



Sequential Pd(0)-Catalyzed Reactions for the Construction of Multiple Substituted Furans. A Short Synthesis of the F₅ Furan Fatty Acid^{1a}

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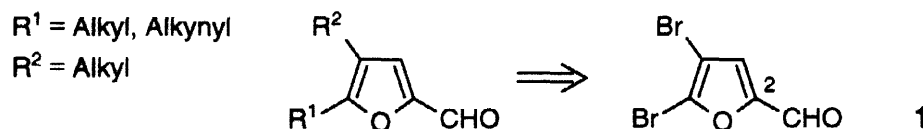
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Abstract: 4,5-Dibromofurfural (**1**) undergoes a regioselective Pd(0)-catalyzed C-C bond forming reaction at its C-5 position to yield the corresponding furans **3**. The second bromine substituent in C-4 position can be substituted by a methyl group in a subsequent Pd(0)-catalyzed cross coupling reaction. The furan fatty acid **12** and its benzyl ester **13** were prepared in a short synthetic sequence using this method. © 1998 Elsevier Science Ltd. All rights reserved.

Multiple substituted furans belong to the biologically most important heterocycles many varieties of which are found in nature. Some prominent examples of alkyl- and alkenylsubstituted furans include furan fatty acids,¹ calicogorgins,² furanocembranolides,³ and furanoterpenes.⁴ A synthetic approach to these compounds can be developed along two opposing strategic lines. Either the side chains are appropriately established at the carbon backbone prior to cyclization or the substituents are later introduced by regioselective reactions.⁵

Our own studies for a selective synthesis of substituted furans are based on Pd(0)-catalyzed C-C bond forming reactions⁶ which occur on 2-acceptor substituted di- or tribromofurans. Of particular interest was the yet unexplored regioselectivity of these processes with regard to the ligand type at the metal center and the reaction conditions. The electron withdrawing substituent in C-2 position was expected to facilitate an oxidative addition of Pd(0) in C-5 and C-3 position of the corresponding bromofurans. In addition, it enhances the stability of the heterocycle towards oxidation. The readily accessible 4,5-dibromofurfural (**1**)⁷ appeared to be an ideal starting material for the synthesis of 2,3,5-trisubstituted furans.⁸



The Sonogashira variant⁹ of the Heck reaction was chosen as test reaction to evaluate the regioselectivity of Pd(0)-catalyzed bond forming reactions on furan **1** [equation (1)]. During the cross coupling of the intermediately formed copper acetylide an oxidative addition of Pd(0) in the halogen-carbon bond takes place as the primary step. This step resembles mechanistically a nucleophilic aromatic substitution.¹⁰ Based on the

analogy with known reactions of this type¹¹ a selection appeared to be possible. Among the palladium catalysts we checked $\text{PdCl}_2(\text{PPh}_3)_2$ turned out to be best suited for a rapid and selective transformation. Contrary to that, the use of $\text{Pd}(0)$ in the presence of more than two equivalents of phosphine resulted in a considerably slower reaction.¹² As pointed out in table 1 the reaction with various alkynes (**2**) proceeded in good yields with the desired regioselectivity.¹³

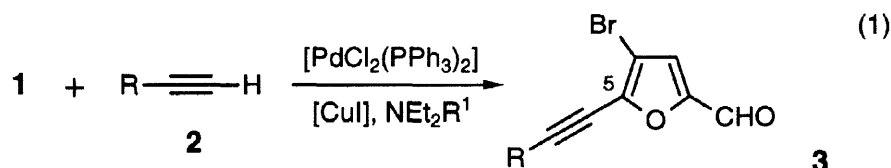
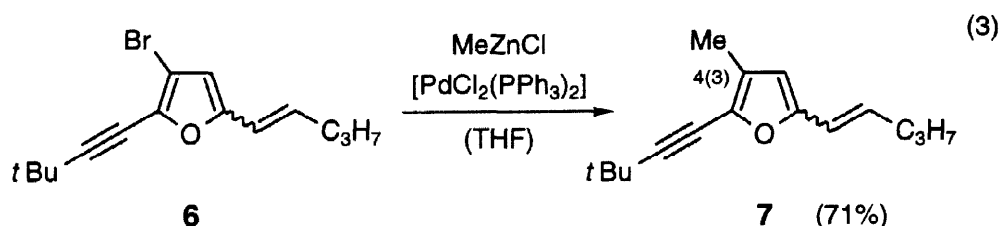
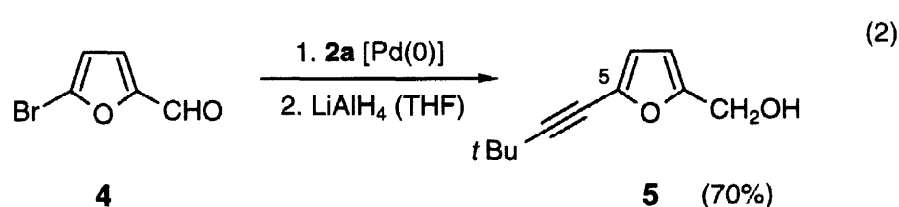


Table 1: Pd(0)-catalyzed coupling of 4,5-dibromofurfural (**1**) with various alkynes **2**

