N-Alkylation of *N*-trimethylsilyl derivatives of lactams, amides, and imides with alkyl sulfonates*

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The reaction of *N*-trimethylsilyl derivatives of amides and imides with alkyl sulfonates on heating affords the corresponding *N*-alkyl derivatives and trimethylsilyl sulfonates.

Key words: *N*-alkyllactams, *N*-alkylamides, *N*-alkylimides; synthesis, "silyl method" of alkylation.

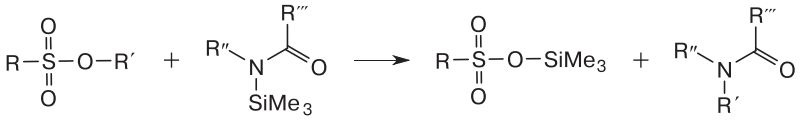
Methods of alkylation, based on the reaction of amides with various alkylation agents (dialkyl sulfates,[1—5] diazoalkanes,[6,7] diacetales,[8] alkyl halogenides[9], *etc.*) and with variations of conditions, that lead to N- or O-alkylation products, are widely used nowadays.

"Silyl method" is one of common and convenient methods for the N-alkylation of amides and imides. For example, the reactions of *N*-trimethylsilyl derivatives of lactams with active halogen derivatives such as benzyl bromide, chloro- and bromoacetyl acid esters,[10] chloroacetamide derivatives (*N*-chloroacetyl-L-proline, *N*-chloroacetyl-L-valine,[11] and 3-chloroacetyl-5-oxazolidone[12]), α-chloro ethers,[13] acetylated aldonic acid halides,[14] leads to *N*-substituted lactams. *N*-TMS-derivatives of amides, imines, and imides also participate in the reactions of this type, and *N*-trimethylsilyloxymethyl and similar derivatives of these compounds[15] or oxazolidin-5-ones[16] in the presence of electrophilic catalysts can serve as alkylation agents in this case. Known nootropic drugs such as nootropil and phenotropil as well as their topologic countertypes containing peptide bonds[17] were synthesized by amination of the products mentioned above that comprise ester bonds. Thus, "silyl version" of N-alkylation means the introduction of methyl group with non-alkylic substitutes to a nitrogen atom of amide or imide.

The current work contains data of use of sulfonic esters based on primary alcohols RSO_2OR' in N-alkylation of lactams, amides and imides. This helps to avoid alkaline medium in the course of alkylation and to obtain simple *N*-alkyl derivatives. For instance, heating of a mixture of alkyl sulfonates **1a—c** with trimethylsilyl derivatives of lactams **2a—c**, *N*-TMS-succinimide **2d,** and amides **2e**,**f** at 140—170 °C for several hours leads to TMS-sulfonates **3a—c** and the corresponding alkylation products **4a—h** (Scheme 1).

The starting silylated lactams **2a—c** are shown as *N*-silyl tautomers for simplicity. Tautomerism of silyllactams, *i.e.* equilibrium of their N- и O-derivatives ("silyltautomerism") was described in Ref. 18. TMS-derivatives of amides **2e**,**f** and succinimide **2d** are also shown as *N*-silyltautomers.

Scheme 1



1a—c **2a—f** **3a—c** **4a—h**

1	R	R′
a	Bu	Me
b	Ph	Et
c	Me	*n*-C_5H_{11}

2	R″—R‴
a	$(CH_2)_3$
b	$CH_2CH(Ph)CH_2$
c	$(CH_2)_4$
d	$C(O)CH_2CH_2$

2	R″	R‴
e	Me	Me
f	Ph	Me

3	R
a	Bu
b	Ph
c	Me

4	R′	R″—R‴
a	Me	$(CH_2)_3$
b	Me	$CH_2CH(Ph)CH_2$
c	Et	$(CH_2)_3$
d	*n*-C_5H_{11}	$(CH_2)_3$
e	Et	$(CH_2)_4$
f	Et	$C(O)CH_2CH_2$

4	R′	R″	R‴
g	Et	Me	Me
h	Et	Ph	Me

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Note, TMS-sulfonates **3a—c** that form in these reactions probably serve as catalysts for alkylation similar to what was found for trimethylsilyl triflate and trimethylsilyl halogenides,[10] *i.e.* these reactions are autocatalytic.

The herein synthesized *N*-alkyl derivatives of lactams, amides, and imides were described in the literature repeatedly. Their spectral characteristics, for instance their IR spectra and ^{1}H NMR spectra, are similar to those reported.

In conclusion, we developed the new method for *N*-alkylation of lactams, aliphatic amides, and imides, comprising reaction of their *N*-trimethylsilyl derivatives with alkyl sulfonates at 140—170 °C for several hours in absence of solvents. The advantage of this method is obtaining of *N*-alkylation products without thermal or catalytic initiation.

