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LETTERS

Improved preparation of tosyldiazomethane

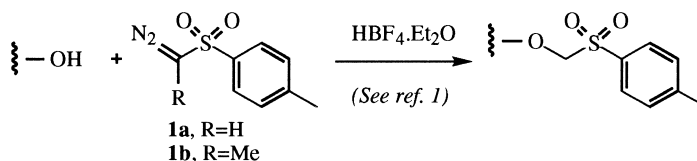
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Abstract

Treatment of the carbamate **2a** by *i*-amyl nitrite and TMSCl in presence of a reduced amount of pyridine, followed by decomposition of the resulting nitroso derivative **3a** with activated alumina afforded in high yield the pure, crystalline, diazosulfone **1a**, a process which could be extended to the preparation of the parent diazosulfone **1b**. © 2000 Elsevier Science Ltd. All rights reserved.

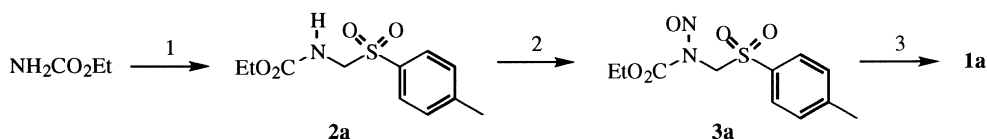
As part of a synthetic work, we had to prepare various tosylmethyl ethers and an obvious, straightforward way for doing so was, as indicated, to react the corresponding alcohols with tosyldiazomethane **1a** in presence of an acid catalyst (Scheme 1).¹ The preparation of the diazo-sulfone **1a** was thus examined.



Scheme 1.

According to the organic syntheses directions,² the carbamate **2a**, which was formed efficiently by stirring for a few days a solution of ethyl carbamate and sodium *p*-toluenesulfinate in 30% formalin diluted with methanol and formic acid, was reacted with nitrosyl chloride in pyridine, used both as a reactant and a solvent (Scheme 2). Dilution with water of the crude reaction mixture then afforded the *N*-nitroso derivative **3a**, the treatment of which with basic alumina in ether afforded the desired diazo compound **1a**.

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Scheme 2. Reagents and conditions: according to Ref. 1: (1) sodium *p*-toluenesulfinate in formalin/formic acid; (2) NOCl in pyridine; (3) basic alumina in ether/ CH_2Cl_2

Some pure **1a** could indeed be obtained this way. However, after repeated experiments on various scales (ca. 0.1 to 10 g), we noticed that not only the yields but also the physical state and, to a lesser extent, the purity³ of this product varied rather erratically. Hence, though in a few cases the final treatment of **3a** with basic alumina afforded as reported, though in lower yield, the diazosulfone **1a** as a yellow solid, in many instances an impure orange to reddish oil resisting crystallisation was isolated in variable yields. With the aim to elucidate the origin of this inconsistency, we re-examined each step of this otherwise valuable procedure.⁴

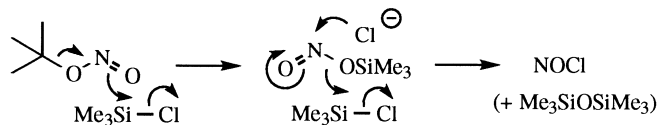
It could obviously be surmised that much of these difficulties originated from the conditions of the final **3a**–**1a** conversion. As pointed out in the relevant publication,² the time required for observing complete disappearance of the starting nitroso derivative **3a** was highly dependent on the specification—i.e. basic or neutral—of the used alumina, the former being, with regards to the kinetic of this process, the more efficient. The trouble, however, also noticed in this publication, was the formation of red-coloured side-products at the surface of the alumina when the basic form was used. Though no other product than **1a** appeared (TLC) to be eluted during ensuing filtration and washing operations, trace amounts of these impurities could be present however, thus preventing the crystallisation of the oily **1a** thus obtained. The attempted use of neutral alumina looked at first beneficial since only a faint pink colour developed in these conditions. But, in agreement with previous observations,² though the clean formation of **1a** could be substantiated (TLC, NMR), the reaction then proceeded only very slowly and repeated treatments of the resulting **1a**–**3a** mixture with alumina, detrimental to the yield owing to the moderate stability of **1a**, were necessary to observe a full conversion of **3a**.

