REACTIONS WITH AZIRIDINES - 39[1].
RING OPENING OF ACTIVATED 2,2-DIMETHYLAZIRIDINES
BY GRIGNARD REAGENTS. A MECHANISTIC STUDY.

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Abstract - Reaction of activated 2,2-dimethylaziridines 1 with Grignard reagents RMgHal in boiling THF can yield the products 2 of normal aziridine ring opening, the rearranged opening products 3, and the methallylamides 4 (isomers of 1). The product distribution depends on R, Hal, and experimental conditions, and very strongly on the nature of the activating group A. It is shown that 1 is opened (reversibly for A = sulfonyl) forming 10 through a Lewis acid assisted attack of $Hal^{\ominus}$ on the tert carbon of 1 (abnormal opening by $Hal^{\ominus}$). Evidence is presented to show that 4 as well as 3 come from this intermediate.

INTRODUCTION

In a recent report on the reaction of 1e with Grignard reagents RMgHal Zjawiony et al.[2] found the expected "normal" nucleophilic ring opening (2e) with R = benzyl or alkyl. However, with R = aryl they obtained also the rearranged substitution products 3e. They interpreted the formation of 3e by an attack of the Grignard reagent on a Schiff base intermediate 5e that was supposed to form thermally at 120-130°C. This assumption of a thermal formation of 5e is not well compatible both with the known[3] one-step isomerization 1 → 4 for A = acyl or sulfonyl and with the statement of the authors that 4e forms up to at least 50% at higher temperatures.

Recently, we needed a sample of 2aP for a mechanistic study of Friedel-Crafts reactions. When we caused 1a to react with PhMgBr in THF, we obtained (Scheme 1; Table 1, run 1) a mixture of 2aP and 3aP along with some 4a. This finding prompted an investigation[5] whose results have mechanistic as well as preparative bearings. The rearranging substitution seems to be an analogue of the known[6-10] oxirane rearrangements. However, the aziridine case introduces further variables, viz. nucleofugality and basicity of the leaving group $NA^{\ominus}$ as well as structure and steric demands of the activating group A. So, the present work may shed more light not only on the aziridine chemistry but also on the oxirane chemistry.

$$\underset{1}{\text{N-A}} \xrightarrow[\text{THF reflux}]{\text{RMgHal}} \underset{2}{R-\text{NH-A}} + \underset{3}{R-\text{NH-A}} + \underset{4}{\text{NH-A}}$$
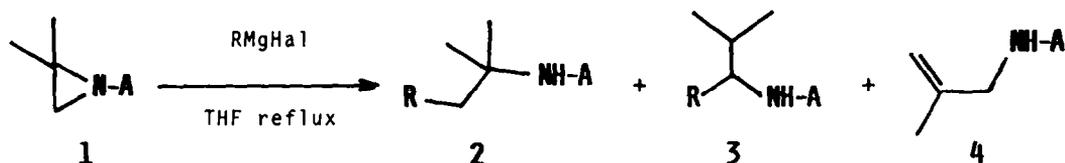
Activating

Group A: a = Ts   Substituent

  b = 2,5-dichlorobenzenesulfonyl ("Diclosyl", Dcs)   R: B = benzyl

  c = Pivaloyl (COCMe$_3$, Piv)   M = methyl

  d = COPh   P = phenyl

  e = POPh$_2$

SCHEME 1

Table 1. Reactions of Aziridines 1 with an Excess[a] of RMgHal in Boiling THF.

Run	1	A	R	Hal	Time [h]	Yields[b] [%] 2	3	4	1	Yield Ratio 2/3	2/(3 + 4)
1[c]	1a	Ts	Ph	Br	4	(48)	(25)	(13)	–	66/34	56/44
2[d]	1a	Ts	Ph	Br	5.5	(15)	(15)	(10)	(60)	50/50	38/62
					22	(28)	(28)	(9)	(35)	50/50	43/57
3[e]	1a	Ts	Ph	Br	4	(58)	(29)	(8)	–	67/33	61/39
4	1a	Ts	Ph	Br	4	(61)	(35)	(4)	–	64/36	61/39
5	1a	Ts	Ph	Br	4	(57)	(37)	(4)	–	61/39	5o/42
6	1a	Ts	Ph	Br	22	(63)	(34)	(2)	–	65/35	64/36
7	1a	Ts	Ph	I	5	(11)	(56)	(29)	–	16/84	11/89
8	1a	Ts	Ph	I	22	(16)	(55)	(24)	–	22/78	17/83
9	1a	Ts	Ph	I	96	(8)	(55)	(29)	–	13/87	9/91
10[f]	1a	Ts	PhCH$_2$	Br	22	36	56	–	–	39/61	39/61
11	1a	Ts	Me	I	5	–	95	(<1)	–	0/100	0/100
12	1b	Dcs[g]	Ph	Br	1	(28)	–	–	(72)	100/0	100/0
13	1b	Dcs[g]	Ph	Br	22	97	(0.8)	(0.4)	–	99/1	99/1
14	1c	Piv	Ph	Br	4	–	96	–	–	0/100	0/100

[a] 5 mmol 1 and 25 mmol RMgHal (prepared from 25 mmol Mg and 25 mmol RHal) in 80 ml THF if not otherwise stated.

[b] Yields in parentheses from ^{1}H-NMR spectroscopic data.

[c] 10 mmol 1a and 12.5 mmol PhMgBr in 60 ml THF.

[d] 10 mmol 1a and 10 mmol PhMgBr in 200 ml THF.

[e] 2.2 mmol 1a and 12.7 mmol PhMgBr in 80 ml THF. Quenching with D$_2$O.

