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Expeditious Approach to 5-Aroyl-pyrrolidinones by a Novel PIFA-Mediated Alkyne Amidation Reaction

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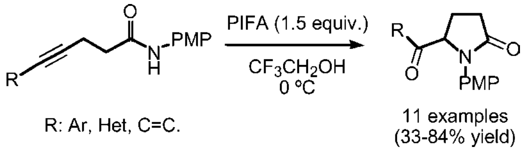
ABSTRACT



A novel metal-free approach to the alkyne amidation reaction is presented. The oxidation of properly substituted amides by the hypervalent iodine reagent PIFA provides the generation of a nitrenium ion that can react intramolecularly with a triple bond, leading to the construction of the title compounds.

The intramolecular addition of nitrogen functionalities across carbon−carbon multiple bonds is a highly efficient route to nitrogen-containing heterocycles. Fueled by the development of new catalyst systems, inter- and intramolecular alkyne hydroamination is becoming an interesting approach to the formation of linear or cyclic amines or imines that meets today's requirements for atom economy.[1] The employment of alkaline metals,[2] transition metal complexes,[3] lanthanides,[4] and actinides[5] as catalysts offers a representative overview of the research in this area.[6] However, the employment of high quantities of either toxic or expensive metal salts, the high sensitivity of some of these complexes to air and moisture, and the low tolerance to different functional groups are the major drawbacks of this transformation. Therefore, the application of these protocols to target-oriented synthesis is still very limited.[7] Thus, the development of new protocols for alkyne amination reactions remains an important goal in synthetic organic chemistry.

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(1) Recent reviews: (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (b) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(2) (a) Cid, M. M.; Domínguez, D.; Castedo, L.; Vázquez-López, E. M. *Tetrahedron* **1999**, *55*, 5599−5610. (b) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

(3) Early transition metals: (a) Bystschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935. (b) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956. (c) Tillack, A.; Garcia Castro I.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541. Palladium: (d) Yamamoto, Y.; Kadota, I.; Lutete, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (e) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc. 2002*, *124*, 12670. (f) Jacobi, P. A.; Brielman, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013. Ruthenium: (g) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222. Rhodium: (h) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339. Silver: (i) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855.

(4) (a) Sukwon, H.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (b) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770.

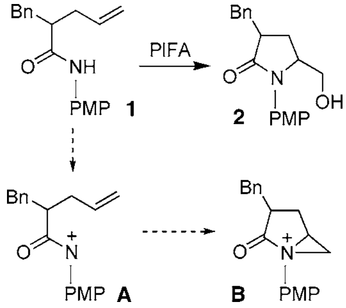
(5) (a) Stubbert, B. D.; Stern, C. L.; Marks, T. J. *Organometallics* **2003**, *22*, 4836. (b) Straub, T.; Haskel, A.; Neyround, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017.

(6) Some electrophilic reagents also promote related processes. See for example: (a) I_2: Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (b) $KMnO_4$: Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5*, 2287. (c) IPy_2BF_4: Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.

10.1021/ol0510623 CCC: $30.25

Recently, we reported that the action of the hypervalent iodine reagent[8] [phenyliodine(III)bis-trifluoroacetate] (PIFA) on *N*-*p*-methoxyphenyl-4-pentenamides of type **1** (see Scheme 1) can provide the construction of the 5-hydroxymethylpyrrolidinone derivative **2** efficiently.[9] The generation of an acylnitrenium ion **A** and its subsequent trapping by the olefin fragment to form, via intermediate **B**, the final heterocycle featuring the vicinal hydroxyamino moiety are the essential key steps of this transformation.

