A Study of the Friedel-Crafts Acylation of 1-Benzenesulfonyl-1*H*-pyr-
role in the Preparation of 3-Aroylpyrroles

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In this work, we studied the aluminum chloride catalyzed reaction of 1-benzenesulfonyl-1*H*-pyrrole with a series of eleven aroyl chlorides. The products formed were not isolated, but hydrolyzed to the target 3-aroylpyrroles in overall yields, usually, higher than 50%. However, in the cases with the π electron rich 1-phenyl-1*H*-pyrrole-3-carbonyl chloride and 1-methyl-1*H*-indole-3-carbonyl chloride significant C-2 substitution occured, resulting in the isolation of the corresponding 1-benzenesulfonyl-2-aroylpyrroles as the predominant or the sole products. The desired C-3 isomers were synthesized starting with 1-triisopropyl-silanyl-1*H*-pyrrole.
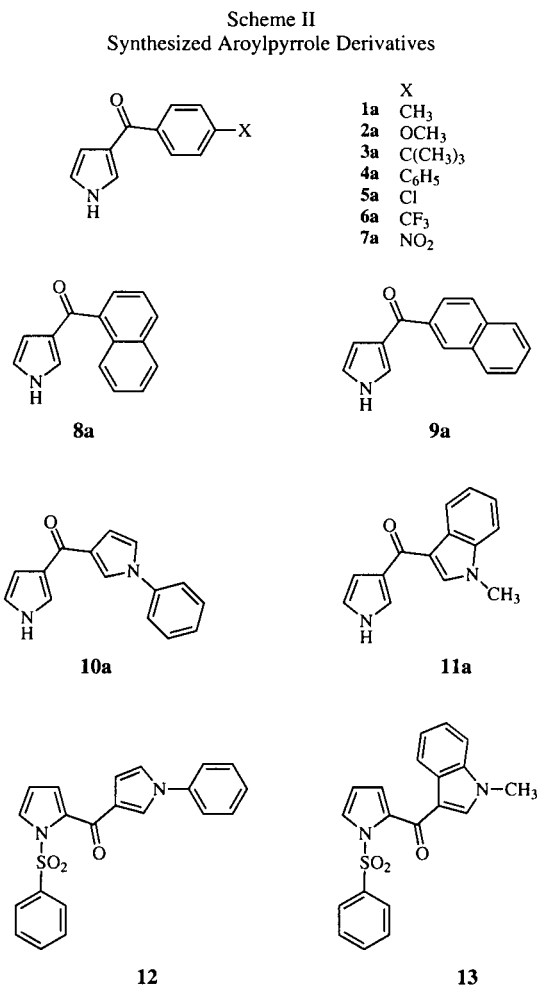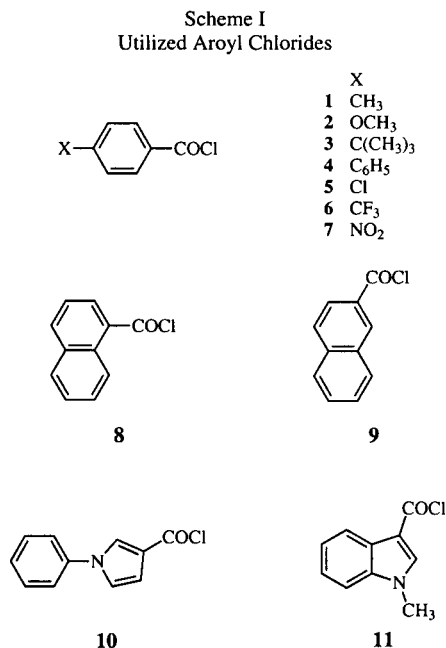
Introduction.

As a part of our ongoing effort to develop potent aldose reductase inhibitors [1,2], we needed a number of 3-aroylpyrroles as starting materials. The main methodology to prepare these compounds involves Friedel-Crafts acylation of 1-benzenesulfonyl-1*H*-pyrrole, followed by a base catalyzed hydrolysis of the *N*-sulfonyl substituent [3-5]. However, it has been reported that with certain aroyl halides (*e.g.* 3,5-dichloro-2-methoxy-benzoyl chloride [6]) the main product is the corresponding C-2 isomer. Furthermore, the reaction solvent could influence the position of the electrophilic attack. For example, it has been reported [7] that the reaction of 1-naphtoyl chloride in dichloromethane results in the formation of an equimolar mixture of the C-2 and C-3

isomers, while with nitromethane as a cosolvent only the C-3 isomer is formed.

