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The Mechanism of the *ortho*-Methylation of Nitrobenzenes by Dimethylsulfonium Methylide

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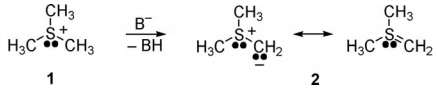
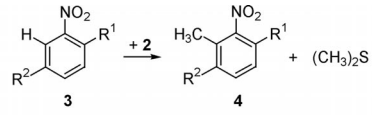
Nitrobenzenes carrying an *ortho* substituent are selectively methylated at the free *ortho* position by reaction with dimethylsulfonium methylide. The importance of the *ortho* substituent is demonstrated by the failure of the methylation of nitrobenzene and 3- and 4-nitroanisole. This is explained by the out-of-plane geometry of the nitro group in the *ortho*-substituted derivative, which enables a specific interaction between the ylide and the nitro group favourable for attack of the methylide C atom at the neighbouring free *ortho* position. As shown by appropriate deuterium-labelling studies, the addition is followed by an E1-like β-elimination with displacement of dimethyl sulfide and subsequent protonation of the elimination product.

Introduction

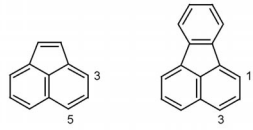
The acidic nature of α-protons in sulfonium ions such as **1** was demonstrated as early as 1955.[1] When the iodide of **1** was dissolved in a solution of sodium deuteroxide in D_2O under reflux, an almost complete exchange of hydrogen by deuterium could be noted after 3 h. It has been concluded that the marked acid strengthening effect of the positive sulfur atom is not likely to be due to an electrostatic interaction between the positive charge and the developing negative charge alone. An extra stabilization by d-orbital interaction was postulated, and consequently the resulting conjugate base **2** was considered as a resonance hybrid of an ylide and an ylene canonical structure. Although the π(pd) approach is very popular amongst chemists, experimental and theoretical investigations have put a strong question mark on this view. A discussion of the pro and contra arguments on the π(pd) model and MO-theoretical descriptions to account for the stabilizing effect of sulfur on adjacent negative charges without 3d-orbital participation can be found, for example, in ref.[2,3]



Dimethylsulfonium methylide (**2**) and other sulfonium ylides can be easily prepared by deprotonation of the corresponding sulfonium salts with strong bases (e. g. sodium hydride, methylsulfinyl carbanion) in dipolar, aprotic solvents at approximately 0 °C and used for countless synthetic applications.[4] The best known is the transformation of aldehydes and ketones into oxiranes (Corey–Chaykowski reaction).[5] A further demonstration of the utility of **2** is the synthesis of 1-azabicyclo[1.1.0]butanes from 2*H*-azirines.[6] More recently, Kitano and Ohashi[7] reported on the successful *ortho*-methylation of nitrobenzene derivatives **3** by reaction with **2**. A literature search revealed that acenaphthylene (**5**) and fluoranthrene (**6**) also undergo selective methylation when exposed to **2**.[8] These aromatics are substituted at positions 3 and 5 (ca. 24:1) and 1 and 3 (ca. 12:1), respectively. Similar methylation reactions of aromatic compounds with dimethyloxosulfonium methylide[9,10] and methylsulfinyl carbanion[11] are occasionally described in the older literature.



R^1 = OCH_2Ph, OCH_3, morpholino
R^2 = CF_3, Cl, CH_3



The literature data[7,8] suggest that electrophilic aromatic compounds that do not possess a good leaving group (nucleofuge) can be methylated by dimethylsulfonium methylide (**2**). The unique and high selectivity renders this methylation reaction synthetically interesting.

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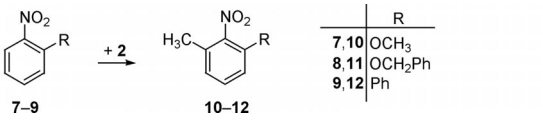
In this paper, the dependence of the *ortho*-methylation of nitrobenzenes by **2** on structural conditions is examined. Furthermore, the sequence of steps involved in building up the *ortho*-methyl substituent is elucidated by appropriate deuterium labelling studies.

