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2,5-Disubstituted furans from 1,4-alkynediols

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Abstract—1,4-Alkynediols serve as readily available starting materials for isomerisation to 1,4-diketones, which can be converted in situ into the corresponding furans by acid-catalysed dehydration. A range of 2,5-disubstituted furans was prepared using the ruthenium-based catalyst $Ru(PPh_3)_3(CO)H_2$ with Xantphos at 1 mol % loading.

Substituted furans represent an important class of compounds that can be found in many natural products and pharmaceutically important compounds.[1] For example, ranitidine (Fig. 1) is one of the most successful anti-ulcer drugs currently available.[2] Many routes to furans have been described, but the majority are variants on the original dehydrating ring closure of a 1,4-dicarbonyl species known as the Paal–Knorr synthesis.[3] The general features of this method are that almost all 1,4-dicarbonyl species (or their derivatives) can be cyclised, and the reaction can be catalysed by strong mineral acids, Lewis acids and dehydrating agents. However, the limitation of the Paal–Knorr synthesis lies in the availability and stability of the starting dicarbonyl compound, especially those containing an aldehyde moiety and those with substituents that may be unstable towards acid.

There have been many reports detailing more elaborate approaches to the synthesis of furans including the use of an epoxyketone,[4] or an acetalketone,[5] which share a common γ-hydroxy-α,β-unsaturated carbonyl intermediate; terminal alkynes have been used as starting materials;[6] allenyl- and alkynyl-ketones have also been cyclised in the presence of a transition-metal catalyst.[7–12]

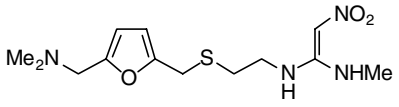
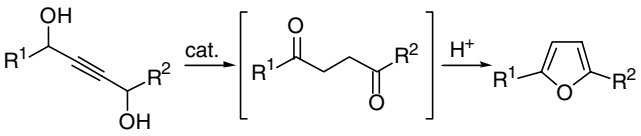


Figure 1. The anti-ulcer drug ranitidine.

Of particular interest was the report by Lu et al. describing the palladium-catalysed isomerisation of 1,4-alkynediols to their respective 1,4-dicarbonyl compounds.[13] This was shortly followed by a further report describing that in the presence of an acid resin, in situ ring closure occurred to give the corresponding furan.[14] The reaction conditions required 4 mol % Pd at 130 °C to effect furan formation.

We have recently been using ruthenium and iridium complexes as transfer hydrogenation catalysts to effect a range of one-pot tandem reactions involving alcohols as starting materials.[15,16] It appeared viable that these catalysts might also be used to effect furan formation from 1,4-alkyne diols **1**. These diols could be oxidised to the 1,4-dicarbonyl species with concomitant reduction of the alkyne moiety, either by intermolecular transfer hydrogenation or by isomerisation. The resulting 1,4-diketone **2** could then undergo a Paal–Knorr cyclisation to afford furan derivative **3** (Scheme 1). 1,4-Alkynediols are stable and readily available or easily synthesised from propargyl alcohols and an aldehyde, providing an alternative route to the formation of 1,4-dicarbonyl compounds in situ.

We decided that the attempted conversion of 1-phenylpent-2-yne-1,4-diol **1a** into diketone **2a** and furan **3a**



1 2 3

Scheme 1. Isomerisation/cyclisation approach to furans.

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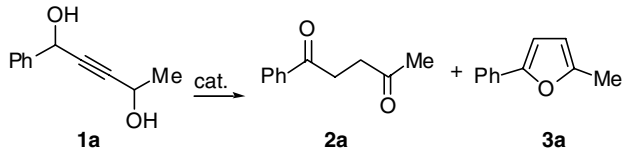


1a 2a 3a

Scheme 2. Formation of diketone and furan.

