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Synthesis of 3-Substituted Furans by Hydroformylation

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Abstract: A simple and novel method for the synthesis of 3-substituted furans by the hydroformylation of substituted propargylic alcohols is described using rhodium acetate and triphenylphosphine in dichloromethane. The hydroformylation reaction proceeds in a regioselective manner under mild reaction conditions. This novel methodology is versatile and can be applied to the synthesis of a variety of 3-aryl-substituted furans.

Keywords: hydroformylation, propargyl alcohols, rhodium, Sonogashira reaction, 3-substituted furans

Introduction

The furan ring is widely distributed as a key structural unit in many natural products,[1] some of which exhibit interesting biological activities. Furans have applications not only as pharmaceuticals,[2] but also as flavouring[3] and fragrance compounds.[4] Furthermore, substituted furans are useful and versatile synthetic intermediates for the preparation of a variety of heterocyclic and acyclic organic compounds.[5]

Furans substituted at the 3-position are generally important because they form the basis for the structures of several natural products.[1] Synthetic access to these compounds is not straightforward, due to difficulties encountered in the preparation of 3-furyl synthons.[6] In 1971, Botteghi et al.[7] reported that 3-substituted furans can be synthesized through the hydroformylation of allylic alcohols. This is the first method used for the synthesis of 3-substituted furans using hydroformylation reaction conditions.

There are few examples of the regioselective hydroformylation of alkynes to yield aldehydes.[8] Buchwald et al.[9] reported the first useful catalytic hydroformylation reactions of symmetrical and unsymmetrical alkynes using a rhodium catalyst. This reaction occurs under mild reaction conditions and leads to α,β-unsaturated aldehydes. The hydroformylation reaction can also be used to synthesize biologically important molecules, such as pyrroles. Although several methods for their synthesis have been reported in the literature, the first rhodium-catalyzed hydroformylation of β-alkynylamines to give β-substituted pyrroles was described by Jackson et al. in 1991.[10]

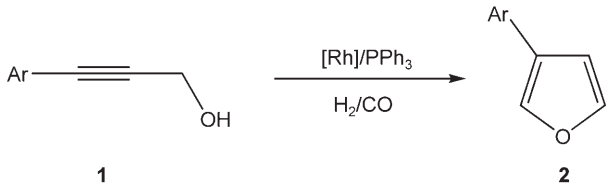
Despite the fascinating methods described in the literature, the preparation of 3-substituted furans remains an important synthetic goal for chemists due to their prominence in natural products chemistry.[11] Nevertheless, there is still a need to create simple synthetic routes for these five-membered ring heterocycles.

Results and Discussion

In this manuscript, we disclose the results of a novel rhodium-catalyzed hydroformylation reaction of propargylic alcohols **1** to form 3-aryl-substituted furans, **2**, in good yields. Neutral conditions are used and a wide variety of functional groups can be tolerated for this reaction. To our knowledge, there are no examples of the preparation of 3-aryl-substituted furans by rhodium-catalyzed hydroformylation reactions of substituted propargylic alcohols.

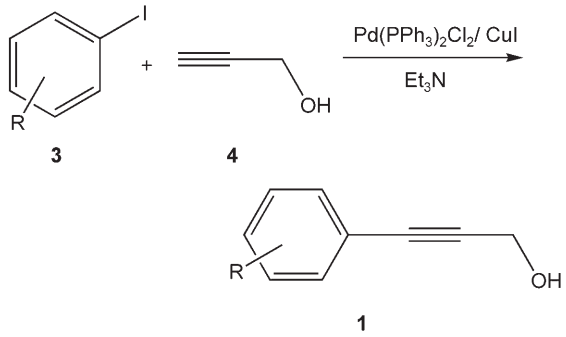
First, we became interested in investigating the synthesis of 3-aryl-substituted furans *via* a rhodium-mediated process. It occurred to us that a general route to furans could involve the hydroformylation of aryl-substituted propargylic alcohols in the presence of syn gas, followed by cyclization with concomitant dehydration to give the desired 3-substituted furan (**2**) in reasonable yields.

The required substituted phenylpropargylic alcohols (**1**) were readily prepared by Pd/Cu-catalyzed Sonoga-



Scheme 1. Formation of 3-substituted furans by rhodium-catalyzed hydroformylation reactions of substituted propargylic alcohols.

shira cross-coupling of the appropriate aromatic iodide (**3**) with propargylic alcohol (**4**).[12] This catalytic process requires the use of a palladium(0) complex, which is performed in the presence of a base. Thus, when the reaction was effected in the presence of CuI, 100% conversion was observed within 2 h at room temperature. Et_3N was used as the solvent and the base, giving satisfactory yields of the products.

