A New Preparation of Functionalized 3-Alkanoylpyrroles and 7-Oxoisoindoles

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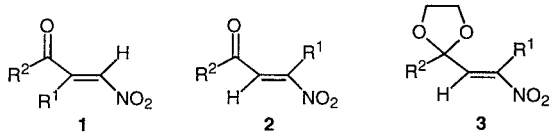
Reaction of the ethylene acetals of β-nitroenones **3** with isocyanoacetates followed by acidic hydrolysis allowed the synthesis of 3-alkanoylpyrrole-2-carboxylates **9a–f** and 7-oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylates **9g–i** in good yield. 3-Alkanoyl-4-nitropyrroles **11a,b** were obtained using **3** and tosylmethyl isocyanide.

Conjugated nitroalkenes are important synthetic intermediates which act as excellent Michael acceptors.[1] Addition of isocyanoacetates or tosylmethyl isocyanide (TosMIC) to nitroalkenes followed by ring closure to the isocyano carbon allowed the preparation of pyrrole-2-carboxylates[2,3] and 3-nitropyrroles,[4,5] respectively. These compounds have proved to be biologically active compounds and useful key intermediates for the preparation of natural products, among which are the porphyrins.[6]

We have reported preparations[7] and numerous synthetic applications[8] of β-nitroenones **1**. We showed that these compounds undergo Michael addition reaction on the nitroalkene function with various nucleophiles (e.g. alkoxides, thiolates, enolates). A positional reversal compared to α,β-enones took place; all these nucleophiles added α to the carbonyl group, generally in good yield.

Only polymeric materials were obtained when β-nitroenones **1** were allowed to react with isocyanoacetates or tosylmethyl isocyanide. Therefore, it appeared worthwhile to study the behavior of β-nitroenones **2**, possessing a hydrogen on the carbon α to the carbonyl group, towards these isocyano derivatives. Thus, reaction of **2** with isocyanoacetates or tosylmethyl isocyanide should allow the preparation of 3-alkanoyl-substituted pyrroles **9** and **11** (see Schemes 2 and 3).

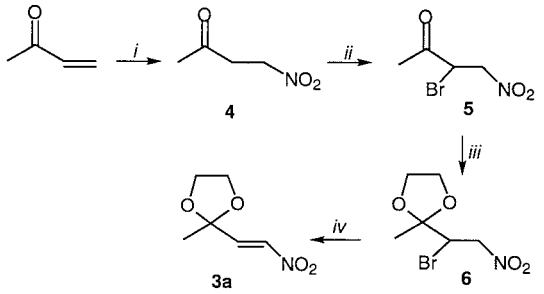


1 **2** **3**

Over the last decades, several methods have been described for the preparation of 2- and/or 5-unsubstituted 3-alkanoylpyrroles which allow further reactions for the preparation of porphyrins and related structures: (i) addition of tosylmethyl isocyanide to α,β-unsaturated ketones;[9] (ii) condensation of aminoacetaldehyde with acylpyruvates;[10] (iii) reaction of 1,3-dicarbonyl compounds with β-nitrostyrene followed by treatment with ammonia;[11] (iv) blocking of the pyrrole nitrogen with bulky and/or electron-withdrawing substituents (*t*-$BuMe_2Si$, i-Pr_3Si, $SO_2C_6H_5$), acylation and removal of the protecting group;[12] (v) using protecting substituents on the 2-position of the pyrrole ring directing the acylation reaction on position 4.[13]

The aim of this work is to describe a new and convenient synthesis of compounds **9** and **11**. We first investigated the reaction of tosylmethyl isocyanide and isocyanoacetates with β-nitroenones **2**. Nitropyrroles were obtained only in poor yield: for example, 3-acetyl-4-nitropyrrole **(11a)** was obtained in only 14% yield starting from 4-nitrobut-3-en-2-one (**2a**, R^1=H; R^2=CH_3) and TosMIC at −80 °C in THF. Preparations of 3-alkanoylpyrrole-2-carboxylates were all unsuccessful.

Therefore, we investigated these reactions with ethylene acetals **3**. Compounds **3** were prepared using two different procedures. The ethylene acetals of 1-nitropent-1-en-3-one (**3b**, R^1 = H; R^2 = Et) and of 3-nitrocyclohex-2-en-1-one (**3c**, R^1-R^2 = $-(CH_2)_3-$) were obtained according to Vankar's method.[14] The synthesis of the ethylene acetal of 4-nitrobut-3-en-2-one **(3a)** was achieved as summarized in Scheme 1.



4 **5** **3a** **6**

(i) $NaNO_2$, THF/AcOH (74%); (ii) Br_2, TsOH, CH_2Cl_2 (100%); (iii) $(CH_2OH)_2$, TsOH, C_6H_6, Δ (58%); (iv) Et_3N, CH_2Cl_2, 0 °C (100%).