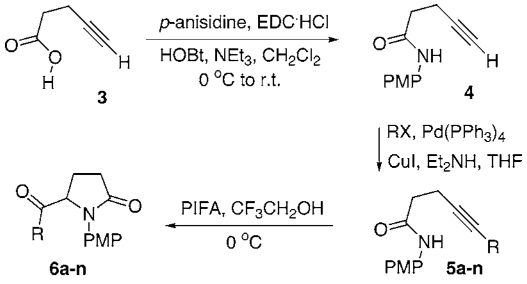
Scheme 1. PIFA-Mediated Olefin Amidohydroxylation



The hypothesis that we will confirm in this Letter can be stated as follows. If the success of the former cyclization relies on the intramolecular nucleophilic attack of the olefin to the deficient nitrogen, we can presume that a similar behavior would operate starting from the analogous alkynylamides of type **5**. By inspection of the related literature, we found that the formation of paired imines/enamines is the final destiny of the triple bond in almost all occasions.[10] Therefore, we envisaged that the design of a procedure that could eventually incorporate functionality across both positions of the triple carbon−carbon bond in one single step would be more desirable in order to enrich the versatility of such functional groups as a synthon for a diverse array of modern synthetic methods.

The required β-alkynylamide precursors **5a**−**n** were prepared in a two-step sequence, as outlined in Scheme 2. Amide **4** was synthesized via EDC·HCl/HOBt[11] coupling of commercially available 4-pentynoic acid (**3**) with *p*-anisidine. Finally, the substitution at the terminal position of the triple bond[12] in amide **4** was introduced by a Sonogashira cross-coupling reaction[13] using appropriately substituted iodides or bromides (RX) in variable yields (32−81%) as shown in Table 1.

Scheme 2. PIFA-Mediated Alkyne Amidohydroxylation



entry	conditions	yield (%)
1	PIFA, CH_2Cl_2, 0 °C	0^a
2	PIFA, CH_3CN, 0 °C	0^a
3	**PIFA, CF_3CH_2OH, 0 °C**	**6a (62)**
4	PIDA, CF_3CH_2OH, 0 °C	0^a

[a] Unreacted starting material was recovered. EDC·HCl: *N*-(3-Dimethylaminopropyl)-*N′*-ethyl-carbodiimide hydrochloride. HOBt: 1-Hydroxybenzotriazole. PMP: *p*-Methoxyphenyl.

Amide **5a** was selected to optimize the cyclization process. We tested common aprotic solvents such as CH_2Cl_2 and CH_3CN (see Scheme 2), concluding that the use of a fluorinated alcohol such as trifluroethanol as a solvent[14] was essential for an efficient transformation into the corresponding 5-aroylpyrrolidinone **6a**. Another related hypervalent iodine reagent [phenyliodine(III) diacetate] (PIDA) was also tested with negative results.

One of the primary driving forces of this 5-*exo-dig* cyclization reaction is the aptitude of the triple bond to behave as a nucleophile. Thus, by modifying the nature of the aryl ring, we attempted to find a direct relationship between the feasibility of the final cyclization and the electron density around the triple bond. As expected (see Table 1), despite of the lack of reactivity of derivatives **5j**−**l** under a variety of reaction conditions, a series of pyrrolidinones **6a**−**h** were obtained in moderate to good (58−84%) yields. On the other hand, pyrrolidinone **6i** could be obtained but in a lower (33%) yield as a result of the diminished donating properties of the halogen atom.

Trying to expand the scope of the presented cyclization, the behavior of other π-extended systems of olefinic nature was also tested. Thus, enyne amides **5l**−**n** reacted with PIFA under standard conditions (see Table 1). Thus, while vinyl-substituted alkynylamide **5l** afforded only complex mixtures of polymeric materials, **5m**,**n** yielded the desired heterocycles **6m**,**n**, respectively, in good yields.

The described transformation can be rationalized as shown in Scheme 3. We propose that the nitrenium ion **C**, generated

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[7] Some exceptions: (a) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823. (b) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (c) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323.

[8] Some selected reviews about hypervalent iodine chemistry: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665. (b) Wirth, T. *Top. Curr. Chem.* **2003**, 224, 1. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89. (e) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997.