An alternative methodology for the formation of the target 3-aroylpyrroles could involve Friedel-Crafts acylation of the sterically hindered 1-triisopropylsilanyl- [8] or

Scheme II
Synthesized Aroylpyrrole Derivatives

	X
1a	CH₃
2a	OCH₃
3a	C(CH₃)₃
4a	C₆H₅
5a	Cl
6a	CF₃
7a	NO₂

8a

9a

10a

11a

12

13

Scheme I
Utilized Aroyl Chlorides

	X
1	CH₃
2	OCH₃
3	C(CH₃)₃
4	C₆H₅
5	Cl
6	CF₃
7	NO₂

8

9

10

11

1-(*tert*-butyldimethylsilanyl)-1*H*-pyrrole [9] followed by fluoride anion catalyzed desilanylation. This sequence of reactions has been reported with benzoyl chloride and gives moderate overall yields.

Results and Discussion.

In the present work, we studied the aluminum chloride catalyzed reaction of 1-benzenesulfonyl-1*H*-pyrrole with the aroyl chlorides **1-11** (Scheme I). The reactions were performed in 1,2-dichloroethane and, if the yield was low, also in dichloromethane with nitromethane as a cosolvent. The products formed were not isolated, but subjected to hydrolytic conditions with sodium hydroxide in a mixture of water/1,4-dioxane. We chose this method of hydrolysis because the alternative with methanolic potassium hydroxide has been shown to result in the formation of 1-methylpyrrole derivatives as side products [5]. The final 3-aroylpyrroles (Scheme II) were usually isolated by a simple recrystallization from toluene/petroleum ether with overall yields generally higher than 50% (Table). In the

group was not removed under the employed mild hydrolytic conditions. The importance of the π electron availability in the acylating halide as to determine the position of substitution is further demonstrated with 1-methyl-1*H*-indole-3-carbonyl chloride (**11**). In this case, the sole or the predominant product was the C-2 substituted isomer which was similarly isolated as its 1-benzenesulfonyl derivative **13**. The desired C-3 isomer **11a** was synthesized from 1-triisopropylsilanyl-1*H*-pyrrole; in this reaction no C-2 isomer was formed. The use of 1-triisopropylsilanyl-1*H*-pyrrole was also investigated for the preparation of **6a** and **10a**. Again, only the corresponding C-3 isomers were isolated, but in moderate yields.

In conclusion, our study shows that the electronic nature of the aromatic ring in the acylating aroyl halide influences the position of substitution of 1-benzenesulfonyl-1*H*-pyrrole but not of 1-triisopropylsilanyl-1*H*-pyrrole, where steric hindrance is the predominant factor.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. Infrared spectra were recorded with a Perkin-Elmer 597 spectrophotometer, nuclear magnetic resonance spectra with a Bruker AW-80 spectrometer with internal tetramethylsilane reference. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Flash chromatography was carried out using Merck 9385 silica gel. Petroleum ether refers to the fraction of bp 40-60°. The aroyl chlorides **10** and **11** were synthesized, respectively, from 1-phenyl-1*H*-pyrrole-3-carboxylic acid [10] and 1-methyl-1*H*-indole-3-carboxylic acid [11] by the action of oxalyl chloride and a catalytic amount of dimethylformamide in tetrahydrofuran. The method of preparation, the yields and the melting points of the synthesized aroylpyrroles are compiled in the Table.

Aroylation of 1-Benzenesulfonyl-1*H*-pyrrole.

Method A.

To a suspension of aluminum chloride (30 mmoles) in 1,2-dichloroethane (50 ml) the appropriate aroyl chloride (28 mmoles) was added slowly and the resulting mixture was stirred for 10 minutes at room temperature. Then, a solution of 1-benzenesulfonyl-1*H*-pyrrole (25 mmoles) in 1,2-dichloromethane was added slowly and the mixture was stirred at room temperature for 90 minutes. The reaction was quenched with ice and water and the product was extracted to chloroform. The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (100 ml) and to this a 5*N* solution of sodium hydroxide was added. The reaction mixture was vigouriously stirred at room temperature for 17-48 hours. The organic layer was collected and the aqueous was thoroughly extracted with ethyl acetate. The combined organic layer and extracts were washed with saturated sodium chloride solution, dried over anhydrous

