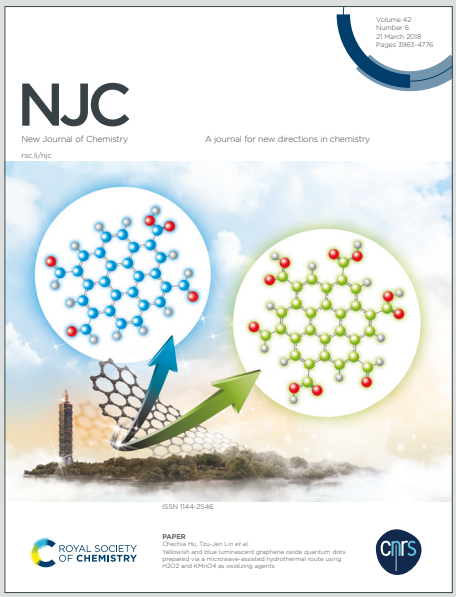
NJC

New Journal of Chemistry

A journal for new directions in chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. B. Atar, J. Kang and A. H. Jadhav, *New J. Chem.*, 2020, DOI: 10.1039/C9NJ05738B.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

View Article Online
DOI: 10.1039/C9NJ05738B

COMMUNICATION

[bmim]Cl: Promoted domino protocol of isocyanides-based [4 + 1]-cycloaddition reaction for the synthesis of diversely functionalized 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile under solvent free condition.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Amol Balu Atar*[a], Jongmin Kang[a], and Arvind H. Jadhav[b]

A domino protocol of aldehydes, isocyanides and 2-pyridylacetonitrile in presence of [bmim]Cl as a promoter and solvent for the synthesis of 3-alkylamino-2-alkyl/arylindolizine-1-carbonitrile is described. A wide range of alkyl, aryl and hetero-aryl aldehydes reacted with 2-pyridylacetonitrile and isocyanides, leading to an indolizine derivatives with high selectivity, high atom economy, and good to excellent yields. These straight forward and highly efficient method allows the synthesis of bis indolizine-1-carbonitrile derivatives.

Introduction

Fused indolizines, which are most representative *N*-fused heterocyclic compounds, having potential application in the field of medicinal chemistry and organic synthesis.[1] The biological activities of fused indolizines nucleus have been discovered in the form of anticancer,[2] anti-inflammatory,[3] antimicrobial,[4] anti-tubercular,[4] antifungal,[5] antioxidant,[6] and inhibitor for vascular endothelial growth factor (VEGF).[7] Especially, the 3-substituted indolizine-1-carbonitrile derivatives exhibited activity against phosphatase inhibitors.[8] Apart from medical application, the fused indolizines nucleus has also displayed more newly distinctive fluorescent and photophysical properties which provide new potential applications in materials science.[9] Furthermore, fused indolizines nucleus act as herbicides and fungicides in the agricultural sector.[10,11] Examples of some active substituted indolizines are depicted in Figure 1.

Due to the broad range of applications, the significant interest extend on this specific skeleton has led to substantial development of numerous elegant approaches for the expeditious assembly of the indolizine core. These includes transition-metal-catalyzed intramolecular cycloisomerization,[12] cyclocondensations,[13] cycloadditions,[14] cyclization/elimination[15] and multicomponent coupling reactions.[16] However, the most reported methods have several drawbacks, due to the limited scope, harsh reaction conditions, require the use of transition-metal catalysts and additives, and involve tedious work-up processes and long reaction times, which strongly affect the economics as well as the environmentally friendly nature of the reaction.

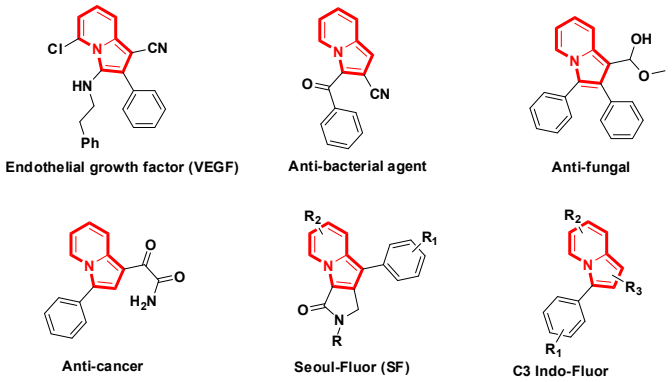


Figure 1. Selected examples of active indolizines.

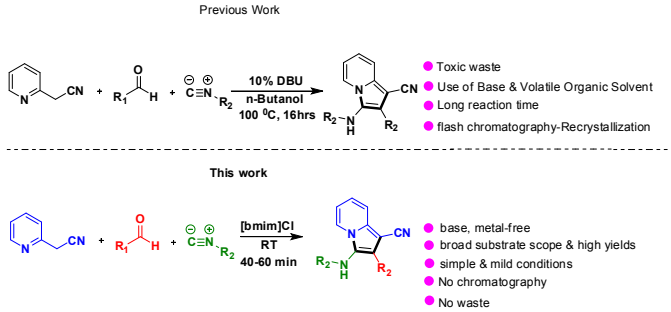
Recently, multicomponent coupling reactions (MCRs) have emerged as powerful and versatile synthetic tools for the organic chemist in the field of modern organic chemistry and is one of the popular research areas of the scientific community that drives increasing efforts.[17] MCRs have been considered and used as one of the most important tools for the construction of novel and structurally complex molecules in a single pot ensuring high efficiency, safe, high selectivity, atom- and step-economical synthesis strategy.[18] Recently, isocyanide-based multicomponent reactions followed by other synthetic conversions emerged as a powerful tool for designing fused multicyclic skeletons.[19] Therefore, the development of novel protocol with MCRs approaches continues to attract the attention of organic chemists.[20] In addition, currently attention focused on the replacement of volatile organic solvents by

[a]*Department of Chemistry, Sejong University, Seoul 143-747, South Korea*
[b]*Centre for Nano and Material Science(CNMS), Jain University, Jain Global Campus, Bangalore 562112, Karnataka, India*
**E-mail: amol.atar@sejong.ac.kr*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C9NJ05738B

environmentally friendly solvents in organic synthesis.[21] In this context, room temperature ionic liquids (**RTILs**) is the most convenient eco-friendly solvent due to unique properties such as nonvolatility, thermal stability, solvation ability, and easy recyclability.[22] Importantly, RTILs may play a dual role as both catalysts and solvents in the organic synthesis.[23] With these aspects of green metrics in mind, the development of catalyst-free, RTILs promoted multicomponent reactions in environmentally benign media would be of considerable interest.

On the basis of the above analysis and continuing our research program on the sustainable synthesis of biologically active heterocyclic compounds, [24-29] we report herein a highly efficient route to constructing 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives via [bmim]Cl promoted one-pot three-component reactions of aldehydes, isocyanides and 2-pyridylacetonitrile under base and solvent-free condition at room temperature. The classical synthetic method for constructing 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives is the reaction of aldehydes, isocyanides and 2-pyridylacetonitrile in the presence of 1, 4-diazabicyclo [2.2.2] octane and volatile organic solvent such n-butanol at 100 ^{0}C temperature was previously reported.[30-31] Although, these synthetic methods create important contributions to the synthesis of 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives, but they often require skin corrosive/eye irritative toxic 1, 4-diazabicyclo [2.2.2] octane as base with volatile organic solvent n-butanol at higher temperature. Instead of these methods, our approach for the synthesis indolizine-1-carbonitrile derivatives via [bmim]Cl promoted one-pot three-component reactions is very simple, efficient, no any waste formation, milder condition and produces excellent yields (Scheme 1).

