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Urea Derivatives from Carbon Dioxide and Amines by Guanidine Catalysis: Easy Access to Imidazolidin-2-ones under Solvent-Free Conditions

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Abstract. A novel methodology to easily access imidazolidin-2-ones from propargylamines, primary amine and CO_2 with TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) or MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) as catalysts under solvent-free conditions is here reported. Bicyclic guanidines, able to catalyze the formation of oxazolidinones from secondary propargylamines and CO_2, are now presented for the first time as effective organocatalysts for the chemical fixation of CO_2 into linear and cyclic ureas. Plausible reaction pathways are proposed on the basis of experimental findings.

Keywords: Bicyclic guanidines; Carbon dioxide fixation; Organocatalysis; Propargylic amines; Ureas

1. Introduction

Imidazolidin-2-one is an ubiquitous structural motif found in a plethora of heterocyclic compounds that display a wide range of biological activities (Figure 1) [1]. Substituted imidazolidin-2-ones are also chiral auxiliaries in asymmetric synthesis [2] and valuable intermediates for organic chemists [3], allowing, for instance, a facile access to hydantoins [4]. The most common approach to imidazolidin-2-ones consists in the carbonylation of diamines with phosgene [5], carbon monoxide [6], dialkyl carbonate [7], or carbon dioxide [8]. Alternative methodologies involve metal-catalyzed diamination of olefins [9], aziridine ring expansion [10] or cyclization of preformed urea derivatives [11] (Scheme 1). Among these, processes exploiting the inexpensive, abundant, non-flammable and nontoxic CO_2 as carbonylating agent represent an attractive route to cyclic ureas from the environmental point of view [8]. In this context, Munoz et al. reported the formation of cyclic ureas under mild conditions with a

stoichiometric amount of DPPA as phosphorylating agent [8b]. However, the co-production of salts and a stoichiometric amount of phosphine oxide induced to develop efficient catalysts for the reaction between diamines and CO_2, that, without any suitable additive, requires quite harsh conditions (>150 °C, >6 MPa) [8c,d].

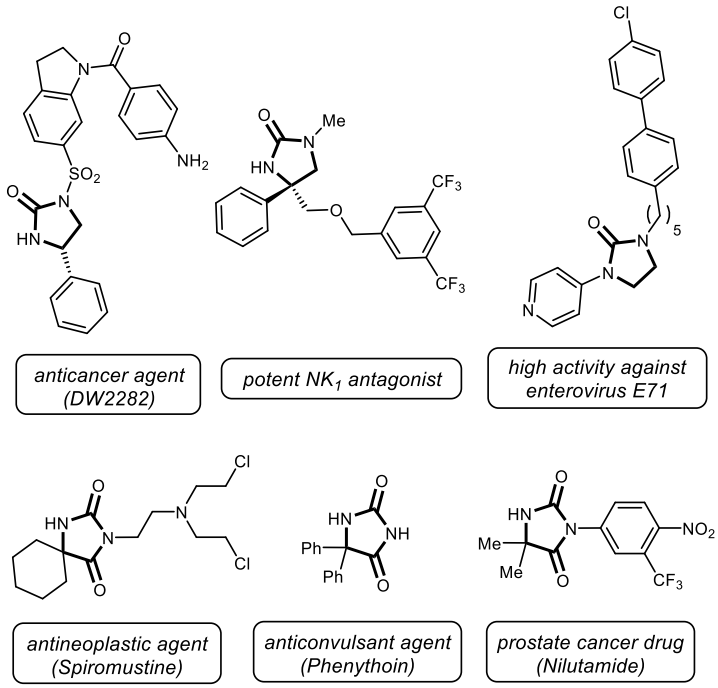
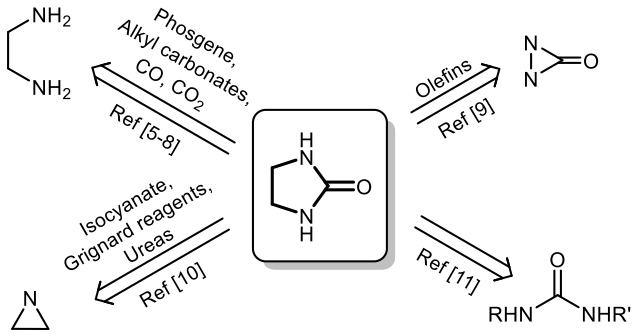


Figure 1. Selected bioactive imidazolidin-2-ones (up) and hydantoins (down).



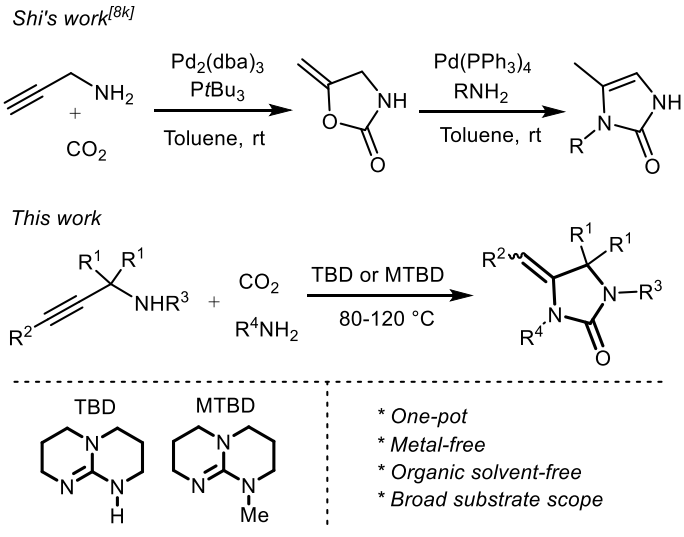
Scheme 1. Conventional strategies to imidazolidin-2-one derivatives.

