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Synthesis of furans, pyrroles and pyridazines by a ruthenium-catalysed isomerisation of alkynediols and in situ cyclisation

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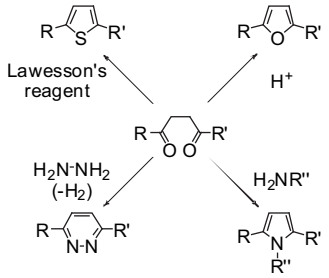
ABSTRACT

Alkyne-1,4-diols are readily available substrates which are isomerised to 1,4-diketones using $Ru(PPh_3)_3(CO)H_2$/xantphos as a catalyst. In situ cyclisation into furans, pyrroles and pyridazines has been achieved under suitable conditions.

1. Introduction

In 1884 Paal and Knorr simultaneously reported that treatment of 1,4-diketones with strong mineral acids or with concentrated ammonia or ammonium acetate produced 2,5-disubstituted furans and pyrroles respectively.[1,2] Similarly, the use of a source of nucleophilic sulfur will result in thiophene derivatives,[3] whilst pyridazines can be formed in the presence of hydrazine (Scheme 1).[4]



Scheme 1. Synthesis of heterocycles from 1,4-diketones.

For furan synthesis,[5] various acid catalysts may be used, including strong mineral acids such as HCl as well as organic acids such as acetic acid, TFA and *p*-TsOH.[6,7] Lewis acids, including zinc halides and $BF_3 \cdot Et_2O$ have been used for furan synthesis from 1,4-dicarbonyls.[8] The availability of 1,4-dicarbonyl compounds can be a limiting factor, and a number of transition metal catalysed approaches to furans have been developed using alternative starting materials.[9]

Of particular relevance to our work are the reports of Lu et al. who used a palladium catalyst to isomerise 2-butyne-1,4-diol derivatives to 1,4-dicarbonyl surrogates in the presence of acidic resin to afford the corresponding 2,5-disubstituted furans.[10] However, the high catalyst loading and temperature required as well as the requirement for a strong acid to be present to facilitate the cyclisation reaction were limitations. Similarly, 2-butyne-1,4-diones have been used as precursors to furans. Reduction of the alkyne functionality using palladium on carbon with formic acid as the reductant was combined with sulfuric acid co-catalyst for the cyclisation under microwave conditions.[11]

A variety of other alkyne substrates have also been successfully used for furan synthesis, catalysed by palladium,[12,13] silver,[14] gold,[15] ruthenium[16] and copper complexes.[17] Mortreux has reported a one-pot route to furans and pyrroles using a rhodium catalysed 1,4-carbonylative addition of arylboronic acids to vinylketones to synthesise 1,4-dicarbonyls. The dicarbonyls are then cyclised in situ to afford the corresponding furan and pyrrole derivatives.[18] In addition, the isomerisation of propargylic alcohols into enals and enones with ruthenium catalysts is a known transformation.[19,20]

We have recently used a variety of ruthenium-based catalysts for oxidative reactions of alcohols[21] and for redox-neutral borrowing hydrogen reactions.[22] In particular, the use of xantphos[23] with

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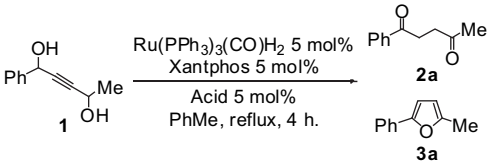
$Ru(PPh_3)_3(CO)H_2$ was found to be effective for catalysing the formation of C–C bonds from alcohols,[24] the conversion of alcohols into methyl esters,[25] and the conversion of alcohols into alkenes.[26] We therefore chose to examine this catalyst combination for reactions involving the isomerisation of alkyne-1,4-diols and report our results herein. Preliminary results indicated that $Ru(PPh_3)_3(CO)H_2$/xantphos was a more effective catalyst than other Ru and Ir complexes that we had screened.[27]

