Application of the PIFA–mediated alkyne amidation reaction to the formal synthesis of *(±)-clausenamide*

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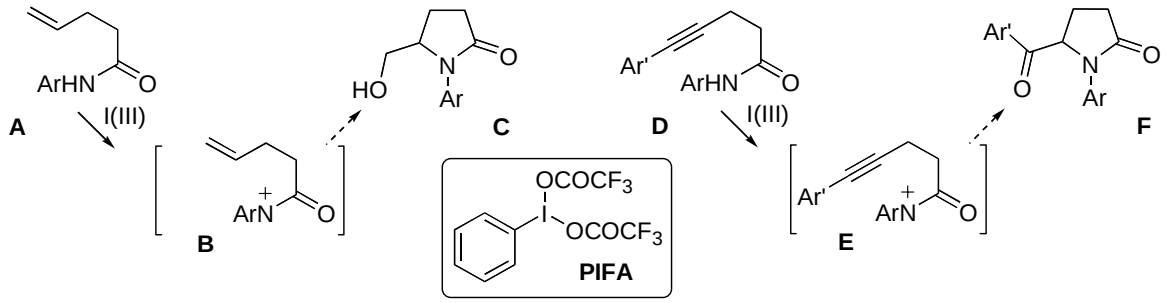
Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

Abstract
The hypervalent iodine reagent PIFA promotes the intramolecular electrophilic cyclization of easily accessible *N*-aryl and *N*-methylalkynylamides leading to the formation of the pyrrolidinone skeleton in a very efficient way. This strategy has found application in the preparation of a key intermediate in the total synthesis of *(±)-clausenamide* alkaloid.

Keywords: Hypervalent iodine, pyrrolidinone, clausenamide, cyclization

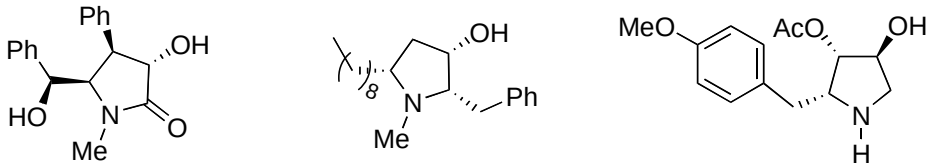
Introduction

When properly substituted amides are treated with the hypervalent iodine reagent PIFA,[1] [*bis*(trifluoroacetoxy)iodo]benzene, an acylnitrenium ion (**B** and **E**) is formed provided that an electron-releasing group is attached to the nitrogen to stabilize such deficient species (see Scheme 1).[2] If under such conditions the substrate contains an additional nucleophilic group, a heterocyclic compound can be formed after an intramolecular cyclization process. We have applied this strategy to amides containing olefins (**A**) or alkynes (**D**), as the nucleophilic component of the reaction, to afford, respectively, a series of 5-hydroxymethylpyrrolidinones (**C**)[3] or 5-aroylpyrrolidinones (**F**).[4]



Scheme 1

Such pyrrolidine nucleus is found in many natural products and it constitutes an interesting motif with pharmaceutical interest. Some selected examples include the liver protecting agent *(-)-clausenamide*,[5] the antibiotic *(-)-anisomicine*,[6] and the potent fungicide *(+)-preusine*[7] (see Figure 1). Considering its close structural similarity to pyrrolidinones of type **F**, we embarked in the formal synthesis of one of these related natural products by using our PIFA-mediated strategy that transforms alkynylamides into 5-aroylpyrrolidinones as the key step of the synthesis.