Polyethylene-glycol supported potassium hydroxide (KOH/PEG1000) [8e] is an efficient heterogeneous catalyst at 8 MPa CO_2 pressure and 150 °C, while CeO_2 was found to be active at 160 °C and lower pressure (0.5 MPa) but 20 mol% of catalyst was needed [8f]. Ph_3SbO/P_4S_{10} [8g] catalyzed the synthesis of imidazolidinones at lower temperatures (80-150 °C) and 4.9 MPa, however only dialkylamines were employed. Aromatic *ortho*-diamines led to the synthesis of benzimidazolones in the presence of $TBA_2[WO_4]$ as catalyst [8h] at 140 °C and with atmospheric pressure of CO_2, or by means

of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)-based ionic liquid at 120 °C and 9 MPa CO_2 pressure under solvent free conditions [8j]. Generally, harsh conditions or a very narrow reaction scope are the main drawbacks of these methodologies. On the other hand, we have to mention the two-steps synthesis of imidazolidin-2-ones at very mild reaction conditions under palladium catalysis starting from α-unsubstituted propargylamines, CO_2 and an additional amine (Scheme 2, *Shi's work*). The methyleneoxazolidin-2-one intermediate, generated with $Pd_2(dba)_3$ and P*t*Bu_3 as ligand at room temperature, gave, in the presence of an aliphatic amine and $Pd(PPh_3)_4$ as catalyst, the imidazolidin-2-one derivative in satisfactory yield [8k]. The presence of α-substituents led, however, to very poor results.

In the last decades, guanidines have constituted an important class of organic superbases able to catalyze various types of base-mediated organic reactions [12]. In particular, bicyclic guanidines, featuring a rigid framework and unique electronic and chemical properties, have shown to be active catalysts in CO_2 chemical fixation [12]. In this context, both homogeneous and heterogeneous catalytic systems have been discovered for the conversion of CO_2 into value-added chemicals [12i]. For instance, organosuperbases, such as 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), have displayed high efficiency in the formation of oxazolidinones from secondary propargylamines and CO_2 [13]. Moreover, in the course of our research on new methodologies for CO_2 activation [14], we have recently demonstrated that bicyclic guanidines act as organocatalysts for the synthesis of cyclic carbonates and, in the presence of primary amines, carbamates by carboxylation of propargyl alcohols with carbon dioxide as reagent and solvent [14a].

Herein, we report a new one-pot synthesis of 5-methyleneimidazolidin-2-ones based on the use of bicyclic guanidines as catalysts, starting from propargylamines, primary amines and CO_2 under solvent-free and mild conditions (Scheme 2, *this work*). This one-pot transformation represents a further advancement in the direction of carbon dioxide conversion into high value-added chemicals [12i, 15].



Scheme 2. Syntheses of imidazolidin-2-ones by palladium (*Shi's work*) and bicyclic guanidine catalysis (*This work*).

2. Experimental section

2.1. General Information

All reagents were used as received from commercial sources without further purification unless otherwise stated. Solvents were dried over activated molecular sieves for 24 h. All reactions were analyzed by TLC and by GC using a 30 m SE-30 capillary column. Column chromatography was performed on silica gel 60 (70–230 mesh). Melting points were measured with an Electrothermal apparatus and are uncorrected. Electron impact mass spectra [*m/z*, relative intensity (%)] were determined with a GC-MS apparatus at 70 eV ionization energy. IR spectra were run on a Nicolet FT-IR 5700 spectrophotometer paired with a Diamond Smart Orbit accessory. Elemental analyses were performed with a Carlo Erba EA 1108-Elemental Analyzer. Unless otherwise indicated NMR spectra were recorded on Bruker AVANCE 300 and 400 spectrometers in deuterated chloroform (unless otherwise indicated), using the solvent residual signals as internal reference (7.26 and 77.00 ppm, respectively for ^{1}H and ^{13}C). Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively.

2.2. Typical Experimental Procedure for the Catalytic Synthesis of Symmetric Urea 1 (Table 2)

An oven dried 125-mL stainless-steel autoclave was charged with *n*-butylamine (365 mg, 5.0 mmol) and TBD (69 mg, 0.5 mmol, 10 mol%). The autoclave was sealed, purged at room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (44g) at room temperature (by weighing it before and after the pressurization). The reaction mixture was stirred at 100 °C for 24 h, after that the autoclave was cooled, degassed and opened. The reaction crude was recovered with CH_2Cl_2 and the symmetric urea **1a** was obtained in 63% yield by ^{1}H NMR using methylbenzoate as internal standard. Recrystallization of the residue from diethyl ether/petroleum ether (1:1) gave **1a** as white solid (0.499 g, 58%).

2.3. Typical Experimental Procedure for the Catalytic Synthesis of Compounds 2 and 3 (Scheme 4)

An oven dried 125-mL stainless-steel autoclave was charged with 2-methyl-3-butyn-2-amine (415 mg, 5.0 mmol) and MTBD (76 mg, 0.5 mmol, 10 mol%). The autoclave was sealed, purged at

room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (44g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using EtOAc and the resulting organic solution was analyzed by GC, GC-MS and ^{1}H NMR. The solvent was removed and the residue was purified *via* column chromatography (1:1 hexane:ethyl acetate) to afford product **2a** (0.34 g, 35%) and **3a** (0.32 g, 31%). *1,1,5,5-tetramethyl-1,5-dihydroimidazo[1,5-a]pyridin-3(2H)-one* (**2a**): pale yellow solid: mp 198-199 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (br s, 1H), 5.67 (dd, *J* = 9.7, 5.8 Hz, 1H), 4.89 (d, *J* = 9.7 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 1H), 1.57 (s, 6H), 1.30 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.4, 147.6, 125.9, 118.3, 89.0, 56.3, 55.0, 28.9, 28.0; IR (ATR): ν = 3244, 2943, 2842, 1719, 1660, 1575, 1542, 1461, 1354, 1329 cm^{-1}; MS (EI): *m/z* = 192 (M^+, 20), 177 (40), 162 (10), 134 (100), 118 (10), 106 (10), 92 (10); anal. calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57; O, 8.32; found: C 68.93, H 8.32, N 14.51. *4,4-dimethyl-1-(2-methyl-3-oxobutan-2-yl)-5-methyleneimidazolidin-2-one* (**3a**): white solid: mp 128-129 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.53 (s, 1H), 4.09 (d, *J* = 2.7 Hz, 1H), 4.03 (d, *J* = 2.7 Hz, 1H), 2.03 (s, 3H), 1.41 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 206.2, 156.5, 152.5, 80.5, 63.9, 55.7, 29.0, 23.6, 21.6; IR (ATR): ν = 3345, 3252, 2981, 2901, 2837, 1726, 1647, 1577, 1424, 1360, 1282 cm^{-1}; MS (EI): *m/z* = 210 (M^+, 5), 167 (100), 153 (5), 124 (80), 111 (30), 96 (15), 82 (15); anal. calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32; O, 15.22; found: C 62.64, H 8.70, N 13.29.

