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THE MUKAIYAMA REACTION OF KETENE BIS(TRIMETHYLSILYL) ACETALS WITH α-HALO ACETALS

A CONVENIENT BUTENOLIDE SYNTHESIS

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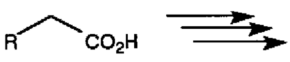
Summary: Ketene bis(trimethylsilyl) acetals were reacted with α-halo acetals giving β-alkoxy-γ-halo acids which were converted to butenolides by reaction with two equivalents of base. This constitutes a novel and short butenolide synthesis.

The butenolide unit is widely distributed in nature and diverse methods for its synthesis exist.[1] However, many of these are not general[1] whilst others rely upon the elaboration of an existing 5-membered heterocycle.[1,2] More specifically, for the transformation of a carboxylic acid into a butenolide (1 ⟶ 2), an activated acid substrate such as malonate[1] or α-phenylthio acid[3] is often required.



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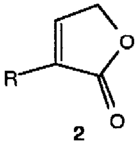

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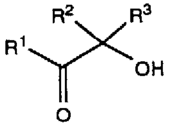

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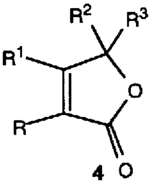
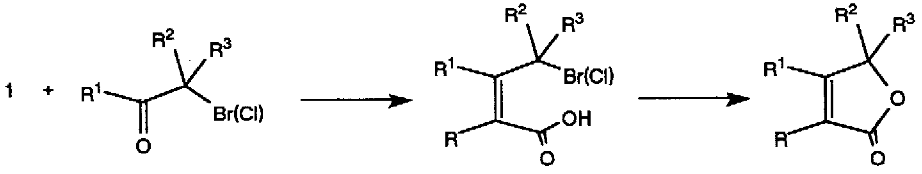


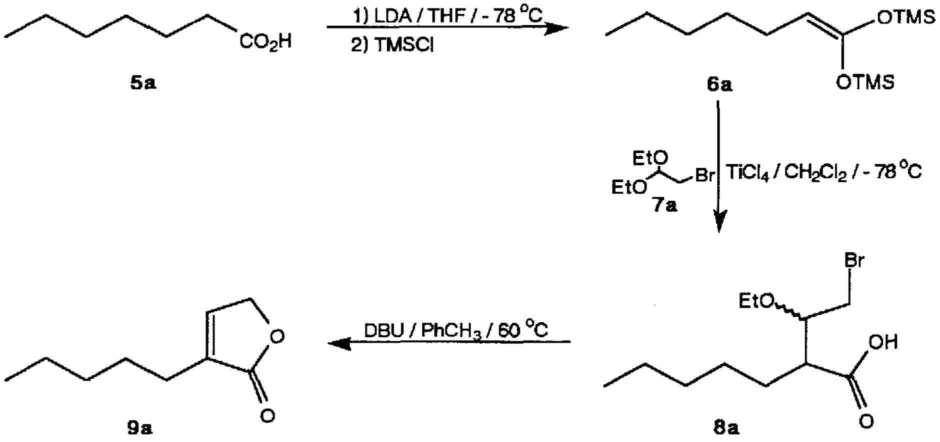
4

Alternatively, R in (1) needs to be suitably functionalized for elaboration into a butenolide.[1] The condensation of acyloins (3) with active methylene compounds to give butenolides (4) is known[1] but fails for glycolaldehyde-derived simple α-monosubstituted butenolides (4, R^1, R^2, R^3, = H).[4] Recent investigations have addressed the conversion of (1) into (2), providing some solutions,[5,6] although the procedures together with the preparation of starting materials can be lengthy. Formally this transformation represents a Knoevenagel condensation of a carboxylic acid with an α-halo carbonyl compound followed by cyclisation (Equation 1). We wish to report that, in connection with other work,[4] we have developed a short and simple three-step sequence to effect precisely this overall conversion.



