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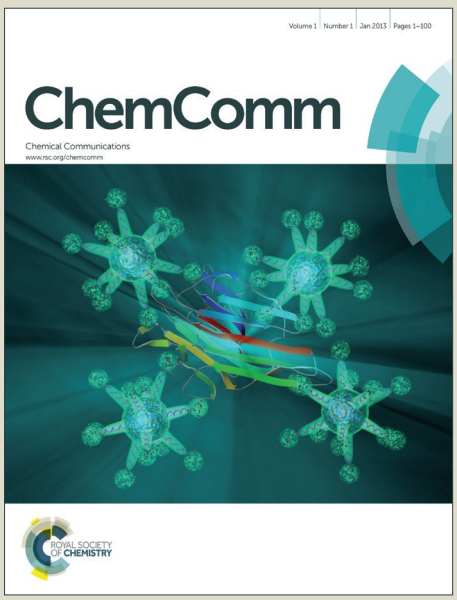

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Intermolecular Dearomative C2-Arylation of N-Ac Indoles Activated by $FeCl_3$

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We report the $FeCl_3$-mediated direct addition of electron-rich arenes to the C2-position of electrophilic N-Ac indoles in mild conditions (room temperature, air). No functional group is required on the arene nucleophile: one of its C-H bond is added to the C2=C3 double bond of the indole nucleus in a Friedel-Crafts-type reaction. This dearomatisation process delivered a broad range of C2-arylated indolines.

The functionalization of indoles derivatives via dearomatisation reactions is a field of intense synthetic efforts due to the biological relevance of the heterocyclic scaffolds obtained.[1] In this context, we have recently described several methods for the dearomative C3-arylation of indoles[2] via $FeCl_3$-activation of 3-substituted N-Ac indoles[3] or oxidation of indoles with NIS[4] or from N-hydroxyindoles[5] using the electrophilicity of indoles.[6] Our next goal was to achieve the related C2-arylation of indoles due to the presence of the C2-arylindoline motif in several natural products such as phalarine, hinckdentine A or tabernaebovine (Figure 1).[7]

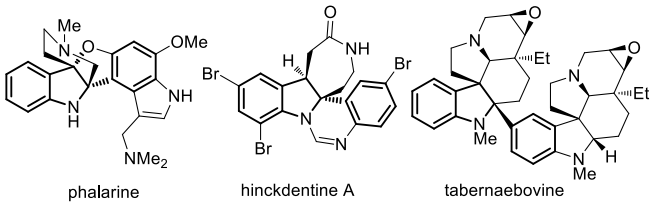
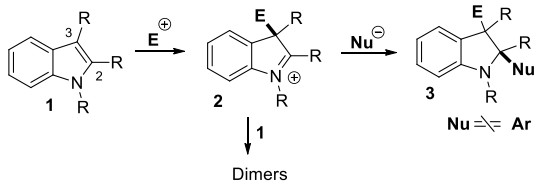


Figure 1. C2-arylindoline-containing natural products.

The arylative dearomatisation of indoles also allows to transform a flat heterocycle into a 3-D structure which is more poised to explore chemical space in the context of drug discovery.[8]

Indoles **1** are widely known to be highly nucleophilic at the C3-position leading in presence of electrophiles or acid to indolium ions **2** which can be trapped by nucleophiles at the C2-position and delivered functionalized indolines **3**, usually in the intramolecular mode (Scheme 1).[9] Due to the propensity of indolium ions **2** to form dimeric compounds via attack of indole **1** at C2,[10] intermolecular addition of aryl nucleophiles to indoliums such as **2** are very rare.[11] Only few nucleophiles such as allyboranes or hydrides could be added to **2** in the intermolecular mode.[12]



Scheme 1. Innate reactivity of the indole nucleus.

