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Article

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Nucleophilic substitution of azide acting as a pseudo leaving group: one-step synthesis of various azaheterocycles

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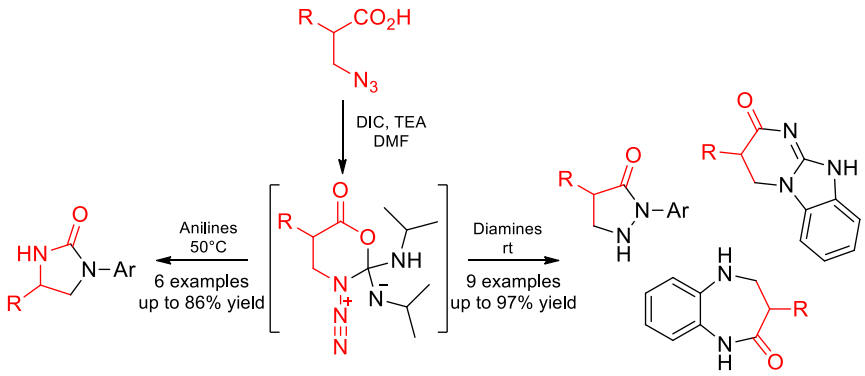
ABSTRACT GRAPHIC



ABSTRACT

The reaction of 3-azidopropanoic acid with the carbodiimide-based coupling reagent DIC leads to a six-membered ring intermediate acting as a versatile precursor to a diverse set of azaheterocycles, including mono-, bi- and tricyclic compounds.

INTRODUCTION

Since the first description of phenyl azides by Grieß in 1864,[1] organic chemistry involving organic azides has been extensively developed, leading to the synthesis of amino acids as well as a diverse range of azaheterocycles.[2] Over the last decades, organic azides have been reported to exhibit a wide range of chemical reactivities. Because of their 1,3-dipolar character, azides react with electron-deficient compounds at N_1 and with electron-rich compounds at N_3, providing access to [3+2] cycloaddition reactions with unsaturated substrates.[3] Organic azides can also behave as pseudo-nitrenes and allow for the formation of a new bond to nitrogen N^1, with loss of molecular nitrogen.[4] In contrast, the pseudohalogenic character of aliphatic azides is less well known. Although azides have been reported to undergo elimination to form alkenes,[5] to our knowledge no nucleophilic substitution has ever been reported of an azido group in an aliphatic chain. Herein, we describe the unexpected reactivity of 3-azidopropionic acid with standard coupling reagents such as carbodiimides, opening access to a variety of azaheterocyclic systems under mild conditions.

RESULTS and DISCUSSION

During our work on chemical probe synthesis using Click chemistry, we planned to couple the short spacer 3-azidopropanoic acid **1** (Scheme 1) with a phenylhydrazine derivative, using classical reaction conditions (COMU, TEA, DMF, rt, 5h). Surprisingly, the expected hydrazide was not formed, and only pyrazolidin-3-one **2a** was isolated in moderate yield (Table 1, entry 1). Other classical coupling reagents were also screened (Table 1); while the phosphonium salt PyBOP and the uronium salt HATU afforded **2a** in low yields, the carbodiimides DIC and DCC led to excellent yields (entries 4 and 5). However, the water-soluble EDCI afforded **2a** in only 38% yield. Several bases were screened, with DIEA giving a similar result as that with TEA (Table 1, entries 4 & 7). In contrast, the weakly basic N-methylmorpholine (NMM) was found to be less efficient (entry 8), and no reaction occurred with the strongly basic DBU (entry 9). The mineral base K_2CO_3 (entry 10) was entirely ineffective. Besides DMF, other solvents such as DMSO or MeCN gave **2a** in moderate yields (entries 11 & 12), while dioxane or DCM led to lower yields (entries 13 & 14).

Scheme 1. One-step synthesis of 3-azidopropionic acid 1 as described by Kuang at al.[6]

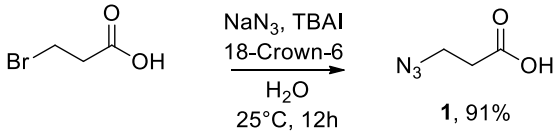
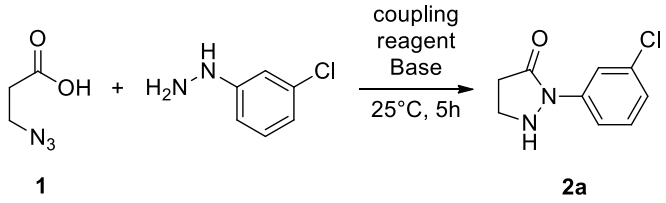


Table 1. Optimization of the pyrazolidin-3-one 2a synthesis[a]



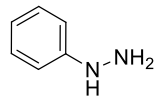
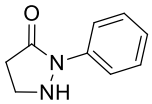
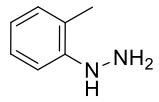
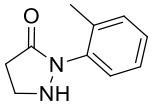
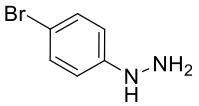
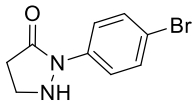
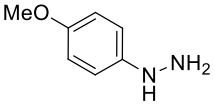
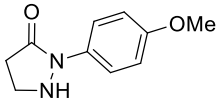
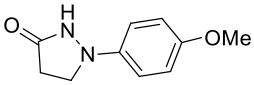
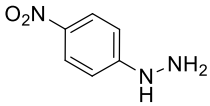
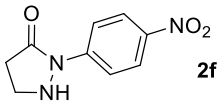
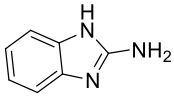
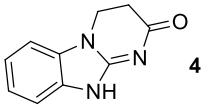
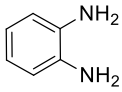
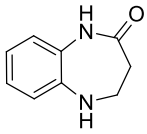
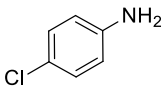
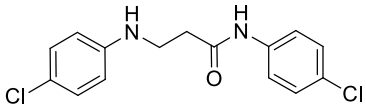
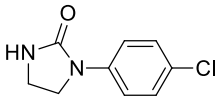
1 **2a**