Table 1. Preliminary catalyst screen[a]

Catalyst	Temperature/time	Conv.[b]	2a/3a[b]
$[Ir(COD)Cl]_2$/dppp[c]	110/42	83	57:31
$[IrCp^*Cl_2]_2$/dppp[d]	110/42	95	87:8
$[RhCp^*Cl_2]_2$/dppp[d]	110/42	22	22:0
$Rh(PPh_3)_3(CO)H$/dppp	110/42	37	14:22
Grubbs[e]	80/24	38	28:10
$[Ru(p\text{-cymene})Cl_2]_2$/dppf[d]	80/24	56	36:20
$Ru(PPh_3)_3(CO)H_2$	80/24	21	21:0

[a] Reaction conditions: Alkyne diol (1 mmol) was dissolved in PhMe (1 mL) in the presence of the catalyst (5 mol % Ir or Ru) and ligand (5 mol %) and heated.
[b] Determined by ^1H NMR analysis.
[c] Cs_2CO_3 (5 mol %) added.
[d] Cs_2CO_3 (10 mol %) added.
[e] Grubbs' first generation metathesis catalyst; $Ru(PCy_3)_2Cl_2(=CHPh)$.

would be an appropriate choice for initial screening reactions (Scheme 2).

The catalysts screened (Table 1) have all been used in transfer hydrogenation reactions,[17] and represented likely candidates for the isomerisation reaction. We were pleased to find that all of these catalysts showed activity for the isomerisation process, and in most cases, the reaction proceeded further to provide furan **3a** as well as the diketone **2a**. The ruthenium complexes showed somewhat greater catalytic activity, facilitating reaction even at 80 °C.

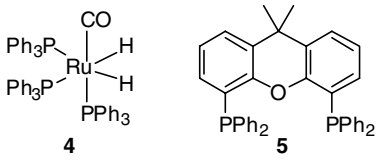
We have previously observed remarkable catalyst acceleration when bidentate ligands have been employed in conjunction with ruthenium catalysts.[18] Therefore, we investigated a range of phosphines as additives for this transformation. Considering that the cyclisation step for the formation of furan is favoured by acidic conditions, the addition of base to facilitate catalyst activation is not ideal. We therefore concentrated our efforts on optimising the conditions using ruthenium dihydride complex $Ru(PPh_3)_3(CO)H_2$ **4**, with a range of ligands to attempt to improve catalytic activity (Table 2).

The reactions with addition of tricyclohexylphosphine and dppp {1,3-bis(diphenyphosphino)propane} resulted in poor conversions, with the dppp ligand shutting down the reaction. Addition of ligands possessing wider bite angles such as dppf {1,1′-bis(diphenyphosphino)ferrocene} showed improvement. However, it was Xantphos ligand **5**[19] that showed the best catalytic activity, providing acceptable conversion of substrate to ketone with additional furan formation. On repeating the reaction with inclusion of 5 mol % of acetic acid co-catalyst, conversion of the substrate proceeded to 81% yield, with the

Table 2. Ligand screen using $Ru(PPh_3)_3(CO)H_2$[a]

Ligand	2a[b] (%)	3a[b] (%)	Conv.[b] (%)
None	21	0	21
PCy_3	15	1	16
Dppp	0	0	0
Dppf	21	0	21
Xantphos	56	12	68
Xantphos[c]	18	63	81

[a] Reaction conditions: Alkyne diol (1 mmol) was dissolved in PhMe (1 mL) in the presence of the $[Ru(PPh_3)_3(CO)H_2]$ catalyst (5 mol %) and ligand (5 mol %) and heated to 80 °C for 24 h.
[b] Analysed by ^1H NMR.
[c] Reaction with addition of 5 mol % of AcOH.



