The First Reaction of Dimethoxycarbene with an Imine Moiety

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The nucleophilic dimethoxycarbene (DMC; **2**) generated by thermal decomposition of 2,5-dihydro-1,3,4-oxadiazole derivative **1** in boiling toluene reacts smoothly with *N*-(9*H*-fluoren-9-ylidene)-4-methylbenzenesulfonamide (**7b**) to yield carbonimidoate derivative **10**. A multi-step reaction pathway, initiated by the attack of DMC onto the C=N bond and followed by the migration of the sulfonyl group (or *via* a sulfinate anion) is proposed to explain the formation of the final product. In contrast to the formal ketimine **7b**, *N*-benzylidene-4-methylbenzenesulfonamide (**7a**), a formal aldimine, does not react with DMC under comparable conditions.

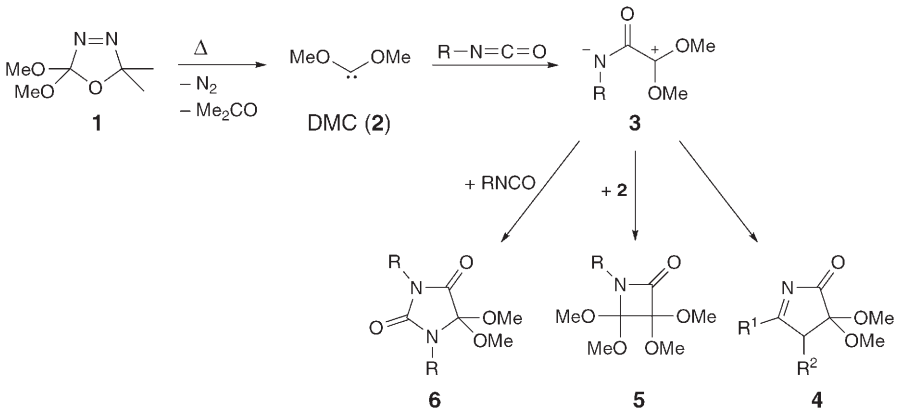
1. Introduction. – Dimethoxycarbene (= dimethoxymethylene; **2**; DMC) belongs to the class of nucleophilic carbenes. The first method for its generation, based on the thermal decomposition of a 7,7-dimethoxy-8,9,10-trinorbornadiene derivative at 140°, was reported by *Hoffmann et al.* [1]. Another method, used by *Moss* and co-workers, is the thermal or photochemical decomposition of 3,3-dimethoxy-3*H*-diazirine, but it has not been used for preparative purposes [2]. The thermal decomposition of 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole (**1**), elaborated by *Warkentin* and co-workers [3][4], opened new perspectives for numerous synthetic applications of DMC as a versatile building block. In a recent paper, **1** was used for the generation of DMC in the gas-phase under flash vacuum pyrolysis (FVP) conditions, and subsequent analysis of the pyrolysate at 10 K enabled the conformational analysis of the carbene [5]. For practical applications of DMC, the introduction of the modified precursor, in which one Me group is replaced by a 4-methoxyphenyl residue, is of significant practical importance, because the decomposition can be carried out already at 50° [6].

In the chemistry of carbenes, the reactions with multiple bonds are of special importance [7]. The addition to C=C bonds, known as cyclopropanation reactions, are widely applied in the synthesis of complex molecules [8]. Reactions with hetero-π-systems are also extensively elaborated to prepare three-membered heterocycles (oxiranes, thiiranes, aziridines) or products resulting from the interception of the initially formed ylide species [7].

