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Tandem in situ Generation of Azomethine Ylides and Base Sensitive Nitroethylene Dipolarophiles

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Abstract—We have studied the behaviour of 2-acetoxy-nitroethane derivatives in the presence of triethylamine and of an azomethine ylide generated also by the action of this base in the same reaction mixture. Under these conditions the nitro-olefins are generated and react in situ with the corresponding dipoles, giving pyrrolidine derivatives in moderate to good yields.

The potential of the simplest nitro-olefin, nitroethylene as a versatile reagent for organic synthesis has found limited application. Nitroethylene, which was first described early this century by Wieland and Sakkelarios[1] is known to polymerise readily in the presence of any trace of water and reacts violently with base. This behaviour prevents its use in many types of reaction. In spite of this sensitivity nitroethylene itself has been applied as a very electron-deficient and highly reactive dienophile in Diels–Alder reactions with electron-rich[2] or unactivated[3] dienes, and also as a useful acceptor for nucleophilic radicals.[4] A wide variety of nucleophiles have been used in conjugate additions to nitroethylene.[5] Avoiding the facile base-mediated polymerisation in these cases is crucial to the successful application of these additions in the synthesis of important natural products.[5k,l,6]

Nitroethylene is also a good dipolarophile in 1,3-dipolar cycloadditions, but only a few examples have been published to date; reaction with 9-diazafluorene led to a nitrocyclopropane derivative,[7] whilst the reaction with 1-azidoadamantene gave a 1*H*-1,2,3-triazole[8] by the further reaction of the original cycloadduct in both cases. An interesting observation, which can be rationalised from FMO considerations, is that the regiochemistry of nitroethylene reactions with nitrones[9] and nitrile oxides[10] is often reversed from those observed with less electron deficient alkenes.[11]

However there is no report on the cycloadditions of the azomethine ylides or nitrile ylides to nitroethylene. Presumably this is mostly due to the base-related generation of these unstable species. During our earlier work[12] we also noticed serious difficulties in the synthetic applications of oxindole nitroethylene derivatives which also readily polymerize in the presence of nucleophiles.

In order to avoid the difficulty in handling and storing these nitroethylenes, we considered the possibility of employing some more convenient surrogates. We describe here[13] the tandem in situ generation of azomethine ylides and nitroethylene. This process leads in one stereoselective step to 3-unsubstituted-4-nitropyrrolidine cycloadducts.

Results and Discussion

There are many reports in the literature on the base-catalysed formation of azomethine ylides.[14,15] In contrast, only a few reports on the thermal in situ generation and reaction of nitroethylene are known; from 2-nitroethyl phenyl sulfoxide,[16] 2-benzyloxy-[5f–i] or 2-acetoxy-nitroethane[5a–d] and from 2-nitroethanol in the presence of dehydrating agent.[3a]

First we decided to study the behaviour of 2-acetoxy-nitroethane in the presence of triethylamine and of an azomethine ylide generated also by the action of this base. Under the basic reaction conditions, β-elimination of the acetate group would generate the required nitroethylene in situ, and the concentration of the latter could be maintained sufficiently low to minimise base-induced polymerisation. The imine precursors for the dipoles were prepared using the standard method[17] from aromatic aldehydes and glycine ester, while the 2-acetoxy-nitroethane was obtained by the acylation of 2-nitroethanol with acetic anhydride.[5b]

The cycloaddition reactions were carried out in dry toluene in the presence of silver acetate as a catalyst, to avoid

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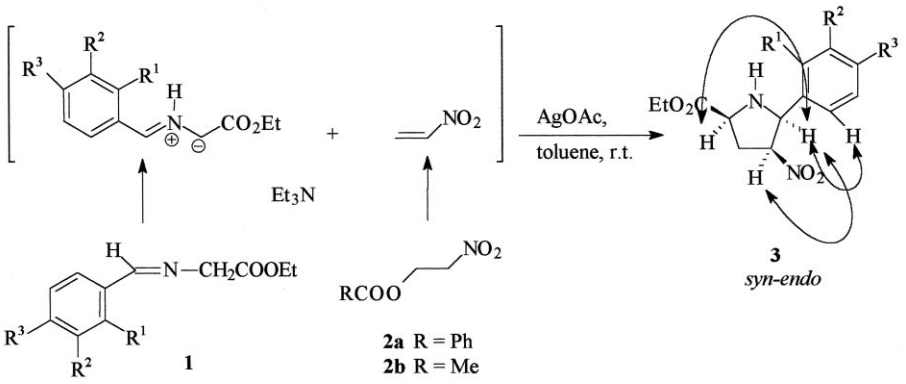


Scheme 1.

