ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 7437

Received 28th April 2014,
Accepted 15th May 2014

DOI: 10.1039/c4cc03129f

www.rsc.org/chemcomm

Copper-catalyzed 5-*endo*-trig cyclization of ketoxime carboxylates: a facile synthesis of 2-arylpyrroles†

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A novel and facile copper-catalyzed 5-*endo*-trig cyclization of ketoxime carboxylates for the synthesis of 2-arylpyrroles has been developed. The reaction tolerates a range of functional groups and is a practical procedure for rapid synthesis of 2-arylpyrroles in high yields under mild conditions.

Pyrroles are some of the most important heterocycles which are ubiquitous scaffolds in countless natural products, drugs, and functional materials.[1] Particularly, 2-arylpyrrole motifs are prevalent in drugs and materials, such as antipsychotic drugs (a), chromogenic and fluorescent anion sensors (b), BODIPY dyes (c) and ligands for transition metals (d) (Fig. 1).[2] In the past few decades, a number of methods have been developed for the synthesis of various pyrroles.[3] However, a general protocol for the synthesis of 2-arylpyrroles has rarely been developed.[4] Therefore, the development of novel and efficient methods for the straightforward synthesis of 2-arylpyrroles that are compatible with various functional groups and use readily available starting materials remains desirable.

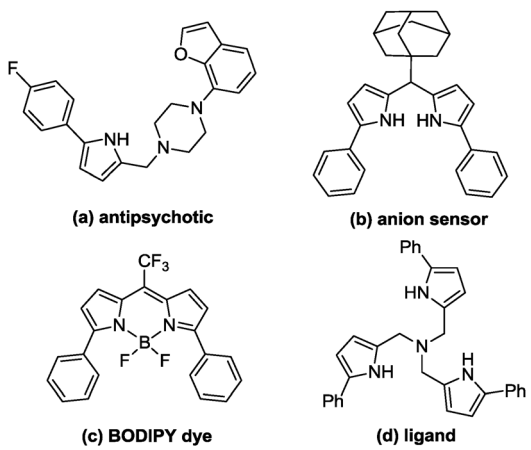

Fig. 1 Some compounds containing the 2-arylpyrrole framework.

Ketoximes and their derivatives are versatile building blocks in organic synthesis because of their ready accessibility and high reactivity.[5] In recent years, much attention has been paid to the transition-metal catalyzed transformation of ketoximes and their derivatives.[6] Particularly, transition-metal catalyzed cross coupling of ketoximes for construction of azaheterocycles is an active area of research. For example, Cu or Rh-catalyzed coupling of ketoxime carboxylates with vinylboronic acids, aldehydes, alkenes, pyridines, or *N*-sulfonylimines has emerged for construction of a series of azaheterocycles.[7] Cu-catalyzed coupling of ketoxime carboxylates with activated alkynes has been developed for the synthesis of di-ester substituted pyrroles.[8] Alternatively, intramolecular cyclization of ketoximes is a promising route for construction of azaheterocycles.[9] Cu or Pd-catalyzed 5-*exo*-trig cyclization of ketoximes has recently been developed for the synthesis of isoxazolines,[10] indoles,[11] and dihydropyrroles.[12] However, 5-*endo*-trig cyclization of ketoximes has not yet been realized due to their disfavored cyclization pattern according to Baldwin's rules. Our interest in the Cu-catalyzed transformation of ketoximes[7b,13] prompted us to study the intramolecular cyclization of ketoxime carboxylates. In this paper, we report on a facile and efficient Cu-catalyzed anti-Baldwin 5-*endo*-trig cyclization of ketoxime carboxylates for the synthesis of 2-arylpyrroles.

We began our study by investigating the Cu-catalyzed intramolecular cyclization of 1-phenylbut-3-en-1-one oxime acetate **1a** in DCE at 120 °C. We were pleased to find that the 2-phenyl-1*H*-pyrrole **2a** was obtained in 63% yield in the presence of CuI under argon (Table 1, entry 1). Encouraged by this result, further studies were performed for developing a synthetically useful procedure for the synthesis of 2-arylpyrroles. Therefore, various copper catalysts, such as CuCl, CuBr, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2$, were screened to determine if they improved the reaction efficiency (Table 1, entries 1–6). CuBr was found to be the most effective catalyst for the transformation, giving the desired 2-phenyl-1*H*-pyrrole **2a** in 85% yield (Table 1, entry 3). A control experiment confirmed that no

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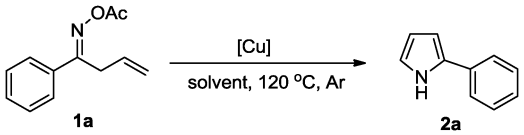
† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectral data for all products. See DOI: 10.1039/c4cc03129f