Experimental

IR spectra in solid phase were recorded at Bruker Tensor-2 spectrometer with use of incomplete internal reflection module (IIRM). ^{1}H NMR spectra were registered at 20 °C with Bruker Avance II 300 instrument (^{1}H, 300 MHz) in $CDCl_3$; in pulse mode with consequent Fourier transform and with ^{2}H-stabilization of the resonance conditions. Me_4Si was used as an internal standard.

Alkyl sulfonates **1a—c** were commercial reagents (Aldrich). NMR spectroscopy was used as purity control method. Initial *N*-silylated lactams, *N*-TMS-2-pyrrolidone (**2a**),[19] *N*-TMS-4-phenyl-2-pyrrolidone (**2b**),[17] *N*-TMS-azepan-2-one (**2c**),[20] *N*-TMS-succinimide (**2d**),[21] *N*-TMS-*N*-methylacetamide (**2e**),[22] *N*-TMS-acetanilide (**2f**)[23] were obtained as described; their constants and yields correspond with literature data.

Synthesis of *N*-alkyl-substituted derivatives 4a—h (general procedure). A mixture of alkyl sulfonate **1** (0.05—0.1 mol) with equimolar amount of *N*-silyl derivative of **2** was heated for 3—5 h at 140—170 °C, then fractioned.

***N*-Methyl-2-pyrrolidone (4a).** Yield 72%, b.p. 94—97 °C (18 Torr), n_D^{20} 1.4705 (see Ref. 24: b.p. 94—96 °C (20 Torr), n_D^{20} 1.4700). Trimethylsilyl sulfonate **3a** was also obtained (yield 75%), b.p. 115—120 °C (18 Torr), n_D^{20} 1.4298 (see Ref. 25: b.p. 72—73 °C (3 Torr), n_D^{20} 1.4300).

***N*-Methyl-4-phenyl-2-pyrrolidone (4b).** Yield 66%, b.p. 182—184 °C (15 Torr), n_D^{20} 1.5510 (see Ref. 26: b.p. 127—130 °C (1 Torr), n_D^{20} 1.5538). Trimethylsilyl sulfonate **3a** was also obtained (yield 72%), b.p. 117—120 °C (15 Torr), n_D^{20} 1.4320.

***N*-Ethyl-2-pyrrolidone (4c).** Yield 59%, b.p. 102—105 °C (20 Torr), n_D^{20} 1.4660 (see Ref. 27: b.p. 93—97 °C (16 Torr), n_D^{20} 1.4650). Trimethylsilyl sulfonate **3b** was also obtained (yield 72%), b.p. 160—163 °C (20 Torr), n_D^{20} 1.4935.

***N*-Penthyl-2-pyrrolidone (4d).** Yield 58%, b.p. 117—120 °C (18 Torr), n_D^{20} 1.4620 (see Ref. 28: b.p. 87—88 °C (1 Torr), n_D^{20} 1.4619). Trimethylsilyl sulfonate **3c** was also obtained (yield 51%), b.p. 100—102 °C (18 Torr), n_D^{20} 1.4240 (comp. Ref. 26: b.p. 80—82 °C (8 Torr), n_D^{20} 1.4235).

***N*-Ethylazepan-2-one (4e).** Yield 78%, b.p. 125—128 °C (16 Torr), n_D^{20} 1.4790 (see Ref. 29: b.p. 97 °C (5.5 Torr), n_D^{20} 1.4772). Trimethylsilyl sulfonate **3b** was also obtained (yield 86%), b.p. 155—157 °C (16 Torr), n_D^{20} 1.4940.

***N*-Ethylsuccinimide (4f).** Yield 86%, the product crystallized when standing, m.p. 24 °C. (see Ref. 30: b.p. 119—121 °C (15 Torr), m.p. 26 °C).

***N*-Ethyl-*N*-methylacetamide (4g).** Yield 87%, b.p. 185—189 °C (750 Torr), n_D^{20} 1.4280 (see Ref. 31: b.p. 180 °C (750 Torr)). Trimethylsilylsulfonate **3b** was also obtained (yield 45%), b.p. 168—172 °C (25 Torr), n_D^{20} 1.4950.

***N*-Ethylacetanilide (4h).** Yield 78%, b.p. 126—130 °C (12 Torr), m.p. 53—54 °C (see Ref. 32: b.p. 138 °C (20 Torr), m.p. 53—54 °C, n_D^{20} 1.4772). Trimethylsilylsulfonate **3b** was also obtained (yield 71%), b.p. 145—146 °C (12 Torr), n_D^{20} 1.4950.

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