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A new and practical PIFA-promoted olefin amidohydroxylation: six- versus five-membered ring formation

Sonia Serna, Imanol Tellitu,* Esther Domínguez,* Isabel Moreno and Raúl SanMartín

Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco–Euskal Herriko Unibertsitatea (UPV/EHU), PO Box 644, 48080 Bilbao, Spain

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Dedicated to Professor A. Varvoglis on the occasion of his 65th birthday

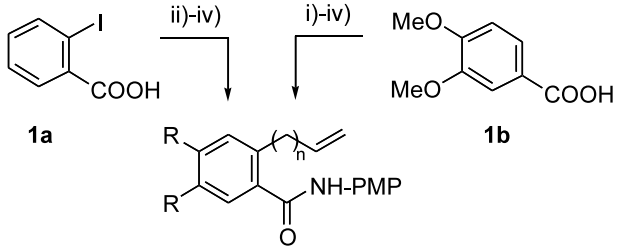
Abstract—A novel access to the isoindolinone and isoquinolin-2-one skeletons from adequately substituted aromatic precursors is described. The key intramolecular cyclization step was performed by the action of phenyliodine(III)bis(trifluoroacetate) (PIFA) on the corresponding vinyl or allyl substituted *N*-(*p*-methoxyphenyl)benzamide derivatives leading to the heterocyclic compounds through 5-*exo*-trig and 6-*exo*-trig processes, respectively.

In the search for novel approaches to the preparation of different heterocyclic derivatives, our group has recently focussed on the enormous potentiality that some hypervalent iodine reagents can provide in organic synthesis.[1] For example, the clean transformations achieved, the mild conditions employed, and the low toxicity associated to it, prompted us to include one of these iodine(III) reagents, PIFA [phenyliodine(III)-bis(trifluoroacetate)], in our synthetic plans as a promising agent to carry out new reactions for the access to a number of heterocycles. The desirability of this type of reactions can be appreciated considering the importance of heterocyclic derivatives, mainly *N*-heterocycles, in chemical biology and drug discovery fields.

Thus, the synthesis of a series of phenanthridines, phenanthrenes and phenanthrenoids by the construction of the biaryl linkage,[2] and the synthesis of different heterocyclic-fused quinolinones[3] and 1,4-benzodiazepin-2-ones[4] by an electrophilic aromatic amidation process have been recently reported in which the I(III) reagent PIFA displays a prominent contribution. Therefore, when the mildly oxidant reagent PIFA reacts with arene rings or properly substituted amides, radical-cation[5] and *N*-acylnitrenium[6] intermediates are generated, respectively. Finally, in the presence of nucleophilic species, the so-obtained electrophilic intermediates are trapped inter- or intramolecularly to form new linkages.

Following these master lines, we have explored the feasibility of this strategy in the synthesis of isoindolinone and isoquinolinone skeletons through a PIFA-promoted olefin amidation process.[7] This process, could be eventually employed in the construction of a number of related natural and synthetic products of interest by the direct formation of C–N bonds. The preliminary results are now presented in this letter.

The retrosynthetic disconnection of the target molecules led us to conclude that amides **2a**,**b** and **3a**,**b** would be the precursors of choice since, with these substrates in hand, two important aspects of the cyclization step could be studied. Firstly, the presence or absence (**2**/**3b**



Scheme 1. Preparation of precursors **2a**,**b** and **3a**,**b**. *Reagents and conditions*: (i) PIDA, I_2, AcOH, Ac_2O, H_2SO_4, rt; (ii) $SOCl_2$, Tol, reflux; (iii) *p*-anisidine, pyridine, CH_2Cl_2, rt; (iv) tributylvinyltin, $Pd(PPh_3)_2Cl_2$, diox., reflux (70% overall for **2a** from **1a**, and 49% overall for **2b** from **1b**); (iv) allyltributyltin, $Pd(PPh_3)_2Cl_2$, diox., reflux (90% overall for **3a** from **1a**, and 58% overall for **3b** from **1b**).

* Corresponding authors.