Results

In a first set of experiments, we applied reaction conditions close to that reported by Kitano and Ohashi.[7] To a suspension of NaH in DMSO/THF (3:1) kept in an ice bath was added an equimolar amount of trimethylsulfonium iodide (**1**·I^-). After stirring for 10 min, a solution of 0.5 equiv. of the nitrobenzene derivative in DMSO was added, and the mixture was allowed to react at 20 °C for several hours. With this protocol, nitrobenzene (**6**) did not undergo any methylation reaction.

Inspection of the substitution pattern of the nitrobenzene derivatives **3** raised the suspicion that a substituent *ortho* to the nitro group is important. Therefore, *ortho*-substituted nitrobenzenes **7**–**9** were subjected to the above reaction conditions.

In contrast to **6**, *ortho*-substituted derivatives **7**–**9** produced the methyl-substituted nitrobenzenes in yields between 40 and 50% calculated with respect to the consumed starting materials. At 0 °C, the conversion into the methylation products proceeded very slowly. To obtain an acceptable turnover, the reaction temperature had to be raised to approximately 20 °C after mixing. At this temperature, the product yields attained a plateau after 15 to 20 h.



3-Methyl-2-nitro-biphenyl (**12**) obtained from **9** has been reported twice in the literature.[12] Denny et al. synthesized **12** by a Gomberg–Bachmann arylation of benzene with the diazonium salt of 3-methyl-2-nitroaniline.[12a] No spectroscopic data are given for **12**; however, the reported m. p. of 85–85.5 °C is in accordance with our product (m. p. 85–85.5 °C). In contrast, in ref.[12b] compound **12** is described as an oil showing MS, ^{1}H NMR and ^{13}C NMR spectroscopic data in substantial disagreement with our results.

As in the case of nitrobenzene (**6**), the attempted methylation of 3-nitroanisole (**13**) and 4-nitroanisole (**14**) failed.

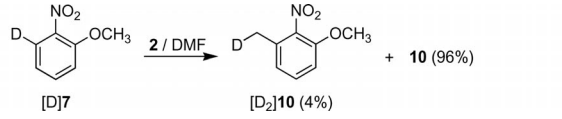
During our studies with perdeuteriated trimethylsulfonium iodide (see below), we noted that applying the above deprotonation procedure brought about an almost complete deuterium depletion by exchange with the protons of the solvent DMSO. To circumvent this complication, reagent **2** was prepared in DMF by direct deprotonation with NaH. All experiments described so far were repeated under these conditions with essentially identical results.

In order to obtain further insights into the course of the methylation reaction, 2-nitroanisole (**7**) was chosen as model compound for deuterium labelling studies. To achieve this goal, 3-deuterio-2-nitroanisole ([D]**7**) and perdeuteriotrimethylsulfonium iodide ([D_9]**1**·I^-) were synthesized.

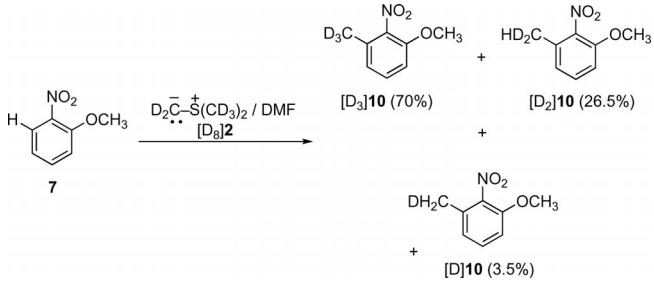
It is known that nitrobenzene suffers from a H/D exchange in the position *ortho* to the NO_2 group with *t*BuOK in *t*BuOD.[13] We achieved a maximum deuterium incorporation at position 3 of 20% (^{1}H NMR, MS) for compound **7**. This deuteriation degree could be insufficient for unequivocal conclusions. A deuterium incorporation of 95% was obtained by adaptation of a technique reported for 2-deuterionitrobenzene.[14] With this elegant method, the iodo substituent of 3-iodo-2-nitroanisole is replaced by deuterium on reduction with sodium borohydride in D_2O/diglyme.

