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DIMETHYL ISOPROPYLIDENE MALONATE, THE "FORGOTTEN" DIENOPHILE

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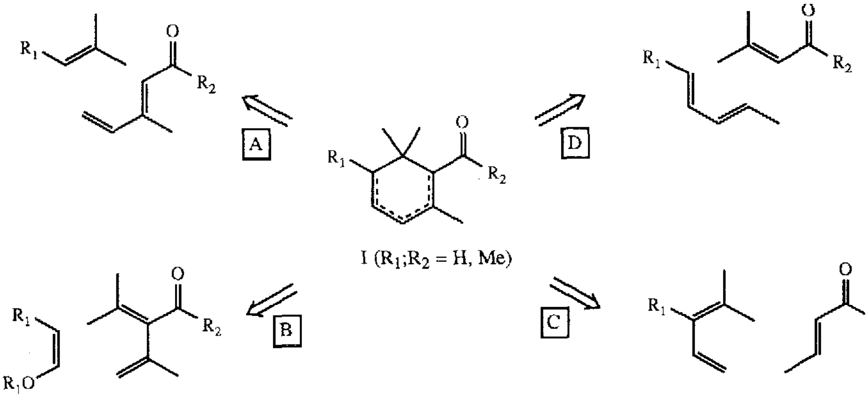
Summary: Despite the reported unreactivity of dimethyl isopropylidene malonate **1a** as a *Diels-Alder* dienophile, moderate yields of cycloadducts are obtained with various dienes in refluxing $CHCl_3$ in the presence of catalytic amounts of $AlCl_3$.

The construction of the 6-substituted 1,1,5-trimethylcyclohexane substructure I, a characteristic lipophilic moiety of many fragrances [1] and carotenoids [2], via a *Diels-Alder* approach (of type A [3], B [3], C[4] or D[5], *cf. Figure)* has been extensively investigated.

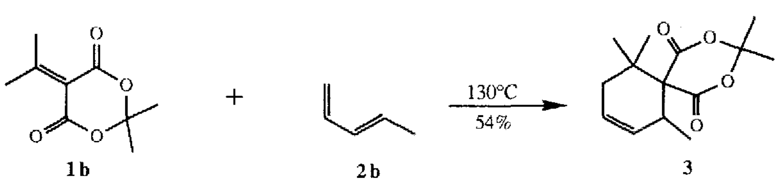
Figure



I (R_1;R_2 = H, Me)

With regard to the type D *Diels-Alder* reaction, *Cookson et al.*, in 1974, reported the unreactivity of dimethyl isopropylidene malonate (**1a**) with trans-1,3-pentadiene (**2b**) under a variety of conditions [3]; in contrast, *Dauben* subsequently described the uncatalysed cycloaddition of isopropylidene malonate **1b** with the same diene to afford cycloadduct 3 in 54% yield [5b] (*cf. Scheme 1*).

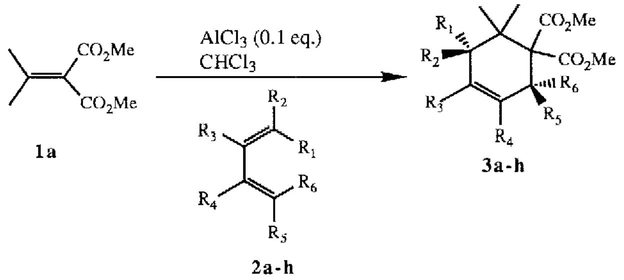
Scheme 1

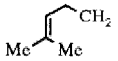


1b **2b** 3

This discrepancy encouraged us to re-investigate the *Diels-Alder* reactivity of **1a** with various 1,3-dienes; our results are summarised in the *Table*.

