Methyl Shifts in 1,4-Dipoles from Sulfonyl Isocyanates and Ketene *O,N*-Acetals

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At low temperature, sulfonyl isocyanates **1** react with ketene *O,N*-acetals **2** to give 1,4-dipoles **3**. On warming, dipoles **3** rearrange in a formal $O \rightarrow N$ methyl shift to give malonamides **4**. A crossover experiment starting from **2a** and **2b** with a deuterated *O*-methyl group gave scrambling of the label and thus confirmed the intermolecular nature of the methyl transfer.

Methyl-Verschiebungen in 1,4-Dipolen aus Sulfonylisocyanaten und Keten-*O,N*-acetalen

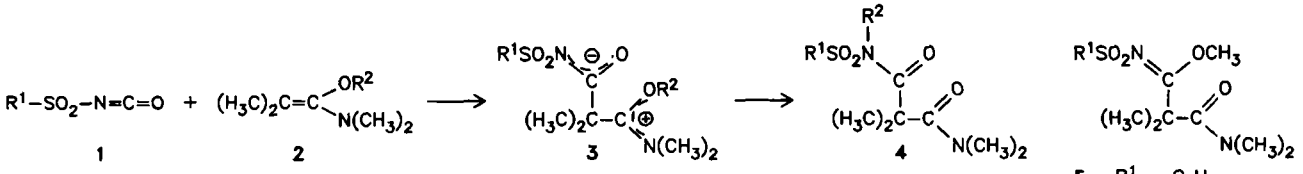
Bei niedriger Temperatur reagieren Sulfonylisocyanate **1** und Keten-*O,N*-acetale **2** zu 1,4-Dipolen **3**. Beim Erwärmen lagern sich die Dipole **3** in einer formalen $O \rightarrow N$-Methyl-Wanderung zu Malonamiden **4** um. Ausgehend von **2a** und **2b** mit deuterierter *O*-Methyl-Gruppe gab ein Kreuzungsversuch halbdeuterierte Produkte und bewies so, daß die Methyl-Verschiebung intermolekular verläuft.

1,4-Dipoles have been frequently invoked as intermediates in [2 + 2] cycloadditions between highly electrophilic heterocumulenes and electron-rich olefins[1-4]. Besides cyclization, zwitterions derived from olefins with hydrogen on the nucleophilic terminus of the C=C bond may undergo a hydrogen shift to give acyclic products[2,5]. If the cationic portion of a 1,4-dipole is substituted by a siloxy group, a 1,5-silyl migration to the anion part readily ensues[2,3,6]. Remarkably, even methyl shifts from methoxy residues have been observed[4,7]. Among the reported cases, the reaction between sulfonyl isocyanates **1** and 1-alkoxy-1-(dimethylamino)alkenes ("ketene *O,N*-acetals") such as **2** presents an exceptional example as the intermediate dipole can be isolated and allows the mechanism of methyl transfer to be studied[4]. Our preliminary investigation indicated an intramolecular pathway which would refute predictions based on the feasibility of an endocyclic S_N-reaction[8] or of a 6-*endo*-tet process[9]. Therefore, a reinvestigation of the title reaction seemed desirable.

Synthesis and Structure Elucidation of Rearranged Products

Sulfonyl isocyanates **1b,c** and dimethylketene *O,N*-acetal **2a** have been reported to react at low temperature to give zwitterions **3c,d**[4]. The same type of reaction has now been observed for isocyanate **1a**. On standing at room temperature or on brief refluxing of solutions in acetonitrile, zwitterions **3a,c,d** rearrange to give isomers which are less polar than **3** and not prone to hydrolysis. Characteristic features of the products are two IR absorptions in the double-bond range around 1680 and 1630 cm^{-1} and, at least on cooling of the sample, magnetic non-equivalence of the methyl residues in the dimethylamino group. Based on this evidence, cyclization of **3** to β-lactams can be ruled out, but distinction between **4** and **5**, the two possible products of methyl transfer, is less straightforward. Following HSAB theory[10], a shift of the cationic methyl group to oxygen as the hard terminus of the ambident anion portion in **3** to give **5** was originally favored[4]. However, the ^{13}C-NMR spectrum of the product from zwitterion **3a** (**3d**) shows a signal at δ = 31.7 (33.1) in the *N*-methyl range and two carbonyl resonances at δ = 170.9, 175.3, (170.4, 173.4) in accord with constitution **4**.