[9] Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *Tetrahedron* **2004**, *60*, 6533.

[10] Imines/enamines obtained could be further modified in a second step: (a) Garcia Castro, I.; Tillack, A.; Hartung, C. G.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 3217. (b) Haak, E.; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2002**, 457. (c) Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2002**, 1213.

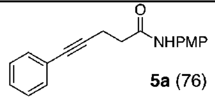
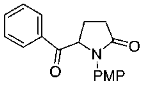
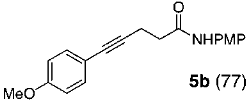
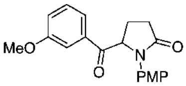
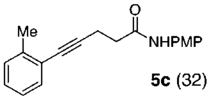
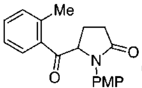
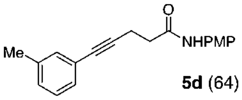
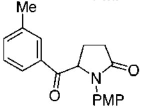
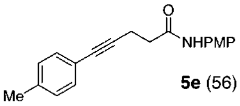
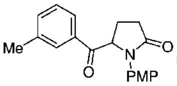
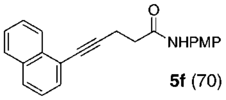
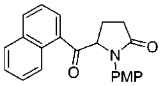
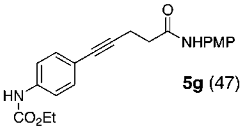
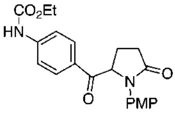
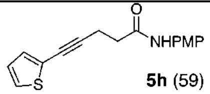
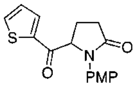
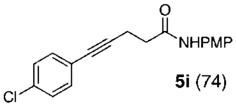
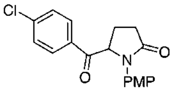
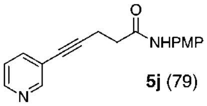
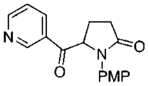
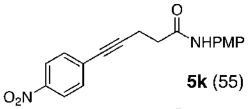
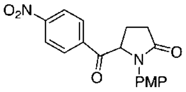
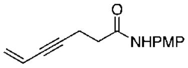
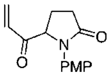
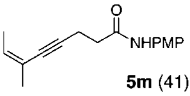
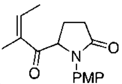
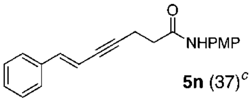
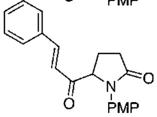
[11] Sukekatsu, N. *Chem. Lett.* **1997**, 1.

[12] PIFA reacts with terminal alkynes to produce α-hydroxy ketones; see: Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837.

[13] For a mini account, see: Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

[14] Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18.

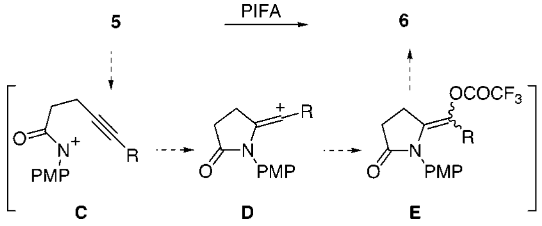
Table 1. 5-Substituted Pyrrolidinones **6** Prepared[a]

entry	Alkynylamides **5** (%)	Pyrrolidinones **6** (%)
1	 **5a** (76)	 **6a** (62)
2	 **5b** (77)	 **6b** (84)
3	 **5c** (32)	 **6c** (77)
4	 **5d** (64)	 **6d** (70)
5	 **5e** (56)	 **6e** (58)
6	 **5f** (70)	 **6f** (69)
7	 **5g** (47)	 **6g** (71)
8	 **5h** (59)	 **6h** (74)
9	 **5i** (74)	 **6i** (33)[b]
10	 **5j** (79)	 **6j** (0)
11	 **5k** (55)	 **6k** (0)
12	 **5l** (81)[c]	 **6l** (0)
13	 **5m** (41)[c]	 **6m** (51)
14	 **5n** (37)[c]	 **6n** (68)

[a] Standard reaction conditions: 1.5 equiv of PIFA in CF_3CH_2OH as a solvent (50 mM based on the amide) at 0 °C for 1−3 h. [b] Reaction carried out at 65 °C. [c] Bromides were used instead of the corresponding iodides.