2.4. Typical Experimental Procedure for the Catalytic Synthesis of imodazolidin-2-ones 8 (Table 4)

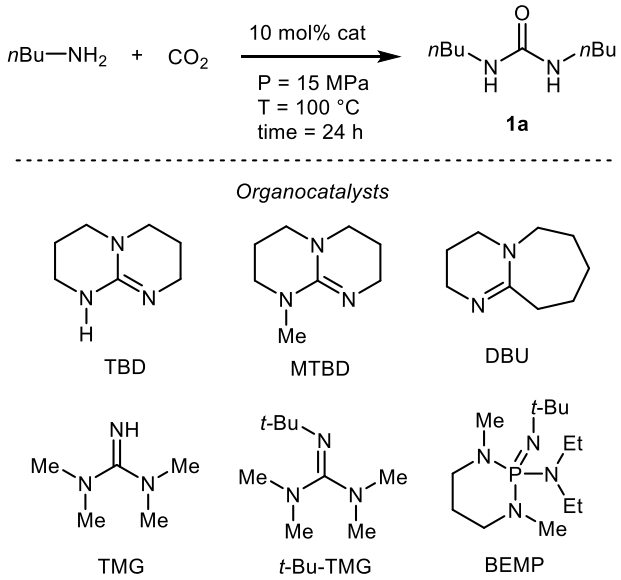
An oven dried 45-mL stainless-steel autoclave was charged with 1-ethynylcyclohexan-1-amine (246 mg, 2 mmol), *n*-butylamine (584 mg, 8 mmol) and TBD (28 mg, 0.2 mmol). The autoclave was sealed, purged at room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (8g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 100 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using EtOAc and after removal of the solvent, the residue was purified *via* column chromatography to give **8a** (373 mg, 84% yield) as a pale yellow solid (m.p.: 112.8-113.4 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (br s, 1H), 3.95 (br s, 1H), 3.87 (br s, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.78-1.16 (m, 14H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.7, 77.5, 59.1, 39.5, 38.5, 28.5, 24.9, 22.2, 19.9, 13.7; IR (ATR): ν = 3359, 2963, 2941, 2916, 2870, 1702, 1630, 1527, 1392, 1353; MS (EI): *m/z* = 222 (M^+, 80), 207 (20), 193 (15), 180 (70), 167 (100), 151 (20), 137 (30), 123 (30), 111 (50), 94 (10). Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 69.9; H, 9.9; N, 12.5.

3. Results and discussion

3.1. Reaction of Alkylamines with CO_2 in the Presence of Organic Superbases

The first investigations were focused to test the activity of several organic superbases in the formation of simmetric ureas from alkylamines and CO_2. In the model reaction, *n*-butylamine reacted with CO_2 in the presence of 10 mol% of catalyst under solvent-free conditions. The mixture was kept at 100 °C under stirring for 24 h and the results are reported in Table 1. Among the tested superbases, TBD and MTBD gave the best yields of **1a** with selectivity above 98% (Table 1, entries 1 and 2). Under these conditions the other catalysts were less effective, suggesting that only strong bases having pK_a (MeCN) in the range 25-27 afford satisfactory yields. The basicity, however, is not the only factor influencing the reaction described here [12f]. It becomes evident with the use of a phosphazene base, such as BEMP (p$K_a^{(MeCN)}$>27), which did not bring forward any improvement in comparison with bicyclic guanidines. The course of the reaction turns out to be influenced not only by basicity but also by other structural effects likely due to steric hindrance and hydrogen bridges. A similar trend was previously observed in the organocatalyzed-synthesis of oxazolidinones from secondary propargylamines and CO_2 [13].

Table 1. Organocatalyzed-synthesis of **1a** from *n*-butylamine and CO_2.[a]



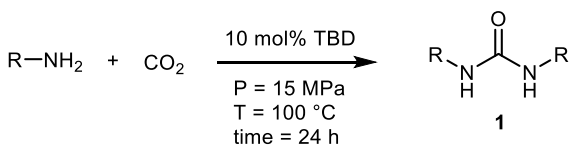
Entry	cat	pK_a[b]	Solvent	Yield [%][c]
1	TBD	26.03	-	63
2	MTBD	25.49	-	53

3	DBU	24.34	-	24
4	TMG	23.30	-	8
5	*t*-Bu-TMG	n.d.[d]	-	19
6	BEMP	27.58	-	37
7	TBD		MeCN (1 mL)	64[e]
8	TBD		MeCN (2 mL)	67[e]
9	TBD		MeCN (4 mL)	69[e]

[a] Reaction conditions: stainless-steel autoclave (125 mL capacity) was charged with *n*-butylamine (5 mmol), CO_2 (15 MPa at 100 °C), cat (10 mol%), 24 h. [b] p*K*a is referred to its conjugate acid in MeCN.[12] [c] Yield of **1a** was determined via ^{1}H NMR analysis using methylbenzoate as internal standard. [d] Not determined, but a value between 23.5 and 24.5 could be assigned [13]. [e] A small amount of *N*-butylacetamide (<5%), obtained by hydrolysis of MeCN and subsequent transamidation, was detected by GC-MS analysis.

In this case, the catalytic performance of TBD at 100 °C is modest (63% yield) but remarkable, since almost all existing catalytic systems give, without dehydrating agents, comparable results at higher reaction temperatures (>140 °C) [8,16]. The role of TBD was further remarked by Kleij et al. in the valuable synthesis of non-symmetric ureas from cyclic carbonates and anilines [12d]. Further optimization work did not improve the reaction output (see Table S1 in SI). Noteworthy, the addition of organic aprotic polar solvents was similarly negative. Only MeCN in small amount, produced slightly better results (Table 1, entries 7-9 and Table S2 in SI). This can be ascribed to its reaction with water [16a], whose removal from the equilibrium promotes the urea formation. We then explored the generality of this protocol testing other primary amines (Table 2). Apparently, under the employed reaction conditions, only linear alkylamines, such as *n*-hexylamine and *n*-octylamine, gave satisfactory results (Table 2, entries 1-3). A more hindered saturated amine, such as cyclohexyl amine, led to poor yield of the corresponding urea and the unconverted substrate was recovered at the end of the reaction (Table 2, entry 4). Unsaturated or less nucleophilic amines did not react at all (Table 2, entries 5-7) as well as secondary amines.