To prove the constitution of the rearranged products, independent syntheses of **4c,d** and **5a,b** by selective *O*- or *N*-methylation of amides **4f,g**[4] were attempted. Based on ^1H NMR and thin-layer chromatographic evidence, reactions with methyl iodide in acetonitrile, dimethyl sulfate, or



	R^1
1a	CH_3
b	C_6H_5
c	$4\text{-}H_3CC_6H_4$

	R^2
2a	CH_3
b	CD_3

3, 4	R^1	R^2
a	CH_3	CH_3
b	CH_3	CD_3
c	C_6H_5	CH_3
d	$4\text{-}H_3CC_6H_4$	CH_3
e	$4\text{-}H_3CC_6H_4$	CD_3
f	C_6H_5	H
g	$4\text{-}H_3CC_6H_4$	H

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diazomethane using standard procedures[11,12] gave the same methylation products as obtained from **3c,d** and only trace amounts of the isomer, if any. However, addition of diazomethane to **4f,g** with silica gel catalysis[13] furnishes mixtures of *N*-methly products **4** and *O*-methyl isomers **5** which can be separated by chromatography and unambiguously identified by spectroscopic means (see Experimental). By comparison, the constitution of *N*-methyl derivatives **4c,d** could be unequivocally established for the products from dipoles **3c,d**.

Mechanism of Methyl Transfer

A cross-over experiment involving zwitterion **3c** and the dipole from **1c** and **2** ($R^2 = C_2H_5$) gave only one product of methyl transfer (**4c**) and one secondary amide (**4g**)[4]. This result would only prove an intramolecular pathway for the rearrangement, if the rate constants of methyl transfer in **3c** and of ethylene elimination from **3** ($R^1 = 4\text{-}H_3CC_6H_4$, $R^2 = C_2H_5$) happen to be the same magnitude. To clarify this mechanistic point, we turned to a rigorous experiment employing **2a** and the deuterated analogue **2b**. Now a difference in rate constants can only be due to a secondary isotope effect which should be negligible, if the deuterium incorporation is monitored by NMR spectroscopy. For better chromatographic separation of the products, isocyanates **1a** and **c** were used in the reaction with **2b** and **2a** to give **3b** and **3d**, respectively. Subsequently, the mixture was rearranged to **4a/b** along with **4d/e**. The deuterium content of the isolated products was measured by comparing the integrated intensity of the *N*-methyl signal to those of the other aliphatic hydrogens in the ^{1}H-NMR spectrum. Within the limits of experimental error, equal distribution of deuterium was found as expected for an intermolecular reaction pathway.

An alternative explanation for the scrambling of the deuterium label would be reversible formation of **3** from **1** and **2** allowing for reaction of regenerated **1a** or **c** with **2a** as well as **2b** and concealing the mechanism of the **3**→**4** step. To assess this possibility, deuterated zwitterion **3e** was prepared and allowed to rearrange in the presence of 1.35 equivalents of the undeuterated alkene **2a**. Isolated **4** then showed hydrogen incorporation of up to 81% rather than in the **2a/2b** ratio. This result allows to exclude appreciable reversibility in the formation of **3**, but demonstrates the ability of *O,N*-acetal **2a** to methylate dipole **3e** under the reaction conditions; a probable pathway from the resulting ionic species to product **4** would be hydrolysis on work-up.

Another mechanistic problem that could be tackled with the compounds at hand was whether imidates **5** are intermediates in the transformation of **3** to **4**. When **5b** was refluxed in [D_3]acetonitrile under the conditions which led from **3** to **4**, ^{1}H-NMR spectroscopy confirmed that the compound remained unchanged. This proves that the activation energy for the Chapman rearrangement[14] of **5** to give **4** is much higher than for the **3**→**4** process, and the intermediacy of **5** in the formation of **4** from **3** can be excluded.

In conclusion, the present study confirms the intermolecular methyl transfer in **3** and, consequently, is in line with theory[8,9]. Mutatis mutandis, an intermolecular mechanism should hold for alkyl shifts in other zwitterions[4,7,15]. However, it should be noted that the present evidence gives no clue as to the exact nature of the intermolecular process.

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Experimental

Melting points: uncorrected, Leitz hot-stage microscope. – IR spectra: Perkin-Elmer 257. – ^{1}H-NMR spectra: Varian T 60. – ^{13}C-NMR spectra: Bruker WP 60 and WH 270. – Mass spectra (MS): Varian MAT CH 7. – Preparative TLC: silica gel plates (20 × 90 cm), fluorescent indicator.

