Pergamon

Tetrahedron Letters 41 (2000) 5281–5286

TETRAHEDRON
LETTERS

Palladium-catalyzed synthesis of stereodefined 3-[(1,1-unsymmetrically disubstituted)methylidene]isobenzofuran-1(3*H*)-ones and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]furan-2(5*H*)-ones

Renzo Rossi,[a,*] Fabio Bellina,[a] Matteo Biagetti,[a] Antonella Catanese[a] and Luisa Mannina[b]

[a]*Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, I-56126 Pisa, Italy*
[b]*Corso di Laurea in Scienze Ambientali, Università del Molise, Via Mazzini 8, I-86170 Isernia, Italy*

Received 2 March 2000; accepted 16 May 2000

Abstract

Treatment of (hetero)aryl halides with 2-(1-alkynyl)benzoic acids or (*Z*)-2-en-4-ynoic acids in the presence of K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$ provides reaction mixtures in which stereodefined 3-[(1,1-unsymetrically disubstituted)methylidene]isobenzofuran-1(3*H*)-ones and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]furan-2(5*H*)-ones, respectively, are the major products. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium and reactions; isobenzofuranones; furanones; alkynes.

In recent years considerable attention has been devoted to the synthesis of natural and unnatural oxygen-containing heterocycles by protocols which involve transition metal-catalyzed intramolecular addition reactions of carboxylic acids to alkynes.[1]

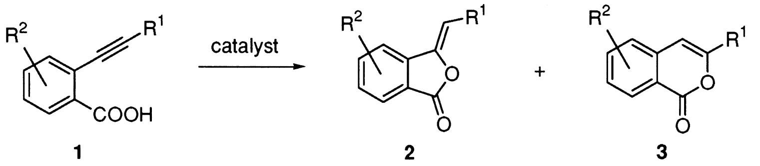
As part of our ongoing interest in this field,[2] we recently described a new and efficient procedure for the regioselective synthesis of natural and unnatural (*Z*)-3-(1-alkylidene)isobenzofuran-1(3*H*)-ones **2** and 3-substituted isocoumarins **3**, which involves the transition metal-catalyzed cyclization reaction of readily prepared 2-(1-alkynyl)benzoic acids **1** (Scheme 1).[2f]

More recently, in a continuation of these investigations, we found that treatment of 2-(1-alkynyl)-benzoic acids of general formula **4**[2f] with 1.2 equiv. of (hetero)aryl halides **5** in degassed acetonitrile at 70°C under an argon atmosphere, in the presence of 4 equiv. of K_2CO_3 and 5 mol% $Pd(PPh_3)_4$, provides mixtures of 3-substituted 4-(hetero)arylisocoumarins **6**[3] and stereoisomerically pure 3-[(1,1-unsymmetrically disubstituted)methylidene]isobenzofuran-1(3*H*)-ones **7** in high yields, in which these last compounds are the major products (Table 1).[4]

---

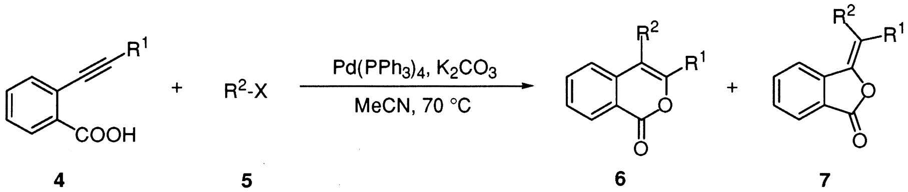
[*] Corresponding author. Tel: +39 50918214; fax: +39 50918260; e-mail: rossi@dcci.unipi.it

PII: S0040-4039(00)00806-6



Scheme 1.