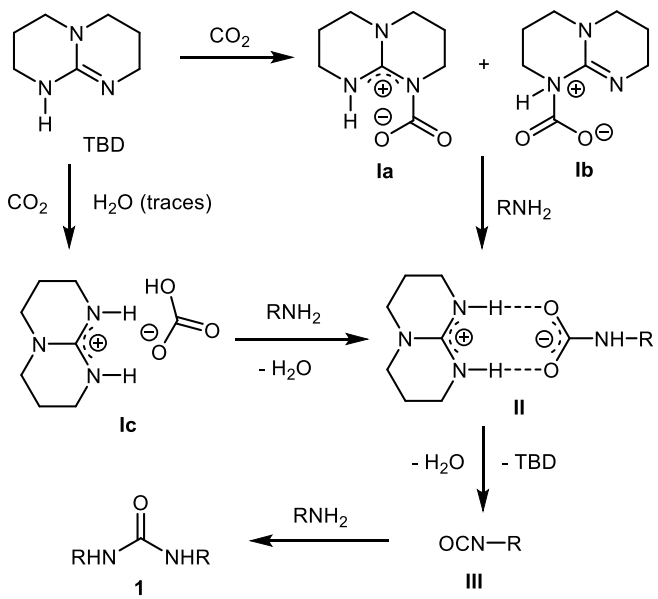
Table 2. Scope and limitations for the TBD-catalyzed synthesis of symmetric ureas **1** from RNH_2 and CO_2.[a]



Entry	R	Yield [%][b]
1	*n*-Butyl	**1a**, 63
2	*n*-Hexyl	**1b**, 65
3	*n*-Octyl	**1c**, 57
4	Cyclohexyl	**1d**, 12
5	Allyl	-
6	Benzyl	-
7	Phenyl	-

[a] Reaction conditions: stainless-steel autoclave (125 mL capacity) was charged with RNH_2 (5 mmol), liquid CO_2 (15 MPa at 100 °C), TBD (0.5 mmol), 24 h. [b] Determined via ^1H NMR analysis using methylbenzoate as internal standard.

Referring to known data and the above described results we can propose a plausible mechanism involving bicyclic guanidines as catalysts (Scheme 3). Three species (**Ia-c**) resulting from TBD-CO_2 system have been postulated on the basis of NMR experiments and TGA-FTIR analyses (Scheme 3) [17].



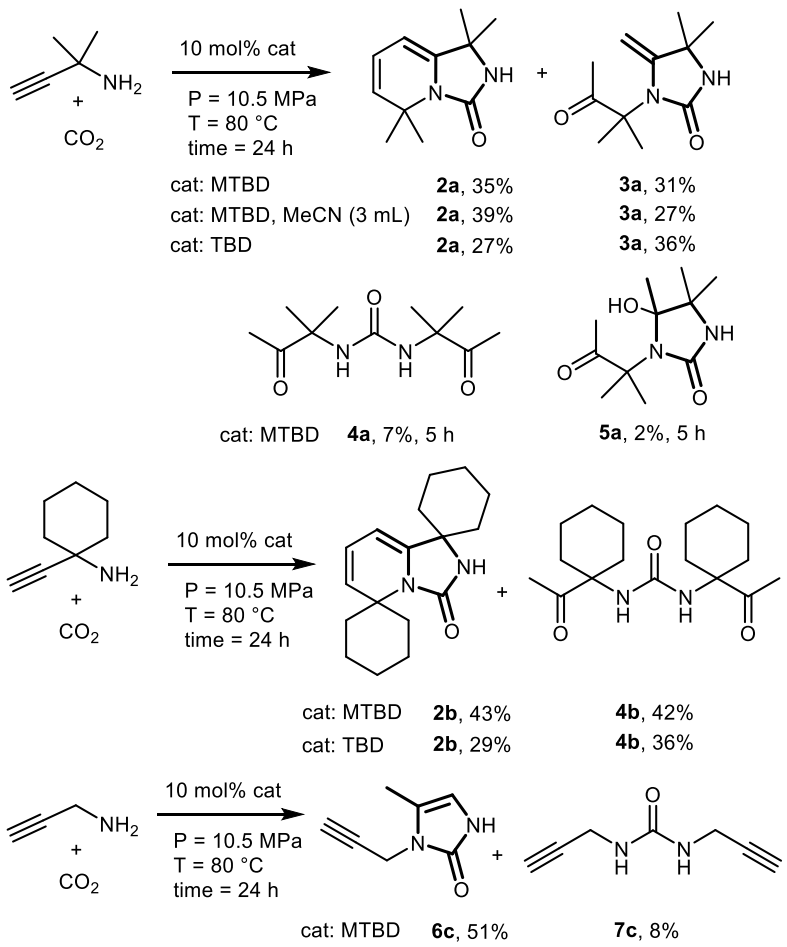
Scheme 3. Proposed mechanism for bicyclic guanidine-catalyzed urea formation.

In particular **Ia** has been synthesized and characterized by working under strictly anhydrous conditions [12g]. Traces of water can favor bicarbonate-guanidinium salt **Ic** over the zwitterionic adducts **Ia** and **Ib**. In all cases, reversibility of intermediates **Ia-c** [17] allows the primary amine to attack the electrophilic carbon of CO_2 generating carbamate **II**. Stable hydrogen bridges, shown in the solid state

by X-ray analysis for acetate or trifluoroacetate/TBDH salts [18], can be reasonably assumed even for the carbamate-guanidinium ionic pairs **II**. Furthermore, a similar intermediate has been quantitatively isolated from propargylamine, TBD and CO_2 at room temperature by He and co-workers [12e]. Then, elimination of water from **II** leads to the formation of isocyanate **III**, which readily react with another amine providing urea **1**. Isocyanate **III** was not detected in our experiments, however, according to literature [8c,h,j] its formation *in situ* seems to be reasonable and the rate determining step at the same time.

