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EFFICIENT *N*-SULFENYLATION OF DIHYDROPYRROLE DERIVATIVES USING *N*-SULFENYLPHTHALIMIDES

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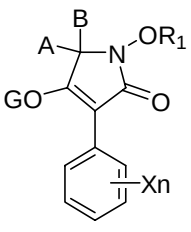
Abstract- Ultrasound treatment of dihydropyrrole derivatives with *N*-sulfenylphthalimides in the presence of base gave the corresponding *N*-sulfenyldihydropyrrole derivatives.

Recently we have reported the preparation of a series of *N*-oxydihydropyrrole derivatives (**1**)[1] that demonstrate high insecticidal activity. These compounds are characterized by the oxygen atom attached to the nitrogen of the dihydropyrrole ring. Then we were interested in the biological effect caused by replacement of the oxygen with a sulfur atom, and intended to seek an efficient method to prepare the *N*-sulfenyldihydropyrrole derivatives (**2**).



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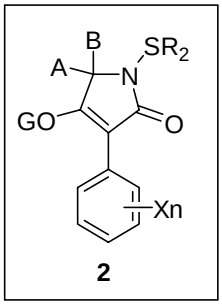

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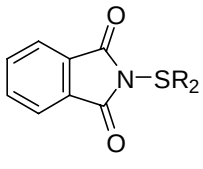

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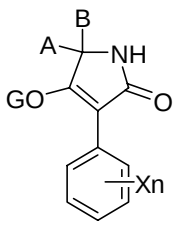

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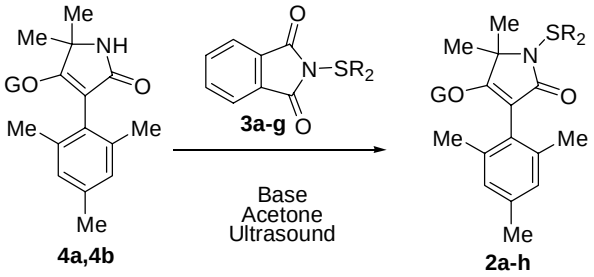
While several methods for *N*-sulfenylation in the β-lactam system have been reported,[2] none of the related synthetic methods could be effectively used for our dihydropyrrole system (**2**). To take advantage of the utility of *N*-sulfenylphthalimides (**3**)[3] as reagents for *N*-sulfenylation, we examined their reactions with dihydropyrrole derivatives (**4**).[4] While our first trial of the reaction between **4a** and **3a** using sodium hydride (NaH) or lithium diisopropyl amide (LDA) as a base in tetrahydrofuran provided the desired *N*-sulfenylated product (**2a**) in moderate yields (45 % for NaH and 27 % for LDA), the reaction of **4b** with **3a** under the same reaction conditions did not give the desired product (**2h**), resulting only in the removal of methoxycarbonyl group of **4b** [compounds (**4a**), (**4b**), (**3a**), (**2a**) and (**2h**) are listed in Table 1]. Further attempts using other bases and solvents did not improve the yield. But finally we found that ultrasound treatment[5] of various derivatives of **3** and **4** in the presence of base, such as potassium carbonate (K_2CO_3), gave the desired *N*-sulfenyldihydropyrrole derivatives **2a-h** in moderate to good yields. The results are summarized in Table 1.

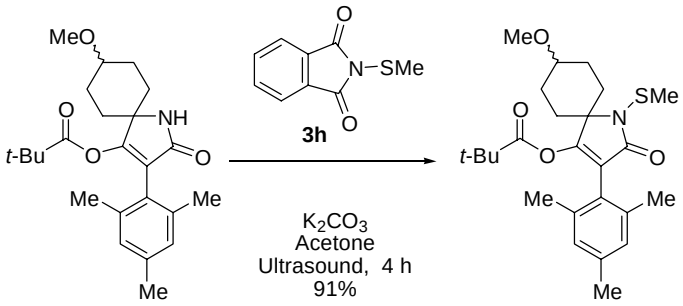
Table 1. *N*-sulfenylation of dihydropyrrole derivatives (**4a**, **4b**) with *N*-sulfenylphthalimides (**3a-g**).



Entry	**4**	G	**3**	R_2	Base	Time(h)	**2**	Yield(%)
1	**4a**	*t*-BuCH_2C(O)	**3a**	Et	Et_3N	4	**2a**	46
2	**4a**	*t*-BuCH_2C(O)	**3a**	Et	Li_2CO_3	4	**2a**	22
3	**4a**	*t*-BuCH_2C(O)	**3a**	Et	Na_2CO_3	4	**2a**	40
4	**4a**	*t*-BuCH_2C(O)	**3a**	Et	$NaHCO_3$	4	**2a**	53
5	**4a**	*t*-BuCH_2C(O)	**3a**	Et	K_2CO_3	4	**2a**	59
6	**4a**	*t*-BuCH_2C(O)	**3b**	Pr	K_2CO_3	4	**2b**	72
7	**4a**	*t*-BuCH_2C(O)	**3c**	*i*-Pr	K_2CO_3	5	**2c**	61
8	**4a**	*t*-BuCH_2C(O)	**3d**	Bu	K_2CO_3	2	**2d**	44
9	**4a**	*t*-BuCH_2C(O)	**3e**	*i*-Bu	K_2CO_3	4	**2e**	44
10	**4a**	*t*-BuCH_2C(O)	**3f**	Bn	K_2CO_3	3	**2f**	45
11	**4a**	*t*-BuCH_2C(O)	**3g**	Ph	K_2CO_3	2	**2g**	38
12	**4b**	MeOC(O)	**3a**	Et	K_2CO_3	1.5	**2h**	74

