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(*E*)-5-Tosyl-4-pentenamide: A Vinyl Sulfone for the One-Pot General Synthesis of Indolizidine Derivatives

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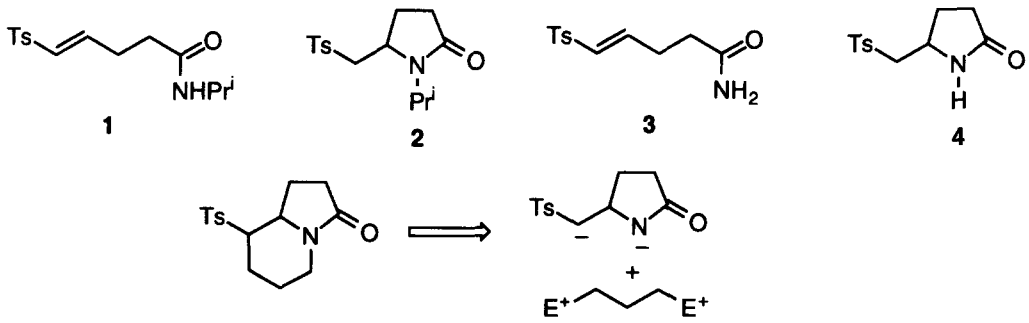
Abstract: (*E*)-5-tosyl-4-pentenamide (**3**), easily prepared from 4-pentenoic acid by stereoselective iodosulfonylation-dehydroiodination and further amidation with oxalyl chloride and ammonia, reacts with sodium hydride at room temperature in DMF and then with 1,3-dielectrophiles such as 1,3-dihalides and α,β-unsaturated esters to provide stereoselectively differently substituted indolizidines **6**.

Indolizidine alkaloids are natural products with a wide variety of structural and stereochemical features, which have been isolated from plants, fungi and animal sources. They have aroused considerable interest because of their important biological properties, specially their polyhydroxy derivatives as inhibitors of several glycosidases.[1] A plethora of strategies based in convergent and divergent methods have been developed for the particular synthesis of these type of bicyclic compounds .[2,3] However, more general methods for the synthesis of different substituted indolizidines should be desirable.

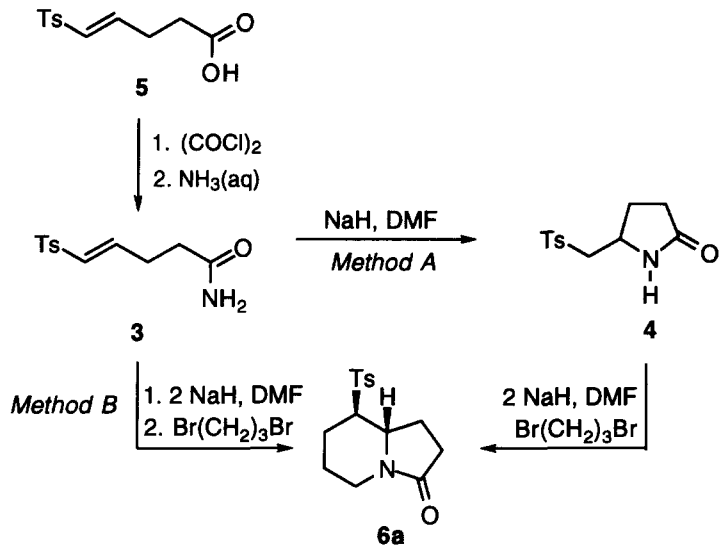
We have recently described the synthetic applications of the readily accesible (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide (**1**) in the preparation of 6-hydroxy-substituted (2*E*,4*E*)-dienamides acting as a δ-acyldienyl anion equivalent.[4] This vinyl sulfone has a high tendency to cyclize after deprotonation of the NH group to the corresponding γ-lactam **2** through an intramolecular conjugate addition. The substituted lactam **4**, which could be prepared from the primary pentenamide[5] **3**, should be an appropriate 1,3-dinucleophile for the synthesis of the 1-azabicyclo[4.3.0]nonane skeleton of indolizidine alkaloids by reaction with 1,3-dielectrophiles.



1 **2** **3** **4**

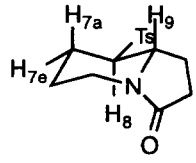
The starting sulfone (*E*)-5-tosyl-4-pentenoic acid (**5**) was prepared by *in situ* iodosulfonylation-dehydroiodination of 4-pentenoic acid in 71% yield,[4] this acid was transformed into amide **3** (mp 122-123°C)

by treatment with oxalyl chloride and further reaction with aqueous ammonia in 85% yield (Scheme 1). Initially this amide was cyclized[6] to 2-(tosylmethyl)-γ-lactam (**4**, mp 134-135°C) by treatment with NaH in DMF at room temperature for 1 h in 90% yield. Subsequent reaction of lactam **4** in the presence of 2 equiv of NaH with 1,3-dibromopropane gave indolizidine **6a** in 53% yield (Scheme 1, Method A). When the same procedure was carried out one-pot allowing the pentenamide **3** to cyclize for 1 h and then adding the electrophile, the same indolizidine **6a** was obtained in 42% yield (Scheme 1, Method B).

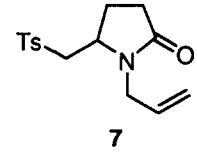


Scheme 1.