Equation 1

The method, exemplified in Scheme 1 for the preparation of α-n-pentyl butenolide (**9a**) from heptanoic acid (**5a**), involves the titanium tetrachloride ($TiCl_4$) - promoted alkoxyalkylation[8] of a ketene bis(trimethylsilyl) acetal (ketene BTMS acetal) (**6**)[9b] by an α-halo acetal (**7**). Treatment of the resultant β-alkoxy-γ-halo acid (**8**) with two equivalents of base affords the butenolide (**9**).[10]



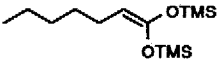
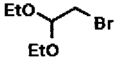
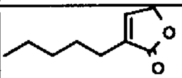
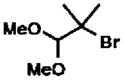
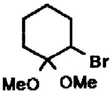
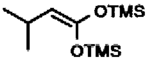
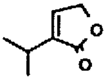
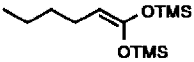
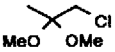
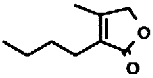
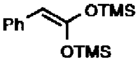
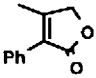
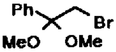
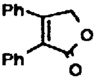
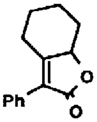
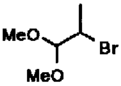
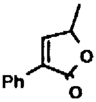
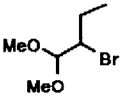
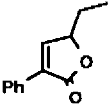
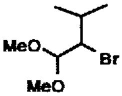
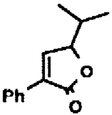
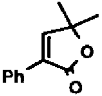
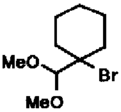
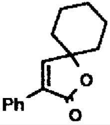
Scheme 1

The preparation of β-hydroxy and β-alkoxy esters and -carbonyl compounds by means of the Mukaiyama reaction is well known.[8] However, the use of ketene BTMS acetals (**6**) in this reaction for the direct formation of β-hydroxy - and β-alkoxy acids has to our knowledge not yet been reported.[11]

In a typical procedure, commercially available bromoacetaldehyde diethyl acetal (**7a**) (4 ml, 26.5 mmol) in dry CH_2Cl_2 (200 ml) at -78 °C was treated sequentially with $TiCl_4$ (2.9 ml, 26.5 mmol) and the ketene BTMS acetal of heptanoic acid (**6a**)[9b] (8 g, 29.2 mmol, 1.1 equiv.) in dry CH_2Cl_2 (20 ml) dropwise over 15 min. After stirring for 1 hr. at -78 °C the solution was quenched with a solution of KH_2PO_4 (1.8 g) and Na_2HPO_4 (1.9 g) in H_2O (110 ml) and allowed to warm to room temperature. Normal extractive work-up gave the γ-bromo-β-ethoxy acid (**8a**) as a colourless oil, (diastereomer ratio not determined). Treatment of this crude product with DBU (2 equiv.) in dry toluene at 60°C for 24 hrs., acid- and bicarbonate wash, concentration in vacuo and distillation (b.p. 86 - 88 °C / 0.5 mm) gave α-n-pentyl butenolide (**9a**) (48% overall in three steps from heptanoic acid (**5a**)).

Table 1 shows a variety of other butenolides which were subsequently[12] prepared using our methodology. Mono-, di- and trisubstituted butenolides are accessible. The procedure fails in the preparation of more highly ring - substituted α-alkyl butenolides. Thus both the aldehyde derived bromoacetal (**7b**) and the ketone derived (**7c**) gave complex mixtures when reacted with ketene acetals (**6a**) and (**6b**). The branched chain carboxylic acid - derived ketene acetal (**6b**) does however react with bromoacetaldehyde diethyl acetal giving, after base treatment of the intermediate γ-bromo acid, the butenolide (**9b**). The γ-halo acids (**8**) can routinely be taken on crude thus obviating any need for purification of intermediates. In the case of phenylacetic acid - derived butenolides (**9d** - **k**) the cyclisation / elimination reaction becomes simplified to stirring of the intermediates (**8**) with excess anhydrous K_2CO_3 in acetone at room temperature. Filtration through a short silica plug and crystallisation from diisopropyl ether or 95% ethanol gives pure butenolides.