2. Results and discussion

2.1. Synthesis of 2,5-disubstituted furans

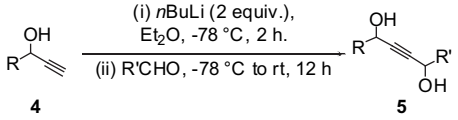
We chose the reaction of alkynediol **1** as a model substrate, and in the presence of 5 mol % $Ru(PPh_3)_3(CO)H_2$/xantphos we obtained a mixture of dicarbonyl compound **2a** (56%) and the desired furan **3a** (12%) after heating at 80 °C in toluene for 24 h. In the presence of 5 mol % acetic acid, the selectivity towards furan formation was more favourable, providing diketone **2a** (18%) and furan **3a** (63%). A comparison of acetic acid with propanoic acid and benzoic acid revealed that all three acids provided an almost identical reaction outcome. Stronger acids, including trifluoroacetic acid, *p*-toluenesulfonic acid and sulfuric acid completely inhibited the isomerisation step. We also attempted the reaction in the presence of scandium triflate, but under these conditions, minimal product formation occurred. When the reaction was run in the presence of 5 mol % potassium *tert*-butoxide, the isomerisation step was successful (57% **2a**), although under the basic conditions very little furan formation was seen (2% **3a**) (Scheme 2).



Scheme 2. Formation of diketones and furans from alkyne-1,4-diols.

After further optimisation reactions, we were able to lower the catalyst loading to 1 mol % $Ru(PPh_3)_3(CO)H_2$, 1 mol % xantphos and 5 mol % benzoic acid. The reaction was run for 24 h in toluene at reflux. Under these conditions, all of the model compound **1** was consumed, with 15% of diketone **2a**, 85% of furan **3a**, as judged from analysis of the ^{1}H NMR spectrum. The furan **3a** could be isolated in 80% yield.

With an acceptable procedure for furan formation, we wished to examine a range of substrates under these reaction conditions. A series of alkyne-1,4-diols was successfully synthesised in modest to good yield by treatment of commercially available propargylic alcohols with 2 equiv of *n*-butyllithium, followed by addition of the appropriate aldehyde (Scheme 3).



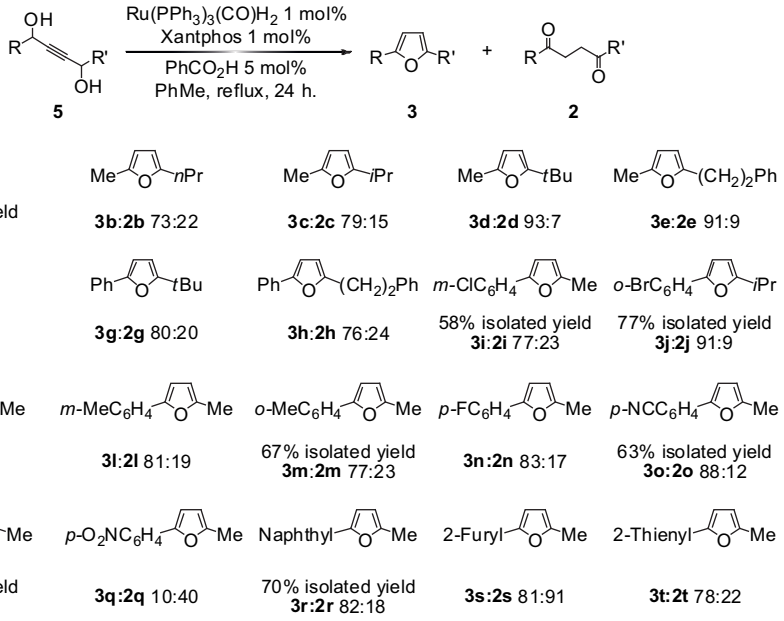
Scheme 3. Synthesis of alkyne-1,4-diols.

These alkyl/alkyl and aryl/alkyl substituted alkyne-1,4-diols were converted into the required furan derivatives with good to excellent selectivities and with good functional group tolerance. The majority of reactions proceeded with conversions greater than 95% with more than 70% furan produced. The conversion and ratio of furan to diketone were determined by analysis of the ^{1}H NMR spectra, and for more volatile samples by GC–MS. In several cases, the product furan was purified by column chromatography with a reasonable isolated yield. It was only the alkyne-1,4-diol containing the *para*-substituted nitro group that proved problematic, as this substrate was only sparingly soluble in toluene at reflux (Scheme 4).

