

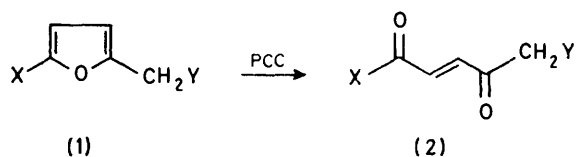
Michael Addition to *trans*-Enediones: A Facile Route to 2,3,4,5-Tetra-substituted Furans

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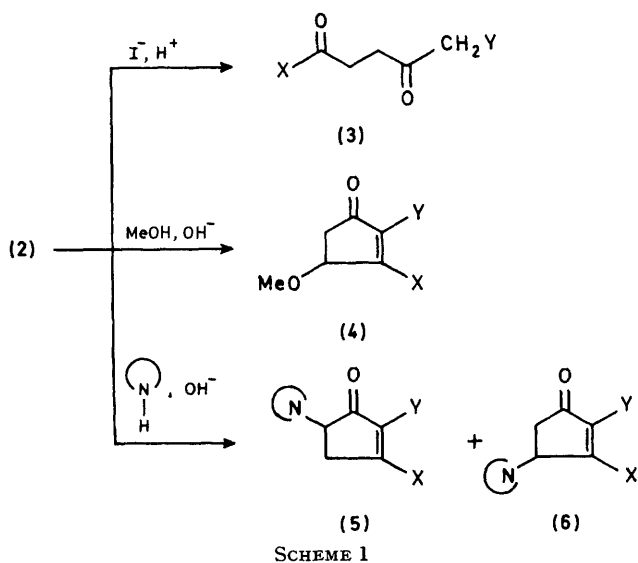
The enediones (2) are useful starting materials for a two-step synthesis of tetrasubstituted furans, which are not otherwise easily available. Michael addition of active methylene compounds to the enediones (2) led to the two regioisomeric adducts (8) and (9), which then cyclized to furans under very mild conditions.

THE addition of nucleophilic reagents to the activated carbon-carbon double bond of enediones has been little investigated, probably because the preparation of these substrates is difficult.

Recently we reported a useful synthesis of *trans*-enediones (2) by the oxidative ring opening of 2,5-dialkylfurans (1) with pyridinium chlorochromate (PCC) (yields >90%).¹



Compounds (2) were synthetically useful as Michael acceptors,¹⁻³ the first step in their reactions being the addition of a nucleophile to the olefinic double bond with either acid or base catalysis (Scheme 1).

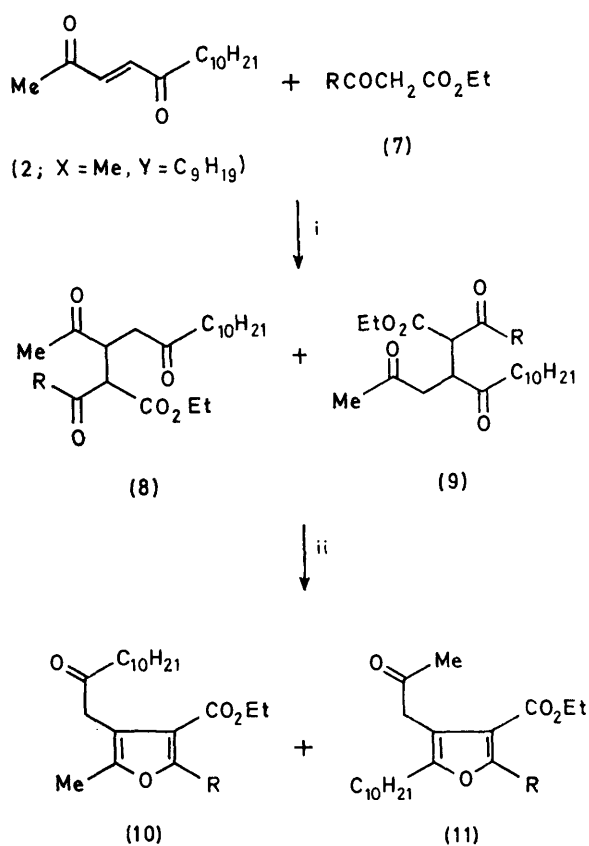


SCHEME 1

We now report a new application of the Michael addition of some active methylene compounds to (2) achieved under mild and simple conditions of phase-transfer catalysis, that allows the easy synthesis of 2,3,4,5-tetrasubstituted furans, a class of compound which is not easily available.