TABLE 1 **PREPARATION OF BUTENOLIDES**

Ketene BTMS acetal[9b]		α-Halo acetal[13]		Butenolide[14] / (Yield (%))[15] / M.P. (°C)	
	6a		7a		9a[16] / (48) b.p. 86 - 88 °C / 0.5 mm
6a			7b	—	
6a			7c	—	
	6b	7a			9b / (40)
6b		7b		—	
6b		7c		—	
	6c		7d		9c[17] / (56)
	6d	7d			9d[18] / (66) 84.5 - 86
6d			7e		9e[19] / (65) 104 - 105
6d		7c			9f / (60) 74.5 - 76.5
6d			7f		9g[20] / (47) 47 - 48
6d			7g		9h[21] / (45) Oil
6d			7h		9i / (50) 89 - 90
6d		7b			9j[22] / (58) 69.5 - 70.5
6d			7i		9k / (52) 103.5 - 104.5

Owing to the ready availability of α-halo carbonyl compounds[13] and of carboxylic acids, this method should prove a versatile and convergent synthesis for α-arylbutenolides possessing the whole range of possible substitution patterns and of simple monosubstituted α-alkylbutenolides. Our attempts at preparing (**9a**), for example by using chloroacetaldehyde and heptanoic acid in a manner analogous to that published by Padwa[7] led only to polymeric products.[12] Hence our method should prove an attractive and direct alternative to the strategy outlined in Equation 1 in those cases where simple α-monosubstituted butenolides such as (**9a**) are desired (Equation 1, R^1, R^2, R^3 = H) but cannot be prepared using the labile (and unpleasant!) chloroacetaldehyde. We are currently applying this procedure to the synthesis of some natural products and will report the results in due course.

Acknowledgements

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10) A preparation of tetronic acids, similar in concept to our butenolide synthesis, has been published: J. D. White, T. Nishiguchi and R. W. Skeean, **J. Am. Chem. Soc.**, 1982, **104**, 3923.
11) The facile hydrolysis of the Si-O bond during aqueous work-up in this procedure ensures the isolation of the carboxylic acid. The same Mukaiyama reaction can be performed with the ketene methyltrimethylsilyl acetal derived from methyl heptanoate.[9a] However, the subsequent conversion of the γ-bromo-β-ethoxy methyl ester to the butenolide is much less efficient.
12) The first part of this work (the preparation of α-n-pentyl butenolide) is taken from: F. W. J. Demnitz, PhD Thesis, University of Cambridge, 1983.
13) These compounds can be conveniently prepared in good yields by the ketalization of commercially available haloketones (for **7d**, **7e**), by bromination (NBS, CCl_4) and ketalization ($HC(OMe)_3$, MeOH, p-TsOH) of cyclohexanone (for **7c**) or by bromination (Br_2, $CHCl_3$, p-dioxane, -15°C) followed by ketalization (addition of MeOH, $HC(OMe)_3$ to reaction: one pot) of the requisite commercially available aldehydes (**7b**, **7f** - **i**). All halo acetals (except **7e** - m.p.: 46 - 47 °C) are distillable and can be stored over anhydrous K_2CO_3 in the refrigerator for extended periods.
14) All new compounds (**9b**, **f**, **i**, **k**) were characterized by nmr, ir, ms, hrms and/or microanalysis. Butenolides (**9a**, **c**-**e**, **g**, **h**, **j**) are known compounds.[16 - 22]
15) Yields are unoptimized and quoted for three steps from carboxylic acid (**5**).
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21) The preparation of this compound has been mentioned in the patent literature but no physical or spectroscopic data are given: **Chem. Abstr.**, 1985, **102**, P95527p.
22) A. Padwa, T. Brookhart, D. Dehm and G. Wubbels, **J. Am. Chem. Soc.**, 1978, **100**, 8247.

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