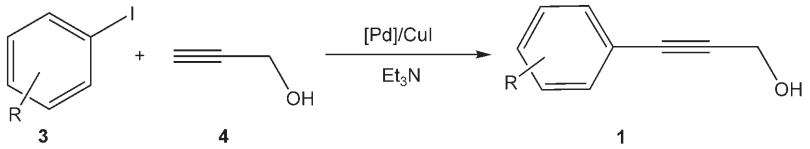


Using this method, a variety of substituted phenylpropargylic alcohols was synthesized in yields ranging from 38% to 89% (Table 1). The reaction could tolerate different substituents on the phenyl ring, including electron-donating and -withdrawing groups. It is well understood that the relative reactivity of the aryl halides is Ar–I > Ar–Br > Ar–Cl. This factor is important for the reaction of aryl halides containing electron-withdrawing substituents in which case the rate of coupling is faster than the reoxidation of the Pd(0) complex.[13] Aryl iodides containing electron-withdrawing substituents more readily underwent oxidative addition giving higher yields (entries 1, and 2). With electron-rich substrates, the corresponding coupling reactions proceeded more slowly (entries 5–9). In addition, the cross-coupling reaction was influenced by steric factors as well (entry 3).

The influence of the catalyst, solvent, substrate/catalyst ratio, CO/H_2 pressure, and temperature on the hydroformylation reaction of 3-phenyl-2-propyn-1-ol to 3-phenylfuran was extensively investigated. Initially, we examined the hydroformylation reaction of 3-phenyl-2-propyn-1-ol with carbon monoxide and hydrogen, in the presence of $[Rh(OAc)_2]_2$ as the catalyst in anhydrous CH_2Cl_2.

Different catalysts were tested to determine their effect on the formation of 3-phenyl-substituted furans. Initial catalyst screening indicated that the use of $[Rh(OAc)_2]_2$ with added phosphine ligand displayed the highest catalytic activity towards the formation of the hydroformylation product. Use of the zwitterionic rhodium complex or $Rh(dppb)(COD)^+BF_4^-$ catalyst with added PPh_3 and at a pressure of 700 psi CO/H_2

Table 1. Synthesis of substituted phenylpropargylic alcohols.[a]



Entry	R	Product	Yield [%][b]
1	*p*-$COCH_3$	**1b**	84[13]
2	*p*-CF_3	**1c**	80[14]
3	1-naphthyl	**1d**	75[15]
4	2-thiophene	**1e**	89[16]
5	*p*-NH_2	**1f**	38
6	*o*-OH	**1g**	45
7	*p*-C_2H_5	**1h**	55
8	*p*-CH_3	**1i**	58[17]
9	*p*-OCH_3	**1j**	49[18]
10	*m*-OCH_3	**1k**	42
11	*m*-Br	**1l**	83

[a] *Reaction conditions:* Iodoarene (1 mmol), propargylic alcohol (1.1 mmol), 10 mL of Et_3N, $Pd(PPh_3)_2Cl_2$ (0.01 mol %), CuI (0.02 mol %), room temperature for 2 h.
[b] Yield of isolated product based on **3**.

(1:1) at 60 °C for 24 h in CH_2Cl_2 gave very low product yields (<10%). Other catalysts, such as $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PhCN)_2$, $Pd(PCy_3)_2$, $Pd(PPh_3)_4$, $(CH_3CN)_4Pd(BF_4)_2$ and $[Rh(COD)Cl]_2$, did not form the furan, and only the starting material was recovered.

The influence of the ratio of CO/H_2 was evaluated by using the $[Rh(OAc)_2]_2/PPh_3$ catalyst system in CH_2Cl_2 at 60 °C. It was found that the optimum CO/H_2 pressure for the hydroformylation reaction was 350/350 psi. The formation of hydrogenated by-products, instead of the hydroformylated product, was favoured at low CO and high H_2 pressure.