Table



Entry	R2	R3	R4	R5	R6	R1	Temp. °C	Time h	Yield of 3a-h % isolated
a	H	Me	H	H	H	H	35	18	71
b	H	H	H	Me	H	H	43	18	50
c	H		H	H	H	H	62	18	41
d	H	Me	Me	H	H	H	62	18	72
e	H	Me	H	Me	H	H	62	18	71
f	Me	H	H	Me	H	H	62	87	25[1]
g	H	H	H	H	–CH_2–		62	18	44
h	H	H	H	H	CH_2–CH_2		62	24	20[1]

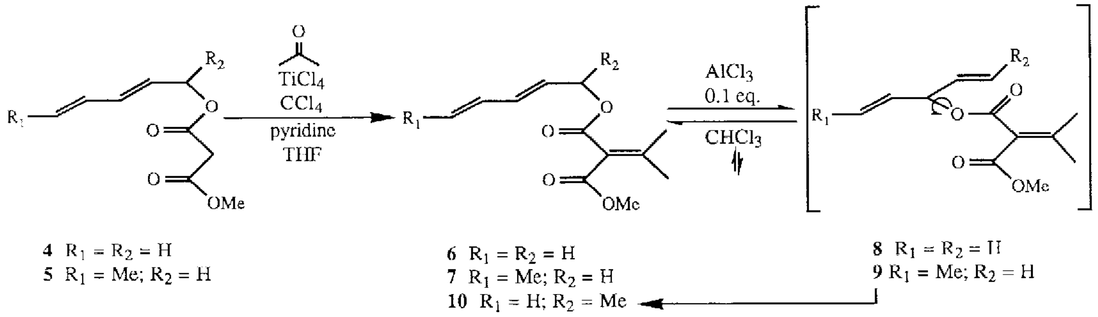
[1] $AlCl_3$ (0.3 equiv.)

Reaction of **1a** with isoprene (**2a**) in refluxing $CHCl_3$ in the presence of $AlCl_3$ (0.1 mole equiv.) afforded *Diels-Alder* adduct **3a** in 71% yield. In comparison, the sterically more demanding **2b** gave cycloadduct **3b** in 50% yield. This steric effect was also observed in the series of dienes **2d** (72% yield), **2e** (71% yield) and **2f** (25% yield with $AlCl_3$ (0.3 mole equiv.) and a prolonged reaction time). The lower reactivity of **2f** is partially due to steric hindrance, since even cyclic s-*cis* fixed dienes such as cyclopentadiene (**2g**, 44% yield) and 1,3-cyclohexadiene (**2h**, 20% yield, $AlCl_3$, 0.3 mole equiv.) also exhibit unusually low reactivity.

The ready retro *Diels-Alder* reaction of **3g** and **3h** is indicated by the absence of molecular ions in their MS and predominant fragments at 66 m/e and 80 m/e, corresponding to **2g** and **2h** respectively.

Several examples of activated trisubstituted dienophiles are known to perform intramolecular [4 + 2] cycloadditions [6] and such an approach was also briefly examined. Accordingly the esters **4** and **5** [7] were condensed with acetone ($TiCl_4/CCl_4$/pyridine/THF) [8] to afford the isopropylidene malonates **6** and **7** in 52% and 60% yields respectively (*Scheme 2*).

Scheme 2



4 $R_1 = R_2 = H$
5 $R_1 = Me; R_2 = H$

6 $R_1 = R_2 = H$
7 $R_1 = Me; R_2 = H$
10 $R_1 = H; R_2 = Me$

8 $R_1 = R_2 = H$
9 $R_1 = Me; R_2 = H$

After prolonged heating in refluxing $CHCl_3$ in the presence of $AlCl_3$ (0.1 mole equiv.), **6** was recovered unchanged. Increasing the temperature (refluxing xylene) or the amount of catalyst (0.3 → 1 mole equiv.) as well as employing Me_2AlCl or $LiClO_4$ [9] was also not successful. When **7** was refluxed in $CHCl_3$ with $AlCl_3$ (0.1 mole equiv.), a 1.7:1 mixture of **7** and **10** (*Scheme 2*) was recovered in 82% yield. We believe that, in analogy with Mg^{2+} or Cu^{2+} catalysed rearrangements [10], the putative ester **9** could be a plausible intermediate for the isomerisation of **7** to **10** [11] *via* a double allylic rearrangement.

