molbank

MDPI

Short Note

(*S*)-4-Isopropyl-5,5-diphenyloxazolidin-2-one

Raffaella Mancuso [1,*], Rossana Miliè [1], Ida Ziccarelli [1], Mariangela Novello [1], Nicola Della Ca' [2] and Bartolo Gabriele [1,*]

[1] Laboratory of Industrial and Synthetic Organic Chemistry, Department of Chemistry and Chemical Technologies, University of Calabria, Via Pietro Bucci 12/C, 87036 Arcavacata di Rende (CS), Italy; milierossana1@libero.it (R.M.); idaziccarelli@gmail.com (I.Z.); novello.mariangela@gmail.com (M.N.)

[2] Department of Chemistry, Life Sciences and Environmental Sustainability (SCVSA), University of Parma, Parco Area delle Scienze 17/A, 43124 Parma, Italy; nicola.dellaca@unipr.it

* Correspondence: raffaella.mancuso@unical.it (R.M.); bartolo.gabriele@unical.it (B.G.); Tel.: +39-0984-492816 (R.M.); +39-0984-492815 (B.G.)

Received: 27 July 2018; Accepted: 27 August 2018; Published: 31 August 2018

Abstract: (*S*)-4-Isopropyl-5,5-diphenyloxazolidin-2-one has been synthesized for the first time by the enantiospecific oxidative carbonylation of commercially available (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol. The cyclocarbonylation reaction was carried out at 100 °C in 1,2-dimethoxyethane (DME) as the solvent for 15 h, under 20 atm of a 4:1 mixture of CO–air and in the presence of the catalytic system PdI_2/KI (substrate:KI:PdI_2 molar ratio = 100:10:1), to give the oxazolidinone derivative in 81% isolated yield.

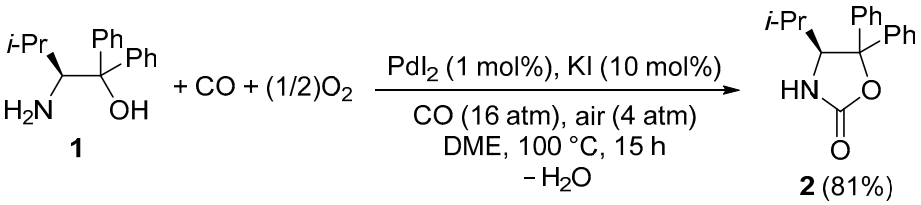
Keywords: β-amino alcohols; carbonylation; cyclocarbonylation; oxazolidinones; palladium

1. Introduction

Oxazolidin-2-ones are a very important class of heterocyclic derivatives. Many compounds possessing the oxazolidinone scaffold present important pharmacological activities, antimicrobial activity in particular [1]. Moreover, chiral oxazolidinones are widely used as chiral auxiliaries in organic synthesis [2].

Among the possible synthetic methods for preparing oxazolidin-2-ones from acyclic substrates, the direct metal-catalyzed oxidative carbonylation of β-amino alcohols with CO is one of the most attractive, in consideration of the large availability and inexpensiveness of carbon monoxide and the excellent atom economy of the process, which produces water as the only coproduct, and its enantiospecificity (when starting from enantiopure substrates) [3]. Many oxazolidin-2-one derivatives have been prepared by this approach using different types of catalytic systems [3]. Between them, the PdI_2/KI catalytic system, developed by our research group, has proved valuable for the preparation of a plethora of oxazolidinones starting from the corresponding β-amino alcohols under relatively mild reaction conditions [3–6].

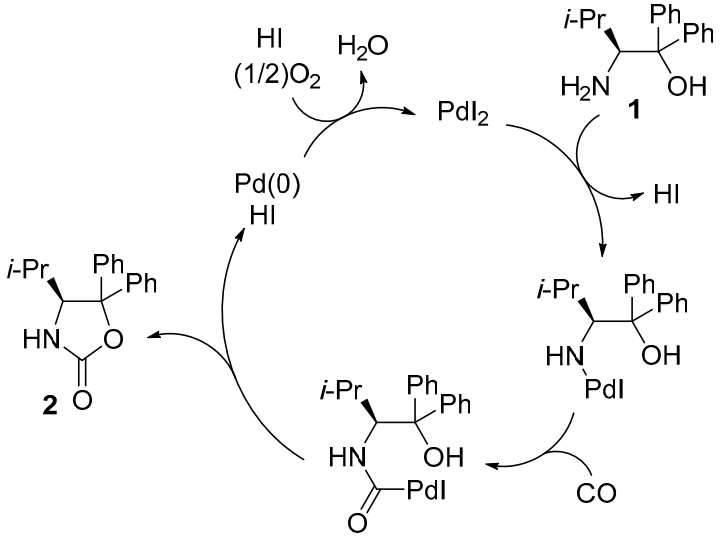
In this Short Note, we report a further application of our method to the use of sterically demanding (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**1**) as the starting material, for the first synthesis of (*S*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**2**) by a direct carbonylation approach (Scheme 1). In fact, this derivative, which is a useful chiral auxiliary [7], has been synthesized so far from **1** by alternative methods, which involve the use of activated carbonyl derivatives instead of CO [7–11].



