A Facile Synthesis of 3-Acyl-1-alkylpyrroles

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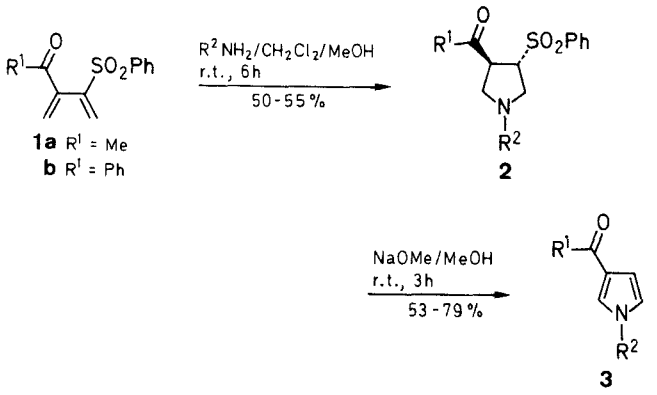
The title compounds **3** were synthesized in good yield by the reaction of dienes **1** with primary aliphatic amines followed by treatment with sodium methoxide.

Acylpyrroles are intermediates of considerable importance, and hence numerous synthetic methods for their synthesis have been developed. The 2-acylpyrroles are readily prepared by direct acylation of pyrrole derivatives.[1,2] The 3-acylpyrroles are less easily obtained.[3] Three different approaches have been utilized with varying degrees of success. The first one requires the introduction of an electron-withdrawing group at the 2-position which directs the subsequent acylation at C-4. Removal of the C-2 substituent then gives the desired 3-acylpyrroles.[4] In the second approach a substituent is introduced on the nitrogen atom of the pyrrole to exert either a steric[5] or an electronic[6] effect to achieve selective C-3 acylation. The third approach consists of an acid-catalyzed rearrangement of 2-acyl-1-alkylpyrroles to the corresponding 3-acylpyrroles.

All the above methods for the synthesis of 3-acylpyrroles start with suitable pyrrole derivatives themselves. We now describe a new synthesis of 3-acylpyrroles by a [4 + 1] annulation reaction[8] of an electron-deficient diene with an aliphatic amine. The dienes **1** were prepared by the 3-chloroperoxybenzoic acid (MCPBA) oxidation of the corresponding sulfides.[9] It should be noted that diene **1** readily undergoes dimerization in the neat form at room temperature, but can be stored as a dilute solution in dichloromethane in the freezer. Treatment of **1** with 1 equivalent of a primary aliphatic amine in dichloromethane/methanol (1:1) at room temperature gave the pyrrolidine intermediate **2** which were shown by ^{1}H-NMR to have the *trans* configuration (Table). Although pyrrolidines **2a**, **2b**, and **2e** were purified by chromatography and fully characterized, for preparative purpose it is better to use the crude **2** for the next step, because severe decomposition of **2** occurred during column chromatography. Dehydrosulfonylation of **2** with sodium methoxide followed by air oxidation during workup gave directly the desired 3-acyl-1-alkylpyrroles **1** in good yield. As shown in the Table a variety of aliphatic primary amines could be successfully used.



2,3	R^1	R^2	2,3	R^1	R^2
a	Me	Bu	**e**	Me	$PhCH_2$
b	Me	*i*-Bu	**f**	Me	$CH_2(CH_2)_2OH$
c	Me	*s*-Bu	**g**	Ph	*i*-Bu
d	Me	*t*-Bu	**h**	Ph	*t*-Bu

In summary, we have developed a facile synthesis of 1-acyl-3-alkylpyrroles **3** by utilizing a [4 + 1] annulation reaction of primary aliphatic amines with the highly

