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Efficient synthesis of 5-substituted 2-aryl-6-cyanoindolizines via nucleophilic substitution reactions

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Preliminary Communication

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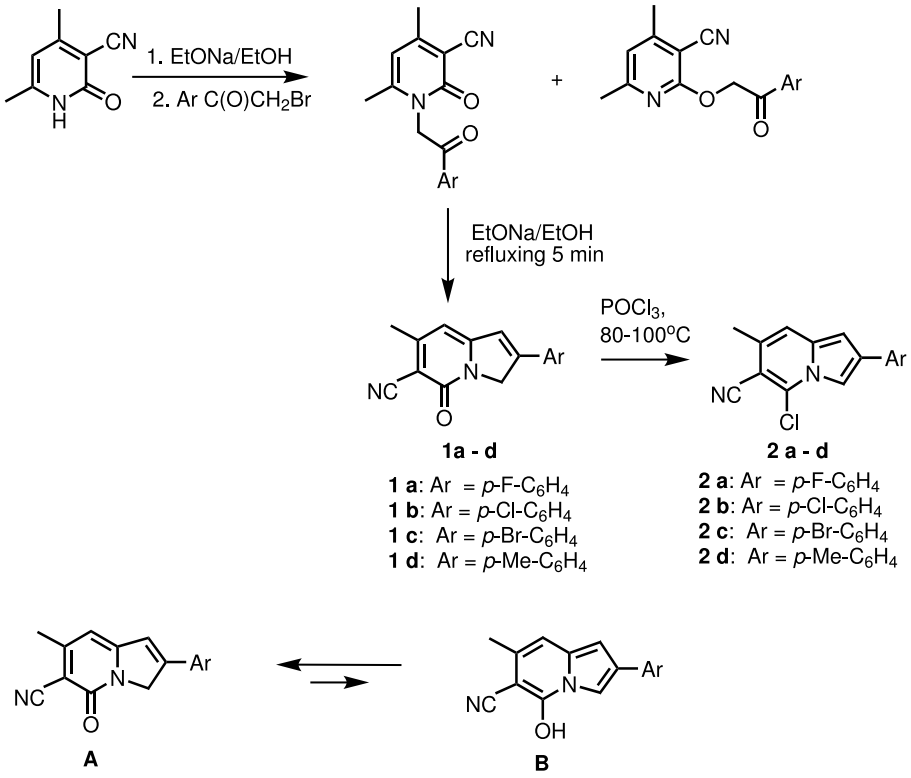
Abstract

2-Aryl-6-cyano-7-methyl-5-indolizinones were successfully converted into 2-aryl-5-chloro-6-cyano-7-methylindolizines. The obtained 5-chloroindolizines readily underwent nucleophilic substitution at position 5 leading in high yields to novel 5-functionalised indolizines.

Indolizines are an important class of heterocyclic compounds since many natural alkaloids contain in their structure a saturated (swainsonine) or aromatic (camptothecin) indolizine moiety. While the chemistry of indolizines has been widely investigated[1] the chemistry of 5-substituted indolizines remains very poor because there are only a few reliable ways for their synthesis.

8-Nitroindolizines may undergo amination at position 5 (S_NH substitution) under the action of secondary amines.[2] 2-Phenylindolizine can be lithiated at position 5, and the resulting indolizyl lithium can react with some electrophiles (CO_2, PhCHO, PhCN, Me_3SiCl, MeI) leading to variety of new products in good yields.[3] An interesting method for preparing 5-substitutied indolizines by recyclization of oxazolo[3,2-a] pyridinium salts was developed in our laboratory.[4,5] Using this strategy a series of 5-substituted indolizines have been prepared in good yields, but (although the method seems to be quite reliable) it is currently restricted only by secondary amines.

In seeking for a synthetic approach to 5-substituted indolizines we have assumed that indolizines bearing an appropriate leaving group (*e.g.* halogen) at position 5 may undergo nucleophilic substitution. Herein we discuss the synthesis of previously unknown 5-chloroindolizines and their use as precursors



Scheme 1: Synthesis of 2-aryl-5-chloro-6-cyano-7-methylindolizines **2**. Possible tautomeric structures **A** and **B** for 2-aryl-6-cyano-7-methyl-5-indolizinones **1**.

