SHORT PAPER

J. Chem. Research (S),
2000, 339–341

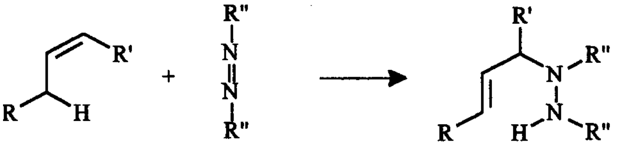
Tandem ene addition/Diels-Alder cycloaddition reactions of methyl linoleate with 4-phenyl-1,2,4-triazoline-3,5-dione and diethyl azodicarboxylate†

Jill F. McLellan,[a] Roy M. Mortier,[b] Stefan T. Orszulike[b] and R. Michael Paton[a]*

[a]*Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK,*
[b]*Castrol International, Technology Centre, Whitchurch Hill, Pangbourne, Reading RG8 7QR, UK*

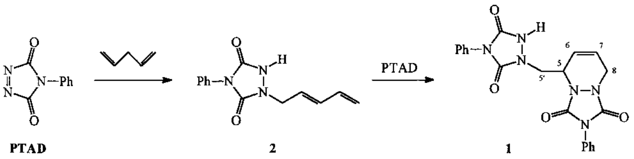
Treatment of methyl linoleate with 4-phenyl-1,2,4-triazoline-3,5-dione affords 1:1 adducts resulting from ene addition, and 1:2 adducts formed by ene addition followed by Diels Alder cycloaddition. The corresponding reaction of diethyl azodicarboxylate yields predominantly 1:1 ene products.

Electron-deficient azo compounds, such as diethyl azodicarboxylate (DEAD) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), readily undergo ene additions[1,2] to electron-rich alkenes possessing an allylic hydrogen. The products have structures in which the ‘ene’ double bond has migrated from the α, β- to the β,γ-position and the ‘enophile’ is attached as a hydrazino substituent at the resulting allylic carbon atom (Scheme 1). We have previously reported[3] that mono-unsaturated lipids, including methyl oleate and oleyl acetate undergo such ene reactions with DEAD and PTAD under mild conditions to afford 1:1 adducts, and that this process can be utilised to modify the liquid wax ester jojoba oil.[4,5] We now describe the reactions of these activated azo enophiles with methyl linoleate, which was selected as a model for the 1,4-diene-containing components of triglycerides such as those present in sunflower, safflower and grape-seed oils.



Scheme 1

Preliminary experiments were carried out with 1,4-pentadiene, which mimics the central methylene-interupted diene fragment of methyl linoleate. A solution of PTAD in dichloromethane was treated with an excess of 1,4-pentadiene and the mixture stirred at 0°C until the distinctive red colour of the enophile had faded. Removal of the solvent and unreacted diene afforded a white solid (93%) which was identified from its spectroscopic properties as 2:1 adduct **1**. In the ^{13}C NMR spectrum there are signals characteristic of both 1-alkyl-4-phenylurazole[3,6] and *s*-triazolo[1,2-*a*]pyridazine-1,3-dione[6,7] moieties; these include four carbonyl peaks (151.59, 152.75, 153.48 and 153.68 ppm) and two alkene CH peaks (122.06 and 123.29 ppm) for C-6 and C-7, in addition to signals attributable to 5-CH, 5′-CH_2, 8-CH_2 and the carbons of two phenyl rings. In the ^1H NMR spectrum there are peaks for the alkene protons (6-H, 7-H) and the diastereotopic protons attached to C-5′ and C-8, in addition to signals for 5-H and ten phenyl ring protons. Formation of compound **1** is consistent with a mechanism (Scheme 2) involving initial ene addition of PTAD to 1,4-pentadiene, followed by hetero Diels–Alder cycloaddition of a second PTAD to the conjugated diene unit in the 1:1 adduct **2**. PTAD is known to be both a powerful enophile and dienophile towards electron-rich alkenes and 1,3-dienes.[2]



Scheme 2

Having established the tandem ene / Diels–Alder nature of the addition of PTAD to 1,4-pentadiene, the corresponding reaction with methyl linoleate was examined. A 1:1 mixture of PTAD and methyl linoleate in dichloromethane was stirred at 0°C. The red colour faded rapidly and after 2.5 minutes the solution was pale yellow. Removal of the solvent and chromatography of the residue afforded, in order of elution, unreacted methyl linoleate (32%), a mixture of 1:1 adducts (36%), and a mixture of 2:1 adducts (32%).