Perdeuteriated trimethylsulfonium iodide ([D_9]**1**) was prepared by dissolving the unlabelled iodide in 0.3 M NaOD in D_2O. The course of the deuterium exchange can be monitored by the decline of the CH_3 singlet (δ = 2.93 ppm) and a complementary increase of the HDO signal (δ = 4.89 ppm) in the ^{1}H NMR spectrum. After 16 h, the CH_3 singlet completely disappeared, and a small, badly resolved septet for CHD_2 (δ = 2.90 ppm) remained. A deuteriation degree of approximately 97% was determined by comparison with dioxane as internal reference. A slightly lower deuterium degree (95%) was found after work-up and recrystallization from methanol.

The deuteriated 2-nitroanisole [D]**7**, when reacted with **2** in DMF, furnished 3-methyl-2-nitroanisole containing to an extent of 4% a monodeuteriated methyl group ([D]**10**).



When the perdeuteriated trimethylsulfonium salt [D_9]**1**·I^- was deprotonated in DMF followed by addition of compound **7**, the resulting methylation product showed the isotopic distribution given below.



Any influence of the aqueous work-up of the reaction mixtures on the deuteriation degree of the methyl group in **10** could be excluded. Scavenging of the reaction mixture of **7** and **2** with D_2O gave **10** with no detectable deuterium incorporation.

Discussion

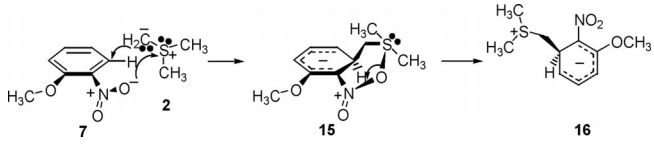
From the literature data[7] and the experiments described in this communication, it becomes evident that an *ortho*

substituent is an essential prerequisite for the methylation of the free *ortho* position of nitrobenzenes by dimethylsulfonium methylide (**2**). The nitrobenzene derivatives **3** reported in ref.,[7] to be accessible to the methylation at the free *ortho* position, have an *ortho*-alkoxy or -morpholino substituent with respect to the NO_2 group in common. Similarly, 2-nitroanisole (**7**), 2-benzyloxynitrobenzene (**8**) and 2-nitrobiphenyl (**9**) undergo the methylation when reacted with sulfur ylide **2**. By way of contrast, the attempted methylation of nitrobenzene (**6**) itself and 3- (**13**) and 4-methoxynitrobenzene (**14**) failed when treated under identical conditions. After aqueous work-up, the starting materials were almost completely recovered, and no methylation products could be detected.

The nucleophilic nature of the methylation reaction is reflected by the reaction conditions (dipolar aprotic solvents) and the orientation (*ortho* to the electron-withdrawing NO_2 group). Thus, it appears conceivable that the reaction is started by a nucleophilic addition of the reagent to the free *ortho* position of the nitrobenzene derivative.

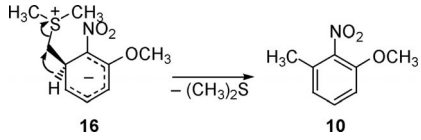
The main structural difference between nitrobenzene (**6**) and its *ortho*-substituted derivatives is the out-of-plane geometry in the latter. From X-ray crystallographic studies, it follows that an *ortho*-methoxy group causes a dihedral angle of approximately 35°.[15] For 2-nitrobiphenyl (**9**), a dihedral angle of 44.7° between the phenyl ring and the nitro group has been reported.[16] Polar and steric interactions between NO_2 and the *ortho* substituents (OCH_3, Ph) favour an orthogonal geometry, whereas the resonance effect of the NO_2 group and the aromatic ring has its maximum at a planar conformation. The balance of these two influences leads to the dihedral angles given above.

If it is assumed that the positively charged sulfur atom in dimethylsulfonium ylide is attracted by a negatively charged oxygen atom of the nitro group, the out-of-plane geometry would facilitate an approach with an orientation of the methylide C atom favourable for nucleophilic addition at C-3. The interaction of the positive sulfur atom with the oxygen atom of the nitro group enhances the nucleophilicity of the methylide C atom and, thus, assists C–C bond formation. This type of interaction would explain the specific substitution at the *ortho* position (no *para*-product could be detected within the limits of the analytical techniques TLC and NMR spectroscopy). Furthermore, because of the almost coplanar geometry of the nitro group in nitrobenzene (**6**), a similar approaching of the sulfur ylide cannot occur in this case. This type of interaction may be represented by the formation of a tetracoordinate sulfurane **15** as intermediate complex,[17] preceding the Meisenheimer complex **16** (Scheme 1).



