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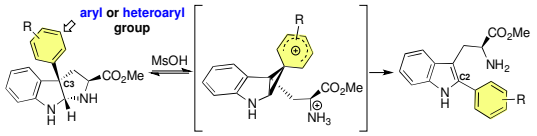

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Acid-Mediated Aryl Migration Reaction of C-3 Aryl Substituted Pyrrolidinoindolines

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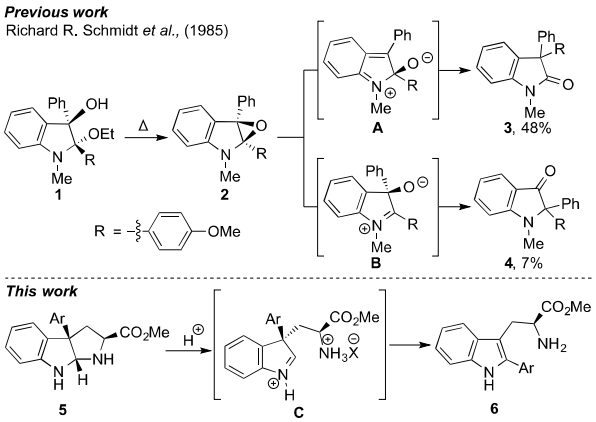
ABSTRACT

Aryl migration reactions of C-3 aryl substituted pyrrolidinoindoline compounds to provide highly conjugated C-2 aryl indole compounds have been discovered. The developed reactions have a wide substrate scope and proceed in high yield under simple acidic conditions. A unique cationic cyclopropane intermediate as the transition state is proposed.

Introduction

The indole architecture, which is composed of benzene and pyrrole rings, exhibits a specific reactivity derived from its unique electron states. A wide variety of indole alkaloids that come from tryptophan have been isolated as natural products. In biosynthesis, the diversity of indole alkaloid compounds stems from the specific reactivities of indole; reactions can be induced by both nucleophilicity and electrophilicity, and the structure can undergo migration processes[1]. Recently, the specific reactivity of indole and its derivatives have been widely applied in the fields of chemical biology and material chemistry[2]. Although a large number of specific indole reactions have been reported, it remains a developing area. Therefore, expanding the range of indole reactions is an important topic in current organic chemistry.

Whereas several oxidative migration reactions of aryl groups from the C-2 to the C-3 position to form oxindole core or alkyl group migration reactions from the C-3 to the C-2 position to form pseudoindoxyl core have been documented[3], to our knowledge, only two examples of an aryl migration reaction from the C-3 position of indolenine to the C-2 position of the pseudoindoxyl core has been reported (Schmidt and Beitzke; Scheme 1)[3h, 4]. Therefore, thermolysis of aniline derivative **1** induced aryl migration via iminium ion intermediate **A** (C-2 to C-3) to provide C-3 diaryl compound **3** as a major component. The minor rearrangement product was the C-2 diaryl product, which was formed via cationic indolenine intermediate **B** (C-3 to C-2) [4]. We envisioned that a similar cationic indolenine intermediate **C** could be generated from pyrrolidinoindoline derivative **5** under acidic conditions to promote aryl migration from C-3 to C-2 toward thermodynamically stable indole **6**.



Scheme 1. Migration of aryl group on indole related molecules.

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Herein, we report the acid-mediated aryl migration reactions of an aryl group on the C-3 position of pyrrolidinoindoline to the C-2 position of indoles via a cationic indolenine intermediate.

Result and discussion

To investigate the proposed aryl migration reaction, pyrrolidinoindoline derivatives were prepared using Qin's

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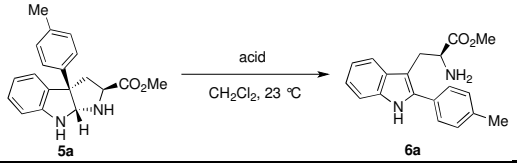
protocol[5] followed by removal of the Boc group (see details in the Supporting Information). The migration of C-3 tolyl derivative **5a** was used to screen a selection of acids with a range of pK_a values (Table 1).

