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Note

Search for new silylating agents

II. Comparative gas–liquid chromatographic evaluation of N-trimethylsilyl-acetanilide and its *p*-ethoxy derivative

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In the search for new silylating agents, we considered the N-trimethylsilyl derivatives of acetanilide and *p*-ethoxyacetanilide, which hydrolyzed rapidly upon exposure to air moisture and hydrolyzed vigorously in contact with water. These features were indicative of a high reactivity of the N-silyl moiety. Preliminary tests confirmed our expectations and encouraged us to carry out a more thorough study on the silylation strength of these two reagents.

Both reagents belong to the group of silylated derivatives of acetamide, which includes the commonly used reagent N,O-bis(trimethylsilyl)acetamide (BSA). N-Trimethylsilylacetanilide (TMSA) was first reported by Klebe and Bush[1] in 1965. Its *p*-ethoxy congener, N-trimethylsilyl-*p*-ethoxyacetanilide (TMSEA), was prepared in this laboratory by silylation of *p*-ethoxyacetanilide with trimethylchlorosilane in the presence of triethylamine.

As in Part I[2], the silylating strengths of both reagents were estimated by using BSA, N-trimethylsilylimidazole (TMSIM) and trimethylsilyldiethylamine (TMSDEA) as references. As substances for silylation, 15 organic compounds carrying primary, secondary, tertiary and phenolic hydroxyl groups, as well as carboxylic, thiophenolic, amine, amide and imide functions, were used.

EXPERIMENTAL

Materials

TMSA was obtained as follows. To 27 g (0.2 moles) of acetanilide dissolved in 200 ml of benzene, 20.2 g (0.2 moles) of triethylamine was added followed by 54.3 g (0.5 moles) of trimethylchlorosilane, which was added dropwise with stirring. The reagent mixture was refluxed for 3 h, cooled and a precipitate of $(C_2H_5)_3N \cdot HCl$ was filtered off. The filtrate was evaporated under reduced pressure to remove benzene and the oily residue obtained was fractionally distilled to give the desired compound: b.p. 222°; n_D^{20} 1.4986; d_4^{20} 0.9745 g·cm^{-3}; MR_D calcd. 61.98, found 62.27 (literature data[3]: b.p. 105°/13 mm Hg; n_4^{20} 1.4971). The yield was 78%.

Similarly, TMSEA was obtained in 75% yield by silylation of *p*-ethoxyacet-

TABLE I

SILYLATION CONDITIONS AND RESULTS

*Compound silylated**	*Silylation time (min)*	*Temperature (°C)*	*Solvent*	*Molar excess of silylating agent*	*Retention time (sec)*		*Conversion (%)*				
					Compound	*TMS derivative*	*BSA*	*TMSEA*	*TMSA*	*TMSIM*	*TMSDEA*
1	3	20	Pyridine	10-fold	126	180	88.8	97	97.8	96.8	13.0
2	300	30	CH_3CN	10-fold	84	132	100	100	100	100	62.2
3	180	60	Pyridine	10-fold	72	84	86	63	99	89	80
4	1	20	Pyridine	Double	258	321	100	97.6	91	99.5	93.5
5	600	Reflux	CH_3CN	10-fold	105	213	100	40	4.3	59.5	100
6	1	20	CH_3CN	10-fold	78	270	100	100	100	73	100
7	30	50	Pyridine	10-fold	600	780	86	100	100	100	91
8	120	60	Pyridine	40-fold	175	—**	61	56	50	45	16
9	15	20	Pyridine	10-fold	162/180***	150/210***	75	95	97	98	71
10	10	30	Pyridine	20-fold	48	77/89§	0/98§	0/100§	0/100§	2/87§	0/98§
11	360	30	CH_3CN	20-fold	60	156	19	100	100	100	52.5
12	15	20	CH_3CN	10-fold	63	51	100	100	12.5	0	0.6
13	1080	20	DMF	10-fold	39	54	98	100	89	71	96
14	360	30	CH_3CN	20-fold	111	129	50-1TMS/50-2TMS	42	95	82	100
15	2	20	DMF	20-fold	78	108	100	100	67	0	91

* Numbers correspond to the compounds given in Table II.

