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Directed Metalation of 1-Ester-Substituted Indolizines: Base/Electrophile-Controlled Regioselective Functionalization

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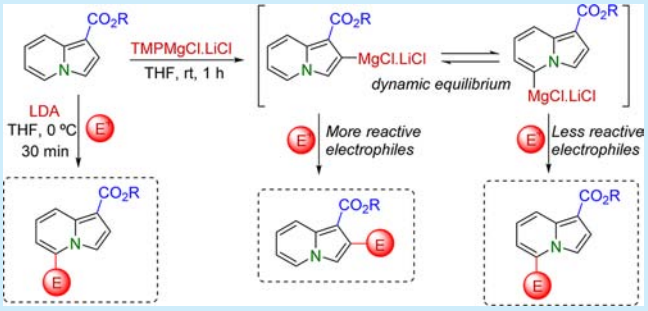
Supporting Information

ABSTRACT: A variety of C-2 and C-5 difunctionalized indolizines have been prepared through the reaction of 1-ester-substituted indolizines with organometallic bases followed by a reaction with different electrophiles. Metalation takes place under mild conditions allowing the isolation of a number of difunctionalized indolizines in good yields. The regioselectivity of the reaction appears to be governed by the nature of the base and electrophile.



In recent years, the pharmacological potential of indolizines, an *N*-bridgehead bicyclic ring system fused with an electron-rich pyrrole and an electron-poor pyridine, has been receiving attention due to its many useful applications.[1] Many of the natural and synthetic indolizines have shown substantial biological activities, for instance, they can function as cardiovascular agents, anti-inflammatories, antibacterials, and central nervous system depressants.[2] They are also known as calcium entry blockers, phosphatase inhibitors, and 5-hydroxytryptamine receptor antagonists.[3] Furthermore, indolizine derivatives have demonstrated long wavelength absorption and fluorescence with high quantum efficiency in the visible light region.[4] Hence, there is a growing interest in the synthesis of functionalized indolizines.[5]

In recent years, directed metalation has been widely used as an efficient method for regioselective functionalization of aromatics and heteroaromatics.[6] However, literature data on the metalation of the indolizinyl ring are scarce. In pioneering work, Gubin et al. have shown the regioselective deprotonation of 2-phenylindolizine with *n*-BuLi.[7] Following the work of Gubin, Babaev et al. performed additional investigations;[8] however, only three slightly functionalized substrates were studied. Recently, we have reported the preparation of a variety of novel 2,5-diarylindolizines through the Pd-catalyzed cross-coupling reactions of aromatic halides with organozinc reagents prepared from 2-aryl-indolizines.[4b]

Following our interest in the functionalization of aromatic and heterocyclic compounds using organometallic reagents, in this work we have investigated the regioselective functionalization of 1-ester-substituted indolizines using organometallic bases. Interesting base/electrophile regioselectivity control has been achieved leading to a number of difunctionalized indolizines in good yields.

Initially, we studied the directed metalation of ethyl indolizine-1-carboxylate (**1a**)[9] with different lithium and magnesium amides using iodine as an electrophile (Table 1). In the first set of experiments, the metalation of **1a** was examined with TMPLi (TMP = 2,2,6,6-tetramethyl-piperamidyl) in THF at 0 °C, followed by changing the base equivalents and reaction time in the subsequent reactions (Table 1, entries 1−7). From Table 1, it was observed that all reactions presented preferential iodine incorporation at the C-5 ring position of the substrate. Additionally, compound **3a** was obtained with a high conversion rate and regioselectivity after 30 min of reaction using 1.4 equiv of the base (entry 5).

Notably, it was also observed that (i) smaller amounts of TMPLi decrease the reaction conversion rate (entries 1−3), (ii) greater amounts of the base have a negative impact on the reaction regioselectivity (entry 7), and (iii) the reaction time is directly related to the formation of a diiodide byproduct from the double substitution of positions C-2 and C-5 (entry 4). On the other hand, the bases LHMDS and Et_2NLi were ineffective for the lithiation of **1a** (entries 8−11). In contrast, reactions using 1.4 equiv of LICA or LDA displayed similar conversion and regioselectivity to those using TMPLi (entries 12 and 13). Moreover, substitution of THF for diethyl ether had no effect on the yield or regioselectivity of the reaction using LDA (entry 15).