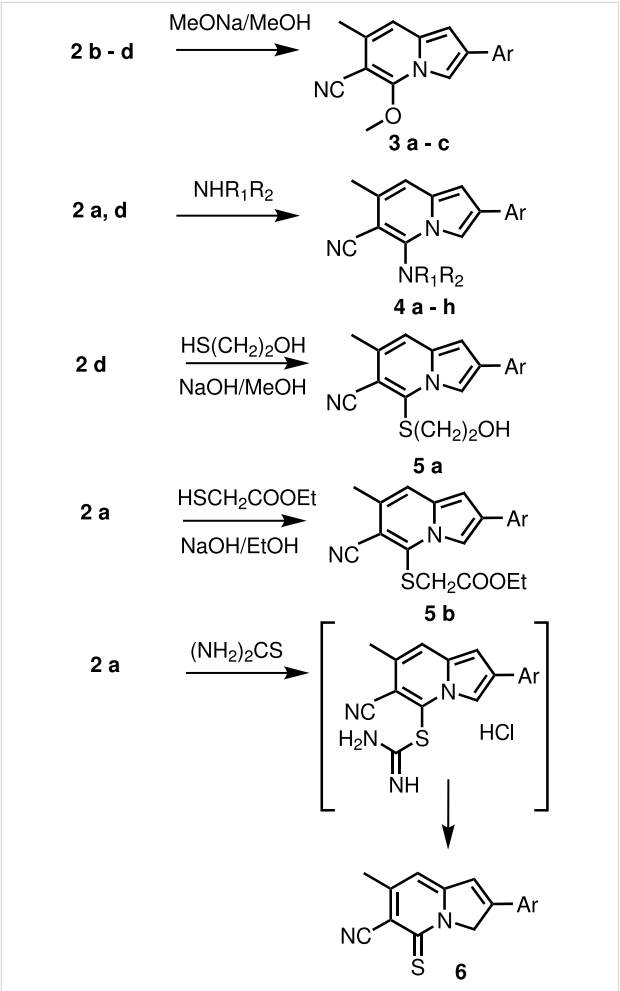
to novel 5-substituted indolizines via nucleophilic displacement reactions.

The synthesis of 2-aryl-5-chloro-6-cyano-7-methylindolizines **2** is shown in Scheme 1. 2-Aryl-6-cyano-7-methyl-5-indolizinones **1 a** – **d** were prepared according to protocol of Gevald.[6] Our modification of the original method included separation of N- and O-isomers of phenacyl pyridines before cyclization (using the difference in their solubility in chloroform). Although ^{1}H-NMR (see Supporting Information File 2) and Nuclear Overhauser Effect confirmed the structure **A** for indolizinones **1**, we assumed the existence of tautomerism between forms **A** and **B** involving hydrogen interchange between oxygen and C-3 carbon (Scheme 1). Although the amount of tautomer **B** is negligibly small, one would expect that treatment of **1 a** – **d** with phosphorous oxychloride may lead to substitution of oxo/oxy-group to chlorine giving the products **2 a** – **d**. (It is well known that analogous 2-hydroxypyridines which exist in the pyridone tautomeric form can be easily converted to 2-chloroderivatives by reaction with $POCl_3$.).[7] Indeed, heating of indolizinones **1 a** – **d** in $POCl_3$ at 80–100°C during 10 hours without any solvent followed by pouring into a mixture of ice/sodium acetate and filtration of the green precipitate afforded crude 5-chloroindolizines. After column chromatography (eluent – carbon tetrachloride) yellow solids were obtained. Performing this reaction in the presence of two-fold molar excess of trimethylbenzylammonium chloride or TEBAC increased the yields of **2 a** – **d** up to 30–75%. In the ^{1}H NMR spectra of these products[†] the initial signal of 3-CH_2 group at ~5 ppm (intensity 2H) disappeared, and a new aromatic signal 3-CH (with intensity 1H) appeared at 7.99 – 8.11 ppm.

