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A SIMPLE AND EFFICIENT ROUTE TO β-SUBSTITUTED PYRROLES

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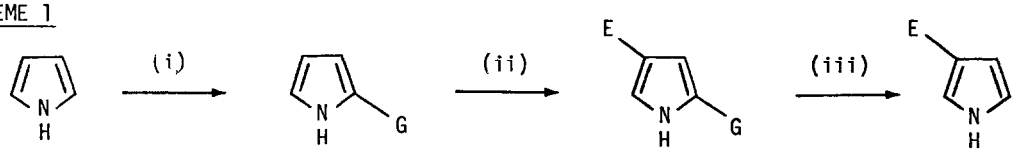
SUMMARY: N-Phenylsulfonylpyrrole undergoes Friedel-Crafts acylation exclusively at the β-position of the pyrrole ring, thus allowing a simple and efficient synthesis of β-acylated pyrroles.

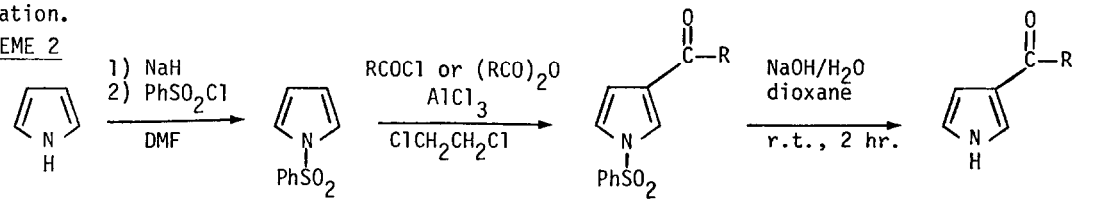
Electrophilic substitution of pyrroles occurs predominantly at the α-position, whereas access to the less favored β-substituted pyrroles has been a stubborn problem in synthetic heterocyclic chemistry[1]. The best method[2] so far is the pathway shown in Scheme 1:

SCHEME 1



The essence of this pathway is the introduction of an electron-withdrawing group at the α-position (step i) followed by electrophilic substitution of the intermediate (step ii) and the removal of the α-substituent (step iii). However, each of the three steps has its own limitations[2,3]. An alternative approach based on the photochemical addition of pyrroles and aliphatic carbonyl compounds has been reported[4]. However, pyrrole itself appeared to be reluctant to react in such photoadditions. In this communication we describe a new and efficient method of preparing β-acylpyrroles, involving an unprecedented regiospecific Friedel-Crafts acylation.

SCHEME 2

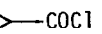


I II III IV

The key to the present method, shown in Scheme 2, is the use of a phenylsulfonyl group[5,6] on the annular nitrogen atom in the acylation step. The phenylsulfonyl substituent serves two purposes: it deactivates the α-position (relative to the β-position) and suppresses the formation of diacylated products during the Friedel-Crafts acylation step. Aluminum chloride catalyzed acylations of N-phenylsulfonylpyrrole (II) with various acylating agents exclusively produced β-substituted pyrroles in quantitative yields. [Traces (~1:500) of the α-acylated pyrroles could be detected only by careful HPLC of the total crude reaction products.] The final step, removal of the phenylsulfonyl group, is simple and efficient. Mild basic hydrolysis of the β-acylated N-phenylsulfonylpyrroles (III) produced β-acylated N-H-pyrroles (IV) quantitatively (Table I).

TABLE I

Aluminum Chloride Catalyzed Acylations of N-Phenylsulfonylpyrrole[a]

RUN	ACYLATING AGENT	% YIELD III[b] (m.p., °C)	% YIELD IV[b] (m.p., °C)
1	$(CH_3CO)_2O$	99 (97-99)	93 (112-114)
2	CH_3COCl	98 (97-99)	
3	PhCOCl	97 (70-72)	98 (96-97)
4		99 (84-86)	97 (104-105)
5	$Cl(CH_2)_3COCl$	98 (69-71)	84 (104-105)[c]
6	Succinic anhydride	96 (121-123)	84 (173-175)

a Run in 1,2-dichloroethane at 25° for 1-2 hr. with 1.1 eq. of acyl chloride and 1.2 eq. of $AlCl_3$ or 3 eq. of acid anhydride and 6 eq. of $AlCl_3$.