[f] 5 mmol 1a and 17.8 mmol PhCH$_2$MgBr in 80 ml THF. The Grignard reagent was prepared from 29 mmol PhCH$_2$Br and gave 5.6 mmol bibenzyl.

[g] Dcs = 2,5-Dichlorobenzenesulfonyl; Piv = COCMe$_3$.

RESULTS AND DISCUSSION.

Table 1 shows our results that were obtained in most runs from a large excess of RMgHal. Because of the difficult product separation we estimated the yields of 2aP, 3aP, and 4a in runs 1-9 by ^{1}H-NMR analysis which allowed a clear distinction of the three products. The most striking features of Table 1 are (1) the influence of the activating group A on the competing substitution reactions as shown by the ratio 2/3 in the second last column of Table 1, (2) the formation of 4 in many runs, and (3) the general absence of products arising from a formal attack of $R^{\ominus}$ on the tert carbon of 1 ("abnormal" opening of 1). The latter point indicates that an SET process[11] is not involved.

The yields of 2aP in runs 1-5 show a tendency that suggest a rate dependence on the concentrations of both 1a and PhMgBr, in accord with the bimolecular kinetics of an S_N2 reaction. Such S_N2-like normal opening of 1 is an attack in a distorted neopentyl position. A good leaving group $NA^{\ominus}$ is therefore required to overcome the steric hindrance[11,12]. In other words, this S_N2 opening is kinetically favoured by strong activation: Dcs > Ts >> Piv. With A = Dcs (Diclosyl), practically only the normal product 2 is obtained (runs 12 and 13), while with A = Piv no 2 was formed (run 14). It is not clear whether this dramatic product dependence on A is simply a kinetic effect in the formation of 2. A possible retardation of the competing formation of 3 for A = Dcs is considered below in the discussion of Scheme 3. Such a retardation may perhaps be involved also in the marked change of the product ratio 2/3 when going from A = Ts (run 6) to the slightly stronger activating A = Dcs (run 13).
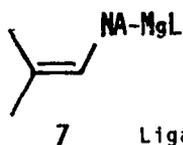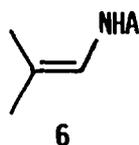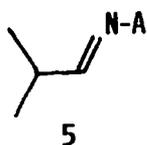
5   6   7   Ligand of Magnesium:
L = Hal or R

The higher yields of 4a in runs 1-3 as compared to runs 4-6 may be correlated with the absence of a large excess of PhMgBr in runs 1 and 2 and with the low concentrations in run 3, i. e. with a slowing down of the reaction that therefor perhaps could not go to completion in runs 1-3. This finding may suggest a transformation of 4 or its anion, respectively, into another product, e. g. into 5 via 7. However, such an explanation is not supported by the results of runs 7-9. An intermediate role of 4a or its magnesium salt could definitely be ruled out when a sample of 4a was recovered unchanged after treatment with a five-fold excess of

PhMgBr or MgBr$_2$ in boiling THF for two days. On
the other hand, we cannot exclude such a transfor-
mation of **4c** under the reaction conditions of
Table 1, since the corresponding process has pre-
viously been observed for **4d** in strongly basic me-
dium[14]. The reason for the probably general differ-
ence in isomerization behaviour between N-allylated

4-C⁻
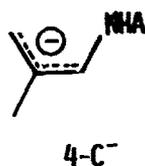
carboxamides and sulfonamides is supposed to be the large basicity difference of
their N-anions. The tautomerization of the N-anion of **4** into the carbanion **4-C**⁻
will be thermodynamically more unfavourable for A = sulfonyl than for A = acyl[15].

In similar experiments we excluded a simple thermal formation of **4** under the
experimental conditions of Table 1. **1a** was recovered unchanged after 20 days in
boiling THF or 6 days in boiling toluene. A better immediate precursor of **4** would
be **8** or its magnesium salt **10**, respectively. A solution of **9a** in THF gave rapidly
a quantitative yield of **4a** on addition of aqueous sodium hydroxide solution, thus
mimicking the basic conditions of work-up for the reactions of Table 1. This fast
dehydrohalogenation is probably the result of an intramolecular E2 mechanism in
which the rapidly formed sulfonamide anion of **9a** (pK$_a$ of **9a** near 11) serves as
base. This assumption found support from the same experiment with **9c** (pK$_a$ probably
about 20[16]) that led to only 25% **4c** along with 29% unreacted **9c** and 31% of what is
supposed to be **12** on grounds of ^{1}H-NMR data.

8

9a,c,d: Hal = Br

10
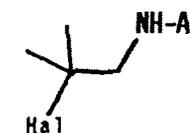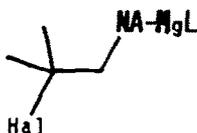
11a,c: Hal = L = Br

Ligand of Magnesium:

L = Hal or R

12c,d
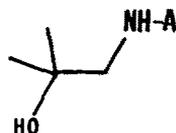
If the magnesium salt **10** is the precursor of **4** in the reactions of Table 1,
it may also be the precursor of the supposed intermediate **5**. Some experiments,
whose results are shown in Scheme 2 and Table 2, supported this view. Refluxing **1a**
with MgBr$_2$ in THF followed by evaporation and immediate flash chromatography (run
1, Table 2) yielded a not separable mixture (^{1}H-NMR analysis) of 50% **9a** (emerging
from the primary product **11a**), 7% **4a**, and 31% of a third product. The IR spectrum
(1632 cm^{-1}, strong band) and in particular the ^{1}H-NMR spectrum of this mixture
were compatible with **6a** as the third product: (δ in ppm) Me 1.46 (s); Me 1.58 (s);

C=CH 6.93 (d, J = 9.6 Hz); comparison with $\underline{6d}$[14,17]: Me 1.72 (s); Me 1.77 (s); C=CH

