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A Formal [3+2] Cycloaddition Process with Nonactivated Aziridines to Polysubstituted Indolizidines

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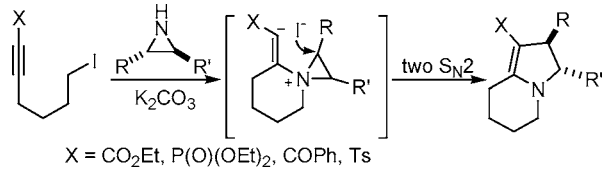
ABSTRACT



Heating a mixture of ethyl 7-iodo-2-heptynoate (or its analogues), 2-aryl aziridines, and K_2CO_3 in dry CH_3CN delivers polysubstituted indolizidines. This reaction goes through an S_N2/formal [3+2] cycloaddition process and represents the first synthetically useful example of the formal [3+2] cycloaddition process through a C–N bond cleavage of nonactivated aziridines.

Aziridines and their reactions are of great importance because of their synthetic and pharmacological values. In recent years enormous efforts have been directed to the development of new transformations based on the ring opening of aziridines.[1−6]

Among emerging reactions, [3+2] cycloaddition represents undoubtedly one of the most important reaction patterns due to its facility to quickly assemble complex pyrrolidine skeletons.[1,3−6] However, most attention has been paid to reactions involving azomethine ylides generated from the C−C bond cleavage of aziridines.[3,4] By way of contrast, C−N bond cleavage derived formal [3+2] cycloaddition reactions are largely unexplored (Scheme 1). This kind of transformation has only been observed in the Lewis acid-promoted ring opening of activated azidizines,[5] and the

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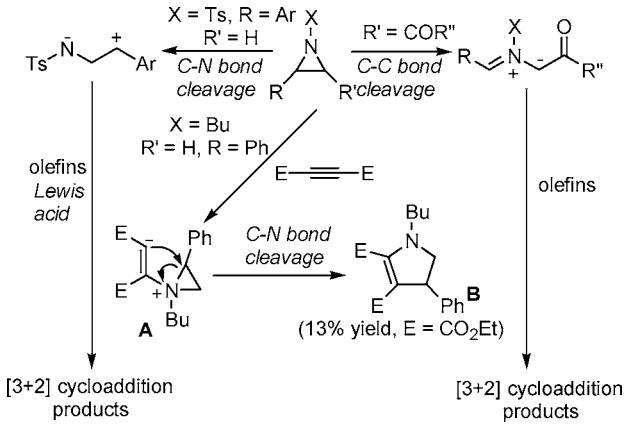
Scheme 1



reaction of 1-butyl-2-phenylaziridine, a nonactivated aziridine, with dimethyl acetylenedicarboxylate.[6] In the latter case, it was proposed by Mattay that initial addition of 1-butyl-2-phenylaziridine to dimethyl acetylenedicarboxylate provided a dipolar intermediate **A**, and subsequent attack of the carbanion in **A** on the aziridine ring afforded a formal [3+2] cycloaddition product **B** via C−N bond cleavage. Several side products were formed in this case, which led to only a 13% yield of **B** being isolated. During our studies on the development of cascade processes using ethyl 7-iodo-2-heptynoate and its analogues,[7] we recently found that the above formal [3+2] cycloaddition worked well in an intramolecular manner, delivering the desired cycloaddition products in good yields. This result represents the first synthetically useful example of the formal [3+2] cycloaddition process through the C−N bond cleavage of nonactivated aziridines. However, the mechanism of this process was found to be slightly different from that of Mattay's process. Herein, we wish to disclose this result.

As shown in Table 1, reaction of ethyl 7-iodo-2-heptynoate **1a**[7] and 2-phenyl aziridine **2a** in dry CH_3CN at 50 °C in the presence of 1.2 equiv of anhydrous K_2CO_3 provided indolizidine **3a** in 92% yield (Table 1, entry 1). We next found that most 2-aryl aziridines worked well in this procedure delivering the corresponding indolizidines in good yields (entries 1−5). However, when 2-(4-nitrophenyl)aziridine **2f**, a substrate possessing a strong electron-withdrawing group at the aromatic ring, was employed, higher reaction temperature was required and only a moderate yield was noted (entries 6 and 7). This result implied that electron density at the aromatic ring played an essential role in this process. Indeed, the trend in reactivity and yields for **2c**−**e** had already hinted at this hypothesis (entries 3−5). 2-Vinyl aziridines were also participants in this process as evidenced by the reaction of 2-styryl aziridine **2g** with **1a**, which gave indolizidine **3g** in 45% yield (entry 8). However, no desired product was observed in the case of the 2-alkyl aziridine **2h** (entry 9). These differences indicated that a π-system