Table 1. Results of the cycloadditions under different conditions

Entry	Base (equiv.)	Temp.	Nitroethylene precursor (equiv.)	Product[a]	Yield[b] (%)
1	Et_3N (2)	0°C	**2b** (1)	**3a**	42
2	Et_3N (2)	−78°C	**2b** (1)	**3a**	22
3	Et_3N (2)	0°C→rt	**2b** (1.2)	**3a**	55
4	Et_3N (1)	0°C→rt	**2b** (1.2)	**3a**	8
5	Et_3N (2)	rt	**2a** (1)	**3a**	15
6	Et_3N (2)	0°C	**2a** (1.5)	**3a**	12
7	Et_3N (2)	0°C	**2b** (2.5)	**3a**	44

[a] Isolated yield after column chromatography.
[b] R^1=R^2=R^3=H.

formation of the isomeric azomethine ylides and the Michael addition products obtained in previous investigations (Scheme 1).

The cycloadditions gave the expected products in all cases as a single isomer in moderate yield. The results are summarised in Tables 1 and 2. Lower temperatures decreased the yield (Table 1, entry 2) while excess of dipolarophile (Table 1, entry 7) reduced the amount of polymeric by-products arising from the anionic polymerisation of the nitroethylene. These impurities and the unreacted imine were easily separated, in all cases, by column chromatography. The use of different nitroethylene sources (entries 5 and 6) or other bases (DABCO, DBU) did not improve the results. The substituents on the aromatic ring do not have any significant effect on the yield (Table 2).

The structure and stereochemistry of one cycloadduct (**3c**) were confirmed by HH-COSY and n.O.e. experiments, which showed clearly the formation of the 'normal' regioisomer. The *syn*-azomethine ylide reacted with the nitroethylene through the preferred *endo*-transition state to give the all-*cis* cycloadduct (Table 3).

The cycloadducts are prone to epimerize at position 4 upon standing in solution, due to the strongly activated nature of the proton adjacent to the nitro-group. After several days all of the cycloadducts had epimerized to give a 1:1 mixture of the *endo* and *exo* products, shown by the two sets of signals in the carbon spectra.

We have investigated the use of this methodology for the in situ generation of nitroethylene in the presence of another dipole derived from isoquinolinium salts **4a** and **4b** by deprotonation with triethylamine.[18] When the suspension of **4a** or **4b** was treated with base in dichloromethane in the presence of **2** the reaction mixture soon became homogeneous and after the usual work-up resulted in the *endo* cycloadducts **5a** and **5b** (Scheme 2). The stereochemistry of the cycloadducts was again determined by n.O.e. studies (Table 4).

We next started to investigate the possible replacement of the nitromethylene-oxindole **9** in similar base mediated

Table 2. Results of the cycloadditions described in Scheme 1

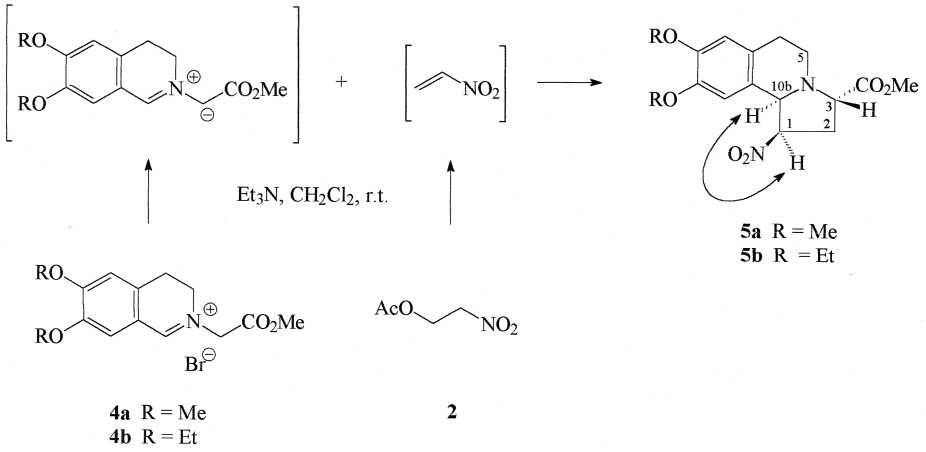
Entry	Product	R^1	R^2	R^3	Yield[a] (%)
1	**3b**	H	H	OMe	56
2	**3c**	Cl	H	Cl	64
3	**3d**	H	H	CH_3	54
4	**3e**	H	H	Cl	55
5	**3f**	H	H	CF_3	62
6	**3g**	CH_3	H	H	58
7	**3h**	OMe	OMe	H	54
8	**3i**	NO_2	H	H	35

[a] Isolated yield after column chromatography.

