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α-Trifluoromethylmethylene and α-Trifluoromethylethylidene γ-Butyrolactones

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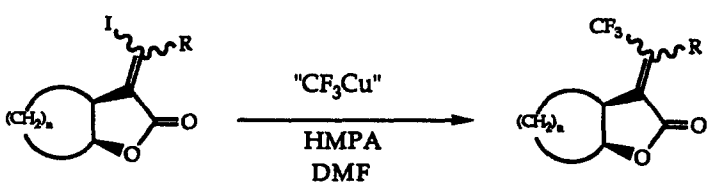
Abstract: *Trifluoromethylation of iodoalkylidene lactones can be achieved stereospecifically via zinc organocuprate reagents to yield a new series of α-trifluoromethylalkylidene-γ-butyrolactones.*

Despite extensive synthetic interest in α-methylene lactones with view to their potential biological activity it is surprising to find that few α-trifluoromethylalkylidene lactones have been prepared. Indeed, the only report of such a unit is from investigations into ylid chemistry where an iminophosphorane pentyrolactone was formed by reaction of trifluoroacetonitrile with the corresponding ylid[1,2]. The synthesis of these compounds will enable their biological activities to be compared with those of other unsaturated lactones. This may lead to the development of compounds which have increased selectivity as anti-tumour and anti-bacterial agents without the overriding cytotoxicity associated with small unsubstituted exomethylene lactones.

By utilising the preparation of iodoalkylidene lactones described earlier[3,4], we can stereoselectively synthesise (*E*)-iodoalkylidene lactones from a range of alkenes. Photolysis allows the (*Z*) isomer to be isolated.

Treatment of a variety of (*E*) and (*Z*)-iodoalkylidene lactones with a "CF_3Cu" reagent in HMPA/DMF[5,6] at 60°C gave almost quantitative yields of trifluoromethylated products with **retention of stereochemistry** (Scheme 1, Table 1). With the trimethylsilyl substituted lactone (4), reaction with the trifluoromethylating reagent produced the desilylated lactone (9), again with retention of stereochemistry. The desilylation is most probably brought about by the presence of fluoride ion in the reagent[5]. It is advantageous to prepare (9) *via* the TMS lactone since the cyclisation to form (4) from its precursor occurs in a 93% yield as opposed to a 37% yield for the cyclisation to form (2)[3].

It was found that the trifluoromethylation of the methyl substituted lactones (3) and (7) could only be achieved at 60°C, with no reaction being observed at room temperature, whereas the unsubstituted lactones formed the trifluoromethylated derivatives at room temperature in comparable yields. This general decrease



Scheme 1.

Table 1. Trifluoromethylalkylidene lactone synthesis.

Reactant	Temperature /°C	Product	Isolated Yield %
(1) 	25 (60)	(8) 	80 (98)
(2) 	25 (60)	(9) 	95 (89)
(3) 	60	(10) 	75
(4) 	60	(9) 	98
(5) 	60	(11) 	90
(6) 	60	(12) 	84
(7) 	60	(13) 	94

in reactivity is expected for the alkylated derivatives and may arise from a combination of steric and electronic effects. These relative reactivities are also reflected in the preliminary biological assay results[7].

The trifluoromethyl substitution of the iodoalkylidene lactones which is described in this communication represents facile access to a new class of compounds, the trifluoroalkylidene lactones. A particularly attractive feature is the high stereoselectivity of the reaction which is manifested even with the substrates which yield (*E*) / (*Z*) mixtures with lithium dimethyl cuprate[8].

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6. All reactions were carried out under a nitrogen atmosphere. All reagents and solvents were dried prior to use. A typical procedure is to make an aproximately 1 molar solution of "$ZnCF_3$" by adding CF_2Br_2 (2.0 ml, 21.9 mmol) portionwise to activated zinc dust (2.86 g, 43.8 mmol) in DMF (10 ml), allowing a small degree of reflux to occur, followed by stirring for 2 h at room temperature. Filtration *via* a Schlenk funnel under nitrogen gave a thick brown solution of the organozinc reagent. To this reagent (1.0 ml, 1.0 mmol) in HMPA (1.0 ml) at 0°C was added CuBr (0.14 g, 1.0 mmol). The mixture was stirred for 5 min before addition of the iodoester (0.5 mmol) in DMF (0.5 ml), then allowed to warm to room temperature over 0.5 h followed by heating at 60-70°C for 30-40 min. The product was poured into water and extracted into ether, dried ($MgSO_4$) and filtered though a silica plug to yield the trifluoromethylated product. The product was identified by NMR, IR, MS and microanalysis.
7. All compounds except (10) are cytotoxic, with the (Z) isomers (11) and (12) found to have the greatest cytotoxicity with IC_{50} values of aprox. 2.7 µg/ml. There is an increase in anti-bacterial activity for the fused 5 over the fused 6-membered lactones.
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