Usually, the C2-arylative dearomatisation of indoles rely on intramolecular reactions with the aryl substituent attached to the nitrogen of the indole nucleus. In that cases, the aryl group is introduced by transformation of an aryl-halogen bond via palladium-catalysed[13] or radical reactions.[14]

In the intermolecular mode, the C2-arylation of indoles could take place by the 1,4 addition of Grignard reagents to indoles containing a strong electronwithdrawing group at C3.[15] An elegant palladium-catalyzed 3-oxy-2-arylation of 3-unsubstituted indoles with phenylboronic acids and TEMPO was described.[16] These methods rely on the use of a functional group on the aromatic nucleophile. Alternatively, during the total synthesis of dideepoxytabernaebovine, a rare and straightforward addition of electron rich arenes to an indolium

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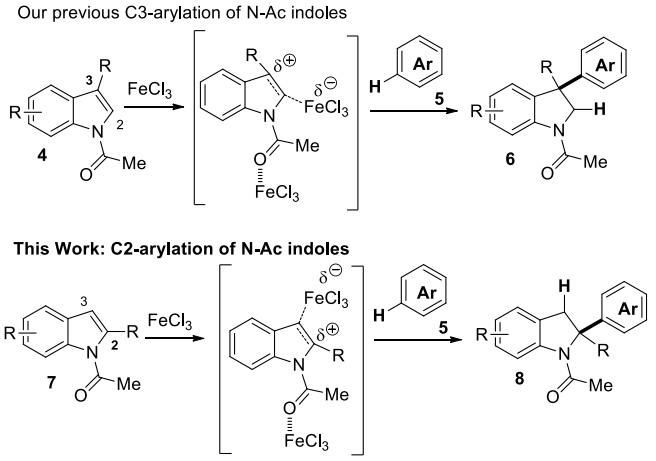
intermediate such as **2** was deployed.[11a] A formal [4+2] cycloaddition with a N-phenyl iminium intermediate was also described.[17] We achieved the 3-oxy-2-arylation of indoles during the DDQ-mediated oxidative coupling between phenols and 3-substituted N-Ac-indoles activated by $FeCl_3$.[18]

Despite these achievements, we felt like that a general method for the C2-arylation of indoles from the functionalization of the C-H bond of the aromatic nucleophile was lacking. To achieve the C2-regioselective addition of a C-H bond across the C2=C3 double bond of indoles, our experience in the activation of N-Ac-indoles by $FeCl_3$ was crucial to induce a Friedel-Crafts process.[3] We discovered that the $FeCl_3$-mediated hydroarylation of 3-unsubstituted N-Ac-indoles, proceeds at the C2-position. We can postulate that the complexation of $FeCl_3$ by the oxygen of the acetyl lead to the sequestration of the nitrogen lone pair by conjugation, the C2=C3 bond could then be activated by an acid species and formally lead to a positive charge at C2 or C3.[3b] If a substituent is present at C3, the positive charge could be more stabilized at C3 by the formation of a tertiary benzylic carbocation.[3a,b] If the C3 position lacks substitution, the resulting secondary benzylic carbocation at C3 would be less stabilized than a positive charge at C2, due to the effect of the lone pair of the nitrogen. The latter would lead to the C2-regioselective hydroarylation of indoles which is the subject of this report (Scheme 2).

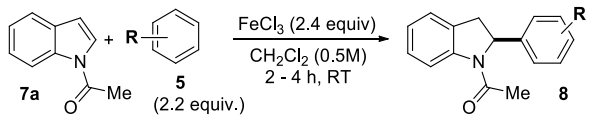


Scheme 2. Arylative dearomatisation of N-Ac indoles mediated by $FeCl_3$.

