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N-HALOAMIDINES. VI[1].
REACTION OF N-CHLORO-N'-BENZENESULFONYLBENZAMIDINES WITH ENAMINES.

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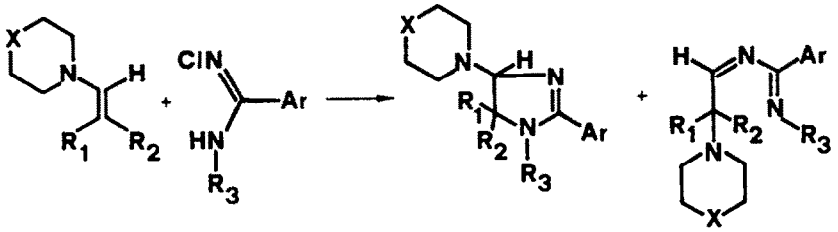
Abstract. The reaction between N-chloro-N'-benzenesulfonylbenzamidines and ß,ß-disubstituted enamines affords N-(benzenesulfonyl)-N'- [(2-chloro-2-substituted-1-amino)-propyl]-benzamidines. When both ß-substituents are methyl groups the open chain adducts have been isolated and characterized; whereas, when one of the two substituents is a phenyl group, they have been characterized only by PMR because of the easy cyclization to 1-benzenesulfonyl-4,5-dihydroimidazoles.

In previous works we reported that enamines derived from 2,2-disubstituded aldehydes react with N-chloro-N'-aryl and N-chloro-N'-aroylamidines according to two different pathways. The substituents at the enamine double bond and at the N' atom of the benzamidine determine the reaction products which can be the 1-aryl(or aroyl)-4-amino-imidazolines 1 and/or the isomeric N-(2-amino-ethylidene)-N'aryl(or aroyl)-amidines 2, (Scheme 1)[2,3,4].

SCHEME 1



1 2

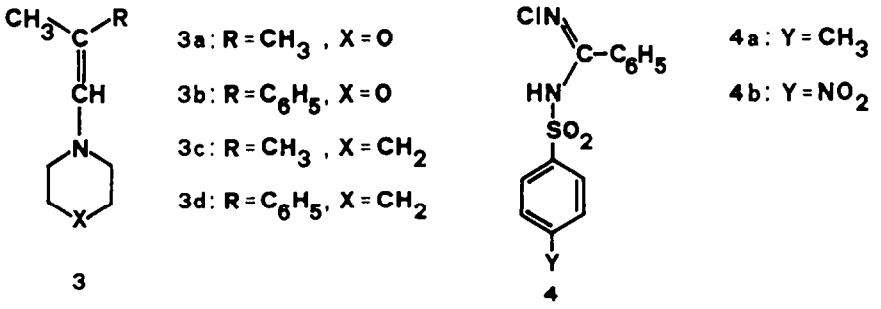
The formation of the imidazoline 1 appears to be favoured when R_1 and/or R_2 are phenyl groups, whereas compounds 2 represent the main products of the rearrangement when R_1 and R_2 are alkyl groups or when R_3 is an aroyl group.

We wish now to report our results when the same enamines 3 were reacted with N-chloro-N'-benzenesulfonylbenzamidines 4 ($R_3 = SO_2Ar$). The aim of this study was to find an entry to a new class of imidazole derivatives and to investigate whether the presence of the sulfonyl group on the N-chloroamidine allows a better understanding of the mechanisms underlying the reactions between N-chloroamidines and enamines.

