CHEMISTRY OF 2,2-DIMETHYL-1,3-DIOXOLE. TWO-CARBON HOMOLOGATION OF CARBONYL COMPOUNDS TO α-KETOALDEHYDES AND DIHYDROXYACETONYL MOIETIES†

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Abstract-----The lithium salt of 2,2-dimethyl-1,3-dioxole adds readily to aldehydes and ketones to form the blocked dihydroxyacetonyl moiety. Only in favorable cases, however, can deblocking be accomplished without rearrangement. More commonly, acid-catalyzed deblocking leads to concomitant dehydration and results in excellent yields of α-ketoaldehydes rather than substituted dihydroxyacetones.

Recently there has been a considerable exploration of the chemistry of lithium salts of vinyl ethers as reversed polarity equivalents of carbonyl compounds. The dihydroxyacetonyl moiety is found in several important drugs, including glucocorticoids and the clinically useful antitumor anthracycline antibiotic, doxorubicin (1) and this moiety cannot be formed by the above procedures. Introduction of this moiety onto preexisting ketonic precursors presently adds undesirable length to already lengthy synthetic sequences so alternative processes are under continual examination.

Additionally, there has been substantial interest in the antiviral properties shown by a variety of α-dicarbonyl compounds despite present difficulties in synthesizing them. It seemed to us that the known dienophile, 2,2-dimethyl-1,3-dioxole (3) offered a potentially attractive means of preparing the above substances through an intermediate masked form and we record here some of our more

†Dedicated to Prof. Herbert C. Brown, on the occasion of his 70th birthday.
significant findings.

Preparation of 3 by pyrolysis of the stable crystalline anthracene adduct (7) produces the desired dioxole 3 in variable yield (35-50%) as described. Examination of the byproducts by glc-ms led to the identification of 2-methylfuran [SE-30 column, isothermal at 60°C, retention time = 85 sec.; m/z 82; pmr (CCl₄) 2.868 (3H, s, CH₃), 5.84, 6.14 and 7.12 (3xArH)], acetone [r.t. = 78 sec.; m/z 58,42; pmr (CCl₄) 2.046 (6H, s, CH₃CO)], isopropyl alcohol [r.t. = 78 sec.; m/z 60; pmr (CCl₄) 1.186 (6H, d, J = 6Hz, CH₃CHO-), 3.90 (1H, hept., J = 6Hz, Me₂CHO-) and water. Under cracking conditions, fragmentation of dioxole 2 to diradical 8 and subsequent rearrangements and fragmentations can easily account for the observed products. Even storage over KOH in the freezer (as recommended) leads to partial decompentation of pure 3 into these products.

As summarized in Table 1, 2,2-dimethyl-1,3-dioxole readily forms a lithio salt (t-BuLi, TMEDA, THF, -65°C) which reacts with representative aldehydes and ketones (2) to form adducts (4) in good to excellent yields. Unfortunately for the direct preparation of glucocorticoids and anthracyclines, only on a milligram scale in the absence of more than trace quantities of catalytic acid could the original target products (5) be obtained. Despite numerous attempts, the usual product was the enol of the α-ketoaldehyde (6). Adducts such as 17 are of considerable contemporary interest and have been transformed to glucocorticoids. The required additional steps diminish the attractiveness of 3 as a synthon although the dehydration does allow for epimerization to the natural stereochemistry at C-17. The elimination of the tertiary OH group is readily rationalized in retrospect as involving participation of one of the vinyl oxygens as shown in formula 18. This decomposition pathway is not readily available to the Baldwin adduct and adequately rationalizes the different outcome. Where a highly stable carbonium ion is involved (as with 12), the adduct is transient and the only detectable product is 13, formed directly in 46% yield.

Thus, use of 2,2-dimethyl-1,3-dioxole provides a convenient route for the two-carbon homologation of ketones and aldehydes to α-ketoaldehydes and these products can be, if desired, isolated and reacted in blocked form (10, 15). This should make these presently difficultly accessible compounds more freely available for study.

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REFERENCES AND NOTES


5. All products gave satisfactory pmr, ms and, regarding the aldehydes, microanalyses.


8. \( \text{Ir (KBr)} \) 3480 cm\(^{-1}\), 2938, 2880, 1605, 1496; pmr (CCl\(_4\)) 0.885 (s, 3H, 19-CH\(_3\)), 1.20-2.44 (m, 14H, CH\(_2\) and 1H, vinyl), 1.52 (br.s., 6H, dioxole (CH\(_3\))\(_2\), 2.60-3.02 (m, 2H, ArCH\(_2\)), 3.64 (s, 3H, OCH\(_3\)), 5.94 (s, 1H, vinyl-H), 6.42 (br.s., 1H, 4-ArH), 6.50 (d, d, J = 1.5, 8.0 Hz, 1H, 2-Ar-H), 7.00 (d, d, J = 10, 8.0 Hz, 1H, 1-Ar-H); eims m/e 384 (M\(^+\) = 49%), 366 (20%), 326 (100%), etc. Anal. Calcd. for C\(_{24}\)H\(_{32}\)O\(_4\): C, 74.96; H, 8.39. Found: C, 75.27; H, 8.73.

9. \( \text{Ir (CH\(_2\)Cl\(_2\))} \) 3490 cm\(^{-1}\), 2960, 2880, 1736, 1668, 1640, 1500, 1332; pmr (CDCl\(_3\)) 1.006 (s, 3H, 19-CH\(_3\)), 1.18-3.10 (m, 15H, CH\(_2\), CH), 3.76 (s, 3H, OCH\(_3\)), 5.60, 5.96 (2xbr.s., 1H ea., 17-CH, OH), 6.62 (s, 1H, 4-ArH), 6.60-6.84 (d, d, J = 10, 8.5 Hz, 1H, 2-Ar-H), 7.06-7.34 (d, d, J = 1.0, 8.5 Hz, 1H, 1-Ar-H), 9.36 (s, 1H, CHO); eims m/e 326 (M\(^+\), 100%), 311 (5%), 297 (7%), 269 (21%), etc. Anal. Calcd. for C\(_{21}\)H\(_{26}\)O\(_3\)\(_2\): C, 73.22, H, 8.19. Found: C, 72.88; H, 7.98.

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