Gold-catalysed rearrangement of *O*-vinyl oximes for the synthesis of highly substituted pyrroles†

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***O*-Vinyl oximes were synthesised from the reaction of oximes with activated alkynes and subsequently rearranged using gold catalysis to afford highly substituted pyrroles in an efficient and regiocontrolled process. Additionally, pyrroles were formed directly from oximes and activated alkynes in a multifaceted catalysis process.**

The mild and selective synthesis of pyrroles using metal catalysis has received considerable research interest in recent years due to the prevalence of nitrogen-containing heterocycles in pharmaceuticals, agro-chemicals and biologically active natural products.[1] One procedure for the convergent synthesis of pyrroles is the reaction of oximes[2] with alkynes under thermal superbasic conditions (DMSO/LiOH), the Trofimov reaction (Fig. 1).[3,4] Importantly, this reaction allows for the direct formation of both a C–C and C–N bond from unactivated alkynes. This powerful transformation is underutilised due to the harsh reaction conditions that result in poor yields and low levels of product chemo-/regioselectivity.[5] However, due to the potential of the Trofimov reaction in synthesis, catalytic variants seeking to improve the yield and selectivity whilst removing the need for strongly basic conditions have been developed. For example, earlier this year Anderson *et al.* described an iridium-catalysed isomerisation of *O*-allyl oximes under reductive conditions that afforded 4-methyl-5-unsubstituted pyrroles.[6] Recently, we reported a nucleophilic catalysis method for the regioselective synthesis of pyrroles from oximes and activated alkynes.[7] This one-pot procedure relies on a two-stage microwave process to initially form the *O*-vinyl oxime *in situ*, followed by thermal rearrangement.[8] In an effort to lower the reaction temperature, improve the yield and increase the substrate scope of the nucleophilic catalysis/thermal rearrangement protocol, we examined a novel method using noble metal catalysis. A number of synthetically useful reactions involving oximes have employed gold catalysis,[9] though not for their intermolecular addition to alkynes.[10] This communication describes the unprecedented gold-catalysed rearrangement of vinyl oximes to pyrroles as well as a one-pot procedure for the direct formation of pyrroles from oximes and activated alkynes.

Our initial investigations were aimed at the synthesis of the requisite *O*-vinyl oximes using nucleophilic catalysis. Thus, *O*-vinyl oximes **4a–5e** were synthesised by the reaction of oximes **1** with electron deficient alkynes **2** or **3** using the nucleophilic catalyst DABCO under our previously reported conditions (Scheme 1).[7,11] The oximes were used as diastereomeric mixtures in the subsequent transformations.

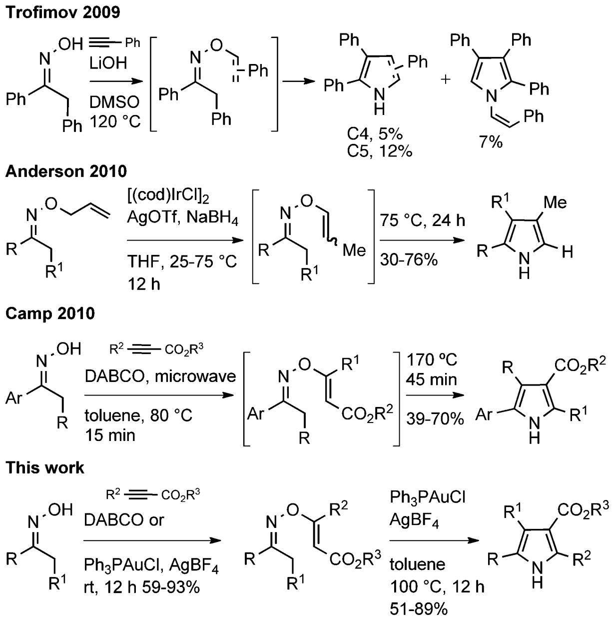
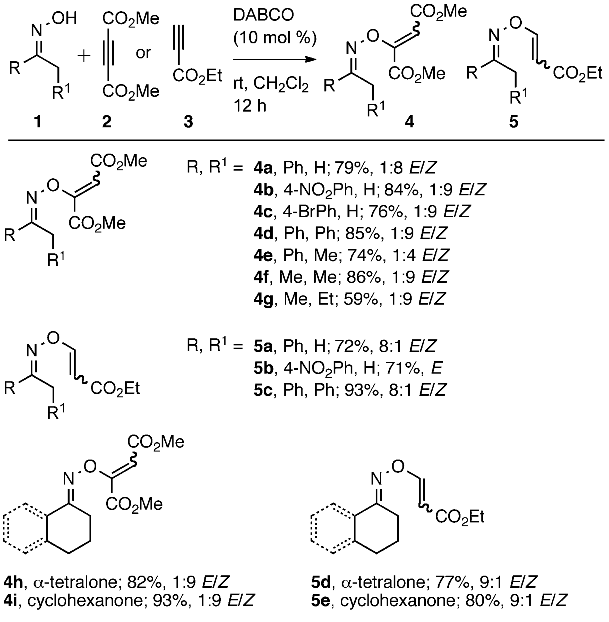


Fig. 1 Synthesis of pyrroles *via* the Trofimov reaction and *via* rearrangement of substituted oximes.