3.2. Reaction of Primary Propargyl Amines with CO_2 in the Presence of Bicyclic Guanidines

An unexpected behaviour was observed for primary propargyl amines (Scheme 4). 2-Methyl-3-butyn-2-amine, 1-ethynylcyclohexan-1-amine and 2-propynamine readily reacted with CO_2 under lower reaction temperatures compared to aliphatic amines. Unlike secondary propargyl amines that under similar conditions afforded smoothly oxazolidinones [13], primary propargyl amines led mainly to urea derivatives. In particular starting from 2-methyl-3-butyn-2-amine and MTBD as catalyst, compounds **2a** and **3a** were isolated in almost equimolar amount (35 and 31% respectively) [19]. Both products arise from two molecules of propargyl amine and one of CO_2. At shorter reaction time intermediates **4a** and **5a** were also observed in low amounts (7 and 2% respectively after 5 h, see the effect of the reaction time on the yield of compounds **2**-**5a** in Figure S1 of SI). Their formation is significant for the mechanism discussion (see Scheme 5). As expected, the addition of MeCN (3 mL) to the reaction with 2-methyl-3-butyn-2-amine increased to some extent the yield of **2a** (39%) and reduced those of **3a** (27%). Compound **2b**, analogous of **2a**, was obtained in 43% yield together with symmetric urea **4b** bearing two carbonyl groups (42%) starting from the more hindered 1-ethynylcyclohexan-1-amine (Scheme 4). Imidazolidinone **6c** (51%) and dipropargyl urea **7c** (8% yield) were obtained under the same conditions from 2-propynamine (Scheme 4). Formation of products **3a**, **4a**-**b** and **5a** involves the addition of one or two molecules of water to the triple bonds. Notably, the addition of water to triple bonds occurs easily under our reaction protocol without metals [20]. In particular, we verified experimentally that hydration of both the triple bonds of dipropargyl urea leading to **4a** and **4b** was promoted by TBD and MTBD only in the presence of CO_2 likely through the action of guanidinium bicarbonate species [21].



Scheme 4. TBD or MTBD-catalyzed synthesis of urea derivatives from primary propargyl amines and CO_2.

On the contrary, urea **7c** and imidazolidinone **6c**, probably due to their steric configuration were not involved in water addition. An analogous behavior was noticed in the reactions of propargyl alcohols with CO_2 under similar conditions [14a]. Further investigations on this subject are in progress.

All compounds have been fully characterized and structures of **2b**, **4b** and intermediate **5a** were also confirmed by X-ray crystallography (Figure 2).

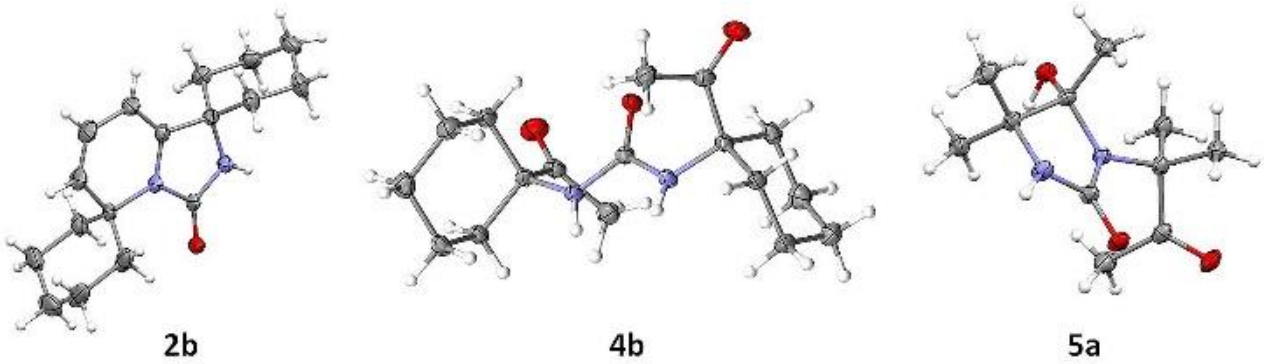
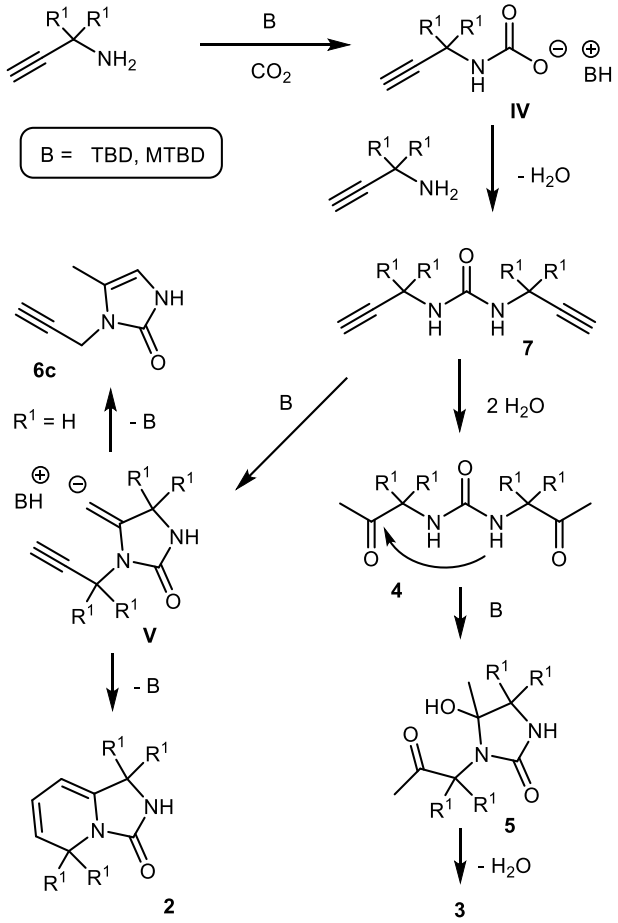


Figure 2. X-ray structures for compounds **2b**, **4b** and **5a**.

Taking into account the reaction progress diagram (Figure S1 in SI), proposed reaction pathways for the formation of compounds **2**-**7** are presented in Scheme 5. According to Scheme 3, the catalytic cycle should start with the fast formation of intermediate **IV** (analogous to **II** in Scheme 3), which can evolve, likely *via* isocyanate, towards urea **7** by H_2O elimination. Then, acetylenic urea **7** can lead to compound **2** by a sequential double cyclization process. Firstly an NH group attacks the triple bond on the internal carbon with formation of the intermediate **V**. The latter undergoes a further annulation step by nucleophilic attack of the carbanion to the near triple bond without any mediation of metals, providing compound **2**.



