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Tin-Free Intermolecular Addition of Primary Alkyls to Imines via the Dimethylzinc–Air Radical Process

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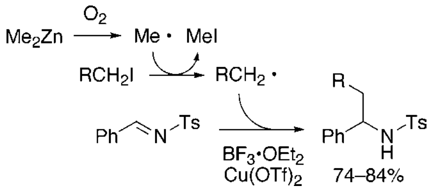
ABSTRACT



A dimethylzinc–air initiator was applied to the generation of primary alkyl radicals from alkyl iodides. The addition of the generated primary alkyl radicals to *N*-tosylimines was accelerated by the action of boron trifluoride–diethyl etherate and copper(II) triflate to give the corresponding adducts in good yields after 2–3 h. Air oxygen was essential for the reaction to proceed, showing involvement of a radical process in the reaction.

Development of environmentally sustainable reactions is an important goal of recent organic chemistry. To this end, it is essential to avoid the use and production of toxic compounds in organic reactions. Although trialkyltin hydrides, which enable many transformations via radical processes, are among the most versatile reagents in organic synthesis, difficulty in complete removal and toxicity of tin compounds are critical drawbacks, especially for industrial applications.[1] Herein, we describe a new tin-free method for the generation and reaction of primary alkyl radicals.[2]

Since our discovery of the radical addition of ethers to imines by the action of dimethylzinc and air,[3] we have investigated direct generation of carbon-centered radicals via C−H bond cleavage and their reactions.[4,5] Dimethylzinc reacts with air oxygen to release methyl radical, which abstracts α-hydrogen of ethers to generate α-alkoxyalkyl radicals. Recently, we have also developed direct generation of cycloalkyl radicals from plain cycloalkanes and their addition reaction to *N*-tosylimines.[4d,6] In continuation with our investigation, we then attempted direct generation of a primary alkyl radical from a chain alkane. However, the reaction of *N*-tosylimine **1a** with hexane in the presence of dimethylzinc and air as an initiator only gave a 1:1 mixture of 1-methylpentyl adduct and 1-ethylbutyl adduct in 25% combined yield after 45 h without the production of hexyl adduct. Thus, we decided to generate primary alkyl radicals from alkyl iodides.

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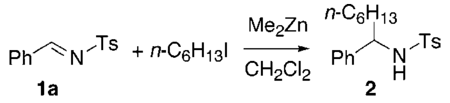
For the generation of alkyl radicals, triethylborane–air initiation has been a popular tin-free method.[7] Ethyl radical, generated from triethylborane, abstracts iodine from alkyl iodides[8] or hydrogen from solvent ethers[9] to give carbon-centered radicals. However, the scope of this method is limited to the generation of secondary, tertiary, and stabilized alkyl radicals. Production of primary alkyl radicals by the triethylborane method is inefficient because ethyl radical is as stable as other primary alkyl radicals. The most common solution to this problem is the use of a stoichiometric amount of tributyltin hydride as a source of a tin radical that efficiently abstracts halogen.[10] Because a methyl radical is less stable than primary alkyl radicals (bond dissociation energy in kJ/mol; Me–H = 439 vs Et–H = 421),[11] we expected that a methyl radical, generated from dimethylzinc, should be able to abstract an iodine atom from a primary alkyl iodide to give a primary alkyl radical.

First, the reaction of imine **1a** and hexyl iodide was carried out by using a large excess amount of the iodide and dimethylzinc, without solvent. The expected generation of hexyl radical seemed to take place, giving hexyl adduct **2** in 40% yield after 110 h (Table 1, entry 1). In the presence of 6 equiv of boron trifluoride–diethyl etherate,[4d] the reaction was accelerated to give **2** in 62% yield after 10 h with 5 equiv of the iodide, 6 equiv of dimethylzinc, and dichloromethane as solvent (entry 2).

To our delight, the reaction was further accelerated with 0.1 equiv of copper(I) iodide[12] to give **2** in 64% yield after 6 h (entry 3). Other copper salts were also tested. The results with copper(I) halides (entries 3–5) were less satisfactory than those with other copper(I) and copper(II) salts (entries 6–10). Copper(II) triflate gave the best results to afford **2** in 71% yield after 1.5 h (entry 10). Without boron trifluoride–diethyl etherate, the reaction was rather slower, giving **2** in 45% yield even after 24 h (entry 11). [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium also accelerated the reaction, but less efficiently, to give **2** in 57% yield after 4 h (entry 14). Interestingly, when nickel(II) acetylacetonate was used as an additive, the addition of a methyl group took place very quickly to give methyl adduct in 97% yield after 0.5 h (entry 15). Finally, it was found that the reaction with copper(II) triflate was as efficient when cooled in an ice–water bath to give **2** in 74% yield after 1.5 h (entry 12). Under argon atmosphere, the reaction was dramatically retarded (entry 13). These results suggest that the initiation of a radical process by dimethylzinc and air oxygen is required for the reaction.