Scheme 1 Synthesis of *O*-vinyl oximes *via* nucleophilic catalysis.

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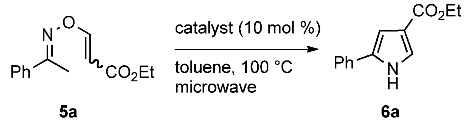
Table 1 Optimisation of the noble metal-catalysed rearrangement of *O*-vinyl oximes

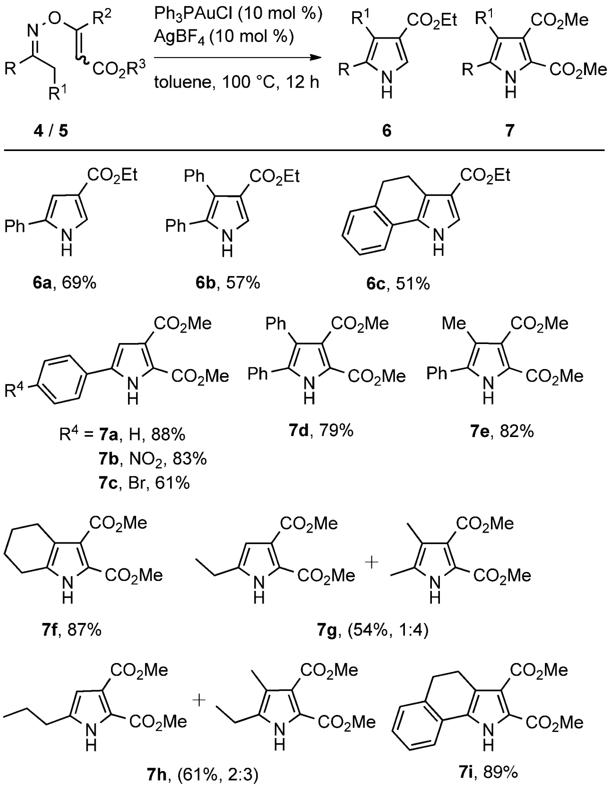


Entry	Catalyst	Time/min	Yield (%)
1	Ph_3PAuCl, AgOTf	10	10[a]
2	Ph_3PAuCl, AgOTf	40	52
3	Ph_3PAuCl, $AgBF_4$	10	13[a]
4	Ph_3PAuCl, $AgBF_4$	40	68
5	$PtCl_4$	10	NR
6	$AuCl_3$	10	NR
7	Au(I)[b]	10	NR
8	None	40	NR
9	PPh_3	40	NR
10	$AgBF_4$	40	NR

[a] Percent conversion to product based on ^1H NMR analysis. [b] Au(I) = (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine] gold(I).

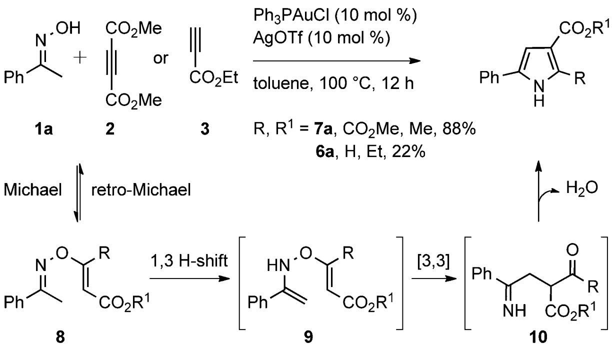
The second phase of the work was directed towards the catalytic rearrangement of *O*-vinyl oxime **5a** to pyrrole **6a**. Noble metals are known to catalyse related [3,3]-sigmatropic rearrangements,[12] including the Overman[13] and Claisen reactions.[14] Toluene was found to be the best solvent for the clean formation of pyrrole **6a** from *O*-vinyl oxime **5a**. A variety of noble metal catalysts were screened under microwave irradiation conditions, and the catalytic system derived from Ph_3PAuCl and $AgBF_4$ was optimal (for selected examples, see Table 1). Thus, rearrangement of **5a** in the microwave at 100 °C afforded the desired pyrrole **6a** in 68% yield. Experiments involving prolonged heating, inclusion of PPh_3 or $AgBF_4$ and the use of other gold(I) catalysts indicated that the specific gold-complex is necessary for the reaction to proceed at 100 °C. To the best of our knowledge this is the first example of noble metal catalysis of both the rearrangement of *O*-vinyl oximes to pyrroles and of N–O bond cleavage.

