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New route synthesis of indolizines via 1,3-dipolar cycloaddition of pyridiniums and alkynes

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ABSTRACT

A convenient synthesis of 2,3-di and 1,2,3-trisubstituted indolizines has been achieved via a 1,3-dipolar cycloaddition of pyridiniums and alkynes. Various alkynes and diynes were used instead of dimethyl acetylenedicarboxylate (DMAD) and its analogues in the traditional method. The corresponding 1,2,3-trisubstituted indolizines are useful building blocks for the construction of complex indolizine derivatives.

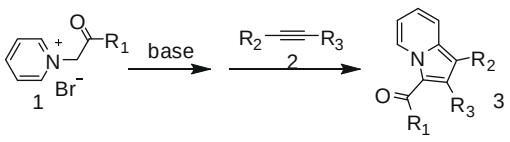
Bridgehead nitrogen heterocycles are important natural products. Among those, indolizines have received much attention in recent years[1] due to their intriguing molecular structures featured with a 10 π-delocalized electrons, and their important biological activities. These molecules have found various pharmaceutical applications as anti-tuberculosis agents,[2] PLA_2 inhibitors,[3] histamine H_3 receptor antagonists,[4] 5-HT_3 receptor antagonists,[5] MPtpA/MPtpB phosphatases inhibitors, associated with many infectious diseases,[6] and as 15-lipoxygenase inhibitors.[7] Thus, there is a growing interest in the synthesis of indolizine derivatives.

Indolizines can be prepared by the 1,3-dipolar cycloaddition reaction between pyridiniums and carboxylic acid[8,1c] in the presence of a mild base, and many five-membered heterocycles[9] can be generated from this method. Recently, many new synthetic approaches have been developed to prepare functionalized indolizines.[10] However, transition-metal catalyst is often required, and in some cases the starting materials were not easy to synthesize. Thus, it is necessary to develop a practical synthetic route for the efficient synthesis of indolizine derivatives. The classic 1,3-dipolar cycloaddition between pyridinium-related heteroaromatic ylides and alkynes is very attractive due to its versatility and efficiency.[11,12] Surprisingly, only DMAD and its analogues have been used in this process.[13] From our continuous research interest in the 1,3-dipolar cycloaddition,[14] we anticipated that various alkynes could be suitable dipolarophiles to extend the classic synthesis of indolizine derivatives.

Herein, we report a new synthesis of a series of indolizine derivatives in high yields via the 1,3-dipolar cycloaddition between pyridinium (**1**) and alkyne (**2**) (Scheme 1), and the representative X-ray structure of one of the indolizine derivatives.

The starting ylide was derived from 1-(2-oxo-2-phenylethyl) pyridinium bromide (**1a**) in the presence of K_2CO_3 in DMF at room temperature. To this mixture was added phenylacetylene (**2a**), the resulting mixture was heated at 120 °C in the sealed flask using the oil bath. After 10 h, the major product **3a** was formed in good yield which was monitored by TLC. After purification via column chromatography, compound **3a** was isolated in 85% yield and was characterized by NMR, IR, and MS.

Optimization of this 1,3-dipolar cycloaddition process between **1a** and **2a** is summarized in Table 1. In DMF, this reaction smoothly generated the desired product **3a** in 85% yield (Table 1, entries 2 and 3) in 2–10 h from 90 °C to reflux. Two equivalents of base was necessary to achieve high yield (Table 1, entries 2 and 6), while



Scheme 1. Preparation of indolizines through the classic 1,3-dipolar cycloaddition reaction.

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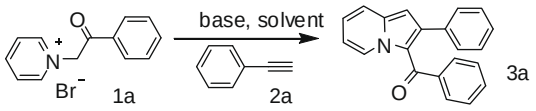
Table 1
Optimization of the reaction condition for the 1,3-dipolar cycloaddition of pyridinium **1a** and alkyne **2a** to generate **3a**



Entry	Base[a]	Solvent	Temp (°C)	Time (h)	Yield[d] (%)
1	K_2CO_3	DMF	120	10	85
2	K_2CO_3	DMF	90	2	85
3	K_2CO_3	DMF	Reflux	2	85
4	K_2CO_3	CH_3CN	Reflux	2	75
5	K_2CO_3	THF	Reflux	2	78
6[b]	K_2CO_3	DMF	90	10	30
7	K_2CO_3	DCM	rt	10	5
8[c]	K_2CO_3	H_2O	90	2	40
9	Et_3N	DMF	90	2	66