In the case of the nucleophilic dimethoxycarbene, the most extensively studied reactions with relevant practical applications (two- or multi-component reactions) are

focused on the use of ketones [4][9] or mixtures of acetylene dicarboxylate (= but-2-ynedioate) and an aldehyde [10] as substrates. Recently, DMC was shown to react smoothly with cycloaliphatic thioketones [11] and carbodithioates [12]. Cyclopropanones, cyclobutanones, and cyclopentanone react with DMC to give ring-enlarged products [9], whereas 9*H*-fluoren-9-one and cyclohexanone yield methyl α-hydroxycarboxylates *via* the initially formed oxiranes [13][14]. Analogous reactions with 'cage' ketones lead to the corresponding α-hydroxy esters [15]. The reactions of DMC with C=N bonds are limited to isocyanates, which occur *via* a zwitterionic intermediate **3**. In the case of unsaturated isocyanates with $R = CR^1=CHR^2$, subsequent 1,5-cyclization leads to pyrrolones **4** (*Scheme 1*). This methodology has been widely applied for the preparation of a variety of natural products [16]. In addition, decomposition of **1** in the presence of aryl isocyanates in chlorobenzene was shown to yield tetramethoxy-β-lactams **5** in competition with the formation of isatin derivatives **6** [17].

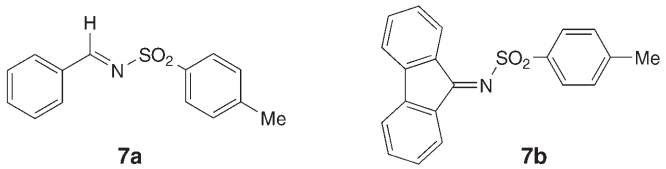
Scheme 1



To the best of our knowledge, no reports on the reactions of DMC with aldimines or ketimines have been published to date. In a recent paper, we described that electron-deficient imines derived from hexafluoroacetone failed to react with DMC [18]. The present study is aimed at the examination of the reactivity of formal imines, which are activated by a sulfonyl group attached to the N-atom, toward DMC.

2. Results and Discussion. – For the study presented in this paper, *N*-tosylimines of benzaldehyde and 9*H*-fluoren-9-one, *i.e.*, *N*-substituted 4-methylbenzenesulfonamides **7a** and **7b**, were selected. Both substrates were easily available by condensation of 4-methylbenzenesulfonamide with the corresponding carbonyl compound in the presence of Et_3N and $TiCl_4$ [19].

The decomposition of **1** was carried out in the presence of **7** in boiling toluene under Ar. In both cases, the reaction was finished after 7 h, and the crude products were analyzed by ^{1}H-NMR spectroscopy. The formal imine **7a** failed to react with DMC, and the dimer of the latter was the main product containing MeO groups. It was identified by the chemical shift of four equal MeO groups (δ 3.53), which fits well with the

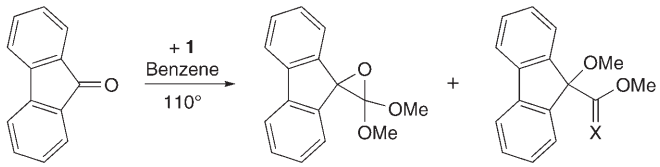


7a **7b**

reported data [20]. Other minor products formed in this reaction underwent decomposition during the attempted chromatographic separation on silica gel.

The TLC analysis of the reaction mixture obtained with **7b** showed the absence of the starting **7b**, and the ^{1}H-NMR analysis revealed the presence of two equally intense MeO signals located at δ 3.10 and 4.00, and one Me signal at δ 2.33 for the *p*-tolyl residue. These data suggested the formation of a new product corresponding to a 1:1 stoichiometry of DMC and **7b**. After crystallization from hexane, yellowish crystals with an intense absorption at 1663 cm^{-1} in the IR spectra (KBr) were obtained, and the presence of a C=N bond was confirmed by the ^{13}C-NMR spectrum (δ 161.8). The spectroscopic evidence excluded the structure of an aziridine for the isolated product. The result obtained with **7b** should be compared with those described by *Pole* and *Warkentin* in the case of the reaction of DMC with 9*H*-fluoren-9-one, where the oxirane **8** was observed in the reaction mixture along with the rearranged product **9** [13] (*Scheme 2*). In the light of the data of the product isolated from the reaction with **7b**, the structure corresponding to **9** with X = *p*-MeC$_6$H$_4$SO$_2$N could be proposed. However, the X-ray crystal-structure determination solved the problem, unambiguously disclosing the unexpected structure **10** (*Fig.*).

