

An improved, easy and efficient method for the generation of nitrile oxides from nitronates for *in situ* 1,3-dipolar cycloaddition

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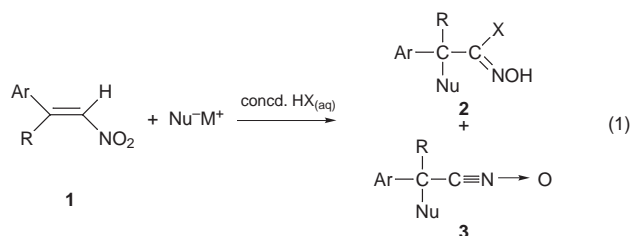
Received (in Cambridge) 4th December 1998, Accepted 3rd March 1999

The Michael addition of the diethyl allyl malonate anion to β -nitrostyrenes **1** generated nitronates **5**. Nitronates **5** could be converted into nitrile oxides **7** to undergo intramolecular nitrile oxide–olefin cycloaddition (INOC) to form medium to high yields (51–95%) of five-membered carbocycles **8** and **9** by using ethyl chloroformate in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). High yields (91%) of tricyclic compounds **11** and **12** were obtained when **1a** reacted with the anion of **10** under similar experimental conditions and procedures.

Introduction

Isoxazole and isoxazoline are useful intermediates in organic synthesis. Typically, these ring systems are synthesized from the [3+2] cycloaddition of nitrile oxides with an alkyne or alkene.¹ Nitrile oxides can be generated *in situ* from dehydration of the corresponding primary nitroalkanes² or dehydrohalogenation of the hydroximoyl chlorides.³

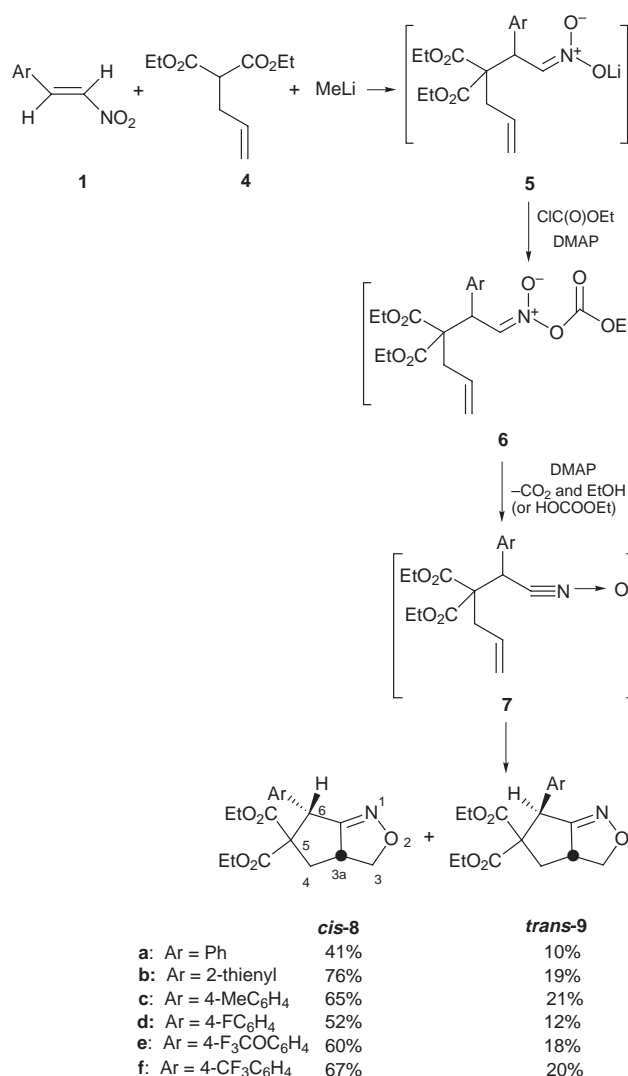
We have recently reported that high yields of the hydroximoyl halides **2** and/or the nitrile oxides **3** can be generated when β -nitrostyrenes **1** react with various nucleophiles and the resulting nitronates are added to ice cold concentrated hydrohalic acids [eqn. (1)]. Different heterocyclic products could be gener-



ated when hydroximoyl halides **2** were treated with triethylamine to generate nitrile oxides to undergo intramolecular nitrile oxide–olefin cyclizations (INOC).⁴ The characteristic of the one-pot synthesis of bicyclic compounds is to combine Michael addition, the generation of hydroximoyl halides by the use of concentrated hydrohalic acids and then nitrile oxides by the use of triethylamine in the same flask. It has also been reported that primary nitroalkanes react with benzenesulfonyl chloride or ethyl chloroformate to generate nitrile oxides to undergo INOC to generate various cycloadducts.⁵ Based on our previous study and literature reports,^{2–5} we developed an improved, easy and efficient method proceeding through a sequence of nitroalkene conjugate addition–nitronate transformation– β -elimination to generate nitrile oxides to undergo intramolecular cycloaddition to afford medium to high yields of five-membered carbocycles in one flask.

