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A new method for the acylation of pyrroles

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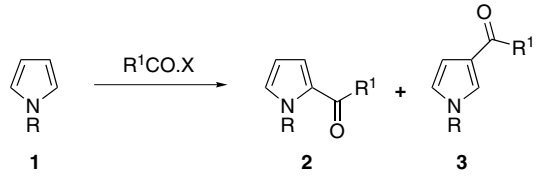
Abstract—*N*-Tosylpyrroles can be very efficiently converted into the corresponding 2-acylpyrroles by reaction with carboxylic acids and trifluoroacetic anhydride; little or none of the isomeric 3-acyl derivatives are formed.

Because of their very high reactivity towards electrophilic substitution and general sensitivity to acid-catalysed polymerisation, there are few very efficient methods available for the selective acylation of pyrroles **1**; mixtures of 2- and 3-acylated product **2** and **3** are often obtained (Scheme 1). Perhaps the best and most proven method is by Vilsmeier reaction with phosphorus oxychloride and *N*,*N*-dimethyl acetamide, which leads to respectable yields of 2-acetylpyrrole.[1] The same method, when applied to the general series of *N*,*N*-dimethylcarboxamides, is also viable and delivers good yields (75–80%) of 2-acylpyrroles, uncontaminated by significant amounts of the corresponding 3-acyl isomers or bis-acyl derivatives.[2] This is certainly not the case with direct acetylation with acetic anhydride, which gives mixtures of 2- and 3-acetylpyrrole in moderate overall yields.[3] A similar but even less efficient result has been obtained using triethyl orthoacetate and $BF_3{\cdot}OEt_2$ as catalyst.[4] The formation of both possible isomers (Scheme 1) also plagues otherwise reasonably efficient methodology based on the thermal rearrangement of *N*-acetylpyrroles[5] or on the acylation of pyrryl Grignard reagents with a variety of electrophiles at the carboxylic acid oxidation level.[6] Less direct but nevertheless efficient alternatives, which do not appear to suffer from formation of 3-acyl isomers, include condensations of pyrrole with a 1,3-benzoxathiolium tetrafluoroborate followed by mercury(II) oxide-induced hydrolysis[7] or an *N*-methylnitrilium salt, obtained by *N*-methylation of the corresponding nitrile using Meerwein's reagent, followed by hydrolysis of the resulting imine.[8] Clearly, an obvious way to moderate the excessive reactivity of a 'free' pyrrole is to derivatise it by placing an electron withdrawing group on the nitrogen. In this respect, sulfonyl derivatives have been the most widely studied. Unfortunately, the problem of mixed product formation (Scheme 1) has been found to persist in acylations of such derivatives ($R = SO_2Ar$), at least under Friedel–Crafts conditions using aluminium trichloride as the catalyst and various aroyl chlorides,[9] although not when the electrophile is an alkanoyl chloride and the catalyst is $BF_3{\cdot}OEt_2$.[10,11] A more recent report[12] has outlined a general method for the selective 2-acylation of a range of pyrrole derivatives (*N*-Boc; *N*-SO_2Ar) as well as of pyrrole itself, by exposure to an acid chloride and zinc powder in toluene. Yields are generally 80% or better from these highly regioselective acylations. It was against this background that we felt somewhat uncertain as to the best method to use for the preparation of a series of deactivated (i.e., *N*-derivatised; preferably *N*-tosyl) 2-acylpyrroles, which were required for a separate study.[13] Clearly, the use of anhydrides would be rather wasteful, especially when the precursor acid is relatively precious. However, we were intrigued by the contrast between the foregoing results and those reported by Kakushima et al.[14] These authors report that either an acid chloride or the corresponding anhydride, in combination with boron trifluoride etherate, will acylate an *N*-tosylpyrrole slowly and largely in the 2-position



1 2 3

Scheme 1.