Scheme 5. Proposed reaction pathways for the formation of compounds **2**-**7**.

Formation of **2a** and **3a** from **7a** has been demonstrated under our reaction conditions (Scheme S1 in SI). The other isolated intermediate **4** is generated from acetylenic urea **7** by addition of H_2O. The fast intramolecular nucleophilic attack of NH to the carbonyl group of **4** affords intermediate **5** which, after elimination of H_2O, leads to product **3**. The alternative pathway from **IV** to compound **3**, involving an oxazolidinone intermediate and the addition of a second molecule of propargylamine, cannot be rule

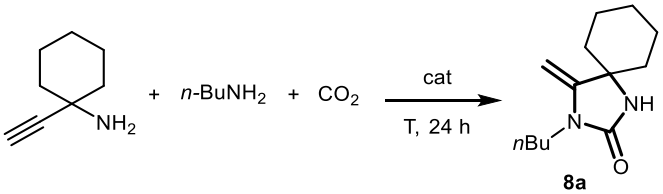
out [12d]. Finally, when R^1 is H, compound **6c** can be obtained from **V** by neutralization and isomerization steps.

Clearly, the limited selectivity and generality of these reactions prevent any meaningful synthetic application at present stage, however, based on these singular structures, some considerations can be done. Concerning the urea formation, the reported findings show a higher activity of primary propargylamines in comparison with saturated alkylamines, which are often totally unreactive at 100 °C (see Table 2, entries 4-7). Moreover, taking into account the proposed pathways, it is supposed that the presence of an alkylamine in the reaction mixture, would compete with the second molecule of propargylamine for the formation of a non-symmetric urea (Scheme 5). The subsequent annulation step would provide an imidazolidinone scaffold incorporating two different amines. This new transformation should benefit from improved reaction scope and selectivity as well, thanks to the considerable different reactivity between acetylenic and not acetylenic amines.

3.3. The Propargyl Amines/Primary Amines/CO_2 system under TBD/MTBD Catalysis: A New Route to Imidazolidinones

To verify our hypothesis we initially treated 1-ethynylcyclohexan-1-amine with *n*-butylamine and CO_2 in the presence of 10 mol% of TBD at 80 °C without any organic solvent (Table 3, entry 1). We were pleased to find that, under these conditions, the desired imidazolidinone **8a** was obtained with an encouraging 22% yield (calculated by ^{1}H NMR analysis on the reaction crude) together with compounds **2b** and **4b** which were formed in 12 and 11% yield, respectively.

Table 3. Organocatalyzed-synthesis of **8a** from 1-ethynylcyclohexan-1-amine, *n*-butylamine and CO_2.[a]



8a

Entry	cat	*n*-$BuNH_2$ (equiv)	P CO_2 (MPa)	T (°C)	Conv[b] (%)	Yield[c] (%) **8a**
1	TBD	1	5	80	61	22
2	TBD	1	7	100	82	31
3	TBD	2	7	100	90	42

4	**TBD**	**4**	**7**	**100**	**99**	**88**
5	TBD[d]	4	7	100	72	56
6	-	4	7	100	50	23
7	MTBD	4	7	100	74	43
8	DBU	4	7	100	69	49
9	TBD	4	3	100	83	65
10	TBD	4	10	100	85	70

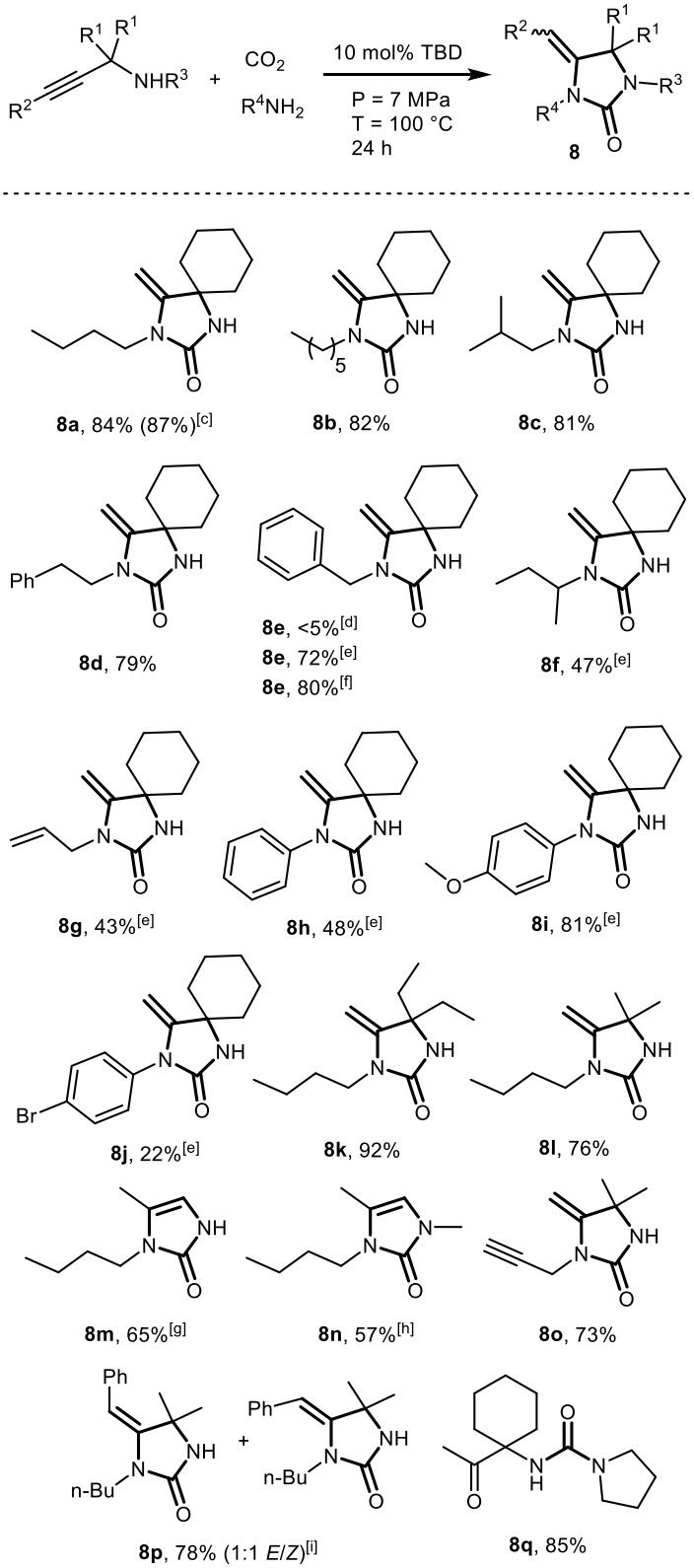
[a] Reaction conditions: 1-ethynylcyclohexan-1-amine (2 mmol), *n*-butylamine, CO_2, cat (10 mol%), 45 ml autoclave, 24 h. [b] Conversion of 1-ethynylcyclohexan-1-amine was determined by GC analysis. [c] Yield of **8a** was determined via ^{1}H NMR analysis using methylbenzoate as internal standard. [d] 5 mol%.

