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CYCLOADDITION REACTIONS OF POLYSUBSTITUTED FURANS WITH OXYALLYL CARBOCATIONS

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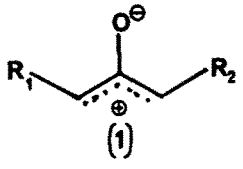
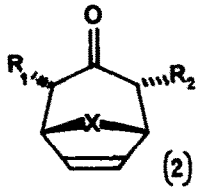
Abstract - New and improved routes to polysubstituted furans are described, together with a survey of their reactivity in cycloaddition reactions with oxyallyl carbocations, producing polysubstituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones.

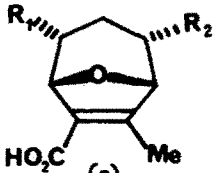
Oxyallyl carbocations (1) are now well established as key intermediates for the construction of bicyclo[3.2.1]oct-6-en-3-ones (2) (X = CH_2, O, NR), and their reactions with simple monosubstituted furans have been most extensively studied.[1,2,3] We were interested in synthesising oxa-analogues (3) of the plant growth promoting agent helminthosporic acid (4)[4], and envisaged an approach via cycloadducts of general structure (5). This necessitated the synthesis of a number of 2,3-di- and 2,3,4-trisubstituted furans, and reactions of these furans with oxyallyl carbocations (1). Since few such reactions of oxyallyls with complex furans have been recorded, we document in this paper full results of our studies; and in addition provide details of new and improved routes to the furans themselves.



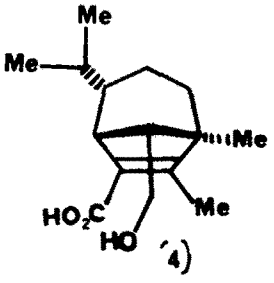
(1)



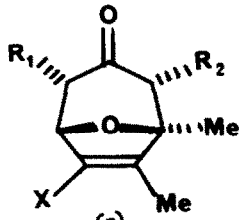
(2)



(3)



(4)



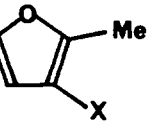
(5)

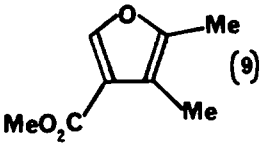
Synthesis of Furans

Two furans were of particular interest: 2,3-dimethylfuran (6, X=Me) and methyl-2,3-dimethyl-4-furoate (9).

An examination of the various reported routes[4] to (6) suggested that the method of Winberg et al. as modified by Rice and Dyer was the most practical. This route involves formation of 3-chloromethyl-2-methylfuran (7) by reaction of 3-hydroxymethyl-2-methylfuran (8) with thionyl chloride, with subsequent reduction of (7) with $LiAlH_4$ to yield (6) in an overall yield of 36%. However, these authors allude to the great instability of (7), and certainly in our hands this method gave very variable results. Through efficient neutralisation (with solid Na_2CO_3) of the HCl produced during chlorination, and by the use of diglyme (in place of ether) for the reduction, we have improved the overall yield to 61%.

(6) X = Me
(7) X = CH_2Cl
(8) X = CH_2OH





An alternative route (FIG. ONE) involved condensation of acetoin and dimethylacetylene dicarboxylate (acetone/anhydrous K_2CO_3 at reflux) with subsequent dehydration to form dimethyl-4,5-dimethylfuran-2,3-dicarboxylate (56% overall yield based on acetoin). Ester hydrolysis (2M.aq.NaOH) yielded 2,3-dimethylfuran-4,5-dicarboxylic acid, and subsequent double decarboxylation could be accomplished with copper and quinoline at 200°. Under these conditions 2,3-dimethylfuran (6) distils (b.pt. 92-4°) out of the reaction mixture, and other furans with b.pts. less than 200° should be equally accessible by this route.

The more complex furan (9) was obtained by the route shown in FIG. TWO. A Diels-Alder cycloaddition between 2-methylfuran and acetylene dicarboxylate was followed by selective hydrogenation, and a retro-Diels-Alder reaction to produce diethyl-2-methylfuran-3,4-dicarboxylate. Half-saponification (an adaption of the method of Edwards et al.[5]) yielded two ester-acids in the ratio of 7:2, and the major (desired) isomer was reduced ($LiBH_4$/THF) to alcohol-acid, and thence to 2,3-dimethyl-4-furoic acid by catalytic hydrogenation. This last step has yet to be optimised, and the yield is based on a flash chromatography and a recrystallisation to separate side-products and unreacted alcohol-acid. Other 2-methylfurans are obviously accessible using this same route.