2.2. Synthesis of pyrroles from alkyne-1,4-diols

Since pyrroles can be prepared from the same 1,4-dicarbonyl precursors as furans, our attention turned to the combined ruthenium catalysed isomerisation of alkyne-1,4-diols with in situ cyclisation to the pyrrole in the presence of an amine.[28]

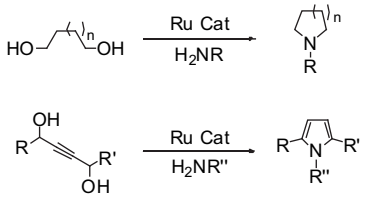
There have been several other approaches to the synthesis of pyrroles from alkyne-containing precursors, including a copper-catalysed cycloisomerisation of alkynylimines,[29] palladium-catalysed cyclisation of *Z*-enynamines,[30] gold-catalysed reactions of



Scheme 4. Furans prepared by isomerisation and in situ cyclisation.

various substrates,[31] and a titanium-catalysed process involving initial hydroamination of 1,4 and 1,5-diynes with primary amines.[32]

The conversion of simple diols into saturated *N*-substituted heterocycles using ruthenium based catalysts has been reported and is described in reviews (Scheme 5).[33] Based on this, the use of alkyne-1,4-diols would be expected to lead to the pyrrole and there exists a previous report by Watanabe et al. of the transition metal catalysed conversion of alkyne-1,4-diols into a pyrrole using $Ru(PPh_3)_3Cl_2$ as a catalyst.[34] However this system requires 150 °C to effect isomerisation and 63% conversion was the best case in this example. This system was unsuccessful when anilines were used as the amine components.



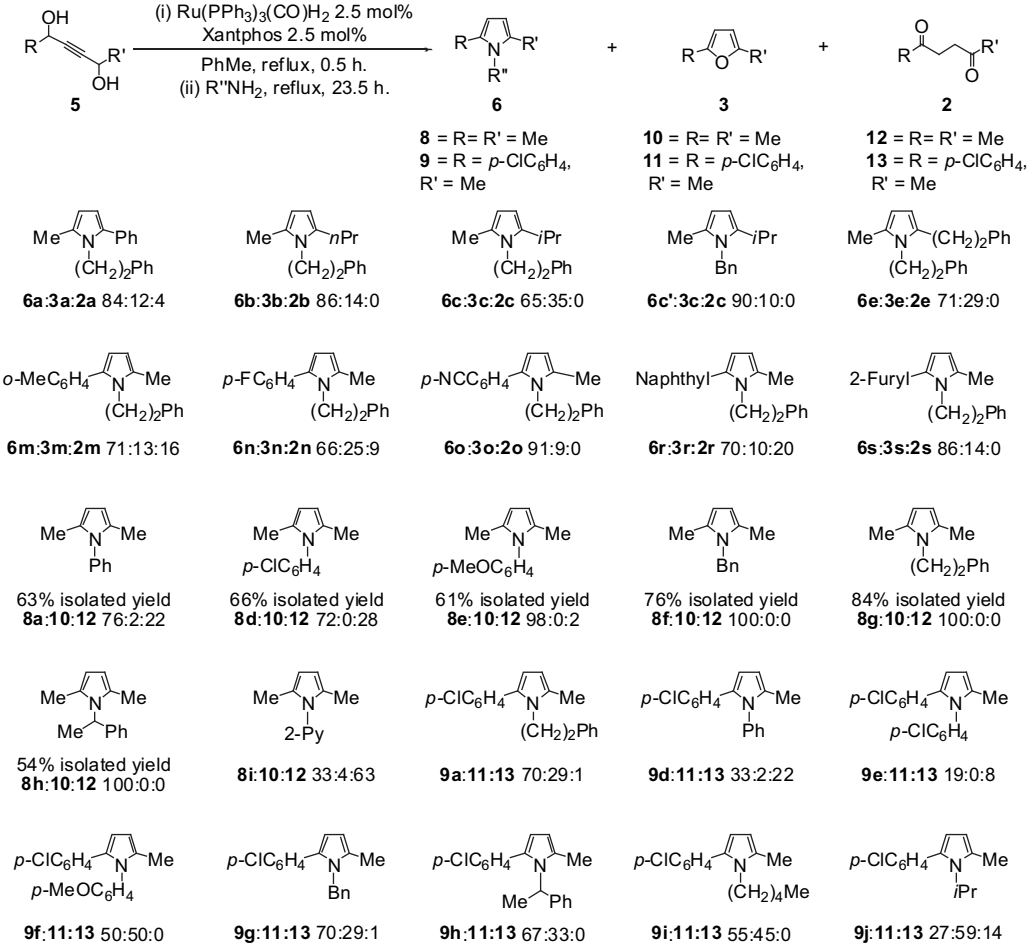
Scheme 5. Cyclisation reactions of diols with amines.

