One-pot Synthesis of α-Alkoxy Azides from Carbonyl Compounds Catalyzed by Iron(III) Chloride

Megumi Omura, Katsuyuki Iwanami, and Takeshi Oriyama*
Department of Chemistry, Faculty of Science, Ibaraki University, 2-1-1 Bunkyo, Mito 310-8512

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In the presence of alkoxytrimethylsilane and a catalytic amount of iron(III) chloride, the reaction of various carbonyl compounds with trimethylsilyl azide afforded the corresponding α-alkoxy azides. This reaction could be suitable especially for azidation of aromatic aldehydes and proceeds under mild conditions in a convenient one-pot manner.

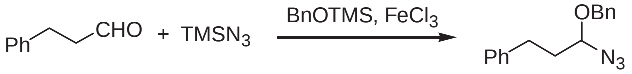
The azide group has been used extensively in organic synthesis. Several methods for the introduction of the azide group have been reported.[1] Trimethylsilyl azide has been frequently employed for this purpose because of its handy property.[2] There are some reports on the reactivity of trimethylsilyl azide toward carbonyl compounds. Addition of trimethylsilyl azide to aldehydes in the presence of a catalytic amount of zinc(II) chloride provided α-siloxy azides, but these reactions were applied only to aliphatic aldehydes.[3] After that, α-siloxy azides derived from aromatic aldehydes were reported to be very unstable and difficult to isolate.[4] α-Alkoxy azides were synthesized starting from acetals with hydrazoic acid in the presence of a stoichiometric amount of magnesium(II) bromide.[5] Aliphatic aldehydes were reacted with an excess of hydrazoic acid in the presence of alcohol and a catalytic amount of titanium(IV) chloride to afford α-alkoxy azides, but a similar reaction of aromatic aldehydes has not occurred.[6] On the other hand, we have recently demonstrated hybrid transformations including "nucleophilic addition to a carbonyl group" and "O-protection of a hydroxy group" in a simple one-pot procedure. These reactions of carbonyl compounds with various silyl nucleophiles and alkoxytrimethylsilane were effectively promoted by iron(III) chloride.[7]

In this communication, we wish to describe the first example of the direct conversion of various carbonyl compounds to the corresponding α-alkoxy azides under the influence of a catalytic amount of iron(III) chloride.

First, we examined the reaction of 3-phenylpropanal with 1.5 equiv. of trimethylsilyl azide and 2.4 equiv. of benzyloxytrimethylsilane in the presence of 5 mol % of iron(III) chloride in nitromethane at room temperature according to the procedure reported in our previous paper,[7c] and the desired product was obtained in 52% yield (Table 1, Run 1). After a preliminary investigation, we found that the reaction proceeded in acetonitrile at −40 °C to give the highest yield of the product (Run 6).[8]

Next, various aliphatic aldehydes were tested under these optimized reaction conditions (Table 2). 3-Methylbutanal, isobutanal, and cyclohexanecarbaldehyde were uniformly transformed into the corresponding α-benzyloxy azides in excellent yields (Runs 2–4). Even in the case of sterically hindered pivalaldehyde, the desired product was obtained in 57% yield (Run 5).

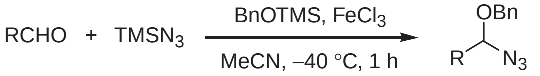
Table 1. Optimization of the reaction conditions[a]



Run	Solvent	Temp.	Time/h	Yield/%[b]
1	$MeNO_2$	rt	1	52
2	$MeNO_2$	0 °C	1	71
3	$MeNO_2$	−20 °C	1	85
4	CH_2Cl_2	−20 °C	1	74
5	MeCN	−20 °C	1	79
6	MeCN	−40 °C	1	91
7	EtCN	−40 °C	1	84
8	EtCN	−78 °C	24	47

[a]Molar ratio of aldehyde:BnOTMS:$TMSN_3$:$FeCl_3$ = 1:1.2:1.5:0.05. [b]Isolated yield of purified product.

Table 2. Synthesis of α-benzyloxy azides from various aliphatic aldehydes[a]



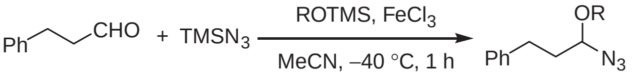
Run	RCHO	Yield/%[b]
1	$PhCH_2CH_2CHO$	91
2	$(CH_3)_2CHCH_2CHO$	90
3	*i*-PrCHO	97
4	*cyclo*-$C_6H_{11}CHO$	93
5	*t*-BuCHO	57

[a]Molar ratio of aldehyde:BnOTMS:$TMSN_3$:$FeCl_3$ = 1:1.2:1.5:0.05. [b]Isolated yield of purified product.

Furthermore, this reaction was similarly effective for various alkoxytrimethylsilanes to give the corresponding α-alkoxy azides as summarized in Table 3. Reaction with allyloxytrimethylsilane gave α-allyloxy azide in 63% yield (Run 2). Silyl ethers of primary and cyclic secondary alcohols gave the corresponding α-alkoxy azides in high yields (Runs 3 and 4). However, when *t*-butoxytrimethylsilane was used, the corresponding product was obtained in only 12% yield (Run 5).