Cycloaddition Reactions

A number of methods were employed for the generation of oxyallyl carbocations and these, together with the results obtained in cycloaddition reactions, are shown in TABLES 1 and 2. The n.m.r. data for the cycloadducts is collected in TABLE 3.

In terms of practical utility, the results clearly indicate that as the complexity of the furan increases, so the yield of cycloadduct decreases; and when more than one -M group is present, cycloadducts are not obtained. In addition, although there is some evidence for regioselectivity, probably due to steric factors, the outcome of the reactions is not predictable. As usual in oxyallyl cycloaddition, the 2,4-di-equatorial products are favoured.

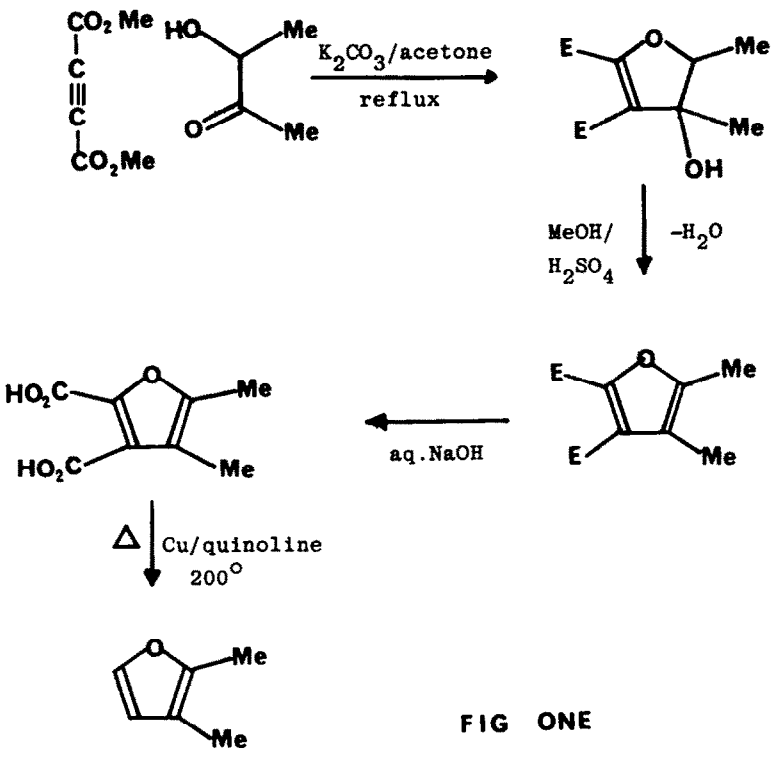


FIG ONE

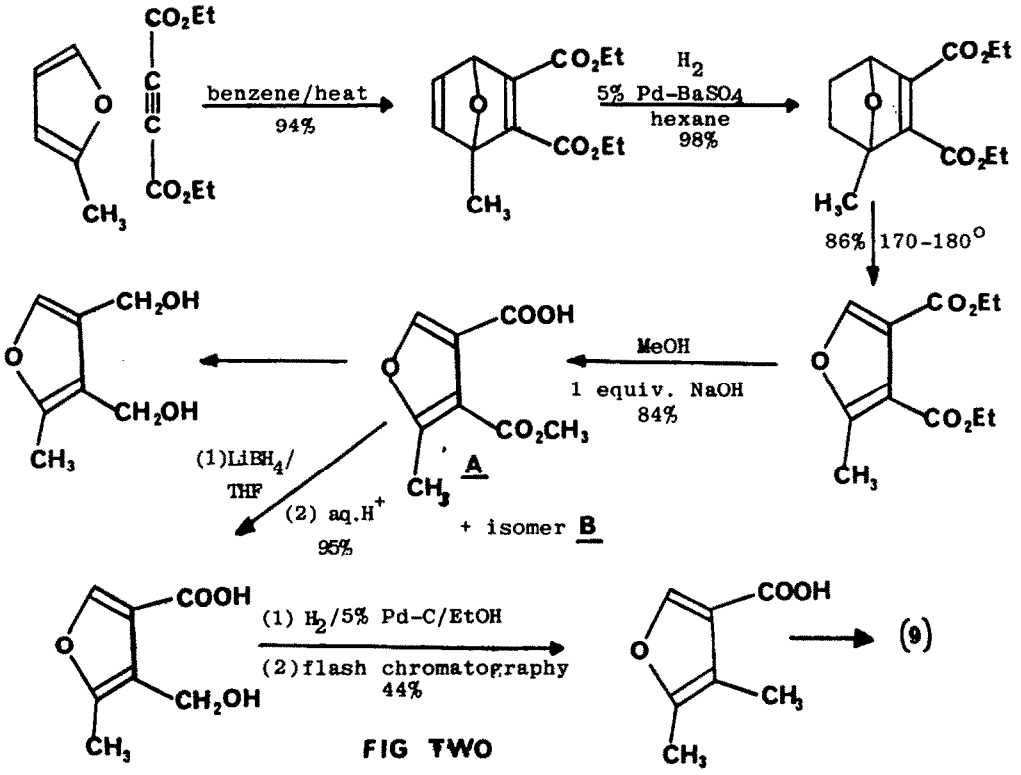
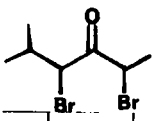


