Pergamon

Tetrahedron Letters 42 (2001) 3851–3854

TETRAHEDRON LETTERS

Synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones and unsymmetrically disubstituted 3,4-dialkyl-2(5*H*)-furanones by palladium-catalyzed cross-coupling reactions

Fabio Bellina,* Chiara Anselmi and Renzo Rossi

Dipartimento di Chimica e Chimica Industriale, University of Pisa, via Risorgimento 35, I-56126 Pisa, Italy

Received 12 April 2001

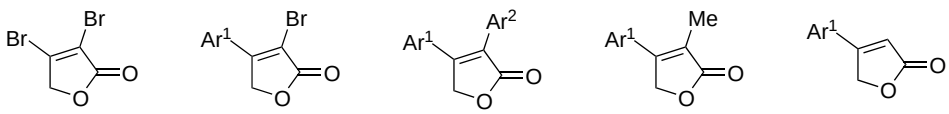
Abstract—Easily available 3,4-dibromo-2(*5H*)-furanone undergoes a regioselective cross-coupling reaction with alkylboronic acids in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ and $AsPh_3$ and a large molar excess of Ag_2O to provide the corresponding 4-alkyl-3-bromo-2(5*H*)-furanones in satisfactory yields. These monobromo derivatives have proven to be useful precursors to unsymmetrically substituted 3,4-dialkyl-2(5*H*)-furanones which include the racemic form of naturally occurring seiridin.

In recent years 3,4-disubstituted 2(5*H*)-furanones have attracted considerable attention as synthetic target compounds[1] due to the wide range of biological activities they cover,[2] their occurrence in nature[3] and their use as synthetic intermediates.[4]

Recently, in connection with our ongoing projects related to the design and use of simple and efficient protocols for the synthesis of natural and unnatural bioactive oxygen-containing heterocycles,[5] we developed a new procedure for the selective synthesis of 4-aryl-3-bromo-2(5*H*)-furanones **2** involving the reaction of easily available 3,4-dibromo-2(5*H*)-furanone **1** with aryl(trialkyl)stannanes in the presence of the catalyst precursor consisting of 5 mol% $PdCl_2(PhCN)_2$ and 10 mol% $AsPh_3$ or that obtained by treatment of 2.5 mol% $Pd_2(dba)_3$ with 10 mol% $AsPh_3$.[6] These monobromo derivatives were then used as precursors to unsymmetrically disubstituted 3,4-diaryl-2(5*H*)-furanones **3**, 4-aryl-3-methyl-2(5*H*)-furanones **4** and 4-aryl-2(5*H*)-furanones **5**.[6]

More recently, we investigated a new method for the efficient and selective synthesis of unsymmetrically substituted 3,4-dialkyl-2(5*H*)-furanones of general formula **6**.[7] In particular, encouraged by the successful outcome of the palladium-catalyzed monoarylation reactions of **1**,[6] we explored the possibility of preparing compounds **6** by selective palladium-catalyzed alkylation of **1** at the 4-position,[8] followed by a palladium-catalyzed methylation reaction of the resulting 4-alkyl-3-bromo-2(5*H*)-furanones **7**.

After unsuccessful attempts to prepare compounds **7** in satisfactory yields by treatment of **1** either with 1.1 equiv. of 9-alkyl-9-borabicyclo[3.3.1]nonanes **8**[9] in a ca. 1:3 mixture of THF and dioxane at 60°C in the presence of 3 equiv. of K_3PO_4, 5 mol% $Pd(OAc)_2$ and 10



* Corresponding author. Tel.: +39 50918282; fax: +39 50918260; e-mail: bellina@dcci.unipi.it

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00609-8

mol% PPh_3 or with 1.1 equiv. of alkylboronic acids **9**[10] in refluxing THF for 23 h, in the presence of 3 equiv. of Ag_2O and catalytic quantities of $Pd(PPh_3)_4$, we were pleased to observe that the reaction of **1** with 1.1 equiv. of **9** in THF under reflux for 18–23 h, in the presence of 3 equiv. of Ag_2O, 5 mol% $PdCl_2(MeCN)_2$ and 20 mol% $AsPh_3$, proceeded regioselectively to give the desired cross-coupled products **7** in yields ranging from 69 to 79% (Table 1).[11,12]

Interestingly, the reaction, which was amenable to the preparation of multigram quantities of compounds **7**, in all the cases examined (entries 1–4, Table 1) did not provide any trace of the product derived from the cross-coupling at the bromine-bearing carbon atoms C-3 and C-4.

