The Sulfenylation of Substituted Imines

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Conditions for mono- and bissulfenylation of *N*-methyl-3,3-dimethylpyrrolidine-2,5-dione are described and compared to a closely related six-membered imide, *N*-methyl-3-ethyl-3-phenylpiperidine-2,6-dione. The influence of solvent, base and electrophile on product distribution is explored.

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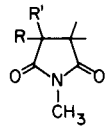
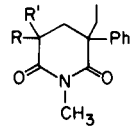
As part of a project to investigate chemotherapeutic agents for breast cancer, we have systematically studied the sulfenylation of imides. Unlike the sulfenylation of other carbonyl substrates (2) the sulfenylation of imides (3) is litte known. In addition to our previous report (4) on the sulfenylation of substituted glutarimides, we would like to report here the results of our studies on the sulfenylation of the substituted succinimide **1**. These results are compared to those of the sulfenylation of the substituted glutarimide **2**.

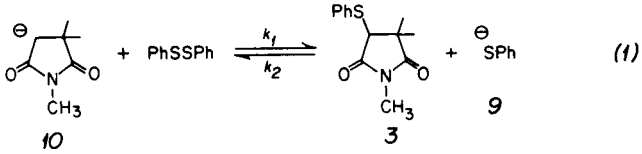




1: R = R' = H
3: R = H, R' = SPh
5: R = R' = SPh

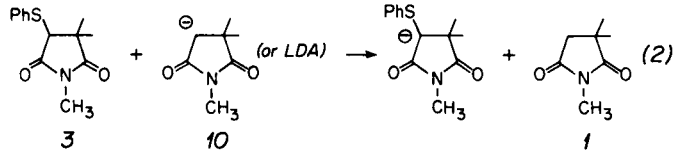
2: R = R' = H
4: R = H, R' = SCH_3

The product distribution of the reaction of **1** with various ratios of lithium diisopropylamide (LDA), electrophile [diphenyl disulfide (**6**) or phenyl benzenethiosulfonate (**7**)] and hexamethyphosphoramide (HMPA) are tabulated in Table I. The reaction of **1** with **6** both parallel and differ from that of glutarimide **2** with dimethyl disulfide (**8**) (Table II) (4). In general, the higher yields of **3** than that of **4** are attributed in part to the higher reactivity of the diphenyl disulfide and to the higher stability of the phenylthiolate anion (**9**). The latter would favor 3 in the equilibrium (equation 1). The reverse of equation 1



10 *3* *9* (1)

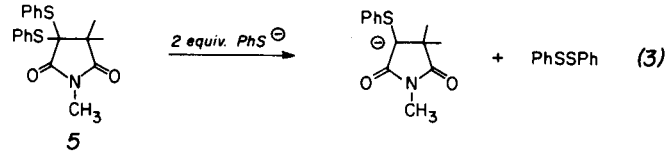
was proven by the reaction of **9** with **3** (5,6). The lower yield of **3** with a 1:1:1 ratio than that with a 1:2:2 ratio was attributed to proton transfer (7) (equation 2). With added HMPA, the yields of **3** and **4** increased when a 1:2:2:2



3 *10* *1* (2)

ratio, as opposed to a 1:2:2 ratio, was employed. It is likely that HMPA increases the reactivity of the forward reaction more than that of the reverse reaction in equation 1. It is interesting to note that HMPA did not increase the yields of **3** and **4** when a 1:1:1:1 ratio, as opposed to a 1:1:1 ratio, was employed. This can be attributed to the equal enhancement in reactivity of **10** by adding HMPA in both equation 1 and 2.

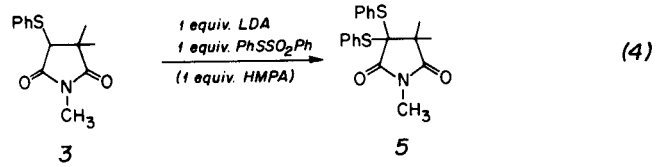
Unlike esters and lactams, bissulfenylation did not occur when diphenyl disulfide was employed, even with added HMPA. Lack of bissulfenylation may reflect an unfavorable equilibrium for the sulfenylation of **3** with diphenyl disulfide. This was demonstrated by the desulfenylation of **5** with two equivalents of phenylthiolate anion to give 92% yield of **3** (equation 3).