Results and discussion

We started with N-Ac indole **7a** as the electrophilic indole and we investigated a broad range of aromatic nucleophiles **5** at room temperature in dichloromethane in presence of 2.4 equivalents of $FeCl_3$ (Table 1). Anisole **5a** reacts selectively at the C2-position of **7a** in a 86% yield with a 1:1 mixture of addition products from the *para* and *ortho* positions of **5a** (entry 1). Arenes containing a strong electrondonating group such as 4-methyl anisole **5b**, 1,4-dimethoxybenzene **5c**, 1,3-dimethoxybenzene **5d**, 4-methylphenol **5e** delivered regioselectively and efficiently the C2-arylated N-Ac indoles **8b-e** in 86-46% yields (entries 2-5).[19] Xylenes **5f-h** were also good partners for the regioselective C2-hydroarylation leading to **8f-h** in 60-47% yields (entries 6-8). Fluorine-containing arene **5i** also delivered **8i** in 57% yields (entries 9). Finally, less electron rich arenes **5j,k** surprisingly delivered moderate yields of 3-arylated indolines **6j,k** (entries 10, 11). It seems that the regioselectivity of the hydroarylation is also dependant of the arene nucleophile. The rational for this observation is, presently, unclear to us.

Table 1. Scope of aromatic nucleophiles **5**.

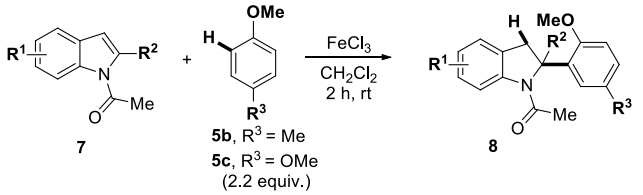


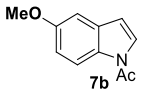
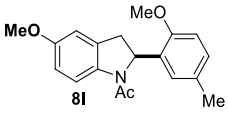
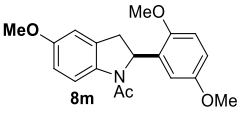
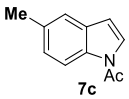
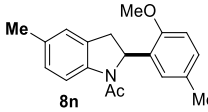
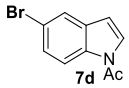
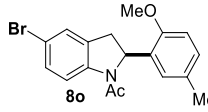
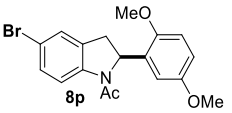
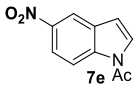
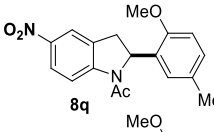
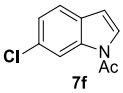
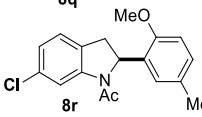
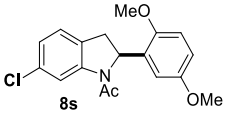
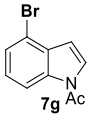
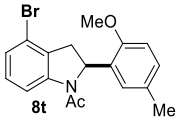
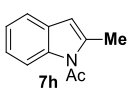
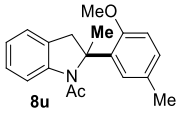
Entry	Arene **5**	Product	Yield[a]
1	**5a**	**8a** / **8a'**	86% (1:1)
2	**5b**	**8b**	86%
3	**5c**	**8c**	59%
4	**5d**	**8d**	48%
5	**5e**	**8e**	46%
6	**5f**	**8f**	54%
7	**5g**	**8g**	60%
8	**5h**	**8h**	47%
9	**5i**	**8i**	57%
10	**5j**	**6j**	22%
11	**5k**	**6k**	27%

a) Isolated yield.

We then turned our attention to the scope of N-Ac indoles **7** with 4-methylanisole **5b** and 1,4-dimethoxybenzene **5c** as nucleophiles (Table 2).

Table 2. Scope of electrophilic indoles **7**.

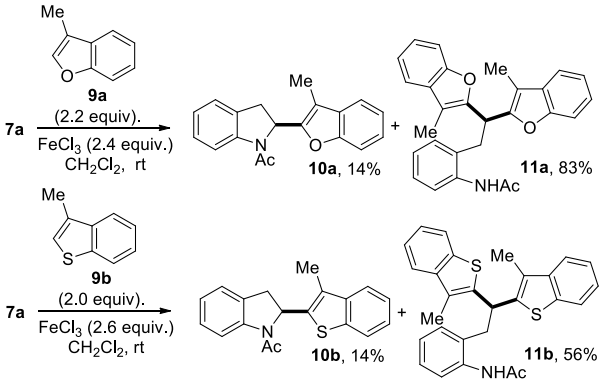


Entry	Indole **7**	R^3	Product **8**	Yield[a]
1		-Me		67%
2	**7b**	-OMe		35%
3		-Me		74%
4		-Me		83%
5	**7d**	-OMe		54%
6		-Me		40%
7		-Me		55%
8	**7f**	-OMe		62%
9		-Me		85%
10		-Me		30%[b]

a) Isolated yield; b) 28% of 3-acetyl-2-methyl-indoles was isolated.