Table
Method of Preparation, Yields and Melting Points of the Synthesized Aroylpyrroles

Acylating Aroyl Chloride	Method [a]	Product	Yield %	Mp° (lit [3] mp)
1	A	1a	59	130 (128-129.2)
2	A	2a	65	105-106 (105-106.5)
3	A	3a	49	141-142
4	A	4a	61	183-184
5	A	5a	75	121-122 (119-120)
6	A	6a	17	121-122
	B		29	
	C		35	
7	A	7a	68	166
8	A	8a	56	102-103 [b]
9	A	9a	75	72-74
10	A	10a	35	149-150
		12	41	109-111
	B	10a	21	
		12	7	
	C	10a	31	
11	A	13	46	176-177
	B	13	43	
		11a	6	158
	C	11a	32	

[a] See Experimental; [b] A preparation for this compound has been reported in reference [7] but not the corresponding physicochemical properties.

reaction with 4-trifluoromethylbenzoyl chloride the yield of the final product **6a** was low and was not substantially improved by the use of nitromethane as a cosolvent. It was noted that, in the case of the Friedel-Crafts acylation with the π electron rich 1-phenyl-1*H*-pyrrole-3-carbonyl chloride (**10**), significant C-2 substitution occured resulting in the isolation of **12**, in which the 1-benzenesulfonyl

sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from toluene/petroleum ether.

Method B.

Aluminum chloride (30 mmoles) was dissolved in the minimum amount of nitromethane and 1-phenylsulfonyl-1*H*-pyrrole (28 mmoles) dissolved in dichloromethane (140 ml) was added to the stirred mixture. Then, the appropriate aroyl chloride (30 mmoles) was added and the mixture was stirred at room temperature for 1 hour. The workup and hydrolysis procedure is similar to that of Method A. The crude product was first flash chromatographed on silica gel with ethyl acetate/petroleum ether as the eluent and further recrystallized from toluene/petroleum ether.

Aroylation of 1-Triisopropylsilanyl-1*H*-pyrrole.

Method C.

The appropriate aroyl chloride (6 mmoles) was added slowly to a stirred slurry of aluminum chloride (6.6 mmoles) in dichloromethane (15 ml) at 0° under a nitrogen atmosphere. After 0.25 hour, a solution of 1-triisopropylsilanyl-1*H*-pyrrole (6 mmoles) in dichloromethane (3 ml) was added. The mixture was stirred for 0.5 hour at 0° and 0.5 hour at room temperature and then poured into an ice-water mixture. The organic phase was separated and combined with a dichloromethane extract of the aqueous phase. The organic phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran and to this tetra-*n*-butylammonium fluoride (6 mmoles) was added. The reaction was stirred at room temperature for 15 minutes. The solution was diluted with ethyl acetate and the organic phase was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was flash chromatographed on silica gel with ethyl acetate/petroleum ether as the eluent and further recrystallized from toluene/petroleum ether.

(4-*tert*-Butylphenyl)(1*H*-pyrrol-3-yl)methanone (**3a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 9.30 (br s, 1H, NH), 7.75 (d, 2H, phenyl-H), 7.50 (d, 2H, phenyl-H), 7.15-7.30 (m, 1H, pyrrole C-2-H), 6.65-6.85 (m, 2H, pyrrole C-4-H and C-5-H), 1.35 (s, 9H, CH$_3$).
Anal. Calcd. for C$_{15}$H$_{17}$NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.02; H, 7.61; N, 5.99.

Biphenyl-4-yl(1*H*-pyrrol-3-yl)methanone (**4a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 11.00 (br s, 1H, NH), 7.40-8.05 (m, 9H, biphenyl-H), 7.20-7.30 (m, 1H, pyrrole C-2-H), 6.60-6.85 (m, 2H, pyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{17}$H$_{13}$NO: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.22; H, 5.17; N, 5.45.

(1*H*-Pyrrol-3-yl)(4-trifluoromethylphenyl)methanone (**6a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 9.20 (br s, 1H, NH), 7.85-8.00 (m, 4H, phenyl-H), 7.25-7.45 (m, 1H, pyrrole C-2-H), 6.65-6.90 (m, 2H, pyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{12}$H$_8$NOF$_3$: C, 60.26; H, 3.37; N, 5.86. Found: 60.15; H, 3.21; N, 5.77.