These problems could finally be solved by first heating at ca. 300°C commercial (Grade I) basic alumina in an oven for 12 h, the dry powder thus obtained being then slurried in ether with cooling (ice bath) and vigorous stirring before being treated by a solution of **3a** in CH_2Cl_2 , any adventitious moisture being constantly excluded during all operations. After several hours of stirring at rt, a simple elimination of the solids by filtration, followed by evaporation of the solvents, gave reproducibly the pure (TLC, NMR) diazosulfone **1a** as an oil crystallising almost instantly in the cold (ca. –30°C).

Another crucial point appeared to be the quality of the nitroso compound used: the purer the starting nitroso derivative, the higher the yield in crystalline diazosulfone **1a**. Unfortunately, due to the use of pyridine as solvent in the nitrosation step, the isolation of **3a** proceeded unsatisfactorily: whereas in a few cases **3a** crystallised out readily by dilution of the reaction mixture with water as recommended,² in most experiments this dilution resulted only in the slow appearance of a gummy solid having a strong smell of pyridine, and a classical extraction, followed by a purification by chromatography was necessary to obtain pure **3a** in reduced yield.

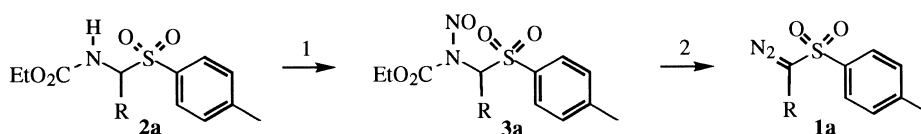
In order to avoid the use of a large excess of pyridine, we became interested by a report on the clean conversion of oximes into the corresponding ketones by treatment with a mixture of *t*-butyl nitrite and TMSCl.⁵ Though not explicitly mentioned in this publication, it could be supposed

that TMSCl induced first the formation of the *O*-TMS derivative of nitrous acid, then possibly decomposed into nitrosyl chloride as indicated (Scheme 3).



Scheme 3.

In the event, simply mixing **2a** with an organic nitrite and TMSCl in an inert solvent and in presence of a reduced amount of an amine base would have resulted in the formation of **3a** (Scheme 4). This proved to be the case.



Scheme 4. Reagents and conditions: (1) *i*-amyl nitrite (1.4 equiv.), pyridine (1.4 equiv.), TMSCl (2.8 equiv.), CH₂Cl₂; rt, 1 day; (2) activated basic alumina, ether/CH₂Cl₂; overnight, then crystallisation from ether/hexane

Sequential addition of *i*-amyl nitrite, preferred over *t*-butyl nitrite for its higher stability, and TMSCl to a CH₂Cl₂ solution of **2a** and pyridine, each reagents being in slight excess, resulted after one day of stirring at rt in the obtention of pure **3a** in high yield (Table 1). Moreover, submitting this compound to the treatment with activated alumina as above afforded almost quantitatively the diazosulfone **1a** as an orange oil which crystallised on standing in the freezer overnight (90% yield overall, from **2a**).⁶ Interestingly, submitting the carbamate **2b**, which was formed by condensing acetaldehyde and *p*-toluenesulfinic with ethyl carbamate, to the same two-step procedure gave similarly, the parent, crystalline, diazosulfone **1b** (Table 1).⁷

Table 1
Preparation of the diazosulfones **1** from carbamates **2** by the *i*-amyl nitrite-TMSCl process

R	Nitrosocarbamate 3 , Yield, m. p.	Diazosulfone 1 , Yield, m. p.
H	3a , 90.8%,* 88-89 °C	1a , 67.2%,* 34-35 °C(dec)
Me	3b , 61.2%, 57-58 °C	1b , 72.6%,* 39-42 °C (dec)

* After recrystallisation

Slow recrystallisation of **1a** was then attempted in an ether/hexane mixture, at low temperature, as described (Fig. 1).² To our delight, one of the crystals thus obtained (67.2%) proved suitable for X-ray analysis, which was run by maintaining the temperature at -100 °C throughout in order to minimise the decomposition of **1a**.⁸

As can be seen on the Chem-3D structure computed from the resulting crystal data, the length of the carbon–nitrogen bond (ca. 1.294 Å) is close to the value (ca. 1.32 Å) obtained for the carbon–nitrogen bond in diazomethane,^{9a} which suggested at first sight that the term tosyldiazomethane

