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Si-BEZA – catalytic pyridinium triflate: a mild and powerful agent for the silylation of alcohols

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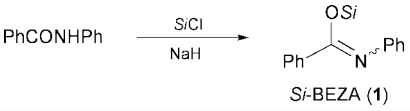
A highly efficient method of silylation using a novel agent, *Si*-BEZA (silylbenzamide), together with a pyridinium triflate catalyst was developed, wherein a variety of silyl groups can be introduced into sterically crowded alcohols under mild conditions.

The silylation of alcohols is indispensable for organic syntheses as the most reliable protective method.[1–3] Despite the well-established method, there still remains a strong need for improved efficiency. In view of the restrictions involved during elaborate syntheses of complex compounds, the development of mild and efficient silylation methods has become increasingly important for: (1) smooth silylation against sterically crowded and functionalized alcohols under mild conditions, (2) introduction of bulky silyl groups into unreactive alcohols, and (3) mild alternatives to some bulky-sized silyl triflates, one of the most powerful agents, because the preparation of silyl triflates sometimes requires tedious procedures.

Thus, we were prompted to explore a more efficient system. Consistent with the interest in the mild and effective silylations,[4,5] we wish to introduce here a novel, efficient, and powerful silylation agent, *Si*-BEZA [**1**, *O*-(trisubstituted silyl)benzamide] together with catalytic $PyH^{+}\cdot OTf^{-}$ (**2**, pyridinium triflate). The present method is of general interest, because it covers several types of silylations [TMS, TES, TBMDS, TIPS (triisopropylsilyl), and TBDPS (*tert*-butyldiphenylsilyl)] against sterically crowded, functionalized, aliphatic, allylic, and phenolic hydroxy groups under mild conditions.

Preparation and handling of both *Si*-BEZA (**1a–e**) and $PyH^{+}\cdot OTf^{-}$ (**2**) are quite easy (Table 1).† Compared with the

Table 1 Preparation of *Si*-BEZA[a]

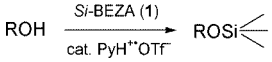


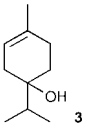
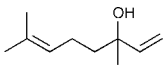
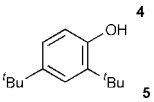
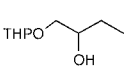
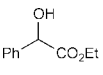
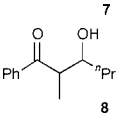
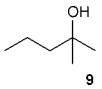
Si-BEZA (**1**)

Si-BEZA (**1**)	Yield (%)	Purification
TMS- (**1a**)	54	Distillation[b]
TES- (**1b**)	48	Distillation[b]
TBDMS- (**1c**)	83	Recrystallization[c]
TIPS- (**1d**)	74	Chromatography[d]
TBDPS- (**1e**)	74	Chromatography[d]

[a] In MeCN at 20 to 25 °C for 10 h. Molar ratio; benzamide:*Si*Cl:NaH = 1.0:1.0:1.0. [b] By Kügelrohr. [c] From hexane. [d] Use of neutral alumina.

Table 2 Silylation of alcohols using *Si*-BEZA with $PyH^{+}\cdot OTf^{-}$ catalyst[a]



Alcohol	*Si*-BEZA (**1**)	cat. $PyH^{+}\cdot OTf^{-}$ (equiv.)	Solv.	Temp./°C	Time/min	Yield[b] (%)
 3	**1a** (TMS)	0.05	THF	25	5	95
	1b (TES)	0.1	THF	25	10	99
	1c (TBDMS)	0.2	THF	50	150	96
 4	**1c**	0.2	THF	25	30	99
	1d (TIPS)	0.2	THF	50	840	97
 5	**1a**	0.05	BTF[c]	25	5	99
	1b	0.1	BTF[c]	25	10	99
	1c	0.2	BTF[c]	50	60	99
	1c	0.2	THF	50	60	10 ~ 20
 6	**1e** (TBDPS)	0.1	THF	25	30	98
 7	**1e**	0.1	THF	25	30	99
 8	**1e**	0.1	THF	25	60	90
 9	**1e**	0.2	THF	50	1200	23
	1e	0.4	THF	Reflux	2400	83[d]

[a] Molar ratio; alcohol:**1** = 1.0:1.5. [b] Isolated. [c] Benzotrifluoride. [d] 5.0 equiv. of **1e** was used.