(4-Nitrophenyl)(1*H*-pyrrol-3-yl)methanone (**7a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 11.15 (br s, 1H, NH), 8.30 (d, 2H, phenyl-H), 7.95 (d, 2H, phenyl-H),

7.20-7.40 (m, 1H, pyrrole C-2-H), 6.60-6.85 (m, 2H, pyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{11}$H$_8$N$_2$O$_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.77; H, 3.74; N, 12.57.

Naphthalen-1-yl(1*H*-pyrrol-3-yl)methanone (**8a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 9.30 (br s, 1H, NH), 7.25-8.30 (m, 7H, napthyl-H), 6.90-7.10 (m, 1H, pyrrole C-2-H), 6.60-6.80 (m, 2H, pyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{15}$H$_{11}$NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.11; H, 4.90; N, 6.24.

Naphthalen-2-yl(1*H*-pyrrol-3-yl)methanone (**9a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 9.60 (br s, 1H, NH), 7.30-8.40 (m, 7H, napthyl-H), 7.20-7.30 (m, 1H, pyrrole C-2-H), 6.75-6.85 (m, 2H, pyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{15}$H$_{11}$NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.13; H, 4.95; N, 6.17.

(1-Phenyl-1*H*-pyrrol-3-yl)(1*H*-pyrrol-3-yl)methanone (**10a**).

This compound had ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d$_6$): 11.30 (br s, 1H, NH), 7.80-7.88 (m, 1H, phenylpyrrole C-2-H), 7.35-7.63 (m, 6H, phenyl-H and pyrrole C-2-H), 6.63-6.93 (m, 4H, pyrrole C-4-H and C-5-H and phenylpyrrole C-4-H and C-5-H).
Anal. Calcd. for C$_{15}$H$_{12}$N$_2$O: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.18; H, 5.19; N, 11.51.

(1-Methyl-1*H*-indol-3-yl)(1*H*-pyrrol-3-yl)methanone (**11a**).

This compound had ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d$_6$): δ 10.50 (br s, 1H, NH), 8.55-8.30 (m, 1H, indole C-4-H), 7.70 (s, 1H, indole C-2-H), 7.20-7.50 (m, 4H, pyrrole C-2-H, indole C-5-H, C-6-H and C-7-H), 6.60-6.90 (m, 2H, pyrrole C-4-H and C-5-H), 3.80 (s, 3H, CH$_3$).
Anal. Calcd. for C$_{14}$H$_{12}$N$_2$O: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.93; H, 5.46; N, 12.13.

(1-Benzenesulfonyl-1*H*-pyrrol-2-yl)(1-phenyl-1*H*-pyrrol-3-yl)methanone (**12**).

This compound had ^{1}H nmr (deuteriochloroform): δ 8.03-8.21 (m, 2H, HArSO$_2$), 7.33-7.70 (m, 9H, phenyl-H, HArSO$_2$ and pyrrole C-5-H), 6.95-7.08 (m, 1H, phenylpyrrole C-2-H), 6.73-6.94 (m, 2H, pyrrole C-3-H and phenylpyrrole C-4-H), 6.25-6.40 (m, 1H, pyrrole C-4-H).
Anal. Calcd. for C$_{21}$H$_{16}$N$_2$O$_3$S: C, 67.01; H, 4.28; N, 7.44. Found: C, 66.80; H, 4.18; N, 7.22.

(1-Benzenesulfonyl-1*H*-pyrrol-2-yl)(1-methyl-1*H*-indol-3-yl)methanone (**13**).

This comound had ^{1}H nmr (deuteriochloroform): δ 8.05-8.35 (m, 3H, HArSO$_2$ and indole C-5-H), 7.20-7.70 (m, 8H, indole C-2-H, C-6-H, C-7-H and C-8-H, HArSO$_2$ and pyrrole C-5-H), 6.60-6.75 (m, 1H, pyrrole C-3-H), 6.25-6.40 (m, 1H, pyrrole C-4-H), 3.76 (s, 3H, CH$_3$).
Anal. Calcd. for C$_{20}$H$_{16}$N$_2$O$_3$S: C, 65.92; H, 4.43; N, 7.69. Found: C, 66.31; H, 4.52; N, 7.26.

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