Journal of Chromatography, 116 (1976) 315–320

CHROM. 8631

SEARCH FOR NEW SILYLATING AGENTS

I. COMPARATIVE GAS–LIQUID CHROMATOGRAPHIC EVALUATION OF TRIMETHYLSILYL DERIVATIVES OF PIPERIDINE, PYRROLIDINE AND MORPHOLINE

RYSZARD PIEKOS, KRZYSZTOF OSMIAŁOWSKI, KRZYSZTOF KOBYŁCZYK and JANUSZ GRZYBOWSKI

Institute of Chemistry and Analytics, Medical Academy, 80-416 Gdansk (Poland)

(First received April 29th, 1975; revised manuscript received July 15th, 1975)

SUMMARY

The effectiveness of the N-trimethylsilyl derivatives of piperidine (TMSPI), pyrrolidine (TMSPY) and morpholine (TMSM) as silylating reagents has been compared for 16 representative organic compounds having hydroxyl, carboxyl, amino, imino and mercapto groups as substituents. Conventional silylating agents such as N,O-bis(trimethylsilyl)acetamide (BSA), trimethylsilyldiethylamine (TMSDEA) and N-trimethylsilylimidazole (TMSIM), were used as reference reagents. In general, TMSPI and TMSPY were stronger silyl donors than TMSDEA and TMSIM, and in some instances were as effective as BSA.

INTRODUCTION

Silylation of various classes of organic compounds having active hydrogen atoms is well recognized as a rapid and convenient method for preparing trimethylsilyl (TMS) derivatives amenable to gas–liquid chromatography (GLC). Commonly used silylating reagents involve trimethylchlorosilane (TMCS), hexamethyldisilazane (HMDS), trimethylsilyldiethylamine (TMSDEA), N-trimethylsilylimidazole (TMSIM), N,O-bis(trimethylsilyl)acetamide (BSA), N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA), as well as mixtures of two or more silylating agents, *e.g.*, TRI-SIL. These reagents are characterized in an excellent monograph[1] and recent surveys[2,3]. Other silylating agents, reviewed by Wurst[4], appear to be of minor importance.

The most powerful silyl donor appears to be BSA, which was first reported by Birkofer *et al.*[5] and used for silylation by Klebe *et al.*[6]. However, as we have found, BSA cannot be used as a universal silylating agent for silylation of all classes of organic compounds.

In this paper, the silylating strengths of the N-trimethylsilyl derivatives of piperidine (TMSPI), pyrrolidine (TMSPY) and morpholine (TMSM), which were

first reported by Birkofer *et al.*[7] in 1960, have been compared. Two of them (TMSPI and TMSPY) are superior to TMSDEA and TMSIM and, for some compounds, to BSA.

EXPERIMENTAL

Materials

All the silylating agents used were prepared by known procedures[6–9]. Their physical constants (b.p. and n_D^{20}) were consistent with the literature values listed in Table I, and they were chromatographically homogeneous (GLC).

TABLE I

PHYSICAL CONSTANTS OF THE SILYLATING REAGENTS

Reagent	*Abbreviation*	*Molecular formula*	*Molecular weight*	*Boiling point (°C/mm)*	n_D^{20}	*Reference*
N,O-Bis(trimethylsilyl)-acetamide	BSA	$C_8H_{21}ONSi_2$	204.44	71–73/35	—	6
Trimethylsilyldiethyl-amine	TMSDEA	$C_7H_{19}NSi$	145.32	127	1.4109	8
N-Trimethylsilyl-imidazole	TMSIM	$C_6H_{12}N_2Si$	140.26	91/12	1.4756	7
N-Trimethylsilyl-piperidine	TMSPI	$C_8H_{19}NSi$	157.33	161/760	1.4423	7
N-Trimethylsilyl-pyrrolidine	TMSPY	$C_7H_{17}NSi$	143.31	142/760	1.4333	7
N-Trimethylsilyl-morpholine	TMSM	$C_7H_{17}ONSi$	159.31	160	1.4407	9

4-Chloro-3,5-dimethylphenol (Fluka, Buchs, Switzerland), *tert.*-amyl alcohol (Schuchardt, Munich, G.F.R.), cetyl alcohol (Riedel-De Haen, Seelze–Hannover, G.F.R.), *sec.*-butanol (Polskie Odczynniki Chemiczne, P.O.Ch., Gliwice, Poland), benzenethiol (Koch–Light, Colnbrook, Great Britain), phthalimide (P.O.Ch.), *p*-toluenesulphonamide (P.O.Ch.), dimethylformamide (DMF) (Reakhim, U.S.S.R.) and cholecalciferol (vitamin D_3) (Koch–Light) were pure commercial products and were used as supplied. 2,4,6-Tri-*tert.*-butylphenol (Serva, Heidelberg, G.F.R.), D-xylose (E. Merck, Darmstadt, G.F.R.), ethanolamine (Carlo Erba, Milan, Italy), aniline (P.O.Ch.), pyridine (P.O.Ch.) and acetonitrile (Fluka) were of analytical grade. Cholesterol was the official Polish product, and the remaining reagents were of pharmacopoeial grade.

