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N-SULFONYLAMIDINES. PART III. A NEW REARRANGEMENT REACTION OF N-ALKYLSULFONYL-AMIDINES SYNTHESIS OF ENAMINES, ß-AMINOSULFONYL-ENAMINES AND 4H-THIAZETE-S,S-DIOXIDES

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Abstract - On reaction with lithium diisopropylamide, N-alkylsulfonylamidines (1) (a new class of amidines) rearrange by intramolecular attack of the carbanion generated α to the SO_2 group on the amidine carbon. Through a cyclic thiazetidine intermediate three main classes of compounds are formed, i e enamines (8), ß-aminosulfonylenamines (9) and 4H-thiazete-S,S-dioxides (6) In the rearrangement products 8 and 9 the two carbon moieties of the amidine formerly linked to the N and S atoms, respectively, become linked together, with the formation of a new C-C bond.

Since several years we are interested in the study of the synthetic possibilities of tertiary N-sulfonylamidines These compounds have been shown to react at the electrophilic amidine carbon with nucleophilic reagents as lithium aluminium hydride (synthesis of amines[1]) or organolithium compounds (synthesis of ketones[2]) As far as we are aware, only N-arylsulfonylamidines have been described till now and considered in the above studies

In the present paper we describe several hiterto unknown N-benzylsulfonyl- and N-alkylsulfonylamidines (1), which are expected to display a larger reactivity pattern owing to the possibility to undergo deprotonation α to the SO_2 group, possibly leading to intramolecular cyclization reactions.

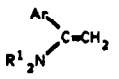
RESULTS AND DISCUSSION

The amidines 1a-i were prepared by reaction of the appropriate sulfonylazide 2a-c with the corresponding enamines 3a-g. The preparation of azides 2a-c was performed by reacting the corresponding sulfonyl chlorides with sodium azide according to a described procedure[3] The morpholino enamines 3a-e,g were obtained from the corresponding ketones

by reaction with an excess of morpholine and titanium tetrachloride[4], whereas for 3f the acid-catalyzed reaction of acetophenone diethyl ketal with N-methylaniline was employed[5].

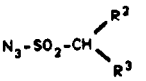
The cycloaddition reaction of azides (2) and enamines (3) affords labile and not isolable 1,2,3-triazoline intermediates (4) which readily lose diazomethane ultimately yielding products 1 (Scheme 1). This spontaneous cycloreversion reaction is well known for the analogous 5-amino-1-arylsulfonyl-1,2,3-triazolines without substituents in position 4[6].

Scheme 1

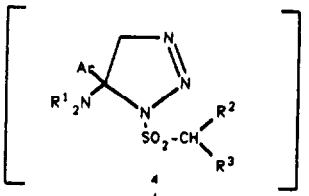


3	Ar	NR'_2
a	C_6H_5	morpholino
b	2-CH_3-C_6H_4	morpholino
c	4-CH_3-C_6H_4	morpholino
d	N-methyl-2-pyrrolil	morpholino
e	2-thienyl	morpholino
f	C_6H_5	$N(CH_3)C_6H_5$
g	3-pyridil	morpholino

+



2	R^2	R^3
a	C_6H_5	H
b	CH_3	C_2H_5
c	CH_3	CH_3



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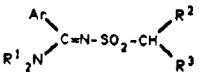
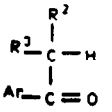
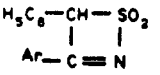


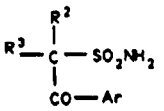
1	Ar	NR'_2	R^2	R^3
a	C_6H_5	morpholino	C_6H_5	H
b	2-CH_3-C_6H_4	morpholino	C_6H_5	H
c	4-CH_3-C_6H_4	morpholino	C_6H_5	H
d	N-methyl-2-pyrrolil	morpholino	C_6H_5	H
e	2-thienyl	morpholino	C_6H_5	H
f	C_6H_5	$N(CH_3)C_6H_5$	C_6H_5	H
g	3-pyridil	morpholino	C_6H_5	H
h	C_6H_5	morpholino	CH_3	CH_3
i	C_6H_5	morpholino	CH_3	C_2H_5

