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Iodine Promoted Cyclofunctionalization Reaction of 2,4-Dialkenyl-1,3-Dicarbonyl Compounds

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Abstract: The reactions of 2,4-dialkenyl-1,3-dicarbonyl compounds with I_2 lead to 5-iodoalkyl-4,5-dihydrofuran rings in good yield under mild conditions. © 1997 Elsevier Science Ltd.

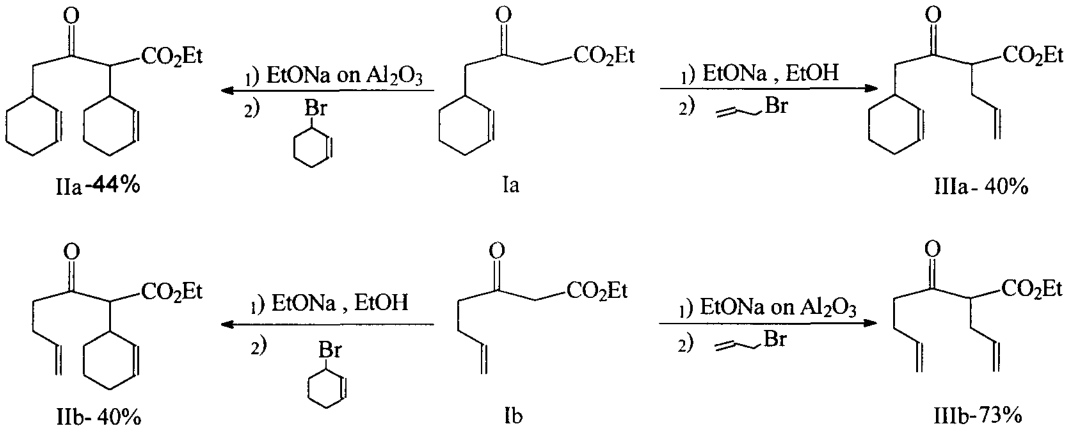
The addition of an electrophile to an alkene bearing a nucleophilic group at a suitable position generates an intermediate onium species that is intramolecularly trapped by the nucleophilic moiety. Such cyclization is named cyclofunctionalization and indicates that the original double bond involved in the ring formation reaction becomes attached to a group that can be submitted to further manipulations[1]. The internal nucleophile can be OH, CO_2H, CO_2^-, SR, NHR, CONR.[2] The reaction gives good yields of the cyclic products with various electrophiles such as I_2, Br_2, $HgCl_2$, ArSX[2], ArSeX[3], $ArTeCl_3$ and $TeCl_4$[4].

Some time ago the regio- and stereoselective cyclofunctionalization of 2-alkenyl-1,3-dicarbonyl compounds leading to iodoalkyl and phenylselenoalkyl dihydrofurans[5], and more recently similar cyclofunctionalization of α–alkenyl–β–enaminone compounds to cyclic β-enamino esters and β-enamino ketones[6] have been reported. Furans and their derivatives have been the key intermediates in many natural products syntheses which have a variety of applications as pharmaceuticals, flavour and fragrance compounds[7], and have also been starting materials for heterocyclic and acyclic compounds[8]. In view of our interest in the chemistry of cyclofunctionalization reactions of 2-alkenyl-1,3-dicarbonyl compounds, we undertook a systematic investigation of the reaction of 2,4-dialkenyl-1,3-dicarbonyl compounds with iodine.

In this paper we report an efficient and easy synthesis of 2,3,5-trisubstituted dihydrofuran rings, by reacting 2,4-dialkenyl-1,3-dicarbonyl compounds with iodine, in the presence of anhydrous Na_2CO_3 in CH_2Cl_2 solution. The yields of the purified products were in most cases, in the range of 72-94%. To our knowledge, these are the first examples of such electrophile-promoted O-cyclization of 2,4-dialkenyl-3-ketoesters.

