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Acylation of *N*-*p*-toluenesulfonylpyrrole under Friedel–Crafts conditions: evidence for organoaluminum intermediates

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Abstract

The Friedel–Crafts acylation of *N*-*p*-toluenesulfonylpyrrole under Friedel–Crafts conditions has been reinvestigated. Evidence is presented in support of the hypothesis that when $AlCl_3$ is used as the Lewis acid, acylation proceeds via reaction of an organoaluminum intermediate with the acyl halide. This leads to the production of the 3-acyl derivative as the major product. With weaker Lewis acids ($EtAlCl_2$, Et_2AlCl) or less than 1 equiv of $AlCl_3$ the relative amount of 2-acyl product is increased. A mechanistic rationalization is presented to explain these data.

Keywords: Acylpyrrole; Organoaluminum intermediates; Friedel–Crafts reaction; Reaction mechanism

1. Introduction

It has been known for many years that electrophilic substitution reactions of pyrrole and many substituted pyrroles occur predominantly at the 2-position.[1] Historically, in order to prepare 3-substituted pyrrole derivatives, a variety of multi-step indirect syntheses were employed. However, in work carried out in 1980s, it was found that an easily removable bulky nitrogen substituent, triisopropylsilyl[1,2] or, alternatively, an *N*-benzenesulfonyl group[1,3,4] provided acylation primarily at the 3-position of the *N*-substituted pyrrole under Friedel–Crafts conditions.

The regioselectivity observed in the case of *N*-triisopropylsilylpyrrole was attributed to steric hindrance at the pyrrole 2-position,[2b] however, the reactions of *N*-benzenesulfonylpyrrole are less straightforward than those of *N*-triisopropylsilylpyrrole.[1,3,4] In particular, while acylation under Friedel–Crafts conditions using relatively simple acyl halides with $AlCl_3$ produces the 3-acyl compound with good regioselectivity,[3,4] the use of weaker Lewis acids, such as $SnCl_4$ or boron trifluoride etherate produces the 2-isomer as the major product.[4b] Also, Friedel–Crafts alkylation of *N*-benzenesulfonylpyrrole using *tert*-butyl chloride gave an excellent yield of the 3-isomer, while isopropyl chloride under the same conditions gave a mixture of 2- and 3-isomer.[3b] Kakushima et al. considered several possible explanations for the regiochemistry observed in the acylation of *N*-benzenesulfonylpyrrole including initial acylation at C-2 followed by rearrangement to the 3-isomer and steric or electronic effects.[4b] Evidence was presented that the observed regiochemistry could be explained neither by rearrangement of a 2-substitued compound nor by steric effects. It was suggested that with $AlCl_3$ charge control prevailed to give 3-acylation via a highly polarized species formed by interaction of the Lewis acid with acyl chloride. With weaker Lewis acids, a less polarized species reacts by orbital control to provide the 2-acyl compound as the major product. Although the authors favored this hypothesis over the others they stated that none of these explanations is completely consistent with their experimental results.

Several years ago, we reported the synthesis and pharmacology of a series of cannabimimetic 1-alkyl-3-(1-naphthoyl)-pyrroles (**1**, R=*n*-C_3H_7 to *n*-C_7H_{15}).[5] Based upon the assumption that cannabimimetic pyrroles interact with the CB_1 receptor by aromatic stacking in a manner similar to

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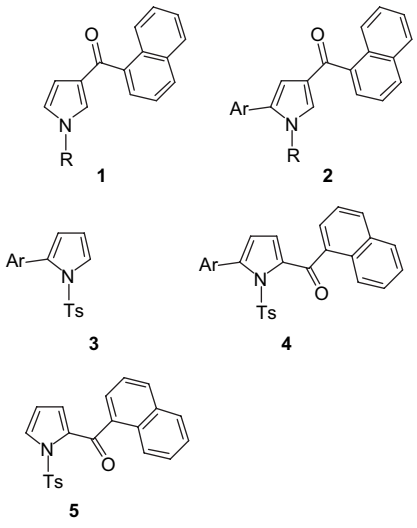
indoles and indenes,[6] it was concluded that the addition of another aromatic substituent to naphthoylpyrroles **1** could lead to compounds with increased receptor affinity. Accordingly, the synthesis of a series of 1-alkyl-2-aryl-4-(1-naphthoyl)-pyrroles (**2**, Ar=phenyl and substituted aryl, R=*n*-alkyl) was carried out.[7] The initial synthetic approach to these compounds included as a key step the Friedel–Crafts acylation of an *N*-*p*-toluenesulfonyl-2-arylpyrrole, which was successfully applied to the synthesis of *N*-*p*-toluenesulfonyl-2-phenyl-4-(1-naphthoyl)pyrrole (**2**, Ar=C_6H_5, R=Ts) by the $AlCl_3$ catalyzed reaction of 1-naphthoyl chloride with *N*-*p*-toluenesulfonyl-2-phenylpyrrole (**3**, Ar=C_6H_5) under standard Friedel–Crafts conditions in which the substrate is added to a mixture of $AlCl_3$ and the acyl halide. These conditions are similar to those of reaction conditions A (see Section 5) in which the acyl chloride is stirred with the catalyst and the substrate is then added.



When this approach was extended to the $AlCl_3$ catalyzed reaction of 1-naphthoyl chloride with *N*-*p*-toluenesulfonyl-2-(4-methoxyphenyl)pyrrole (**3**, Ar=$C_6H_4OCH_3$) a complex mixture of products was obtained. We have successfully employed a modified Friedel–Crafts acylation procedure developed by Okauchi et al. and Ottoni et al. in the synthesis of a number of 3-acylindoles.[8–10] In this method the substrate is stirred with the catalyst for approximately 30 min and the acyl halide is added subsequently. These are experimental conditions B (see Section 5). Reaction of pyrrole **3** (Ar=$C_6H_4OCH_3$) with Et_2AlCl followed by the addition of 1-naphthoyl chloride gave a single product in 47% unoptimized yield. This compound was identified as *N*-*p*-toluenesulfonyl-2-(4-methoxyphenyl)-5-(1-naphthoyl)pyrrole (**4**, Ar=$C_6H_4OCH_3$) on the basis of its ^1H NMR spectrum, which showed the pyrrole protons as doublets (J=3.4 Hz) at δ 6.12 and δ 6.68. These chemical shifts and coupling constants are consistent with those of a 2,5-disubstituted pyrrole.[11]