The use of the $Ru(PPh_3)_3(CO)H_2$/xantphos catalyst combination was a logical choice, based on our earlier experiences with furan formation. Preliminary reactions required a fairly high catalyst loading, although after a few optimisation experiments, we established that an in situ pre-complexation of the xantphos to the ruthenium was beneficial, as was the use of 2 equiv of amine. We therefore used the conditions shown in Scheme 6 for the formation of a range of pyrroles from alkyne-1,4-diol precursors. In a few cases, the pyrrole was formed as the exclusive product (**8f**, **8g** and **8h**), although generally, at least some furan formation was observed, as well as uncyclised diketone. Even anilines could be used under these conditions, although there was a lower selectivity for pyrrole formation (**8d**, **8i**, **9d** and **9e**). When the more nucleophilic aniline, *p*-methoxyaniline, was used, pyrrole formation was highly selective in the formation of the 2,5-dimethyl substituted product (**8e**), but not when one of the substituents was an aryl group (**9f**). Selectivities were either determined by analysis of the ^1H NMR spectra or by GC–MS. In several cases, the product pyrrole was purified by column chromatography, and isolated in a reasonable yield.

We speculate that the major mechanistic pathway is via complete isomerisation of the alkynediol into the corresponding diketone, followed by pyrrole formation. An analysis of the crude NMR spectra of reactions which were terminated early indicates the absence of any nitrogen-containing compounds other than starting material and product. Whilst we investigated the use of longer reaction times in order to drive the reaction towards the formation of a greater proportion of pyrrole, there was minimal beneficial effect. It is therefore possible that, at least in the case where anilines are used, that an equilibrium is established.

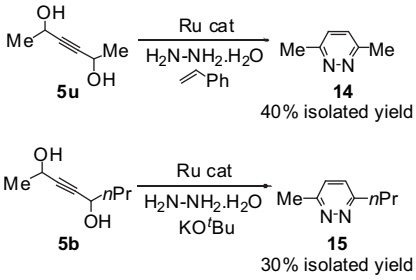
2.3. Synthesis of pyridazines from alkyne-1,4-diols

We decided to apply the isomerisation/cyclisation sequence to the formation of pyridazines. We anticipated that isomerisation of an alkyne-1,4-diol would, as before, lead to a 1,4-diketone, which



Scheme 6. Pyrroles prepared by isomerisation and in situ cyclisation.

would undergo cyclisation and in situ oxidation to give a pyridazine. The oxidative step could be driven by aromatisation, either by donation of hydrogen to a suitable acceptor or by loss of H_2 gas. We considered the transformation of alkyne-1,4-diols **5u** and **5b**, leading to pyridazines **14** and **15** (Scheme 7). Preliminary experiments demonstrated that the reaction was unsuccessful if the hydrazine was added at the start of the reaction, as the isomerisation step was inhibited, and hence hydrazine was added three hours after the start of the reaction. We found that the most successful reaction conditions involved either the addition of styrene as a hydrogen acceptor or activation of the catalyst using KO*t*-Bu. Alternative oxidants led to less satisfactory results; crotononitrile inhibited the isomerisation step, while cyclohexene and hexene provided a mixture of products with minimal pyridazine formation. Increasing the amount of base led to incomplete isomerisation, as did the use of the alternative bases KOH or K_2CO_3. Surprisingly, the combined use of styrene and KO*t*-Bu led to a complex mixture of products.



Scheme 7. Synthesis of pyridazines **14** and **15**. Conditions: $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %), xantphos (2.5 mol %), reflux 3 h, then addition of hydrazine hydrate (1 equiv) and further heating—see Experimental section for details.

3-Hexyne-2,5-diol **5u** was converted into pyridazine **14** with moderate isolated yield. Whilst there was complete consumption of starting material and no remaining diketone, several minor impurities were observed in the ^{1}H NMR spectrum, including a dimerised product known to be generated during pyridazine formation.[4] Similarly, 3-octyne-2,5-diol **5b** was converted into pyridazine **15**, again with only moderate isolated yield.

