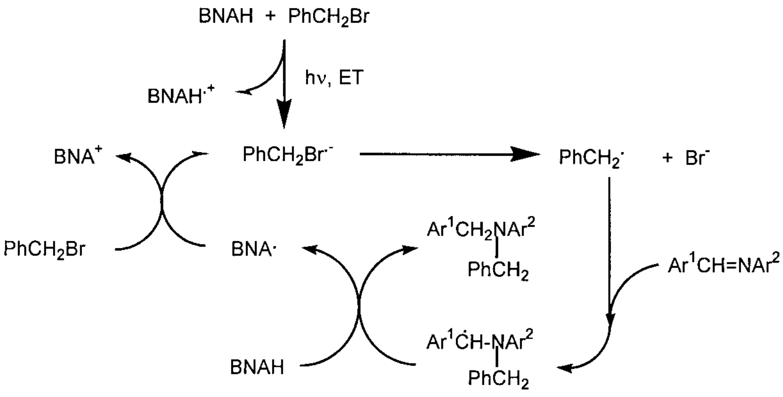
Scheme 1.

Table 1
BNAH-mediated photoinduced benzyl radical addition of aromatic imines

Substrate	Ar^1	Ar^2	t/h	Conversion (%)	Product (yield, %)
1a	Ph	Ph	4	94	**3a** (87)
1b	Ph	4-Cl-C_6H_4	4.5	91	**3b** (84)
1c	PhCH=CH	Ph	3	92	**3c** (81)
1d	3,4-$(CH_2O_2)C_6H_3$	Ph	3	90	**3d** (86)
1e	4-Br-C_6H_4	Ph	3	88	**3e** (82)
1f	Ph	4-$CH_3OC_6H_4$	2.5	95	**3f** (64), **4f** (21)
1g	4-$CH_3OC_6H_4$	Ph	3	90	**3g** (83)
1h	4-F-C_6H_4	Ph	5	92	**3h** (75), **4h** (14)

It is seen from Table 1 that the benzyl group added exclusively to the nitrogen atom in **1** giving *tert*-amine **3** in the case of **1a**–**e** and **1g**. However, when a strongly electron-donating group was attached to the Ar^2 moiety (**1f**) or a strongly electron-withdrawing group was attached to the Ar^1 moiety (**1h**), the carbon-addition products **4f** and **4h** were also obtained. This is understood because the benzyl radical is electrophilic due to the delocalization of the unpaired electron to the phenyl ring; it preferentially attacks the electronegative nitrogen atom of the C=N bond of **1**. It has been found previously that, in the intramolecular free radical addition reaction of imines, aryl radicals could add to either the nitrogen or carbon atom depending on the combination of both kinetic and thermodynamic factors coupled with relative radical stability and substituent effect.[1b,2–5] Our result demonstrates clearly that, in the present case, the polar effect is the predominant factor which governs the regioselectity of the reaction.

It was found that BNAH was oxidized to the corresponding pyridinium salt (BNA^+Br^-) and a small amount of toluene (yields range from 1 to 4% in all cases) was generated during the reaction as evidenced by gas chromatography. No reaction took place either in the dark or under irradiation in the absence of benzyl bromide. This is consistent with previous reports that imines are not reduced by BNAH thermally or photochemically unless the imine is activated by coordinating with a proton, an alkyl group or a metal ion.[9] Therefore, photoinduced electron transfer between BNAH and benzyl bromide is clearly the initiating step for the reaction, as outlined in Scheme 2. The oxidation potential and the excitation energy of BNAH are 0.57 V versus SCE and 3.17 eV, respectively,[10] and the reduction potential of benzyl bromide is ca. –1.11 V versus Ag/AgBr electrode.[11] Therefore, the photoinduced electron transfer between BANH and benzyl bromide is energetically feasible.[12] It is well known that carbon–halogen bonds in the radical anion of alkyl halides are extremely weak and the bond breaking may occur concertedly with electron transfer via the so-called mesolytic cleavage process,[13] generating alkyl radical as the vital intermediate. In



Scheme 2.

the present case, the benzyl radical thus formed attacks the C=N bond in imines, producing a new carbon-centered and/or nitrogen-centered radical. The latter abstracts a hydrogen from BANH giving **3** and/or **4** and BNA· radical. This radical may transfer an electron to another molecule of benzyl bromide, giving BNA^+ as the final product and generating the radical anion of benzyl bromide to continue the radical chain reaction.[10] The by-product toluene may be formed by the free radical chain reaction between benzyl radical and BNAH, as reported previously.[10,14]

In conclusion, this work provides a new approach to initiate free radical addition reactions, which may be extended to other synthetically useful reactions, such as intramolecular radical cyclizations.

Acknowledgements

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