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Formal [3+2] cycloaddition of 1-cyanocyclopropane 1-ester with pyridine, quinoline or isoquinoline: a general and efficient strategy for construction of cyanoindolizine skeletons†

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An efficient and straightforward synthetic protocol has been developed for the preparation of cyanoindolizine derivatives *via* a cycloaddition reaction between 1-cyanocyclopropane 1-ester and pyridine or benzopyridine for the generation of a wide range of structurally interesting and pharmacologically significant compounds.

Indolizines are important classes of organic compounds that are not only widely used as synthetic building blocks and various kinds of functional materials,[1] but they also occur in numerous natural products and pharmaceuticals as privileged scaffolds.[2] Among them, the cyanoindolizines have attracted more attention recently. Cyanoindolizine derivatives were investigated extensively as highly potent non-nucleoside inhibitors of HIV-1 reverse transcriptase,[3] a xanthine oxidase with inhibitory activities for the prevention or treatment of a disease associated with the abnormal serum uric acid level,[4] anticancer agents,[2,5] potent inhibitors of *Acinetobacter baumannii* OXA-24 carbapenemase,[6] anti-inflammatory, and antimalarial agents.[7]

The synthesis of indolizine derivatives has made much progress,[8] most traditionally synthetic strategies require starting from pyridinium *N*-methylides[8b,9] or pyridines with specific C2 functionalization.[10] In contrast, only some annulation reactions of the pyridine ring that involve [3+2] cycloaddition have recently been reported.[11,12] In recent years, some previous studies revealed that donor–acceptor cyclopropanes are versatile building blocks in Lewis acid-promoted formal cycloadditions for the construction of various cyclic skeletons.[13] The formal [3+2] cycloaddition reaction of donor–acceptor (D–A) cyclopropanes has emerged as a powerful method for the simple access to useful molecules for materials or biological applications. The ring-opening of the strained substituted cyclopropanes can give easily a 1,3-dipolar intermediate upon thermolysis or under catalysis by Lewis acids[14] which affords formal [2+3]-cycloaddition with alkenes,[15] aldehydes,[16] ketones,[17] isocyanates,[18] imines,[19] diazenes,[20] pyrazolines,[21] azomethine imine ylides,[22] nitrones,[23] acetylenes,[24] nitriles[25] to structure various five-membered carbo- and heterocycles. To the best of our knowledge, no example using 1-cyanocyclopropane 1-ester and pyridine as starting materials to construct the cyanoindolizine core was reported. These products were described as potent central nervous system (CNS) depressant agents, anticancer, anti-inflammatory, and antimalarial agents as shown in Fig. 1.[2,5,7] Herein we report a facile and straightforward method to synthesize substituted cyanoindolizines from 1-cyanocyclopropane 1-esters and pyridines *via* an iodine-catalyzed formal [3+2] cycloaddition reaction.

The starting materials, 2-aroyl-3-aryl-1-cyanocyclopropane carboxylates, were prepared in good yields under mild conditions according to the reported procedure.[26] In order to explore the synthesis of title cyanoindolizines *via* the [3+2] cycloaddition reactions of substituted cyclopropane with pyridines, the reaction between ethyl 2-(*p*-bromophenyl)-3-(*p*-chlorobenzoyl)-1-cyano cyclopentanecarboxylate and pyridine was chosen as a model reaction to optimize the reaction conditions. The results are summarized in Table 1.

To start, the reaction was conducted with 1 equiv. of ethyl 3-(*p*-bromophenyl)-2-(*p*-chlorobenzoyl)-1-cyanocyclopropane carbonate and 1 equiv. of pyridine using a catalytic amount of the Lewis acid $AlCl_3$, $ZnCl_2$, BF_3Et_2O, $FeCl_3$ and I_2 in toluene at 120 °C.

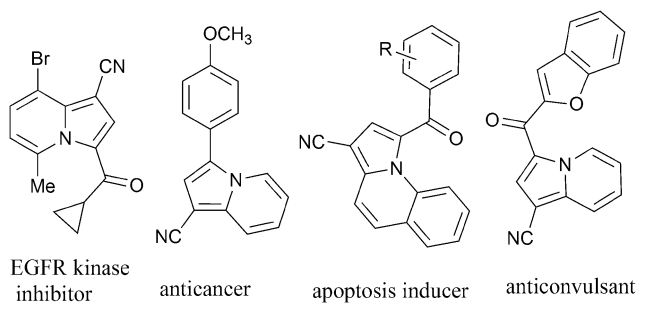

Fig. 1 Examples of bioactive cyanoindolizines.