6.73 (d, J = 10.2 Hz). The structure of the supposed $\underline{6a}$ was confirmed in a second

experiment (run 2, Table 2) when the reaction mixture was worked up under condi-

tions that favour the hydrolytic cleavage of $\underline{6a}$: 37% $\underline{9a}$ and 50% tosylamide ($TsNH_2$)

were obtained from the organic layer, while isobutyraldehyde was detected in the

aqueous layer by the formation of its 2,4-dinitrophenylhydrazone. Excess of $MgBr_2$

(run 3 of Table 2) did not change the ratio $\underline{6a}/\underline{9a}$ (deduced from $TsNH_2/\underline{9a}$ in run 2)

even with extended reaction (run 4). So, in this reaction of $\underline{1a}$ with $MgBr_2$ the

isomerization of $\underline{1a}$ to $\underline{6a}$ does not go to completion, perhaps because of the meta-

thetic reaction $\underline{6a}$ + $\underline{11a}$ → $\underline{7a}$ + $\underline{9a}$ supposing that $\underline{6a}$ is formed from the interme-

diate $\underline{11a}$ through the general reaction sequence $\underline{10}$ → $\underline{5}$ → $\underline{6}$ (vide infra).

$$MgBr_2$$

1a ——————————▶ 6a/7a   +   9a/11a

     THF reflux

                                                          silica gel

                        silica   or H_2O

                        gel

                         6a   9a

                         H_2O

        $TsNH_2$ + $Me_2CH-CH=O$ ——————▶ 2,4-dinitrophenylhydrazone
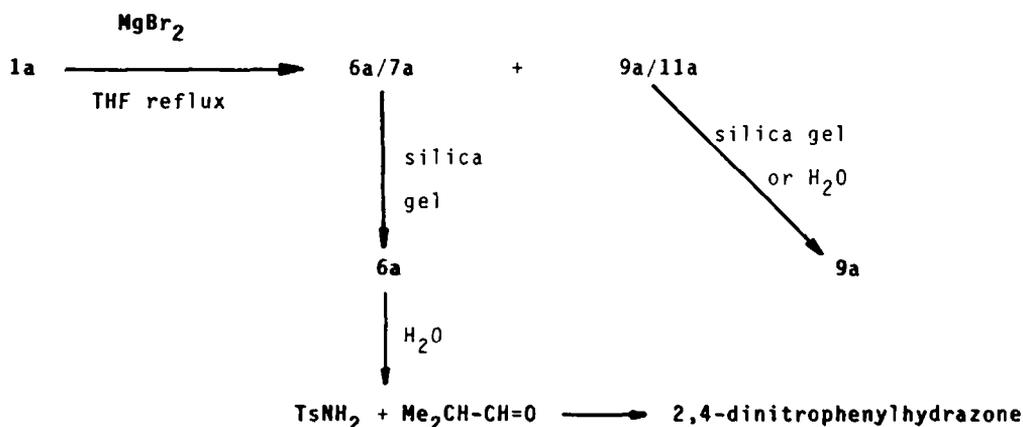
S C H E M E   2

Table 2. Reactions of $\underline{1a}$ with $MgBr_2$ in Boiling THF.

Run	$\underline{1a}$ [mmol]	$MgBr_2$ [mmol]	THF [ml]	React. Time [days]	Hydrolytic Work-Up	Yields[a] [%]
1	5	5	80	2.5	no[b]	(7%) $\underline{4a}$, (31%) $\underline{6a}$, (50%) $\underline{9a}$
2	10	10	80	2.5	sustained homogeneous[c]	50% $TsNH_2$, 37% $\underline{9a}$, Me_2CHCHO[d]
3	5	20	80	2.5	short heterogeneous[e]	(56%) $\underline{6a}$, (41%) $\underline{9a}$
4	2.5	30	40	7	short heterogeneous[e]	(57%) $\underline{6a}$, (38%) $\underline{9a}$

[a] Yields in parentheses from ¹H-NMR spectroscopic data.

[b] Evaporation, followed by flash chromatography (silica gel, CH_2Cl_2).

[c] Work-up as in Table 1: after adding ice, the mixture was concentrated in vacuo (bath temp. ~70°C) and then partitioned (CH_2Cl_2/water).

[d] Identified by the formation of its 2,4-dinitrophenylhydrazone.

[e] Short partitioning between CH_2Cl_2 and water.

The most important aspects of these experiments are the "abnormal" opening of
1 by halide and the formation of the enamide structure 6/7. As for the latter, a
carbenium ion is an unlikely precursor in a Grignard solution, since rapid depro-
tonation should convert it to 4 that would be the final product at least for A =
sulfonyl (see above). So, the enamide structure arises probably from 10. A direct
conversion of 10 into 6 would be mechanistically obscure and would not lead to 3
in the reaction of 1 with RMgHal, since at least for A = sulfonyl the nitrogen of
6 would rapidly be deprotonated (forming 7), thus preventing a tautomerization of
6 into 5. The latter argument holds also for a direct conversion of 10 into 7.
This reasoning was confirmed by a 72% yield of 6a when 1a reacted with a mixture
of 1 equivalent of PhMgBr and 4 equivalents of $MgBr_2$ (vide infra). Therefore it
appears reasonable to propose the reaction sequence 10 → 5 → 6, the first step
having its analogue in the chemistry of epoxides[6-10]. A Grignard reagent would
then add to 5 forming, after protonation, the rearranged substitution product 3.
This proposal requires that the latter addition is faster than the tautomeriza-
tion 5 → 6. A formation of 3 by addition of RMgHal to the C=C double bond of 6 or
7 could be ruled out by quenching the reaction with D_2O (run 3 of Table 1): the
^{1}H-NMR spectrum of the product mixture did not reveal an incorporation of deute-
rium into the isopropyl group of 3aP. Since we did not observe 5a in the reactions
of Table 2 we suppose that the tautomerization is accelerated by $MgBr_2$. So, the
products 3, 4, and 6 come probably from 10, implying that in the reaction of 1
with RMgHal a certain pool of 10 is built up and maintained until the reaction
goes to completion. In run 2 of Table 1, which was performed as a rough kinetic
experiment, the amount of 4a (probably at least in part indicative of 10) remained
constant after the initial increase while the increase in 2aP and 3aP as well as
the decrease in 1a continued after the first 1.5 hours.