4 5

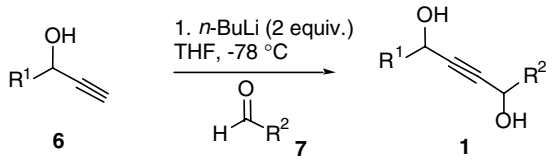
Figure 2. Structures of the complex and ligand used.

formation of furan favoured over that of ketone. This is supportive of the acidic conditions needed to help cyclisation of a ketone to a furan, therefore ruthenium dihydride complex $Ru(PPh_3)_3(CO)H_2$ **4** with Xantphos **5** and acid co-catalyst provides the most favourable catalytic system for the conversion of alkyne diols into furans (Fig. 2).

Using the combination of complex **4** with ligand **5** for the conversion of alkynediol **1a** into furan **3a**, we found that other carboxylic acids could be used, including propanoic acid, benzoic acid and toluic acid. However, the use of stronger acids such as toluenesulfonic acid, sulfuric acid and trifluoroacetic acid completely stopped the reaction. The use of scandium triflate as an additive retarded the reaction significantly, with barely detectable amounts of ketone and furan present in the reaction mixture. Interestingly, the use of potassium *tert*-butoxide as an additive afforded diketone **2a** as the major product (59% conversion, 30:1 **2a**:**3a**).

With the ruthenium dihydride $Ru(PPh_3)_3(CO)H_2$ and Xantphos system working well at 80 °C with 5 mol % loading, we chose to increase the reaction temperature and decrease the catalyst loading. We therefore decided on the use of 1 mol % $Ru(PPh_3)_3(CO)H_2$ **4**, 1 mol % Xantphos **5** and 5 mol % (RCO_2H) in toluene at reflux for 24 h as our standard set of conditions, and applied this to a range of 1,4-alkynediols. 1,4-Alkynediols were prepared by treatment of the commercially available propargylic alcohol **6** with 2 equiv of *n*-butyllithium, followed by the addition of the appropriate aldehyde **7**. These reactions were not optimised, but led to acceptable yields of 1,4-alkynediol products **1** (Scheme 3, Table 3).[20]

With a suitable system in place, various alkynediols were converted into 2,5-disubstituted furans. Alkyl/alkyl substituted alkynediols and aryl/alkyl substituted alkyn-

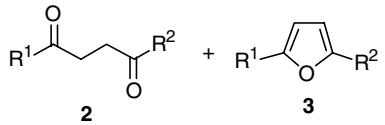


Scheme 3. Preparation of 1,4-alkynediols.

Table 3. Alkynediols synthesised (isolated yields)

Diol	R^1	R^2	Yield (%)
1a	Me	Ph	82
1b	Me	^{n}Pr	65
1c	Me	^{i}Pr	63
1d	Me	^{t}Bu	78
1e	Me	CH_2CH_2Ph	51
1f	H	Ph	52
1g	Ph	^{t}Bu	74
1h	Ph	CH_2CH_2Ph	35
1i	Me	*m*-ClC_6H_4	57
1j	Me	*o*-BrC_6H_4	76
1k	Me	*p*-MeC_6H_4	59
1l	Me	*m*-MeC_6H_4	58
1m	Me	*o*-MeC_6H_4	58
1n	Me	*p*-FC_6H_4	48
1o	Me	*p*-NCC_6H_4	55
1p	Me	*p*-$MeOC_6H_4$	64
1q	Me	*p*-$O_2NC_6H_4$	44
1r	Me	*p*-$MeO_2CC_6H_4$	67
1s	Me	Naphthyl–	70
1t	Me	2-Furyl–	38
1u	Me	2-Thienyl–	22

Table 4. Conversion of alkynediols into furans[a]



Diol	Conversion (%)	Ketone **2** (%)	Furan **3** (%)
1a	100	15	85
1b	95[b]	22[b]	73[b]
1c	94[b]	15[b]	79[b]
1d	100[b]	7[b]	93[b]
1e	100[b]	9[b]	91[b]
1f	100	4	96
1g	100[c]	20	80
1h	100[c]	24	76
1i	100	23	77
1j	100	18	82
1k	100[c]	19	81
1l	100[c]	19	81
1m	100	23	77
1n	100	17	83
1o	100	12	88
1p	100	20	80
1q	50[c]	10	40
1r	100	0	100
1s	100	18	82
1t	100	19	81
1u	100	22	78

