Cu(I)-Catalyzed Regioselective Synthesis of Substituted Allyl Furans and Thiophenes Using Organostannanes

Norma S. Nudelman,* Cecilia Carro

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P.3, C. Universitaria, 1428 Buenos Aires, Argentina

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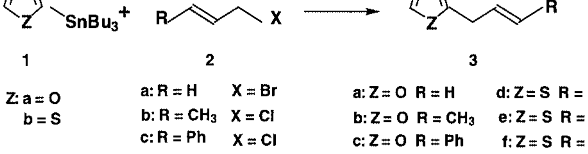
Abstract: 2-Allyl-substituted furans and thiophenes were efficiently synthesized from organostannyl derivatives as starting materials using Cu(I) as catalyst. The effect of DMF and NMP as solvents are discussed, as well as other solvent and temperature effects.

Key words: furans, thiophenes, copper catalyst, organostannanes

Furans with functionalized C2 substituents are of interest as intermediates for the synthesis of various natural products and can also serve as pivotal intermediates in synthetic strategy by virtue of their specific chemistry and latent functionality.[1,2] The Pd-catalyzed cross-coupling of organic electrophiles such as vinyl halides or triflates with organostannanes (Stille reaction)[3] has become an extremely powerful tool in organic synthesis and this reaction has been extensively used to the synthesis of substituted furans and thiophenes. The cross-coupling of different organic halides with heterocyclic stannanes has been reported.[4]

Recently, the beneficial influence of *co-catalytic* Cu(I) on nonproductive or sluggish Stille cross-coupling reaction catalyzed by palladium has been reported [5-9] as well as the cross-coupling mediated by *stoichiometric* amounts of copper salts.[10,11] The use of *catalytic* amounts of CuX in the presence NaCl was recently reported[12] and we have previously described a Cu(I) catalyzed methodology for C-C bond formation using α-heteroactivated-aliphatic stannyl derivatives.[13]

Nevertheless in spite of the potential utility of the use of Cu(I) as unique catalyst, this modification to the Stille reaction[14] have not been examined for the synthesis of allyl-substituted furans and thiophenes. The present paper reports the cross-coupling of 2-(tributyl stannyl)furan and 2-(tributylstannyl)thiophene with allyl halides in the presence of *catalytic* amount of CuCl (10 mol%) (without any Pd catalyst) as an efficient method for the synthesis of allyl-substituted furans and thiophenes (Scheme 1).



Scheme 1

Table 1 CuCl-Catalyzed Cross-Coupling of 2-(tributylstannyl) furan, **1a**, with allyl bromide, **2a**, at 55 °C.[a]

Entry	Solvent	Time (h)	Yield(%)[b]	
			3a	1a
1	THF	1	21	45
2	THF	13	32	3
3	Et_3N	1	2	82
4	Et_3N : THF (1:1)	1	2	74
5	Et_3N : THF (1:9)	1	15	72
6	Et_3N : NMP (1:1)	1	28	66
7	Et_3N : NMP (1:9)	1	32	47
8	THF:HMPA (1:1)	1	76	13
9	THF:NMP (9:1)	14	76	0
10	THF:NMP (1:1)	1	70	17
11	THF:NMP (1:1)	6	77	8
12	THF:NMP(1:1)	14	82	3
13	NMP	1	82	6
14	NMP[c]	1	86	4
15	NMP[c]	3	81	0
16	NMP[c]	8	83	0

[a] [CuCl] 10 mol %; [b] ~ 10 % of furan was also detected in the reaction mixtures; in solvents containing THF or Et_3N, furan could not be quantitatively determined by CG; [c] Reaction at 90°C.

In a first set of experiments, the copper catalyzed cross-coupling of 2-(tributylstannyl)furan, **1a**, with allyl bromide, **2a**, was fully examined to find the best reaction conditions. Table 1 shows the several solvents and binary mixtures that were tested, changes in reaction times and temperature were also examined. It can be observed in Table 1 the remarkable effect of adding HMPA (entries 1,8) or NMP (e.g. entries 1, 10; 2, 9; etc.) to the THF.

Increasing the reaction time from 1 h to 14 h has not a highly convenient effect (see entries 10, 12); in pure NMP the yield rises up to 82% in only one hour, following the reaction for more than one hour did not improve the yield. A small increase in yield was observed by increasing the temperature (entries 13, 14); some recovery of the reagent was observed after 1 hour but on longer reaction times at 90 °C decomposition of both, the reactant and the coupling product, occurs (Table 1, entries 15, 16). Under these reaction conditions, no homocoupling of stannane was observed and the only side-products were furan or thiophene and Bu_3SnX.