The reaction of 1-chloro-1-(dimethylamino)-2-methyl-1-propene with sodium methoxide was employed to synthesize **2a**[4,16] and, using [D_3]methoxide under the same conditions, also provided **2b** (33%).

The generation of zwitterions **3c,d** was reported previously[4]. Analogously, when equimolar amounts of **1a**[17] and **2a** were mixed in CD_3CN at −20°C, the ^{1}H-NMR spectrum confirmed quantitative formation of *3-(dimethylimonio)-3-methoxy-2,2-dimethyl-N-(methylsulfonyl)propionamidate* (**3a**): ^{1}H-NMR (CD_3CN): δ = 1.01 (s; 6H, CCH_3), 2.33 (s; 3H, SO_2CH_3), 2.83 (s; 6H, NCH_3), 3.76 (s; 3H, OCH_3).

N,N,N',2,2-Pentamethyl-N'-(methylsulfonyl)propanediamide (**4a**): A solution of 0.49 g (4.05 mmol) of isocyanate **1a**[17] in 5 ml of dry acetonitrile was added dropwise to a solution of 0.54 g (4.19 mmol) of **2a** in 5 ml of dry acetonitrile over a period of 20 min under cooling with an ice-salt mixture. After 3 days at room temperature, ^{1}H-NMR spectroscopy proved the absence of **3a** and almost complete formation of **4a**. The solvent was evaporated and the residue purified by preparative TLC (eluent ethyl acetate/dichloromethane 1:3). Yield 0.63 g (62%), m.p. 106–107°C (from CCl_4). – IR (KBr): 1680 cm^{-1} (sulfonylated amide), 1625 ($CONMe_2$). – ^{1}H NMR ($CDCl_3$): δ = 1.48 (s; 6H, CCH_3), 3.02 [s; 6H, $N(CH_3)_2$], 3.20 (s; 3H, NCH_3), 3.40 (s; 3H, SO_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 23.8 (CCH_3), 31.7 (SO_2NCH_3), 36.8 [$N(CH_3)_2$], 41.7 (SO_2CH_3), 50.1 (CMe_2), 170.9, 175.3 (C=O).

$C_9H_{18}N_2O_4S$ (250.3) Calcd. C 43.19 H 7.25 N 11.19 S 12.81
Found C 42.59 H 7.12 N 10.99 S 12.92

Methylation of Amides **4f/g**: Samples of 2.5 mmol of **4f** or **g**[4] and 3.5 g of silica gel (70–230 mesh) were covered with 10 ml of ether and dispersed by ultrasonication for 30 min. At 0°C, diazomethane generated from 2.8 g (27 mmol) of *N*-methyl-*N*-nitrosourea was added. After 1 h, the reaction mixture was filtered and the residue washed with 20 ml of ethyl acetate/2-propanol/triethylamine (94:5:1). After evaporating the solvents, the products were isolated by preparative TLC (eluent chloroform/acetone 19:1) to give:

N,N,N',2,2-Pentamethyl-N'-(phenylsulfonyl)propanediamide (**4c**): 0.045 g (6%), m.p. 176–177°C. – IR (KBr): 1675 cm^{-1} (sulfonylated amide), 1620 ($CONMe_2$). – ^{1}H NMR ($CDCl_3$): δ = 1.37 (s; 6H, CCH_3), 2.81, 2.98 [broad s; 3H each, $N(CH_3)_2$], 3.33 (s; 3H, SO_2NCH_3), 7.4–8.1 (m; 5H, Ar-H). – MS (70 eV): *m/z* (%) = 312 (1, M^+), 171 (6), 155 (20), 142 (39, $OC-CMe_2-CONMe_2$), 141 (40, $PhSO_2$), 114 (24, $Me_2C-CONMe_2$), 86 (41), 77 (67, Ph), 72 (100, $CONMe_2$).