The abnormal opening of 1 to form 10 can be explained (1) by electrophilic
assistance through one of the magnesium compounds present and (2) by the high nu-
cleophilicity of the halide ion of the latter. The Lewis acid-Lewis base inter-
action (13 in Scheme 3) forces the ring opening into the borderline region[12]. An
S_N1-like formation of a carbenium ion is unlikely both for A = sulfonyl (see
above) and for A = acyl that should lead to the corresponding oxazoline: compare
ref.[12] and the literature cited therein. The double activation in 13 is expected[12]
to change the reactivity order of 1 so that 11c should form faster than 11a. A
fast formation of 11c is possibly involved in run 14 of Table 1, although the
extraordinary result of run 14 may be caused by a cooperation of various effects
including the above discussed slowing down of the competing formation of 2cP. Ir-
reversibility of the formation of 11c may be another one of these effects. While
the anions of N-(2-halogenoalkyl) sulfonamides form rapidly[18] the corresponding
aziridines by intramolecular displacement of the halide, for the analogous

carboxamides this cyclization is confined to some special cases[19]. The reaction

1 → 10 can therefore be expected to be reversible for A = sulfonyl, but less pro-

bably for A = acyl. Absence of the reverse reaction may enhance the over-all rate

1 → 5 and thus contribute to the result of run 14. Further aspects are considered

in the discussion of Scheme 3.

A normal opening of 1 by halide has to be taken into consideration for

strongly activated 1, but the reversibility would preclude an essential influence

of this opening on the final products.

Final proof for the deduced reaction pathway comes from two reactions of 8.

Reaction of 5 mmol 9a with 30 mmol PhMgBr yielded (after loss of some material du-

ring work-up due to emulsification) a mixture of 15% 2aP, 34% 3aP, and 11% 4a

(^{1}H-NMR analysis). The formation of 2aP requires the intermediacy of 1a, thus pro-

ving the reversibility of the abnormal opening by bromide. The second experiment

performed in the same manner with 9c provided (^{1}H-NMR analysis) 43% 3cP and 43% 6c,

but no 2cP. The structure of 6c was deduced from the ^{1}H-NMR spectrum and confirmed

by NMR comparison with authentic material[17]: (δ in ppm) Me 1.63 (s); Me 1.71 (s);

C=CH 6.53 (d, J = 10.1 Hz). A further experiment corroborated the magnesium halide

catalysis of the tautomerization 5 → 6 as well as the deprotonation of 6 in a

Grignard solution. Reaction of 5 mmol 1a with 5 mmol PhMgBr and 20 mmol $MgBr_2$ pro-

vided (^{1}H-NMR analysis) 5% 2aP, 13% 3aP, 10% 4a, and 72% 6a. The ratio 2aP/3aP is