Results and discussion

Addition of the β -nitrostyrenes **1** (1 equivalent) to diethyl allyl malonate anion (1.5 equivalent), prepared from diethyl allyl malonate **4** and base, at 0 °C generated nitronates **5**. Instead of using sodium hydride, methyl lithium was used as base to increase the solubility in this study. After addition of



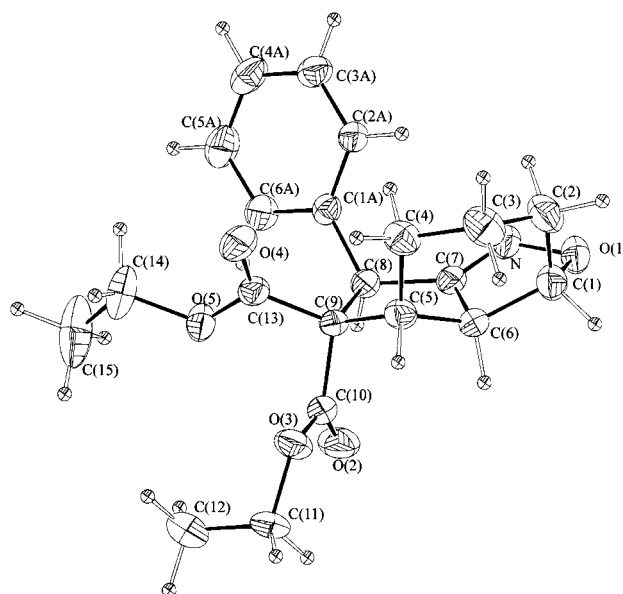
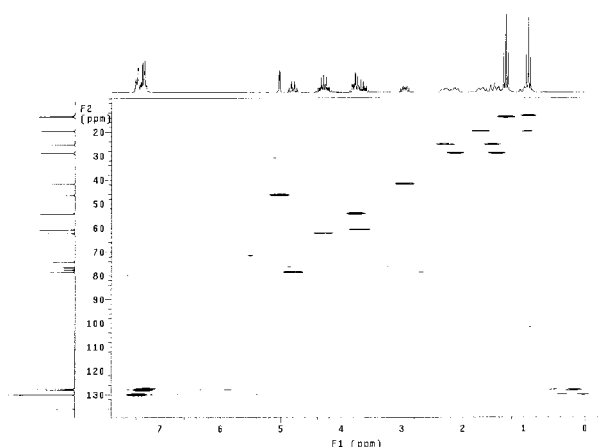
Scheme 1

the β -nitrostyrenes **1**, nitronates **5** were converted into nitronate esters **6** by slowly adding ethyl chloroformate (2 equivalents) and 4-dimethylaminopyridine (DMAP 0.1 equivalent) to the solution at the same temperature. The solution was warmed up to room temperature and was stirred for 2–10 hours. 51–95% of **8** (*cis* isomer) and **9** (*trans* isomer) were isolated by flash column

Table 1 Crystallographic and refinement data for compound **11**

Molecule	Compound 11
Empirical formula	C ₂₁ H ₂₅ NO ₅
Crystal system	Orthorhombic
Space group	<i>P bca</i>
Cell dimensions	
<i>a</i> /Å	12.613(3)
<i>b</i> /Å	15.097(6)
<i>c</i> /Å	20.378(10)
<i>V</i> /Å ³	3880(3)
Crystal size/mm	0.60 × 0.45 × 0.30
Formula weight	371.43
<i>Z</i>	8
<i>F</i> (000)	791.89
<i>D_c</i> /g cm ⁻³	1.272
<i>μ</i> /mm ⁻¹	0.04
<i>λ</i> /Å	0.70930
2 θ (max)	54.8
Diffractometer	Nonius (CAD-4)
Scan mode	$\theta/2\theta$
<i>hkl</i> mode	0 < <i>h</i> < 16, 0 < <i>k</i> < 19, 0 < <i>l</i> < 26
No. unique reflections	4445
No. observed <i>I_o</i> > 2.5 σ (<i>I_o</i>)	2569
Parameters	245
<i>R</i> ^a	0.049
<i>R_w</i> ^a	0.045
Goodness of fit ^a	1.33
Maximum Δ / σ	0.001
D-map maximum, e Å ⁻³	0.170
D-map minimum, e Å ⁻³	-0.230

