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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 4substituted furan-2(5H)-ones involving a Heck reaction on 2,5-dihydrofuran and subsequent iterative NBS oxidation is described. Copyright © 1996 Published by Elsevier Science Ltd

 γ -Butyrolactones¹and 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 ¹O₂ 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-E⁴ and manoalide⁵ 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 4aryl- 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 PhN₂+BF₄- (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-BF3.Et₂O 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/BF₃.Et₂O/CH₂Cl₂/0° to RT; (ii) NBS/cat. AlBN/CCl₄/reflux; (iii) CH₂=CH-CH₂TMS/ BF₃.Et₂O/CH₂Cl₂/-78°; (iv) MeOH/Et₃N/RT.

forming reaction with allyltrimethylsilane/BF3.Et2O 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 CCl₄, thus avoiding the usual practice of using toxic selenium-based reagents. Further oxidation to the 5-alkoxyfuran-2(5H)-ones (as shown for $7b \rightarrow 9$) 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.

R	4(%) ^a	5(%) ^a	6(%, trans:cis) ^{a,b}	7(%) ^a
Н	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 ₂ Et	4e (80)	5e (90)		
o-Me	4f (26)		6f (92, 95:5)	
^a Values in parenthesis refer to yields of isolated material				
Turry characterized by it, -ri & -C NMR data.				
by 'H & 'C NMR analysis				

Table 1

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