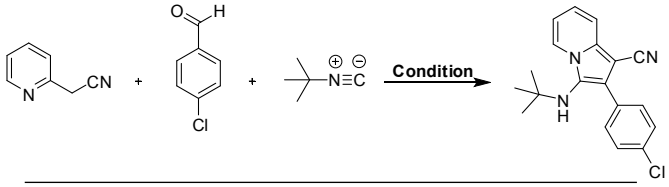


Scheme 1. Synthesis 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives

Result and discussion-

In exploration of efficient conditions for the non-toxic clean protocol, the reaction of 2-pyridylacetonitrile (**1a**) with 4-chlorobenzaldehyde (**2a**) and tert butyl isocyanide (**3a**) under catalyst and solvent-free conditions at various temperatures was first investigated (Table 1). Initially by using model substrate, the reaction was carried at room temperature under catalyst and solvent-free condition. The result shows that, after 24hrs stirring at room temperature there is no any progress and TLC indicating starting material as it is (Table 1, entry 1). Then further by using similar condition, the reaction was carried out at various temperatures. These results shows that there is no any product formation and indicated that need promoter to accomplish the reaction (Table 1, entries 2, 3, 4).

Table 1 [a]Screening of various types of promoters and solvents for the synthesis of compound **4a**



Entry	Catalyst(equiv) /Solvent	Condition	Time (h)	Yield[b] (%)
1	----	RT	24	----
2	----	50 ^{0}C	20	----
3	----	80 ^{0}C	16	----
4	----	120 ^{0}C	10	----
5	**[bmim]Cl (1)**	**RT**	**40 min**	**96**
6	[bmim]Cl (1)	50 ^{0}C	30 min	92
7	[bmim]Cl (1)	80 ^{0}C	30 min	90
8	[bmim]Cl (1)	120 ^{0}C	20 min	87
9	[bmim]Cl (0.2)	RT	60 min	50
10	[bmim]Cl (0.5)	RT	60 min	65
11	[bmim]Cl (0.7)	RT	60 min	78

[a]Reactions and conditions: 2-pyridylacetonitrile (1 mmol), 4-chlorobenzaldehyde (1 mmol), tert butyl isocyanide (1 mmol), [b]Isolated yields.

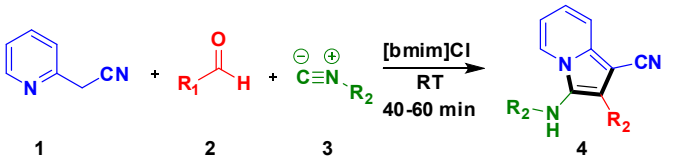
To avoid various volatile organic solvents and clarify the clean process, the reaction of 2-pyridylacetonitrile (**1a**) with 4-chlorobenzaldehyde (**2a**) and tert butyl isocyanide (**3a**) conducted in the 1-butyl-3-methylimidazolium chloride [bmim]Cl. Surprisingly, the yield of corresponding product 4a were obtained 96% within 40 min at room temperature (Table 1, entry 5). Second, we performed the reaction at different temperatures in [bmim]Cl (Table 1, entries 6, 7, 8). The results revealed that raising the temperature and decreased the reaction time was disadvantageous for the reaction. Finally, we also studied the amount of [bmim]Cl for this one pot reaction and found that 1 equivalent of [bmim]Cl is the optimum amount to obtain the highest yield of the target compound **4a** (Table 1, entries 5, 9, 10, 11) at room temperature.

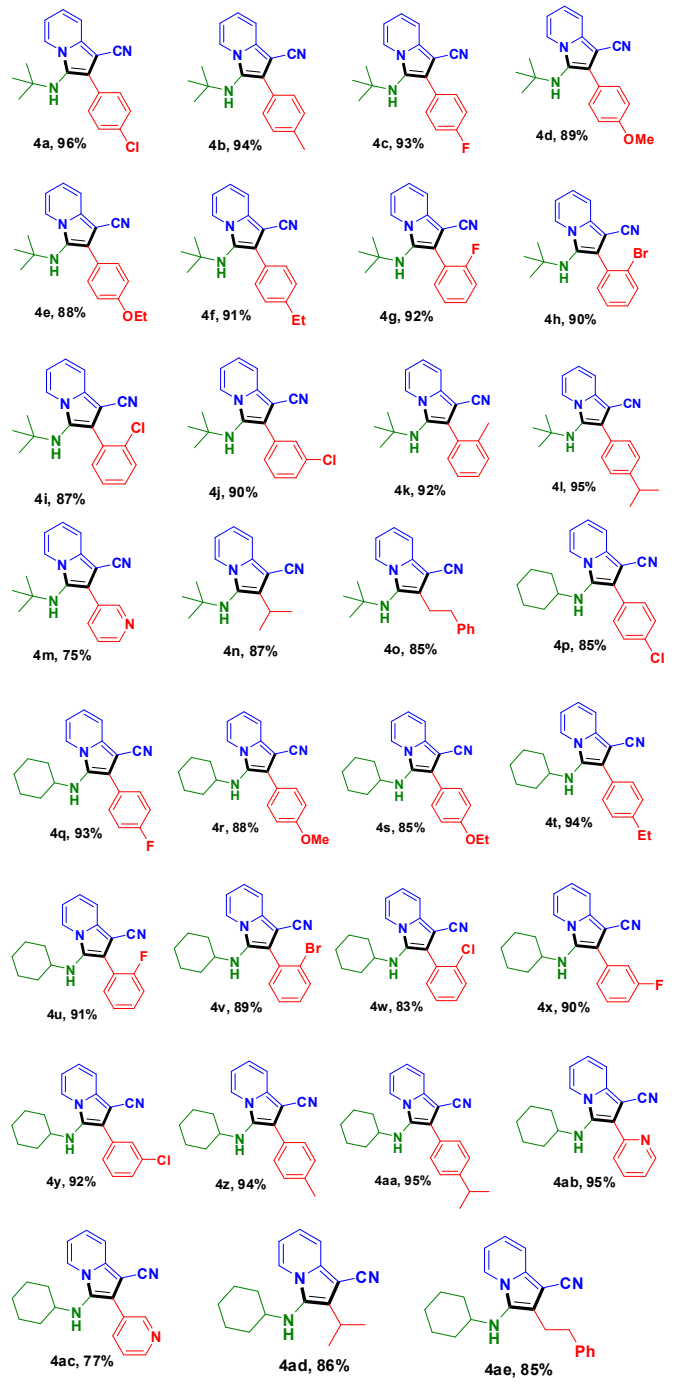
To develop the diversity orientated of 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives, we further investigated the scope and generality of use of various substituted aryl/heteroaryl/aliphatic aldehydes in the presence of 2-pyridylacetonitrile and tert butyl isocyanide/cyclohexyl isocyanide under optimal conditions and the results are listed in Table 2. The results revealed that the various substituted aryl aldehydes proceeded the reaction smoothly and gave the products in good yields. Furthermore, heteroaryl aldehydes was tested for this one pot reaction. The results shows that, as compared to various substituted aryl aldehydes, the heteroaryl aldehydes gave relatively lower yields of corresponding target molecules. In contract with aromatic heteroaryl aldehydes, aliphatic aldehyde gave relatively higher yields of the

View Article Online
DOI: 10.1039/C9NJ05778B

corresponding 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitril derivatives.

