Tetrahedron Vol. 46, No. 21, pp. 7587-7598, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

A USEFUL SYNTHESIS OF PYRROLES FROM NITROOLEFINS

Derek H. R. Barton[a,c], Jocelyne Kervagoret[b,c], and Samir Z. Zard* [b,c]

a) Department of Chemistry, Texas A & M University, College Station, Texas U.S.A
b) Laboratoire de Synthèse Organique, Ecole Polytechnique, 91128 Palaiseau, France
c) Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-Sur-Yvette, France

(*Received in USA* 5 *February* 1990)

Abstract : *Nitroolefins or β–acetoxy-nitro compounds react with α– isocyano-esters in the presence of an organic base to give pyrroles in good yield.*

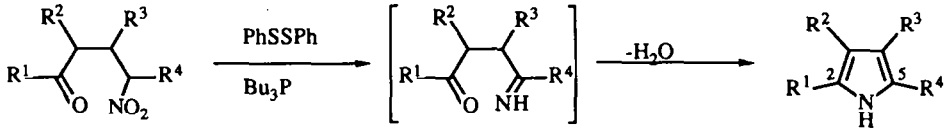
Porphyrins and bile pigments are of paramount importance among natural and unnatural products containing pyrrole subunits. Porphyrins in particular have been at the centre of numerous and wide ranging studies related to, *inter alia*, photosynthesis, electron transfer, oxygen transport, vitamin B12 biosynthesis as well as catalytic systems based on its chemistry, activation of hydrocarbons using mimics of cytochrome P450, and so on and so forth[1]. Metalloporphyrins isolated from soil samples represent "biological markers" in the geochemical study of petroleum and shales[2]. In addition to all these crucially important areas of research, some porphyrins have found promising use in the photodynamic treatment of certain types of cancer. This therapeutic approach is based on the observation that some cancerous cells tend to accumulate more of the porphyrinic compound than normal cells, and can therefore be selectively destroyed by singlet oxygen produced by irradiation with a suitable laser beam[3].

In the light of the foregoing introductory comments, it is not surprising that a vast amount of work has and is being devoted to the development of practical methods for the synthesis of pyrrole building blocks containing appropriate substitution patterns[4]. In the context of porphyrins and bile acid pigments, the most popular procedures have so far been based on the Paal-Knorr reaction and related variants involving the reaction of α-amino ketones (normally generated *in situ* by reduction, usually with zinc dust, of the α-keto-oxime) with ß-ketoesters or ß-diketones[1,4]. Although experimentally such reactions are often capricious in inexperienced hands, the procedures for obtaining some of the more important pyrrole units for porphyrin synthesis have been optimized and standardised over the years and are now widely used.

We have, for some years, been interested in the chemistry of aliphatic nitro compounds, and our explorations in this area have led to useful methods for the synthesis of pyrroles[5,6]. In particular, we conceived that the base catalysed reaction of nitro-olefins with α-isocyanoacetates would lead to pyrroles with an ideal substitution pattern for the synthesis of porphyrins and bile pigments. This work, which was

reported earlier as a short preliminary communication[6], will now be described in detail.

Nitro compounds, and especially nitro-olefins, have previously served for the preparation of pyrroles[7]. The so-called Grob-Camenisch reaction involving the condensation of nitro-olefins with enamino-ketones or -esters, is well-known, and several variants of it have since appeared in the literature[4,7]. We had earlier shown, as part of of our study of the tributylphosphine-diphenyl disulphide deoxygenating system for oximes and nitoalkanes[5], that the easily accessible 1,4-nitro ketones were smoothly reduced by this reagent combination to an intermediate imino-ketone, which underwent spontaneous cyclisation and dehydration to produce the corresponding pyrroles in good yield, as depicted in scheme 1.

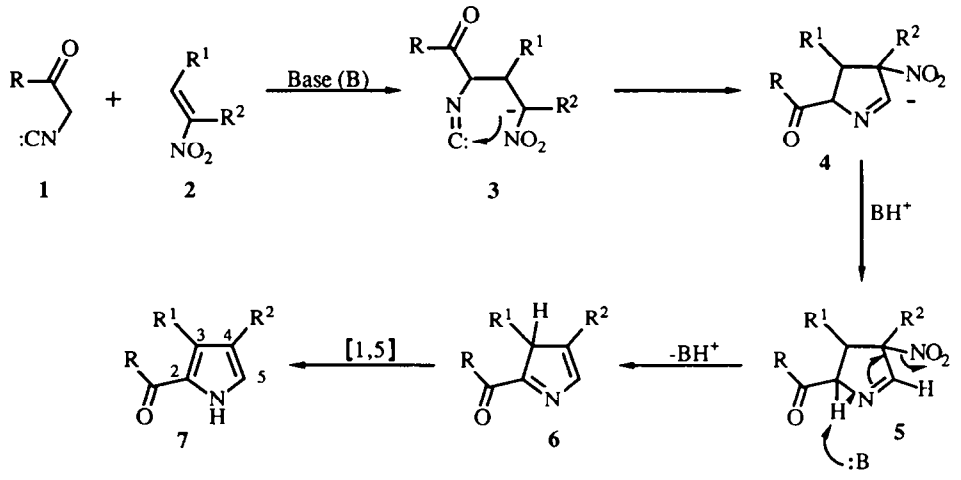


Scheme 1

Inherent limitations in the reducing system however restrict the utility of this method to pyrroles which must be substituted in the 2- *and* 5- positions, although one of the substituents may be an ester group, removable in principle through saponification and decarboxylation.