Pyridine was dried over potassium hydroxide and distilled before being used; DMF and acetonitrile were dried with molecular sieve 4A.

Procedure

In order to evaluate the silylating strength of the reagents used, they were allowed to react with 16 representative compounds having hydroxyl, carboxyl, imino, amino or mercapto groups, or mixtures of these groups. The conditions adopted were such as to incompletely silylate the compounds, and are specified in Table II.

TABLE II

SILYLATION CONDITIONS AND RESULTS

No.	Silylated compound	Reaction conditions				Retention time (sec)		Percentage conversion with silylating reagent					
		Time (min)	Temp. (°C)	Solvent	Molar excess reagent	Compound	TMS deriv.	BSA	TMSPI	TMSPY	TMSIM	TMSDEA	TMSM
1	Cetyl alcohol	3	20	Pyridine	10	126	180	88.8	85.1	97.1	96.8	13	72.4
2	*sec.*-Butanol	300	30	Acetonitrile	10	84	132	100	100	100	100	62.2	100
3	*tert.*-Amyl alcohol	180	60	Pyridine	10	72	84	86	72.6	85.4	89	80	70.4
4	4-Chloro-3,5-dimethylphenol	1	20	Pyridine	2	258	321	100	100	100	99.5	93.5	86.1
5	2,4,6-Tri-*tert.*-butylphenol	600	Reflux	Acetonitrile	10	105	213	100	85.4	91.4	59.5	100	20.2
6	Benzenethiol	1	20	Acetonitrile	10	78	270	100	100	13.8	73.2	100	95.3
7	Cholesterol	30	50	Pyridine	10	600	780	86	100	100	100	91	94.5
8	D-Xylose	120	60	Pyridine	40	175	x*	60.9	48	41.6	45.4	15.9	12.0
9	Vitamin D_3	15	20	Pyridine	10	162	150**	74.5	61.9	98.6	97.3	62.4	38.4
10	Salicylic acid	10	30	Pyridine	20	48	77	0	0	23.3	4.7	0	0
							89***	98.2	98.5	75	86.5	97.6	97.7
11	Ethanolamine	180	60	Pyridine	30	—	120§	100	70	3	Ill-defined peak	2	100
12	Aniline	360	30	Acetonitrile	20	60	156	19.4	6.1	78.9	100	52.5	89
13	*p*-Acetophenetidine	60	60	Pyridine	10	114	84	99.5	7.1	0	0	53	1.5
14	Phthalimide	1080	20	Dimethylformamide	10	39	54	97.8	93.7	41.2	71	96	91.3
15	*p*-Toluenesulphonamide	360	30	Acetonitrile	20	111	129	50 (1TMS) 50 (2TMS)	100	91.3	81.8	100	100
16	5,5-Diethylbarbituric acid	2	20	Dimethylformamide	20	78	108	100	37.7	16.2	0	91.2	66.2

* Four peaks appeared, apparently due to mono-, di-, tri- and tetrasilylated derivatives; the percentage conversion was based on the last-named derivative.

** The main peak was accompanied by another one, probably due to vitamin D_3 as impurity[10].

*** The two values refer to the mono- and disilylated derivatives.

§ Trisilyl derivative.

Reactions were carried out, with exclusion of atmospheric moisture, in 10-ml rubber-stoppered vials. To 0.1–0.5 ml of a 0.2–1.0 *M* solution of the organic compound in pyridine, DMF or acetonitrile was added 0.1–0.5 ml of the silylating agent from a micro-burette. The mixture was then shaken vigorously for about 30 sec and allowed to stand for the period indicated in Table II. With compounds having sterically hindered functional groups, silylation was performed at 30, 50 or 60° to accelerate the conversion (*cf.* Table II); in these instances, pressure in the vial was reduced by means of a syringe.

From 0.1 to 0.8 μl of the resulting reaction mixture was injected into the gas chromatograph.

GLC conditions

A Pye series 104 gas chromatograph with a flame-ionisation detector was used, the chromatograms being recorded on a Philips PM 8010 chart recorder. Peak areas were calculated by multiplying the peak width at half height by the maximum peak height.

Two glass columns were used: (1) a 1.5 m × 4 mm I.D. column packed with 3% of OV-1 on 100–120-mesh Diatomite CQ; and (2) a 0.9 m × 4 mm I.D. column packed with 3% of SE-30 on the same support. Argon was used as carrier gas, the attenuation factor was 2×10^4 or 5×10^4, and the remaining operating conditions were as in Table III.

The relative retention times of the silylating agents and of the parent amines were determined by using the 0.9-m column. The operating conditions were: column temperature, 85°; detector temperature, 220°; injection-port temperature, 210°; carrier gas, argon at 75 ml/min. Under these conditions, the absolute retention time of imidazole exceeded 455 sec.