Table 3. Selected ^1H and ^{13}C NMR chemical shifts, H–H couplings and measured n.O.e. interactions for compound **3c**

	δ_H	[$J_{H,H}$ (Hz)]	$^1H\{^1H\}$ n.O.e.[a]		δ_C
H-4	5.44 dd	$J_{3,4}$=2.4	H-5, **H-3**	C-4	86.2
H-5	4.85 dd	$J_{4,5}$=6.4	Ar-6′H, H-4, H-2	C-5	64.5
H-2	4.04 dd	$J_{2,3}$=6.3 and 9.4	H-3, H-5	C-2	58.4

[a] Entries are for n.O.e.>2%; entries in bold for n.O.e.>5%.



Scheme 2.

cycloadditions. This nitroethylene, prepared from isatin in three steps (Scheme 3), was used in Diels–Alder and 1,3-dipolar cycloadditions only under neutral conditions. From this valuable nitro-olefin, complex spirooxindolo compounds could be obtained in one cycloaddition step.

The chloro derivative **8**, a known intermediate for the preparation of **9**, did not serve as a precursor for the in situ formation of **9**. However, treating the mixture of isoquinolinium salt **4** and **7** in toluene with two equivalents of triethylamine at room temperature gave the five membered heterocycle **10** stereoselectively and in good yield (Scheme 4). The structure and stereochemistry of these cycloadducts were suggested by comparison of the results the ^{1}H NMR experiments of **10a** with our earlier data.[12] Besides the clear stereochemical relationship of the pyrrolidine ring protons, the different regioselectivity compared to the cycloadditions to 3-(methoxycarbonyl-methylene)-1,3-dihydro-2*H*-indol-2-one[12] in this case seems to be strongly supported by the intense n.O.e. of the H-4 and H-4′ signals obtained by the irradiation of H-3′ (Table 5).

In conclusion, the method reported here provides a fairly general and mild method for the tandem in situ generation of 1,3-dipoles and nitroethylenes for the preparation of 4-nitropyrrolidines, although the yields rarely exceed the modest.

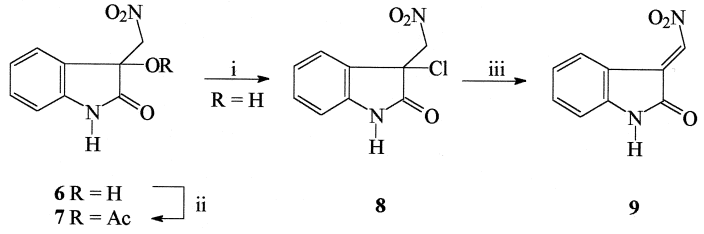
Table 4. Selected ^{1}H NMR chemical shifts, H–H couplings and measured n.O.e. interactions for compound **5a**

	δ_H	[$J_{H,H}$ (Hz)]	^{1}H{^{1}H} n.O.e.[a]
H-1	5.48 dt	$J_{1,2}$=2 Hz	**H-10**, **H-10b**, H-5
H-10*b*	4.84 d	$J_{10b,1}$=6.5 Hz	**H-10**, **H-1**
H-3	4.28 t	$J_{3,2}$=7.1 Hz	H-2, **H-5**

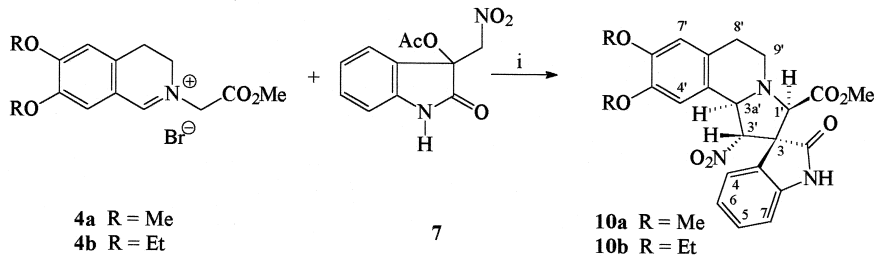
[a] Entries are for n.O.e.>2%; entries in bold for n.O.e.>5%.

Experimental

Column chromatography was performed using Merck Kieselgel 60, 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. IR spectra were measured



Scheme 3. *Reagents and conditions*: (i) $SOCl_2$; (ii) AcCl; (iii) Et_3N, 0°C, 1–5 s.



Scheme 4. *Reagents and conditions*: (i) Et_3N, toluene, rt.

