Regioselective Pd(0)-Catalyzed Coupling Reactions on Methyl 2,3-Dibromofuran-5-carboxylate as a Facile Entry into 2,3,5-Tri- and 2,3-Disubstituted Furans

T. Bach*, L. Krüger

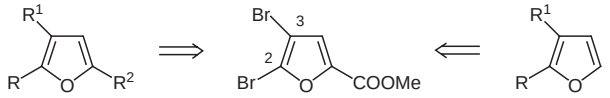
Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

Fax: + 49(0)6421/288917; E-mail: bach@chemie.uni-marburg.de

Received 12 August 1998

Abstract: Regioselective Pd(0)-catalyzed cross-coupling reactions on the title compound **1** occur at the C-2 carbon atom in excellent yields with a variety of organometallic reagents. The products **2** react under Pd(0)-catalysis at the 3-position with MeZnCl or $SnMe_4$ to yield 2,3,5-trisubstituted furans. A subsequent decarboxylation gives access to 2,3-disubstituted furans as exemplified by the synthesis of rosefuran (**5**).

Multiply-substituted furans are frequently found in nature and they exhibit interesting biological and pharmacological properties. The furanocembranes,[1] the furan fatty acids,[2] the calicogorgins,[3] and the furanoterpenes[4] represent some of the many examples. The 2,3,5-tri- and the 2,3-disubstitution patterns are widespread among the naturally occurring furans and it is therefore desirable to devise a general approach to these two classes of compounds.[5] We speculated that the readily available title compound, methyl 2,3-dibromofuran-5-carboxylate (**1**),[6] might be an ideal starting material to access both 2,3-di- and 2,3,5-trisubstituted furans if it was possible to achieve a regioselective reaction at the bromine-bearing carbon atoms C-2 and C-3. In particular, Pd(0)-catalyzed coupling reactions[7] appeared to be well-suited for such a purpose as they would allow a direct C-C-bond formation even with functionalized reagents (Scheme 1).



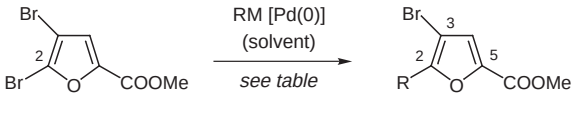
1

Scheme 1

In earlier studies we have shown that 4,5-dibromofurfural undergoes a regioselective Sonogashira type coupling[8] at the 5(2)-position[9] but this starting material is less suited for the reaction with organometallic compounds such as organozinc reagents[10] and stannanes.[11] The latter fact precluded a sequential reaction as the formyl group had to be transformed into a less sensitive functional group before conducting a cross-coupling at the 4(3)-position. The title compound **1** appeared to be superior for this purpose. In addition, it seemed useful for the synthesis of 2,3-disubstituted furans because the decarboxylation of the free acid was expected to be a facile and high-yielding process.[5]

In a first set of experiments we tried to find the best conditions to achieve a regioselective cross-coupling at the 2-position of furan **1** (Scheme 2). As we had hoped for, a variety of reagents underwent a clean reaction at the more reactive C-2 carbon atom (see table, DMA = *N*,*N*-dimethylacetamide). The reaction is facilitated by the acceptor substituent in 5-position which lends additional stability to the heterocycle.

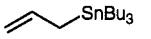
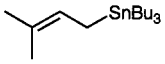
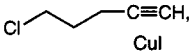
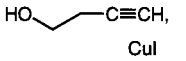
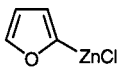
A broad variety of substituents can be attached to the C-2 carbon atom by this method. Several Pd-catalysts were screened but the commonplace $Pd(PPh_3)_2Cl_2$ proved to be best suited for most cross-coupling reactions. In the Stille reaction, $Pd(PPh_3)_4$ was slightly superior (entries 1 and 2).[12] Mechanistically, we assume the oxidative addition[13] to be the selectivity determining step in these reactions. It is



1 **2**

Scheme 2

Table: Pd(0)-Catalyzed Cross Coupling with Furan **1** (Scheme 2)