The presence of a phosphine ligand was essential for the reaction catalyzed by $[Rh(OAc)_2]_2$, as no conversion of aryl-substituted propargylic alcohol occurred in the absence of triphenylphosphine. To investigate the effect of the added phosphine ligand on the reaction, various types of phosphine ligands were employed when 3-phenyl-2-propyn-1-ol was used as the reactant, and the results are summarized in Table 2. Different bidentate ligands were employed for the hydroformylation reaction. 1,3-Bis(diphenylphosphino)propane (dppp) and 1,4-bis(diphenylphosphino)butane (dppb) were less effective than PPh_3, giving 15% and 18% yields, respectively (entries 2 and 3). Pruett and Smith reported that phosphites are more effective than phosphines for the hydroformylation of allylic alcohols.[19] However, the use of triphenyl phosphite $[P(OPh)_3]$ in our system did not afford the hydroformylated product (entry 4). From these experiments, we concluded that PPh_3 was the ligand of choice for our catalytic system (entry 1).

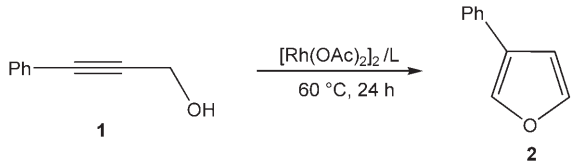
The influence of the solvent on the yield of the hydroformylation reaction was also studied, using different anhydrous solvents. The results of the solvent study are summarized in Table 3. Using rhodium acetate-triphenylphosphine as the catalyst system, we found that the reaction occurred giving good product yields when CH_2Cl_2 is the solvent (entry 3). Other solvents, such as toluene, benzene or ether afforded somewhat lower yields compared to CH_2Cl_2 (entries 1, 2 and 4).

The effect of temperature was next investigated by employing 3-phenyl-2-propyn-1-ol in the presence of $[Rh(OAc)_2]_2/PPh_3$ in CH_2Cl_2, and the results are summarized in Table 4.

The optimum temperature suitable for the hydroformylation reaction was found to be 65–70 °C. When the reaction was performed at 100 °C, the yield of hydroformylated product was much lower (entry 3) and lower regioselectivity and chemoselectivity were observed. Among other side reactions, hydrogenation of the substrate, and condensation reactions are the most important.[20]

The conversion and the formation of by-products are also found to be controlled by the catalyst concentration. Besides the temperature and the reaction time, the catalyst feed is the third parameter to influence the conversion (Table 5).

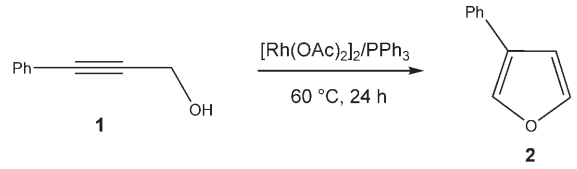
Table 2. Effect of the ligand on the hydroformylation of 3-phenyl-2-propyn-1-ol.[a]



Entry	Ligand	Yield of **2** [%][b]
1	PPh_3	65
2	dppp	15
3	dppb	18
4	$P(OPh)_3$	–

[a] *Reaction conditions:* $[Rh(OAc)_2]_2$ (0.02 mmol), ligand (0.08 mmol), phenylpropargylic alcohol (1 mmol), 2.5 mL of solvent, 700 psi CO/H_2 (1:1), 65 °C, 24 h.
[b] GC yield.

Table 3. Effect of the solvent on the hydroformylation of 3-phenyl-2-propyn-1-ol.[a]



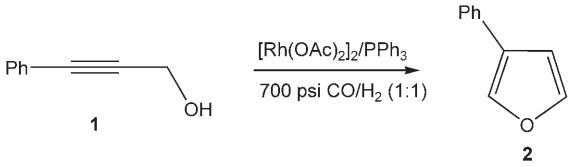
Entry	Solvent	Yield of **2** [%][b]
1	Toluene	57
2	Benzene	49
3	CH_2Cl_2	65
4	Et_2O	43

[a] *Reaction conditions:* $[Rh(OAc)_2]_2$ (0.02 mmol), PPh_3 (0.08 mmol), phenylpropargylic alcohol (1 mmol), 2.5 mL of solvent, 700 psi CO/H_2 (1:1), 65 °C, 24 h.
[b] GC yield.

The maximum yield of the hydroformylated product was obtained when 5/20 mol % of $[Rh(OAc)_2]_2/PPh_3$ was used (entry 3), and below that the yields were somewhat lower (entries 1 and 2). Clearly, the number of phosphines coordinated to rhodium determines the regioselectivity. At high PPh_3 concentration, rather low product yield was obtained (entry 4). This could be due to the high ligand concentration which competes with the substrate for binding to the active rhodium species.