Scheme 1. Enantiospecific synthesis of **2** by PdI_2/KI-catalyzed oxidative carbonylation of commercially available **1**.

2. Results and Discussion

The enantiospecific cyclocarbonylation of **1** was carried out at 100 °C in 1,2-dimethoxyethane (DME) as the solvent (substrate concentration: 0.5 mmol of **1** per mL of DME), under 20 atm (at 25 °C) of a 4:1 mixture of CO-air, in the presence of catalytic amounts of PdI_2 (1 mol%) in conjunction with KI (10 mol%). After 15 h reaction time, the TLC analysis of the reaction crude showed the complete conversion of the substrate and the formation of a product, which was isolated by crystallization and identified as **2** by full spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR) and spectrometric (MS) characterization. Oxazolidinone **2** was smoothly formed in an isolated yield as high as 81%, which is a noteworthy result, considering the high steric hindrance present in the substrate. Mechanistically, the formation of **2** can be rationalized as shown in Scheme 2 (anionic iodide ligands are omitted for clarity): nitrogen palladation (with formal elimination of HI) is followed by CO insertion (to give a carbamoylpalladium iodide intermediate) and intramolecular nucleophilic displacement by the hydroxyl group to give **2**, Pd(0) and a second mol of HI. Pd(0) is then reoxidized back to PdI_2 by the action of oxygen, in the presence of the HI generated before.



Scheme 2. Proposed catalytic cycle for the formation of oxazolidinone **2** from **1**.

3. Materials and Methods

Solvents and chemicals were reagent grade and used without further purification. Reactions were analyzed by thin layer chromatography (TLC) on silica gel 60 F254 (Merck s.p.a., Vimodrone, Milano, Italy). Starting material **1** was commercially available (Sigma-Aldrich Italia s.r.l., Milano, Italy). Evaporation refers to the removal of solvent under reduced pressure. Melting point is uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 25 °C on a 300 MHz spectrometer (Bruker DPX Avance 300, Bruker Italia s.r.l., Milano, Italy) in DMSO-d_6 solutions with Me_4Si as the internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and Hz, respectively. IR spectrum was

taken with a JASCO FTIR 4200 spectrometer (JASCO Europe s.r.l., Cremella, Italy). Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus (Shimadzu Italia s.r.l., Milano, Italy) at 70 eV ionization voltage. Optical rotation was measured on an Atago Polax-2L polarimeter (Atago Italia s.r.l., Rozzano, Italy).

Synthetic procedure for the preparation of **2**. A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (7.1 mg, 0.020 mmol), KI (32.5 mg, 0.20 mmol), and a solution of **1** (500.0 mg, 1.96 mmol) in DME (3.9 mL). While stirring, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm) and then heated at 100 °C for 15 h. After cooling, the autoclave was degassed and solvent evaporated. Some of the crude product was already present in the suspension in the reaction mixture. The crude oxazolidin-2-one **2** was purified by the crystallization in $CHCl_3$/hexane. Yield: 448 mg, 81% based on starting **1**. Pure **2** was a white solid, m.p. = 246–247 °C. $[\alpha]_D^{25}$ (acetone, $c = 7.02 \times 10^{-3}$ g·mL^{-1}) = −253.6 (lit. [12]: $[\alpha]_D^{25}$ ($CHCl_3$, c = 2×10^{-3} g·mL^{-1}) = −255.2); IR (KBr): ν = 1767 (s), 1744 (s), 1493 (w), 1450 (m), 1366 (m), 1315 (w), 1250 (m), 1227 (m), 1185 (m), 1042 (m), 1003 (m), 976 (m), 764 (m), 745 (m), 706 (m) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.14 (s, 1H, NH), 7.68 (d, J = 7.4, 2H, aromatic), 7.47 (d, J = 7.4, 2 H, aromatic), 7.40–7.20 (m, 6H, aromatic), 4.44 (s, C*H*NH), 1.92–1.75 (m, 1H, C*H*Me$_2$), 0.91 (d, J = 6.7, 3 H, CH_3CHCH$_3$), 0.50 (d, J = 6.7, 3 H, CH$_3$CHCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 157.3, 145.2, 139.7, 128.3, 128.0, 127.6, 127.1, 125.4, 125.0, 87.6, 64.1, 29.0, 20.1, 14.4; GC/MS: m/z = 281 (M$^+$, 3), 238 (2), 195 (9), 194 (14), 184 (14), 183 (100), 167 (10), 165 (18), 152 (5), 116 (3), 105 (56), 91 (4), 77 (18). The spectroscopic data were in good agreement with those reported [10]. Copies of the IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra are given in the Supplementary Materials.