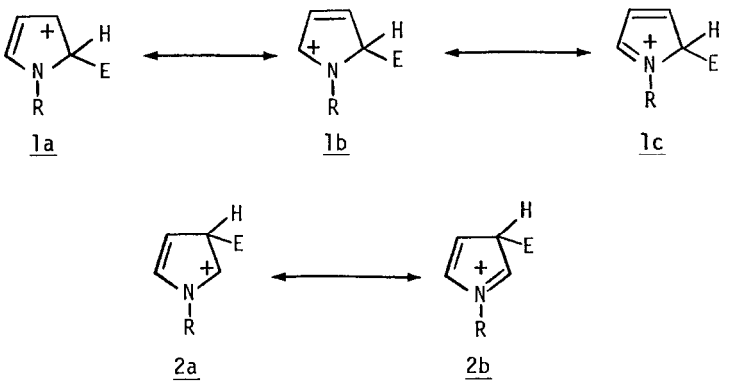
b Isolated yields; all new compounds gave satisfactory elemental analyses.

c During the hydrolysis a concomitant cyclization to the cyclopropyl ketone of run 4 occurred.

The remarkable regiospecificity in the Friedel-Crafts acylation step as well as high overall yield recorded here clearly constitute a method of choice for the synthesis of β-acylated pyrroles. By simple manipulation of the carbonyl function, this method opens the way to the synthesis of a wide variety of β-substituted pyrroles.

The mechanism of this Friedel-Crafts acylation and the role of the phenylsulfonyl group are not yet known with certainty. We have considered several possible explanations which might account for the observed regiospecificity. The relative stabilities of the two σ-complexes 1 and 2 (Scheme 3) have been claimed to control orientation of electrophilic substitution of pyrrole[1], and the overwhelming α-substitution observed in the literature is explained by the energetically more favored σ-complex 1.

SCHEME 3



CNDO/2 calculations on the six conformers (rotation around the N-S bond) for both the α- and β-protonated N-phenylsulfonylpyrroles 1a and 2a (R = $PhSO_2$ and E = H), respectively, clearly indicate that the σ-complex 1a is the more stable (Table II). The above analysis seems to indicate that the relative stabilities of the σ-complexes would not provide an explanation of the observed β-substitution in our case.

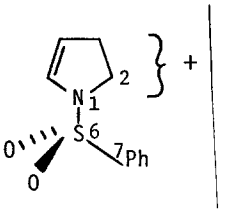
TABLE II

Relative Stabilities of the Conjugate Acids of N-Phenylsulfonylpyrrole[a]

NUMBER	DIHEDRAL ANGLES (degree)[b]	RELATIVE ENERGIES (Kcal/mole)	
		1a	2a
1	0	1.64	5.76
2	60	0[c]	7.89
3	90	0.16	6.70
4	120	0.92	5.03
5	150	0.51	4.96[c]
6	180	0.04	5.31

[a] Relative energies obtained from CNDO/2 calculations using the Merck Molecular Modeling System[7].

[b] The dihedral angle is defined in terms of atoms 2-1-6-7.



[c] Minimum energy conformations.

It could be argued that, owing to the steric hindrance of the phenylsulfonyl group, substitution occurs at the less hindered β-position. However, we feel that such a steric argument alone would be insufficient to explain the pronounced regiospecificity[8].

Thus, in the search for a better rationale for this regiospecificity we have calculated MO properties of pyrroles. Table III shows that N-phenylsulfonylpyrrole has a large dipole moment, suggesting that the unusual regiospecificity of its Friedel-Crafts acylation may be primarily controlled by the polarizability or "hardness" of the electrophile. The reaction of N-phenylsulfonylpyrrole with "hard" electrophiles could be "charge-controlled" and occurs predominantly at the β-position due to its greater atomic charge (Table III). For "softer" electrophiles, the α-position would be the more reactive, as the reaction becomes "frontier-controlled"[1(b),8]. Follow-up on this idea as well as the question of acid-mediated rearrangement of acylpyrroles[9] and synthetic applications will be discussed in detail in subsequent papers.

TABLE III

Calculated Ground State Molecular Properties
of N-Substituted Pyrroles[a]

SUBSTITUENT	HOMO			ATOMIC CHARGE DENSITIES (net charges)		DIPOLE MOMENT
	a.u.	coefficients				
		C(α)	C(β)	C(α)	C(β)	(D)
H	-0.435	0.56	0.38	0.038	-0.048	1.98
$C_6H_5SO_2$	-0.450	0.59	0.38	0.050	-0.040	5.38

[a] These data obtained from CNDO/3 calculations[b] using Bak's geometry[10] for the pyrrole nucleus and standard geometries for the substituent.
[b] CNDO/3 calculations performed using the Merck Molecular Modeling System[7]. CNDO/2 calculations for N-phenylsulfonylpyrrole did not converge.

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