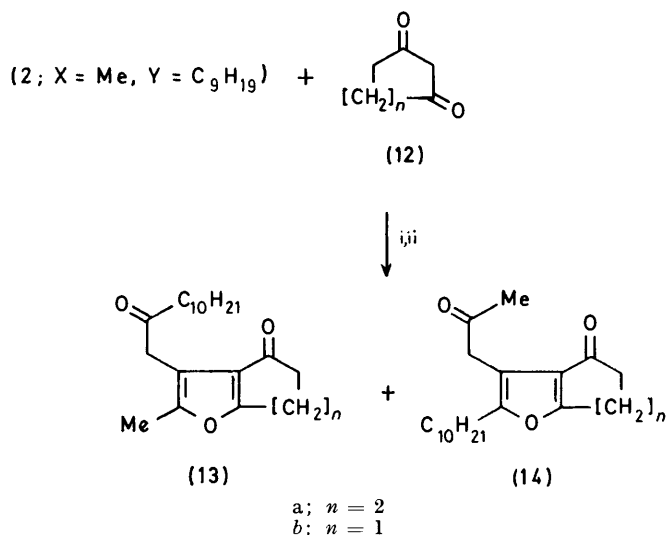
Since the normal procedure for generation of car-

banions from active methylene compounds [50% sodium hydroxide in the presence of triethylbenzylammonium chloride (TEBAC)] led to substantial decomposition, the reaction was generally carried out by using equimolar quantities of the starting compound (2; X = Me, Y = C₉H₁₉), an active methylene compound, and anhydrous sodium carbonate in benzene at 75–80 °C in the presence of catalytic amounts of TEBAC (Schemes 2 and 3).



SCHEME 2 Reagents: i, Na₂CO₃, TEBAC ii, HCl, Et₂O

The formation of the Michael adducts, monitored by t.l.c., proceeded satisfactorily with both β-ketoesters (7) and the cyclic 1,3-diones (12), but they could not be isolated because of their reactivity during purification.



SCHEME 3 Reagents: i, Na₂CO₃, TEBAC; ii, HCl, Et₂O

Only for (7b) was it possible to isolate the addition product, an inseparable mixture of the two regioisomeric adducts (8) and (9) in nearly 1 : 1 ratio as shown by ¹H n.m.r. spectroscopy.*

In spite of their lability, all the Michael adducts were of synthetic value; treatment, without purification, with hydrogen chloride-saturated diethyl ether caused their conversion into the corresponding more stable 2,3,4,5-tetrasubstituted furans (10), (11), (13), and (14) in good yields (Table).

TABLE
Preparation and characterization of (10), (11), (13), and (14)

Product	Reaction time/h	M.p. (t/°C)	% Yield ^a
(10a)	0.5	31—32	34
(11a)		44—45	32
(10b)	1.0	28—30	27
(11b)		<i>b</i>	45
(13a)	12.0	Syrup	35
(14a)		48—50	23
(13b)	0.5	32—34	17
(14b)		46—48	18

* All the yields refer to isolated chromatographically pure compounds. ^b Compound (11b) decomposed extensively during attempted crystallization.

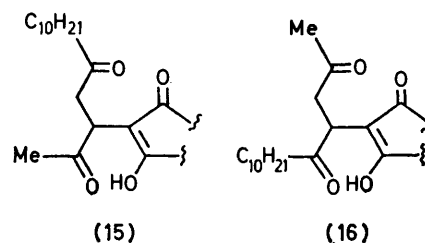
Normal routes to furans from 1,4-diones require much more drastic conditions; in fact, the saturated analogue of (2; X = Me, Y = C₉H₁₉) was unaffected by the foregoing treatment. However, the Michael addition allowed the preparation of 1,4-diones particularly

* Determined from the relative intensity of the methyl resonances: δ 2.08 (s, 1.5 H) and 1.98 (s, 1.5 H) for (8b) and (9b), respectively.

activated by the presence of an easily enolizable group.

The mildly acidic conditions clearly promoted conversion into the enolic forms (15) and (16), which then cyclized to furans by the usual path.