Therefore, whilst the isomerisation/cyclisation approach may be used for pyridazine formation, only moderate isolated yields were achieved due to the formation of impurities under these reaction conditions.

The conversion of alkynediol **1** into a thiophene was attempted with Lawesson's reagent [$(p$-$MeOC_6H_4PS_2)_2$],[35] using the $Ru(PPh_3)_3$-$(CO)H_2$/xantphos combination in toluene at reflux. However, only starting material was recovered, presumably due to inhibition of the catalyst by Lawesson's reagent.

3. Conclusion

In summary, alkynediols undergo a ruthenium-catalysed isomerisation reaction which leads to 1,4-diketones. In situ cyclisation in the presence of acid generates furans, whilst in the presence of amines or hydrazine, the corresponding pyrroles or pyridazines are formed.

4. Experimental

4.1. General

General experimental details, along with the synthesis of alkynediols **5a**–**5v** and furans and pyrroles which were analysed by GC–MS are provided in Supplementary data.

4.2. Representative procedure for the synthesis of 2,5-disubstituted furans

*4.2.1. 2-Methyl-5-phenylfuran (**3a**)*

To an oven dried, argon purged Young's tap carousel tube was added 1-phenylpent-2-yne-1,4-diol **5a** (352 mg, 2 mmol), $Ru(PPh_3)_3(CO)H_2$ (18.3 mg, 0.01 mmol), xantphos (11.5 mg, 0.01 mmol) and acid co-catalyst (acetic, propanoic or benzoic 5.7 μL, 7.4 μL, 12.2 mg respectively, 0.05 mmol). Degassed anhydrous toluene (1 mL) was added and the reaction heated to reflux for 24 h. The solvent was removed in vacuo and the crude reaction mixture analysed by ^{1}H NMR spectroscopy. Conversion was determined by the analysis of the peak integral ratios characteristic of 1-phenyl-2,5-hexadione **2a** and 1-phenyl-5-methyl furan **3a** in the ^{1}H NMR spectrum of the crude reaction mixture. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.47) and the title compound was afforded as a clear oil (256.5 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, 2H, J=7 Hz, 1.3 Hz), 7.27 (t, 2H, J=7.3 Hz), 7.12 (m, 1H), 6.44 (d, 1H, J=3.2 Hz), 5.96 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.70, 152.34, 131.60, 128.98, 128.63, 127.13, 123.70, 108.07, 106.24, 14.10; FTIR (neat) 3077, 3025, 2951, 2918, 1883, 1683, 1595, 1545, 1479, 1444, 1203, 1021, 791, 760, 692 cm^{-1}.

*4.2.2. 2-(3-Chlorophenyl)-5-methylfuran (**3i**)*

According to the general procedure using 1-(3-chlorophenyl)pent-2-yne-1,4-diol **5i** (421 mg, 2 mmol) 2-(3-chlorophenyl)-5-methylfuran **3i** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.48) and the title compound was afforded as a clear oil (226 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.50 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 6.57 (d, 1H, J=3.2 Hz), 6.07 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.03, 151.24, 135.04, 133.22, 130.26, 126.98, 123.67, 121.70, 108.31, 107.43, 14.09.

*4.2.3. 2-(2-Bromophenyl)-5-methylfuran (**3j**)*

According to the general procedure using 1-(2-bromophenyl)pent-2-yne-1,4-diol **5j** (510 mg, 2 mmol) 2-(2-bromophenyl)-5-methylfuran **3j** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.46) and the title compound was afforded as a clear oil (328 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J=7.9, 1.7 Hz), 7.64 (dd, 1H, J=7.9, 1.2 Hz), 7.35 (m, 1H), 7.09 (m, 2H), 6.14 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.59, 149.97, 134.49, 131.83, 128.68, 128.19, 127.71, 119.54, 112.54, 108.07, 14.07.

*4.2.4. 2-Methyl-5-p-tolylfuran (**3k**)*

According to the general procedure using 1-*p*-tolylpent-2-yne-1,4-diol **5k** (380 mg, 2 mmol) 2-methyl-5-*p*-tolylfuran **3k** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.45) and the title compound was afforded as a clear oil (278 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, 2H, J=8.2 Hz), 7.01 (d, 2H, J=8.2 Hz), 6.33 (d, 1H, J=3.2 Hz), 5.89 (dd, 1H, J=3.2, 1.0 Hz), 2.21 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.04, 151.94, 131.64, 129.40, 128.80, 124.13, 108.80, 105.59, 21.95, 14.14.

