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2-Chloro-1,3-dithiane - A Formyl Cation Equivalent

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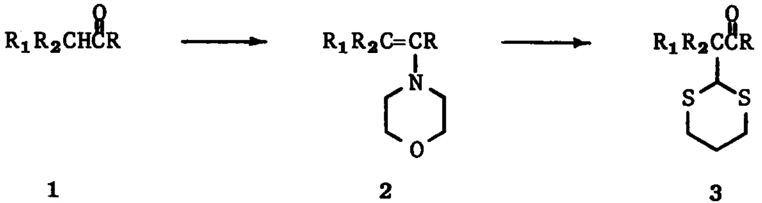
In connection with another project, we had need for a series of substituted malondialdehydes in which only one of the carbonyl groups was protected as a dithioacetal. We have found that aliphatic aldehydes possessing at least one α-hydrogen (1) can be converted to the desired half-protected malondialdehydes (3) by alkylation of their respective morpholino enamines (2) with 2-chloro-1,3-dithiane.[2] 1,3-Dithiane itself has been widely exploited as a "formyl anion equivalent", but it does not appear to have been generally recognized that 2-chloro-1,3-dithiane is, in effect, a "formyl cation equivalent" - a readily accessible synthetic equivalent to a formyl halide.[3,4] We are communicating our preliminary results at this time in view of a recent publication which describes the reaction of 2-chloro-1,3-dithiane as an alkylating agent with several phosphorus compounds and with the anion of diethyl malonate.[5]

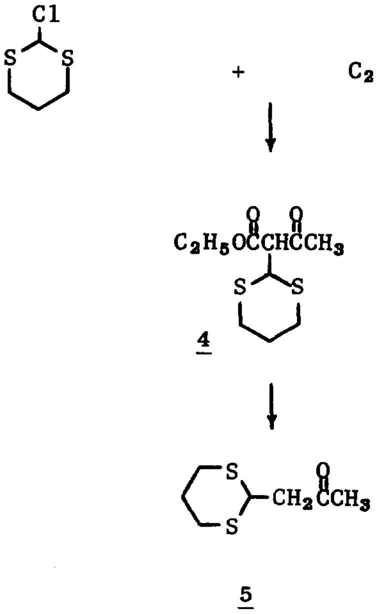


1 2 3

The following procedure is representative. A solution of 2.40 g (20 mmol) of 1,3-dithiane in 15 ml of dry benzene was stirred at room temperature under nitrogen and to it was slowly added, over 20 min, 2.80 g (21 mmol) of powdered N-chlorosuccinimide. After addition was complete, the mixture was stirred at r.t. for another 20 min, rapidly filtered with minimum exposure to air, and the filtrate immediately concentrated on a rotary evaporator at r.t.

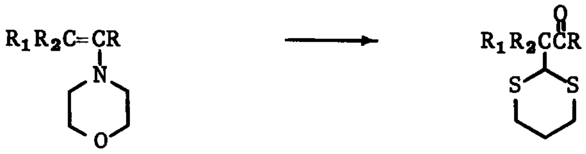
to a volume of 5 ml. The residual material was then dissolved in a mixture of 10 ml of dry THF and 10 ml of dry ether. A 100-ml, 3-necked round-bottomed flask, fitted with two addition funnels and a magnetic stirring bar, was cooled with an ice bath and 10 ml of dry ether added. Under a nitrogen atmosphere, the above solution of 2-chloro-1,3-dithiane, and another solution of 1-(morpholino)-1-butene (2.82 g, 20 mmol) in 20 ml of dry ether, was added dropwise simultaneously over 15 min. During this time a solid precipitated. After addition was complete, the mixture was vigorously stirred at r.t. for 10 min, and 20 ml of 10% HCl was then added directly to the mixture. The two-phase mixture was stirred at r.t. for 0.5 hr,[6] the ether layer separated and the aqueous phase extracted twice with 10 ml portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered and evaporated and the resulting oil distilled under reduced pressure to give 2.05 g (53%) of α-(1,3-dithian-2-yl)butyraldehyde as a yellow oil, bp 97°/0.01 torr.

3-Pentanone, cyclopentanone and cyclohexanone were also α-formylated via their morpholino enamines by the above procedure. More acidic substrates can be alkylated directly; thus, ethyl acetoacetate was converted to 4 which, without isolation, was decarboethoxylated with sodium chloride in DMSO to give the known α-(1,3-dithian-2-yl)acetone (5).[7] Attempts to formylate the dianion of ethyl acetoacetate led only to proton transfer, with recovery of unchanged starting material. Thus, the utility of 2-chloro-1,3-dithiane as a formylating agent appears to be limited by the basicity of the nucleophile.



Classical methods for α-formylation of carbonyl compounds include the use of ethyl formate and base, Vilsmeier reactions utilizing dimethylformamide and Lewis acids, and related processes utilizing dimethylformamide dimethylacetal, or trialkyl orthoformates. The present procedure is complementary, with the advantage that it introduces directly a base-stable protected formyl substituent. We plan to report at a later time on the utilization in synthesis of these half-protected alkyl malondialdehydes.

Table 1. Synthesis of α-(1,3-Dithian-2-yl)aldehydes and Ketones



	bp°/torr mp°	Yield,%
$R_1 = R_2 = CH_3$, $R = H^{a,b}$	56-57 (sublimes)	73
$R_1 = CH_3$, $R_2 = R = H^c$	97/0.01	53
$R_1 = C_2H_5$, $R_2 = R = H^c$	112/0.01	50
$R_1 = CH_3$, $R_2 = H$, $R = C_2H_5$	95/0.01	65
$R_1 = R = (CH_2)_3$, $R_2 = H^d$	113/0.01 75-76 (ethanol)	41
$R_1 = R = (CH_2)_4$, $R_2 = H^e$	125-128/0.01	40

(a) All new compounds exhibited satisfactory nmr and ir spectra, as well as combustion analyses (C,H ±0.4%). (b) This enamine has been described previously: E. Benzing, Angew. Chem., 71, 521 (1959). (c) These enamines were prepared by the method of R. Dulou, E. Elkik and A. Veillard, Bull. Soc. Chim. France, 967 (1960). (d) This product solidifies after distillation and can be subsequently recrystallized. (e) This product was analyzed as its 2,4-dinitrophenylhydrazone.

REFERENCES

1. NIH Postdoctoral Fellow (CA 05017-B), 1975-77.
2. (a) K. Arai and M. Oki, Tetrahedron Lett., 2183 (1975): (b) K. Arai and M. Oki, Bull. Chem. Soc. Japan, 49, 553 (1976).
3. Formyl chloride is unknown, but formyl fluoride has been used in Friedel-Crafts and Schotten-Baumann formylations, and with some S, O and N nucleophiles. It does not, however, appear to have been used for the formylation of enamines or enolates (G. A. Olah and S. J. Kuhn, J. Am. Chem. Soc., 82, 2380 (1960)).
4. 1,3-Dithienium tetrafluoroborate (E. J. Corey and S. W. Walinsky, J. Am. Chem. Soc., 94, 8932 (1972)) is closely related structurally to 2-chloro-1,3-dithiane, but it has never been used as a formylating agent.
5. C. Kruse, N. Broekhof, A. Wijsman and A. van der Gen, Tetrahedron Lett., 885 (1977).
6. When the morpholino enamines of ketones are used, the heterogeneous solution is gently warmed for 0.5 hr before work-up.
7. D. Coffen, K. C. Bank, and P. E. Garrett, J. Org. Chem., 34, 605 (1969).