Table 5. Selected ^{1}H NMR chemical shifts, H–H couplings and measured n.O.e. interactions for compound **10a**

	δ_H	J (Hz)	^{1}H{^{1}H} n.O.e. interactions[a]
H-3′	5.66 d	7.0	**H-4**, **H-4′**
H-3a′	5.19 d	7.0	H-4′, H-1′
H-1′	4.34 s	–	H-3a′

[a] Entries are for n.O.e.>2%; entries in bold for n.O.e.>5%.

on NICOLET FT-IR and Shimadzu IR-435 instruments. Low resolution electron impact mass spectra were obtained on Varian CH5-D and GCMS-QP5050A mass spectrometers. NMR spectra were recorded on Brucker 250 and Brucker AM-200 instruments at 30°C; chemical shifts are given relative to δ_{TMS}=0.00 ppm.

1,3-Dipolar cycloadditions between ethyl (arylideneamino)-acetates and nitroethylene generated in situ—general procedure

Ethyl (arylideneamino)acetate (10 mmol) and 2-acetoxy-nitroethanol (12 mmol) were dissolved in dry toluene (50 mL), then AgOAc (2.5 g, 15 mmol) and MS 4 Å were added. The reaction mixture was cooled to 0°C and triethylamine (2.8 mL, 20 mmol) was added slowly to the well stirred reaction mixture. After 10 min at 0°C the reaction mixture was allowed to warm to room temperature. When the reaction was completed (judged by TLC), saturated aqueous ammonium chloride (25 mL) was added, the precipitate was filtered off and the residue was extracted with ether. The combined organic fractions were dried over magnesium sulfate, evaporated and the residue was purified by column chromatography to yield the cycloadducts.

Ethyl 4-nitro-5-phenylpyrrolidine-2-carboxylate (3a). White powder, mp 77–79°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.32 (s, 5H, Ph), 5.18 (td, 1H, J=3.2 and 5.5 Hz, H-4), 4.55 (d, 1H, J=5.6 Hz, H-5), 4.30 (q, 2H, J=7.2 Hz, OCH_2), 4.04 (t, 1H, J=8.4 Hz, H-2), 2.95 (br s, 1H, NH), 2.51 (m, 2H, H_2-3), 1.33 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.0 (C=O), 134.2 (Ph-1′C), 128.6 (Ph-2′ and 6′C), 128.5 (Ph-4′C), 126.1 (Ph-3′ and 5′C), 96.7 (C-4), 68.5 (C-5), 61.6 (OCH_2), 59.2 (C-2), 35.9 (C-3), 14.1 (CH_3); MS *m/z* (relative intensity, %): 265 (M^{+1}, 5), 218 (4), 191 (36), 144 (100), 177 (28), 91 (10), 77 (10); IR (KBr, cm^{-1}): 2984, 2928, 1730, 1547, 1436, 1372, 1261, 1201, 1111 (Found: C, 59.17; H, 6.19; N, 10.51%. $C_{13}H_{16}N_2O_4$ requires C, 59.08; H, 6.10; N, 10.60).

Ethyl 5-(4-methoxyphenyl)-4-nitropyrrolidine-2-carboxylate (3b). White powder, mp 82–83°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.24 (d, 2H, J=8.9 Hz, Ar-2′H and 6′H), 6.87 (d, 2H, J=8.9 Hz, Ar-3′H and 5′H), 5.15 (td, 1H, J=2.8 and 5.6 Hz, H-4), 4.54 (d, 1H, J=5.4 Hz, H-5), 4.32 (q, 2H, J=7.0 Hz, OCH_2), 4.05 (dd, 1H, J=6.4 and 9.3 Hz, H-2), 3.79 (s, 3H, OCH_3), 2.74 (m, 2H, H_2-3), 1.35 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.1 (C=O), 159.7 (Ar-4′C), 127.2 (Ar-2′ and 6′C), 122.1 (Ar-1′C), 114.1 (Ar-3′ and 5′C), 89.3 (C-4), 68.3 (C-5), 61.7 (OCH_2), 59.3 (C-2), 55.1 (OCH_3), 35.9 (C-3), 14.2 (CH_3); MS *m/z* (relative intensity, %): 294 (M^+, 7), 247 (35), 221 (62), 174 (100), 159 (16), 147 (88), 132 (35); IR (KBr, cm^{-1}): 2982, 2923, 1731, 1547, 1439, 1377, 1262, 1121 (Found: C, 57.24; H, 6.02; N, 9.55. $C_{14}H_{18}N_2O_5$ requires C, 57.14; H, 6.16; N, 9.52).

