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Ruthenium-catalysed conversion of 1,4-alkynediols into pyrroles

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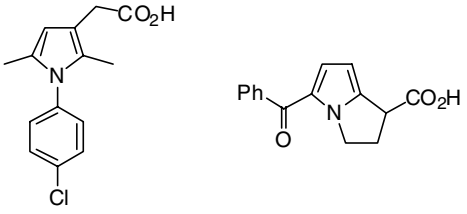
Abstract—Various 1,2,5-substituted pyrroles have been synthesised from 1,4-alkynediols using a ruthenium catalysed isomerisation to give the corresponding 1,4-dicarbonyl compounds, which undergo in situ cyclisation to pyrroles in the presence of amine.

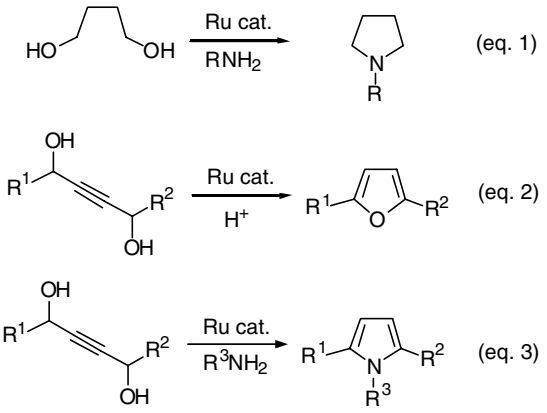
Pyrroles form an important class of compounds as natural products and in the pharmaceutical industry, for example the non-steroidal anti-inflammatory compounds, Clopirac and Ketorolac (Fig. 1).[1]

The conversion of simple diols into saturated N-heterocycles using ruthenium catalysts (Scheme 1, Eq. 1) has been reported by several groups,[2] including our own.[3] In this chemistry, the ruthenium catalyst removes hydrogen from an alcohol to give an aldehyde, forming an imine, which is then reduced to an amine, and then repeating the sequence to give cyclisation. In the preceding Letter,[4] we have shown that the ruthenium complex $Ru(PPh_3)_3(CO)H_2$ with the bidentate phosphine Xantphos is able to effect isomerisation of 1,4-alkynediols to 1,4-dicarbonyl compounds, with in situ cyclisation to the corresponding furans (Scheme 1, Eq. 2). Herein, we report the conversion of 1,4-alkynediols into pyrroles by isomerisation and N-heterocyclisation (Scheme 1, Eq. 3). There exists one previous report of the transition metal catalysed conversion of a 1,4-alkynediol into a pyrrole (using $Ru(PPh_3)_3Cl_2$ as catalyst at 150 °C) which gave a 63% conversion in the best case, but was unsuccessful when anilines were used as the amine component.[5] Other approaches to the synthesis of furans and pyrroles using transition metal catalysts are documented in a recent review.[6]



Clopirac Ketorolac

Figure 1. Pyrrole-containing anti-inflammatory drugs.



Scheme 1. Ruthenium catalysed heterocyclisation reactions.

Since the combination of $Ru(PPh_3)_3(CO)H_2$ with Xantphos had proven to be successful for the isomerisation of 1,4-alkynediols into 1,4-diketones and furans,[4,7] we chose to use this catalyst for the isomerisation of alkynediol **1** using amine **2** to allow N-heterocyclisation to take place via diketone **3** to give pyrrole **5**; some furan **4** was obtained as a byproduct (Scheme 2).

We had established that Xantphos[8] as ligand gave the best reactivity and selectivity in furan formation and

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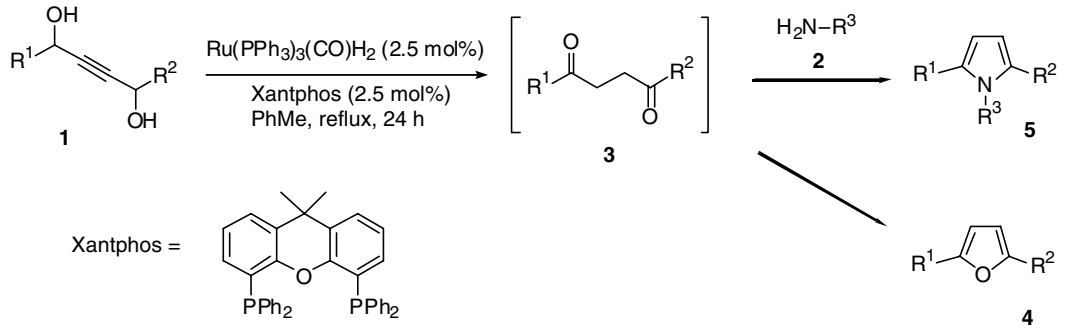


