Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of substituted pyrroles via Ru(II)-catalyzed coupling of alkynes with enamides

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ARTICLE INFO

Article history:
Received 3 January 2013
Revised 22 February 2013
Accepted 5 March 2013
Available online xxxx

Keywords:
Pyrrole
Enamide
Coupling reaction
Alkyne
Ruthenium

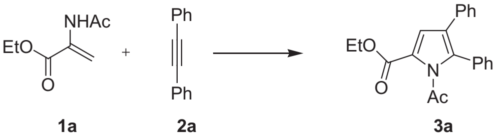
ABSTRACT

An efficient ruthenium-catalyzed oxidative cyclization of enamides with alkynes in water or dimethoxyethane leading to the pyrrole derivatives is reported. Typically, a mixture of ethyl 2-(acetylamino)acrylate, diphenylacetylene, [Ru(p-cymene)Cl_2] (2 mol %), KPF_6, and $Cu(OAc)_2$ in water was heated under refluxing conditions providing the N-acetylated pyrrole product in 95% yield.

Pyrrole scaffold is an important core structure in many pharmaceuticals,[1] natural products,[2] and functional materials.[3] Hence, the development of synthesis of pyrrole derivatives has driven attention to chemists. After pioneering Knorr-pyrrole synthesis,[4] a vast number of methods have been developed over the years such as cycloaddition,[5] metal catalyzed cyclization,[6] multicomponent and tandem reactions.[7] Among them, the transition metal catalyzed C–H bond functionalization strategy for the pyrrole synthesis ought to be a more atom-economical approach and thus receives much attention.

In recent days the utility of enamides as precursors appears, which causes C–C and C–N bond forming reactions leading to the pyrrole ring synthesis (Scheme 1).[8] Glorius[9] and Fagnou[10] have independently reported Rh(III) catalyzed oxidative coupling of enamides with internal alkynes, they synthesized a number of substituted pyrroles in good to moderate yields. However, the methods described above required expansive rhodium complexes as the catalysts. The use of cheaper, environmentally benign alternative catalysts is still desirable in organic transformation. Very recently we have reported Ru(II) catalyzed synthesis of *N*-acetyl enamides.[11] Inspired by aforementioned reports, our endeavor begins to find the utility of Ru(II) catalyzed reaction of enamides with unactivated alkynes. In this work, we wish to report an efficient synthesis of substituted pyrroles by oxidative cyclization of *N*-acetyl enamides with various symmetrical and unsymmetrical alkynes in the presence of [Ru(p-cymene)Cl_2], KPF_6, $Cu(OAc)_2{\cdot}H_2O$ as oxidant and DME as solvent, notably water also as a compatible solvent for many substrates.[12]

We began our study on the coupling of ethyl pyruvate derived *N*-acetylenamide **1a** with 1,2-diphenylacetylene (Tolan) (**2a**) (Eq. (1)). In a typical experiment, a mixture of enamide **1a**, alkyne **2a**, [Ru(p-cymene)Cl_2] (3 mol %, based on **1a**), KPF_6 (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) in a solvent was heated at 100 °C for 12 h. The reaction resulted in the formation of the substituted pyrrole **3a** in 75% isolated yield (Table 1, entry 1). The product was confirmed by NMR and mass analysis. Without KPF_6 or $Cu(OAc)_2{\cdot}H_2O$, the reaction rate was sluggish, indicating the requirement of KPF_6 and stoichiometric amount of oxidant for a better performance.



(1)

Further solvent screening, acetonitrile appeared to be unsuitable for the catalysis, but in the case of acetone, the product formation was moderate only at elevated temperature (Table 1, entries 2–4 and 26). Chloro solvents (DCE and $CHCl_3$) and DME performed well and yielded the desired pyrrole in high yields (Table 1, entries 5–8). Surprisingly, water was compatible with this reaction and the desired product was obtained in high yield 95% at 2 mol % catalyst loading (entry 9), notably the reaction rate drastically increased as compared to the organic solvents. Lowering the catalyst loading down to 1 mol % (Table 1, entry 10), the product conversion

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http://dx.doi.org/10.1016/j.tetlet.2013.03.013

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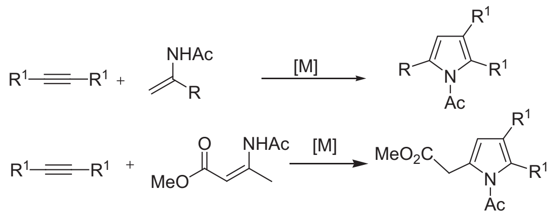

Scheme 1. Preparation of pyrroles via oxidative coupling of enamides with alkynes.

lowered even with the increase of the reaction time. In these screens, we found that the catalyst loading at 2 mol % level showed an optimal condition for the reaction in either water or DME. The turn over frequency for producing **3a** in water medium reaches 23.5 [(mol of product)/(mol of catalyst)·h], which is superior to the other reported data.[12] In addition, several oxidants such as $K_2S_2O_8$, oxone, and AgOAc were examined (Table 1, entries 11–25), but in lower yields or inactive for this reaction.