A higher temperature (100 °C) was beneficial for conversion but marginal for yield (Table 3, entry 2). Since byproducts **2b** and **4b** are clearly originated from the reaction of the sole propargylamine with CO_2, their amounts can be presumably reduced by increasing the concentration of the less reactive alkylamine, which contributes to the formation of **8a**. As expected, when a twofold amount of *n*-butylamine was employed selectivity toward **8a** improved (Table 3, entry 3). A further excess of alkylamine (4 equiv) led to 88% yield of imidazolidinone (Table 3, entry 4). Interestingly, under these reaction conditions formation of urea **1a** was rather limited (only a 2% of the starting *n*-butylamine gave the corresponding symmetric urea **1a**). The reaction still proceeded with 5% of TBD (56%, Table 3, entry 5), and even in the absence of organocatalyst a 23% yield of the desired cyclic urea was obtained (Table 3, entry 6). MTBD, which gave comparable results for the synthesis of urea **1a** (Table 1), was here less effective (43%, Table 3, entry 7) while DBU, often used as CO_2 activator [8j,13,22], afforded **8a** with 49% yield at 69% conversion of propargylamine (Table 3, entry 8). As we have previously observed in preliminary optimization study for the synthesis of symmetric ureas **1** (Table S1 in SI), the pressure of CO_2 seems to be crucial for the formation of imidazolidinone **8a**, being 7 MPa the best compromise (Table 3, entry 4, 9-10).

With the optimized conditions in hand (Table 3, entry 4), the scope of this three-component cyclization was demonstrated with a series of primary amines using TBD as the best catalyst (Table 4). High yields of isoxazolidin-2-ones **8a-c** were obtained by the reaction of 1-ethynylcyclohexan-1-amine with CO_2 and simple alkylamines, such as *n*-butyl, *n*-hexyl or *i*-butylamine. Remarkably, the yield of **8a** was not affected when the reaction was performed on gram-scale (87%). The presence of a phenyl ring on C-2 of the alkylamine did not significantly influence the reaction outcome, being cyclic urea **8d** isolated with 79% yield. Surprisingly, when a phenyl was placed on C-1, as in benzylamine, the yield of the corresponding product **8e** was less than 5%. A good yield of the desired product was obtained at

120 °C (72%) and an even better result was achieved using MTBD in place of TBD (80%). This singular behavior could be ascribed to the higher stability of the carbamate intermediate arising from benzylamine. A more hindered primary amine, such as *s*-butylamine, gave only 47% yield of the corresponding cyclic urea **8f**. Also in this case, a temperature of 120 °C was required. An unsaturated amine, such as allylamine, led to the corresponding cyclic urea **8g** in moderate 43% yield at 120 °C. Aniline, despite its quite low nucleophilicity, afforded imidazolidinone **8h** in satisfactory yield [12d]. Electronic properties strongly affected the reaction output since 4-OMe-aniline, having an electronically rich aromatic ring, gave **8i** with an excellent 81% yield while a worse performance was reached using 4-Br-aniline (**8j**, 22%). The scope of different primary propargylamines with *n*-$BuNH_2$ was then explored (Table 4). Under our reaction protocol, 3-ethylpent-1-yn-3-amine readily reacted with CO_2 and *n*-$BuNH_2$ providing the urea derivative **8k** in excellent yield (92%), while the less hindered 2-methylbut-3-yn-2-amine furnished the corresponding imidazolidinone in slightly lower yield (**8l**, 76%). Simple unsubstituted propargylamine generated compound **8m**, displaying the most stable endocyclic double bond, in 65% yield at 80 °C. The reaction also worked well with 2-methyl-4-phenylbut-3-yn-2-amine, bearing an internal triple bond, which, under the usual conditions, was successfully converted into imidazolidinone **8p** as a *ca.* 1:1 mixture of *E/Z* diastereoisomers (78% total yield). We also tested the reactivity of secondary propargylamines. It is well-known that secondary propargylamines show a strong tendency to give the corresponding oxazolidin-2-ones by reaction with CO_2 [12e,23]. Using our protocol, a 57% yield of cyclic urea **8n** was obtained starting from *N*-methylprop-2-yn-1-amine and *n*-$BuNH_2$. Unlikely, other secondary propargylamines afforded only oxazolidinone derivatives in high yields, confining the applicability of this protocol mostly to primary ones. The combination of two different propargylamines, that are 2-methylbut-3-yn-2-amine and prop-2-yn-1-amine led to the selective formation of **8o** in 73% yield, whose structure was unequivocally determined by single-crystal X-ray diffraction analysis (Figure 3). Finally, by reacting an acetylenic amine with a secondary amine, such as pyrrolidine, the linear ketourea **8q** was obtained in high yield (85%). In general, all reactions showed good to excellent selectivity with respect to the primary amine (R^4NH_2), which can be hypothetically recovered at the end of the reaction and recycled.

Table 4. Scope of the TBD-catalyzed synthesis of imidazolidinones **8** from propargyl amines, primary amines and CO_2.[a,b]



[a] Reaction conditions: propargylamine (2 mmol), R^4NH_2 (8 mmol), CO_2 (7 MPa), TBD (10 mol%), 45 ml autoclave, 100 °C, 24 h. [b] Isolated yield. [c] Gram-scale reaction (see SI for details) [d] Conversion of propargylamine was less than 10%. [e] 120 °C. [f] MTBD (10 mol%) at 120 °C. [g] 80 °C. [h] A 30% yield of 3-methyl-5-methyleneoxazolidin-2-one was also obtained. [i] determined by ^1H NMR.