Table 1. The Addition of Hexyl to Imine **1a** Initiated by Me_2Zn–Air[a]

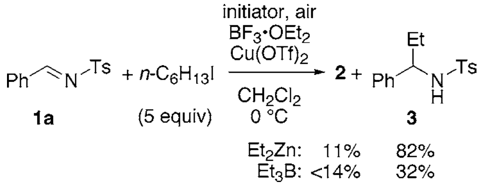


entry	Me_2Zn (equiv)	n-$C_6H_{13}I$ (equiv)	additives (equiv)	temp	time (h)	yield (%)
1[b]	9	60	none	rt	110	40
2	6	5	$BF_3{\cdot}OEt_2$ (6)	rt	10	62
3	6	5	$BF_3{\cdot}OEt_2$ (6) CuI (0.1)	rt	6	64
4	4	5	$BF_3{\cdot}OEt_2$ (4) CuBr (0.1)	rt	3	53
5	4	5	$BF_3{\cdot}OEt_2$ (4) CuCl (0.1)	rt	3	47
6	4	5	$BF_3{\cdot}OEt_2$ (4) CuCN (0.1)	rt	3	65
7	4	5	$BF_3{\cdot}OEt_2$ (4) $Cu(ClO_4)(MeCN)_4$ (0.1)	rt	3	64
8	4	5	$BF_3{\cdot}OEt_2$ (4) $(CuOTf)_2{\cdot}C_6H_6$ (0.1)	rt	3	63
9	4	5	$BF_3{\cdot}OEt_2$ (4) $CuCl_2$ (0.1)	rt	3	63
10	2	5	$BF_3{\cdot}OEt_2$ (2) $Cu(OTf)_2$ (0.1)	rt	1.5	71
11	2	5	$Cu(OTf)_2$ (0.1)	rt	24	45
12	2	5	$BF_3{\cdot}OEt_2$ (2) $Cu(OTf)_2$ (0.1)	0 °C	1.5	74
13[c]	2	5	$BF_3{\cdot}OEt_2$ (2) $Cu(OTf)_2$ (0.1)	0 °C	1.5	5
14	2	5	$BF_3{\cdot}OEt_2$ (2) $PdCl_2(dppf){\cdot}CHCl_3$ (0.1)	rt	4	57
15	2	5	$BF_3{\cdot}OEt_2$ (2) $Ni(acac)_2$ (0.1)	rt	0.5	0[d]

[a] The reaction was conducted under ordinary air atmosphere with a $CaCl_2$ drying tube unless otherwise mentioned. [b] Without solvent CH_2Cl_2. [c] Under argon atmosphere. [d] Methyl adduct was obtained in 97% yield.

Other radical initiators, diethylzinc[13] and triethylborane,[14] were tested with regard to their reaction efficiency. The reactions were conducted under the same conditions as in Table 1, entry 12. Diethylzinc or triethylborane, in place of dimethylzinc, gave ethyl adduct **3** as the major product in 82% and 32% yield, respectively (Scheme 1). Adduct **2** was the minor product as expected.[15]

Scheme 1. The Reaction of **1a** and n-$C_6H_{13}I$ Initiated by Et_2Zn or Et_3B in the Presence of $BF_3{\cdot}OEt_2$ and $Cu(OTf)_2$



Other primary alkyl iodides were also applicable to the reaction. Butyl adduct **4a** was obtained in 80% yield (Table 2, entry 1). The addition of 4-acetoxybutyl proceeded without

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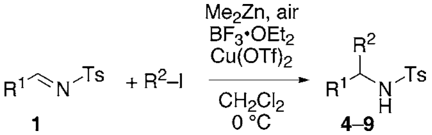
Table 2. The Addition of Alkyls to Imines **1** Initiated by Me_2Zn−Air in the Presence of $BF_3{\cdot}OEt_2$ and $Cu(OTf)_2$[a]