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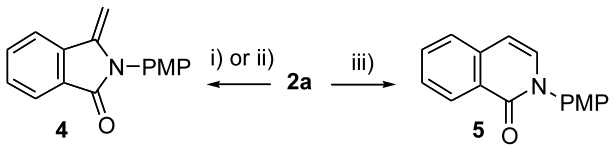
versus **2**/**3a**) of electron-donating groups in the aromatic ring will inform about the electronic requirements of the reaction. And, secondly, both vinyl and allyl groups include, a priori, the possibility of *exo*-trig versus *endo*-trig cyclization modes.

The preparation of precursors **2** and **3** started (see Scheme 1) from commercially available 2-iodobenzoic acid (**1a**) and 3,4-dimethoxybenzoic acid (**1b**). In the latter case, a combination of PIDA [phenyliodine-(III)diacetate)] and iodine was employed to incorporate the halogen atom in the required position with complete regioselectivity.[8] Then, amide formation, using *p*-anisidine, and Stille processes, employing either tributylvinyltin or allyltributyltin, rendered the desired precursors **2a**,**b** and **3a**,**b** in 49–90% overall yields.

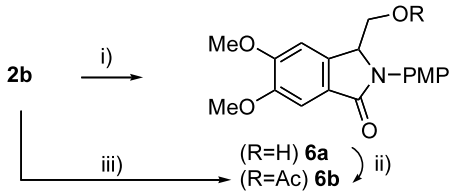
With these substrates in hand, optimization of the cyclization conditions included solvent selection, temperature, and the presence of additives such as TFA[9] or $BF_3{\cdot}OEt_2$.[10] Under all the employed experimental conditions the starting materials reacted completely to afford complex mixtures of products. Thus, when amide **2a** reacted (see Scheme 2) with PIFA in the presence of $BF_3{\cdot}OEt_2$ using CH_2Cl_2 as solvent at –20°C, isoindolinone **4** was obtained in a modest 23% yield through a 5-*exo*-trig process.[11] Conversely,[12] by using TFA instead of $BF_3{\cdot}OEt_2$, isoquinolinone **5** was obtained through an, a priori, less favored[13] 6-*endo*-trig cyclization mode in a 28% yield. Finally, amide **2a** was made to react with PIFA in CF_3CH_2OH as solvent[14] at low temperature in the absence of any activating agent. Under these conditions isoindolinone **4** was obtained in a very poor yield (16%).

In order to improve results, we envisaged that an increased nucleophilicity of the styrene fragment would facilitate the cyclization onto the electronically deficient nitrogen atom generated. For that purpose, amide **2b** was prepared and made to react with PIFA in CF_3CH_2OH as solvent at low temperature in the absence of any activating agent (see Scheme 3).[15] As anticipated, the 5-*exo*-trig cyclization took place smoothly to afford isoindolinone **6a** in 95% yield.[16] This compound was subsequently acetylated to yield derivative **6b** for a full structural identification.

Although the PIFA mediated carbon–nitrogen bond formation readily provided access to *N*-heterocyclic derivatives, the exact mechanism of the reaction is not



Scheme 2. Reaction of amide **2a** with PIFA. *Reagents and conditions*: (i) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20°C (23%); (ii) PIFA, CF_3CH_2OH, –20°C (16%); (iii) PIFA, TFA, CH_2Cl_2, 0°C (28%).



Scheme 3. Reaction of amide **2b** with PIFA. *Reagents and conditions*: (i) PIFA, CF_3CH_2OH, –20°C (95%); (ii) Ac_2O, pyridine, rt (99%); (iii) PIDA, CF_3CH_2OH, –20°C (27%).

apparent. Nevertheless, to the view of the obtained results we can propose that this novel intramolecular amidohydroxylation process takes place through the formation of a nitrogen-centered cation (see Fig. 1).[6,17]

The species **II**, generated from **I** by the action of PIFA, is intramolecularly attacked by the olefine fragment to form the heterocyclic core **III** stabilized as an aziridinium ion by the donating properties of the *para*-methoxyphenyl (PMP) group. This new intermediate is opened by a free trifluoroacetate group (delivered from PIFA), and the resulting non-isolated[18] ester **V** is hydrolyzed during the work up (Na_2CO_3, H_2O) to render derivative **6a**. In this case, conversely to **4** (≈**IV**), the elimination process is not facilitated because of the diminished acidity of the benzylic proton.[19]

