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An efficient microwave-assisted synthesis of cotinine and iso-cotinine analogs from an Ugi-4CR approach

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A convenient base-mediated two-step synthesis of cotinine analogs and a one-pot base-free synthesis of iso-cotinine derivatives featuring an Ugi-4CR/cyclization protocol, are reported. These approaches exploit the reactivity of the peptidyl position present in the Ugi adducts, allowing the facile construction of the *γ*-lactam core, as well as the introduction of a *N*-substituted methyl group into the analogs in a straightforward manner. A plausible mechanism for the cyclization step is discussed.

Introduction

The nocive side effects that tobacco consumption has on human health continue to be the subject of numerous studies to expand the understanding of the relationship between nicotine (**1**) and its secondary metabolites with the central nervous system (CNS).[1] In humans, and in most mammalian species, 80-85% of consumed nicotine is converted in the liver into cotinine (**2**) [(5S)-1-methyl-5-(3-pyridyl)-pyrrolidin-2-one] mainly by cytochrome P450 2A6 (CYP2A6) (Figure 1, A).[2] Research conducted in 1962 by Borzelleca et al.,[3] and Bowman et al.,[4] on the effects of cotinine in humans, showed that this compound has a relatively safe pharmacological profile, which opened the door for further studies in this area and revealed this molecule as an important biological target.[5] Cotinine (**2**) has proved to be 100 times less toxic than nicotine (**1**) with a longer plasma half-life of 19-24 h respect to nicotine (2-3 h), apart from not having addictive or cardiovascular effects on humans, despite its structural similarity with nicotine **1**.[6]
Pre-clinical studies have shown that cotinine facilitates the elimination of fear memories and improve attention and working memory in a mouse model for Alzheimer disease (AD),[7] reduce fear and anxiety in a mouse model of post-traumatic stress disorder (PTSD),[8] as well as antipsychotic drug-like properties.[9] Cotinine itself has been used by Janda for the preparation of haptens used in the generation of cotinine-specific-antibodies.[10] Presumably, cotinine also stimulates nicotinic cholinergic receptors[11] and could influence the release of neurotransmitters, along with the inhibition of androgen biosynthesis, and perhaps contributes to lower blood pressure of smokers.[12]
Despite the outstanding biological profile of cotinine (**2**), there is a lack of efficient synthetic methods that allow the preparation of this molecule and its derivatives, and the known procedures for their construction rely mainly on the C-H oxidation at C-2 from the corresponding nicotine analogs using highly toxic oxidants.[13,10] Additionaly, the combinatorial synthesis of cotinine and iso-cotinine analogs from simple starting materials that would contribute to expand the chemical space remains unexplored. Some commercially available cotinine analogs are depicted in Figure 1B[14] and exemplify the need to develop new strategies that would allow the preparation of this important core (5-heteroaryl-γ-lactam) as well as the synthesis of novel cotinine isomers (iso-cotinine) with the pyrrolidinone ring at nonnatural position in a fast, simple and economical fashion.