entry	imine	R^1	R^2	time (h)	adduct	yield (%)
1	**1a**	Ph	Bu	1.5	**4a**	80
2	**1a**	Ph	AcO(CH$_2$)$_4$	1.5	**5**	77
3	**1a**	Ph	Cl(CH$_2$)$_4$	1.5	**6**	84
4[b]	**1a**	Ph	Cl(CH$_2$)$_3$	1.5	**7**	77
5[c]	**1a**	Ph	*i*-Pr	0.5	**8**	95
6[c]	**1a**	Ph	*c*-C$_6$H$_{11}$	1.0	**9**	91
7	**1b**	4-ClC$_6$H$_4$	Bu	2	**4b**	82
8[b]	**1c**	4-MeOC$_6$H$_4$	Bu	2	**4c**	83
9[d]	**1d**	1-Naph	Bu	3	**4d**	57
10[d]	**1e**	2-Naph	Bu	3	**4e**	58
11[e]	**1f**	PhCH$_2$CH$_2$	Bu	2	**4f**	67
12[b]	**1g**	*c*-C$_6$H$_{11}$	Bu	3	**4g**	69

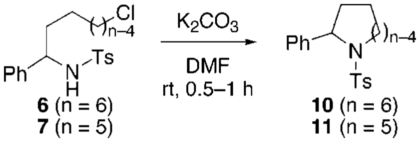
[a] Unless otherwise mentioned, iodide (5 equiv), Me_2Zn and $BF_3{\cdot}OEt_2$ (2 equiv each), and $Cu(OTf)_2$ (0.1 equiv) were used. [b] Me_2Zn and $BF_3{\cdot}OEt_2$ (3 equiv each) were used. [c] Iodide, Me_2Zn, and $BF_3{\cdot}OEt_2$ (1.5 equiv each) were used. [d] Me_2Zn (3 equiv), $BF_3{\cdot}OEt_2$ (5 equiv), and $Cu(OTf)_2$ (0.2 equiv) were used. [e] Me_2Zn (2 equiv) and $BF_3{\cdot}OEt_2$ (3 equiv) were used.

problems to give **5** in 77% yield (entry 2). The reaction with chloroalkyl iodides gave chloroalkyl adducts **6** and **7** without the production of the corresponding iodoalkyl adducts (entries 3 and 4). When secondary alkyl iodides were used as alkyl sources, the reactions required only 1.5 equiv each of the iodide, boron trifluoride−diethyl etherate, and dimethylzinc to give adducts **8** and **9** in high yields after 0.5 or 1 h (entries 5 and 6).

The reaction proceeded with other *N*-tosylimines **1**. The reaction with imines **1b** and **1c** having an electron-withdrawing 4-chloro or donating 4-methoxy group on the aromatic rings gave **4b** and **4c** in 82% and 83% yield, respectively (entries 7 and 8). With imine **1d** and **1e** bearing a naphthyl group, **4d** and **4e** were obtained in 57% and 58% yield, respectively (entries 9 and 10). Aliphatic hydrocinnamaldehyde and cyclohexanecarbaldehyde imines **1f** and **1g** were also good acceptors, giving the corresponding adducts **4f** and **4g** in 67% and 69% yield, respectively (entries 11 and 12).

As a utility of this reaction, cyclization of adducts **6** and **7** into piperidine and pyrrolidine, respectively, was carried out. To this end, treatment of **6** with potassium carbonate in DMF for 1 h gave 2-phenylpiperidine **10** in 96% yield (Scheme 2). 2-Phenylpyrrolidine **11** was also obtained from **7** in 95% yield.[16] Other 2-substituted piperidines and pyrrolidines may be easily synthesized in the same manner.

Scheme 2. Cyclization of **6** and **7** to Form 2-Phenylpiperidine **10** and Pyrrolidine **11**



In conclusion, we have developed a new tin-free method for the generation of primary alkyl radicals and their addition to *N*-tosylimines. The use of a stoichiometric amount of boron trifluoride−diethyl etherate and a catalytic amount of copper(II) triflate accelerated the reaction and improved the efficiency of the reaction. The reaction was extremely slow under argon atmosphere, showing that a radical process initiated by dimethylzinc and air oxygen should be involved.[17]

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

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(16) Attempts to obtain **10** in a one-pot reaction by heating the reaction mixture after the radical addition failed, probably due to low nucleophilicity of the zinc amide formed by the alkyl addition.

(17) An alternative pathway of nonradical addition of dialkylzincs generated from alkyl iodides and dimethylzinc may be negligible because only a trace amount (<1%) of methyl adduct was obtained in the reaction under argon atmosphere (Table 1, entry 13). Moreover, the iodine−zinc exchange between alkyl iodides and dimethylzinc is unlikely because the process would involve displacement of the less stable methyl radical by more stable primary or secondary alkyl radicals: Micouin, L.; Knochel, P. *Synlett* **1997**, 327−328.