shifted from about 64:36 in runs 3-5 of Table 1 or 50:50 in run 2 to 28:72 under

the influence of the added magnesium halide. The change in the ratio

normal/abnormal opening (shown in the last column of Table 1) is even more im-

pressive: from 60:40 in runs 3-5 and 43:57 in run 2 to 5:95 in the last

experiment.
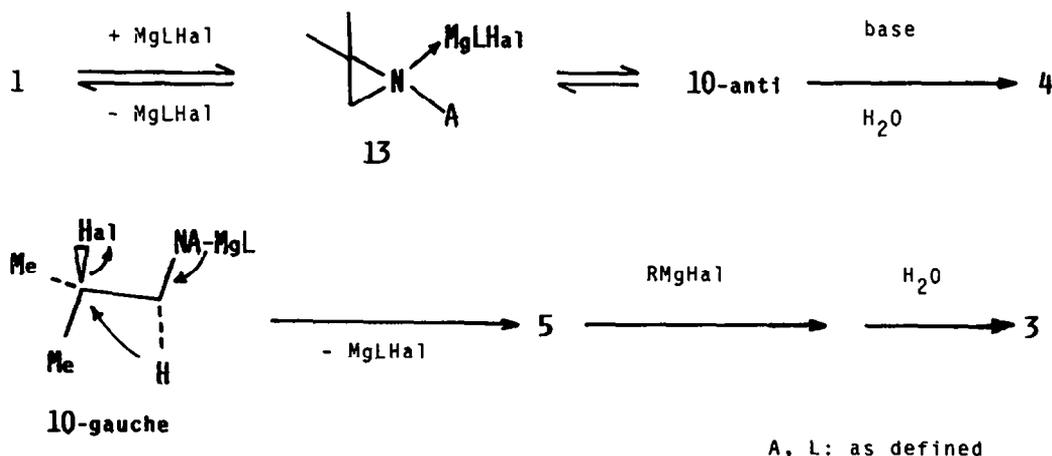
S C H E M E   3

The various pieces of evidence along with the presented arguments allow to establish a reaction scheme for the products 3 and 4: Scheme 3. The first step, i. e. the (reversible) formation of 13, may be sterically hindered as perhaps happens with 1b due to the chlorine atom at the ortho position of Dcs. Formation of 13 is followed by a borderline aziridine opening, yielding 10. This ring opening is reversible for A = sulfonyl, but the equilibrium seems to depend on the nature of the halide among other factors, I favouring 10 more than Br: comp. the last column in Table 1, runs 3-9. In analogy to the epoxide reactions[7-10] we suppose the next event to be the one-step formation of 5 by a halide displacement through a neighbouring hydride and by simultaneous elimination of MgLHal. In order to meet the stereoelectronic requirements for this process, 10 has to adopt a gauche conformation. Finally, 5 adds RMgHal in a fast reaction forming the magnesium salt of 3. The transformation 10 → 5 may be faster for A = Piv than for A = Ts (a) due to the difference in basicity and energy of the anionic part of 10, (b) due to a lower energy of the product 5c owing to conjugation, and (c) perhaps due to a different coordination of the magnesium implicating a different stereoelectronic situation. For A = Piv coordination to the oxygen of A may be favoured while usually an electrophilic assistance of aziridine ring opening will probably operate by binding to the nitrogen (comp. the discussion in ref.[12]). We consider the addition of RMgHal to 5 to be the fastest step in the sequence 1 → 10 → 5 → 3.

4 is formed from 10 exclusively (runs 6-9 of Table 1) or partly during the reaction and partly during work-up. The latter may even dominate (run 2 of Table 1). The rate ratio for the competing conversions of 10 into 4 or 5 seems to depend on Hal (comp. runs 7-9 with runs 4-6) and on R (comp. runs 4-6 with run 10 und runs 7-9 with run 11). The first influence can be explained by a steric effect on the conformational equilibrium of 10. The second influence seems also to be a steric effect, that would be comprehensible if, refining the rough picture of Scheme 3, the conversion 10 → 5 is a cyclic process (comp. ref.[7-10]) producing MgLHal without intercurrent ions.

The competition between the two transformations of the imine 5 (into 6/7 or into 3) is very sensitive to the composition of the reagent as was shown above (1) by the reaction of 1a with the mixture of PhMgBr and MgBr$_2$ and (2) by the reaction of 9c with PhMgBr. We assume that also in the reaction of 9a with PhMgBr formation of 6a accounts for a part of the observed material loss, since 6a can only be detected if special care is taken to avoid its hydrolytic cleavage. Hydrolysis of 6a produces TsNH$_2$ that, dissolved in the strongly alkaline aqueous phase, would offer an explanation for the otherwise not observed extensive and sustained emulsification. The marked influence of the reagent composition is easy to understand on the basis of the proposed MgHal$_2$ catalysis of the tautomerization 5 → 6.

EXPERIMENTAL

IR spectra (KBr tablets or film) were recorded on a Perkin-Elmer 283 spectrometer.
^{1}H-NMR spectra (CDCl$_3$, internal TMS) were recorded on a Varian T 60-A spectrometer, operating at 60 MHz, on a Bruker HX 90-E spectrometer, operating at 90 MHz, or on a Bruker WM 250 spectrometer, operating at 250 MHz. Chemical shifts are recorded in ppm, coupling constants in Hz. The letters br, vbr, sh, s, d, t, q, m, and mc denote broad, very broad, shoulder, singlet, doublet, triplet, quadruplet, multiplet, and multiplet centered at, respectively. Mass spectra were obtained from a Varian MAT 311-A spectrometer. Microanalyses were obtained from a Heraeus CHN-Rapid instrument.

Starting Materials.

THF was anhydrous. Magnesium bromide: magnesium bromide etherate (99%) was purchased from Aldrich and used in the supplied form. Aziridines 1a-c were prepared[20] from 2,2-dimethylaziridine and the respective acid chloride according to a known procedure. For 1c see ref. 20.

1-(2,5-Dichlorobenzenesulfonyl)-2,2-dimethylaziridine (1b). Yield 92%; m.p. 88°C; IR (KBr) ν 1325, 1160/cm; H-NMR (90 MHz) δ 1.60 (s, 6H, Me, Me), 2.66 (s, 2H, CH$_2$), 7.27-8.10 (m, 3H, ArH); MS e/m (150°C, 37-Cl peaks omitted) 279 (M, 0.7), 238 (DcsNHCH$_2$, 4), 209 (Dcs, 7), 161 (3), 145 (dichlorophenyl, 9), 109 (8), 70 (M – Dcs, 100). Anal. Calcd for C$_{10}$H$_{11}$Cl$_2$NO$_2$S: C, 42.87; H, 3.96; N, 5.00. Found: C, 42.80; H, 4.04; N 4.83.

N-Methallyl-4-toluenesulfonamide (4a). A solution of 0.1 mol sodium methoxide, 0.1 mol tosylamide, and 0.1 mol methallyl chloride in 300 ml methanol was refluxed for 4 h. The mixture was evaporated to dryness, dissolved in CH$_2$Cl$_2$, and washed with water. Subsequent chromatography (CH$_2$Cl$_2$) provided 29% 4a. Oil; IR (film) ν 3295, 1660, 1322, 1158/cm; H-NMR (90 MHz) δ 1.67 (s, 3H, Me), 2.40 (s, 3H, Me of Ts), 3.45 (d, 6.6 Hz, 2H, N-CH$_2$), 4.78 (br s, 1H, C=CH), 4.85 (br s, 1H, C=CH), 5.35 (br t, 6.6 Hz, 1H, NH), 7.26-7.35 (m, 2H, m-H of Ts), 7.72-7.81 (m, 2H, o-H of Ts); MS m/e (60°C) 225 (M, 13), 210 (M – Me, 2), 184 (TsNHCH$_2$, 2), 155 (Ts, 24), 91 (67), 70 (M – Ts, 100). Anal. Calcd for C$_{11}$H$_{15}$NO$_2$S: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.52; H, 6.73; N, 5.93.