Four isomeric 1:1 adducts (**3a, 3b, 4a, 4b**) can be envisaged, as depicted in Scheme 3. Regioisomers **3a** and **3b** result from bonding of the urazole to C-10 and C-12, respectively, of the linoleate and consequentially the alkene groups in the produce form a 1,5-diene The other pair of isomers **4a**/**4b** are formed by attachment of the enophile at C-9/C-13 with concomitant shift of the alkenes into conjugation. The ^1H and ^{13}C NMR spectra reflect the complexity of the mixture. A full assignment (Table 1) can, however, be accomplished for the key region involving the urazole and diene moieties by selective decoupling experiments, which reveal that the major 1:1 products are compounds **3a** and **3b**. The signal at 2.70 ppm for the methylene protons at C-11 in methyl linoleate is absent in the product, while there is a new inter-double bond methylene group CH_2(e) with diastereotopic protons (e_A and e_B); these give rise to distinctive dddd-mutliplets at 2.35 and 2.54 ppm, with a mutual geminal coupling of 15.0 Hz. The signals for H(d) adjacent to the urazole and the *trans*-alkene protons H(b)/H(c) (J = 15.5 Hz) are broadly similar to those reported[3] for the corresponding 1:1 adducts between PTAD and methyl oleate. The other olefinic proton protons H(f) and H(g) show a 10.5 Hz mutual coupling, confirming that the *cis* geometry at this location in the starting material is retained. Traces (~10%) of the conjugated 1:1 adducts **4a** and **4b** were also present, as evidenced by signals characteristic of the *E*,*Z*-1,3-diene unit [H(d) 5.58, H(e) 6.52,m H(f) 5.87 ppm; $J_{d,e}$ 15.0, $J_{e,f}$ 11.0 $J_{f,g}$ 10.5 Hz]. The ^{13}C NMR spectrum of the mixture

