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New Methods and Reagents in Organic Synthesis. 28.[1] A Convenient and Efficient Preparation of Trimethylsilyldiazomethane ($TMSCHN_2$) using Diphenyl Phosphorazidate (DPPA)

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The stable and safe compound trimethylsilyldiazomethane ($TMSCHN_2$), which is useful for organic synthesis, was prepared in high yield by diazo-transfer reaction of trimethylsilylmethylmagnesium chloride with diphenyl phosphorazidate [DPPA, $(C_6H_5O)_2P(O)N_3$].

Keywords——trimethylsilyldiazomethane; diphenyl phosphorazidate; trimethylsilylmethylmagnesium chloride; diazo-transfer reaction; nuclear magnetic resonance spectrum; Widmer fractionating column

Previously, we have reported that trimethylsilyldiazomethane ($TMSCNH_2$, **1**), which is a stable and safe substitute for hazardous diazomethane, can be effectively used for the Arndt–Eistert synthesis,[2] homologation of ketones[3] and aldehydes,[4] and methyl esterification of carboxylic acids,[5] as depicted in Chart 1.

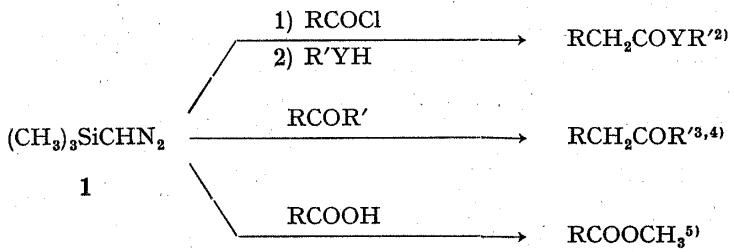
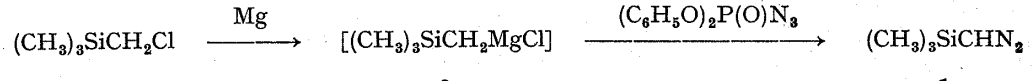


Chart 1

Unfortunately, the lack of ready availability of **1** has prevented wide use of this reagent in organic synthesis. The known multi-step preparations[6,7] of **1** from chloromethyltrimethylsilane (**2**) are very tedious and result in low yield, though we[2b] slightly improved Seyferth's method.[6] Recently, Barton *et al.*[8] have reported a short-step preparation of **1**, though in only 38% yield, by a diazo-transfer reaction of *p*-toluenesulfonyl azide(TsN_3) with trimethylsilylmethyl lithium. We now wish to describe a convenient and efficient preparation of **1** by means of a modified diazo-transfer reaction as shown in Chart 2.



2 **3** **1**

Chart 2

First, we chose the combination of trimethylsilylmethylmagnesium chloride (**3**)[9] and TsN_3 for this reaction since the preparation of the former from **2** was easier than that of trimethylsilylmethyl lithium[8] and the latter is often used as a diazo-transfer reagent.[10] Treatment of **3** with TsN_3 in diethyl ether, however, gave **1** in only 17% yield. Changing the azide from TsN_3 to commercially available diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[11]

Table I. Reaction of Trimethylsilylmethylmagnesium Chloride (3) with Azides

Run	Solvent	Azide	Conditions for preparation of Grignard reagent		Conditions for diazo-transfer reaction		Yield[a] of 1 (%) (Purity, w/w%)
			Temp. (°C)	Time (h)	Temp. (°C)	Time (h)	
1	Et_2O	TsN_3	Room temp.	19	0	6	17
					Room temp.	34	(41)[b]
2	Et_2O	DPPA	Room temp.	20	0	2	85
					Room temp.	3	(70)[b]
3	Et_2O	DPPA	Room temp.	3	0	2	79
							(In hexane)[c]
4	n-Bu_2O	DPPA	30	3	0	2	58
			Room temp.	17	Room temp.	3	(96)[d]
5	n-Bu_2O	DPPA	30	3	0	1.5	55
							(92)[d]
6	THF	DPPA	Room temp.	3	0	2	58
							(In hexane)[e]

a) Based on DPPA. *b*) Mixture of **1** and diethyl ether. *c*) Concentration: 2.25 mmol/ml. *d*) Mixture of **1** and di-*n*-butyl ether. *e*) Concentration: 0.7 mmol/ml.

had a significant effect on the yield of **1**. Thus, the reaction of **3** and DPPA proceeded smoothly to give **1** in excellent yield compared with the previous procedures.

As shown in Table I, the reaction proceeded within 5 hours and diethyl ether was found to be the best reaction solvent, though di-*n*-butyl ether or tetrahydrofuran could be used. $TMSCHN_2$ (**1**) containing diethyl ether was easily converted to its hexane solution free from the ether (run 3) as described in "Experimental." This solution was stable and could be stored without decomposition for periods exceeding 6 months at room temperature with protection from light. The use of di-*n*-butyl ether as a reaction solvent increased the purity of **1** above 90%, though the yields were moderate.