Ethyl 5-(2,4-dichlorophenyl)-4-nitropyrrolidine-2-carboxylate (3c). White powder, mp 95°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.41 (d, 1H, J=8.1 Hz, Ar-6′H), 7.40 (d, 1H, J=2.0 Hz, Ar-3′H), 7.26 (dd, 1H, J=2.0 and 8. 1 Hz, Ar-5′H), 5.44 (td, 1H, J=2.4 and 6.5 Hz, H-4), 4.85 (d, 1H, J=6.4 Hz, H-5), 4.33 (q, 2H, J=6.1 Hz, OCH_2), 4.04 (dd, 1H, J=6.3 and 9.4 Hz, H-2), 2.81 (m, 2H, H_2-3), 1.35 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 171.9 (C=O), 135.1 (q), 133.7 (q), 131.1 (q), 129.3 (CH), 127.9 (CH), 127.6 (CH), 86.7 (C-4), 64.5 (C-5), 61.7 (OCH_2), 58.4 (C-2), 35.0 (C-3), 14.2 (CH_3); MS *m/z* (relative intensity, %): 333 (M^+, 3), 286 (8), 259 (60), 212 (100), 185 (42), 177 (45), 149 (14), 115 (16); IR (KBr, cm^{-1}): 3344, 2981, 1734, 1588, 1552, 1468, 1429, 1373, 1309, 1292, 1209, 1148, 1095 (Found: C, 46.75; H, 4.12; N, 8.36. $C_{13}H_{14}Cl_2N_2O_4$ requires C, 46.87; H, 4.24; N, 8.41).

Ethyl 5-(4-methylphenyl)-4-nitropyrrolidine-2-carboxylate (3d). White powder; mp 67°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.19 (d, 2H, J=7.6 Hz, Ar), 7.14 (d, 2H, J=7.6 Hz, Ar), 5.16 (td, 1H, J=3.0 and 5.7 Hz, H-4), 4.54 (d, 1H, J=5.7 Hz, H-5), 4.32 (q, 2H, J=7.1 Hz, OCH_2), 4.02 (dd, 1H, J=6.7 and 9.0 Hz, H-2), 2.70 (m, 2H, H_2-3), 2.32 (s, 3H, Ar-CH_3), 1.34 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.0 (C=O), 138.1 (Ar-4′C), 131.1 (Ar-1′C), 129.1 (Ar-2′ and 6′C), 125.9 (Ar-3′ and 5′C), 89.2 (C-4), 68.1 (C-5), 61.4 (OCH_2), 59.0 (C-2), 35.8 (C-3), 20.9 (Ar–CH_3), 14.0 (CH_3); MS *m/z* (relative intensity, %): 278 (M^+, 5), 232 (7), 205 (56), 158 (100), 143 (18), 131 (63), 115 (15), 91 (19), 79 (26); IR (KBr, cm^{-1}): 3309, 2981, 2927, 2867, 1728, 1549, 1437, 1375, 1263, 1203, 1115, 1038, 919 (Found: C, 60.25; H, 6.63; N, 10.1. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07).

Ethyl 4-nitro-5-(4-trifluoromethylphenyl)pyrrolidine-2-carboxylate (3f). White powder; mp 76°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.61 (d, 2H, J=8.4 Hz, Ar), 7.46 (d, 2H, J=8.4 Hz, Ar), 5.25 (td, 1H, J=3.6 and 5.6 Hz, H-4), 4.63 (d, 1H, J=5.6 Hz, H-5), 4.32 (q, 2H, J=7.2 Hz, OCH_2), 4.07 (t, 1H, J=8.6 Hz, H-2), 2.76 (m, 2H, H_2-3), 1.34 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 171.9 (C=O), 138.5 (Ar-1′C), 130.7 (quartet, J=32.5 Hz, CF_3), 126.8 (Ar-3′ and 5′C), 126.2 (Ar-4′C), 125.6 (Ph-2′ and 6′C), 88.9 (C-4), 67.7 (C-5), 61.8 (OCH_2), 59.1 (C-2), 35.7 (C-3), 14.1 (CH_3); MS *m/z* (relative intensity, %): 332 (M^+, 1), 286 (3), 259 (19), 212 (100), 185 (20), 172 (9), 115 (11); IR (KBr, cm^{-1}): 3323, 2991, 2908, 1740, 1620, 1555, 1420, 1373, 1330, 1209, 1166, 1125, 1069, 1017 (Found: C, 50.74; H, 4.57; N, 8.41. $C_{14}H_{15}F_3N_2O_4$ requires C, 50.61; H, 4.55; N, 8.43).