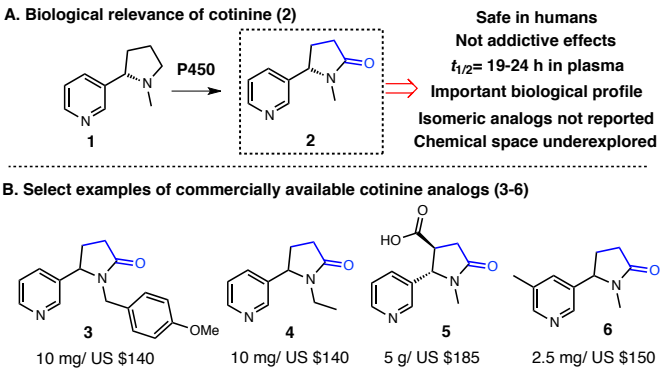
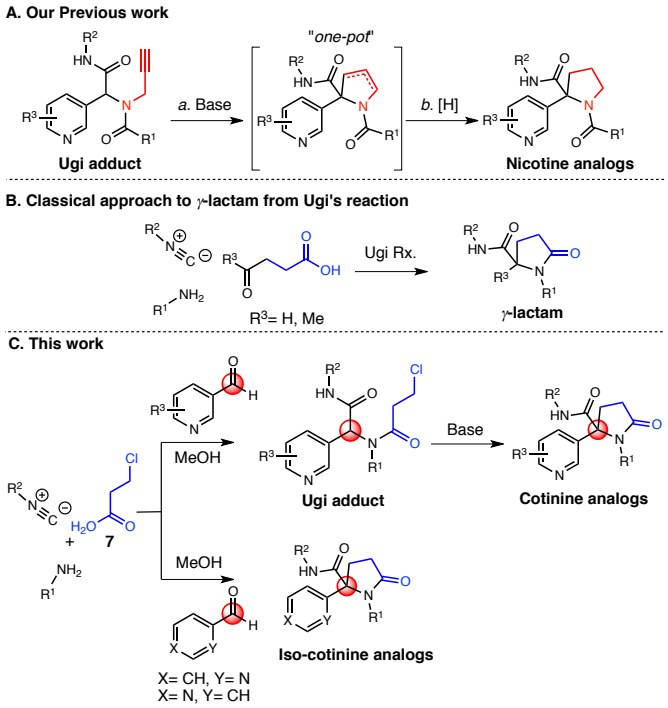


Figure 1 (A) Biological relevance of cotinine (**2**). (B) Select examples of commercially available cotinine analogs **3-6**.

On the other hand, isocyanide-based multicomponent reactions (IMCRs) have become a powerful tool for the synthesis of different scaffolds with notable molecular complexity.[15] Among these transformations, the Ugi reaction (Ugi-4CR) plays a central role, due to its high atom economy as well as the versatility of the Ugi adducts to undergo further transformations.[16] Under the Ugi protocol, a set of four components (an aldehyde, amine, carboxylic acid and isocyanide) are assembled into a peptide-like adduct, with the release of a molecule of H_2O. In recent years, there has been an emerging and increasing interest in the exploration of the peptidyl position as alternative reactive center in Ugi adducts for the synthesis of various molecular arrangements, some possessing quaternary centers.[17] Recently, we developed a synthetic protocol for the rapid access to nicotine analogs from Ugi-4CR through a 5-*endo* cycloisomerization-reduction process, where an intramolecular cyclization between an allenamide group[18] and an enolate generated

in the peptidyl position is performed (Scheme 1A).[19] With this precedent, and the fact that several syntheses of 5-substituted γ-lactams using the Ugi reaction, are restricted, in most cases, to reagents with a tethered combination of an acid and a ketone/aldehyde, along with the other components usually employed in this transformation (Ugi-4C-3CR, Scheme 1B),[20,16b] we envisioned the possibility of building the γ-lactam nuclei (cotinine and iso-cotinine analogs) by exploiting the reactivity of the peptidyl position of Ugi adducts bearing a 3-chloropropionic moiety (Scheme 1, C). Herein, we disclose the results of the synthetic strategy depicted in Scheme 1C.



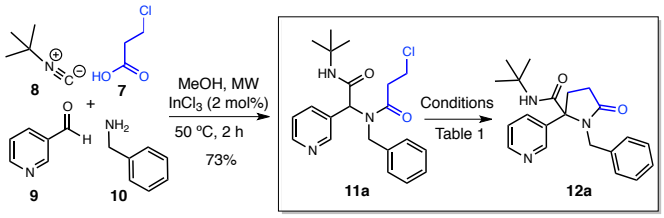
Scheme 1 State of the art: (A) Our previous work on nicotine analogs. (B) Classical approach to γ-lactam nuclei from Ugi Rx. (C) Proposal toward the construction of cotinine and iso-cotinine analogs.

