Intramolecular cycloadditions of *N*-alkenoyl aryl azides

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Depending upon the reaction conditions, intramolecular cycloadditions of variously substituted *N*-alkenoyl aryl azides **4** give the [1,2,3]triazolobenzodiazepine **5**, bridgehead aziridines **6** or imines **7**. The dipolarophilic activity of the C=N double bond of the latter compounds is also exploited in the synthesis of [1,2,4]triazolobenzodiazepines **10** by means of nitrilimine cycloadditions.

Introduction

Organic azides occupy a prominent role in the field of 1,3-dipolar cycloaddition chemistry.[1] In the last two decades, a copious literature has been devoted to the intramolecular version of this methodology,[2] thus providing a versatile tool for new synthetic targets[3] and mechanistic investigations.[4] The present paper describes the results which we obtained from the intramolecular cycloaddition of the azides **4a**–**c** bearing the acrylamide moiety as the dipolarophile.

Results and discussion

Our synthetic sequence starts from *N*-benzyl-2-nitrobenzylamine **1**, which was readily obtained through literature procedures.[5] Alkenoylation of **1** and subsequent reduction of the aromatic nitro group of **2** gave the *N*-alkenoyl-2-amino-*N*-benzylbenzylamines **3**. Diazotisation of the latter followed by treatment with sodium azide gave the *N*-alkenoyl-2-azido-*N*-benzylbenzylamines **4** with yields ranging from fair to quantitative (Scheme 1). Due to its lability even at room temperature, unsubstituted **4a** was not fully characterised, since it partially undergoes spontaneous intramolecular cycloaddition to the [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepinone **5** during the reaction work-up. The complete conversion from **4a** to **5** was achieved by stirring a 0.1 M ethereal solution of the crude azide at room temperature. Methyl- and phenyl-substituted azides **4b**,**c** were far more stable than **4a** since, under the above reaction conditions, quantitative amounts of the starting materials were recovered. It was found that substrates **4b**,**c** reacted smoothly in refluxing toluene and in the presence of a little (1%) triethylamine, giving the azirino[1,2-*a*][1,4]benzodiazepinones **6b**,**c** and the 2-ethyl[1,4]benzodiazepin-3-one **7b**. Products, as well as reaction times, eluents and yields, are given in Table 1. Basic reaction media and eluents were needed because of the known lability of compounds such as **6** towards acidic species,[6] which can cause extensive resinification of the latter. Structural assignments for products **5**–**7** are unambiguous and rely upon analytical and spectral data. In particular, the *J*-values found for the protons of the aziridine ring of **6** (3.4–3.6 Hz) agree well with those reported for similar nitrogen bridgehead aziridines[7] and speak in favour for the *trans* arrangement of such protons, thus accounting for the depicted (1*S**,1a*R**) relative stereochemistry of **6b** and **6c**.

The above results deserve some comments in order to explain the observed reaction paths. It is well known that several Δ^2-1,2,3-triazolines thermally decompose to give aziridines and imine derivatives.[8] By occurring at room temperature, intramolecular cycloaddition of **4a** allows the isolation of **5** with good yields. Similar tricyclic structures, which are involved in the thermal decomposition of substituted azides **4b**,**c**, undergo loss of nitrogen followed by prototropic migration to give products **6** and/or **7**. The lack of imine derivatives when starting from azide **4c** may be ascribed to the stabilising effect of the phenyl group on the adjacent electron-deficient carbon atom.

This picture is substantiated by thermal decomposition of **5**, which was carried out in refluxing toluene and just gave a mixture of the aziridine **6a** and imine **7a** (Table 1 and Scheme 2). The latter decomposition was also carried out in $CDCl_3$ at 60 °C with monitoring of the reaction progress by ^{1}H NMR analyses. The disappearance of the signals of **5** was accompanied by the simultaneous appearance of two sets of signals easily attributable to **6a** and **7a**. At this point it needs to be added that the absence of geminal coupling in the case of **6a** parallels that observed for similar nitrogen bridgehead aziridines.[6,9]

As a further stage of our work, we undertook the synthesis of [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-4-ones **10** by means of nitrile imine cycloaddition onto the C=N double bond of imines **7a**,**b** (Scheme 3). Hence, treatment of the latter with the hydrazonoyl chloride **8**[10] in the presence of triethylamine, which generates nitrilimine intermediates **9**, gave cycloadducts **10** with good yields and full regioselectivity. The latter is consistent with similar behaviour of benzodiazepines as dipolarophiles.[11] To gain deeper insight about this point, we performed PM3 calculations[12] on the imine **7a**[13] (Table 2). The LUMO atomic coefficients of C and N (C=N double bond of **7a**) are quite different, so accounting for the exclusive formation of isomer **10** when the cycloaddition follows the usual HOMO-dipole (LUMO-dipolarophile) control.[14]