Repetition of the reaction of *N*-*p*-toluenesulfonyl-2-phenylpyrrole (**3**, Ar=C_6H_5) with 1-naphthoyl chloride under conditions A with $AlCl_3$ catalysis gave a product mixture containing approximately equal amounts of *N*-*p*-toluenesulfonyl-2-phenyl-4-(1-naphthoyl)pyrrole (**2**, Ar=C_6H_5, R=Ts) and *N*-*p*-toluenesulfonyl-2-phenyl-5-(1-naphthoyl)pyrrole (**4**, Ar=C_6H_5). Under conditions B with $AlCl_3$ catalysis, reaction of pyrrole **3** (Ar=C_6H_5) with 1-naphthoyl chloride gave a 9:1 mixture of the 2,4-isomer (**2**, Ar=C_6H_5, R=Ts) and the 2,5-isomer (**4**, Ar=C_6H_5). The ^1H NMR spectrum of pyrrole **2** (Ar=C_6H_5, R=Ts) shows one of the pyrrole protons as a doublet (J=1.8 Hz) at δ 6.72. The other pyrrole proton is obscured by the peaks due to the naphthoyl and toluenesulfonyl protons. The structures of pyrroles **2** (Ar=C_6H_5, R=Ts) and **4** (Ar=$C_6H_4OCH_3$) were confirmed by X-ray crystallography.[12]

In our synthesis of *N*-alkylpyrroles **1**, it was found that the $AlCl_3$ catalyzed Friedel–Crafts reaction of *N*-*p*-toluenesulfonylpyrrole with 1-naphthoyl chloride in dichloromethane gave mixtures of *N*-*p*-toluenesulfonyl-3-(1-naphthoyl)pyrrole (**1**, R=Ts) and *N*-*p*-toluenesulfonyl-2-(1-naphthoyl)pyrrole (**5**) with ratios of 3-acylpyrrole to the 2-isomer ranging from 2:1 to 4:3.[5,13] These acylations were carried out under conditions essentially identical to procedure A using 1.2 equiv of $AlCl_3$ and 1.2 equiv of 1-naphthoyl chloride, however, the reactions were carried out at ambient temperature rather than 0 °C. Acylation with 1-naphthoyl chloride in 1,2-dichloroethane again provided a mixture of the 2- and 3-isomer. These results contrast with those of other workers described above and those of Sattambolo et al.[3,4,14] We were unable to explain neither these variable results nor the acylation experiments using *N*-*p*-toluenesulfonylpyrroles **3** (Ar=C_6H_5 and $C_6H_4OCH_3$) and a systematic reinvestigation of the acylation reactions of *N*-*p*-toluenesulfonylpyrrole was undertaken.

2. Results

Initially, the effects of solvent and concentration upon the course of the $AlCl_3$ catalyzed acylation of *N*-*p*-toluenesulfonylpyrrole with 1-naphthoyl chloride under standard Friedel–Crafts conditions (method A) were investigated. The results of these experiments are summarized in Table 1 and show that in both dichloromethane and 1,2-dichloroethane, *N*-(*p*-toluenesulfonyl)-3-(1-naphthoyl)pyrrole (**1**, R=Ts) comprised at least 98% of the product mixture. The use of chloroform as the reaction solvent increased the amount of the 2-(1-naphthoyl)

Table 1
Effect of solvent on acylation (method A) of *N*-*p*-toluenesulfonylpyrrole using excess 1-naphthoyl chloride and $AlCl_3$[a]

Solvent	Concn[b] (M)	**1** R=Ts	**5**	*N*-Ts–pyrrole
$ClCH_2CH_2Cl$	0.159	>98	<2	0
$ClCH_2CH_2Cl$	0.422	>99	<1	0
$CHCl_3$	0.411	83	17	0
CH_2Cl_2	0.514	>98	<1	<1
CH_2Cl_2	0.799	>99	<1	0
CH_2Cl_2	0.211	98	1	1
CH_2Cl_2	0.422	98	2	0

[a] Acylation performed in designated solvent system with 2 equiv of $AlCl_3$ and 1.18 equiv of 1-naphthoyl chloride for 2 h. Product ratios determined by ^1H NMR.
[b] Concentration relative to *N*-*p*-toluenesulfonylpyrrole.

isomer (**5**) to 17% of the product mixture. This increase in the relative amount of **5** may be due to the difference in polarity between chloroform and either dichloromethane or 1,2-dichloroethane.

The effect of the relative amount of $AlCl_3$ under reaction conditions A was explored and the results are summarized in Table 2. Decreasing the relative amount of $AlCl_3$ from 2 to 1 equiv increased the relative amount of the 2-(1-naphthoyl) isomer to 15% of the product mixture. Reducing the amount of $AlCl_3$ to 0.9 equiv increased the amount of the 2-isomer to 25%. A further decrease in the amount of catalyst to 0.1 equiv resulted in 95% recovery of the starting material and the formation of an approximately equimolar mixture of the 2- and 3-isomer. When the reaction was carried out at room temperature under conditions duplicating as nearly as possible to those of Lainton et al.,[5,13] the product mixture contained 90% of the 3-isomer (**1**, R=Ts) and 10% of the 2-isomer (**5**). At room temperature with 0.9 equiv of $AlCl_3$ the relative amount of the 2-isomer was increased to 32%. Changing the catalyst to 2 equiv of $AlBr_3$ gave results indistinguishable from those with $AlCl_3$. When a milder Lewis acid, $SnCl_2$, was employed as catalyst the major product (72% of the product mixture) was the 2-(1-naphthoyl) isomer (**5**). The product mixture from this reaction also contained 6% of the 3-(1-naphthoyl) isomer (**1**, R=Ts) and 22% recovered starting material. These results are in accord with those of Kakushima et al. who reported that acylation of *N*-benzenesulfonylpyrrole using mild Lewis acids, such as $SnCl_4$, $ZnCl_2$ or $BF_3{\cdot}OEt_2$, led to predominant formation of the 2-acyl product.[4b]