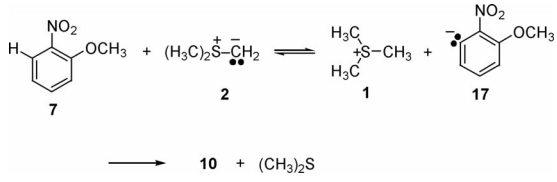
Scheme 1. The *ortho*-directing effect of the nitro group in the reaction of **7** with dimethylsulfonium methylide (**2**).

For the reaction to proceed from the Meisenheimer intermediate **16** to the methylation product **10**, a 1,2-hydride shift under displacement of dimethyl sulfide (Scheme 2) may be anticipated as the most obvious mechanism. Indeed, this rationalization, which corresponds to the insertion of the CH_2 group of the sulfur ylide **2** in the aromatic CH bond, has been implicated to explain the overall reaction of compounds **3**,[7] **5**[8] and **6**.[8] However, the outcome of the methylation of 3-deuterio-2-nitroanisole ([D]**7**) by sulfur ylide **2** excludes this mechanism. Instead of the predicted complete retention of the deuterium labelling, only very little deuterium incorporation in the methyl group (4%) was found.



Scheme 2. 1,2-Hydride shift in Meisenheimer complex **16**.

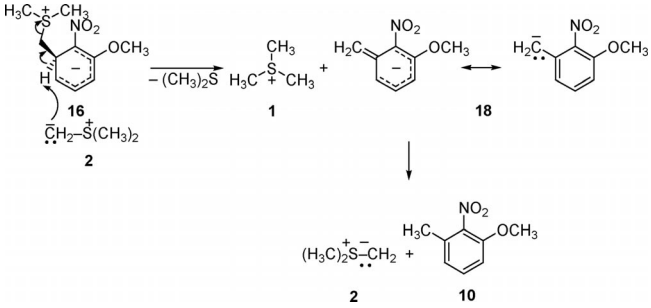
A mechanistic scenario without the intervention of a Meisenheimer complex should also be addressed shortly. It is well known that *ortho*-H atoms of nitroarenes are acidic enough to enable the establishment of an acid–base equilibrium with strong bases.[13] Transferred to the reaction under study, such a process could generate small equilibrium concentrations of the conjugate base **17** and the sulfonium ion **1**, as aryl anion **17** is a strong nucleophile and could attack a methyl group of **1** in an S_N2 reaction with the formation of the methylation product **10**. This mechanistic rationalization is, however, less likely, because it would be difficult to understand why nitrobenzene (**6**) does not show any methylation by action of **2** although its acidity should be similar or even higher than that of 2-nitroanisole (**7**). Indeed, the labelling result obtained from the reaction of [D]**7** with **2** disprove the deprotonation-S_N2 sequence of Scheme 3. According to this mechanism, deprotonation of [D]**7** should furnish a monodeuteriated sulfonium ion, and the subsequent S_N2 attack of the aryl anion should occur without any significant discrimination between the deuteriated and undeuteriated methyl groups, because no primary kinetic isotope effect can be involved. Therefore, about one third of the methylation product should consist of monodeuteriated product [D]**10**.



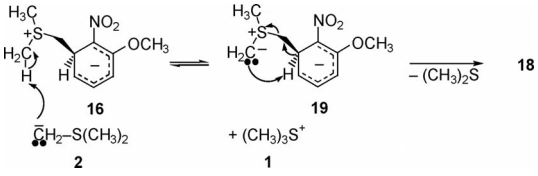
Scheme 3. The aryl anion mechanism.

For the overall substitution of a hydrogen atom in electron-deficient arenes by carbanions bearing a leaving group X at the carbanion centre, Makosza et al.[18] developed the

concept of vicarious nucleophilic substitution. These reactions are initiated by fast addition of the carbanion to yield a Meisenheimer complex (σ^H adduct) bearing a hydrogen atom at the sp^3 carbon atom. The addition is followed by a base-induced elimination of HX and completed by final protonation of the elimination product. Analogously, the transformation of Meisenheimer intermediate **16** into methylation product **10** could proceed by loss of the hydrogen atom at the sp^3 carbon atom as proton and concomitant expulsion of the dimethyl sulfide as neutral nucleofugal group. Two alternative mechanisms can be written for the loss of a proton and dimethyl sulfide from the Meisenheimer intermediate; these are β-elimination (Scheme 4) and α′,β-elimination[19] (Scheme 5).



