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Functionalization of pyridyl ketones using deprotolithiation-*in situ* zincation

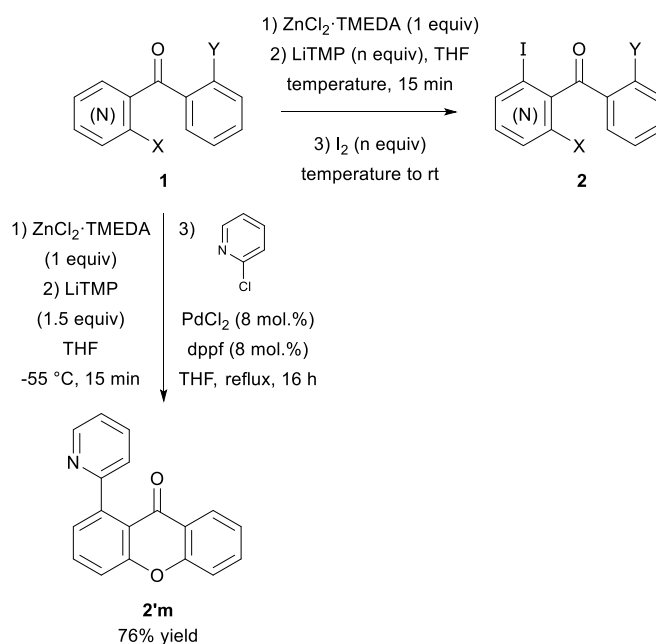
Madani Hedidi,^{a,b,c} William Erb,^{a,*} Frédéric Lassagne,^a Yury S. Halauko,^{d,*} Oleg A. Ivashkevich,^d Vadim E. Matulis,^e Thierry Roisnel,^f Ghenia Bentabed-Ababsa^{b,*} and Florence Mongin^a

The metallation of aryl ketones was achieved by using LiTMP in the presence of ZnCl₂-TMEDA, as evidenced by subsequent interception with iodine or by palladium-catalysed cross-coupling reaction. One of the synthesized iodo ketones has been further elaborated to reach derivatives of biological interest.

Pyridines play a large part in biological processes (nicotine, niacin, NADP, vitamin B₆...), in pharmaceuticals and agrochemicals,¹ as well as in organic materials.² In addition, pyridyl ketones bearing a halogen at the position adjacent to the carbonyl function are key intermediates to access heterocyclic scaffolds of interest such as azaflorenones,³ azaxanthenes,⁴ naphthyridones,⁵ and thieno-,⁶ pyrazolo-⁷ and isoxazolo-pyridines.⁸

Even if deprotonative lithiation⁹ has been largely used to regioselectively functionalize pyridines,¹⁰ the method has never been extended to pyridyl ketones due to their low compatibility with organolithiums. Mixed lithium-nonalkali metal combinations have been developed to achieve chemoselective deprotometallation of aromatics.¹¹ In this context, the 1:1 mixture of homometallic amides LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) and Zn(TMP)₂,¹² obtained by mixing in a 3:1 ratio LiTMP and ZnCl₂-TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) in THF (THF = tetrahydrofuran), was successfully employed with a large range of sensitive substrates.¹³ Such a synergy, attributed to reversible deprotolithiation shifted by zinc-mediated transmetallation¹² (or 'trans-metal trapping'¹⁴), has since been extended to the use of LiTMP in the presence of ZnCl₂·2LiCl, MgCl₂ or CuCN·2LiCl.¹⁵

Herein, we report the efficiency of aryl ketones as directing groups for LiTMP-mediated deprotometallation of pyridines and other arenes in the presence of ZnCl₂-TMEDA as *in situ* trap (Scheme 1, Table 1).



Scheme 1 Zincation of aryl ketones **1** using LiTMP in the presence of ZnCl₂-TMEDA followed by iodolysis or palladium-catalysed cross-coupling to afford ketones **2** and **2'**.

Thus, after optimization of the reaction conditions (using four different reaction temperatures from -70 to -10 °C and different amounts of LiTMP from 1 to 3 equiv), treatment of 2-benzoylpyridine (**1a**) in THF containing ZnCl₂-TMEDA (1 equiv) with LiTMP (1.5 equiv) at -30 °C for 15 min and then iodine led to the 3-iodo derivative **2a** in 50% yield (entry 1). Similarly, 4-benzoylpyridine (**1b**) was converted to the 3-iodo derivative **2b** by using LiTMP (2 equiv); with this substrate benefiting from two free positions adjacent to the benzoyl group, a second deprotonation was observed to some extent, as evidenced by the competitive formation of the diiodo **2b'** (entry 2).

3-Benzoylpyridine (**1c**) is more prone to nucleophilic attack onto the ring than its 2- and 4-isomers.¹⁶ As a consequence, deprotolithiation-zincation could only be evidenced by subsequent iodolysis at temperatures below -50 °C. Using LiTMP (1.5 equiv) at -55 or -70 °C for 15 min and then iodine provided the 4-iodo derivative **2c** in 30 or 37% yield, respectively (entry 3).