Scheme 1

Methyl isocyanoacetate **(7a)** is commercially available. Benzyl and decyl isocyanoacetate (**7b** and **7c**) were prepared starting from glycine in 49 and 68% yield, respectively.[3] α-Isocyanoacetates **7** condensed smoothly at room temperature with nitroalkenes **3** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in a tetrahydrofuran/*tert*-butyl alcohol mixture to give compounds **8**. Hydrolysis of the acetal group of **8** with a catalytic amount of concentrated sulfuric acid in acetone in the presence of silica gel[15] yielded the 3-alkanoylpyrrole-2-carboxylates **9a–f** and the 7-oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylates **9g–i** in good overall yields after purification by chromatography (Scheme 2). The better yields obtained with nitroacetal **3c** than with compounds **3a** and **3b** are due to the ease of polymerization of these acyclic substrates under basic conditions and to the difficult addition of the intermediate primary nitronate on the isocyanide function. Results obtained and spectroscopic data of compounds **8** and **9** are reported in the experimental (Tables 1 and 2).

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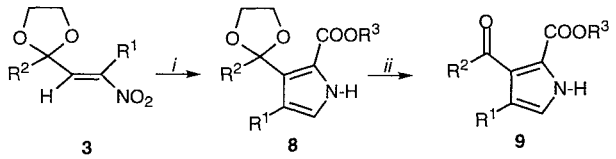
Table 1. 3-Alkanoylpyrrole-2-carboxylate Ethylene Acetals **8a–f** and 7-Oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate Ethylene Acetals **8g–i** Prepared.

Products[a]	Yield (%)	IR ν (cm^{-1})	EI-MS (70 eV) *m/z*	^1HNMR ($CDCl_3$/TMS) δ, *J* (Hz)
8a	57	3313, 1691	211 (M^+), 196, 164, 152, 137, 120, 87	9.22 (s, 1H, NH), 6.79 (dd, 1H, J = 2.7, J' = 2.8, N–C*H*=CH), 6.38 (dd, 1H, J = 2.7, J' = 2.8, N–CH=C*H*), 4.09–3.98 (m, 2H, acetal-CH_2), 3.93–3.84 (m, 2H, acetal-CH_2), 3.87 (s, 3H, $COOCH_3$), 1.96 [s, 3H, $C(OCH_2CH_2O)CH_3$]
8b	47	3345, 1683	287(M^+), 272, 244, 227, 196, 184, 164, 152, 137, 120, 105, 91, 65	9.32 (s, 1H, NH), 7.56–7.29 (m, 5H, aromatic-H), 6.77 (dd, 1H, J = J' = 2.8, N–C*H*=CH), 6.39 (dd, 1H, J = J' = 2.8, N–CH=C*H*), 5.32 (s, 2H, $COOCH_2Ph$), 4.09–3.95 (m, 2H, acetal-CH_2), 3.94–3.82 (m, 2H, acetal-CH_2), 1.85 [s, 3H $C(OCH_2CH_2O)CH_3$]
8c	33	3332, 1687	–	9.20 (s, 1H, NH), 6.80 (dd, 1H, J = J' = 2.7, N–C*H*=CH), 6.39 (dd, 1H, J = J' = 2.7, N–CH=C*H*), 4.29 (t, 2H, J = 6.7, $COOCH_2$), 4.07–4.01 (m, 2H, acetal-CH_2), 3.91–3.86 (m, 2H, acetal-CH_2), 1.87 [s, 3H, $C(OCH_2CH_2O)CH_2$], 1.79–172 (m, 2H, $COOCH_2CH_2$), 1.34–1.21 [m, 14H, $COO(CH_2)_2(CH_2)_7$], 0.90 [t, 3H, J = 6.7, $(CH_2)_9CH_3$]
8d	54	3333, 1692	225 (M^+), 196, 164, 149, 137, 121, 93, 65	9.17 (s, 1H, NH), 6.79 (dd, 1H, J = J' = 2.7, N–C*H*=CH), 6.37 (dd, 1H, J = J' = 2.7, N–CH=C*H*), 4.10–3.96 (m, 2H, acetal-CH_2), 3.91–3.80 (m, 2H, acetal-CH_2), 3.86 (s, 3H, $COOCH_3$), 2.22 (q, 2H, J = 7.3, CH_2CH_3), 0.89 (t, 3H, J = 7.3, CH_2CH_3)
8e	56	3347, 1688	301 (M^+), 272, 166, 137, 91, 65	9.26 (s, 1H, NH), 7.48–7.29 (m, 5H, aromatic-H), 6.74 (dd, 1H, J = J' = 2.7, N–C*H*=CH), 6.35 (dd, 1H, J = J' = 2.7, N–CH=C*H*), 5.29 (s, 2H, $COOCH_2Ph$), 4.05–3.96 (m, 2H, acetal-CH_2), 3.90–3.81 (m, 2H, acetal-CH_2), 2.20 (q, 2H, J = 7.3, CH_2CH_3), 0.87 (t, 3H, J = 7.3, CH_2CH_3)
8f	16	3332, 1689	–	9.18 (s, 1H, NH), 6.78 (dd, 1H, J = J' = 2.8, N–C*H*=CH), 6.36 (dd, 1H, J = J' = 2.8, N–CH=C*H*), 4.25 (t, 2H, J = 6.7, $COOCH_2$), 4.01–3.98 (m, 2H, acetal-CH_2), 3.90–3.86 (m, 2H, acetal-CH_2), 2.21 [q, 2H, J = 7.5 $C(OCH_2CH_2O)CH_2$], 1.74–1.68 (m, 2H, $COOCH_2CH_2$), 1.32–1.21 [m, 14H, $COO(CH_2)_2(CH_2)_7$], 0.92 [t, 3H, J = 7.5, $C(OCH_2CH_2O)CH_2CH_3$], 0.91 [t, 3H, J = 6.7, $(CH_2)_9CH_3$]
8g	81	3329, 1691	237 (M^+), 209, 193, 177, 162, 146	9.18 (s, 1H, NH), 6.62 (d, 1H, J = 2.9, N–CH=C), 4.36–4.29 (m, 2H, acetal-CH_2), 4.13–4.07 (m, 2H, acetal-CH_2), 3.83 (s, 3H, $COOCH_3$), 2.56–2.50 (m, 2H, ring-CH_2), 1.96–1.88 (m, 2H, ring-CH_2), 1.87–1.82 (m, 2H, ring-CH_2)
8h	86	3325, 1690	313 (M^+), 285, 269, 222, 194, 177, 162, 150, 134, 118, 91, 77, 64	9.51 (s, 1H, NH), 7.39–7.30 (m, 5H, aromatic-H), 6.52 (d, 1H, J = 2.8, N–CH=C), 5.24 (s, 2H, $COOCH_2Ph$), 4.01–3.96 (m, 2H, acetal-CH_2), 3.95–3.89 (m, 2H, acetal-CH_2), 2.49 (t, 2H, J = 5.8, ring-CH_2), 1.90–1.87 (m, 2H, ring-CH_2), 1.86–1.78 (m, 2H, ring-CH_2)
8i	64	3316, 1690	–	9.34 (s, 1H, NH), 6.57 (d, 1H, J = 2.9, N–CH=C), 4.37–4.28 (m, 2H, acetal-CH_2), 4.22 (t, 2H, J = 7.0, $COOCH_2$), 4.13–4.04 (m, 2H, acetal-CH_2), 2.57–2.50 (m, 2H, ring-CH_2), 1.95–1.90 (m, 2H, ring-CH_2), 1.88–1.82 (m, 2H, ring-CH_2), 1.73–1.64 (m, 2H, $COOCH_2CH_2$), 1.37–1.20 [m, 14H, $COO(CH_2)_2(CH_2)_7$], 0.88 [t, 3H, J = 7.0, $(CH_2)_9CH_3$]

