Room-Temperature and Transition-Metal-Free Intramolecular α-Arylation of Ketones: A Mild Access to Tetracyclic Indoles and 7-Azaindoles

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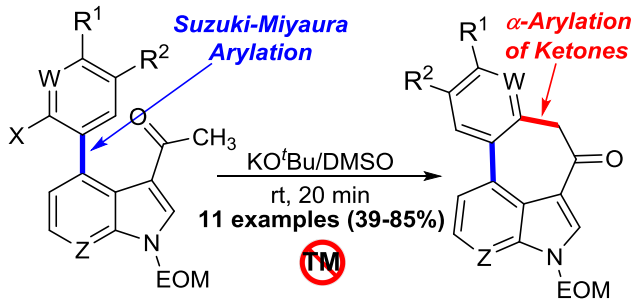
Chérif Adouama,[a] María E. Budén,*[b] Walter D. Guerra,[b] Marcelo Puiatti,[b] Benoît Joseph,[a] Silvia M. Barolo,[b] Roberto A. Rossi*[b] and Maurice Médebielle*[a]

[a] Univ Lyon, Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS, UMR 5246, 1 rue Victor Grignard, 69622 Villeurbanne Cedex, France

[b] INFIQC, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, X5000HUA Córdoba, Argentina

Supporting Information Placeholder



ABSTRACT: A novel approach for the synthesis of tetracyclic indoles and 7-azaindoles is reported. The strategy involves four steps, with a fast rt intramolecular α-arylation of ketones as key step. The reaction was inspected synthetically to achieve the synthesis of eleven novel tetracyclic structures with moderate to very good yields (39-85%). Theoretical combined with experimental studies led us to propose a probable polar mechanism (concerted S_NAr).

Indoles and 7-azaindoles are important heterocycles found in many natural products and pharmaceutical agents.[1] Among indole alkaloids, 3,4-fused indoles have been considered attractive synthetic targets due to their biological activities and synthetic challenges. Examples include the well-known *N*-methylwelwitindolinone C and their isothiocyanate derivatives,[2] 9-deacetylfumigaclavine C,[3] lysergic acid,[4] among others. New synthetic approaches to prepare these compounds and analogues represent still a challenge for organic chemists.

Although various methodologies to prepare 3,4-fused tricyclic indoles are reported,[5] synthetic approaches to prepare 3,4-fused tetracyclic indoles are less explored. Currently one of the most preferred methods to prepare such skeletons is metal-catalyzed reactions (mostly Pd). For example, Rawal *et. al.* in their route to the welwitindolinone alkaloids,[6] used Pd-catalyzed intramolecular enolate arylations. In the same way, other authors used this methodology to generate a variety of tetracyclic indoles and naturals products derivatives in good to excellent yields.[7] Also, Garg *et al*. developed indolyne cyclization (*via* benzyne) as key step to prepare welwitindolinone alkaloids[8] and Pd-catalyzed intramolecular Heck reaction were used as a key transformation for the synthesis of lysergic acid[9] and (-)-hapalindole U and (+)-ambiguine H.[10]

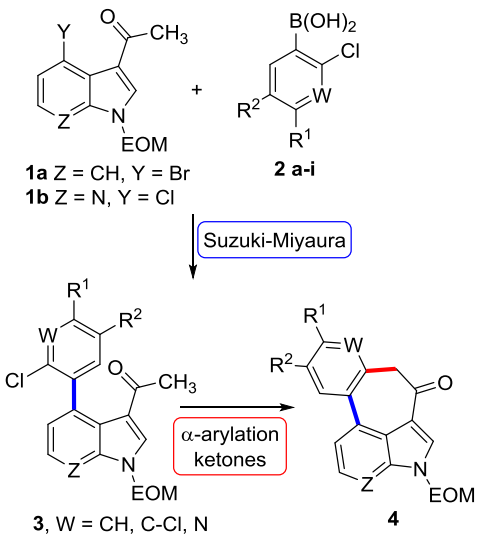
Inter- and intramolecular α-arylation of ketones involving metal catalyzed processes has been widely employed.[11] However, there are still many issues due to the use of hazardous reagents, additives, and expensive, sensitive reagents, which need to be overcome. The $S_{RN}1$ reaction has been successfully applied as a mild alternative for the arylation of α-carbonyl compounds and noteworthy in the context of natural products synthesis.[12]

These previous reports encourage us to study a novel approach to prepared unprecedented 3,4-fused tetracyclic indoles and 7-azaindoles **4**, based on α-arylation of ketones from haloindole derivatives (Scheme 1). To the best of our knowledge there is only one example reporting the synthesis of such type of skeleton[13] albeit obtained from a Rh-catalyzed reaction. The synthetic strategy involves, as first step the construction of compounds **3**, where 3-acetyl-4-bromoindole (**1a**) or 3-acetyl-4-chloro-7-azaindole (**1b**) derivatives are substituted in C_4 position by an *o*-aryl halide group, *via* Suzuki-Miyaura reaction (Scheme 1). Then, ketones **3** could undergo an intramolecular α-arylation, to form the 3,4-fused tetracyclic indoles and 7-azaindoles **4** (Scheme 1).