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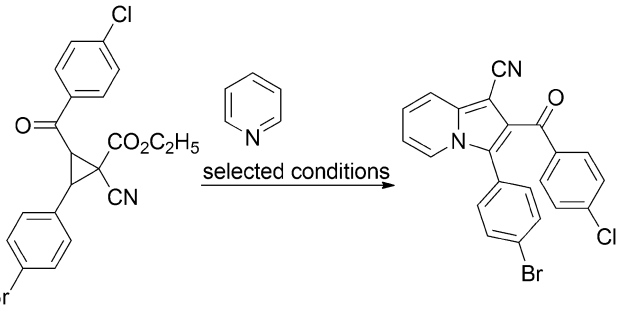
† Electronic supplementary information (ESI) available: Reaction conditions and spectra. CCDC 978204, 978827, 970814, 939543 and 939542. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc03267e

Table 1 Optimization of reaction conditions in the synthesis of **2a**



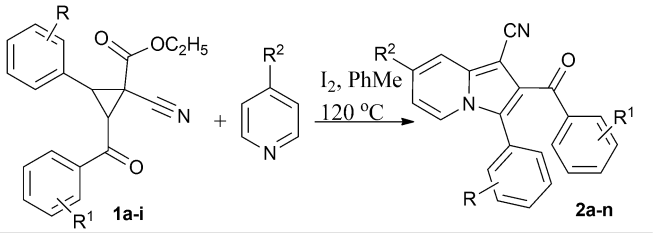
Entry	Catalyst	Solvent	T (°C)	t (h)	Yield[a] (%)
1	10% $AlCl_3$	Toluene	120	20	0
2	10% $ZnCl_2$	Toluene	120	20	0
3	10% BF_3	Toluene	120	20	0
4	10% $FeCl_3$	Toluene	120	20	0
5	10% I_2	Toluene	120	20	53
6	20% I_2	Toluene	120	20	84
7	50% I_2	Toluene	120	20	78
8	100% I_2	Toluene	120	20	73
9	200% I_2	Toluene	120	20	71
10	20% I_2	DMF	120	20	74
11	20% I_2	Toluene	60	20	9
12	20% I_2	Toluene	90	20	62
13	20% I_2	Toluene	130	20	74
14	20% I_2	Toluene	140	20	64
15	20% I_2	Toluene	120	8	26
16	20% I_2	Toluene	120	15	54
17	20% I_2	Toluene	120	24	83

[a] Isolated yield.

As a result, the use of Lewis acid $AlCl_3$, $ZnCl_2$, BF_3Et_2O, or $FeCl_3$ did not lead to [3+2] cycloaddition at all (Table 1, entries 1–4). Pleasingly, while molecular iodine was used as a Lewis acid the 3-(*p*-bromophenyl)-2-(*p*-chlorobenzoyl)-1-cyanoindolizine (**2a**) was obtained as the only isolable product in 53% yield (entry 5). When the amount of iodine was increased further to 20 mol%, the reaction was complete after 20 h and the isolated yield was the best, 84% (entry 6). The yield was reduced slightly when the amount of iodine was increased from 50 mol% to 200% (entries 7–9). Switching the solvent to DMF decreased the yield to 74% (entry 10). When conducted at 60 °C, the reaction nearly did not take place (entry 11). While the reaction was carried out at 90 °C, the reaction was incomplete after 20 h and the isolated yield was only 62% (entry 12). Lower yield was obtained when the reaction was conducted at 130–140 °C (entries 13 and 14). Additionally, the lower yields of **2a** were also observed when this reaction was carried out at 8–15 h (entries 15 and 16), or 24 h (entry 17). A series of experiments revealed that the optimal results were obtained when the reaction of 1-cyanoindolizine **2a** and pyridine together with 20 mol% iodine was carried out in toluene, the resultant mixture was stirred for 20 h at 120 °C, whereby the yield of **2a** reached 84% (Table 1, entry 6).