We next developed a more practical method for the gold-catalysed rearrangement of *O*-vinyl oximes under thermal conditions that eliminated the need for microwave irradiation. For example, stirring *O*-vinyl oxime **4a** in the presence of PPh_3AuCl and $AgBF_4$ in toluene at 100 °C for 12 h gave the desired pyrrole **7a** in good yield (Scheme 2). Several features of the gold-catalysed method are noteworthy. Microwave irradiation was not required to rearrange and dehydrate the *O*-vinyl oxime to form the pyrrole. The reaction proceeded at 100 °C in contrast to the 170 °C required for a thermal rearrangement. This method proved particularly amenable to α-methyl-α-aromatic ketoxime substrates. Interestingly, substituents at the R^1-position and non-aromatic groups at the R-position, substrates that are incompatible with our thermal nucleophilic catalysis conditions,[7] also gave good yields of the corresponding pyrroles **7e**, **7g–h**. Additionally, the pyrroles were isolated as the unsubstituted free *NH* compounds with little to no polymerisation observed. The *O*-vinyl oximes that did not rearrange to give the desired pyrroles afforded significant amounts of the oximes precursor indicating the predominance of the known retro-Michael reaction (*vide infra*).



Scheme 2 Gold-catalysed rearrangement of *O*-vinyl oximes to form pyrroles.

Finally, a gold-catalysed one-pot synthesis of pyrroles from activated alkynes and oximes was investigated. The gold should act as a multifaceted catalyst (MFC)[15] and promote the two mechanistically distinct steps of the reaction; the addition of the oxime to the alkyne and the subsequent rearrangement to the pyrrole. The acetylene moiety is a strong σ-donor and weak π-acceptor[16] towards the highly Lewis-acidic gold catalysts[17] making attack of the oxime oxygen onto the intrinsically electrophilic gold–alkyne complex highly favorable. Thus, reaction of acetophenone oxime **1a** with **2** in the presence of PPh_3AuCl and AgOTF afforded the desired pyrrole **7a** in good yield (Scheme 3). Experiments involving prolonged heating of **1a** and **2** and the addition of AgOTf only gave starting material. Similar to the rearrangement of *O*-vinyl oximes **5** to pyrroles **6**, the reaction of **1a** with mono-ester **3** gave a lower yield of pyrrole **6a**. This is possibly due to the



Scheme 3 Gold multifaceted catalysis reaction for the synthesis of pyrroles.

competing retro-Michael reaction followed by insertion of the catalyst into the alkynyl CH bond to form a gold–alkyne compound.[18] The overall process may follow a pathway that is similar to the Trofimov reaction. Initial gold-catalysed addition of oxime **1a** to the alkyne gives *O*-vinyl oxime **8**, which could then undergo a 1,3-hydrogen shift to afford diene **9**. A gold-catalysed cyclisation induced rearrangement[15] to give 1,4-iminoaldehyde **10**, followed by cyclodehydration would give the pyrrole, in a manner analogous to the Paal–Knorr pyrrole synthesis. The gold-complex catalyses both the formation of the *O*-vinyl oxime and its rearrangement to the pyrrole, but the precise role of the catalyst in each of these proposed steps is unclear and future efforts will be directed towards characterising intermediates to elucidate the reaction mechanism.[19]

In summary, we have developed a simple and effective gold-catalysed synthesis of pyrroles from *O*-vinyl oximes. In particular, we note the amenability of this novel method to the regioselective generation of di-, tri- and tetra-substituted pyrroles. A functional group handle at C3/C4 of the pyrrole is also incorporated, whilst the need for strongly basic conditions or high temperatures was eliminated. A mild gold-catalysed one-pot synthesis of pyrrole from activated alkynes and oximes was also developed. Importantly, the formation of pyrroles and other heterocycles should be accessible from the intermolecular addition of oximes to unactivated alkynes.[20] On going work is concerned with the further development of the one-pot gold-catalysed pyrrole formation reaction of both activated and unactivated alkynes as well as application of this method towards the synthesis of biologically active natural products. The results of these studies will be reported in due course.

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