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Iodoenolcyclization. III. A General Approach to Tetrasubstituted Furans from 2-Alkenyl-1,3-Dicarbonyl Compounds.

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Abstract: *2,3,4,5-tetrasubstituted furans were easily obtained from of 2-alkenyl-1,3-dicarbonyl compounds by an efficient three steps synthesis.*

Furans constitute one of the most important classes of heteroaromatic compounds. Efficient syntheses of furans continue to be of interest[1] due to the widespread occurrence of this system in Nature[2]; (they can be found in a variety of commercially important pharmaceuticals[3], and flavour and fragrance compounds[4]). The furan ring, because of its importance as a synthetic intermediate[5], is currently the subject of many synthetic studies. Substituted furans have been usually synthesised by regioselective introduction of carbon substituents into a simple furan[6], or from acyclic precursors[7] Few reports about the utilization of 1,3-dicarbonyl compounds as furan-ring precursors are reported in the literature.[8]

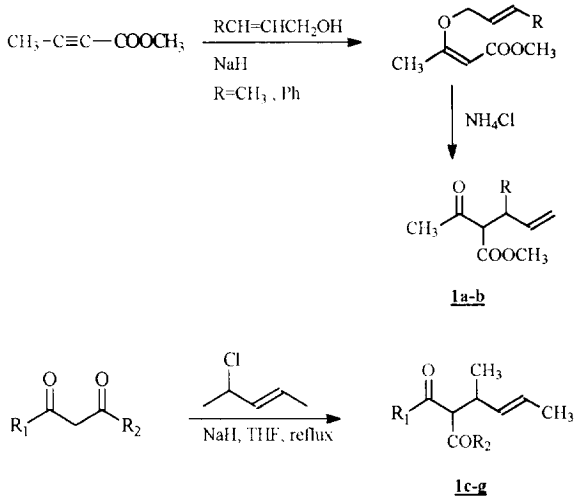
In a previous paper we reported a new approach to furan derivatives by I_2-induced cyclization of 2-alkenyl-1,3-dicarbonyl compounds.[9] Now we report an extension of this methodology. In fact we have demonstrated that the compounds **1** are easily converted to 2,3,4,5-tetrasubstituted furans **2**.(Scheme 1).

SCHEME 1

1 **2**

Starting materials **1a-g** were available with the following methods. (Scheme 2). The β-ketoesters **1a-b** were obtained by the conjugate addition of the sodium alcoholate to the methyl butynoate, followed by Claisen rearrangement of the enolether products.[10] Dicarbonyl compounds **1c-g** were prepared by the direct alkylation[11] of the active methylene compounds with 4-chloro-2-pentene.[12]

SCHEME 2



The 2,3,4,5-tetrasubstituted furans **2a-g** were obtained by a simple sequence involving, in the key-step, an iodoenolcyclization of 2-alkenyl-1,3-dicarbonyl compounds **1a-g**, as shown in Scheme 3. Compounds **1a-g** underwent a very efficient regioselective ring closure leading to the intermediates **3a-g**. We never observed the formation of the pyran nucleus.[13] The iodoalkyl-dihydrofurans **3a-g** gave the furans **2a-g** after dehydrohalogenation by hindered tertiary amine and acid-catalyzed rearrangement of the corresponding alkylidenedihydrofurans **4a-g**.

The results summarized in Table 1 indicate that this method is of general application because it works with aryl and alkyl β-ketoesters and β-diketones (linear and cyclic). Moreover the efficiency of the reaction is also independent from the nature of R_3 and R_4 (Scheme 3). Phenyl, methyl and ethyl groups gave excellent results in all experiments (See Table 1).

SCHEME 3

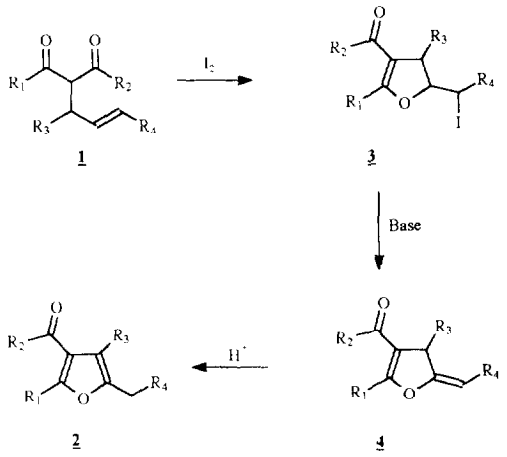


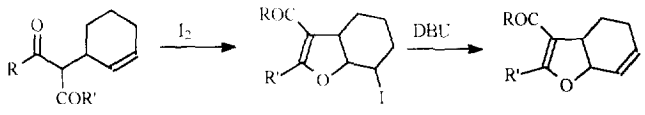
TABLE 1

Entry	R_1	R_2	R_3	R_4	Yields[a,c](%)
2a	Me	OMe	Ph	H	87
2b	Me	OMe	Me	H	70[b]
2c	Me	OMe	Me	Me	80
2d	Ph	OEt	Me	Me	90
2e	Ph	Ph	Me	Me	92
2f	Et	Et	Me	Me	95
2g	$CH_2CH_2CH_2CH_2$		Me	Me	92

[a] Isolated yields. [b] Lower yield is due to the volatility of **2b**. [c] Overall yields from **1**.

In conclusion we have shown that this reaction has general value; its limit is the synthesis of the 2-alkenyl-1,3 dicarbonyl compounds **1**. We observed a different result when the double bond were in a cyclic system as for **5**. In this case, after elimination with DBU, **6** gave the regioisomer **7** which cannot aromatise. Work is in progress to determine the advantages and the limits of this approach to furan-ring synthesis.

SCHEME 4



5a R = R' = Ph
5b R = OEt R' = Ph

6

7a 95%
7b 90%

As a general procedure a solution of compound **1** (2 mmol) in dry CH_2Cl_2 (4ml) was added to a mixture of anhydrous Na_2CO_3 (4mmol) and iodine (4mmol) in dry CH_2Cl_2 (40ml). The reaction was stirred at room temperature until the substrate disappeared (TLC, GC monitoring). Et_2O was added and organic phase was washed with sodium thiosulfate, brine, and dried over Na_2SO_4. Removal of the solvent gave compound **3**. This crude material was dissolved in anhydrous benzene (0.2M) and 1,8-diazabicyclo-(5,4,0)undec-7-ene (DBU) (6.0mmol) was added. The mixture was refluxed overnight under argon. The solution was poured in HCl dil. and the acidic solution extracted with Et_2O. The organic layer was washed with brine to neutrality; then dried over Na_2SO_4, and the solvent was removed in vacuo. The resulting compound **4** was dissolved in dry Et_2O (0.05M) and few drops of H_2SO_4 (10) were added. The solution was stirred under argon at room temperature until completion of the reaction (TLC, GC monitoring).Then the solution was diluted with Et_2O and washed with brine. After the usual work-up the furans **2** were obtained in pure form by column chromatography on silica gel.

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12) 4-Chloro-2-pentene was prepared reacting $SOCl_2$ (6.0ml) with 4-Hydroxy-2-pentene (1.2ml) (reaction monitored by I.R.). Excess of $SOCl_2$ was removed by distillation.
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