

Monoalkylidenes of Meldrum's Acid

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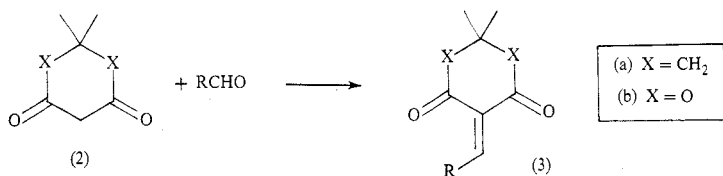
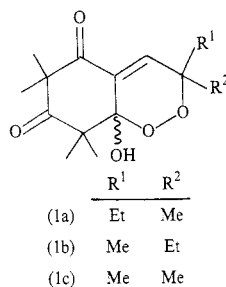
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Abstract

Meldrum's acid has been found to react with equimolar quantities of aldehydes and secondary cyclic aliphatic amines to yield the corresponding Mannich bases which decompose under acidic conditions to afford the monoalkylidene derivatives in excellent yields.

Introduction

In the course of studies on structure-activity relationships in analogues of the G-regulators (1), growth regulators from *Eucalyptus grandis*,¹ we have had occasion to synthesize a range of 2-alkylidene 1,3-diones (3). The preferred approach was by reaction (Scheme 1) between the appropriate 1,3-diones (2) and carbonyl components—perhaps the C-C bond-forming reaction most used in synthesis and one where the generality is always stressed in standard texts. In practice, however, the multiplicity of reaction conditions presented in the literature bears testimony to the frustrations encountered in the application of this general reaction. The successful outcome seems to depend in each case upon a fine balance between the rates of various stages in the reaction and upon their reversibility. In the present communication we outline the situation encountered with synthesis of alkylidene derivatives of some cyclic 1,3-diones and the development of a successful approach to the problem.

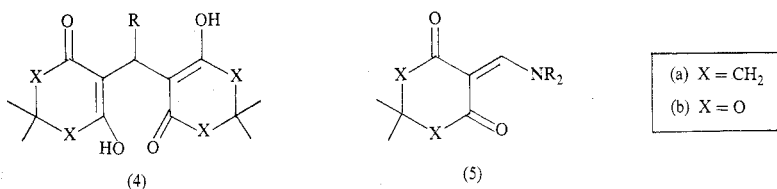


Scheme 1

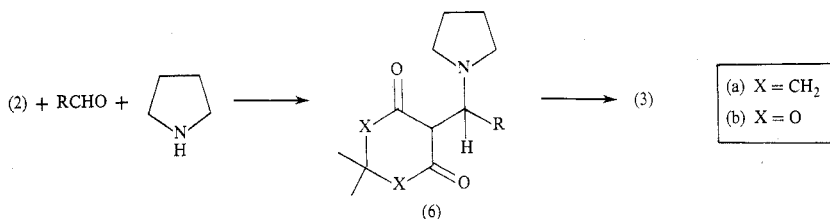
¹ Crow, W. D., Nicholls, W., and Sterns, M., *Tetrahedron Lett.*, 1970, 4723.

Discussion

Several methods have been reported for the preparation of monoalkylidene derivatives (3b) of Meldrum's acid (2b) by reaction with aldehydes. The method of Cope² gives fair-to-good yields with aromatic or hindered aliphatic aldehydes, it gives only polymers with the straight-chain aliphatic aldehydes. The major disadvantage of the normal base^{3,4} or Lewis acid⁵ catalysed Knoevenagel condensation is that the rate of Michael addition of (2b) to the product (3b) is, unfortunately, often comparable to the rate of formation of (3b) itself, leading to extensive formation of the double condensation product (4b). This is, of course, the normal product from dimedone. More recently, a longer and tedious approach⁶ has involved 1,4-addition of Grignard reagents to the vinylogous amides (5b), followed by acid hydrolysis to (3b). In practice, this method gives only fair yields from Meldrum's acid (2b), a 50% yield with *N,N*-dimethylbarbituric acid (2, X = NMe) and fails with dimedone (2a). The failure in this case is almost certainly due to enolization in (5a) since the analogous (but non-enolizable) derivatives from syncarpic acid reacted smoothly to give the desired products.