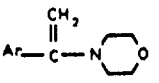


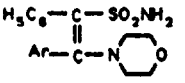


5	Ar	R^2	R^3
a	C_6H_5	C_6H_5	H
b	4-CH_3-C_6H_4	C_6H_5	H
c	2-thienyl	C_6H_5	H
d	C_6H_5	CH_3	C_2H_5

6	Ar
a	C_6H_5
b	4-CH_3-C_6H_4
c	N-methyl-2-pyrrolil
d	2-thienyl







7	Ar	R^2	R^3
a	C_6H_5	C_6H_5	H
b	4-CH_3-C_6H_4	C_6H_5	H
c	2-thienyl	C_6H_5	H
d	C_6H_5	CH_3	CH_3

8	Ar
a	2-CH_3-C_6H_4
b	N-methyl-2-pyrrolil

9	Ar
a	C_6H_5
b	2-CH_3-C_6H_4
c	4-CH_3-C_6H_4
d	N-methyl-2-pyrrolil
e	3-pyridil

Amidines 1 were made to react with bases, aiming to generate a carbanionic intermediate α to the SO_2 group, possibly able to react intramolecularly with the C=N bond

Though several bases could be considered in principle it had to be born in mind that the electrophilic reactivity of the C=N amidine bond is relatively low and moreover the acidity of the CH_2 group α to SO_2 is not very high Only strong bases appeared to be suitable Sodium hydride, potassium t-butoxide, diazabicycloundecene and lithium diisopropylamide (LDA) were tried An appreciable result was obtained only using LDA in tetrahydrofuran at low temperature Under these conditions amidines 1a–i rapidly reacted affording reaction mixtures from which one or more of compounds 5, 6, 7, 8, 9 were

isolated by column chromatography on silica gel In several cases relatively high amounts of untractable tarry products were formed, making the chromatographic elaboration of the reaction mixture difficult and slow In these cases the loss of products formed in low amount and/or the hydrolysis of moisture sensitive compounds was unavoidable The yields listed in Table 1 are for isolated and purified products

Table 1

Starting amidine	Products isolated (Yield %)				
1a	5a(28)	6a(2)	7a(5)	-	9a(38)
1b	-	-	-	8a(20)	9b(42)
1c	5b(28)	6b(13)	7b(12)	-	9c(27)
1d	-	6c(6)	-	8b(19)	9d(14)
1e	5c(30)	6d(1)	7c(5)	-	-
1f	-	6a(1)	7a(4)	-	-
1g	-	-	-	-	9e(35)
1h	-	-	7d(32)	-	-
1i	5d(30)	-	-	-	-

The structure of all reaction products 5 - 9 was confirmed on analytical and spectroscopic data

Ketones **5a-d** were easily identified through their IR and ^{1}H-NMR spectra and/or by comparison with authentic samples The enamines **8a,b** were characterized by the typical high-field shift of the enamine proton[7] and by hydrolysis to the corresponding known ketones respectively. The thiazete-S,S-dioxide compounds 6 show in the IR spectrum a band at 1520 cm^{-1} associated with the C=N bond In the ^{1}H-NMR spectrum a singlet at 6 0-6 1 δ is associated with H-4 ^{13}C-NMR resonances are observed for **6a** at 95 ppm for C-4 and 181 3 ppm for C-3 Mass spectra of compound **6a** is characterized by the absence of the molecular ion Instead, an M-SO_2 peak is present Another important peak is at M-SO_2=NH evidencing a typical loss of sulfimide[8] The enamines 9 and the related ketones 7 could be unequivocally identified by spectroscopic methods (IR, ^{1}H-NMR, MS)

