Aqueous Medium Radical Addition to Ketimines with a Phenolic Hydroxyl Group

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Abstract: Intermolecular alkyl radical addition to ketimines having 2-phenolic hydroxyl group proceeded effectively in aqueous media, providing the novel method for construction of all-substituted sp^3-hybridized carbon center.

Key words: radical, imine, ketimine, water, aqueous media

The carbon-nitrogen double bond of imines has emerged as a radical acceptor.[1] However, studies on the intermolecular reaction of imines have concentrated on reaction of aldimines.[2–5] The difficulty in achieving the construction of all-substituted sp^3-hybridized carbon center based on the intermolecular radical addition to ketimines has remained unresolved.[6] Nothing has been known about the radical addition to ketimines using a conventional radical initiator such as Et_3B or AIBN. Therefore, the screening of reactive and stable ketimino radical acceptors is the new focus of our efforts. In this paper, we report the intermolecular radical reaction of ketimines with a 2-phenolic hydroxyl group, which exhibit the excellent reactivity even under the mild aqueous medium reaction conditions.

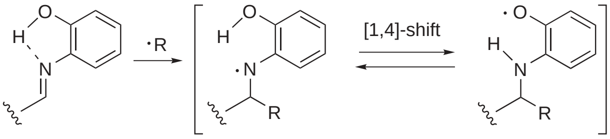
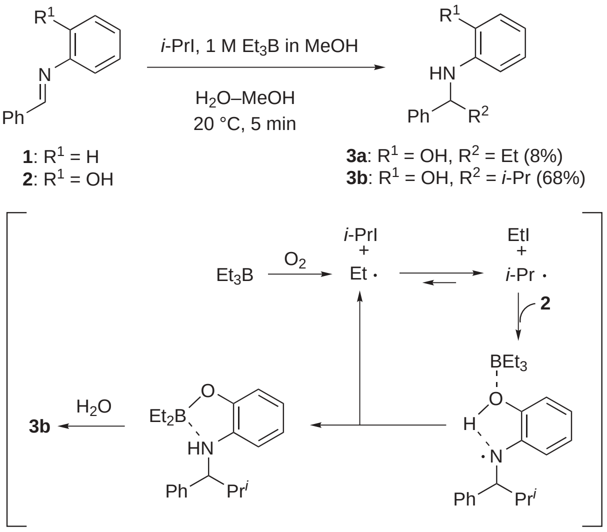


Figure 1 Effect of phenolic hydroxyl group on the stability and reactivity of imine derivatives in radical reaction

The use of water in radical reactions has generated considerable interest from both economical and environmental points of view.[7] As part of our program directed toward the development of radical reactions of imines in aqueous media,[8,9] the aqueous-medium radical addition to imines having a hydroxyl group has been newly investigated (Figure 1). As a simple effect of phenolic hydroxyl group, the activation and stabilization of C=N bond in aqueous media would be provided by an intramolecular hydrogen bond. Particularly, we expected that the extra stabilization of intermediate aminyl radical, provided by the [1,4]-hydrogen shift from the hydroxyl group and the delocalization on aromatic ring,[10] would give the accelerated addition rates.

To confirm the effect of phenolic hydroxyl group, we first investigated the radical addition to aldimines **1** and **2** in aqueous media (Scheme 1). As expected, aldimine **2** having a hydroxyl group exhibits a good reactivity, comparable to that of *N*-sulfonyl imines having a strong electron-withdrawing substituent reported in our previous studies.[11] The reaction of **2** was conducted in H_2O–MeOH (1:4, v/v) at 20 °C under tin-free iodine atom-transfer conditions using *i*-PrI and 1.0 M Et_3B in MeOH as a radical initiator. The reaction proceeded within five minutes to give the desired isopropylated product **3b** in 68% yield, along with an 8% yield of the ethylated product **3a** as a result of competitive addition of ethyl radical generated from Et_3B. In this reaction, Et_3B worked not only as a radical initiator but also as a radical chain terminator to trap the intermediate radical to give a chain-propagating ethyl radical.[12] In contrast, aldimine **1** did not give the desired adduct under the aqueous-medium conditions, because of the competitive hydrolysis of the C=N bond. These results show that the aldimines having phenolic hydroxyl group are highly promising water-resistant radical acceptors.