Entry	Coupling Reagent	Base	Solvent	Yield[b]
1	COMU	TEA	DMF	49
2	PyBOP	TEA	DMF	16
3	HATU	TEA	DMF	11
4	DIC	TEA	DMF	91 (82)[c]
5	DCC	TEA	DMF	89
6	EDCI	TEA	DMF	38
7	DIC	DIEA	DMF	78
8	DIC	NMM	DMF	57
9	DIC	DBU	DMF	0
10	DIC	K_2CO_3	DMF	23
11	DIC	TEA	DMSO	71
12	DIC	TEA	MeCN	60
13	DIC	TEA	Dioxane	43
14	DIC	TEA	DCM	24

[a] Reactions were carried out on a scale of 0.26 mmol of arylhydrazine hydrochloride and 0.47 mmol of **1** in the presence of coupling reagent (0.51 mmol) and base (0.78 mmol) in 3 mL of solvent under argon atmosphere. [b] Yield determined by HPLC/UV using caffeine as internal standard. [c] Isolated yield

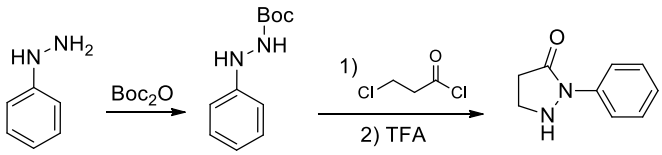
When the reaction was conducted on small or large scale (0.2 mmol or 2 mmol of phenylhydrazine, respectively), **2b** was recovered in excellent yield (Table 2). A set of experiments employing substituted phenylhydrazines illustrated the transformation's general substituent tolerance. The sterically hindered o-tolylhydrazine afforded **2c** in 80% yield. With the electron-withdrawing 4-nitrophenyl group, the reaction mixture had to be heated at 50°C to afford **2f** in 44% yield. In contrast, the electron-donating group 4-methoxyphenyl led to an increase in the nucleophilicity of the nitrogen bearing the aromatic ring, affording **2e** in only 18% yield and its regioisomer 1-(4-methoxyphenyl)pyrazolidin-3-one **3** in 39% yield.

Table 2. DIC-mediated cyclization using various amines

Entry	Amine	Product (isolated yield)[a]
1		 **2b** (92%) - (97%)[b]
2		 **2c** (80%)
3		 **2d** (56%)
4		 **2e** (18%)  **3** (39%)
5		 **2f** (44%)[c]
6		 **4** (85%)
7		 **5** (87%)
8		 **6** (25%)  **7c** (< 5%)

[a] Reactions were carried out on a scale of 0.26 mmol of amine hydrochloride and 0.47 mmol of **1** in the presence of coupling reagent (0.51 mmol) and base (0.78 mmol) in 3 mL of solvent under argon atmosphere. [b] Reactions were carried out on a scale of 2 mmol of arylhydrazine. [c] Reaction was heated at 50°C.

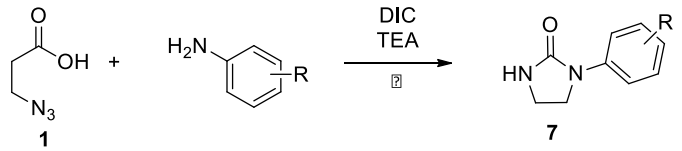
Scheme 2. Reported synthesis of 2-arylpyrazolidin-3-one 2b[7]

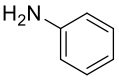
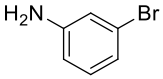
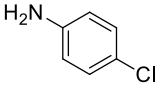
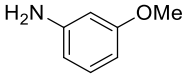
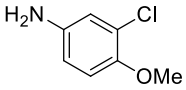
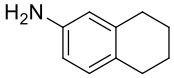
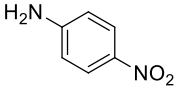
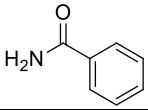


As a comparison, 2-arylpyrazolidin-3-ones **2b** was previously described synthesis starting with Boc-protection of the hydrazine NH_2 group, followed by cyclization with 3-chloropropanoyl chloride and finally, N-Boc deprotection. This three-step strategy afforded 2-phenylpyrazolidin-3-one **2b** in 52% global yield (Scheme 2).[7]

We next extended the reaction to other nucleophiles bearing two amino groups. Thus, 2-aminobenzimidazole and 1,2-diaminobenzene afforded [6+5+6] tricyclic guanidine **4**,[8] and the [6+7] bicyclic compound **5**, respectively, in excellent yields. In contrast to the arylhydrazines and aryldiamines studied, aliphatic amines or hydrazines are too reactive and lead to complex mixtures. However, the monoamine 4-chloroaniline afforded the target compound **6** in poor yield, and a number of by-products were also formed. Among the by-products, we were able to identify the cyclic urea 1-(4-chlorophenyl)imidazolidin-2-one **7c** as a component of the product mixture (Table 2, entry 8). Nevertheless, the recovery of cyclic urea **7c** suggested a mechanism involving a Curtius rearrangement. Indeed, by just heating the reaction mixture at 50°C, imidazolidin-2-one **7a** could be obtained in 86% yield (Table 3, entry 3). Higher temperatures did not improve the yield of **7a**. A set of substituted anilines were screened, and imidazolidinones **7a–f** were obtained in yields ranging from 52% to 86% (table 3, entries 6 – 10). No reaction occurred with the electron-withdrawing 4-nitroaniline (Table 3, entry 11). Similarly, benzamide appeared to be not enough nucleophilic to react (Table 3, entry 12).