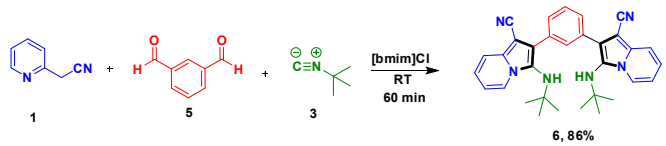
Table 2[a] Eco-friendly synthesis 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives[b]





[a]Reactions and conditions: 2-pyridylacetonitrile (1 mmol), aldehydes (1 mmol), isocyanides (1 mmol), [bmim]Cl (1 mmol)
[b]Isolated yields.

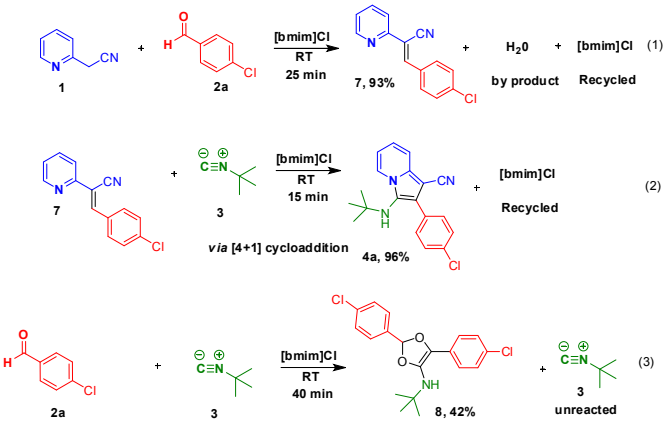
Interestingly, isophthalaldehyde (**5**) having a bis aldehyde functionality was also found to be suitable for this reaction to give 2, 2'-(1, 3-phenylene) bis(3-(tert-butylamino)indolizine-1-carbonitrile) (**6**) in satisfy to good yields within one hours (Scheme 2).



Scheme 2 Reaction of **5** with **1** and **3** to give **6**

To prove the path of reaction mechanism of this one pot process, control experiments were conducted. Firstly, the by using model substrate the reaction of 4-chlorobenzaldehyde (**2a**) and 2-pyridylacetonitrile (**1**) conducted for the formation of Knoevenagel adduct (Z)-3-(4-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile **7** in the presence of [bmim]Cl. From this reaction Knoevenagel adduct **7** was formed in 93% yields (Scheme 3, (1)). Secondly, the Knoevenagel adduct **7** and tert butyl isocyanide (**3a**) was reacted by using [bmim]Cl at room temperature (Scheme 3, (2)). The targeted compound 3-(tert-butylamino)-2-(4-chlorophenyl) indolizine-1-carbonitrile **4a** was obtained in 96% yields. Furthermore, we study the reaction of 4-chlorobenzaldehyde (**2a**) and tert butyl isocyanide (**3a**) in the presence of [bmim]Cl. The results reveals that the formation of N-tert-butyl-2, 5-bis (4-chlorophenyl)-1, 3-dioxol-4-amine **8** in 42% yields with unreacted tert butyl isocyanide (**3a**) (Scheme 3, (3)). This study reveals that the reaction was proceed through Knoevenagel condensation followed by [4+1] cycloaddition.

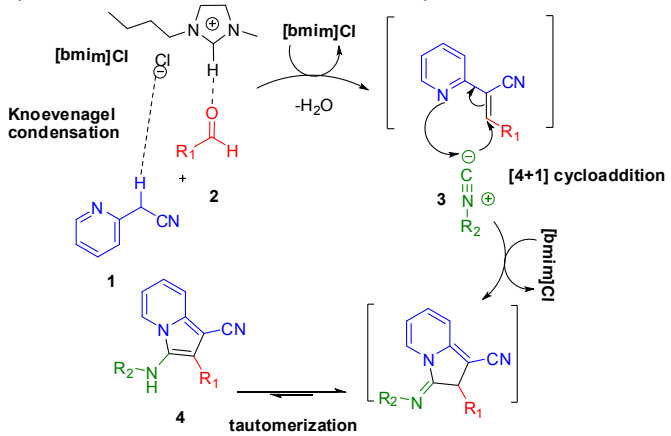
Scheme 3. Control experiments



Based on the above experimental results and on the basis of literature,[32] a tentative reaction pathway for this isocyanides-based [4 + 1]-cycloaddition reaction is exemplified in Scheme 4. Initially, Knoevenagel adduct was formed by the action [bmim]Cl. It is hypothesized that, anion Cl^- of the [bmim]Cl has high hydrogen bond accepting basicity are beneficial in weakening the H–C bond. Similarly, cations can constitute complexes with oxygen atoms of the aldehydes, weakening the C=O bond. It should be pointed out that, among ILs, [bmim]Cl is often used to promote dehydration of various substrates.[33]

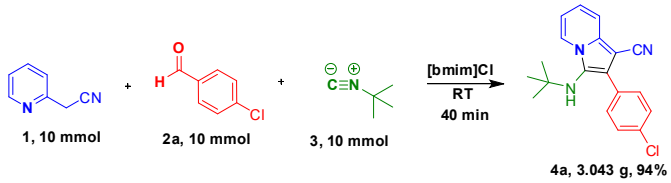
View Article Online
DOI: 10.1039/C9NJ05738B

Further, the proceeded by isocyanides-based [4 + 1]-cycloaddition reaction to form the final product **4**.



Scheme 4. Plausible Reaction Mechanism

Finally, to see whether newly developed synthesis of 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives is suitable for more practical applications, the reaction of 2-pyridylacetonitrile (**1**) with 4-chlorobenzaldehyde (**2a**) and tert butyl isocyanide (**3a**) was carried out in a large scale, 10 mmol. From this reaction, **4a** were obtained 94% in yields (Scheme 5).



Scheme 5. Gram-scale synthesis of **4a**

From the perspective of clean methods, the reusability reaction media is also important to fulfill the green metrics. Therefore, the recovery and reusability of the room temperature ionic liquid [bmim]Cl was investigated by using model reaction (Table 3). After completion of the reaction as monitored by TLC, the crude product was precipitated in [bmim]Cl. Due to the insolubility of [bmim]Cl in organic solvents, the crude product was extracted from with ether. The recycled [bmim]Cl was washed with ether and dried under vacuum. Then recovered [bmim]Cl successively applied for the formation 3-(tert-butylamino)-2-(4-chlorophenyl) indolizine-1-carbonitrile 4a by using model reaction. The results reveals that, recycling and reusability of the [bmim]Cl shows high activity and formed the target product in excellent yield (Table 3).

Table 3. Recycling and reuse of [bmim]Cl

Entry	Reaction cycle	Yield[a] (%)
1	First (fresh run)	96
2	Second cycle	94
3	Third cycle	92
4	Fourth cycle	92

[a]Isolated yield

Conclusion

In summary, room temperature based ionic liquid [bmim]Cl promoted domino protocol for the synthesis of 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives under milder condition has been developed. This protocol is suitable with a wide range of functional groups and bring diversity oriented indolizine derivatives in moderate to good yields. The current protocols indicated a clean reaction, a base and solvent-free process, easily accessible reactants, and environmentally friendly reaction conditions with high atom economy.

Experimental section

Materials and techniques

Chemicals were purchased from Aldrich, Merck, and Alfa Aesar chemical companies. The NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) on a Bruker 500 MHz NMR. High resolution mass spectra (HRMS) were recorded on a Jeol JMS-700 mass spectrometer.

General procedure for the synthesis of diversely functionalized 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile 4

To a mixture of 2-pyridylacetonitrile (1 mmol), isocyanides (1 mmol) and aldehydes (1 mmol) was added 100 mol % [bmim]Cl and the reaction mixture was kept room temperature with constant stirring for stipulated time (see table 2). After completion of the reaction as monitored by TLC, the crude product was extracted with ether. The combined organic layers were washed with brine solution, and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the solvent was removed under vacuum. The solid crude product was recrystallized from ethanol to afford pure compound 4.