Table 1
Palladium-catalyzed synthesis of compounds **6** and **7**$^{(a)}$

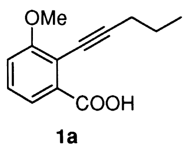


Entry	Reagents					Reaction	Products			
	4	R^1	**5**	R^2	X	time (h)	**6** + **7**	**6**/**7** molar ratio$^{(b)}$	Yield (%) of **6**	Yield (%) of **7**
1	**4a**	C_3H_7	**5a**	C_6H_5	I	5.5	**6a** + **7a**	11/89	9	76
2	**4a**	C_3H_7	**5b**	2-thienyl	I	6.5	**6b** + **7b**	13/87	3	48
3	**4a**	C_3H_7	**5c**	2,4-$Cl_2C_6H_3$	I	29.5	**6c** + **7c**	18/82	14	70
4	**4a**	C_3H_7	**5d**	5-pyrimidyl	Br	22.5	**6d** + **7d**	11/89	n.d.	77
5	**4b**	C_6H_5	**5e**	4-$MeOC_6H_4$	I	22.5	**6e** + **7e**	<4/>96	n.d.	90

(a) Reactions performed in acetonitrile in the presence of 4 equiv of K_2CO_3 and 5 mol % $Pd(PPh_3)_4$.
(b) Evaluated in the crude reaction mixture.

Compounds **7** were separated from the corresponding regioisomers **6** by MPLC on silica gel and were differentiated from these isocoumarins on the basis of their IR spectra. In fact, compounds **7** displayed a carbonyl absorption band at 1765–1778 cm^{-1}, whereas in compounds **6** the carbonyl absorption frequency was observed at 1722–1724 cm^{-1}. On the other hand, the stereochemistry of compounds **7** was assigned by NOESY experiments.

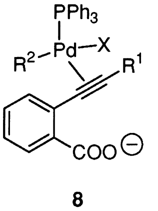
As shown in Table 1, this Pd-catalyzed process gave compounds **7** in moderate to good yields and its regioselectivity proved to be higher when the carboxylic acid, which was used as a starting material, was a 2-[1-(aryl)ethynyl]benzoic acid such as **4b**. Nevertheless, a typical 2-(1-alkynyl)-benzoic acid bearing a substituent in the 3-position such as compound **1a** failed to undergo this Pd-catalyzed reaction with (hetero)aryl halides.



1a

It must also be noted that, unlike that recently reported for the Pd-catalyzed cyclization reaction of 1,2-allenic carboxylic acids with aryl halides,[5] we observed that the presence of catalytic amounts of Ag_2CO_3 did not affect the Pd-catalyzed reaction of compounds **4** with (hetero)aryl halides **5**. In fact, the regioselectivity and the yields of the reactions performed in the presence of 5 mol% $Pd(PPh_3)_4$ and 5 mol% Ag_2CO_3 were found to be very similar to those observed for the same reactions which were carried out in the absence of this silver salt.

As far as the mechanism of this Pd-catalyzed process is concerned, on the basis of previous work on Pd-catalyzed reactions between aryl halides and carboxylic acids which contain an alkynyl moiety[2a,2c,6] we can propose that it involves the following reaction sequence: (1) oxidative addition of the (hetero)aryl halide **5** to Pd(0); (2) coordination of the so formed Pd(II) complex to the carboxylate anion derived from **4**; (3) intramolecular oxypalladation of the resulting complex **8**; and (4) reductive elimination of Pd(0) and compounds **6** and **7**.

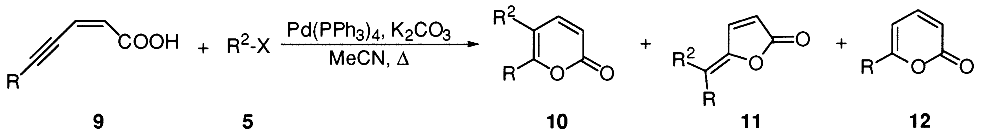


8

We also found that a process which was similar to that employed for the synthesis of compounds **6** and **7** occurred when easily prepared (*Z*)-2-en-4-ynoic acids **9**[7] were reacted with (hetero)aryl halides **5** in acetonitrile at 70–85°C in the presence of 4 equiv. of K_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$. In fact, in the case of (*Z*)-2-alken-4-ynoic acids such as **9a** (entries 1 and 2, Table 2) these reactions provided, although in modest yields, mixtures of 6-substituted 5-aryl-2*H*-pyran-2-ones

