A Simple and Convenient Synthesis of Alkyl Azides under Mild Conditions

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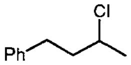
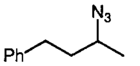
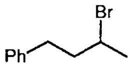
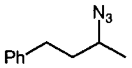
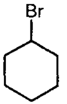
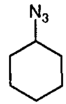
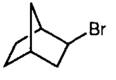
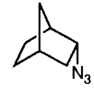
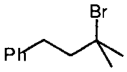
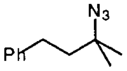
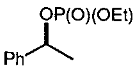
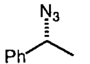
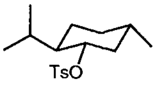
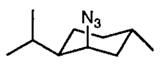
Various primary and secondary alkyl azides have been synthesized in high yields by the fluoride anion induced S_N2 substitution reactions of the corresponding alkyl halides, phosphates, or tosylates and trimethylsilyl azide.

Organoazides are one of the most important synthetic intermediates for the preparation of nitrogen-containing organic compounds, because the azido functionality not only reacts with nucleophiles and electrophiles but also serves as a nitrene precursor on thermolysis or photolysis. In recent years trimethylsilyl azide has been used as a convenient reagent to introduce the azido moiety into organic molecules.[1-3] For instance, Nishiyama and Karigomi[4] reported that trimethylsilyl azide reacts with activated organic halides such as allylic and benzylic halides in hexamethylphosphoric triamide to provide the corresponding azides. Reactions of trimethylsilyl azide with

Table 1. Reaction of Trimethylsilyl Azide and Alkyl Halides in the Presence of Tetrabutylammonium Fluoride

	Substrate **1**	Product **2**	Temp. (°C)	Time (h)	Yield[a] (%)
a	$CH_3(CH_2)_{11}Cl$	$CH_3(CH_2)_{11}N_3$	50	28	95
b	p-$CH_3C_6H_4CH_2Cl$	p-$CH_3C_6H_4CH_2N_3$	r.t.	24	97
c	$(C_6H_5)_2CHCl$	$(C_6H_5)_2CHN_3$	40	120	>99
d			50	120	96
e	$C_6H_5(CH_2)_2Br$	$C_6H_5(CH_2)_2N_3$	r.t.	12	97
f			r.t.	18	>99
g			70	8	91
h	 (*exo*/*endo* = 98/2)	 (*exo*/*endo* = 9/91)	70	216	97[b]
i			r.t.	17	22[c]
j	$CH_3(CH_2)_{11}I$	$CH_3(CH_2)_{11}N_3$	r.t.	24	>99
k	 (96% o.p.)	 (96% *ee* [d])	70	24	79
l	$CH_3(CH_2)_{11}OTs$	$CH_3(CH_2)_{11}N_3$	r.t.	9	96
m			70	168	90

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[a] Yield of pure, isolated product unless otherwise stated; purity confirmed by ^1H NMR.

[b] Total yield of *exo*- and *endo*-isomers determined by ^1H NMR spectroscopy.

[c] Yield determined by ^1H NMR spectroscopy; two olefins [2-methyl-4-phenylbut-1-ene: ^1H NMR $\delta = 1.77$ (s, 3H), 2.29–2.42 (m, 2H), 2.64–2.78 (m, 2H), 4.74–4.74 (m, 2H) (17%); 2-methyl-4-phenylbut-2-ene: ^1H NMR $\delta = 1.72$ (s, 3H), 1.74 (s, 3H), 3.34 (d, $J = 7.3$ Hz, 2H), 5.33 (t, $J = 7.3$ Hz, 1H) (48%)] were formed by elimination reaction together with **2i**.

[d] Enantiomeric excess was determined after converting **2k** to 1-phenylethylamine (Pd—C catalyzed hydrogenation) using HPLC analysis [DAICEL Chiralcel OD using 1% propan-2-ol in hexane for elution (1 mL/min); (R)-(+)-form: 15.1 min and (S)-(−)-form: 20.3 min].

unactivated alkyl halides, however, hardly proceed because of its low nucleophilicity compared with alkali metal azide compounds. In 1986, Olah et al. developed a procedure for the preparation of tertiary azides from tertiary halides using trimethylsilyl azide in the presence of a catalytic amount of tin(IV) chloride.[5] This method, however, does not work well in the case of secondary halides. We have found that various unactivated alkyl halides, phosphates, and tosylates can be converted to the corresponding azides in high yields by the reaction with trimethylsilyl azide in the presence of fluoride anion under mild conditions.

$$\underset{\mathbf{1a-m}}{\mathrm{R\text{-}X}} \xrightarrow[22-99\%]{\substack{(\mathrm{CH_3})_3\mathrm{SiN_3}\,/\,(n\text{-}\mathrm{C_4H_9})_4\mathrm{NF} \\ \mathrm{THF,\ r.t.-70\,^\circ C,\ 12-216\ h}}} \underset{\mathbf{2a-m}}{\mathrm{R\text{-}N_3}}$$

Addition of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.5 equiv) to a mixture of trimethylsilyl azide (1.5 equiv) and an alkyl halide (1.0 equiv) triggered off the reaction. Representative results are shown in Table 1.