A more interesting approach to pyrrole building blocks for porphyrin synthesis consisted in taking advantage of the strong ability of a nitro group to activate an olefin towards Michael additions as well as of its propensity to act as a leaving group in situations where El_{CB} type eliminations are favorable. These considerations become clear on inspection of the reaction manifold displayed in scheme 2 , where the nucleophile in the Michael addition is an activated isocyano derivative **1** . The first step leads to an adduct **3** which can cyclise to **4** through internal attack of the nitronate on the isocyano group. Similar cyclisations constitute the basis of a powerful methodology for the construction of heterocyclic rings uncovered by the group of Schöllkopf[8] some twenty years ago. The cyclic intermediate **5** resulting from proton exchange can now eliminate a nitronate ion through a vinylogous El_{CB} mechanism to give pyrrole **7**, after aromatisation through a [1,5] sigmatropic shift of hydrogen. The overall mechanism is similar to that proposed by Van Leusen and co-workers[9] for the condensation of toluenesulphonylmethyl isocyanide **1e** with electron deficient olefins which also leads to pyrroles but with a different substitution pattern. In this case, the group that is eliminated is the toluenesulphinate (c.f. Scheme 5).

The pyrroles produced by the present approach would be ideal building blocks for porphyrins and bile pigments since they are unsubstituted in the 5-position, and the 2-position can be protected by an easily removable group such as an ester. The substituents in the 3- and 4- position originate from the nitro-olefin component and can be readily varied in view of the exceptionally rich chemistry of the nitro group.



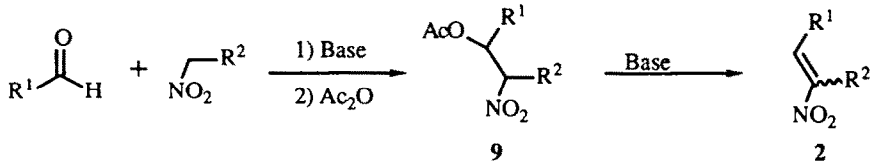
Scheme 2

Since the t-butyl ester function is one of the most useful yet perhaps the most difficult to introduce by the conventional Paal-Knorr and related reactions, we chose to study the proposed condensation using mostly t-butyl isocyanoacetate **1a** even though comparable results were observed with other activated isocyano derivatives. Indeed, when substituted ß-nitrostyrene **2a** was added to a solution of isocyanoacetate **1a** and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in a 1:1 mixture of isopropanol and tetrahydrofuran at room temperature, a smooth reaction took place to give the expected pyrrole **7a** in 80% yield after chromatographic purification. The reaction was slightly faster and the yield better (90%) when DBU was replaced by the stronger guanidine base **8a**. Similarly the ethyl ester derivative **7b** was prepared (91%) using ethyl isocyanoacetate **1b** and nitrostyrene **2b**. In view of its superior performance, the guanidine base, available to us from a parallel project[10] concerned with powerful but hindered organic bases, was selected for most of this study. In one instance, the commercially available N,N,N',N'-tetramethyl guanidine was tried and found to be quite suitable (*vide infra*).

The condensation to give pyrroles could also be extended to aliphatic nitro olefins. For example, pyrrole **7c** with a steroid substituent was produced in 91% yield from derivative **2c** using similar experimental conditions. With simpler nitro-olefins such as 2-nitropropene **2d**, however, the yield of the corresponding pyrrole **7d** dropped dramatically with the best result (48%) being obtained by adding slowly the highly reactive olefin to a solution of the isocyanoester and base.

As a palliative to the difficulty in handling and storing small, very base sensitive nitroolefins, we considered the possibility of employing ß-acetoxy nitroalkanes **9** as more convenient surrogates. Under the basic reaction conditions, ß-elimination of the acetate group (scheme 3) would generate the requisite nitroolefin *in situ* ; furthermore, the concentration of the latter could be maintained sufficiently low to minimise base induced polymerisation. Indeed, starting from 1-acetoxy-2-nitropropane **9a** instead of 2-nitropropene itself, the yield of pyrrole **7d** was easily raised to 70%. It is interesting to note that the methyl ester analogue **7e** is the trail marker pheromone of the Texas leaf-cutting ant, *Atta texana* (Buckley)[11a]. This compound had been synthesised some years ago by Sonnet[11b] from pyrrole itself, and earlier by

Rappoport[11c] by a somewhat longer route. Using the present condensation, this simple pheromone can be conveniently and directly obtained in 60% by simply using methyl isocyanoacetate in the above experiment (a mixture of t-butanol and tetrahydrofuran was used in this case to avoid problems of transesterification observed when isopropanol was the co-solvent).