Ethyl 5-(2-methylphenyl)-4-nitropyrrolidine-2-carboxylate (3g). White powder; mp 91°C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.33–7.17 (m, 4H, Ar), 5.25 (td, 1H, J=2.6 and 6.4 Hz, H-4), 4.70 (d, 1H, J=5.8 Hz, H-5), 4.31 (q, 2H, J=7.1 Hz, OCH_2), 4.01 (dd, 1H, J=4.2 and 7.8 Hz, H-2), 2.78 (m, 2H, H_2-3), 2.39 (Ar–CH_3), 1.35 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.7 (C=O), 137.8

(q), 135.7 (q), 130.7 (CH), 128.1 (CH), 128.1 (CH), 126.4 (CH), 90.7 (C-4), 66.5 (C-5), 61.8 (OCH_2), 58.8 (C-2), 35.7 (C-3), 19.3 (Ar–CH_3), 14.1 (CH_3); MS *m/z* (relative intensity, %): 278 (M^+, 5), 231 (5), 205 (50), 158 (100), 143 (16), 131 (53), 115 (17), 91 (17), 78 (24); IR (neat, cm^{-1}): 3349, 2982, 2935, 1738, 1552, 1462, 1371, 1209, 1130, 1034 (Found: C, 60.29; H, 6.67; N, 10.12. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07).

Ethyl 5-(2,3-dimethoxyphenyl)-4-nitropyrrolidine-2-carboxylate (3h). pale yellow oil; ^1H NMR ($CDCl_3$, 200 MHz): 7.02–6.82 (m, 3H, Ar), 5.27 (dt, 1H, *J*=2.5 and 5.3 Hz, H-4), 4.74 (d, 1H, *J*=5.3 Hz, H-5), 4.27 (q, 2H, OCH_2), 4.12 (dd, 1H *J*=6.5 and 9.1 Hz, H-2), 3.93 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.75 (m, 2H, H-3), 1.29 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.0 (C=O), 151.9 (q), 146.2 (q), 127.3 (q), 124.0 (q), 117.1 (CH), 112.8 (CH), 88.3 (C-4), 63.5 (C-5), 61.8 (C-2), 60.6 (OCH_2), 58.7 (OCH_3), 55.7 (OCH_3), 36.3 (C-3), 14.1 (CH_3); MS *m/z* (relative intensity, %): 324 (M^+, 13), 277 (15), 251 (52), 204 (100), 189 (27), 177 (15), 162 (32); IR (neat, cm^{-1}): 3343, 2989, 2938, 1739, 1554, 1463, 1377, 1207, 1132, 1031 (Found: M^+, 324.1323. $C_{15}H_{20}N_2O_6$ requires 324.1321).

Ethyl 4-nitro-5-(2-nitrophenyl)pyrrolidine-2-carboxylate (3i). Pale yellow oil; ^1H NMR ($CDCl_3$, 250 MHz): 8.19 (s, 1H, Ar-2′H), 8.12 (d, 1H, *J*=8 Hz), 7.64 (d, 1H, *J*=8 Hz), 7.48 (t, 1H, *J*=8 Hz), 5.23 (dt, 1H, *J*=2.5 and 6 Hz, H-4), 4.66 (d, 1H, *J*=6 Hz, H-5), 4.27 (q, 2H, *J*=7 Hz, OCH_2), 4.04 (dd, 1H, *J*=4 and 7 Hz, H-2), 2.76 (m, 2H, H-3), 1.26 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 171.9 (C=O), 148.5 (q), 137.3 (q), 132.5 (CH), 130.1 (CH), 123.9 (CH), 122.3 (CH), 89.0 (C-4), 67.4 (C-5), 62.1 (CH_2), 59.2 (C-2), 35.6 (C-3), 14.3 (CH_3); IR (neat, cm^{-1}): 3326, 2998, 1741, 1622, 1557, 1425, 1379, 1201, 1167, 1069, 1030 (Found: M^+, 309.0964. $C_{13}H_{15}N_3O_6$ requires 309.0961).

1,3-Dipolar cycloadditions of isoquinolinium salts 4a and 4b and nitroethylenes generated in situ—general procedure

The corresponding acetoxy-nitroethylene (1.5 mmol) and isoquinolinium salt (1 mmol) were dissolved in dry toluene (8 mL) and dry triethylamine (2 mmol) was added dropwise with good stirring. After 1 h at room temperature ether (10 mL) and saturated aqueous ammonium chloride solution (20 mL) were added. The organic layer was dried over magnesium sulfate, filtered and evaporated to yield the cycloadducts, which were purified by recrystallisation.