(-)-clausenamide *(+)-preusine* *(-)-anisomicine*

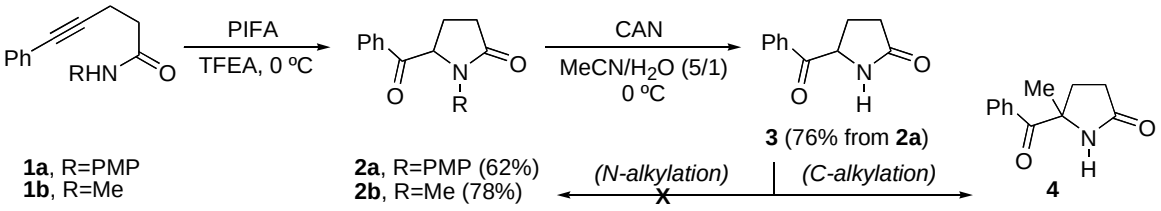
Figure 1

Results and Discussion

(±)-Clausenamide is the main component of aqueous extract of the leaves of *Clausena lansium*, a plant extensively employed in chinese folk medicine.[8] This alkaloid has shown efficiency as a liver–protecting agent against chemical toxins,[9] as an inductor effect over P450 cytochrome,[10] and also as a protector against cerebral hypoxia.[11] In fact, the possible application of this compound for the prevention and/or treatment of degenerative processes, such as Alzheimer's disease, is under study.[12] Due to the low concentration of the alkaloid in the natural media, an efficient chemical synthesis is highly desirable.[13] Therefore, to accommodate its preparation to our synthetic design, in combination with previous procedures, properly substituted substrates had to be prepared.

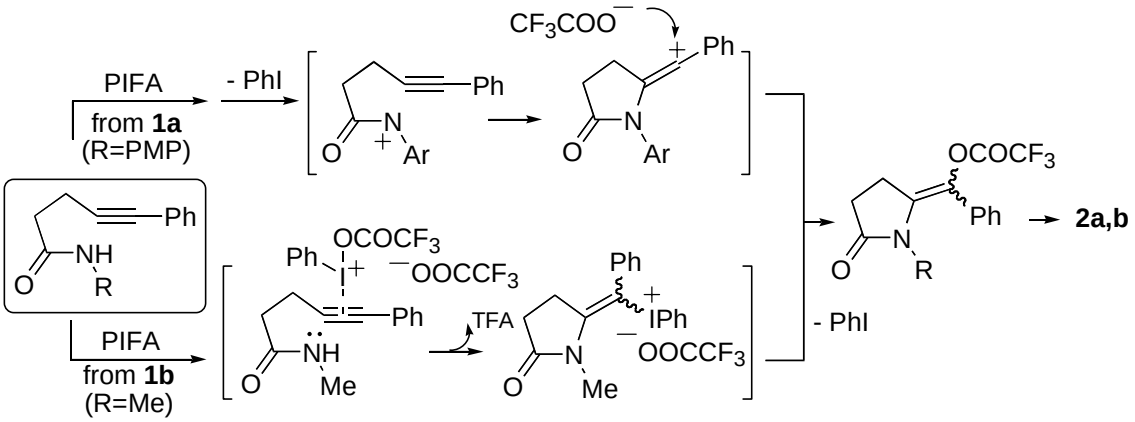
Our first attempt (see Scheme 2) started with the cyclization of the preformed[14] alkynylamide **1a**, which on treatment with PIFA in trifluoroethanol[15] at 0 ºC afforded the desired pyrrolidinone **2a** in 62% yield. Location of the methyl group at nitrogen required further removal of the PMP

group and a subsequent *N*-methylation process. Although elimination of the aryl group was easily accomplished by using ceric ammonium nitrate, all efforts to *N*-methylate pyrrolidinone **3** furnished the *C*-alkylated product **4**.