*4.2.5. 2-Methyl-5-m-tolylfuran (**3l**)*

According to the general procedure using 1-*m*-tolylpent-2-yne-1,4-diol **5l** (380 mg, 2 mmol) 2-methyl-5-*m*-tolylfuran **3l** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.45) and the title compound was afforded as a clear oil (307 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.36 (t, 1H, J=7.6 Hz), 7.15 (d, 1H, J=7.6 Hz), 6.63 (d, 1H, J=3.2 Hz), 6.16 (m, 1H), 2.49 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.99, 152.25, 138.64, 131.66, 129.03, 128.09, 124.45, 121.04, 108.19, 106.27, 29.62, 21.96, 14.16.

*4.2.6. 2-Methyl-5-o-tolylfuran (**3m**)*

According to the general procedure using 1-*o*-tolylpent-2-yne-1,4-diol **5m** (380 mg, 2 mmol) 2-methyl-5-*o*-tolylfuran **3m** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.32) and the title compound was afforded as a clear oil (308 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H, J=8.0 Hz), 7.40–7.26 (m, 3H), 6.55 (d, 1H, 3.2 Hz), 6.21 (m, 1H), 2.62 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.31, 151.91, 134.54, 131.62, 131.00, 128.11, 127.73, 127.06, 110.10, 108.00, 22.48, 14.13.

*4.2.7. 4-(5-Methylfuran-2-yl)benzonitrile (**3o**)*

According to the general procedure using 4-(1,4-dihydroxypent-2-ynyl)benzonitrile **5o** (402 mg, 2 mmol) 4-(5-methylfuran-2-yl)benzonitrile **3o** was synthesised. The crude reaction mixture was purified by column chromatography (5:1 petroleum ether 40–60 °C/diethyl ether R_f=0.51) and the title compound was afforded as a white solid (230.9 mg, 63%). Mp 112–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 2H, J=8.6 Hz), 7.55 (d, 2H, J=8.6 Hz), 6.63 (d, 1H, J=3.3 Hz), 6.05 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ .40, 150.73, 135.29, 132.92, 123.74, 119.53, 109.92, 109.69, 108.89, 14.17; HRMS (ESI-TOF): calcd for $C_{12}H_9OH^+$: 184.0762, found 184.0754 (MH^+); FTIR (neat) 3125, 2981, 2225, 1611, 1541, 1415, 1023, 831 cm^{-1}.

*4.2.8. 2-(4-Methoxyphenyl)-5-methylfuran (**3p**)*

According to the general procedure using 1-(4-methoxyphenyl)pent-2-yne-1,4-diol **5p** (412 mg, 2 mmol) 2-(4-methoxyphenyl)-5-methylfuran **3p** was synthesised. The crude reaction mixture was purified by column chromatography (5:1 petroleum ether 40–60 °C/diethyl ether, R_f=0.77) and the title compound was afforded as a yellow solid (241.7 mg, 64%). Mp 37–41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H, J=8.9 Hz), 6.81 (d, 2H, J=8.9 Hz), 6.31 (d, 2H, J=3.2 Hz), 5.94 (m, 1H), 3.74 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.99, 152.70, 151.59, 129.45, 128.64, 125.12, 114.44, 107.89, 104.60, 55.70, 14.11; FTIR (neat) 3105, 3000, 2981, 2838, 1579, 1614, 1497, 1019, 831, 784 cm^{-1}.

*4.2.9. 2-Methyl-5-(naphthalen-2-yl)furan (**3r**)*

According to the general procedure using 1-(naphthalen-2-yl)-pent-2-yne-1,4-diol **5r** (452 mg, 2 mmol) 2-methyl-5-(naphthalen-2-yl)furan **3r** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.34) and the title compound was afforded as a clear oil (291.1 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (m, 1H), 7.89 (m, 1H), 7.81 (d, 1H, J=8.2 Hz), 7.73 (dd, 1H, J=7.3, 1.2 Hz), 7.52 (m, 3H), 6.62 (d, 1H, J=3.1 Hz), 6.19 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.66, 152.04, 134.41, 130.65, 129.30, 128.87, 128.42, 126.77, 126.20, 126.03, 126.01, 125.74, 110.58, 107.87, 14.19; FTIR (neat) 3048, 2981, 2949 m 2919, 1588, 1508, 1392, 1023, 770 cm^{-1}.