Methyl 8,9-dimethoxy-1,2,3,5,6,10*b*-hexahydro-1-nitropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5a). Yield: 63%; pale yellow powder; mp 88–90°C; ^1H NMR ($CDCl_3$, 250 MHz): 6.58 (s, 2H, H-7 and H-10), 5.48 (dt, 1H, *J*=6.5 and 2.0 Hz, H-1), 4.84 (d, 1H, *J*=6.5 Hz, H-10*b*), 4.28 (t, 1H, *J*=7.1 Hz, H-3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.77 (s, 3H, CH_3O), 3.31–3.18 (m, 1H, H-2), 3.08–2.95 (m, 1H, H-2), 2.90–2.51 (m, 4H, H-5 and H-6); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.1 (C=O), 147.9 (C-8), 147.2 (C-9), 128.2 (C-10*a*), 122.4 (C-6*a*), 111.3 (C-7), 109.4 (C-10), 89.2 (C-1), 64.8 and 64.7 (C-3 and C-10*b*), 55.9 (OCH_3), 55.6 (OCH_3), 52.2 (CH_3O_2C), 45.8 (C-5), 33.5 (C-2), 27.8 (C-6); IR (nujol, cm^{-1}): 1727, 1606, 1542, 1508, 1211, 1116, 1012; MS *m/z* (relative intensity, %): 337 (M^+,100), 321 (9), 306 (10), 292 (37), 192 (72), 114 (65), 85 (58), 57 (67) (Found: C, 63.27; H, 6.48; N, 9.25. $C_{16}H_{20}N_2O_6$ requires C, 63.14; H, 6.62; N, 9.20).

Methyl 8,9-diethoxy-1,2,3,5,6,10*b*-hexahydro-1-nitropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5b). Yield: 66%; pale yellow powder; mp 121–123°C; ^1H NMR ($CDCl_3$, 250 MHz): 6.60 (s, 1H, H-10), 6.59 (s, 1H, H-7), 5.46 (dt, 1H, *J*=6.6 and 2.0 Hz, H-1), 4.82 (d, 1H, *J*=6.6 Hz, H-10*b*), 4.28 (t, 1H, *J*=7.1 Hz, H-3), 4.04 (m, 4H, 2×CH_2CH_3), 3.77 (s, 3H, CH_3OOC), 3.30–3.18 (m, 1H, H-2), 3.09–2.94 (m, 1H, H-2), 2.90–2.50 (m, 4H, H-5 and H-6), 1.42 (t, 6H, *J*=7.5 Hz, 2×CH_2CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): 173.3 (C=O), 148.1 (C-8), 146.9 (C-9), 128.5 (C-10*a*), 122.5 (C-6*a*), 113.3 (C-7), 112.0 (C-10), 89.3 (C-1), 64.9 and 64.75 (C_3 and 10*b*), 64.8 and 64.4 (CH_2), 52.3 (CH_3OOC), 45.9 (C-5), 33.6 (C-2), 27.9 (C-6), 14.9 (CH_2CH_3), 14.8 (CH_2CH_3); IR (nujol, cm^{-1}): 1725, 1543, 1385, 1378, 1300, 1332, 1254, 1216, 1152, 1117; CIMS *m/z* (relative intensity, %): 365 (M^+, 100), 349 (11), 337 (13), 320 (29), 305 (10), 291 (10), 220 (30) (Found: C, 59.44; H, 6.60; N, 7.49. $C_{18}H_{24}N_2O_6$ requires C, 59.33; H, 6.64; N, 7.69).

Methyl 5′,6′-dimethoxy-3′-nitro-2-oxo-1,1′,2,2′,3′,3a′,8′,9′-octahydro spiro[indolo-(3,2′)-pyrrolo[2,1*a*]isoquinoline]-1-carboxylate (10a). Yield: 73%; pale yellow powder; mp 207–209°C; ^1H NMR ($CDCl_3$, 250 MHz): 8.90 (s, 1H, NH), 7.52 (d, 1H, *J*=7.5 Hz, H-4), 7.24 (t, 1H, *J*=7.5 Hz, H-5), 7.03 (t, 1H, *J*=7.5 Hz, H-6), 6.88 (d, 1H, *J*=7.5 Hz, H-7), 6.66 (s, 1H, H-4′), 6.63 (s, 1H, H-7′), 5.66 (d, 1H, *J*=7.0 Hz, H-3′), 5.19 (d, 1H, *J*=7.0 Hz, H-3*a*′), 4.34 (s, 1H, H-1′), 3.86 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.29 (s, 3H, CH_3O), 3.50–3.08 (m, 2H, CH_2), 2.91 (t, 1H, *J*=11.7 Hz, CH_2), 2.46 (d, 1H, *J*=16 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): 175.9 (ester C=O), 168.7 (C-2), 148.5 (C-6′), 148.3 (C-5′), 141.6 (C-7a), 130.4 (C-6), 127.6 (C-3*b*′), 126.9 (C-3*a*), 125.9 (C-4), 123.4 (C-7*a*′), 123.2 (C-5), 111.8 (C-7′), 110.4 and 108.9 (C-7 and C-4′), 94.9 (C-3′), 67.6 (C-3*a*′), 59.9 (C-1′), 59.3 (C-3), 56.1 (2×OCH_3), 52.1 (CO_2CH_3), 45.3 (C-9′), 22.9 (C-8′); MS *m/z* (relative intensity, %): 454 (M^+, 100), 407 (19), 264 (22), 218 (25), 204 (15), 192 (80), 161 (54); IR (nujol, cm^{-1}): 3304, 1760, 1735, 1617, 1553, 1540, 1469, 1453, 1402, 1367, 1333, 1306, 1257, 1204 (Found: C, 61.07; H, 5.01; N, 9.27. $C_{23}H_{23}N_3O_7$ requires C, 60.92; H, 5.11; N, 9.27).