Table 1 Optimization of the reaction conditions[a]

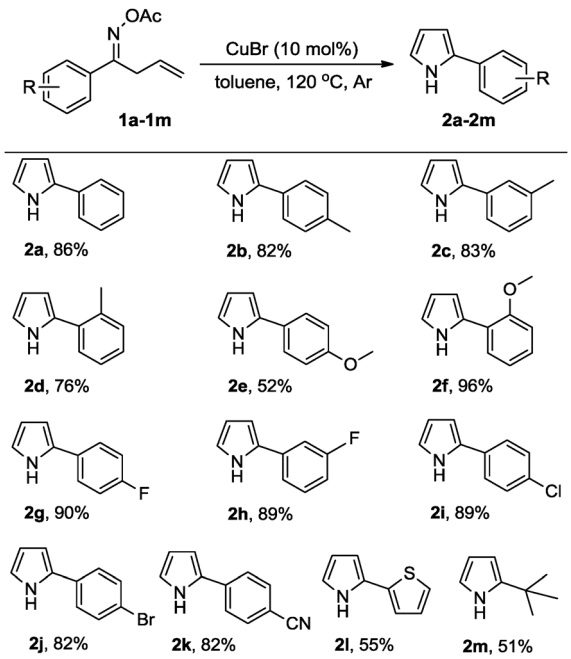


Entry	[Cu] Catalyst	Solvent	Yield[b] (%)
1	CuI	DCE	63
2	CuCl	DCE	72
3	CuBr	DCE	85
4	$CuCl_2$	DCE	60
5	$CuBr_2$	DCE	44
6	$Cu(OAc)_2$	DCE	73
7	—	DCE	n.r.[c]
8	CuBr	THF	56
9	CuBr	1,4-Dioxane	74
10	CuBr	CH_3CN	39
11	**CuBr**	**Toluene**	**86**
12	CuBr	DMF	Trace

[a] Reaction conditions: 1-phenylbut-3-en-1-one oxime acetate **1a** (0.2 mmol), [Cu] (10 mol%) in solvent (3 mL) at 120 °C under Ar. [b] Isolated yields. [c] n.r. = no reaction.

reaction occurs in the absence of a copper catalyst (Table 1, entry 7). Screening of different solvents, such as THF, 1,4-dioxane, CH_3CN, toluene and DMF, suggested that toluene was the first choice for the reaction, with which the reaction was complete in half an hour to give **2a** in 86% yield (Table 1, entries 8–12). Finally, the optimal reaction conditions were: substrate (1.0 equiv.), CuBr (10 mol%) in toluene at 120 °C under Ar.

With the optimized conditions in hand, we then investigated a series of ketoxime acetates to extend the substrate scope (Scheme 1). This transformation displayed good functional group tolerance and proved to be an efficient method for the synthesis of 2-arylpyrroles.

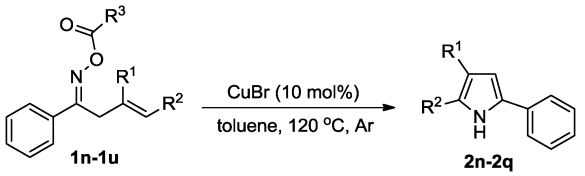


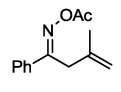
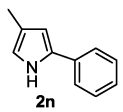
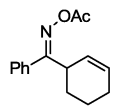
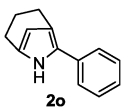
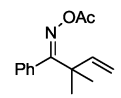
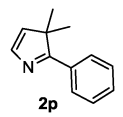
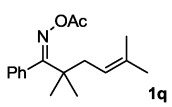
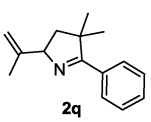
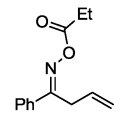
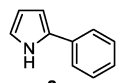
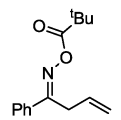
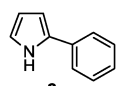
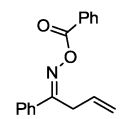
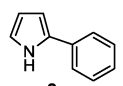
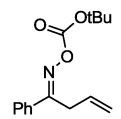
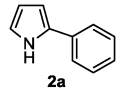
Scheme 1 Cu-catalyzed cyclization of ketoxime acetates. Reaction conditions: **1** (0.3 mmol), CuBr (10 mol%) in toluene (3 mL) at 120 °C under Ar; isolated yields.