We conclude by pointing out that, even though enediones have been known for a long time, this is the first example of the successful Michael addition of active



methylene compounds to (2). Furthermore, the easy conversion of the Michael adducts, in spite of their reactivity, into furan derivatives is of significance synthetically since alternative routes for the preparation of complex furans are not at present available.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. ¹H N.m.r. spectra were recorded with a Perkin-Elmer R 32 spectrometer for CCl₄ solutions with Me₄Si as an internal standard. I.r. spectra were recorded with a Perkin-Elmer 257 Infracord spectrometer for 1% solutions in CCl₄. Commercial Merck silica gel was used for column chromatography. Merck pre-coated silica gel plates were used in t.l.c. and preparative t.l.c. The chromatograms were visualized by spraying with 5 N-H₂SO₄ and heating at 110 °C for 10 min. Mass spectra were obtained with an AEI MS-12 spectrometer at 70 eV, by using direct insertion at a source temperature of 150 °C.

2,3,4,5-Tetrasubstituted Furans: General Procedure.—A mixture of pentadec-3-ene-2,5-dione (2; X = Me, Y = C₉H₁₉) (200 mg, 8.4 mmol), the appropriate active methylene compound (8.4 mmol), dry Na₂CO₃ (98 mg, 8.4 mmol), and TEBAC (20 mg) in benzene (20 ml) was stirred at 75–80 °C for 24 h (7a and b) or 48 h (12a and b), and then diluted with Et₂O and the organic phase washed with brine. The organic phase was dried (Na₂SO₄) and the solvent removed *in vacuo* to give the crude Michael adducts, which were immediately treated with hydrogen chloride-saturated Et₂O (20 ml). When t.l.c. showed the reaction was complete [benzene–Et₂O (4 : 1) as eluant for (7a and b) and benzene–ethyl acetate (1 : 1) for (12a and b)], the solution was diluted with Et₂O, washed several times with brine, and dried (Na₂SO₄). Removal of solvent under reduced pressure and purification by column or preparative thin-layer chromatography gave the furans (10), (11), (13), and (14).

Ethyl 2,5-dimethyl-4-(2-oxododecyl)-3-furoate (10a) and *ethyl 5-n-decyl-2-methyl-(2-oxopropyl)-3-furoate* (11a). The isomeric esters (10a) and (11a) were purified by preparative t.l.c. with benzene–diethyl ether (9 : 1) as eluant; (10a) gave needles from MeOH–H₂O (Found: C, 72.1; H, 9.9. C₂₁H₃₄O₄ requires C, 72.0; H, 9.8%); ¹H n.m.r., δ 4.17 (2 H, q, J 7 Hz, OCH₂Me), 3.44 (2 H, s, 4-CH₂), 2.46 (3 H, s,

2-Me), 2.34 (2 H, t, J 7 Hz, COCH_2), 2.11 (3 H, s, 5-Me), 1.30 (3 H, partially obscured t, J 7 Hz, OCH_2Me), 1.27 (16 H, m, $8 \times \text{CH}_2$), and 0.80 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r. ν_{max} 1720br cm^{-1} ; m/e : 350 (M^+); (11a) gave plates from $\text{MeOH-H}_2\text{O}$ (Found: C, 72.1; H, 9.6%); ^1H n.m.r., δ 4.19 (2 H, q, J 7 Hz, OCH_2Me), 3.47 (2 H, s, 4- CH_2), 2.47 (3 H, s, 2-Me), 2.34 (2 H, t, J 6 Hz, 5- CH_2), 2.04 (3 H, s, COMe), 1.27 (19 H, m, $8 \times \text{CH}_2$ and OCH_2Me), and 0.88 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r. ν_{max} 1740 and 1720 cm^{-1} ; m/e : 350 (M^+).