---

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

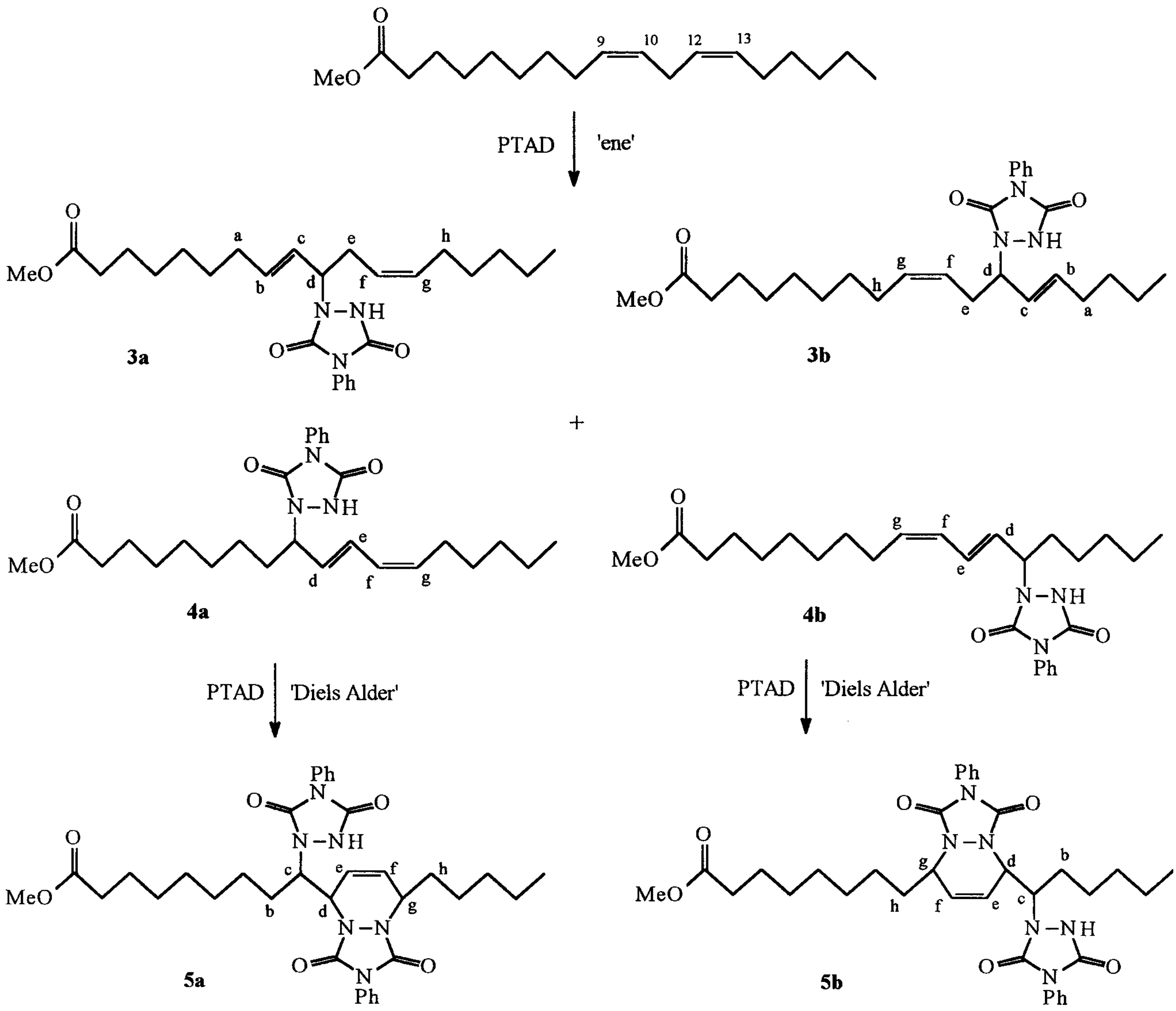
Table 1 Selected NMR data [$CDCl_3$; 360 MHz (^1H), 90 MHz)^2H)] for adducts **3, 5** and **6**

δ_H/pp,	**3**	**5**	**6**	δ_C/ppm	**3**	**5**	**6**
H(a)	1.96 (m)	a	a	(c(a)	31.29, 31.48	a	25.48
H(b)	5.74 (ddd)	a	a	C(b)	134.95, 135.17	a	31.09
H(c)	5.43 (dd)	4.36, 4.85 (m)	4.59 (m)	C(c)	124.95	53.63,^{b} 54.04^b	59.70
H(d)	4.65 (q)	4.59, 4.65 (m)	5.56 (dd)	C(d)	57.80, 57.84	55.65^b, 56.90^b	130.45
H(e)	2.35 (dddd)	5.91, ~6.0^c (dd)	6.40 (dd)	C(e)	30.24	119.10	127.62
	2.54 (dddd)			C(f)	123.42, 123.53	121.76	127.62
H(f)	5.30 (dt)	~6.0^c	5.90 (t)	C(g)	132.66, 132,82	54.42,^{b} 54.65^b	132.46
H(g)	5.45 (m)	4.55 (m)	5.40 (dt)	C(h)	26.64	a	27.40
H(h)	1.96 (m)	1.78 (m)	2.12 (q)	C=O	151.23, 173.66	151.7–153.4,^{d} 173.78	
	1.55.69, 156.41, 173.96						

