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Tin-Free Radical Addition of Acyloxymethyl to Imines

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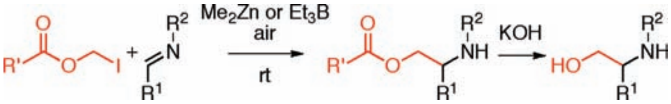
ABSTRACT



Acyloxymethyl radicals were generated from the corresponding iodomethyl esters and successfully underwent addition to the C═N bond of *N*-Ts, *N*-PMP, and *N*-Dpp imines by the action of dimethylzinc or triethylborane. Ethyl acetate, toluene, and benzene as well as dichloromethane were suitable solvents. The utility of acyloxymethyl radicals as a hydroxymethyl anion equivalent was highlighted by the facile hydrolysis of the acyloxy moiety of the adducts to give the corresponding amino alcohol derivatives in good to high yield.

Synthetically useful transformations that are otherwise difficult to accomplish have been achieved through reactions involving radical species.[1] In addition, these reactions are usually carried out under mild conditions. An α-oxygenated alkyl radical is classified as a stabilized nucleophilic radical and is accordingly an α-oxygenated carbanion equivalent, while the anion counterpart, α-alkoxycarbanion, is a relatively unstable species. Examples of the most successful methods to generate α-oxygenated carbanion are tin−lithium exchange of (1-alkoxyalkyl)tin compounds[2] and iodine−magnesium exchange of iodomethyl carboxylates.[3] Usually, strictly anhydrous and deoxygenated atmosphere, strongly basic conditions, and also low temperature are required for this type of carbanion chemistry. In contrast, α-alkoxy and α-hydroxyalkyl radicals have been generated via C−H bond cleavage under milder conditions and utilized in C−C bond forming reactions as nucleophilic α-oxygenated carbon units.[4] The major problem of this strategy was, however, the requirement of a large amount (usually 20−250 equiv) of the corresponding ether or alcohol as a radical source. The generation of this class of radical via C−heteroatom bond cleavage using a tin compound has been utilized in sugar chemistry as well as in a number of total syntheses.[5] Although α-oxygenated C-centered radicals were efficiently generated from the radical sources in these examples, the use of organotinhydrides is a critical drawback, especially from an ecological point of view, because of difficulty in complete removal and toxicity of tin compounds.[6] Moreover, the radical source, α-halogenated ether is rather unstable and easily hydrolyzed under ordinary atmosphere. α-Acyloxyalkyl radical is also expected to react as a nucleophilic α-oxygenated carbon unit. The corresponding radical source, α-halogenated alkyl benzoate and pivalate are so stable

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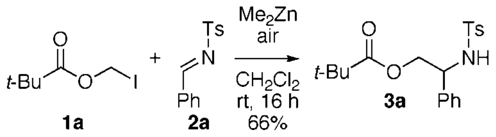
10.1021/ol8014978 CCC: $40.75

toward hydrolysis[7] that the purification by silica gel column chromatography is possible. However, the synthetic utility of α-acyloxyalkyl radical has scarcely been studied. Besides, reported examples are limited to addition to an intramolecular C═C bond,[8,9] with the exception of one example of intermolecular addition of propanoyloxymethyl radical, generated from iodomethyl propanoate using an organotin reagent.[10,11]

We have studied the dimethylzinc−air-initiated direct generation of α-alkoxyalkyl radicals from ethers through hydrogen abstraction and their reactions for the functionalization of ethers.[12] We also succeeded in the tin-free generation of primary alkyl radicals from the corresponding alkyl iodides via dimethylzinc−air-radical process.[13−15] Herein, we report the tin-free generation of acyloxymethyl radicals from the corresponding iodomethyl esters and their reaction with imines to show their utility as hydroxymethyl anion equivalents.

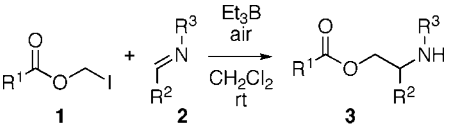
First, we examined the reaction of iodomethyl pivalate (**1a**)[16] with *N*-tosylbenzaldimine (**2a**). To a solution of **1a** (3 mmol) and **2a** (1 mmol) in dichloromethane (1 mL) was added a 1.0 M solution of dimethylzinc in hexane (1 mL, 1 mmol). The mixture was stirred at room temperature under ordinary atmosphere, while a solution of dimethylzinc (1 mL, 1 mmol) was added every 2 h. After addition of a total amount of 5 mmol of dimethylzinc, the mixture was stirred for another 6 h at room temperature to give adduct **3a** in 66% yield (Scheme 1).