Reactions of primary alkyl bromide **1e**, alkyl iodide **1j**, and alkyl tosylate **1l** proceeded smoothly at ambient temperature. As for alkyl chlorides, reaction of *p*-methylbenzyl chloride (**1b**) afforded the product in high yield at ambient temperature, while a slightly elevated temperature was required for the complete reaction of unactivated primary alkyl chloride **1a**. Secondary alkyl bromide **1f** was also active enough to react at room temperature and even alkyl chloride **1d** yielded the corresponding azide as a sole product at 50 °C. The azidation reaction of cyclic secondary bromide **1g** using phase transfer catalysis was reported to give an unignorable amount of elimination product.[6] In contrast, the formation of the byproduct was suppressed in the present method to less than < 1%. Only in the case of tertiary bromide **1i**, however, were considerable amounts of elimination products obtained in addition to the desired azide **2i**. Stereochemistry of the present reaction was investigated by the reactions of *l*-(−)-menthyl tosylate (**1m**), 2-bromonorbornane (*exo*/*endo* = 98:2) (**1h**), and (*S*)-(−)-1-phenylethyl diethyl phosphate (**1k**). *l*-(−)-Menthyl tosylate (**1m**) gave only (+)-neomenthyl azide (**2m**), which showed that this substitution proceeds with complete inversion of configuration. Even for 2-bromonorbornane (*exo*/*endo* = 98:2) (**1h**), a high level of the inversion pathway was attained to give 2-azidonorbornane (*exo*/*endo* = 9:91) (**2h**). In particular, complete inversion of configuration was observed in the reaction at the stereogenic center of the benzylic position of **1k**.

Thus, the present method works well with alkyl bromides and chlorides, as well as alkyl iodides, tosylates, and phosphates. Because of its high tendency to yield competitive elimination products, unactivated alkyl halides, especially alkyl chlorides, have hardly been employed as starting materials in the reaction using alkali metal azides, even with the aid of phase transfer catalysts. In our new method, however, almost all kinds of alkyl halides including unactivated secondary halides and some tertiary halides afford the corresponding azides in very high yields under mild conditions. To the best of our knowledge, no other superior method has been reported so far for the preparation of optically active azides. This high efficiency of the trimethylsilyl azide–tetrabutylammonium fluoride system might be due to the high nucleophilicity of the azide moiety of the pentacoordinate silicate intermediate. Since reduction of the azide group to an amine constitutes a synthetically important process and the reaction is of wide applicability, the present method seems to be very useful for the synthesis of various nitrogen-containing compounds.

Unless otherwise stated, all commercial reagents were used without further purification. All manipulations of moisture-sensitive materials were conducted under Ar purified by passing through BASF-R3-11 catalyst by the use of standard Schlenk techniques. NMR spectra were taken with JEOL EX-270 (^{1}H 270 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were measured on JASCO IR-810 grating spectrometer. Optical rotations were measured on a JASCO DIP-360 spectrophotometer. HPLC analyses were conducted on a TOSOH CCPM equipped with CO-8000 injection unit and UV-8000 detector. Column chromatography was carried out by using Waco-gel C-200. Tetrahydrofuran was dried by distillation from sodium and benzophenone under Ar. Dodecyl chloride (**1a**)[7] and dodecyl *p*-toluenesulfonate[8] (**1l**) were prepared from dodecan-1-ol. 2-Chloro-4-phenylbutane (**1d**)[9] and 2-bromo-4-phenylbutane (**1f**)[10] were prepared from 4-phenylbutan-2-ol. (*S*)-(−)-1-Phenylethyl diethyl phosphate (**1k**) ($[\alpha]_D^{27}$ −43.8° (c = 2.45, $CHCl_3$); 96% optical purity[11]) was synthesized from (*S*)-(−)-1-phenylethanol (97% optical purity, Wako Pure Chemical

Table 2. IR and ^{1}H NMR Spectral Data for Products **2a–m**

Product	Lit. Data	IR (film) ν_{N_3} (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
2a (= **2j**, **2l**)	14	2094	0.88 (t, 3H, J = 6.6), 1.26–1.40 (m, 18H), 1.55–1.60 (m, 2H), 3.25 (t, 2H, J = 6.9)
2b	15	2098	2.36 (s, 3H), 4.28 (s, 2H), 7.20 (s, 5H)
2c	16	2098	5.70 (s, 1H), 7.26–7.42 (m, 10H)
2d (= **2f**)	17	2100	1.29 (d, J = 6.6, 3H), 1.73–1.84 (m, 2H), 2.65–2.76 (m, 2H), 3.40–3.47 (m, 1H), 7.17–7.32 (m, 5H)
2e	15	2088	2.88 (t, 2H, J = 7.3), 3.49 (t, 2H, J = 7.3), 7.20–7.34 (m, 5H)
2g	18	2090	1.20–1.93 (m, 10H), 3.30–3.77 (m, 1H)
2h	19	2098	*endo*-form: 1.00–2.37 (m, 10H), 3.86–3.93 (m, 1H) *exo*-form: 1.00–2.37 (m, 10H), 3.48–3.50 (m, 1H)
2i	20	2098	1.33 (s, 6H), 2.29–2.42 (m, 2H), 2.64–2.78 (m, 2H), 7.14–7.31 (m, 5H)
2k	21	2110	1.53 (d, J = 6.9, 3H), 4.61 (q, J = 6.9, 1H), 7.29–7.42 (m, 5H)
2m	22	2106	0.77–1.28 (m, 13H), 1.42–1.77 (m, 4H), 1.97–2.06 (m, 1H), 3.98 (br, 1H)

Industries Ltd.) as reported.[12] *l*-(−)-Menthyl tosylate (**1m**)[13] was prepared from *l*-(−)-menthol.

Alkyl Azides 2a–m; General Procedure:

In a 50 mL round-bottomed flask fitted with a three-way stopcock, an alkyl halide (1.0 equiv) and trimethylsilyl azide (1.5 equiv) were placed under Ar. To the resulting solution was added a 1.0 M solution of tetrabutylammonium fluoride in THF (1.5 equiv). After stirring the reaction mixture under the conditions given in Table 1, the resulting solution was removed under reduced pressure and the residue was chromatographed on silica gel with pentane as eluent, and evaporation of the solvent afforded the corresponding azides **2a–m**.

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