Formation of bicyclic pyrroles from the catalytic coupling reaction of 2,5-disubstituted pyrroles with terminal alkynes, involving the activation of multiple C–H bonds†

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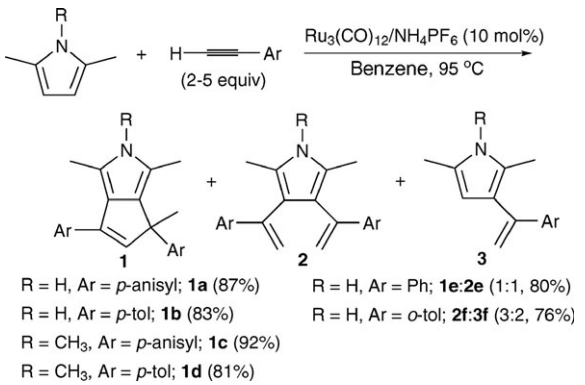
Received (in College Park, MD, USA) 12th March 2008, Accepted 25th March 2008
First published as an Advance Article on the web 21st April 2008
DOI: 10.1039/b804263b

Substituted bicyclic pyrroles are produced directly from the coupling reaction of 2,5-disubstituted pyrroles with terminal alkynes, involving the activation of multiple C–H bonds and regioselective cyclisation.

Transition metal-catalysed C–H bond activation and functionalisation reactions of nitrogen heterocyclic compounds have attracted considerable attention, in part due to their prominent role in the synthesis of natural products and pharmaceutical agents.[1] Highly regioselective catalytic C–H bond insertion reactions of nitrogen-containing aromatic compounds, such as pyridines, indoles and pyrroles, have been reported in recent years.[2] Direct oxidative coupling reactions of arene C–H bonds[3] and the C–H bond oxidative annulation of indoles[4] have also been achieved using Cu and Pd catalysts. Despite such remarkable progress, however, catalytic C–H bond activation methods have rarely been employed for constructing nitrogen-containing heterocyclic compounds. We recently developed a new catalytic coupling reaction between arylamines and alkynes, which involved the regioselective activation of sp^2 C–H bonds to yield tricyclic quinoline products.[5] In an effort to extend the scope of catalytic C–H bond activation reactions, we have begun to explore the coupling reactions of pyrroles and indoles. This report delineates the coupling reaction between 2,5-disubstituted pyrroles and terminal alkynes, which involves multiple C–H bond activation and cyclisation steps.

Treatment of 2,5-dimethylpyrrole (1.0 mmol) with 4-ethynylanisole (2.0 mmol) in the presence of $Ru_3(CO)_{12}/NH_4PF_6$ (1 : 3, 10 mol% Ru) in benzene (5 mL) at 95 °C for 36 h cleanly produced the cyclisation product, **1a** (eqn (1)). Since **1a** was found to be air sensitive, the analytically pure product was isolated by column chromatography under a nitrogen atmosphere (87% yield), and was fully characterised by both spectroscopic methods and elemental analysis.‡ The initial catalyst activity survey showed that both $Ru_3(CO)_{12}$ and NH_4PF_6 were essential for catalytic activity. Other neutral and cationic ruthenium compounds, such as $RuCl_3{\cdot}3H_2O$, $(PPh_3)_3RuHCl$, $(PCy_3)_2(CO)RuHCl$ and $[(PCy_3)_2(CO)(MeCN)_2RuH]^+BF_4^-$, did not give any coupling products under similar reaction conditions. The analogous reaction of *N*-phenylpyrrole with 4-ethynylanisole produced a mixture of 1 : 1 and 1 : 2 coupling products, without forming any cyclisation product.



(1)

The coupling reaction was found to be strongly influenced by the steric and electronic nature of alkynes. In contrast to terminal alkynes with a *para*-electron-donating group, such as 4-ethynylanisole or 4-ethynyltoluene, which readily produced the cyclisation products **1a–1d**, the coupling reaction with phenylacetylene gave a 1 : 1 mixture of the cyclisation and 1 : 2 insertion products, **1e** and **2e**. The coupling reaction with sterically demanding 2-ethynyltoluene (2 equiv.) produced a 3 : 2 mixture of the coupling products **2f** and **3f** under similar conditions. Neither arylalkynes with an electron-withdrawing group, such as 4-ethynyltrifluorotoluene or 4-fluorophenylacetylene, nor the aliphatic terminal alkynes, gave any coupling products under similar conditions. A prolonged reaction time at a higher temperature did not convert **2** or **3** into cyclisation product **1**. Instead, the cyclotrimerisation products from the homocoupling of the terminal alkynes were produced predominantly in these cases.