RESULTS

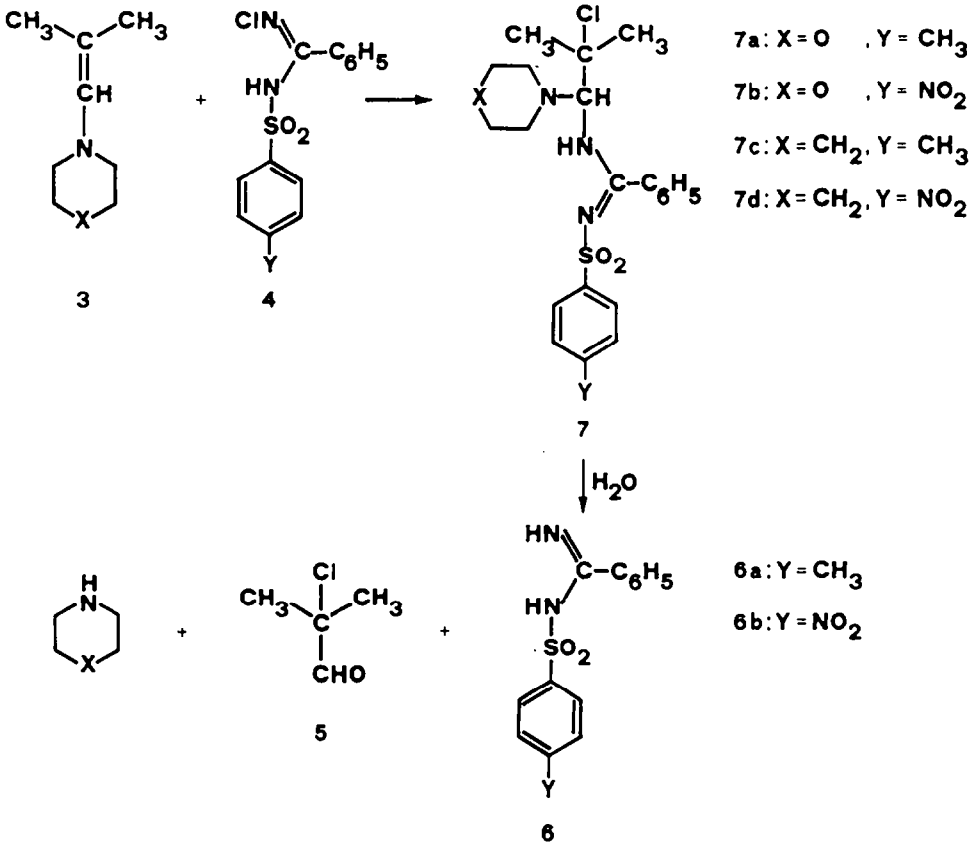
Enamines **3a–d** were reacted with N-chloro-N'-benzenesulfonylbenzamidines **4a** and **4b** (Scheme 2), in chloroform at room temperature.

SCHEME 2



Two different behaviours depending on the enamine structure were observed. Enamines deriving from 2-methylpropanal (**3a** and **3c**) when reacted with N-chloroamidines **4a** and **4b** gave after chromatographic purification over silica gel, 2-chloro-2-methylpropanal **5**, N-sulfonylamidine **6a** and **6b** and morpholine or piperidine (Scheme 3).

SCHEME 3

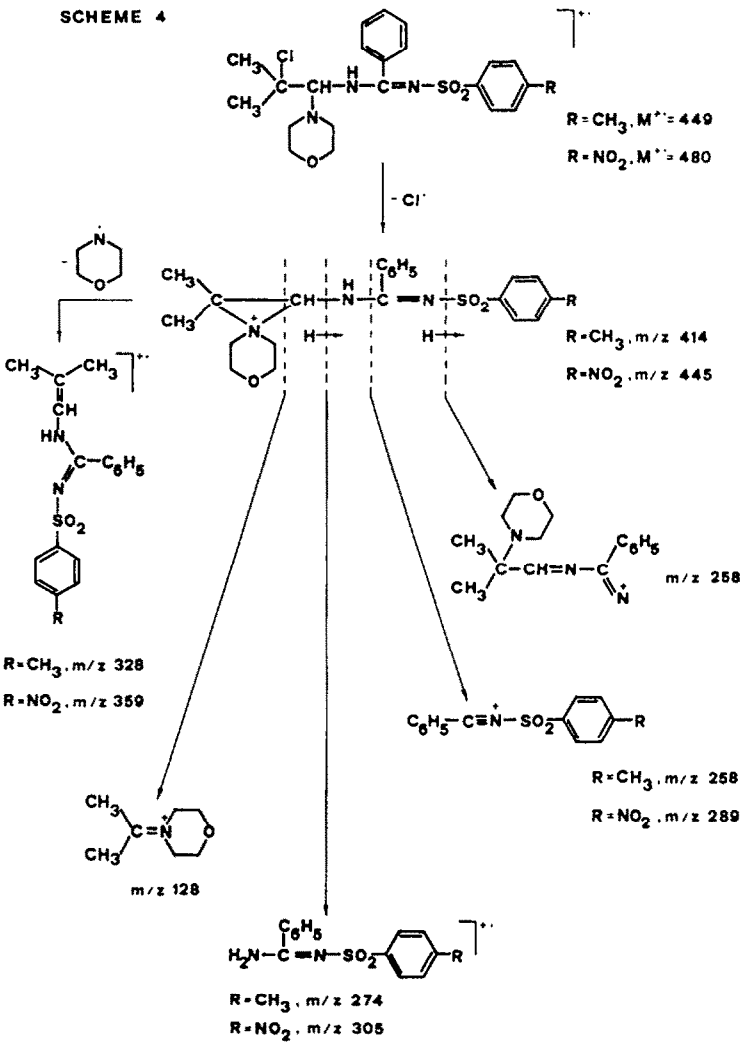


These products, however, could be the result of a hydrolytic process taking place during the purification. To verify this hypothesis the purification of the reaction mixture was examined with greater care.