It was clear that NMP was the solvent of election and the reactions of 2-(tributylstannyl)furan, **1a**, and 2-(tributylstannyl) thiophene, **1b**, with different allyl halides using

Table 2 CuCl-Catalyzed Cross-Croupling of stannyl derivatives of furan **1a**, and thiophene, **1b**, with allyl halides at 90 °C.[a]

Entry	Organo stannane	Allyl halide	Solvent	Yield (%)		
				Product		HZ[b]
1	**1a**	2a	NMP	**3a**	86	10
2		2b	DMF	**3b**	85	12
3		2c	NMP	**3c**	70	10
4	**1b**	2a	NMP	**3d**	85	15
5		2b	DMF	**3e**	83	11
6		2b	DMF	**3e**	88	11
7		2c	DMF	**3f**[c]	44	20
8		2c	DMF	**3f**[d]	49	23
9		2c	NMP	**3f**[e]	47	30

[a] [CuCl] 10 mol %. All reactions were run for one hour (except entries 6, 8 and 9, time=3h), see footnote.[14] [b] **HZ** means furan for the reaction of **1a** and thiophene for the reaction of **1b**. [c] 14% of **1b** and 11% of bithiophene were obtained. [d] 6% of **1b** and 13% of bithiophene were obtained. [e] 3% of **1b** and 3% of bithiophene were obtained.

CuCl as catalyst were studied, the results are summarized in Table 2. High yields of the coupling product, **3a-f**, are obtained by the general procedure,[15] similar results were found by using either allyl chloride or bromide. On the contrary, in the absence of CuCl, the reaction between **1a** and **2a** did not proceed at all, and 99% of **1a** was recovered after 7.5 hs (in NMP, at 90 °C). It can be observed that the use of DMF gives similar results (Table 2). The reaction mixtures were carefully examined looking for isomeric product. For the allylic systems tested, the reaction is highly regioselective and coupling only occurs in the α position, products arising via an allylic rearrangement were never observed. Considering E/Z selectivity, for cases were two isomeric products are likely (eg. **2b** and **2c)** only the E isomers were obtained. The reaction of *Z*-1-bromo-2-pentene with **1b** gave the coupling product in 83% and only the *Z*-isomer was observed.

In the original disclosure of the copper effect,[6b] it was suggested that transmetallation of the R group from $RSnBu_3$ to copper salts could be the responsible for the catalysis and recent studies support the tin to copper transmetallation.[5] The remarkable effect of NMP might be to facilitate the Sn/Cu transmetallation (perhaps by coordination at Sn in the transition state) and/or stabilize the intermediate organocopper.[17] Thus, while the ^{119}Sn NMR chemical shift of **1a** and **1b** are almost insensitive to the solvent change, that of Bu_3SnCl is shifted 60 ppm upfield in Cl_3CD:NMP 9:1 relative to Cl_3CD.[18]

It is also interesting to note that in THF, the cross-coupling product was obtained in low yield (32%) (Table 1, entry 2) and the 2-(tributylstannyl)furan, **1a**, was recovered only in 3% yield, whereas in NMP yield and recovery were much better (Table 1, entries 14, 15).

This CuCl-mediated cross-coupling protocol is highly efficient for the synthesis of α-allyl-substituted furans and thiophenes, and it is economical in terms of cost and time. Under these conditions, the coupled product was obtained as the only product in excellent yield. CuCl possesses a good spectrum of properties: inexpensive, easy and rapid synthesis, and rapid reactions. This new process provides allylfurans and thiophenes in good yields under neutral reaction conditions.

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(15) *General Procedure*: A vial containing CuCl (10% mol) and a Teflon-coated stir bar was capped with a non-air stopper, evacuated and filled with dry nitrogen alternatively, several times. Anhydrous NMP or DMF (2 ml) and the organostannane[16] (0.65 mmol) were added by a syringe and the vial was put in a bath at 90 °C. The allyl halide (1.2 equiv.) was added and the reaction mixture stirred for 1h. Quantitative analyses were carried out by gas chromatography. *Isolation of the compounds*: the reaction mixture was cooled to rt, and 0.1 ml of satd. KF soln. was added. After filtration, the reaction mixture was extracted with ether, the organic layer dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by neutral alumina column chromatography using CH_2Cl_2 as eluant. Satisfactory spectra

data (^{1}H NMR, 13C NMR and mass spectra) were obtained for all the compounds. Isolated yields were slighly lower (5-7%) than those obtained by GC.

(16) The organostannanes were prepared similarly to other organotin derivatives as described in: Nudelman, N. S.; Carro C. *J. Organometal. Chem.* **1998**, *563*, 31-36.

(17) We thank one of the referees for this suggestion about the role of NMP.

(18) By studying the reaction mixture of **1a** and **2a** or **2b** in the presence of CuCl, by ^{119}Sn- and ^{13}C- NMR evidences for the presence of a $(\text{furil-Cu})_n$ intermediate and Bu_3SnX species were gathered. (to be published elsewhere)

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