N-(2-Bromo-2-methylpropyl)-4-toluenesulfonamide (9a). A solution of 10 mmol 1a in 20 ml CH$_2$Cl$_2$ was stirred with 3.4 g hydrobromic acid (48%) for 10 min. Evaporation of the organic layer provided 95% 9a. M.p. 84°C; IR (KBr) ν 3275, 1325, 1160/cm; H-NMR (90 MHz) δ 1.74 (s, 6H, Me, Me), 2.43 (s, 3H, Me of Ts), 3.15 (d, 6.8 Hz, 2H, CH$_2$), 5.15 (br t, 6.8 Hz, 1H, NH), 7.27-7.36 (m, 2H, m-H of Ts), 7.71-7.80 (m, 2H, o-H of Ts); MS m/e (80°C, 81-Br peaks omitted) 305 (M, 3), 226 (M – Br, 7), 184 (TsNHCH$_2$, 71), 155 (Ts, 74), 91 (100). Anal. Calcd for C$_{11}$H$_{16}$BrNO$_2$S: C, 43.15; H, 5.27; N, 4.57. Found: C, 43.05; H, 5.18; N, 4.76.

N-(2-Bromo-2-methylpropyl)-trimethylacetamide (9c). Preparation was analogous to 9a. Yield 94%; m.p. 39°C; IR (KBr) ν 3380, 1648, 1532/cm; H-NMR (90 MHz) δ 1.25 (s, 9H, tBu), 1.73 (s, 6H, Me, Me), 3.52 (d, 6.1 Hz, 2H, CH$_2$), 6.20 (vbr s, 1H, NH); MS m/e (25°C, 81-Br peaks omitted) [235.0565 (235.0558 required)] 235 (M, 0.8), 220 (M – Me, 0.4), 192 (0.9), 156 (M – Br, 35), 114 (PivNHCH$_2$, 37), 85 (Piv, 43), 57 (tBu, 100). Anal. Calcd for C$_9$H$_{18}$BrNO: C, 45.77; H, 7.68; N, 5.93. Found: C, 45.96; H, 7.56; N, 5.90.

Reactions of 1 with Grignard Reagents (Table 1).

General Procedure. If not otherwise stated in Table 1, the Grignard solution was prepared from 30 mmol magnesium turnings in 20 ml boiling THF by dropwise addition of 25 mmol RHal, dissolved in 20 ml THF, and by maintaining this mixture under reflux for 15 min. A solution of 5 mmol 1 in 40 ml THF was added under reflux and the mixture stirred under reflux for a further time given in Table 1. After cooling to room temp. cold water (D$_2$O in run 3) was added. The mixture was concentrated in a rotatory evaporator. The aqueous residue was shaken with CH$_2$Cl$_2$. The obtained organic layer was washed with water and evaporated to dryness. The residue was analyzed by H-NMR or separated by chromatography on silica gel with CH$_2$Cl$_2$ or mixtures of CH$_2$Cl$_2$ and ethyl acetate, the percentage of the latter increasing from 0% to 100% in some cases. In run 13, 97% 2bP was eluted with 4:1 of the latter solvent mixture; elution with 3:2 yielded a mixture of (H-NMR) 0.8% 3bP, 0.4% 4b, and 0.4% 2bP.

N-(1,1-Dimethyl-2-phenethyl)-4-toluenesulfonamide (2aP). Obtained from an insufficient chromatographic separation of run 1 by recrystallizing the first eluate from ethanol. M.p. 121°C; IR (KBr) ν 3280, 1320, 1155/cm; H-NMR (90 MHz) δ 1.14 (s, 6H, Me, Me), 2.36 (s, 3H, Me of Ts), 2.84 (s, 2H, CH$_2$) 5.31 (br s, 1H, NH), 7.15-7.23 (m, 2H, m-H of Ts), 7.23 (s, 5H, Ph), 7.69-7.78 (m, 2H, o-H of Ts); MS m/e (130°C) 288 (M – Me, 0.7), 260 (M – iPr, 0.6), 212 (M – benzyl, 80), 155 (Ts, 42), 91 (100). Anal. Calcd for C$_{17}$H$_{21}$NO$_2$S: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.32; H, 7.12; N, 4.64.

N-(1-Phenyl-2-methylpropyl)-4-toluenesulfonamide (3aP). Obtained from one eluate of an insufficient chromatographic separation of run 9 by recrystallization from ethanol. M.p. 142°C; IR (KBr) ν 3290, 1325, 1165/cm; H-NMR (250 MHz) δ 0.73 (d, 6.7 Hz, 3H, Me), 0.94 (d, 6.7 Hz, 3H, Me), 1.85-1.99 (m, 1H, CH of iPr), 2.32 (s, 3H, Me of Ts), 4.02 (mc, 1H, N-CH), 5.29 (br d, 8.4 Hz, 1H, NH), 6.91-7.11 (m, 7H, Ph, m-H of Ts), 7.47-7.51 (m, 2H, o-H of Ts); MS e/m (100°C) 303 (M, 0.1), 260 (M - iPr, 84), 155 (Ts, 44), 104 (9), 91 (100). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.03; H, 7.10; N, 4.33.

