EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200916

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Special Collection

A Multicomponent Approach to Imidazo[2,1-*b*]thiazole Derivatives by Sequential PdI_2/KI-Catalyzed Deprotective Oxidative Aminocarbonylation – Dearomative Cyclization – Aromatization

Lucia Veltri,*[a] Roberta Amuso,[a] Tommaso Prestia,[a] Paola Vitale,[b] and Bartolo Gabriele*[a]

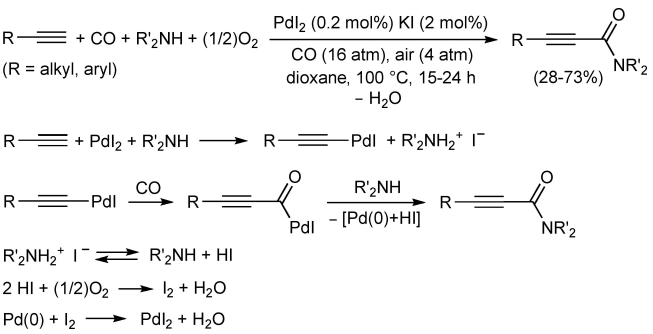
Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday

We report a direct, multicomponent approach to an important class of fused-ring heterocycles, namely, imidazo[2,1-*b*]thiazole derivatives starting from simple and readily available building blocks (*N*-Boc-*N*-propargylthiazol-2-amines, carbon monoxide, a secondary amine, and oxygen). The process takes place under the catalysis of the simple PdI_2/KI system under relatively mild conditions (100 °C under 20 atm of a 4:1 mixture of CO-air), and leads to 2-(imidazo[2,1-*b*]thiazol-5-yl)-*N*,*N*-dialkylacetamides in yields up to 87%. The mechanistic pathway leading to carbonylated imidazo[2,1-*b*]thiazole occurs through an ordered sequence of steps, involving amine-induced *N*-deprotection, oxidative aminocarbonylation of the triple bond (with C*sp*–H activation and formation of a 2-ynamide intermediate), dearomative cyclization (by intramolecular conjugate addition of thioazolic nitrogen to the 2-ynamide moiety) and aromatization by proton-shift isomerization. When starting from *N*-Boc-*N*-(propargyl)benzo[*d*]thiazol-2-amine, tricyclic benzimidazothiazoles were formed in moderate yields.

Introduction

The PdI_2/KI catalytic system, disclosed by our research group in 1992, is one of the most versatile catalysts for carbonylation reactions, in particular under oxidative conditions.[1] In the course of the years, it has proved to be active in the carbonylation of a plethora of substrates, with formation of carboxylic acid esters, amides, and various carbonylated heterocycles.[1,2]

Among the carbonylation processes that this simple but highly active catalyst is able to promote, the oxidative monoamincarbonylation of terminal alkynes to give, upon C*sp*–H activation, high value added 2-ynamides,[3] is one of the most important (Scheme 1). The process, disclosed by our research group in 2001,[4] starts with the formation of an alkynylpalladium iodide intermediate from the reaction between the terminal alkyne, PdI_2, and a secondary amine acting as a base. Carbon monoxide insertion then takes place, followed by nucleophilic displacement by the amine, to give the final product and Pd(0). The PdI_2 catalyst is finally regenerated by the action of oxygen, which oxides the two mol of HI formed during the process to I_2, followed by oxidative addition of the latter to Pd(0) (Scheme 1; anionic iodide ligands are omitted for clarity).[4]



Scheme 1. PdI_2/KI-catalyzed oxidative aminocarbonylation of terminal alkynes leading to 2-ynamides.[4]

In addition to the intrinsic significance of 2-ynamide derivatives, obtained from unfunctionalized 1-alkynes, the PdI_2/KI-catalyzed oxidative aminocarbonylation approach can also be very useful for the one-pot preparation of carbonylated heterocycles, when starting from terminal alkynes bearing a suitably placed nucleophilic group. In fact, with such substrates, the initially formed 2-ynamide intermediate can undergo inter-[5] or intramolecular[6] conjugate addition eventually lead-