^a $R = \sum |F_o - F_c| / \sum F_o$, $R_w = [\sum w(F_o - F_c)^2 / \sum w(F_o)^2]^{1/2}$, $GOF = [\sum w(F_o - F_c)^2 / (N_{obsd} - N_{param})]^{1/2}$.

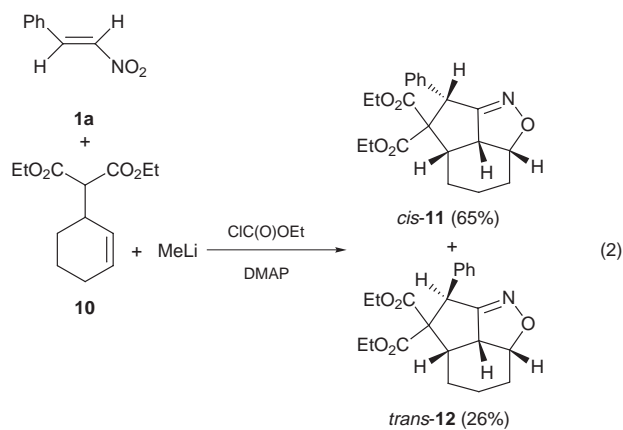
**Fig. 1** Molecular structure of compound **11**.**Fig. 2** HETCOR spectrum of compound **11**.

chromatography and the ratios of **8**:**9** were from 3.1:1 to 4.3:1.

Our previous study found that 56–90% of the same products **8** and **9** were formed and the ratios of **8**:**9** were from 3.5:1 to 7.5:1 when the sodium nitronates **5** were slowly added to ice-cold concentrated hydrochloric acid and the extraction solution was treated with triethylamine. The formation of products **8** and **9** was proposed to proceed through the generation of the nitrile oxides **7** as intermediate during the reaction.⁴ In this study, similar intermediates, nitrile oxides, were also proposed to be generated and the formation of nitrile oxides **7** was proposed to proceed through the elimination of CO₂ and EtOH (or HOC(O)OEt) from the nitronate ester **6**. The nitrile oxides then undergo INOC to generate compounds **8** and **9**. All experimental results are shown and a possible mechanism is proposed in Scheme 1.

Compounds **8** and **9** are easily isolated and purified by flash column chromatography. All the spectral data of products **8a**–**9a**–**e** are consistent with the literature report.^{4d} It is also easy to determine the stereochemistries of compounds **8f** and **9f** according to their ¹H NMR spectrum. For example, the C3a methine proton of *trans*-**9f** appears at ~4.60 ppm compared with that at ~3.80 ppm in *cis*-**8f** due to the deshielding effect of the aryl group.

After obtaining medium to high yields of compounds **8** and **9** in one pot, we tried to react β -nitrostyrene **1a** with the anion of **10** under similar experimental conditions and procedures. 65% of *cis* isomer **11** and 26% of *trans* isomer **12** were isolated after column chromatography [eqn. (2)]. The stereochemistry of compound *cis*-**11** has been determined by X-ray crystallography and the structure is shown in Fig. 1 and the crystal data are listed in Table 1.⁶ Similar to compounds **8f** and **9f**, the C(6) methine proton of *trans*-**12** appears at ~4.58 ppm and that of *cis*-**11** appears at ~3.76 ppm. The heteronuclear correlation spectroscopy (HETCOR) spectrum of compound *cis*-**11** is also shown in Fig. 2. Based on these spectra, all the proton and carbon chemical shifts can be assigned and all the data are shown in the Experimental section.



Compared with literature reports,^{1–5} several advantages are as follows: (a) the β -nitrostyrenes, ethyl chloroformate and DMAP are commercially available and inexpensive, (b) the experimental procedures are simple and the experimental conditions are mild, (c) all reactions occur in the same flask and the intermediates need not be isolated and (d) the final products are easily purified because the by-products are CO₂ gas and EtOH (or HOC(O)OEt) which is soluble in water during the workup procedure.