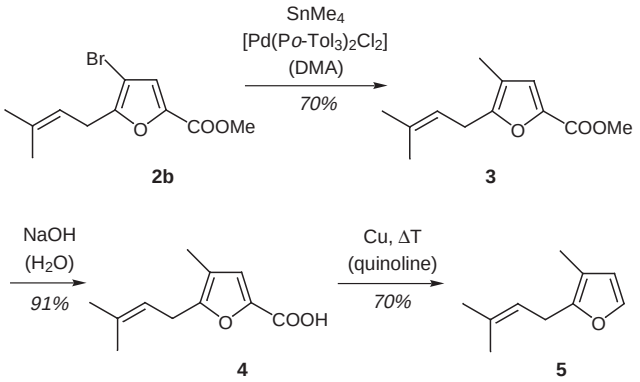
Entry	RM	Catalyst [a]	Solvent	Temp.[b]	Product	Yield [%]
1		A	DMA	90°C	**2a**	73
2		A	DMA	90°C	**2b**	79
3	*t* BuC≡CH, CuI	B	NEt_2H	r.t.	**2c**	72
4	PhC≡CH, CuI	B	NEt_2H	r.t	**2d**	80
5		B	NEt_2H	r.t.	**2e**	94
6		B	NEt_2H	r.t.	**2f**	73
7	PhZnCl	B	THF	r.t.	**2g**	66
8		B	THF	r.t.	**2h**	76
9	MeZnCl	B	THF	r.t.	**2i**	84

[a] Catalysts: A = $Pd(PPh_3)_4$; B = $PdCl_2(PPh_3)_2$. [b] All reactions were run overnight under an argon atmosphere at the indicated temperature, see footnote.[12]

known that nucleophilic substitution reactions on 2,3-dibrominated furans which bear an acceptor substituent in the 5-position occur preferentially at C-2.[5,14] The 3-position is less reactive towards attack of a nucleophile and the oxidative addition of Pd(0) should consequently be retarded at this site. In the course of the reactions listed in the Table no hints were found for the formation of disubstituted products.

It was clear that more drastic conditions or a more nucleophilic Pd(0)-species were necessary to achieve a coupling at the 3-position of the monobrominated substrates **2**. As most naturally occurring furans bear a methyl group at this site we tried to optimize the coupling reaction with a methyl donor, e.g. MeZnCl or $SnMe_4$. After considerable experimentation the tri(*o*-tolyl)phosphane (P*o*-Tol_3) ligand turned out to be the ligand of choice and $Pd(Po\text{-}Tol_3)_2Cl_2$ was successfully employed as the catalyst. Scheme 3 illustrates the conversion of bromofurane **2b** to the methylated product **3**.[15] The yields for the methyldebrominations

conducted so far range between 65 and 75%. Although the reaction time was slightly longer it appears as if $Pd(Po\text{-}Tol_3)_2Cl_2$ was also more reactive than $Pd(PPh_3)_2Cl_2$. These findings are in accord with recent suggestions about the more readily formed reactive intermediate '$Pd(Po\text{-}Tol_3)$'.[16]



Scheme 3

As an application of the regioselective cross-coupling we have completed a short synthesis of rosefuran (**5**).[17] Saponification of the ester **3** gave the free carboxylic acid **4** which was thermally decarboxylated to yield the desired target compound.[18,19]

In summary, sequential Pd(0)-catalyzed coupling reactions on the title compound **1** can lead to a variety of 2,3,5-tri- and 2,3-disubstituted furans in good yields. The wide selection of organometallic reagents which can be sucessfully employed and the fact that many functional groups are tolerated in the course of the cross-coupling are beneficial for synthetic applications some of which are currently being studied in our laboratory.

Acknowledgements. This work was generously supported by the *Deutsche Forschungsgemeinschaft* (Ba 1372/5-1 and Graduiertenkolleg 'Metallorganische Chemie'), and by the *Fonds der Chemischen Industrie*. We thank the *Degussa AG* for a gift of chemicals. Thanks are also due to Prof. Dr. P. Knochel and his group for helpful discussions.

References and Notes

(1) Rodríguez, A. D.; Shi, J-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425-4432 and refs. cited therein.

(2) Glass, R. L.; Krick, T. P.; Sand, D. M.; Rahn, C. H.; Schlenk, H. *Lipids* **1975**, *10*, 695-702. Hannemann, K.; Puchta, V.; Simon, E.; Ziegler, H.; Ziegler, G.; Spiteller, G. *Lipids* **1989**, *24*, 296-298 and refs. cited therein.

(3) Ochi, M.; Yamada, K.; Kawakami, H.; Tatsukawa, A.; Kotsuki, H., Shibata, K. *Tetrahedron Lett.* **1992**, *33*, 7531-7534.