FIG TWO

TABLE 1: Cycloadditions with  /Cu/NaI/MeCN

Furan	Major Product(s) A	Ratio of A:other isomers	Total yield / %	Scale /mmol
	ca. 1:1		35-52	20
			22	50
	ca. 3:1	84:16	60	37
		85:15	44	10
		39:34	73	2x50
	no apparent reaction	-	-	10
	ca. 1:1		35+	5
	no apparent reaction	-	-	10
	no apparent reaction	-	-	1
			42	2
	major		55	10

TABLE 2: Cycloadducts from polyhaloketones, after reduction using Zn-Cu couple

Poly-haloketone	Reducing Agent	Furan	Major product(s)	Total yield / %	Scale /mmol
	Zn-Ag/ THP		no apparent reaction	-	25
	(a)Zn-Ag/ THP		major	7 of 27	12 15
	(b)Cu/NaI/ MeCN		no apparent reaction	-	12
	(c) Zn/ $(EtO)_3B$/ THP		no apparent reaction	-	28
	Zn-Ag/ THP		formation of cycloadducts indicated by n.m.r.	7	35
	Et_3N/ CF_3CH_2OH			46	30
	Et_3N/ CF_3CH_2OH		no apparent reaction	-	21
			cycloadducts indicated by n.m.r.	11	9

Table 3 : ^{1}H n.m.r. data of cycloadducts. All spectra run in $CDCl_3$ (Me_4Si internal standard δ = 0 ppm); a - 60 MHz, b - 100 MHz, c - 220 MHz; δ value / ppm; m-multiplicity; J - coupling constant / Hz; * - a, b or c.

' Numbering of basic skeleton

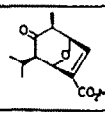
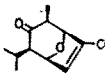
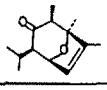
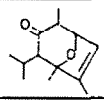
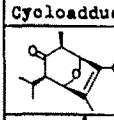
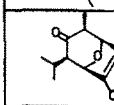
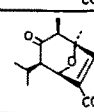
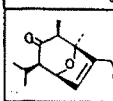
Cycloadduct	*		1-H	1-Me	2-H	2-Me	4-H	5-H	5-Me	6-H	6-Me	7-H	7-Me
	b	δ	4.92	-	2.91	0.94	2.65	5.30	-	-	-	7.05	-
		m	dd		dq	d	dd	d				d	
		J	2, 5		5, 7	7	4, 10	4				2	
	a	δ	5.05	-				5.1	-	7.1	-	-	-
		m	d					dd		d			
		J	5					2, 4		2			
	b	δ	-	1.47	2.50	0.84-1.08	2.56	5.00	-	6.16	-	6.02	-
		m		s	q	d	dd	dd		dd		d	
		J			7	7	4.5, 7	1.8, 4.5		1.8, 5.5		5.5	
	a	δ	4.8	-		0.9-1.1		-	1.5	6.05-6.15	-	6.05-6.15	-
		m	dd			complex			s	complex		complex	
		J	1.5, 5										
	a	δ	-	1.45	2.55	0.85-1.13	2.54	4.85	-	5.75	-	-	1.8
		m		s	q		dd	complex		complex			d
		J			7.5		5, 7	3, 5		2, 3			2
	c	δ	4.62	-	2.65	1.16	2.53	-	1.46	-	1.85	5.91	-
		m	complex		dq	d	dd		s		comp.	complex	
		J	2, 5		5, 7	7	2.4, 0.7					2	

Table 3 (continued): ^{1}H n.m.r. data of cycloadducts.

