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Synthesis of benzofurans via Pd^{2+}-catalyzed oxidative cyclization of 2-allylphenols

Alexander I. Roshchin, Sergey M. Kel'chevski, Nikolai A. Bumagin *

Department of Chemistry, M.V. Lomonosov Moscow State University, Moscow 119899, Russia

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Abstract

Substituted 2-methylbenzofurans were obtained from 2-allylphenols via Pd^{2+}-catalyzed oxidative cyclization using $Cu(OAc)_2$–LiCl as a reoxidant and wet DMF as a solvent. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: 2-Allylphenols; Catalysis; Benzofuranes; Isocoumarines; Palladium(II)

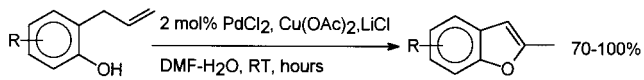
1. Introduction

Olefin π-complexes of divalent palladium are well known to react with nucleophilic reagents [1]. In the presence of suitable reoxidant the process can be made catalytic in palladium; this reaction, known as 'Wacker oxidation' [2], has significant value in organic chemistry [3]. Substrates, having both double bond and nucleophilic group in the same molecule, react in the intramolecular fashion, forming heterocycles [1,4]. Specifically, Murahashi et al. have discovered that Pd^{2+}-catalyzed oxidative cyclization of 2-allylphenol leads to bezofuran [5]; however, synthetic utility of this reaction has not been explored.

We report here that oxidative cyclization of 2-allylphenols can be performed easily and under mild conditions using palladium dichloride as a catalyst, $Cu(OAc)_2$–LiCl as a reoxidant, and aqueous dimetylformamide as a solvent. A number of functionalized 2-methylbezofurans were obtained in high yields.

2. Results and discussion

The influence of reaction conditions on product yield was first investigated with 2-allylphenol (Table 1). In dry DMF with 2 mol% $Pd(OAc)_2$ and excess $Cu(OAc)_2$ at 100°C this substrate forms 2-methylbenzofuran quite easily (entry 1). With 2 mol% $PdCl_2$ as a catalyst the reaction proceeds a little faster (entry 2), and, on addition of excess chloride (LiCl), can be performed at room temperature (r.t.) (entry 4), reduced form of copper being CuCl precipitate.



The reaction is further accelerated with moist dimethylformamide. This catalytic system (entry 5) turned out to be the most efficient and required only 25 min at ambient temperature for completion. It is worth noting here, that acceleration of palladium-catalyzed reactions in aqueous media was repeatedly observed and utilized [6]. Particularly in this case, possible explanation is that palladium atom of intermediate π-complex is more positively charged, making easier the nucleophilic attack. Nevertheless, neat water (a poor

* Corresponding author. Tel.: +7 095 9391383; e-mail: bna@bumagin.chem.msu.su

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Table 1
Pd^{2+}-catalyzed cyclization of 2-allylphenol to 2-methylbenzofuran

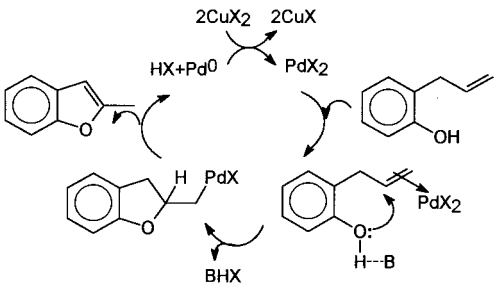
Entry	$PdCl_2$ (mol%)	$Cu(OAc)_2$ (eq)	LiCl (eq)	H_2O (% vol.)	T (°C)	Reaction time (min)	Yield[a] (%)
1	2[b]	3	—	—	100	120	92
2	2	3	—	—	100	60	100 (95)
3	2	3	1	—	25	180	45
4	2	3	3	—	25	110	90
5	2	3	3	15	25	25	95 (90)
6	2	3	3	100	25	180	0
7	2	$CuCl_2$, 3	LiOAc, 3	15	25	<60	100
8	0.5	3	3	—	100	<20	60
9	0.5	3	3	15	25	90	80
10	2	0.2	3	—	25	3 days	50

Eq, equivalents.
[a] GLC yield based on starting allylphenol; isolated yield in parentheses
[b] 2 mol% $Pd(OAc)_2$.

solvent for allylphenol) is unsuitable for the cyclization and gives rise only to resinous products (entry 6).

With reoxidant $CuCl_2$ the cyclization proceeds only in the presence of excess acetate (entry 7), so base is requisite for this reaction. The amount of palladium catalyst can decrease to 0.5 mol% at the cost of prolonged reaction time (entry 8) or elevated temperature (entry 9). When amount of copper is diminished to 0.2 equivalents, the oxidation becomes sluggish (entry 10, Table 1).