Some conclusions can be drawn from the present work: (*i*) the product output of the intramolecular cycloadditions of the *N*-alkenoyl aryl azides **4a**–**c** is strongly dependent upon reaction conditions and the kind of substituent placed on the alkenoyl moiety; (*ii*) we were able to synthesise, for the first time, the 3,3a,5,6-tetrahydro[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-4-one skeleton of **5** by means of a direct intramolecular azide cycloaddition; and (*iii*) our cycloadditive methodology provides a clean synthetic entry to compounds **5**, **7** and **10** of potential pharmacological interest.

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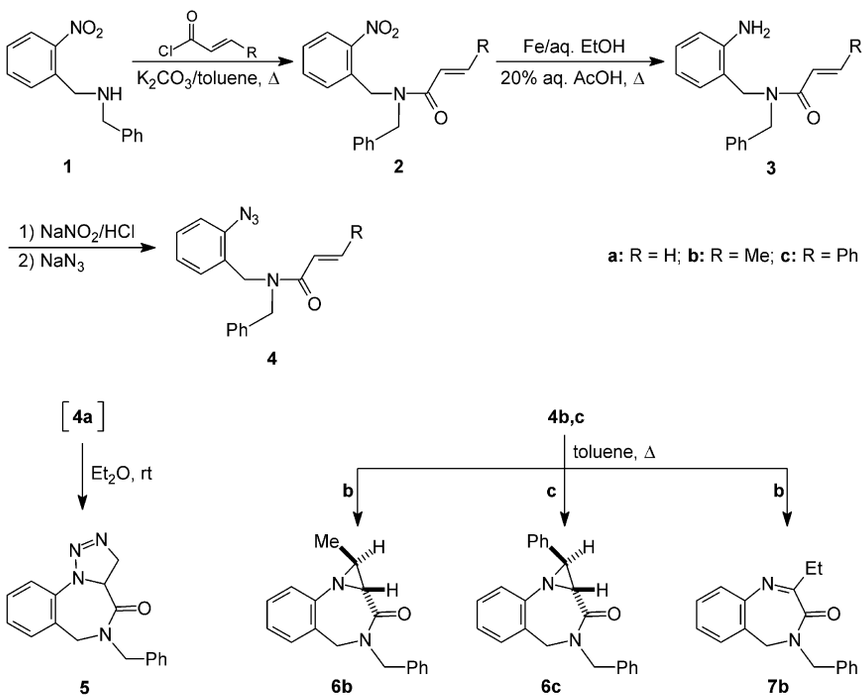
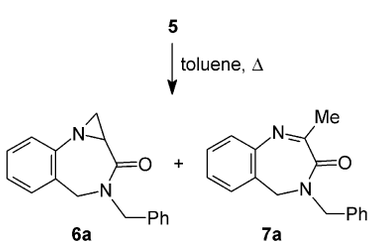
Table 1 Reaction of azides **4** and 1,2,3-triazolobenzodiazepine **5**

Compd	Time (*t*/h)	Products and yields (%)[c]			Eluent
		5	**6**	**7**	
4a[a]	20	74[d]			
4b[b]	1		11	79	*n*-Hexane–CH_2Cl_2–Et_2O–Et_3N 20 : 20 : 20 : 1
4c[b]	1		90[e]		
5[b]	1		42	56	*n*-Hexane–AcOEt–Et_3N 30 : 30 : 1

[a] In diethyl ether, rt. [b] In refluxing toluene. [c] Isolation yields. [d] From diisopropyl ether. [e] From *n*-hexane–benzene.



Scheme 1



Scheme 2

Table 2 PM3 Calculations on the imine **7a**[a]

Frontier molecular orbital[b]	Energy/eV	Atomic coefficients	
		C	N
HOMO	−9.177	+0.35	+0.13
LUMO	−0.889	+0.59	−0.25

[a] Geometry of **7a** was fully optimised with the PM3 method. [b] FMO of the C=N double bond of **7a**, bond length 135.1 pm.