[a] Satisfactory microanalyses obtained for all new compounds: C ± 0.42, H ± 0.29, N ± 0.25.



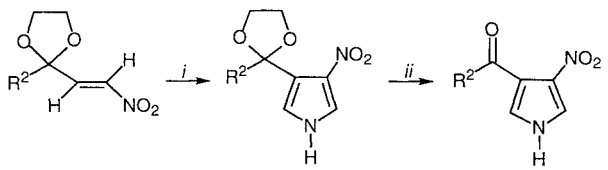
3 8 9

(i) $CNCH_2CO_2R^3$ (**7a** R^3 = Me, **7b** R^3 = Bn, **7c** R^3 = decyl), DBU, THF/*t*-BuOH, r.t.; (ii) H_2SO_4, silica gel, acetone

8, 9	R^1	R^2	R^3	8, 9	R^1	R^2	R^3
a	H	Me	Me	**f**	H	Et	decyl
b	H	Me	CH_2Ph	**g**	$-(CH_2)_3-$		Me
c	H	Me	decyl	**h**	$-(CH_2)_3-$		CH_2Ph
d	H	Et	Me	**i**	$-(CH_2)_3-$		decyl
e	H	Et	CH_2Ph				

Scheme 2

We extended the use of nitroalkenes **3** for the preparation of compounds **11**. The synthesis of pyrroles **10** was conveniently achieved by reaction of **3a** and **3b** with tosylmethyl isocyanide in tetrahydrofuran at −80 °C in the presence of potassium *tert*-butoxide. Cleavage of the acetal group afforded 3-alkanoyl-4-nitropyrroles **11** in excellent yield (Scheme 3).