5 (3)

The bissulfenylated adduct **5** may be obtained by utilization of the more reactive agent **7**, since its gegenion, phenylsulfinate, is more stable; therefore, the reverse reaction will not occur (Table I, entry 5,6).

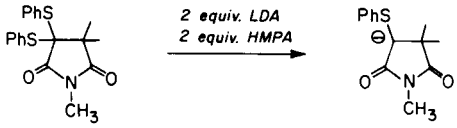
The sulfenylation of **3** with one equivalent of LDA and one equivalent of **7**, with or without added HMPA, gave a 98% yield of **5** (equation 4). Treatment of **3** with 1.5



3 *5* (4)

equivalents of LDA and 1.5 equivalents of **7** gave a mixture of **3** and **5**. This result prompted an investigation of the stability of **5** in the presence of LDA. Surprisingly,

reaction of **5** with LDA gave a 97% yield of **3** (equation 5). A related desulfenylation reaction induced by a Grignard reagent was reported recently (8).



(5)

5

A rationale behind the much lower yield of **5** for the direct sulfenylation of **1** than that of **3** remains to be answered. The desulfenylation of **5** and **3** with diisopropylamine was ruled out since the reaction of **5** or **3** with diisopropylamine gave only starting material. Further investigation is required to answer this question.

In summary, the mechanism of the sulfenylation of imides is complex. However, with proper ratio of substrate: base:electrophile:HMPA, maximized yields of the desired products may be obtained.

EXPERIMENTAL

Infrared spectra were obtained on potassium bromide film on a Perkin-Elmer 567 or 5996 spectrophotometer. Proton magnetic resonance spectra were recorded at 90 MHz in deuteriochloroform on a Bruker WH-90 spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilene (TMS). Mass spectral analyses were determined on a Nuclide 12-90-G magnetic sector spectrometer. Thin-layer chromatography was performed on Merck 60F-254 (0.25mm) plates which were visualized with molybdophosphoric acid in ethanol. Merck 230-400 mesh silica gel 60 was employed for column chromatography. Reactions were run under nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from calcium hydride.

General Procedure for Sulfenylation.

To a 24 ml semtum-capped side arm round bottom flask equipped with a magnetic stirring bar was added a hexane solution of *n*-butyllithium. Hexane was partially removed under the combination of a stream of nitrogen and reduced pressure. The flask was cooled to -78° and a solution of tetrahydrofuran and diisopropylamine was added via syringe. After 45 minutes, a tetrahydrofuran solution of **1** or **3** was introduced dropwise *via* a syringe. After one hour, the sulfenylating reagent was added and the reaction mixture was stirred at 0° for three hours and at ambient temperature for sixteen hours. Water was added and the mixture was extracted with four 20 ml portions of ethyl acetate. The combined organic extracts were washed with 5% hydrochloric acid and saturated sodium chloride. The organic solution was dried (sodium sulfate), filtered, and concentrated *in vacuo* to give an oil. The reaction product was purified by column chromatography (70:1 absorbent ratio) with a mixture of hexane and ether (11:9) as eluent.

Sulfenylation of *N*-Methyl-3,3-dimethylpyrrolidine-2,5-dione (**1**) with Diphenyl Disulfide (**6**). Synthesis of *N*-Methyl-3,3-dimethyl-4-phenylthiopyrrolidine-2,5-dione (**3**).

Table I

Sulfenylation of *N*-Methylsuccinimide **1**

Electrophile	Ratio of 1:LDA:Electrophile:HMPA	Yield **1** (%)	Yield **3** (%)	Yield **5** (%)
PhSSPh (6)	1:2:2:2	10	90	0
6	1:1:1:1	32	58	0
6	1:2:2:0	23	69	0
6	1:1:1:0	36	58	0
$PhSSO_2Ph$ (7)	1:2:2:2	10	23	65
7	1:2:2:0	17	14	62

Table II

Sulfenylation of *N*-Methylglutarimide **2**

Electrophile	Ratio of 2:LDA:Electrophile:HMPA	Yield **2** (%)	Yield **4** (%)
CH_3SSCH_3 (8)	1:2:2:2	35	65
8	1:1:1:1	52	44
8	1:2:2:0	57	42
8	1:1:1:0	58	38

1:2:2:2 Ratio of 1:LDA:6:HMPA.