Table 3. Optimization of the imidazolidinones 7 synthesis[a]



Entry	Aniline	Temp. (°C)	Time (h)	7	Yield
1		rt	5	**7a**	8[b]
2		rt	24		32[b]
3		50	5		86[b] (79)[c]
4		70	5		82[b]
5		90	5		73[b]
6		50	5	**7b**	61[c]
7		50	5	**7c**	66[c]
8		50	5	**7d**	70[c]
9		50	5	**7e**	73[c]
10		50	5	**7f**	52[c]
11		50	5	**7g**	0
12		50	5	**7h**	0

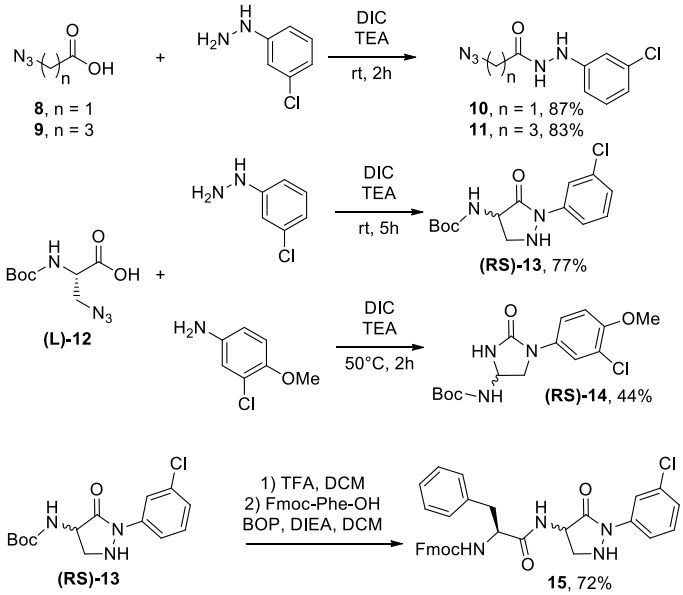
[a] Reactions were carried out on a scale of 0.39 mmol of arylamine and 0.70 mmol of **1** in the presence of coupling reagent (0.78 mmol) and base (0.78 mmol) in 4.5 mL of solvent under argon atmosphere. [b] Yield determined by HPLC/UV using internal standard. [c] Isolated yield

We next focused on homologs of 3-azidopropanoic acid **1** (Scheme 3). When using 2-azidoacetic acid[9] **8** or 4-azidobutanoic acid[10] **9** with 3-chlorophenylhydrazine, the expected cyclic products were not obtained. Instead, the corresponding 2-azidoacetohydrazide **10** and 4-azidobutanehydrazide **11** were obtained in good yields, highlighting the importance of the β-position of the azido group in the transformation.

Additional insights were gained when the chiral serine azido derivative **12** (described by Panda et al)[11] was subjected to the transformation. Reaction of **(L)-12** with 3-chlorophenylhydrazine in the presence of DIC and TEA at 50°C led to completely racemized pyrazolidin-3-one **(RS)-13** in 77% yield.

The analogous reaction of **(L)-12** with 3-chloro-4-methoxyaniline afforded the racemic cyclic urea **(RS)-14** in 44% yield (Scheme 3). Loss of chirality in **13** was verified by the introduction of a second chiral group (Scheme 3). Briefly, the Boc group was cleaved with trifluoroacetic acid, and the resulting amino function was coupled with Fmoc-L-Phe-OH to form **15** in 72% global yield. ^{1}H and ^{13}C NMR analysis established that **15** was recovered as a mixture of two diastereoisomers in a [1:1] ratio, highlighting the racemic form of the precursor **13**. The racemization was confirmed by starting with the enantiomer **(D)-12** (data not show).

Scheme 3. DIC-mediated cyclization using various azido derivatives



This set of experiments allowed us to gain an insight into the possible mechanism by which this reaction may be operating. In the reaction leading to 2-arylpyrazolidin-3-ones **2**, the presence of the aryl group at the 2-position led us to hypothesize that the initial nucleophilic attack by the hydrazine displaces the azido group. However, an unmodified azido group is not considered to be a good leaving group. Consequently, we postulate the formation of an intermediate showing electrophilic nature at the position bearing the azide. In the absence of a coupling reagent, no reaction occurred, and hence, we proposed **A** as the first intermediate of a possible mechanism (Figure 1).

