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Synthesis of cinnamyl substituted dihydrofuranones by the Heck cross-coupling reaction

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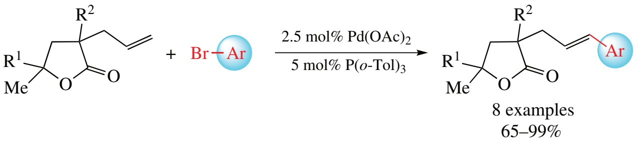
The Heck cross-coupling of 3-allyldihydrofuran-2(3*H*)-ones with aryl bromides [Pd(OAc)$_3$, P(*o*-Tol)$_3$] afforded the corresponding 3-cinnamyl derivatives. The structure of the products was confirmed by NMR spectroscopy, mass spectrometry and X-ray diffraction.



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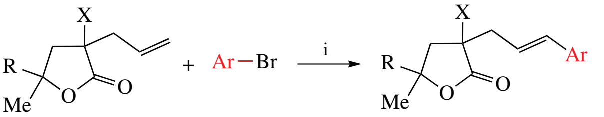
One of the unique methods in modern organic chemistry, allowing one to synthesize difficult-to-find chemical compounds, is the cross-coupling of alkenyl, alkynyl and halovinyl derivatives with different aryl halides.[1] The Heck reaction has a wide range of applications for the synthesis of functionally substituted hydrocarbons, polymer compounds, dyes and biologically active compounds.[2] However, compounds containing butanolide ring were not comprehensively studied in the Heck reaction, although butanolide moiety is a widespread pharmacophore fragment within natural compounds. Biological properties of lactone-containing terpenoids and alkaloids isolated from plant raw materials and various microorganisms were documented.[3–8] These studies stimulated further research in the field of lactone chemistry, *e.g*., an analogue of nemotin,[9] bicyclo-γ-lactones exhibiting antimicrobial properties[10] and antitumor activity,[11] bis-spiro-γ-lactones[12] and Nimbacin,[13,14] (–)-neopallavicin,[15] natural (±)cidarmicines A and B[16] were stereoselectively synthesized. Numerous preparations in practical medicine dealing with furan-2-one derivatives (pilocarpine, spironolactone, podophilox, drospiron, *etc*.) as active aglycons, make it obvious that studies of furan-2-one chemistry are topical.

Within our ongoing studies on furan-2-ones, we have shown that propynyl- and 2-chloropropenyl derivatives can be successfully used as starting materials in the Sonogashira and Suzuki–Miyaura reactions,[17,18] while furan-2-one moiety was tolerant to the catalysis conditions. The thus obtained furan-2-one–arylacetylene conjugates turned to be good inhibitors of alkaline phosphatases, being 14–80 times more active than the known preparations Levamisole and L-Phenylalanine.[17]

In view of the aforesaid, we herein prepared new furan-2-one derivatives of potent utility employing the Heck cross-coupling.[19–24] The optimization of the reaction conditions was carried out with model 3-allyl-5,5-dimethyldihydrofuran-2(3*H*)-one **1b** and methyl 4-bromobenzoate (Scheme 1, Table 1). The optimal catalytic system was found to be a convenient and effective combination of Pd(OAc)$_2$ and P(*o*-Tol)$_3$ (see Table 1, entry 9). The optimal ratios per one mole of the starting allyl derivatives **1a–d** (in DMF at 100 °C for 24 h) were as follows: 2.5 mol% Pd(OAc)$_2$, 5 mol% P(*o*-Tol)$_3$, 2.5 equiv. of aryl bromide, 3 equiv. of K$_2$CO$_3$. Then arylation of a series of compounds **1a–d** was carried out under optimal conditions (see Scheme 1).

The structure of the obtained compounds **2a–h** was determined by the ^{1}H, ^{13}C NMR spectroscopy, mass spectrometry and X-ray diffraction analysis. In addition, the counter-synthesis of compound **2e** was carried out (Scheme 2).

Structure of compound **2g** was ultimately established by X-ray diffraction (Figure 1).[†]



1a–d **2a–h**

ii **1a** R = Me, X = CO$_2$Et
→ **1b** R = Me, X = H
ii **1c** R = H, X = CO$_2$Et
→ **1d** R = X = H

	R	X	Ar	Yield (%)
a	Me	CO$_2$Et	Ph	67
b	Me	CO$_2$Et	4-MeO$_2$CC$_6$H$_4$	68
c	H	CO$_2$Et	4-MeO$_2$CC$_6$H$_4$	93
d	H	CO$_2$Et	3-F$_3$CC$_6$H$_4$	81
e	Me	H	Ph	65
f	Me	H	4-MeO$_2$CC$_6$H$_4$	99
g	H	H	4-MeO$_2$CC$_6$H$_4$	76
h	H	H	4-F$_3$CC$_6$H$_4$	74

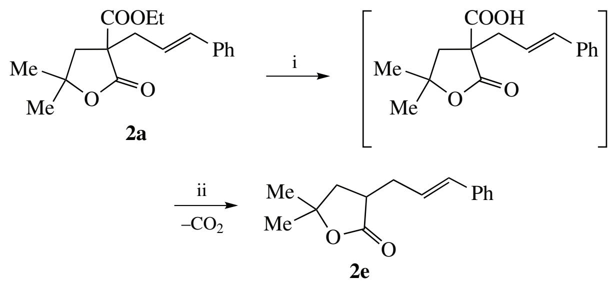
Scheme 1 *Reagents and conditions*: i, ArBr (2.5 equiv.), Pd(OAc)$_2$ (2.5 mol%), P(*o*-Tol)$_3$ (5 mol%), K$_2$CO$_3$ (3 equiv.), DMF, 100 °C, 24 h; ii, NaOH (3.5 equiv.), H$_2$O, Δ.