[a] Prof. Dr. L. Veltri, Dr. R. Amuso, Dr. T. Prestia, Prof. Dr. B. Gabriele
Laboratory of Industrial and Synthetic Organic Chemistry (LISOC),
Department of Chemistry and Chemical Technologies
University of Calabria
Via Pietro Bucci 12/C, 87036 Arcavacata di Rende (CS), Italy
E-mail: lucia.veltri@unical.it
bartolo.gabriele@unical.it
[b] Prof. Dr. P. Vitale
Department of Pharmacy – Pharmaceutical Sciences
University of Bari "Aldo Moro"
Via E. Orabona 4, 70125 Bari, Italy

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200916

Special Collection Part of the "Cesare Gennari's 70th Birthday" Special Collection.

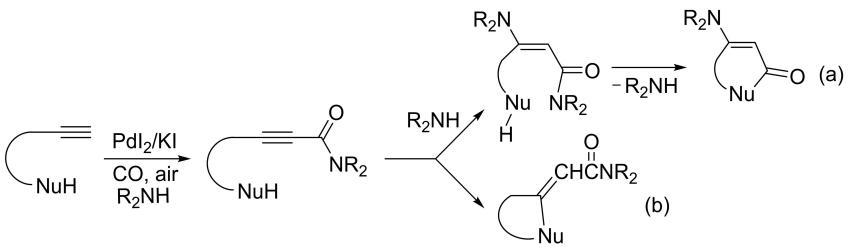
ing to carbonylated hetero- or carbocycles, as shown in Scheme 2a and Scheme 2b, respectively.

In this work, we have studied the possibility to apply this kind of reactivity to readily available *N*-propargylthiazol-2-amines, in order to realize a multicomponent, one-step carbonylative approach to 2-(imidazo[2,1-*b*]thiazol-5-yl)-*N*,*N*-dialkylacetamides, as shown in Scheme 3.[7] These compounds, in fact, could be formed by dearomative cyclization of the initially formed 2-ynamide intermediate **I** (by intramolecular conjugate addition of the thiazole nitrogen to the triple bond, assisted by the exocyclic amino group) followed by aromatization-triggered proton-shift isomerization of the ensuing intermediate **II**. A simple approach like this would therefore represent a new entry[8] to an important class of heterocyclic derivatives, whose core is known to be present in many bioactive compounds of pharmacological interest.[9,10]

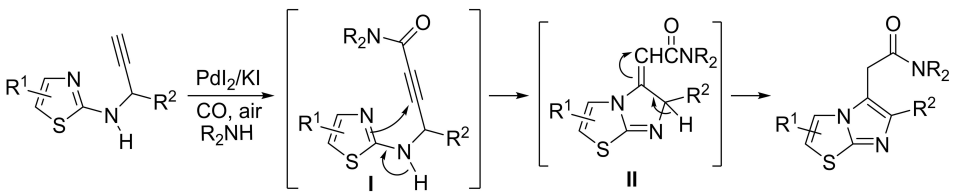
Results and Discussion

We started our study by synthesizing *N*-Boc-(prop-2-yn-1-yl)thiazolamine **1a** by the reaction between commercially available 2-aminothiazole with $(Boc)_2O$ followed by propargylation of the ensuing *N*-Boc-2-aminothiazole with propargyl bromide (see the Supporting Information for details). Considering the possibility of in situ *N*-deprotection under PdI_2/KI-catalyzed oxidative carbonylation conditions, already observed in other contexts,[6a,11] we used **1a** directly as possible model substrate for testing our work hypothesis, thus possibly avoiding an additional prior deprotection step. Substrate **1a** was initially allowed to react with CO (16 atm), diethylamine **2a** (3 equiv), and O_2 as the external oxidant (from air; 4 atm) in MeCN as the solvent (substrate initial concentration, 0.20 mmol of **1a** per mL of MeCN) at 100 °C in the presence of PdI_2 (1 mol%) and KI (1 equiv). After 6 h reaction time, substrate conversion was quantitative, and analysis of the reaction mixture revealed the formation of the desired *N*,*N*-diethyl-2-(imidazo[2,1-*b*]thiazol-5-yl)acetamide **3aa** (58% GLC yield), which was isolated in 54% yield (Table 1, entry 1), together with equimolar amounts of *tert*-butyl diethylcarbamate (as detected in GLC-MS). This preliminary result was quite interesting, since it confirmed the validity of our work hypothesis, as shown in Scheme 3, as well as the possibility to realize in situ *N*-Boc deprotection (at either the substrate or *N*-Boc-2-ynamide intermediate level) caused by transamination of the *N*-Boc moiety with Et_2NH (Scheme 4). In any case, it is worth mentioning that the formation of the bicyclic product could not be taken for granted, as cyclization of intermediate **I** to give **II** implies dearomatization of the thiazole ring. Therefore, the formation of product **3aa** in an acceptable yield, already in the first experiment under unoptimized conditions, appears to be of particular significance.