Cycloadduct	*		1-H	1-Me	2-H	2-Me	4-H	5-H	5-Me	6-H	6-Me	7-H	7-Me
	b	δ	5.07	-	2.92	0.94	2.68	5.00	-	-	2.16	-	-
		m	dd		dq	d	dd	d			d		
		J	0.5, 4.5		4.5, 7	7	4.5, 10.5	4.5			0.5		
	b	δ	4.68	-	2.98	0.98-1.08	2.65	5.29	-	-	-	-	2.14
		m	d		dq	d	dd	dd					d
		J	4.5		4.5, 7	7	3.8, 10	3.8, 0.5					0.5
	b	δ	-	1.48	2.70	1.00	2.60	5.24	-	-	-	-	2.06
		m		s	q	d	dd	dd					d
		J			7	7	3.8, 10.5	10.8, 3.8					0.8
	c	δ	-	1.47	2.62	0.90	2.59	4.98	-	6.10	-	-	-
		m		ss	q	d	dd	ddd		d			
		J			7	7	4, 8	1, 2, 4		2			
	b	δ	-	1.45	2.32& 2.48	-	2.52	5.03	-	6.16	-	6.02	-
		m		s	AB		dd	dd		dd		d	
		J			15		4.5, 7	1.8, 4.5		1.8, 6		6	
	a	δ	5.0	-		-		-	1.5	6.1	-	6.1	-
		m	complex						s	complex		comp.	
	b	δ	-	1.5	2.16-2.80	-	2.16-2.80	5.06	-	6.20	-	6.05	-
		m		s	AB		AB	dd		dd		d	
		J			5, 16		5, 16	1, 5		1, 6		6	

For the production of multigramme quantities of highly substituted cycloadducts like (3), the best strategy is to use α,α'-dibromo-α,α'-disubstituted ketones in conjunction with 2,3-dialkylfurans, and with copper and sodium iodide[7] as co-reagents. Alternatively, reaction of tetrachloroacetone[8] with 2,3-dialkylfurans, followed by reductive removal of residual chlorines, yields cycloadducts which may be alkylated via their enol silyl ethers.[9]

The chemistry of cycloadducts (5), and in particular their conversion into species related in structure to helminthosporic acid (4), will be described in a subsequent paper.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (liquid films for oils and Nujol mulls for solids); ^{1}H n.m.r. spectra were recorded with a Varian T-60 (60 MHz), Varian HA 100 (100 MHz) or Bruker WH 360 (360 MHz) instruments (tetramethylsilane as internal standard); and mass spectra were recorded on an A.E.I. MS12 spectrometer. Kieselgel GF_{254} Merck) was used for analytical t.l.c., and flash chromatography was performed with Merck silica gel (230-400 mesh). Organic solvents were distilled from calcium hydride when required anhydrous, and petrol is pet. ether (40-60).

3-Hydroxymethyl-2-methylfuran (8)

Methyl 2-methyl-3-furoate (25 g, 178 mmol) was added to a refluxing suspension of lithium aluminium hydride (an excess) in anhydrous ether. Refluxing was continued until starting material had been consumed. Completion of the reaction was tested by addition of further LAH until no more reaction was evident. The reaction mixture was cooled in ice and was worked up by addition of water (n ml), NaOH (15%, n ml) and water (3n ml) (where n = number of g of LAH used). The reaction mixture was filtered and the solids were washed with methanol doped ether. The solvent was removed and the residue was distilled. 3-Hydroxymethyl-2-methylfuran (8) (18.25 g, 91%) was obtained as a colourless liquid, b.p. 56 - 9°C/3 mm (lit.,[4] 70°/7 mm), n_D^{16} 1.4876 (lit.,[4] n_D^{25} 1.4840).

3-Chloromethyl-2-methylfuran (7)

Pet. ether (30-40°) (200 ml) was added to finely ground sodium carbonate (18.5 g, 175 mmol) under nitrogen. Pyridine (12.5 ml, 161 mmol) was added and the reaction mixture was cooled to -15 to -25°C. Thionyl chloride (11.6 ml, 159 mmol) was added dropwise over 10 min with stirring. A solution of 3-hydroxymethyl-2-methylfuran (8) (17.75 g, 158 mmol) in pet. ether (30-40°) (30 ml) and dry ether (20 ml) was added over 20 min, maintaining the reaction mixture at -15 to -25°C. The reaction mixture was stirred for 1 h, was filtered and the solids were washed with pet. ether (30-40°) and ether. The solvents were removed using a dry-ice/acetone trap to give a straw coloured residue which was kept at 0°C or below.