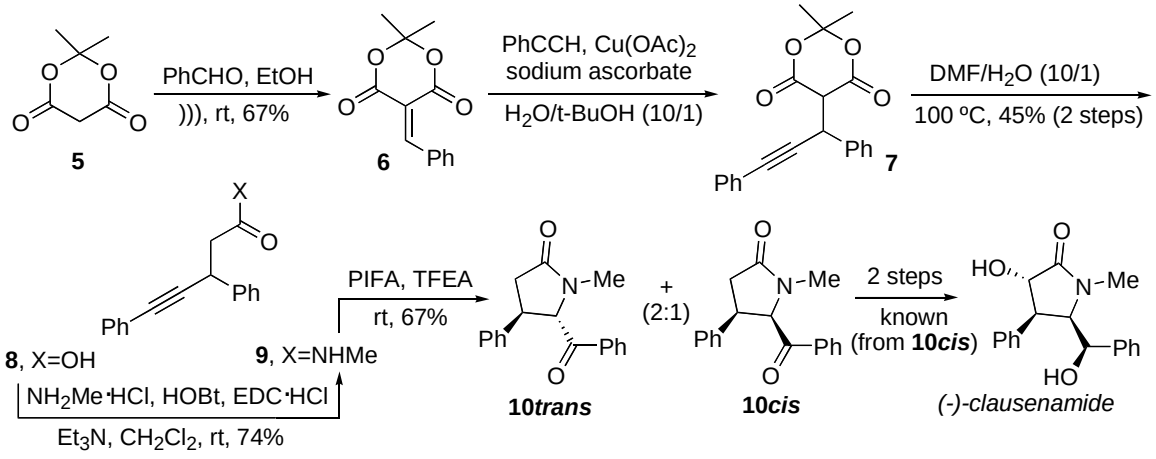
Scheme 2

At this moment we were considering that the presence of an aryl group (i.e. PMP) in substrate **1a** was essential for the stabilization of the acylnitrenium intermediate of type **B** presumably formed after treatment with PIFA.[16] But to the view of the difficulties associated with the *N*-methylation step, and trying to simplify the synthesis, we designed a second attempt starting from the *N*-methylalkynylamide **1b**. To our delight, treatment of **1b** with the hypervalent iodine reagent under the same reaction conditions yielded the corresponding *N*-methylpyrrolidinone **2b** in a superior 78% yield. Conversely to this anticipated mechanistic scenario, the success on the cyclization of *N*-alkynylamides of type **1b**, where a positive charge on nitrogen would not be adequately stabilized, led us to propose an alternative mechanism (see Scheme 3). Thus, activation of the triple bond by PIFA (instead of nitrogen oxidation) gives an electrophilic intermediate that reacts intramolecularly with the nucleophilic amide. Substitution by a trifluoroacetate ligand, with concomitant release of PhI, renders the corresponding enol acetate, which after basic work up yields the final *N*-methylpyrrolidinone **2b**.



Scheme 3

Considering this new piece of information, the synthetic design towards the *clausenamide* alkaloid was modified according to Scheme 4 in which a more elaborated precursor **9** that includes the N-methyl and the phenyl groups had to be prepared. Therefore, alkylidene adduct **6** was satisfactorily prepared by condensation of commercially available Meldrum's acid (**5**) with benzaldehyde in EtOH under sonication. Conjugate addition of phenylacetylene to **6** yielded **7**, which after a decarboxylation process led to the formation of the required β-alkynyl carboxylic acid **8** in 45% yield over two steps. Then, carboxylic acid **8** was transformed into the *N*-methylamide **9** in high yield employing HOBt and EDC·HCl as activating reagents. Finally, application of our PIFA–mediated cyclization conditions afforded pyrrolidinone **10** as a *cis/trans* mixture (1:2 ratio).[17] The desired *cis*-isomer could be separated by flash column chromatography (EtOAc/hexanes, 8/2) as a solid that was crystallized from Et_2O, and its stereochemical identification was achieved by comparison with the previously reported data that claimed a coupling constant of 8Hz for protons H–4 and H–5 in a *cis* relationship. Finally, pyrrolidinone **10*cis*** can be easily transformed into *(±)-clausenamide* in two steps following procedures previously described in the literature.[13e]



Scheme 4

Experimental Section

General Procedures. All reagents were purchased and used as received. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as KBr plates or as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. NMR spectra were recorded at ambient temperature on a Bruker ACE-250 apparatus at 250 MHz (250 MHz for ^1H and 62.83 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.00 for ^{13}C) as internal standard. Coupling constants, *J*, are

reported in hertz. DEPT experiments were used to assist with the assignation of the signals. HRMS spectra were measured by using a Waters GCT Mass Spectrometer.

Typical procedure for the heterocyclization reaction. Synthesis of pyrrolidinones 2a,b, and 10

5-Benzoyl-*N*-(4-methoxyphenyl)pyrrolidin-2-one (2a). A solution of amide **1a** (100 mg, 0.36 mmol) in CF_3CH_2OH (5 mL) was cooled to 0 ºC and a solution of PIFA (95 mg, 0.54 mmol) in 6 mL of the same solvent was added dropwise. The reaction mixture was stirred at 0 ºC for 1 hour. Aqueous Na_2CO_3 10% (5 mL) was added and extracted with CH_2Cl_2 (3x10mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc/MeOH, 96/4), followed by crystallization from hexanes, afforded pyrrolidinone **2a** as a white solid (66 mg, 62%). mp 136-138 ºC (MeOH). ^{1}H NMR ($CDCl_3$) δ 2.04-2.19 (m, 1H), 2.54-2.70 (m, 3H), 3.73 (s, 3H), 5.62-5.67 (m, 1H), 6.65 (d, *J*=8.9, 2H), 7.35 (d, *J*=8.9, 2H), 7.50 (t, *J*=7.5, 2H), 7.63 (t, *J*=7.5, 1H), 7.96 (d, *J*=7.5, 2H). ^{13}C NMR ($CDCl_3$) δ 23.3, 30.3, 55.3, 64.2, 114.1, 124.5, 128.3, 129.0, 131.1, 133.8, 134.0, 157.3, 174.5, 196.3. IR (film) ῡ 1694, 1513. MS (EI) *m/z* (%) 295 (13), 191 (12), 190 (100). HRMS calculated for $C_{18}H_{17}NO_3$ 295.1208 found 295.1205.