The mixed lithium−magnesium amides TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ have proven to be highly active and soluble bases allowing smooth metalations of various substrates with

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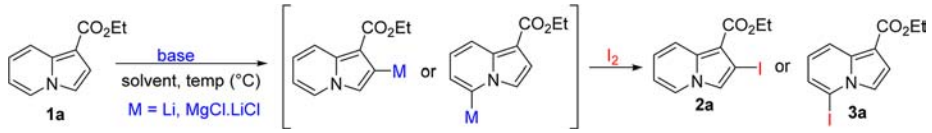
Table 1. Survey of Reaction Conditions for Regioselective Metalation of 1a



						iodo incorporation			
entry	base	equiv	solvent	temp (°C)	time (h)	% C-2	% C-5	% total	(**2a**:**3a**)
1	TMPLi	1.1	THF	0	1	0	13	13	>99 (**3a**)
2	TMPLi	1.2	THF	0	1	0	56	56	>99 (**3a**)
3	TMPLi	1.3	THF	0	1	0	65	65	>99 (**3a**)
4	TMPLi	1.4	THF	0	1	9	65	100[a]	12:88
5	TMPLi	1.4	THF	0	0.5	1	96	97	1:99
6	TMPLi	1.4	THF	0	3	28	36	99[a]	44:56
7	TMPLi	1.5	THF	0	0.5	10	85	99[a]	10:90
8	LiHMDS	1.4	THF	0	1	0	0	0	–
9	LiHMDS	1.4	THF	25	1	0	0	0	–
10	Et_2NLi	1.4	THF	0	1	0	0	0	–
11	Et_2NLi	1.4	THF	25	1	0	0	0	–
12	LICA	1.4	THF	0	0.5	5	94	99	5:95
13	LDA	1.4	THF	0	0.5	2	96	98	2:98
14	LDA	1.5	THF	0	0.5	3	93	98[a]	3:97
15	LDA	1.4	Et_2O	0	0.5	4	94	98	4:96
16	LDA	1.4	THF	0	3	32	35	99[a]	48:52
17	TMPMgCl·LiCl	1.5	THF	25	1	79	6	85	92:8
18	TMPMgCl·LiCl	1.8	THF	25	1	85	5	90	94:6
19	TMPMgCl·LiCl	1.8	THF	40	1	59	17	76	77:23
20	TMP_2Mg·2LiCl	1.8	THF	25	1	45	28	90[a]	61:39

[a]A diiodide byproduct from the double substitution of positions C-2 and C-5 was observed.

excellent functional group compatibility.[10] Interestingly, metalation of **1a** with TMPMgCl·LiCl has allowed preferential iodation at the C-2 ring position (entries 17−19). A good conversion and high selectivity (94:6) were achieved when 1.8 equiv of the base were used in THF at rt (entry 18). Despite also showing preference for the C-2 position, the diamide TMP_2Mg·2LiCl was less selective giving a 61:39 ratio mixture of **2a** and **3a** isomers respectively (entry 20).

To rationalize the base-controlled regioselective metalation of **1a** a computational thermochemistry study has been performed (Figure 1). The use of computational chemistry for calculating

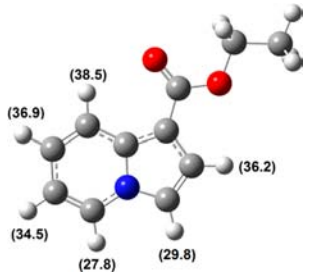


Figure 1. pK_a values of indolizine **1a** (in unities of pK_a) for H-atoms, calculated with PCM/B3LYP/6-31+G(d,p) model using THF as solvent and pyridine as reference compound.

pK_a values is currently an important tool to guide the experimental planning.[11] In addition, this strategy has been used to evaluate the CH-acidity influence on the regioselectivity of metalations in aromatic and heterocyclic substrates.[10h,i,12]

The pK_a values in THF for indolizine **1a** were obtained using the B3LYP/6-31+G(d,p) model[13] employing the Gaussian 03 program. Isodesmic reactions were performed to describe the reactivity of C−H bonds using pyridine as a standard molecule. Gibbs energy of solvation values were computed using the PCM model[14] and used to estimate the pK_a values, as suggested in early studies.[12] Details of computational calculations can be assessed in Supporting Information (SI). According to the computational study, in THF the most acidic H-atom of indolizine **1a** is located at the C-5 position (pK_a 27.8; see Figure 1). These data are in agreement with the experimental results observed when lithium amides were used to metalate this substrate. Furthermore, the preference of the base TMPMgCl·LiCl for the C-2 position is clearly related to the directing metalation effect promoted by the ester group and may be rationalized by the complex-induced proximity effect concept.[15] Thus, deprotonation of the C-2 position becomes favored by the initial formation of a complex between the ester group and the organomagnesium reagent affording kinetic rather than the expected thermodynamic products.