The results presented in Table 1 in which acylation of *N*-*p*-toluenesulfonylpyrrole was carried out with 2 equiv of $AlCl_3$ were generally reproducible and it was found that the amount of $AlCl_3$ could be reduced to 1.2 equiv without loss of regioselectivity. However, in some experiments this procedure afforded up to 20% of the 2-naphthoyl isomer (**5**). In an effort to explain this decline in regioselectivity the effect of the purity of the $AlCl_3$ was explored. A series of reactions were performed at a pyrrole concentration of 0.422 M in dry dichloromethane using 2.0 equiv of $AlCl_3$ and 1.17 equiv of 1-naphthoyl chloride for 2 h. Samples of $AlCl_3$ from different suppliers of different labeled purities and of different ages were investigated. Aliquots were taken at 5, 30, 60, 90, and 120 min to examine changes in relative amounts of reaction products with respect to time. The reaction was monitored by ^1H NMR and GC/MS. The data show that the relative amount of the 2-naphthoyl isomer remains constant at 1–10% throughout the reaction and as would be expected the amount of starting material decreases as the reaction proceeds. All samples of $AlCl_3$ tested provided at least 90% of 3-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole (**1**, R=Ts). There was no significant difference between very high purity (99.9% under argon) $AlCl_3$ and material of 98% purity, or between materials from different suppliers. It was observed that older samples of $AlCl_3$ gave proportionately larger amounts of the 2-isomer (**5**) and that the reaction was somewhat slower than when fresh $AlCl_3$ was used. This is consistent with the observation that fewer equivalents of $AlCl_3$ enhance the formation of the 2-isomer (**5**). Regioselective formation of the 3-isomer (**1**, R=Ts) was achieved with the older samples of $AlCl_3$ when an excess (at least 2 equiv) was used.

Under reaction conditions A, using $AlCl_3$ as catalyst, the only variable that appreciably affected the relative amounts of 2- and 3-acylation product was the number of equivalents of $AlCl_3$ that were used. It appears probable that the product distribution that we reported earlier was caused by the use of impure or aged $AlCl_3$, with perhaps a small increase in the amount of the 2-isomer (**5**) caused by carrying out the reaction at room temperature, rather than 0 °C.[5,13]

The results of the acylation of *N*-*p*-toluenesulfonylpyrrole with 1-naphthoyl chloride under conditions B using $AlCl_3$, $EtAlCl_2$ or Et_2AlCl in 1,2-dichloroethane are summarized in Table 3. With an initial *N*-*p*-toluenesulfonylpyrrole concentration of 0.075 M, $AlCl_3$ gave a product mixture containing greater than 98% of the 3-(1-naphthoyl) isomer (**1**, R=Ts). $EtAlCl_2$ provided a 2.5 to 1 ratio of the 2-(1-naphthoyl) isomer (**5**) to the 3-isomer (**1**, R=Ts). With Et_2AlCl these ratios increased to greater than 16 to 1. With both $EtAlCl_2$ and Et_2AlCl from 6% to 14% of starting material was recovered. At a concentration of *N*-*p*-toluenesulfonylpyrrole of 0.221 M the reactions using $EtAlCl_2$ and Et_2AlCl are considerably more regioselective than those carried out at the lower concentration of starting material. With $EtAlCl_2$ the ratio of 2-naphthoyl isomer **5** to the 3-naphthoyl isomer (**1**, R=Ts) was greater than 15 to 1 and with Et_2AlCl greater than 95% of **5** was

Table 2
Acylation of *N*-*p*-toluenesulfonylpyrrole with 1.18 equiv of 1-naphthoyl chloride using varying amounts of $AlCl_3$ (method A)

Lewis acid (equiv)	Solvent	**1** R=Ts[a]	**5**[a]	*N*-Ts–pyrrole[a]
$AlCl_3$ (2.0)	$ClCH_2CH_2Cl$	98	2	0
$AlCl_3$ (1.2)[b]	CH_2Cl_2	90	10	0
$AlCl_3$ (1.2)[c]	CH_2Cl_2	90	10	0
$AlCl_3$ (1.1)	$ClCH_2CH_2Cl$	>98	<2	0
$AlCl_3$ (1.1)	CH_2Cl_2	>88	<2	10
$AlCl_3$ (1.0)	$ClCH_2CH_2Cl$	85	15	0
$AlCl_3$ (0.9)	CH_2Cl_2	75	25	0
$AlCl_3$ (0.9)[c]	CH_2Cl_2	68	32	0
$AlCl_3$ (0.1)	$ClCH_2CH_2Cl$	<3	<2	95

[a] Ratios determined by ^1H NMR.
[b] Reaction was carried out at room temperature, following the procedure of Lainton et al. (Ref. 5).
[c] Reaction was carried out at room temperature.

Table 3
Effect of Lewis acid and concentration upon acylation of *N*-*p*-toluenesulfonylpyrrole via method B[a]

Concentration of *N*-Ts–pyrrole (M)	Lewis acid	**1** R=Ts[b]	**5**	*N*-Ts–pyrrole
0.075	$AlCl_3$	>98	<2	0
0.221	$AlCl_3$	>99	<1	0
0.075	$EtAlCl_2$	27	67	6
0.221	$EtAlCl_2$	6	93	<1
0.075	Et_2AlCl	<5	80	15
0.221	Et_2AlCl	<5	>95	0

[a] Acylation performed in 1,2-dichloroethane with the indicated Lewis acid and 2.18 equiv of 1-naphthoyl chloride for 2 h at 0 °C.
[b] Ratios determined by ^1H NMR.

obtained. In none of these experiments was a significant amount of starting material recovered. The reactions summarized in Table 3 were also carried out in dichloromethane, however, there were no significant differences in product distribution from those carried out in 1,2-dichloroethane (data not shown).