Experimental

Mps were measured with a Büchi apparatus in open capillary tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR and ^{13}C NMR spectra were taken with a Bruker AC 300 or AMX 300 instrument for samples in $CDCl_3$ solutions at room temperature unless otherwise stated. Chemical shifts are given as ppm from tetramethylsilane; *J*-values are given in Hz. Because of severe overlapping of the signals, ^{1}H NMR spectra of compounds **2a**, **3a** and **7a** were taken in DMSO-d_6 solutions at 100 °C.

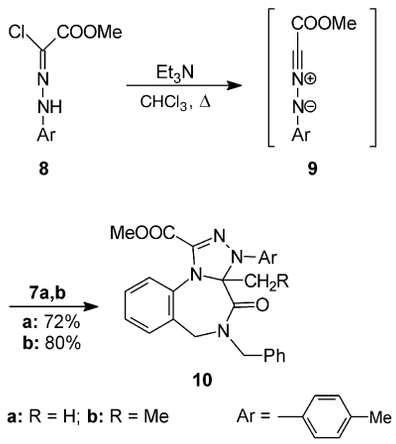
General procedure for the preparation of *N*-benzyl-2-nitro-*N*-(1-oxoalk-2-enyl)benzylamines 2

A solution of **1** (4.00 g, 16.5 mmol) in dry toluene (110 cm^3) was treated with K_2CO_3 (4.30 g, 31.2 mmol). The appropriate alkenoyl chloride (16.5 mmol) as a solution in dry toluene (4.0 cm^3) was added dropwise at 90 °C. The mixture was refluxed for 9 h, then the undissolved material was filtered off. The organic layer was washed with water (50 cm^3) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford acrylamides **2a**–**c** as undistillable oils, not analytically pure.

Compound **2a** (4.78 g, 98%) was a colourless oil; ν_{max} (neat)/cm^{-1} 1650; δ_H (DMSO-d_6; 100 °C) 4.56 (2H, s), 4.82 (2H, s), 5.70 (1H, dd, *J* 10.8, 3.0), 6.22 (1H, dd, *J* 17.5, 3.0), 6.68 (1H, dd, *J* 17.5, 10.8), 7.20–7.95 (9H, m); *m*/*z* (EI) 296 (M$^+$).

Compound **2b** (5.01 g, 98%) was a colourless oil; ν_{max} (neat)/cm^{-1} 1660; δ_H ($CDCl_3$; 60 °C) 1.94 (3H, d, *J* 8.0), 4.70 (2H, s), 4.94 (2H, s), 6.25 (1H, br s), 7.10–7.60 (9H, m), 8.05 (1H, br s); *m*/*z* (EI) 310 (M$^+$).

Compound **2c** (4.42 g, 72%) was a pale yellow oil; ν_{max} (neat)/cm^{-1} 1650; δ_H ($CDCl_3$) 4.72 (2H, s), 4.91 (1H, d, *J* 14.7), 4.98 (1H, d, *J* 14.7), 6.68 (1H, d, *J* 16.2), 7.10–7.70 (14H, m), 7.82 (1H, d, *J* 16.2); *m*/*z* (EI) 372 (M$^+$).



Scheme 3

General procedure for the preparation of 2-amino-*N*-benzyl-*N*-(1-oxoalk-2-enyl)benzylamines 3

A solution of a nitro compound **2** (11.0 mmol) in ethanol (15 cm^3) was treated with iron dust (4.92 g, 0.088 mol) and 20% aq. acetic acid (6.0 cm^3), and then refluxed for 4 h under vigorous stirring. The mixture was taken up with ethyl acetate (80 cm^3) and filtered over Celite. The organic layer was washed successively with 5% aq. sodium hydrogen carbonate (40 cm^3) and water (2 × 50 cm^3), and dried over sodium sulfate. Evaporation of the solvent gave amines **3a**,**b** as undistillable oils, not analytically pure, and solid amine **3c**.

Amine **3a** (2.19 g, 75%) was a pale yellow oil; ν_{max} (neat)/cm^{-1} 3420, 3350, 3235, 1640; δ_H (DMSO-d_6; 100 °C) 4.46 (2H, s), 4.60 (2H, s), 4.74 (2H, br s), 5.62 (1H, dd, *J* 10.7, 3.5), 6.20 (1H, dd, *J* 16.7, 3.5), 6.53 (1H, dt, *J* 7.2, 2.0), 6.68 (1H, dd, *J* 16.7, 10.7), 6.85–7.35 (8H, m); *m*/*z* (EI) 266 (M^+).