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[11] IR spectra: Perkin-Elmer 297 spectrometer, cm^{-1}; ^1H and ^{13}C-NMR spectra ($CDCl_3$): Bruker WH 360 (360 and 90 MHz), δ [ppm] rel. to TMS (= 0 ppm); coupling constants J in Hz
MS: Varian MAT 112 spectrometer (ca 70 ev); intensities in % relative to the base peak (100%).
3a) IR 2950, 1730, 1435, 1240.
^1H-NMR 1.09 (s, 6H), 1.63 (s, 3H), 2.09 (brs, 2H), 2.66 (m, 2H), 3.68 (s, 6H), 5.26 (m, 1H).
^{13}C-NMR 23.3q; 26.0q; 30.7t; 34.8s; 43.9t; 51.9q; 59.2s; 116.3d; 133.65s; 171.4s.
MS $M^{+\cdot}$ 240 (9); 180 (43); 165 (25); 121 (**100**); 105 (36).
3b) IR 2950, 1730, 1435, 1050.
^1H-NMR 0.91 (s, 3H), 1.03 (d, J=7, 3H), 1.17 (s, 3H), 1.7 (m, 1H), 2.77 (m, 1H), 3.11 (m, 1H), 3.66 (s, 3H), 3.77 (s, 3H), 5.35 (dxd, J_1=9, J_2=3, 1H), 5.63 (m, 1H).
^{13}C-NMR 18.4q; 26.0q; 27.6q; 33.4d; 35.3s; 39.9t; 51.1q; 51.7q; 64.3s; 124.8d; 128.3d; 170.0s; 171.5s.
MS $M^{+\cdot}$ 240 (4); 180 (23); 176 (38); 121 (**100**); 105 (36); 82 (48).