In our earlier work, we obtained somewhat different results when benzoyl chloride was used in place of 1-naphthoyl chloride to acylate *N*-*p*-toluenesulfonylpyrrole.[5,13] In particular, when dichloromethane was used as solvent a mixture of 2- and 3-acylation products was obtained. However, in 1,2-dichloroethane, 3-benzoyl-*N*-*p*-toluenesulfonylpyrrole was the only detectable product. With the exception of temperature, the reactions described in Refs. 5 and 13 were carried out under conditions virtually identical to those of acylation method A. In the current study, acylation of *N*-*p*-toluenesulfonylpyrrole with benzoyl chloride or acetyl chloride using procedure A and 2 equiv of $AlCl_3$ gave as the only product 3-acyl-*N*-*p*-toluenesulfonylpyrrole, plus a trace of recovered starting material (Table 4). Similar results were obtained with acetyl chloride and 2 equiv of $AlCl_3$, however, the product mixture contained 5% of starting material. When acetic anhydride was employed as the acylating agent under the same conditions with 2 equiv of $AlCl_3$, the product mixture contained 80% of 3-acetyl-*N*-*p*-toluenesulfonylpyrrole, less than 3% of the 2-isomer, and 17% recovered *N*-*p*-toluenesulfonylpyrrole. This result contrasts with that reported by Kakushima et al., who reported that the $AlCl_3$ catalyzed reaction of acetic anhydride with *N*-*p*-benzenesulfonylpyrrole gave predominantly (>98%) the 3-isomer.[4b] However, the results reported by Kakushima et al. were obtained using 6 mol equiv of catalyst rather than the 2 equiv used in the present work. It has been established that acid anhydrides react with 1 equiv of $AlCl_3$ to give the acyl chloride plus an aluminum salt of a carboxylic acid.[15] As would be predicted, our results with acetic anhydride and 2 equiv of $AlCl_3$ are similar to those using acetyl chloride and 1 equiv of $AlCl_3$. When the acylation of *N*-*p*-toluenesulfonylpyrrole with acetic anhydride was repeated using 1.5 equiv of $AlCl_3$ the product mixture contained 48% of 3-acetyl-*N*-*p*-toluenesulfonylpyrrole, 37% of the 2-isomer, and 15% starting material. Decreasing the amount of $AlCl_3$ further to 1.2 equiv gave a product mixture containing 19% of the 3-acyl product, 61% of the 2-isomer, and 20% recovered *N*-*p*-toluenesulfonylpyrrole. With 1 equiv of $AlCl_3$ acetic anhydride gave a product mixture that contained 12% of 3-acetyl-*N*-*p*-toluenesulfonylpyrrole, 36% of the 2-isomer, and 52% starting material.

Table 4
Effect of acylating agents upon the acylation of *N*-*p*-toluenesulfonylpyrrole[a]

Acylating agent	**1** R=Ts[b]	**5**[b]	*N*-Ts–pyrrole[b]	Acylation method
Benzoyl chloride	>99	0	<1	A
Acetyl chloride	>99	0	<1	A
Acetyl chloride[c]	>95	Trace	<5	A
Acetic anhydride	80	<3	17	A
Acetic anhydride[d]	48	37	15	A
Acetic anhydride[e]	19	61	20	A
Acetic anhydride[c]	12	36	52	A
Acetyl chloride	84	1	15	B
Acetyl chloride[f]	59	34	7	B

[a] Acylation performed in 1,2-dichloroethane with 2 equiv of $AlCl_3$ and 1.2 equiv of 1-naphthoyl chloride for 2 h.
[b] Ratios determined by ^{1}H NMR.
[c] $AlCl_3$ (1 equiv).
[d] $AlCl_3$ (1.5 equiv).
[e] $AlCl_3$ (1.2 equiv).
[f] $EtAlCl_2$ used as Lewis acid.

Under acylation conditions B using $AlCl_3$ and acetyl chloride, *N*-*p*-toluenesulfonylpyrrole gave the 3-acetyl compound as the predominant product (Table 4). However, when the acylation was carried out using $EtAlCl_2$ as the Lewis acid, the product mixture consisted of 59% of the 3-acyl product, 34% of 2-acetyl-*N*-*p*-toluenesulfonylpyrrole, and 7% *N*-*p*-toluenesulfonylpyrrole.

A qualitative estimate of the rate of the $AlCl_3$ catalyzed reaction of *N*-*p*-toluenesulfonylpyrrole with 1-naphthoyl chloride under acylation conditions A was carried out by removing aliquots from the reaction mixture at timed intervals throughout the procedure. Analysis of the aliquots by ^{1}H NMR showed that the mixture of acylation products contained >98% 3-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole (**1**, R=Ts) and <2% 2-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole (**5**) after 5 min. The starting material was completely consumed within 2 h, however, with highly active $AlCl_3$ the reaction was complete within 30 min. In earlier work, Kakushima et al. reported that the $AlCl_3$ catalyzed reaction of *N*-benzenesulfonylpyrrole with acetyl chloride at −78 °C went to completion in 12 min to afford almost exclusively the 3-acyl isomer.[4b]

Pyrroles normally undergo electrophilic substitution at the 2-position and a possible route for the acylation of *N*-arylsulfonylpyrroles at C-3 would involve initial acylation at C-2, followed by rearrangement to the 3-acyl isomer. Although migrations of 2-acyl, sulfinyl, and sulfonyl groups to the corresponding 3-isomers have been observed in substituted pyrroles under acidic conditions at mild temperatures,[16] Kakushima et al. considered that this was an unlikely reaction path for the formation of 3-isomers in the Friedel–Crafts reaction of *N*-benzenesulfonylpyrrole.[4b] This conclusion was based upon the observation that 2-acetyl-*N*-benzenesulfonylpyrrole formed a stable complex with $AlCl_3$ from which it could be recovered unchanged after aqueous work up. In our hands similar results were obtained with 2-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole (**5**), which after stirring with $AlCl_3$ in dichloromethane for 2 h was recovered unchanged. Similar treatment of the 3-isomer (**1**, R=Ts) also provided unchanged starting material.