The spectral and analytical data of the model representative compound is given here:

4a: 3-(tert-butylamino)-2-(4-chlorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.56 (d, *J* = 10Hz, 1H), 7.78-7.75 (m, 2H), 7.59 (d, *J* = 10Hz, 1H), 7.56-7.54 (m, 2H), 7.21-7.18 (m, 1H), 6.97-6.94 (m, 1H), 4.63 (s, 1H), 0.85 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.8, 132.7, 132.7, 131.5, 128.9, 126.0, 125.0, 124.7, 123.8, 117.3, 116.9, 113.0, 78.5, 55.9, 30.2. HRMS m/z calcd for $C_{19}H_{18}ClN_3$ [M+] 323.8193, found 323.8190.

4b: 3-(tert-butylamino)-2-p-tolylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 5Hz, 1H), 7.63 (d, *J* = 10 Hz, 2H), 7.57 (d, *J* = 10Hz, 1H), 7.28 (d, *J* = 10Hz, 2H), 7.16 (t, *J* = 12Hz, 1H), 6.92 (t, *J* = 12Hz, 1H), 4.56 (s, 1H), 2.36 (s, 3H), 0.83 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 137.1, 134.7, 130.8, 129.6, 129.4, 126.1, 125.7, 124.8, 123.5, 117.6, 116.7, 112.7, 78.7, 55.8, 30.2, 21.2. HRMS m/z calcd for $C_{20}H_{21}N_3$ [M+] 303.4008, found 303.4002.

4c: 3-(tert-butylamino)-2-(4-fluorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 10Hz, 1H), 7.79-7.76 (m, 2H), 7.58 (d, *J* = 10Hz, 1H), 7.32 (t, *J* = 15Hz, 2H), 7.18-7.15 (m, 1H), 6.94-6.91 (m, 1H), 4.60 (s, 1H), 0.83 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 163.0, 161.1, 134.7, 131.8, 131.7, 130.2, 130.2, 125.9, 125.1, 124.9, 123.7, 117.4, 116.8, 115.8, 115.7, 112.9, 78.7, 55.7, 30.2. HRMS m/z calcd for $C_{19}H_{18}FN_3$ [M+] 307.3647, found 307.3643.

4d: 3-(tert-butylamino)-2-(4-methoxyphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.54 (d, *J* = 5Hz, 1H), 7.67-7.65 (m, 2H), 7.56 (d, *J* = 10Hz, 1H), 7.17-7.14 (m, 1H), 7.04 (d, *J* = 10Hz, 2H), 6.93-6.90 (m, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 0.84 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 159.1, 134.6, 130.9, 126.0, 125.9, 125.6, 124.8, 123.4, 117.7, 116.7, 114.3, 112.7, 78.6, 55.7, 55.5, 30.2. HRMS m/z calcd for $C_{20}H_{21}N_3O$ [M+] 319.4002, found 319.4007.

4e: 3-(tert-butylamino)-2-(4-ethoxyphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.53 (d, *J* = 10Hz, 1H), 7.66 (d, *J* = 5Hz, 2H), 7.55 (d, *J* = 10Hz, 1H), 7.16-7.13 (m, 1H), 7.02 (d, *J* = 10Hz, 2H), 6.92-6.89 (m, 1H), 4.53 (s, 1H), 4.12-4.04 (m, 2H), 1.34 (t, *J* = 10Hz, 3H), 0.83 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 158.4, 149.9, 144.9, 138.1, 134.6, 130.9, 126.0, 124.8, 123.3, 120.6, 117.7, 116.7, 112.7, 78.6, 63.4, 55.7, 30.2, 15.1. HRMS m/z calcd for $C_{21}H_{23}N_3O$ [M+] 333.4268, found 333.4273.

4f: 3-(tert-butylamino)-2-(4-ethylphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 10Hz, 1H), 7.65 (d, *J* = 10Hz, 2H), 7.57 (d, *J* = 10Hz, 1H), 7.31 (d, *J* = 10Hz, 2H), 7.18-7.15 (m, 1H), 6.93-6.90 (m, 1H), 2.67-2.63 (m, 2H), 1.22 (t, *J* = 15Hz, 3H), 0.83 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 143.4, 134.7, 131.1, 129.6, 128.2, 126.1, 125.8, 124.8, 123.5, 117.6, 116.7, 112.8, 78.7, 55.8, 30.2, 28.4, 15.9. HRMS m/z calcd for $C_{21}H_{23}N_3$ [M+] 317.4274, found 317.4270.

4g: 3-(tert-butylamino)-2-(2-fluorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.56 (d, *J* = 10Hz, 1H), 7.68-7.65 (m, 1H), 7.60 (d, *J* = 10Hz, 1H), 7.50-7.46 (m, 1H), 7.38-7.30 (m, 2H), 7.21-7.18 (m, 1H), 6.96-6.93 (m, 1H), 4.25 (s, 1H), 0.82 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 160.8, 158.9, 134.5, 132.8, 130.7, 130.6, 126.6, 124.9, 123.8, 121.4, 121.3, 120.3, 116.8, 116.2, 116.1, 112.9, 80.0, 55.5, 29.9. HRMS m/z calcd for $C_{19}H_{18}FN_3$ [M+] 307.3647, found 307.3644.

4h: 2-(2-bromophenyl)-3-(tert-butylamino) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 5Hz, 1H), 7.77 (d, *J* = 10Hz, 1H), 7.60-7.56 (m, 2H), 7.50-7.47 (m, 1H), 7.37-7.34 (m, 1H), 7.19-7.16 (m, 1H), 6.95-6.92 (m, 1H), 4.08 (s, 1H), 0.84 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.6, 134.3, 133.4, 133.1, 130.4, 128.0, 126.3, 125.5, 124.8, 124.3, 123.7, 117.1, 116.9, 112.9, 80.5, 55.3, 30.0. HRMS m/z calcd for $C_{19}H_{18}BrN_3$ [M+] 368.2703, found 368.2705.

4i: 3-(tert-butylamino)-2-(2-chlorophenyl) indolizine-1-carbonitrile

yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 10Hz, 1H), 7.62-7.57 (m, 3H), 7.47-7.43 (m, 2H), 7.21-7.17 (m, 1H), 6.96-6.93 (m, 1H), 4.13 (s, 1H), 0.82 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.3, 133.6, 133.3, 130.3, 130.0, 127.5, 126.5, 124.8, 123.8, 116.9, 115.9, 112.9, 80.4, 55.3, 29.9. HRMS m/z calcd for $C_{19}H_{18}ClN_3$ [M+] 323.8193, found 323.8191.

4j: 3-(tert-butylamino)-2-(3-chlorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 10Hz, 1H), 7.85 (s, 1H), 7.70 (d, *J* = 10Hz, 1H), 7.57 (d, *J* = 10Hz, 1H), 7.50 (t, *J* = 15Hz, 1H), 7.45-7.41 (m, 1H), 7.18 (t, *J* = 15Hz, 1H), 6.95-6.92 (m, 1H), 4.68 (s, 1H), 0.84 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 150.1, 143.6, 138.2, 135.9, 134.9, 133.6, 130.7, 129.3, 128.4, 127.8, 126.2, 124.9, 124.4, 123.9, 117.2, 113.0, 78.5, 55.8, 30.2. HRMS m/z calcd for $C_{19}H_{18}ClN_3$ [M+] 323.8193, found 323.8195.