Conclusion

The Michael addition of the diethyl allyl malonate anion to

β -nitrostyrenes **1** to generate nitronates and the use of ethyl chloroformate in combination with DMAP to convert the nitronates into nitrile oxides to undergo intramolecular nitrile oxide-olefin cycloaddition (INOC) to form five-membered carbocycles in one-pot is a novel and practically useful development. Some new and known compounds are synthesized and reported in this paper. The application of this methodology to synthesize other compounds by using different nucleophiles is being studied and will be reported in the future.

Experimental

All reactions were performed in flame or oven-dried glassware under positive pressure of nitrogen or argon. Air and moisture sensitive compounds were introduced by the use of a syringe or cannula through a rubber septum. Compounds **1a–f**, ethyl chloroformate and 4-dimethylaminopyridine were purchased from Aldrich. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl and was degassed prior to reactions. Analytical thin layer chromatography was performed with E. Merck silica gel 60F254 glass plates and flash chromatography by the use of E. Merck silica gel 60 (230–400 mesh). GCMS were recorded on a HP 5890 GC/HP 5970B MSD, HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL EX-400 or Varian Gemini-200. All NMR data were obtained in CDCl_3 solution and chemical shifts (δ) were given in ppm relative to TMS. Elemental analysis was performed on a Perkin-Elmer 2400 instrument. All melting points were determined with a MEL-TEMP II apparatus and were uncorrected.

Typical procedures for the reaction of **1a** with the anion of diethyl allyl malonate (see Scheme 1)

At 0°C , 6 mmol (1.4 M, 5.86 mL) of methyllithium in diethyl ether was added to a solution of 5 mmol (1.000 g) of diethyl allyl malonate in 20 mL of THF and the solution was stirred for 30 minutes under nitrogen. At the same temperature, 5 mmol (0.745 g) of β -nitrostyrene **1a** in 30 mL of THF was slowly added to the solution described above. After the **1a** had disappeared (checking by TLC), 0.5 mmol (0.061 g) of 4-dimethylaminopyridine and 25 mmol (2.39 mL) of ethyl chloroformate were slowly added to the solution at 0°C and then the solution was warmed up to room temperature and was stirred for 10 hours. The solution was slowly added to 250 mL of ice-cold brine and extracted with CH_2Cl_2 (50 mL \times 3) and the extraction solution was washed with dilute aqueous sodium bicarbonate solution (100 mL) and distilled water (250 mL \times 2), dried over MgSO_4 , filtered and the solvent was evaporated to obtain the crude products. Flash column chromatography was used to purify the mixture using hexane-ethyl acetate as eluent to obtain 0.680 g of *cis* isomer **8a** (41%) and 0.167 g of *trans* isomer **9a** (10%). Similar procedures were enacted when **1b–f** reacted with diethyl allyl malonate anion to obtain products **8b–f** and **9b–f** and all the experimental results are shown in Scheme 1. All ^1H and ^{13}C NMR spectra of isolated products **8a–e** and **9a–e** were consistent with the literature report^{4d} and the spectral data of **8f** and **9f** were as follows.

8f (cis isomer). ^1H NMR (CDCl_3) δ 7.56 (d, J 8.4, 2H, Ar), 7.48 (d, J 8.4, 2H, Ar), 5.08 (d, J 0.8, 1H, 6-H), 4.65 (dd, J 9.4 and 8.0, 1H, 3-H), 4.42–4.07 (m, 3H, $\text{COOCH}_2\text{CH}_3$ and 3-H), 3.99–3.65 (m, 2H, $\text{COOCH}_2\text{CH}_3$ and 3a-H), 3.53–3.37 (m, 1H, $\text{COOCH}_2\text{CH}_3$), 2.71 (dd, J 13.6 and 10.6, 1H, 4-H), 2.58 (dd, J 13.6 and 8.4, 1H, 4-H), 1.27 (t, J 7.2, 3H, $\text{COOCH}_2\text{CH}_3$) and 0.77 (t, J 7.2, 3H, $\text{COOCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 170.54, 169.79, 167.90, 139.69 (Ar), 130.45 (Ar), 129.97 (q, J 32.65, Ar), 124.84 (q, J 3.8, Ar), 123.93 (q, J 270.50, CF_3), 75.13 (C-3), 69.63 (C-5), 62.37 ($\text{COOCH}_2\text{CH}_3$), 61.56 ($\text{COOCH}_2\text{CH}_3$), 51.42 (C-3a), 46.03 (C-6), 35.02 (C-4), 13.63 ($\text{COOCH}_2\text{CH}_3$)