Supplementary Materials: The following are available online, IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra for product **2**.

Author Contributions: Conceptualization, B.G. and R.M. (Raffaella Mancuso); Methodology, all authors; Validation, R.M. (Raffaella Mancuso), and N.D.C.; Investigation, R.M. (Raffaella Mancuso), R.M. (Rossana Miliè), I.Z. and M.N.; Writing-Review & Editing, B.G.; Supervision, B.G.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Roger, C.; Roberts, J.A. Clinical Pharmacokinetics and Pharmacodynamics of Oxazolidinones. *Clin. Pharmacokinet.* **2018**, *57*, 559–575. [CrossRef] [PubMed]
2. Zadsirjan, V.; Heravi, M.M. Oxazolidinones as Chiral Auxiliaries in the Asymmetric 1,4-Conjugate Addition Reaction Applied to the Total Synthesis of Natural Products: A Supplemental Mini-Review. *Curr. Org. Synth.* **2018**, *15*, 3–20. [CrossRef]
3. Gabriele, B. Synthesis of Heterocycles by Palladium-Catalyzed Carbonylative Reactions. In *Advances in Transition-Metal Mediated Heterocyclic Synthesis*; Solé, D., Fernández, I., Eds.; Academic Press-Elsevier: London, UK, 2018; Volume 3, pp. 55–127, ISBN 978-0-12-811651-7.
4. Gabriele, B.; Mancuso, R.; Salerno, G. Oxidative Carbonylation as a Powerful Tool for the Direct Synthesis of Carbonylated Heterocycles. *Eur. J. Org. Chem.* **2012**, *2012*, 6825–6839. [CrossRef]
5. Mancuso, R.; Raut, D.S.; Della Ca', N.; Fini, F.; Carfagna, C.; Gabriele, B. Catalytic Oxidative Carbonylation of Amino Moieties to Ureas, Oxamides, 2-Oxazolidinones, and Benzoxazolones. *ChemSusChem* **2016**, *8*, 2204–2211. [CrossRef] [PubMed]
6. Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. An Improved Procedure for the Palladium-Catalyzed Oxidative Carbonylation of β-Amino Alcohols to Oxazolidin-2-ones. *J. Org. Chem.* **2003**, *68*, 601–604. [CrossRef] [PubMed]
7. Hintermann, T.; Seebach, D. A Useful Modification of the *Evans* Auxiliary: 4-Isopropyl-5,5-diphenyloxazolidin-2-one. *Helv. Chim. Acta* **1998**, *81*, 2093–2126. [CrossRef]
8. Gibson, C.L.; Gillon, K.; Cook, S. A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries. *Tetrahedron Lett.* **1998**, *39*, 6733–6736. [CrossRef]

9. Gawley, R.E.; Zhang, P. 1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary ^{13}C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinolyloxazolines. *J. Org. Chem.* **1996**, *61*, 8103–8112. [CrossRef] [PubMed]
10. Alexander, K.; Cook, S.; Gibson, C.L.; Kennedy, A.R. Highly Effective and Recyclable Chiral Auxiliaries: A Study of the Synthesis and Use of Three 4-Isopropyl-5,5-diaryloxazolidin-2-ones. *J. Chem. Soc., Perkin Trans. 1* **2001**, *2001*, 1538–1549. [CrossRef]
11. O'Hagan, D.; Tavasli, M. A Short Synthesis of (*S*)-α-(Diphenylmethyl)alkyl Amines from Amino Acids. *Tetrahedron: Asymm.* **1999**, *10*, 1189–1192. [CrossRef]
12. Yu, L.-T.; Ho, M.-T.; Chang, C.-Y.; Yang, T.-K. Asymmetric Zinc-Reformatsky Reaction of Evans Chiral Imide with Acetophenones and Its Application to the Stereoselective Synthesis of Triazole Antifungal Agents. *Tetrahedron Asymm.* **2007**, *18*, 949–962. [CrossRef]