$C_{14}H_{20}N_2O_4S$ (312.4) Calcd. C 53.83 H 6.45 N 8.97 S 10.26
Found C 53.94 H 6.53 N 9.03 S 10.50

Methyl 3-(Dimethylamino)-2,2-dimethyl-3-oxo-N-(phenylsulfonyl)propanimidate (**5a**): 0.027 g (3%), m.p. 74°C, b.p. ca. 130°C/0.3 Torr. – IR (KBr): 1635 cm^{-1} (C=O), 1610 (C=N). – ^1H NMR ($CDCl_3$): δ = 1.67 (s; 6H, CCH_3), 3.30 (broad s; 6H, NCH_3), 3.80 (s; 3H, OCH_3), 7.4–8.2 (m; 5H, Ar-H). – MS (70 eV): *m/z* (%) = 312 (14, M^+), 171 (16), 155 (13), 141 (52, $PhSO_2$), 114 (7, $Me_2C-CONMe_2$), 101 (16), 100 (10), 86 (14), 77 (80, Ph), 72 (100, $CONMe_2$).

$C_{14}H_{20}N_2O_4S$ (312.4) Calcd. C 53.83 H 6.45 N 8.97 S 10.26
Found C 54.09 H 6.47 N 9.02 S 10.32

N,N,N',2,2-Pentamethyl-N'-(4-methylphenylsulfonyl)propanediamide (**4d**): 0.215 g (26%), m.p. 164°C. – IR (KBr): 1685 cm^{-1} (sulfonylated amide), 1640 ($CONMe_2$). – ^1H NMR ($CDCl_3$): δ = 1.36 (s; 6H, CCH_3), 2.45 (s; 3H, $ArCH_3$), 2.83, 2.99 [each broad s; 3H, $N(CH_3)_2$], 3.35 (s; 3H, SO_2NCH_3), 7.38, 7.96 (each d, *J* = 8 Hz; 4H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 21.9 ($ArCH_3$), 23.8 (geminal CH_3), 33.1 (NCH_3), 37.1 [$N(CH_3)_2$], 50.3 (CMe_2), 127.7, 129.0, 135.7, 143.6 (Ar-C), 170.4, 173.4 (C=O). – MS (70 eV): *m/z* (%) = 326 (1, M^+), 262 (8, M – SO_2), 171 (4, M – Tos), 155 (92, Tos), 142 (55, $CO-CMe_2CONMe_2$), 114 (31, $Me_2C-CONMe_2$), 91 (70, C_7H_7), 86 (30), 72 (100, $CONMe_2$).

$C_{15}H_{22}N_2O_4S$ (326.4) Calcd. C 55.20 H 6.79 N 8.58 S 9.82
Found C 55.25 H 6.74 N 8.56 S 10.15

Methyl 3-(Dimethylamino)-2,2-dimethyl-3-oxo-N-(4-methylphenylsulfonyl)propanimidate (**5b**): 0.083 g (10%), m.p. 88°C, b.p. ca. 130°C/0.5 Torr. – IR (KBr): 1635 cm^{-1} (C=O), 1595 (C=N). – ^1H NMR ($CDCl_3$): δ = 1.63 (s; 6H, CCH_3), 2.45 (s; 3H, $ArCH_3$), 3.13 (broad s; 6H, NCH_3), 3.80 (s; 3H, OCH_3), 7.37, 7.93 (each d, *J* = 8 Hz; 4H, Ar-H). – MS (70 eV): *m/z* (%) = 326 (19, M^+), 171 (23, M – Tos), 155 (69, Tos), 139 (11), 128 (11), 114 (7, $Me_2C-CONMe_2$), 101 (25), 100 (13), 91 (93, C_7H_7), 86 (12), 72 (100, $CONMe_2$).

$C_{15}H_{22}N_2O_4S$ (326.4) Calcd. C 55.20 H 6.79 N 8.58 S 9.82
Found C 55.35 H 6.80 N 8.56 S 9.76

Cross-over Experiment: At –20°C in separate flasks, dipoles **3b** and **d** were prepared by mixing 5 ml of acetonitrile solutions each of 5.0 mmol of **1a** with **2b** and of **1c** with **2a**. Formation of **3** was confirmed by taking ^1H-NMR spectra of evaporated samples. The reaction mixtures were then combined at –20°C and refluxed for 10 min. After concentration, the products were isolated by TLC (eluent dichloromethane/ethyl acetate 3:1). Yields 0.55 g (44%) **4a/b** (NCH_3 content 52.2 ± 4.9%) and 0.70 g (45%) **4d/e** (NCH_3 content 54.1 ± 4.9%).