4k: 3-(tert-butylamino)-2-o-tolylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.54 (d, *J* = 5Hz, 1H), 7.58 (d, *J* = 10Hz, 1H), 7.38-7.25 (m, 4H), 7.19-7.16 (m, 1H), 6.95-6.92 (m, 1H), 4.25 (s, 1H), 2.30 (s, 3H), 0.80 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 137.0, 134.3, 133.2, 131.5, 130.5, 128.4, 126.4, 126.1, 126.0, 124.8, 123.4, 117.5, 116.8, 112.7, 80.2, 55.1, 30.1, 20.2. HRMS m/z calcd for $C_{20}H_{21}N_3$ [M+] 303.4008, found 303.4005.

4l: 3-(tert-butylamino)-2-(4-isopropylphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.55 (d, *J* = 10Hz, 1H), 7.66 (d, *J* = 5Hz, 2H), 7.57 (d, *J* = 10Hz, 1H), 7.34 (d, *J* = 5Hz, 2H), 7.16 (t, *J* = 15Hz, 1H), 6.91 (t, *J* = 15Hz, 1H), 4.56 (s, 1H), 2.95-2.90 (m, 1H), 1.23 (d, *J* = 10Hz, 6H), 0.83 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 148.0, 134.7, 131.2, 129.6, 126.7, 126.1, 125.8, 124.8, 123.4, 117.6, 116.7, 112.7, 78.7, 55.8, 33.6, 30.2, 24.3. HRMS m/z calcd for $C_{22}H_{25}N_3$ [M+] 331.4540, found 331.4544.

4m: 3-(tert-butylamino)-2-(pyridin-3-yl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.95 (s, 1H), 8.60-8.56 (m, 2H), 8.14-8.12 (m, 1H), 7.60 (d, *J* = 5Hz, 1H), 7.53-7.51 (m, 1H), 7.22-7.19 (m, 1H), 6.96 (t, *J* = 10Hz, 1H), 4.64 (s, 1H), 0.86 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 150.1, 148.7, 137.0, 135.1, 129.9, 126.4, 125.0, 123.9, 123.9, 122.8, 117.0, 116.9, 113.0, 78.7, 55.7, 30.3. HRMS m/z calcd for $C_{18}H_{18}N_4$ [M+] 290.3623, found 290.3625.

4n: 3-(tert-butylamino)-2-isopropylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.38 (d, *J* = 5Hz, 1H), 7.45 (d, *J* = 10Hz, 1H), 7.08-7.04 (m, 1H), 6.82-6.79 (m, 1H), 4.42 (s, 1H), 3.31-3.22 (m, 1H), 1.34 (d, *J* = 10Hz, 6H), 1.10 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 135.3, 131.9, 124.9, 122.7, 118.0, 116.3, 112.0, 76.3, 55.0, 30.3, 25.2, 23.1. HRMS m/z calcd for $C_{16}H_{21}N_3$ [M+] 255.3580, found 255.3581.

4o: 3-(tert-butylamino)-2-phenethylindolizine-1-carbonitrile

Yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.40 (d, *J* = 10Hz, 1H), 7.50 (d, *J* = 5Hz, 1H), 7.33-7.26 (m, 4H), 7.22-7.19 (m, 1H), 7.11-7.07 (m, 1H), 6.85-6.82 (m, 1H), 4.24 (s, 1H), 3.06-2.96 (m, 4H), 1.10 (s, 9H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 141.9, 134.6, 128.9, 128.6, 126.5, 126.3, 125.2, 124.8, 122.9, 117.6, 116.5, 112.1, 78.9, 55.4, 36.1, 30.3, 28.0. HRMS m/z calcd for $C_{21}H_{23}N_3$ [M+] 317.4274, found 317.4276.

View Article Online DOI: 10.1039/D0NJ05778B

4p: 2-(4-chlorophenyl)-3-(cyclohexylamino) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.42 (d, *J* = 5Hz, 1H), 8.40 (d, *J* = 10Hz, 2H), 7.60-7.55 (m, 3H), 7.17 (t, *J* = 15Hz, 1H), 6.95 (t, *J* = 10Hz, 1H), 4.82 (d, *J* = 5Hz, 1H), 2.66-2.62 (m, 1H), 1.59-1.53 (m, 4H), 1.40-1.38 (m, 1H), 1.07-0.97 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.6, 132.6, 131.9, 130.8, 129.0, 127.6, 124.1, 123.4, 121.0, 117.4, 117.0, 113.3, 78.0, 56.1, 33.6, 25.7, 24.6. HRMS m/z calcd for $C_{21}H_{20}ClN_3$ [M+] 349.8566, found 349.8567.

4q: 3-(cyclohexylamino)-2-(4-fluorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.41 (d, *J* = 5Hz, 1H), 7.82-7.80 (m, 2H), 7.58 (d, *J* = 5Hz, 1H), 7.33 (t, *J* = 15Hz, 2H), 7.14 (t, *J* = 15Hz, 1H), 6.93 (t, *J* = 15Hz, 1H), 4.79 (d, *J* = 5Hz, 1H), 2.64-2.61 (m, 1H), 1.56-1.49 (m, 4H), 1.38-1.34 (m, 1H), 1.08-0.93 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 162.9, 161.0, 134.4, 131.1, 131.0, 129.3, 127.4, 124.0, 123.2, 121.5, 117.5, 117.0, 116.0, 115.8, 113.1, 78.2, 56.0, 33.6, 25.7, 24.6. HRMS m/z calcd for $C_{21}H_{20}FN_3$ [M+] 333.4020, found 333.4028.

4r: 3-(cyclohexylamino)-2-(4-methoxyphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.40 (d, *J* = 5Hz, 1H), 7.72 (d, *J* = 5Hz, 2H), 7.56 (d, *J* = 10Hz, 1H), 7.14-7.10 (m, 1H), 7.06 (d, *J* = 10Hz, 2H), 6.93-6.90 (m, 1H), 4.71 (d, *J* = 5Hz, 1H), 3.81 (s, 3H), 2.66-2.63 (m, 1H), 1.57-1.50 (m, 4H), 1.40-1.36 (m, 1H), 1.09-0.92 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 159.0, 134.3, 130.2, 126.9, 125.1, 123.9, 122.9, 122.4, 117.7, 116.8, 114.4, 113.0, 78.1, 55.9, 55.5, 33.6, 25.7, 24.6. HRMS m/z calcd for $C_{22}H_{23}N_3O$ [M+] 345.4375, found 345.4371.

4s: 3-(cyclohexylamino)-2-(4-ethoxyphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.39 (d, *J* = 5Hz, 1H), 7.70 (d, *J* = 10Hz, 2H), 7.56 (d, *J* = 5Hz, 1H), 7.12 (t, *J* = 15Hz, 1H), 7.03 (d, *J* = 10Hz, 2H), 6.91 (t, *J* = 15Hz, 1H), 4.70 (d, *J* = 5Hz, 1H), 4.09-4.05 (m, 1H), 2.66-2.62 (m, 1H), 1.57-1.50 (m, 4H), 1.36-1.34 (m, 4H), 1.08-0.92 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 158.3, 134.3, 130.2, 126.9, 125.0, 123.9, 122.8, 122.4, 117.8, 116.8, 114.8, 112.9, 78.1, 63.4, 55.9, 33.6, 25.7, 24.6, 14.1. HRMS m/z calcd for $C_{23}H_{25}N_3O$ [M+] 359.4641, found 359.4639.

