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Unprecedented 'ring transformation-rearrangement' of pyran-2-ones into 5,6-dihydropyran-2-ones through insertion of acetol ☆

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ABSTRACT

One-pot efficient synthesis of functionalized 5,6-dihydropyran-2-ones has been delineated by reacting 2*H*-pyran-2-ones and acetol in the presence of a base at room temperature. The formation of 5,6-dihydropyran-2-ones revealed that the reaction proceeded in a unique 'ring transformation-rearrangement' sequence.

Pyran-2-ones and their partially reduced 5,6-dihydropyran-2-ones are an important class of biologically interesting natural products isolated from higher plants, marine and animal sources.[1] Many of the natural 5,6-dihydropyran-2-ones such as (+)-parasorbic acid[2] (**I**), tarchonanthuslactone[3] (**II**), (−)-goniothalamin[4] (**III**), and (+)-kurzilactone[5] (**IV**) possess interesting pharmacological and cytotoxic[6] properties (Fig. 1). Synthetic compounds bearing this ring skeleton display anti-HIV,[7] anti-cancer,[8] antileukemic,[9] and a broad range of many other relevant pharmacological properties.[10] The wide pharmacological potential of this bioactive scaffold has aroused considerable interest in developing novel approaches to their synthesis.

Numerous synthetic methodologies of 5,6-dihydropyran-2-ones have been reported in the literature. The construction of 5,6-dihydropyran-2-ones skeleton can be achieved by the reaction of glycals with $InCl_3$/IBX reagent,[11] lactonization of substituted δ-hydroxy acid derivatives,[12] oxidation of substituted dihydropyran derivatives,[13] and by ring-closing metathesis.[4,14] Although these reactions have been widely employed for the synthesis of natural and unnatural dihydropyran-2-ones, the scope of these reactions is limited due to the difficulties in obtaining suitably functionalized acyclic substrates, specialized organometallic reagents, harsh reaction conditions, and formation of undesired byproducts. Herein we report a one-pot highly convenient protocol for the synthesis of 5,6-dihydropyran-2-ones through base-induced ring transformation-rearrangement of pyran-2-ones using acetol as a source of O-nucleophile.

During our studies on the chemistry of 2*H*-pyran-2-ones, we found that 4-methylsulfanyl/amino-2-oxo-6-aryl-2*H*-pyran-3-carbonitriles are susceptible to Michael addition of a conjugate base of methylene carbonyl compounds at position 6, leading to the formation of a benzene ring at room temperature (Scheme 1).[15] The success of our efficient novel pathway to a benzene ring system under mild basic conditions encouraged us to explore this methodology for the synthesis of functionally congested benzenes, unsymmetrical biaryls, teraryls, quateraryls, and oligoarenes under mild basic conditions at room temperature.[16] Recently we have demonstrated that our methodology can be applied to prepare fluorescent blue materials for efficient organic light emitting diodes.[17]

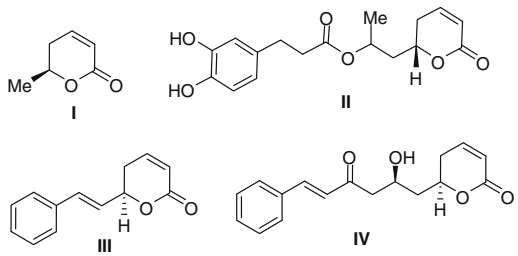

Figure 1. Examples of natural 5,6-dihydropyranones: (+)-parasorbic acid (**I**), tarchonanthuslactone (**II**), (−)-goniothalamin (**III**), and (+)-kurzilactone (**IV**).

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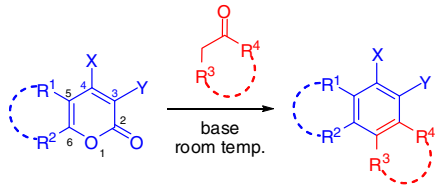
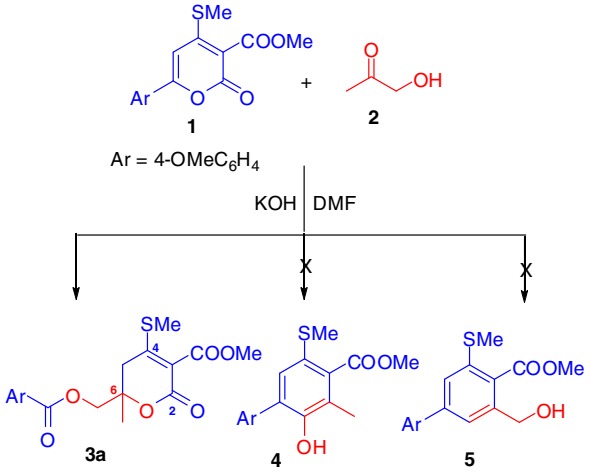


Scheme 1. C-Nucleophile induced ring transformed product.



Scheme 2. Synthesis of methyl 6-(4-methoxy-benzoyloxymethyl)-6-methyl-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carboxylic acid ester (**3**).

When we applied our ring transformation strategy[15] on methyl 6-(4-methoxyphenyl)-4-(methylthio)-2-oxo-2*H*-pyran-3-carboxylate (**1**) using acetol (**2**) as a source of nucleophile to prepare substituted phenol (**4**) and/or benzyl alcohol (**5**) derivatives as shown in Scheme 2, we isolated an unknown compound in 70% yield (Scheme 2). A careful examination of the spectroscopic analysis of the isolated compound including HSQC and HMBC NMR data revealed its structure as methyl 6-((4-methoxybenzoyloxy)-methyl)-6-methyl-4-(methylsulfanyl)-2-oxo-5,6-dihydro-2*H*-pyran-3-carboxylate (**3a**).