The Okauchi–Ottoni modification of the Friedel–Crafts acylation of indoles differs from the classical procedure in that the substrate is stirred with the Lewis acid for some time, usually 30 min, prior to the addition of the acylating agent.[8] This is similar to our acylation procedure B, while procedure A is a normal Friedel–Crafts procedure. Although Okauchi et al. did not comment upon the mechanism of the modified procedure,[8a] Ottoni et al. suggested that an intermediate organometallic complex was formed between the indole and the Lewis acid.[8b] In earlier work, we obtained evidence for such an intermediate when 1-pentylindole was treated with

dimethylaluminum chloride and subsequently quenched with D_2O to afford a 3-deuterio compound.[10] In contrast to the results of Ottoni et al.,[8b] who found that their organotin intermediates were insoluble in dichloromethane in the absence of nitromethane, the organoaluminum intermediates in our work and presumably those of Okauchi et al. are soluble in dichloromethane.[8a,10]

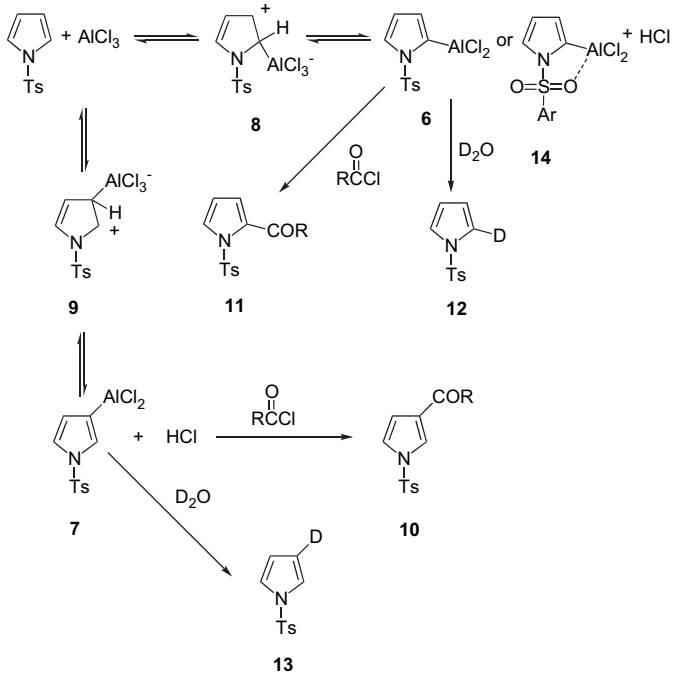
Kakushima et al. reported that a mixture of *N*-benzenesulfonylpyrrole and $AlCl_3$ in 1,2-dichloroethane remains heterogeneous and that there is no evidence of complex formation by ^1H NMR and UV.[4b] However, in our hands the stirred mixture of *N*-toluenesulfonylpyrrole and 0.9 equiv of $AlCl_3$ in 1,2-dichloroethane provides a homogeneous green solution within 4 min, which fades to pale tan over time. In our hands *N*-benzenesulfonylpyrrole behaves similarly. D_2O quenching experiments similar to those carried out on 1-pentylindole were carried out with the solution of *N*-*p*-toluenesulfonylpyrrole and $AlCl_3$ in 1,2-dichloroethane. In this procedure, 1.5 equiv of $AlCl_3$ was added to a solution of *N*-*p*-toluenesulfonylpyrrole in 1,2-dichloroethane at 0 °C and the reaction was stirred at that temperature for 30 min. After quenching with D_2O the ^1H NMR spectra of the reaction products were examined. The ^1H NMR signals at δ 6.28 and δ 7.15, which are assigned to the pyrrole protons of *N*-*p*-toluenesulfonylpyrrole, were considerably diminished. The $AlCl_3$ reaction with D_2O quench was carried out three times and in all cases the ^{13}C NMR signals for both pyrrole carbons were diminished. Qualitatively, it was observed that in the ^1H NMR spectra of the products of all three runs the intensity of the pyrrole C-2 protons was diminished more than those at C-3. An effort was made to obtain quantitative data by integration of the ^1H NMR spectra. The results were highly variable over the three runs, with substitution at C-2 of 40±27% and at C-3 of 28±14%. In one run aliquots were taken at 30 s, 2, 10, 20, and 60 min with substitution at C-2 of 30±6% and at C-3 of 21±4%, with essentially no change in substitution pattern over the course of the reaction.

Some difficulty was encountered in obtaining the ^1H NMR spectrum of the homogeneous solution of *N*-*p*-toluenesulfonylpyrrole and $AlCl_3$ in 1,2-dichloroethane-d_4. However, when the sample was prepared in a dry, inert atmosphere the ^1H NMR spectrum was obtained. This spectrum was not particularly well resolved, but clearly showed the loss of the signals at δ 6.29 and δ 7.17, which are assigned to the protons at C-3 and C-2, respectively, of *N*-*p*-toluenesulfonylpyrrole. The doublets at δ 7.30 and δ 7.74 (J=8 Hz), assigned to two of the protons on the phenyl ring of *N*-*p*-toluenesulfonylpyrrole are no longer present. Several pairs of doublets with J=7–8 Hz are present in the aromatic region of the spectrum, the most prominent of which appear at δ 7.80 and δ 7.83. The bulk of the aromatic protons appear as a broad multiplet and it was not possible to obtain integration data, nor was it possible to assign any of these signals to specific protons. Also, in addition to the aromatic methyl peak at δ 2.36 there was a second peak of slightly greater intensity at δ 2.46. An attempt was made to obtain a ^{13}C spectrum of this solution, however, the compound slowly decomposed during the time required to obtain the spectrum. Quenching the solution of *N*-*p*-toluenesulfonylpyrrole and $AlCl_3$ in 1,2-dichloroethane with water provided only recovered *N*-*p*-toluenesulfonylpyrrole. When a solution of *N*-*p*-toluenesulfonylpyrrole in 1,2-dichloroethane was treated with $EtAlCl_2$ or Et_2AlCl and the mixture was quenched with D_2O the products showed no incorporation of deuterium as indicated by the ^1H NMR spectrum.

3. Discussion

The data summarized in Tables 1–4 and presented above indicate that the mechanism of acylation of *N*-*p*-toluenesulfonylpyrrole with $AlCl_3$ is different from that with weaker Lewis acids. In particular, the observation that quenching a 1,2-dichloroethane solution of *N*-*p*-toluenesulfonylpyrrole and $AlCl_3$ with D_2O results in the incorporation of deuterium at C-2 and C-3, combined with the fact that these solutions are homogeneous with an ^1H NMR spectrum different from that of *N*-*p*-toluenesulfonylpyrrole provides strong evidence for the intermediacy of organoaluminum compounds derived from *N*-*p*-toluenesulfonylpyrrole in the acylation reactions. This is in direct contrast to the results reported by Kakushima et al. and we have no explanation for the differences in our results and those reported previously.[4b] The deuterium incorporation reactions were carried out several times as was the observation that the $AlCl_3$, *N*-*p*-toluenesulfonylpyrrole, and 1,2-dichloroethane system was homogeneous. Thus, the mechanism of this reaction is probably similar to that of the Okauchi and Ottoni indole acylation procedure.[8,10]