Methyl 5′,6′-diethoxy-3′-nitro-2-oxo-1,1′,2,2′,3′,3a′,8′,9′-octahydro spiro[indolo-(3,2′)-pyrrolo[2,1*a*]isoquinoline]-1-carboxylate (10b). Yield: 75%; pale yellow powder; mp 183–185°C; ^1H NMR ($CDCl_3$, 250 MHz): 9.00 (s, 1H, NH), 7.55 (d, 1H, *J*=7.5 Hz, H-4), 7.26 (t, 1H, *J*=7.5 Hz, H-5), 7.05 (t, 1H, *J*=7.5 Hz, H-6), 6.90 (d, 1H, *J*=7.5 Hz, H-7), 6.69 (s, 1H, H-4′), 6.66 (s, 1H, H-7′), 5.66 (d, 1H, *J*=7.3 Hz, H-3′), 5.21 (d, 1H, *J*=7.3 Hz, H-3*a*′), 4.37 (s, 1H, H-1′), 4.10 (q, 2H, *J*=7.0 Hz, CH_2), 3.98 (q, 2H, *J*=7.0 Hz, CH_2), 3.31 (s, 3H, CH_3O_2C), 3.41–3.14 (m, 2H, CH_2), 2.91 (t, 1H, *J*=13.5 Hz, CH_2), 2.47 (d, 1H, *J*=16 Hz, CH_2), 1.46 (t, 3H, CH_3), 1.39 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 175.9 (ester C=O), 168.8 (C-2), 148.2 (C-6′), 148.1 (C-5′),

141.6 (C-7a), 130.4 (C-6), 127.7 (C-3*b*′), 127.0 (C-3*a*), 125.9 (C-4), 123.4 (C-7*a*′), 123.2 (C-5), 113.8 (C-7′), 111.1 and 110.3 (C-7 and C-4′), 94.9 (C-3′), 67.7 (C-3′*a*), 64.9 (CH_2), 64.7 (CH_2), 59.9 (C-1′), 59.4 (C-3), 52.1 (CO_2CH_3), 45.3 (C-9′), 23.0 (C-8′); 14.9 (CH_3), 14.8 (CH_3); CIMS *m*/*z* (relative intensity, %): 482 (M^+, 100), 466 (6), 435 (15), 292 (12), 220 (44); IR (nujol, cm^{-1}): 1760, 1718, 1615, 1565, 1513, 1254, 1227, 1203, 1142, 1103 (Found: C, 62.18; H, 5.77; N, 8.71. $C_{25}H_{27}N_3O_7$ requires C, 62.36; H, 5.65; N, 8.73).

3-Acetoxy-3-nitromethyl-2,3-dihydroindol-2-one (7). 3-Hydroxy-3-nitromethyl-2,3-dihydroindol-2-one 6 (2.08 g, 10 mmol) was heated under reflux in acetyl chloride (20 mL) overnight in Ar atmosphere. After the removal of solvent the remaining solid was triturated with ether to yield a white powder (2.32 g, 93%); mp 136–137°C; ^{1}H NMR (DMSO-d_6, 250 MHz): 7.35 (d, 1H, *J*=7.5 Hz, H-4), 7.32 (t, 1H, *J*=7.5 Hz, H-5), 7.00 (t, 1H, *J*=7.5 Hz, H-6), 6.89 (d, 1H, *J*=7.5 Hz, H-7), 5.20 (d, 1H, *J*=12.9 Hz, CH_2), 5.06 (d, 1H, *J*=12.9 Hz, CH_2), 2.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.1 (ester C=O), 168.0 (C-2), 142.9 (C-7*a*), 130.9 (C-6), 124.3 (C-4), 123.9 (C-3*a*), 122.1 (C-5), 110.4 (C-7), 77.9 (CH_2), 76.5 (C-3), 20.3 (CH_3); IR (nujol, cm^{-1}): 3348, 1754, 1731, 1614, 1548, 1318, 1231, 1040, 964; MS *m*/*z* (relative intensity, %): 251 (M^+, 4), 191 (34), 174 (5), 161 (15), 146 (40), 61 (100) (Found: C, 52.88; H, 4.04; N, 11.27. $C_{11}H_{10}N_2O_5$ requires C, 52.80; H, 4.03; N, 11.20).

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