Figure 1. Possible mechanism

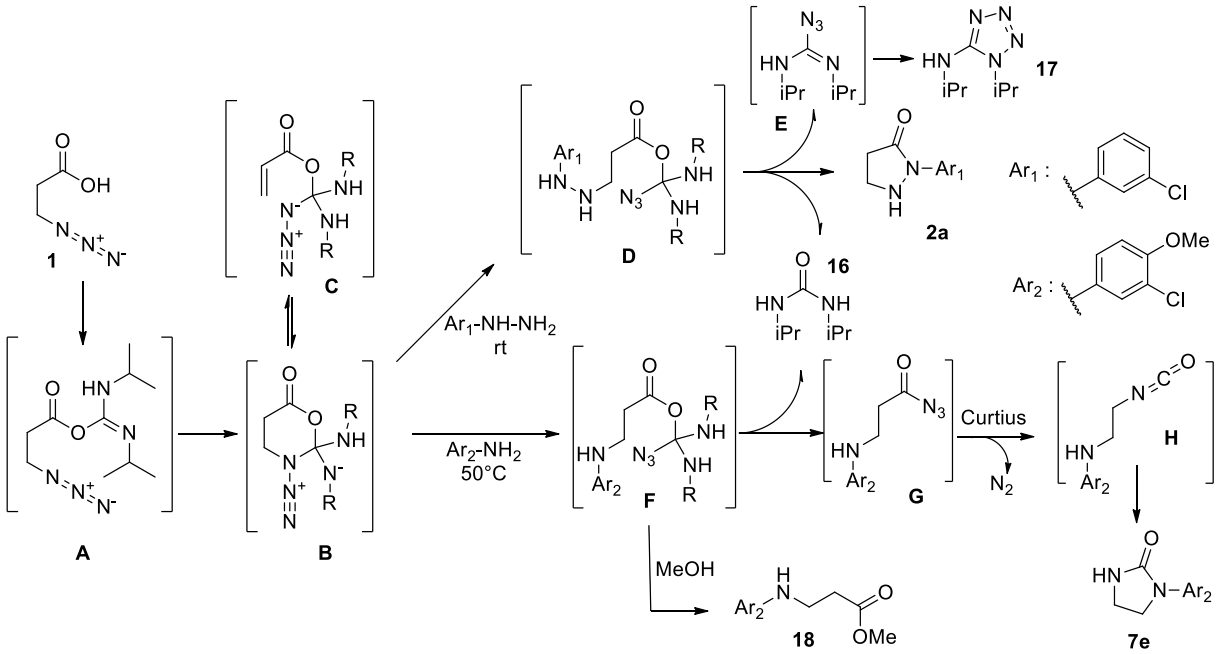


Figure 2. Concomitant formation of 2a and 17

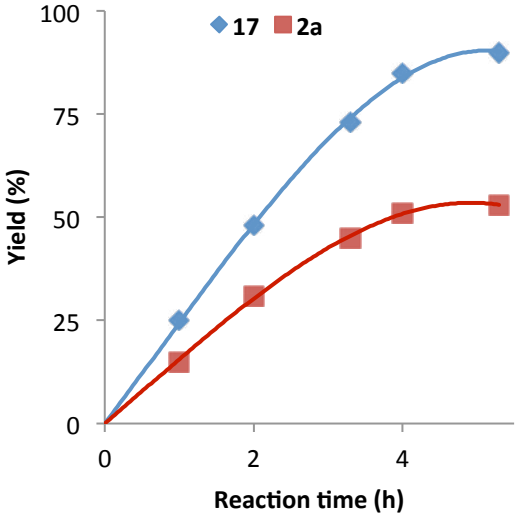
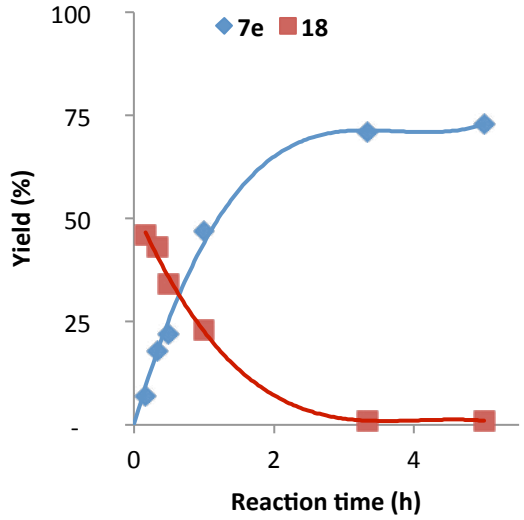


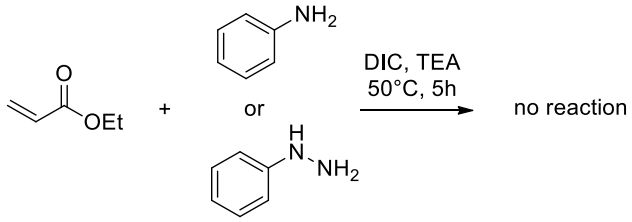
Figure 3. Kinetics of formation of the urea 7e through the intermediate F. The reaction was quenched with methanol at different times. **7e** and **18** were quantified by HPLC/UV. By measuring the disappearance of **18** resulting from the reaction of intermediate **F** with methanol, we were able to observe the concomitant formation of **7e** with the disappearance of **F** during the course of the reaction.



Then, taking into account that the known ability of the nitrogen N_1 of the azido group to react with electrophilic centers such as ketones and aldehydes,[12] and that the reaction did not proceed with homologous azidoalkanoic acids **8** and **9**, we proposed the formation of the six-membered ring intermediate **B**, resulting from the intramolecular nucleophilic attack of the azido N_1 at oxygen bearing carbon of the ureido ether moiety of intermediate A. Moreover, we have seen with the chiral serine azido derivative **(L)-12** that the reaction led to compound **(RS)-13** through a complete racemization of the chiral center originally present. One way to explain this racemization is to consider an equilibrium between **B** and the corresponding acrylate derivative **C**. To validate this hypothesis, the reaction was followed by NMR analysis in the absence of hydrazine, in order to identify the reaction intermediates. After a few minutes in *DMF-d7*, quantitative ^{13}C and ^{1}H NMR analysis indicated the complete disappearance of the starting carboxylic acid **1**, which was replaced by a mixture of two new compounds in a [9:1] ratio.[13] The minor compound **C** gave the characteristic peaks of an acrylate derivative, while the major compound **B** still showed both CH_2 groups. This mixture appeared stable for more than 1 h in *DMF-d7* at 25°C. Addition of hydrazine led to the rapid

disappearance of both compounds **B** and **C**. In model studies carried out under the experimental conditions described in Table 2, no 1,4-azaMichael addition was observed between ethyl acrylate and phenylhydrazine or aniline (Scheme 4).

Scheme 4. Reaction between ethyl acrylate and phenylhydrazine or aniline



This result suggests **B** as the likely key intermediate. Moreover, equilibrium between **B** and **C** is probably achieved very fast, as only traces of acrylhydrazide derivatives were detected by LCMS at the end of the reaction. Intermediate **B** could then react quickly with the NH_2 group of the arylhydrazine, opening the ring to form intermediate **D**. A final intramolecular ring closure then occurs, leading to **2a**, along with by-products such as the expected urea **16** and the 5-aminotetrazole **17**. By HPLC, we were able to observe the concomitant formation of **2a** and **17** (Figure 2). The tetrazole ring results from the electrocyclization of intermediate **E**, as proposed by Batey et al.[14] An earlier electrocyclization has been also considered, but in this case, the azide group would not have been available for the Curtius rearrangement. Intermediate **B** can also react with aniline, leading to **F** after ring opening. Nucleophilic attack of the amino group to form a four-membered ring was not observed, and with heating (50°C), Curtius rearrangement occurred via intermediate **G**, leading to urea **7e**. Kinetic experiments were performed using HPLC/UV after quenching of the reaction with methanol (Figure 3). During the first 20 min following the aniline addition, the major compound was found to be the ester **18**, its proportion gradually decreased along with the appearance of **7e**. The reaction rate appeared to be determined by the Curtius rearrangement.

CONCLUSION

We have shown for the first time that an aliphatic azido group can act formally as a pseudo leaving group in a nucleophilic substitution under mild conditions. This reaction proceeds through an original mechanism, opening a highly-efficient access to a variety of azaheterocycles, including mono-, di- and tricycles.

