Double Coupling Reactions of 3,4-Bis(stannyl)furanone: Facile Preparation of Diaryl- and Dibenzylfuranones

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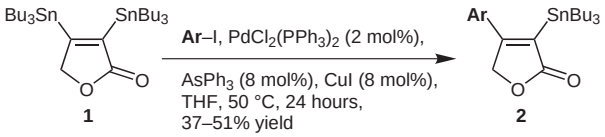
Abstract: The palladium-catalyzed cross-coupling reaction of 3,4-bis(tributylstannyl)furan-2(5*H*)-one using chelating ligand or polar solvent gives mixtures of single and double coupled products, even when one equivalent of halide coupling partner is used. After optimization, the double coupling reaction was shown to be general, with the use of two equivalents of aryl iodides giving 3,4-disubstituted furanones, The reaction using benzyl bromides proceeds at lower temperatures than the corresponding coupling using aryl iodides, giving dibenzylfuranones. The methodology has been exemplified in a synthesis of (±)-hinokinin.

Key words: furanon, butenolide, Stille coupling, diarylfuranone, lignan, hinokinin

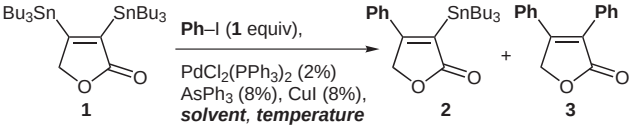
There is considerable interest in efficient methods to prepare furan-2(5*H*)-ones, due to the methodological challenges involved and the presence of these heterocycles at the core of many bioactive structures, both natural and synthetic. We have previously reported the utility of stannylated furanones,[1] and have shown that palladium-catalyzed cross-couplings of 3,4-bis(tributylstannyl)furanone (**1**) are regioselective, leading to 3-tributylstannyl-4-arylfuran-2(5*H*)-ones **2** (Scheme 1).[2] Subsequent Stille coupling of **2** leads to dissymmetric diarylfuranones.[3]



Scheme 1 Regioselective Stille coupling of 3,4-bis(stannyl)furan-2(5*H*)-one

We observed during these studies that use of a chelating ligand or a polar solvent led to the obtention of a mixture of 4-substituted and 3,4-disubstituted furanones (Table 1).[2] Thus, even using a single equivalent of iodide coupling partner, significant amounts of 3,4-diphenylfuranone (**3**) were obtained in addition to the usual coupling product **2** (Ar = Ph) when reactions were carried out using $Pd(dppb)_2$ as catalyst, or using $PdCl_2(PPh_3)_2$ as catalyst in DMF solution. Furthermore, the average yield per coupling reaction was significantly higher than those normally observed under the standard conditions (i.e., when preparing only 4-aryl-3-stannylfuranones). In the light of this observation, and with the knowledge that diarylfuranones and related compounds, such as lignans (dibenzylfuranones), are interesting small-molecule targets, we set about optimizing the conditions of the dicoupling reaction.

Table 1 Double Coupling of **1** with Iodobenzene[2]



Entry	Solvent	Temp (°C)	Yield of **2** (%)	Yield of **3** (%)
1	THF	50[a]	27	29
2	DMF	50	29	28
3	DMF	70	28	28
4	DMF	90	25	36
5	MeOH	50	12	27

[a] $Pd(dppb)_2$ (2 mol%) used as catalyst.

We commenced with an examination of the reaction using $Pd(dppb)_2$ as catalyst, but to our surprise (and in contrast to the data shown in Table 1) found that the reaction of **1** with two equivalents of iodobenzene was complex. Spectroscopic examination of crude reaction mixtures indicated a diverse range of products, most of which could not be isolated in a pure state, and the processes furnished diphenyl furanone **3** in a maximum yield of 25%; this implies an average yield per coupling of 51%, indicating that the first coupling reaction was no more efficient[4] than under the 'normal' conditions. Using a range of chelating diphosphines, similar results were obtained.