Scheme 1

The development of reactive ketimino radical acceptors is a challenging problem. The next substrates of choice were ketimines **4**–**7** prepared from methyl pyruvate, since electron-deficient glyoxylic aldimines have shown an excellent reactivity toward nucleophilic carbon radicals in our previous work (Scheme 2).[3] All reactions were carried out by using 2.5 equivalents of Et_3B. The reaction of

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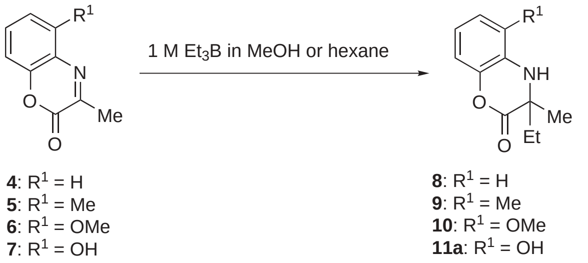
ketimines **4**–**6** proceeded slowly to give the low yields of desired ethylated products **8**–**10**, along with the recovered starting materials **4**–**6** (Table 1, entries 1–3). As expected, ketimine **7** exhibited an excellent reactivity in aqueous media. The ethyl radical addition to **7** afforded the ethylated product **11a** in 94% yield within five minutes without formation of other by-products (entry 4). To identify the reactivity of ketimine **7**, the reaction was tested in organic solvent at lower reaction temperature. High chemical yields were also observed in MeOH or toluene even at –78 °C (entries 5 and 6). Additionally, the lower reactivity of ketimines **4**–**6** was observed in non-H-bonding solvent such as CH_2Cl_2 or toluene. Among the different types of imino radical acceptors, the oxime ethers and hydrazones are well known to be excellent radical acceptors, because of the stabilization of the intermediate aminyl radical provided by the lone pair on the adjacent heteroatoms.[1] However, the reaction of ketoxime ethers did not proceed even in the presence of $BF_3{\cdot}OEt_2$. Thus, these results indicated that 2-phenolic hydroxyl group is important for the reactivity of ketimine **7**.



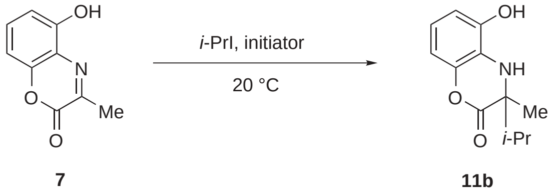
Scheme 2

Table 1 Ethyl Radical Addition to Ketimines **4**–**7**

Entry	Imine	Solvent	Temp (°C)	Time (min)	Yield (%)[a]
1[b]	**4**	H_2O–MeOH	20	60	35 (30)
2[b]	**5**	H_2O–MeOH	20	60	19 (41)
3[b]	**6**	H_2O–MeOH	20	60	48 (10)
4[b]	**7**	H_2O–MeOH	20	5	94
5[b]	**7**	MeOH	–78	30	92
6[c]	**7**	Toluene	–78	60	84

[a] Isolated yields. Yield in parentheses is for the recovered starting material.
[b] Reactions were carried out using 1.0 M Et_3B in MeOH.
[c] Reaction was carried out using 1.0 M Et_3B in hexane.

We next investigated the aqueous medium addition of an *iso*propyl radical to ketimine **7** by using several radical initiators (Scheme 3). The isopropylated product **11b** was also obtained in 87% yield under iodine atom-transfer conditions using *i*-PrI and Et_3B without Bu_3SnH (Table 2, entry 1). We recently reported that indium has the potential to induce radical reactions as a single-electron transfer radical initiator in aqueous media.[8c–e,9] The indium-mediated reaction of **7** proceeded slowly to give the product **11b** in 60% yield, along with a small amount of reduced product (entry 2). Although a significant amount of the reduced product was formed by using Zn in aqueous NH_4Cl–MeOH, a good yield of the product **11b** was obtained by using Zn–CuI in H_2O–MeOH (entries 3 and 4).[13]

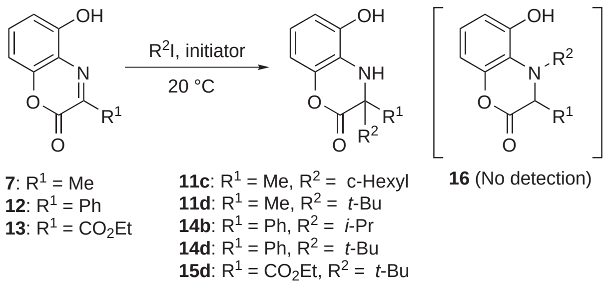


Scheme 3

Table 2 *Iso*propyl Radical Addition to **7** in Aqueous Media

Entry	Initiator	Solvent	Time (min)	Yield (%)[a]
1[b]	Et_3B	H_2O–MeOH	5	87 (> 30:1)[e]
2[c]	In	H_2O–MeOH	30	60[f]
3[c]	Zn	aq NH_4Cl–MeOH	5	17[f]
4[d]	Zn, CuI	H_2O–MeOH	5	83

[a] Isolated yields.
[b] Reaction was carried out using *i*-PrI (30 equiv) and Et_3B in MeOH (2.5 equiv).
[c] Reactions were carried out using *i*-PrI (7 equiv) and In or Zn (7 equiv).
[d] Reaction was carried out using *i*-PrI (7 equiv), Zn (7 equiv), CuI (1 equiv).
[e] Ratio for **11b**:**11a** is determined by ^1H NMR analysis.
[f] The reduced product was formed as a by-product.