** Three peaks appeared due to di-, tri- and tetrasilylated derivatives. The percentage conversion is based on the last derivative.

*** The main peak was accompanied by a subsidiary peak, probably due to vitamin D_2 impurity[4].

§ The pairs of values refer to the monosilylated ($COOSiMe_3$) and disilylated ($COOSiMe_3$ + $OSiMe_3$) derivatives, respectively.

anilide using identical molar amounts of the reagents. The reagent mixture was refluxed for 5 h. A fraction collected at 138°/4 mm Hg had the following properties: n_D^{20} 1.5032; d_4^{20} 1.024 g·cm^{-3}; MR_D calcd. 73.18, found 72.63; C calcd. 62.10%, found 61.87%; H calcd. 8.42%, found 8.33%. It was identified as the expected compound.

The physical constants of the remaining silylating agents and organic compounds subjected to silylation have been reported in the Part I[2], except for N-methylformamide, which was a pure reagent supplied by Fluka (Buchs, Switzerland).

Procedure

To evaluate the silylating strengths of the reagents used, 15 representative organic compounds were selected, carrying various functional groups (Table I). The silylation conditions adopted were such as to incompletely silylate the compounds. Reactions were carried out with the exclusion of air moisture in 10-ml rubber-stoppered vials in which 0.1–0.5 ml of a 0.2–1.0 *M* solution of an organic compound to be silylated was placed. To this solution, 0.1–0.5 ml of a silylating agent was added by means of a microburette, the mixture was shaken vigorously for about 30 sec and allowed to stand over a period and at a temperature indicated in Table I. Pressure that developed in some instances in the vial upon heating was reduced by means of a syringe.

Gas–liquid chromatography conditions

A Pye Series 104 gas chromatograph with a flame ionization detector was used and two columns: (1) a 1.5 m × 4 mm I.D. glass column packed with 3% OV-1 on 100–120 mesh Diatomite CQ and (2) a 0.9 m × 4 mm I.D. glass column packed with 3% SE-30 on 100–120 mesh Diatomite CQ. Argon was used as the carrier gas. The remaining operating conditions are given in Table II.

TABLE II

OPERATING CONDITIONS USED FOR GLC DETERMINATIONS OF SILYL DERIVATIVES

No.	*Compound silylated*	*No. of column*	*Argon flow-rate (ml/min)*	*Column temp. (°C)*	*Detector oven temp. (°C)*	*Injector port temp. (°C)*
1	Cetyl alcohol	2	75	190	240	200
2	*sec.*-Butanol	2	20	50	80	45
3	*tert.*-Amyl alcohol	1	30	80	210	105
4	4-Chloro-3,5-dimethylphenol	1	30	140	220	170
5	2,4,6-Tri-*tert.*-butylphenol	1	30	190	220	210
6	Thiophenol	2	16	120	230	135
7	Cholesterol	2	75	240	250	225
8	D-Xylose	2	30	190	240	185
9	Vitamin D_3	2	71	240	250	230
10	Salicylic acid	2	75	160	240	180
11	Aniline	2	16	130	230	160
12	N-Methylformamide	2	25	60	110	140
13	Phthalimide	2	8	180	220	210
14	*p*-Toluenesulphonamide	2	6	255	270	240
15	5,5-Diethylbarbituric acid	2	20	195	240	175

TABLE III

RELATIVE RETENTION TIMES (t_r) OF THE SILYLATING AGENTS AND OF THE PARENT COMPOUNDS

No.	*Silylating agent*	t_r	*Parent compound*	t_r
1	BSA	1.00*	Monosilylacetamide**	1.00***
2	TMSEA	4.83	*p*-Ethoxyacetanilide	6.78
3	TMSA	2.00	Acetanilide	2.56
4	TMSDEA	0.43	Diethylamine	0.23
5	TMSIM	1.08	Imidazole	— §
6	HMDS	0.65		

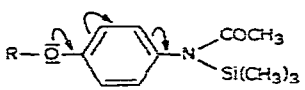
* Absolute retention time 18 sec.
** Partial desilylation product of BSA.
*** Absolute retention time 16 sec.
§ A badly tailing peak with a long retention time.