9 **2**

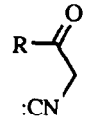
Scheme 3

ß-Acetoxy-nitro derivatives are readily obained by base catalysed addition of a primary nitroalkane to an aldehyde (the Henry reaction) followed by acetylation. For example, **9a** was obtained by reacting nitromethane with acetaldehyde followed by acetylation. The addition requires only a mild base and proceeds generally in high yield. This confers to the present approach an important practical advantage since the substituents in the 3- and 4- positions derive from the nitroalkene precursor and may therefore be varied by altering the nitroalkane and aldehyde partners in the Henry reaction. The convergence and simplicity of this approach are highlighted by the following examples.

Addition of 1-nitropropane to propionaldehyde and subsequent acetylation gives 3-acetoxy-4-nitrohexane **9b**, which produces the 3,4-diethyl substituted pyrrole **7f** in 55% yield on reaction with the isocyano-ester **1a** in the presence of the guanidine base. This compound is a useful starting material for the preparation of octaethyl porphyrin which is often used as a model in the study of porphyrin chemistry[1].

If the Henry addition is conducted starting with nitropropane and acetaldehyde followed by acetylation and condensation with the isocyano-ester, the sequence leads to pyrrole **7g** possessing 3-methyl and 4-ethyl substituents in 95% yield. This substitution pattern may be easily reversed by simply starting with 1-nitroethane and propionaldehyde. This time pyrrole **7h** with 3-ethyl and 4-methyl groups is produced, albeit in a slightly lower yield (68%). Access to these two pyrroles by a conventional approach would have required two separate and, in any case, lengthier sequences.

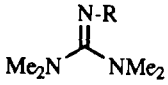
In addition to methyl and ethyl groups, several naturally occuring porphyrins (e.g. the coproporphyrins) contain a propionate side chain. This important moiety may be introduced quite easily into a pyrrole building block in the following manner. Thus reaction of a mixture of methyl 4-nitrobutanoate, itself prepared by Michael addition of nitromethane onto methyl acrylate, and acetaldehyde (neat) in the presence of a small amount of N,N-dimethyl-4-aminopyridine (DMAP) followed by dilution with dichloromethane and addition of acetic anhydride gives nitroester **9e** in almost quantitative yield. DMAP acts both as a basic catalyst for the Henry addition and as a promoter for the acetylation step allowing a substantial simplification of the experimental procedure by dispensing with the isolation and purification of the intermediate nitro-alcohol. This convenient "one-pot" variant was used for the prepration of nitroacetates **9c** and **9e**, at a late stage in our study, and was not tested for the other acetoxy-nitro derivatives. These were obtained earlier by conventional procedures, but there is no reason to believe that this simplification should not be applicable to them too. Finally, condensation of **9e** with isocyanoacetate **1a** afforded the desired pyrrole **7i** in excellent yield (97%). For the sake of comparison, it is worth mentioning



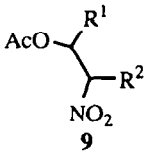
1

1e

a ; R= t-BuO-
b ; R= EtO-
c ; R= MeO-
d ; R= Me_2N

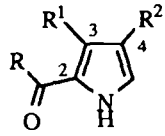


8a ; R= t-Bu
8b ; R=H



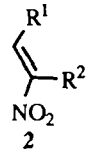
9

a ; R^1= H , R^2= Me
b ; R^1= R_2= Et
c ; R^1= Me, R^2=Et
d ; R^1= Et , R^2= Me
e ; R^1= Me, R^2= -$CH_2CH_2CO_2Me$



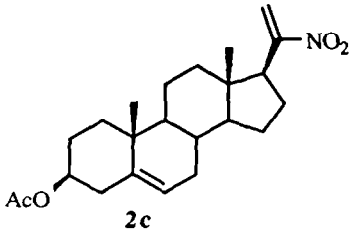
7

a ; R= t-BuO- , R^1= *p*-$MeOC_6H_4$- , R^2= Me
b ; R= EtO- , R^1= *p*-$PhCH_2OC_6H_4$- , R^2= Me
d ; R= t-BuO- , R^1= H , R^2= Me
e ; R= MeO- , R^1= H , R^2= Me
f ; R= t-BuO- , R^1= R^2= Et
g ; R= t-BuO- , R^1= Me , R^2= Et
h ; R= t-BuO- , R^1= Et , R^2= Me
i ; R= t-BuO- , R^1= Me , R^2= -$CH_2CH_2CO_2Me$
k; R= Me_2N- , R^1= Me , R^2= Et

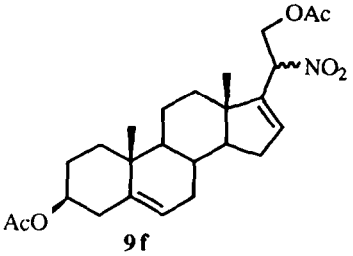


2

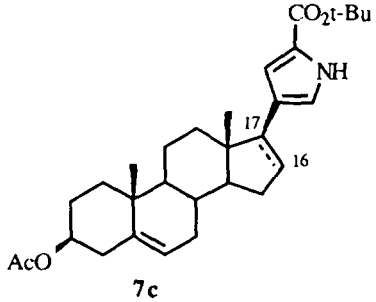
a ; R^1= *p*-$MeOC_6H_4$- , R^2= Me
b ; R^1= *p*-$PhCH_2OC_6H_4$- , R^2= Me
d ; R^1= H , R^2= Me
e ; R^1= *p*-$MeOC_6H_4$- , R^2=H