When present at pyridine 2-position, halogens are known to acidify the 4-position, as shown by p*K*_a values calculated in THF.^{13a} The 2-halogeno 3-benzoylpyridines **1d-h** were thus prepared.¹⁷ Accordingly, when similarly reacted by using LiTMP at -55 °C, the iodo derivatives **2d-g** were isolated in improved yields, in line with the long range effects of fluorine and chlorine (entries 4-7). In contrast, the reaction from **1h** proved more complex, giving the iodide **2h** in a modest yield (entry 8).

^a Chimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226, Université de Rennes 1-CNRS, Bâtiment 10A, Case 1003, Campus de Beaulieu, 35042 Rennes, France.
E-mail : william.erb@univ-rennes1.fr

^b Laboratoire de Synthèse Organique Appliquée, Faculté des Sciences, Université d'Oran 1 Ahmed Ben Bella, BP 1524 El M'Naouer, 31000 Oran, Algeria.
E-mail : badri_sofi@yahoo.fr

^c Present address: Département de Chimie, Faculté des Sciences, Université Hassiba Benbouali de Chlef, Hay Es-Salem, RN 19, 02000 Chlef, Algeria.

^d UNESCO Chair of Belarusian State University, 14 Leningradskaya Str., Minsk 220030, Belarus.
E-mail : hys@tut.by

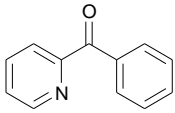
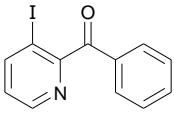
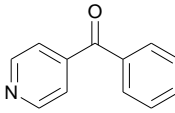
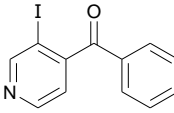
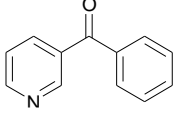
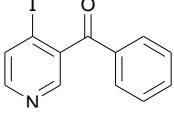
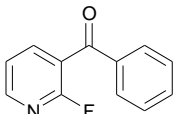
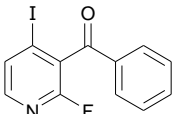
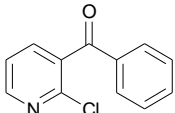
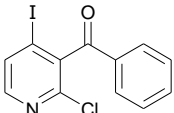
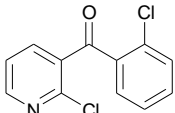
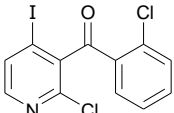
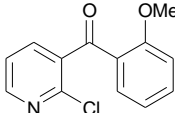
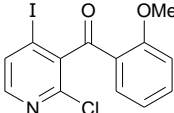
^e Research Institute for Physico-Chemical Problems of Belarusian State University, 14 Leningradskaya Str., Minsk 220030, Belarus.

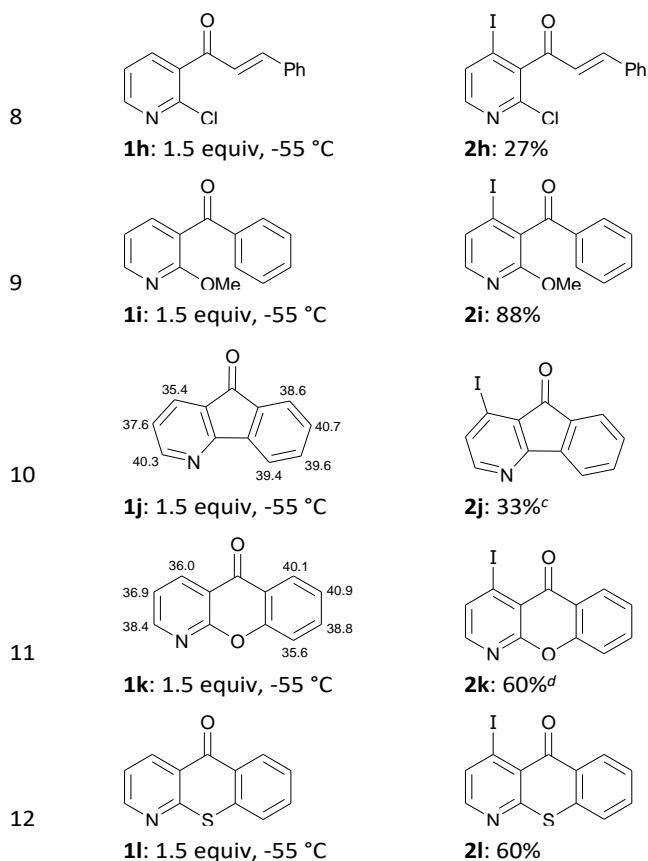
^f Centre de Diffractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226, Université de Rennes 1-CNRS, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes, France.