In the case of the reaction between morpholinoenamine **3a** and N-chloroamidines **4a** and **4b** work up at low temperature and in anhydrous conditions resulted in the isolation of a white solid as the sole reaction product (**7a** and **7b**). The structure of N-(4-methyl-benzenesulfonyl)-N'-[(2-chloro-2-methyl-1-morpholino)-propyl]-benzamidine **7a** and N-(4-nitrobenzenesulfonyl)-N'-[(2-chloro-2-methyl-1-morpholino)-propyl]-benzamidine **7b** was assigned to these compounds on the basis of analytical and spectral data[5] which also allow to assign the position of the double bond. The fragmentation patterns of **7a** and **7b** are shown in Scheme 4.

EI mass spectra of compounds **7a** and **7b** do not show the molecular ion, but only a very small $[M-Cl]^+$ ion. This behaviour is clearly due to the instability of these molecules. At first glance the fragmentation pattern seems to be in agreement with a structure where the morpholine ring is directly connected to the carbon atom bearing the two methyl groups. The base peak at m/z 128 in both spectra is particularly favourable for this hypothesis. However the mass spectrometric data can also be explained assuming that the $[M-Cl]^+$ ion has the aziridinium structure as shown in Scheme 4. All observed fragments can be derived from this precursor by simple cleavages accompanied by hydrogen migrations[5].