Results and discussion

Cotinine analogs: Initially, the Ugi adduct model **11a** was synthesized in 73% yield by the equimolar reaction of 3-chloropropionic acid **7**, *tert*-butylisocyanide **8**, 3-pyridinecarboxaldehyde **9** and benzylamine **10**, in methanol under microwave heating conditions [50 ºC, 100 W, 2 h, 2 mol % $InCl_3$]. With the model substrate **11a** in hand, we initiated the screening of a set of bases, solvents and temperatures to find the best cyclization conditions (Table 1).

In the initial experiments, we tested the use of Cs_2CO_3 (10 eq) and *t*-BuOK (1.0 eq) in THF (Table 1, entries 1-2); however, the cyclization reaction did not occur whatsoever. Interestingly, increasing the number of *t*-BuOK (2.5 eq) equivalents generated the expected cotinine analog **12a** at room temperature, although in low yield (30%) (entry 3). To our delight, when *t*-BuOK (2.0 eq) in CH_3CN at 110 ºC (MW) was used, the reaction proceeded smoothly, affording the desired cyclization product in 66% yield (entry 4). Consequently, the variation in reaction time under the same conditions produced better yields (78%) (entry 5). Similarly, the organic base DBU was evaluated in CH_3CN, albeit proved to be less effective for the desired transformation (entries 5-7). The use of DMF as the solvent, and DBU as the base (entries 8-10), generated similar results to those obtained in entries 4-5. With these results, we decided to use *t*-BuOK in CH_3CN as the standard conditions to facilitate the purification process (Table 1, entry 5). The methodology was then applied to a series of Ugi adducts **11b-r** obtained in a similar way to **11a** [MeOH, 50 ºC, 100 W, 2 h, 2 mol % $InCl_3$], using different amines, 3-pyridinecarboxaldehydes, isocyanides and 3-chloropropionic acid **7** as a model reagent (Table 2).

Table 1 Optimization of cyclization conditions



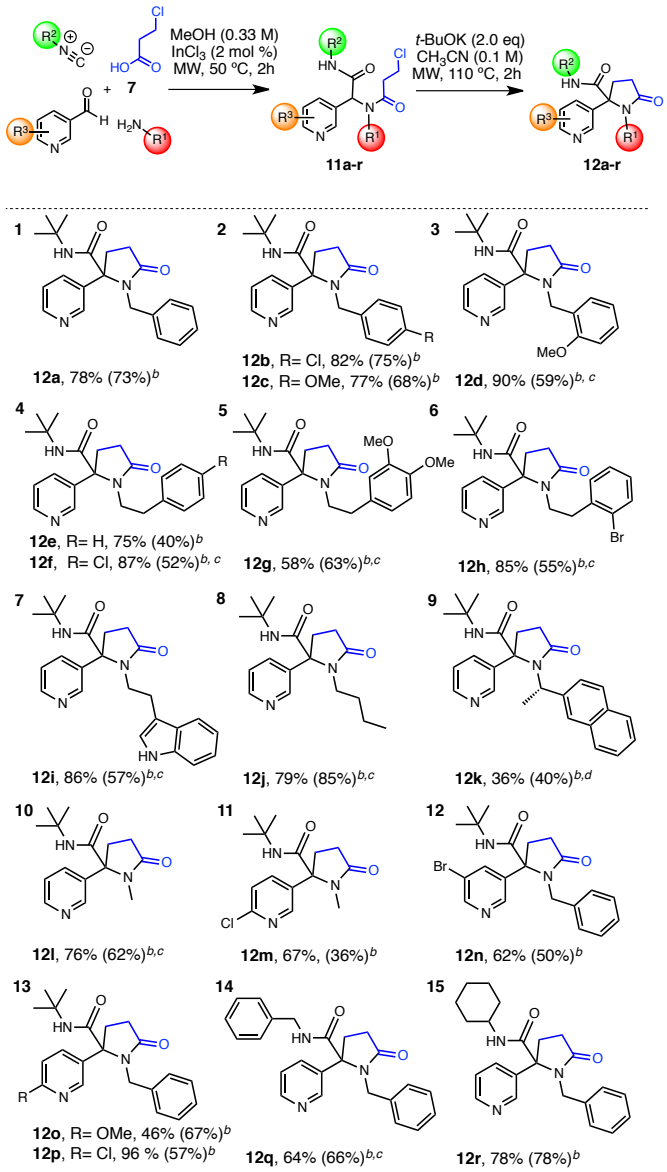
Entry[a]	Solvent	Base	T(ºC), source	Time (h)	Yield (%)[b]
1	THF	Cs_2CO_3 (10)	50, MW	0.5	-
2	THF	*t*-BuOK (1.0)	25, RT	1.0	-
3	THF	*t*-BuOK (2.5)	25, RT	1.5	30
4	CH_3CN	*t*-BuOK (2.0)	110, MW	1.0	66
5	**CH_3CN**	***t*-BuOK (2.0)**	**110, MW**	**2.0**	**78**
6	CH_3CN	DBU (2.0)	110, MW	1.0	50
7	CH_3CN	DBU (2.0)	110, MW	3.0	47
8	DMF	DBU (1.0)	110, MW	1.0	66
9	DMF	DBU (2.0)	110, MW	2.0	76
10	DMF	DBU (2.0)	110, MW	3.0	77