*4.2.10. 2-Methyl-5-(thiophen-2-yl)furan (**3t**)*

According to the general procedure using 1-(thiophen-2-yl)pent-2-yne-1,4-diol **5t** (364 mg, 2 mmol) 2-methyl-5-(thiophen-2-yl)furan **3t** was synthesised. The crude reaction mixture was purified by column chromatography (hexane, R_f=0.70) and the title compound was afforded as a clear oil (126 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, 1H, J=2.0 Hz), 7.14 (m, 2H), 6.21 (d, 1H, J=3.2 Hz), 5.87 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.66, 149.96, 133.41, 126.46, 125.32, 118.23, 107.75, 106.34, 14.09.

4.3. Representative procedure for the synthesis of pyrroles

*4.3.1. 2,5-Dimethyl-1-phenyl-1H-pyrrole (**8a**)*

To an oven dried, argon purged Young's tap carousel tube was added 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol), $Ru(PPh_3)_3(CO)H_2$ (45.8 mg, 0.05 mmol), xantphos (28.8 mg, 0.05 mmol) and degassed anhydrous toluene (2 mL). The reaction was heated at reflux to preform the active catalytic species. After 30 min, aniline (364 μL, 4 mmol) was added and the reaction heated at reflux for a total of 24 h. The solvent was removed in vacuo and the crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 76% pyrrole formation. GC–MS retention time 13.59 min, *m*/i (EI) 171 (M^+), 172 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.37) and the title compound was afforded as a pale yellow oil (212 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 3H), 7.13 (m, 2H), 5.82 (s, 2H), 1.95 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.43, 129.44, 129.20, 128.66, 128.02, 106.04, 13.40.

*4.3.2. 1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (**8d**)*

According to the representative procedure using 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol) and 4-chloroaniline (510 mg, 4 mmol) 1-(4-chlorophenyl)-2,5-dimethyl-1*H*-pyrrole **8d** was synthesised. The crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 72% pyrrole formation. GC–MS retention time 15.52 min, *m*/*z* (EI) 205 (M^+), 206 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.39) and the title compound was afforded as a pale yellow oil (353 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 2H, J=8.6 Hz), 7.08 (d, 2H, J=8.6 Hz), 5.82 (s, 2H), 1.94 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.93, 133.93, 129.90, 129.70, 129.13, 106.43, 13.35.

*4.3.3. 1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole (**8e**)*

According to the representative procedure using 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol) and 4-methoxyaniline (492 mg, 4 mmol) 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole **8e** was synthesised. The crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 98% pyrrole formation. GC–MS retention time 16.27 min, *m*/*z* (EI) 201 (M^+), 202 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.28) and the title compound was afforded as a pale yellow oil (249 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 2H, J=8.9 Hz), 6.89 (d, 2H, J=8.9 Hz), 5.80 (s, 2H), 3.78 (s, 3H), 1.94 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.27, 132.17, 129.62, 129.43, 114.60, 105.65, 55.85, 13.34.

*4.3.4. 1-Benzyl-2,5-dimethyl-1H-pyrrole (**8f**)*

According to the general procedure using 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol) and benzylamine (437 μL, 4 mmol) 1-benzyl-2,5-dimethyl-1*H*-pyrrole **8f** was synthesised. The crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 100% pyrrole formation. GC–MS retention time 15.12 min, *m*/*z* (EI) 186 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.30) and the title compound was afforded as a pale yellow oil (279 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 3H), 6.81 (d, 2H, J=7.1 Hz), 5.78 (s, 2H), 4.93 (s, 2H), 2.06 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.94, 129.09, 128.40, 127.38, 126.04, 105.77, 47.10, 12.82.

*4.3.5. 2,5-Dimethyl-1-phenethyl-1H-pyrrole (**8g**)*

According to the representative procedure using 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol) and 2-phenethylamine (504 μL, 4 mmol) 2,5-dimethyl-1-phenethyl-1*H*-pyrrole **8g** was synthesised. The crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 100% pyrrole formation. GC–MS retention time 16.40 min, *m*/*z* (EI) 200 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina

(19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.36) and the title compound was afforded as a pale yellow oil (336.6 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 3H), 7.02 (m, 2H), 5.69 (s, 2H), 3.87 (t, 2H, J=7.6 Hz), 2.80 (t, 2H, J=7.6 Hz), 2.07 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ .96, 129.24, 129.01, 127.76, 127.03, 105.58, 45.67, 37.95, 12.75.