Scheme 4

We next investigated the reaction with other radical precursors (Scheme 4). In the reaction of **7**, other radical precursors such as *c*-hexyl-I and *tert*-BuI worked well to give the desired products **11c** and **11d** by using Et_3B or Zn–CuI as a radical initiator (Table 3, entries 1–4). The *iso*propyl radical addition to ketimine **12**, highly stabilized by conjugation with a phenyl substituent, proceeded smoothly to give the adduct **14b** in 95% yield (entry 5). The reaction of **12** with a bulky *tert*-butyl radical also proceeded effectively (entry 6). The reaction of ketimine **13** having an additional ester group proceeded regioselectively to give the desired product **15d** without formation of Michael-type product **16** (entry 7).

Table 3 Alkyl Radical Addition to **7**–**13** in Aqueous Media

Entry	Imine	RI	Initiator	Yield (%)[a]
1[b]	**7**	c-Hexyl-I	Et$_3$B	89 (9:1)[d]
2[b]	**7**	*t*-BuI	Et$_3$B	59 (>30:1)[d]
3[c]	**7**	c-Hexyl-I	Zn, CuI	81
4[c]	**7**	*t*-BuI	Zn, CuI	90
5[b]	**12**	*i*-PrI	Et$_3$B	95 (>30:1)[d]
6[b]	**12**	*t*-BuI	Et$_3$B	62 (>30:1)[d]
7[b]	**13**	*t*-BuI	Et$_3$B	95 (>30:1)[d]

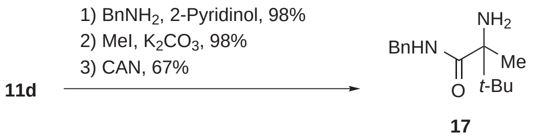
[a] Isolated yields.

[b] Reactions were carried out using RI (30 equiv) and Et$_3$B in MeOH (2.5 equiv) in H$_2$O–MeOH for 5 min.

[c] Reactions were carried out using RI (7 equiv), Zn (7 equiv), CuI (1 equiv) in H$_2$O–MeOH for 5 min.

[d] Ratios are for the desired alkylated product to ethylated product determined by ^{1}H NMR analysis.

The product **11d** was converted to α,α-disubstituted amino acid derivative **17** (Scheme 5). The reaction of **11d** with benzylamine in the presence of 2-pyridinol gave amide, which was converted to methyl ether. The methyl ether was treated with CAN to afford **17**.



Scheme 5

In conclusion, we have demonstrated the utility of imines having 2-phenolic hydroxyl group in radical reactions. These are the first examples of intermolecular reaction of ketimines using Et$_3$B or Zn as a conventional radical initiator.

General Procedure for Radical Addition to Ketimines by Using Et$_3$B.

To a solution of ketimine **7**, **12**, or **13** (0.25 mmol) in H$_2$O–MeOH (1:4, v/v, 2.5 mL) were added RI (7.50 mmol) and Et$_3$B (1.0 M in MeOH, 0.63 mL, 0.63 mmol) at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was evaporated, diluted with sat. NaHCO$_3$ and then extracted with EtOAc. The organic phase was dried over MgSO$_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane–EtOAc = 4:1, 2-fold development) afforded product.

Representative Characterization Data of Product 11a.

Colorless oil; IR (CHCl$_3$): 1762 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ = 6.72 (1 H, br t, *J* = 8.3 Hz), 6.62 (1 H, br d, *J* = 8.3 Hz), 6.60 (1 H, br d, *J* = 8.3 Hz), 3.86 (1 H, br s), 1.83 (1 H, m), 1.68 (1 H, m), 1.47 (3 H, s), 0.97 (3 H, t, *J* = 7.6 Hz). ^{13}C NMR (CDCl$_3$): δ = 170.1, 144.5, 141.9, 120.4, 119.4, 111.3, 108.4, 57.7, 29.7, 22.7, 7.4. MS (EI$^+$): *m/z* (%) = 207 (40) [M$^+$], 150 (100). HRMS (EI$^+$): *m/z* calcd for C$_{11}$H$_{13}$NO$_3$ [M$^+$]: 207.0895. Found: 207.0892.

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