Reaction of the Deuterated Dipole **3e** *with Undeuterated Ketene Acetal* **2a**: Acetonitrile solutions of 2 ml each of 0.42 g (2.1 mmol) of **1c** and 0.26 g (2.0 mmol) of **2b** were mixed at –20°C, and 0.35 g (2.7 mmol) of **2a** was added. The reaction mixture was refluxed for 60 min and concentrated. Product **4d/e** was isolated using a chromatotron (silica gel, 4 mm; eluent petroleum ether/ethyl acetate 4:1). Yield 0.15 g (23%) **4d/e** (NCH_3 content 80.9 ± 3.2% from integration of the ^1H-NMR signals).

CAS Registry Numbers

1a: 3611-92-5 / **2a**: 55019-20-0 / **3a**: 105728-83-4 / **4a**: 105728-80-1 / **4c**: 105728-81-2 / **4d**: 105728-82-3 / **4f**: 55019-60-8 / **4g**: 55019-57-3 / **5a**: 55019-54-0 / **5b**: 55019-51-7

[1] cf. R. Huisgen, P. Otto, *J. Am. Chem. Soc.* **91** (1969) 5922; H. U. Wagner, R. Gompper, *Tetrahedron Lett.* **1970**, 2819; D. Becker, N. C. Brodsky, *J. Chem. Soc., Chem. Commun.* **1978**, 237; E. Schaumann, H.-G. Bäuch, G. Adiwidjaja, *Angew. Chem.* **93** (1981) 600; *Angew. Chem. Int. Ed. Engl.* **20** (1981) 613, 702; E. Schaumann, H.-G. Bäuch, S. Sieveking, G. Adiwidjaja, *Chem. Ber.* **116** (1983) 55; A. H. Al-Husaini, H. W. Moore, *J. Org. Chem.* **50** (1985) 2595.

[2] W. T. Brady, R. D. Watts, *J. Org. Chem.* **46** (1981) 4047.

[3] P. W. Raynolds, J. A. DeLoach, *J. Am. Chem. Soc.* **106** (1984) 4566.

[4] E. Schaumann, S. Sieveking, W. Walter, *Chem. Ber.* **107** (1974) 3589.

[5] S. Hünig, H. Hoch, *Fortschr. Chem. Forsch.* **14** (1970) 235.

[6] Sagami Chemical Research Center (Inventors I. Ojima, S. Inaba), *Jpn. Kokai Tokkyo Koho* 78 34,758 (14.9.1976) [*Chem. Abstr.* **90** (1979) 6527]; see also: W. Adam, J. del Fierro, F. Quiroz, F. Yany, *J. Am. Chem. Soc.* **102** (1980) 2127.

[7] H. J. Bestmann, *Angew. Chem.* **89** (1977) 361; *Angew. Chem. Int. Ed. Engl.* **16** (1977) 349; H. J. Bestmann, R. W. Saalfrank, *J. Chem. Res. S* **1979**, 313; *M* **1979**, 3670; E. Schaumann, H.-G. Bäuch, S. Sieveking, G. Adiwidjaja, *Chem. Ber.* **115** (1982) 3340.

[8] L. Tenud, S. Farooq, J. Seibl, A. Eschenmoser, Helv. Chim. Acta **53** (1970) 2059; J. F. King, M. J. McGarrity, *J. Chem. Soc., Chem. Commun.* **1979**, 1140; **1982**, 175.

[9] J. E. Baldwin, M. J. Lusch, *Tetrahedron* **38** (1982) 2939. Review: F. M. Menger, *ibid.* **39** (1983) 1013.

[10] T.-L. Ho, *Chem. Rev.* **75** (1975) 1.

[11] M. Julia, H. J. Mestdagh, *Tetrahedron* **39** (1983) 433, and references cited therein.

[12] The experiments were carried out by cand. chem. *R. Beyer* and cand. chem. *W. Hils* as part of advanced organic laboratory work.

[13] H. Nishiyama, H. Nagase, K. Ohno, *Tetrahedron Lett.* **1979**, 4671.

[14] J. W. Schulenberg, S. Archer, *Org. React.* **14** (1965) 1.

[15] E. Schaumann, J. Dietz, E. Kausch, G. C. Schmerse, *Chem. Ber.* **120** (1987) 339, following paper in this issue.

[16] L. Ghosez, B. Haveaux, H. G. Viehe, *Angew. Chem.* **81** (1969) 468; *Angew. Chem. Int. Ed. Engl.* **8** (1969) 454; J. Marchand-Brynaert, L. Ghosez, *J. Am. Chem. Soc.* **94** (1972) 2870.

[17] W. H. Daly, H. J. Holle, *J. Org. Chem.* **39** (1974) 1597.

[240/86]