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corresponding silyl triflates (especially, TBDMS, TIPS, and TBDPS), **1c–e** are considerably moisture-insensitive. Without catalyst **2**, the reaction did not proceed. Namely, *Si*-BEZA (**1**), itself, is adequately stable and **2** acts as a useful trigger. An analogous pyridinium salt, PPTS did not promote the silylation. Diphenylammonium triflate[6] is also a good catalyst, we chose **2** due to its convenience. Careful NMR experiments of **1c** revealed that the structure was not an *N*-TBDMS amide but a *O*-TBDMS imidate. The high silylation potential originated from the strong driving force of the reactive *O*-silyl imidate transformed into thermodynamically stable benzamide with the release of the silyl moiety. Table 2 lists the results of the silylation of sterically crowded (silylation-resistant) and/or functionalized alcohols.‡ Indeed, silylation-resistant terpinen-4-ol (**3**), linalool (**4**), and 2,4-di-*tert*-butylphenol (**5**) were successfully silylated in excellent yield under mild conditions. In the case of **5**, BTF solvent was more suitable than THF. Several functionalized alcohols, *i.e.*, allylic **4**, tetrahydropyranyl **6**, ester **7** and aldol **8** tolerated the present conditions. To our knowledge, this is the first example of the bulky TBDPS group being practically introduced into a tertiary alcohol **9**.[7]

The present method has another practical merit of easy work-up procedure. After the reaction was completed, solid benzanilide was easily filtered from the mixture containing the desired silyl ester and/or separated by standard column chromatography. Two parallel experiments for silylations using TIPS-BEZA (**1d**) with linalool (**4**) and *o*-cresol (**10**) demonstrate that the ability of **1d** is considered to rival or surpass the most powerful method using *Si*OTfs–2,6-lutidine[8] under standard conditions (Figs. 1 and 2). Small amounts of polymerization was found to occur, when linalool (**4**) was subjected to silylation using TIPSOTf–2,6-lutidine (Fig. 1).

In conclusion, this original reagent, *Si*-BEZA (**1**), with catalytic PyH$^+$·OTf$^-$ (**2**) is structurally simple, yet, exhibits powerful and highly efficient silylations.

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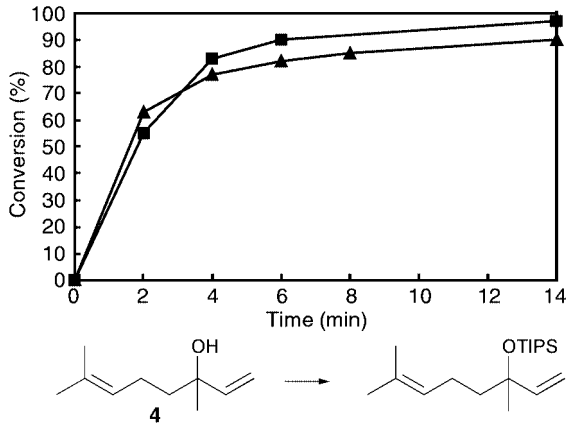

Fig. 1 Comparable experiments of triisopropylsilylation of linalool (**4**) conversion (GC%) ■: TIPS-BEZA (**1d**; 1.5 equiv.)–PyH$^+$·OTf$^-$ (**2**; 0.2 equiv.)–THF, 50 °C. ▲: TIPSOTf (1.5 equiv.)–2,6-lutidine (2.5 equiv.)–DMF, 50 °C.

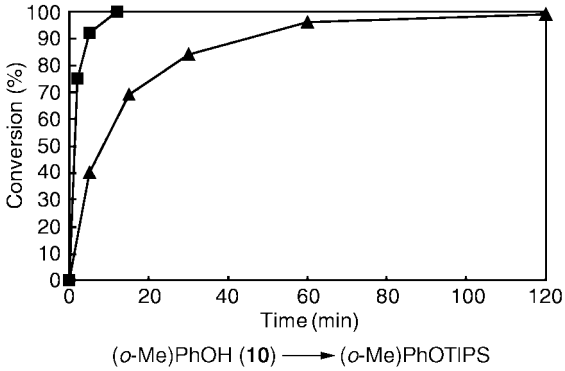

Fig. 2 Comparable experiments of triisopropylsilylation of *o*-cresol (**10**) conversion (GC%) ■: TIPS-BEZA (**1d**; 1.5 equiv.)–PyH$^+$·OTf$^-$ (**2**; 0.2 equiv.)–BTF, 25 °C. ▲: TIPSOTf (1.5 equiv.)–2,6-lutidine (2.5 equiv.)–CH_2Cl_2, 25 °C