With the availability of 4-alkyl-3-bromo-2(5*H*)-furanones **7a–d** (entries 1–4, Table 1), we explored their conversion into the 3,4-dialkyl-2(5*H*)-furanones of general formula **6**. Thus compounds **7** were reacted with 3 equiv. of tetramethylstannane **10** in 1-methyl-2-pyrrolidinone (NMP) at 80°C for 23–68 h, in the presence of the catalyst precursor consisting of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% $AsPh_3$ and 10 mol% CuI or that obtained by treatment of 2.5 mol% $Pd_2(dba)_3$ with 10 mol% $AsPh_3$ and 10 mol% CuI. Disappointingly, the final reaction mixtures, which at the beginning were homogeneous and green colored and after a few minutes at 80°C became dark and heterogeneous, proved to contain mixtures of unreacted compounds **7**, the desired cross-coupled products **6** and hydrodebrominated compounds **11** in which the monobromo derivatives **7** were the major components.

10 **11**

Nevertheless, to our delight we found that the reaction of compounds **7** to form the desired products **6** proceeded cleanly and without the formation of the byproducts **11** if a large molar excess (3 equiv.) of **10** was used as the reagent in NMP at 85°C and the catalyst precursor consisted of 5 mol% $PdCl_2[P(o\text{-}Tol)_3]_2$ and 10 mol% CuI. As shown in Table 2, this protocol allowed us to prepare compounds **6a–c** in 88–95% yield. It is interesting to note that when the cross-coupling was over, the reaction mixtures became dark and heterogeneous.

Finally, it is worth mentioning that treatment of the prepared **6c** with 1.5 equiv. of $TiCl_4$ in CH_2Cl_2 at 0°C for 45 min, followed by aqueous workup and purification by MPLC on silica gel of the resulting crude reaction product, afforded racemic seiridin **12** in 91% yield.[13,14] The spectral properties of this compound were in satisfactory agreement with those of the naturally occurring homochiral compound isolated from *Seiridium cardinale*.[3b]

Table 1. Palladium-catalyzed synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones **7**[a]

$$\mathbf{1}+\mathbf{9} \xrightarrow[Ag_2O,THF,\ reflux]{PdCl_2(MeCN)_2,\ AsPh_3} \mathbf{7}$$

Entry	Alkylboronic acid		Reaction time (h)	Product **7**	Yield (%)
	9	R			
1	**9a**	n-C_8H_{17}	22	**7a**	71
2	**9b**	t-C_4H_9O-$(CH_2)_6$	23	**7b**	70
3	**9c**	t-C_4H_9O-$CH(CH_3)$-$(CH_2)_5$	23	**7c**	69
4	**9d**	n-C_4H_9	18	**7d**	79

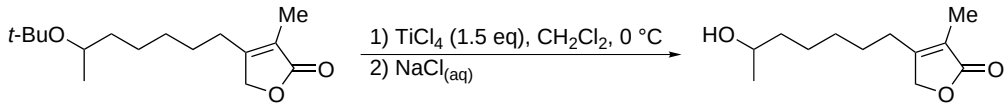
[a] All reactions were performed in THF under reflux in the presence of 3 equiv. of Ag_2O, 5 mol% $PdCl_2(MeCN)_2$ and 20 mol% $AsPh_3$.

Table 2. Palladium-catalyzed synthesis of 3,4-dialkyl-2(5*H*)-furanones **6**[a]

$$\mathbf{7}+\mathbf{10} \xrightarrow[NMP,\ 85°C]{PdCl_2[P(o\text{-}Tol)_3]_2,\ CuI} \mathbf{6}$$

Entry	4-Alkyl-3-bromo-2(5*H*)-furanone		Reaction time (h)	Product **6**	Yield (%)
	7	R			
1	**7a**	n-C_8H_{17}	18	**6a**	90
2	**7b**	t-C_4H_9O-$(CH_2)_6$	20	**6b**	88
3	**7c**	t-C_4H_9O-$CH(CH_3)$-$(CH_2)_5$	18	**6c**	95

[a] All reactions were performed in NMP at 85°C with 3 equiv. of tetramethylstannane **10** in the presence of 5 mol% $PdCl_2[P(o\text{-}Tol)_3]_2$ and 10 mol% CuI.



6c (91 % yield) **12**

In summary, we have developed an unprecedented, general and efficient procedure for the regioselective synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones **7**. We have also demonstrated that these monobromo derivatives are useful precursors to unsymmetrically substituted 3,4-dialkyl-2(5*H*)-furanones which include the racemic form of naturally occurring seiridin **12**.

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the University of Pisa.