Ethyl 5-methyl-4-(2-oxododecyl)-2-phenyl-3-furoate (10b) and *ethyl 5-n-decyl-4-(2-oxopropyl)-2-phenyl-3-furoate* (11b). The isomeric *esters* (10b) and (11b) were purified by preparative t.l.c. with benzene-diethyl ether (8:2) as eluant; (10b) gave needles from $\text{MeOH-H}_2\text{O}$ (Found: C, 75.5; H, 8.7. $\text{C}_{28}\text{H}_{36}\text{O}_4$ requires C, 75.7; H, 8.8%); ^1H n.m.r., δ 7.69 (2 H, m, ArH), 7.38 (3 H, m, ArH), 4.17 (2 H, q, J 7 Hz, OCH_2Me), 3.53 (2 H, s, 4- CH_2), 2.40 (2 H, t, J 7 Hz, COCH_2), 2.26 (3 H, s, 5-Me), 1.40–1.21 (19 H, m, $8 \times \text{CH}_2$ and OCH_2Me), and 0.89 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1730–1710br cm^{-1} ; m/e : 412 (M^+); (11b) (Found: C, 75.5; H, 9.0%); ^1H n.m.r., δ 7.69 (2 H, m, ArH), 7.27 (3 H, m, ArH), 4.17 (2 H, q, J 7 Hz, OCH_2Me), 3.53 (2 H, s, 4- CH_2), 2.56 (2 H, t, J 7 Hz, 5- CH_2), 2.10 (3 H, s, COMe), 1.27 (16 H, m, $8 \times \text{CH}_2$), 1.22 (3 H, partially obscured t, J 7 Hz, OCH_2Me), and 0.90 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1740–1710br cm^{-1} ; m/e 412 (M^+).

6,7-Dihydro-2-methyl-3-(2-oxododecyl)benzofuran-4(5H)-one (13a) and *2-n-decyl-6,7-dihydro-3-(2-oxopropyl)benzofuran-4(5H)-one* (14a). The *benzofurans* (13a) and (14a) were purified by preparative t.l.c. with benzene-diethyl ether (9:1) as eluant; (13a) was a syrup (Found: C, 75.6; H, 9.65. $\text{C}_{21}\text{H}_{32}\text{O}_3$ requires C, 75.9; H, 9.7%); ^1H n.m.r. δ 3.52 (2 H, s, 3- CH_2), 2.68 (2 H, t, J 6 Hz, 7- H_2), 2.50–2.00br (4 H, m, COCH_2 and 5- H_2), 2.17 (3 H, s, 2-Me), 1.60

(2 H, m, 6- H_2), 1.28 (16 H, m, $8 \times \text{CH}_2$), and 0.89 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1720br. and 1675 cm^{-1} ; m/e : 332 (M^+); (14a) gave prisms from $\text{MeOH-H}_2\text{O}$ (Found: C, 76.0; H, 9.55); ^1H n.m.r., δ 3.52 (2 H, s, 3- CH_2), 2.80 (2 H, m, 7- H_2), 2.60–2.00br (4 H, m, 2- CH_2 and 5- H_2), 2.10 (3 H, s, COMe), 1.60 (2 H, m, 6- H_2), 1.20 (16 H, m, $8 \times \text{CH}_2$), and 0.89 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1730, 1715, and 1675 cm^{-1} ; m/e : 332 (M^+).

5,6-Dihydro-2-methyl-3-(2-oxododecyl)cyclopenta[b]furan-4-one (13b) and *2-n-decyl-5,6-dihydro-3-(2-oxopropyl)cyclopenta[b]furan-4-one* (14b). The *cyclopentafurans* (13b) and (14b) were purified by column chromatography on silica gel with benzene-acetonitrile-water (68.5:23.3:8.2) as eluant; (13b) gave plates from $\text{MeOH-H}_2\text{O}$ (Found: C, 75.2; H, 9.7. $\text{C}_{20}\text{H}_{30}\text{O}_3$ requires C, 75.4; H, 9.5%); ^1H n.m.r., δ 3.96 (2 H, s, 3- CH_2), 2.65 (2 H, m, 6- H_2), 2.40–2.20br (4 H, m, COCH_2 and 5- H_2), 2.15 (3 H, s, 2-Me), 1.22 (16 H, m, $8 \times \text{CH}_2$), and 0.90 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1720 and 1698 cm^{-1} ; m/e : 318 (M^+); (14b) gave plates from $\text{MeOH-H}_2\text{O}$ (Found: C, 75.6; H, 9.6%); ^1H n.m.r. δ 3.96 (2 H, s, 3- CH_2), 2.75 (2 H, m, 6- H_2), 2.40–2.20br (4 H, m, 5- H_2 and 2- CH_2), 2.04 (3 H, s, COMe), 1.26 (16 H, m, $8 \times \text{CH}_2$), and 0.80 (3 H, m, $[\text{CH}_2]_9\text{Me}$); i.r., ν_{max} 1720 cm^{-1} ; m/e : 318 (M^+).

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