Scheme 2



8 **9** X = O

A mechanistic interpretation of the formation of **10** is presented in *Scheme 3*. Under the assumption that the nucleophilic DMC attacks the imino C-atom to form the zwitterion **11** in analogy to the reactions with carbonyl groups, ring closure to give the aziridine **12** is necessary to explain the further reaction pathway *via* the intermediate azomethine ylide (= iminium ylide) **13**. The appearance of the latter is conclusive as the C=N bond attached to the fluorene moiety is preserved in the product **10**. However, this interpretation is not compatible with the observed lack of reactivity in the case of **7a**, which is believed to be more reactive toward nucleophilic reagents. Therefore, the attack of DMC at the N-atom of **7b**, leading directly to **13**, is a plausible alternative. Finally, a 1,2-sulfonyl migration leads to the isolated product **10**, but the release of sulfinate to form an ion pair, which recombines to yield **10**, cannot be excluded.

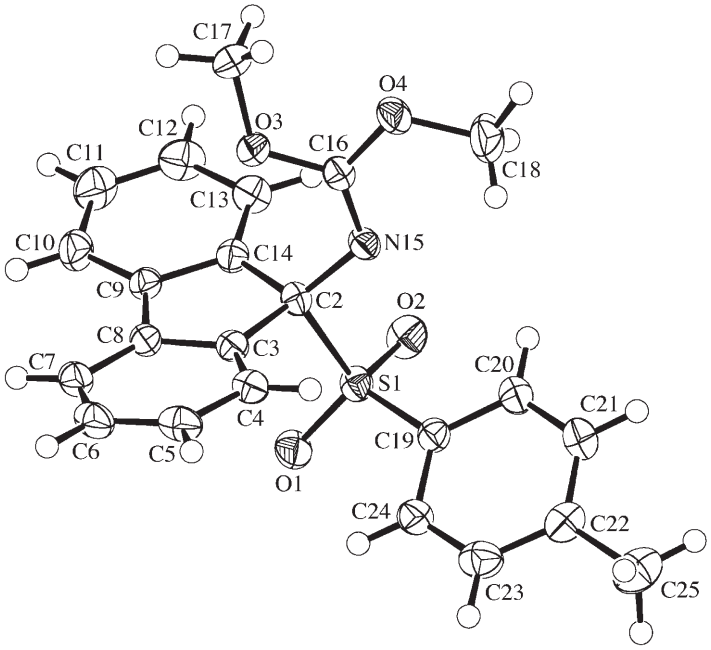


Figure. *ORTEP Representation* [21] *of the molecular structure of one of the three symmetry-independent molecules of* **10** (50% probability ellipsoids, arbitrary atom numbering)

3. Conclusions. – The formation of **10** as the sole product of the reaction of the formal imine **7b** with DMC suggests that the transient azomethine ylide **13** isomerizes *via* migration of the sulfonyl group (or *via* a sulfinate anion). The reaction pathway leading to **13** is not clear, but the intermediacy of aziridine **12** formed *via* **11** is doubtful. One of the arguments of this interpretation is that aziridines bearing electron-donating substituents at a C-atom and/or electron-withdrawing substituents at the N-atom are not suitable precursors for the thermal generation of azomethine ylides [22]. Despite the mechanistic consideration, the presented results show that DMC can in principal react with an electron-deficient C=N moiety. In contrast to the analogous reaction with an electron-deficient ethene derivative [23], the expected [2 + 1] cycloadduct has not been detected. Instead, isomeric products, resulting from further conversion of the intermediate aziridine or its precursor, are formed.