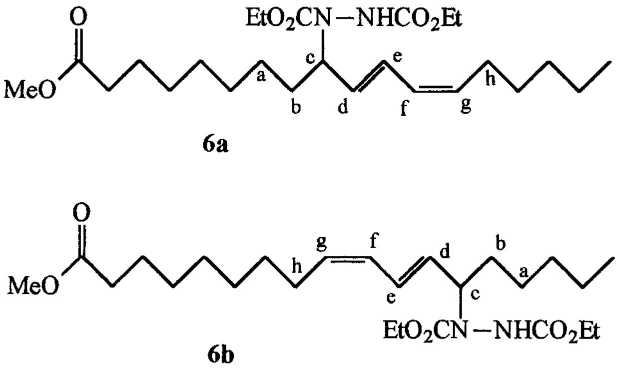
$^{(a)}$Not determined, within CH_2 envelope; $^{(b)}$alternative assignments; $^{(c)}$overlapping signals; $^{(d)}$ 8 peaks.

confirms that the non-conjugated diene adducts are the major products and provides further evidence for the presence of conjugated dienes, **4a**/**4b** as minor components. The doubling of some carbon signals is consistent with the formation of both regioisomers **3a** and **3b** in similar amounts.

The 2:1 products were identified as tandem Diels–Alder adducts **5a** and **5b** resulting from the hetero-Diels–Alder reaction of PTAD to conjugated dienes **4a** and **4b** by comparison of their NMR spectra with those of model compound **1**. There are three asymmetric centres in each product, two of which are part of the pyridazoline ring; two diastereomers are thus possible, and these can be distinguished by NMR spectroscopy. In the ^1H NMR spectrum there are two distinct sets of signals for each of the methine protons H(c), H(d) and H(g). The signals for H(c) adjacent to the urazole substituent are well separated ($\Delta\delta$ = 0.49 ppm) thus allowing the diastereomeric ratio to be estimated as 54:46. Two pairs of signals were also evident for the olefinic protons H(e) and H(f). Six peaks in the ^{13}C NMR spectrum for the three methine carbons provides further evidence for the presence of two diastereomers. The ease of Diels Alder adduct formation between triazolinediones and 1,3-dienes[6–8] accounts for only traces of conjugated dienes **4a**/**4b** being detected in the 1:1 adduct fraction.



DEAD is less reactive than PTAD as both enophile and dienophile,[3] and the addition reactions with alkenes required heating. After 48 hours at 77°C a 1:1 mixture of DEAD and methyl linoleate in CCl_3CH_3 afforded unreacted methyl linoleate (13%), a fraction containing 1:1 adducts (67%), and a fraction containing 2:1 products (11%). A repeat experiment using an excess of DEAD (2:1) resulted in complete consumption of the linoleate and yielded 38% 1:1 adducts and 36% 2:1 products. The principal component at the 1:1 adduct fraction was shown by NMR spectroscopy (Table 1) to be compounds **6a** and **6b**. In the ^{1}H NMR spectrum there is a characteristic absorption pattern for the *E*,*Z*-conjugated diene unit [H(d) 5,56, H(e) 6, 40, H(f) 5.90, H(g) 5.40 ppm; $J_{d,e}$ 15.1, $J_{e,f}$ 11.3, $J_{f,g}$ 10.5 Hz]. The initial ene reaction with DEAD appears to be much more periselective than that with PTAD; in the former case the enophile reacts almost exclusively at C-9/C-13 and one of the more reactive interdiene methylene hydrogens, whereas with PTAD similar amounts of products result from attack at C-9/C-12 and C-10/C-12. These results show that 1,5-dialkyl-substituted-1,4-dienes, such as those found in the lipid component of high-linoleate vegetable oils, react readily with electron-deficient azo enophiles, and that this process therefore offers scope for the functionalisation of such oils.



6a

6b

Scheme 3

Experimental

General procedure for the reactions of PTAD and DEAD: The enophile was added to a solution of the ene component in dichloromethane and the mixture stirred until the colour had faded; the reaction was also monitored by TLC. The solvent was removed *in vacuo* and the products isolated from the residue by dry flash chromatography (Fluka GF_{254} silica, gradient elution with hexane/Et_2O). Reactions with PTAD were carried out in CH_2Cl_2 at 0°C and those with DEAD in 1,1,1-trichloroethane under reflux (~77°C). The elemental compositions of the products were determined by high resolution mass spectrometry, and their structures established from their ^{1}H and ^{13}C NMR spectra, which were recorded in $CDCl_3$ at 360 MHz (^{1}H) and 90 MHz (^{13}C). FAB mass spectra used a thioglycerol matrix.