Table 2

Palladium-catalyzed synthesis of compounds **10** and **11** and **12**[(a)]



Entry	Reagents					Reaction conditions (h/°C)	Products			
	10	R	**5**	R^2	X		**10+11+12**	**10/11/12** molar ratio	Yield (%) of **10**	Yield (%) of **11**
1	**9a**	C_4H_9	**5e**	$4\text{-}MeOC_6H_4$	I	23.5/70	**10a+11a+12a**	11/76/13[(b)]	5	38
2	**9a**	C_4H_9	**5f**	3-methyl-6-pyridyl	Br	22.0/82	**10b + 11b**	12/88[(b)]	7	34
3	**9b**	C_6H_5	**5c**	$2,4\text{-}Cl_2C_6H_3$	I	22.5/70	**11c + 12b**	47/53[(c)]	---	26[(d)]

(a) Reactions performed in acetonitrile in the presence of 4 equiv of K_2CO_3 and 5 mol % $Pd(PPh_3)_4$.

(b) This molar ratio was evaluated in the crude reaction mixture.

(c) Evaluated on the basis of the amounts of **11c** and **12b** which were isolated by MPLC of the crude reaction mixture on silica gel.

(d) A 30 % yield of compound **12b** was also isolated.

10, and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]furan-2(5*H*)-ones **11**, in which these last compounds, which were isolated as single stereoisomers, were the major products. On the other hand, the Pd-catalyzed reaction between aryl halide **5c** and a typical (*Z*)-5-aryl-2-buten-4-ynoic acid, i.e. **9b**, gave a mixture in which the stereoisomerically pure 5-ylidenefuran-2(5*H*)-one **11c** and the 6-substituted 2-pyrone **12b** were the sole reaction products (entry 3, Table 2). These compounds were isolated in 26 and 30% yield, respectively. Interestingly, a 6-substituted 2-pyrone, which derived from the Pd-catalyzed heteroannulation reaction of the corresponding (*Z*)-2-en-4-ynoic acid, was also obtained from the Pd-catalyzed reaction between **9a** and **5e** (entry 1, Table 2).

The products of the Pd-catalyzed coupling reactions of (*Z*)-2-en-4-ynoic acids **9** with (hetero)-aryl halides were separated by MPLC on silica gel and well differentiated by NMR analysis.[8] In fact, either in the 5,6-disubstituted 2*H*-pyran-2-ones **10** or in compounds **12** the value of the $^3J_{H3-H4}$ coupling constant was in the range 9.4–10.0 Hz,[9] whereas stereodefined 5-ylidenefuran-2(5*H*)-ones **11** displayed values of the $^3J_{H2-H3}$ coupling constant in the range 5.3–5.9 Hz.[10] On the other hand, the stereochemistry of these last compounds was assigned by NOESY experiments.

In conclusion, a useful and simple protocol for the Pd-catalyzed synthesis either of stereodefined 3-[(1,1-unsymmetrically disubstituted)methylidene]isobenzofuran-1(3*H*)-ones or stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]furan-2(5*H*)-ones has been developed. Studies are in progress on the development of a new and efficient procedure for selective synthesis of the regioisomers of these compounds, i.e. 3,4-unsymmetrically disubstituted isocoumarins **6** and 5,6-unsymmetrically disubstituted 2*H*-pyran-2-ones **10**, respectively.

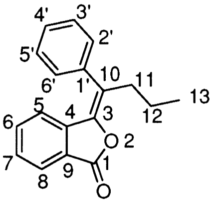
Acknowledgements

We gratefully acknowledge the financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the University of Pisa.