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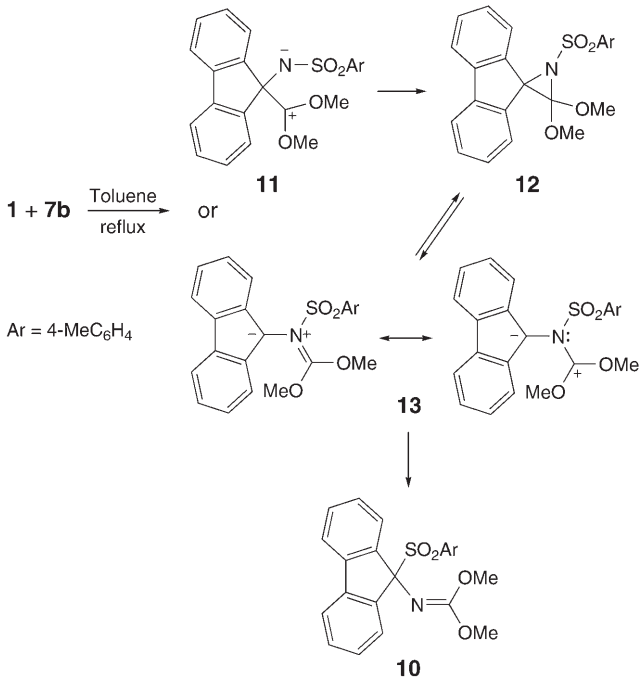
Experimental Part

1. *General*. M.p.: *Meltemp 2* apparatus, in capillary; uncorrected. IR Spectra: *Nexus-FT-IR* spectrophotometer, in KBr. ^{1}H- and ^{13}C-NMR Spectra: *Bruker 200* and *400* spectrometer (200 and 100 MHz, resp.); δ in ppm rel. to $SiMe_4$ (= 0 ppm) as an internal standard, J in Hz. CI-MS: *Finnigan Mat-*

Scheme 3



90 spectrometer; in *m*/*z* (rel. %). Elemental analyses were performed in the Analytical Laboratory of the University of Zürich.

2. *Starting Materials.* The 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole (**1**) was prepared according to [3]. The formal imines **7a** and **7b** were synthesized from 4-methylbenzenesulfonamide and benzaldehyde (0°, CH_2Cl_2) or 9*H*-fluoren-9-one (boiling CH_2Cl_2, Et_3N), respectively, in the presence of $TiCl_4$ and Et_3N: *N*-benzylidene-4-methylbenzenesulfonamide (**7a**), pale yellow crystals, m.p. 109–111° ([24]: 107°); *N*-(9*H*-fluoren-9-ylidene)-4-methylbenzenesulfonamide (**7b**), orange-yellow crystals, m.p. 184–186° ([19]: 182–184°).

