Tellurium and Iodine Promoted Cyclofunctionalization of Alkenyl Substituted β-Keto Esters

H. M. C. Ferraz*, M. K. Sano, A. C. Scalfo

Instituto de Química, Universidade de São Paulo, C.P. 26077, 05599-070-São Paulo-SP, Brazil

Fax 55-11-815-5579; E-mail: hmferraz@quim.iq.usp.br

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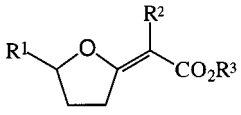
Abstract: This work describes the use of aryltellurium trichloride and iodine as suitable cyclization reagents for alkenyl substituted β-keto esters. The reaction takes place via the enolic form of the dicarbonyl compounds, giving the corresponding five-membered cyclic ethers in good yields.

Key words: cyclization, carbonyl compounds, tellurium and iodine compounds

The development of new methods for preparing tetrahydrofuran derivatives continues to be an active research area, since they are useful intermediates in the synthesis of many natural products.[1] In particular, the tetrahydrofuran moiety of general pattern **1**, containing an exocyclic double bond, has been applied in many studies toward the synthesis of Nonactic Acid,[2-5] the monomeric structure of an important class of antibiotics called Nonactins.[6]



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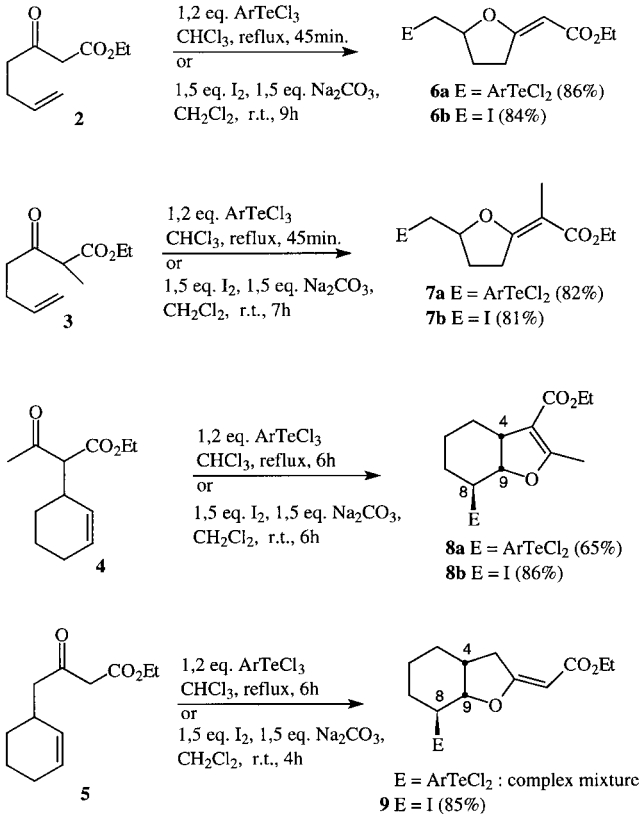
The tellurocyclofunctionalization of unsaturated substrates has been the subject of continuous studies in our laboratories. Starting from γ,δ-unsaturated carboxylic acids, it is possible to obtain tellurolactones in good to excellent yields,[7] while alkenols lead to the corresponding cyclic telluroethers, also in good yields.[8-10]

Ley et al.[11] have already shown that alkenyl-substituted-β-dicarbonyl compounds can be cyclized using selenium electrophiles, and that one can selectively achieve the product of an *O*-cyclization (kinetic control) or that of a *C*-cyclization (thermodynamic control), depending upon the reaction conditions. Antoniolleti et al.,[12,13] as well as Iqbal and Pandey,[14] have reported a similar iodo-*O*-cyclization of a series of alkenyl-substituted β-keto esters and ketones, all of them bearing the alkenyl chain at the α-position. An analogous iodine-promoted cyclization of β-enamino esters and ketones, which led to synthetically valuable precursors for the pyrrole nucleous, has already been described by us.[15] Nevertheless, the tellurocyclofunctionalization of alkenyl β-keto esters appears to be unprecedented.

As an extension of our previous works,[8,9,15] and in analogy to those cited above, we investigated the behaviour of a series of α- and γ-alkenyl-β-keto esters toward aryltellurium trichloride. For comparison purposes, the same substrates were also submitted to treatment with iodine. The paper by Stefani et al.[16] prompts us to disclose our first results on the cyclization of four of these β-keto esters, namely **2-5,** which are closely related to those studied by them. The results are summarized in Scheme 1.



