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Selective Palladium-Mediated Synthesis of Racemic 4,5-Disubstituted 5*H*-Furan-2-ones from 3-Ynoic Acids and Organic Halides

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Abstract: Racemic 4,5-disubstitued 5*H*-furan-2-ones have been selectively synthesized by addition of 1.2-1.6 equiv of aryl, alkenyl or 1-alkynyl halides and catalytic amounts of $Pd(OAc)_2$ and a soft ligand such as tri-2-furylphosphine or triphenylarsine to the reaction mixtures obtained by treatment of 3-ynoic acids with 1.1 equiv of *t*-BuOK in DMSO at 20 °C.

5*H*-Furan-2-ones include several biologically important natural products[1] and are useful synthetic intermediates.[2] Therefore, several methods have been reported in the literature for the synthesis of these substances.[3,4] Among these methods it is worthy of mention, owing to its simplicity and efficiency, that which involves a Pd-mediated hydrocarbonylation of propargyl mesylates followed by an Ag-catalyzed cyclization of the resultant allenic acids.[4a] Interestingly, this method allows the preparation of enantiomerically enriched 3,5-disubstituted 5*H*-furan-2-ones from propargyl mesylates having high enantiomeric excess, but it is unsuitable for the synthesis of 5*H*-furan-2-ones substituted at position 4.

In the context of our studies on the synthesis of 5-membered unsaturated lactone derivatives by intramolecular addition of carboxylic acids to alkynes in the presence of Pd or Ag catalysts,[5,6] recently we developed a new simple method for the selective synthesis of racemic 4,5-disubstituted 5*H*-furan-2-ones, **3**, starting from 3-ynoic acids **1** and organic halides **2** such as (hetero)aryl bromides or iodides, alkenyl bromides or 1-alkynyl bromides. We now wish to describe this new synthetic procedure as well as to outline its limitations. In particular, we found that sequential addition of a catalyst system constituted of 5 mol % $Pd(OAc)_2$ and 10 mol % tri-2-furylphosphine or triphenylarsine and 1.2-1.6 equiv of an organic halide **2** to the reaction mixture obtained by stirring 1 equiv of a 3-ynoic acid **1** with a suspension of 1.1 equiv of *t*-BuOK in DMSO at 20 °C for 0.5 h under argon, followed by stirring the resultant reaction mixture at 20 -70 °C for 16-48 h, provided a compound **3** in 15-76 % isolated yield (Eq 1).

Interestingly, compounds **3** so prepared proved to be not contaminated by detectable amounts of the corresponding 4,5-disubstituted 3*H*-furan-2-ones. The results obtained in the synthesis of several compounds of general formula **3** are summarized in the Table. As shown from the results of entries 1 and 2 of this table, tri-2-furylphosphine or triphenylarsine could be used as ligands, but tri-2-furylphosphine gave better results as

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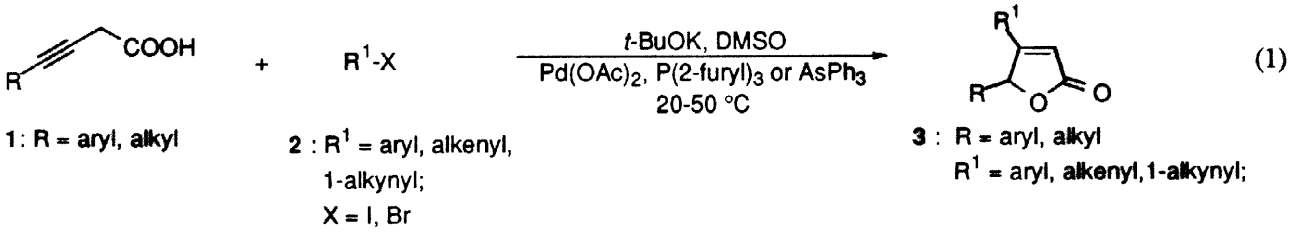
regards either the yield or the reaction time. The results reported in this table also show that the yields of the reactions affording 5-alkyl-4-aryl-5*H*-furan-2-ones (entries 1-4 and 6) were satisfactory and significantly higher than those of the reactions which provided either a typical 5-alkyl-4-alkenyl-5*H*-furan-2-one (entry 5) or a 5-alkyl-4-(1-alkynyl)-5*H*-furan-2-one such as **3g** (entry 9).