The precursors **1a** and **1b** were prepared in two steps from commercially available 4-bromoindole and 4-chloro-7-

azaindole.[14,15] The following step is Pd-catalyzed cross-coupling reaction of **1a** or **1b**, with different 2-halophenyl boronic acids (**2a-i**)[15] and 3-acetyl-4-arylindole and 7-azaindole derivatives (**3a-n**) were obtained in moderate to excellent yields (29-98%).[15] Thus, fifteen precursors were prepared to evaluate electronic factors in the cyclization reaction.

SCHEME 1. Synthetic Strategy for 3,4-fused tetracyclic indoles and 7-azaindoles (4)



The key step in the sequential synthesis of tetracyclic indoles and 7-azaindoles involves an intramolecular α-arylation of indole-derived methyl ketones, **3a-o**. The dark reaction of indole **3a** (Z = W = CH, $R^1 = CF_3$, R^2 = H) with KO^{t}Bu (5 equiv) in DMSO, gave the cyclization product **4a** in 85% yield (entry 1).[16] The yield of **4a** did not increase in the presence of pinacolone enolate ion or Fe^{2+} salts.[17] Lower conversion and reduced yield of cyclized product **4a** was found when the reaction was performed in shorter time or with lower amount of base (entries 2 and 3). The reaction is inhibited in the presence of *p*-dinitrobenzene (*p*-DNB) which is used as a good electron acceptor in ET reactions (Table 1, entry 4). However, because of its strong electron-withdrawing character, S_NAr displacements of a nitro group is observed with a large variety of nucleophiles.[15,18,19] In addition it is possible that the enolate might react with *p*-DNB by an electron-transfer interrupting therefore the cyclization process. Moreover, the addition of TEMPO also caused inhibition of the reaction (entry 5). However, the absence of adduct does not allow us to confirm the presence of radicals as intermediates.

In comparison, 3-acetyl-4-(2-chlorophenyl)-indole (**3b**, W = Z = CH, $R^1 = R^2$ = H) was less reactive than **3a**, giving only a 37% yield of **4b** after 20 min (entry 6, Table 1). If the reaction was pushed further, similar conversion and lower yield of **4b** were obtained (entry 7, Table 1).[20] Moreover, the effect of photostimulation was evaluated using a fluorescent lamp (250 W), giving full conversion and slight increase of the yield of **4b** (46% yield, entry 8).[20] Interestingly, use of NaO^{t}Bu, NaH or NBu_4OH in DMSO[15] in the reaction with **3a** didn't provide **4a**, while KHMDS in DMSO only provided **3a** in 20% yield. In addition, the reaction of indole **3a** or 7-azaindole derivative **3c** with KO^{t}Bu in THF could provide **4a** and **4c** in 65% and 48% yields, respectively (Scheme 2).[15, 21]

To extend the application of the developed methodology, we evaluated the reactivity of a different 3-acetyl-4-arylindoles (**3d-h**). Thus, while the precursors substituted with EWG or without substitution reacted well giving the tetracyclic indoles with moderate to very good yields (for **4b**, **4d**, **4g** and **4h**) (Scheme 2), those substituted with EDG did not (**4e** and **4f**). The same behavior was observed when 3-acetyl-4-aryl-7-azaindole precursors were employed, giving good yields for EWG and without substitution (**4i-4j** and **4m-4n**, 39-84% yields). However, when the photostimulated reaction of **3k** (Z = N, R^2 = OMe) was carried out in $NH_{3(liq)}$ as a solvent, the cyclization product **4k** was obtained in 53% yield.[22] It worth noting that in dark condition no product **4k** was found, the substrate **3k** was recovered completely, ruling out S_NAr mechanism in NH_3 solvent at this temperature (-33 °C). These results reinforce the fact that changes in the experimental conditions (temperature, solvent and photostimulation), may change the involved mechanism.[23]