Table 1. The effect of acid on the migration reaction of **5a**.[a]

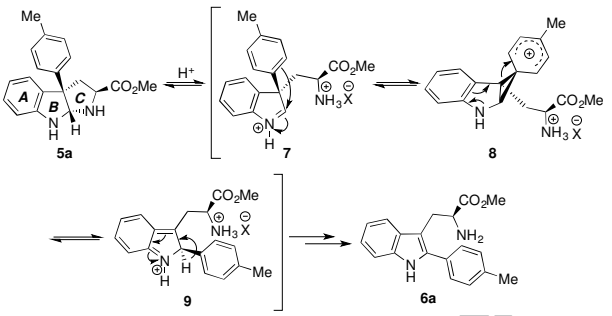


Entry	Acid [equiv.]	pK_a in H_2O	Time [h]	Yield [%][b]
1	CH_3CO_2H [30.0 equiv.]	4.76	24	N. R.
2	CH_2ClCO_2H [30.0 equiv.]	2.86	24	N. R.
3	$CHCl_2CO_2H$ [30.0 equiv.]	1.29	24	trace
4	CCl_3CO_2H [30.0 equiv.]	0.65	24	45 (quant.) [c]
5	CF_3CO_2H [30.0 equiv.]	–0.25	24	85 (99) [c]
6	CH_3SO_3H [30.0 equiv.]	–2.6	1	quant.
7	CF_3SO_3H [30.0 equiv.]	–14.0	0.25	99
8	CH_3SO_3H [10.0 equiv.]	–2.6	2	quant.

[a] Reaction conditions: **5a** (0.05 mmol), CH_2Cl_2 (0.5 mL, 0.1 M). [b] Yield of the isolated product. [c] Base on recovered starting material.

When weaker acids such as dichloroacetic acid, monochloroacetic acid, or acetic acid (30 equiv., CH_2Cl_2, 23 °C) were employed, the desired migrated product was not observed (pK_a > 1.29; Table 1, entries 1–3). In contrast, the use of either trichloroacetic acid (pK_a 0.65) or trifluoroacetic acid (pK_a –0.25) led to the desired rearrangement reaction to give C-2 tolyl indole **6a**, although the reaction was not complete after 24 h (entries 4 and 5). Finally, methanesulfonic acid (MsOH, pK_a –2.6) and trifluoromethanesulfonic acid (TfOH, pK_a –14) were both found to be suitable for promotion of the aryl migration reaction. Therefore, when 30 equivalents of either MsOH or TfOH were added to **5a** in CH_2Cl_2, **6a** was obtained in quantitative yield (MsOH, 1 h; TfOH, 15 min; entries 6 and 7). The amount of acid could be reduced to 10 equivalents, although longer reaction times were required (MsOH, 2 h; entry 8).

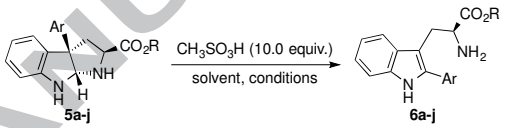
The proposed reaction mechanism is shown in Scheme 2. Under acidic conditions, the secondary amine on ring *C* was converted into the salt; this ring was then opened to generate cationic indolenine intermediate **7**. Subsequently, the tolyl group migrated from the C-3 to the C-2 position to afford intermediate **9** via cationic cyclopropane intermediate **8**. This was followed by tautomerization to provide the highly conjugated thermodynamically stable indole compound **6a**.

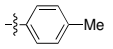
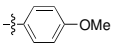
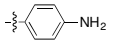
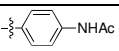


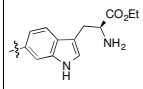
Scheme 2. Proposed reaction pathway.

Next, the substrate scope of the reaction was investigated. Compounds **5b**–**h** and **5j** were prepared using the procedure described for **5a**. Compound **5i** was prepared using our previously developed dimerization reaction of tryptophan derivatives[6].

Table 2. Scope of the reaction.[a]

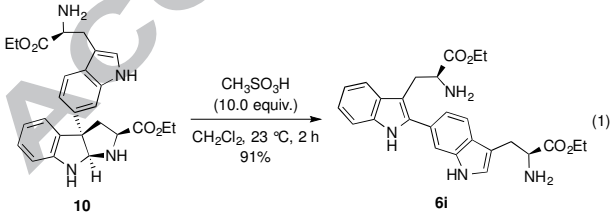


Entry	Ar	R	solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	 **5a**	Me	CH_2Cl_2	23	2	quant.
2	 **5b**	Me	CH_2Cl_2	23	2	99
3	 **5c**	Me	CH_2Cl_2	23	2	95
4	 **5d**	Me	CH_2Cl_2	23	2	96
5	 **5e**	Me	CH_2Cl_2	23	2	quant.
6	 **5f**	Me	CH_2Cl_2	23	4	23 [c]
7	**5f**	Me	$(ClCH_2)_2$	80	2	93
8	 **5g**	Me	$(ClCH_2)_2$	80	2	73 [d]

9	 **5h**	Me	CH_2Cl_2	23	2	96
10	 **5i**	Et	CH_2Cl_2	23	2	93
11	 **5j**	Me	CH_2Cl_2	23	2	36 [e]
12	**5j**	Me	$(ClCH_2)_2$	80	2	88