We propose that the water, which is eliminated during the reaction, could be captured by adding molecular sieves to the reaction mixture. Hence, the addition of 0.1 g of 4 Å molecular sieves to each reaction mixture of phenylpropargylic alcohol in the presence of 700 psi CO/H_2 (1:1), at 60 °C for 24 h in CH_2Cl_2 increased the yield of product **2** from 38% to 47%.

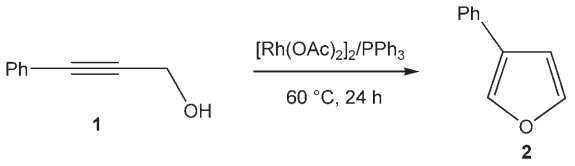
Table 4. Effect of the temperature on the hydroformylation of 3-phenyl-2-propyn-1-ol.[a]



Entry	Temperature [°C]	Yield of **2** [%][b]
1	65	65
2	80	54
3	100	35

[a] *Reaction conditions:* $[Rh(OAc)_2]_2$ (0.02 mmol), PPh_3 (0.08 mmol), phenylpropargylic alcohol (1 mmol), 2.5 mL of solvent, 700 psi CO/H_2 (1:1), 24 h.
[b] GC yield.

Table 5. Effect of the catalyst/ligand ratio on the hydroformylation of 3-phenyl-2-propyn-1-ol.[a]



Entry	Catalyst/ligand [mol %]	Yield of **2** [%][b]
1	3/6	53
2	3/9	59
3	5/20	65
4	5/25	56

[a] *Reaction conditions:* $[Rh(OAc)_2]_2$, PPh_3, 2.5 mL of CH_2Cl_2, phenylpropargylic alcohol (1 mmol), 700 psi CO/H_2 (1:1), 65 °C, 24 h.
[b] GC yield.

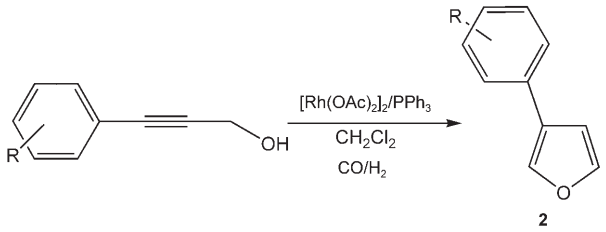
After establishing the optimum reaction conditions for the hydroformylation of 3-phenyl-2-propyn-1-ol, different substituted phenylpropargylic alcohols were employed in the hydroformylation reaction in order to determine the effect of substituents.

The synthesis of 3-substituted furans is sensitive to electronic effects. Phenyl rings with electron-withdrawing groups gave lower yields (Table 6, entries 1 and 2) than those with electron-donating groups (entries 5, 6, 7 and 8).

It is interesting to note that alkylpropargylic alcohols did not give the expected cyclic products when the phenyl group was substituted with an alkyl group such as C_2H_5, $Me(CH_2)_5$ or $Me(CH_2)_6$.

The reactions were complete within 24 h, and the crude mixtures were directly analyzed by ^1H NMR spectroscopy and GC analysis (using biphenyl as the internal standard). Although the 3-substituted furan **2** was the major product (GC and ^1H NMR), the isolated yield was lower after performing column chromatography.

Table 6. Hydroformylation of substituted propargyl alcohols under optimized reaction conditions.[a]