2,3-Dimethylfuran (6)

The straw coloured residue was taken up in diglyme (Na dried, 100 ml) and the solution was cooled in ice. Lithium aluminium hydride (4.5 g, 119 mmol) was added in ten portions over 15 min. The ice bath was removed and the reaction mixture was allowed to reach 30°C. The reaction was soon complete, but the reaction mixture was left stirring overnight at room temperature. Water (20 ml) was added and the volatiles were removed at about 0.2 mm, and were collected in a flask immersed in a liquid nitrogen trap (50-70 ml). The flask was warmed to 0°C and the water separated. The organic phase was washed with a small quantity of water, followed by weak $CuSO_4$ solution (to remove H_2S), and finally with water (3 x). A small quantity of copper bronze, charcoal and anhydrous K_2CO_3 were added and the mixture was stirred for 10 min at 0°C. 2,3-Dimethylfuran (6) (9.3 g, 61% from the alcohol) was obtained by distillation, b.p. 92 - 4°C [lit.,[4] 94 - 5°C (738 mm)], δ (60 MHz, $CDCl_3$): 1.9 (3H, s, 3-Me), 2.2 (3H, s, 2-Me), 6.15 (1H, d, 4-H), 7.2 (1H, d, 5-H).

Synthesis of 4,5-dimethylfuran-2,3-dioic acid

Acetoin dimer (5.39 g, 61 mmol), dimethyl acetylenedicarboxylate (DMAD) (8 ml, 65 mmol) and anhydrous potassium carbonate (8.49 g, 61 mmol) were combined in AR acetone (100 ml). The reaction mixture was refluxed for 20 h to give a dark brown solution, which was allowed to cool and then poured onto

ice-water (60 ml) and extracted with ether (3 x 50 ml). The organic layer was concentrated in vacuo. The resulting dark brown residue was filtered through a column of silica using 3:1 e:p as eluent. The solvent was removed to give an orange oil (10.05 g), which was dissolved in AR methanol (100 ml). Conc. H_2SO_4 (20 drops) was added and the mixture turned from orange to yellow. The reaction mixture was refluxed for 4 h, and was then allowed to cool. The reaction was worked up by addition of ice-water (100 ml) and extraction with ether. The combined organic extracts were washed with $NaHCO_3$ solution (10%, 100 ml) and NaCl (100 ml), and were concentrated in vacuo. The resulting orange-brown residue was taken up in ether (50 ml), dried ($MgSO_4$) and concentrated to give dimethyl 4,5-dimethylfuran-2,3-dioate (7.32 g, 56% crude yield from acetoin dimer) as a dark orange-brown syrup, δ (60 MHz, $CDCl_3$): 2.0 (3H, s, 4-Me), 2.3 (3H, s, 5-Me), 3.9 (6H, s, 2 x OMe). The diester (7.22 g, 34 mmol) was stirred with NaOH solution (2M, 100 ml) at room temperature for 3 days. Dilute HCl (2M) was added to acidify the reaction mixture. A cream fine precipitate came out of solution, which was filtered and dried at 120°C for several hours. 4,5-Dimethyl-2,3-furan-dicarboxylic acid (4.67 g, 74%) was obtained as an off-white powder, m.p. 243 - 4°C, ν_{max}(nujol): 3400 (OH); 1705 (C=O); 1620 (C=C) cm^{-1}.

2,3-Dimethylfuran (6)

The diacid (4.67 g, 25 mmol), Cu powder (642 mg, 10 mmol) and quinoline (redistilled from BaO; 8 ml, 68 mmol) were placed in a 50 ml round-bottomed flask fitted with a 15 cm Vigreux column connected to a distillation condenser and a receiver cooled in an ice-salt bath. The reaction mixture was heated on a Woods-metal bath. At bath temperature 150°C the reaction mixture started to effervesce quite dramatically. When the bath temperature was at 210 - 275°C, a colourless liquid distilled over, b.p. 50 - 100°C. When no more material distilled over, heating was stopped. The cold receiver contained 2.13 g of material including some water, which was carefully removed with a pasteur pipette. The 2,3-dimethylfuran was dried ($MgSO_4$) and a sample removed to record an n.m.r. spectrum. The remaining material was found to weigh 1.39 g (57%), δ (60 MHz, $CDCl_3$): 1.9 (3H, s, 3-Me), 2.2 (3H, s, 2-Me), 6.15 (1H, d, 4-H), 7.2 (1H, d, 5-H).

