Ruthenium-Catalyzed Oxidative Amidation of Alkynes to Amides

Andrea Álvarez-Pérez,† Miguel A. Esteruelas,§ Susana Izquierdo,§ Jesús A. Varela,† and Carlos Saá∗,†

†Centro Singular de Investigación en Química Biológica e Materiales Moleculares (CiQUS), Departamento de Química Orgánica, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
§Departamento de Química Inorgánica-Instituto de Síntesis Química y Catálisis Homogénea (ISQCH)—Centro de Innovación en Química Avanzada (ORFEO—CINQA), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

Supporting Information

ABSTRACT: Complex CpRuCl(PPh3)2 catalyzes reactions of terminal alkynes with 4-picoline N-oxide and primary and secondary amines to afford the corresponding amides. The reactions occur in chlorinated solvent and aqueous medium, showing applications in peptide chemistry. Stoichiometric studies reveal that the true catalysts of the processes are the vinylidene cations [CpRu(η^2-C=CHR)(PPh3)]^+ which are oxidized to the Ru(η^2-CO)-ketenes by the N-oxide. Finally, nucleophilic additions of primary and secondary amines to the free ketenes yield the corresponding amides.

Amide bonds play a crucial role in living organisms and are present in a great number of pharmacologically active compounds. Furthermore, they are widely used as synthetic materials, including nylon, hydrogels, supported catalysts, etc.† The conventional approach to amide formation is the condensation of an amine with a carboxylic acid via an active ester. In recent years, new catalytic methods, which offer alternatives for selective amide bond formation, have emerged to overcome some of the limitations of these standard protocols.‡ In this context, the use of surrogates for the oxidative transformations of terminal alkynes into ketenes, their use remains largely underused.§ Although terminal alkynes are promising surrogates of acyls in reactions with amines, through catalytic oxidative amidations, their use remains largely underused.³

We initially tested the oxidative amidation of phenylacetylenes 1a and 1b with secondary amines 2a and 2b using Rh catalysts (Lee’s conditions, Table 1). To our initial surprise, while 1a and 1b reacted smoothly with aniline 2a to give the secondary amides 3aa and 3ab in fairly good yields (entry 1), 1a and 1b were recovered when reacted with N-Mephenethylamine 2b either in CH2CN or DCE or in the presence of catalyst RhCl((PPh3)3 (entry 2).⁴ It was mandatory to use the ammonium salt of 2b in order to obtain the corresponding amides 3aa and 3ab in fairly good yields (entry 3). B. After this singular behavior of secondary amines under Rh catalysts (aniline 2a vs alkyamine 2b), we decided to compare these results against ruthenium catalysts. To our delight, we found that the use of electron-rich CpRu catalysts in noncoordinating DCE as solvent gives good to excellent yields of amides 3aa, 3ab, 3ba, and 3bb in two sets of conditions using the free amines (entries 1 and 2). Both N-oxide (entry 4) or Ru catalyst (entry 5) are required for the reaction to take place (see the SI for other conditions tried).

The substrate scope varying the nature of the alkyne was then examined under optimized conditions A (Scheme 2). Either electron-poor or electron-rich heteroaryl alkynes also gave rather good yields of tertiary amides 3cb and 3db. In addition, aliphatic and functionalized aliphatic alkynes (Cl, OBn) as well as enynes...
were also tolerated to give tertiary amides 3eb, 3fb, 3gb, and 3hb, respectively, in fairly good yields. Second, other secondary amines were also tested. Thus, five- and six-membered cyclic amines reacted smoothly to give good to excellent yields of cyclic tertiary amides 3ac, 3ad, 3ae, and 3af, respectively. In addition, the linear N,O-dimethylhydroxylamine and dibenzylamine gave the interesting Weinreb amide 14 3ag and dibenzyl-protected amide 3ah in rather good yields.

We also evaluated whether this oxidative amidation is suitable for the preparation of the interesting secondary amides (peptide bonds). As we already did with the secondary amines, we tested and compared the oxidative amidations of phenylacetylene 1a with three different primary amines 2i–k under Rh and Ru catalytic conditions (Table 2). While the employment of Rh catalyst (Lee’s conditions)5,15,2a proved relatively efficient for the preparation of anilide 4ai from aniline 2i (entry 1, 72%), it gave lower to negligible yields in the case of phenethyl and benzyl amides 4aj and 4ak from the free amines 2j and 2k (entries 2 and 3). Once again, it was mandatory to use the ammonium salts of 2j, k in order to obtain the corresponding amides 4aj and 4ak in excellent yields (entries 2 and 3). In contrast, amides 4ai–ak were always obtained in excellent yields from the free amines 2i–k using Ru catalysts (entries 1–3). Scaling was also possible since amide 4ak could be obtained in 94% isolated yield using 1 mmol of alkyne 1a.