Amine **3b** (2.46 g, 80%) was a pale yellow oil; ν_{max} (neat)/cm^{-1} 3450, 3350, 3230, 1660; δ_H ($CDCl_3$) 1.84 (3H, dd, *J* 6.9, 1.7), 4.50 (2H, s), 4.54 (2H, s), 4.75 (2H, br s), 6.24 (1H, dq, *J* 14.8, 1.5), 6.60–7.45 (10H, m); *m*/*z* (EI) 280 (M^+).

Amine **3c** (2.84 g, 76%) mp 79 °C (from diisopropyl ether) (Found: C, 81.21; H, 5.94; N, 8.28. $C_{23}H_{22}N_2O$ requires C, 80.70; H, 6.43; N, 8.19%); ν_{max} (Nujol)/cm^{-1} 3440, 3340, 3230, 1660; δ_H ($CDCl_3$) 4.60 (2H, s), 4.65 (2H, s), 4.72 (2H, br s), 6.73 (1H, dt, *J* 7.8, 1.2), 6.83 (1H, d, *J* 15.4), 6.92 (1H, dd, *J* 8.0, 1.7), 7.11 (1H, dt, *J* 7.8, 1.7), 7.20–7.40 (11H, m), 7.82 (1H, d, *J* 15.4); *m*/*z* (EI) 342 (M^+).

General procedure for the preparation of 2-azido-*N*-benzyl-*N*-(1-oxoalk-2-enyl)benzylamines 4

A solution of an amine **3** (8.0 mmol) in 2 M hydrochloric acid (20 cm^3) was stirred and cooled to 0 °C. Sodium nitrite (1.10 g, 16.0 mmol) was added portionwise over a period of 30 min, and cold diethyl ether (50 cm^3) was added to the reaction mixture. Sodium azide (2.60 g, 40.0 mmol) was then added portionwise under vigorous stirring and ice-cooling. After 1 h, the organic layer was separated, washed successively with 5% aq. sodium hydrogen carbonate (50 cm^3) and water (50 cm^3), and dried over sodium sulfate. The solvent was removed under reduced pressure to give brown oily residues.

Acryloyl azide **4a** (2.29 g, 98%), ν_{max} (neat)/cm^{-1} 2130, 1650, was used without further purification.

In the remaining cases, the residue was chromatographed on a silica gel column with diethyl ether as eluent to give azides **4b**,**c** as undistillable oils, not analytically pure.

Azide **4b** (1.71 g, 70%) was a pale yellow oil; ν_{max} (neat)/cm^{-1} 2130, 1660; δ_H ($CDCl_3$) 1.84 (3H, d, *J* 6.9), 4.43 (2H, s), 4.61 (2H, s), 6.22 (1H, dq, *J* 15.0, 1.5), 7.00–7.40 (10H, m); *m*/*z* (EI) 306 (M^+).

Azide **4c** (1.47 g, 50%) was a pale yellow oil; ν_{max} (neat)/cm^{-1} 2125, 1650; δ_H ($CDCl_3$) 4.56 (1H, d, *J* 15.6), 4.62 (1H, d, *J* 15.6), 4.67 (2H, s), 6.73 (1H, d, *J* 15.5), 7.10–7.40 (14H, m), 7.82 (1H, d, *J* 15.5); *m*/*z* (EI) 280 (M^+).

5-Benzyl-3,3a,5,6-tetrahydro[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-4-one 5

A solution of **4a** (2.10 g, 7.2 mmol) in dry diethyl ether (72 cm^3) was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was crystallised from diisopropyl ether to give tricycle **5** (1.56 g, 74%) as a colourless solid, mp 85 °C (Found: C, 69.90; H, 5.55; N, 19.10. $C_{17}H_{16}N_4O$ requires C, 69.85; H, 5.52; N, 19.16%); ν_{max} (Nujol)/cm^{-1} 1675; δ_H ($CDCl_3$) 3.82 (1H, d, *J* 16.7), 4.37 (1H, d, *J* 14.9), 4.58 (1H, dd, *J* 16.6, 12.1), 5.00 (1H, d, *J* 14.9), 5.44–5.63 (3H, m), 6.85–7.30 (8H, m), 7.83 (1H, dd, *J* 7.8, 1.8); δ_C ($CDCl_3$) 50.16 (t), 50.56 (t), 53.93 (d), 68.52 (t), 116.65 (d), 122.04 (d), 127.7–129.8, 136.23 (s), 165.46 (s); *m*/*z* (EI) 292 (M^+).