After establishing the best reaction conditions for selective C-2 or C-5 metalation of indolizine **1a**, we examined the reaction of the corresponding organometallic intermediates with different electrophiles such as TMSCl, halides, aldehydes, aryl iodides, diphenyldiselenide, and DMF. To evaluate the effect of the substituent, an indolizine attached to a more hindered ester group (**1b**) was also studied (Table 2). Thus, after lithiation of **1a** and **1b** using Condition A (LDA in THF at 0 °C for 30 min), a number of C-5 substituted 1-ester indolizines (**3**) were produced with high regioselectivity and isolated yields ranging from 62% to 85% (entries 1−14). Furthermore, after transmetalation of the organomagnesium intermediate with $ZnCl_2$, a Negishi cross-coupling reaction in the presence of $Pd_2(dba)_3$ and P(2-furyl)$_3$

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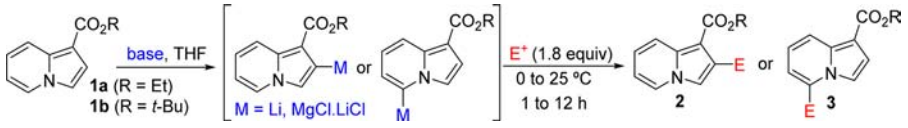
Table 2. Selective Directed Metalation of 1 Followed by Reactions with Electrophiles



entry	cond.[c]	R	electrophile	E	(2:3)[b]	product[e]	yield (%)[a]
1	A	Et	I_2	I	2:98	**3a**	80
2	A	Et	$HCONMe_2$	CHO	>99	**3b**	79
3	A	Et	$(CH_3)_2CHO$	$CH(OH)(CH_3)_2$	3:97	**3c**	70
4	A	Et	Cl_3CCCl_3	Cl	>99	**3d**	72
5	A	Et	C_6H_5CHO	$CH(OH)(C_6H_5)$	>99	**3e**	81
6	A	Et	TMSCl	TMS	2:98	**3f**	75
7	A	Et	$(C_6H_5Se)_2$	SeC_6H_5	10:90	**3g**	72
8	A	Et	*p*-ClC_6H_5I[d]	*p*-ClC_6H_5	>99	**3h**	69
9	A	*t*-Bu	I_2	I	>99	**3i**	85
10	A	*t*-Bu	$HCONMe_2$	CHO	>99	**3j**	69
11	A	*t*-Bu	Cl_3CCCl_3	Cl	>99	**3k**	62
12	A	*t*-Bu	TMSCl	TMS	>99	**3l**	72
13	A	*t*-Bu	$(CH_3)_2CHO$	$CH(OH)(CH_3)_2$	>99	**3m**	80
14	A	*t*-Bu	C_6H_5CHO	$CH(OH)(C_6H_5)$	4:96	**3n**	65
15	B	Et	I_2	I	94:6	**2a**	85
16	B	*t*-Bu	I_2	I	80:20	**2b**	60
17	B	Et	$(CH_3)_2CHO$	$CH(OH)(CH_3)_2$	83:17	**2c**	69
18	B	Et	C_6H_5CHO	$CH(OH)(C_6H_5)$	91:9	**2d**	75
19	B	*t*-Bu	$(CH_3)_2CHO$	$CH(OH)(CH_3)_2$	94:6	**2e**	75
20	B	Et	$(C_6H_5Se)_2$	SeC_6H_5	92:8	**2f**	41
21	B	Et	$HCONMe_2$	CHO	67:33	**2g**	55
22	B	*t*-Bu	$HCONMe_2$	CHO	70:30	**2h**	50
23	B	Et	Cl_3CCCl_3	Cl	2:98	**3d**	39
24	B	*t*-Bu	Cl_3CCCl_3	Cl	3:97	**3k**	31
25	B	Et	*p*-ClC_6H_5I[d]	*p*-ClC_6H_5	>99	**3h**	70