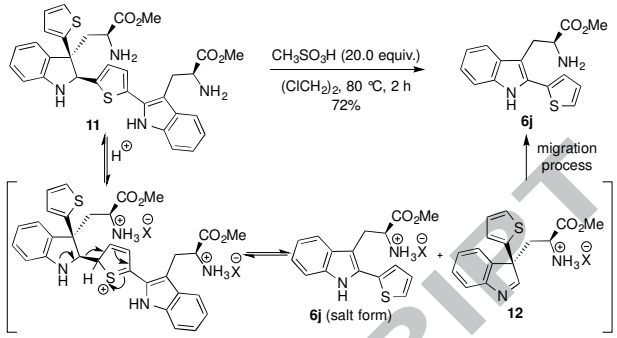
[a] Reaction conditions: **5** (0.1 mmol), solvent (1 mL, 0.1 M). [b] Yield of the isolated product. [c] Starting material **5f** was recovered in 73% yield. [d] Deacetyl rearrangement compound **6f** was obtained in 13% yield. [e] Dimeric compound **11** was obtained in 63 % yield.

When **5b** was used as substrate under the optimized reaction conditions (10 equiv. MsOH, CH_2Cl_2, 23 °C), rearrangement compound **6b** was obtained in 99% yield (Table 2, entry 2). *o*-methoxybenzene derivative **5c** was transformed to **6c** ragio-selectivily in superb yeild (95%, Table 2, entry 3). Naphthalene derivatives **5d** and **5e** were also suitable substrates, giving **6d** and **6e** in 96% and quantitative yield, respectively (entries 4 and 5). On the other hand, aniline derivative **5f** was less reactive under the established conditions (MsOH 10.0 equiv., 23 °C); in this case, the reaction gave **6f** in reaction to the iminium ion might be inhibited. After optimization, a higher reaction temperature was identified as being required to obtain excellent conversion (MsOH 10.0 equiv., 1, 2-dichloroethane, 80 °C, 93%; entry 7). When the reaction with acetylated **5g** was carried out under the heating conditions described for **5f** (entry 7), **6g** was obtained in 73% yield along with deacetylated **6f** in 13% (entry 8). C3-indole derivatives **5h**[7] and **5i** also provided migrated products **6h** and **6i** in excellent yield (96% and 93%, respectively; entries 9 and 10). In addition, the relative stereochemistry of the ethoxycarbonyl group did not have any effect on the migration reaction (Eq. 1). Therefore, tryptophan dimeric derivative **10**[6], which is the diastereomer of **5i**, was converted into **6i** in excellent yield under same reaction conditions (91%).



10 **6i**

Interestingly, the migration reaction of thiophene derivative **5j** gave dimeric compound **11**, which was formed by Friedel–Crafts addition of the desired product **6j** to the cationic indolenine intermediate; compound **11** was obtained in 63% yield as the major product (desired **6j** was obtained in 36% yield as the minor compound; entry 11). This unexpected side reaction derived from the high nucleophilicity of the thiophene moiety. Therefore, we considered the retro reaction from dimeric compound **11** to the salt form of **6j** and cationic indolenine intermediate **12** (Scheme 3).



Scheme 3. Retro reaction and migration of dimeric thiophen derivative **11**.

Scheme 3. Retro reaction and migration of dimeric thiophen derivative **11**.

If these equilibrium conditions were established in situ, thermodynamically stable **6j** would be obtained selectively. Therefore, isolated dimeric compound **11** in 1, 2-dicholoroethane was treated with MsOH at 80 °C for 2 h. As a result, the desired monomer **6j** was obtained in good yield (72%). The optimized reaction conditions were then directly applied to **5j**. In this case, the yield of **6j** improved dramatically without any production of **11** (88% yield; Table 2, entry 12). The discovered equilibrium reaction suggested that C-2 thiophene adducts such as **11** could be employed as a cationic indolenine equivalent.

Conclusions

We have developed aryl migration reactions of C-3 aryl substituted pyrrolidinoindoline compounds to provide highly conjugated C-2 aryl indole compounds via a cationic indolenine intermediate. The developed reactions proceed in high yield under simple acidic conditions and show excellent substrate generality. Therefore, the novel reaction mode of indole-related compounds has been expanded to further enhance the field of indole chemistry. Applications of the migration reaction to π-conjugated compounds for use in chemical biological studies and material chemistry are underway.

Acknowledgements

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7. Qin and co-workers reported that the coupling product at the C-2 position of the *N*-Me indole that connected the tryptophan C-3 position was obtained using their reported protocol. However, using their reported protocol, we obtained the C-3 coupling product **5h** as the major product. The stereochemistry of **5h** was determined by 2D NMR and NOEDF analysis after removal of the Boc group (see details in the Supporting Information).

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://

*Highlights

The novel reaction mode of indole-related compounds has been discovered.

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