Since $Ru_3(CO)_{12}/NH_4PF_6$ was not particularly effective for the coupling reactions with electron-poor arylalkynes, we next surveyed the efficacy of gold catalysts to promote the formation of cyclisation products. When 2,5-dimethylpyrrole was treated with phenylacetylene (2 equiv.) in the presence of 5 mol% of $Au(PPh_3)Cl/AgOTf$ (1 : 1) in benzene for 24 h, **1e** was formed exclusively, though the catalyst lost its activity after 60% conversion. Control experiments indicated that both $Au(PPh_3)Cl$ and AgOTf were required for catalytic activity, and other selected gold compounds, such as $AuCl_3$

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† Electronic supplementary information (ESI) available: The experimental procedure and characterization data of organic products. See DOI: 10.1039/b804263b

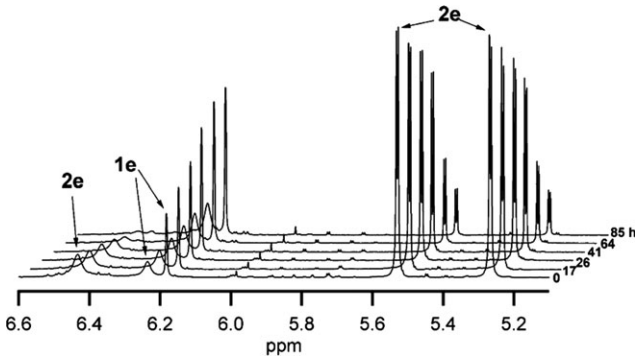
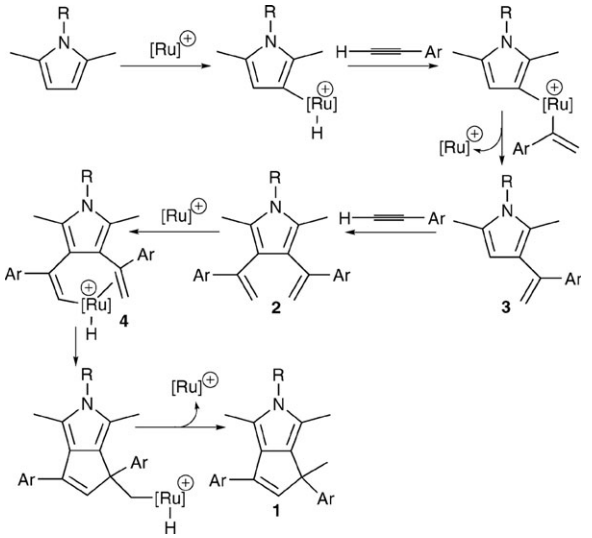


Fig. 1 Partial ^{1}H NMR spectra of the reaction mixture of **1e** and **2e**.

and $NaAuCl_4$, failed to catalyse the coupling reaction. When the $Au(PPh_3)Cl/AgOTf$ (5 mol%) catalyst was treated with a 1 : 1 mixture of **1e** and **2e**, **2e** was cleanly converted to **1e** to produce an 8 : 1 mixture of **1e** and **2e** after 10 h at 95 °C. By using the combined catalytic system, $Ru_3(CO)_{12}/NH_4PF_6$ and $Au(PPh_3)Cl/AgOTf$, cyclisation product **1e** was obtained from the coupling reaction of 2,5-dimethylpyrrole with phenylacetylene (>95% conversion, 81% combined yield, **1e** : **2e** = 85 : 15). This result indicates that the gold catalyst was particularly effective in promoting the cyclisation step of the coupling reaction. While gold catalysts have been successfully utilised in C–H bond activation reactions,[6] the synergistic effect of Ru/Au catalysts is not entirely clear at the present time.