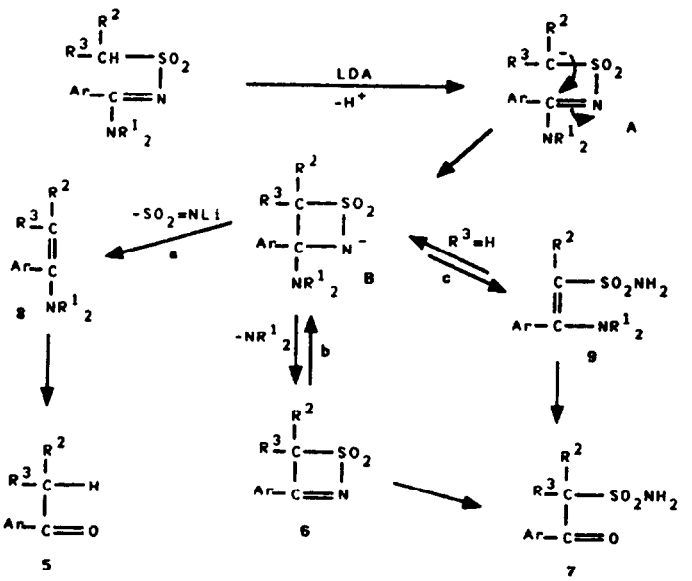
The pattern shown in Scheme 2 is proposed to rationalize the formation of compounds 5 to 9 starting from the amidine 1

The strong base LDA deprotonates the starting compound in position α to the SO_2 group resulting in the formation of a carbanionic intermediate (A) which undergoes intramolecular cyclization through nucleophilic addition to the amidine C=N bond. The cyclic intermediate (B) is thus formed, from which all the three primary reaction products (i e 6, 8 and 9) are derived The formation of enamines 8 (path a) occurs by SO_2=NLi elimination (possibly a cycloreversion reaction) The elimination of secondary amine (path b) leads to the formation of the thiazete compound (6) A third possibility

(path c) arises, clearly only when one of the R groups is H, i e. ring opening to produce enamines 9. The ketone products 5 and 7 are produced through partial hydrolysis of the corresponding enamines 9 and 8. The extent of this hydrolysis depends on the time required for chromatographic separation, which may be relatively long. In a separate experiment it has been observed that pure 8a or 9a are slowly hydrolyzed during chromatography. It has to be stressed that ketone 7 may also arise from the thiazete derivative 6 through hydrolytic cleavage. This has been demonstrated in a separate experiment in which 6a yielded 7a when heaten in moist ethanol with a trace amount of acid. This fact is also confirmed by the formation of 7d from 1h since its production occurs mandatorily by this route

Moreover, an equilibrium exists between compounds 9 and 6 via intermediate (B) A demonstration is offered by the reaction of 9a with LDA in anhydrous tetrahydrofuran A partial conversion into 6a was observed, similarly, when 6a was brought to reaction with morpholine a reaction mixture was obtained from which after elaboration 5a was isolated suggesting the reversibility of path b

Scheme 2



The most interesting feature of the above reactions has to be seen in the new rearrangement according to which products are obtained in which the two carbon moieties of the amidine formerly linked to N and S atoms respectively, become linked together, thus making available a new reaction useful for the formation of carbon-carbon bonds

EXPERIMENTAL SECTION

Melting points were taken on a BUCHI 510 instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Varian EM 360 and Brucker AC 200 spectrometers, chemical shifts being given in ppm from Me_4Si. IR spectra were recorded on a PYE UNICAM SP3-200 S Philips instrument. Ready to use silica gel plates were employed for TLC.

Materials:

LDA was freshly prepared just before each reaction.

Enamines 3a, e, f, have been described previously (3a[7] ; 3e[4] ; 3f[5]), products 3b, c, d, g are unknown and were prepared by analogous procedures (3b: b.p. 118°C, 1 mm Hg; 3c: b.p. 115°C, 1 mm Hg; 3d: b.p. 130°C, 1 mm Hg; 3g: b.p. 120°C, 0.5 mm Hg).

Azide 2a has been described (2a[11],); 2b , c are unknown and were prepared according to a known procedure[10,3] (2b: b.p. 90°C, 20 mm Hg; 2c: b.p. 74°C, 20 mm Hg).

N-Sulfonylamidines (1):

General procedure:

Azides 2 (30 mmol) were dissolved in anhydrous methylene chloride (50 ml) and slowly dropped in a stirred solution of enamines 3 (30 mmol) in the same solvent (50 ml) in a nitrogen atmosphere. Products 2 and 3 react rapidly and after 2 or 3 hours the reaction mixture was worked up. After evaporation of the reaction solvent, the white solid residue was crystallized. Analytical and spectroscopic data are listed in Table 2.