With the aim of achieving a higher **3aa** yield, we then screened some reaction parameters. Lower GLC yields of **3aa** were observed when MeCN was replaced with another non-nucleophilic solvent such as dioxane (48%, Table 1, entry 2) or when using a lower excess of **2a** (2 equiv; **3aa** GLC yield was 46%, Table 1, entry 3). On the other hand, a higher **3aa** GLC yield was obtained with 4 equiv. of **2a** (60%; Table 1, entry 4) or with 0.5 equiv. of KI (76%; Table 1, entry 5). A further decrease of the amount of KI to 0.1 equiv. did not improve the product yield (Table 1, entry 6). A lower **3aa** GLC yield with respect to the parent experiment was observed when lowering the temperature to 80 °C (Table 1, entry 7), by raising the total pressure to 40 atm (Table 1, entry 8), or when the process was carried out under more concentrated conditions (Table 1, entry 9). Conversely, dilution of the reaction mixture to an initial



Scheme 2. Synthesis of carbonylated heterocycles by PdI_2/KI-catalyzed oxidative monoaminocarbonylation of terminal alkynes bearing a suitably placed nucleophilic group: formation of the 2-ynamide intermediate followed by (a) intermolecular conjugate addition-cyclization or (b) intramolecular conjugate addition.

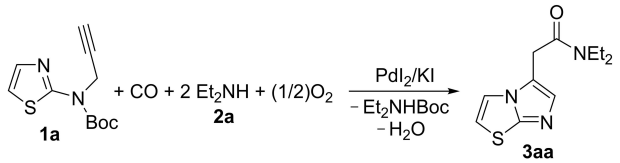


Scheme 3. *This work hypothesis:* Formation of 2-(imidazo[2,1-*b*]thiazol-5-yl)-*N*,*N*-dialkylacetamides by PdI_2/KI-catalyzed oxidative aminocarbonylation of *N*-propargylthiazol-2-amines to give **I**, followed by dearomative cyclization to **II** and proton-shift aromatization.

Research Article
doi.org/10.1002/ejoc.202200916

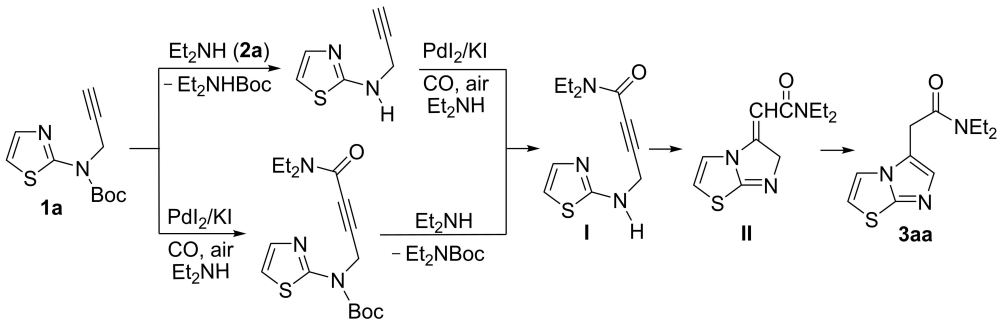
Chemistry Europe
European Chemical Societies Publishing

Table 1. PdI_2/KI-catalyzed oxidative aminocarbonylation of *N*-Boc-*N*-propargylthiazol-2-amine **1a** under different conditions.[a]