Under the optimized reaction conditions, several substituted alkynes **2a**–**j** reacted efficiently with *N*-acetyl enamide **1a** to give the corresponding substituted pyrrole derivatives **3a**–**j** in high yields (Scheme 2). Thus, halogen (chloro and bromo) substituted biaryl alkynes reacted with enamide **1a** smoothly and yielded the corresponding pyrrole derivatives **3b** and **3c**, respectively, in quantitative yields, but in the case of water medium the product yield was moderate due to the lower solubility. To improve the reactivity in water medium we tried various conditions like changing the additive and using phase transfer catalyst, finally all attempts were unsuccessful. With electron rich alkynes the oxidative coupling proceeded smoothly and afforded the corresponding annulated products **3d** and **3e** in 87% and 99% yields, respectively, in the organic medium. Similarly, electron deficient alkyne reacted smoothly and yielded the annulated product **3f** almost in quantitative yield. These results indicate that there is no reactivity difference between electron poor and rich alkynes in oxidative annulation reactions.

Further, the scope of the reaction extended to symmetrically substituted biaryl and heteroaryl alkynes, which were reacted smoothly with **1a** and furnished the desired products **3g** and **3h** in 81% and 99% yields, respectively. Aliphatic alkynes such as 3-hexyne and 4-octyne reacted similarly to aromatic alkynes and yielded the corresponding pyrrole derivatives **3i** and **3j** in high yields. Compared to the previous report,[12] this condition exhibits higher reactivity for biaryl, heteroaryl, and aliphatic alkynes.

Regioselective synthesis of organic molecules is a challenging task. Under the optimized conditions described above, we also extended to test the regioselectivity with unsymmetrical alkynes **(2k–m)**, (Scheme 3). *N*-Acetyl enamide **1a** underwent oxidative annulation with 1-phenyl-1-propyne (**2k**) affording coupling product **3k** in high yield 97% with excellent level of regioselectivity, the bulky group reside proximal to amide nitrogen. This selectivity pattern is quite similar with the previous reports by other's works.[10,12] Similarly 1-phenyl-1-pentyne (**2l**) and 1-(3-phenylprop-2-ynyloxy)benzene (**2m**) also regioselectively reacted with enamide **1a** exclusively providing annulated products **3l** and **3m** in 92% and 90%, respectively, with high regioselectivity.

The scope of ruthenium(II) catalyzed oxidative annulation reaction was further examined with various aryl-substituted enamides with 1,2-diphenylacetylene (**2a**) (Scheme 4). Thus, phenyl, *o*-methylphenyl, and 2-naphthyl substituted *N*-acetyl enamides underwent oxidative annulation with alkyne **2a** under the optimized condition, providing corresponding annulated products **3n**–**p** in good to moderated yields, but these substrates required little higher catalyst loading for better performance. Furthermore, we examined the cyclization of 1,3-diyene with enamide under the

Table 1
Optimization of reaction conditions[a]

Entry	[Ru(*p*-cymene)Cl_2] (mol %)	Oxidant (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] %
1	3	$Cu(OAc)_2$ (1.0)	*t*-AmOH	100	12	75
2	3	$Cu(OAc)_2$ (1.0)	Acetone	rt	12	NR
3	3	$Cu(OAc)_2$ (1.0)	Acetone	60	12	50
4	3	$Cu(OAc)_2$ (1.0)	MeCN	100	12	NR
5	3	$Cu(OAc)_2$ (1.0)	$CHCl_3$	90	6	92
6	3	$Cu(OAc)_2$ (1.0)	DCE	110	12	90
7	3	$Cu(OAc)_2$ (1.0)	DME	110	12	97
8	2	$Cu(OAc)_2$ (1.0)	DME	100	12	97
9	2	$Cu(OAc)_2$ (1.0)	H_2O	100	2	95
10	1	$Cu(OAc)_2$ (1.0)	H_2O	100	6	85
11	2	$Zn(OAc)_2$ (1.0)	H_2O	100	20	30
12	2	$Cu(OAc)_2$ (0.5)	H_2O	100	2	70
13	2	$K_2S_2O_8$ (1.0)	H_2O	100	12	NR
14	2	Oxone (1.0)	H_2O	100	12	NR
15	2	AgOAc (1.0)	H_2O	100	12	10
16	2	$Zn(OAc)_2$ (1.0)	DME	100	12	25[c]
17	2	$Cu(OAc)_2$ (0.5)	DME	100	12	72[c]
18	2	$K_2S_2O_8$ (1.0)	DME	100	12	20[c]
19	2	Oxone (1.0)	DME	100	12	10[c]
20	2	AgOAc (1.0)	DME	100	12	10[c]
21	2	$Zn(OAc)_2$ (1.0)	MeCN	100	12	10[c]
22	2	$Cu(OAC)_2$ (0.5)	MeCN	100	12	NR
23	2	$K_2S_2O_8$ (1.0)	MeCN	100	12	NR
24	2	Oxone (1.0)	MeCN	100	12	NR
25	2	AgOAc (1.0)	MeCN	100	12	5[c]
26	2	$Cu(OAc)_2$ (1.0)	Acetone	100	12	80[c]
27	—	$Cu(OAc)_2$ (1.0)	DME	110	12	NR
28	2	—	DME	110	12	Trace
29	—	—	DME	110	12	NR

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.1 equiv), KPF_6 (20 mol %), and [Ru(*p*-cymene)Cl_2] in solvent, DCE = 1,2-dichloroethane, DME = dimethoxyethane.
[b] Isolated yields.
[c] Yield determined by NMR using mesitylene as the internal standard, NR = no reaction.