Scheme 4. The β-elimination (E2)-protonation sequence.



Scheme 5. The α′,β-elimination-protonation sequence.

In both cases, dimethylsulfonium methylide (**2**) would act as base. The trimethylsulfonium ion **1**, thus formed, could be the proton source for the final protonation step of the elimination product **18**. The trimethylsulfonium ion is a Brønsted acid with pK_a = 18.2 in DMSO.[20] The pK_a of 3-methyl-2-nitroanisole is unknown; however, when the values reported for 2-nitrotoluene in water (pK_a = 20.6,[21] 25[22]) are taken as a rough measure, it becomes clear that anion **18** should be protonated by the trimethylsulfonium ion. The possibility that the elimination product **18** survives and becomes protonated only in the aqueous work-up can be excluded, because performing the reaction between 2-nitroanisole (**7**) and dimethylsulfonium methylide (**2**) under anhydrous conditions followed by scavenging with D_2O results in no deuterium incorporation.

The β-elimination (Scheme 4) and the α′,β-elimination (Scheme 5) pathways differ in the origin of the proton that is added to dimethylsulfonium methylide (**2**) to transform this to trimethylsulfonium ion **1**. In the β-elimination process, the H atom attached to the sp^3 C atom of Meisenheimer intermediate **16** is transferred to ylide **2**. Thus, in the case of the deuteriated 2-nitroanisole ([D]**7**, 95%), trimethylsulfonium ion is obtained with two unlabelled methyl groups and one methyl group which is to an extent of 95% CH_2D ([D]**10**). If this partly deuteriated sulfonium ion protonates anion **18** at the carbanionic methylene group, in a statistical manner a methylation product should be formed with 89.4% CH_3 (**10**) and 10.6% CH_2D ([D]**10**). The experimental ratio is 96:4. The deviation between the experimental and statistical distribution can be explained by a primary kinetic isotope effect, k_H/k_D = 2.8, for the proton/deuteron transfer.

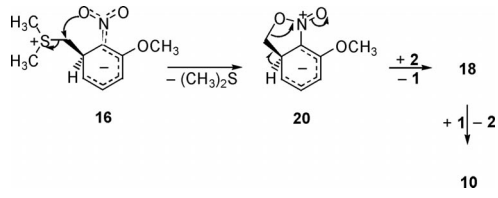
By way of contrast, in the α′,β-elimination mechanism (Scheme 5), ylide **2** captures a proton from one of the methyl groups fixed at the sulfonium sulfur atom of intermediate **16**. The hydrogen atom at the sp^3 carbon atom is then lost as part of the expelled dimethyl sulfide in a subsequent *syn*-elimination step from intermediate **19**. In the case of 3-deuterio-2-nitroanisole ([D]**7**), the consequence of this reaction sequence should be the complete loss of the deuterium labelling in the methylation product.

Therefore, the results obtained from the methylation reaction of isotopomer [D]**7** are best explained with a β-elimination rather than an α′,β-elimination step preceding the final protonation. The fact that an isotope effect has to be included to match the experimental deuterium incorporation into the methyl group with this reaction scheme means that the reaction rate of proton transfer to elimination product **18** has some influence on the overall rate of the reaction sequence outlined in Scheme 4.

