Tetrahedron Letters,Vol.27,No.20,pp 2319-2322,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

PHOTOCHEMICAL 2-ALKYLATION OF CYCLOHEXANE-1,3-DIONES WITH ENOL ETHERS

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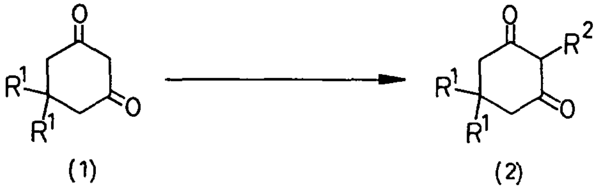
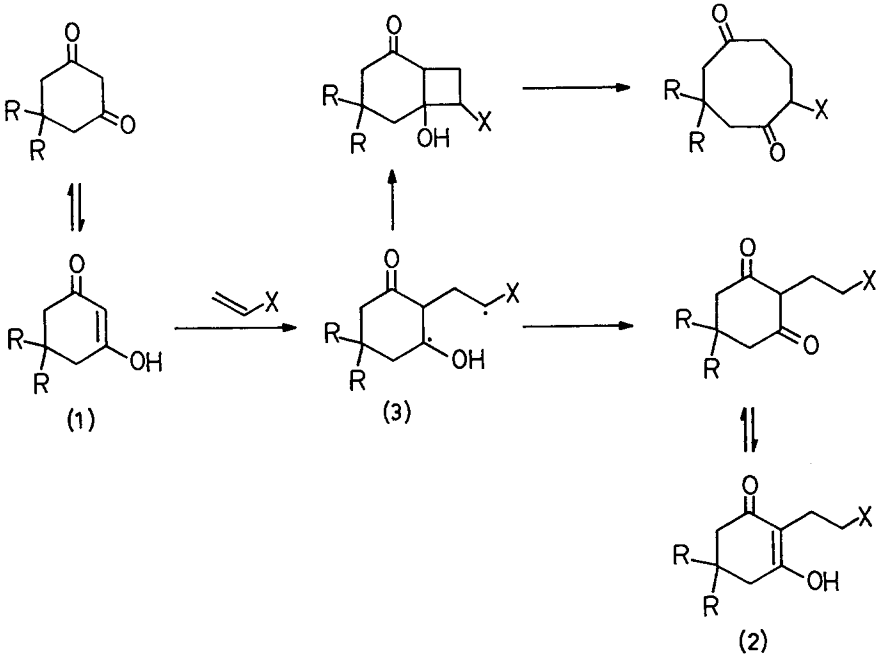
Abstract: Cyclohexane-1,3-diones may be photochemically 2-alkylated with enol ethers under mild conditions.

As part of an ongoing synthetic programme we required a means of preparing 2-alkylcyclohexane-1,3-diones under mild conditions from the parent diketones. (1 => 2)



With such substrates, base mediated alkylation procedures frequently result in O-alkylation except in the case of "soft" electrophiles,[1] and whilst Michael addition of cyclic 1,3-diketones to vinyl ketones via C-2 is frequently possible[2] the side chain carbonyl moiety introduces problems of functional group differentiation. Certain 2-alkyl-1,3-cyclohexanediones are available via selective 2-alkylation of the Birch reduction products of 1,3-dimethoxybenzenes,[3] but this route requires strongly basic conditions and is inapplicable to the preparation of derivatives with additional geminal disubstitution (eg. 2, R^1 = Me).

Irradiation of cyclohexane-1,3-diones in the presence of alkenes is known to result in 2+2 cycloaddition followed by reverse aldol cleavage of the cycloadduct to give ring expanded products (De Mayo reaction[4], Figure, path a), but low yields of 2-alkylated by-products have also been reported.[5] On the assumption that such divergence results from hydrogen atom abstraction by the initial diradical (Figure, path b), we investigated the use of substituted alkenes which would lead to a stabilized diradical intermediate 3 in the hope of favouring the hydrogen abstraction pathway.