As depicted in Scheme 1, reaction of *N*-*p*-toluenesulfonylpyrrole with $AlCl_3$ leads reversibly to a mixture of 2- (**6**) and 3-organoaluminum (**7**) species via cations **8** and **9**, respectively. Alternatively, organoaluminum species **6** and **7** may interconvert via an intramolecular process.[16] The acid



Scheme 1.

catalyzed equilibration of substituted pyrroles is exceedingly facile and there is evidence both in favor of and against an intramolecular process. Reaction of organoaluminum intermediate **7** with the acyl chloride leads to the 3-acylpyrrole derivative (**10**). The reaction of organoaluminum compounds with acyl halides to provide ketones is a known reaction, which is facilitated in the presence of $AlCl_3$ or organoaluminum halides.[17] Under the conditions that provide 3-acylpyrrole derivatives regioselectively there is either excess $AlCl_3$ present or the organoaluminum intermediates may serve to enhance the reaction of **7** with the acyl chloride. Reactions of organoaluminum intermediate **6** with the acyl chloride will lead to the 2-substituted pyrrole derivative (**11**). Quenching the homogeneous solution of organoaluminum intermediates with D_2O leads to a mixture of 2- and 3-deuteriopyrrole derivatives (**12** and **13**, respectively) in which the 2-deuterio isomer prevails in an approximately 3:2 ratio.

Although in principle the path outlined in Scheme 1 would lead to a mixture of 2- and 3-acylation products, the rate of conversion of the 2-substituted organoaluminum intermediate **6** to pyrrole **11** would be expected to be slower than the corresponding conversion of the 3-substituted intermediate **7** to pyrrole **10**. In analogy to steric effects invoked to explain the high regioselectivity in reactions of *N*-triisopropylsilylpyrrole, it would be anticipated that the rate of reaction of the 2-organoaluminum intermediate (**6**) with an acyl chloride would be slower than the rate of reaction of the less sterically encumbered 3-isomer (**7**) with the acyl chloride. Also, there may be a direct electronic interaction of the electrophilic aluminum atom of **6** with an oxygen of the sulfonyl group via a five-membered structure as depicted in **13** (Scheme 1). Such an interaction would stabilize the 2-organoaluminum intermediate (**6**) and decrease the rate of reaction with the acyl halide. A combination of these factors provides a rationalization for the regioselective formation of the 3-acyl isomers in the acylation of *N*-*p*-toluenesulfonylpyrrole using $AlCl_3$. Thus, *the regioselective acylation of N-p-toluenesulfonylpyrrole with $AlCl_3$ is not a Friedel–Crafts acylation, but is rather the reaction of an organoaluminum intermediate with an acyl chloride.* In the absence of at least 1 equiv of $AlCl_3$, excess *N*-*p*-toluenesulfonylpyrrole will be present and will be acylated with organoaluminum compounds **6** and/or **7** acting as catalyst. The regiochemistry of this acylation would be similar to that of the acylation of *N*-*p*-toluenesulfonylpyrrole using a Lewis acid that did not form an organometallic intermediate prior to acylation.

As noted above under conditions B, in which the substrate is treated with $AlCl_3$ and the acylating agent is subsequently added, the formation of an organoaluminum species, such as **6** and **7**, was confirmed experimentally. This confirmation consists of both the direct determination of the ^1H NMR spectrum of the mixture of organoaluminum intermediates and trapping them via deuterium quenching. Under acylation conditions A the acyl halide is stirred with $AlCl_3$, which generates a reversibly formed complex between $AlCl_3$ and the acyl halide in which the $AlCl_3$ is coordinated with the carbonyl oxygen of the halide.[18–20] *N*-*p*-Toluenesulfonylpyrrole may compete with this complex for $AlCl_3$, which will lead to cations **8** and **9**, which are in turn converted into organoaluminum compounds **6** and **7**. It is not necessary to postulate a sequence of this sort under acylation conditions B because species **6** and **7** are formed prior to the addition of the acyl halide.

In the presence of weaker Lewis acids,[21] such as $EtAlCl_2$ and Et_2AlCl (Table 3), or as reported by Kakushima who employed $SnCl_4$, $TiCl_4$, $ZnCl_2$, and $FeCl_3$ as catalysts the reaction is considerably less regioselective.[4b] With $BF_3\cdot Et_2O$ as catalyst Kakushima obtained 2-acylpyrrole as the major product. In the case of $EtAlCl_2$, Et_2AlCl, and presumably the other weaker Lewis acids, these acylations do not involve organometallic pyrrole derivatives. Bigi et al. found that in relatively nonpolar solvents, such as dichloromethane and 1,2-dichloroethane, a polarized Lewis acid ($AlCl_3$) acyl halide complex is formed with no NMR indication of a significant concentration of acylium ion.[20] For the series RCOCl in which R was CH_3, CH_2Cl, $CHCl_2$, and CCl_3, these authors found that the degree of Lewis acid induced polarization of the complex between the acyl halide and the Lewis acid decreased incrementally with the inductively electron withdrawing effect of the α-halogens. These authors also found that the rate of acylation was reduced by electron withdrawing substituents on the acyl halide. Similar effects would be expected with decreasing strength of the Lewis acid while holding the electronegativity of the alkyl or aryl substituent on the acyl halide relatively constant.

A number of years ago, Olah suggested that in aromatic substitution reactions, strongly electrophilic reagents provide early transition states resembling a π-complex, while less electrophilic reagents provide a transition state similar to the resonance stabilized Wheland intermediate.[22] Although this suggestion has been criticized,[23] ab initio calculations indicate that electrophilic aromatic substitution reactions may proceed through a single transition state, which would vary from an early π-complex-like with reactive electrophiles to σ-complex-like with less reactive electrophiles.[24] This in effect is an application of the Hammond postulate to electrophilic aromatic substitution reactions in which a reactive electrophile provides a reactant-like transition state, while a less reactive electrophile leads to a product-like transition state. For the addition of an electrophile to an aromatic compound the product-like transition state will resemble a delocalized cation (Wheland intermediate).