It must also be noted that the crude reaction mixture, which was obtained from the Pd-catalyzed reaction between **1a** and **2f** (entry 9), contained compound **3g** contaminated by significant amounts of two other products the carbon skeleton of which derived only from **2f**. One of these products was 6,8-tetradecadiyne, **4**.

Table. Palladium-catalyzed synthesis of 4,5-disubstituted 5*H*-furan-2-ones, **3**, starting from 3-ynoic acids, **1**, and organic halides, **2**.

Entry	3-Ynoic acid		Organic halide			Ligand	Reaction conditions	Product			Isolated yield
	1	R	2	R^1	X		(h / °C)	3	R	R^1	(%)
1[b)]	**1a**	CH_3	**2a**	C_6H_5	I	P(2-furyl)3	16 / 20	**3a**	CH_3	C_6H_5	65
2	**1a**	CH_3	**2a**	C_6H_5	I	$AsPh_3$	24 / 20	**3a**	CH_3	C_6H_5	46
3	**1a**	CH_3	**2b**	C_6H_5	Br	P(2-furyl)3	16 / 70	**3a**	CH_3	C_6H_5	58
4	**1b**	C_3H_7	**2c**	2-thienyl	I	P(2-furyl)3	22 / 20	**3b**	C_3H_7	2-thienyl	76
5	**1b**	C_3H_7	**2d**	$H_3C-\overset{I}{C}=CH_2$	Br	P(2-furyl)3	16 / 20 then 6 / 50	**3c**	C_3H_7	$H_3C-\overset{I}{C}=CH_2$	29
6	**1a**	CH_3	**2e**	$2,4\text{-}Cl_2C_6H_3$	I	P(2-furyl)3	16 / 20	**3d**	CH_3	$2,4\text{-}Cl_2C_6H_3$	55
7	**1c**[c)]	C_6H_5	**2a**	C_6H_5	I	P(2-furyl)3	48 / 20	**3e**	C_6H_5	C_6H_5	22
8	**1c**[c)]	C_6H_5	**2e**	$2,4\text{-}Cl_2C_6H_3$	I	P(2-furyl)3	23 / 20	**3f**	C_6H_5	$2,4\text{-}Cl_2C_6H_3$	18
9	**1a**	CH_3	**2f**	$C_5H_{11}-C\equiv C-$	Br	P(2-furyl)3	6.5 / 50	**3g**	CH_3	$C_5H_{11}-C\equiv C-$	15
10	**1d**	H	**2a**	C_6H_5	I	P(2-furyl)3	22 / 20	**3h**	H	C_6H_5	-----

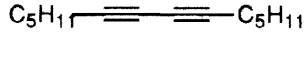
a) Unless otherwise reported these reactions were carried out using a molar ratio **2** : **1** = 1.6; b) The molar ratio **2** : **1** used in this reaction was 1.2; c) Compound **1c** was contaminated by *ca.* 30 % of 4-phenyl-2,3-butadienoic acid.

On the other hand, when it was attempted to increase the yield of **3g** by using 1-iodo-1-heptyne instead of 1-bromo-1-heptyne, **2f**, the Pd-catalyzed reaction provided compound **4** as the only reaction product. This diyne very likely derived from a Pd-catalyzed reductive coupling of the 1-halo-1-alkyne.