Scheme 2. Isomerisation and heterocyclisation of 1,4-alkynediols.

used this ligand for pyrrole-forming reactions. The addition of base is normally required to activate catalysts containing a metal–halide bond, although this is not expected to be necessary for metal hydrides.[9] In comparison with reactions performed in the absence of base, we found that the addition of Cs_2CO_3 neither hindered

Table 1. Formation of pyrroles from various 1,4 alkynediols and benzylamine or 2-phenethylamine[a]

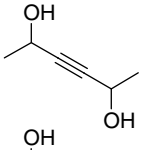
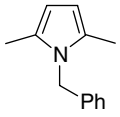
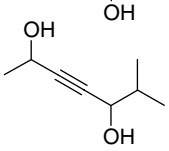
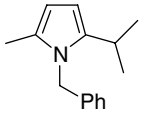
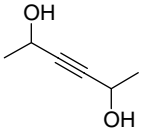
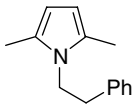
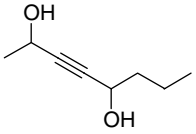
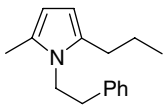
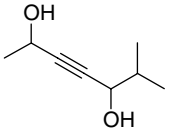
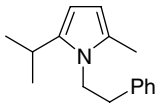
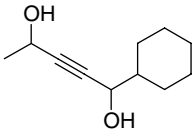
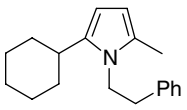
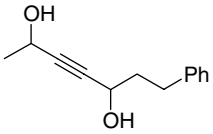
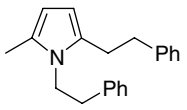
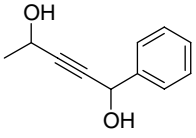
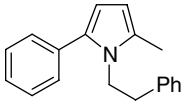
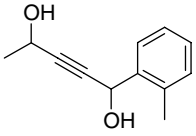
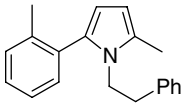
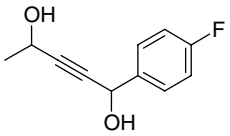
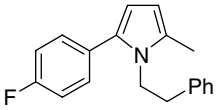
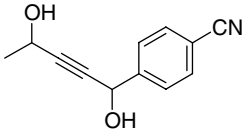
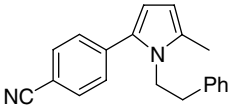
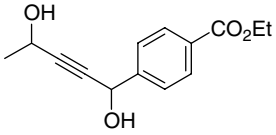
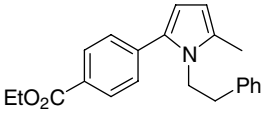
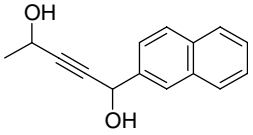
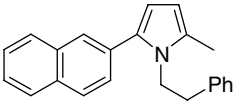
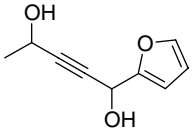
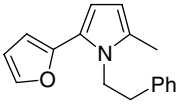
Entry	Starting material	Product	Conversion[b] (%)	Diketone **3**[b] (%)	Furan **4**[b] (%)	Pyrrole **5**[b] (%)
1[c]			100	0	0	100
2[c]			100	0	10	90
3			100	0	0	100
4			100	0	14	86
5			100	0	35	65
6			100	0	38	62
7			100	0	29	71
8			100	4	12	84
9			100	16	13	71

Table 1 (*continued*)

Entry	Starting material	Product	Conversion[b] (%)	Diketone **3**[b] (%)	Furan **4**[b] (%)	Pyrrole **5**[b] (%)
10			100	9	25	66
11			100	0	9	91
12			100	0	37	63
13			100	20	10	70
14			100	0	14	86

