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N-*p*-TOLUENESULFONYLPYRROLES FROM 1,3-DIENES

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This paper is dedicated to Professor E. C. Taylor on the occasion of his seventieth birthday.

Abstract: 1,3-Dienes can be converted to N-*p*-toluenesulfonylpyrroles in two steps: 1) [4+2]-cycloaddition with N-sulfinyl-*p*-toluenesulfonamide and 2) conversion of the 3,6-dihydro-1,2-thiazine oxide adduct to a pyrrole using triethylamine-trimethylphosphite.

In connection with our research into new methodologies for construction of the analgesics ketorolac (**1**) and tolmetin (**2**), we were interested in using the carbon framework of inexpensive sorbic acid (**3**) to supply all the carbons of a pyrrole-2-acetate.[1] Deconjugation of a sorbate ester[2] and a 1,3-diene to pyrrole transformation would accomplish this objective.

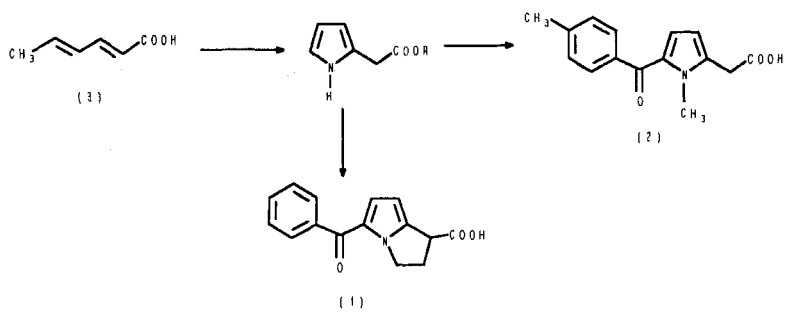

Figure 1. Pyrrole-2-acetate as a Ketorolac and Tolmetin Precursor

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The conversion of a 1,3-diene to a pyrrole is precedented. Cycloaddition [4+2] with nitrosoarenes affords 3,6-dihydro-1,2-oxazines. These cycloadducts are converted to N-arylated pyrroles by base treatment[3] or photolysis.[4] There is one report of cycloaddition with *p*-toluenesulfonylnitrite to produce 2-*p*-toluenesulfonyl-3,6-dihydro-1,2-oxazine. This cycloadduct was similarly converted to N-*p*-toluenesulfonylpyrrole.[3b] Cycloaddition [4+2] with N-sulfinylaniline affords a 3,6-dihydro-1,2-thiazine oxide. 2-Aryl-3,6-dihydro-1,2-thiazine oxides are efficiently converted to N-arylated pyrroles by reaction with sodium hydroxide in refluxing methanol.[5] Dienes can be converted to pyrroles and furans via 3,6-dihydro-1,2-dioxins.[6] Finally, palladium-promoted 1,4-cycloamination of dienes affords pyrroles.[7] Several of these methods presently suffer rather severe limitations. Two are generally applicable only to preparation of N-arylated pyrroles. While the conversion to an N-*p*-toluenesulfonylpyrrole would allow us to access N-unsubstituted and N-alkylated pyrroles, *p*-toluenesulfonylnitrite is both unstable and prepared using potent nitrosating agents such as dinitrogen tetraoxide.[8] We now report that adducts from the well-known [4+2]-cycloaddition of 1,3-dienes with commercially available N-sulfinyl-*p*-toluenesulfonamide[9] can be converted to N-*p*-toluenesulfonylpyrroles in reasonable yields.

Reaction of 2-*p*-toluenesulfonyl-3,6-dihydro-1,2-thiazine oxide with 0.5 equivalents of triethylamine in methanol at 25°C afforded N-tosylpyrrole in low (19%) yield. Neglecting the fate of the S-O bond, a simple mechanism based on the work described above[10] would involve: proton abstraction from the position adjacent to sulfur, cleavage of the S-N bond, formation of the N-C bond, and "HSOH" elimination. In considering the fate of the S-O bond, we evaluated the effect of reducing agents on the yield of N-tosylpyrrole. The yield quadrupled when an equivalent of trimethylphosphite was added.