The relative *trans*-configuration for compound **6a** was deduced from the analysis of the corresponding coupling constants (see below) being the tosyl group at the equatorial position. In both procedures A and B, competitive dehydobromination was observed and *N*-allyl-2-(tosylmethyl)-γ-lactam (**7**) was also isolated in 23 and 30% yield, respectively. The formation of this by-product indicated that it is the nitrogen which attacks to the electrophile first, and then the second alkylation takes place at the α-position of the sulfone group to give the thermodynamically more stable *trans*-indolizidine.[7]



$J_{8\text{-}9}$ = 10.4 Hz
$J_{8\text{-}7a}$ = 12.5 Hz
$J_{8\text{-}7e}$ = 3.7 Hz



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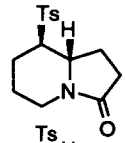
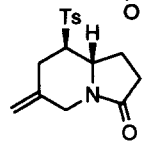
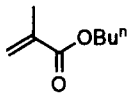
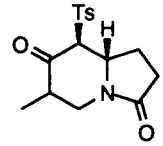
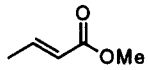
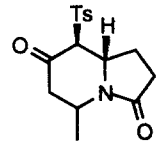
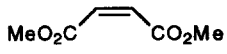
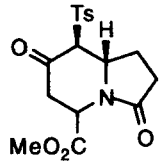
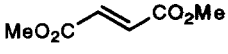
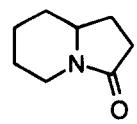
In order to study the scope of this procedure other 1,3-dielectrophiles such as 3-chloro-2-(chloromethyl)-1-propene and α,β-unsaturated esters were used following both methods A and B (Table 1). From the data of Table 1 can be observed that similar yields and stereochemical results were obtained using both methods (entries 1 and 2, 3 and 4, 6 and 7). The configuration between the tosyl and the bicyclic system was always *trans* according to the typical values of 9.8 and 10.4 Hz for the coupling constants between H_8-H_9 for ketones **6c**-

Table 1. Synthesis of Indolizidine Derivatives **6**

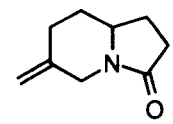
entry	electrophile	method[b]	product[a] no.	structure	yield (%)[c]	mp (°C)[d]
1	Br⁄⁄Br	A[e]	**6a**		53	145-146
2		B[e]	**6a**		42	
3	Cl⁄=⁄Cl	A[e]	**6b**		66	161-162
4		B[e]	**6b**		65	
5		B[f,g]	**6c**		44[h]	180-181[h]
6		A[f]	**6d**		50[i]	159-160[j]
7		B[f]	**6d**		47[i]	
8		B[f]	**6e**		65[k]	140-141[j]
9		B[f]	**6e**		60[k]	

[a] All products were pure (TLC, 300MHz ^{1}H NMR) and gave satisfactory spectral data (IR, ^{1}H and ^{13}C NMR, and MS). [b] Method A: the lactam **4** was treated with NaH and the electrophile for 90 min. Method B: the amide **3** was treated with NaH and after 1 h was added the electrophile and stirred for additional 90 min. [c] Isolated yield based on lactam **4** (Method A) or amide **3** (Method B), after column chromatography on silica gel. [d] Hexane/EtOAc. [e] 2 equiv of NaH were used. [f] 1 equiv of NaH was used. [g] Reaction time with the electrophile: 7 h. [h] 8/1: *cis/trans* (C_6-C_8) diastereomers mixture. [i] 19/1: *cis/trans* (C_5-C_8) diastereomers mixture. [j] For the *cis*-diastereomer. [k] 4/1: *cis/trans* (C_5-C_8) diastereomers mixture.

6e and derivatives **6a-6b**, respectively. The new stereocenter in compounds **6c-6e** has mainly *cis* relative configuration respect to the tosyl group being determined by NOE experiments.[7] The reaction with dimethyl maleate or fumarate gave the same mixture of diastereomeric indolizidines **6e** (Table 1, entries 8 and 9). The reduction of 8-tosyl substituted derivatives **6a** and **6b** with sodium amalgam in MeOH (Na_2HPO_4)[8] at 0°C for 90 min gave the corresponding indolizidines **8a** and **8b** in 80 and 94 % yield, respectively.



8a



8b

In summary, we have found that the reaction of (*E*)-5-tosyl-4-pentenamide (**3**), readily accessible from 4-pentenoic acid, with NaH and then with 1,3-dielectrophiles is an adequate convergent methodology for the stereoselective, general and simple preparation of indolizidines by a cascade process in which 4-(tosylmethyl)-γ-lactam participates as 1,3-dinucleophile. The possibility to choose the structure of the amide[9] and the electrophile as well as to carry out further modifications in the obtained indolizidines[10] increase the scope of this methodology.

Typical procedure (Method B): to a suspension of NaH (13 mg, 0.33 mmol for esters and 26 mg, 0.66 mmol for dihalides) in dry DMF (2 ml) was added a suspension of amide **3** (76 mg, 0.3 mmol) in DMF (2 ml) under argon. The reaction mixture was stirred at room temperature for *ca.* 1 h and then the dielectrophile (0.33 mmol) was added. After 90 min (7 h for compound **6c**) it was hydrolyzed with sat. aqueous NH_4Cl and after extractive work-up, the residue was purified by column chromatography (silica gel) to afford pure compounds **6**, which were recrystallized with hexane/EtOAc.[11]

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