EXPERIMENTAL SECTION

General Experimental methods. Chemicals and solvents were purchased from commercial suppliers. Abbreviations : COMU : (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate; DCC : N,N'-Dicyclohexylcarbodiimide; DIC : N,N'-Diisopropylcarbodiimide; EDCI : N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; PyBOP : (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate. Analytical thin-layer chromatography was performed using silica gel plates and plates were visualized by exposure to ultraviolet light. Compounds were purified using flash chromatography on silica gel (particle size 0.040-0.063mm), or on reverse phase column. Yields refer to isolated compounds, estimated to be >97% pure as determined ^{1}H NMR or HPLC. ^{1}H and ^{13}C NMR spectra were recorded on 300, 400 or 500MHz spectrometers for proton and 100 or 125MHz for carbon. 500MHz spectrometer was equipped with cryoprobe to provide quantitative and high sensitivity carbon spectra. . All chemical shift values and coupling constants J are quoted in ppm and in Hz, respectively. Infra-Red analysis were performed by FT-IR. Analytical RP-HPLC-MS was performed using a C18 column (30 mm × 1 mm; 1.9 µm) using the following parameters : 1) The solvent system : A (acetonitrile) and B (0.05% TFA in H2O); 2) A linear gradient : t = 0 min, 98%B; t = 5 min, 5% B; t = 6 min, 5%B; t = 7 min, 98%B; t = 9 min, 98%B; 3) Flow rate of 0.3 mL/min; 4) Column temperature : 50°C; 5) The ratio of products was determined by integration of spectra recorded at 210 nm or 254 nm; 6) Ionization mode : MM-ES+APCI. High-resolution spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI)

WARNING! Low molecular weight carbon azides used in this study are potentially explosive. As free azide ion is formed during the reaction, there is also a potential for the formation of hydrazoic acid as well. Appropriate protection measures should always be taken when handling these compounds.

General methods:

Method A : Preparation of the compounds **2a-f, 3, 4, 5, 6, 10, 11, 13**

Diisopropylcarbodiimide DIC (2eq, 81µL, 0.51mmol) and Et_3N (3eq, 109µL, 0.78mmol) were mixed together, then 3-azidopropanoic acid **1** (1.8eq., 0.47mmol) in DMF (5mmol/mL) was added dropwise and the reaction mixture was stirred at 25°C for 5min. Then, a solution of amine hydrochloride (1eq, 0.26mmol) in DMF (0.09mmol/mL) was argon flushed for 10min and added dropwise to the reaction. The reaction vial was wrapped with an aluminum foil to protect from light and the reaction mixture was stirred at 25°C for 5h under argon. Solvent was concentrated under vacuum and the crude product was purified by flash chromatography on reverse phase using H_2O(0.05%TFA)/MeOH to give the expected products: **2a-f, 3, 4, 5, 6, 10, 11, 13**.

Method B : Preparation of the compounds **7a-f, 14**

DIC (2eq, 120µL, 0.78mmol) and Et_3N (2eq, 109µL, 0.78mmol) were mixed together, then 3-azidopropanoic acid **1** (1.8eq, 0.70mmol) in DMF (5mmol/mL) was added dropwise and the reaction mixture was stirred at 25°C for 5min. Then, a solution of aniline (1eq, 0.39mmol) in DMF (0.09mmol/mL) was argon flushed for 10min and added dropwise to the reaction. The reaction vial was wrapped with an aluminum foil to protect from light and the reaction mixture was stirred at 50°C for 5h under argon. Solvent was concentrated under vacuum and the crude product was purified by flash chromatography on silica gel using EtOAc/heptane to give the expected products: **7a-f, 14**.

2-(3-Chlorophenyl)pyrazolidin-3-one, ***2a***.[15] Following the general method A, **2a** was obtained as an oil (42mg, 0.21mmol, 82%). ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.91 (s, 1H), 7.76 (d, *J* = 8.1Hz, 1H), 7.32 (m, 1H), 7.11 (d, *J* = 7.8Hz, 1H), 3.43 (t, *J* = 7.6Hz, 2H), 2.76 (t, *J* = 7.6Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): δ

172.0, 139.9, 134.5, 129.8, 124.1, 118.1, 116.0, 43.7, 35.6; IR (cm^{-1}): 1688, 1591, 1481, 777; HPLC t_R = 2.69 min; ESI-MS: m/z 197.0, $[M+H]^+$.

2-Phenylpyrazolidin-3-one, ***2b***.[16] Following the general method A, **2b** was obtained as an oil (38mg, 0.24mmol, 92%). ^1H NMR (CD_3OD, 400MHz): δ 7.78 (d, *J* = 7.8Hz, 2H), 7.34 (t, *J* = 7.9Hz, 2H), 7.10 - 7.22 (m, 1H), 3.43 (t, *J* = 7.7Hz, 2H), 2.74 (t, *J* = 7.7Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 174.5, 140.2, 129.7, 125.7, 120.2, 44.4, 36.4; IR(cm^{-1}): 1682, 1595, 1495, 755; HPLC t_R = 1.30 min; ESI-MS: m/z 161.3, $[M+H]^+$.

2-(2-Methylphenyl)pyrazolidin-3-one, ***2c***. Following the general method A, **2c** was obtained as an oil (37mg, 0.20mmol, 80%). ^1H NMR (CD_3OD, 400MHz): δ 7.19 - 7.34 (m, 4H), 3.54 (t, *J* = 7.7Hz, 2H), 2.75 (t, *J* = 7.7Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (CD_3OD, 100MHz): δ 174.3, 137.4, 137.2, 132.1, 129.8, 128.1, 127.7, 45.2, 34.3, 18.1; IR(cm^{-1}): 1681, 1495, 762; HPLC t_R = 1.16 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{10}H_{12}N_2O$ 177.1022; found 177.1018.

2-(4-Bromophenyl)pyrazolidin-3-one, ***2d***. Following the general method A, **2d** was obtained as a white solid (35mg, 0.15mmol, 56%). mp: 126 – 128°C; ^1H NMR (CD_3OD, 400MHz): δ 7.71 - 7.80 (d, *J* = 9.0Hz, 2H), 7.43 - 7.53 (d, *J* = 9.0Hz, 2H), 3.42 (t, *J* = 7.7Hz, 2H), 2.74 (t, *J* = 7.7Hz, 2H); ^{13}C NMR (100MHz, CD_3OD) δ 174.7, 139.6, 132.7, 121.5, 118.0, 44.4, 36.4; IR (cm^{-1}): 1672, 1588, 1485, 1075; HPLC t_R = 2.81 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_9H_9BrN_2O$ 240.9971; found 240.9968.