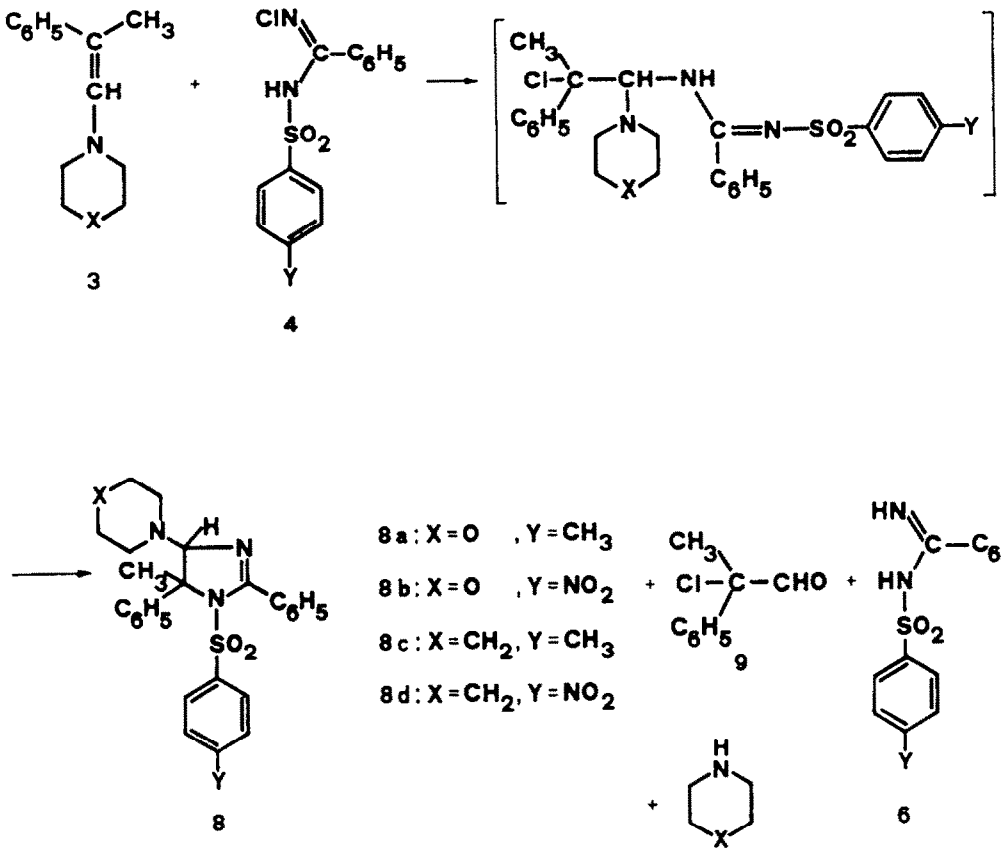
SCHEME 4



In the case of the piperidinoenamine 3c, the addition products 7c and 7d could not be isolated but only detected because of their easy hydrolisability during the work up. They were detected in the crude reaction mixture with tha aid of PMR spectroscopy. Compounds 7a–d, as expected give in hydrolytic conditions, 2-chloro-2-methyl-propanal 5, N-sulfonylamidines 6a and 6b and morpholine or piperidine. All attempts to transform the compounds 7a–d into imidazolines 1 or ethylidene-amidines 2 failed: in every case only tarry products have been obtained.

A different reaction pathway was observed when N-chloroamidines 4a or 4b were reacted with enamines derived from 2-phenylpropanal 3b and 3d. In this case, 1-sulfonyl-4,5-dihydro-imidazoles 8a–d (Scheme 5) were isolated after column chromatography, as the main products besides little amounts of 2-chloro-2-phenylpropanal 9 and sulfonylamidines 6a and 6b. The open chain adducts were not isolated but only detected immediately after the addition of the reagents by PMR spectroscopy.

SCHEME 5



1-Sulfonyl-4,5-dihydro-imidazoles **8a-d** represent a new class of imidazole derivatives. The compounds prepared and their relevant physicochemical properties are listed in the following table.

TABLE 1. 1-Sulfonyl-4,5-dihydro-imidazoles, **8a-d**.

No	Eluent for chromatography	Yield[a] %	m.p. [°C] (solvent)	Molecular formula	Elemental analysis,%[b] C	H	N	Spectroscopic data
8a	dichlorometane/ ethylacetate 90/10	48	181 (ethanol)	$C_{27}H_{29}N_3O_3S$ (475,60)	67,95 (68,00)	6,20 (6,15)	8,78 (8,84)	^{1}H-NMR: 4,56[c](H4)
8b	ethylacetate/ cyclohexane 80/20	16	136-141 (ethanol)	$C_{26}H_{26}N_4O_5S$ (506,56)	61,45 (61,64)	5,20 (5,17)	10,85z (11,06)	^{1}H-NMR: 4,73[d](H4)
8c	cyclohexane/ ethylacetate 70/30	33	185 (ethanol)	$C_{28}H_{31}N_3O_2S$ (473,61)	70,98 (71,00)	6,57 (6,60)	8,82 (8,87)	^{1}H-NMR: 4,53[c](H4)
8d	cyclohexane/ ethylacetate 70/30	12	161-163 (isopropanol)	$C_{27}H_{28}N_4O_4S$ (504,59)	64,49 (64,26)	5,67 (5,59)	11,06 (11,10)	^{1}H-NMR: 4,73[c](H4)