2,3-Diethoxycarbonyl-1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene

2-Methylfuran (16 ml, 161 mmol) and diethyl acetylene-dicarboxylate (24.5 g, 144 mmol) were refluxed in benzene (150 ml) for 3 h. The solvent was removed on the rotary evaporator to give a yellow oil, which was purified by flash chromatography (3:2 p:e) to give recovered acetylene dicarboxylate (4.24 g, 25 mmol) and 2,3-diethoxycarbonyl-1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (28.4 g, 94%, calculated from the amount of reacted acetylene) as a yellow oil, ν_{max} (film): 1710 (C=O), 1640 (C=C); δ 100 MHz, $CDCl_3$): 1.30 (6H, 2 x t, 2 x $CH_2\underline{CH}_3$), 1.76 (3H, s, 1-Me), 4.25 (4H, 2 x q, 2 x $OC\underline{H}_2CH_3$), 5.57 (1H, d, 4-H), 6.96 (1H, d, 6-H), 7.16 (1H, dd, 5-H); R_f ca. 0.3 (3:2 p:e).

2,3-Diethoxycarbonyl-1-methyl-7-oxabicyclo[2.2.1]hept-2-ene

A solution of the diene (6.06 g, 24 mmol) in n-hexane (70 ml) was added by syringe to a stirring suspension of 5% Pd-$BaSO_4$ (200 mg) in n-hexane (30 ml) under N_2. The reaction vessel was evacuated and placed under a balloon of H_2. The reaction mixture was stirred at room temperature for 1.5 - 2 h. (Small scale reactions were carried out at 0°C). Completion of reaction was determined roughly by t.l.c., and more accurately by n.m.r. spectroscopy. The reaction

mixture was filtered through "hyflo", and the filtrate was concentrated to give 2,3-diethoxycarbonyl-1-methyl-7-oxabicyclo[2.2.1]hept-2-ene (5.97 g, 98%) as a yellow oil, ν_{max}(film): 1725 (C=O), 1640 (C=C) cm^{-1}; δ (100 MHz, $CDCl_3$): 1.30 (6H, 2 x t, 2 x $OCH_2\underline{CH}_3$), 1.67 (3H, s, 1-Me), 1.42 - 2.44 (4H, complex, 2 x 5-H and 2 x 6-H), 4.26 (4H, 2 x q, 2 x $OC\underline{H}_2CH_3$), 5.16 (1H, d, J 4.5 Hz, 4-H); R_f ca. 0.3 (3:2 p:e).

Diethyl 2-methyl-3,4-furandicarboxylate

Neat product from the previous step (11.26 g, 44 mmol) was heated at 160 - 180°C for 2 h. The resulting brown oil was allowed to cool, and diethyl 2-methyl-3,4-furandicarboxylate (8.66 g, 86%; 75% overall from the acetylene) was obtained by vacuum distillation as a colourless oil, b.p. 90°C/0.7 mm; ν_{max}(film): 1730 (C=O), 1610 (C=C) cm^{-1}; δ (60 MHz, $CDCl_3$): 1.3 (6H, 2 x t, 2 x $OCH_2\underline{CH}_3$), 2.5 (3H, s, 2-Me), 4.3 (4H, 2 x q, 2 x $OC\underline{H}_2CH_3$), 7.7 (1H, s, 5-H); (m/z): 226.0851 (24%, M^+, $C_{11}H_{14}O_5$ requires 226.0841), 180.0416 (94%, $C_9H_8O_4$), 153.0193 (100%, $C_7H_5O_4$); R_f ca. 0.6 (2:1 e:p).