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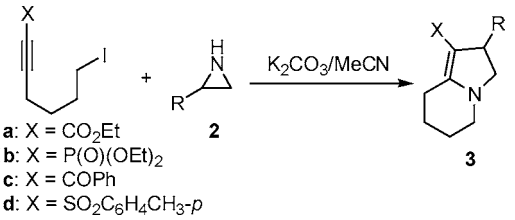
Table 1. Reaction of Iodides **1** with Aziridines **2**[a]



entry	iodide	R	temp (°C)/ time (h)	product/ yield (%)[b]
1	**1a**	Ph (**2a**)	50/16	**3a**/92
2	**1a**	naphthyl (**2b**)	50/12	**3b**/89
3	**1a**	4-MeC_6H_4 (**2c**)	50/12	**3c**/93
4	**1a**	4-ClC_6H_4 (**2d**)	65/24	**3d**/83
5	**1a**	4-BrC_6H_4 (**2e**)	65/18	**3e**/80
6	**1a**	4-$NO_2C_6H_4$ (**2f**)	50/24	**3f**/<5[c]
7	**1a**	4-$NO_2C_6H_4$ (**2f**)	85/24	**3f**/55[d]
8	**1a**	PhCH=CH (**2g**)	65/24	**3g**/45
9	**1a**	$PhCH_2$ (**2h**)	65/12	**3h**/—[d]
10	**1b**	Ph (**2a**)	60/12	**3i**/90
11	**1c**	Ph (**2a**)	30/18	**3j**/55
12	**1d**	Ph (**2a**)	30/12	**3k**/60

[a] Reaction conditions: iodides **1** (0.20 mmol), aziridine **2** (0.24 mmol), and anhydrous K_2CO_3 (0.24 mmol) in 3 mL of dry MeCN. [b] Isolated yield. [c] Some simple S_N2 product was determined. [d] Some unidentified decomposed products were determined.

connected to the 2-position of the aziridines is necessary for this process. For iodides with other electron-withdrawing groups, phosphonate **1b** displayed similar activity to **1a**, giving indolizidine **3i** in 90% yield (entry 10), while ketone **1c** and *p*-toluenesulfone **1d** showed higher reactivity than **1a**, their transformations being complete at 30 °C. However, they all gave moderate yields due to formation of unidentified side products (entries 11 and 12). The structures of all products were determined by ^1H NMR spectroscopy and were further confirmed by an X-ray structural analysis of **3k** as shown in Figure 1.

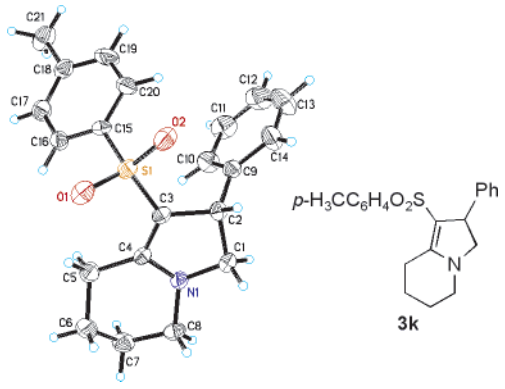
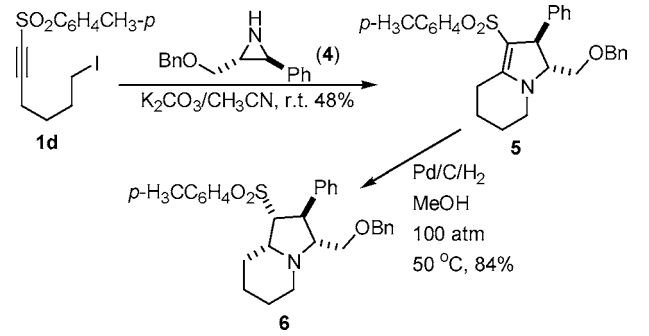


Figure 1. X-ray structure of **3k**.

To probe the possible reaction mechanism, a reaction of *trans*-α,β-disubstituted aziridine **4** with iodide **1d** was

conducted and it was found that **5** was isolated as the only bicyclic product in 48% yield (Scheme 2). Hydrogenation

Scheme 2



of **5** produced trisubstituted indolizidine **6**, which gave a fine crystal and allowed us to determine the stereochemistry by X-ray analysis. To our surprise, the 1-benzoxymethyl and 2-phenyl groups in **6** were trans to each other as shown in Figure 2. On the basis of Mattay's mechanism, the config-

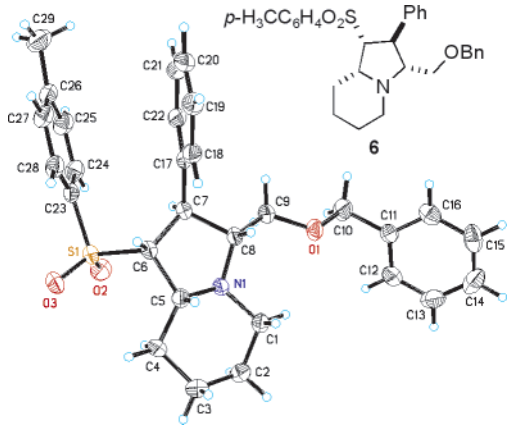
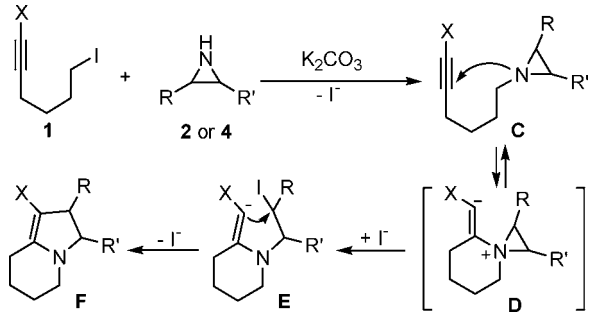