[a]All reactions were carried out in 0.1 mmol scale (0.1 M). [b]Yield of isolated products. MW= microwave.

Initially, the nature of the amine was evaluated finding that several Ugi adducts derived from benzylamines (H, 4-Cl, 4-OMe, 2-OMe, **11a-d**) and phenethylamines (H, 4-Cl, 3,4-diMeO, 2-Br, **11e-h**) afforded the corresponding cotinine analogs **12a-h** in good to excellent overall yields (58-90%, entries 1-6, Table 2). Similarly, Ugi adducts **11i-j** bearing a heteroaromatic or aliphatic amine, such as tryptamine and *n*-butylamine, afforded the cyclization products **12i-j** successfully (86 and 79% respectively, entries 7-8). The use of an optically active amine (*S*)-(-)-1-(2-naphthyl)ethylamine for adduct **11k** resulted in a 1:1.8 diastereoisomeric mixture of the γ-lactam nuclei **12k** in low yield (36%) and with evidence of a slight diastereoselectivity (entry 9). Interestingly, this methodology provides the possibility of introducing the *N*-methyl group into the corresponding analogue rapidly. Thus, Ugi adducts **11l-m** derived from methylamine (40 wt. % in H_2O) afforded the corresponding cotinine analogs **12l-m** in good yield (67-76%, entries 10-11).

With respect to the heteroaromatic moiety in the Ugi adducts **11n-p**, we found that electron-donating (6-OMe) and electron-withdrawing (5-Br, 6-Cl) groups have a strong influence on the γ-lactam formation (46, 62 and 96% yield, respectively, entries 12-13). In addition, other isocyanides such as benzyl and cyclohexylisocyanide were also tested in the methodology, providing good results (64-78%, entries 14-15). In some cases, shorter reaction times were necessary due to the sensibility of the corresponding Ugi adducts, requiring only 10 minutes for the cyclization to be completed (Table 2, **12d**, **12f-j**, **12l**, **12q**).