2-(4-Methoxyphenyl)pyrazolidin-3-one, ***2e***. Following the general method A, **2e** was obtained as white solid (9mg, 0.047mmol, 18%). mp: 114 – 115°C; ^1H NMR (CD_3OD, 400MHz): δ 7.65 (d, *J* = 9.0Hz, 2H), 6.91 (d, *J* = 9.0Hz, 2H), 3.78 (s, 3H), 3.42 (t, *J* = 7.7Hz, 2H), 2.73 (t, *J* = 7.7Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 173.7, 158.4, 133.2, 122.3, 114.8, 55.9, 44.3, 36.0; IR (cm^{-1}): 1681, 1508, 1245, 1032, 830; HPLC t_R = 1.74 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{10}H_{12}N_2O_2$ 193.0972; found 193.0968.

2-(4-Nitrophenyl)pyrazolidin-3-one, ***2f***. Following the general method A (the reaction mixture was heated at 50°C), **2f** was obtained as a yellow solid (28mg, 0.11mol, 44%). mp: 186 – 187°C; ^1H NMR

(DMSO-d_6, 400MHz): δ 8.27 (d, *J* = 9.3Hz, 2H), 8.03 (d, *J* = 9.3Hz, 2H), 6.47 (t, *J* = 8.4Hz, 1H), 3.38 (m, 2H), 2.73 (t, *J* = 7.4Hz, 2H); ^{13}C NMR (DMSO-d_6 ,100MHz): δ 173.9, 144.6, 142.1, 124.9, 117.2, 43.0, 35.2. IR (cm^{-1}): 1693, 1593, 1510, 1496, 1312, 847. ; HPLC t_R = 2.31 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_9H_9N_3O_3$ 208.0717; found 208.0710.

1-(4-Methoxyphenyl)pyrazolidin-3-one, ***3***. Following the general method A, **3** was obtained as a white solid (19mg, 0.10mmol, 39%). mp: 145 – 147°C (lit.[17] mp: 144 – 146°C); ^{1}H NMR (CD_3OD, 400MHz): δ 7.01 (d, *J* = 9.0Hz, 2H), 6.88 (d, *J* = 9.0Hz, 2H), 3.81 (t, *J* = 7.9Hz, 2H), 3.75 (s, 3H), 2.50 (t, *J* = 7.9Hz, 2H); ^{13}C NMR (CD_3OD ,100MHz): δ 177.2, 157.5, 146.5, 119.6, 115.5, 57.0, 56.0, 30.7; IR (cm^{-1}): 1673, 1508, 1247, 1034, 833; HPLC t_R = 2.10 min; ESI-MS: m/z 193.0, $[M+H]^+$.

2,10-Dihydropyrimido[1,2-a]benzimidazol-4(3H)-one, ***4***. Following the general method A, **4** was obtained as a white solid (41mg, 0.22mmol, 85%). mp: 264 – 165°C (lit.[18] mp: 260 – 262°C); ^{1}H NMR (DMSO-d_6, 400MHz): δ 11.43 (s, 1H), 7.40 (m, 2H), 7.03 - 7.19 (m, 2H), 4.24 (t, *J* = 7.0Hz, 2H), 2.88 (t, *J* = 7.0Hz, 2H); ^{13}C NMR (DMSO-d_6, 100MHz): δ 168.1, 148.1, 141.8, 132.9, 121.2, 120.6, 117.2, 108.8, 40.1, 36.9, 30.0; IR (cm^{-1}): 1681, 1516, 1453, 746; HPLC t_R = 0.98 min; ESI-MS: m/z 188.2, $[M+H]^+$.

1,3,4,5-Tetrahydro-2H-1,5-benzodiazepin-2-one, ***5***. Following the general method A, **5** was obtained as a white solid (37mg, 0.23mmol, 87%). mp: 138 – 140°C (lit.[19] mp: 140 – 141°C); ^{1}H NMR (CD_3OD ,400MHz): δ 6.88 - 6.99 (m, 2H), 6.74 - 6.87 (m, 2H), 3.56 - 3.64 (m, 2H), 2.54 - 2.65 (m, 2H). ^{13}C NMR (CD_3OD, 100MHz): δ 176.5, 141.2, 128.2, 126.6, 123.3, 121.2, 121.2, 47.6, 36.6; IR (cm^{-1}): 1662, 1175, 1131; HPLC t_R = 0.86 min; ESI-MS: m/z 163.0, $[M+H]^+$.

N-(4-Chlorophenyl)-3-[(4-chlorophenyl)amino]propanamide, ***6***. Following the general method A (3.6 eq. of 4-chloroaniline were used (120mg, 0.94 mmol), **6** was obtained as a white solid (20mg, 0.065mmol, 25%). mp: 138 - 140°C (lit.[20] mp: 141°C); ^{1}H NMR (CD_3OD, 400MHz): δ 7.56 (d, *J* = 8.8Hz, 2H), 7.29 (d, *J* = 8.8Hz, 2H), 7.08 (d, *J* = 8.8Hz, 2H), 6.64 (d, *J* = 8.8Hz, 2H), 3.46 (dd, *J* = 6.7Hz, 2H), 2.65 (dd, *J* = 6.7Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 172.8, 148.7, 138.8, 130.1, 130.0, 129.8, 122.7,

122.6, 115.3, 41.2, 37.6; IR (cm^{-1}): 3306, 2924, 1657, 1492,1090; HPLC t_R = 4.48 min; ESI-MS: m/z 309.0, $[M+H]^+$.

1-Phenylimidazolidin-2-one, ***7a****.* Following the general method B, **7a** was obtained as a white solid (50mg, 0.31mmol, 79%). mp: 163 - 164°C (lit.[21] mp: 162 - 163°C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.54 (d, *J* = 7.8Hz, 2H), 7.32 - 7.42 (m, 2H), 7.03 - 7.15 (m, 1H), 3.91 - 4.03 (m, 2H), 3.55 - 3.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 159.8, 140.0, 128.9, 122.8, 118.0, 45.4, 37.5; IR(cm^{-1}): 3264, 1682; HPLC t_R = 2.22 min; ESI-MS: m/z 163.0, $[M+H]^+$.