Notes and references

† Benzanilide was added to a stirred suspension of NaH (1.0 equiv.) in MeCN (*ca.* 0.5 M) at 0–5 °C and stirred at rt for 1 h. To the mixture was added silyl chloride (1.0 equiv.) at 0–5 °C, followed by stirring at room temp. for 2–10 h. After evaporation of MeCN, the residue was extracted with hexane, and NaCl and the small amount of benzanilide remaining were removed. Hexane was evaporated to give crude *Si*-BEZA (**1a–e**), which was purified by distillation (TMS, TES), recrystallization from hexane (TBDMS), or neutral alumina column chromatography with hexane–ether (*ca.* 20 : 1) (TIPS, TBDPS). TfOH was added to a stirred solution of pyridine (1.0 equiv.) in toluene at 0–5 °C and stirred at rt for 15 min. Toluene was evaporated to give the crude solid, which was washed with ether to give pure PyH·OTf$^-$. TMS-BEZA (**1a**); yellow oil; 190 °C (oven temp.) at 0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.26–0.69 (9H, br s), 6.62–8.16 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.22, 120.21—123.89 (br), 126.98—131.48 (br), 148.01. TES-BEZA (**1b**); yellow oil; 200 °C (oven temp.) at 0.2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07–1.41 (15H, m), 6.50–8.12 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.01, 6.56, 120.17–131.78 (br), 148.00. TBDMS-BEZA (**1c**); Colorless crystals; mp 73–74 °C; ^{1}H NMR (300 MHz, −40 °C, $CDCl_3$) δ −0.29 (3.7H, s), 0.39 (2.3H, s), 0.79 (5.6H, s), 0.99 (3.4H, s), 6.68–7.99 (10H, m); (20 °C, $CDCl_3$) δ −0.52–1.57 (15H, m), 6.53–8.36 (10H, m); (140 °C, d^7-DMF) 0.16 (6H, s), 0.94 (9H, s), 6.78–6.86 (2H, m), 6.91–6.99 (1H, m), 7.15–7.24 (2H, m), 7.27–7.40 (3H, m), 7.54–7.65 (2H, m). ^{13}C NMR (100 MHz; −40 °C, $CDCl_3$) δ −4.89, −4.23, 17.87, 18.19, 25.36, 25.73, 120.88, 122.14, 122.51, 123.34, 127.62, 128.00, 128.26, 128.33, 128.89, 129.56, 129.77, 130.74, 131.51, 135.16, 146.95, 148.29, 154.28, 156.40; (20 °C, $CDCl_3$) δ −4.28, 18.26, 25.79, 120.18–123.72 (br), 126.61–130.79 (br), 147.87 (not *amide* but *imidate*). ^{29}Si NMR (80 MHz; −40 °C, TMS) δ 23.10, 23.25. ^{15}N-enriched TBDMS-BEZA (**1c**) was prepared from ^{15}N-aniline (>99% purity). ^{15}N NMR of this sample (40 MHz; −40 °C, CH_3NO_2) δ −123.43, −123.29. TIPS-BEZA (**1d**); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–1.61 (21H, m), 6.63–7.62 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.43, 18.16, 120.73–122.81 (br), 127.80, 128.90, 129.46, 129.81, 148.47. TBDPS-BEZA (**1e**); pale yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–1.46 (9H, m), 6.24–7.90 (20H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.59, 27.30, 120.78, 122.49, 127.39, 127.86, 128.70, 129.40, 129.51, 130.01, 133.08, 135.17, 135.54, 147.60, 154.76.

‡ A typical procedure. TBDMS-BEZA (**1c**; 476 mg, 1.5 mmol) was added to a stirred solution of terpinen-4-ol (**3**; 154 mg, 1.0 mmol) and PyH·OTf$^-$ (46 mg, 0.2 mmol) in THF (2.0 cm^3) at 20–25 °C. After stirring at 50 °C for 2.5 h, the mixture was quenched with water and extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane) to give 1-(*tert*-butyldimethylsiloxy)-1-isopropyl-4-methyl-3-cyclohexene (257 mg, 96%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 0.88 (3H, d, *J* 6.7 Hz), 0.89 (3H, d, *J* 6.7 Hz), 1.61–2.30 (10H, m), 5.20–5.25 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.33, −2.04, 17.06, 17.15, 18.65, 23.07, 26.00, 28.78, 32.23, 33.79, 35.92, 75.72, 119.40, 133.49.

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