Entry	Solvent	KI [equiv]	**2a** [equiv]	**2a** concentration[b]	*T* [°C]	P_{CO} [atm]	P_{air} [atm]	Yield of **3aa** [%][c]
1	MeCN	1.0	3	0.20	100	16	4	58 (54)
2	dioxane	1.0	3	0.20	100	16	4	48
3	MeCN	1.0	2	0.20	100	16	4	46
4	MeCN	1.0	4	0.20	100	16	4	60
5	MeCN	0.5	3	0.20	100	16	4	76
6	MeCN	0.1	3	0.20	100	16	4	58
7	MeCN	1.0	3	0.20	80	16	4	50
8	MeCN	1.0	3	0.20	100	32	8	55
9	MeCN	1.0	3	0.40	100	16	4	45
10	MeCN	1.0	3	0.05	100	16	4	72

[a] All reaction were carried out for 6 h in the presence of PdI_2 (1 mol%). [b] Mmol of **1a** per mL of solvent. [c] GLC yield (isolated yield) based on starting **1a**.



Scheme 4. Possible pathways leading to **3aa** from **1a** and **2a**.

1a concentration of 0.05 mmol of **1a** per mL of MeCN was beneficial (GLC yield of **3aa** was 72%; Table 1, entry 10).

Based on this brief optimization study, the next experiment was carried out using PdI_2 (1 mol%) in conjunction with KI (50 mol%), 4 equiv. of **2a**, in MeCN as the solvent (**1a** initial concentration = 0.05 mmol per mL of MeCN), under 20 atm of a 4:1 mixture of CO-air, at 100 °C for 6 h. Under these conditions, imidazothiazolacetamide **3aa** was obtained in 81% GLC yield (78% isolated, Table 2, entry 1). Similar results were obtained when changing the amine to diisopentylamine **2b** (isolated yield of **3ab**, 87%; Table 2, entry 2) or to cyclic amines morpholine **2c** (yield of **3ac**, 80%; Table 2, entry 3) and piperidine **2d** (yield of **3ad**, 71%; Table 2, entry 4). On the other hand, dibutylamine **2e** and cyclohexylethylamine **2f** required a higher reaction time (15 h) to achieve a good isolated yield of the corresponding products **3ae** and **3af** (66%; Table 2, entries 5 and 6). Substrates bearing an electron-donating (Me) or -withdrawing (CO_2Et) group at the C-4 position of the thiazole ring (**1b** and **1c**, respectively) also reacted quite well, and led, with diethylamine **2a**, to the formation of the corresponding imidazothiazolacetamides **3ba** and **3ca** in 71% and 58% yields, respectively (Table 2, entries 7 and 8, respectively). The presence of an alkyl substituent α to the triple bond (substrates **1d** and **1e**) was tolerated, with final isolated yields of the corresponding products **3da** and **3ee** of 84% and 60%, after 20 h or 15 h reaction time, respectively, (Table 2, entries 9 and 10).

To further expand the synthetic scope of the process, we also tested the reactivity of *N*-Boc-*N*-(propargyl)benzo[*d*]thiazol-2-amine **1f** with both Et_2NH **2a** and Bu_2NH **2e**. With this substrate, dearomative cyclization was expected to be more difficult with respect to **1**, owing the higher aromatic stability conferred by the additional fused benzene ring. In spite of this, the desired benzimidazothiazolacetamide **3fa** and **3fe** were indeed obtained under the usual conditions in acceptable yields (57% and 51%; Table 2, entries 10 and 11 respectively).