Scheme 1



The reaction using diethylzinc, in place of dimethylzinc, failed to give the expected product **3a** but instead the ethyl adduct in 78% yield along with the reduced product, *N*-benzyltoluenesulfonamide, in 9% yield. When a hexane solution of triethylborane[17] was used instead of dimethylzinc, the reaction proceeded more cleanly to give **3a** in 96% yield after 20 h (Table 1, entry 1). The ester functionality of **1** and **3** was inert under these conditions. It is worthy of note that the reaction can be conducted at room temperature under ordinary atmosphere. In contrast, the reaction of methoxymethyl radical, generated from methyl iodomethyl ether with dimethylzinc−air, required −78 °C to give the methoxymethylated analogue of **3a** in 95% yield, and the reaction at room temperature resulted in a complex mixture including no desired adduct.[18]

Table 1. Addition of Acyloxymethyl Radicals, Generated from **1**, to Imines **2** Mediated by Et$_3$B−Air[a]



entry	1/R^1	2	R^2	R^3	Et$_3$B (equiv)	time (h)	3/yield (%)
1	**1a**/*t*-Bu	**2a**	Ph	4-tolSO$_2$	9	20	**3a**/96
2	**1b**/Ph	**2a**	Ph	4-tolSO$_2$	5	14	**3b**/79
3	**1a**/*t*-Bu	**2b**	Ph	4-MeOC$_6$H$_4$	5	7	**3c**/89
4	**1b**/Ph	**2b**	Ph	4-MeOC$_6$H$_4$	5	8	**3d**/84
5[b]	**1a**/*t*-Bu	**2c**	Ph	Ph$_2$PO	20	48	**3e**/80
6	**1a**/*t*-Bu	**2d**	4-ClC$_6$H$_4$	4-tolSO$_2$	8	20	**3f**/88
7	**1a**/*t*-Bu[c]	**2e**	4-MeC$_6$H$_4$	4-tolSO$_2$	18	48	**3g**/82
8[d]	**1a**/*t*-Bu	**2f**	4-MeOC$_6$H$_4$	4-tolSO$_2$	9	22	**3h**/94
9	**1a**/*t*-Bu	**2g**	Ph(CH$_2$)$_2$	4-tolSO$_2$	8	24	**3i**/67

[a] **1** (3 equiv) and Et$_3$B (3 equiv) were initially added, and the rest of Et$_3$B was portionwise added (1 equiv/2 h). [b] Toluene was used as a solvent in place of CH$_2$Cl$_2$. BF$_3$·OEt$_2$ (total 6 equiv) was added in four portions. [c] 9 equiv. [d] BF$_3$·OEt$_2$ (total 3 equiv) was added in three portions.

Iodomethyl benzoate (**1b**)[19] was also a good radical precursor to give benzoyloxymethylated adduct **3b**[20] in 79%

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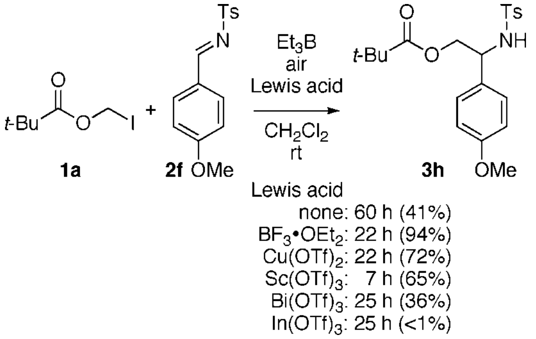
yield after 14 h under similar conditions (entry 2). The reaction proceeded smoothly with *N*-(4-methoxyphenyl) (PMP) imine **2b**, and products **3c** and **3d** were obtained in 89% and 84% yields after 7 and 8 h, respectively (entries 3 and 4). Interestingly, the reactions of *N*-PMP imines were faster than those with more electron-deficient *N*-tosyl imines. The reaction of *N*-diphenylphosphinoyl (Dpp) imine **2c** also proceeded in toluene by using 20 equiv of triethylborane to give **3e** in 80% yield in the presence of trifluoroborane diethyl etherate (entry 5). In the absence of trifluoroborane diethyl etherate, the reaction produced **3e** in only 20% yield and **2c** was recovered in 40% yield after 48 h using 20 equiv of triethylborane. The products were also obtained in good yields in the reaction of *N*-tosyl imines **2d** and **2e** derived from 4-chloro and 4-methylbenzaldehyde (entries 6 and 7), although the latter required 9 equiv of **1a** and prolonged reaction time.