Turning our attention to the use of a more polar solvent, initial screening studies indicated DMF as the ingredient of choice. Thus, the reaction of **2** with iodobenzene (2 equiv) at 90 °C was a smooth process, and **3** was obtained in 56% yield (indicating an average coupling yield of 75%). Using a range of aryl iodides, it was found that a slight diminution in temperature (to 80 °C) did not adversely affect the yields of dicoupled products and simultaneously minimized the amount of unidentifiable side-products obtained. We also found that the reactions

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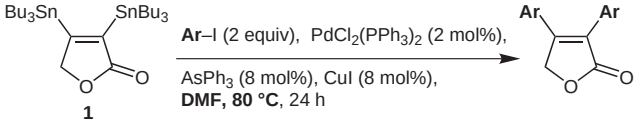
were just as rapid as the original monocoupling processes; under these conditions, diarylfuranones were obtained in good yields (Table 2). A few points arising from the data shown in Table 2 merit further comment. Thus, the presence of an sp^3 *ortho*-substituent in the iodide partner diminishes the yield of the coupling (entry 8), whilst an sp^2 *ortho*-substituent has little effect (entry 4). A nitro group has a deleterious effect (entry 7) but a ligating substituent (entry 6) does not. As we have often observed in analogous reactions,[2] a mixture of geometric isomers of 2-bromostyrene couples with **1** to give only *E*-configured alkenes in the product. Finally, the reaction of benzyl bromide under these conditions proceeded in moderate yield, to give 3,4-dibenzylfuranone (entry 9).

Table 2 Double Coupling of **1** with Aryl Iodides[5]

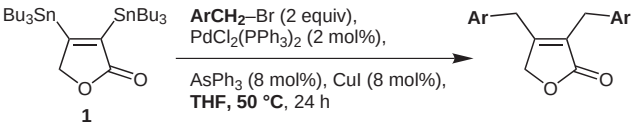


Entry	Ar	Yield (%)	Efficiency (%)[a]
1	Ph	56	75
2	4-Tol	50	71
3	3-F_3C-C_6H_4	43	66
4	2-Thienyl	47	69
5	3-Thienyl	43	66
6	4-MeS-C_6H_4	39	63
7	3-O_2N-C_6H_4	27	52
8	2-F_3C-C_6H_4	18	43
9	Bn[b]	29	54
10	PhCH=CH[b,c]	36[d]	60

[a] Average yield per coupling reaction.
[b] Bromide used in place of iodide.
[c] A 2:1 mixture of *E*/*Z* isomers was used.
[d] Only *E*,*Z*,*E* isomer obtained.

Given the higher reactivity of benzylic halides compared with aryl halides, we were slightly disappointed with the yield obtained upon coupling of benzyl bromide with **1** (though we remained mindful of the anomalous reactivity associated with such substrates in other cross-coupling reactions).[6] Thus, we reexamined the conditions used to prepare dibenzylfuranone and found after some experimentation that THF was a more appropriate solvent and that lower reaction temperatures could be used, improving yields substantially (Table 3). In the case of the unsubstituted halides, both chloride and bromide gave good yields of coupled products, but when substitution was present in the aryl ring, chlorides react less well than the corresponding bromides (low yields of coupled products were isolated from complex product mixtures).

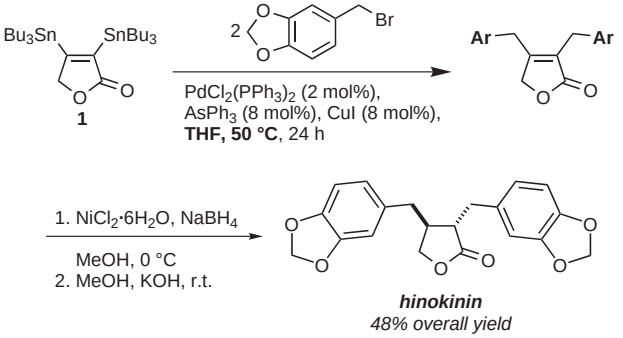
Table 3 Optimized Coupling of **1** with Benzyl Bromides[7]



Entry	Ar	Yield (%)	Efficiency (%)[a]
1	Ph	45	67
2	Ph[b]	44	66
3	4-MeO-C_6H_4	25	50
4	1-Naphthyl	39	62
5	2-Naphthyl	43	66
6	Piperonyl	51	71

[a] Average yield per coupling reaction.
[b] Chloride used in place of bromide.

