A NEW METHOD FOR THE SYNTHESIS OF DIOXOLENONES VIA THE CARBOXYLATION OF KETONE ENOLATES WITH ANISYL CYANOFORMATE

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Abstract: The generality of the intramolecular dioxolenone photocycloaddition we have described depends on the availability of the requisite functionalized dioxolenones. We report herein a general approach to the preparation of dioxolenones, via carboxylation of ketone enolates with anisyl cyanoformate and condensation of the resulting ketoesters with acetone.

We have recently reported that the intramolecular photoaddition of dioxolenones to alkenes results in the formation of six-, seven-, and eight-membered rings, i.e., $1 \rightarrow 3$, in good yields with excellent regiochemical control.² The generality of this method depends critically on the availability of the requisite dioxolenones, $1.^{3,4}$ In this Letter, we describe an efficient and general approach to the synthesis of dioxolenones by annulation onto a pre-existing ketone, as outlined below, $4 \rightarrow 6$.



The conversion of t-butyl β -ketoesters to dioxolenones can be accomplished in excellent yields in a single chemical step using either the conditions described by Sato⁴ or our own recently reported procedure.² A general approach to the synthesis of acid labile ketoesters would therefore lead to a general synthesis of dioxolenones. Towards that end, we were intrigued by the report that methyl cyanoformate, 7, reacts in excellent yields with a variety of ketone and ester enolates to give β -ketoesters.^{5,6} In a straightforward extension of this work, we attempted to carboxylate the lithium enolate of cyclopentanone with tert-butyl cyanoformate, 8,⁷ although none of the desired ketoester was obtained. However, anisyl cyanoformate, 9,⁸ reacts with a variety of ketone and ester enolates in excellent yields and permits an efficient two step procedure for the homologation of a ketone to the corresponding dioxolenone, 4 \div 6.⁹

As illustrated in the Table, 9 reacts with the lithium enolates of ketones (Entries 1-6) to give excellent yields of the anisyl ketoesters. In contrast 8 gives a ca. 65% yield of the tert-butyl cyclohexanone carboxylate. The reaction of 9 with ester enolates (Entries 7 and 8) proceeds in excellent yields for the synthesis of both enolizable and non-enolizable malonates, in which the two esters are differentiated. In this kinetic process, unlike the Claisen condensation for the synthesis of malonic acid esters, the formation of the conjugate base of the malonate to drive an unfavorable equilibrium is not required, so that both non-enolizable (Entry 7) and enolizable (Entry 8) malonates can be formed. We note also that the dianion¹⁰ of methyl cyclohexanone 2-carboxylate (Entry 9) reacts with 9 to give a 63% yield of the corresponding diester. Conjugate addition of lithium dimethylcuprate to enones (Entries 4 and 5) followed by reaction of the enolate generated in situ with 9 led to the formation of the substituted ketoesters in nearly quantitative yields. This exceedingly efficient one-step conjugate addition/trapping sequence attests to the uniqueness of the cyanoformates as regeants for carboxylation.

A representative experimental procedure for the carboxylation follows: A solution of 3 mmol ketone in 2 ml of tetrahydrofuran (THF) was added to a solution of lithium diisopropylamide, prepared from 4.5 mmol of diisopropylamine and 4 mmol of butyllithium (1.9M in hexanes) in 20 ml THF at 0° C. The mixture was stirred at 0° C for 30 min, and then cooled to -78° C. Hexamethylphosphoramide (3 mmol) and anisylcyanoformate (4 mmol) in 2 ml of THF were added and the mixture was stirred at -78° C for 30 min. The reaction mixture was partitioned between water and diethyl ether, and the organic layer washed with water, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue chromatographed¹¹ to yield the desired product.

To complete the proposed sequence, $4 \rightarrow 6$, outlined above, the conversion of the anisyl ketoesters to the desired dioxolenones was next examined. The conversion of the anisyl ketoesters (Entries 1-6) to the corresponding dioxolenones proceeds in excellent yields (see Table) in a single synthetic operation (anhydride, trifluoroacetic acid, acetone, $-78^{\circ}C \rightarrow RT$, 12 h) using either a large excess of acetic anhydride (55 equivs) with 1:1 trifluoroacetic acid/acetone (10 ml/mmol ketoester) as solvent (Method A) or 2 equivs of trifluoroacetic anhydride in the same solvent (Method B). The application of this sequence to the synthesis of highly functionalized photosubstrates, 1, is currently in progress in our laboratories and our progress will be described in due course.



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References:

- 1. Recipient of a Merck Grant for Faculty Development, 1985-1986.
- a) J. Winkler, J. Hey, F. Hannon, Heterocycles, 1986, in press; b) J. Winkler, J. Hey, P. Williard, J. Am. Chem. Soc. 108 6425 (1986); c) J. Winkler, J. Hey, Tet. Letters, 1986, in press; d) J. Winkler, P. Hershberger, J. Springer, Tet. Letters, 1986, in press.
- For the first example of the <u>inter</u>molecular photocycloaddition of dioxolenones, see S. Baldwin, J. Wilkinson, J. Am. Chem. Soc. 102 3634 (1980).
- M. Carroll, A. Bader, J. Am. Chem. Soc. 75 5400 (1953); M. Sato, H. Ogasawara, K. Oi, T. Kato, Chem. Pharm. Bull. 31 1896 (1983).
- 5. L. Mander, S. Sethi, Tet. Letters 5425 (1983).
- For the application of the Mander reagent to the carboxylation of enolates, see a) F. Ziegler, A. Kneisley, R. Wester, Tet. Letters 1221 (1986); b) F. Ziegler, R. Wester, Tet. Letters 1225 (1986); c) F. Ziegler, T. Wang, Tet. Letters 2291 (1985); d) F. Ziegler, S. Klein, U. Pat, T. Wang, J. Am. Chem. Soc. 107 2730 (1985); e) F. Kunisch, K. Hobert, P. Welzel, Tet. Letters 5433 (1985).
- 7. L. Carpino, J. Org. Chem. 29 2820 (1964).
- a) M. Leplawy, W. Stec. Bull. Acad. Polon. Sci., Ser. Sci. Chim. 12 21 (1964) (Chem. Abstracts 61 1933 (1964); b) O. Achmatowicz, K. Belniak, C. Borecki, M. Leplawy, Roczniki Chem. 39 1442 (1965) (Chem. Abstracts 64 17457g).
- All new compounds were characterized by full spectroscopic (NMR, IR, MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

10. S. Huckin, L. Weiler, J. Am. Chem. Soc. 1974, 96, 1082.

11. W. Still, M. Kahn, A. Mitra, J. Org. Chem. 43 2923 (1978). (Received in USA 11 November 1986)

1054