Alkyne	R	R ¹	Time ^[a] [h]	Product	Yield [%]
2a	<i>t</i> -Bu	Et	24	3a	84
2b	Ph	H	24	3b	81
2c	HOCH ₂ CH ₂	H	24	3c	68
2d	MeOCH ₂	Et	24	3d	68
2e	ClCH ₂ CH ₂ CH ₂	H	18	3e	71

^[a] Time required for complete transformation at room temperature with an amine NEt_2R^1 as solvent

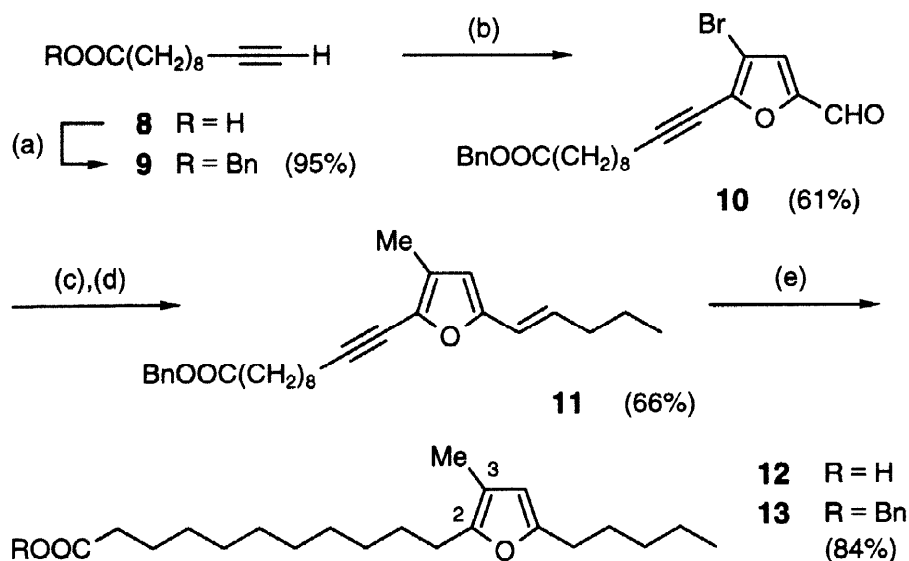
Proof for the introduction of the alkynyl moiety in the C-5 position was obtained by the hydrodebromination of product **3a** with LiAlH_4 which yielded the 2-furylmethanol **5** due to the concomitant reduction of the aldehyde. Independent synthesis of this material from 5-bromofurfural (**4**) showed that the Pd(0)-catalyzed coupling had selectively occurred in the C-5 position of 4,5-dibromofurfural.



Since most naturally occurring furans carry a methyl group in 4(3)-position we intended to substitute the bromine in compounds **3** by coupling with a methyl metal reagent. It was expected, however, that the common

reagents employed for this coupling are not compatible with the aldehyde group in furan **3**. The compound **3a** was therefore converted into alkene **6** by a Wittig reaction (91% yield). The transformation into an alkene was deliberate with respect to further synthetic targets which we intended to prepare and which carry an alkyl side chain (*vide infra*). By variation of the coupling reagent and of the Pd-catalyst we finally obtained 2,3,5-trisubstituted furans (e.g. **7**) under optimized conditions which guaranteed a reasonable yield in the second Pd(0)-catalyzed step [equation (3)]. The Pd(0)-catalyzed coupling of alkynes and alkylzinc¹⁴ reagents allows a high compatibility with functional groups.

Both substituents in C-2 and C-3 position of the F₅ fatty acid **12**^{1a} were introduced by Pd(0)-catalyzed reactions. The commercially available 10-undecynoic acid (**8**) served as building block for the C₁₁-side chain. After transformation into its benzyl ester **9** a regioselective coupling with 4,5-dibromofurfural (**1**) yielded aldehyde **10**. After a Wittig reaction (85% yield) the corresponding alkene was converted to furan **11** by coupling with MeZnCl. Treatment of compound **11** with hydrogen in the presence of Pd(OH)₂ effected the hydrogenation of the multiple bonds to the benzyl ester **13**¹⁵ and after prolonged reaction time the hydrogenolytic deprotection to the acid **12**.



Reagents and conditions: (a) 1. (COCl)₂ (2 equiv.), DMF (cat.) in CH₂Cl₂; 0 °C; 2 h; 2. BnOH (1.2 equiv.), NEt₃ (1.2 equiv.), DMAP (cat.) in CH₂Cl₂; rt; 2 h. (b) **1**, PdCl₂(PPh₃)₂ (0.05 equiv.), CuI (0.1 equiv.) in Et₂NH; rt; 24 h. (c) Ph₃P=CHC₃H₇ (1 equiv.) in THF; reflux; 3 h. (d) MeZnCl (3 equiv.), PdCl₂(PPh₃)₂ (0.04 equiv.) in THF; reflux; 16 h. (e) H₂, Pd(OH)₂/C (0.02 equiv.) in EtOAc; rt; 1 h.

The total yield of this synthetic sequence (34% for **13** starting from **1**) as compared to that of other syntheses of substituted furans¹⁶ is evidence for the efficiency of the strategy we have chosen. Further applications of the method described above are currently under way in our laboratory.

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