The presence of trifluoroborane also facilitated the reaction of electron-rich 4-methoxybenzaldehyde imine **2f**. In the presence of trifluoroborane diethyl etherate (3 equiv), adduct **3h** was obtained in 94% yield after 22 h (entry 8). In the absence of trifluoroborane diethyl etherate, **3h** was obtained in only 41% yield along with recovered **2f** in 45% yield after 60 h using 9 equiv of **1a** and 20 equiv of triethylborane (Scheme 2). Catalytic amounts (0.2 equiv) of other additives, copper(II) triflate and scandium triflate also promoted the reaction to give **3h** in 72% and 65% yields after 22 and 7 h, respectively, using 9 equiv of triethylborane. On the contrary, bismuth triflate and indium triflate failed to facilitate the reaction to give **3h** in 36% and <1% yields, respectively, after 25 h. As shown in entry 9, the reaction is also applicable to aliphatic imine **2g** derived from hydrocinnamaldehyde to give **3i** in 67% yield.

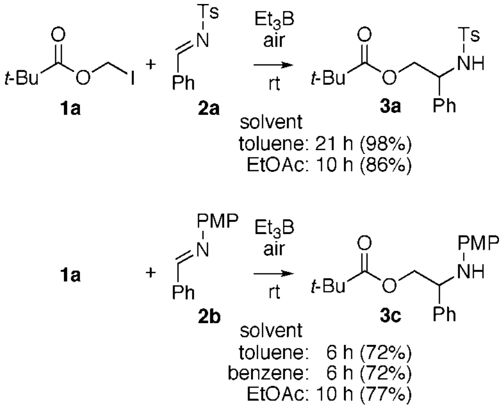
Scheme 2



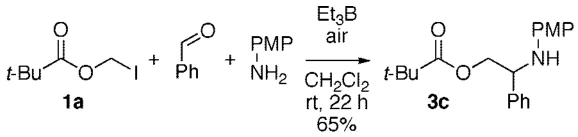
Dichloromethane was replaceable with toluene, benzene, or environmentally acceptable ethyl acetate, as shown in Scheme 3. The products were obtained in good to high yield comparable to the corresponding reaction in dichloromethane. It is noteworthy that ethyl acetate, which is usually incompatible with a carbanion, was usable in these radical conditions. This wide choice of solvents is one of the advantages of this reaction.

The reaction of benzaldehyde with **1a** (3 equiv) and triethylborane (5 equiv in three portions) failed to proceed, resulting in quantitative recovery of the starting aldehyde. This result encouraged us to perform a three-component reaction. To a mixture of **1a** (3 equiv), benzaldehyde, and *p*-anisidine (1 equiv) was added triethylborane (10 equiv in eight portions). Addition of pivaloyloxymethyl radical exclusively took place to imine **2b**, generated in situ, to give adduct **3c** in 65% yield after 22 h (Scheme 4). No addition product to the C=O bond of benzaldehyde was detected.

Scheme 3

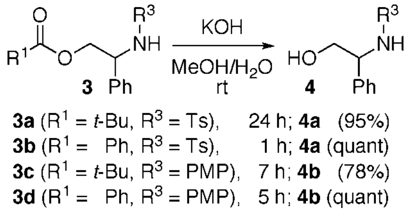


Scheme 4



Demasking of the alcohol moiety of pivalate and benzoate product **3** was readily achieved by basic hydrolysis with potassium hydroxide in aqueous methanol at room temperature to give the corresponding amino alcohols **4**[21] in good to high yield (Scheme 5).

Scheme 5



In summary, we have developed the reaction of acyloxymethyl radicals, generated from the corresponding iodomethyl

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esters, with a variety of imines. The utility of acyloxymethyl radicals as hydroxymethyl anion equivalents was highlighted by the easy demasking of the alcohol moiety in standard basic conditions. It is advantageous that the reaction can be conducted without tin reagents under ordinary atmosphere at room temperature with a choice of ecological solvents. Furthermore, the radical precursor, iodomethyl ester, is rather stable and easy to handle.

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

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