*4.3.6. 2,5-Dimethyl-1-(1-phenylethyl)-1H-pyrrole (**8h**)*

According to the representative procedure using 3-hexyne-2,5-diol **5u** (228 mg, 2 mmol) and 1-phenethylamine (516 μL, 4 mmol) 2,5-dimethyl-1-(1-phenylethyl)-1*H*-pyrrole **8h** was synthesised. The crude reaction mixture was analysed by GC–MS, which showed 100% conversion with 100% pyrrole formation. GC–MS retention time 15.73 min, *m*/*z* (EI) 200 (MH^+). The crude reaction mixture was purified by column chromatography using neutral alumina (19:1 petroleum ether (bp 40–60 °C)/diethyl ether, R_f=0.59) and the title compound was afforded as a pale yellow oil (215 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 3H), 6.96 (d, 2H, J=7.1 Hz), 5.72 (s, 2H), 5.39 (q, 1H, J=7.1 Hz), 2.00 (s, 6H), 1.78 (d, 3H, J=7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.85, 128.86, 128.69, 127.22, 126.42, 106.50, 52.86, 19.71, 14.22.

4.4. Synthesis of 3,6-dimethylpyridazine (14)

To an oven dried, argon purged carousel tube was added $Ru(PPh_3)_3(CO)H_2$ (23 mg, 0.025 mmol) and xantphos (14 mg, 0.025 mmol). Degassed anhydrous toluene (1 mL) was added and the reaction heated to reflux for 1 h. The reaction was cooled to room temperature before 3-hexyne-2,5-diol **5u** (0.11 mL, 1 mmol) was added and the reaction returned to reflux for 3 h. The reaction was cooled to room temperature and hydrazine hydrate (0.049 mL, 1 mmol) was added. The reaction was heated at reflux for 17 h before cooling and addition of styrene (0.12 mL, 1 mmol). The reaction was then heated at reflux for a further 4 h. The solvent was removed in vacuo and the pyridazine removed from the ruthenium residue by extracting with hexane. Purification by column chromatography (9:1 diethyl ether/methanol, R_f=0.21) and the title compound was afforded as a yellow oil (43 mg, 40%). ^{1}H NMR (250 MHz; $CDCl_3$) δ 7.17 (s, 2H), 2.60 (s, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 158.00, 127.43, 22.15. GC–MS retention time 9.3 min, *m*/*z* (EI) 108 (MH^+).

4.5. Synthesis of 3-methyl-6-propylpyridazine (15)

To an oven dried, argon purged carousel tube was added $Ru(PPh_3)_3(CO)H_2$ (23 mg, 0.025 mmol) and xantphos (14 mg, 0.025 mmol). Degassed anhydrous toluene (1 mL) was added and the reaction heated to reflux for 1 h. The reaction was cooled to room temperature before oct-3-yne-2,5-diol **5b** (142 mg, 1 mmol) was added and the reaction heated at reflux for 3 h. After cooling to room temperature, hydrazine hydrate (0.049 mL, 1 mmol) and potassium *tert*-butoxide (11 mg, 0.1 mmol) were added; the reaction was then heated at reflux for a further 20 h. The solvent was removed in vacuo and the pyridazine removed from the ruthenium residue by extracting with hexane. Purification by column chromatography (9:1 diethyl ether/methanol, R_f=0.32) yielded the title compound as a yellow oil (41 mg, 30%). ^{1}H NMR (250 MHz; $CDCl_3$) δ 7.21 (s, 1H), 7.20 (s, 1H), 2.84 (t, 2H, J=7.7 Hz), 2.60 (s, 3H), 1.79–1.64 (m, 2H), 0.91 (t, 3H, J=7.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 161.4, 157.9, 127.0, 126.3, 37.9, 23.0, 22.1, 13.8; *m*/*z* (ES) 137.1069, $C_8H_{13}N_2$ $[M+H]^+$ requires 137.1079, GC–MS retention time 12.0 min, *m*/*z* (EI) 136 (MH^+).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.108.

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