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Direct synthesis of pyrroles *via* a silver-promoted three-component reaction involving unusual imidazole ring opening†

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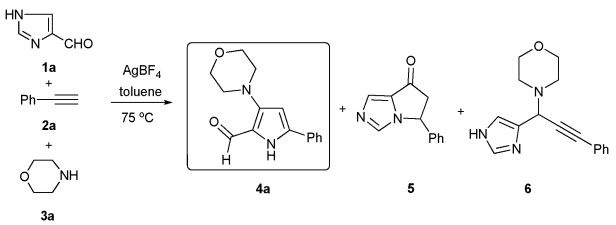
A novel silver-promoted three-component reaction toward the synthesis of multifunctionalized pyrroles has been developed. This reaction involves an unusual imidazole ring decomposition, presumably *via* 1,5-isomerization and subsequent hydrolysis.

Pyrrole is one of the most important heterocyclic structural motifs present in a large number of natural and synthetic molecules[1] with a wide range of utilities in medicinal chemistry[2] and material science.[3] Consequently, the importance of this heterocyclic motif has promoted the development of practical and diversified synthetic methods.[4,5] The traditional methods rely on the cyclization of amines with ketones or diketones discovered by Knorr and Paal in 1880's.[6] However, shortcomings including low yields and stepwise reactions limited the usage of this type of reactions. Recently, metal-catalyzed synthesis of pyrroles is becoming increasingly popular due to its high efficiency of constructing pyrrole motifs.[7] Examples include Rh(III) catalyzed coupling of alkynes with activated enamines,[5b] Rh(I) catalyzed [4+1] cycloaddition reactions,[7e] Cu(II) or Mn(II) promoted 1,4-addition of acetoacetate to vinyl azides[7f] and more. In addition, multicomponent reactions were also explored.[8] Despite all these achievements, it is still a big challenge to produce multifunctionalized pyrroles from readily available and easily varied substrates *via* a simple procedure.

In continuation with our interest in the syntheses of heterocycles through multicomponent reactions,[9] we observed that the silver promoted three-component reactions of imidazole-4-carboxaldehyde **1a**, phenylacetylene **2a** and morpholine **3a** afforded two unexpected products 3-aminopyrrole **4a** (structure was confirmed by X-ray structural analysis, see ESI†) and ketone **5** as well as propargyl amine **6** (Scheme 1). 3-Aminopyrrole is an important class of pyrrole which exhibits antibacterial, antiviral, anticonvulsant, analgesic, antiinflammatory, and antipyretic activities.[10] These features promoted us to investigate this unexpected and interesting reaction. We envisioned that this three-component reaction could be a promising method to synthesize functionalized pyrroles with high efficiency.



Scheme 1 Unexpected three-component reaction.

Our investigations commenced with the development of an optimal set of reaction conditions (see ESI†). After screening numerous conditions, it was found that the use of a quantitative amount of $AgBF_4$ and 1.5 equivalents of diisopropylethylamine (DIPEA) as the additive in wet *N*-methyl-2-pyrrolidinone (NMP) at 75 °C resulted in formation of the desired pyrrole **4a** in 62% yield. Further optimizations revealed that when a catalytic amount of $AgBF_4$ (0.2 equiv.) was used in combination with 1.2 equivalents of other silver additives with none or weak Lewis acidity, such as $AgNO_3$, Ag_2CO_3, Ag_2O and AgF, the desired pyrrole was still obtained in acceptable yields. Among the silver additive tested, $AgNO_3$ was found to be most compatible with this system, displaying the highest efficiency (**4a**, 61%). Water was proven to be necessary in the reaction system, when anhydrous solvents were used instead of wet solvents, only a trace amount of the desired pyrrole was observed. In all cases, ketone **5** was obtained as the inevitable by-product.

With these optimized conditions in hand, we embarked on an investigation of the substrate scope of this interesting transformation and the results are summarized in Table 1. A variety of terminal alkynes were tested. Among them, all aryl alkynes proceeded smoothly under the current conditions and gave the corresponding pyrroles in good yields. The aryl alkynes with electron-withdrawing groups produced the desired pyrroles in slightly higher yields (**4g–i**) than those bearing electron-donating groups (**4c–f**). The yields decreased dramatically when alkyl alkynes were employed (**4j–k**). Secondary amines other than morpholine and piperidine could be incorporated and the corresponding pyrroles were generated in good yield (**4l**).