In an earlier publication⁷ we reported the use of the Mannich reaction to prepare 2-alkylidene 1,3-diones (3a) employing acid-catalysed breakdown of the Mannich bases (6a) (see Scheme 2). The essential feature of the method was the use of an aprotic solvent (dichloromethane) for the initial condensation, and actual isolation of the Mannich base by evaporation of the solvent prior to decomposition in aqueous acid. While the method was generally effective for 2-substituted aldehydes, it failed with unsubstituted aldehydes, giving rise to the double condensation products (4). In some cases this problem arises from the facile elimination of the base [to form (3)] while the first stage of the reaction is in progress; in other cases Mannich base forma-



Scheme 2

² Cope, A. C., *J. Am. Chem. Soc.*, 1941, **63**, 3455.

³ Schuster, R., Polansky, O. E., and Wessely, F., *Monatsh. Chem.*, 1964, **95**, 53.

⁴ Margaretha, P., and Polansky, O. E., *Tetrahedron Lett.*, 1969, 4983.

⁵ Lehnert, W., *Tetrahedron Lett.*, 1970, 4723.

⁶ Ziegler, F. E., Guenther, T., and Nelson, R. V., *Synth. Commun.*, 1980, **10**, 661.

⁷ Bolte, M. L., Crow, W. D., and Yoshida, S., *Aust. J. Chem.*, 1982, **35**, 1421; Crow, W. D., Bolte, M. L., Osawa, T., Paton, D. M., and Yoshida, S., in 'IUPAC Pesticide Chemistry: Human Welfare and the Environment' (Pergamon Press: Oxford 1983).

tion is seen to proceed, but the base elimination in aqueous solution is accompanied by Michael addition of water to (3) and reversion to (2). In both cases the coexistence of (2) and (3) leads to the dimeric condensation product (4), that is, to 'failure' of the method.

In order to overcome this problem we made two simple but effective modifications to the system. The first modification has been to prepare the Mannich bases (6) in dry ether, whereupon they may be isolated by filtration without heating: this ensures that no 1,3-dione is carried over into the second stage. The elimination of the base, leading to formation of the 2-alkylidene 1,3-diones (3), is carried out in the absence of effective nucleophiles by treating the Mannich base in dry dichloromethane with a slight excess of *p*-toluenesulfonic acid, thus avoiding generation of (4) during the process.*

The reaction proceeded smoothly in every case, although a longer reaction time (30 min) was needed for the preparation of the Mannich base from benzaldehyde. The course of the reaction and the yields are quite independent of the nature of the amine used; similar results were obtained with morpholine or piperidine. On the other hand, the reaction is quite sensitive to temperature and hence a low reaction temperature is recommended to avoid nucleophilic attack of the amine on Meldrum's acid and also to avoid polymerization of the aldehydes—especially when straight-chain aldehydes are used. The Mannich bases are quite stable when stored at low temperature but decompose at room temperature in a period of a few days. Yields of Mannich base (6b) were 100% for R = Et, Pr, Prⁱ, Buⁱ, Ph, CH(Et)Bu, and for all these substituents the yield of alkylidene was likewise 100% except for R = Et or Pr (98%). All Mannich bases were characterized by spectroscopic means and by combustion analysis, while the alkylidenes were identified by comparing the spectral and melting point data with those already reported in the literature.⁶ As seen from the results, the method should prove useful on account of its simplicity, high yields and ease of workup.

Experimental

Meldrum's acid (500 mg, 3.47 mmol) in dry ether (10 ml) was stirred for 5 min at salt-ice bath temperature under nitrogen. To this was added dry pyrrolidine (0.3 ml, 3.5 mmol), followed by a dropwise addition of freshly distilled propanal (0.25 ml, 3.5 mmol). After 10 min at the same temperature, the reaction product was filtered off and washed with cold dry ether to yield the Mannich base (5) (880 mg, 100%) as a colourless solid. The Mannich base (5) (510 mg, 2 mmol) was dissolved in dry methylene chloride (5 ml) and to this was added *p*-toluenesulfonic acid (400 mg, 2.1 mmol) at 0° with the exclusion of moisture. After 10 min at 0° it was diluted with ether (50 ml) and the milky white ether solution was washed with water and dried (Na₂SO₄). Evaporation of solvent afforded the alkylidene (3b; R = Et) (360 mg, 98%), identical with an authentic specimen.⁴

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* When aqueous acid is used, the Mannich bases eliminate the amine to yield the alkylidenes which are very prone to attack of water and undergo retroaldol reaction. The liberated Meldrum's acid then undergoes Michael addition to unchanged alkylidene to give a bis adduct (4).