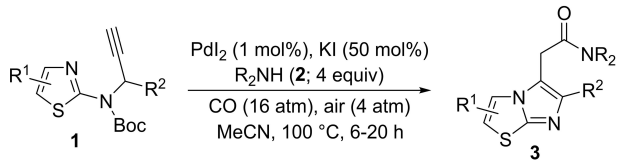
Conclusion

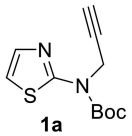
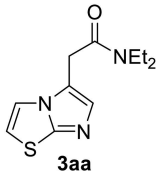
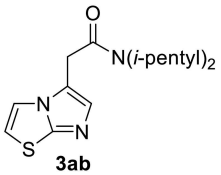
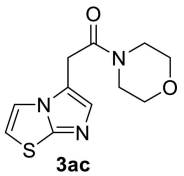
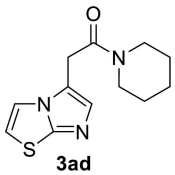
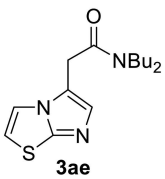
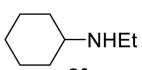
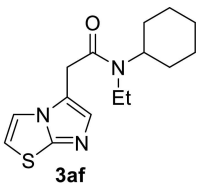
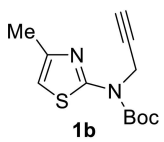
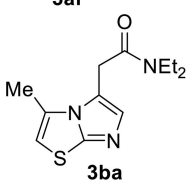
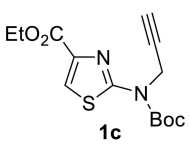
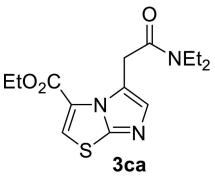
In conclusion, we have reported a new approach to the synthesis of an important class of functionalized bicyclic heterocycles, namely, 2-(imidazo[2,1-*b*]thiazol-5-yl)-*N*,*N*-dialkylacetamides **3**, starting from readily available *N*-Boc-*N*-propargylthiazol-2-amines **1**, carbon monoxide, a secondary amine **2**, and oxygen in a multicomponent fashion. The process leading to **3**

Research Article
doi.org/10.1002/ejoc.202200916

Chemistry Europe
European Chemical Societies Publishing

Table 2. Synthesis of imidazothiazolacetamides **3** by PdI_2/KI-catalyzed oxidative aminocarbonylation of *N*-Boc-*N*-propargylthiazol-2-amines **1** with CO, O_2, and a secondary amine **2**.[a]

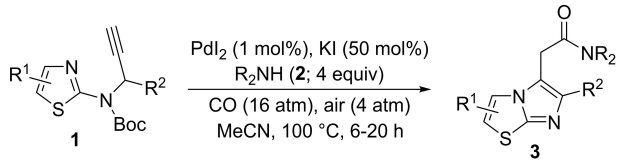


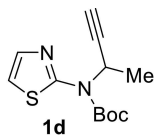
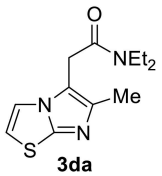
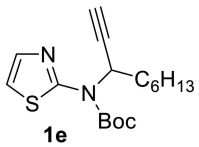
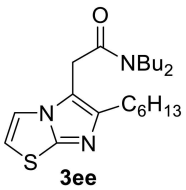
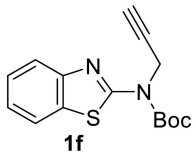
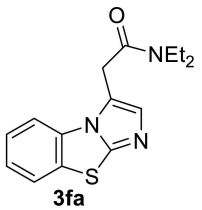
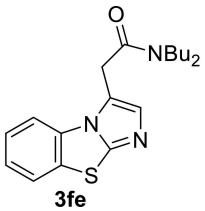
Entry	1	2	3	Yield of 3[%][b]
1	 **1a**	Et_2NH **2a**	 **3aa**	78
2	**1a**	$(i\text{-pentyl})_2NH$ **2b**	 **3ab**	87
3	**1a**	 **2c**	 **3ac**	86
4	**1a**	 **2d**	 **3ad**	80
5[c]	**1a**	Bu_2NH **2e**	 **3ae**	66
6[c]	**1a**	 **2f**	 **3af**	80
7	 **1b**	**2a**	 **3ba**	71
8	 **1c**	**2a**	 **3ca**	58

Research Article
doi.org/10.1002/ejoc.202200916

Chemistry Europe
European Chemical Societies Publishing

Table 2. continued



Entry	1	2	3	Yield of 3[%][b]
9[d]	 1d	2a	 3da	84
10[c]	 1e	2e	 3ee	60
11	 1f	2a	 3fa	57
12	1f	2e	 3fe	51