Although in the acylations of *N*-*p*-toluenesulfonylpyrrole with 1-naphthoyl chloride the acyl halide is not varied, the electrophilic character of the Lewis acid complex with 1-naphthoyl chloride will vary as a function of the Lewis acidity of the catalyst. $AlCl_3$ is the strongest Lewis acid of those used for the acylation of *N*-*p*-toluenesulfonylpyrrole and it reacts directly with the substrate to form an organoaluminum intermediate with an approximate ratio of 2- to 3-substitution of 3 to 2. The Merck group carried out CNDO/2 calculations on the 2- and 3-cations derived from *N*-benzenesulfonylpyrrole, and found that the 3-cation, obtained by substitution at C-2, was significantly more stable than the 2-cation, derived from substitution at C-3, a conclusion that is also predicted by classical valence bond theory.[4a] CNDO/3 calculations for the ground state of *N*-benzenesulfonylpyrrole indicated that the electron density

at C-3 is greater than that at C-2, while the HOMO coefficient is greater at C-2. Similar results would be expected for *N*-*p*-toluenesulfonylpyrrole. According to this hypothesis, regioselective substitution with hard electrophiles will proceed through charge control to provide substitution at C-3, while soft electrophiles will lead to the 2-isomer through frontier-orbital effects.[4a] As noted by Bray et al. other workers have made similar suggestions regarding electrophilic substitution of pyrrole.[2b]

An indication of the relative nucleophilicity of C-2 and C-3 in *N*-*p*-toluenesulfonylpyrrole can be found in the ^{1}H NMR chemical shifts of the protons at C-2 (δ 7.15) and C-3 (δ 6.28).[25] For pyrrole the chemical shifts of the C-2 and C-3 protons are δ 6.73 and δ 6.17, respectively, while for *N*-triisopropylsilylpyrrole the C-2 proton appears at δ 6.80 and the C-3 proton at δ 6.32.[2b] *N*-Triisopropylsilylpyrrole undergoes Friedel–Crafts acylation exclusively at C-3 and it was concluded that this was due primarily to steric effects inasmuch as the ^{1}H NMR chemical shifts of *N*-triisopropylsilylpyrrole are very similar to those of pyrrole itself. The similarity of these NMR chemical shifts was considered to be indicative of no significant electronic effect caused by N-silylation.[2b] In contrast, while the chemical shift of H-3 of *N*-*p*-toluenesulfonylpyrrole is relatively unchanged with respect to those of pyrrole and *N*-triisopropylsilylpyrrole, H-2 is shifted quite far downfield, suggesting an electron withdrawing effect at C-2 caused by the *p*-toluenesulfonyl group.

Based upon these considerations, the Hammond postulate would predict that reaction at the 3-position of *N*-*p*-toluenesulfonylpyrrole by highly electrophilic species via a reactant-like transition state would be enhanced relative to pyrrole itself. Less electrophilic species would be expected to preferentially attack at C-2 via a product-like transition state to produce the energetically favored, delocalized 3-carbocation. The evidence discussed above indicates that the mechanism of reaction of *N*-*p*-toluenesulfonylpyrrole with an acyl halide using $AlCl_3$ is not a Friedel–Crafts acylation, but is instead the reaction of an intermediate organoaluminum species with the acyl halide. The weaker Lewis acids, $EtAlCl_2$ and Et_2AlCl provide mixtures of 2- and 3-acylation products (Table 3). With $BF_3{\cdot}Et_2O$, which forms a very weak complex with acetyl chloride, the acylation of *N*-benzenesulfonylpyrrole is reported to give exclusively the 2-acyl product.[4b] Similar results were reported by Kimbaris and Varvounis in the acylation of *N*-*p*-toluenesulfonylpyrrole with 2-nitrobenzoyl chloride.[26] With $AlCl_3$ these authors obtained a 4:1 mixture of 3-acyl to 2-acyl product and with $SnCl_4$ the ratio was 1:5. More recently Song et al. reported that exclusive 2-acylation of *N*-*p*-toluenesulfonylpyrrole and substituted *N*-*p*-toluenesulfonylpyrroles could be achieved by employing a mixture of the appropriate carboxylic acid and trifluoroacetic anhydride.[27] Although these authors do not discuss the mechanism of this reaction, it almost certainly proceeds via a mixed anhydride, with the strongly electron withdrawing trifluoroacetyl moiety inducing enhanced positive character to the carbonyl group derived from the carboxylic acid to give a weakly electrophilic species that would be expected to react via a product-like transition state and provide the 2-acyl product.

4. Conclusions

In summary, acylations of *N*-*p*-toluenesulfonylpyrrole with $AlCl_3$ appear to proceed via reaction of an organoaluminum intermediate with the acyl chloride. Acylations using weaker Lewis acids proceed by a normal Friedel–Crafts reaction through a polarized complex formed from the acylating agent and the Lewis acid. The electrophilicity of this complex is determined by a combination of the nature of the acylating agent and the strength of the Lewis acid. In these reactions the regiochemistry will be determined by the character of the transition state leading to the intermediate carbocation. With highly reactive electrophiles, a reactant-like transition state will favor the 3-substituted product, while less reactive electrophiles will provide a product-like transition state that resembles the more stable cation resulting from attack at C-2.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300AC or 500 MHz spectrometers or a JEOL 500 MHz spectrometer. Mass spectral analyses were performed on a Hewlett-Packard 5890A capillary gas chromatograph equipped with a mass sensitive detector. Ether and THF were distilled from Na–benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Sorbent Technologies silica gel (32–63 μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and/or ^{13}C NMR. TLC was carried out using 200 μm silica gel plates using the indicated solvents. GLC analyses were performed on the Hewlett-Packard 5890A GC/MS using a 60 m carbowax column and helium gas as a carrier. An initial column temperature of 60 °C was employed and the temperature was increased at a rate of 1.5 °C/min to a maximum temperature of 300 °C with a total run time of 20 min. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