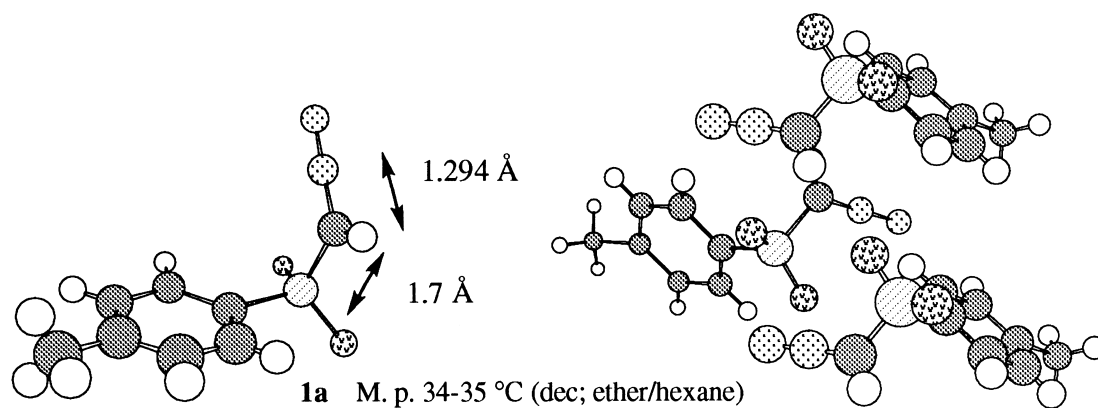


Figure 1.

used to designate **1a** is justified. However, the relatively short bond (1.7 Å)^{9b} of the sulfur atom with the carbon atom bearing the diazo residue is indicative of some delocalisation of the negative charge on the sulfonyl group, which is consistent with previous NMR^{9c} and IR^{9d} studies. Additionally, besides being chiral, each molecule of tosyldiazomethane **1a** is arranged in the crystal unit so that each central nitrogen atom, which should theoretically share a positive charge, is bonded to one of the two oxygen atoms of the neighbouring SO₂ residue, a complexation which is reminiscent of the metal-SO₂ interaction displayed by anionised sulfones in the crystalline state.^{9b}

In conclusion, new conditions for converting efficiently the carbamate **2** into the corresponding *N*-nitroso derivatives **3** has been found and, although this has not yet been fully explored, it can be predicted that the combination of an alkyl nitrite with TMSCl used presently should also be useful for performing related nitrosylation reactions. Additionally, improved conditions for the known alumina-induced decomposition of compounds **3** into the diazosulfones **1** have been identified. Both improvements contribute to making this method for preparing diazosulfones much efficient, permitting inter alia to obtain a crystal of **1a** suitable for an apparently unprecedented X-ray analysis. Further study of this interesting class of diazo compounds is actively pursued, the results of which will be published in due course.