4t: 3-(cyclohexylamino)-2-(4-ethylphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.41 (d, *J* = 5Hz, 1H), 7.69 (d, *J* = 5Hz, 2H), 7.57 (d, *J* = 5Hz, 1H), 7.32 (d, *J* = 5Hz, 2H), 7.14-7.11 (m, 1H), 6.92 (t, *J* = 15Hz, 1H), 4.74 (d, *J* = 5Hz, 1H), 2.68-2.63 (m, 2H), 1.57-1.49 (m, 4H), 1.39-1.37 (m, 1H), 1.22 (t, *J* = 15Hz, 3H), 1.09-0.91 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 143.3, 134.4, 130.3, 128.7, 128.3, 127.2, 123.9, 122.9, 122.4, 117.7, 116.9, 113.0, 78.2, 56.0, 33.6, 28.4, 25.7, 24.6, 15.8. HRMS m/z calcd for $C_{23}H_{25}N_3$ [M+] 343.4647, found 343.4653.

4u: 3-(cyclohexylamino)-2-(2-fluorophenyl) indolizine-1-carbonitrile

Yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.37 (d, *J* = 5Hz, 1H), 7.64-7.58 (m, 2H), 7.50-7.46 (m, 1H), 7.38-7.31 (m, 2H), 7.13 (t, *J* = 15Hz, 1H), 6.93 (t, *J* = 15Hz, 1H), 4.54 (d, *J* = 5Hz, 1H), 2.64-2.61 (m, 1H), 1.57-1.46 (m, 4H), 1.36-1.32 (m, 1H), 1.01-0.88 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 160.9, 158.9, 134.0, 132.6, 130.6, 130.5, 128.1, 124.9, 123.9, 123.0, 120.6, 120.5, 117.0, 116.9, 116.2, 116.0, 115.9, 113.0, 79.7, 55.5, 33.4, 25.6, 24.5. HRMS m/z calcd for $C_{21}H_{20}FN_3$ [M+] 333.4020, found 333.4023.

4v: 2-(2-bromophenyl)-3-(cyclohexylamino) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.36 (d, *J* = 10Hz, 1H), 7.78 (d, *J* = 10Hz, 1H), 7.58 (d, *J* = 10Hz, 1H), 7.52-7.48 (m, 2H), 7.40-7.36 (m, 1H), 7.13 (t, *J* = 15Hz, 1H), 6.93 (t, *J* = 15Hz, 1H), 4.52 (d, *J* = 5Hz, 1H), 2.61-2.57 (m, 1H), 1.60-1.46 (m, 4H), 1.39-1.36 (m, 1H), 1.05-0.83 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.1, 133.5, 133.2, 132.9, 130.5, 128.0, 124.7, 123.9, 122.7, 120.3, 117.1, 113.0, 80.2, 55.3, 33.5, 33.4, 25.7, 24.6. HRMS m/z calcd for $C_{21}H_{20}BrN_3$ [M+] 394.3076, found 394.3079.

4w: 2-(2-chlorophenyl)-3-(cyclohexylamino) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.35 (d, *J* = 5Hz, 1H), 7.63-7.45 (m, 5H), 7.13 (t *J* = 15Hz, 1H), 6.93 (t, *J* = 15Hz, 1H), 4.52 (d, *J* = 5Hz, 1H), 2.61-2.57 (m, 1H), 1.56-1.35 (m, 5H), 1.08-0.83 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 133.9, 133.6, 133.1, 132.0, 130.3, 129.8, 128.1, 127.5, 123.9, 122.8, 118.7, 117.1, 116.9, 113.0, 80.1, 55.2, 33.4, 25.7, 24.5. HRMS m/z calcd for $C_{21}H_{20}ClN_3$ [M+] 349.8566, found 349.8571.

4x: 3-(cyclohexylamino)-2-(3-fluorophenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.42 (d, *J* = 5Hz, 1H), 7.64-7.51 (m, 4H), 7.22-7.14 (m, 2H), 6.94 (t, *J* = 15Hz, 1H), 4.74 (d, *J* = 5Hz, 1H), 2.72-2.68 (m, 1H), 1.60-1.53 (m, 4H), 1.43-1.39 (m, 1H), 1.13-0.97 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 163.6, 161.7, 135.5, 135.4, 134.6, 130.8, 130.8, 127.8, 125.2, 125.2, 124.0, 123.3, 121.0, 117.2, 117.0, 115.7, 115.5, 114.6, 114.4, 113.2, 78.3, 56.2, 33.6, 25.7, 24.6. HRMS m/z calcd for $C_{21}H_{20}FN_3$ [M+] 333.4020, found 333.4021.

4y: 2-(3-chlorophenyl)-3-(cyclohexylamino) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.43 (d, *J* = 5Hz, 1H), 7.88 (d, *J* = 5Hz, 1H), 7.74 (d, J = 5Hz, 1H), 7.59 (d, *J* = 5Hz, 1H), 7.52 (t, *J* = 15Hz, 1H), 7.43 (d, *J* = 10Hz, 1H), 7.17 (t, *J* = 15Hz, 1H), 6.95 (t, *J* = 15Hz, 1H), 4.89 (d, *J* = 5Hz, 1H), 2.65-2.62 (m, 1H), 1.58-1.51 (m, 4H), 1.41-1.37 (m, 1H), 1.11-0.93 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 135.1, 134.6, 133.7, 130.8, 128.5, 127.8, 127.6, 124.1, 123.5, 120.5, 117.3, 117.1, 113.3, 78.0, 55.2, 33.7, 25.7, 24.6. HRMS m/z calcd for $C_{21}H_{20}ClN_3$ [M+] 349.8566, found 349.8569.

4z: 3-(cyclohexylamino)-2-p-tolylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.41 (d, *J* = 5Hz, 1H), 7.67 (d, *J* = 10Hz, 2H), 7.57 (d, *J* = 5Hz, 1H), 7.29 (d, *J* = 10Hz, 2H), 7.13 (t, *J* = 15Hz, 1H), 6.92 (t, *J* = 15Hz, 1H), 4.73 (d, *J* = 5Hz, 1H), 2.67-2.63 (m, 1H), 2.35 (s, 3H), 1.56-1.50 (m, 4H), 1.39-1.36 (m, 1H), 1.09-0.93 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 137.1, 134.4, 130.0, 129.6, 128.9, 127.2, 123.9, 123.0, 122.4, 117.7, 116.9, 113.0, 78.2, 56.0, 33.6, 25.7, 24.6, 21.3. HRMS m/z calcd for $C_{22}H_{23}N_3$ [M+] 329.4381, found 329.4387.

DOI: 10.1039/C9NJ05738B

4aa: 3-(cyclohexylamino)-2-(4-isopropylphenyl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.40 (d, *J* = 10Hz, 1H), 7.71 (d, *J* = 5Hz, 2H), 7.56 (d, *J* = 10Hz, 1H), 7.34 (d, *J* = 10Hz, 2H), 7.12 (t, *J* = 15Hz, 1H), 6.90 (t, *J* = 15Hz, 1H), 4.74 (d, *J* = 5Hz, 1H), 2.95-2.89 (m, 1H), 2.67-2.63 (m, 1H), 1.57-1.49 (m, 4H), 1.39-1.35 (m, 1H), 1.23 (d, *J* = 10Hz, 6H), 1.10-0.90 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 147.9, 134.4, 130.4, 128.9, 127.2, 126.8, 123.9, 122.9, 122.3, 117.7, 116.9, 113.0, 78.2, 56.0, 33.7, 33.6, 25.7, 24.6, 24.2. HRMS m/z calcd for $C_{24}H_{27}N_3$ [M+] 357.4913, found 357.4910.