The general sulfenylation procedure described above was employed. Hexane was partially removed from 2.7 ml (4.1 mmoles) of *n*-butyllithium. To this solution was added 3 ml of tetrahydrofuran and 0.58 ml (4.1 mmoles) of diisopropylamine. The solution was stirred at −78°C for 45 minutes whereupon a solution of 0.282 g (2.00 mmoles) of **1** in 0.5 ml of tetrahydrofuran and 0.72 ml (4.1 mmoles) of hexamethylphosphoramide was introduced *via* a syringe. The reaction mixture was stirred at 0° for one hour. A solution of 0.5 ml of tetrahydrofuran and 0.872 g (4.00 mmoles) of diphenyl disulfide was introduced *via* a syringe. The mixture was stirred at 0° for three hours and at ambient temperature for sixteen hours. Water was added and the product isolated with ethyl acetate. Purification by column chromatography gave 0.44 g (9%) of monosulfenylated **3** as an oil and 0.014 g (10%) of the starting **1**: ir (film): 3070, 2980, 2940, 2880, 1785, 1720, 1585, 1580, 1480, 1470, 1440 cm^{-1}; nmr (deuteriochloroform): δ 7.31 (m, 5H), 3.77 (s, 1H), 2.93 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06. Found: C, 62.81; H, 6.11.

N-Methyl-3,3-dimethyl-4,4-di(phenylthio)-pyrrolidine-2,5-dione (**5**).

The general sulfenylation procedure described above was employed. Hexane was partially removed from 0.65 ml (1.0 mmole) of *n*-butyllithium. To this solution was added 3 ml of tetrahydrofuran and 0.14 ml (1.0 mmole) of diisopropylamine. The solution was stirred at −78° for 45 minutes and 0.24 g (1.00 mmole) of **3** in 0.5 ml of tetrahydrofuran was introduced *via* a syringe. The reaction mixture was stirred at −78° for one hour and 0.275 g (1.10 mmoles) of phenyl benzenethiosulfonate in 0.5 ml of tetrahydrofuran was added. The mixture was stirred at 0° for three hours and at ambient temperature for sixteen hours. Water was added and the product isolated with ethyl acetate. Purification by column chromatography on 30 g of silica gel using a mixture of hexane and ether (7:3) as eluent gave 0.351 g (98%) of oily bissulfenylated **5**; ir (film): 3070, 3000, 2980, 2940, 1965, 1780, 1720, 1590, 1580, 1480, 1450 cm^{-1}; nmr (deuteriochloroform): δ 7.17-7.78 (m, 10H), 2.66 (s, 3H), 1.40 (s, 6H).

Anal. Calcd. for $C_{19}H_{19}NO_2S_2$: C, 63.83; H, 5.36. Found: C, 63.93; H, 5.46.

Desulfenylation of *N*-methyl-3,3-dimethyl-4,4-di(phenylthio)pyrrolidine-2,5-dione (**5**) with Lithium Diisopropylamide.

To a solution of 2 ml of tetrahydrofuran and 0.64 (1.0 mmole) of *n*-butyllithium at −78% was added 0.14 ml (1.0 mmole) of diisopropylamine dropwise. The reaction mixture was stirred at −78° for 45 minutes and 0.178 g (0.500 mole) of **5** in a mixture of 0.75 ml of tetrahydrofuran and 0.17 ml (1.0 mmole) of hexamethylphosphoramide was added *via* a syringe. The mixture was stirred at 0° for three hours and ambient temperature for sixteen hours. Water was added and the product isolated with ethyl acetate. Purification by column chromatography on 14 g silica gel using a mixture of hexane and ether (7:3) as eluant gave 0.121 g (97%) of **3**.

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