[a] Unless otherwise noted, all reactions were carried out with 0.5 equiv. of KI and 4 equiv. of R_2NH **2** in MeCN (0.05 mmol of starting **1** per mL of solvent) at 100 °C for 6 h. [b] Isolated yield based on starting **1**. [c] The reaction was carried out for 15 h. [d] The reaction was carried out for 20 h.

takes place through an ordered sequence of mechanistic steps, involving *N*-Boc deprotection, triple bond oxidative aminocarbonylation with C*sp*–H activation, dearomative intramolecular conjugate addition (by nucleophilic attack of the thiazole nitrogen to the ensuing 2-ynamide intermediate) and aromative isomerization. The process, although less efficiently, has also been applied to the one-step synthesis of tricyclic 2-(benzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)-*N*,*N*-dialkylacetamides **5** starting from *N*-Boc-*N*-(propargyl)benzo[*d*]thiazol-2-amine **4**.

The approach disclosed here therefore opens the way to the direct carbonylative synthesis of important polycyclic heterocyclic derivatives in one step and under relatively mild conditions (100 °C under 20 atm of a 4:1 mixture of CO-air), with the catalysis of the particularly simple PdI_2/KI catalytic system and with oxygen (from air) as the simplest external oxidant.

Experimental Section

General experimental methods: Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ or DMSO-d_6 at 500 MHz and 125 MHz, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. All reactions were analyzed by TLC on silica gel 60 F254 and by GC-MS analysis using a GC-MS apparatus at 70 eV ionization voltage equipped with a 95% methyl polysiloxane – 5% phenyl polysiloxane capillary column (30 m × 0.25 mm, 0.25 μm). Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure. The HRMS spectra were taken on Q-TOF-MS mass spectrometer, equipped with an electrospray ion source (ESI) operated in dual ion mode. 10 μL of the sample solutions (CH_3OH) were introduced by continuous infusion at a flow rate of 200 L min^{-1} with the aid of a syringe pump. Experimental conditions were performed as follows: capillary voltage, 4000 V; nebulizer pressure, 20 psi; flow rate of drying gas, 10 L/min; temperature of sheath gas, 325 °C; flow rate of sheath gas, 10 L/ min; skimmer voltage, 60 V; OCT1 RF Vpp, 750 V; fragmentor voltage, 170 V. The spectra data were recorded in the *m/z* range of 100–1000 Da in a centroid pattern of full-scan MS analysis mode. The MS/MS data of

the selected compounds were obtained by regulating diverse collision energy (18–45 eV).

Preparation of substrates: *N*-Boc-*N*-propargylthiazol-2-amines **1** were prepared and characterized as described in the Supporting Information. All other materials were commercially available and were used without further purification.

General procedure for the synthesis of 2-(imidazo[2,1-*b*]thiazol-5-yl)-*N*,*N*-dialkylacetamides 3 (Table 2): A 35 mL stainless steel autoclave was charged in the presence of air with PdI_2 (1.5 mg, 4.16×10^{-3} mmol), KI (35.0 mg, 0.21 mmol) and a solution of *N*-Boc(prop-2-yn-1-yl)thiazol-2-amine **1** (0.42 mmol; **1a**: 100 mg; **1b**: 106 mg; **1c**: 130 mg, **1d**: 106 mg; **1e**: 135 mg; **1f**: 121 mg] and amine (1.67 mmol) [**2a**: 122 mg; **2b**: 262 mg; **2c**: 145 mg; **2d**: 142 mg; **2e**: 215 mg; **2f**: 212 mg) in anhydrous CH_3CN (8.4 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm). After being stirred at 100 °C for 6–20 h (see Table 2), the autoclave was cooled, degassed and opened. After evaporation of the solvent, products **3** were purified by column chromatography on silica gel using as eluent $CHCl_3$-hexane from 8:2 to 100:0. Characterization data for products **3** are given in the Supporting Information.