Subsequently, imidazole aldehydes bearing substituents at 1- or 2- or 5-position were examined and the results are

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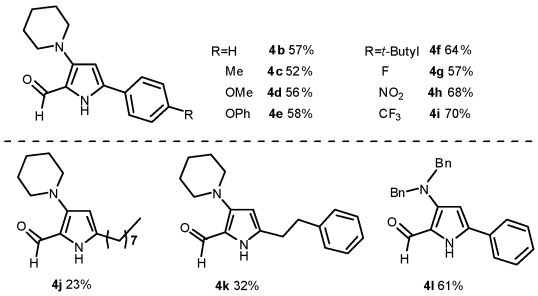
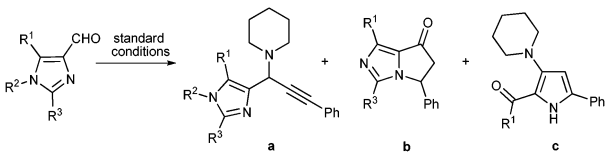
Table 1 Silver promoted three-component reaction: substrate scope[a,b]



[a] Unless otherwise specified, all reactions were carried out using aldehyde (0.3 mmol, 1 equiv.), alkyne (0.45 mmol, 1.5 equiv.) and secondary amine (0.36 mmol, 1.2 equiv.) with $AgBF_4$ (0.06 mmol, 0.2 equiv.), $AgNO_3$ (0.36 mmol, 1.2 equiv.) and DIPEA (0.45 mmol, 1.5 equiv.) in wet NMP (NMP : H_2O = 20 : 1, 0.6 mL) at 75 °C. [b] Isolated yields.

Table 2 Reaction with substituted imidazole-4-carboxaldehyde[a,b]



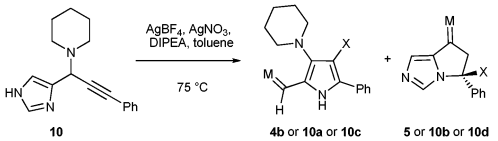
	Starting material	Product (yield)		
1	**7** (R^1, R^3 = H; R^2 = Trt)	**7a** (72%)	—	—
2	**8** (R^1, R^2 = H; R^3 = Me)	**8a** (21%)	**8b** (23%)	—
3	**9** (R^2, R^3 = H; R^1 = Me)	—	**9b** (56%)	**9c** (11%)

[a] All reactions were carried out using aldehyde, phenylacetylene and piperidine under standard reaction conditions. [b] Isolated yields.

depicted in Table 2. It is not surprising that the reaction with *N*-substituted imidazole-4-carboxaldehyde **7** only generated the sole propargylic amine **7a** in 72% yield. Noteworthily, when 2-methyl imidazole-4-carboxaldehyde **8** were employed, ketone **8b** and uncyclized products **8a** were obtained in low yields and only a trace amount of the desired pyrrole-2-carboxaldehyde was observed by mass spectroscopy. When 5-methylimidazole-4-carboxaldehyde **9** was introduced under the standard reaction conditions, 2-acetylpyrrole **9b** was formed in 56% yield together with 11% yield of the corresponding ketone **9c**. This observation strongly indicated that the carbonyl carbon of the pyrrole product came from the C5 of imidazole aldehyde, which suggested that unusual ring opening reactions were involved in the reaction. Therefore, we deduced that the unusual ring decomposition was caused by hydrolysis.

To elucidate the hydrolysis process, controlled reactions and isotopic labelling were performed, as shown in Table 3. In these reactions, propargylamine **10** was prepared as the substrate. As depicted before, the reaction did not proceed under anhydrous conditions. However, when 10 equivalents of H_2O were employed, pyrrole **4b** and ketone **5** were obtained in 51% yield and 11% yield respectively. Interestingly, when D_2O was

Table 3 Isotopic labelling reaction[a]

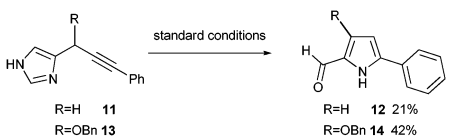


Entry	Additive	Products	Note
1	None	—	—
2	H_2O (10 equiv.)	**4b**, **5**	M = O, X = H
3	D_2O (10 equiv.)	**10a**, **10b**	M = O, X = D
4	$H_2{}^{18}O$ (10 equiv.)	**10c**, **10d**	M = ^{18}O, X = H[b]