References

1. (a) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett*. **2000**, *41*, 17–20; (b) Mahon, R.; Richecoeur, A. M. E.; Sweeney, J. B. *J. Org. Chem*. **1999**, *64*, 328–329; (c) Bella, M.; Piancatelli, G.; Pigro, M. C. *Tetrahedron* **1999**, *55*, 12387–12398; (d) Bonini, C.; Chiummiento, L.; Evidente, A.; Funicello, M. *Tetrahedron Lett*. **1995**, *36*, 7285–7286; (e) Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489–5494; (f) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett*. **1994**, *35*, 7897–7900; (g) Crisp, G. T.; Meyer, A. G. *J. Org. Chem*. **1992**, *57*, 6972–6975; (h) Demnitz, F. W. J. *Tetrahedron Lett*. **1989**, *30*, 6109–6112; (i) Wakharkar, R. D.; Deshpande, V. H.; Landge, A. B.; Upadhye, B. K. *Synth. Commun*. **1987**, *17*, 1513–1517; (j) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem*. **1984**, *49*, 3819–3824; (k) Delaunay, J.; Orliac-Le Moing, A.; Simonet, J. *Tetrahedron* **1988**, *44*, 76089–76094; (l) Douboudin, J. G.; Jousseaume, B. *J. Organomet. Chem*. **1979**, *168*, 233–240; (m) Mornet, R.; Gouin, L. *Bull. Chem. Soc. Fr*. **1977**, 737–741; (n) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 242–247.
2. (a) Desmond, R.; Dolling, U.; Marcune, B.; Tillyer, R.; Tschaen, D. US Patent 5,585,504, 17 Dec 1996; *Chem. Abstr*. **1996**, 125, P86474s; (b) Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Therien, M. PCT Int. Appl. WO9500,501, 5 Jan 1995; *Chem. Abstr*. **1996**, 124, P201998j; (c) Aoki, K.; Tokuda, T.; Hishi, H.; Satake, K.; Fumayama, S. Japanese Patent 7,328,646, 03 Sept 1973; *Chem. Abstr*. **1974**, 80, P117147w; (d) Sparapano, L.; Evidente, A. *Nat. Toxins* **1995**, *3*, 166–173 and references cited therein.
3. (a) Evidente, A.; Sparapano, L. *J. Nat. Prod*. **1994**, *57*, 1720–1725; (b) Evidente, A.; Randazzo, G.; Ballio, A. *J. Nat. Prod*. **1986**, *49*, 593–601; (c) Tantivatana, P.; Ruangrunsi, N.; Vaissiriroj, V.; Lankin, D. C.; Bhacca, N. S.; Borris, R. P.; Cordell, G. A.; Johnson LeRoy, F. *J. Org. Chem*. **1983**, *48*, 268–270; (d) Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 803–806.
4. (a) Janini, T. E.; Sampson, P. *J. Org. Chem*. **1997**, *62*, 5069–5073; (b) Ref. 1a; (c) Ref. 1e.
5. (a) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857–2870; (b) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479–487; (c) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533–2545; (d) Rossi, R.; Bellina, F.; Biagetti, M; Catanese, A.; Mannina, L. *Tetrahedron Lett*. **2000**, *41*, 5281–5286; (e) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1163–1172; (f) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7799–7802; (g) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7599–7602; (h) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 3017–3020; (i) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135–156.
6. Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749–1752.
7. For previous syntheses of unsymmetrically substituted 3,4-dialkyl-2(5*H*)-furanones, see: (a) Ref. 1c; (b) Ref. 1d; (c) Ref. 1e; (d) Ref. 1h; (e) Ref. 1l; (f) Ref. 1m; (e) Ref. 1n.
8. For some relevant examples of regioselective palladium-catalyzed reactions involving $C_{sp}{}^2$-hybridized organic dihalides that have two identical halogen atoms in different structural environments, see: (a) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem*. **2000**, *65*, 337–342; (b) Ref. 6; (c) Bach, T.; Krüger, L. *Eur. J. Org. Chem*. **1999**, 2045–2057; (d) Rossi, R.; Bellina, F.; Carpita, A. *Recent Res. Devel. Synth. Org. Chem*. **1998**, *1*, 47–75 and references cited therein; (e) Rossi, R.; Bellina, F. *Org. Prep. Proced. Int*. **1997**, *29*, 137–176 and references cited therein; (f) Shen, W.; Wang, L. *J. Org. Chem*. **1999**, *64*, 8873–8879; (g) Langli, G.; Gundersen, L.-L.; Rise, F. *Tetrahedron* **1996**, *52*, 5625–5638; (h) Wang, L.; Shen, W. *Tetrahedron Lett*. **1998**, *39*, 7625–7628; (i) Trauner, H.; Le Floch, P.; Lefour, J.-M.; Ricard, L.; Mathey, F. *Synthesis* **1995**, 717–726; (j) Wang, D.; Haseltine, J. *J. Heterocyclic Chem*. **1994**, *31*, 1637–1639.
9. A range of 9-alkyl-9-borabicyclo[3.3.1]nonanes **8** were prepared, and used in situ, from the corresponding 1-alkenes and 9-borabicyclo[3.3.1]nonane.
10. The alkylboronic acids **9** used in this study, save butylboronic acid **9d** which was commercially available, were prepared by treatment of the corresponding 1-alkenes with 1.05 equiv. of 1,3,2-benzodioxaborole (catecholborane) at 100°C for 2.5–3 h, followed by hydrolysis at 0°C of the crude 2-alkyl-1,3,2-benzodioxaboroles so obtained. It must be noted that, since dry *n*-alkylboronic acids undergo atmospheric oxidation to give products contaminated with boric acid [Snyder, H. R.; Kuck, J. A.; Johnson, J. R. *J. Am. Chem. Soc*. **1938**, *60*, 105–111; Torssell, K.; Larson, E. N. V. *Acta Chem. Scand*. **1957**, *11*, 404–405], compounds **9** were freshly prepared and maintained under an atmosphere of nitrogen or argon.
11. For Suzuki reactions carried out under similar experi-