[a] Reaction conditions: 1,4-Alkynediol (1 mmol), $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %) and Xantphos (2.5 mol %) were dissolved in dry PhMe (1 mL) and heated to reflux. After 30 min, amine (2 mmol) was added to the reaction mixture. After 24 h, the reaction mixture was cooled, diluted with MeOH:PhMe (1:1, 10 mL) and injected into the GC–MS without further purification.
[b] Determined by GC–MS.
[c] $PhCH_2N{=}CHPh$ also formed as a minor by-product.

nor enhanced reactivity. We had hoped that in those cases where furan formation was a significant problem, that the presence of base may deter this process, but it had essentially no effect on the product distribution, and we therefore did not add base (or acid) to these reactions.

Optimisation of the reaction conditions showed that addition of amine after 30 min of heating the catalyst, ligand and starting material in toluene was ideal. Therefore the 1,4-alkynediols, shown in Table 1, were treated with $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %) and Xantphos (2.5 mol %) and heated at reflux in toluene for 30 min, prior to the addition of two equivalents of the amine (benzylamine or 2-phenylethylamine). Heating at reflux was then continued to give a total reaction time of 24 h.[10]

The reactions were highly selective for pyrrole formation from unhindered substrates, leading to the formation of 2,5-dimethylpyrroles (Table 1, entries 1 and 2). More hindered substrates still afforded pyrroles selectively, although in some cases, the corresponding furan was a significant by-product (Table 1, entries 5–7, 10, 12). However, many functional groups were tolerated, including halide, nitrile, ester and furyl.

We also wished to investigate the range of amines that could be used in these pyrrole-forming reactions. In reactions to form the 2,5-dimethyl substituted pyrroles, we were pleased to find that aniline could be used as the amine (Table 2, entry 1), although some diketone remained uncyclised under these conditions, probably reflecting the lower nucleophilicity of anilines with respect to aliphatic amines. The aniline containing the strongly electron-withdrawing *p*-nitro group failed to provide any of the corresponding pyrrole product (Table 2, entry 3). However, as expected, the aniline containing the electron-donating *p*-methoxy group (Table 2, entry 4) reacted with excellent selectivity towards pyrrole formation. 2-Aminopyridine (Table 2, entry 8) was also a problematic amine, giving an unsatisfactory conversion into pyrrole under these reaction conditions.

Formation of pyrroles possessing a 2-(*p*-chloro)-substituent was generally less selective towards pyrrole formation, although reasonable conversions were obtained in favourable cases, where the amine was an unbranched aliphatic primary amine (Table 2, entries 12, 13, 16). The use of a branched aliphatic amine provided an acceptable conversion for 1-phenylethylamine (Table 2, entry 14) but not in the case of isopropylamine, which may be due to an issue of volatility (bp 34 °C). The

Table 2. Formation of pyrroles from other amines[a]

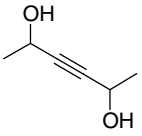
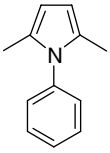
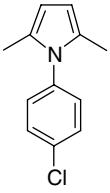
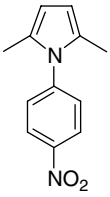
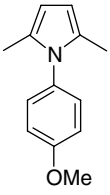
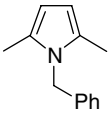
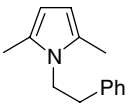
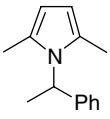
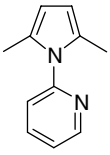
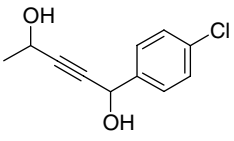
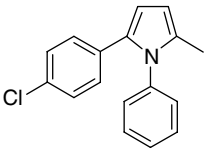
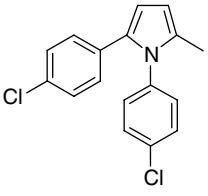
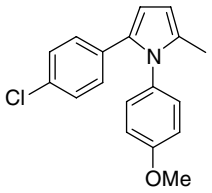
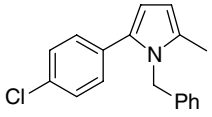
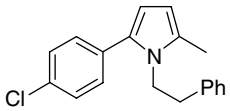
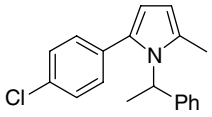
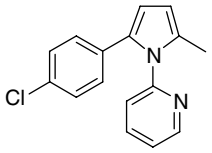
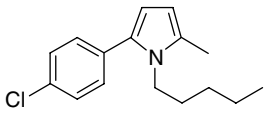
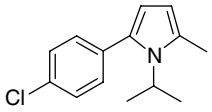
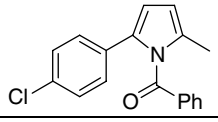
Entry	Starting material	Product	Conversion[b] (%)	Diketone **3**[b] (%)	Furan **4**[b] (%)	Pyrrole **5**[b] (%)
1			100	22	2	76
2			100	28	0	72
3			100	83	17	0
4			100	2	0	98
5			100	0	0	100
6			100	0	0	100
7			100	1	0	99
8			100	63	4	33
9			100	6	61	33
10			100	12	69	19