2c

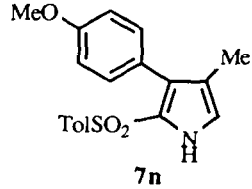


9f



7c

7j ; $\Delta^{16,17}$

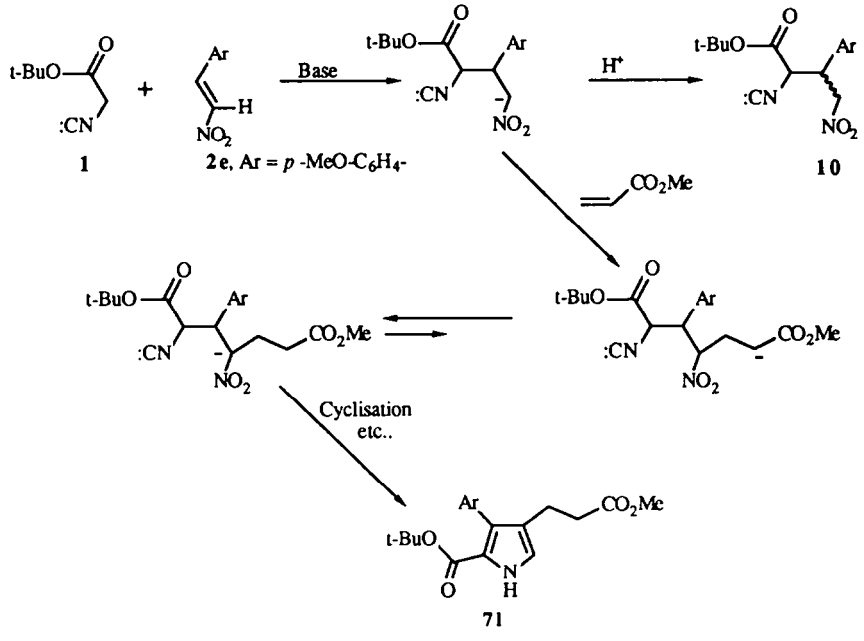


7n

that the same pyrrole was synthesised by Clezy and co-workers[12] a few years ago, in several linear steps involving a Paal-Knorr reaction with an overall yield of the order of 10%.

Finally access to vinylic pyrroles may be illustrated by the efficient (87%) preparation of pyrrole **7j** from nitrosteroid **9f**. The latter substance was an intermediate from an earlier project related to the construction of the corticosteroid side chain from 17-ketosteroids[13].

Although esters, and especially the t-butyl ester, are particularly useful protecting groups for the 2-position in the pyrrole, amides are increasingly finding use in the preparation of porphyrins by the so-called oxo-bilane route[14]. In this approach, the amide group, usually the N,N-dimethyl amide, is converted into the corresponding Vilsmaier salt and coupled to another pyrrole to give after hydrolysis a dipyrryl ketone. In a sense, the group in the 2-position is not "wasted". However, pyrrole amides are not always easily available through the Paal-Knorr condensation. Access to such pyrrole amides by the present method requires simply the use of an isocyanoamide instead of an isocyanoester. For example, condensation of **1d** with nitroester **9c** in the usual manner produced the corresponding pyrrole **7k** in high yield (77%).



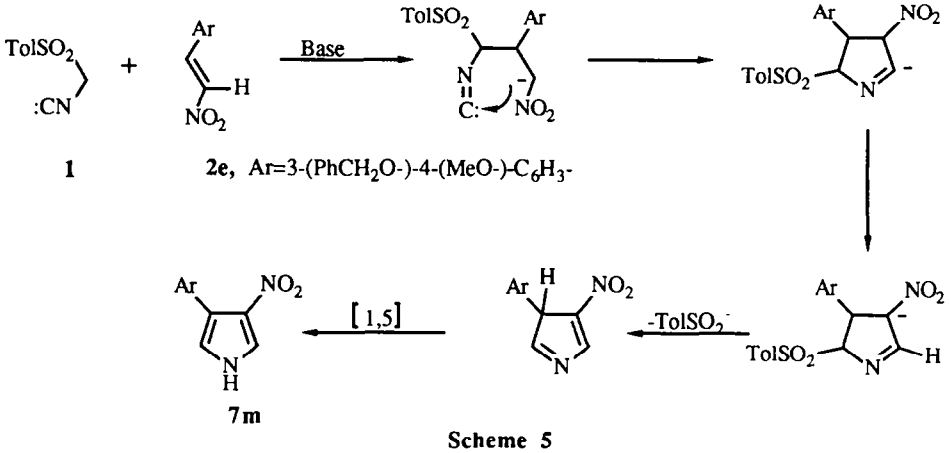
Scheme 4

In all the examples so far presented, the nitro olefin , whether prepared beforehand or generated *in situ*, contained a substituent geminal to the nitro group (i.e. $R_2 \neq H$ in **2**). When the condensation was attempted under the same reaction conditions as above on an unsubstituted derivative such as **2e** and using isocyanoester **1a**, a complex mixture was produced in which none of the expected pyrrole was found. When the reaction was conducted at -70°C and the mixture neutralised at low temperature with a weak acid, the Michael adduct **10** could be isolated as a mixture of diasterioisomers (scheme 4) as indicated by its nmr spectrum. It seems therefore that, in this case, the cyclisation step is much slower due to the lower

nucleophilicity of the primary nitronate anion, and, if cyclisation is taking place at all, it is not leading to pyrroles. The fact that cyclisation does not occur (or occurs very slowly) at low temperature, as demonstrated by the isolation of compound **10**, could be used to advantage for the expedient elaboration of complex pyrroles, as shown by the following example.