Table. Dienes **1**, Pyrrolidines **2** and 3-Acyl-1-alkylpyrroles **3** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (12 eV) m/z (%)
1a	65	$C_{12}H_{12}O_3S$ (236.3)	1695, 1308, 1144	2.30 (s, 3H), 6.00 (m, 2H), 6.35 (s, 1H), 6.75 (s, 1H), 7.50–8.10 (m, 5H)	236 (M^+, 27), 160 (100)
1b	80	$C_{17}H_{14}O_3S$ (298.4)	1674, 1307, 1144	5.70 (s, 1H), 6.1 (s, 1H), 6.3 (s, 1H), 6.60 (s, 1H), 7.10–7.90 (m, 10H)	298 (M^+, 20), 105 (100)
2a	50	$C_{16}H_{23}NO_3S$ (309.4)	1716	0.85 (t, 3H, J = 7), 1.10–1.55 (m, 4H), 2.10 (s, 3H), 2.35 (m, 2H), 2.40–3.20 (m, 4H), 3.60 (dt, 1H, J = 7.8, 6), 4.30 (dt, 1H, J = 8.5, 6), 7.55–8.10 (m, 5H)	309 (M^+, 11), 124 (100)
2b	55	$C_{16}H_{23}NO_3S$ (309.4)	1716	0.85 (d, 6H, J = 7), 1.20 (m, 1H), 2.10 (s, 3H), 2.20 (m, 2H), 2.50–3.20 (m, 4H), 3.55 (dt, 1H, J = 7.8, 6), 4.20 (dt, 1H, J = 8.5, 6), 7.50–8.10 (m, 5H)	309 (M^+, 2), 49 (100)
2e	55	$C_{19}H_{21}NO_3S$ (343.4)	1716	2.10 (s, 3H), 2.50–3.15 (m, 4H), 3.60 (m, 3H), 4.25 (dt, 1H, J = 8.5, 6), 7.35 (br s, 5H), 7.55–8.10 (m, 5H)	343 (M^+, 6), 158 (100)
3a	60	$C_{10}H_{15}NO$ (165.2)	1651, 1529	0.90 (t, 3H, J = 7), 1.10–1.70 (m, 4H), 2.30 (s, 3H), 3.85 (t, 2H, J = 7), 6.60 (m, 2H), 7.25 (m, 1H)	165 (M^+, 100), 150 (49)
3b	53	$C_{10}H_{15}NO$ (165.2)	1653, 1533	0.90 (d, 6H, J = 7), 1.90 (m, 1H), 2.30 (s, 3H), 3.70 (d, 2H, J = 7), 6.55 (m, 2H), 7.25 (m, 1H)	165 (M^+, 90), 150 (100)
3c	58	$C_{10}H_{15}NO$ (165.2)	1655, 1529	0.90 (t, 3H, J = 7), 1.40 (d, 3H, J = 7), 1.70 (m, 2H), 2.30 (s, 3H), 3.80 (m, 1H),6.55 (m, 2H), 7.25 (m, 1H)	165 (M^+, 100), 150 (76)
3d	60	$C_{10}H_{15}NO$ (165.2)	1655, 1527	1.55 (s, 9H), 2.40 (s, 3H), 6.60 (m, 1H), 6.80 (m, 1H), 7.50 (m, 1H)	165 (M^+, 100), 94 (75)
3e	55	$C_{13}H_{13}NO$ (199.3)	1655, 1529	2.40 (s, 3H), 5.10 (s, 2H), 6.65 (m, 2H), 7.00–7.50 (m, 6H)	199 (M^+, 100), 150 (49)
3f	56	$C_9H_{13}NO_2$ (167.2)	3396, 1651, 1531	2.00 (m, 2H), 2.30 (s, 1H), 2.35 (s, 3H), 3.60 (t, 2H, J = 7), 4.00 (t, 2H, J = 7), 6.65 (m, 2H), 7.35 (m, 1H)	167 (M^+, 100), 152 (79)
3g	79	$C_{15}H_{17}NO$ (227.3)	1631, 1525	0.90 (d, 6H, J = 7), 1.90 (m, 1H), 3.75 (t, 2H, J = 7), 6.60 (m, 2H), 7.25 (m, 1H), 7.40–7.90 (m, 5H)	227 (M^+, 100), 150 (21)
3h	76	$C_{15}H_{17}NO$ (227.3)	1633, 1522	1.55 (s, 9H), 6.65 (m, 1H), 6.85 (m, 1H), 7.40–7.90 (m, 6H)	227 (M^+, 100), 171 (43)

[a] Yield of isolated product after chromatography. The yield of **3** refers to the overall yield from **1** without prior purification of **2**.
[b] Satisfactory HRMS obtained.

electron-deficient dienes **1**. This new synthetic method has the advantages of easy access of starting materials and simple and mild reaction conditions. Some alkyl substituents on the nitrogen may also serve as protective groups.

Silica gel Merck (60 H) was used for flash column chromatography. All reagents were of reagent grade and were purified prior to use.

The following instruments were used for recording the spectral data. IR: Analect RFX-65 FT-IR spectrophotometer; NMR: Varian EM 360 spectrometer; MS: JEOL JMD-100 spectrometer; HRMS: JEOL JMS-HX 110 spectrometer.

2-Acyl-3-phenylsulfonyl-1,3-butadienes 1a,b: General Procedure:
To a solution of 2-acetyl- or 2-benzoyl-3-(phenylthio)-1,3-butadiene[8] (1.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C is added dropwise a solution of MCPBA (0.50 g, 2.88 mmol, 2.4 equiv) in CH_2Cl_2 (5 mL). After stirring for 1 h at 0 °C and 1 h at r.t., the mixture is washed with 5% aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), and evaporated. The crude product is purified by flash chromatography on silica gel using hexane/EtOAc (1:1) as eluent.

***N*-Substituted 3-Acyl-4-phenylsulfonylpyrrolidines 2; General Procedure:**
To a solution of diene **1a/1b** (1.0 mmol) in CH_2Cl_2 (3 mL) and MeOH (3 mL) at r.t. is added the required amine (1.2 mmol). After stirring for 6 h, the solvent is evaporated, and the crude product is purified by flash chromatography on silica gel using hexane/EtOAc (1:1) as eluent to give the *trans* diastereoisomers **2**.

3-Acylpyrroles 3; General Procedure:
The crude product **2** (0.80 mmol) is disssolved in MeOH (5 mL), and NaOMe (4 mmol) is then added. The mixture is stirred for 3 h at r.t., and CH_2Cl_2 (30 mL) is added. The organic solution is washed with water (2 × 10 mL), dried ($MgsO_4$), and evaporated. The crude product is purified by flash chromatography on silica gel using hexane/EtOAc (1:1) as eluent to give **3**.

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