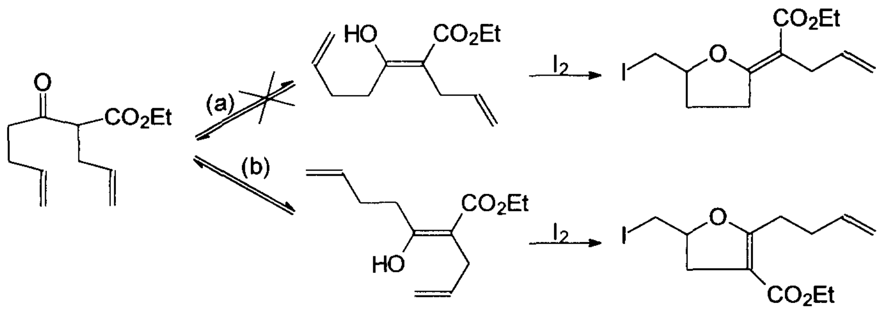
The starting materials Ia and Ib were prepared by described methods[9-11] and the second alkylation was performed by a simple and controlled procedure, which involved a solvent-free reaction on the surface of neutral aluminum oxide impregnated with sodium ethoxide in order to avoid O-alkylation and di-alkylation[12]. The yields were in the range of 40-73% (Scheme 1).

Scheme 1



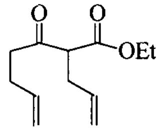
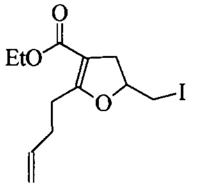
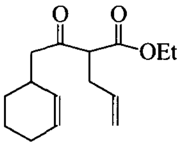
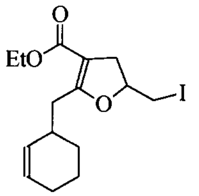
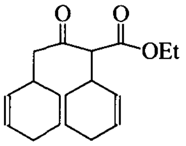
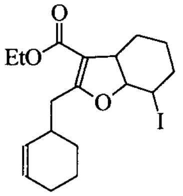
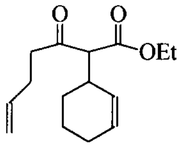
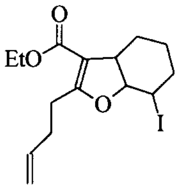
Compounds IIa, IIIa, IIb and IIIb were submitted to the cyclization reaction employing iodine as the electrophile partner. As exemplified in scheme 2, two possible cyclic products could be obtained, resulting respectively from the participation of the α or γ alkenyl groups. Isolation of dihydrofuran products showed that route **b** was operating. The olefin selectivity can be rationalized on the basis of conformation of the transition states of the enolic forms where the OH group and the olefinic chain are appropriately positioned.

Scheme 2



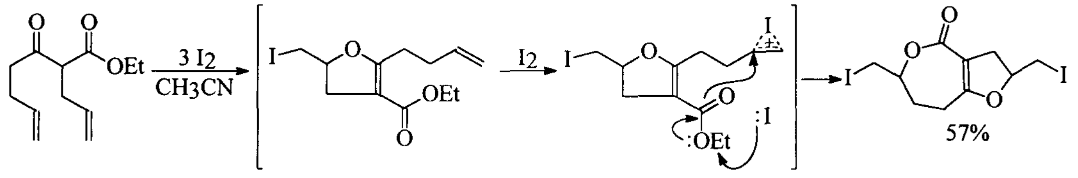
In a typical general procedure, iodine (1.2mmol) and dry sodium carbonate (1.2mmol) was added to a dry CH_2Cl_2 solution of 2,4-dialkenylated-3-ketoester (1mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for the time indicated in Table 1 and the progress of the reaction was monitored by TLC. The product was extracted with ether, washed with a solution of sodium thiosulfate and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2. For yields see Table 1.

Table 1 - Iodine promoted preparation of 2,3,5-trisubstituted dihydrofuran rings

Starting Material	Product	Reaction time hr	Yield[a,b] %
		**3**	**91**
		**20**	**92**
		**3**	**94**
		**20**	**72**

All the new compounds were fully characterized by IR, ^1H and ^{13}C-NMR, and mass spectroscopy. Elemental analysis gave values in agreement with the proposed structures.

By using three equivalents of iodine in CH_3CN the formation of a lactone ring[13] accompanies the first cyclization in a "one pot"procedure. At the present one example of this reaction was achieved in moderate yield[14] (57%).



In summary, our methodology described herein provides a new useful and general entry for the mono- and dicyclization of 2,4-dialkenyl-1,3-dicarbonyl compounds.

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14-Spectral data for lactone compound:IR (neat) 1741 cm-^{1} ; ^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.75-1.95 (m, 1H), 2.25-2.42 (m, 1H), 2.51-2.63 (m, 1H), 2.85-3.09 (m, 2H), 3.16-3.39 (m, 5H), 4.41-4.57 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$)δ: 7.02, 9.22, 29.15, 31.53, 74.93, 82.97, 93.83, 168.82, 171.25.

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