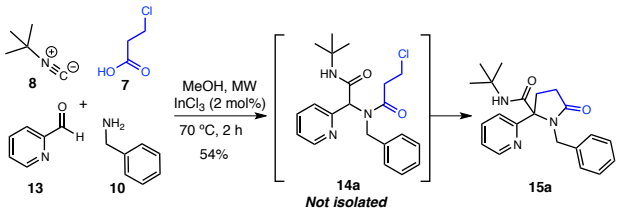
Table 2 Scope of the methodology (cotinine analogs)[a]



[a]Isolated products. [b] In parenthesis, yields of the corresponding Ugi adduct. [c]Reaction time for cyclization: 10 minutes. [d] A 1:1.8 diastereomeric ratio was measured by ^{1}H NMR for **12k**

Iso-cotinine analogs: In 2010, Che and Yang et al.[21] reported the synthesis of chromeno[3,4-c]-pyrrole-3,4-diones through a base-free Ugi-4CR/Michael addition protocol. In this approach, a highly reactive enol species, formed at the peptidyl position of the Ugi adducts derived from 2- and 4-pyridinecarboxaldehyde, was the key to perform the one-pot intramolecular cyclization with the Michael acceptor. Based on this precedent, we envisioned the possibility of performing the synthesis of iso-cotinine analogs from these isomeric aldehydes via an intramolecular nucleophilic substitution (S_N2) between the enol tautomer and the 3-chloropropionic moieties present in the corresponding Ugi adduct by means of a related strategy. Thus, an experiment using a similar set of reagents and conditions [MeOH, MW, 70 °C, 100 W, 2 h, 2 mol % $InCl_3$] used for the synthesis of the Ugi adduct model **11a** (Table 1), except for the aldehyde component (2-pyridinecarboxaldehyde **13**) and the reaction temperature was conducted.

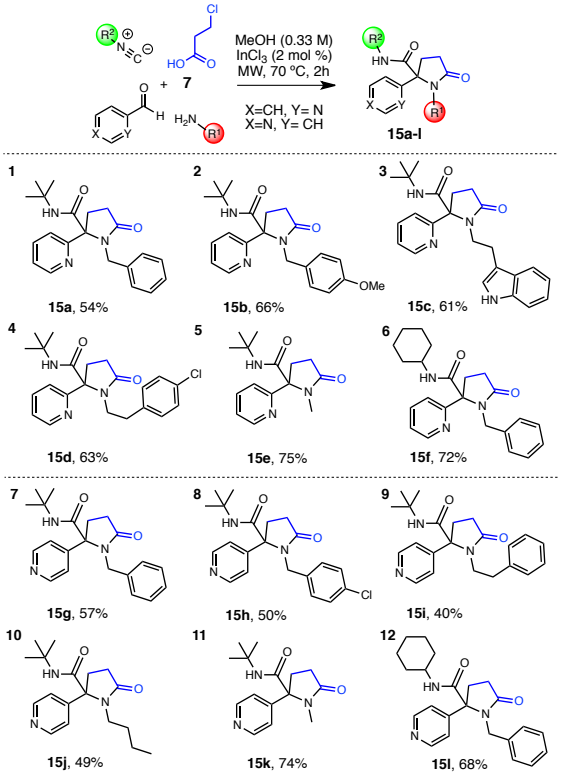
To our delight, the γ-lactam nuclei **15a** (iso-cotinine analog) was obtained in good yield (54%) through a remarkably efficient base-free one-pot process, without the need to isolate the transient Ugi adduct **14a** (Scheme 2).



Scheme 2 One-pot synthesis of iso-cotinine analog **15a**.

In order to explore the scope of this transformation displaying high atom economy, a survey of different amines and isocyanides along with 2- and 4-pyridinecarboxaldehyde and 3-chloropropionic acid **7** as a model reagent was conducted. In the case of 2-pyridinecarboxaldehyde, diverse γ-lactams **15a-e** derived from benzylamines (H, 4-MeO), tryptamine, 4-chlorophenethylamine and methylamine (40 wt. % in H_2O) were obtained in good yields (54-75%, entries 1-5, Table 3). Also, the use of cyclohexylisocyanide afforded the iso-cotinine analog **15f** in 72% yield (entry 6). In the case of 4-pyridinecarboxaldehyde, a similar behavior during the cyclization step was observed when benzyl and 4-chlorobenzylamine were evaluated (**15g-h**, 50-57%, entries 7-8). Likewise, other amines such as phenethylamine, *n*-butylamine and methylamine (40 wt. % in H_2O) afforded the γ-lactam core **15i-k** in good overall yield (40-74%, entries 9-11, Table 3). Consistently, the use of a different isonitrile also generated the expected γ-lactam nuclei **15l** (68%, entry 12, Table 3).