3c)	IR	2940, 1730, 1430, 1050.
	^{1}H-NMR	1.09 (s, 6H); 1.6 (s, 3H); 1.67 (s, 3H); 1.93 (m, 2H); 2.04 (m, 2H); 2.1 (brs, 2H); 2.68 (m, 2H); 3.68 (s, 6H); 5.05 (t, J=7, 1H); 5.28 (m, 1H).
	^{13}C-NMR	17.7q; 25.7q; 26.0q; 26.4t; 30.7t; 34.7s; 37.3t; 42.1t; 51.9q; 59.4s; 116.3d; 124,2d, 131.3s; 137.3 s; 171.4s.
	MS	M$^{+\cdot}$ 308 (3); 265 (20); 248 (16); 233 (24); 179 (50); 119 (**100**); 69 (90); 41 (80).
3d)	IR	2940, 1735, 1435, 1245, 1060.
	^{1}H-NMR	1.08 (s, 6H); 1.57 (s, 3H); 1.61 (s, 3H); 2.07 (s, 2H); 2.58 (s, 2H); 3.68 (s, 6H).
	^{13}C-NMR	18.5q; 18.8q; 25.9q; 34.75s; 36.5t; 45.5t; 51.9q; 59.9s; 121.1 s; 124.9s; 171.4 s.
	MS	M$^{+\cdot}$ 254 (20); 194 (62); 179 (45); 152 (37); 135 (**100**); 119 (30); 91 (20).
3e)	IR	2950; 1725; 1430; 1240; 1050.
	^{1}H-NMR	0.88 (s, 3H); 1.0 (d, J=7, 3H); 1.17 (s, 3H); 1.56 (d, J=16, 1H), 1.67 (s, 1H); 2.54 (d, J=16, 1H); 3.1 (m, 1H); 3.65 (s, 3H); 3.74 (s, 3H); 5.04 (s, 1H).
	^{13}C-NMR	18.7q; 23.1q; 26.1q; 27.5q; 33.7d; 35.8s; 44.7t;51.1q; 51.7q; 64.1s; 122.4d; 131.9s; 170.1s; 171.6s.
	MS	M$^{+\cdot}$ 254 (10); 194 (70); 179 (62); 135 (**100**); 119 (30); 96 (32).
3f)	IR	2960; 1730; 1430; 1240; 1040; 790.
	^{1}H-NMR	0.91 (d, J=7, 3H); 1.03 (d, J=7, 3H); 1.2 (s, 3H); 1.24 (s, 3H); 1.84 (m, 1H); 2.98 (m, 1H); 3.68 (s, 3H); 3.7 (s, 3H); 5.32 (dxt, J$_1$=11, J$_2$=2, 1H); 5.64 (dxt, J$_1$=11, J$_2$=3.5).
	^{13}C-NMR	15.0q, 17.6q; 19.5q; 25.1q; 36.3d; 37.6s; 39.6d; 51.3q; 51.8q; 64.0s; 129.8d; 130.0d; 170.4s; 172.1s.
	MS	M$^{+\cdot}$ 254 (2); 222 (7); 194 (27); 179 (25); 162 (27); 147 (29); 135 (**100**); 119 (40); 82 (50); 67 (57).
3g)	IR	2950; 1730; 1430; 1235; 1050.
	^{1}H-NMR	1.2 (s, 3H); 1.22 (s, 3H); 1.45 (d, J=7, 1H); 2.07 (d, J=7, 1H); 2.36 (brs; 1H); 3.35 (brs, 1H); 3.62 (s, 3H); 3.72 (s, 3H); 6.07 (dxd, J$_1$=7; J$_2$=3; 1H); 6.35 (dxd, J$_1$=7, J$_2$=3, 1H).
	^{13}C-NMR	27.2q; 28.6q; 45.3t; 48.1s; 51.7q; 52.2q; 52.4d; 55.5d; 65.9s; 135.0d; 140.4d; 170.3s; 172.3s.
	MS	M$^{+\cdot}$ 238 (0); 173 (15); 141 (90); 109 (28); 66 (**100**).
3h)	IR	2950, 1725, 1430.
	^{1}H-NMR	0.9 (s, 3H); 1.1 (m, 2H); 1.44 (s, 3H); 1.98 (m, 1H); 2.06 (m, 2H); 3.02 (m, 1H); 3.63 (s, 3H); 3.66 (s, 3H); 6.25 (t, J=7, 1H); 6.37 (t, J=7, 1H).
	^{13}C-NMR	18.6t; 22.2t; 25.55q; 29.9q; 38.05d; 41.65s; 44.35d; 51.4q; 51.8q; 64.1s; 132.2d; 134.1d; 171.2s; 171.7s.
	MS	M$^{+\cdot}$ 252 (0); 221 (4); 173 (30); 141 (97); 109 (13); 80 (**100**).
6)	IR	2940; 1700; 1650; 1420; 1220.
	^{1}H-NMR	2.07 (s, 3H), 2.09 (s, 3H); 3.77 (s, 3H); 4.72 (d, J=7; 2H); 5.16 (d, J=8, 1H); 5.26 (d, J=18, 1H); 5.79 (dxt, J$_1$=7, J$_2$=17, 1H); 6.33 (m, 2H).
	^{13}C-NMR	23.1q; 23.2q; 51.9q; 64.9t; 118.6t; 124.3s; 126.8d; 134.8d; 136.0d; 155.8s; 165.4s; 165.9s.
	MS	M$^{+\cdot}$ 224(0); 192(4); 141 (**100**); 109 (72); 82 (30); 67 (70).
7)	IR	2950; 1720; 1640; 1435; 1240; 1100; 1050.
	^{1}H-NMR	1.77 (d, J=7, 3H); 2.05 (s, 3H); 2.08 (s, 3H); 3.76 (s, 3H); 4.68 (d, J=7, 2H); 5.63 (txd, J$_1$=7, J$_2$=14, 1H); 5.75 (qxd, J$_1$=7, J$_2$=14, 1H); 6.05 (dxd, J$_1$=11, J$_2$=14, 1H); 6.27 (dxd, J$_1$=11, J$_2$=14).
	^{13}C-NMR	18.1q; 23.1q; 23.2q; 51.9q; 65.4t; 123.45d; 124.5 s; 130.6 d; 131.2d; 135.0d; 155.6s; 165.55s; 165.9s.
	MS	M$^{+\cdot}$238 (2); 141 (96); 109 (68); 79 (**100**).
10)	IR	2950; 1720; 1245; 860.
	^{1}H-NMR	1.37 (d, J=7, 3H); 2.05 (s, 3H); 2.1 (s, 3H); 3.76 (s, 3H); 5.13 (d, J=9, 1H); 5.29 (d, J=16, 1H), 5.51 (quint, J=7, 1H), 5.7 (dxd, J$_1$=7, J$_2$=16, 1H); 6.3 (m, 2H).
	^{13}C-NMR	20.0q; 23.0q; 23.2q; 51.8q; 71.1d; 118.4t; 124.6s; 132.3d; 132.4d; 136.1d; 155.4s; 165.1s.
	MS	M$^{+\cdot}$ 238 (2); 206 (5); 163 (7); 141 (**100**); 109 (62); 81 (70).

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