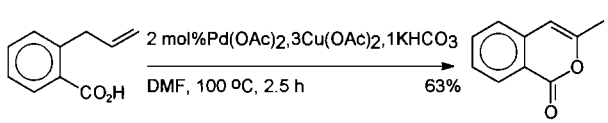
After initial optimization, the cyclization of a number of substituted 2-allylphenols was carried out; the results are presented in Table 2. Introduction of donor groups (methyl, acetamido, etc.) leads to slower reaction, but yields are still high (entries 1–4, Table 2). Influence of other substituents is more complicated. 2-Allyl-4-bromophenol reacts rapidly, although slower than parent 2-allylphenol (entry 5). Meanwhile, ethyl salicilate derivative requires several hours at high temperature and unprotected 3-allylsalicilic acid does not form any cyclic product at all (entry 6). 2-Allyl-4-nitrophenol also demands drastic conditions and, moreover, mainly forms six-membered chromene derivatives rather than benzofuran (entry 7, Table 2).



So, under the conditions, optimized for cyclization of 2-allylphenol, substituents of any sort decrease the reaction rate. One conceivable reason is that phenolic hydroxyl needs to be deprotonated to act as nucleophile towards olefin fragment, directly or through coordination to palladium (catalytic cycle of intramolecular nucleophilic addition is given on Scheme). In such a situation, donor groups lower acidity of phenol and make its deprotonation more difficult, whereas electron-withdrawing groups stabilize phenolate anion and decrease its nucleophility. Particular inertness of 3-allylsalicilic acid may be attributed to its chelating ability.

Predominant formation of six-membered rings in the case of nitro derivative is difficult for explanation so far. Competition of 5-*exo* and 6-*endo* cyclizations is not unusual for Pd^{2+}-catalyzed oxidation, but mechanistic reasons for this remain still unclear [5]. Methyl ether of 2-allylphenol undergoes usual intermolecular Wacker oxidation to methyl ketone, which is remarkably slower than cyclizations under our conditions (entry 8, Table 2).

This catalytic system can be extended on other substrates: for example 2-allylbenzoic acid [7] is readily transformed to 3-methyl-isochromen-1-one. Quite expectedly, with the less nucleophilic carboxylate group, the reaction requires high temperature. Cyclization proceeds smoothly in dry DMF; addition of water not only slows the reaction, but also favors formation of byproducts with five-membered ring (cf. ([7]b) and entry 7 in Table 2).

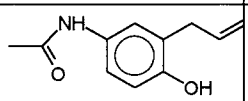
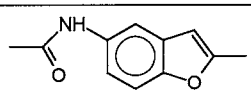
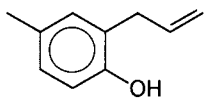
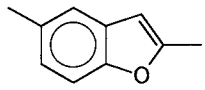
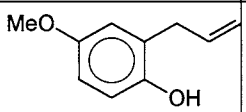
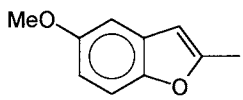
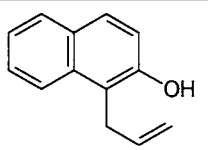
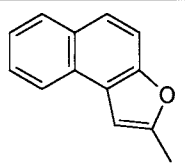
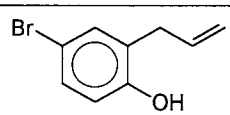
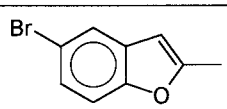
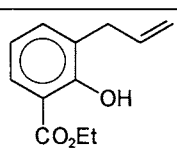
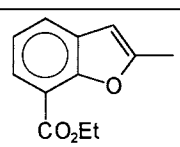
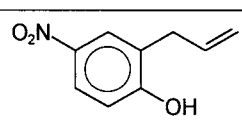
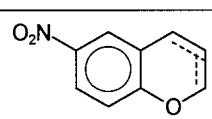
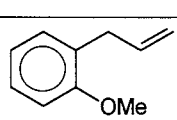
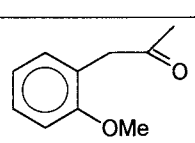


Further study of these and related Pd^{2+}-catalyzed heterocycle syntheses is under way in our group.

3. Experimental

Commercial 2-allylphenol was distilled before use. Other 2-allylphenols were obtained through standard procedure, including *o*-allylation of phenol and termic

Table 2
Synthesis of substituted benzofurans

entry	2-allylphenol	product	T, °C	time, h	yield, % (isolated)
1			25	4	92
2			25	10	95
3			25	5	90
4			25	10	85
5			25	0.5	83
6			100	6	73
7			100	1.5	50
8			100	3	40(GLC)

Claisen rearrangement of allylphenyl ether. 2-Allylbenzoic acid was obtained from 2-bromobenzoic acid through low-temperature lithiation.