Figure 2. Mechanism for N-Tosylpyrrole Formation

The availability of many functionalized dienes, the stability of N-tosylpyrroles, the opportunities for capitalizing on unique N-tosylpyrrole reactivity,[11] and the ease of detosylation all suggest that this new process can be an important new addition to pyrrole synthetic methodology. Examples of the N-tosylpyrrole preparation, including the preparation of an N-tosylpyrrole-2-acetate (entry 7), are presented in the **Table.**

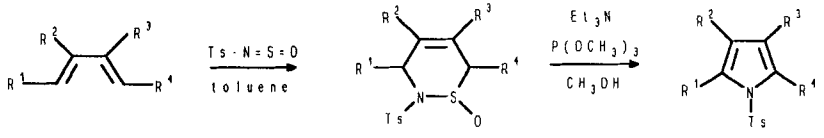

Figure 3. Two-Step Preparation of N-Tosylpyrroles from 1,3-Dienes

Table. Preparation of N-Tosylpyrroles

	R^1	R^2	R^3	R^4	[4+2] YIELD (%)	PYRROLE YIELD (%)
1	H	H	H	H	78	80
2	H	H	CH_3	H	86	64
3	H	H	Cl	H	94	67
4	H	H	Ph	H	90	64
5	CH_3	H	H	H	86	74
6	Ph	H	H	H	83	73
7	CH_2COOCH_3	H	H	H	87	76
8	CH_3	H	CH_3	H	83	72
9	H	CH_3	CH_3	H	85	15

The curent method is effective for preparation of 2-substituted (entries 2-4) or 3-substituted pyrroles (entries 5-7). The [4+2]-cycloaddition is similarly efficient with many disubstituted butadienes. However, we have been unable to convert the dihydrothiazine oxides from 3-methyl-1,3-pentadiene, *trans,trans*-2,4-hexadiene or *cis,trans*-2,4-hexadiene to the 2,3- or 2,5-disubstituted pyrroles at ambient temperature. The yield of 2,4-disubstituted pyrrole was good (entry 8); the yield of 3,4-disubstituted pyrrole was low (entry 9).

Many of the dihydrothiazine oxides were prepared by literature methods.[12-14] While most previous synthetic applications of dihydrothiazine oxides have capitalized on the regio- and stereoselectivity in the cycloaddition, mixtures of isomeric cycloadducts can be used in the the current application.

EXPERIMENTAL:

New dihydrothiazine oxides were prepared as follows: the diene (1.2 equivalents) was added via syringe to a 25°C solution of 5.00 g (23.0 mmol) N-sulfinyl-*p*-toluenesulfonamide in 20 mL dry toluene (dry N_2). The solution was then stirred at 25°C overnight. The resulting mixture was concentrated *in vacuo*. The residue was triturated with ethyl acetate-hexanes and the precipitate filtered and washed with hexanes. The dihydrothiazine oxides were recrystallized from ethyl acetate or ethyl acetate-hexanes.

Methyl 2-*p*-toluenesulfonyl-3,6-dihydrothiazine-1-oxide-3-acetate. 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.82 (dd, J=4, 16 Hz, 1H), 2.98 (dd, J=10.5, 16 Hz, 1H), 3.31 (ddd, J=3, 6, 16 Hz, 1H), 3.38-3.46 (m, J=6, 16 Hz, 1H), 3.67 (s, 3H), 4.86-4.92 (m, 1H), 5.69-5.76 (m, 1H), 6.12-6.18 (m, 1H), 7.35 (d, J=8 Hz, 2H), 7.77 (d, J=8 Hz, 2H); IR (KBr) 1739, 1356, 1349, 1193, 1165, 1104, 1090 cm^{-1}; m.p. 122-123°C. Elemental Analysis (Expected, Observed)[15]: C (48.96, 49.03); H (4.99, 5.03); N (4.08, 4.11).