N-(1,1-Dimethyl-3-phenylpropyl)-4-toluenesulfonamide (2aB). M.p. 113°C; IR (KBr) ν 3285, 1320, 1160/cm; H-NMR (250 MHz) δ 1.21 (s, 6H, Me, Me), 1.75-1.82 (m, 2H, N-C-CH₂), 2.34 (s, 3H, Me of Ts), 2.57-2.64 (m, symmetrical to m at 1.75-1.82 but somewhat broader, 2H, N-C-C-CH₂), 5.26 (br s, 1H, NH), 7.01-7.31 (m, 7H, Ph, m-H of Ts), 7.81-7.84 (m, 2H, o-H of Ts); MS m/e (140°C) 317 (M, 0.3), 302 (M - Me, 2), 226 (M - benzyl, 7), 212 (M - PhCH₂CH₂, 57), 155 (Ts, 39), 146 (M - TsNH₂, 49), 131 (146 - Me, 16), 105 (PhCH₂CH₂, 7), 91 (100). Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30; N, 4.41. Found: C, 67.86; H, 7.24; N, 4.01.

N-(1-Benzyl-2-methylpropyl)-4-toluenesulfonamide (3aB). M.p. 97°C; IR (KBr) ν 3295, 1325, 1165/cm; H-NMR (250 MHz) δ 0.85 (d, 6.8 Hz, 3H, Me), 0.88 (d, 6.8 Hz, 3H, Me), 1.78-1.85 (m, 1H, CH of iPr), 2.40 (s, 3H, Me of Ts), 2.44-2.77 (m, 2H, CH₂), 3.23-3.38 (m, 1H, N-CH), 4.31 (br d, 8.4 Hz, 1H, NH), 6.95-7.32 (m, 7H, Ph, m-H of Ts), 7.57-7.60 (m, 2H, o-H of Ts); MS m/e (120°C) 274 (M - iPr, 11), 226 (M - benzyl, 62), 155 (Ts, 37), 91 (100). Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30; N, 4.41. Found: C, 67.91; H, 7.24; N, 4.05.

N-(1,2-Dimethylpropyl)-4-toluenesulfonamide (3aM). Oil; IR (film) ν 2980, 1342, 1168/cm; H-NMR (250 MHz) δ 0.81 (d, 6.8 Hz, 6H, Me, Me), 0.93 (d, 6.8 Hz, 3H, N-C-Me), 1.58-1.74 (m, 1H, CH of iPr), 2.43 (s, 3H, Me of Ts), 3.12-3.24 (m, 1H, N-CH), 4.36 (br d, 9.3 Hz, 1H, NH), 7.28-7.31 (m, 2H, m-H of Ts), 7.75-7.78 (m, 2H, o-H of Ts); MS m/e (50°C) 241 (M, 0.9), 198 (M - iPr, 37), 171 (TsNH₂, 5), 155 (Ts, 48), 91 (100). Anal. Calcd for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.93; N, 5.80. Found: C, 60.11; H, 7.62; N, 5.67.

N-(1,1-Dimethyl-2-phenethyl)-2,5-dichlorobenzenesulfonamide (2bP). M.p. 157°C; IR (KBr) ν 3260, 1335, 1160/cm; H-NMR (90 MHz) δ 1.16 (s, 6H, Me, Me), 2.86 (s, 2H, CH₂), 5.15 (br s, 1H, NH), 6.96-7.83 (m, 7H, Ph, m-H and p-H of Dcs), 8.19 (mc, 1H, o-H of Dcs); MS m/e (120°C, 37-Cl peaks omitted) 266 (M - benzyl, 100), 209 (Dcs, 30), 145 ($C_6H_3Cl_2$, 35), 91 (10). Anal. Calcd for $C_{16}H_{17}Cl_2NO_2S$: C, 53.64; H, 4.78; N, 3.91. Found: C, 53.65; H, 4.67; N, 3.65.

N-(1-Phenyl-2-methylpropyl)-2,5-dichlorobenzenesulfonamide (3bP). Obtained only in a mixture with 2bP and 4b. H-NMR (90 MHz) δ 0.72 (d, 6.6 Hz, 3H, Me), 0.99 (d, 6.6 Hz, 3H, Me), 1.88-2.05 (m, 1H, CH of iPr), 4.04 (mc, 1H, N-CH), 5.62 (br d, 8.5 Hz, 1H, NH), 6.91-7.49 (m, Ph, m-H and p-H of Dcs of 3bP + 2bP + 4b), 8.05 (mc, o-H of Dcs of 3bP + 2bP + 4b); strong peak typical of 3bP in a MS of the mixture with 2bP and 4b m/e (120°C) 314 (M - iPr).

N-Methallyl-2,5-dichlorobenzenesulfonamide (4b). Obtained only in a mixture with 2bP and 3bP. H-NMR (90 MHz) δ 1.67 (s, 3H, Me), 3.50 (d, 6.8 Hz, 2H), 4.86 (vbr s, 2H, C=CH₂), two m for ArH see H-NMR of 3bP (preceding compd.); peak typical of 4b in a MS of the mixture with 2bP and 3bP m/e (120°C) 279 (M).

N-(1-Phenyl-2-methylpropyl)-trimethylacetamide (3cP). M.p. 102°C; IR (KBr) ν 3320, 1648, 1532/cm; H-NMR (250 MH) δ 0.83 (d, 6.8 Hz, 3H, Me), 0.94 (d, 6.8 Hz, 3H, Me), 1.20 (s, 9H, tBu), 1.95-2.20 (m, 1H, CH of iPr), 4.75 (mc, 1H, N-CH), 6.00 (br s, 1H, NH), 7.25 (s, 5H, Ph); MS m/e (40°C) 233 (M, 15), 190 (M - iPr, 100), 132 (M - PivNH₂, 7), 106 (32), 91 (23), 85 (Piv, 27), 57 (tBu, 100). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.94; N, 6.00. Found: C, 76.87; H, 10.13; N, 5.64.

Experiments Concerning the Reaction Mechanism

Run 2 of Table 1. Rough kinetic results. Aliquot parts were worked up according to the General Procedure of the Grignard reactions and analyzed by H-NMR.