Next, the reaction was conducted with various aromatic aldehydes (Table 4). We examined the reaction of benzaldehyde under the same reaction conditions as that of aliphatic aldehydes, and the corresponding product was obtained in 52% yield. However, the reaction of aromatic aldehydes proceeded smoothly to give the corresponding α-benzyloxy azides in high yields via in situ formation of acetal according to the procedure reported in our previous paper[7b] (Run 1).[9] Aromatic aldehydes having electron-donating (Runs 2–4, 6) or -withdrawing (Runs 7 and 8) groups, and naphthaldehydes (Runs 9 and 10) reacted readily under the above reaction conditions in good to excellent yields. Although mesitaldehyde did not react (Run 5), cinnamaldehyde

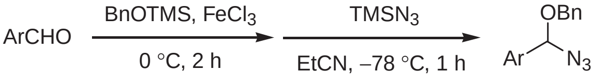
Table 3. Synthesis of various α-alkoxy azides[a]



Run	ROTMS	Yield/%[b]
1	BnOTMS	91
2	$CH_2{=}CHCH_2OTMS$	63
3	*n*-BuOTMS	89
4	*c*-$C_6H_{11}OTMS$	89
5	*t*-BuOTMS	12

[a]Molar ratio of aldehyde:ROTMS:$TMSN_3$:$FeCl_3$ = 1:1.2:1.5:0.05. [b]Isolated yield of purified product.

Table 4. Synthesis of α-benzyloxy azides from various aromatic aldehydes and ketones[a]



Run	ArCHO	Yield/%[b]
1	PhCHO	94
2	2-MeC_6H_4CHO	85
3	3-MeC_6H_4CHO	76
4	4-MeC_6H_4CHO	80
5	2,4,6-$Me_3C_6H_2CHO$	0
6	4-BrC_6H_4CHO	96
7[c]	4-NCC_6H_4CHO	69
8[c]	4-$MeO_2CC_6H_4CHO$	60
9	1-Naphthaldehyde	90
10	2-Naphthaldehyde	85
11	(*E*)-PhCH=CHCHO	61
12[d]	Cyclohexanone	95
13[d,e]	4-Phenylcyclohexanone	81

[a]Molar ratio of aldehyde:BnOTMS:$TMSN_3$:$FeCl_3$ = 1:2.4:1.5:0.02. [b]Isolated yield of purified product. [c]Reaction of the second step was carried out at −40 °C for 24 h. [d]5 mol % of the catalyst was used. [e]Reaction of the second step was performed for 2 h.

afforded the corresponding α-benzyloxy azide in 61% yield (Run 11). Similarly, cyclic ketones gave the desired adducts (Runs 12 and 13).

In conclusion, the present one-pot synthesis of α-alkoxy azides from a variety of carbonyl compounds catalyzed by iron(III) chloride has advantageous features: 1) both azidation of carbonyl compounds and protection of the hydroxy function proceed, 2) novel one-pot synthesis of α-alkoxy azides from aromatic aldehydes, 3) various alkyl-ether types of a protective group for the hydroxy function are obtained by using the corresponding alkoxytrimethylsilanes, 4) extremely mild reaction conditions, 5) experimental convenience. Further studies on these hybrid types of reaction are now in progress.

References and Notes

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8 Typical experimental procedure for the synthesis of α-benzyloxy azides from aliphatic aldehydes as follows: To a suspension of anhydrous iron(III) chloride (3.7 mg, 0.023 mmol) and 3-phenylpropionaldehyde (61.9 mg, 0.46 mmol) in acetonitrile (2 mL) were added benzyloxytrimethylsilane (108 µL, 0.55 mmol) and trimethylsilyl azide (83.3 mg, 0.72 mmol) in acetonitrile (1 mL) under argon atmosphere. After stirring for 1 h at −40 °C, the reaction mixture was quenched with a phosphate buffer (pH 7). The organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. 1-Benzyloxy-3-phenylpropyl azide (112.6 mg, 91%) was isolated by thin-layer chromatography on silica gel.

9 Typical experimental procedure for the synthesis of α-benzyloxy azides from aromatic aldehydes as follows: To a suspension of anhydrous iron(III) chloride (1.5 mg, 0.0093 mmol) and benzaldehyde (47 µL, 0.46 mmol) was added benzyloxytrimethylsilane (220 µL, 1.1 mmol) and stirred at 0 °C under argon atmosphere. After 2 h, trimethylsilyl azide (95 µL, 0.72 mmol) in propionitrile (1.5 mL) was added and stirred for 1 h at −78 °C. The reaction mixture was quenched with a phosphate buffer (pH 7). The organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. (α-Azido-α-benzyloxymethyl)benzene (103.5 mg, 94%) was isolated by thin-layer chromatography on silica gel.