The previous experiment was thus repeated but the quenching by acid replaced by addition of excess methyl acrylate and warming to room temperature. This gave pyrrole **7l** containing the important propionate side chain directly in 62% yield. As outlined in scheme 4, Michael addition of the intermediate primary nitronate onto the acrylate followed by a proton shift leads to a secondary nitronate which undergoes the cyclisation sequence normally. In a sense, this variation turns into an advantage what originally was a limitation.

It is possible to show that by increasing the temperature, cyclisation of the primary nitronate onto the isocyanide function does take place, at least to a certain extent. To this end, toluenesulphonylmethyl isocyanide (TOSMIC) was used as the activated isocyanide partner since the the sulphone group can also act as a leaving group in such condensations, as was shown in important work by Van Leusen and co-workers[9]. Loss of the sulphone generates the double bond necessary for aromatisation and leads to the formation of a 3-nitro pyrrole, as outlined in scheme 5. Indeed, addition of nitroolefin **2e** to a mixture of TOSMIC and DBU in tertrahydrofuran-isopropanol at -78°C followed by warming to -20°C and quenching gave the expected pyrrole **7m** in low yield (14%). In spite of the low (but unoptimised) yield, this condensation can serve after further improvement as an entry into 3-nitro pyrroles which are only accessible with difficulty by other routes.



Scheme 5

If the starting nitro olefin contains a geminal substituent such as in **2a**, reaction with TOSMIC in the presence of DBU leads to a sulphonyl pyrrole (**7n**, 52% yield). In this instance, as with the condensations involving the isocyanoacetates, it is the nitro group that acts as the leaving group.

In conclusion, this approach to pyrroles has many desirable features, namely simplicity, wide scope, and, perhaps most importantly, convergence and economy of steps. Indeed since the appearance of the preliminary communication, several groups have reported its use in the synthesis of various substituted porphyrins[15].

Coda : Shortly after the appearance of our preliminary Communication we received a helpful letter from Prof. J. E. Baldwin, F.R.S. who kindly drew our attention to a review by Prof. D. Hoppe[8b]. In this article mention is made of a Diploma Thesis (D. Stafforst, Göttingen, 1971) supervised by Prof. Schöllkopf, where a pyrrole was synthesised by the base catalysed addition of an isocyanide to a nitroolefin. A diligent search of *Chemical Abstracts* both before and after the receipt of Prof. Baldwin's letter showed that no prior reference to this pyrrole synthesis had appeared in the primary literature. However, *Chemical Abstracts* does record a Patent issued to Schöllkopf and Stafforst in which double Michael addition to nitro olefins is reported.

Prof. Baldwin has kindly informed us that he has used this pyrrole synthesis in his famous work on capped porphyrins. However no reference is given in these publication to the method of pyrrole synthesis used.

We are therefore glad to acknowledge the existence of all this unpublished work. Nevertheless, the fruitful idea of one of us was not influenced by unpublished, and therefore inaccessible, literature.

Acknowledgement. We thank Professors J. E. Baldwin and U. Schöllkopf for friendly correspondence.

Experimental

M.p's were determined with a Kofler hot stage apparatus. ^{1}H-NMR spectra (60MHz) are for deuterated chloroform solutions with tetramethylsilane as internal standard, unless otherwise stated. IR spectra are of nujol mulls for solid samples or neat in the case of liquids unless otherwise specified. Isocyanides **1b** and **1e** are commercially available compounds; **1a**, **1c**, and **1d** were prepared according to literature procedures[16]. THF is tetrahydrofuran.

t-Butyl 3-(*p* -methoxy-phenyl)-4-methylpyrrole-2-carboxylate **7a**

To a solution of nitroolefin **2a**[17] (200 mg) and isocyanide **1a** (169 mg) in a 1:1mixture of THF and isopropanol (5 ml) was added the guanidine base **8a** (180 mg). The resulting solution was then heated to 50°C for 3 hours, poured into water, and extracted with dichloromethane. The organic layer was dried over sodium sulphate and filtered through a short column of silica gel (eluent: dichloromethane). Evaporation under vacuum of the solvent gave the desired pyrrole **7a** as a pale crystalline solid (272 mg; 90%); m.p. 142-144 °C (from CCl_4-pentane); ν_{max} 3250, 1640 cm^{-1}; δ_H 10.0 (1H, broad), 7.45 (2H, d, J=9Hz), 7.10 (2H, d, J=9Hz), 6.90 (1H, d, J=2Hz), 3.90 (3H, s), 2.00 (3H, s), 1.40 (9H, s) (Found: C, 70.77; H, 7.49; N, 4.62. Calc. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87).