0.5 h	84% 1a	4% 2aP	4% 3aP	8% 4a
1.5 h	73% 1a	8% 2aP	8% 3aP	11% 4a
2.5 h	68% 1a	10% 2aP	10% 3aP	12% 4a
3.5 h	65% 1a	11% 2aP	11% 3aP	13% 4a
4.5 h	63% 1a	12% 2aP	12% 3aP	13% 4a
5.5 h	60% 1a	15% 2aP	15% 3aP	10% 4a

Hydrolysis of 9a,c yielding 4a or 4c and 12c, respectively. A solution of 3 mmol 9a in 10 ml THF was thoroughly mixed with 20 ml 10% aqueous sodium hydroxide solution. Shaking with CH₂Cl₂, separation of the two layers, and evaporation of the dried organic layer provided 98% 4a. 9c provided in the same manner a mixture (H-NMR) of 29% educt 9c, 25% 4c, and 31% 12c. The structure of the latter product was deduced from a singlet at 1.23 ppm and a doublet (6.0 Hz) at 3.22 ppm. This assignment is supported by comparison of the pair 9c/12c with the corresponding pair 9d/12d[17,21]: 9d singlet at 1.77 ppm and doublet (6.0 Hz) at 3.70 ppm; 12d singlet at 1.28 ppm and doublet (6.0 Hz) at 3.47 ppm.

N-Methallyl-trimethylacetamide (4c). Authentic material (for spectral comparison) was prepared by heating 1c 21 h to 100°C and recrystallizing from CH₂Cl₂/hexane.

M.p. 61°C; IR (KBr) ν 3340, 1642, 1538/cm; H-NMR (60 MHz) δ 1.23 (s, 9H, tBu), 1.70 (s, 3H, Me), 3.75 (d, 7.0 Hz, 2H, CH_2), 4.77 (vbr s, 2H, C=CH_2), 6.00 (vbr s, 1H, NH). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.03; N, 9.02. Found[23]: C, 69.91; H, 11.10; N, 9.19.

Reactions of 1a with $MgBr_2$ (Table 2) yielding 4a, 6a, 9a, tosylamide, and isobutyraldehyde, respectively.
Run 1. The evaporated reaction mixture was taken up in CH_2Cl_2 and immediately subjected to flash chromatography (silica gel, 5 cm × 5 cm, CH_2Cl_2). The eluate was analyzed by H-NMR.
Run 2. Work-up according to the General Procedure of the reactions with Grignard reagents. The aqueous layer and the first washing of the organic layer were caused to react with 2,4-dinitrophenylhydrazine/sulfuric acid[22a] yielding the 2,4-dinitrophenylhydrazone of isobutyraldehyde, m.p. 181°C (lit.[22b] 182°C), mixed m.p. 181°C, IR and H-NMR spectrum identical with the spectra of authentic material. The product mixture obtained from the organic layer was chromatographed (CH_2Cl_2/ethyl acetate 4:1) yielding succesively 37% 9a and 50% tosylamide.
Run 3 and run 4. The reaction mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2, shortly washed twice with a small amount of water, dried, and evaporated. The residue was analyzed by H-NMR.

N-(2,2-Dimethylvinyl)-4-toluenesulfonamide (6a). Obtained in mixtures only. IR (KBr) ν 3295, 1632, 1338/cm; H-NMR (90 MHz) δ 1.46 (br s, 3H, Me), 1.60 (br s, 3H, Me), 2.40 (s, 3H, Me of Ts), 5.79 (br d, 9.6 Hz, 1H, C=CH), 6.49 (br d, 9.6 Hz, 1H, NH), 7.25-7.33 (m, 2H, m-H of Ts), 7.71-7.79 (m, 2H, o-H of Ts); MS m/e (100°C, rel. intensity in a mixture with 2aP and 3aP) 225 (M, 24), 155 (Ts, 35), 91 (100), 70 (C_4H_8N, 96).
Attempts to isolate and purify 6a (and 6c, vide infra), by chromatography or recrystallization were unsuccessful, partly due to the instability of the product.

Reactions of 9a,c with PhMgBr yielding 2aP, 3aP, and 4a, or 3cP and 6c, respectively.
Reaction of 9a. Reaction and work-up was analogous to the General Procedure of the reactions with Grignard reagents. The aqueous residue, obtained by addition of cold water to the reaction mixture and subsequent concentrating in vacuo, gave a stable emulsion on shaking with CH_2Cl_2. This emulsion could partially slowly (about 5 h) be broken by addition of NaCl and $MgSO_4$. The arising organic layer was dried, evaporated, and analyzed by H-NMR. The reaction of 9c was performed analogously without the formation of an emulsion.

N-(2,2-Dimethylvinyl)-trimethylacetamide (6c). Obtained only in a mixture with 3cP. H-NMR (90 MHz) δ 1.24 (s, 9H, tBu), 1.63 (br s, 3H, C=C-Me), 1.71 (br s, 3H, C=C-Me), 6.53 (br d, 10.1 Hz, further splitting recognizable, 1H, C=CH), 6.97 (br s, 1H, NH). Authentic material[17] revealed (250 MHz) the multiplet character of the two C=C-Me singlets and of the two doublet lines of C=CH: Coupling Me/Me 0.5 Hz, coupling C=CH/Me 1.4 Hz for both methyls; IR (KBr) ν 3360, 1658 sh, 1644, 1510/cm.

Reaction of 1a with PhMgBr/$MgBr_2$ yielding 2aP, 3aP, 4a, and 6a.
Reaction and work-up were analogous to the General Procedure of the reactions with Grignard reagents. $MgBr_2$ etherate was added to the Grignard solution before the addition of 1a. Each added portion of $MgBr_2$ produced a violet colour that disappeared immediately.

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