Table 2

Prod.	M.p. (°C)	Yield %	Analysis C	H	N	^{1}H-NMR ($CDCl_3$)
1a	148-150	52	62.50 (62.80)	5.70 (5.80)	8.10 (8.10)	3-4(m,8H); 4.2(s,2H); 7-7.5(m,12H).
1b	132	60	63.60 (63.90)	6.00 (6.10)	7.80 (7.80)	2.1(s,3H); 2.8-3.2(m,4H); 3.4-3.9(m,4H); 4.2(s,2H); 6.8-7.5(m,9H).
1c	103	50	63.70 (63.90)	6.30 (6.10)	7.80 (7.80)	2.3(s,3H); 3.1-3.2(m,2H) 3.5-3.6(m,2H); 3.7-3.8 (m,4H); 4.2(s,2H); 7.2(dd,4H,J=8Hz); 7.3-7.5(m,5H).
1d	146	66	58.50 (58.80)	6.10 (6.00)	12.15 (12.10)	3.3-3.8(m,10H); 4.2(s,3H); 6.1-6.2(m,2H); 6.6-6.7(m,1H); 7.3-7.5(s,5H).
1e	145-146	44	54.90 (54.80)	5.30 (5.15)	8.10 (8.00)	3.3-3.8(m,8H); 4.3(s,2H); 7-7.6(m,8H).
1f	128	58	68.30 (68.20)	5.60 (5.70)	8.00 (7.95)	3.4(s,3H); 4.2(s,2H); 6.8-7.5(m,15H).
1g	175	45	59.20 (59.10)	5.60 (5.50)	12.00 (12.20)	3-4(m,8H);4.2(s,2H); 7.2-7.5(m,7H); 8.2-8.3(m,1H); (m, 1H); 8.5-8.7(m,1H).
1h	108	44	57.00 (56.70)	6.65 (6.75)	9.60 (9.45)	1.3(d,6H); 3-4(m,9H); 7.5(s,5H).
1i	97	40	56.80 (56.70)	7.05 (7.10)	9.25 (9.03)	0.8-1.5(m,8H); 3-4(m,9H); 7.3-7.6(m,5H).

Reaction of N-sulfonylamidines 1 with LDA:

General procedure:

To a stirred solution of freshly prepared LDA (95 mmol) in anydrous THF, cooled to -40°C, a suspension of N-sulfonylamidine 1 was rapidly added, in a nitrogen atmosphere. The reaction mixture was then stirred for 12 h at room temperature. After evaporation of the solvent the crude mixture was chromatographed on a silica gel column (eluent petroleum ether containing increasing amounts of diethyl ether). Analytical and spectroscopic data of isolated products are given in Table 3.