Ethyl 3-(*p* -benzyloxy-phenyl)-4-methylpyrrole-2-carboxylate **7b**

To a solution of nitroolefin **2b**[5b] (258 mg) and isocyanide **1b** (170 mg) in a 1:1 mixture of THF and isopropanol (4 ml) was added the guanidine base **8a** (250 mg). The resulting solution was kept at room temperature for 2 hours then concentrated *in vacuo* , and the residue purified by column chromatography on silica gel (eluent: ether-hexane 1:1) to give the desired pyrrole **7b** as a white crystalline solid (320mg; 91%); m.p. 126-128 °C (from methanol); ν_{max} 3250, 1640 cm^{-1}; δ_H 9.60 (1H, broad), 7.60 (5H, bs), 7.50 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz), 6.90 (1H, d, J=2Hz), 5.20 (2H, s), 4.25 (2H, q, J=7Hz) 2.05 (3H, s), 1.15 (3H, t, J=7Hz) (Found: C, 75.21; H, 6.31; N, 3.97. Calc. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18).

When this experiment was repeated using DBU instead of the guanidine base **8**, the same pyrrole was obtained in 80% yield.

t-Butyl 4-(3β-acetoxy-androst-5-en-17β-yl)-pyrrole-2-carboxylate **7c**

To a solution of nitrosteroid **2c**[13] (63 mg) and isocyanide **1a** (60 mg) in a 1:1mixture of THF and isopropanol (2 ml) was added the guanidine base **8a** (60 mg). The resulting solution was kept at room temperature overnight then concentrated *in vacuo* , and the residue purified by column chromatography on silica gel (eluent: dichloromethane) to give the desired pyrrole **7c** as a pale crystalline solid (73 mg; 91%); m.p. 225-228 °C (from dichloromethane-methanol); $[\alpha]_D$ -40° (c=0.2 in $CHCl_3$) ν_{max} 3400, 1720, 1680 cm^{-1}; δ_H 9.35 (1H, broad), 6.80 (1H, s), 6.75 (1H, s), 5.45 (1H, m), 2.05 (3H, s), 1.60 (9H, s), 1.05 (3H, s), 0.50 (3H, s) (Found: C, 74.36; H, 9.18; N, 3.63. Calc. for $C_{30}H_{43}NO_4$: C, 74.81; H, 9.00; N, 2.91).

t-Butyl 4-methylpyrrole-2-carboxylate **7d**

a) From 2-nitropropene **2d**: To a solution of isocyanide **1b** (148 mg) and guanidine base **8a** (200 mg) in a 1:1mixture of THF and isopropanol (1 ml) was added slowly (10-15 minutes), at room temperature, a solution of nitroolefin **2d**[18] (184 mg) in the same solvent mixture (4 ml). The resulting solution was kept at room temperature for 3 hours then concentrated *in vacuo* , and the residue purified by column chromatography on silica gel (eluent: dichloromethane). to give the desired pyrrole **7d** as a white crystalline solid (87 mg; 48%); m.p. 114-115 °C (from hexane); ν_{max} 3250, 1640 cm^{-1}; δ_H (CCl_4) 10.30 (1H, broad), 6.55 (2H, m), 2.05 (3H, s), 1.60 (9H, s) (Found: C, 66.03; H, 8.48; N, 7.86. Calc. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73).

b) From 1-acetoxy-2-nitropropane **9a**: A solution of 2-nitropropan-1-ol[19] (5.0 g), acetic anhydride (8.0 g), and DMAP (200 mg) in dichloromethane (25 ml) was kept at room temperature overnight. Methanol (5 ml) was added to destroy the excess acetic anhydride. After stirring for a further hour, the solution was poured into dilute aqueous sodium bicarbonate (11 g in 60ml) and extracted with dichloromethane. The organic layer was dried over sodium sulphate and filtered through a short column of silica. Evaporation of the solvent gave acetate **9a** as a clear liquid (6.4 g; 91%) which was used directly in the next step.

A solution of **9a** (220 mg) in a 1:1 mixture of THF-isopropanol (3 ml) was added in small portions over 1.5 hours to a solution of isocyanide **1a** (158 mg) and the guanidine base **8** (440 mg) in the same solvent mixture (1 ml). The resulting mixture was kept at room temperature for 5 hours then worked up as above to give the same pyrrole **7d** (143 mg; 70%).

Methyl 4-methylpyrrole-2-carboxylate **7e**

A solution of **9a** (450 mg) in a 1:1mixture of THF-t-butanol (6 ml) was added in small portions over 45 minutes to a solution of isocyanide **1c** (220 mg) and the guanidine base **8a** (0.90 ml) in the same solvent mixture (2 ml). The resulting mixture was kept at room temperature for a further 20 minutes then worked up as above to give pyrrole **7e** as a white crystalline solid (178 mg; 60%); m.p. 72-73 °C (from hexane; lit.[11b] m.p. 72.5-73.5 °C).

t-Butyl 3,4-diethylpyrrole-2-carboxylate **7f**

A solution of 4-nitrohexanan-3-ol[19] (5.0 g), acetic anhydride (10 ml), and DMAP (300 mg) in dichloromethane (15 ml) was kept at room temperature for 3 hours. Methanol (15 ml) was added to destroy the excess acetic anhydride. After stirring for a further 30 minutes, the solution was poured into dilute aqueous sodium bicarbonate (30 g in 150 ml) and extracted with dichloromethane. The organic layer was dried over sodium sulphate and filtered through a short column of silica. Evaporation of the solvent gave acetate **9b** as a clear liquid (6.3 g; 98%) which was used directly in the next step.