4ab: 3-(cyclohexylamino)-2-(pyridin-2-yl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.69 (d, *J* = 5Hz, 1H), 8.24 (d, *J* = 10Hz, 1H), 8.03-7.93 (m, 2H), 7.60 (d, *J* = 10Hz, 1H), 7.34 (t, *J* = 10Hz, 1H), 7.15 (t, *J* = 15Hz, 1H), 6.94 (t, *J* = 15Hz, 1H), 6.18 (d, *J* = 10Hz, 1H), 2.96-2.91 (m, 1H), 1.68-1.41 (m, 5H), 1.15-0.99 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 152.5, 149.5, 137.7, 134.9, 131.3, 124.1, 123.2, 122.4, 121.9, 117.7, 117.5, 116.3, 113.6, 76.8, 55.2, 33.7, 25.6, 24.7. HRMS m/z calcd for $C_{20}H_{20}N_4$ [M+] 316.3996, found 316.3998.

4ac: 3-(cyclohexylamino)-2-(pyridin-3-yl) indolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δH (ppm) 8.97 (s, 1H), 8.60 (dd, *J* = 5, 5Hz, 1H), 8.42 (d, *J* = 10Hz, 1H), 8.15 (t, *J* = 10Hz, 1H), 7.60 (d, *J* = 10Hz, 1H), 7.54-7.51 (m, 1H), 7.19-7.16 (m, 1H), 6.97-6.94 (m, 1H), 4.81 (d, *J* = 5Hz, 1H), 2.71-2.67 (m, 1H), 1.59-1.52 (m, 4H), 1.42-1.38 (m, 1H), 1.11-0.95 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 149.6, 148.7, 136.3, 134.8, 129.1, 127.9, 124.1, 123.9, 123.4, 119.3, 117.1, 113.3, 78.3, 56.1, 33.6, 25.7, 24.6. HRMS m/z calcd for $C_{20}H_{20}N_4$ [M+] 316.3996, found 316.3998.

4ad: 3-(cyclohexylamino)-2-isopropylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.18 (d, *J* = 5Hz, 1H), 7.47 (d, *J* = 10Hz, 1H), 7.05 (t, *J* = 15Hz, 1H), 6.84 (t, *J* = 15Hz, 1H), 4.58 (s, 1H), 3.28-3.23 (m, 1H), 2.71-2.68 (m, 1H), 1.77-1.65 (m, 4H), 1.54-1.51 (m, 1H), 1.34 (d, *J* = 5Hz, 6H), 1.25-1.05 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.7, 129.5, 126.2, 123.9, 122.2, 117.9, 116.5, 112.4, 76.0, 56.5, 33.9, 25.9, 25.0, 23.2. HRMS m/z calcd for $C_{18}H_{23}N_3$ [M+] 281.3953, found 281.3955.

4ae: 3-(cyclohexylamino)-2-phenethylindolizine-1-carbonitrile

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.20 (d, *J* = 5Hz, 1H), 7.51 (d, *J* = 10Hz, 1H), 7.30-7.17 (m, 5H), 7.06 (t, *J* = 15Hz, 1H), 6.84 (t, *J* = 15Hz, 1H), 4.43 (d, *J* = 5Hz, 1H), 2.97 (s, 4H), 2.64-2.61 (m, 1H), 1.72-1.62 (m, 4H), 1.51-1.47 (m, 1H), 1.22-1.07 (m, 5H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 141.8, 134.0, 128.8, 128.7, 127.8, 126.4, 123.8, 122.6, 122.3, 117.5, 116.7, 112.5, 78.6, 56.6, 36.3, 27.4, 25.8, 25.0. HRMS m/z calcd for $C_{23}H_{25}N_3$ [M+] 343.4647, found 343.4642.

6: 2, 2'-(1, 3-phenylene)bis(3-(tert-butylamino)indolizine-1-carbonitrile)

Pale yellow solid; ^{1}H NMR (500 MHz, DMSO) δ_H (ppm) 8.56 (d, *J* = 10Hz, 2H), 7.97 (s, 1H), 7.74 (d, *J* = 10Hz, 2H), 7.61-7.58 (m, 3H), 7.19 (t, *J* = 15Hz, 2H), 6.94 (t, *J* = 15Hz, 2H), 4.45 (s, 2H), 0.90 (s, 18H); ^{13}C NMR (500 MHz, DMSO) δ_C (ppm) 134.8, 134.1, 130.6, 129.1, 128.8, 126.3, 126.1, 124.9, 123.5, 117.3, 116.8, 112.8, 79.2, 55.9, 30.3. HRMS m/z calcd for $C_{32}H_{32}N_6$ [M+] 500.6367, found 500.6370.

References

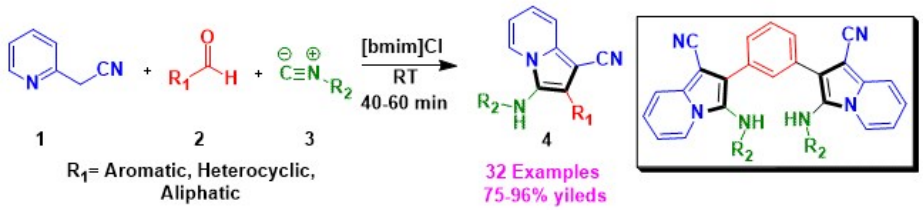
1. J. P. Michael, *Nat. Prod. Rep.* 2008, **25**, 139.
2. C. Bailly, *Curr. Med. Chem.: Anti-Cancer Agents* 2004, **4**, 363.
3. A. K. Das, S. Som, *Orient. J. Chem*. 2006, **2**, 415.
4. S. Lingala, R. Nerella, R. Cherukupally, A. K. Das*, Int. J. Pharm. Sci. Rev. Res.* 2011, **6**, 128.
5. P. Sharma, A. Kumar, S. Sharma, N. Rane, *Bioorg. Med. Chem. Lett.* 2005, **15**, 937.
6. S. Teklu, L. L. Gundersen, F. Riseand, M. Tilset, *Tetrahedron*, 2005, **61**, 4643.
7. A. Hazra, S. Mondal, A. Maity, S. Naskar, P. Saha, R. Paira, K. B. Sahu, P. Paira, S. Ghosh, C. Sinha, A. Samanta, S. Banerjee, N. B. Mondal, *Eur. J. Med. Chem.* 2011, **46**, 2132.
8. T. Weide, L. Arve, H. Prinz, H. Waldmann, H. Kessler, *Bioorganic & Medicinal Chemistry Letters*, 2006, **16**, 59.
9. J. Wan, C. J. Zheng, M. K. Fung, X.K. Liu, C. S. Lee, X. H. Zhang, *J. Mater. Chem.* 2012, **22**, 4502.
10. (*a*) S. C. Smith, E. D. Clarke, S. M. Ridley, D. Bartlett, D. T. Greenhow, H. Glithro, A. Y. Klong, G. Mitchell, G. W. Mullier, *Pest Manage. Sci.* 2005, **61**, 16–24; (*b*) G. Mitchell, S. C. Smith, E. D. Clarke, U. K. Zeneca, US Patent 92191410, 1994.
11. M. Birch, G. E. M. Sibley, D. Law, J. D. Oliver, World Patent, WO2009144473A1, 2009.
12. (*a*) K. H. Oh, S. M. Kim, S. Y. Park, J. K. Park, Org. Lett. 2016, **18**, 2204; (*b*) X. Meng, P. Liao, J. Liu, X. Bi, Chem. Commun. 2014, **50**, 11837; (*c*) L. Zhang, X. Li, Y. Liu, D. Zhang, Chem. Commun. 2015, **51**, 6633.
13. (*a*) D. Chandra Mohan, C. Ravi, V. Pappula, S. Adimurthy, J. Org. Chem. 2015, **80**, 6846; (*b*) M. Kucukdisli, T. Opatz, Eur. J. Org. Chem. 2014, 20, 5836; (*c*) J. Barluenga, G. Lonzi, L. Riesgo, L. A. Lopez, M. Tomas, J. Am. Chem. Soc. 2010, **132**, 13200.
14. (*a*) F. Li, J. Chen, Y. Hou, Y. Li, X. Y. Wu, X. Tong, Org. Lett. 2015, **17**, 5376; (*b*) J. Brioche, C. Meyer, J. Cossy, Org. Lett. 2015, **17**, 2800; (*c*) F. Wang, Y. Shen, H. Hu, X. Wang, H. Wu, Y. Liu, J. Org. Chem. 2014, **79**, 9556; (*d*) A. R. Katritzky, G. Qiu, B. Yang, H.Y. He, J. Org. Chem. 1999, **64**, 7618.
15. (*a*) B. Sahoo, M. N. Hopkinson, F. Glorius, Angew. Chem., Int. Ed. 2015, **54**, 15545; (*b*) R. R. Liu, J. J. Hong, C. J. Lu, M. Xu, J. R. Gao, Y. X. Jia, Org. Lett. 2015, **17**, 3050; (*c*) L. Xiang, Y. Yang, X. Zhou, X. Liu, X. Li, X. Kang, R. Yan, G. Huang, J. Org. Chem. 2014, **79**, 10641.
16. (*a*) B. Yan, Y. Liu, Org. Lett. 2007, **9**, 4323; (*b*) Y. Bai, J. Zeng, J. Ma, B. K. Gorityala, X. W. Liu, J. Comb. Chem. 2010, **12**, 696; (*c*) F. Wang, Y. Shen, H. Hu, X. Wang, H. Wu, Y. Liu, J. Org. Chem. 2014, **79**, 9556; (*d*) J. Sun, F. Wang, H. Hu, X. Wang, H. Wu, Y. Liu, J. Org. Chem. 2014, **79**, 3992; (e) S. U. Dighe, S. Hutait, S. Batra, ACS Comb. Sci. 2012, **14**, 665.
17. (*a*) L. F. Tietze, Chem. Rev. 1996, 96, 115; (*b*) L. F. Tietze, Wiley, Weinheim. 2014 DOI:10.1002/9783527671304
18. (*a*) C. C. Razvan, E. Ruijter, R. V. A. Orru, Green Chem., 2014,16, 2958; (*b*) G. Yanlong, Green Chem., 2012,**14**, 2091; (c) W. zhang, Green Chem., 2009,**11**, 911, (d) S. Shaabani, R. Xu, M. Ahmadianmoghaddam, L. Gao, M. Stahorsky,