1-(3-Bromophenyl)imidazolidin-2-one, ***7b****.* Following the general method B, **7b** was obtained as a light yellow solid (57mg, 0.24mmol, 61%). mp: 127 - 129°C (lit.[22] mp: 127 - 130°C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.72 (s, 1H), 7.47 (dt, *J* = 6.8, 2.4Hz, 1H), 7.12 - 7.23 (m, 2H), 5.65 (brs, 1H), 3.89 (dd, *J* = 8.0Hz, 2H), 3.58 (dd, *J* = 8.0Hz, 2H); ^{13}C NMR ($CDCl_3$,100MHz): δ 159.6, 141.3, 130.0, 125.5, 122.6, 120.5, 116.1, 45.1, 37.3; IR (cm^{-1}): 3257, 2922, 1678, 1479; HPLC t_R = 3.18 min; ESI-MS: m/z 241.0, $[M+H]^+$.

1-(3-Chlorophenyl)imidazolidin-2-one, ***7c****.* Following the general method B, **7c** was obtained as a white solid (51mg, 0.26mmol, 66%). mp: 105 - 107°C; ^{1}H NMR (CD_3OD, 400MHz): δ 7.52 (d, *J* = 9.0Hz, 2H), 7.29 (d, *J* = 9.0Hz, 2H), 3.92 (dd, *J* = 8.0Hz, 2H), 3.53 (dd, *J* = 8.0Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 140.8, 129.9, 129.0, 120.9, 46.9, 38.6; IR (cm^{-1}): 3446, 2923, 1696, 1496, 845; HPLC t_R = 2.97 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_9H_9ClN_2O$ 197.0476; found 197.0471.

1-(3-Methoxyphenyl)imidazolidin-2-one, ***7d****.* Following the general method B, **7d** was obtained as a light yellow solid (52mg, 0.27mmol, 70%). mp: 118 - 121°C (lit.[23] mp: 123°C); ^{1}H NMR (CD_3OD, 400MHz): δ 7.25 (t, *J* = 2.4Hz, 1H), 7.21 (t, *J* = 8.3Hz, 1H), 6.99 (ddd, *J* = 8.2, 2.4, 0.8Hz, 1H), 6.62 (ddd, *J* = 8.3, 2.4, 0.8Hz, 1H), 3.93 (dd, *J* = 8.0Hz, 2H), 3.78 (s, 3H), 3.52 (dd, *J* = 8.0Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 161.6, 142.8, 130.5, 111.5, 109.4, 105.7, 55.7, 46.8, 38.4; IR (cm^{-1}): 3448, 2928, 1693, 841; HPLC t_R = 2.54 min; ESI-MS: m/z 193.0, $[M+H]^+$.

1-(3-Chloro-4-methoxyphenyl)imidazolidin-2-one, ***7e****.* Following the general method B, **7e** was obtained as a white solid (65mg, 0.28mmol, 73%). mp: 160 - 162°C; ^{1}H NMR (CD_3OD, 400MHz): δ 7.68 (d, *J* = 2.5Hz, 1H), 7.30 (dd, *J* = 9.0, 2.5Hz, 1H), 7.03 (d, *J* = 9.0Hz, 1H), 3.90 (dd, *J* = 8.3Hz, 2H), 3.85 (s, 3H), 3.52 (dd, *J* = 8.3Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 162.1, 152.4, 135.5, 126.8, 123.5, 122.0, 119.1, 113.7, 101.4, 78.1, 75.8, 56.9, 46.9, 38.4; IR (cm^{-1}): 2927, 1697, 1504, 843; HPLC t_R = 2.86 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{10}H_{11}ClN_2O_2$ 227.0582; found 227.0578.

1-(5,6,7,8-Tetrahydronaphthalen-2-yl)imidazolidin-2-one, ***7f****.* Following the general method B, **7f** was obtained as a white solid (44mg, 0.20mmol, 52%). mp: 186 - 188°C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.17 (d, *J* = 8.3Hz, 1H), 7.12 (s, 1H), 6.95 (d, *J* = 8.3Hz, 1H), 5.43 (brs, 1H), 3.81 (dd, *J* = 8.0Hz, 2H), 3.47 (dd, *J* = 8.0Hz, 2H), 2.58 - 2.75 (m, 4H), 1.66 - 1.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 159.2, 136.5, 136.5, 130.9, 128.4, 117.8, 115.0, 44.7, 36.6, 28.7, 27.8, 22.3, 22.2; IR (cm^{-1}): 3236, 2928, 1682; HPLC t_R = 3.16 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{16}N_2O$ 217.1335; found 217.1337.

2-Azido-N'-(3-chlorophenyl)acetohydrazide, ***10****.* Following the general method A, **10** was obtained as a light yellow oil (51mg, 0.23mmol,87%). ^{1}H NMR (CD_3OD, 400MHz): δ 7.14 (t, *J* = 8.0Hz, 1H), 6.75 - 6.81 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 4.00 (s, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 170.3, 151.3, 135.9, 131.3, 120.7, 113.7, 112.3, 51.8; IR (cm^{-1}): 3276, 2107, 1681, 1598, 773; HPLC t_R = 2.83 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_8H_8ClN_5O$ 226.0490; found 226.0479.

4-Azido-N'-(3-chlorophenyl)butanehydrazide, ***11****.* Following the general method A, **11** was obtained as a light brown oil (55mg, 0.22mmol, 83%). ^{1}H NMR (CD_3OD, 400MHz): δ 7.12 (t, *J* = 8.0Hz, 1H), 6.73 - 6.79 (m, 2H), 6.70 (d, *J* = 8.3Hz, 1H), 3.38 (t, *J* = 6.7Hz, 2H), 2.37 (t, *J* = 7.3Hz, 2H), 1.92 (m, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 174.9, 151.6, 135.9, 131.3, 120.5, 113.6, 113.1, 112.2, 51.9, 31.8, 25.9; IR (cm^{-1}): 3270, 2094, 1662, 1596, 771; HPLC t_R = 3.28 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{10}H_{12}ClN_5O$ 254.0803; found 254.0795.