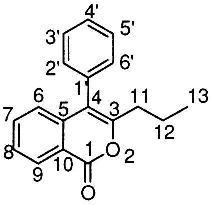
References

1. For leading references, see: (a) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711–3716; (b) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871–872; (c) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121–128; (d) Kotora, M.; Negishi, E. *Tetrahedron* **1997**, *53*, 6707–6738, and references cited therein; (e) Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561–568; (f) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145–1148.
2. (a) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135–156; (b) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017–3020; (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599–7602; (d) Rossi, R.; Bellina, F.; Biagetti, M., Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799–7802; (e) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479–488; (f) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533–2545.
3. For the synthesis of 3,4-disubstituted isocoumarins, see: (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. *J. Org. Chem.* **1995**, *60*, 3270–3271; (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770–8779.
4. All new compounds were characterized by NMR and IR spectroscopy, mass spectrometry and elemental analysis. As an example the spectral data of compounds **7a** and **6a** are given. Compound **7a** ($R^1=C_3H_7$; $R^2=$ Ph) had: mp 95–97°C. MS, *m*/*z* (%): 265 (8), 264 (26), 235 (92), 207 (69), 178 (14), 91 (8), 51 (100). IR (KBr): ν 1772, 1057, 1030, 986, 766, 707, 693 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.87 (1H, d, $J=7.5$ Hz, H-8), 7.48 (2H, m, H-3′ and

H-5′), 7.46 (1H, m, H-4′), 7.38 (1H, ddd, J = 7.5, 7.3 and 0.8 Hz, H-7), 7.32 (2H, m, H-2′ and H-6′), 7.31 (1H, m, H-6), 6.45 (1H, d, J = 7.9 Hz, H-5), 2.75 (2H, t, J = 7.3 Hz, H-11), 1.49 (2H, m, sext, J = 7.3 Hz, H-12), 0.97 ppm (3H, t, J = 7.3 Hz, H-13). A NOESY experiment showed the presence of cross-peaks between the resonances of the following protons: H-5 and H-2′; H-5 and H-3′; H-6 and H-3′; H-6′ and H-11; H-6′ and H-12; H-6′ and H-13. ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.23 (C-1), 142.47 (C-3), 138.75 (C-4), 137.78 (C-1′), 133.78 (C-6), 129.24 (C-3′), 129.24 (C-5′), 129.10 (C-6′), 129.10 (C-2′), 129.10 (C-7), 128.51 (C-4′), 127.45 (C-10), 125.47 (C-9), 125.12 (C-8), 122.72 (C-5), 35.68 (C-11), 20.72 (C-12), 13.87 ppm (C-13). Compound **6a** ($R^1 = C_3H_7$; $R^2 = Ph$) had: mp 83–86°C. IR (KBr): ν 1722, 1637, 1100, 777, 767, 709, 687 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (1H, ddd, J = 7.9, 1.4 and 0.5 Hz, H-9), 7.58 (1H, ddd, J = 8.0, 7.2 and 1.4 Hz, H-7), 7.48 (2H, m, H-3′ and H-5′), 7.45 (1H, m, H-8), 7.43 (1H, m, H-4′), 7.25 (2H, m, H-2′ and H-6′), 6.94 (1H, ddd, J = 8.0, 1.4 and 0.5 Hz, H-6), 2.34 (2H, t, J = 7.5 Hz, H-11), 1.68 (2H, sext, J = 7.5 Hz, H-12), 0.86 ppm (3H, t, J = 7.5 Hz, H-13). A NOESY experiment showed the presence of cross-peaks between the resonances of the following protons: H-6 and H-2′; H-6′ and H-11; H-6′ and H-12; H-6′ and H-13. ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.79 (C-1), 154.97 (C-3), 138.83 (C-5), 134.49 (C-7), 134.38 (C-1′), 130.66 (C-2′), 130.66 (C-6′), 129.42 (C-9), 128.91 (C-3′), 128.91 (C-5′), 128.08 (C-4′), 127.38 (C-8), 124.75 (C-6), 120.05 (C-10), 116.39 (C-4), 33.23 (C-11), 20.97 (C-12), 13.63 ppm (C-13).



