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CARBON-CARBON BOND FORMATION BY 'DOUBLE ACTIVATION' THE SYNTHESIS OF PIPEROLIDE AND FADYENOLIDE INTERMEDIATES

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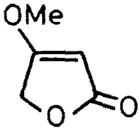
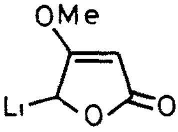
Summary Butenolide anions do not react with orthoesters and butenolides do not react with carbocations derived from acetals and orthoesters However double activation of the butenolide (as the carbanion) and the alkoxyalkanes (as the stabilised carbocations) leads to high yield carbon-carbon bond formation of some generality

The central role of carbanions[1] and carbocations[2] in organic synthesis is well known However the two species, unless heavily stabilised, are generally thought to be incompatible in normal, homogeneous reaction conditions Thus each type is generally reacted with a neutral substrate though inadvertent activation of a neutral substrate by a gegenion, such as lithium, has been verified [3] A very recent report[4] of the reactions of preformed lithium enolates of ketones with trimethyl orthoformate in the presence of boron trifluoride etherate, possibly proceeding by reaction of the enolate with dimethoxymethonium ion ($\overset{+}{C}H(OMe)_2$) formed in situ[5], prompts us to report our independent findings on the reactions of methyl tetronate derived anions[6] with acetals and ketals pretreated with Lewis acids, particularly boron trifluoride etherate The two papers taken together suggest that 'double activation' is a powerful and general tool for carbon-carbon bond formation.

For the preparation of piperolide[7] and fadyenolide[8] and various analogues we required efficient syntheses of compounds (8) (9) and (12) Attempts to react carbanion (2) with trimethyl orthoformate (4a), despite wide variation in reaction conditions failed to yield any of the desired product (8a) Similarly methyl tetronate itself failed to react with (4a) activated by titanium tetrachloride



(1)



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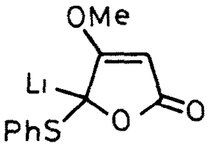


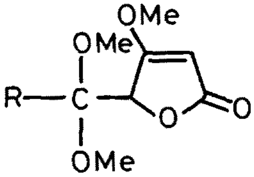
(3)

$RC(OMe)_3$ (4)

$RCH(OMe)_2$ (5)

$C(OMe)_4$ (6)

$HC(OMe)_2NMe_2$ (7)



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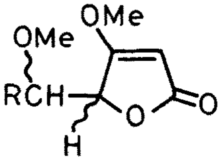

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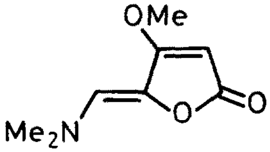

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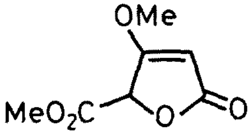

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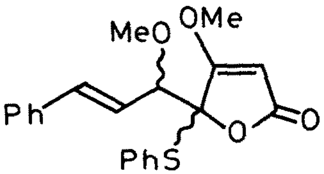

(12)

(a) R = H, (b) R = Me; (c) R = Ph; (d) R = PhCH$\overset{t}{=}$CH

We therefore tried syphoning solutions of (2) at -78°C into slurries of alkoxy-stabilised carbonium ions (R$\overset{+}{C}$(OMe)$_2$) or R$\overset{+}{C}$HOMe produced at -78°C by the action of boron trifluoride etherate (in equivalent quantities to the carbanion used) on acetals or ortho esters, (for a typical procedure see ref 9) We were pleased to find that in these mild conditions good yields of the required products resulted (Table)

TABLE

The reaction of methoxy-stabilised carbonium ions with methyl 5-lithiotetronates

Ortho ester/Acetal	Carbanion	Product	Yield[a,b]	m p °C
$C(OMe)_4$ [c]	2 [c]	11	81	79
$HC(OMe)_3$ [d]	2 [d]	8a	85	oil
$CH_3C(OMe)_3$ [d]	2 [d]	8b	81	78-79
$PhC(OMe)_3$ [c]	2 [c]	8c	84	101-102
$HC(OMe)_2NMe_2$ [c]	2 [c]	10	59	57-58
$PhCH(OMe)_2$ [c]	2 [c]	9c	78	e
$PhCH\ CH\ CH(OMe)_2$ [c]	2 [c]	9d	74	e
$PhCH\ CH\ CH(OMe)_2$ [c]	3 [c]	12	72	e

a) All yields are of isolated products b) All products gave satisfactory C, H analyses and spectral data c) Ether used as solvent d) 10 1 mixture of ether and THF used as solvent e) Mixture of *erythro* and *threo*- products

Several general points can be made (i) All the reactions are regiospecific in that carbon-carbon bond formation occurs only at C-5 of the butenolide unit (ii) The stabilised carbonium ion can be derived from a tetra-, tri- or di-alkoxyalkane making the reaction type one of wide generality (iii) Only monoalkylation of the carbanion occurs (iv) The reactions proceed under mild conditions to give good yields of products not otherwise readily available in general

With regard to specific reactions several comments are required (i) In the case of condensation with (5d), reaction of (2) or (3) *only* occurs at C-1 of the acetal unit, a great contrast to the condensation of (2) with cinnamaldehyde itself,[6,10] which proceeds almost entirely by 1,4-condensation to yield complex mixtures (ii) Condensation with (6) gave the ester (11) rather than the expected ortho ester (8, R = OMe), which could not be isolated (iii) Bredereck's reagent (7) could be used, but elimination occurred so that (10) was isolated in moderate yield In fact (10) is better made by the direct interaction of (7) and (1) with heating

The indications from our work and that of Noyori[4] are that the double activation concept covers a wide range of carbanions and alkoxy-stabilised cations Such reactions may well be first choice for carbon-carbon bond formation and should certainly be considered when difficulty is encountered in the reactions of either carbanions or carbocations with neutral substrates

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9 Carbanion (2) was generated by addition of methyl tetronate (1) (0 285g, 2 5 mmole) in ether (25 ml) to n-butyl lithium (1 7 ml of 1 48M solution in hexane, diluted with ether (50 ml)) at -78°C In a separate flask compound (6) (0 7g, ∼5 mmole) in ether (10 ml) was added dropwise with stirring to freshly distilled BF$_3$ Et$_2$O (0 31g, 2 5 mmole) at -78°C Stirring was continued for 20m and the solution of (2) added over 5m to the slurry by means of nitrogen pressure on a cooled double ended needle The reaction mixture was allowed to warm to room temperature (2h), diluted with ether (25 ml) and washed with aq NaHCO$_3$ (1 x 15 ml), water (2 x 15 ml) dried (MgSO$_4$), filtered and evaporated Recrystallisation from ether gave (11), m.p 79°C, 0 35g, 81 4% yield

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