5-Benzoyl-*N*-methylpyrrolidin-2-one (2b). According to the typical procedure pyrrolidinone **2b** was obtained from amide **1b** as a brown solid (78%). mp 97–98 ºC (hexanes). ^{1}H NMR ($CDCl_3$) δ 1.93–2.08 (m, 1H), 2.36–2.57 (m, 3H), 2.83 (s, 3H), 5.05–5.10 (m, 1H), 7.49 (dd, *J*=8.3, 7.3, 2H), 7.61 (d, *J*=7.3, 1H), 7.94 (d, *J*=8.3, 2H). ^{13}C NMR ($CDCl_3$) δ 22.9, 28.9, 29.1, 63.9, 128.2, 128.9, 130.0, 133.9, 175.3, 196.3. IR (KBr) ῡ 1690. MS (EI) *m/z* (%) 203 (M^+, 1), 98 (100). HRMS calculated for $C_{12}H_{13}NO_2$ 203.0946, found 203.0952.

5-Benzoyl-*N*-methyl-4-phenylpyrrolidin-2-one (10). According to the typical procedure pyrrolidinone **10** was obtained from **9** as a *trans*/*cis* mixture (2/1) in a 67% combined yield. The desired *cis*-isomer could be separated by flash column chromatography (EtOAc/hexanes, 8/2) as a solid that was crystallized from Et_2O. All spectroscopic data were in agreement with the literature.[13e] mp 118–119 ºC (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.72–3.00 (m, 5H), 4.02 (q, *J*=8.3, 1H), 5.42 (d, *J*=8.3, 1H), 6.92-7.10 (m, 5H), 7.18-7.22 (m, 2H), 7.25-7.60 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 29.2, 36.0, 42.3, 67.5, 126.3, 126.5, 127.2, 127.8, 133.7, 135.0, 135.2, 175.0, 196.2. IR (KBr) ῡ 1700, 1680.

5-Benzoylpyrrolidin-2-one (3). To a cold solution (0 ºC) of the pyrrolidinone **2a** (1.44 g, 4.87 mmol) in CH_3CN/H_2O (5/1, 60 mL) ceric ammonium nitrate was added (13.4 g, 24.4 mmol) in one portion. The reaction was stirred at 0 ºC for 30 min. The reaction was diluted with EtOAc (25 mL), washed with saturated aqueous $NaHCO_3$ (2x50 mL), H_2O (1x50 mL), and brine (1x50 mL). The organic layer was dried over Na_2SO_4, filtered, and solvent evaporated under reduced pressure. Purification of the crude by flash chromatography (EtOAc/MeOH, 96/4) afforded 656 mg (71%) of the desired product **3** as a white solid. mp 155-156 ºC (n-pentane). All spectroscopic data were in agreement with the literature.[18]

5-Benzoyl-5-methylpyrrolidin-2-one (4). Pyrrolidinone **3** (200 mg, 1.05 mmol) was added to a solution of NaH (43 mg, 60% in mineral oil, 1.05 mmol) in THF (3 mL). The mixture was stirred

at room temperature for 5 minutes followed by the addition of MeI (0.066 mL, 1.05 mmol). The new solution was left to react for 6 hours under these conditions. Then, 10 mL of NaCl (aq. satd.) was added and the mixture extracted with chloroform (3x20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford pyrrolidinone **4** (20%) as a colorless oil that was crystallized from n-pentane. mp 92-94 ºC (n-pentane). ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H), 2.35-2.68 (m, 4H), 7.00 (br s, 1H), 7.45-7.56 (m, 3H), 7.88 (d, *J*=6.7, 2H). ^{13}C NMR ($CDCl_3$) δ 27.2, 29.9, 32.4, 67.2, 128.6, 129.1, 133.1, 133.6, 176.0, 200.3. IR (KBr) υ 3229, 1684.