3a (R^2 = Me) **10a** (98%) **11a** (100%)
3b (R^2 = Et) **10b** (90%) **11b** (100%)

(i) TosMIC, *t*-BuOK, THF, −80 °C; (ii) H_2SO_4, silica gel, acetone

Scheme 3

As mentioned in the literature with β-nitrostyrene bearing a methyl group in the β position, 7-oxo-1-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (**12**) was obtained in 61 % yield

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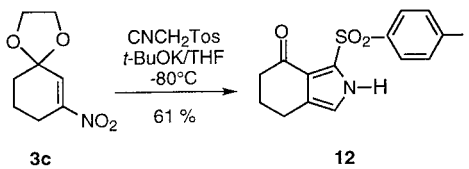
Table 2. 3-Alkanoylpyrrole-2-carboxylates **9a–f** and 7-Oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylates **9g–i** Prepared

Products[a]	Yield (%)	mp (°C)	IR ν (cm^{-1})	MS (70 eV) m/z	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
9a	98	82	3345, 1724, 1648	167 (M^+), 152, 120, 94, 64	9.51 (s, 1H, NH), 6.88 (dd, 1H, $J = J' = 2.7$, N–C*H*=CH), 6.64 (dd, 1H, $J = J' = 2.7$, N–CH=C*H*), 3.90 (s, 3H, $COOCH_3$), 2.64 (s, 3H, CH_3)	196.6 (C=O), 160.3 (COO), 129.9 (pyrrole-C), 121.1 (pyrrole-CH), 112.9 (pyrrole-CH), 52.0 ($COOCH_3$), 30.6 ($COCH_3$)
9b	94		3374, 1722, 1651	243 (M^+), 228, 212, 200, 184, 136, 108, 91, 64	9.61 (s, 1H, NH), 7.47–7.26 (m, 5H, aromatic-H), 6.87 (dd, 1H, $J = J' = 2.8$, N–C*H*=CH), 6.65 (dd, 1H, $J = J' = 2.8$, N–CH=C*H*), 5.35 (s, 2H, $COOCH_2Ph$), 2.60 (s, 3H, $COCH_3$)	197.3 (C=O), 160.1 (COO), 135.7 (aromatic-C), 130.8 (pyrrole-C), 129.1 (pyrrole-C), 128.9 (aromatic-C), 121.8 (aromatic-C), 121.4 (pyrrole-CH), 113.4 (pyrrole-CH), 67.3 ($COOCH_2$), 31.2 ($COCH_3$)
9c	90		3314, 1718, 1666	–	9.60 (s, 1H, NH), 6.88 (dd, 1H, $J = J' = 2.5$, N–C*H*=CH), 6.63 (dd, 1H, $J = J' = 2.5$, N–CH=C*H*), 4.31 (t, 2H, $J = 7.5$, $COOCH_2$), 2.63 (s, 3H, $COCH_3$), 1.79–1.19 [m, 16H, $COOCH_2(CH_2)_8$], 0.88 [t, 3H, $J = 7.5$, $(CH_2)_8CH_3$]	196.8 (C=O), 160.1 (COO), 130.0 (pyrrole-C), 124.3 (pyrrole-C), 121.1 (pyrrole-CH), 112.9 (pyrrole-CH), 65.4 ($COOCH_2$), 32.9 (CH_2), 31.9 (CH_2), 30.8 ($COCH_3$), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.6 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 14.1 [$(CH_2)_9CH_3$]
9d	92		3319, 1723, 1655	181 (M^+), 152, 121, 93, 64	9.90 (s, 1H, NH), 6.91 (dd, 1H, $J = J' = 2.9$, N–C*H*=CH), 6.61 (dd, 1H, $J = J' = 2.9$, N–CH=C*H*), 3.91 (s, 3H, $COOCH_3$), 3.00 (q, 2H, $J = 7.4$, $COCH_2CH_3$), 1.20 (t, 3H, $J = 7.4$, $COCH_2CH_3$)	200.8 (C=O), 161.0 (COO), 133.5 (pyrrole-C), 130.3 (pyrrole-C), 121.9 (pyrrole-CH), 112.8 (pyrrole-CH), 52.4 ($COOCH_3$), 31.7 (CH_2), 8.8 (CH_2CH_3)
9e	97		3312, 1716, 1651	257 (M^+), 228, 200, 166, 150, 91, 65	9.45 (s, 1H, NH), 7.45–7.31 (m, 5H, aromatic-H), 6.85 (dd, 1H, $J = J' = 2.8$, N–C*H*=CH), 6.57 (dd, 1H, $J = J' = 2.8$, N–CH=C*H*), 5.32 (s, 2H, $COOCH_2Ph$), 2.95 (q, 2H, $J = 7.3$, $COCH_2CH_3$), 1.10 (t, 3H, $J = 7.3$, $COCH_2CH_3$)	200.5 (C=O), 159.8 (COO), 135.4 (aromatic-C), 130.4 (pyrrole-C), 128.7 (aromatic-C), 128.5 (aromatic-C), 121.5 (pyrrole-CH), 112.5 (pyrrole-CH), 66.9 ($COOCH_2$), 36.2 ($COCH_2$), 8.3 (CH_3)
9f	94		3321, 1719, 1653	–	9.53 (s, 1H, NH), 6.87 (dd, 1H, $J = J' = 2.7$, N–C*H*=CH), 6.56 (dd, 1H, $J = J' = 2.7$, N–CH=C*H*), 4.29 (t, 2H, $J = 7.5$, $COOCH_2$), 2.99 (q, 2H, $J = 7.5$, $COCH_2CH_3$), 1.83–1.14 [m, 16H, $COOCH_2(CH_2)_8$], 1.16 (t, 3H, $J = 7.5$, $COCH_2CH_3$), 0.88 [t, 3H, $J = 7.5$, $(CH_2)_9CH_2$]	200.6 (C=O), 160.3 (COO), 130.0 (pyrrole-C), 121.2 (pyrrole-C), 120.9 (pyrrole-CH), 112.4 (pyrrole-CH), 65.4 ($COOCH_2$), 36.2 ($COCH_2$), 32.8 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.6 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 14.1 [$(CH_2)_9CH_3$], 8.4 [$COCH_2CH_3$]
9g	93	138	3313, 1728, 1671	193 (M^+), 165, 133, 105, 78, 64	9.87 (s, 1H, NH), 6.77 (d, 1H, $J = 3.0$, N–CH=), 3.91 (s, 3H, $COOCH_3$), 2.80–2.66 (m, 2H, ring-CH_2), 2.60–2.54 (m, 2H, ring-CH_2), 2.13–2.00 (m, 2H, ring-CH_2)	194.6 (C=O), 161.3 (COO), 130.9 (pyrrole-C), 123.4 (pyrrole-C), 121.3 (pyrrole-C), 118.1 (pyrrole-CH), 52.6 ($COOCH_3$), 41.2 ($COCH_2$), 25.0 (CH_2), 22.5 (CH_2)
9h	96	106	3299, 1723, 1661	269 (M^+), 162, 135, 134, 107, 91, 77, 64	10.13 (s, 1H, NH), 7.51–7.45 (m, 2H, aromatic-H), 7.36–7.24 (m, 3H, aromatic-H), 6.70 (d, 1H, $J = 3.0$, N–CH=), 5.34 (s, 2H, $COOCH_2Ph$), 2.73–2.65 (m, 2H, ring-CH_2), 2.57–2.50 (m, 2H, ring-CH_2), 2.08–1.99 (m, 2H, ring-CH_2)	194.7 (C=O), 160.4 (COO), 136.2 (aromatic-C), 130.9 (pyrrole-C), 128.8 (aromatic-C), 128.5 (aromatic-C), 128.4 (aromatic-C), 123.7 (pyrrole-C), 121.2 (pyrrole-C), 118.5 (pyrrole-CH), 67.1 ($COOCH_2$), 41.2 ($COCH_2$), 41.2 ($COCH_2$), 25.0 (ring-CH_2), 22.5 (ring-CH_2)
9i	100		3371, 1721, 1665	–	9.95 (s, 1H, NH), 6.76 (d, 1H, $J = 2.5$, N–CH=), 4.30 (t, 2H, $J = 7.5$, $COOCH_2$), 2.78–2,67 (m, 2H, $COCH_2$), 2.61–2.52 (m, 2H, ring-CH_2), 2.12–1.98 (m, 2H, ring-CH_2), 1.84–1.70 (m, 2H, $COOCH_2CH_2$), 1.48–1.16 [m, 14H, $COO(CH_2)_2(CH_2)_7$], 0.87 [t, 3H, $J = 7.5$, $(CH_2)_9CH_3$]	194.5 (C=O), 161.0 (COO), 130.7 (pyrrole-C), 123.3 (pyrrole-C), 121.8 (pyrrole-C), 118.1 (pyrrole-CH), 65.8 ($COOCH_2$), 41.2 ($COCH_2$), 32.2 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 26.2 (CH_2), 25.1 (ring-CH_2), 23.0 (CH_2), 22.5 (ring-CH_2), 14.5 (CH_3)