Scheme 1

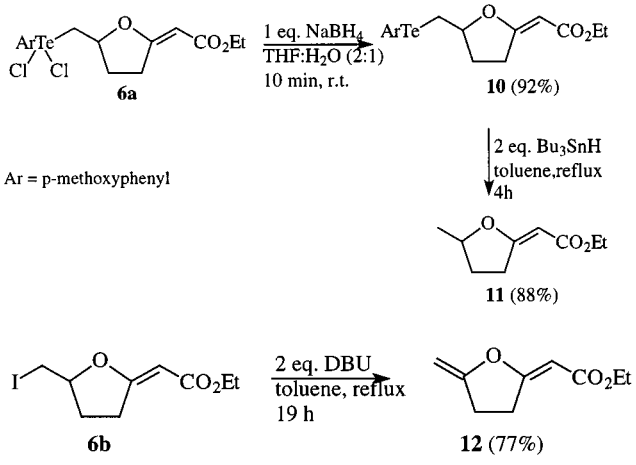
Ar = *p*-methoxyphenyl

To the best of our knowledge, the above results constitute the first examples of the synthesis of 2,5-disubstituted tetrahydrofurans bearing exocyclic double bonds, either by iodo- or by tellurocyclization. Unfortunately, the β-keto ester **5** fails in reacting with *p*-methoxyphenyltellurium

trichloride, and only the iodocyclic derivative **9** was obtained. It must be mentioned that a product similar to **8b**, bearing a phenyl instead of the methyl group, has already been described by Antonioletti.[13]

The *E* double bond geometry for products **6a**, **6b**, **7a**, **7b** and **9** was assigned on the basis of the chemical shifts of the C_3-ring methylene protons, in the 300 MHz ^{1}H NMR spectrum, as well as by comparison with the seleno analogues.[17] The bicyclic products **8a**, **8b** and **9** exhibit *cis* fused rings, assigned by analogy with other examples[8,18] and by the coupling constants between H-C_4 and H-C_9, which indicate an axial-equatorial relationship (**8a**:3.49-3.61δ(m, H-C_4); 5.33δ(t, J = 9.6Hz, H-C_9); 4.06-4.31δ(m, H-C_8); **8b**:3.19δ(br q, J = 7.7Hz, H-C_4); 4.73δ(dd, J = 7.7 and 4.9Hz, H-C_9); 4.55-4.59δ(m, H-C_8); **9**:2.60-2.70δ(m, H-C_4); 4.59δ(t, J = 4.9Hz, H-C_9); 4.47((q J = 4.9Hz, H-C_8)). The assigned configurations are a direct consequence of the well-known mechanism of the electrophile-promoted cyclization, which proceeds via a *trans*-diaxial addition to the double bond.[19]

The previously mentioned structural moiety **1** is represented in our series of examples by the cyclic esters **6a**, **6b**, **7a** and **7b**. In order to explore the synthetic potential of these derivatives, compound **6a** was treated with $NaBH_4$, giving the telluride **10**, which was in turn reduced with Bu_3SnH to afford the α-methyl derivative **11** in excellent yield. On the other hand, dehydroiodination of **6b** with DBU provided the formation of the α-methylene derivative **12,** also in good yield (Scheme 2).



Scheme 2

In conclusion, we believe the methodology here described should be useful for constructing synthetically valuable cyclic ethers. The extension of these studies to other substrates is under way in our laboratory.

Experimental

The β-keto esters **2-5** were prepared by previously described methods.[20,21] All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra.

General procedure for iodocyclization: A mixture of I_2 (1.5 mmol), anhydrous Na_2CO_3 (1.5 mmol) and β-keto ester (1 mmol) in dry CH_2Cl_2 (20 ml) was stirred at room temperature till the starting material disappeared (GC). Then AcOEt was added and the organic phase was washed with sodium thiosulfate solution (0.1 N), brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated.

General procedure for tellurocyclization: A mixture of β-keto ester (2 mmol) and *p*-methoxyphenyltellurium trichloride (2.2 mmol) in 30 ml of recently distilled chloroform was heated under reflux for the time indicated in Scheme 1. The solvent was evaporated and the residue filtered through silica gel using chloroform as eluent.

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