Table 3 Scope of the methodology (iso-cotinine analogs)[a]



[a]Isolated products.

On the other hand, the structure of the cotinine analog **12f** was demonstrated by X-ray crystallography (See supporting information) (Figure 2).[22]

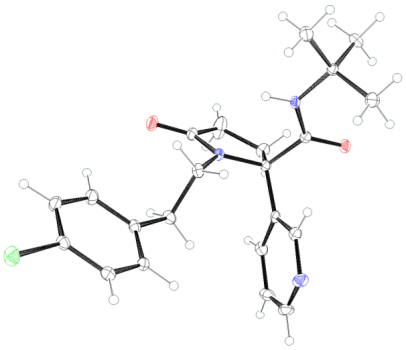
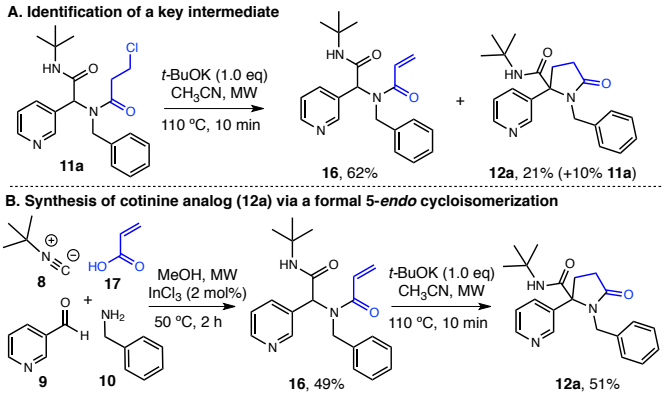


Figure 2 X-ray crystallographic structure of **12f**, thermal ellipsoids are drawn at 30 % probability for all atoms except for hydrogen.

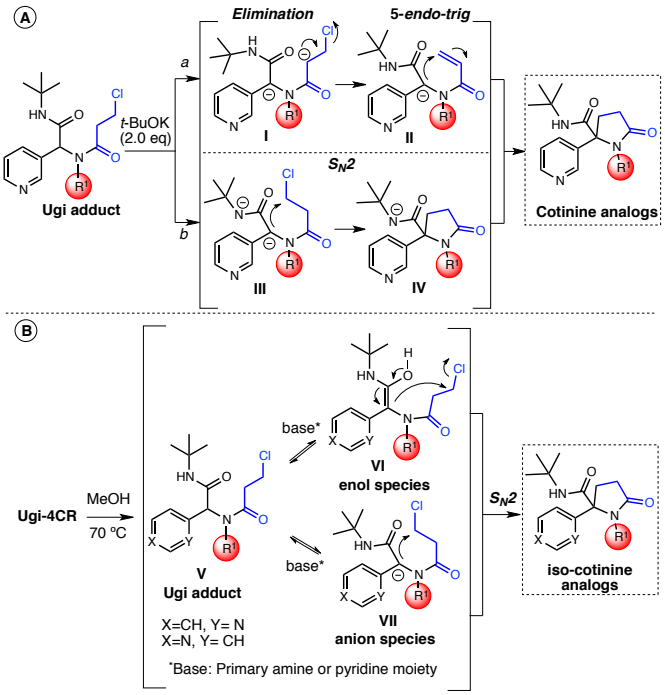
During the initial experiments, the course of the reactions was monitored by thin-layer chromatography (TLC), which allowed us to isolate and identify a key intermediate in the cyclization process of **11a**. In order to gain further mechanistic insights, a cyclization control experiment for **11a** was conducted under the same conditions (CH_3CN, MW, 110 ºC) although using 1.0 eq. of *t*-BuOK and a shorter reaction time (10 min). Interestingly, the Ugi-elimination adduct **16** was isolated after purification by flash column chromatography, along with the cotinine analog **12a** and some starting material **11a** in 62, 21 and 10% yield, respectively (Scheme 3A). This observations suggests that an elimination process and subsequent intramolecular Michael addition onto the α,β-unsaturated amide represents the main route for cyclization, over the nucleophilic substitution reaction pathway. To further confirm this hypothesis, Ugi adduct **16** derived from acrylic acid **17** was synthesized similarly to **11a** and subjected to the conditions previously described (Scheme 3A), providing the corresponding cotinine analog **12a** in 51% yield via a formal 5-*endo*-*trig* cycloisomerization[23] (Scheme 3B).