Commercial DMF (Reakhim) was purified using standard techniques and stored over Molecular Sieve 4 Å. NMR spectra were recorded on Bruker AM-300 Spectrometer at 300 MHz.

3.1. Palladium(II)-catalyzed cyclization of 2-allylphenols to benzofurans (general procedure)

In a typical experiment to $Cu(OAc)_2 \cdot H_2O$ (3 mmol) in DMF (2.5 ml) were added 2-allylphenol (1.0 mmol), 0.3 ml 10 M LiCl (aq) and 0.2 ml 0.1 M $PdCl_2$ (aq). The suspension was stirred in air atmosphere at r.t. until all phenol is consumed (TLC, GLC) and poured into 50 ml of water, containing 5 ml of 25% ammonia. Benzofuran was extracted with 2×20 ml of petroleum ether or benzene, extract washed with 15% aqueous alkali and evaporated to give colorless to yellow oil. If required, this could be purified by means of flash column chromatography (silica gel, $CHCl_3$ or ether–hexane). Product yields are given in Table 2, ^{1}H-NMR spectra are shown in Table 3.

3.2. Cyclization of 2-allyl-4-nitrophenol

When subjected to cyclization as described above, this compound gives a complicated mixture of products in overall yield of 65%. GC–MS indicates main

Table 3
^{1}H-NMR spectra of products (300 MHz; chemical shifts, δ; J, Hz)

No. in Table 2 Substituent	Solvent	CH_3	H^3	Ar–H	Other	Ref.
1 5-AcNH	DMSO-d_6	2.42 s	6.52 s	7.30 d 1H $J = 1.4$, 7.37 d 1H $J = 8.8$ 7.84 s 1H	2.05 s CH_3CO 9.91 s NH	[10][a]
2 5-Me	$CDCl_3$	2.48 s	6.33 s	7.05 d 1H 7.33 m 2H	2.48 s $ArCH_3$	([11]a)
3 5-MeO	$CDCl_3$	2.48 s	6.34 s	6.82 d 1H 6.98 d 1H 7.30 s 1H	3.85 s O–CH_3	([11]b)
4 5,6-C_6H_4	$CDCl_3$	2.48 d $J = 1$	6.42 m	7.05–8.1 m 6H	—	([11]a)
5 5-Br	$CDCl_3$	2.49 s	6.35 s	7.31 m 2H 7.62 s 1H	—	—
6 7-EtO_2C	$CDCl_3$	3.00 s	6.41 q $J = 1.1$	7.23 q 1H $J = 8$ 7.64 dd 1H $J = 7.4$, 1.1 7.85 dd 1H $J = 7.7$, 1.4	1.9 t CH_2–CH_3 $J = 7.2$ 4.47 d O–CH_2 $J = 7.2$	—
7 6-nitro-[^{2}H]chromene	DMSO-d_6	—	—	6.88 d 1H $J = 8.7$ 7.95 d 1H $J = 2.8$ 7.98 dd 1H $J = 8.7$, 2.8 7.49 t 1H $J = 8.4$	5.00 dd 2H $J = 3.4$, 2.0 6.01 dt 1H $J = 10.1$, 3.4 6.61 dt 1H $J = 10.1$, 2.0	[8]
— 3-Methyl-isochromen-1-one	Acetone-d_6	2.24 s	6.43 s	7.77 t 1H $J = 8.6$ 7.85 d 1H $J = 7.7$ 8.13 d 1H $J = 8.0$	—	[9]

[a] Melting point 139°C (135–137°C [10]).

product (44% area ratio) with $m/e = 177$ along with several others (two more with $m/e = 177$, also 179 and 195).

Crystallization from methanol gives almost pure main product (30% on starting phenol), m.p. 123°C, ^{1}H-NMR is identical to that of 6-nitro-[^{2}H]chromene [8] (Table 3).

3.3. 3-Methylisochromen-1-one

A mixture of 2-allylbenzoic acid (0.162 g, 1.0 mmol), $KHCO_3$ (0.100 g, 1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.600 g), $Pd(OAc)_2$ (0.0052 g, 0.02 mmol) in 2 ml DMF was stirred at 100°C in air for 2 h. Then it was poured in 20 ml of water and extracted with ether. The extract was washed with aqueous K_2CO_3, dried over Na_2SO_4 end evaporated. The product was purified by flash column chromatography as described above. Yield 0.101 g (63%). ^{1}H-NMR spectrum is essentially identical to that known from literature [9] (Table 3).

If the reaction is carried out in the same manner in the presence of 5% of water, it gives 0.070g (43%) of an oil, ^{1}H-NMR of which indicates presence of 50% 3-methylisochromen-1-one (singlet at δ 6.43, =CH–), 30% 3-ethylidenphtalide (quadruplet at δ 5.86, =CH–Me) and 20% 3-vinylphtalide (doublets at δ 5.62 and 5.42, $=CH_2$).

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