To our knowledge, this process represents one of the most efficient methods available for the preparation of dibenzylfuranones. As a demonstration of the power of the methodology, we prepared (±)-hinokinin[8] by double coupling of piperonyl bromide with **1**, followed by nickel(II)-mediated conjugate reduction (Scheme 2).[9] Though the key intermediate is apparently an ideal substrate for asymmetric conjugate reduction,[10] to date we have obtained only moderate ee values using a range of chiral modifiers in this process. The identification of an effective chiral reduction method for this furanone is a focus of our efforts at this time.



Scheme 2 Synthesis of hinokinin

In summary, we have modified the conditions for Stille coupling of bis(stannyl)furan-2(5*H*)-one (**1**) to enable the direct preparation of diaryl- and dibenzylfuranones. We are currently engaged in the exploitation of this methodology in synthesis of a range of natural and synthetic lignans and will report on these efforts in due course.

Acknowledgment

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(3) For other routes to 3,4-disubstituted furanones, see, for instance: (a) Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749. (b) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17. (c) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 233. (d) Mornet, R.; Gouin, L. *Bull. Soc. Chim. Fr.* **1977**, 737. (e) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972. (f) Wakharkar, R. D.; Deshpande, V. H.; Landge, A. B.; Upadhye, B. K. *Synth. Commun.* **1987**, *17*, 1513. (g) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1989**, *49*, 3819. (h) Delaunay, J.; Orliac-Le Moing, A.; Simonet, J. *Tetrahedron* **1988**, *44*, 3819. (i) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897; and references therein.

(4) It is not possible to directly discern the yields of the individual coupling reactions: assuming a maximum yield of 100% for the second coupling (normally a more efficient process, see ref. 2), the maximum possible yield for the first step is 51%. Our original observations in monocoupling of **1** with PhI gave **2** (Ar = Ph) in a yield of 51%.

(5) **Representative Experimental Procedure.**
To a flame-dried flask (under argon atmosphere) charged with $PdCl_2(PPh_3)_2$ (2 mol%), CuI (8 mol%), $AsPh_3$ (8 mol%) was added 3,4-bis(tributylstannyl)furan-2(5*H*)-one (500 mg, 0.76 mmol) as a solution in dry, deoxygenated DMF, followed by iodobenzene (310 mg, 1.52 mmol), also added dropwise as a solution in DMF (2.0 mL). After reaction was complete (24 h) the mixture was diluted with aq KF (1 M, 10.0 mL) and extracted with Et_2O (3 × 30.0 mL), washed with H_2O (3 × 15.0 mL) and brine (3 × 15.0 mL). Solvent was removed under reduced pressure and the crude product was purified via flash chromatography (silica gel, 3:2 PE–Et_2O; R_f = 0.24). Recrystallization (CH_2Cl_2–PE) gave 3,4-diphenylfuran-2(5*H*)-one as pale yellow crystals (56%, 101 mg); mp 104–105 °C (CH_2Cl_2–PE). IR ($CHCl_3$): 1751, 1646, 1489 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.10 (2 H, s), 7.23–7.33 (10 H, m). ^{13}C NMR (60 MHz, $CDCl_3$): δ = 71.0 (OCH_2), 126.6, 127.9, 129.2, 129.3, 129.4, 129.7, 130.6, 131.0, 131.2, 156.6, 173.9. MS (CI, NH_3): *m/z* calcd for $C_{16}H_{13}O_2$: 237.0916. Found $[MH]^+$: 237.0915; *m/z* (%) = 179.0 (15).