3,5-Dimethyl-2-*p*-toluenesulfonyl-3,6-dihydro-1,2-thiazine-1-oxide. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J=8 Hz, 3H), 1.84 (s, 3H), 2.43 (s, 3H), 3.23-3.36 (m, 2H), 4.53-4.60 (m, 1H), 5.67-5.68 (m, 1H), 7.34 (d, J=8 Hz, 2H), 7.80(d, J=8 Hz, 2H); IR (KBr) 1595, 1348, 1185, 1165, 1097 cm^{-1}; m.p. 88-92°C. Elemental Analysis (Expected, Observed): C (52.15, 52.20); H (5.72, 5.80); N (4.68, 4.76).

The general procedure for N-tosylpyrrole formation is as follows: the dihydrothiazine oxide (3.0 mmol) was added to a rapidly stirring solution of 0.21 mL (0.15 g, 1.5 mmol) triethylamine, 0.44 mL (0.46 g, 3.75 mmol)

trimethylphosphite, and 20 mL methanol. The mixture was stirred at 25°C overnight. The volatiles were removed *in vacuo*. The residue was separated between 25 mL 1 N HCl and 50 mL ethyl ether. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The N-tosylpyrrole was isolated from the residue by radial chromatography on silica gel using 10-20% v/v ethyl acetate in hexanes as eluent. The N-tosylpyrroles were recrystallized from hexanes or ethyl acetate-hexanes.

3-Methyl-1-(*p*-toluenesulfonyl)pyrrole. 300 MHz ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.38 (s, 3H), 6.10-6.11 (m, 1H), 6.87 (m, 1H), 7.05 (dd, J=2.7 Hz, 1H), 7.26 (d, J=8 Hz, 2H), 7.72 (d, J=8 Hz); IR (KBr) 1596, 1472, 1363, 1172, 1105, 1066 cm^{-1}; m.p. 59.5-60°C. Elemental Analysis (Expected, Observed): C (61.25, 61.20); H (5.57, 5.64); N (5.95, 5.98).

3-Chloro-1-(*p*-toluenesulfonyl)pyrrole. 300 MHz ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 6.20-6.22 (m, 1H), 7.07-7.10 (m, 2H), 7.30 (d, J=8 Hz, 2H), 7.74 (d, J=8 Hz, 2H); IR (KBr) 3142, 1596, 1536, 1368, 1207, 1172, 1062 cm^{-1}; m.p. 59-59.5°C. Elemental Analysis (Expected, Observed): C (51.66, 51.62); H (3.94, 3.97); N (5.48, 5.55).

3-Phenyl-1-(*p*-toluenesulfonyl)pyrrole. 300 MHz ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 6.58-6.60 (m, 1H), 7.18-7.47 (m, 9H), 7.77 (d, J=8 Hz, 2H); IR (KBr) 1595, 1369, 1173, 1136, 1063 cm^{-1}; m.p. 128-129.5°C. Elemental Analysis (Expected, Observed): C (68.66, 68.66); H (5.08, 5.15); N (4.71, 4.75).

2-Phenyl-1-(*p*-toluenesulfonyl)pyrrole. 300 MHz ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.13-6.15 (m, 1H), 6.29 (t, J=3.3 Hz, 1H), 7.08 (d, J=8 Hz, 2H), 7.2-7.37 (m, 7H), 7.42-7.44 (m, 1H); IR (KBr) 1596, 1366, 1190, 1176, 1129, 1057 cm^{-1}; m.p. 124-124.5°C. Elemental Analysis (Expected, Observed): C (68.66, 68.98); H (5.08, 5.12); N (4.71, 4.77).

Methyl 1-(*p*-Toluenesulfonyl)pyrrole-2-acetate. 300 MHz ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.63 (s, 3H), 3.79 (s, 2H), 6.16-6.18 (m, 1H), 6.23 (t, J=3.3 Hz, 1H), 7.26-7.30 (m, 3H), 7.67 (d, J=8 Hz, 2H); IR (KBr) 1748, 1734, 1597, 1362, 1175, 1151 cm^{-1}; m.p. 80-80.5°C. Elemenal Analysis (Expected, Observed): C (57.32, 57.52); H (5.15, 5.23); N (4.78, 4.84).

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