PTAD with 1,4-pentadiene: Using a reactant ratio = 1:3 this reaction afforded 2-phenyl-5-(4-phenyl-1-urazolymethyl)-*s*-triazolo[1,2-*a*]pyridazine-1,3-dione (**1**) as a white solid (93%), *m/z* (FAB) 419.14676 (M^+ + 1, $C_{21}H_{19}N_6O_4$ requires 419.14677); $\delta_H$ppm 8.95 (1 H, br s, NH), 7.23–7.47 (10 H, m, PhH), 5.92 (1 H, dt, H-7), 5.69 (1 H, dm, H-6), 4.83 (1 H, m, H-5), 4.24 (1 H, ddd, H-8a), 3.97, 3.95 (2 H, m, H-5′a and H-8b), 3.60 (1 H, dd, H-5′b); $J_{X\text{-}Y}$/Hz 5′a-5′b 15.1, 5′a-5 7.2, 5′b-5 2.6, 5-6 ~4, 6-7 10.4, 6-8a ~2, 6-8b ~2, 7-8a 4.0, 7-8b ~2, 8a-8b 15.9; δ_C/ppm 151.59, 52.75, 153.48, 153.68 (C=O), 125.80, 125.92, 128.30, 128.98, 130.62, 130.85 (2 C_6H_5), 122.06 123.29 (C-6, C-7), 50.89 (C-5), 44.35, 46.68 (C-5′ and C-8).

PTAD with methyl linoleate: Reaction ratio = 1:1. From the reaction mixture were isolated, in order of elution, unreacted methyl linoleate (32%), 1:1 adducts (**3a/3b, 4a/4b**) (36%) *m/z* (FAB) 470.30189 (M^+ + 1, $C_{27}H_{40}N_3O_4$ requires 470.30186), and 2:1 adducts (**5a/5b**) (32%) (*m/z* (FAB) 645.34010 (M^+ + 1, $C_{35}H_{45}N_6O_6$ requires 645.34003); selected NMR data are given in Table 1.

DEAD with methyl linoleate: Using a 1:1 reactant ratio the following products were isolated: unreacted methyl oleate (13%), 1:1 adducts (**6a/6b, 7a/7b**) (67%) *m/z* (FAB) 469.32775 (M^+ + 1, $C_{25}H_{45}N_2O_6$ requires 469.32774), and 2:1 adducts (11%) (*m/z* (FAB) 643.39179 (M^+ + 1, $C_{31}H_{55}N_4O_{10}$ requires 643.39179). A repeat experiment using a 2:1 reactant ratio afforded unreacted methyl linoleate (trace), 1:1 adducts (38%) and 2:1 adducts. (36%).

Received 30 April 2000; accepted 3 June 2000
Paper 00/305

References

1 G.V. Boyd in The Chemistry of Double-Bonded Functional Groups, Patai, S, (ed.), Wiley, New York, 1989, Ch 8.
2 S. Radl, *Adv. Heterocycl.Chem.*, 1996, **67**, 119.
3 J.F. McLellan, R.M. Mortier, S.T. Orszulik, and R.M. Paton, *Chem. Ind. (Lond.)*, 1993, 94.
4 J. Wisniak, The Chemistry and Technology of Jojoba Oil, American Oil Chemists Society, Champaign, 1987.
5 F.D. Gunstone, Endeavour, New Series, 1990, **14**, 40.
6 V. Bolik, A.L. Hamilton, J.F. McLellan, R.M. Mortier, S.T. Orszulik, and R.M. Paton, unpublished observations.
7 J F. Jensen, C.S Foote. *J. Am. Chem. Soc.*, 1987, **109**, 6376.
8 G. Dobson, *J. Am. Oil Chem. Soc.*, 1998, **75**, 137.