Since the stable and safe compound $TMSCHN_2$ (**1**) can be easily prepared by means of the modified diazo-transfer reaction of **3** with DPPA, this reagent may be widely used for organic synthesis. Further work on the synthetic utility of **1** as well as on the generality of DPPA as a diazo-transfer reagent is now under way in our laboratories.

Experimental

^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL MH-100 spectrometer. Reactions were carried out under an argon atmosphere. For concentration and distillation, a Widmer fractionating column was used. Tetrahydrofuran and diethyl ether were dried by distillation from benzophenone ketyl and lithium aluminum hydride, respectively. Di-*n*-butyl ether was dried over sodium wire. DPPA used for reactions was obtained from Daiichi Pure Chemicals Co., Ltd.

Reaction of Trimethylsilylmethylmagnesium Chloride (3) with TsN_3——Run 1: Trimethylsilylmethylmagnesium chloride (**3**),[9] prepared from chloromethyltrimethylsilane (**2**, 4.41 g, 36 mmol) and magnesium turnings (1.05 g, 43.2 mg-atom) in diethyl ether (25 ml), was added dropwise to TsN_3 (6.38 g, 32.4 mmol) in diethyl ether (100 ml) below 0°C. The mixture was stirred at 0°C for 6 h, then at room temperature for 34 h. The resulting precipitate was filtered off and washed with diethyl ether. The combined organic layer was washed with cold 1% aqueous sodium hydroxide solution, and cold water, and dried over sodium sulfate. Diethyl ether was removed at atmospheric pressure with bath temperature below 45°C. The remaining solution was distilled under reduced pressure (15 mmHg) at 0—30°C (bath temperature) to afford a yellow solution, which was further concentrated at atmospheric pressure to give a yellow mixture (1.51 g) of **1** and diethyl ether. NMR analysis of the mixture showed that the yield of **1** was 17% (41 w/w% purity). NMR of **1** (δ in C_6H_6): -0.03 (s, $SiCH_3$), 2.23 (s, CHN_2). NMR of diethyl ether (δ in C_6H_6): 1.09 (t, $J=6.8$ Hz, CH_3CH_2), 3.27 (q, $J=6.8$ Hz, CH_3CH_2).

Reaction of Trimethylsilylmethylmagnesium Chloride (3) with DPPA——(i) Run 2: Grignard reagent (**3**), prepared from **2** (3.68 g, 30 mmol) and magnesium turnings (0.88 g, 36 mg-atom) in diethyl ether (20 ml), was added dropwise to DPPA (7.43 g, 27 mmol) in diethyl ether (40 ml) below 0°C. The mixture was stirred

at 0°C for 2 h, then at room temperature for 3 h. After cooling to 0°C, the mixture was treated with ice-water. The resulting precipitate was filtered off and washed with diethyl ether. The combined organic layer was washed with cold water, dried over sodium sulfate, and then distilled as described above for run 1 to give a mixture (3.76 g) of **1** and diethyl ether. NMR analysis of the mixture showed that the yield of **1** was 85% (70 w/w% purity).

(ii) Run 3: The reaction was repeated as described for run 2 to give a mixture (*ca.* 5 ml) of **1** and diethyl ether. Hexane (10 ml) was added to the mixture. The solution was concentrated at atmospheric pressure to give a yellow hexane solution (9.49 ml) of **1**. NMR analysis of the solution with dibenzyl as an internal standard showed that the yield of **1** was 79% (concentration: 2.25 mmol/ml) and no diethyl ether was present.

The reaction times are shown in Table I.

(iii) Run 4: The reaction was repeated as described for run 2 using di-*n*-butyl ether as a solvent. After completion of the reaction, the mixture was worked up as usual. The crude product was distilled under reduced pressure (15 mmHg) below 45°C (bath temperature) to afford a yellow liquid, which was further distilled under reduced pressure (90—103 mmHg) at 87—94°C (bath temperature) to give a yellow mixture (1.85 g) of **1** and di-*n*-butyl ether. NMR analysis of the mixture showed that the yield of **1** was 58% (96w/w% purity). NMR of **1** (δ in C_6H_6): −0.03 (s, $SiCH_3$), 2.23 (s, CHN_2). NMR of di-*n*-butyl ether (δ in C_6H_6): 0.73—1.70 (m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 3.29 (t, J=6 Hz, CH_2O).

The reaction times are shown in Table I.

(iv) Run 5: The reaction was carried out as described for run 4 to give a mixture (1.86 g) of **1** and di-*n*-butyl ether (yield: 55%, purity: 92 w/w%).

The reaction times are shown in Table I.

(v) Run 6: The reaction was repeated as described for run 3 on one-third scale using tetrahydrofuran as a solvent. After completion of the reaction, ice-water was added to the mixture, then it was distilled under reduced pressure (15 mmHg) at 0—30°C (bath temperature) to give a mixture of **1** and tetrahydrofuran. Hexane (7 ml) was added to the mixture and the whole was washed well with cold water to give a yellow hexane solution (7.3 ml) of **1**. NMR analysis of the solution showed that the yield of **1** was 58% (concentration: 0.7 mmol/ml) and no tetrahydrofuran was present.

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