Unexpectedly, rather low yields were obtained in the synthesis of compounds **3e** and **3f** starting from 4-phenyl-3-butynoic acid **1c**, which was contaminated by *ca.* 30 % of 4-phenyl-2,3-butadienoic acid, and **2a** and **2e**, respectively (entries 7 and 8).

Finally, it is also worthy of mention that an attempt to extend our procedure for the synthesis of 4,5-disubstituted 5*H*-furan-2-ones to the preparation of a typical 4-aryl-5*H*-furan-2-one starting from 3-butynoic acid, **1d**, and an aryl iodide such as **2a**, proved to be unsuccessful (entry 10).[8] In fact, the crude reaction mixture did not contain even traces of the desired product, **3h**. Attempts to synthesize **3h** using **5** in place of **1d**

also failed. The carboxylate of **5** is easily prepared by base-catalyzed isomerization of **1d**.[9] Nevertheless, a 4-(1-alkynyl) substituted 5*H*-furan-2-one, *i.e.* compound **8**, was synthesized, although in modest yield (28 %), by treatment of 4-bromo-5*H*-furan-2-one, **7**, which is easily available from tetronic acid **6**[10] with 1.2 equiv of 1-hexynylzinc chloride in THF at 45 °C for 6 h, in the presence of 5 mol % $Pd(PPh_3)_4$.[11-13]



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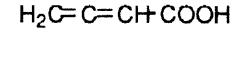
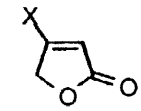


5



6 : X = OH
7 : X = Br
8 : X = C_4H_9-C≡C—

In conclusion, we have developed a simple catalytic procedure which allows the selective preparation of 5-alkyl-4-aryl-5*H*-furan-2-ones **3**, in satisfactory yields. Unfortunately, the yields of the desired furanones are rather low either when the organic halides used in this procedure are alkenyl or 1-alkynyl bromides or when the 3-ynoic acid used is 4-phenyl-3-butynoic acid **1c**. Disappointingly, this new synthetic method can not be used to prepare 4-substituted 5*H*-furan-2-ones. As to the reaction mechanism of the Pd-catalyzed synthesis of compounds **3**, very likely it involves an attack of the carboxylate anions generated from **1** onto the triple carbon-carbon bond of these ynoic acids which is electrophilically activated by complexation to the Pd(II) species derived from oxidative addition of the organic halides **2** to a Pd(0) species. Reductive elimination from the resulting σ–bonded intermediates leads to 3*H*-furan-2-ones, which undergo a base-catalyzed isomerization to the corresponding 5*H*-furan-2-ones.

Biological tests to evaluate the fungicidal activity of compounds **3**, which have been synthesized according to this new catalytic procedure, are currently underway.