Having established the optimal conditions for the synthesis of 1-cyanoindolizine **2a**, to determine the scope of the protocol, a number of available 1-cyano-cyclopropanecarboxylates were condensed with pyridine or 4-(dimethylamino)pyridine under optimized reaction conditions. The results are summarized in Table 2. Both electron-deficient and electron-rich aromatic groups were similarly viable affording the products in moderate

Table 2 Synthesis of cyanoindolizine derivatives from pyridine and 1-cyanocyclopropane 1-ester



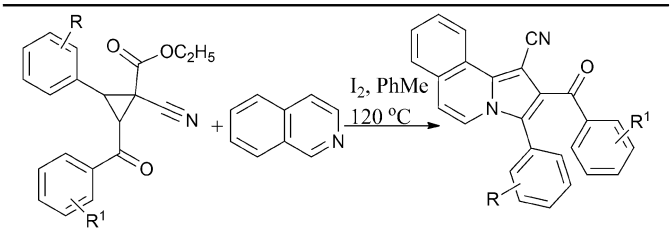
Entry	R	R^1	R^2	Yield[a] (%)
1	*p*-Br	*p*-Cl	H	84 (**2a**)
2	*o*-Cl	*p*-Cl	H	79 (**2b**)
3	*p*-CH_3	*p*-Cl	H	81 (**2c**)
4	*m*-Br	H	H	63 (**2d**)
5	*m*-Br	*p*-Cl	H	76 (**2e**)
6	*p*-OCH_3	*p*-Cl	H	80 (**2f**)
7	*o*-Cl	H	H	75 (**2g**)
8	*p*-Br	*p*-Cl	NMe_2	85 (**2h**)
9	*p*-CH_3	p-Cl	NMe_2	76 (**2i**)
10	*o*-OCH_3	p-Cl	NMe_2	71 (**2j**)
11	*p*-Br	H	NMe_2	84 (**2k**)
12	*p*-Cl	H	NMe_2	82 (**2l**)
13	*m*-Br	H	NMe_2	75 (**2m**)
14	*o*-Cl	H	NMe_2	76 (**2n**)

[a] Isolated yield.

to good yields. Pleasingly, simple benzo-fused pyridines (quinoline and isoquinoline) were found to work well, leading to more complex cycloadducts in variable yields. Thus, quinoline and isoquinoline afforded substituted pyrrolo[1,2-*a*]quinoline and pyrrolo[2,1-*a*]isoquinoline in yields of *ca.* 80%, respectively, upon reaction with 1-cyanocyclopropane 1-ester (Tables 3 and 4).

Generally, 1-cyanocyclopropane 1-ester with a range of substituents such as methyl, methoxy, chloro, and bromo at *ortho*-, *meta*- or *para*-positions of phenyl groups all worked well to give 1-cyanoindolizine derivatives. Substrates with *para*-position phenyl groups gave the products in higher yields than those with *ortho*-, or *meta*-position phenyl groups. Besides pyridine and 4-(dimethylamino)pyridine, substrate quinoline and isoquinoline also reacted well with 1-cyanocyclopropane 1-esters to give 1-cyanobenzoindolizine derivatives.

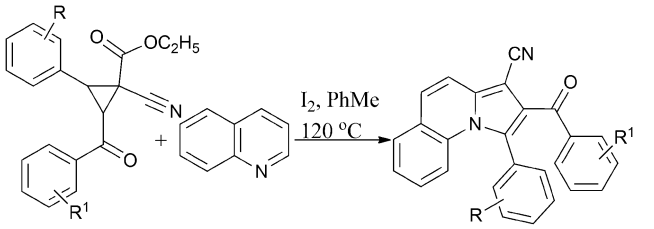
Table 3 Synthesis of 1-cyanobenzoindolizine derivatives from isoquinoline and 1-cyanocyclopropane 1-ester



Entry	R	R^1	Yield[a] (%)
1	*p*-Br	H	77 (**3a**)
2	*m*-Br	H	69 (**3b**)
3	*p*-Br	*p*-Br	79 (**3c**)
4	*o*-OCH_3	H	68 (**3d**)

[a] Isolated yield.

Table 4 Synthesis of 1-cyanobenzoindolizine derivatives from quinoline and 1-cyanocyclopropane 1-ester



Entry	R	R^1	Yield[a] (%)
1	*o*-CH_3	*p*-Cl	65 (**4a**)
2	*m*-Br	H	64 (**4b**)
3	*p*-CH_3	*p*-Cl	72 (**4c**)

[a] Isolated yield.