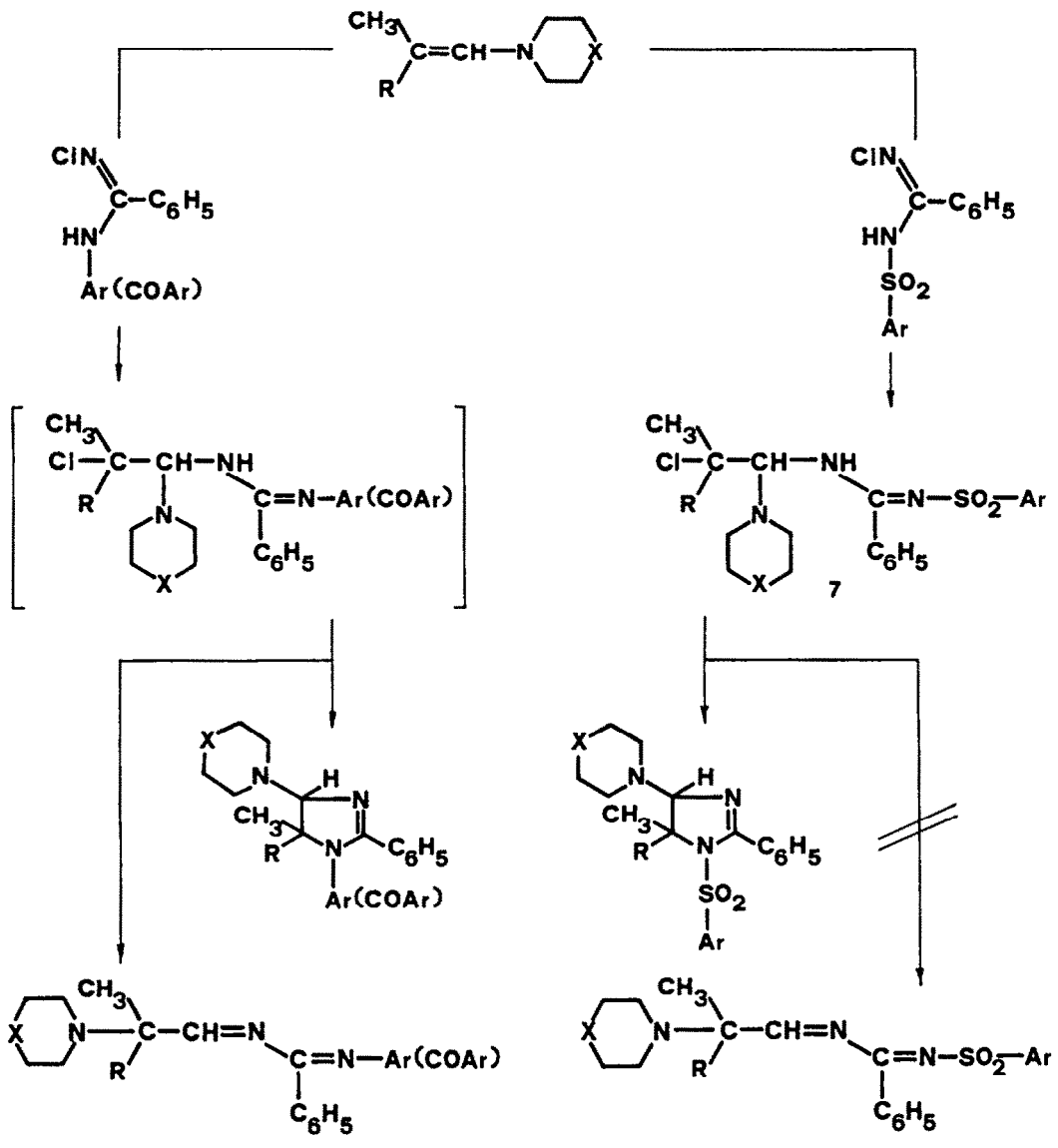
a) of isolated product.
b) calculated values in parentheses.
c) recorded in $CDCl_3$, δ from TMS.
d) recorded in $CDCl_3$/DMSO 95:5, δ from TMS.

DISCUSSION

The mechanism proposed for this reaction is depicted in Scheme 6 and parallels in part the mechanism suggested for the reaction involving the same enamines and N-chloro-N'-aryl(or aroyl)-benzamidines[(2)] (also reported in the Scheme 6).

The major effect induced by the sulfonyl group is the increased stability of the open chain intermediate 7 which could be detected and in some cases even isolated. Another experimental evidence is the absence of the rearrangement product 2 in the reaction mixtures whatever conditions employed. To our opinion these facts are strictly connected and they are due to the acidic character of the hydrogen bound to the amidine moiety. The predictable intramolecular protonation of the amino group hinders the rearrangement process thus stabilizing the open chain intermediate mainly when the cyclization process is unfavoured by the low reactivity of the halogenated carbon atom (R= CH_3). In the case of the intermediates deriving from enamines **3b** and **3d**, (R= C_6H_5), the greater reactivity of the halogenated carbon atom favours the cyclization process to the imidazole ring.

SCHEME 6



EXPERIMENTAL

M. ps were taken with a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian A-360 instrument at 60 MHz with Me_4Si as internal standard. IR spectra were recorded on a Perkin Elmer 1310 spectrometer and Mass spectra on a Varian MAT 311-A mass spectrometer using the electron ionization technique (electron energy 70 eV) and the direct introduction (probe temperature 120°C; ion source temperature 250°C).

Enamines (3a-d).
The enamines employed in this work are known compounds and were prepared according to described methods[2].

N-Sulfonylbenzamidines (6a-b).
N-(4-methyl-benzenesulfonyl)-benzamidine 6a is a known compound[6] N-(4-nitrobenzenesulfonyl)-benzamidine 6b is new and was prepared by reaction between benzamidine hydrochloride and 4-nitrobenzenesulfonyl chloride in acetone/acq. NaOH, according to the procedure of ref. 6. Yield: 65%; m.p. 177

-180°C; elem. anal., found % (calcd for $C_{13}H_{11}N_3O_4S$): C 50,97(51,13); H 3,58(3,63); N 13,79(13,76); IR (nujol), ν_{max} 3300 and 3450 (NH) cm^{-1}.