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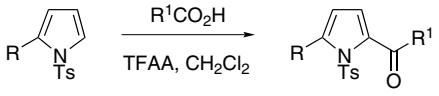
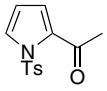
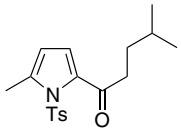
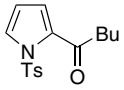
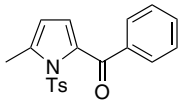
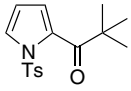
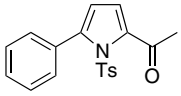
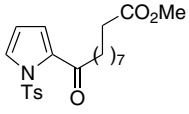
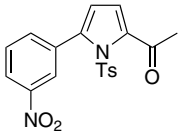
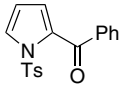
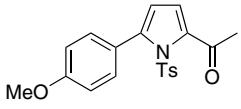
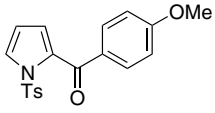
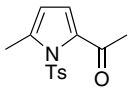
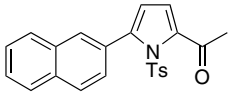
(42–83% yields) with 5–15% of the 3-acyl derivative also being formed. By contrast, the use of the stronger Lewis acid, $AlCl_3$, was reported to give only 3-acyl derivatives (generally >95%) quite rapidly at ambient temperature. In our hands, the former method, when applied to 2-methyl-*N*-tosylpyrrole using $BF_3{\cdot}OEt_2$, gave only moderate yields of the desired 2-acyl-*N*-tosyl-5-methylpyrroles, together with substantial amounts of the 3-acyl isomer from various alkanoyl chlorides. Attempts to secure useful yields using other Lewis acids (e.g., $ZnCl_2$, $SnCl_4$, $TiCl_4$) were also not successful. However, we noted that these authors had commented that 2-acetyl-*N*-tosylpyrrole could also be obtained, but in excellent yield, using a 'large excess'of acetic acid and trifluoroacetic anhydride. The fact that a somewhat related mixture of trifluoroacetic anhydride (TFAA) and phosphoric acid had been used to induce thiophene acylation[15] led us to investigate this method in more detail. We were also attracted by the additional favourable prospect of being able to use carboxylic acids directly, rather than the derived acid chlorides, anhydrides or amides.

Initial experiments established that 2-methyl-*N*-tosylpyrrole could indeed be acetylated using a large excess (>10 equiv) of acetic acid in a 1:1 mixture of TFAA and dichloromethane at ambient temperature. Whilst none of the corresponding 3-acetyl isomer was detected, we were a little surprised to observe that a by-product was rather the 2,4-diacetyl derivative. The large excess of reagents is evidently sufficient to overcome the deactivating effect of the first acetyl group. At least, a 2,4-disubstitution pattern is what would be expected from a second acetylation. Subsequent optimisation experiments defined a more efficient procedure, in which acetylation was achieved using 4 equiv or less of the carboxylic acid. Under these conditions, no 2,4-diacyl products were detected. The results using this method with a range of *N*-tosylpyrroles and carboxylic acids are collected in Table 1.[16]

Table 1. Acylation of *N*-tosylpyrroles by carboxylic acids and trifluoroacetic acid



Entry; acid [equiv] conditions	Yield (%)	Product[16]	Entry; acid [equiv] conditions	Yield (%)	Product[16]
1; R = H. HOAc [4.0]; 20 °C, 30 h, CH_2Cl_2.	94		**8;** R = Me. $Me_2CH(CH_2)_2CO_2H$ [1.5]; 20 °C, 4 h, CH_2Cl_2.	87	
2; R = H. $BuCO_2H$ [4.0]; 20 °C, 16 h then reflux, 7 h CH_2Cl_2.	90		**9;** R = Me. $PhCO_2H$ [4.0]; 20 °C, 42 h, CH_2Cl_2.	96	
3; R = H. *t*-$BuCO_2H$ [4.0]; reflux, 119 h, $Cl(CH_2)_2Cl$.	72		**10;** R = Ph. HOAc [2.0]; 20 °C, 43 h, CH_2Cl_2.	74	
4; R = H. $MeO_2C(CH_2)_8CO_2H$ [1.5] reflux, 48 h, CH_2Cl_2.	73		**11;** R = *m*-$O_2NC_6H_4$ HOAc [2.0]; reflux, 48 h, $Cl(CH_2)_2Cl$.	57	
5; R = H. $PhCO_2H$ [2.0]; reflux, 70 h, $Cl(CH_2)_2Cl$.	84		**12;** R = *p*-$MeOC_6H_4$. HOAc [2.0]; 20 °C, 35 h, CH_2Cl_2.	40[a]	
6; R = H. *p*-$MeOC_6H_4CO_2H$ [2.0]; 20 °C, 48 h, CH_2Cl_2.	84				
7; R = Me. HOAc [3.6]; 0 °C, 2 h, CH_2Cl_2.	83		**13;** R = 2-naphthyl. HOAc [2.0]; 20 °C, 95 h, CH_2Cl_2.	79	

[a] The 5-trifluoroacetyl derivative was also isolated in 11% yield.