TABLE 1. Intramolecular α-Arylation Reactions of 3-acetyl-4-(2-chloroaryl)indoles (3a and 3b)

entry	KO^{t}Bu (equiv)	additive (equiv)	time (min)	yield (%)[b]
1	5	---	40	**3a** ---; **4a** 85
2	5	---	20	**3a** 7; **4a** 78
3	2	---	40	**3a** 36; **4a** 49
4	5	*p*-DNB (0.4)	20	**3a** 78; **4a** 7
5	5	TEMPO (0.4)	20	**3a** 81; **4a** 4
6	5	---	20	**3b** 56; **4b** 37
7	5	---	120	**3b** 53; **4b** 8
8	5	hv, 250 W	20	**3b** ---; **4b** 46

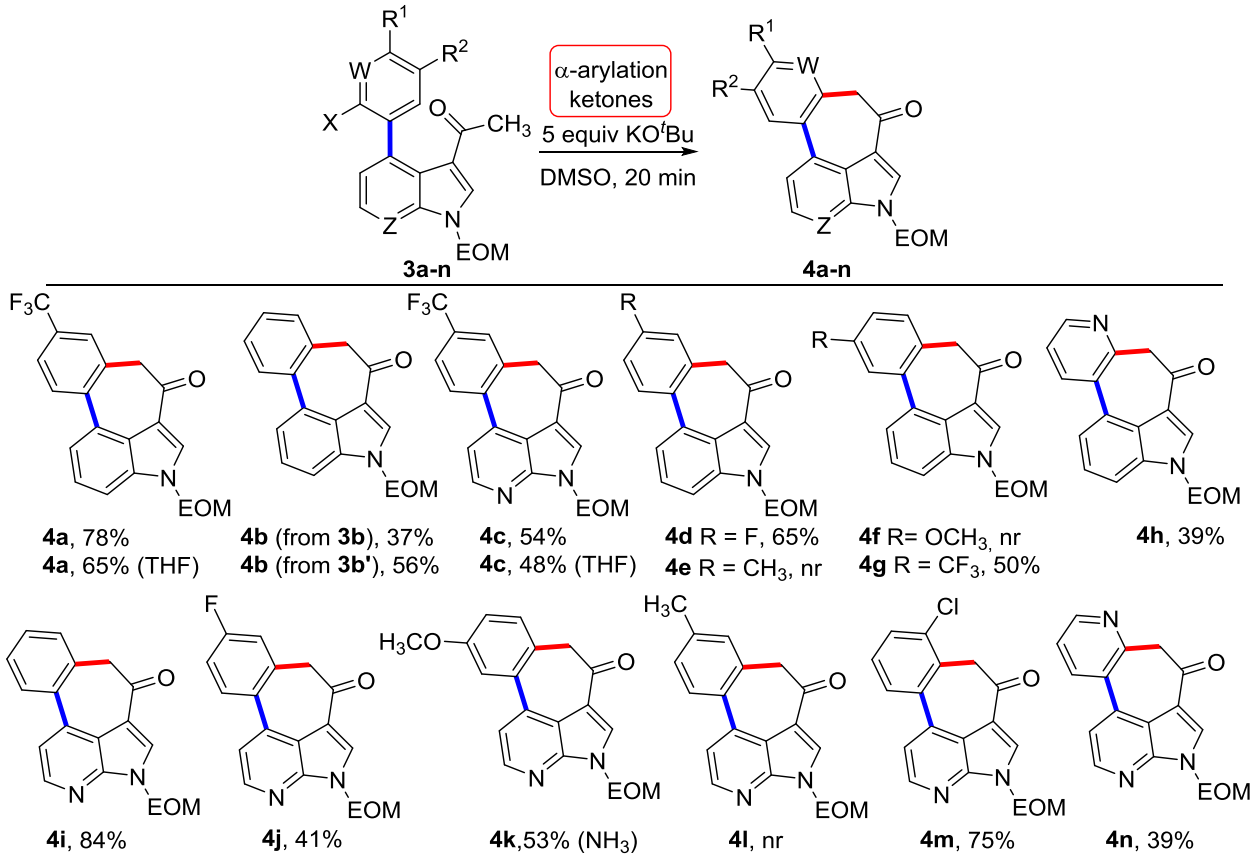
[a]The reaction was carried out under Ar atmosphere using **3** (1 equiv, 0.2 mmol), KO^{t}Bu (5 equiv), in DMSO. [b] Isolated yield.