Thermal behaviour of (*E*)-2-azido-*N*-benzyl-*N*-[1-oxobut-2-enyl]-benzylamine 4b

A solution of azide **4b** (1.56 g, 5.0 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry toluene (50 cm^3) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with *n*-hexane–dichloromethane–diethyl ether–triethylamine 20 : 20 : 20 : 1 as eluent. First fractions contained *4-benzyl 2-ethyl-4,5-dihydro-[1,4]benzodiazepin-3-one* **7b** (1.10 g, 79%) as a colourless oil (Found: C, 77.72; H, 6.44; N, 9.57. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06%); ν_{max} (Nujol)/cm^{-1} 1660; δ_H ($CDCl_3$) 1.32 (3H, t, *J* 7.4), 2.98 (2H, q, *J* 7.4), 3.99 (2H, s), 4.66 (2H, s), 6.80 (1H, dd, *J* 7.8, 1.2), 7.06 (1H, dt, *J* 8.0, 1.4), 7.20–7.35 (7H, m); δ_C ($CDCl_3$) 10.44 (q), 30.69 (t), 47.55 (t), 48.97 (t), 125.6–128.66, 136.00 (s), 146.07 (s), 162.37 (s), 168.52 (s); *m*/*z* (EI) 278 (M^+).

Further elution gave (1*S**,1a*R**)-3-benzyl-1-methyl-1,1a,3,4-tetrahydroazirino[1,2-*a*][1,4]benzodiazepin-2-one **6b** (0.18 g, 11%) as a colourless oil (Found: C, 77.75; H, 6.60; N, 9.55. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06%); ν_{max} (Nujol)/cm^{-1} 1640; δ_H ($CDCl_3$) 1.53 (3H, d, *J* 5.5), 2.33 (1H, dq, *J* 5.5, 3.6), 3.06 (1H, d, *J* 3.6), 3.58 (1H, d, *J* 14.8), 4.13 (1H, d, *J* 14.9), 4.96 (1H, d, *J* 14.9), 5.01 (1H, d, *J* 14.8),† 6.70–7.30 (9H, m); δ_C ($CDCl_3$) 27.35 (q), 53.33 (t), 62.83 (t), 69.03 (d), 116.50–132.20, 135.74 (s), 143.67 (s), 157.10 (s), 162.12 (s); *m*/*z* (EI) 278 (M^+).

Thermal behaviour of (*E*)-2-azido-*N*-benzyl-*N*-[1-oxo-3-phenylprop-2-enyl]benzylamine 4c

A solution of azide **4c** (1.84 g, 5.0 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry toluene (50 cm^3) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was crystallised from *n*-hexane–benzene to give *(1S*,1aR*)-3-benzyl-1-phenyl-1,1a,3,4-tetrahydroazirino[1,2-a][1,4]benzodiazepine-2-one* **6c** (1.53 g, 90%) as a colourless solid, mp 90 °C (Found: C, 81.22; H, 5.90; N, 8.30. $C_{23}H_{20}N_2O$ requires C, 81.15; H, 5.92; N, 8.23%); ν_{max} (Nujol)/cm^{-1} 1640; δ_H ($CDCl_3$) 3.32 (1H, d, *J* 3.4), 3.42 (1H, d, *J* 3.4), 3.67 (1H, d, *J* 14.9), 4.22 (1H, d, *J* 14.8), 5.00 (1H, d, *J* 14.8),‡ 5.09 (1H, d, *J* 14.9), 6.70–7.40 (14H, m); δ_C ($CDCl_3$) 45.41 (t), 47.88 (d), 48.50 (t), 49.33 (d), 121.9–129.7, 136.45 (s), 137.78 (s), 149.25 (s), 165.89 (s); *m*/*z* (EI) 340 (M^+).

Thermal behaviour of the 1,2,3-triazolobenzodiazepine 5

A solution of compound **5** (1.47 g, 5.0 mmol) and triethylamine (0.36 g, 3.6 mmol) in dry toluene (50 cm^3) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with

† After irradiation at δ 3.58: δ 5.01 (1H, s).
‡ After irradiation at δ 4.22: δ 5.00 (1H, s).

n-hexane–ethyl acetate–triethylamine 30 : 30 : 1 as eluent. First fractions contained *4-benzyl-2-methyl-4,5-dihydro-[1,4]benzodiazepin-3-one* **7a** (0.74 g, 56%) as a colourless oil (Found: C, 77.16; H, 6.14; N, 10.51. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.10; N, 10.60%); ν_{max} (Nujol)/cm^{-1} 1650; δ_H (DMSO-d_6; 100 °C) 2.48 (3H, s), 4.17 (2H, s), 4.58 (2H, s), 7.00–7.40 (9H, m); δ_C ($CDCl_3$) 25.17 (q), 47.84 (t), 49.40 (t), 124.80–130.3, 136.08 (s), 164.35 (s); *m*/*z* (EI) 264 (M^+).