*tButyl [1-(3-chlorophenyl)-5-oxopyrazolidin-4-yl]carbamate, **(RS)-13**.* Following the general method A (pre-activation of the acid **12** with DIC and TEA was performed at 50°C for 5 min), **(RS)-13** was obtained as a white solid (62mg, 0.20mmol, 77%). mp: 148 - 150°C; ^{1}H NMR (CD_3OD, 400MHz): δ 7.92 (s, 1H), 7.78 (d, *J* = 8.2Hz, 1H), 7.32 (t, *J* = 8.2Hz, 1H), 7.12 (d, *J* = 8.2Hz, 1H), 4.65 (t, *J* = 9.3Hz, 1H), 3.68 (dd, *J* = 11.3, 9.3Hz, 1H), 3.17 (t, *J* = 11.3Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (CD_3OD, 100MHz): δ 172.3, 158.0, 141.5, 135.4, 131.0, 125.3, 119.3, 117.5, 55.9, 50.1, 28.7; IR (cm^{-1}): 1688, 1592, 1366, 777; HPLC t_R = 3.96 min; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{14}H_{18}ClN_3O_3$ 334.0934; found 334.0929.

*tButyl [1-(3-chloro-4-methoxyphenyl)-2-oxoimidazolidin-4-yl]carbamate, **(RS)-14**.* Following the general method B (pre-activation of the acid **12** with DIC and TEA was performed at 50°C for 5 min), **(RS)-14** was obtained as a white solid (59mg, 0.17mmol, 44%). mp: 280 - 282°C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.51 (d, *J* = 2.3Hz, 1H), 7.38 (dd, *J* = 9.0, 2.3Hz, 1H), 6.89 (d, *J* = 9.0Hz, 1H), 5.40 - 5.53 (m, 2H), 5.28 - 5.38 (m, 1H), 4.16 (dd, *J* = 8.5Hz, 1H), 3.88 (s, 3H), 3.59 (dd, *J* = 8.5, 3.4Hz, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 151.2, 133.0, 122.7, 120.4, 117.7, 112.5, 56.4, 52.1, 28.3; IR (cm^{-1}): 3257, 2975, 1689, 1507; HPLC t_R = 3.77 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{15}H_{20}ClN_3O_4$ 342.1215; found 342.1209.

(9H-fluoren-9-yl)methyl((2S)-1-((1-(3-chlorophenyl)-5-oxopyrazolidin-4-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate, **15**. **(RS)-13** (21mg, 0.067mmol) was solubilized in 0.5mL of CH_2Cl_2 and 0.5mL of TFA. The solution was stirred 1h at r.t. The reaction was monitored by HPLC. Solvents were concentrated under vacuum to afford a light yellow solid directly used in the next step. Fmoc-Phe-OH (34mg, 0.087mmol) was solubilized in 1mL of CH_2Cl_2 followed by the addition of DIEA (44µL, 0.27mmol) and BOP (35mg, 0.080mmol). The obtained solution was added to the deprotected amine. The reaction solution was stirred overnight at r.t. Solvent was concentrated under vacuum and the obtained residue was diluted in EtOAc. The organic layer was washed with NaHCO3 sat., HClaq. 1N, brine, dried over Na2SO4 and concentrated under vacuum. The crude product was purified by

chromatography on silica gel using EtOAc/Heptane: 7/3 to afford the diastereomeric mixture **15** as a white solid (28mg, 0.048mmol, 72%). ^{1}H NMR (DMSO-d_6, 400MHz): δ 8.57 (m, 1H), 7.82 - 7.93 (m, 3H), 7.75 - 7.82 (m, 1H), 7.59 - 7.75 (m, 3H), 7.36 - 7.47 (m, 3H), 7.21 - 7.36 (m, 6H), 7.13 - 7.21 (m, 2H), 6.20 - 6.33 (m, 1H), 4.76 - 4.96 (m, 1H), 4.23 - 4.38 (m, 1H), 4.05 - 4.16 (m, 2H), 3.49 - 3.69 (m, 1H), 2.93 - 3.16 (m, 2H), 2.77 - 2.92 (m, 1H); ^{13}C NMR (DMSO-d_6, 100MHz): δ 172.4, 172.3, 170.8, 170.7, 156.3, 156.3, 144.2, 144.2, 141.1, 141.1, 140.8, 140.8, 138.5, 138.4, 133.6, 133.6, 131.0, 131.0, 129.7, 129.7, 128.6, 128.5, 128.1, 128.1, 127.5, 127.5, 126.8, 126.7, 125.9, 125.8, 123.9, 123.9, 120.5, 120.5, 117.2, 117.2, 116.2, 116.2, 66.2, 66.2, 56.6, 56.6, 53.4, 53.3, 48.9, 48.6, 47.0; IR (cm^{-1}): 3275, 2926, 1709, 1686, 1657, 1531, 1262; HPLC t_R = 5.18 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{33}H_{29}ClN_4O_4$ 581.1950; found 581.1957.

*N,N''''-dipropan-2-ylcarbamimidic azide, Compound **17*** . Following the general method A, **17** was quantified by HPLC. mp: 139 - 140°C; ^{1}H NMR (DMSO-d_6, 400MHz): δ 6.57 (d, *J* = 7.0Hz, 1H), 4.56 (dt, *J* = 13.3, 7.0Hz, 1H), 3.80 (dq, *J* = 13.3, 7.0Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (DMSO-d_6,100MHz): δ 154.0, 47.2, 45.5, 22.4, 21.5; IR (cm^{-1}): 3268, 2978, 1673, 1594, 1139; HPLC t_R = 2.21 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_7H_{15}N_5$ 170.1400; found 170.1395.

*Methyl 3-[(3-chloro-4-methoxyphenyl)amino]propanoate, Compound **18**.* Following the general method B, reaction was quenched with MeOH, and **18** was quantified by HPLC. mp: 43 - 44°C; ^{1}H NMR (CD_3OD, 400MHz): δ 6.86 (d, *J* = 8.8Hz, 1H), 6.70 (d, *J* = 3.0Hz, 1H), 6.55 (dd, *J* = 8.8, 3.0Hz, 1H), 3.76 (s, 3H), 3.67 (s, 4H), 3.33 (dd, *J* = 6.8Hz, 3H), 2.57 (dd, *J* = 6.8Hz, 2H); ^{13}C NMR (CD_3OD, 100MHz): δ 174.3, 148.6, 144.6, 124.4, 116.1, 115.8, 113.5, 57.5, 52.1, 41.2, 34.6; IR (cm^{-1}): 3390, 2951, 1729, 1504, 1230, 1059,1018; HPLC t_R = 3.13 min; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{11}H_{14}ClNO_3$ 244.0735; found 244.0734.

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Supporting information

^{1}H and ^{13}C NMR spectra of intermediates **B** and **C**, along with spectra of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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