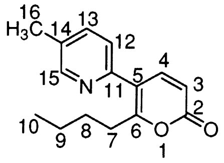
7a



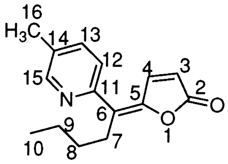
6a

5. Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387–6389.
6. (a) Arcadi, A.; Burini, A.; Cacchi, S.; Del Mastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976–982; (b) Boussy, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811–2814; (c) Boussy, D.; Gore, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129–3130; (d) Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254–2255; (e) Wu, M.-J.; Wei, L.-M.; Lin, C.-F. *10th Symposium on Organometallic Chemistry directed towards Organic Synthesis*; Versailles, France, 18–22 July 1999, Abstracts P-521.
7. These compounds were synthesized in 80–90% overall yield by reaction of methyl (*Z*)-3-bromopropenoate with 1.2 equiv. of a 1-alkyne in Et_3N at 20°C in the presence of 2 mol% $PdCl_2(PPh_3)_4$ and 4 mol% CuI, followed by saponification of the so obtained methyl (*Z*)-2-en-4-ynoates with 1 M LiOH at 20°C and acidification of the resulting lithium carboxylates.
8. Compounds **10**, **11** and **12** gave satisfactory IR, MS, NMR and analytical data. As an example the physical and spectral data of compounds **11b** and **10b** are given. Compound **11b** had: MS, *m*/*z* (%): 243 (17), 214 (16), 200 (100), 187 (28), 172 (35), 144 (26), 118 (16). IR (film): ν 1780, 1757, 1549, 1479, 1108, 888, 813 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (1H, d, J = 2.1 Hz, H-15), 7.84 (1H, d, J = 5.6 Hz, H-4), 7.57 (1H, dd, J = 8.0 and 2.1 Hz, H-13), 7.30 (1H, d, J = 8.0 Hz, H-12), 6.21 (1H, d, J = 5.6 Hz, H-3), 2.88 (2H, quint, J = 7.4 Hz, H-7), 2.39 (3H, s, H-16), 1.43 (2H, quint, J = 7.4 Hz, H-8) 1.35 (2H, sext, J = 7.4 Hz, H-9), 0.87 ppm (3H, t, J = 7.4 Hz, H-10). A NOESY experiment showed the presence of cross-peaks between the resonances of the following protons: H-4 and H-12, H-12 and H-7, H-12 and H-8, H-12 and H-9. ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.82 (C-2), 152.28 (C-11), 149.89 (C-15), 149.29 (C-5), 143.14 (C-4), 137.48 (C-13), 132.94 (C-14), 128.30 (C-6), 123.36 (C-12), 119.88 (C-3), 30.60 (C-8), 30.19 (C-7), 22.64 (C-9), 18.25 (C-16), 13.81 ppm (C-10). Compound **10b** had: MS, *m*/*z* (%): 243 (10), 214 (20), 201 (100), 186 (24), 158 (19), 130 (17), 77 (14). IR (film): ν 1735, 1566, 1547, 1088, 1071, 1015, 825 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.50 (1H, d, J = 2.1 Hz, H-15), 7.56 (1H, dd, J = 8.0 and 2.1 Hz, H-13), 7.55 (1H, d, J = 9.5 Hz, H-4), 7.21 (1H, d, J = 8.0 Hz, H-12), 6.26 (1H, d, J = 9.5 Hz, H-3), 2.66 (2H, t, J = 7.3 Hz, H-7), 2.83 (3H, s, H-16), 1.70 (2H, quint, J = 7.3 Hz, H-8), 1.31 (2H, sext, J = 7.3 Hz, H-9), 0.86 ppm (3H, t, J = 7.3 Hz, H-10). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.83 (C-6), 162.26 (C-2), 150.20 (C-15), 149.99 (C-11), 146.23 (C-4), 137.36

(C-13), 132.93 (C-14), 123.03 (C-12), 117.07 (C-5), 113.13 (C-3), 31.39 (C-7), 29.61 (C-8), 22.36 (C-9), 18.20 (C-16), 13.65 ppm (C-10).



10b



11b

9. For similar values of this coupling constant in 5-substituted and/or 5,6-disubstituted 2*H*-pyran-2-ones, see: (a) Pirkle, W. H.; Dines, M. *J. Heterocyclic Chem.* **1969**, *6*, 1–3; (b) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1998**, *54*, 13013–13022.
10. For similar values of this coupling constant in 5-ylidene-2(5*H*)-furanones, see: (a) Ref. 1e; (b) Rousset, M.; Abarbri, M.; Thibounet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* **1999**, *1*, 701–703.