Further elution gave *3-benzyl-1,1a,3,4-tetrahydroazirino[1,2-a][1,4]benzodiazepine-2-one* **6a** (0.56 g, 42%) as a colourless oil (Found: C, 77.33; H, 6.11; N, 10.51. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.10; N, 10.60%); ν_{max} (Nujol)/cm^{-1} 1650; δ_H ($CDCl_3$) 2.16 (1H, d, *J* 4.0), 2.74 (1H, d, *J* 5.8), 3.32 (1H, dd, *J* 5.8, 4.0), 3.61 (1H, d, *J* 14.8), 4.18 (1H, d, *J* 14.9), 4.95 (1H, d, *J* 14.9),§ 5.03 (1H, d, *J* 14.8), 6.70–7.30 (9H, m); δ_C ($CDCl_3$) 31.90 (t), 38.81 (d), 47.89 (t), 49.16 (t), 122.00–129.70, 136.39 (s), 165.16 (s); *m*/*z* (EI) 264 (M^+).

3a-Alkyl-5-benzyl-1-methoxycarbonyl-3-(4-methylphenyl)-3,3a,5,6-tetrahydro[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-4-ones 10

A solution of a benzodiazepinone **7a** or **7b** (4.0 mmol) and **8** (0.76 g, 4.0 mmol) in dry chloroform (40 cm^3) was treated with triethylamine (2.02 g, 20.0 mmol) and refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with dichloromethane–*n*-hexane 3 : 1. Crystallisation from diisopropyl ether gave a pure tricycle **10**.

Compound **10a** (1.31 g, 72%) was a yellow solid, mp 188 °C (Found: C, 71.29; H, 5.80; N, 12.39. $C_{27}H_{26}N_4O_3$ requires C, 71.35; H, 5.77; N, 12.33%); ν_{max} (Nujol)/cm^{-1} 1730, 1660; δ_H ($CDCl_3$) 1.65 (3H, s), 2.33 (3H, s), 3.71 (1H, d, *J* 14.7), 3.74 (3H, s), 4.37 (1H, d, *J* 15.1), 4.77 (1H, d, *J* 14.7), 4.92 (1H, d, *J* 15.1), 6.90–7.60 (13H, m); δ_C ($CDCl_3$) 20.76 (q), 24.02 (q), 48.90 (t), 52.02 (t), 52.45 (q), 119.94 (d), 127.40–129.30, 131.57 (d), 133.06 (s), 136.27 (s), 137.42 (s), 137.50 (s), 137.93 (s), 139.88 (s), 168.53 (s); *m*/*z* (EI) 454 (M^+).

Compound **10b** (1.50 g, 80%) was a yellow solid, mp 163 °C (Found: C, 71.84; H, 5.98; N, 12.03. $C_{28}H_{28}N_4O_3$ requires C, 71.78; H, 6.02; N, 11.96%); ν_{max} (Nujol)/cm^{-1} 1730, 1655; δ_H ($CDCl_3$) 1.06 (3H, t, *J* 7.3), 1.95 (1H, dq, *J* 16.7, 7.3), 2.33 (3H, s), 2.62 (1H, dq, *J* 16.7, 7.3), 3.61 (1H, d, *J* 14.9), 3.73 (3H, s), 4.14 (1H, d, *J* 15.1), 4.64 (1H, d, *J* 14.9), 4.96 (1H, d, *J* 15.1), 6.80–7.60 (13H, m); δ_C ($CDCl_3$) 20.55 (q), 22.71 (q), 48.16 (t), 51.73 (t), 52.20 (q), 117.66 (d), 127.20–129.30, 131.75 (s), 131.88 (s), 132.53 (d), 136.16 (s), 137.82 (s), 137.95 (s), 139.19 (s), 139.86 (s), 167.40 (s); *m*/*z* (EI) 468 (M^+).

§ After irradiation at δ 4.18: δ 4.95 (1H, s).

Acknowledgements

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