5.2. 3-(1-Naphthoyl)-N-(p-toluenesulfonyl)pyrrole

5.2.1. Method A

This procedure is a modification of that reported by Cadamuro et al.[28] To a stirred suspension of 0.600 g (4.5 mmol) of $AlCl_3$ in 2.35 mL of dry CH_2Cl_2 under argon was added 0.4 mL (2.6 mmol) of 1-naphthoyl chloride. The mixture was stirred for 10 min cooled to 0 °C and 0.500 g (2.3 mmol) of *N*-*p*-toluenesulfonylpyrrole in 3.0 mL of dry dichloromethane was added. The mixture was allowed to warm slowly to ambient temperature with stirring over 2 h. Water was added to quench the reaction, which was extracted with three portions of dichloromethane, washed with 2 M aqueous NaOH, and dried ($MgSO_4$). Concentration in vacuo afforded a brown oil. Chromatography (petroleum ether/ethyl acetate, 9:1) gave 0.561 g (66%) of 3-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole

as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 6.83 (dd, J=1.6, 3.4 Hz, 1H), 7.20–7.25 (m, 2H), 7.47–7.53 (m, 3H), 7.65 (d, J=7.0 Hz, 1H), 7.72 (d, J=8.1 Hz, 2H), 7.86 (d, J=7.0 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 8.16 (d, J=8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 113.4, 121.5, 124.2, 125.3, 126.3, 126.8, 126.9, 127.0, 128.2, 129.6, 130.2, 130.3, 131.2, 133.6, 134.7, 136.4, 145.9, 191.2; EIMS *m/z* (rel intensity) 65 (21), 91 (58), 127 (26), 191 (12), 220 (100), 375 (52). The spectroscopic data agree with those reported previously.[5]

5.2.2. Method B

This procedure is a modification of Okauchi et al.[8a] To a solution of 0.100 g (0.5 mmol) of *N*-*p*-toluenesulfonylpyrrole and 1 mL of 1,2-dichloroethane under N_2 at 0 °C was added 0.68 mL (0.7 mmol) of 1.0 M ethylaluminum dichloride in dichloromethane. The mixture was stirred for 30 min and 0.15 mL (1.0 mmol) of 1-naphthoyl chloride dissolved in 1 mL of 1,2-dichloroethane was added. The reaction was stirred for an additional 2 h at 0 °C, quenched with water and extracted with three portions of ethyl acetate. After drying ($MgSO_4$) the solution was concentrated in vacuo to give a brown solid. Chromatography (petroleum ether/ethyl acetate, 9:1) afforded 0.031 g (18%) of 3-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole as a yellow oil, the spectroscopic data for which are identical to those reported above.

5.3. 2-(1-Naphthoyl)-N-(p-toluenesulfonyl)pyrrole

Acylation of *N*-*p*-toluenesulfonylpyrrole was carried out by method B, however, using diethylaluminum chloride as catalyst. From 0.100 g (0.5 mmol) of *N*-*p*-toluenesulfonylpyrrole and 0.15 mL (1.0 mmol) of 1-naphthoyl chloride there was obtained after chromatography (petroleum ether/ethyl acetate, 9:1) 0.098 g (58%) of 2-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole as a yellow solid: mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.26 (t, J=3.3 Hz, 1H), 6.6 (dd, J=1.7, 3.6 Hz, 1H), 7.36–7.50 (m, 5H), 7.60 (d, J=6.9 Hz, 1H), 7.84–7.85 (m, 1H), 7.86 (d, J=1.7 Hz, 1H), 7.95 (t, J=8.2 Hz, 2H), 8.06 (d, J=8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 110.5, 124.2, 125.4, 126.3, 126.8, 127.2, 127.9, 128.2, 128.7, 129.4, 130.4, 130.9, 131.5, 133.5, 134.5, 135.8, 136.2, 145.0, 186.0; EIMS *m/z* (rel intensity) 65 (11), 91 (14), 127 (38), 190 (13), 219 (100), 375 (62). The spectroscopic data agree with those reported previously.[5]

5.4. Study on effects of aluminum chloride purity on acylation

Reactions were performed according to acylation method A. Each reaction was carried out in duplicate with samples of aluminum chloride taken from bottles of different ages and from Acros, Aldrich, and Alfa-Aesar. Aliquots were taken at 5, 30, 60, 90, and 120 min and the product mixture was evaluated by ^{1}H NMR spectroscopy.

5.5. 2-Phenyl-4-(1-naphthoyl)-N-p-toluenesulfonylpyrrole

Acylation of 0.100 g (0.3 mmol) of 2-phenyl-*N*-*p*-toluenesulfonylpyrrole[29] was carried out by method A to give, after chromatography (petroleum ether/ether, 9:1), 0.115 g (76%) of 2-phenyl-4-(1-naphthoyl)-*N*-*p*-toluenesulfonylpyrrole: mp 146–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.72 (d, J=1.8 Hz, 1H), 7.05–7.39 (m, 8H), 7.53–7.57 (m, 3H), 7.75–7.81 (m, 2H), 7.89–7.93 (m, 1H), 8.00 (d, J=8.2 Hz, 1H), 8.23–8.27 (m, 1H); EIMS *m/z* (rel intensity) 451 (61), 296 (100), 155 (10), 127 (29), 91 (9). Anal. Calcd for $C_{28}H_{21}NO_2S$: C, 74.48; H, 4.69; N, 3.10. Found: C, 74.27; H, 4.70; N, 3.11.

5.6. 3-Acetyl-N-p-toluenesulfonylpyrrole

Acylation of 0.100 g (0.45 mmol) of *N*-*p*-toluenesulfonylpyrrole with 0.04 mL (0.53 mmol) of acetyl chloride by method A or B gave 0.112 g (95%) of 3-acetyl-*N*-*p*-toluenesulfonylpyrrole: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.43 (s, 3H), 6.67 (dd, J=1.4, 3.2 Hz, 1H), 7.13 (dd, J=3.2, 2.2 Hz, 1H), 7.34 (d, J=8.2 Hz, 2H), 7.72 (t, J=1.8 Hz, 1H), 7.80 (d, J=8.2 Hz, 2H); EIMS *m/z* (rel intensity) 263 (48), 248 (61), 155 (43), 91 (100), 65 (37). The spectroscopic data are consistent with those reported previously.[14]

5.7. 3-Benzoyl-N-p-toluenesulfonylpyrrole

Acylation of *N*-*p*-toluenesulfonylpyrrole was carried out by method A: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 6.79 (dd, J=1.5, 3.0 Hz, 1H), 7.23 (dd, J=2.3, 3.2 Hz, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.39–7.56 (m, 3H), 7.71 (t, J=1.7 Hz, 1H), 7.75–7.82 (m, 4H); EIMS *m/z* (rel intensity) 325 (82), 248 (34), 155 (50), 91 (100). The spectroscopic data are consistent with those reported previously.[30]

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