The formation of both 1 : 1 and 1 : 2 products suggested that product **1** is resulted from the cyclisation of 1 : 2 coupling product **2**. To gain further mechanistic insights, the reaction mixture of **1e** and **2e** (1 : 1) was periodically monitored by ^{1}H NMR at room temperature, after it had been heated at 95 °C in the presence of $Ru_3(CO)_{12}/NH_4PF_6$ (10 mol% Ru) in C_6D_6 (Fig. 1). Over time, the peaks due to **1e** at δ 6.19, as well as the NH peak at δ 6.24, increased at the expense of the peaks due to **2e** (δ 5.27 and 5.53 (C=CH_2)). The rate constant, $k_{obs} = 2.1 \times 10^{-2}$ h^{-1}, of the appearance of **1e** was estimated from a pseudo first-order plot.

The coupling reaction of 1,2,5-trimethylpyrrole with deuterium-labelled 4-ethynylanisole-d_1 (2 equiv., >99% D) in the presence of $Ru_3(CO)_{12}/NH_4PF_6$ (10 mol% Ru) in C_6D_6 was monitored by NMR. After 1 h of heating at 95 °C, the ^{1}H NMR spectrum showed that nearly 15% of the deuterium from 4-ethynylanisole had exchanged with 35% of the β-vinyl hydrogens of the unreacted 1,2,5-trimethylpyrrole, prior to the formation of the coupling products. The product, **2a**-*d*, isolated from a preparative scale reaction of 2,5-dimethylpyrrole with 2 equivalents of 4-ethynylanisole-d_1, contained deuterium at both the α-methyl (33%) and vinyl (37%) positions. Also, in support of rapid H/D exchange between the two substrates, a relatively small deuterium isotope effect was observed from a separate reaction of 1,2,5-trimethylpyrrole with phenylacetylene/phenylacetylene-d_1 when forming 1 : 1 coupling product **3e**. The pseudo first-order plots for the reactions gave $k_{obs} = 1.65 \times 10^{-2}$ and 1.38×10^{-2} h^{-1} from phenylacetylene and phenylacetylene-d_1, respectively, which translated into $k_{CH}/k_{CD} = 1.2$.



Scheme 1 A possible mechanistic pathway.

These results suggest a mechanism involving sequential alkyne insertion and cyclisation steps, as outlined in Scheme 1. The sequential C–H activation and regioselective insertion of alkynes would be mediated by an electrophilic ruthenium catalyst to form 1 : 2 coupling product **2**. The subsequent ruthenium-mediated vinyl C–H bond activation and cyclisation steps could be facilitated by coordination of the adjacent olefin to ruthenium *via* the formation of alkene–hydride species **4**. Cyclisation and reductive elimination would give product **1**.

In summary, the catalytic formation of bicyclic pyrroles has been achieved from the direct coupling reaction of 2,5-dimethylpyrroles with terminal alkynes. The cyclisation reaction involved three consecutive sp^2 C–H bond activation and insertion steps.

Financial support from the US National Institute of Health General Medical Sciences (R15 GM55987) is gratefully acknowledged.

Notes and references

‡ *Representative experimental procedure:* In a glove box, $Ru_3(CO)_{12}$ (0.03 mmol), NH_4PF_6 (0.1 mmol), 2,5-dimethylpyrrole (1.0 mmol) and an alkyne (2.0 mmol) were dissolved in benzene (5 mL) in a medium-walled 25 mL Schlenk tube, equipped with a Teflon stopcock and a magnetic stirring bar. The reaction tube was sealed, brought out of the box and heated in an oil bath at 95 °C for 36–48 h. The tube was opened to air at room temperature and the crude product mixture analysed by GC. The solvent was removed using a rotary evaporator and the organic product was isolated by column chromatography on silica gel (hexane/CH_2Cl_2) under a nitrogen atmosphere.
For **1b**: δ_H(400 MHz; C_6D_6) 7.58–7.03 (8 H, m, Ar), 6.20 (1 H, br s, NH), 6.17 (1 H, s, C=CH), 2.15 (6 H, s, CH_3), 2.08 (3 H, s, CH_3), 1.90 (3 H, s, CH_3) and 1.86 (3 H, s, CH_3); δ_C(75 MHz; C_6D_6) 142.9, 141.4, 138.9, 136.6, 135.1, 135.0, 134.7, 129.1, 127.9, 126.7, 117.0, 114.1, 50.6 (CCH_3), 24.3 (CH_3), 21.1 (CH_3), 20.9 (CH_3), 12.8 (CH_3) and 11.6 (CH_3); *m*/*z* (GC-MS) 327 (M^+); Found: C, 88.02; H, 7.62; N, 4.31. Calc. for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28%.

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