The relative retention times of the silylating agents and their desilylation products are listed in Table III. The times were determined using column No. 2. The operating conditions of the gas chromatograph were: column temperature, 190°; detector oven temperature, 240°; injection port temperature, 250°; carrier gas, argon at the flow-rate of 30 ml/min.

RESULTS AND DISCUSSION

The results of the silylation are listed in Table I. They show TMSEA to be an excellent silylating agent for the silylation of primary (cetyl alcohol), secondary (*sec.*-butanol, cholesterol, vitamin D_3), phenolic (4-chloro-3,5-dimethylphenol, salicylic acid), carboxylic (salicylic acid), thiophenolic, amine (aniline), amide (N-methylformamide) and imide (phthalimide, 5,5-diethylbarbituric acid) functions. Its silylating strength for these functional groups is equal to or even better (cholesterol, vitamin D_3, aniline) than that of BSA, TMSIM (thiophenol, D-xylose, N-methylformamide, phthalimide, 5,5-diethylbarbituric acid) and TMSDEA (cetyl alcohol, *sec.*-butanol, D-xylose, vitamin D_3, aniline, N-methylformamide). It should be borne in mind that the molecule of BSA possesses two trimethylsilyl groups compared with one in any of the remaining silylating agents tested. Therefore, the use of, *e.g.*, a 10-fold excess of BSA and any one of the remaining reagents favours the former.

Theoretical considerations concerning the evaluation of the silylating effectiveness of TMSEA and TMSA indicate that the former should be more effective owing to the availability of an electron-releasing ethoxyl group in the *para*-position. The *para*-alkoxyl substituent has been known to increase the basicity of the nitrogen atom owing to the following electronic effects:



As has been suggested in Part I[2], there seems to be a correlation between the

pK_b values of the parent amines and the silyl donor strength of their N-silyl derivatives: the lower the pK_b value, the higher is the silylating strength. This suggestion seems to be supported by some of the results shown in Table I (*cf.*, for instance, the results of the silylation of 4-chloro-3,5-dimethylphenol, 2,4,6-tri-*tert.*-butylphenol, D-xylose, N-methylformamide, phthalimide and 5,5-diethylbarbituric acid). However, two exceptions were noted (*tert.*-amyl alcohol and *p*-toluenesulphonamide).

Other advantages of TMSA and TMSEA are the following: (1) the simple method of their preparation and associated lower cost compared with BSA and TMSIM; (2) good solubility in organic solvents; and (3) useful gas–liquid chromatographic (GLC) characteristics owing to the appearance of single, sharp peaks of the reagents and of their desilylation products. This feature enables the completeness of silylation of an organic compound to be followed gas chromatographically. In contrast, BSA gives 5 or 6 peaks in the chromatograms and TMSIM tails badly.

TMSA has been especially useful for GLC determinations over the temperature ranges 40–140° and 160–350°. In the former range, the use of BSA, HMDS and TMSDEA is limited owing to the appearance of peaks of these reagents used in excess and of their desilylation products. TMSEA can be used over the ranges 40–160° and 180–350° (*cf.* also Table III). It is obvious that the ranges are suitable for the columns and parameters employed in this work.

For organic compounds whose trimethylsilyl derivatives appear over the range 140–180°, N-trimethylsilylpiperidine (TMSPI) and N-trimethylsilylpyrrolidine (TMSPY), reported in Part I[2] can be employed as equally effective silylating agents.

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