and 12.90 ($\text{COOCH}_2\text{CH}_3$); GCMS (EI) m/z (rel. int.) 399 (M^+ , 30%), 380 (8), 326 (100), 280 (11), 252 (18), 198 (7), 171 (10), 127 (11) and 99 (8); Calc. for $\text{C}_{21}\text{H}_{25}\text{NO}_5$: C, 57.14; H, 5.05; N, 3.51%. Found: C, 56.9; H, 5.0; N, 3.8%.

9f (trans isomer). ^1H NMR (CDCl_3) δ 7.55 (d, J 8.4, 2H, Ar), 7.39 (d, J 8.4, 2H, Ar), 5.06 (s, 1H, 6-H), 4.75–4.49 (m, 2H, 3-H and 3a-H), 4.42–4.16 (m, 2H, $\text{COOCH}_2\text{CH}_3$), 3.93 (dd, J 11.4 and 6.8, 1H, 3-H), 3.70 (dq, J 10.6 and 7.2, 1H, $\text{COOCH}_2\text{CH}_3$), 3.37 (dq, J 10.6 and 7.2, 1H, $\text{COOCH}_2\text{CH}_3$), 2.87 (dd, J 12.8 and 6.8, 1H, 4-H), 1.83 (dd, J 12.8 and 10.6, 1H, 4-H), 1.28 (t, J 7.2, 3H, $\text{COOCH}_2\text{CH}_3$) and 0.73 (t, J 7.2, 3H, $\text{COOCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 170.48, 170.05, 169.11, 140.94 (Ar), 130.07 (q, J 32.65, Ar), 129.33 (Ar), 125.18 (q, J 3.8, Ar), 123.98 (q, J 270.8, CF_3), 75.16 (C-3), 71.36 (C-5), 62.21 ($\text{COOCH}_2\text{CH}_3$), 61.68 ($\text{COOCH}_2\text{CH}_3$), 55.15 (C-3a), 45.43 (C-6), 36.54 (C-4), 13.82 ($\text{COOCH}_2\text{CH}_3$) and 13.00 ($\text{COOCH}_2\text{CH}_3$); GCMS (EI) m/z (rel. int.) 399 (M^+ , 34%), 380 (10), 326 (100), 280 (17), 252 (34), 173 (11), 127 (25) and 99 (16); Calc. for $\text{C}_{21}\text{H}_{25}\text{NO}_5$: C, 57.14; H, 5.05; N, 3.51%. Found: C, 57.1; H, 5.2; N, 3.4%.

Typical procedures for the reaction of **1a** with the anion of **10** [cf. eqn. (2)]

At 0°C , 8 mmol (1.4 M, 7.81 mL) of methyllithium in diethyl ether was added to a solution of 7.5 mmol (1.800 g) of **10** in 50 mL of THF and then the solution was stirred for 30 minutes. At the same temperature, a 0.1 M solution of β -nitrostyrene **1a** in THF [5 mmol (0.745 g) in 50 mL] was slowly added to the solution described above under nitrogen. After the starting material **1a** had disappeared, 0.5 mmol (0.061 g) of 4-dimethylaminopyridine and 25 mmol (2.39 mL) of ethyl chloroformate were added to the solution at 0°C and then the solution was stirred for 10 hours at room temperature. The solution was slowly added to 250 mL of ice-cold brine and extracted with CH_2Cl_2 (50 mL \times 3) and the CH_2Cl_2 solution was washed with dilute sodium bicarbonate solution (100 mL) and distilled water (250 mL \times 2), dried over MgSO_4 , filtered and the solvent was evaporated to obtain an oily mixture. Flash column chromatography was used to purify the mixture using hexane-ethyl acetate as eluent to obtain about 1205 mg of *cis* isomer **11** (65%) and 464 mg of *trans* isomer **12** (26%) after evaporation of solvent.