The ^{1}H NMR spectrum of the product (**3a**) showed four singlets at δ_H 1.56, 2.38, 3.83, and 3.87, each for 3H, in which δ_H 2.38, 3.83, and 3.87 showed the characteristic signals corresponding to the SCH_3, OMe, and COOMe groups, respectively, but a singlet at δ_H 1.56 revealed the presence of a methyl group attached to an aliphatic system (Fig. 2). Four doublets at 2.73, 3.04, 4.40, and 4.45 each for one proton with coupling constants of 17.7, 17.7, 11.8, and 11.8 Hz, respectively, revealed the presence of two methylene groups containing geminal protons. Further DEPT-90 and DEPT-135 studies on ^{13}C NMR experiments for the compound **3a** confirmed the presence of two CH_2 groups. Two doublets at δ_H 6.92 and 7.98 each for 2H showed the characteristic signals of the 4-methoxyphenyl group.

The ESI-mass spectrum of **3a** exhibited molecular ion peak $[M+H]^+$ at *m/z* 381, which indicated the formation of addition product (**3a**) of the reactants **1** and **2.** It was found in agreement with the molecular formula of compound **3a** as $C_{18}H_{21}O_7S$ obtained by HRMS. The mass, NMR and IR studies of product (**3**) led us to speculate that **3** had a 5,6-dihydropyran-2-one ring system with a methyl and a 4-methoxybenzoyloxy methyl groups.

The speculated ring system for **3a** was confirmed by the 2D NMR studies (Fig. 2). In the HMBC spectrum of **3a**, the CH_2 protons (δ 2.73 and 3.04) gave long-range correlation with signals at δ 162.98 (C-4), 114.56 (C-3), 77.19 (C-6), 66.76 (O-CH_2), and 22.17 (CH_3) while other CH_2 protons (δ 4.40 and 4.45) gave long-range correlation with signals at δ 164.42 (CO), 77.19 (C-6), 22.17 (CH_3), and 33.82 (CH_2). This supports the existence of methyl and (4-methoxybenzoyloxy) methyl groups at C-6 position of the 5,6-dihydropyran-2-one ring. The HMBC correlation (Fig. 2) of aromatic protons (δ 7.98) with δ 164.42 (CO) also support the presence of 4-methoxy-benzoyloxy methyl group at C-6 position of the 5,6-dihydropyran-2-one ring. The final analysis of all the spectral data of the compound **3a** led to the structure as 6-(4-methoxy-benzoyloxymethyl)-6-methyl-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carboxylic acid methyl ester.

With the demonstration of the utility of this protocol in general, we attempted a series of reactions with a variety of six-membered lactones (**1a–k**). The pyran-2-ones (**1a–k)** were conveniently prepared in high yields by the reaction of 2-cyano/carbomethoxy-3,3-bis-(methylsulfanyl)-acrylic acid methyl ester with aryl methyl ketones under alkaline conditions, followed by the reaction with secondary amines.[15] The synthesis of functionalized 5,6-dihydropyran-2-ones (**3a–k)** was achieved by stirring an equimolar mixture of 2*H*-pyran-2-ones (**1a–k**), acetol (**2**) and powdered KOH in DMF for 10–24 h at room temperature (Scheme 3).[18]

The reaction was monitored by TLC and after completion, the reaction mixture was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was filtered and purified on a silica gel column using 1% methanol in chloroform as an eluent. The isolated compounds were characterized by spectroscopic analysis.[18]

To understand the reaction mechanism for the formation of 5,6-dihydropyran-2-ones, we stirred a solution of 2*H*-pyran-2-ones **1a–k** in the presence of KOH in DMF at room temperature. We found that the lactones are fairly stable in KOH and no ring opening of the lactones was observed. Interestingly, when we stirred a solution of 6-aryl-2-oxo-4-(piperidin-1-yl)-2*H*-pyran-3-carbonitriles **1h–m** in the presence of sodium alkoxide at room temperature, we isolated alkyl 5-aryl-2-cyano-5-oxo-3-(piperidin-1-yl)-pent-2-enoates (**4a–f**) in good yield (Scheme 4). These results indicated that an alkoxide attacked at C-2 position of the lactones **1h–m** leading to the formation of lactone-ring opened products (**4a–f**).

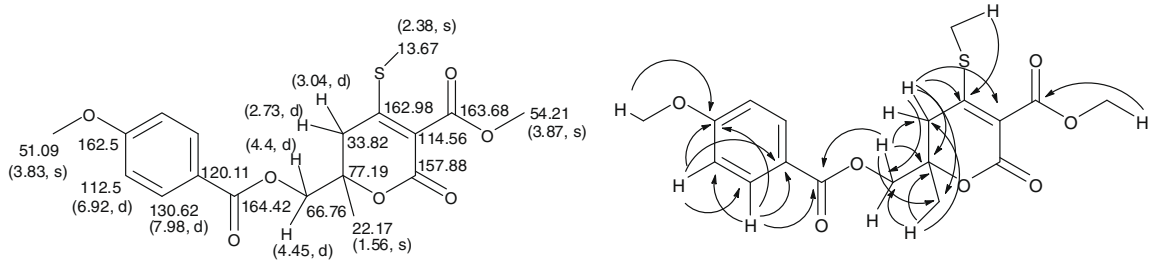


Figure 2. ^{1}H NMR and ^{13}C NMR spectral data of **3a** and selected ^{1}H to ^{13}C-HMBC correlations in $CDCl_3$.