A solution of **9b** (260 mg) in a mixture of THF-isopropanol (3 ml) was added in small portions over 1 hour to a solution of isocyanide **1a** (158 mg) and the guanidine base **8a** (0.5 ml) in the same solvent mixture (1 ml). The resulting mixture was kept at room temperature for 48 hours then worked up as above (eluent dichloromethane: hexane 7:3) to give pyrrole **7f** (139 mg; 55%); m.p. 67-68 °C (from methanol); ν_{max} 3300, 1650 cm^{-1}; δ_H 8.8 (1H, broad), 6.55 (1H, d, J=3Hz), 2.65 (2H, q, J=7Hz),

2.40 (2H, q, J=7Hz), 1.15 (3H, t, J=7Hz), 1.10 (3H, t, J=7Hz) (Found: C, 70.03; H, 9.42; N, 6.32. Calc. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27).

t-Butyl 4-ethyl-3-methylpyrrole-2-carboxylate **7g**

A solution of 2-nitropentan-3-ol[19] (5.0 g), acetic anhydride (8.0 g), and DMAP (200 mg) in dichloromethane (25 ml) was kept at room temperature overnight. Methanol (5 ml) was added to destroy the excess acetic anhydride. Work up as for **9a** above gave the corresponding acetate **9c** as a clear liquid (6.3 g; 95%) which was used directly in the next step.

A solution of **9a** (200 mg) in a mixture of THF-isopropanol (3 ml) was added in small portions over 1 hour to a solution of isocyanide **1a** (158 mg) and the guanidine base **8a** (400 mg) in the same solvent mixture (1 ml). The resulting mixture was kept at room temperature for 48 hours then worked up as above to give pyrrole **7g** (143 mg; 68%) as pale crystals; m.p. 100-101 °C (from methanol); ν_{max} 3300, 1660 cm^{-1}; δ_H 8.80 (1H, broad), 6.60 (1H, d, J=3Hz), 2.70 (2H, q, J=7Hz) 2.00 (3H, s), 1.60 (9H, s), 1.10 (3H, t, J=7Hz) (Found: C, 69.12; H, 9.09; N, 6.92. Calc. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69).

t-Butyl 3-ethyl-4-methylpyrrole-2-carboxylate **7h**

A mixture of 1-nitropropane (9.0 g), freshly distilled acetaldehyde (5.5 g), and DMAP (0.50 g) was kept in an ice-water bath for 30 minutes then in the refrigerator for 48 hours. Dichloromethane (60 ml) was added followed by acetic anhydride (15 ml) and the resulting mixture stirred at room temperature for 5-6 hours then poured into dilute aqueous sodium bicarbonate (30 g in 150 ml) and extracted with dichloromethane. Work up as for **9a** above gave the corresponding acetate **9d** as a colourless liquid (17.2 g; 99%) which was used directly in the next step.

A solution of **9d** (250 mg) in a mixture of THF-isopropanol (3 ml) was added in small portions over 1 hour to a solution of isocyanide **1a** (153 mg) and the guanidine base **8a** (0.5 ml) in the same solvent mixture (1 ml). The resulting mixture was kept at room temperature overnight then worked up as above to give pyrrole **7h** (220 mg; 95%) ; m.p. 93-94 °C (from methanol; lit.[20] m.p. 94-95 °C).

t-Butyl 4-(2-methoxycarbonyl ethyl) -3-methylpyrrole-2-carboxylate **7i**

A mixture of methyl 4-nitropropanoate[21] (1.0 g), freshly distilled acetaldehyde (1.0 g), and DMAP (0.25g) in dicloromethane (5 ml) was kept at room temperature for 30 hours. Dichloromethane (3ml) was added followed by acetic anhydride (4 ml) and the resulting mixture stirred at room temperature for 5-6 hours and the excess acetic anhydride destroyed with methanol (5ml). After stirring for a further 30 minutes, the mixture was poured into dilute aqueous potassium bicarbonate (10 g in 50 ml) and extracted with dichloromethane. Work up as for **9a** above gave the corresponding acetate **9e** as a colourless liquid (1.52 g; 96%) which was used directly in the next step.

A solution of **9e** (335 mg) in a mixture of THF-isopropanol (3 ml) was added in small portions to a solution of isocyanide **1a** (165 mg) and the guanidine base **8a** (0.5 ml) in the same solvent mixture (1ml). The resulting mixture was kept at room temperature for 30 hours then worked up as above (eluent dichloromethane-ether mixtures) to give pyrrole **7i** (302 mg; 97%) ; m.p. 50-53 °C (from hexane-ether); lit.[12] m.p. 51-53 °C).

t-Butyl 4-(3β-acetoxy-androsta-5,16-dienen-17-yl)-pyrrole-2-carboxylate **7j**

Nitrosteroid **9f**[13] (100 mg) was added to a solution of isocyanide **1a** (35 mg) and guanidine base **8a** (100 mg) in a 1:1mixture of THF and isopropanol (2 ml). The resulting solution was kept at room temperature for 5-6 hours then poured into water and extracted with dichloromethane. the organic layer was dried over sodium sulphate then concentrated *in vacuo* , and the residue purified by column

chromatography on silica gel (eluent: dichloromethane) to give the desired pyrrole **7j** (96 mg; 87%); m.p. 218-222 °C (from dichloromethane-methanol); $[\alpha]_D$ -36° (c=0.2 in $CHCl_3$); ν_{max} 3440, 1740, 1660 cm^{-1}; δ_H 9.50 (1H, broad), 6.95 (2H, m), 5.80 (1H, m), 5.40 (1H, m), 2.05 (3H, s), 1.60 (9H, s) 1.10 (3H, s), 0.95 (3H, s).