Potassium carbonate gave the best result among the bases tested (Entries 1-5). Alkylsulfanylation smoothly proceeded to give corresponding *N*-alkylsulfanyldihydropyrrole derivatives (Entries 5-10). Even the sterically hindered *N*-isopropylsulfanylphthalimide (**3c**) reacted, producing **2c** in good yield (Entry 7). The phenylsulfanyl group was also introduced by the reaction with *N*-phenylsulfanyl-phthalimide (Entry 11). The ultrasound method gave *N*-sulfenylated compounds without affecting susceptible substituents such as the alkoxycarbonyloxy group (Entry 12).

Spirocyclohexane derivative (**4c**) (diastereomixture; *ca*. 4:3) was also successfully converted to the *N*-methylsulfanylated form (**2i**) by the same ultrasound treatment. [6]



The products were subjected to biological assays and found to be potent as insecticide. Detailed structure-activity relationships will be discussed elsewhere.

In summary, an efficient synthetic method for the *N*-sulfenylation of dihydropyrrole derivatives has been described. The chemistry established in this article has proven fruitful in providing an array of *N*-sulfenyldihydropyrrole derivatives.

EXPERIMENTAL

General: All melting points are uncorrected. IR spectra were measured on a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer with tetramethylsilane as an internal standard. HRMS spectra were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer.

General procedure for *N*-Sulfenylation of dihydropyrrole derivatives (4a-c) with *N*-sulfenylphthalimides (3a-h).

The suspension of 1 mmol of the diydropyrrole deivative, 1.5 mmol of the *N*-sulfenylphthalimide and 1.2 mmol of base in acetone (4 mL) was sonicated for 4 h. The reaction mixture was poured into brine and the water layer was extracted with ethyl acetate (EtOAc). The combined organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried with anhydrous magnesium sulfate ($MgSO_4$), and evaporated. The resulting residue was chromatographed on silica gel to purify the product.

1-Ethylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2a): white prisms; mp 79-81 ^oC (from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ: 6.82 (2H, s), 2.88 (2H, q, *J*=7.3 Hz), 2.23 (3H, s), 2.18 (2H, s), 2.13 (6H, s), 1.45 (6H, s), 1.28 (3H, t, *J*=7.3 Hz), 0.83 (9H, s); IR (KBr) cm^{-1}: 2951, 1780, 1701, 1678, 1613, 1465, 1366, 1322, 1298, 1231, 1127, 1089; HRMS(EI) Calcd for $C_{23}H_{33}NO_3S$ 403.2181, Found 403.2182.

4-Mesityl-2,2-dimethyl-5-oxo-1-propylsulfanyl-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2b) : white prisms; mp 57-58 ^oC (from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ: 6.81 (2H, s), 2.82 (2H, t, *J*=7.7 Hz), 2.23 (3H, s), 2.12(2H, s), 2.13 (6H, s), 1.72-1.58 (2H, m), 1.45 (6H, s), 1.04 (3H, t, *J*=7.7 Hz), 0.83 (9H, s); IR (KBr) cm^{-1}: 2959, 1781, 1706, 1670, 1611, 1465, 1323, 1227, 1210, 1124, 1086; HRMS(EI) Calcd for $C_{24}H_{35}NO_3S$ 417.2338, Found 417.2338,.

1-Isopropylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethyl-butanoate (2c) : white prisms; mp 89-91 ^oC (from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ: 6.82 (2H, s), 3.41 (1H, sep, *J*=6.6 Hz), 2.23 (3H, s), 2.18 (2H, s), 2.14 (6H, s), 1.45 (6H, s), 1.26 (6H, d, *J*=6.6 Hz), 0.83 (9H, s); IR (KBr) cm^{-1}: 2958, 1777, 1701, 1683, 1613, 1463, 1365, 1320, 1228, 1128, 1092; HRMS(EI) Calcd for $C_{24}H_{35}NO_3S$ 417.2338, Found 417.2337.

1-Butylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2d) : colorless oil; ^1H NMR ($CDCl_3$) δ: 6.81 (2H, s), 2.85 (2H, t, *J*=9.5 Hz), 2.23 (3H, s), 2.18 (2H, s), 2.13 (6H, s), 1.66-1.45 (4H, m), 1.45 (6H, s), 0.91 (3H, t, *J*=7.3 Hz), 0.83 (9H, s); IR (neat) cm^{-1}: 3408, 2959, 1778, 1713, 1681, 1613, 1464, 1310, 1211, 1122, 1093; HRMS(EI) Calcd for $C_{25}H_{37}NO_3S$ 431.2494, Found 431.2493.

