Polarised Diaryl Carbonyl Ylids : The Specificity of Additions to Unsymmetric Dipolarophiles

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<u>Summary</u>: 'Push-pull' carbonyl ylids derived thermally or photochemically from oxiranes (14-16) undergo stereospecific, but uncharacteristically non-regioselective, cycloadditions with unsymmetrical electron-deficient dipolarophiles.

There is considerable synthetic interest in natural lignans which display effective anticancer activity.¹ Intermediates of type (1) occupy a pivotal position in a number of synthetic strategies since they can lead on to bisbenzocyclooctadienes (2) e.g. steganone,² to aryltetralins (3), e.g. podophyllotoxin relatives,³ or to bisbenzyllactones (4) e.g. burseran.⁴



We were attracted by the use of carbonyl ylids (5), derived from readily available stilbene oxides, to obtain 2,5-bisaryl tetrahydrofurans (6) with complete stereo-control at C-3 and C-4 which could provide the desired intermediates, e.g. (7) through benzylic hydrogenolysis, or the selectively functionalised (8), <u>via</u> fragmentation. Such dipolar cycloadditions are well known for stilbene oxide itself, using either heat or light to generate the ylid. In the present work we found that electron transfer sensitised photoreactions were often efficient; thus e.g. irradiation of <u>trans</u>stilbene oxide with 2-butenolide in the presence of 1,4-dicyanonaphthalene afforded only the <u>endo</u> bicyclic lactone (9) in essentially quantitative yield. We have effected related reactions⁵ with 4,4'-dimethoxystilbene oxide. However although symmetrical carbonyl ylids do have synthetic utility, we wished to employ unsymmetrical ylids i.e. (5), $Ar^1 \neq Ar^2$, with unsymmetrical dipolarophiles to open a fully general way to tetrahydrofurans (6): it is clearly necessary that, to be of synthetic value, such reactions be regiospecific. We thus set out to investigate some cycloadditions of this type.

Highly polarised ylids of type (10) ('push-pull' ylids⁶) are readily generated from the corresponding oxiranes; in an extreme case, one such ylid has been isolated as a solid.⁷ Further, all the cases known to us⁸ of intermolecular cycloaddition of carbonyl ylids to unsymmetric dienophiles are highly regioselective, and in agreement we observed that on trapping ylid (10) with ethyl acrylate gave only the adduct (11). Such regioselectivity has been rationalised in terms of control by the HOMO (dipole)-LUMO (dipolarophile) interaction (see 12).⁹ We therefore expected that related highly polarised ylids (13) would undergo regioselective cycloadditions. It was envisaged that a directive nitro group could be readily transformed, for lignan synthesis, into phenolic hydroxyl.



To test this supposition the epoxides (14-16) were prepared by epoxidation of the corresponding <u>E</u>-olefins, which were accessible through conventional Knoevenagel condensations. We were pleased to find that ylids could be generated from (14-16) both thermally and photochemically. Thus heating (15) with maleic anhydride afforded adduct (17) selectively (65%), while irradiation of (14) (low pressure mercury lamp) in the presence of maleic anhydride afforded adduct (18) (68%). The stereochemistry of (17) and (18) was inferred from n.m.r. comparisons with reference compounds and can be seen to arise through the addition of an <u>exo-exo</u> ylid in the <u>endo</u> sense (with respect to aryl groups). The adduct (19) from (15) and dimethylacetylene dicarboxylate, smoothly eliminated hydrogen cyanide on treatment with triethylamine to give an expeditious synthesis of the 2,5-bisarylfuran (20), while adduct (21), from (15) and dimethylfumarate, readily fragmented to enol (22), in the desired sense.



However on heating (110°) the epoxide (15) with ethyl acrylate, a mixture (75%) of adducts (23) and (24) (approximately equal proportions) was obtained. Similar reactions were observed with (14) and (16) and ethyl acrylate. The isomeric esters (23) and (24) were characterised by ¹H.n.m.r.; (23) showed a 3-H, 4-H $_2$, 5H system (δ 3.98, 2.56, 2.75, and 5.34 respectively $J_{3,4}$ 7.6, $J_{3,4}$, 8.5, $J_{5,4}$ 9.7, and $J_{5,4}$, 6.4 Hz), while the regioisomer (24) displayed a $3-H_2$, 4-H, 5-H assembly ($\delta 2.85$, 3.04, 3.80, and 5.60 respectively J_{3,4} 7.6, J_{3',4} 8,4, and J_{4,5} 8.5 Hz). Similarly (16) and ethyl propiolate provided (25) (30%) and (26) (36%), distinguished by the observation of significant nOes (> 5%) between 4-H and 5-H. Isomers (23) and (24) did not equilibrate on separate heating. Thus it appears that the carbonyl ylids derived from (14)-(16) react non-regiospecifically with electron-deficient olefins. Such behaviour has been observed before only in intramolecular reactions where other factors may intervene.¹⁰ It appears likely that in our efforts to induce highly polarised ylids, the dipole frontier orbital energies have been lowered so that the HOMO (dipole) is no longer the controlling feature, but is balanced by LUMO (dipole)-HOMO (dipolarophile) interaction, of opposite direction. Alternatively, the dipole HOMO may not be as biased as expected. This can only be resolved by MO calculations.



We also prepared the oxiran (27) in which the nitro-group was replaced by methylenedioxy, but we were unable to generate and trap (with electrondeficient olefins) an ylid from this compound, either thermally or photochemically; it may be that the frontier orbitals in this case are too elevated in energy for viability.

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