In the intramolecular C-C arylation reaction, a marked difference is observed depending on the electronic nature of the substituent in the ring where the leaving group is located. The reaction of **3** with KO^{t}Bu in excess would afford enolate anion $\mathbf{3}^-$ (Scheme 3). Depending to initiation step, three pathways are possible (Path A, B and C). An intermolecular ET (Path A) affords product **4** by $S_{RN}1$ mechanism. The second possibility is an intramolecular ET (Path B) from $\mathbf{3}^-$ to the aromatic ring where the chlorine is found which gives diradical anion $(\mathbf{3}^{\bullet})^{\bullet-}$. This intermediate has then two different pathways, Path B_1 (radical-radical coupling) or Path B_2 (Substitution Nucleophilic Aromatic *via* Electron Transfer, S_N(ET)Ar), to finally gives product **4**.[18] The third possibility is an addition–elimination mechanism (S_NAr, Path C).

Then, the effect of the leaving group for the precursors **3b** and **3b'** where chlorine and fluorine are the leaving groups, respectively, was analyzed (Scheme 2). The reaction using KO^{t}Bu (5 equiv) in DMSO, leads to the formation of the product **4b** in 37% and 56% yield from **3b** and **3b'**, respectively. It is known that in S_NAr mechanism, fluorine is a much better leaving group than other halogens, which agrees with those results.[18] However, ET mechanisms could not be ruled out because there are precedents where fluorinated and chlorinated analogs react through ET mechanisms with similar conversion.[24] Finally, benzyne mechanism is discarded since the substrate **3m** (W = C-Cl, Z = N, $R^1 = R^2$ = H), which has both

ortho positions to the leaving group blocked, reacted giving the cyclization product **4m** (with chlorine atom retention) in 75% yield (Scheme 2).

SCHEME 2. Synthesis of tetracyclic indoles and 7-aza indoles (4a-n) through α-Arylation Reaction of 3-acetyl-4-(2-chloroaryl)indoles and 3-acetyl-4-(2-chloroaryl)7-aza indoles (3a-n)



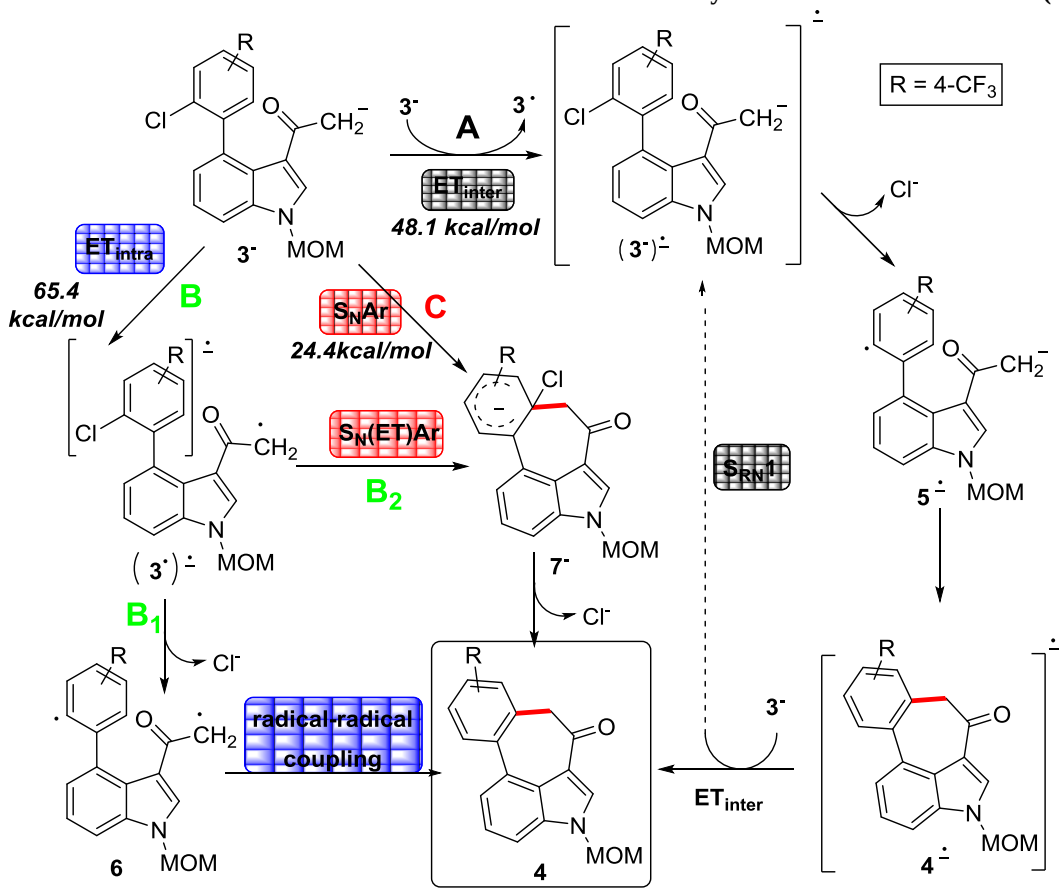
Since the experimental probes were inconclusive, the feasibility of the different steps of the proposed mechanism (A, B and C) was evaluated by computational study (Scheme 3).[15] For ET mechanisms, we employed the Marcus−Hush theory to calculate the activation free energy ($\Delta G_{ET}^{\ddagger}$) involved in an outer-sphere ET.[15, 23] For Path A and B, it was found that the initial $\Delta G_{ET}^{\ddagger}$ is endergonic step (48.1 kcal/mol for intermolecular ET *vs* 65.4 kcal/mol for intramolecular ET). While for S_NAr mechanism the $\Delta G^{\ddagger}$ for the coupling is 24.4 kcal/mol. Besides, computational calculations predict that if a S_NAr occurs, this transformation proceeds through a concerted mechanism and not via a discrete non-aromatic Meisenheimer complex intermediate **7**$^-$.[25] In order to justify the reactivity found only with the potassium enolate, computational calculations were made adding discrete molecules of K^+ or Na^+ as counterions. For both the K and Na salt, it was found that the C-C coupling reactions are exergonic at ΔG = -59.0 and -53.0 kcal/mol, respectively, with activation energies of 24.5 and 27 kcal/mol. Even these differences in activation energy is not large, it agrees with the reactivity showed experimentally.