The substrate scope varying the nature of the alkyne was first examined (Scheme 3). The (trimethylsilyl)acetylene 1i was found to be a good substrate for this amidation reaction to deliver the desilylated N-acetyl amide 4ik in excellent yield. Gratifyingly, functionalized aliphatic alkynes bearing CN, NHAc, OBn, and Cl groups as well as enynes and aromatic diynes were all well tolerated to afford moderate to excellent yields of the corresponding amides 4jk–pk. Then variation of

Table 1. Comparative Results of Rh- and Ru-Catalyzed Oxidative Amidations of Arylacetylenes 1a,b with Secondary Amines 2a,b

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne amine amide</th>
<th>[Rh] (%)</th>
<th>method A (amine 2 equiv) (%)</th>
<th>method B (amine 1 equiv/KPF₆ 1 equiv) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a 2a 3aa</td>
<td>79</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1b 2a 3ba</td>
<td>85</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1a 2b 3ab</td>
<td>c</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1b 2b 3bb</td>
<td>traces</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>1a 2b-HCl 3ab</td>
<td>92</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

**Reaction conditions Rh:** alkyne 1 (0.4 mmol), amine 2 (1.2 equiv), [Rh(cod)Cl]₂ (3 mol %), P(4-FC₆H₄)₃ (12 mol %), 4-picoline N-oxide (1.2 equiv), CH₃CN (0.8 mL), 60 °C. **Reaction conditions Ru:** alkyne 1 (0.4 mmol), CpRuCl(PPh₃)₂ (5 mol %), 4-picoline N-oxide (2 equiv), DCE (3 mL), 100 °C, amine 2 (2equiv) (method A) or amine 2 (1equiv) + KPF₆ (1equiv) (method B). **Starting material recovered either with CH₃CN or DCE as solvents.**

Table 2. Comparative Results of Rh- and Ru-Catalyzed Oxidative Amidations of Phenylacetylene 1a with Primary Amines 2i,j,k

<table>
<thead>
<tr>
<th>entry</th>
<th>R amine amide</th>
<th>[Rh] (%)</th>
<th>[Ru] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph 2i 4ai</td>
<td>72</td>
<td>98⁹</td>
</tr>
<tr>
<td>2</td>
<td>Bn 2j 4aj</td>
<td>23</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(CH₂)₂Ph 2k 4ak</td>
<td>traces</td>
<td>98 (94)⁹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Method B.** A mixture of H₂O/DCE 95:5 was used as solvent. **K₂CO₃ (0.3 equiv) and KPF₆ (1 equiv) were added.** **Isolated yield using 1 mmol of 1a.**

were also tolerated to give tertiary amides 3eb, 3fb, 3gb, and 3hb, respectively, in fairly good yields. Second, other secondary amines were also tested. Thus, five- and six-membered cyclic amines reacted smoothly to give good to excellent yields of cyclic tertiary amides 3ac, 3ad, 3ae, and 3af, respectively. In addition, the linear N,O-dimethylhydroxylamine and dibenzylamine gave the interesting Weinreb amide 14 3ag and dibenzyl-protected amide 3ah in rather good yields.

We also evaluated whether this oxidative amidation is suitable for the preparation of the interesting secondary amides (peptide bonds). As we already did with the secondary amines,
The amine partner was analyzed. Either simple methylamine 2l or functionalized allyl- and propargylamines 2m and 2n gave moderate to good yields of the corresponding amides 4al–an. Pleasingly, 2-(aminomethyl)aniline 2o, a difunctional aniline, and benzyl amine could be conveniently diazotized to give the diamide 4ao in fairly good yield. Natural alkaloids bearing primary amines like (−)-leucine 2p and tryptamine 2q were also acylated to the corresponding amides 4ap and 4aq with very good yields. Interestingly, oxidative amiations with the more challenging chiral secondary (R)-1-phenylethylamine 2r and tertiary tert-butylamine 2s smoothly occurred to give the chiral secondary amide 4ar and N-tert-butylyphenylacetamide 4as with excellent yields.

The oxidative amidation not only occurred in boiling chlorinated solvents but also in aqueous media at 37 °C, which suggests interesting applications in peptide chemistry (Scheme 4). Thus, excellent yields of the secondary amide 4ai (98%) were obtained when the reaction was run either in pure DCE or in a mixture DCE/H2O 5:95 (Table 2). Oxidative amidations of phenylacetylene 1a with methyl ester derivatives of l-amino acids bearing primary amines such as phenylglycine 8a, serine 8b, and MeS-cysteine 8c and secondary amines such as proline 8d smoothly occurred to give the corresponding N-acyl derivatives 9aa–ad in excellent yields. Interestingly, the oxidative amidation is completely chemoselective since reaction only by the more nucleophilic amino group of serine 8b was observed. On the other hand, oxidative amidations of N-nosyl-N-propargyl γ-aminooester 1q16 occurred uneventfully to give the amidoester derivatives 9qd and 9qe in quite good yields.17