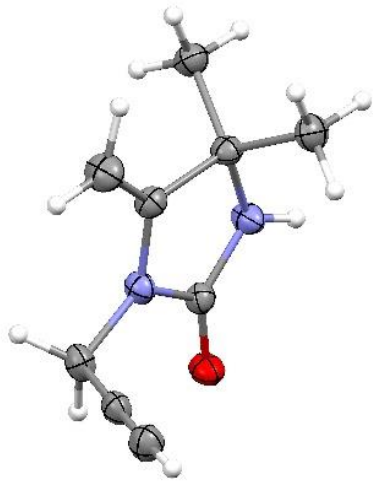
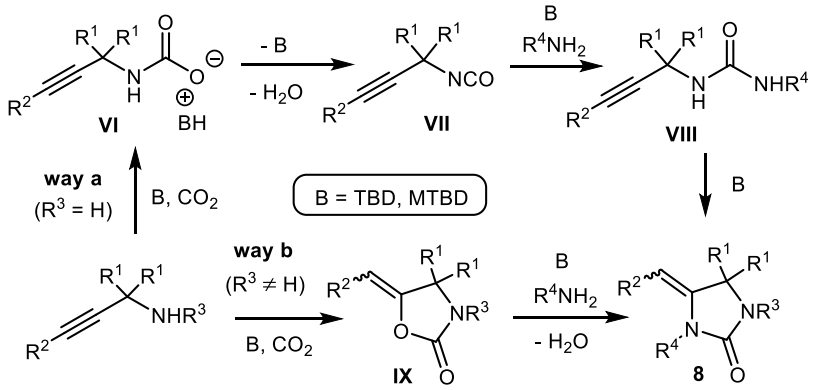


Figure 3. X-ray structure of compound **8o**.

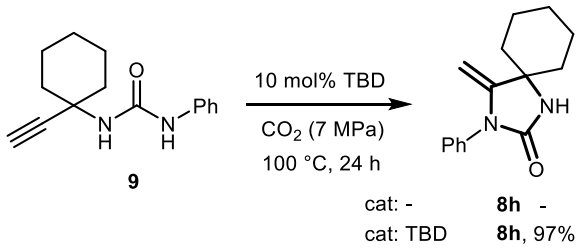
The possible formation pathways for compound **8** are presented in Scheme 6. The more reactive propargylamine forms with CO_2 and the bicyclic guanidine a carbamate intermediate **VI** which undergoes *in situ* dehydration to isocyanate **VII** [8c,h,j]. Then, the excess of primary amine (R^4NH_2) drives the selectivity towards acyclic urea **VIII** and a fast cyclization step affords product **8** (Scheme 6, way *a*). For the above mentioned reasons, formation of carbamate **VI** and isocyanate **VII** appears reasonable and the active role of the base can be highly plausible in both the urea **VIII** formation [12h] and the following cyclization step [11]. In addition, the non-symmetric urea **9**, analogous to **VIII**, was synthesized independently [24], and, under our reaction conditions, it afforded imidazolidinone **8h** in almost quantitative yield (Scheme 7).

The alternative way *b*, involving the initial formation of oxazolidinone **IX** (from the reaction of propargylamine and CO_2), followed by amination, seems less plausible for primary propargylamines (Scheme 6, way *b*). In fact, we have never detected oxazolidinones starting from primary propargyl amines, while linear urea species were frequently found under our reaction conditions. Moreover, Shi and co-workers reported also the formation of oxazolidinones from primary α-substituted propargylamines and CO_2 at room temperature under palladium catalysis (way *b*, formation of intermediate **IX**) [8k], but they essentially failed when they tried to convert them into the corresponding ureas by reaction with primary amines (way *b*, from **IX** to **8**). On the other hand, secondary propargylamines cannot provide urea derivatives according to way *a* (isocyanate) and way *b* in this case is definitely more probable, also in view of their propensity to give oxazolidinones by reaction with CO_2 under various reaction conditions [12e,23]. In our case, among the tested secondary propargylamine, only *N*-methylprop-2-yn-1-amine afforded the corresponding imidazolidinone. Together with **8n**, 3-methyl-5-methyleneoxazolidin-2-one **10** was isolated in 30% yield, supporting our rationale. Moreover, compound **10**, in the presence of *n*-$BuNH_2$ and under the optimized reaction conditions, was partially transformed into imidazolidinone **8n** with high selectivity (35% yield, Scheme

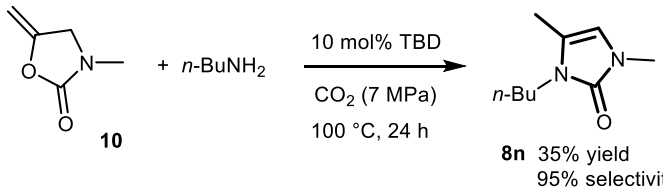
8) confirming that **10** is an intermediate in the formation of **8n** (Scheme 6, way *b*) [25]. All these experimental data suggest that primary and secondary propargylamines may follow different pathways: way *a* seems to be more plausible for primary propargylamines, while way *b*, when is feasible, can be the preferred route for secondary ones.



Scheme 6. Proposed reaction pathways to compounds **8**.



Scheme 7. TBD-catalyzed cyclization of urea **9** to **8h**.



Scheme 8. TBD-catalyzed conversion of 3-methyl-5-methyleneoxazolidin-2-one **10** to imidazolidinone **8n**.

4. Conclusion

In summary, the synthesis of linear and cyclic ureas from carbon dioxide and various amine derivatives under bicyclic guanidine catalysis has been investigated. In particular, we have disclosed a new and general bicyclic guanidine-catalyzed synthesis of 5-methyleneimidazolidin-2-ones by reaction of propargylamines, primary amines and CO_2. The main features of this methodology include (i) a metal-free, ligand-free, VOCs-free (Volatile Organic Compounds) and isocyanate-free protocol for the synthesis of imidazolidinone core, (ii) an easily scalable process, (iii) formation of urea derivatives at

80-120 °C, (iv) proposed reaction pathways based on experimental tests and isolated intermediates, and (v) a further advancement in the direction of carbon dioxide utilization for the synthesis of high-value chemicals.

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