In addition, anions **3a**$^-$ and **3c**$^-$ were characterized by electrochemical techniques, using cyclic voltammetry. For both anions, irreversible reduction steps with relatively high negative reductive potential of **3a**$^-$ (-2.74 V *vs* Ag/Ag$^+$) and **3c**$^-$ (-2.76 V *vs* Ag/Ag$^+$) were measured.[26] Likewise, in both cases an irreversible peak (enolate oxidation) is observed at oxidation potentials around -0.2 V for **3a** and -0.51 V for **3c** (*vs* Ag/Ag$^+$). These results suggested that ET is highly endergonic, according with computational data.

In summary, we presented a transition-metal-free α-arylation of ketones methodology for the synthesis of new 3,4-fused tetracyclic indole and 7-azaindoles (**4**). Following this synthetic strategy, eleven 3,4-fused tetracyclic skeletons were obtained in moderate to very good yields (39-85%), in the final cyclization step. A limitation of the methodology is the presence of EDG (Me and OMe) in the aryl moiety where final ring-closure was not possible. However, only in the case of the 7-azaindole with the OMe group could be obtained the cyclized product in NH_3 under photostimulation, probably by ET mechanisms.

Together with the scope of the reaction, a complete mechanistic picture has been presented with a comparative and detailed study allowing us to conclude that intramolecular α-arylation reaction could take place by concerted S_NAr (similar to Path C), where anion **7**$^-$ represents the structure of the transition state in the potential energy surface instead of a discrete intermediate. This is supported by computational and electrochemical data as well as difference reactivity observed with EWG and EDG substitutions.

SCHEME 3. Different Possible Mechanisms for α-Arylation Reaction of 3a (with MOM protection)



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental Procedure, compound characterization data, computational and electrochemical data (file type, i.e., PDF).

AUTHOR INFORMATION

Corresponding Author

* E-Mail: rossi@fcq.unc.edu.ar
* E-Mail: maurice.medebielle@univ-lyon1.fr
* E-Mail: eugebuden@yahoo.com.ar

Notes

The authors declare no competing financial interest.

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[14] The NH protection with EOM is necessary before cyclization reaction; indeed, the p*K*a of ketones and the NH are anticipated to be close; in presence of KO^{t}Bu deprotonation will take place at both sites and can give rise to unwanted side reactions.

[15] See Supporting Information.

[16] For a related α-arylation, see: Emery, K.; Tuttle, T.; Murphy, J. A. *Tetrahedron* **2016**, *72*, 7875-7887.

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[19] *p*-DNB reacted in presence of KO^{t}Bu in DMSO after 20 min giving the S_NAr product.

[20] Probably, the precursor **3b** and/or the product **4b**, in the reducing medium, decompose to other unidentified compounds.

[21] As a reviewer suggested, it is known that enolates could form aggregates in low polar solvents such as THF, and therefore, probably, the yields of both reactions are lower than in DMSO.

[22] Probably, ET from excited state of the enolate to the aryl moiety is taking place as initiation step.

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[26] We are not aware of any available electrochemical data of 4-halogeno indoles and 4-halogeno-7-azaindoles.