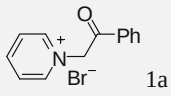
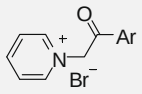
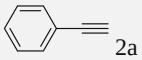
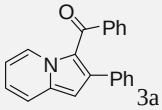
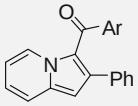
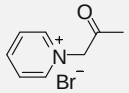
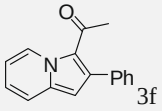
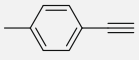
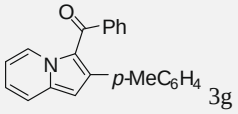
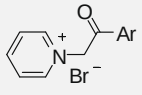
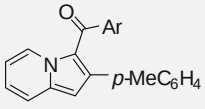
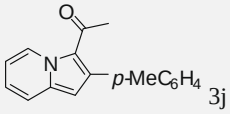
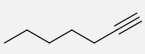
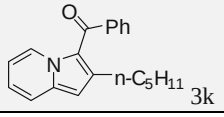
[a] 2 equiv base was used.
[b] 1 equiv base was used.
[c] 1 equiv PTC was used.
[d] Yields refer to pyridinium.

more K_2CO_3 did not increase the reaction yield. Changing solvent to CH_3CN, THF, and H_2O reduced the yields to 75%, 78%, and 40%, respectively. (Table 1, entries 4, 5, and 8). When DCM was used as a solvent, the desired product was obtained in very low yield (Table 1, entry 7). Low yield was obtained when Et_3N was used as a base (Table 1, entry 9). Thus, the optimized reaction condition was in DMF at 90 °C with 2 equiv of K_2CO_3.[15]

We then investigated the scope of this reaction with various pyridiniums **1b**, **1c**, **1d**, **1e,** and **1f**, as shown in Table 2. In most cases, the desired indolizines were smoothly generated in high yields (Table 2, entries 2, 3, and 6). The presence of strong electron-withdrawing group on pyridinium (**1e**) greatly reduced the reaction yield and only trace amount of **3j** was obtained (Table 2, entry 5). Surprisingly, the presence of electron-donating substituent on pyridinium (**1d**) also provided **3d** in relatively low yield (Table 2, entry 4). We attributed this substituent effect to the formation of a potassium salt (phenolate) during the process of ylide formation.

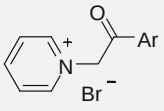
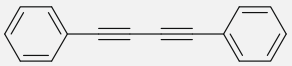
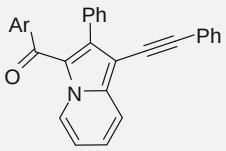
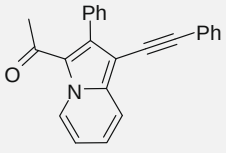
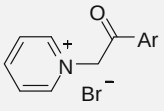
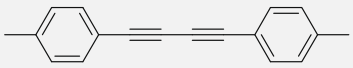
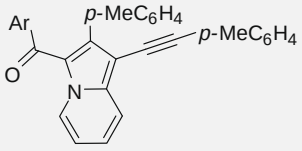
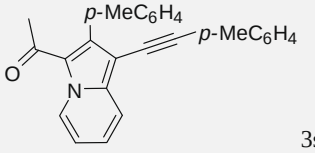
Similar to **2a**, **2b** also gave a good result under this reaction condition and afforded corresponding 2,3-disubstituted indolizines

Table 2
1,3-Dipolar cycloaddition between pyridiniums **1** and alkynes **2** to synthesize 2,3-disubstituted indolizines **3**

Entry	Pyridinium	Alkyne	Product	Yield[a] (%)
1	 	 2a	 	85
2	**1b**	**2a**	Ar = *p*-MeC_6H_4 **3b**	80
3	**1c**	**2a**	Ar = *p*-$MeOC_6H_4$ **3c**	84
4	**1d**	**2a**	Ar = *o*-OHC_6H_4 **3d**	30
5	**1e**	**2a**	Ar = *p*-$NO_2C_6H_4$ **3e**	Trace
6		**2a**		79
7	1a	 2b		81
				
8	**1b**	**2b**	Ar = *p*-MeC_6H_4 **3h**	80
9	**1c**	**2b**	Ar = *p*-$MeOC_6H_4$ **3i**	85
10	**1f**	**2b**		78
11	**1a**	 2c		40

[a] Yields refer to pyridinium.

Table 3
1,3-Dipolar cycloaddition of pyridiniums and diynes to synthesize 1,2,3-trisubstituted indolizines

Entry	Pyridinium	Diyne	Product	Yield[a] (%)
		 2d		
1	**1a**	**2d**	Ar = C_6H_5 **3l**	88
2	**1b**	**2d**	Ar = *p*-MeC_6H_4 **3m**	87
3	**1c**	**2d**	Ar = *p*-$MeOC_6H_4$ **3n**	91
4	**1f**	**2d**	 3o	86
		 2e		
5	**1a**	**2e**	Ar = C_6H_5 **3p**	89
6	**1b**	**2e**	Ar = *p*-MeC_6H_4 **3q**	90
7	**1c**	**2e**	Ar = *p*-$MeOC_6H_4$ **3r**	93
8	**1f**	**2e**	 3s	87

[a] Yields refer to pyridiniums.