2,3-Dimethyl-4-furoic acid

Finely powdered NaOH (508 mg, 13 mmol) was added to a stirring solution of diethyl 2-methyl-3,4-furandicarboxylate (2.9 g, 13 mmol) in AR methanol (35 ml). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the white solid residue was taken up in CH_2Cl_2 (30 ml). The solution was washed well with $NaHCO_3$ solution (5%, 20 ml). The aqueous layer was neutralised with HCl acid (2M) to give a white precipitate, which was extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a mixture (7:2 by n.m.r.) of 3-methoxycarbonyl-2-methyl-4-furoic acid (A) and 4-methoxycarbonyl-2-methyl-3-furoic acid (B) (2.0 g, 84%) as a white solid, from which (A) could be obtained by flash chromatography (1:1 p:e)

A solution of 3-methoxycarbonyl-2-methyl-4-furoic acid (A) (1.13 g, 6 mmol) in dry THF (20 ml) was added by syringe to a stirring solution of lithium borohydride (220 mg, 10 mmol) in THF (10 ml) at 0°C under N_2). The reaction mixture was allowed to reach room temperature and was stirred for 3 h. The reaction mixture was cooled in ice and ice-cold THF-water (1:1, 10 ml) was added slowly with vigorous stirring. The reaction mixture was acidified with 10% HCl acid and the resulting clear solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give 3-hydroxymethyl-2-methyl-4-furoic acid (910 mg, 95% crude yield) as a white solid, δ (60 MHz, $CDCl_3$): 2.3 (3H, s, 2-Me), 4.6 (2H, s, CH_2O), 7.1 (2H, broad s, 2 x OH), 7.9 (1H, s, 5-H).

A solution of 3-hydroxymethyl-2-methyl-4-furoic acid (880 mg, 5.6 mmol) in absolute alcohol (30 ml) was added by syringe to a suspension of 5% palladium on charcoal (100 mg) in absolute alcohol (10 ml) maintained under N_2. The reaction vessel was evacuated and filled with an atmosphere of H_2 by means of a balloon. The reaction mixture was stirred overnight under H_2 at room temperature. The catalyst was removed by filtration through a bed of "hyflo", and the filtrate was concentrated to give a white solid residue (790 mg), which was purified by flash chromatography (2:1 p:e) to give 2,3-dimethyl-4-furoic acid (352 mg, 44%; or 64% if recovered starting material is taken into account) as a white solid. M.pt. 129 - 30° (Lit. 130-1°); δ (60 MHz, $CDCl_3$): 2.1 (3H, s, 3-Me), 2.2 (3H, s, 2-Me), 7.9 (1H, s, 5-H), 10.3 (1H, broad s, OH).

The reaction did not go to completion, and some starting material was recovered from the reaction mixture.

Cycloaddition Reactions

The general methodology is reviewed in ref.3, but representative experimental details for cycloadditions leading to compounds included in Tables 1 and 2 are given below.

Synthesis of 2α-isopropyl-4α,5,6-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one

A solution of 2,4-dibromo-5-methyl-3-hexanone (13.61g, 50 mmol) and 2,3-dimethylfuran (5.14g, 54 mmol) in dry acetonitrile (100 ml) was added dropwise to a stirring suspension of copper powder (reduced by hydrogen; 9.5g, 150 mmol) and sodium iodide (30g, 200 mmol) in dry MeCN (150 ml) maintained under an atmosphere of nitrogen (15 min). The reaction mixture was stirred overnight at room temperature (15 h). Dichloromethane (200 ml) and water (100 ml) were added and the reaction mixture was stirred vigorously for 10 min. The reaction mixture was filtered through "hyflo" and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (75 ml) and the combined organic layers were washed with aqueous ammonia (2M, 5 x 50 ml), with brine (100 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oily, yellow residue was purified by flash chromatography (4:1 p:e) to give one major component and numerous other products. The total yield of all cycloadducts formed in this reaction was 15.31 g (73%). The major isomer, 2α-isopropyl-4α,5,6-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, was obtained as a pale yellow oil (8.09 g, 39%), ν_{max} ($CDCl_3$): 1710 (C=O) cm^{-1}; δ (60 MHz, $CDCl_3$): 0.85 - 1.13 (9H, complex, 4-Me and 2 x i-Me), 1.45 (3H, s, 5-Me), 1.8 (3H, d, J 2 Hz, 6-Me), 1.8 - 2.3 (1H, complex, i-H), 2.54 (1H, dd, J 5 and 7 Hz, 2-H), 2.55 (1H, q, J 7.5 Hz, 4-H), 4.85 (1H, complex, 1-H), 5.75 (1H, complex, 7-H); (m/z): 208.1450 (M^+, 4%; $C_{13}H_{20}O_2$ requires 208.1463), 165.0913 (M^+ - 43, $C_{10}H_{13}O_2$, 100%), 137.0964 ($C_9H_{13}O$, 6%), 123.0804 ($C_8H_{11}O$, 9%), 109.0670 (C_7H_9O, 51%), 95.0494 (C_6H_7O, 15%); R_f *ca.* 0.35 (4:1 p:e).