At the 5-position, indoles containing an electrondonating groups such as methoxy and methyl groups reacted efficiently with **5b** delivering **8l,n** in 67% and 74% yields (entries 1,3). The reaction between 5-methoxy-N-Ac indole **7b** and **5c** afforded moderate yield of **8m** (entry 2). The 5-bromo-N-Ac indole reacted well with **5b,c** leading to **8o,p** in 83% and 54% yields (entries 4, 5). Remarkably, a strong electronwithdrawing group such as a nitro at the 5-position afforded 40% yield of **8q** (entry 6). At the 6-postion the chloro derivative **7f** delivered **8r,s** in 55% and 62% yields with **5b,c** (entries 7, 8). Substitution at the 4-position was also tolerated and 4-bromo-arylated indoline **8t** was obtained in 85% yield (entry 9). Finally, indoline **8u**, containing an arylated quaternary carbon, was obtained in 30% yield from 2-methyl-N-Ac indole **7h** (entry 10). In this case, the hydroarylation reaction is in competition with the migration of the acetyl from the N-position to the C3-position.

In order to obtain more diversified drug-like compounds, we studied the C2-addition of heterocycles such as benzothiophene **9a** or benzofuran **9b** to N-Ac indole **7a** (Scheme 3).



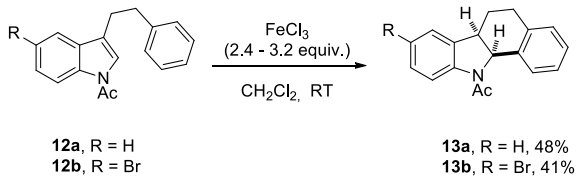
Scheme 3. Addition of heterocycles to N-Ac indole.

Surprisingly, along with the expected C2-hydroarylated compounds **10a,b** we also observed as the major products, the formation of compounds **11a,b**.[19]

Compounds **11a,b** most probably raised from to the unexpected opening of the indole ring of **10a,b** with the cleavage of the C2-NAc bond assisted by the lone-pair of the oxygen or sulfur atom. The resulting benzylic cationic intermediate could then be attacked by the addition of a second heteroarene. Such transformations have been observed during the trimerisation of indoles in acidic conditions [20]

On a final note, we achieved the intramolecular 6-*endo*-trig arylation of **12a,b** which contain an aryl group on the C3-side chain of the indole leading to tetracyclic compounds **13a,b** arylated at the C2-position (Scheme 4).[19] This is in contrast with the usual hydroarylation of 3-substituted N-Ac indoles which proceeds at the C3-position.[3]

The structures of compounds **8b**, **11a** and **13b** were confirmed by X-Ray crystallography (Figure 3).[19]



12a, R = H
12b, R = Br

13a, R = H, 48%
13b, R = Br, 41%

Scheme 4. Intramolecular C2-arylation.

Figure 2. X-Ray structures of compounds **8b**, **11a**, **13b**.

We have achieved the dearomative C2-arylation of N-Ac indoles by functionalization of the C-H bond of electron rich arenes at room temperature, in air with a cheap and non-toxic promotor. A broad scope of N-Ac indoles and arene nucleophiles is tolerated. Presumably, the key of this reaction is the generation of an electrophilic indole by activation of the N-Ac indole with $FeCl_3$ which triggers a Friedel-Crafts reaction.

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19 CCDC 1450298 (**8b**), 1450300 (**11b**) and 1450299 (**13b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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