Despite of the absence or diminished reactivity that PIDA [phenyliodine(III)-diacetate)] had shown, when compared to PIFA, in our previous investigations,[2–4] we decided to check its behavior in a high yielding transformation presented here. Thus, when amide **2b** was reacted with PIDA in trifluoroethanol as solvent (see Scheme 3), ester **6b** was obtained directly in a poor 27% yield along with extensive degradation of the starting material. This result not only confirms the superior reactivity of PIFA over PIDA for the olefine amidation process, but it also supports, by analogy, the proposed structure **V** as an intermediate in the reaction mechanism depicted in Figure 1.

Then, in order to expand the suitability of the designed synthesis, the behavior of amides **3a**,**b** was also studied

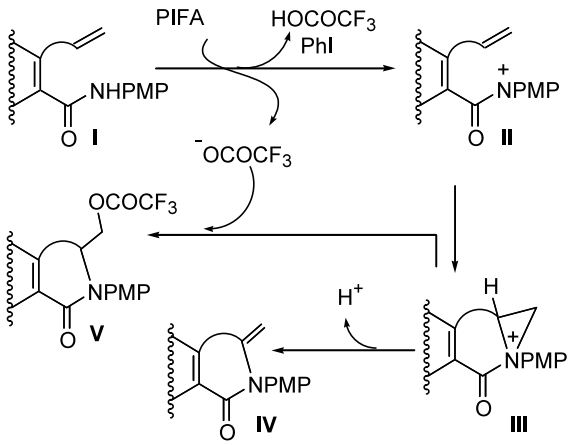
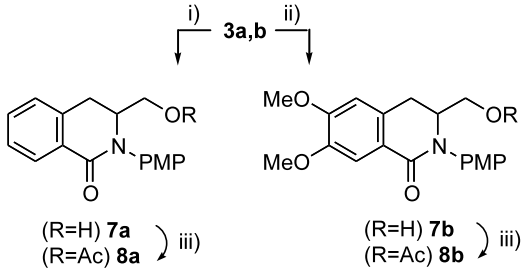


Figure 1. Proposed mechanism for the olefine amidation.



Scheme 4. Reaction of amide **3a**,**b** with PIFA. *Reagents and conditions*: (i) PIFA, CF_3CH_2OH, rt (72% from **3a**); (ii) PIFA, CF_3CH_2OH, rt (93% from **3b**); (iii) Ac_2O, pyridine, rt (99%).

giving the following results (see Scheme 4). When amide **3a** was treated with PIFA in CF_3CH_2OH as solvent at room temperature, a 6-*exo*-trig cyclization took place to afford isoquinolinone **7a** in 72% yield. Analogously, amide **3b** rendered isoquinolinone **7b** in very good yield working at room temperature. So, conversely to the vinyl substituted benzamides, in this case the presence of activating substituents in the aryl ring was not necessary for the reaction to take place with excellent yield. As commented before, a hydroxylation process took place in both cases along with the ring formation. Once again, both heterocyclic compounds were subsequently acetylated as derivatives **8a**,**b** for a full structural identification.

In summary, a novel I(III) mediated intramolecular amidohydroxylation process leading to C–N bond formation is presented and employed in the construction of the isoindolinone and isoquinolinone nucleus. Besides, the additional hydroxylic functional group created will facilitate the construction of new and more complex heterocycles and represents a new tool for future investigations in the field of heterocyclic chemistry.