3. *Reaction of DMC with Formal Imine* **7b**. Under Ar, 1,3,4-oxadiazole **1** (240 mg, 1.5 mmol) and **7b** (333 mg, 1.5 mmol) were dissolved in abs. toluene (3 ml). The mixture was heated under reflux, and the progress of the reaction was monitored by TLC (SiO_2, CH_2Cl_2/hexane). After 4 h, **7b** was completely consumed, heating was stopped, and the solvent was evaporated. The residual viscous oil was triturated with Et_2O, and after several min at r.t., pale yellow crystals were separated by filtration. An anal. pure sample of *dimethyl* N-*[9-[(4-methylphenyl)sulfonyl]-9*H*-fluoren-9-yl]carbonimidoate* (**10**) was obtained by crystallization from hexane: 289 mg (71%). Colorless crystals. M.p. 178–180° (hexane). IR (KBr): 1664v*s* (C=N), 1463*m*, 1451*m*, 1300*s*, 1143*s*, 1090*m*, 752*m*, 670*m*, 580*m*. ^{1}H-NMR (200 MHz): 7.49, 7.01 (*AA′BB′*, *J* = 8, 4 arom. H); 7.43–7.15 (*m*, 8 arom. H); 3.99, 3.11 (2*s*, 2 MeO); 2.33 (*s*, Me). ^{13}C-NMR (100 MHz): 153.2 (*s*, C=N); 143.7, 141.5, 132.4 (3*s*, 6 arom. C); 131.1, 129.8, 127.7, 127.1, 125.6, 119.6 (6*d*, 12 arom. CH); 90.1 (*s*, $(MeO)_2C$); 56.5, 54.9 (2*q*, 2 MeO); 21.6 (*q*, Me). CI-MS (NH_3): 257 (22), 254 (18), 240 (18), 238 (100, $[M - C_7H_7NO_2S]^+$). Anal. calc. for $C_{23}H_{21}NO_4S$ (407.49): C 67.79, H 5.19, N 3.44, S 7.87; found C 67.88, H 5.08, N 3.26, S 7.60.

4. *Attempted Reaction of DMC with Formal Imine* **7a**. Under Ar, 1,3,4-oxadiazole **1** (240 mg, 1.5 mmol) and **7a** (389 mg, 1.5 mmol) were dissolved in abs. toluene (3 ml). The mixture was heated under reflux as in *Exper. 3*. After 4 h, the evolution of N_2 was finished indicating complete decomposition

of **1**; heating was stopped, and the solvent was evaporated. The semi-solid residue was analyzed by ^{1}H-NMR: tetramethoxyethene and significant amounts of **1a** along with some unidentified products in low yield.

5. *X-Ray Crystal-Structure Determination of* **10** (*Fig.*)[1]). All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer [25] by using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford-Cryosystems Cryostream-700* cooler. The data collection and refinement parameters are given below, and a view of the molecule is shown in the *Figure*. Data reduction was performed with HKL Denzo and Scalepack [26]. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [27] was applied. The structure was solved by direct methods with SHELXS97 [28], which revealed the positions of all non-H-atoms. There are three symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the three molecules were tested carefully for a relationship from a higher symmetry space group by using the program PLATON [29], but none could be found. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me groups). The refinement of the structure was carried out on F^2 by full-matrix least-squares procedures, which minimized the function $\Sigma w\left(F_o^2 - F_c^2\right)^2$. A correction for secondary extinction was applied. Five reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [30], and the scattering factors for H-atoms were taken from [31]. Anomalous dispersion effects were included in F_c [32]; the values for f' and f'' were those of [33]. The values of the mass attenuation coefficients are those of [34]. All calculations were performed with the SHELXL97 program [35].

Crystal Data for **10**: $C_{23}H_{21}NO_4S$, M_r 407.47, colorless, prism, crystal dimensions $0.25 \times 0.25 \times 0.30$ mm, monoclinic, space group $P2_1/n$, $Z = 12$, $a = 9.2447(2)$ Å, $b = 18.0563(4)$ Å, $c = 37.0577(8)$ Å, $\beta = 90.7056(8)^\circ$, $V = 6185.4(2)$ Å^3, $D_X = 1.313$ g·cm^{-3}, μ(MoK_α) = 0.186 mm^{-1}, T 160 K, ϕ and ω scans, transmission factors (min; max) 0.859; 0.958, $2\theta_{max} = 60^\circ$, total reflections measured 139999, symmetry independent reflections 18076, reflections with $I > 2\sigma(I)$ 8878, reflections used in refinement 18071, parameters refined 794, R (on F; $I > 2\sigma(I)$ reflections) = 0.0596, $wR(F^2)$ (all reflections) = 0.1653 ($w = (\sigma^2(F_o^2) + (0.0759P)^2)^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.011, secondary extinction coefficient 0.0037(4), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.43; −0.51 e Å^{-3}.

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