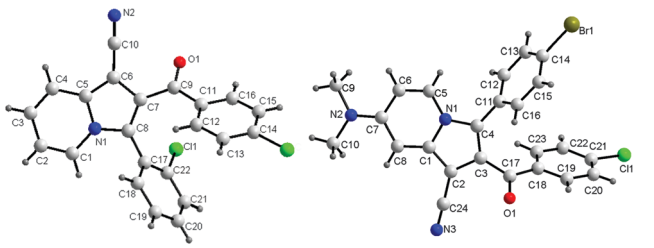


Fig. 2 Molecular structure of 1-cyanoindolizines **2b** and **2h**.

The structures of **2b**, **2h** and **4c** are shown in Fig. 2 and 3.[27] X-ray crystallographic analysis determined that products **2b**, **2h** and **4c** possess a cyano, an aroyl and an aryl contiguous substituent at C(1), C(2), and C(3). On the basis of spectroscopic evidence the structure of compounds **2a–n**, **3a–d** and **4a–c** was identified as 3-aryl-2-aroyl-1-cyanoindolizine or 3-aryl-2-aroyl-1-cyanobenzo indolizine.

To test the generality of this new approach for the construction of the cyanoindolizine, the reactions of pyridine as both a substrate and a solvent with selected 1-cyanocyclopropane 1-ester were examined under identical conditions as above (Scheme 1). Interestingly, 3-cyanoindolizine derivatives **5a–n** can be prepared in good yields, respectively (Table 5, entries 1–14), the result of which suggested that there are different reaction mechanisms for toluene or pyridine as a solvent.

The structures of **5a** and **5b** are shown in Fig. 4.[27] X-ray crystallographic analysis determined that products **5a** and **5b**

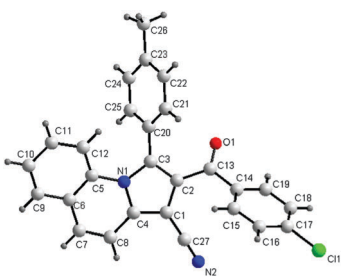
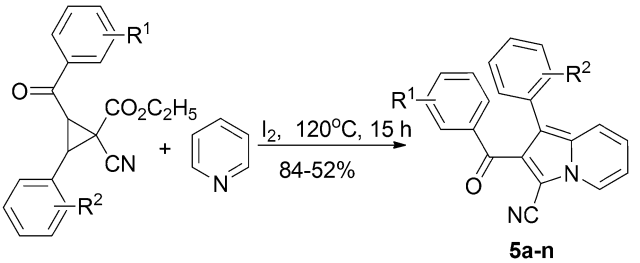


Fig. 3 Molecular structure of 1-cyanoindolizine **4c**.



Scheme 1 Synthesis of 3-cyanoindolizine derivatives from 1-cyanocyclopropane 1-ester and pyridine.

Table 5 Iodine-catalyzed synthesis of 3-cyanoindolizine derivatives

Entry	R^1	R^2	Yield[a] (%)
1	H	*o*-Cl	63 (**5a**)
2	*p*-Br	*p*-Cl	68 (**5b**)
3	H	*o*-Br	52 (**5c**)
4	H	*m*-Br	56 (**5d**)
5	H	*p*-Br	59 (**5e**)
6	H	o-CH_3O	82 (**5f**)
7	*p*-Cl	p-CH_3O	84 (**5g**)
8	H	*m*-Cl	55 (**5h**)
9	H	*p*-Cl	56 (**5i**)
10	H	*p*-NO_2	73 (**5j**)
11	*p*-CH_3	*p*-Br	77 (**5k**)
12	*o*-CH_3	*p*-Br	51 (**5l**)
13	*p*-Br	*p*-Br	53 (**5m**)
14	*p*-Br	*m*-Cl	58 (**5n**)

[a] Isolated yield.

possess an aryl, an aroyl and a cyano contiguous substituent at C(1), C(2), and C(3). On the basis of spectroscopic evidence the structure of compounds **5a–n** was identified as 3-cyano-1-aryl-2-aroylindolizine.