Scheme 3 Mechanistic insights for the formation of **12a**.

This observation is worth to mention, because unactivated α,β-unsaturated amides are considered poor Michael acceptors and information about this behavior in reactions involving Ugi adducts is scarce.[24,17p-q] During the course of our research, Shiri and co-workers reported the base-mediated functionalization of the peptidyl position in Ugi adducts to generate indolyl γ-lactams derivatives from 3-chloropropionic acid **7**. Although no evidence of an elimination/Michael addition process was suggested, we believe that a closely related mechanism could be operating as well.[25]

A plausible mechanism for the synthesis of cotinine and iso-cotinine analogs is shown in Scheme 4. In the case of the cotinine analogs, two possible pathways can be considered for cyclization: (*a*) base-mediated formation of the dianionic species[26,17f,18a,19] **I** and subsequent elimination (E_2) would generated the α,β-unsaturated amide **II**, which undergoes an intramolecular nucleophilic attack/ Michael addition to form the γ-lactam nuclei via a formal 5-*endo*-*trig* cycloisomerization, and (*b*) initial formation of the dianionic intermediate **III** and concomitant bimolecular nucleophilic substitution (S_N2) to afford the cotinine analog after protonation of **IV** (Scheme 4A). In the case of iso-cotinine analogs, as opposed to cotinine derivatives, construction of the pyrrolidinone ring without the addition of an external base can be envisaged via the formation of enol **VI** or anion **VII** and subsequent intramolecular nucleophilic substitution (S_N2). Presumably, the higher acidity of the peptidyl proton[27] in the Ugi adducts derived from 2- and 4-pyridinecarboxaldehydes and the presence of a base already present in the reaction media (e.g. primary amine, pyridine moiety), facilitate the formation of **VI** or **VII** (Scheme 4B). Anion **VII** is further stabilized by resonance, leaving a negative charge on the N atom of the pyridine ring in one of the contributing canonical forms.



Scheme 4 Plausible mechanisms for cyclizations

Conclusions

In summary, we have developed a practical and efficient methodology for the two-steps combinatorial synthesis of cotinine analogs (**12a-r**, 43-96%) featuring an Ugi-4CR/cyclization approach. This protocol exploits the reactivity of the peptidyl position as well as the dual function of the base (*t*-BuOK) as a promoter of reactive intermediate species. The evidence supports a plausible base-mediated elimination/Michael addition process as the primary

pathway for this transformation. Additionally, a novel one-pot base-free process for the construction of iso-cotinine analogs (**15a-l**, 40-75%) through a simple operational process with high atom economy is reported. We strongly believe that our methodology can have some impact for the investigation of new drug candidates based on the cotinine structural motif.

Efforts toward the synthesis of (+/-)-cotinine (**2**) from convertible isocyanides are currently underway and will be published in due course.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Copies of the ^{1}H and ^{13}C NMR spectra for all the products and X-ray crystallographic data for **12f**.

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