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An Expeditious Synthesis of 4-Aryl-γ-Butyrolactones, -Furan-2(5H)-ones and -5-Alkoxyfuran-2(5H)-ones *via* Heck-reaction of Arenediazonium Salts with 2,5-Dihydrofuran

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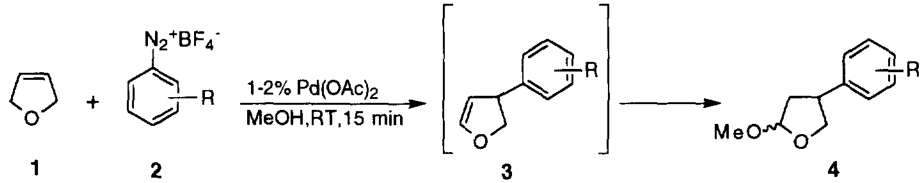
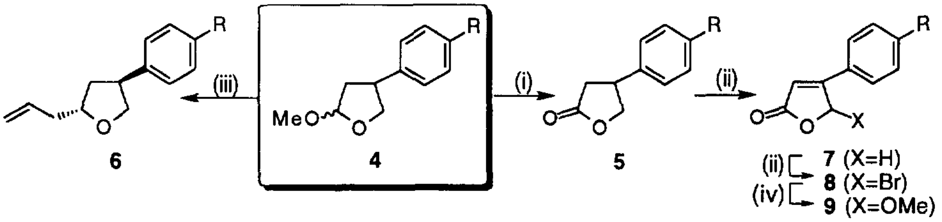
Abstract: An exceptionally simple and short synthetic sequence to 4-substituted furan-2(5H)-ones involving a Heck reaction on 2,5-dihydrofuran and subsequent iterative NBS oxidation is described.

γ-Butyrolactones[1]and Δ^2-butenolides (furan-2(5H)-ones)[2] are versatile synthetic modules in organic synthesis and are the key structural elements present in many biologically active natural products. While there are many methods for the synthesis of 3- and 5-substituted γ-butyrolactones, synthetic routes towards the 4-substituted derivatives are relatively scarce.[1a,b] For 4-substituted furan-2(5H)-ones, only a handful of synthetic methods are known which are usually multistep procedures starting from tetronic acid;[3a-d] and the problem is even more acute for the 5-alkoxy derivatives for which $^1O_2$ reaction of a 4-substituted furan and subsequent rearrangement remains the only reliable synthetic pathway.[3e] As part of a synthetic study towards biologically active marine sesterterpenoids luffariolides A-E[4] and manoalide[5] which possess 4-substituted-γ-butyrolactone, -furan-2(5H)-one or -5-alkoxyfuran-2(5H)-one as structural cores, we had the opportunity to address the above problems and describe herein a unified scheme for the synthesis of these compounds based on a facile Heck reaction of arenediazonium salts with the inexpensive 2,5-dihydrofuran leading to 4-aryl-γ-butyrolactones. In addition, we also describe a new NBS mediated iterative oxidation sequence by which these butyrolactones could be further converted to 4-substituted-5-alkoxyfuran-2(5H)-ones.

At the onset of this work, there was but one isolated example of a Heck reaction of 2,5-dihydrofuran (**1**), with PhI, which required prolonged reaction times (4 days), even under PTC conditions.[6] In order to improve the efficacy of this process, we decided to use arenediazonium salts which we have already shown to be superior Heck components *vis a vis* aryl halides.[7] In the event, Heck reaction of $PhN_2^+BF_4^-$ (**2a**) with **1** in MeOH produced a high yield of the β-phenyl-γ-lactol ether **4a** within 15 min. at RT, presumably *via in situ* acid catalyzed methanolysis of the initial Heck product **3** (Scheme 1). This tandem Heck reaction-vinyl ether capture proved to be quite general for a number of diazonium salts **2a-f**, all of which, except for the sterically hindered *o*-tolyl salt **2f**, gave very good yields of the lactol ethers **4** as a 50:50 mixture of isomers (Table 1). Once in hand, these versatile lactol ethers could on one hand be converted to the corresponding γ-butyrolactones **5** with mCPBA-$BF_3.Et_2O$ or in an interesting synthetic detour, be induced into a highly diastereoselective carbon-carbon bond



Scheme 1: a: R = H; b: R = *p*-OMe; c: R = *p*-Me; d: R = *p*-Cl; e: R = *p*-COOEt; f: R = *o*-Me



Scheme 2: (i) mCPBA/$BF_3.Et_2O/CH_2Cl_2$/0° to RT; (ii) NBS/cat. AIBN/CCl_4/reflux; (iii) CH_2=CH-CH_2TMS/ $BF_3.Et_2O/CH_2Cl_2$/-78°; (iv) MeOH/Et_3N/RT.

forming reaction with allyltrimethylsilane/$BF_3.Et_2O$ to produce, in excellent yields, the potentially useful 2,4-disubstituted tetrahydrofurans **6** as a single isomer (tentatively shown as *trans*)[8] (Scheme 2, Table 1). Returning to our original goal, oxidation of the γ-butyrolactones **5** to the furan-2(5H)-ones **7** was effected in a novel benzylic bromination-dehydrobromination sequence with NBS in CCl_4, thus avoiding the usual practice of using toxic selenium-based reagents. Further oxidation to the 5-alkoxyfuran-2(5H)-ones (as shown for **7b**→**9**) was carried out easily in a two-step procedure again pivoted on an NBS bromination (to give **8**) followed by methanolosis to provide **9** in 55% overall yield. Application of this new methodology in the synthesis of various natural products is underway.

Table 1

R	4(%)[a]	5(%)[a]	6(%, *trans:cis*)[a,b]	7(%)[a]
H	**4a** (80)	**5a** (94)	**6a** (96, 95:5)	**7a** (78)
p-OMe	**4b** (86)	**5b** (88)	**6b** (97, >95:5)	**7b** (71)
p-Me	**4c** (77)	**5c** (80)	**6c** (93, 95:5)	**7c** (47)
p-Cl	**4d** (86)	**5d** (74)	**6d** (94, >95:5)	**7d** (60)
p-CO_2Et	**4e** (80)	**5e** (90)	--	--
o-Me	**4f** (26)	--	**6f** (92, 95:5)	--

[a] Values in parenthesis refer to yields of isolated material fully characterized by IR, ^1H & ^{13}C NMR data.
[b] by ^1H & ^{13}C NMR analysis

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