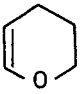
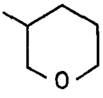
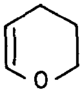
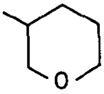
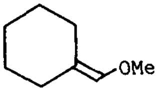


Figure

We now report that the use of enol ethers permits 2-alkylated products to be obtained with the exclusion of any material resulting from the De Mayo pathway. The success of the reaction is critically dependent upon the degree of substitution of the double bond. 1 or 2-substituted enol ethers undergo reaction (the latter at a markedly slower rate) but 2,2-disubstitution renders the alkylation pathway inoperative. Double alkylation of the diketone appears to be highly disfavoured, as in only a few instances were such products tentatively identified by ms. analysis of the crude product.[6] (Table) The addition occurs only at the 2-position of the enol ether and is inhibited in the presence of piperylene which acts as a triplet quencher. Whilst irradiation through quartz or pyrex in a range of reaction solvents (ether, THF, acetonitrile, benzene) was shown to furnish the desired products, use of benzene and irradiation through pyrex consistently gave the highest yields with regards to both reaction components. However the relatively low solubilities of the cyclohexane-1,3-diones in benzene led to the development of a second procedure using benzene/ethanol (95:5) for larger scale reactions (5 mmol). In this instance it was necessary to use excess enol ether (~10 equiv.) due to competing reaction with the ethanol, although the yields of 2-alkylation products based on starting diketone were unaltered.

(1) (2)

Reagents: Method A; enol ether (1.5 equiv.), C_6H_6, hν;
Method B; enol ether (10 equiv.), C_6H_6/EtOH (95:5), hν.

R^1	enol ether	$-R^2$	time (h)	yield (%)
H	$CH_2{=}CHOEt$	$-CH_2CH_2OEt$	96	42[a]
	$CH_2{=}CHOnBu$	$-CH_2CH_2OnBu$	64	49[a]
	$CH_2{=}C(CH_3)OMe$	$-CH_2CH(CH_3)OMe$	96	60
			120	40[b]
Me	$CH_2{=}CHOEt$	$-CH_2CH_2OEt$	24	54
	$CH_2{=}CHOnBu$	$-CH_2CH_2OnBu$	24	60
	$CH_2{=}C(CH_3)OMe$	$-CH_2CH(CH_3)OMe$	24	73
			63	55
		—	100	0

a; Products of double alkylation also detected in the crude product. b; This reaction failed using benzene alone. All other reactions were duplicated using method A and method B; times and yields unaltered under both conditions.

Table

In the standard procedure a deoxygenated solution of the cyclic 1,3-dione in benzene containing 1.5 equivalents of the enol ether was irradiated with a 125 W medium pressure mercury lamp through a pyrex filter in an immersion reactor until starting diketone had been consumed. Removal of solvent and excess enol ether under reduced pressure and base extraction followed by acidification and back extraction (Et_2O) furnished the homogeneous product (tlc., nmr.). Further purification by chromatography or recrystallisation was carried out as appropriate.

A survey of other potential alkene reactants showed that enol acetates and vinyl sulphides did not undergo 2-alkylation. The substrates appear to be limited to cyclic 1,3-diketones as the acyclic analogues and Meldrum's acid furnished no desired products.

In summary this photochemical alkylation approach provides a novel and efficient means of 2-alkylating cyclohexane-1,3-diones under without recourse to basic conditions. We will describe further investigations into the scope and synthetic applications of this procedure in due course.

Acknowledgements: We thank the S.E.R.C. for financial assistance (to N.M.B.)

References

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5. J.E. Pauw and A.C. Weedon, Tetrahedron Lett., 1982, 5485.
6. The alkylated products gave spectroscopic and microanalytical data in accord with their assigned structures. The nmr. spectra indicated that in all cases the products existed in solution almost exclusively in the enol form. eg. (2), R^1=Me, R^2=CH_2CH_2OEt; δ (300 MHz, $CDCl_3$) 1.05(s, 6H, $C(CH_3)_2$), 1.24(t, 3H, J 7Hz, $OCH_2\underline{CH_3}$), 2.23(s, 2H, CH_2CO), 2.34(s, 2H, CH_2C=C), 2.68(t, 2H, J 5Hz, $\underline{CH_2}CH_2OEt$), 3.55(t, 2H, J 5Hz, $CH_2\underline{CH_2}OEt$), 3.59 (q, 2H, J 7Hz, $O\underline{CH_2}CH_3$) and 10.02(s, 1H, OH); i.r. $\nu_{max}(CCl_4)$ 3160, 1650, 1620, 1290, 1090 and 1070 cm^{-1}. m.s., m/z, (%) 212(15, M^+), 183(100), 166(26), 141(32).

(Received in UK 21 March 1986)