Acknowledgements

Financial support by MIUR PRIN 2017YJMPZN project (Mussel-inspired functional biopolymers for underwater adhesion, surface/interface derivatization and nanostructure/composite self-assembly-MUSSEL) to B.G. is acknowledged. Open Access funding provided by Universita della Calabria within the CRUI-CARE Agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Carbonylation · Cyclization · Fused-ring systems · Heterocycles · Palladium

[1] For a recent book and reviews, see: a) *Carbon Monoxide in Organic Synthesis – Carbonylation Chemistry*, (Ed.: B. Gabriele), Wiley-VCH, Weinheim, Germany, **2021**; b) R. Mancuso, N. Della Ca', L. Veltri, I. Ziccarelli, B. Gabriele, *Catalysts* **2019**, *9*, 610; c) B. Gabriele, *Targets Heterocycl. Syst.* **2018**, *22*, 41–55; d) B. Gabriele, *Synthesis of heterocycles by palladium-catalyzed carbonylative reactions, in Advances in Transition-Metal Mediated Heterocyclic Synthesis* (Eds.: D. Solé, I. Fernández), Academic Press-Elsevier, London, **2018**, chapter 3, pp. 55–127; e) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825–6839; f) B. Gabriele, G. Salerno, M. Costa, *Top. Organomet. Chem.* **2006**, *18*, 239–272; g) B. Gabriele, G. Salerno, PdI_2, in *e-EROS (Electronic Encyclopedia of Reagents for Organic Synthesis)* (Ed.: D. Crich), Wiley-Interscience, New York, **2006**.

[2] For very recent examples, see: a) R. Mancuso, P. Russo, R. Miliè, M. Dell'Aera, F. Grande, N. Della Ca', B. Gabriele, *Catal. Today* **2022**, *397–399*, 631–638; b) R. Mancuso, I. Ziccarelli, M. Novello, C. Cuocci, R. Centore, N. Della Ca', D. Olivieri, C. Carfagna, B. Gabriele, *J. Catal.* **2022**, *405*, 164–182; c) R. Mancuso, M. Lettieri, I. Ziccarelli, P. Russo, A. Palumbo Piccionello, B. Gabriele, *Adv. Synth. Catal.* **2021**, *363*, 4612–4620; d) R. Mancuso, I. Ziccarelli, M. Brindisi, C. D. Altomare, L. Frattaruolo, A. Falcicchio, N. Della Ca', A. R. Cappello, B. Gabriele, *Catalysts* **2021**, *11*, 227; e) L. Veltri, T. Prestia, P. Russo, C. Clementi, P. Vitale, F. Ortica, B. Gabriele, *ChemCatChem* **2021**, *13*, 990–999; f) R. Mancuso, R. Strangis, I. Ziccarelli, N. Della Ca', B. Gabriele, *J. Catal.* **2021**, *393*, 335–343.

[3] 2-Ynamides are a very important class of carbonyl derivatives, whose structure is present in many biologically active molecules: a) W.-D. Rudorf, R. Schwarz, *Heterocycles* **1986**, *24*, 3459–3465; b) A. Pinto, L. Neuville, P. Retailleau, J. P. Zhu, *Org. Lett.* **2006**, *8*, 4927–4930; c) S. Eichner, T. Eichner, H. G. Floss, J. Fohrer, E. Hofer, F. Sasse, C. Zeilinger, A. Kirschning, *J. Am. Chem. Soc.* **2012**, *134*, 1673–1679; d) L. A. Hay, T. M. Koenig, F. O. Gina, J. D. Copp, D. Mitchell, *J. Org. Chem.* **1998**, *63*, 5050–5058; e) A. Brennfuhrer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; *Angew. Chem.* **2009**, *121*, 4176–4196; f) W. T. Wu, Z. H. Zhang, L. S. Liebeskind, *J. Am. Chem. Soc.* **2011**, *133*, 14256–14259.

[4] B. Gabriele, G. Salerno, L. Veltri, M. Costa, *J. Organomet. Chem.* **2001**, *622*, 84–88.

[5] a) P. Plastina, B. Gabriele, G. Salerno, *Synthesis* **2007**, 3083–3087; b) B. Gabriele, P. Plastina, G. Salerno, M. Costa, *Synlett* **2005**, 935–938; c) B. Gabriele, G. Salerno, P. Plastina, M. Costa, A. Crispini, *Adv. Synth. Catal.* **2004**, *346*, 351–358.