11 (cis isomer). Mp $97\text{--}98^\circ\text{C}$ (hexane-ethyl acetate); ^1H NMR (CDCl_3) δ 7.41–7.19 (m, 5H, Ph), 5.03 (d, J 1.2, 1H, PhC(8)H), 4.80 (q, J 8.4, 1H, C(1)H), 4.43–4.17 (m, 2H, C(14)H₂), 3.86–3.55 (m, 3H, C(11)H₂ and C(6)H), 2.96 (dt, J 12.2 and 7.2, 1H, C(5)H), 2.34–2.09 (m, 2H, C(4)H and C(2)H), 1.84–1.38 (m, 3H, C(3)H, C(4)H, and C(2)H), 1.30 (t, J 7.2, 3H, C(15)H₃), 1.10–0.84 (m, 1H, C(3)H) and 0.93 (t, J 7.2, 3H, C(12)H₃); ^{13}C NMR (CDCl_3) δ 171.42, 170.10, 166.39, 135.91 (Ph), 130.01 (Ph), 127.89 (Ph), 127.40 (Ph), 78.50 [C(1)], 74.10 [C(9)], 62.27 [C(14)], 60.61 [C(11)], 54.06 [C(6)], 46.34 [C(8)], 41.71 [C(5)], 28.87 [C(2)], 25.26 [C(4)], 19.63 [C(3)], 13.69 [C(15)] and 13.22 [C(12)]; GCMS (EI) m/z (rel. int.) 372 [$\text{M} + 1$], 100%, 371 (M^+ , 51), 299 (14), 298 (85), 297 (42), 252 (18), 224 (21), 206 (13), 167 (7), 135 (22), 115 (11), 91 (6) and 77 (5); HRMS (EI) Calc. for $\text{C}_{21}\text{H}_{25}\text{NO}_5$: M , 371.1732. Found 371.1747 (Calc.: C, 67.91; H, 6.78; N, 3.77%. Found: C, 68.0; H, 6.8; N, 3.8%). The X-ray crystal data are listed in Table 1 and the X-ray molecular structure is presented in Fig. 1. The HETCOR spectrum is also shown in Fig. 2.

12 (trans isomer). Mp $90\text{--}91^\circ\text{C}$ (hexane-ethyl acetate); ^1H NMR (CDCl_3) δ 7.24 (s, 5H, Ph), 5.05 (d, J 2.2, 1H, PhC(8)H), 4.80 (q, J 8.4, 1H, C(1)H), 4.59 (dd, J 8.4 and 7.8, 1H, C(6)H), 4.41–4.12 (m, 2H, C(11)H₂), 3.71 (dq, J 10.6 and 7.2, 1H, C(14)H), 3.20 (dq, J 10.6 and 7.2, 1H, C(14)H), 2.93 (dt, 1H,

J 12.2 and 7.0, C(5)H), 2.13–2.02 (m, 1H, C(4)H), 1.74–1.58 (m, 2H, C(2)H and C(3)H), 1.44–1.26 (m, 1H, C(4)H), 1.27 (t, *J* 7.2, 3H, C(12)H₃), 1.10–0.90 (m, 2H, C(2)H and C(3)H), 0.69 (t, *J* 7.2, 3H, C(15)H₃); ¹³C NMR (CDCl₃) δ 171.57, 169.54, 168.93, 136.79 (Ph), 128.90 (Ph), 128.19 (Ph), 127.54 (Ph), 78.91 [C(1)], 76.42 [C(9)], 61.57 [C(11)], 61.24 [C(14)], 56.94 [C(6)], 44.47 [C(8)], 40.33 [C(5)], 28.37 [C(2)], 24.08 [C(4)], 20.20 [C(3)], 13.90 [C(12)] and 13.02 [C(15)]; GCMS (EI) *m/z* (rel. int.) 372 [(M + 1)⁺, 6%], 371 (M⁺, 27), 299 (18), 298 (100), 297 (37), 252 (14), 224 (19), 206 (10), 165 (7), 115 (12), 91 (9) and 77 (13); HRMS (EI) Calc. for C₂₁H₂₅NO₅: *M*, 371.1732. Found 371.1707 (Calc.: C, 67.91; H, 6.78; N, 3.77%. Found: C, 68.1; H, 6.8; N, 3.6%).

Acknowledgements

Funds provided by the National Science Council of the Republic of China (Grant No. NSC 88-2113-M-003-001), and X-ray data collected and processed by Professor C.-H. Ueng and Mr T.-S. Kuo of the National Taiwan Normal University, are gratefully acknowledged.

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- Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available via the RSC Web page (<http://www.rsc.org/authors>). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/308.

Paper 8/09490J