To gather information about the mechanism of the amination, we reproduced the elemental steps of the catalysis through stoichiometric reactions performed at room temperature. In DCE, the ruthenium complex CpRuCl(PPh3)2 reacts with phenylacetylene (1a) in the presence of KPF6 to give the previously reported vinylidene salt [CpRu(4-Me-py)(PPh3)2]PF6 (1 equiv) as a result of the extraction of the chloride anion and the alkylene-vinylidene tautomerization of the hydrocarbon. Phosphine dissociation is not observed. The addition of a stoichiometric amount of 4-picoline N-oxide to an NMR tube containing a dichloromethane-5 solution of 5 smoothly affords a mixture of 6 (10%), the picoline derivative [CpRu(4-Me-py)(PPh3)2]PF6 (6; 59%), and a Ru–C═O(CH3)2Ph acyl species (31%). Noticeable spectroscopic features of the latter are a singlet at 3.34 ppm due to the CH2 group in the1H NMR spectrum, two singlets at 194.5 and 184.2 ppm corresponding to the CO and CH2 acyl-carbon atoms in the31P{1H} NMR spectrum. Its formation is a strong indirect evidence of the oxidation of the Ru–C bond of 5 to give a Ru(n=CO)-ketene intermediate20 that is trapped by traces of water present in the medium (Scheme 5). The dissociation of the ketene and the subsequent coordination of the generated 4-picoline leads to 6. In addition, it should be pointed out that traces of phosphate oxide are not observed. The formation of the acyl species does not appear to take place under catalytic conditions, i.e., in the presence of an excess of acyl. When 4-picoline N-oxide and benzylamine (2j) were added to the dichloromethane-d2 solution of 5, N-benzyl-2-phenylacetamide (4aj) and 6 were formed. Complex 6 reacts...
The initially formed Ru-vinylidene intermediates. Ketenes are converted to Ru-ketenes via oxidation of terminal alkynes to yield the corresponding amides. The process occurs by outer-sphere process involving the capture of the released ketene from the ruthenium coordination sphere; and (iv) the formation of the amide is an 1,2-addition of the vinylidene, displaces the ketene from the ruthenium N-oxide as external oxidant. Remarkably, the catalysis not only takes place in chlorinated solvents but also in aqueous media, which opens challenging applications in peptide chemistry. The process occurs by the amine. The cycle shown in Scheme 6 summarizes these features.

Scheme 6. Mechanism Proposed for the Ru-Catalyzed Oxidative Amidation of Terminal Alkynes with Amines

In conclusion, efficient ruthenium-catalyzed oxidative amidations of alkynes to primary and secondary amides have been developed using 4-picoline N-oxide as external oxidant. Remarkably, the catalysis not only takes place in chlorinated solvents but also in aqueous media, which opens challenging applications in peptide chemistry. The process occurs by the initial oxidation of the initially formed Ru-vinylidene intermediates. Ketenes are released and trapped by the nucleophilic primary and secondary amines to yield the corresponding amides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01993.

Detailed experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: maester@unizar.es.
*E-mail: carlos.saa@usc.es.

ORCID

Miguel A. Esteruelas: 0000-0002-4829-7590
Jesús A. Varela: 0000-0001-8499-4257
Carlos Saá: 0000-0003-3213-4604

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work has received financial support from MINECO (projects CTQ2014-59015R, CTQ2017-87939R, and CTQ2017-82935-P and the ORFEO-CINQA network CTQ2016-81797-REDC), the Xunta de Galicia (project GRC2014/032, ED431C 2018/04, Centro singular de investigación de Galicia accreditation 2016–2019, ED431G/09), DGA (No.E06_17R), and the European Union (European Regional Development Fund - ERDF). A.A-P. thanks the Spanish MICINN for a predoctoral FPI fellowship. We thank Prof. J. Granja (CiQUS) for a generous gift of aminoester derivatives.

REFERENCES


(11) Catalytic combinations of [Ru(p-cym)Cl2]2 and PPh3 or electron-poor and electron-rich phosphines met with failures. See the Supporting Information for details.


(13) The reaction failed or gave traces of amide formation in the typically used apolar toluene or coordinating CH3CN. See the Supporting Information for details.


(17) Amides 3bj–k, 3bn, and 3br could be also obtained by reaction of alkyne 1b with the corresponding amine 2·HCl in aqueous media at 37 °C. For amide 3bi, free amine 2i was used. Alkyne 1b was partially recovered unchanged. See the Supporting Information for details.


(20) For the observation of Ir(η2-CO)ketene complexes, see: Grotjahn, D. B.; Lo, H. C. Organometallics 1995, 14, 5463–5465.

(21) An alternative mechanistic proposal based on initial formation of aminocarbene (by trapping of the vinylidene 5 with the amine 2) followed by its oxidation with the N-oxide occurs very slowly and was therefore ruled out.