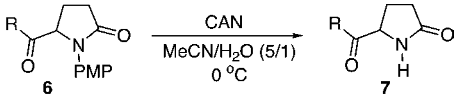
by the action of the mild oxidant PIFA on amides **5**,[15] reacts intramolecularly with the alkyne residue to form a new intermediate **D**. Then, this intermediate, which is stabilized as a linear carbocation by the donating properties of either the aryl ring or the electron-enriched olefins, is trapped by a free ligand delivered by PIFA, resulting in the formation of a nonisolable ester, **E**. Ultimately, after basic hydrolysis during workup, the substituted pyrrolidinone skeleton **6** is formed.

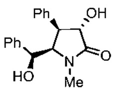
Scheme 3. Mechanism for the Alkyne Amidohydroxylation



Finally, the suitability of the presented novel strategy for the pyrrolidine ring formation oriented to the natural product synthesis would be of higher interest if the required PMP substituent could be removed for further manipulations in the heterocyclic skeleton. In our case, removal of the PMP group from derivatives **6** using ammonium cerium(IV) nitrate (CAN)[16] rendered nicely the desired derivatives **7a**−**e** (Scheme 4). It is noteworthy that pyrrolidinone **7a** contains the main framework of the Clausenamide alkaloid.[17]

Scheme 4. Removal of the PMP Group




(-)-clausenamide

entry	R	**7** (%)
1	phenyl	**a** (71)
2	*p*-methoxyphenyl	**b** (76)
3	*p*-methylphenyl	**c** (62)
4	2-thienyl	**d** (79)
5	(*E*)-stiryl	**e** (72)

In conclusion, a novel, straightforward approach to the intramolecular amidation of alkynes by a PIFA-promoted cyclization reaction has been described and applied to the synthesis of 5-substituted pyrrolidinone derivatives in a few

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[15] (a) Falvey, D. E. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M., Jones, M., Jr., Eds.; John Wiley & Sons: New Jersey, 2004; pp 593. (b) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581.

[16] Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

steps and good overall yields. The designed synthesis allows the preparation of electronically tunable alkyne precursors, and its effect on the reported cyclization has also been evaluated.

Acknowledgment. Financial support from the University of the Basque Country (9/UPV 41.310-13656/2001) and the Spanish Ministry of Science and Technology (CTQ 2004-03706/BQU) is gratefully acknowledged. S.S. thanks the Basque Government for a predoctoral scholarship.

Supporting Information Available: Characterization data for compounds **4**, **5a−n**, **6a−i**,**m**,**n**, and **7a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0510623

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(17) This alkaloid was isolated from an aqueous extract of dry leaves of Chinese folk medicinal *Clausena lansium* and exhibits a potent hepatoprotective and antiamnesiac effect. (a) Yan, Z.; Wang, J.; Tian, W. *Tetrahedron Lett.* **2003**, *44*, 9383. (b) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (c) A close analogue of Clausenamide could be employed for the treatment of osteoporosis; see: Cook, J. H.; Barzya, J.; Brennan, C.; Lowe, D.; Wang, Y.; Redman, A.; Scott, W. J.; Wood, J. E. *Tetrahedron Lett.* **2005**, *46*, 1525. (d) Efforts to apply our strategy to the synthesis of the natural product along with a series of related analogues are currently in progress and will be published elsewhere.