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7. All the new compounds in this study gave satisfactory spectral and microanalytical data. **5*H*-Furan-2-ones 3a** and **3e** are known compounds and their physical and spectral properties were in agreement with those reported in the literature [**3a**: Kita, Y.; Sekihachi, J.; Hayashi, Y.; Da, Y. Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108-1112]; [**3e**: Schrader, L. *Tetrahedron Lett.* **1971**, 2993-2996]. **Some spectral properties of compounds 3b-3d, 3f** and **3g** are as follows. **3b**: MS, *m/z* (%): 208 (26), 166 (100), 137 (78); 109 (90), 65 (20); IR (film): 1746, 1613, 1164, 997, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 0.92 (t, 3H, J = 7.5 Hz), 1.46 (m, 2H), 1.68 (ddm, 1H, J = - 18.6 and 8.0 Hz), 2.08 (ddm, 1H, J = - 18.6 and 8.0 Hz), 5.34 (ddd, 1H, J = 8.0, 2.1 and 1.3 Hz), 6.11 (d, 1H, J = 1.3 Hz), 7.13 (dd, 1H, J = 4.9 and 3.6 Hz), 7.29 (dd, 1H, J = 3.6 and 0.8 Hz), 7.54 ppm (dd, 1H, J = 4.9 and 0.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.62, 17.64, 36.25, 82.02, 112.17, 128.42, 128.86, 132.90, 132.90, 160.49, 172.56 ppm. **3c**: MS, *m/z* (%): 166 (1), 124 (100), 123 (40), 95 (50), 67 (59); IR (film): 1762, 1757, 1752, 1747, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 0.90 (t, 3H, J = 7.5 Hz), 1.38 (m, 2H), 1.54 (m, 1H), 1.96 (m, 1H), 1.98 (dd, 3H, J = 1.5 and 0.8 Hz), 5.18 (ddd, 1H, J = 8.0, 2.8 and 1.5 Hz), 5.24 (q, 1H, J = 0.8 Hz), 5.38 (q, 1H, J = 1.5 Hz), 5.88 ppm (d, 1H, J = 1.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.62, 17.75, 20.65, 36.28, 81.97, 115.17, 120.46, 135.35, 167.53, 172.91 ppm. **3d**: m.p. 98-100 °C; MS, *m/z* (%): 244 (13), 242 (22), 181 (23), 179 (70), 43 (100); IR (KBr): 1741, 1622, 944, 875, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.39 (d, 3H, J = 6.7 Hz), 5.69 (qd, 1H, J = 6.7 and 1.6 Hz), 6.35 (d, 1H, J = 1.6 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.36 (dd, 1H, J = 8.4 and 2.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 18.66, 79.73, 119.59, 127.79, 128.32, 130.56, 130.91, 133.58, 136.98, 165.93, 172.91 ppm. **3f**: MS, *m/z* (%): 304 (8), 241 (12), 170 (15), 105 (100), 77 (37); IR (film): 1752, 1625, 1019, 870, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.48 (br s, 1H), 6.57 (br s, 1H), 7.00 - 7.50 ppm (m, 8H). **3g**: MS, *m/z* (%): 192 (1), 149 (33), 105 (56), 91 (100); IR (film): 1767, 1612, 1282, 1161, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.92 (t, 3H, J = 7.0 Hz), 1.20 - 1.70 (br m, 6H), 1.50 (d, 3H, J = 6.7 Hz), 2.47 (t, 2H, J = 6.9 Hz), 4.96 (q, 1H, J = 6.7 Hz), 6.02 ppm (s, 1H).
8. For other Pd-catalyzed cyclization processes involving 3-ynoic acids in which it was observed that 3-butynoic acid, **1d**, did not give the desired cyclization products, see: *(a)* Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753-2754; *(b)* Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254-2255.
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11. Some spectral properties of compound **8** are as follows. MS, *m/z* (%): 164 (14), 135 (15), 119 (21) 105 (80), 91 (100); IR (film): 1778, 1752, 1610, 1293, 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, 3H, J = 7.0 Hz), 1.30 - 1.55 (m, 4H), 2.39 (t, 2H, J = 6.9 Hz), 1.47 (d, 2H, J = 1.8 Hz), 6.02 ppm (s, 1H).
12. For some examples of Pd-catalyzed cross-coupling reactions between compound **7** and homoallylzinc halides, see: Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5225-5227.
13. It should be noted that a similar reaction between 4-(trifluoromethanesulfonyloxy)-5*H*-furan-2-one [Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489-5494] and 1.2 equiv of 1-octynylzinc chloride in THF at 20 °C for 1.5 h, in the presence of 5 mol % $Pd(PPh_3)_4$, provided 4-(1-octynyl)-5*H*-furan-2-one in 19 % isolated yield. Moreover, a low yield (17 %) of this same compound was also obtained by reaction of 4-(trifluoromethanesulfonyloxy)-5*H*-furan-2-one with 1.2 equiv of 1-octyne in DMF at room temperature for 4 h in the presence of 2.4 equiv of Et_3N, 10 mol % $Pd(PPh_3)_4$ and 20 mol % CuI.