N-Chloro-N'-sulfonylbenzamidines (**4a-b**).
N-Chloro-N'-(4-methyl-benzenesulfonyl)-benzamidine **4a** is a known compound[6] N-Chloro-N'-(4-nitrobenzenesulfonyl)-benzamidine **4b** is new and was prepared from **4b** using tert-butyl hypochlorite as chlorinating agent, according to the procedure of ref. 6. Yield: 99%; m.p. 155°C; elem.anal., found % (calcd for $C_{13}H_{10}ClN_3O_4S$): C 42,38(42,95); H 2,76(2,96); N 11,19(12,37); IR (nujol), ν_{max} 3270 (NH) cm^{-1}.

Reaction of enamines **3a** and **3c** with N-chloroamidines **4a-b**.
A) To a solution of 10 mmol of N-chloroamidine in dry dichloromethane (40ml), cooled at -30°C, 10 mmol of enamine dissolved in dry dichloromethane (20ml) were added dropwise. The mixture was analyzed by tlc until no more haloamidine was detectable, then was freed from the solvent under reduced pressure without heating, and chromatographed on a silica gel column (ratio crude/silica gel 1:40). The column was eluted with ethyl ether yielding progressively 2-chloro-2-methyl-propanal **5**, identified by comparison (tlc, NMR) with an authentic sample; morpholine or piperidine detected by GLC and N-sulfonylamidine **6**, identified by comparison (tlc, IR) with an authentic sample.
B) The crude product obtained by reacting enamine **3a** and N-chloroamidine **4a** was dissolved in dry isopropanol at room temperature and recrystallized at -20°C to yield 2.79g (62%) of N-(4-methylbenzenesulfonyl)-N'-[(2-chloro-2-methyl-1-morpholino)- propyl]-benzamidine **7a** melting at 100-102°C. Elem. anal., found % (calcd for $C_{22}H_{28}ClN_3O_3S$): C 58,87(58,71); H 6,18(6,27); N 9,27(9,34). ^{1}H-NMR ($CDCl_3$), δ: 1,56(s,3H,CH_3); 1,68(s,3H,CH_3); 2,33(s,3H,CH_3); 2,54(m,2H,CH_2-N); 2,80(m,2H,CH_2-N); 3,53 (m,4H,CH_2-O-CH_2); 4,83(d,1H,CH-N); 6,06(d,1H,NH); 6,85-8,00(m,9H,arom.).
C) The crude product obtained by reacting enamine **3c** and N-chloroamidine **4b** was washed several times with dry benzene and filtered to give 3.22g (67%) of N-(4-nitrobenzenesulfonyl)-N'-[(2-chloro-2-methyl-1-morpholino)-propyl]-benzamidine **7b** melting at 118-121°C. Elem. anal., found % (calcd for $C_{21}H_{25}ClN_4O_5S$): C 52,77(52,55); H 5,32(5,25); N 11,92(11,65).
^{1}H-NMR ($CDCl_3$), δ: 1,56(s,3H,CH_3); 1,70(s,3H,CH_3); 2,54(m,2H,CH_2-N); 2,86(m,2H,CH_2-N); 3,60(m,4H, CH_2-O-CH_2); 4,83(d,1H,CH-N); 6,20(d,1H,NH); 7,23-8,26(m,9H,arom.).

Reaction of enamine **3b** and **3d** with N-chloroamidines **4a-b**.
To a well stirred solution of N-haloamidine (3,2 mmol) in dry dichloromethane (15 ml), cooled at -30°C, a solution of enamine (3,2 mmol) in dry dichloromethane (10 ml) was added dropwise over a period of 30 minutes. Stirring was continued at room temperature for 48 h, then the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (ratio crude product/silica gel, 40:1) yielding N-sulfonyl-4,5-dihydro-1midazoles **8a-d** beside 2-chloro-2-phenylpropanale **9**, N-sulfonylamidine **6**, morpholine or piperidine. For data of **8a-d**, see Table 1.

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5) We would like to thank Dr. B.Gioia for helpful discussion on the analysis of the mass spectra.
6) E.Rossi and R.Stradi, Gazz.Chim.It. 111, 299 (1981).