(6) See, for instance: (a) Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703. (b) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725. (c) Kumar, P. *Org. Prep. Proced. Int.* **1997**, *29*, 477. (d) Pan, Y.; Zhang, Z.; Hu, H. *Synthesis* **1995**, 245. (e) Pan, Y.; Zang, Z.; Hu, H. *Synth. Commun.* **1992**, *22*, 2019. (f) Hashem, M. A.; Weyerstahl, P. *Tetrahedron* **1984**, *40*, 2003. (g) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(7) **Representative Experimental Procedure.**
To a flame-dried flask (under an argon atmosphere) charged with benzyl bromide (226 mg, 1.33 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), $AsPh_3$ (8 mol%) and CuI (8 mol%) was added THF (5.0 mL) and the mixture warmed to 50 °C. 3,4-Bis(tributylstannyl)furan-2(5*H*)-one (450 mg, 0.66 mmol) in THF (5.0 mL) was added dropwise via syringe. After reaction was complete the mixture was concentrated under reduced pressure. Purification via flash chromatography (silica gel, PE–Et_2O 1:1; R_f = 0.50) gave 3,4-dibenzylfuranone as a clear colorless oil (78 mg, 45%). IR ($CHCl_3$): 3063, 1754, 1668 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.71 (2 H, s), 3.74 (2 H, s), 4.51 (2 H, s), 6.99–7.02 (2 H, dd, *J* = 7.0, 2.0 Hz), 7.22–7.29 (8 H, m). ^{13}C NMR (60 MHz, $CDCl_3$): δ = 30.0, 34.0, 71.7, 127.0, 127.2, 127.7, 129.0, 129.1, 129.2, 129.5, 136.3, 138.5, 160.3, 175.2. MS (CI, NH_3): *m/z* calcd for $C_{18}H_{16}O_2$: 265.1231. Found $[MH]^+$: 265.1221; *m/z* (%) = 219 (20), 91 (25).

(8) For racemic and asymmetric syntheses of hinokinin, see: (a) Morimoto, T.; Nagai, H.; Achiwa, K. *Synth. Commun.* **2005**, *35*, 857. (b) da Silva, R.; de Souza, G. H. B.; da Silva, A. A.; de Souza, V. A.; Pereira, A. C.; Royo, V. D.; Silva, M. L. A. E.; Donate, P. M.; Araujo, A. L. S. D.; Carvalho, J. C. T.; Bastos, J. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1033. (c) Bennett, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun.* **2004**, 1392. (d) Xia, Y. M.; Liang, Q. R.; Wang, X. L.; Cao, X. P.; Pan, X. F. *Chin. J. Chem.* **2003**, *21*, 1540. (e) Enders, D.; Lausberg, V.; Del Signore, G.; Berner, O. M. *Synthesis* **2002**, 515. (f) Brinksma, J.; van der Deen, H.; van Oeveren, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4159; and references therein.

(9) **Data for (±)-Hinokinin.**
IR ($CHCl_3$): 1769, 1495, 1245, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45–2.60 (3 H, m, $ArCH_2CH$, $ArCH_2CH$ and ArCH2CHCHC=O), 2.86 (1 H, dd, *J* = 14.5, 7.0 Hz, $ArCH_2CHC$=O), 2.99 (1 H, dd, *J* = 14.0, 5.0 Hz, $ArCH_2CHC$=O), 3.87 (1 H, dd, *J* = 9.00, 7.00 Hz, OCH_2), 4.14 (1 H, dd, *J* = 10.0, 7.00 Hz, OCH_2), 5.95 (4 H, m, OCH_2O), 6.46–4.48 (2 H, m, 2 × Ar,), 6.62 (2 H, m, 2 × Ar), 6.64 (2 H, m, 2 × Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2, 38.8 ($ArCH_2$), 41.7 ($ArCH_2CHCHC$=O), 46.9 ($ArCH_2CHCHC$=O), 71.6 (OCH_2), 101.4 (OCH_2O) 108.6, 108.9, 109.2, 109.8, 121.9, 122.6, 131.7, 132.0, 132.1, 146.8, 146.9, 148.3 (2 × Ar), 178.8 (C=O). MS (CI, NH_3): *m/z* calcd for $C_{20}H_{19}O_6$: 355.1181. Found $[MH]^+$: 355.1164; *m/z* (%) = 135 (45).

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