[a] Satisfactory microanalyses obtained (C ± 0.39, H ± 0.24, N ± 0.31).

using the same reaction conditions (TosMIC, *t*-BuOK, THF, −80 °C) and 3-nitrocyclohex-2-en-1-one ethylene acetal (**3c**). Surprisingly, deprotection of the acetal group was observed after hydrolysis with water at −40 °C.



3c **12**

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In summary, protected, as well as unprotected, new 3-alkanoylpyrrole-2-carboxylates, 7-oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylates, and 3-alkanoyl-4-nitropyrroles were prepared in two steps from nitroacetals **3**. This methodology affords 2,3- and 3,4-disubstituted pyrroles with electron-withdrawing groups which are difficult to prepare starting from pyrrole. Such 3-alkanoylpyrroles may be useful synthetic intermediates especially for the preparation of cyclopentenoporphyrins[16] or porphyric insecticides.[17]

All experiments, except acetal hydrolysis reactions, were performed under N_2. Commercially available reagents were purchased from Aldrich or Lancaster. Melting points are uncorrected and were taken on a Tottoli apparatus. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM 400 or Bruker AC 250 spectrometers and the chemical shifts are reported as δ values with units of ppm. ^1H NMR spectra are referenced to TMS at 0.00 ppm as an internal standard and ^{13}C NMR spectra are referenced to $CDCl_3$ at 77.00 ppm or DMSO-d_6 at 40.00 ppm. IR spectra were recorded as thin films between NaCl plates or as KBr disks on a Mattson Genesis Series FTIR. MS were taken on a FISON MD 800 at an ionizing potential of 70 eV and maintaining a source temperature of 200 °C. All reactions were monitored by TLC carried out on Macherey-Nagel SIL G/UV_{254} silica gel plates. Separations were accomplished by column chromatography on silica gel 60 (70–230 mesh) at normal pressure. All organic solvents were appropriately dried and purified before use.