TABLE III

OPERATING CONDITIONS FOR GLC OF SILYL DERIVATIVES

*No.**	*Number of columns*	*Argon flow-rate (ml/min)*	*Column Temp. (°C)*	*Detector temp. (°C)*	*Injection-port temp. (°C)*
1	2	78	190	240	200
2	2	20	50	80	45
3	1	30	80	210	105
4	1	30	140	220	170
5	1	30	190	220	210
6	2	16	120	230	135
7	2	75	240	250	225
8	2	30	190	240	185
9	2	71	240	250	230
10	2	75	160	240	180
11	1	25	115	150	130
12	2	16	130	230	160
13	2	30	190	240	195
14	2	25	180	220	210
15	2	6.3	255	270	240
16	2	20	195	240	175

* The numbers of the compounds correspond to those in Table II.

RESULTS AND DISCUSSION

The results of silylation are shown in Table II. Of particular note is the high silyl-donor effectiveness of TMSPI and TMSPY in the silylation of the hydroxyl groups of alcohols, phenols, cholesterol, vitamin D_3, and the silylation of *p*-toluenesulphonamide and phthalimide (TMSPI only). These two reagents are almost as effective as, and in some instances [*e.g.*, cholesterol, vitamin D_3 (TMSPY) and aniline (TMSPY)] more effective than BSA. TMSM is excellent for the silylation of *sec.*-butanol, benzenethiol, cholesterol, salicylic acid, ethanolamine and *p*-toluenesulphonamide, and TMSPY appears to be suitable for the selective silylation of salicylic acid. This reagent, as well as TMSPI and TMSM, selectively silylated the sulphonamide function to give monosilylated *p*-toluenesulphonamide in excellent yields; under the same conditions, silylation with BSA gave an equimolar mixture of mono- and disilylated products.

The three new reagents are readily soluble in organic solvents, as are their desilylated products, and have low boiling points and low molecular weights. Further, they may be used without any solvent, as many organic compounds are soluble in them at ambient or slightly elevated temperature. On chromatograms, they give single, sharp peaks with short retention times (BSA usually gives a multiple peak, owing to the extreme ease with which it undergoes hydrolysis). TMSIM is less effective and tails badly. The relative retention times of TMSPY, TMSPI and TMSM are shorter than those of TMSIM and BSA (*cf.* Table IV), and the retention times of the parent amines are markedly shorter than that of monosilylacetamide (MSA), a partial desilylation product of BSA.

TABLE IV

RELATIVE RETENTION TIMES (t_r) OF THE SILYLATING REAGENTS AND THEIR PARENT AMINES

No.	*Silylating reagent*	t_r	*Amine*	t_r
1	BSA	1.00*	Monosilylacetamide***	1.00
2	TMSDEA	0.43	Diethylamine	0.23
3	TMSIM	1.08**	Imidazole	—
4	TMSPI	0.83	Piperidine	0.48
5	TMSPY	0.59	Pyrrolidine	0.35
6	TMSM	0.81	Morpholine	0.52
7	HMDS	0.65		

* Absolute retention time, 111 sec.
** Tails badly.
*** Partial desilylation product of BSA; absolute retention time, 87 sec.

There seems to be a close correlation between the pK_b values of the parent amines and the silyl-donor strength of their N-silyl derivatives; for example, the pK_b values of piperidine, pyrrolidine, diethylamine and morpholine are 2.88, 2.73, 3.07 and 5.3, respectively, and the silylating strengths of their TMS derivatives decrease roughly in the same order.

In general, TMSPI is a very promising silylation reagent, which deserves further investigation.

There are also some economic aspects that make TMSPY and TMSPI preferable to TMSIM and BSA. First, the parent amines are cheaper than imidazole, and secondly, the method of preparation of TMSPY and TMSPI is much simpler than that of BSA and the yields are higher.

REFERENCES

1 A. E. Pierce, *Silylation of Organic Compounds*, Pierce Chemical Co., Rockford, Ill., 1968.
2 V. Miller and V. Pacáková, *Chem. Listy*, 67 (1973) 1121.
3 *Papier-Säulen-Dünnschicht-Gas-Chromatographie*, Macherey, Nagel & Co., Düren, G.F.R., 1973, p. 27.
4 M. Wurst, *Chem. Listy*, 65 (1971) 267.
5 L. Birkofer, A. Ritter and W. Giessler, *Angew. Chem.*, 75 (1963) 93.
6 J. F. Klebe, H. Finkbeiner and D. M. White, *J. Amer. Chem. Soc.*, 88 (1966) 3390.
7 L. Birkofer, P. Richter and A. Ritter, *Chem. Ber.*, 93 (1960) 2804.
8 R. O. Sauer and R. H. Hasek, *J. Amer. Chem. Soc.*, 68 (1946) 241.
9 R. A. Pike and R. L. Schank, *J. Org. Chem.*, 27 (1962) 2190.
10 J. G. Bell and A. A. Christie, *Analyst (London)*, 98 (1973) 268.