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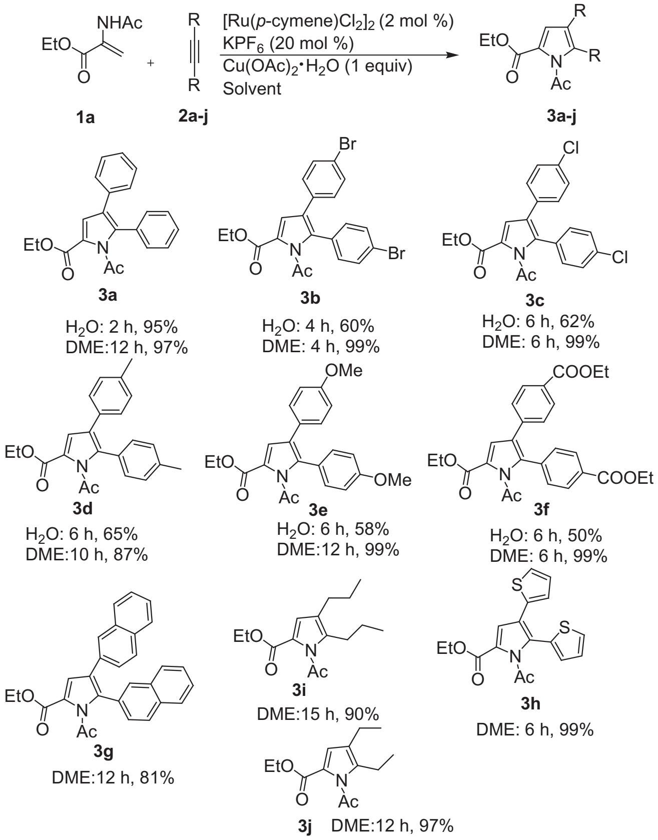
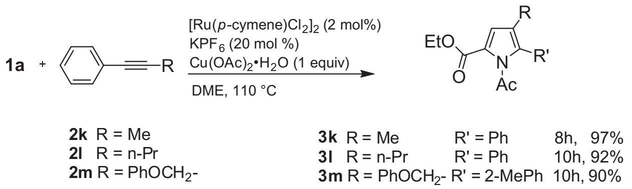
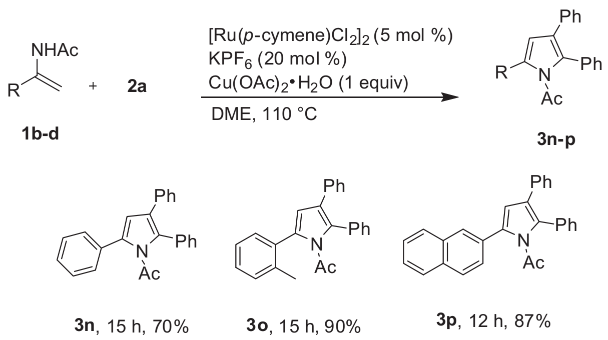


Scheme 2. Symmetrical alkynes in oxidative annulation.

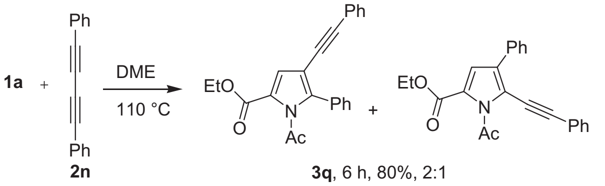


Scheme 3. Study of regioselectivity of alkynes.



Scheme 4. Annulation of various enamides with **2a**.

optimized condition. Gratifyingly, the corresponding annulated product formed, but the regioselectivity is poor and obtained 2:1 regioisomeric product in 80% yield (Eq. (2)).

 (2)

In summary, we have reported an efficient method for the preparation of pyrroles via the ruthenium catalyzed oxidative annulation of enamide with alkyne. In particular, the reaction can be carried out in the aqueous medium. Furthermore, the optimal condition developed in this work requires less amount of [Ru(p-cymene)Cl$_2$] as catalyst (at the level of 2 mol %), which makes this method useful for synthetic application.

Acknowledgment

We thank the National Science Council for the financial support (NSC-100-2113-M002-001-MY3).

Supplementary data

Supplementary data (experimental procedure and spectral data of all pyrrole products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.013.

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