N,N-Dimethyl 3-ethyl-4-methylpyrrole-2-carboxamide **7k**

A solution of **9d** (260 mg) in a 1:1mixture of THF-isopropanol (2 ml) was added in small portions over 45 minutes to a solution of isocyanide **1d** (112 mg) and N,N,N',N'-tetramethylguanidine **8b** (300 mg) in the same solvent mixture (1 ml). The resulting mixture was kept at room temperature for 3 days then worked up as above to give pyrrole **7k** as a pale yellow glass which slowly crystallised (139 mg; 77%); m.p. 87-89 °C (hexane); ν_{max} 3160, 1590, 1570 cm^1; δ_H 9.80 (1H, broad), 6.50 (1H, d, J=2Hz), 3.0 (6H, bs), 2.35 (2H, q, J=7Hz), 2.00 (3H, s), 1.10 (3H, t, J=7Hz).

t-Butyl 4-(2-methoxycarbonyl ethyl) -3-(*p* -methoxyphenyl)-pyrrole-2-carboxylate **7l**

A solution of isocyanide **1a** (150 mg) and guanidine base **8a** (200 mg) in a 1:1mixture of THF and isopropanol (2 ml) was cooled to -70 °C under an inert atmosphere. Nitroolefin **2a** (180 mg) in a small amount of THF (2 ml) was added dropwise over about 5 minutes and the resulting mixture kept at this temperature for 30 minutes. Excess methyl acrylate (0.3 ml) was then added and the cooling bath removed to allow the solution to warm up to room temperature. After 1-2 hours, hexane (10 ml) was added and the solution filtered through a short silica column then evaporated under vacuum. Purification of the residue by chromatography on silica (eluent ether: hexane 1:1) gave pyrrole **7a** (226 mg; 62%); m.p. 100-102 °C (from methanol); ν_{max} 3300, 1720, 1660 cm^{-1}; δ_H 9.55 (1H, broad), 7.30 (2H, d, J=8Hz), 6.90 (2H, d, J=8Hz), 6.75 (1H, d, J=2Hz), 3.80 (3H, s), 3.60 (3H, s), 2.2-2.9 (4H, m), 1.40 (9H, s); m/z 359 (M^+), 303 (M-56) (Found: C, 66.72; H, 7.11; N, 4.14. Calc. for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90).

3-(3-Benzyloxy-4-methoxy-phenyl)-4- nitropyrrole **7m**

To a stirred solution of TOSMIC (293 mg) and DBU (228 mg) in THF-isopropanol (1:1, 4 ml), cooled to -78 °C under an inert atmosphere was added nitro olefin **2e** (285 mg). The resulting mixture was allowed to warm to -20 °C and kept at this temperature for 2 hours then diluted with ether and poured into aqueous citric acid. Extraction (ether) was somewhat difficult due to the presence of an insoluble unidentified material. The organic layer was dried, concentrated, and the residue purified by chromatography on silica (dichloromethane) to give nitro pyrrole **7m** as a yellowish powder (45 mg, 14%); m.p. 190-197 °C; ν_{max} ($CHCl_3$) 3450, 1620, 1520 cm^{-1}; δ_H (200 MHz) 8.9 (1H, broad), 7.63 (1H, appears as a triplet, J=2Hz), 6.9-7.5 (8H, m), 6.57 (1H, appears as a triplet, J=2Hz), 5.30 (3H, s), 3.91 (3H, s); m/z 324 (M^+) (Found: C, 66.42; H, 5.16. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97).

2-(*p* - Toluenesulphonyl-)3-(4-methoxy-phenyl)-4- methylpyrrole **7n**

To a stirred solution of TOSMIC (585 mg) and DBU (456 mg) in THF-isopropanol (1:1, 4 ml) under an inert atmosphere was added nitro olefin **2a** (378 mg) portionwise over 5 minutes. The resulting mixture was stirred at room temperature overnight then concentrated *in vacuo*, and the residue purified by chromatography on silica (dichloromethane: petroleum ether mixtures) to give pyrrole **7n** (327 mg, 52%); m.p. 190 °C (from methanol); ν_{max} 3300 cm^{-1}; δ_H (200 MHz) 9.1 (1H, broad), 7.27 (2H, d, J=8Hz), 7.03 (4H, m), 6.81 (2H, d, J=8Hz), 6.70 (1H, d, J=2Hz), 3.77 (3H, s), 2.23 (3H, s), 1.61 (3H,s). (Found: C, 66.45; H, 5.62. Calc. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61).

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