On the basis of the above experimental results together with related reports, the reaction mechanism shown in Scheme 2 was proposed. First, under basic conditions, iodine promoted the form of cyclopropane enolate anion [**A**][28] and its conjugation cyclopropyl anion, which was followed by ring opening reaction on the cyclopropyl anion to generate anion [**B**]. Then, 1,3-dipolar cycloaddition of anion [**B**] as a 1,3-dipole to pyridine gave the enolate anion [**C**]. Further removal of ethyl formate formed dihydroindolizine [**D**].[29] Finally, the dehydroaromatization of dihydroindolizine [**D**] resulted in the formation of the corresponding 1-cyanoindolizidine under air conditions in the presence of iodine. Similarly, 3-cyanoindolizidine was obtained because the benzyl anion [**B′**] was a stable resonance in pyridine[30] (Scheme 2). The α-carbon anion of [**B**] with two strongly electrondrawing groups (cyano and ester groups) is a stable resonance in a weak polar solvent such as toluene. However, the α-carbon anion of [**B**] possesses larger space steric hindrances and is solvated with difficulty by a strong polar solvent (pyridine), and it is uneasy to obtain a stable structure in pyridine. In contrast, [**B′**] with smaller space steric hindrances is solvated easily by pyridine to form a stable resonance structure.

In conclusion, direct annulation of pyridine derivatives with 1-cyanocyclopropane 1-ester to form cyanoindolizine derivatives

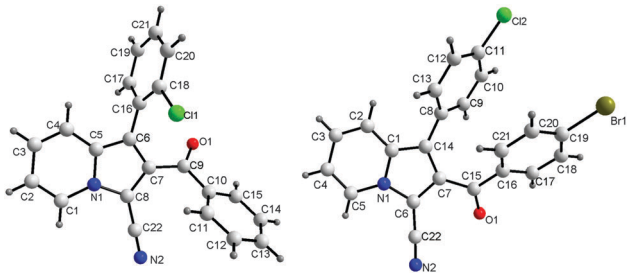
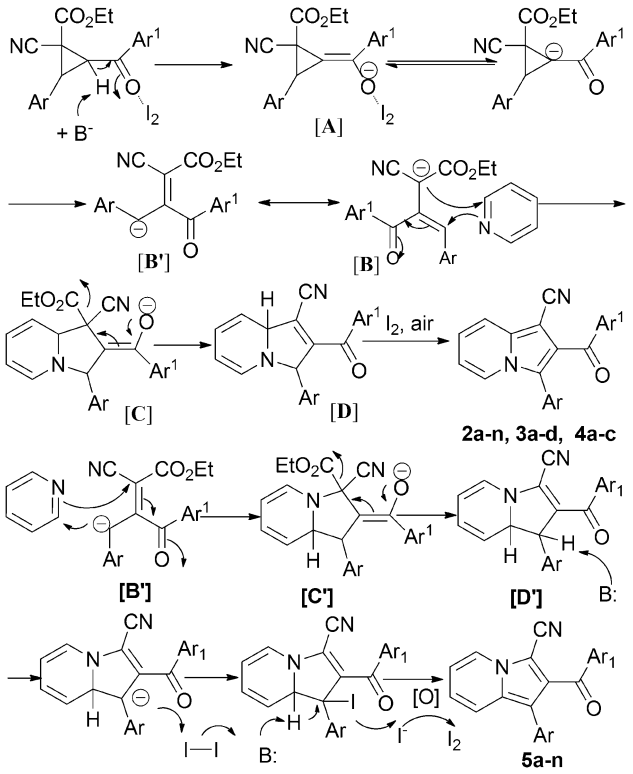


Fig. 4 Molecular structure of 3-cyanoindolizines **5a** and **5b**.



Scheme 2 Possible mechanism in the synthesis of cyanoindolizines.

has been accomplished in a regioselective manner. The reaction proceeds with easy accessibility for 1-cyanocyclopropane 1-ester bearing aryl and aroyl groups, and molecular iodine as a non-expensive catalyst. Due to the described usefulness of cyanoindolizine derivatives, such simple reaction conditions and functional group tolerance offer a new attractive method for access to such structures. It is noteworthy that this is the first successful example of iodine-catalyzed one-pot cyclization of a cyanoindolizidine system with 2-aroyl and aryl groups. Therefore, from these results, it can be envisioned that this method will find many applications in organic chemistry and medicinal chemistry.

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