Acknowledgements

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11. (a) Data of compound **4** can be found in: Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777–4792; (b) In all cases under study, reported in Scheme 2, heterocycles **4** and **5** were isolated from complex mixtures of non-identified compounds. Temperature selection was optimized for each case without modification of the regioselectivity of the cyclization.
12. By altering the reaction conditions, *ortho*-allylanilines have also been transformed regioselectively into indoles via a 5-*exo*-trig process (Hegedus, L. S. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1113–1126) and into quinolines via a 6-*endo*-trig cyclization mode (Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem*. **1996**, *61*, 3584–3585).
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14. Polar and low nucleophilic protic solvents, such as CF_3CH_2OH or $(CF_3)_2CH_2OH$, have been successfully employed in PIFA-mediated reactions. In certain cases, these protic solvents have afforded considerably better yields than the usual CH_2Cl_2 or CH_3CN solvents. See for example: (a) Kita, Y.; Takada, T.; Mihara, S.; Whelan, B. A.; Tohma, H. *J. Org. Chem.* **1995**, *60*, 7144–7148; (b) Ward, R. S.; Pelter, A.; Abd-El-Ghani, A. *Tetrahedron* **1996**, *52*, 1303–1336.
15. Again, a vast array of assays was carried out to establish the optimal conditions. In this case, conversely to the previous experiments, better yields were obtained employing CF_3CH_2OH as solvent without any activating agent.
16. Typical procedure for the amidohydroxylation reaction. Synthesis of 5,6-dimethoxy-3-hydroxymethyl-2-(*p*-methoxyphenyl)-2,3-dihydro-1*H*-isoindolin-1-one (**6a**): Over a solution of amide **2b** (70 mg, 0.3 mmol) in CF_3CH_2OH (3 mL) at −20°C a solution of PIFA (178 mg, 0.4 mmol) in CF_3CH_2OH (3 mL) was added. The mixture was stirred at −20°C until total consumption of the starting material (TLC, 80 min). Then, a solution of Na_2CO_3 (aq. 10%, 10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anh. Na_2SO_4, filtered, and the solvent was removed under vacuum. The resulting oil was crystallized from hexanes/EtOAc (80/20) to render isoindolinone **6a** as a white solid (95%). mp 161–163°C (EtOAc/hexanes); ^{1}H NMR: δ 2.78 (br s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.34 (d, J=3.1, 2H, C$\underline{H}_2$), 4.71 (t, J=3.1, 1H, H-3), 6.84–6.88 (m, 3H, H_{arom}), 7.18 (d, J=8.7, 2H, H_{arom}), 7.70 (s, 1H, H_{arom}); ^{13}C NMR: δ 55.3, 56.1, 56.2 (OCH_3), 64.8 (C-3), 71.5 (CH_2OH), 108.7, 109.9, 113.7, 124.6 (t-C_{arom}), 119.4, 131.1, 139.3, 149.3, 151.3, 152.0 (q-C_{arom}), 156.1 (CO); IR (KBr): 3500–3200 (OH), 1637 (CO); MS (EI) m/z (%): 329 (M^+, 100), 314 (12), 207 (23); HRMS calculated for $C_{18}H_{19}NO_5$ 329.1263, found 329.1261.
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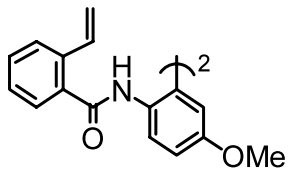
18. The putative structure of trifluoroacetyl ester **V** was proposed based on the close similarity between the proton NMR of the reaction mixture from **2b** to **6a** (prior to basification) and the ester **6b**.
19. The isolation of dimer **9** (trace amounts) probably reveals a contribution of a radical mechanism. For a precedent of the formation of dimeric compounds, see Ref. 2b. The observed deep coloration of the mixture, after the addition of PIFA, can be also in agreement with the formation of radical species (Landais, Y.; Robin, J.-P. *Tetrahedron* **1992**, *48*, 7185–7196).



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^{1}H NMR: δ 3.89 (s, 6H, OCH_3), 5.46 (d, J=10.7, 2H, CH=C$\underline{H}$H), 5.80 (d, J=17.4, 2H, CH=CH$\underline{H}$), 6.96 (dd, J=8.7, 2.4, 2H, H_{arom}), 7.12 (d, J=2.4, 2H, H_{arom}), 7.38–7.52 (m, 4H, H_{arom}), 7.67–7.85 (m, 6H, H_{arom}, C$\underline{H}$=CH_2), 8.09 (d, J=7.5, 2H, H_{arom}); HRMS calculated for $C_{32}H_{28}N_2O_4$ 504.2049, found 504.2041.