The halogen atom in 5-chloro-6-cyanoindolizines **2** should be activated to nucleophilic substitution reactions by the suitable *ortho*-arrangement of the nitrogen atom of the pyridine ring and electron-withdrawing cyano-group. The pattern strongly resembled 2-chloro-3-cyanopyridine, that is why we anticipated successful substitution in reactions of **2** with oxygen, nitrogen, and sulfur nucleophiles. Indeed, 5-chloroindolizines readily underwent nucleophilic substitution to produce previously unknown compounds **3** – **6** in good to excellent yields (Scheme 2). These products are detailed in Table 2. Thus, 5-methoxyindolizines **3 a** – **c** were formed after refluxing **2 b** – **d** in solution of sodium methoxide in methanol overnight in good yields (Scheme 2). Treatment of **2a**, **d** with excess of amines without any solvent gave 5-amino derivatives **4 a** – **h**. In the case of secondary amines (**4 a** – **c**, **e** – **g**) the reaction

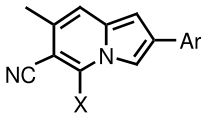
proceeded at room temperature, but reaction with less nucleophilic benzylamine (**4 d**, **h**) required heating for 30 min. Nucleophilic substitution also occured with sulfur nucleophiles. Thus, **2d** reacted with mercaptoethanol under basic conditions leading to **5a**. Conversion **2a** into **5b** was conveniently achieved with ethyl mercaptoacetate in ethanolic sodium hydroxide. Interestingly, **2a** reacted also with thiourea in refluxing butanol giving indolizinethione **6**. The product **6** seems to be the result of decomposition of unstable isothiouronium salt, and the process resembles the known conversion of 2-chloro-3-cyanopyridines to 3-cyanopyridinethiones under the same conditions via a similar intermediate.[8] ^{1}H NMR spectrum of **6**, which was very similar to the spectra of **1**, indicated disappearance of aromatic proton signal H_3 and appearance of a signal at 5.35 ppm with intensity 2H.†

In conclusion, we are the first to obtain 2-aryl-5-chloro-6-cyano-7-methylindolizines from 2-aryl-6-cyano-7-methyl-5-indolizinones and to prove the possibility to employ them in nucleophilic substitution reactions. Moreover, these reactions are the first examples of preparative nucleophilic substitution in indolizines, and our findings open a new way to functionalize the C-5 position (in most cases considered as inactive). The studies of further cyclizations of 5-substituted indolizines involving neighbouring cyano-group and ring position C_3 is underway.



Scheme 2: Nucleophilic substitution in 2-aryl-5-chloro-6-cyano-7-methylindolizines.

Table 1: Properties of 5-substituted 2-aryl-6-cyano-7-methylindolizines



No.	5-X*	R in 2-Ar	Yield %	m.p., °C
2 a	Cl	p-F	30	173–175
2 b	Cl	p-Cl	65	198–200
2 c	Cl	p-Br	54	229–230
2 d	Cl	p-Me	74	157–158
3 a	OMe	p-Cl	50	169–172
3 b	OMe	p-Br	71	197–200
3 c	OMe	p-Me	73	170–173
4 a	pyrrolidyl	p-F	99	189–190
4 b	piperidyl	p-F	91	205–209
4 c	hexamethy-lenimino	p-F	88	186–188
4 d	benzylamino	p-F	58	190–194
4 e	pyrrolidyl	p-Me	74	228–230
4 f	piperidyl	p-Me	71	212–215
4 g	hexamethy-lenimino	p-Me	85	213–216
4 h	benzylamino	p-Me	83	185–187
5 a	$S(CH_2)_2OH$	p-Me	71	132–135
5 b	SCH_2CO_2Et	p-F	70	142–145

Note

*Characteristics of parent indolizinones **1 a** – **d** were identical to those described in literature.[9]

† Supporting information

Supporting Information

Supporting Information File 1

Supporting tables
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-1-9-S1.doc]

Supporting Information File 2

Supporting information
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-1-9-S2.pdf]

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