As expected (entries 1–6), *N*-tosylpyrrole itself proved to be somewhat less reactive than its 2-methyl derivative used in the initial optimisations. While acetic acid reacted smoothly if slowly in dichloromethane at ambient temperature, in order to secure a similarly excellent yield from pentanoic acid, it was necessary to reflux the reaction mixture (entry 2). The much more hindered and electron-rich pivalic acid required prolonged reflux in dichloroethane before a respectable yield (72%; entry 3) of the corresponding acylpyrrole was obtained. Benzoic acid (entry 5) also only reacted slowly under these more vigorous conditions; despite the lengthy reaction times however, no 3-acylated derivatives were evident in ^{1}H NMR spectra of the crude products. In contrast, 4-methoxybenzoic acid reacted smoothly at ambient temperature (entry 6). That the presence of an α-methyl substituent provides significant additional activation is shown by the relatively milder conditions required to acylate 2-methyl-*N*-tosylpyrrole (entries 7–9). Acylations of representative 2-aryl-*N*-tosylpyrroles[17] (entries 10–13) were also similarly selective for the α-pyrryl position and best carried out at ambient temperature for extended periods. Some limitations which were discovered were perhaps not too surprising: direct formylation using formic acid failed to deliver any pyrrole-2-carboxaldehyde derivatives and 2- and 3-furoic acids also failed to act as acylating agents. Under the present conditions, it is also proved impossible to acetylate the alkenylpyrrole **4**; polymers and a variety of decomposition products were formed and not the ketone **5** (Scheme 2).

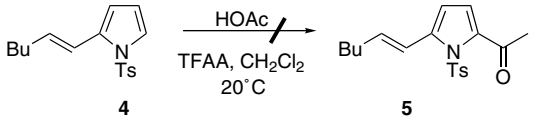
In addition to these limitations there are, however, three additional and positive caveats to this work. Firstly, such acylations can be conducted in an intramolecular fashion. To demonstrate this, we prepared the substituted sulfonamide **6** from 2-methoxycarbonylbenzenesulfonyl chloride and the sodium salt of pyrrole followed by ester saponification. We were delighted to observe that, albeit under relatively vigorous conditions, this was smoothly converted into the hoped-for product **7**, in 78% isolated yield (Scheme 3). To the best of our knowledge, compound **7** represents the parent of a novel heterocyclic ring system.

Secondly, we found that the dihydropyrone **8** was obtained when 2-methyl-*N*-tosylpyrrole was exposed to glutaric acid (0.5 equiv). Further oxidation then gave a moderate but unoptimised return of ca. 40% of the pyrone **9** (Scheme 4). Evidently, a second acylation of *N*-tosylpyrrole does not occur as fast as intramolecular cyclisation of the remaining carboxylic acid group onto the new ketone function, followed by dehydration. Studies of the chemistry of these potentially useful structures are underway.

Thirdly, by reduction of the new carbonyl group, this present method could represent part of an efficient method for overall pyrrole α-alkylation. We initially tried various classical methods for selectively reducing the ketone group in the keto-ester shown in entry 4 of Table 1 (Scheme 5). Unfortunately, both Clemmensen and various versions of the Wolff-Kishner reduction methods failed. However, a more recent method featuring the borane-*t*-butylamine complex as reductant, assisted by aluminium trichloride,[18] did produce the desired product **10** but was somewhat impractical in its original version, due to the claimed requirement for a considerable excess of the reagents. Fortunately, an optimisation study showed this to be unnecessary and delivered cleanly an 85% yield of the ester **10** as shown.