In order to put the validity of this mechanistic rationalization to a test, the methylation of unlabelled 2-nitroanisole (**7**) with the perdeuteriated ylide [D_8]**2** was investigated next. Octadeuteriodimethylsulfonium methylide ([D_8]**2**) was prepared from perdeuteriated trimethylsulfonium iodide ([D_9] 95%) in the usual way. In this case, the methylene group in the intermediate Meisenheimer complex is dideuteriated, and the sulfonium ion transferring a proton/deuteron in the final step contains eight D and one H atoms if incomplete perdeuteriation of the reagent is neglected. If a correction is made for the incomplete perdeuteriation, the methylation product should exhibit the following statistical distribution in the methyl group: 87.6% CD_3 ([D_3]**10**), 12.3% ([D_2]**10**), 0.1% CH_2D ([D]**10**). An isotope effect (k_H/k_D = 2.8) for the proton/deuteron transfer shifts this ratio to 72.5:27.2:0.3. The experimentally determined ratio of 70:26.5:3.5 is close to this prediction and confirms the operation of a β-elimination process. The predicted ratio for the intervention of a β-elimination step corresponds to a total deuteriation degree of the methyl group of 90.7% relative to 88.9% calculated from the experimentally determined isotopomeric distribution. The difference points to an approximately 2% loss of the deuterium originally present. The main reason for this could be the occurrence of some H/D exchange due to the presence of traces of residual water during the preparation of the reagent from perdeuteriated trimethylsulfonium iodide in DMF. For the alternative

α′,β-elimination process to be responsible for the formation of the intermediate **18**, all hydrogen atoms of the methyl group in **10** should ultimately originate from the reagent; thus, the methyl group should be essentially trideuteriated, which is far off the experimental result.

At first glance it appears difficult to rationalize why β-elimination should prevail successfully over the α′,β-elimination mechanism. The protons in the sulfonium subunit of Meisenheimer complex **16** are six times more abundant and certainly more acidic than the single proton at an sp^3 C atom of the six-membered ring. Therefore, it seems more likely that sulfur ylide **2** abstracts a proton from one of the methyl groups attached to the sulfur atom rather than attacking the H atom at the ring as necessary for an E2 transition state. As a possible solution of this conflict, it is suggested that the β-elimination has essentially E1 character due to a nitro-group-assisted expulsion of the leaving group [$(CH_3)_2S$] with formation of intermediate **20**. The loss of the proton starts only when the elimination of the nucleofuge is completed (E1) or has progressed to a large extent (E1-like E2) (Scheme 6). Similar anchimeric assistance by neighbouring group participations of nitro groups are known from solvolysis reactions of *ortho*-nitrobenzyl derivatives; see, for example, ref.[23,24]



Scheme 6. E1 pathway for the β-elimination of dimethyl sulfide from **16**.

The failure of the H atom at the sp^3 C atom of **16** to migrate under replacement of dimethyl sulfide from the exocyclic methylene group (Scheme 2) can also be understood in terms of the intervention of the nitro group. This means that the internal nucleophilic substitution of dimethyl sulfide by the nitro group (Scheme 6) is faster than all other modes to displace this nucleofuge from Meisenheimer complex **16**. It is therefore concluded that a full picture of the methylation mechanism is attained by joining together the reaction steps outlined in Schemes 1 and 6.

Finally, the reaction temperature and the reaction times necessary to attain acceptable turnover rates require some comments. In view of the short mean life-time of several minutes at room temperature reported for sulfonium ylide **2**,[5] the relatively long reaction times and a reaction temperature of 20 °C appear to be a contradiction. To fit the reaction conditions with the sequence of steps elucidated for the overall process, it must be assumed that the addition of **2** to nitrobenzenes is fast, followed by much slower reaction steps. The second molecule of **2** required for the β-elimination is regenerated in the final protonation of **18**. Thus, for each reaction sequence one molecule of **2** is consumed.

Conclusions

The highly selective *ortho*-methylation of nitrobenzenes by dimethylsulfonium methylide requires the presence of a substituent that is *ortho*-oriented with respect to the nitro group. Due to steric and polar interactions, the *ortho*-substitution pattern forces the nitro group in an out-of-plane geometry, which could facilitate the coordination of a negatively charged oxygen atom of the nitro group with the positive sulfur atom of the attacking ylide, thus enabling the addition of the carbanionic ylide C atom to the free *ortho* position. To describe this type of interaction, a sulfurane intermediate as precursor of the conventional Meisenheimer complex is suggested (Scheme 1). The addition of the ylide is followed by an E1-like β-elimination driven by the anchimeric assistance of the nitro substituent (Scheme 6). In the last reaction step, the β-elimination product is protonated by the trimethylsulfonium ion concomitantly formed during the elimination process to complete the introduction of the methyl substituent.