mental conditions, see: (a) Gillmann, T.; Weeber, T. *Synlett* **1994**, 649–650; (b) Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 5034–5036.

12. All new compounds were obtained in analytically pure form. Selected spectral properties of compounds **7a–d** are as follows. Compound **7a**: MS, m/z (%): 276 (2), 274 (2), 178 (35), 176 (38), 95 (66), 57 (73), 41 (100). IR (film): 1774, 1642, 1444, 1346, 1150, 1026, 985, 756, 723 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.76 (2H, s, H-5), 2.49 (2H, t, $J=7.8$ Hz, H-4a), 1.55 (2H, m, H-4b), 1.35 (2H, m, H-4c), 1.29 (4H, m, H-4d and H-4e), 1.28 (2H, m, H-4g), 1.26 (2H, m, H-4f), 0.87 ppm (3H, t, $J=6.9$ Hz, H-4h). Compound **7b**: MS, m/z (%): 305 (11), 303 (11), 247 (17), 245 (19), 59 (87), 57 (100), 41 (72). IR (film): 1774, 1641, 1460, 1444, 1362, 1199, 1028, 985, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.77 (2H, s, H-5), 3.33 (2H, t, $J=6.2$ Hz, H-4f), 2.51 (2H, t, $J=7.6$ Hz, H-4a), 1.67–1.35 (8H, m, H-4b, H-4c, H-4d and H-4e), 1.18 ppm (9H, s, t-C_4H_9). Compound **7c**: MS, m/z (%): 319 (1), 317 (1), 261 (29), 234 (32), 232 (32), 101 (36), 57 (100). IR (film): 1775, 1641, 1462, 1446, 1364, 1198, 1026, 986, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.77 (2H, s, H-5), 3.57 (1H, sext., $J=6.0$ Hz, H-4f), 2.51 (2H, t, $J=7.7$ Hz, H-4a), 1.65–1.32 (8H, m, H-4b, H-4c, H-4d and H-4e), 1.18 (9H, s, t-C_4H_9), 1.11 ppm (3H, t, $J=6.0$ Hz, H-4g). Compound **7d**: MS, m/z (%): 220 (4), 218 (4), 191 (40), 189 (40), 133 (60), 95 (73), 81 (100). IR (film): 1773, 1640, 1444, 1347, 1153, 1028, 986, 756, 722 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.76 (2H, s, H-5), 2.50 (2H, t, $J=7.5$ Hz, H-4a), 1.54 (2H, m, H-4b), 1.39 (2H, sext., $J=7.4$ Hz, H-4c), 0.94 ppm (3H, t, $J=7.4$ Hz, H-4d).
13. For the cleavage of a t-butyl ether under similar experimental conditions, see: Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116–1118.
14. Selected spectral properties of **12** are as follows: MS, m/z (%): 212 (1), 197 (19), 165 (25), 125 (100), 112 (66), 95 (48), 81 (29). IR (film): 3445, 1748, 1674, 1451, 1341, 1130, 1083, 760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.56 (2H, q, $J=1.8$ Hz, H-5), 3.68 (1H, sext., $J=5.5$ Hz, H-4f), 2.32 (2H, t, $J=7.3$ Hz, H-4a), 2.12–2.07 (1H, br s, OH), 1.71 (3H, t, $J=1.8$ Hz, H-3a), 1.52–1.35 (8H, m, H-4bn H-4c, H-4d and H-4e), 1.19 ppm (3H, t, $J=6.3$ Hz, H-4g). ^{13}C NMR ($CDCl_3$): δ 175.43, 160.52, 122.45, 71.29, 67.50, 38.79, 29.26, 27.41, 26.87, 25.21, 23.36, 8.33 ppm.