Ketoxime acetates with electron-donating or electron-withdrawing groups on aryl rings, such as methyl, methoxy, fluoro, chloro, bromo and cyano, all gave the corresponding 2-arylpyrroles **2b–2k** in high to excellent yields. These results indicated that the reaction was insensitive to the electronic effects of the substrates. It should be noted that *ortho*-substituted ketoxime acetates such as **1d** and **1f** proceeded smoothly to give the desired 2-arylpyrroles **2d** and **2f** in 76% and 96% yields, respectively, thus implying that steric hindrance of the substrates has little influence on the reaction. In addition, 2-(thiophen-2-yl)-1*H*-pyrrole **2l** and 2-(*tert*-butyl)-1*H*-pyrrole **2m** could also be synthesized in 55% and 51% yield, respectively, in the reaction.

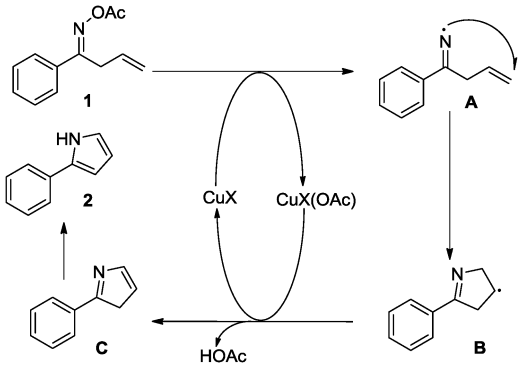
Subsequently, ketoxime acetates bearing different substituents on the olefin moiety were investigated in the reaction (Table 2).

Table 2 Cu-catalyzed cyclization of various ketoxime carboxylates[a]



Entry	Substrate	Product	Yield[b] (%)
1	 1n	 2n	64
2	 1o	 2o	0
3	 1p	 2p	0
4	 1q	 2q	80
5	 1r	 2a	84
6	 1s	 2a	82
7	 1t	 2a	80
8	 1u	 2a	0

[a] Reaction conditions: **1** (0.3 mmol), CuBr (10 mol%), toluene (3 mL), 120 °C, in Ar. [b] Isolated yields.



Scheme 2 Tentative mechanism of the reaction.

The 3-methyl-1-phenylbut-3-en-1-one oxime acetate **1n** was tolerated in the reaction and afforded the 4-methyl-2-phenyl-1*H*-pyrrole **2n** in 64% yield (Table 2, entry 1). However, a complex mixture was observed when the cyclohex-2-en-1-yl(phenyl)methanone oxime acetate **1o** or 2,2-dimethyl-1-phenylbut-3-en-1-one oxime acetate **1p** was used as the substrate (Table 2, entries 2 and 3). Additionally, an unexpected 4,4-dimethyl-5-phenyl-2-(prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrole **2q** was obtained in 80% yield when 2,2,5-trimethyl-1-phenylhex-4-en-1-one oxime acetate **1q** was employed as the substrate (Table 2, entry 4). Finally, different carboxylates of 1-phenylbut-3-en-1-one oxime were studied to examine the reactivity. It was found that propionate, pivalate, and benzoate show similar reactivity to acetate to give 2-phenyl-1*H*-pyrrole **2a** in 80–84% yield (Table 2, entries 5–7). However, no reaction occurred when 1-phenylbut-3-en-1-one oxime *tert*-butyl carbonate **1u** was used as the substrate (Table 2, entry 8).

On the basis of the above results and previous studies, a tentative mechanism for the cyclization reaction is proposed in Scheme 2. Firstly, Cu(I) initiated N–O bond cleavage of the ketoxime acetate generates an imino radical **A** and a Cu(II) species.[13] An anti-Baldwin intramolecular 5-*endo*-trig radical cyclization of intermediate **A** produces an intermediate **B**.[14] Then, single-electron oxidation of intermediate **B** by Cu(II) species forms a 2-phenyl-3*H*-pyrrole intermediate **C** and the active Cu(I) catalyst.[7b,13] Finally, tautomerization of intermediate **C** gives the desired 2-phenyl-1*H*-pyrrole **2**.

In summary, we have developed a novel and efficient Cu-catalyzed intramolecular 5-*endo*-trig cyclization of ketoxime carboxylates for the synthesis of 2-arylpyrroles. The reaction tolerates a range of functional groups and is a good protocol for rapid synthesis of valuable 2-arylpyrroles in high yields under mild conditions. A further study of the reaction scope and mechanism is underway in our laboratory.

This work was supported by generous grants from the National Natural Science Foundation of China (NSFC21272183) and the Fund of the Rising Stars of Shanxi Province (2012KJXX-26).

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