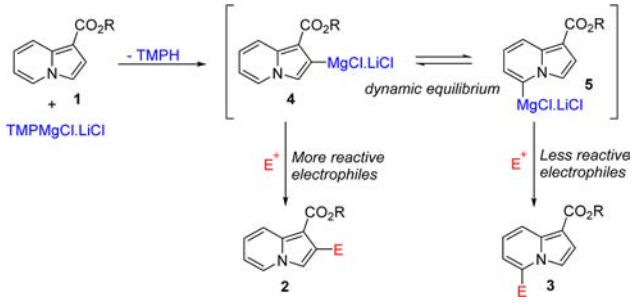
[a]Isolated yield of major product. [b]Determined by GC. [c]Conditions: (A) LDA in THF at 0 °C for 30 min; (B) TMPMgCl.LiCl in THF at 25 °C for 1 h. [d]Obtained by a cross-coupling reaction (60 °C for 12 h). [e]Major product.

produced the expected arylated derivative **3h** in 69% yield (entry 8).

Interestingly, metalation of indolizines **1a** and **1b** under Condition B (TMPMgCl·LiCl in THF at 25 °C for 1 h) followed by reaction with electrophiles showed an electrophile-controlled regioselective functionalization of 1-ester indolizines. Thus, the use of reactive electrophiles such as iodine and aldehydes produced in most of the cases the expected products in good yields and regioselectivity (entries 15−19). Moreover, the use of diphenyldiselenide as an electrophile has provided the isolation of the expected C-2 substituted derivative in a 92:8 selectivity ratio and 41% isolated yield (entry 20). Additionally, when the less reactive electrophile *N*,*N*-dimethylformamide was used, aldehyde derivatives were obtained in modest yields and low regioselectivity (entries 21 and 22). Interestingly, C-5 substituted derivatives were also observed when hexachloroethane was used to quench both organomagnesium intermediates from **1a** and **1b**. However, reactions appeared to be slow and gave the products in low yields (entries 23 and 24). A similar regioselectivity was obtained after a Negishi cross-coupling reaction with *p*-chloroiodobenzene leading to the corresponding arylated derivative in a yield of 70% (entry 25).

The role of the electrophile on the regioselective functionalization of aromatics using organometallic reagents has been previously discussed in the literature.[16] In our system, the observed electrophile-controlled regioselectivity is possibly related to a dynamic equilibration of the organomagnesium intermediates of types **4** and **5** (Scheme 1). Thus, after the *ortho*-magnesiation step with TMPMgCl·LiCl, reactive electrophiles undergo a fast reaction with **4** giving C-2 substituted products with high selectivity. In contrast, less reactive electrophiles or the cross-coupling protocol (60 °C for 12 h) may allow the equilibration of **4** and **5** species giving isomeric mixtures or majority C-5 substituted products (Scheme 1).

Scheme 1. Proposal for the Electrophile-Controlled Functionalization of 1a



To gain further information about the stability of the organomagnesium reagents of type **4** additional experiments were performed. Thus, six metalation reactions were consecutively run on substrate **1a** using the base TMPMgCl·LiCl (1.8 equiv). Reactions were quenched with excess iodine within 1−6 h, and their regioselectivities were evaluated by GC analysis. The results are presented in the SI. As observed, after 1 h of metalation the regioselectivity of the reaction rapidly decreased,

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yielding a 52:48 ratio mixture of regioisomers **2a**:**3a** within 4 h. No considerable difference was observed when D_2O was used as an electrophile, and the C-2 deuterated product was obtained with high selectivity after 1 h of reaction. After 4 h, a 51:49 ratio of deuterated **2**:**3** was obtained. These results are in agreement with Scheme 1 and suggest a dynamic equilibrium of species **4** and **5** may affect the regioselectivity of the reaction. Finally, results present in entries 6 and 16 of Table 1 indicate that a dynamic equilibrium may also be present in the corresponding organolithium intermediates.

In summary, we have described the directed functionalization of 1-ester-substituted indolizines using organometallic bases. Metalation occurs under mild conditions, and the reaction of the corresponding organometallic intermediates with different electrophiles has allowed the synthesis of a number of difunctionalized indolizines in good yields. While lithium amides favor C-5 functionalization, the base TMPMgCl·LiCl gives a majority of C-2 substituted derivatives via *ortho*-metalation. In the case of functionalization reactions mediated by TMPMgCl·LiCl, the reactivity of the electrophile plays an important role in the regioselectivity of the reaction. The scope of this methodology and its applicability toward the synthesis of biologically active molecules are currently being investigated in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and details of the computational study. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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