(4) Subba Rao, G. S. R.; Ravindranath, B.; Sashi Kumar, V. P. *Phytochemistry* **1984**, *23*, 399-401 and refs. cited therein.

(5) Reviews: Eberbach, W. in *Houben-Weyl*, 4th ed., Vol. E6a, part 1; Kreher, R. P., Ed.; Thieme: Stuttgart, 1994; pp 16-185d. Sargent, M. V.; Dean, F. M. in *Compr. Heterocycl. Chem.*, Vol. 4; Katritzky, A. R., Ed.; Pergamon: Oxford, 1984; pp. 599-656. Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167-238, *ibid*. **1982**, *31*, 237-344.

(6) Chadwick, D. J.; Chambers, J.; Meakins, G. D.; Snowden, R. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1766-1773.

(7) Diederich, F.; Stang, P. J., Eds. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, 1998.

(8) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.

(9) Bach, T.; Krüger, L. *Tetrahedron Lett.* **1998**, *39*, 1729-1732.

(10) Review: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117-2188.

(11) Review: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652.

(12) Representative procedure: 2 mmol of ester **1** (568 mg) and 0.08 mmol of $Pd(PPh_3)_2Cl_2$ (56 mg) were dissolved in 8 ml of THF at room temperature. A solution of 4 mmol of 2-furylzinc chloride, prepared by metalation of 4 mmol of furan (272 mg) with *n*-butyllithium (4 mmol, 2.2 ml of a 1.8 M solution) and transmetalation with $ZnCl_2$ (6 mmol, 818 mg), in 8 ml of THF was added via syringe. The mixture was stirred at room temperature for 16 h and subsequently quenched with a saturated aqueous solution of NH_4Cl. After extraction with ether the organic layers were collected, washed with brine and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (pentane/*t*-butylmethyl ether = 98:2) to yield 411 mg of compound **2h** (76%). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 3.85 (s, 3 H), 6.48 (dd, ^3J = 3.5 Hz, ^3J = 1.7 Hz, 1 H), 7.01 (d, ^3J = 3.5 Hz, 1 H), 7.19 (s, 1 H), 7.50 (d, ^3J = 1.7 Hz, 1 H).

(13) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176-5185 and refs. cited therein.

(14) Kada, R.; Knoppová, V.; Kovác, J.; Cepec, P. *Coll. Czech. Chem. Commun.* **1984**, *49*, 984-991.

(15) Representative procedure: 2 mmol of compound **2b** (546 mg), 4 mmol of tetramethylstannane (720 mg, 550 µl) and 0.1 mmol of $Pd(Po\text{-}Tol_3)_2Cl_2$ (70 mg) were dissolved in 10 ml of DMA and heated to 90 °C for 16 h. – CAUTION: Tetramethylstannane is very toxic by inhalation, in contact with skin and if swallowed. Appropriate safety protection and utmost care is required while handling this compound. – The mixture was cooled to room temperature and subsequently quenched with a saturated aqueous solution of NH_4Cl. After extraction with ether the organic layers were collected, washed with brine and dried over $MgSO_4$. The solvent was distilled *in vacuo* and the residue was purified by flash chromatography (pentane/*t*-butylmethyl ether = 90:10) to yield 290 mg of compound **3** (70%). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.69 (d, ^4J = 1.5 Hz, 6 H), 1.96 (s, 3 H), 3.32 (d, ^3J = 7.2 Hz, 2 H), 3.83 (s, 3 H), 5.23 (tsept, ^3J = 7.2 Hz, ^4J = 1.5 Hz, 1 H), 6.94 (s, 1 H).

(16) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969-5970. Hartwig, J. F. *Synlett* **1997**, 329-340.

(17) Büchi, G.; sz. Kovats, E.; Enggist, P.; Uhde, G. *J. Org. Chem.* **1968**, *33*, 1227-1229.

(18) When comparing this route with other ways to 2,3-disubstituted furans which start from 2,3-dibromofuran, e.g. the regioselective halogen-metal exchange,[19] one should note that 2,3-dibromofuran is prepared from ester **1**.

(19) Zaluski, M. C.; Robba, M.; Bonhomme, M. *Bull. Soc. Chim. Fr.* **1970**, 1838-1846. Ly, N. D.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 2085-2088.