5-Benzyliden-2,2-dimethyl-[1,3]-dioxan-4,6-dione (6). A solution of Meldrum´s acid (**5**) (10 g, 69.4 mmol) and benzaldehyde (6.4 mL, 63.1 mmol) in EtOH (100 mL) was sonicated overnight. Then, the mixture was cooled to 0 ºC and the resulting solid was filtered and crystallized from EtOH. This solid (67%) was identified as compound **6** by comparation with reported physical and spectroscopic data.[19] mp 77-79 ºC (EtOH).

2,3-Dimethyl-5-(1,3-diphenyl-2-propynyl)-[1,3]-dioxan-4,6-dione (7). Diester **6** (1.0 g, 4.31 mmol) and sodium ascorbate (342 mg, 1.72 mmol) were added onto a solution of phenylacetylene (0.56 mL, 5.17 mmol) and $Cu(OAc)_2$ (172 mg, 0.86 mmol) in H_2O/^{t}BuOH (10/1, 19 mL). The mixture was stirred for 4 hours, diluted with 10 mL of CH_2Cl_2 and washed with a saturated solution of NH_4Cl (1x40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2) to afford diester **7** as a white solid after crystallization from n-pentane.

3,5-Diphenylpentynoic acid (8). A solution of diester **7** (639 mg, 1.91 mmol) in DMF/H_2O (10/1, 20 mL) was heated at 100 ºC for 1 hour. After cooling the mixture was acidified with HCl (5% aq. pH=2) and extracted with Et_2O (3x50mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford carboxylic acid **8** as a yellowish solid that was crystallized from n-pentane (45% 2 steps). mp 104-105 ºC (n-pentane). ^{1}H NMR ($CDCl_3$) δ 2.83-3.05 (m, 2H), 4.40 (dd, *J*=7.9, 7.1, 1H), 7.29-7.51 (m, 10H), 10.50 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 34.3, 43.0, 83.6, 89.4, 123.1, 127.3, 127.4, 128.0, 128.2, 128.7, 131.7, 140.1, 177.2. IR (KBr) υ 3030, 1709. MS (EI) *m/z* (%) 250 (M^+, 16), 204 (100), 202 (75), 189 (35), 165 (25). HRMS calculated for $C_{17}H_{14}O_2$ 250.0994, found 250.0999.

3,5-Dipheny-*N*-methyl-4-pentynamide (9). A solution of pentynoic acid **8** (600 mg, 2.40 mmol) in 25 mL of CH_2Cl_2 was added onto a solution of EDC·HCl (243 mg, 3.59 mmol) and HOBt (453 mg, 3.35 mmol) in CH_2Cl_2 (20 mL). Then, triethylamine (0.50 mL, 3.59 mmol) was added dropwise and the new solution was stirred at room temperature overnight. Water (20 mL) was added and the mixture extracted with CH_2Cl_2 (3x20mL). The combined organic extracts were washed with HCl (5% aq.), $NaHCO_3$ (satd. aq. solution), and NaCl (satd. aq. solution), and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford an oil that was crystallized from Et_2O to afford amide **9** as a white solid (470 mg, 74%). mp 96-98 ºC

(Et_2O). ^1H NMR ($CDCl_3$) δ 2.59-2.89 (m, 5H), 4.43 (dd, *J*=7.9, 7.1, 1H), 6.12 (br s, 1H), 7.21-7.46 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 26.2, 35.0, 45.5, 83.7, 90.0, 123.1, 127.0, 127.2, 127.9, 128.1, 128.5, 131.5, 140.5, 170.8. IR (KBr) υ 3297, 1647. MS (EI) *m/z* (%) 263 (M^+, 19), 205 (100), 203 (30), 191 (86), 189 (59). HRMS calculated for $C_{18}H_{17}NO$ 263.1310, found 263.1320.

Acknowledgements

Financial support from the University of the Basque Country (UPV 41.310-13656), the Basque Government (GIU 06/87), the Spanish Ministry of Science and Technology (CTQ 2004-03706/BQU, and the Spanish Ministry of Science and Innovation CTQ2007-64501/BQU) is gratefully acknowledged. S. S. thanks the Basque Government for a predoctoral scholarship. The authors gratefully acknowledge PETRONOR, S. A. (Muskiz, Bizkaia) for the generous gift of hexanes.

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