References

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- Most of the crude samples of **1a** thus obtained appeared pure in NMR. In a few cases, however, a weak singlet at 6.8 ppm, possibly indicative of the presence of 1,2-bis-tosylethylene, was also perceptible in the ¹H NMR spectra.
- Sulfones **1** cannot be obtained from the corresponding *p*-tolyl alkylsulfones by using the diazo transfer method of Regitz (see: Dieckmann, J. *J. Org. Chem.* **1965**, 30, 2272–2275). Recently, a procedure based on the related alumina-induced decomposition of 1-diazo-1-tosyl-acetophenone has been proposed (Korneev, S.; Richter, C. *Synthesis* **1995**, 1248–1250). However, owing to the ease with which the starting carbamate **2a** is prepared, this method presents no clear advantage over the van Leusen's process.
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6. All reactions were performed in flame-dried flasks in a dry argon atmosphere and using well-dried solvents and reagents, all vessels used being protected from daylight with a foil of aluminium during any operation. Protocol for the nitrosylation of **2a**: To a stirred solution of **2a** (19 g; 738 mmol) in CH₂Cl₂ (100 ml) were added successively, by means of a syringe: (i) pyridine (8.5 ml; 105 mmol); (ii) *i*-amyl nitrite (14 ml; 105 mmol); (iii) TMSCl (26.7 ml; 210 mmol). The resulting clear solution was stirred for 24 h at rt (should a TLC indicate the presence of residual **2a**, slight excess (0.2 equiv.) of each reagent will be added in the same order, the stirring being pursued until complete disappearance of the starting material). The reaction mixture was then poured into 10% aqueous NaHCO₃ (200 ml). After 30 min stirring, the aqueous layer was extracted with CH₂Cl₂ (2×50 ml). The pooled organic extracts were then washed successively with 1 N HCl (2×150 ml), brine (2×50 ml), 10% NaHCO₃ (50 ml), then brine (20 ml), and dried (MgSO₄). Rotoevaporation (without heating) of the solvents left a pale-yellow powder (21 g) which was recrystallised in CH₂Cl₂/Et₂O to give **2a** (19.2 g; 67 mmol; 90.8%) as a bright-yellow powder; mp 88–89°C (lit.² mp 87–89°C); ¹H NMR: 1.33 (t, J = 7.12 Hz, 3H), 2.4 (s, 3H), 4.42 (q, J = 7.12 Hz, 2H), 5.06 (s, 2H), 7.31 (m, 2H), 7.63 (m, 2H); ¹³C NMR: 14.1, 21.8, 58.5, 65.4, 128.5, 130.6, 135.4, 145.9, 152.4. The **3–1** conversions were performed according to Ref. 2 except that the flask containing the basic alumina (Merck; 3 g/mmol) was first heated in an oven at 300°C for 12 h, then immediately transferred in a desiccator where it was allowed to cool to rt in vacuo. It was then connected to an argon line, and cooled (ice/methanol) before the ether was added. After 12 h stirring at rt, on a 7.2 g scale (25 mmol), the diazosulfone **1a** was obtained as bright-yellow needles (3.3 g; 67.2%) after recrystallisation from a 2:1 ether:hexane mixture.
7. Selected data: **2b**: ¹H NMR: 1.04 (t, J = 6.8 Hz, 3H), 1.56 (d, J = 6.7 Hz, 3H), 2.39 (s, 3H), 3.86 (q, J = 6.8 Hz), 4.85–5.1 (m, 1H), 5.57 (d, J = 10.3 Hz, 1H (NH)), 7.29 (m, 2H), 7.75 (m, 2H); ¹³C NMR: 13.2, 14.5, 21.7, 61.6, 67.4, 129.5, 129.8, 133.4, 145.2, 154.8; **3b**: ¹H NMR: 1.45 (t, J = 7.15 Hz, 3H), 1.67 (d, J = 7.2 Hz, 3H), 2.43 (s, 3H), 4.53 (qd, J = 7.15, 1.6 Hz, 2H), 5.75–5.9 (m, 1H), 7.34 (m, 2H), 7.68 (m, 2H); ¹³C NMR: 13.3, 14.5, 21.8, 61.7, 67.4, 129.4, 129.8, 133.3, 145.3, 154.9; **1b**: ¹³C NMR: 8.95, 21.7, 59.3, 126.7, 130.1, 139.3, 144.4. ¹H and ¹³C NMR at 200 and 50 MHz, respectively, in CDCl₃.
8. Crystal data for **1a**: C₈H₈N₂O₂S, M.W. = 196.23, colourless, orthorhombic, *a* = 7.791(3), *b* = 20.389(6), *c* = 5.653(2) Å, *Z* = 4, *d*_{calc} = 1.45 g cm^{−3}, *μ* = 2.906 mm^{−1}, space group P2₁2₁2₁. Data were collected on a crystal of dimensions 0.35×0.35×0.12 mm³ using a Philips PW1100/16 automatic diffractometer and graphite monochromated CuKα radiation (λ = 1.5418 Å) at −100°C. 672 reflections measured (3° < 2θ < 54°) with 603 having I > 3 σ(I). Empirical absorption corrections, transmission factors between 0.28 and 1. The structure was determined using direct methods. Hydrogen atoms were introduced in structure factor calculations as fixed contributors with d(X–H) = 0.95 Å and B(H) = 1.3*Beqv(X) Å². Refinements against |F| using the OpenMoleN package on a DEC Alpha workstation and anisotropic temperature factors for all non-hydrogen atoms. The absolute structure was determined refining Flack's *x* parameter. Final results: R(F) = 0.052, R_w(F) = 0.068, GOF = 1.657.
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