A small quantity (310 mg) of the next fastest moving component, by t.l.c., (R_f *ca.* 0.32, 4:1 p:e) was also isolated. This was identified by means of its n.m.r. spectrum as 2-isopropyl-1,4,6-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one. δ (220 MHx, $CDCl_3$) 0.92 (6H, 2 x d, J 7 Hz, 2 x i-Me), 1.16 (3H, d, J 7 Hz, 2-Me), 1.46 (3H, s, 5-Me), 1.85 (3H, complex, 6-Me), 1.99 (1H, complex, J 7 and 2.4 Hz, i-H), 2.53 (1H, dd, J 2.4 and 0.7 Hz, 4-H), 2.65 (1H, dq, J 5 and 7 Hz, 2-H), 4.62 (1H, complex, J 2 and 5 Hz, 1-H), 5.91 (1H, complex, J 2 Hz, 7-H).

This cycloaddition reaction was also carried out on the 40 mmol scale and the 50 mmol scale. Similar results to those obtained above were found in both cases.

1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one

1,1,3,3-Tetrachloroacetone (3.3) (3.7 ml, 30 mmol) was added dropwise to a stirring, ice-cold solution of 2-methylfuran (3.13) (30 ml, excess), 2,2,2-trifluoroethanol (TFE, 30 ml) and triethylamine (8.3 ml, 60 mmol). Addition took 20 min, during which white fumes were produced and the reaction mixture turned from pale yellow to dark reddish-brown. The reaction mixture was allowed to warm up to room temperature and was stirred for 3.5 h. Water (50 ml) was added and the reaction mixture was stirred vigorously for 5 min. After extraction with ether (3 x 50 ml), the combined organic layers were washed with water (2 x 100 ml), dried ($MgSO_4$) and concentrated to give a dark brown residue (8.6 g). A mixture of trichloroketone cycloadducts (3.73 g, 52%) was obtained as a pale yellow solid by Kugelrohr distillation, b.p. 80 - 100°C/0.1-0.2 mbar, ν_{max} (nujol): 1750 (C=O), 1600 (weak, C=C) cm^{-1}; δ (100 MHz, $CDCl_3$): 1.68 and 1.79 (0.36 x 3H and 0.64 x 3H, 2 x s, 2 x bridgehead Me), 4.92 - 5.3 (2H, complex, bridgehead H and CO.C<u>H</u>.Cl), 6.3 - 6.7 (2H, complex, CH-CH); R_f *ca.* 0.27 and 0.33 (9:1 p:e).

Dechlorination Step

A solution of the trichloroketone mixture (2.66 g, 11 mmol) in MeOH-NH_4Cl (20 ml) was added to a stirring suspension of zinc/copper couple [from Zn (18 g) and $Cu(OAc)_2.H_2O$ (1 g)] in MeOH-NH_4Cl (30 ml), and the reaction mixture was stirred at room temperature for 36 h. The reaction mixture was filtered through "hyflo" and the solid residue was washed with methanol. The methanolic solution was then stirred with aqueous edtaNa_2H_2 solution (7%, 100 ml) for 15 min. The reaction mixture was extracted with CH_2Cl_2 (5 x 50 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (150 ml), dried ($MgSO_4$) and concentrated to give an oil residue (1.6 g). 1-Methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (1.50 g, 88%, or 46% overall) was obtained by Kugelrohr distillation, b.p. 80 - 100°C/13-15 mm), as a colourless oil; ν_{max} (film): 3060, 2960, 2920, 2890; 1710 (C=O) cm^{-1}; δ (100 MHz, $CDCl_3$): 1.50 (3H, s, 1-Me), 2.16 - 2.80 (4H, complex, J_{gem} 16 Hz, J_{vic} 5 Hz, 2 x 2-H and 2 x 4-H), 5.06 (1H, dd, J 5 and 1 Hz, 5-H), 6.05 (1H, d, J 6 Hz, 7-H), 6.20 (1H, dd, J 1 and 6 Hz, 6-H); (m/z): 138 (M^+, 39%), 95 (M^+ - 43, 100), 81 (C_5H_5O, 55), 53 (44), 43 (71); R_f ca. 0.26 (3:1 p:e).

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