Table 2 (*continued*)

Entry	Starting material	Product	Conversion[b] (%)	Diketone **3**[b] (%)	Furan **4**[b] (%)	Pyrrole **5**[b] (%)
11			100	0	50	50
12			100	1	29	70
13			100	1	29	70
14			100	0	33	67
15			100	42	56	2
16			100	0	45	55
17			100	14	59	27
18			65	15	50	0

[a] Reaction conditions: 1,4-Alkynediol (1 mmol), $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %) and Xantphos (2.5 mol %) were dissolved in dry PhMe (1 mL) and heated to reflux. After 30 min, amine (2 mmol) was added to the reaction mixture. After 24 h, the reaction mixture was cooled, diluted with MeOH–PhMe (1:1, 10 mL) and injected into the GC–MS without further purification.
[b] Determined by GC–MS.

use of anilines with the chloro-containing alkynediol provided a best selectivity of 50% in the case of the electron rich *p*-methoxyaniline (Table 2, entry 11). Benzamide was found to be unreactive towards pyrrole formation (Table 2, entry 18).

In summary, the conversion of 1,4-alkynediols into pyrroles has been achieved with excellent selectivities in favourable cases. The reaction involves isomerisation of the 1,4-alkynediol into a 1,4-diketone and subsequent Paal–Knorr cyclisation into the corresponding pyrrole.

Acknowledgement

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References and notes

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10. For example, the synthesis of 2,5-dimethyl-1-(2-phenylethyl)-pyrrole. 3-Hexyne-2,5-diol (457 mg, 4 mmol), $[Ru(PPh_3)_3(CO)H_2]$ (92 mg, 2.5 mol %), Xantphos (58 mg, 2.5 mol %) and dry toluene (4 mL) were added to a dry clean Schlenk tube under argon, and heated to 110 °C. After 30 min at reflux, 2-phenethylamine (1.0 mL, 8 mmol) was added, and the mixture was heated at reflux for a total of 24 h. The reaction was cooled, diluted with toluene (4 mL) and methanol (4 mL) and a sample was taken for analysis by GC–MS. The solvent was removed in vacuo to give a viscous brown oil which was purified by flash column chromatography eluting with petroleum ether 40:60–diethyl ether (19:1 v/v) to give the title compound as a colourless oil (493 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, $CDCl_3$) $\delta = 7.23$–7.14 (3H, m, Ph-H), 7.02–6.99 (2H, m, *o*-Ph-H), 5.99 (2H, s, C=C*H*–), 3.85 (2H, t, $J = 7.70$ Hz, N–CH_2), 2.79 (2H, t, $J = 7.70$ Hz, CH_2Ph), 2.06 (6H, s, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 139.0$ (*i*-Ph-*C*), 129.3 (Ph-*C*), 129.1 (Ph-*C*), 127.8 (N*C*CH_3), 127.1 (*p*-Ph-*C*), 105.7 (C(CH_3)=*C*H), 45.7 (N-*C*H_2), 38.0 (*C*H_2Ph), 12.8 (*C*H_3). MS (EI): *m*/*z* (%) 200 ([M+1]$^+$, 60), 109 (100), 104 (15), 91 (8).