View Article Online
DOI: 10.1039/C9NJ05738B

J. Olechno, R. Ellson, M. Kossenjans, V. Helan, A. Dömling, Green Chem., 2019, **21**, 225.
19. S. Sadjadi, M. M.Heravi, N. Nazari, RSC Adv., 2016, **6**, 53203.
20. (a) H. G. O. Alvim, J. R. Correa, J. A. F. Assumpção, W. A. da Silva, M. O. Rodrigues, J. L. de Macedo, M. Fioramonte, F. C. Gozzo, C. C. Gatto, B. A. D. Neto, J. Org. Chem. 2018, **83**, 4044; (b) X. D. Corte, E. M. d. Marigorta, F. Palacios, J. Vicario, Molecules, 2019, **24**, 2951; (c) D. Zhu, Y. Yao, R. Zhao, Y. Liu, L. Shi, Chem.-Eur. J. 2018, **24**, 4805; (d) L. Zeng, B. Huang, Y. Shen, S. Cui, Org. Lett. 2018, **20**, 3460; (e) B. Zhao, C. Chen, J. Lv, Z. Li, Y. Yuan, Z. Shi, Org. Chem. Front. 2018, **5**, 2108.
21. (*a*) J. Cornely, L. M. S. Ham, D. E. Meade, V. Dragojlovic, Green Chem., 2003,**5**, 34; (*b*) K. Skowerski, J. Białecki, A. Tracz, T. K. Olszewski, Green Chem., 2014,**16**, 1125; (*c*) M. Nasrollahzadeh, N. Motahharifar, M. Sajjadi, A. M. Aghbolagh, M. Shokouhimehr, R. S. Varma, Green Chem., 2019, DOI: 10.1039/C9GC01822K (*d*) I. T. Horváth, Green Chem., 2008, **10**, 1024.
22. (*a*) T. Welton, Chem. Rev. 1999, **99**, 2071; (*b*) L. Chen, B.Huang, Q. Nie, M. Cai, Appl. Organometal. Chem. 2016, **30**, 446; (c) N. V. Plechkova, K. R. Seddon, Chem. Soc. Rev., 2008, **37**, 123.
23. R. Sheldon, Chem. Commun., 2001, **23**, 2399.
24. A. B. Atar, synlett, 2019, **30**, 1462.
25. A. B. Atar, J. S. Kim, K. T. Lim, Y. T. Jeong, New Journal of Chemistry 2015, **39**, 396.
26. A. B. Atar, Y. S. Jeong, Y. T. Jeong, Tetrahedron 2014, **70**, 5207.
27. A. B. Atar, Y. T. Jeong, Molecular diversity 2014, **18**, 389.
28. A. B. Atar, Y. T. Jeong, Tetrahedron Letters 2013, **54**, 5624.
29. A. B. Atar, Y. T. Jeong, Tetrahedron Letters 2013, **54**, 1302.
30. K. Bedjeguelal, H. Bienayme, S. Poigny, Ph. Schmitt, E. Tam, QSAR Comb. Sci., 2006, **25**, 504.
31. K. Bedjeguelal, H. Bienayme, A. Dumoulin, S. Poigny, P. Schmitt, E. Tam, Bioorganic & Medicinal Chemistry Letters 2006, **16**, 3998.
32. L. M.Ramos, M. O.Rodrigues, B. A. D. Neto, Org. Biomol. Chem. 2019, **17**, 7260.
33. (a) X. Sun, Z. Liu, Z. Xue, Y. Zhang, T. Mu, Green Chem. 2015, **17** ,2719; (b) J. Zhang, X. Yu, F. Zou, Y. Zhong, N. Du, X. Huang, ACS Sustainable Chem. Eng. 2015, **3**, 3338; (c) C. Zhu, H. Wang, C. Cai, K. Bi, B. Cai, X. Song, Q. Liu, L. Ma, ACS Sustainable Chem. Eng. 2019, **7**, 16026. (d) V. Bhaskar, R. Chowdary, S. R. Dixit, S. D. Joshi, Bioorganic Chemistry, 2019, **84**, 202 (e) I.R. Siddiqui, A. Srivastava, A. Srivastava, S. Shamim, Shireen, M. A. Waseem, Arabian Journal of Chemistry, 2018, **11**, 256

View Article Online
DOI: 10.1039/C9NJ05738B

Room temperature based ionic liquid [bmim]Cl catalyzed multicomponent coupling strategy for the synthesis of 3-alkylamino-2-alkyl/aryl/hetero-aryl indolizine-1-carbonitrile derivatives under milder condition.



- isocyanides-based [4 + 1]-cycloaddition
- base, metal-free
- broad substrate scope & high yields
- simple & mild conditions
- No column chromatography
- No Waste, H_20 is side product

247x106mm (72 x 72 DPI)