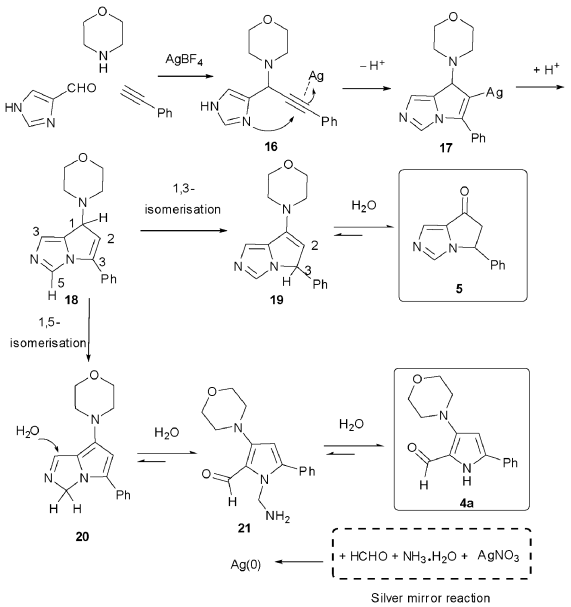
[a] All reactions were carried out using **10** (1 equiv.), $AgBF_4$ (0.2 equiv.), $AgNO_3$ (1.2 equiv.) and DIPEA (1.5 equiv.) and additive in anhydrous toulene at 75 °C. [b] HR/MS (ESI) calcd for **10c**: $C_{16}H_{19}N_2{}^{18}O$ $[M + H]^+$ 257.1540, found 257.1546; calcd for **10d**: $C_{12}H_{11}N_2{}^{18}O$ $[M + H]^+$ 201.0914, found 201.0910.

added to the reaction instead of H_2O, the deuterium atom was observed at the 4-position of pyrrole **10a** due to silver-D exchange. The β-position of ketone **10b** was also deuterized while the α-position remained unchanged.[11] The deuterization of the β-position of ketone indicated that a 1,3-isomerisation occurred. Similarly, a 1,5-isomerisation may be involved in the formation of pyrrole. When $H_2{}^{18}O$ was utilized instead of H_2O, it was observed that the normal oxygen atom of the carbonyl group of **10c** and **10d** was replaced by the ^{18}O atom indicated by HRMS. These experimental results strongly suggested that the carbonyl moiety was formed *via* hydrolysis. Interestingly, our further investigations of this reaction revealed that the substrates **11** and **13** with functional groups other than the amino group in the propargylic position could also tolerate this reaction. However, the corresponding products were generated in low yields as depicted in Scheme 2.

A plausible mechanism for this reaction is outlined in Scheme 3 on the basis of the above experimental proofs. Under optimized conditions, compound **16** was first generated *via* silver catalyzed three-component Mannich–Grignard reaction and it was then converted to compound **18** by cyclization and silver-proton exchange.[9a,12] Presumably, **18** could proceed along two pathways: 1,3-isomerisation and 1,5-isomerisation. The 1,3-isomerisation would afford enamine **19** and, from which, ketone **5** would be formed by hydrolysis. Since imidazole is a quite stable moiety, a direct hydrolysis is unlikely to take place on the aromatic imidazole ring, the 1,5-isomerisation process would destroy aromaticity of the imidazole moiety and simultaneously create a new aromatic pyrrole moiety to generate **20**. Hydrolysis of the imine group of **20** would produce the carbonyl group, subsequent hydrolysis steps resulted in the formation of pyrrole **4a**, formaldehyde and ammonia. In the presence of silver salt, the well known silver mirror reaction would take place consequently to consume the formaldehyde and ammonia, which would push the hydrolysis equilibrium towards



Scheme 2 Reaction with imidazole derivatives.



Scheme 3 A plausible mechanism.

the formation of the desired pyrrole product. The silver mirror was indeed observed in some cases. The reaction precipitate was further characterized by X-ray diffraction (XRD) (see ESI†).

In conclusion, we have developed a novel method for the synthesis of multifunctionalized pyrroles through silver promoted three-component reactions from imidazole aldehydes, secondary amines and terminal alkynes. In this reaction, an unprecedented imidazole decomposition was observed. Studies are ongoing to understand the reaction mechanism and apply this methodology to the synthesis of pyrrole alkaloids such as prodigiosin families.[1d,e]

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