Figure 2. X-ray structure of indolizidine **6**.

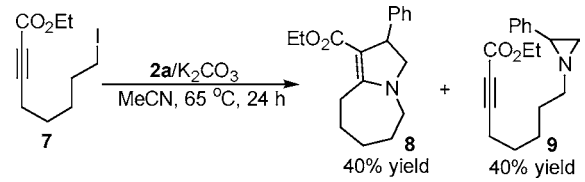
uration of phenyl neighboring carbon should have been inverted and therefore *cis*-**5** should have been obtained. The present result forced us to consider that iodide might be playing a role in the stereochemical outcome because it is known that iodide can serve as a nucleophile to cleave an aziridine ring.[1a] Consequently a possible mechanism for the present process was proposed (Scheme 3). After the S_N2 reaction of **1** and **2** took place to form tertiary amine **C**, an intramolecular Michael reaction between the lone electron pair of nitrogen and the electron-deficient C−C triple bond occurred to provide the 1,3-dipole **D**. The aziridine ring was then opened by the iodide anion to afford intermediate **E**. Next, a third S_N2 reaction occurred between the carbanion in **E** and the resultant iodide moiety to provide the bicyclic products **F**. These reactions proceeded in a cascade manner to display a formal [3+2] process. Obviously, the substituent

Scheme 3



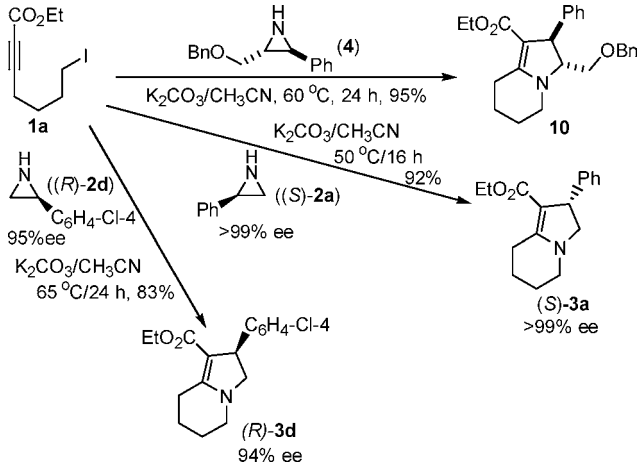
effects[8] in Table 1 discussed above and the stereochemistry outcome observed in Scheme 2 favored this mechanism. In addition, it was supported by the partial conversion of **9** to **8** (both products were produced from the reaction of iodide **7** and **2a** (Scheme 4) when a $CDCl_3$ solution of this compound was left to stand in a NMR tube).

Scheme 4



It is notable that conditions for effecting the reaction of aziridine **4** with iodide **1d** were very critical. At room temperature the reaction was quite sluggish and gave incomplete conversion (Scheme 2). Attempts to improve it by heating the reaction mixture failed to give better results because some decomposition was occurring. By way of contrast, the reaction between **4** and iodide **1a** worked well at 60 °C to afford **10** as a single product in 95% yield

Scheme 5



(Scheme 5). Its stereochemistry was assigned based on the observation for the indolizidine **6**. This result indicated the last two S_N2 reactions outlined in Scheme 3 proceeded in a stereospecific manner. To further confirm this assumption, we next chose to run enantiopure aziridine (*S*)-**2a** (99% ee) in this reaction. As we expected, the ee value of the isolated bicyclic product (*S*)-**3a** was identical with that of the starting material. Using aziridine (*R*)-**2d** (95% ee) gave a similar result. Since enantiopure aziridines are conveniently available,[1c,d,9] this method holds great promise for the assembly of enantiopure polysubstituted indolizidines in great diversity.

In conclusion, we have developed a sequential S_N2/formal [3+2] cycloaddition process starting from nonactivated aziridines, which provides an efficient protocol to assemble polysubstituted indolizidines.[10]

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Supporting Information Available: Experimental procedures and characterization for compounds **3**, **5**, **6**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) In our case the electron-withdrawing substituents decelerated the S_N2 reaction, which was evident in low reactivity of **2f**. For discussion of substituent polar effects, see: Streitwieser, A., Jr. *Solvolytic displacement reactions*; McGraw-Hill: New York, 1962; p 16.

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