[6] For recent examples, see: a) L. Veltri, P. Russo, T. Prestia, P. Vitale, R. Romeo, B. Gabriele, *J. Catal.* **2020**, *386*, 53–59; b) L. Veltri, S. V. Giofrè, P. Devo, R. Romeo, A. P. Dobbs, B. Gabriele, *J. Org. Chem.* **2018**, *83*, 1680–1685; c) L. Veltri, G. Grasso, R. Rizzi, R. Mancuso, B. Gabriele, *Asian J. Org. Chem.* **2016**, *5*, 560–567; d) L. Veltri, R. Mancuso, A. Altomare, B. Gabriele, *ChemCatChem* **2015**, *7*, 2206–2213; e) B. Gabriele, L. Veltri, R. Mancuso, C. Carfagna, *Adv. Synth. Catal.* **2014**, *356*, 2547–2558.

[7] For a recent example of carbonylative heterocyclization with aromatic Csp^2–H activation using alcohols rather than amines as external nucleophiles, see: W. Zhang, M.-N. Zhao, M. Chen, Z.-H. Ren, Z. Guan, *Asian J. Org. Chem.* **2018**, *7*, 1605–1608.

[8] Previous examples of formation of 2-(imidazo[2,1-*b*]thiazol-5-yl)amides include the reaction of 5-(2,2-dibromovinyl)-imidazo[2,1-*b*]thiazole with an excess of amine, the decarboxylation of 2-(imidazo[2,1-*b*]thiazol-5-yl)acetic acid under MW irradiation in the presence of *N*,*N*-dimethylacetamide, and the Ugi reaction employing imidazo[2,1-*b*]thiazole-5-carbaldehyde; see, respectively: a) Q. Huang, S. Zard, *Org. Lett.* **2018**, *20*, 1413–1416; b) V. M. Muzalevskiy, Z. A. Sizova, A. V. Shastin, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2019**, 4034–4042; c) A. S. Trifilenkov, A. P. Ilyin, V. M. Kysil, Y. B. Sandulenko, A. V. Ivachtchenko, *Tetrahedron Lett.* **2007**, *48*, 2563–2567.

[9] For examples of bioactive 2-(imidazo[2,1-*b*]thiazol-5-yl)acetic acid derivatives, see: a) T. A. Tikhonova, I. V. Rassokhina, E. A. Kondrakhin, M. A. Fedosov, J. V. Bulanova, A. V. Rossokhin, I. N. Sharonova, G. I. Kovalev, I. V. Zavarzin, Y. A. Volkova, *Bioorg. Chem.* **2020**, *94*, 103334; b) M. J. Bamford, T. D. Heightman, D. M. Wilson, J. Witherington, *Int. Pat. Appl.* WO2005/087746 (**2005**); c) F. Palagiano, L. Arenare, E. Luraschi, P. de Caprariis, E. Abignente, M. D'Amico, W. Filippelli, F. Rossi, *Eur. J. Med. Chem.* **1995**, *30*, 901–909.

[10] For recent reviews on bioactivity of imidazo[2,1-*b*]thiazole derivatives, see: a) M. A. Shareef, I. Khan, B. N. Babu, A. Kamal, *Curr. Med. Chem.* **2020**, *27*, 6864–6887; b) C. M. Afsina Abdulla, M. Neetha, T. Aneeja, G. Anilkumar, *ChemistrySelect* **2020**, *5*, 10374–10386; c) F. Buron, M.-A. Hiebel, J.-Y. Merour, K. Ple, S. Routier, *Adv. Heterocycl. Chem.* **2018**, *125*, 301–356; d) M. L. Fascio, M. I. Errea, N. B. D'Accorso, *Eur. J. Med. Chem.* **2015**, *90*, 666–683.

[11] See, for example: B. Gabriele, L. Veltri, R. Mancuso, G. Salerno, S. Maggi, B. M. Aresta, *J. Org. Chem.* **2012**, *77*, 4005–4016.

Manuscript received: July 29, 2022
Revised manuscript received: October 5, 2022
Accepted manuscript online: October 6, 2022