4-Nitrobutan-2-one (4):
4-Nitrobutan-2-one was prepared by 1,4-addition of $NaNO_2$ to methyl vinyl ketone according to the procedure of Miyakoshi and co-workers.[18]

3-Bromo-4-nitrobutan-2-one (5):
To a stirred solution of 4-nitrobutan-2-one (**4**, 8.0 g, 68 mmol) and a catalytic amount of TsOH · H_2O (130 mg, 0.68 mmol) in CH_2Cl_2 (80 mL) was added bromine (10.94 g, 68 mmol) dropwise at r.t. After 20 min, the mixture was poured into iced water (50 mL) and extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and the solvent was removed at reduced pressure to leave 13.32 g (quantitative) of an oil which was used without purification for the acetalization step.

IR (neat): ν = 1722 (C=O), 1558 (NO_2), 1368 (NO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.09 (dd, 1 H, J = 15.0, 8.5 Hz, CH–NO_2), 4.87 (dd, 1 H, J = 8.5, 4.9 Hz, CH–Br), 4.68 (dd, 1 H, J = 15.0, 4.9 Hz, CH–NO_2), 2.49 (s, 3 H, CH_3).

3-Bromo-4-nitrobutan-2-one Ethylene Acetal (6):
Product **5** (6.5 g, 33 mmol) was placed in a 100 mL three-necked flask equipped with a Dean–Stark apparatus and condenser. Benzene (50 mL), ethylene glycol (15.4 g, 0.249 mol) and TsOH · H_2O (63 mg, 0.33 mmol) were added and the mixture was refluxed for 24 h. After cooling, the mixture was treated with satd aq $NaHCO_3$ (50 mL). The organic layer was separated and washed with brine (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude oil obtained, containing **6** and **3a**, was filtered over silica gel (eluent: EtOAc/hexane 10/90) and used immediately in the next step.

4-Nitrobut-3-en-2-one Ethylene Acetal (3a):
Complete elimination of hydrobromic acid was realized by treatment of the previous mixture (1.77 g, 7.38 mmol) with Et_3N (782 mg, 7.75 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After disappearance of the starting bromonitroacetal (TLC), the reaction mixture was diluted with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (eluent: EtOAc/hexane 8/92) to give 1.17 g (100 %) of pure (*E*)-**3a**.

IR (neat): ν = 1652 (C=C), 1532 (NO_2), 1355 (NO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.15 (d, 1 H, J = 13.0 Hz, CH=C*H*–NO_2), 7.05 (d, 1 H, J = 13.0 Hz, C*H*=CH–NO_2), 4.12–4.01 (m, 2 H, acetal-CH_2), 3.96–3.86 (m, 2 H, acetal-CH_2), 1.56 (s, 3 H, CH_3).

1-Nitropent-1-en-3-one Ethylene Acetal (3b):
According to the procedure of Vankar and Bawa,[14] compound **3b** was prepared by nitromercuration of pent-1-en-3-one ethylene acetal followed by elimination with 2.5 N aq NaOH. The crude product obtained was purified by flash chromatography (EtOAc/hexane 10:90) to give 1.210 g (overall yield from pentan-3-one 18 %) of **3b** as a pale yellow oil.

IR (neat): ν = 1650 (C=C), 1520 (NO_2), 1437 (C=C), 1345 NO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.13 (d, 1 H, J = 13.0 Hz, CH=CH–NO_2), 7.02 (d, 1 H, J = 13.0 Hz, C*H*=CH–NO_2), 4.10–3.90 (m, 4 H, acetal-CH_2), 1.81 (q, 2 H, J = 7.0 Hz, CH_2), 0.96 (t, 3 H, J = 7.0 Hz, CH_3).

3-Nitrocyclohex-2-en-1-one Ethylene Acetal (3c):
The ethylene acetal of nitrocyclohexenone **3c** has previously been described by Vankar.[14]

3-Alkanoylpyrrole-2-carboxylate Ethylene Acetals 8a–f and 7-Oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate Ethylene Acetals 8g–i; General Procedure:
DBU (0.164 g, 1.08 mmol) was added dropwise to a stirred solution of isocyanide **7** (1.08 mmol) in a mixture of THF and *t*-BuOH (1:1, 5 mL) at r.t. After 5 min, a solution of the nitroacetal **3** (1.08 mmol) in the same mixture of solvents (8 mL) was added over a period of 20 min. The resulting solution was kept at r.t. until disappearance of the starting materials (TLC) and was then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: EtOAc/hexane 8:92) to give the desired compounds **8**.