3g–**3j** in 78–85% yield (Table 2, entries 7–10). Unfortunately, when **2c** was used, only 40% **3k** was obtained (Table 2, entry 11), associated with the inert nature of 1-heptyne.

Surprisingly, when **2d**, a byproduct of our multicomponent reaction of sulfonyl azide, terminal alkyne, and 2-(benzylideneamino)phenol, was used to react with **1a**, the corresponding 1,2,3-trisubstituted indolizine **3l** was obtained as the major product in high yield (Table 3, entry 1). Each reaction of **1b**, **1c,** and **1f** with **2d** provided the corresponding 1,2,3-trisubstituted indolizines **3m**, **3n**, and **3o** in 87%, 91%, and 86% yields, respectively (Table 3, entries 2–4). The X-ray structure of **3m** is illustrated in Figure 1.[16] This high regioselectivity might be attributed to the relatively strong electronic negativity on the C_2 and C_3 of **2d** and **2e** than those on the C_1 and C_4 of **2d** and **2e**.

As a development of phenylacetylenic coupling,[17] this process can be used for the efficient construction of a series of 1-alkynyl indolizines by reacting pyridiniums with various diynes.

We propose a plausible mechanism for the synthesis of indolizines as shown in Scheme 2. Pyridinium could be deprotoned by K_2CO_3 to give the corresponding ylide, which would act as a dipolar to react with alkyne and generate indolizine via 1,3-dipolar cycloaddition.

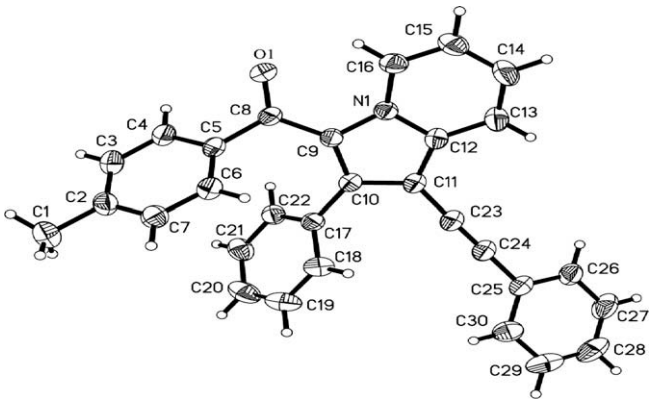
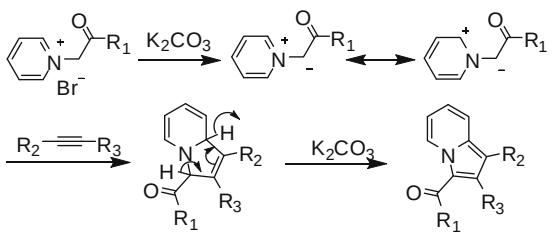


Figure 1. The single-crystal X-ray structure of **3m**.



Scheme 2. Proposed mechanism for the 1,3-dipolar cycloaddition between pyridiniums and alkynes.

In summary, we have synthesized a series of novel indolizine derivatives in good to excellent yields by reacting pyridiniums and alkynes in the presence of a mild base. This synthetic approach was also suitable for the reaction between pyridiniums and diynes, from which a series of novel indolizines were obtained in high yields. Further investigation of this reaction and the electronic properties of the resulting compounds are carried out in our laboratory.

Acknowledgments

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15. *General procedure for the synthesis of indolizines by 1,3-dipolar cycloaddition:* To pyridinium(1 equiv) in DMF was added K_2CO_3 (2 equiv) at room temperature. After 15 min, alkyne (1.2 equiv) was added, and the resulting mixture was heated in oil base at 90 °C for 2 h in a sealed reaction flask. Upon the completion of this reaction, the mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1, v/v) to afford indolizine **3**. Compound **3a**: mp = 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (t, J = 6.6 Hz, 1H, ArH), 7.26–7.34 (m, 2H, ArH), 7.42–7.57 (m, 8H, ArH), 7.84–7.90 (m, 3H, ArH), 10.04 (d, J = 6.9 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.3, 117.6, 122.2, 125.1, 125.4, 126.6, 127.5, 127.9, 128.2, 128.9, 129.0, 130.9, 134.6, 136.4, 140.8, 184.6 ppm. IR (KBr) v: 3055, 3028, 2360, 1600, 1570, 1543, 1469, 1419, 1354, 1230 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1187, found: 298.1220; Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71; O, 5.38. Found: C, 84.66; H, 5.24; N, 4.55; O, 5.24.
16. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 738843]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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