Table 3

Prod.	M.p.(°C)	IR(nujol) cm^{-1}	Analysis C	H	N	^{1}H-NMR ($CDCl_3$)
5a	57	1680	85.50 (85.70)	6.10 (6.15)	/ /	4.4(s,2H); 7.3-8.2(m,10H).
5b	101	1660	85.90 (85.70)	6.90 (6.70)	/ /	2.4(s,3H); 4.3(s,2H); 7.25-7.35(m,7H); 7.9(dd,2H,J=9Hz).
5c	50-51	1670	71.00 (71.30)	4.90 (4.95)	/ /	4.1(s,2H); 6.9-7.8(m,8H).
5d	106 b.p.(12)	1640	81.45 (81.50)	8.50 (8.65)	/ /	1(q,3H,J=7Hz); 1.25(d,3H,J=7Hz); 1.6-1.8(m,2H); 3.2-3.8(m,1H); 7.3-8(m,5H).
6a	125	1520	65.40 (65.40)	4.40 (4.30)	5.60 (5.50)	6.8(s,1H); 7.2-7.7(m,10H).
6b	147	1520	66.00 (66.20)	4.90 (4.80)	5.00 (5.10)	2.4(s,3H); 6.8(s,1H); 7.2-7.6(m,7H); 7.6-7.65(dd,2H,J=9Hz).
6c	125	1520	59.80 (60.00)	5.30 (5.50)	10.70 (10.75)	4.1(s,3H); 6.15(dd,1H,J_{AM}=5Hz,J_{AX}=2.3Hz); 6.35(dd,1H, J_{AM}=5Hz,J_{MX}=1.7Hz); 6.7(s,1H); 7.1-7.5(m,6H).
6d*		1525				6.1(s,1H); 7-7.5(m,8H).
7a	139	3400	61.00 (61.10)	4.85 (4.75)	4.90 (5.10)	5.1(bs,2H exch.); 6.2(s,1H); 7.2-8(m,10H).
7b	173	3300 1650	62.50 (62.70)	5.35 (5.25)	4.95 (4.90)	2.4(s,3H); 5.9(bs 2H exch.); 6.1(s,1H); 7.2(dd,2H,J=8Hz); 7.3-7.5(m,5H); 7.75(dd,2H,J=8Hz).
7c	198	3300 1640	51.20 (51.20)	3.90 (3.90)	4.95 (5.00)	5(bs, 2H exch.); 6(s,1H); 7-7.7(m,8H).
7d	115	3300 1660	52.90 (52.90)	6.00 (5.70)	6.30 (6.30)	1.7(s,6H); 6.4(bs,2H exch.); 7.3-8(m,5H).
8a	136	1590	81.60 (81.70)	7.35 (7.50)	4.90 (5.00)	2.2(s,3H); 2.7-3(m,4H); 3.6-3.8(m,4H); 5.6(m,1H); 6.6-7.2(m,9H).
8b	115	1600	76.20 (76.10)	7.50 (7.45)	10.55 (10.45)	2.8-3(m,4H); 3.2(s,3H); 3.6-3.8(m,4H); 5.6(s,1H); 6.1(m,2H); 6.5-7.2(m,6H).
9a	140-142	3300	62.50 (62.80)	5.75 (5.80)	8.25 (8.15)	2.55(t,4H,J=3.6Hz); 3.4(t,4H,J=3.6Hz); 4.2(bs,2H exch.); 7.3-7.5(m,10H).
9b	180	3350	63.80 (63.90)	6.20 (6.15)	7.85 (7.80)	2.2(s,3H); 2.6-2.8(m,4H); 2.8-3(m,4H); 4.1-4.2(bs,2H exch.); 7.2-7.6(m,9H).
9c	163	3300	63.40 (63.80)	5.90 (6.15)	7.70 (7.80)	2.4(s,3H); 2.6(t,4H,J=4Hz); 3.5(t,4H,J=4Hz); 4.1(bs,2H exch.); 7.2-7.5(m,9H).
9d	140	3300	48.60 (48.60)	6.15 (6.10)	15.35 (15.35)	2.4-2.7(m,8H); 3.6(s,3H); 4.4(bs,2H exch.); 6.15(m,1H); 6.4(m,1H); 6.8(m,1H); 7.3-7.5(m,5H).
9e	200	3400	59.10 (59.10)	5.50 (5.50)	12.20 (12.20)	3.3(s,2H); 3.8-4(m,8H); 7.2-7.6(m,7H); 8.6-8.9(m,2H).

*: uncrystallizable solid which gave only poor analytical results.

Appendix: MS data (m/z): **5a**: EI-MS: 196[M^+], 185, 176, 165, 149, 139, 125; **6a**:[M^+]absent, 193($M-SO_2$),178 ($M-SO_2$=NH), 165, 154, 126, 116, 90, 82, 77, 63, 50; **7a**: 275[M^+], only traces, 211, 195, 165, 152, 105, 77, 69; **9a**: [M^+]absent, 264 ($M-SO_2NH_2$), 234, 220, 206, 193, 178, 165, 154, 126, 116, 104, 96, 89, 77, 71, 63, 51, 42. ^{13}C-NMR data (ppm from TMS): **6a**: 95, 127.3-127.5, 129.5-131, 136, 181.3. **8b**: 34, 49, 67, 107.1, 108.1, 110.5, 122.9-124.5, 127.21, 128.4, 138.6, 141.9; **9a**: 50.8, 67.15, 117, 127.7, 128, 128.7, 128.76, 130.17, 130.29, 130.37, 133.06, 135.84, 137.3, 157.7. **9d**: 34.66, 49.96, 66.57, 108.61, 113.65, 118.99, 126.08, 127.02, 128.47, 133.04, 135.04, 135.17, 148.54.

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