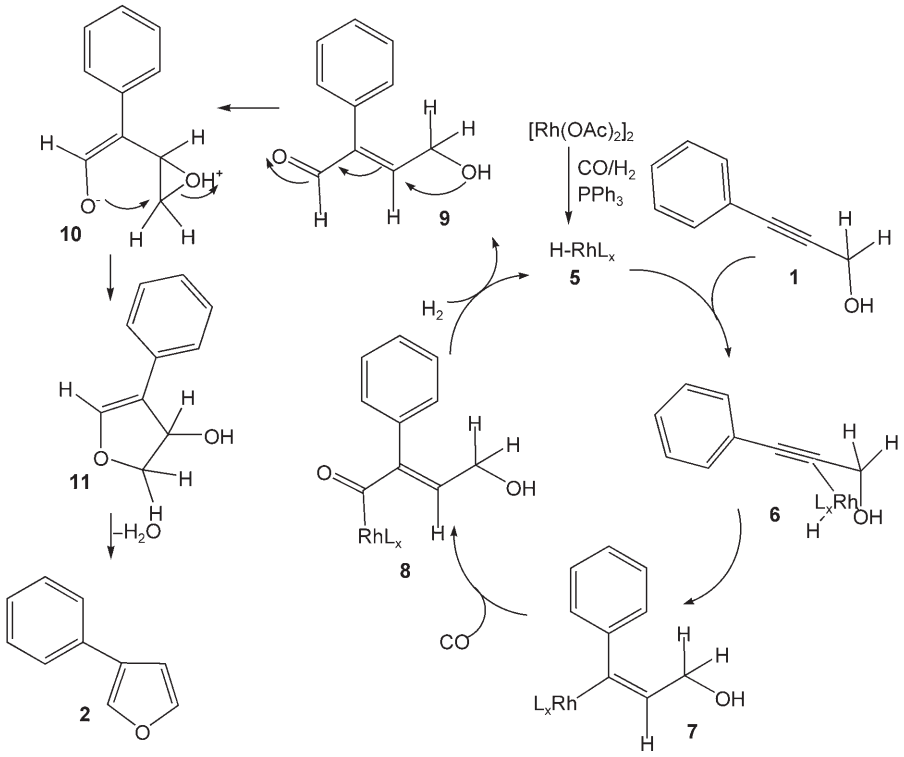


2a R = H;[21] **b** *p*-$CO(CH_3)$; **c** *p*-CF_3; **d** 1-naphthyl;[22] **e** 2-thiophenyl;[22] **f** *p*-NH_2; **g** *o*-OH; **h** *p*-C_2H_5; **i** *p*-CH_3;[21] **j** *p*-OCH_3;[23] **k** *m*-OCH_3;[23] **l** *m*-Br; **m** *m,m*-$(CF_3)_2$; **n** *p*-CN.

Entry	R	Yield of **2** [%][b]
1	**1a**	47
2	**1b**	43 (28)[c]
3	**1c**	44 (32)
4	**1d**	53
5	**1e**	40
6	**1h**	58
7	**1i**	57
8	**1j**	60
9	**1k**	63 (41)
10	**1l**	48
11	**1m**	38
12	**1n**	52

[a] *Reaction conditions:* 0.1 g of 4 Å MS, $[Rh(OAc)_2]_2$ (5 mol %), PPh_3 (20 mol %), 2.5 mL of CH_2Cl_2, arylpropargylic alcohol (1 mmol), 700 psi CO/H_2 (1:1), 65 °C, 24 h.
[b] GC yield.
[c] Yield of isolated product.

A plausible mechanism for the hydroformylation of propargylic alcohols is outlined in Scheme 2. The active rhodium catalyst **5** can be generated by the reaction of $[Rh(OAc)_2]_2$ and PPh_3 in the presence of CO and H_2. The second step may involve coordination of the rhodium hydride complex with the triple bond and weak H-bonding interaction with the alcohol **6**.[24] Next, the rhodium hydride may add in a *cis* fashion to the coordinated alkyne, affording the intermediate **7**.[25] The initial complexation of the rhodium complex could govern the selectivity of the resulting unsaturated product, and the regioselectivity could be mainly determined at this stage.[26] Carbonyl insertion (**8**), and regeneration of the active rhodium catalyst in the presence of a hydrogen molecule may afford the intermediate, **9**. Finally, **9** would undergo cyclization with elimination of a water molecule, providing 3-substituted furans **2**.



Scheme 2. Proposed mechanism for the formation of 3-substituted furans.

Conclusion

In conclusion, a simple and novel method for the synthesis of 3-substituted furans was developed by regioselective hydroformylation of substituted propargylic alcohols using $[Rh(OAc)_2]_2$ and PPh_3 under mild reaction conditions. This method constitutes a simple approach to 3-substituted furans.

Experimental Section

General Procedure for the Hydroformylation of Substituted Propargylic Alcohols

To a 45-mL autoclave containing a glass liner and stirring bar was placed $[Rh(OAc)_2]_2$ (5 mol %), triphenylphosphine (20 mol %), the substituted propargylic alcohol (0.5 mmol), and CH_2Cl_2. The autoclave was flushed three times with carbon monoxide, pressurized to 350 psi, and then hydrogen was introduced up to a total pressure of 700 psi. The autoclave was placed in an oil bath at 60 °C for 24 to 48 hours, and then was allowed to cool to room temperature. The autoclave was depressurized, the reaction mixture filtered through Florisil, and the solvent was removed by rotary evaporation. The resulting yellow residue was directly subjected to ^1H and ^{13}C NMR spectroscopy. The crude was purified by silica gel chromatography or thin layer chromatography using pentane as the eluent to afford the pure product **2**.

Acknowledgements

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