[†] *Crystal data for* **2g**. C$_{16}$H$_{18}$O$_4$, *M* = 274.30, monoclinic, space group *P*2$_1$/*c*, *a* = 5.0081(14), *b* = 29.157(8) and *c* = 9.843(3) Å, *β* = 98.930(8)°, *V* = 1419.9 (7) Å^3, *T* = 123 K, *Z* = 4, d_{calc} = 1.283 g cm^{-3}, *μ* = 0.092 mm^{-1}, *F*(000) = 584.0, the final *R* = 0.0584, *wR*$_2$ = 0.1784 and *S* = 1.020. The measurements were performed on a Bruker Kappa Apex II diffractometer. Since in the molecule of **2g**, the C^2 and C^4 atoms have asymmetric centers, it crystallizes in the chiral space group *P*2$_1$/*c*. Since this compound is established as a two-component stereoisomeric pair, the crystal is a mixture of (*R*,*S*)- and (*S*,*R*)-enantiomers in a ratio of 0.8 : 0.2.

CCDC 1978919 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 1 Optimization of conditions for the Heck coupling between 3-allyl-5,5-dimethyldihydrofuran-2(3*H*)-one **1b** and methyl 4-bromobenzoate (ArBr).

Entry	ArBr (equiv.)	[Pd] (mol%)	Base (equiv.)	Ligand (mol%)	Solvent	*T*/°C	*t*/h	Yield of **2f** (%)
1	1.5	Pd(OAc)$_2$ (1)	Et$_3$N (2)	PPh$_3$ (2)	DMF	80	72	mix
2	2.5	Pd(OAc)$_2$ (3)	Et$_3$N (2)	PPh$_3$ (6)	DMF	80	18	mix
3	1.5	PdCl$_2$ (5)	K$_2$CO$_3$ (2)	PPh$_3$ (2)	DMF	80	24	60
4	1.5	PdCl$_2$ (5)	K$_2$CO$_3$ (2)	BINAP (5)	MeCN	80	24	43
5	1.2	Pd(OAc)$_2$ (5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	100	24	91
6	2.5	Pd(OAc)$_2$ (5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	100	20	89
7	1.5	Pd(OAc)$_2$ (5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	80	24	94
8	2.5	Pd(OAc)$_2$ (2.5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	80	24	93
9	2.5	Pd(OAc)$_2$ (2.5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	100	24	99
10	2.5	Pd(OAc)$_2$ (2.5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	MeCN	80	24	92
11	2.5	PdCl$_2$ (2.5)	Na$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	100	24	94
12	2.5	PdCl$_2$ (2.5)	Na$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	MeCN	100	20	85
13	2.5	Pd(PPh$_3$)$_4$ (2.5)	K$_2$CO$_3$ (3)	–	DMF	100	20	95
14	2.5	Pd(PPh$_3$)$_4$ (2.5)	K$_2$CO$_3$ (3)	–	DMF	80	20	88
15	2.5	Pd(PPh$_3$)$_4$ (2.5)	K$_2$CO$_3$ (3)	–	MeCN	100	20	87
16	1.2	Pd(OAc)$_2$ (5)	K$_2$CO$_3$ (3)	P(*o*-Tol)$_3$ (5)	DMF	100	24	91



Scheme 2 *Reagents and conditions*: i, NaOH, then HCl; ii, Δ.

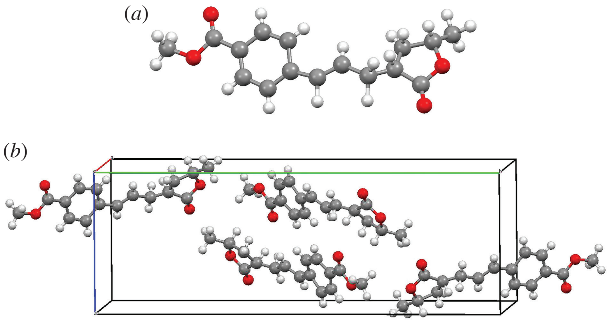


Figure 1 (*a*) Molecular structure of crystalline compound **2g** drawn at the 50% probability level; (*b*) three-dimensional packing of crystalline lattice of compound **2g**.

In summary, 3-allyldihydrofuran-2-ones can be successfully subjected to the Heck cross-coupling reactions with aryl bromides to afford the corresponding promising cinnamyl derivatives. The results obtained expand the range of substances that can potentially find applications in pharmacology and medicine.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.036.

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