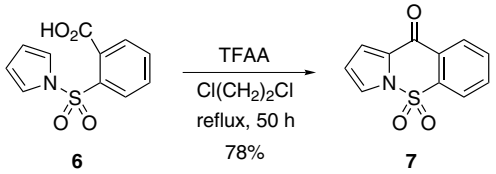
Finally, 'free' pyrroles can also be obtained by this route, followed by subsequent *N*-detosylation. Although we have not examined any alternatives, simply exposing the 2-acyl-*N*-tosylpyrroles to potassium hydroxide in aqueous methanol (3 h, 60 °C) delivers >80% yield of the NH-pyrroles, also uncontaminated by any migration products.[19]

In summary, it would appear that the combination of a carboxylic acid and trifluoroacetic anhydride is a simple and practical method for the selective 2-acylation of *N*-tosylpyrroles. We assume that the mechanism involves mixed anhydride formation between TFAA and the



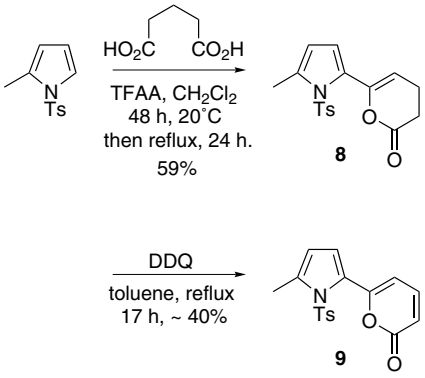
4 5

Scheme 2.

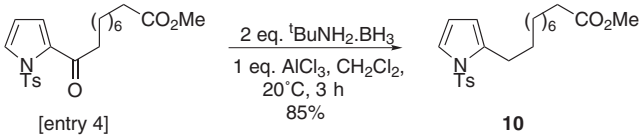


6 7

Scheme 3.



Scheme 4.



Scheme 5.

reacting carboxylic acid. It is perhaps surprising therefore that only in the example involving acetylation of 2-(4-methoxyphenyl)-*N*-tosylpyrrole (entry 12) was an isolable amount of a 2-trifluoroacetyl derivative formed.

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16. A typical procedure is as follows: *5-Methyl-2-(4-methylpentanoyl)-N-(4-toluenesulfonyl)-pyrrole.* To a stirred solution of 2-methyl-*N*-tosylpyrrole (7.173 g, 33 mmol), trifluoroacetic anhydride (50 ml) and dichloromethane (75 ml) maintained at 0 °C was added 4-methylpentanoic acid (6.2 ml, 49 mmol). The resulting solution was stirred without further cooling until TLC analysis showed complete conversion (ca. 4 h) and then the volatiles were removed by rotary evaporation. The residue was stirred briefly with dichloromethane (30 ml) and 10% aqueous sodium carbonate (50 ml) then the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 ml). The combined organic solutions were then washed with brine (50 ml), dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue (SiO_2, 10% EtOAc–40–60° petrol) then separated the acylpyrrole (Table 1, entry 8) (9.56 g, 87%) as a yellow oil, which showed R_f 0.75 (80% Et_2O–40–60° petrol), ν_{max}/cm^{-1} (film) 1679, 1597, 1488, 1366, 1177, 1105 and 812, δ_H (400 MHz, $CDCl_3$) 0.82 (6H, d, *J* 6.3 Hz, 2 × Me), 1.41–1.58 (3H, m, 4′-H and 3-CH_2), 2.34 (3H, s, Ar-Me), 2.46 (3H, s, 5-Me), 2.58–2.69 (2H, m, 2′-CH_2), 5.91 (1H, d, *J* 3.5 Hz, 4-H), 6.69 (1H, d, *J* 3.5 Hz, 3-H), 7.25 (2H, d, *J* 8.2 Hz) and 7.90 (2H, d, *J* 8.2 Hz), δ_C (100 MHz, $CDCl_3$) 16.3 (5-Me), 2.21 (Ar-Me), 22.8 (2 × Me), 28.2 (4′-CH), 34.2 (3′-CH_2), 39.3 (2′-CH_2), 112.6 (4-CH), 121.1 (3-CH), 128.1 (2 × ArCH), 129.9 (2 × ArCH), 136.7, 137.3, 141.0, 145.1 (all ArC) and 192.0 (C=O), *m*/*z* (APCI) 334 ($M + H^+$ 100%) (Found: $M + H^+$, 334.1474. Calcd for $C_{18}H_{24}NO_3S$, 334.1477).
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19. Full analytical and spectroscopic data have been obtained which support all of the structures reported herein.