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SYNTHESIS WITH SILICON DERIVATIVES.
NON SYMMETRICAL DERIVATIZATION OF SYMMETRICAL DIAMINES

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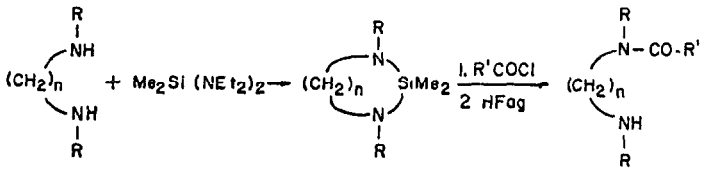
Summary The conversion of symmetrical diamines to monoamides via the use of cyclic silicon-nitrogen compounds as intermediates is described.

The conversion of symmetrical diamines to non-symmetrical derivatives is a difficult problem, which is encountered in the total synthesis of many natural products. Examples are the synthesis of spermidine (1,2) as well as many cyclic spermidine alkaloids (3). In the former case, the preparation of the key precursor, N-acetyl-1,4-diamino butane from 1,4-diamino butane and 1 equivalent acetic anhydride occurs in only 22-23% yield (2,4) and gives as major material unreacted diamine and symmetrical diamide In order to solve the problem of non-symmetrical derivatization, Leznoff et al introduced polymers as selective blocking groups, making use of the dilution principle (5,6) We wish to describe in this communication an alternative method which is based on the use of silicon derivatives and wish to report on the conversion of symmetrical diamines to mono amides The method is based on transforming diamines into cyclic silicon-nitrogen compounds as intermediates. Subsequent reaction with equimolar amounts of acyl halides gives monoamides.

The key of the method resides in the formation of the cyclic silicon-nitrogen compound as intermediate. In this intermediate, the two amino groups have become interdependent and reaction of the first group causes deactivation of the second allowing the preparation of monoderivatives. The detailed experimental procedure is as follows

A solution of 0.0077 M acyl halide in 10 ml tetrahydrofuran is added dropwise to a solution of 0.0077 M cyclic silazane in 25 ml tetrahydrofuran at room temperature The reaction is carried out in a polyethylene bottle and the addition of the reagent with a syringe pump at a speed of 0.15 ml/min After the addition of the reagent is completed, stirring is continued for another 30 min and the reaction mixture subsequently cooled with ice and treated with 1 ml of a 40% aqueous solution of hydrogen fluoride. Stirring is continued for 30 min at room temperature, and the mixture poured into 30 ml of 5% aqueous bicarbonate. After extraction with 3 portions of 30 ml chloroform the organic phase is dried over magnesium sulfate, filtered

and concentrated. The aqueous phase is extracted with chloroform, dried, filtered and concentrated. The oily residue is subsequently separated on an ion exchange resin, AG MP-50, 100-200 mesh hydrogen form. Elution with methanol provdes small amounts of the diamide by-products, elution with 0.5% NH_4OH in methanol the monoamides. The yields for the individual examples and the spectroscopic and physical properties of the products are summarized in Table 1.



1, n=2, R=Et
2, n=2, R=Bz
3, n=3, R=Et

4a R'=Ph
4b, R'=Bu

5a n=2, R=Et R'=Ph
5b n=2, R=Et R'=Bu
6a n=2, R=Bz R'=Ph
6b n=2, R=Bz R'=Bu
7a n=3, R=Et R'=Ph
7b n=3, R=Et R'=Bu

As evident from the examples given in the Table, the method is applicable to diamines with aliphatic and aromatic substituents and to aliphatic and aromatic acyl halides. With aliphatic acyl halides however, no diamides are formed, while with aromatic acyl halides some diamides are obtained as by-products (See footnote in Table 1).

The reaction of cyclic silazanes with acyl halides may be visualized to occur by nucleophilic attack of the silazane nitrogen on the acyl carbon to give the non-symmetrical intermediate I.

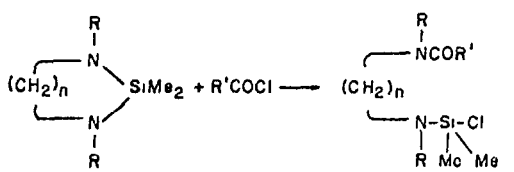


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Table

YIELDS AND SPECTROSCOPIC PROPERTIES OF MONOAMIDES

Compound	Yield %	IR-Spectra[a] ν(cm^{-1})	Mass Spectra m/e	^{1}H-NMR Spectra[b] δ (ppm)					
				HN-	$HNCH_2$-	-$CONCH_2$-	-$COCH_2$-	-ArH	others
5a	75[c]	3500 3310 1630	220	1.6(s)	2.2-2.8 (m)	2.9-3.5 (m)		7.13(s)	0.72-1.34 (2t)
5b	58[d]	3480 3280 1630	186	1.53(s)	2.5-2.8 (m)	3.3-3.5 (m)	2.3(t)		0.86-1.17 (2t) 1.25-1.8 (m)
6a	69[e]	3500 3310 1630	344	1.5(s)	2.7-2.9 (m) 3.4-3.7 (m)	3.4-3.7 (m) 4.64 (broad s.)		7.23- 7.49(m)	
6b	60[d]	3480 3305 1640	310	1.74(s)	2.5-2.9 (m) 3.71(s) 3.75(s)	3.2-3.6 (m) 4.56(s) 4.59(s)	2.1-2.5 (m)	7.15- 7.53(m)	0.9-1.00 (m) 1.36-1.4 (m)
7a	72[f]	3500 3300 1630	234	1.62(s)	1.9-3.2 (m)	3.2-3.6 (m)		7.36(s)	1.0-1.35(m) 1.35-1.9(m)
7b	61[d]	3470 3300 1635	200	1.98(s)	2.4-2.8 (m)	3.1-3.6 (m)	2.23(t)		0.75-1.35(m) 1.35-1.9(m)

[a]The IR-Spectra were recorded in KBr pellets. [b] The NMR-Spectra were recorded in $CDCl_3$ on a Varian 80MHz instrument except for 5a, the spectrum of which was recorded in CCl_4 on a Varian 60MHz instrument. Chemical shifts are given relative to internal TMS. The yields of the corresponding diamides were: c, 22%; d, undetectable; e, 21%; f, 19%.

The electronegative chlorine substituent in intermediate I reduces the reactivity of the second amino group which becomes resistant to further attack. Subsequent cleavage of the silicon-nitrogen bond with aqueous hydrogen fluoride provides the mono amides.

It should be pointed out, that the selection of silicon for amines and tin for diols as reported in an earlier publication (7) is not arbitrary, but based on considering the chemical reactivity of the respective metalloid derivative The high reactivity of silicon nitrogen compounds towards organic substrates (8) together with their ready availability, when compared with tin-nitrogen compounds (9), make silicon the element of choice for amines. For diols, however, tin has to be used since silicon-oxygen compounds are rather inert, while tin-oxygen compounds are reactive towards organic substrates (10).

The major difference between the silicon method and the polymer-method is that the silicon functions as both, protecting and activating group, the polymer only as protecting group. We are currently in progress of applying the method for the preparation of mixed derivatives and for the synthesis of naturally occuring nitrogen compounds.

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