3-Alkanoylpyrrole-2-carboxylates 9a–f and 7-Oxo-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylates 9g–i; General Procedure:
To a mixture of compound **8** (0.46 mmol) and silica gel (1 g) in acetone (4 mL) was added a catalytic amount of concd H_2SO_4. The mixture was stirred at r.t. until disappearance of the starting materials (TLC). The silica gel was then filtered off. The filtrate was washed with 5 % aq $NaHCO_3$ (25 mL) and dried ($MgSO_4$) and concentrated to afford crude compounds **9**, which were purified by chromatography on silica gel (eluent: EtOAc/hexane 10:90). Spectroscopic data for products **8** and **9** are collected in Tables 1 and 2.

3-Alkanoyl-4-nitropyrrole Ethylene Acetals 10a–b; General Procedure:
Tosylmethyl isocyanide (0.222 g, 1.14 mmol) in THF (4 mL) was added dropwise to a stirred solution of *t*-BuOK (0.307 g, 2.74 mmol) in THF (9 mL) at −80 °C. After stirring for 15 min at −80 °C, a solution of nitroacetal **3** (1.26 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 1 h while the temperature was allowed to rise to −40 °C. The reaction was then quenched with water (15 mL). The reaction mixture was extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated.

3-Acetyl-4-nitropyrrole Ethylene Acetal (**10a**):
After workup, the crude product was purified by column chromatography on silica gel (eluent: EtOAc/hexane 40:60) to give 0.24 g (98 %) of **10a** as a colorless powder; mp 197 °C.

IR (KBr): ν = 3279 (NH), 1471 (NO_2), 1364 (NO_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.80 (s, 1 H, NH), 7.80 [s, 1 H, CH=C(NO_2)], 6.78 (s, 1 H, CH), 4.00–3.91 (m, 2 H, acetal-CH_2), 3.78–3.73 (m, 2 H, acetal-CH_2), 1.73 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 123.6 (pyrrole-CH), 121.6 (pyrrole-C), 119.2 (pyrrole-CH), 106.7 [*C*(OCH_2CH_2O)], 64.7 [C(*O*CH_2CH_2O)], 26.0 (CH_3).

EI-MS (70 eV): m/z (%) = 198 (M^+, 1), 183 ($M^+ - CH_3$, 100), 139 ($M^+ - CH_3 - OCH_2CH_2$, 50), 123 ($M^+ - CH_3 - OCH_2CH_2O$, 9), 109 ($M^+ - NO_2 - CH_3 - CH_2CH_2$, 6), 93 ($M^+$

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$-NO_2-OCH_2CH_2-CH_3$, 18), 87 [$C(OCH_2,CH_2O)CH_3$, 10], 65 (pyrrole, 8).

Anal. ($C_8H_{10}N_2O_4$): Calcd C, 48.49; H, 5.09, N, 14.14. Found C, 48.47; H, 4.99; N, 14.07.

4-Nitro-3-propanoylpyrrole Ethylene Acetal **(10b):**
The crude product was purified by column chromatography on silica gel (eluent: EtOAc/hexane 40:60) to give 0.24 g (90%) of **10b** as a colorless powder; mp 164°C.

IR (KBr): ν = 3249 (NH), 1478 (NO_2), 1352 (NO_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.84 (s, 1H, NH), 7.86 [br s, 1H, CH=C(NO_2)], 6.78 (br s, 1H, CH), 3.97–3.85 (m, 2H, acetal-CH_2), 3.81–3.69 (m, 2H, acetal-CH_2), 2.09 (q, 3H, J = 7.4 Hz, CH_2), 0.80 (t, 3H, J = 7.4 Hz, CH_3).

^{13}C NMR (DMSO-d_6): δ = 134.4 (pyrrole-C), 124.0 (pyrrole-CH), 121.1 (pyrrole-C), 120.4 (pyrrole-CH), 109.5 [*C*(OCH_2CH_2O)], 65.4 [C(*OCH*$_2$*CH*$_2$O)], 31.7 (CH_2), 8.4 (CH_3).

EI-MS (70 eV): m/z (%) = 212 (M^+, 1), 183 ($M^+-CH_2CH_3$, 100), 139 ($M^+-CH_2CH_3-OCH_2CH_2$, 40), 101 [$CH_3CH_2C(OCH_2CH_2O)$, 2], 93 [$M^+-NO_2-CH_3CH_2(OCH_2CH_2)$, 15], 65 (pyrrole, 7).

Anal. ($C_9H_{12}N_2O_4$): Calcd C, 50.94; H, 5.70; N, 13.20. Found C, 50.71; H, 5.93; N, 13.17.