1-Isobutylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2e) : white prisms; mp 51-52 °C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.81 (2H, s), 2.73 (2H, d, *J*=7.0 Hz), 2.23 (3H, s), 2.18 (2H, s), 2.13 (6H, s), 1.98-1.82 (1H, m), 1.45 (6H, s), 1.05 (6H, d, *J*=7.0 Hz), 0.83 (9H, s); IR (KBr) cm^{-1}: 2955, 1179, 1697, 1679, 1613, 1465, 1364, 1321, 1214, 1127, 1094; HRMS(EI) Calcd for $C_{25}H_{37}NO_3S$ 431.2494, Found 431.2495.

1-Benzylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2f) : colorless oil; ^{1}H NMR ($CDCl_3$) δ: 7.33-7.26 (5H, m), 6.82 (2H, s), 4.13 (2H, s), 2.24 (3H, s), 2.14 (8H, s), 1.18 (6H, s), 0.81 (9H, s); IR (neat) cm^{-1}: 2961, 1778, 1704, 1682, 1613, 1455, 1312, 1234, 1211, 1123, 1094, 1030; HRMS(EI) Calcd for $C_{28}H_{35}NO_3S$ 465.2338, Found 465.2338.

4-Mesityl-2,2-dimethyl-5-oxo-1-phenylsulfanyl-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (2g) : white prisms; mp 109-111 °C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 7.41-7.20 (5H, m), 6.82 (2H, s), 2.25 (3H, s), 2.19 (6H, s), 2.18 (2H, s), 1.39 (6H, s), 0.83 (9H, s); IR (KBr) cm^{-1}: 2955, 1775, 1706, 1678, 1612, 1584, 1480, 1366, 1317, 1212, 1125, 1092; HRMS(EI) Calcd for $C_{27}H_{33}NO_3S$ 451.2181, Found 451.2181.

1-Ethylsulfanyl-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl methyl carbonate (2h) : white amorphous compound; ^{1}H NMR ($CDCl_3$) δ: 6.86 (2H, s), 3.60 (3H, s), 2.89 (2H, q, *J*=7.3 Hz), 2.26 (3H, s), 2.14 (6H, s), 1.49 (6H, s), 1.28 (3H, t, *J*=7.3 Hz); IR (KBr) cm^{-1}: 2936, 1782, 1712, 1686, 1443, 1221, 1188, 1153, 1036; HRMS Calcd for $C_{19}H_{25}NO_4S$ 363.1504, Found 363.1505.

3-Mesityl-8-methoxy-1-methylsulfanyl-2-oxo-1-azaspiro[4.5]dec-3-en-4-yl pivalate (2i) : white amorphous compound; ^{1}H NMR ($CDCl_3$) δ: 6.82 (2H, s), 3.49, 3.40-3.26 (1H, br s, m), 3.39, 3.38 (3H, s, s), 2.45 (3H, s), 2.23 (3H, s), 2.14 (6H, s), 2.56-2.00, 1.95-1.50 (8H, m, m), 1.02, 0.99 (9H, s, s); IR (KBr) cm^{-1}: 2933, 1769, 1703, 1670, 1612, 1458, 1323, 1207, 1115, 1082; HRMS(EI) Calcd for $C_{25}H_{35}NO_4S$ 445.2287, Found 445.2287.

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3. *N*-Sulfenylphthalimides (**3a**-**h**) were prepared by the reaction of *N*-bromophthalimide with appropriate disulfides according to the following reported methods: G. A. Eberlelin and M. F. Powell, *J. Am. Chem. Soc*., 1984, **106**, 3309; W. K. Gordon, W. L. Alistair, and W. Sharon, *J. Chem. Soc. Perkin Trans.* 1, **1996**, 977.
4. Dihydropyrrole derivative (**4a-c**) were prepared according to the following reported procedures: B. Krauskopf, K. Luerssen, H.-J. Stantel, R. R. Schmidt, U. Wachendorff-Neumann, R. Fisher, and C. Erdelen, EP 456063, 1991 (*Chem. Abstr*., 1992, **116**, 106083h); R. Fischer, T. Bretschneider, B. W. Krueger, C. Erdelen, H. J. Santel, K. Luerssen, R. R. Schmidt, U. Wachendorff-Neumann, and W. Stendel, EP 596298, 1994 (*Chem. Abstr*., 1994, **121**, 280537x).
5. S.V. Lay and C. M. R. Low, 'Ultrasound in Synthesis,' Springer-Verlag, Berlin Heidelberg, 1989.
6. The ratio of diastereomers in the product (**2i**) was almost the same as that in the reactant (**4c**). Both of the diastereomer ratios were determined by ^{1}H NMR spectrometry.