Experimental Section

General Information: ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer. Mass spectra were obtained with a TSQ-70 Triple stage quadrupole and a MAT 95 mass spectrometer. Melting points were determined with a Büchi B-540 apparatus. 2-Nitroanisole (**7**), 2-nitrobiphenyl (**9**) and trimethylsulfonium iodide (**1**) are commercially available products. 2-Benzyloxynitrobenzene (**8**) was synthesized according to a reported procedure.[25] All reactions were performed in thoroughly dried solvents and glassware under a nitrogen atmosphere.

3-Deuterio-2-nitroanisole ([D]7): The deuteriated compound was synthesized by starting from 3-methoxy-2-nitrobenzoic acid. The benzoic acid derivative was converted into 3-methoxy-2-nitro-aniline,[26] which, after diazotization followed by reaction with potassium iodide, furnished 1-iodo-3-methoxy-2-nitrobenzene.[27] Deuteriated compound [D]**7** was prepared by reductive deuteriation of the iodobenzene derivative.[14] To a stirred mixture of diglyme (14 mL) and D_2O (4 mL) was added a solution of 1-iodo-3-methoxy-2-nitrobenzene (560 mg, 2 mmol) in diglyme (2 mL) followed by sodium borohydride (150 mg, 4 mmol). After stirring for 90 min, the reaction mixture was decomposed by HCl (1 M) and extracted with light petroleum (5 × 20 mL). The extracts were washed with brine (2 × 25 mL) and dried with Na_2SO_4. The solvents were removed on a rotary evaporator, and the crude product obtained was purified by flash chromatography (eluent PE 40/60 / CH_2Cl_2, 3:1); yield 313 mg (65%), oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H, CH_3), 7.01 (m, 1 H, 4-H), 7.08 (m, 1 H, 6-H), 7.53 (m, 1 H, 5-H), 7.83 (m, 0.03 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4 (CH_3), 113.4 (C-6), 120.1 (C-4), 125.3 (t, $^1J_{C,D}$ = 29.4 Hz, C-3), 134.2 (C-5), 139.5 (C-1), 152.9 (C-2) ppm. MS (70eV): *m*/*z* (%) = 154 (86) [$M^{+\cdot}$, 95% D], 153 (4), 124 (41) [$M - NO]^+$, 107 (100) [$M - HNO_2]^{+\cdot}$, 93 (63), 78 (96).

Perdeuteriotrimethylsulfonium Iodide ([D_9]1·I^-): This compound was synthesized by dissolving the unlabelled iodide in NaOD (0.3 M) in D_2O (15 mL).[1] The deuterium exchange was conducted at room temperature and followed by ^1H NMR spectroscopy. After approximately 16 h, only a weak multiplet consisting of a quintu-

plet (δ = 2.86 ppm, CD_2H) and a triplet (δ = 2.89 ppm, CDH_2) for the residual protons remained (ca. 3% ^{1}H by integration against internal dioxane). Work-up as described[1] and recrystallization from dry methanol furnished pure [D_9]**1** iodide. ^{1}H NMR (D_2O) spectroscopy with dioxane as internal reference indicates a small increase of the ^{1}H content to 5% after work-up. The deuteriation degree of 95% was confirmed by mass spectrometry. In the heated inlet probe of the EI source, the deuteriated sulfonium iodide decomposes into dimethyl sulfide and iodomethane, whose deuteriation degrees were determined from the corresponding $M^{+\cdot}$ ions.

Methylation of Nitrobenzenes 7–9

General Procedure: Sodium hydride in paraffin (2.5 mmol NaH) was suspended in dry DMF (6.5 mL) and cooled in an ice bath. After addition of trimethylsulfonium iodide (2.5 mmol) and stirring for several min, the nitrobenzenes (1.25 mmol) dissolved in DMF (1 mL) were added, and the mixture was warmed up to room temperature over 16 h. The reaction mixture was poured onto ice and extracted with light petroleum (5 × 20 mL). The extracts were washed with brine (2 × 25 mL), dried with Na_2SO_4, and the solvent was removed. Flash chromatography with mixtures of PE 40/60 and CH_2Cl_2 furnished the methylation products and unreacted starting compounds.