3-Alkanoyl-4-nitropyrroles 11a–b:
Acetals **10** were treated as described above to afford 3-alkanoyl-4-nitropyrroles **11** which were chromatographed on silica gel (eluent: EtOAc/hexane 50:50).

3-Acetyl-4-nitropyrrole **(11a):**
The crude product was purified by column chromatography on silica gel (eluent: EtOAc/hexane 50:50) to give 0.189 g (100%) of **11a** as a colorless powder; mp 152°C.

IR (KBr): ν = 3235 (NH), 1726 (C=O), 1463 (NO_2), 1346 (NO_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 12.30 (s, 1H, NH), 7.92 [d, 1H, J = 1.7 Hz, CH=C(NO_2)], 7.58 (d, 1H, J = 1.7 Hz, CH), 2.41 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 192.7 (C=O), 134.5 (pyrrole-C), 124.8 (pyrrole-CH), 122.5 (pyrrole-CH), 119.5 (pyrrole-C), 28.3 (CH_3).

EI-MS (70 eV): m/z (%) = 154 (M^+, 30), 139 (M^+-CH_3, 100), 123 (M^+-CH_3-O, 9), 93 ($M^+-CH_3-NO_2$, 35), 65 (pyrrole, 20).

Anal. ($C_6H_6N_2O_3$): Calcd C, 46.76; H, 3.92; N, 18.18. Found C, 46.80; H, 3.70; N, 18.10.

4-Nitro-3-propanoylpyrrole **(11b):**
The crude product was purified by column chromatography on silica gel (eluent: EtOAc/hexane 50:50) to give 0.190 g (100%) of **11b** as a colorless powder; mp 132°C.

IR (KBr): ν = 3228 (NH), 1725 (C=O), 1499 (NO_2), 1364 (NO_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 12.28 (s, 1H, NH), 7.93 [d, 1H, J = 2.2 Hz, CH=C(NO_2)], 7.55 (d, 1H, J = 2.2 Hz, CH), 3.80 (q, 2H, J = 7.2 Hz, CH_2), 1.04 (t, 3H, J = 7.2 Hz, CH_3).

^{13}C NMR (DMSO-d_6): δ = 195.4 (C=O), 134.4 (pyrrole-C), 124.7 (pyrrole-CH), 123.3 (pyrrole-CH), 119.6 (pyrrole-C), 34.2 (CH_2), 8.3 (CH_3).

EI-MS (70 eV): m/z (%) = 168 (M^+, 3), 139 ($M^+-CH_2CH_3$, 100), 93 ($M^+-CH_2CH_3-NO_2$, 16), 65 (pyrrole, 12).

Anal. ($C_7H_8N_2O_3$): Calcd C, 50.00; H, 4.80; N, 16.66. Found C, 50.14; H, 4.69; N, 16.70.

7-Oxo-1-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (12):
The reaction was carried out as above using *t*-BuOK (265 mg, 2.36 mmol), tosylmethyl isocyanide (192 mg, 0.98 mmol), and 3-nitrocyclohex-2-en-1-one ethylene acetal (**3c**, 200 mg, 1.08 mmol) in THF at −80°C. Chromatography on silica gel (eluent: CH_2Cl_2) gave 190 mg (61%) of **12** as a colorless powder; mp 233°C.

IR (KBr): ν = 3328 (NH), 1663 (C=O), 1436 (C=C), 1319 (SO_2), 1142 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.70 (s, 1H, NH), 8.06 (d, 2H, J = 8.3 Hz, aromatic-H), 7.30 (d, 2H, J = 8.3 Hz, aromatic-H), 6.77 (d, 1H, J = 2.5 Hz, pyrrole-H), 2.68 (t, 2H, J = 6.1 Hz, $COCH_2$), 2.46 (t, 2H, J = 6.1 Hz, CH_2C=CH), 2.40 (s, 3H, CH_3), 2.06–1.98 (m, 2H, $COCH_2CH_2$).

^{13}C NMR ($CDCl_3$): δ = 193.1 (C=O), 144.5 (pyrrole-C), 137.2 (aromatic-C), 130.6 (pyrrole-C), 129.3 (aromatic-C), 128.6 (aromatic-C), 127.4 (aromatic-C), 121.6 (pyrrole-C), 117.2 (pyrrole-CH), 39.6 ($COCH_2$), 24.4 (ring-CH_2), 21.7 (ring-CH_2), 21.6 (CH_3).

EI-MS (70 eV): m/z (%) = 289 (M^+, 6), 281 (M^+ −isoindole-H, 29), 219 ($M^+-(CH_2)_3CO$, 66), 204 ($M^+-(CH_2)_3CO-CH_3$, 100), 133 (M^+ −Tos−H, 14), 70 [$(CH_2)_3CO$, 54].

Anal. ($C_{15}H_{15}NO_3S$): Calcd C, 62.27; H, 5.23; N, 4.84; S, 11.08. Found C, 62.01; H, 5.30; N, 5.02; S, 11.0.

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