[a] Using benzoic acid (5 mol %), reactions analysed by ^{1}H NMR.
[b] Analysed by GC.
[c] Using propanoic acid (5 mol %).

ediols were converted into the required furan derivatives with good to excellent selectivities with ruthenium dihydride $[Ru(PPh_3)_3(CO)H_2]$ **4** and Xantphos **5** system, which also displayed good functional group tolerance[21] (Table 4).

In summary, we have shown the use of alkynediols as attractive starting materials for the synthesis of 2,5-disubstituted furans. The use of 1,4-alkynediols can overcome some of the problems often associated with the classical Paal–Knorr synthesis such as availability and stability of the 1,4-diketone substrates. Using ruthenium dihydride $[Ru(PPh_3)_3(CO)H_2]$ **4** and Xantphos **5** system with an organic acid co-catalyst, various furans could be made in one tandem reaction.

Acknowledgement

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20. *Procedure for synthesis of 1-phenylpent-2-yne-1,4-diol.* Butyn-2-ol (5 mL, 4.47 g, 65 mmol) was added to anhydrous THF (50 mL) under an Ar atmosphere and cooled to −78 °C. *n*-BuLi (10 N) (12.75 mL, 130 mmol) was added dropwise and the reaction mixture stirred at

−78 °C for 2 h. Benzaldehyde (6.6 mL, 6.89 g, 65 mmol) was added dropwise at −78 °C, and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride solution (50 mL) and the aqueous layer was extracted with EtOAc (2 × 20 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel chromatography (60:40, hexane–EtOAc) and the product was identified by ^{1}H NMR: ^{1}H NMR ($CDCl_3$): δ 7.41–7.18 (5H, m, Ph), 5.3 (1H, s, Ph(OH)*H*C), 4.4 (1H, q, J = 6.6 Hz, C(OH)*H*CH_3), 4.0 (1H, br s, OH), 3.72 (1H, br s, OH), 1.3 (3H, d, J = 6.6 Hz, C(OH)HCH_3). Other alkyne diols were prepared and characterised by the same methods.

21. *General procedure for the synthesis of furans from alkynediols.* Alkynediol (1 mmol), [$Ru(PPh_3)_3(CO)H_2$] (9.2 mg, 1 mol %), Xantphos (5.8 mg, 1 mol %), toluene (1 mL) and acid (5 mol %) were added to a dry clean Radley's carousel tube under nitrogen and heated at 110 °C for 24 h. The reaction was cooled and then quenched with base and extracted with hexane (2 × 5 mL). The combined hexane layers were dried with $MgSO_4$ and concentrated in vacuo to yield the crude reaction mixture, which was analysed by ^{1}H NMR or gas chromatography. *Procedure for the synthesis of 4-(5-methyl-furan-2-yl)-benzoic acid methyl ester* **3r**. The standard procedure was employed at a 5 mmol scale, and then the final product was recrystallised from methanol/water to yield an orange solid (776 mg, 72%), mp 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, $CDCl_3$) δ = 7.96 (2H, d, J = 8.7 Hz, Ph–*H*), 7.61 (2H, d, J = 8.7 Hz, Ph–*H*), 6.61 (1H, d, J = 3.0 Hz, C=C*H*–), 6.03 (1H, d, J = 3.0 Hz, C=C*H*), 3.85 (3H, s, OCH_3), 2.31 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25 °C, $CHCl_3$): δ = 153.74 (Ph–*C*), 151.63 (Ph–*C*), 130.48 (Ph–*C*H), 123.21 (Ph–*C*H), 108.76 (H*C*=C–O), 108.65 (H*C*=C–O), 52.48 (O*C*H_3), 14.21 (*C*H_3).