1-Methoxy-3-methyl-2-nitrobenzene (10): Compound **10** was obtained as a yellow oil; yield: 58 mg of **10** (42% calculated for consumed starting material); the spectroscopic data agree with those given in the SDBS database and ref.[28]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.84 (d, J = 7.8 Hz, 1 H, 4-H), 6.86 (d, J = 8.3 Hz, 1 H, 6-H), 7.29 (t, J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (CH_3), 56.2 (OCH_3), 109.9 (C-6), 122.5 (C-4), 130.6 (C-5), 130.9 (C-3), 142.0 (C-2), 150.7 (C-1) ppm. MS (70 eV): *m/z* (%) = 167 (98) [$M^{+\cdot}$], 150 (100) [[M – OH]$^+$], 135 (9), 120 (8), 105 (26), 91 (67), 77 (37).

Methylation of 3-Deuterio-2-nitroanisole ([D]7): This reaction was performed as described for the unlabelled compound **7** and produced a methylation compound consisting of 96% unlabelled **10** and 4% monolabelled [D]**10**. This follows from the relative intensities for the peaks at *m/z* 167 and 168 (100:13) in the molecular ion region, after correction for the natural ^{13}C 4% deuterium incorporation into the methyl group was calculated. MS analysis of the recovered nitroanisole revealed complete retention of the deuterium incorporation.

Methylation of 2-Nitroanisole (7): This reaction was carried out as described before, except that perdeuteriated trimethylsulfonium iodide was applied. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24–2.30 (m, 0.03 H, composed of a triplet for CDH_2 and a quintuplet for CD_2H, $J_{C,D}$ = 2.3 Hz, the approximate intensity ratio is 1:8), 3.87 (s, 3 H, OCH_3), 6.85 (m, 2 H, 4-H, 6-H), 7.29 (m, 1 H, 5-H) ppm. The molecular ion peak region of the EI-MS showed the following intensity distribution. *m/z* (%) = 171 (9), 170 (100), 169 (37), 168 (5), 167 (< 1). This corresponds to a composition of 70% [D_3]**10**, 26.5% [D_2]**10** and 3.5% [D]**10**.

1-Benzyloxy-3-methyl-2-nitrobenzene (11): Compound **11** was obtained as a yellow oil; yield: 92 mg (44% calculated for consumed starting material). ^{1}H NMR spectroscopic data agree with those reported in ref.[29]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 5.16 (s, 2 H, CH_2), 6.85 (d, J = 7.8 Hz, 1 H, 4-H), 6.89 (d, J = 8.3 Hz, 1 H, 6-H), 7.25 [t (broad), J = 8.1 Hz, 1 H, 5-H], 7.33 (m, 1 H, 4′-H), 7.65 (m, 4 H, 3′/5′-H, 2′/6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4 (CH_3), 71.3 (CH_2), 112.0 (C-6), 123.3 (C-4), 127.4 (C-2′/6′), 128.6 (C-4′), 129.1 (C-3′/5′), 130.9 (C-5), 131.5 (C-3), 136.1 (C-1′), 142.9 (C-2), 150.1 (C-1) ppm. MS (70 eV): *m/z* (%) = 243 (< 1), [$M^{+\cdot}$], 137 (14), 91 (100).

3-Methyl-2-nitrobiphenyl (12): Compound **12** was obtained as colourless crystals (m. p. 85–85.5 °C, ref.[12a]: m. p. 85–85.5 °C); yield 74 mg (50% calculated for consumed starting material). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 7.19 (m, 2 H, 4-H, 6-H), 7.25 (m, 1 H, 5-H), 7.28 (m, 1 H, 4′-H), 7.30–7.39 (m, 4 H, 3′/5′-H, 2′/6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4 (CH_3), 128.0 (C-3′/5′), 128.4 (C-4′*), 128.6 (C-6*), 128.7 (C-2′/6′), 129.7 (C-1′), 130.0 (C-4**), 130.2 (C-5**), 134.3 (C-1), 136.7 (C-3), 150.8 (C-2) ppm. MS (70 eV): *m/z* (%) = 213 (33) [$M^{+\cdot}$], 196 (99), 185 (77), 168 (76), 165 (89), 156 (100), 152 (78), 142 (26), 139 (25) (*,** exchangeable).

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