† Electronic supplementary information (ESI) available: General procedures, experimental procedures and compound characterizations, ¹H and ¹³C NMR spectra of the new compounds, and X-ray crystallographic data. CCDC 1475309 (**2j'**), 1475009 (**2k'**) and 1475010 (**2n'**). For ESI and crystallographic data in CIF see DOI: 10.1039/x0xx00000x

The presence of a methoxy group at 2-position of 3-benzoylpyridine also had a positive impact on the course of the reaction since involving **1i** in the sequence furnished the iodo derivative **2i** in 88% yield (entry 9). Whereas this group does not acidify remote pyridine 4-position,^{13b} it acts by making the pyridine ring less sensitive towards competitive nucleophilic attack. Indeed, based on the ¹H NMR chemical shifts in CDCl₃ of **1c** (8.12 and 8.82 ppm for H4 and H6, respectively) and **1i** (7.72 and 8.32 ppm for H4 and H6, respectively), one can predict as shown by Handy and Zhang¹⁸ that the partial positive charges at C4 and C6 will be reduced for **1i**.

Table 1 Substrates **1a-l**, calculated pK_a(THF) values for **1j** and **1k**, conditions used for the deprotonation-zincation, and iodinated aryl ketones **2a-l** obtained.

Entry	Substrate/n/temperature	Product/yield ^a (%)
1	 1a : 1.5 equiv, -30 °C	 2a : 50%
2	 1b : 2 equiv, -30 °C	 2b : 45% ^b
3	 1c : 1.5 equiv, -55 °C 1c : 1.5 equiv, -70 °C	 2c : 30% 2c : 37%
4	 1d : 1.5 equiv, -55 °C	 2d : 63%
5	 1e : 1.5 equiv, -55 °C	 2e : 73%
6	 1f : 1.5 equiv, -55 °C	 2f : 78%
7	 1g : 1.5 equiv, -55 °C	 2g : 70%



^a Yield after purification by column chromatography. ^b 4-Benzoyl-3,5-diiodopyridine (**2b'**) was also obtained in 10% yield. ^c 1,5-Diiodo-4-azafluorenone (**2j'**) was also obtained in 20% yield. ^d 1,6-Diiodo-4-azaxanthone (**2k'**) was also obtained in 10% yield.

The behaviour of the ketones **1j-l**, possessing reduced flexibility on carbonyl direction, was similarly examined. 4-azafluorenone (**1j**) was converted to the 1-iodo derivative **2j** in a moderate yield, similar to that obtained from 3-benzoylpyridine (**1c**). In the case of **1j**, the phenyl ring was also attacked to a lesser extent at a position facing the pyridine nitrogen to afford the diiodide **2j'** (entry 10, Figure 1). In contrast with the reaction from **1j**, the sequence using 4-azaxanthone (**1k**) and 4-azathioxanthone (**1l**) provided the iodides **2k** and **2l** in higher 60% yields (entries 11 and 12).

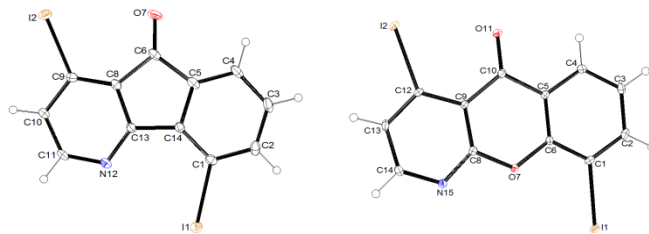
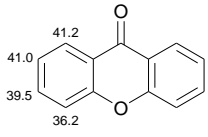
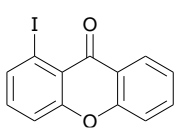
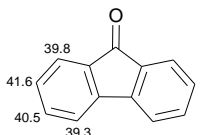
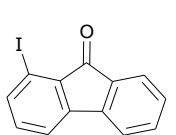
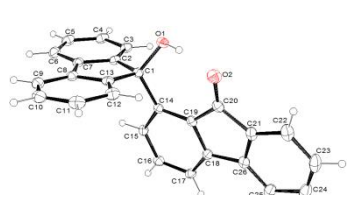
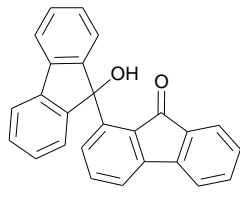


Figure 1 ORTEP diagrams (30% probability) of compounds **2j'** and **2k'**.

In order to evaluate the scope of the method, we chose other aromatic substrates.¹⁹ When compared with its 4-aza analogue **1k**, xanthone (**1m**) similarly led to the 1-iodo **2m** in 72% yield. On the contrary, as previously noted between **1j**

and **1k**, the reaction from **1n** was less efficient than from **1m**. Indeed, 1-iodofluorenone (**2n**) was obtained in 52% yield, but together with the ketone **2n'** (35% yield) resulting from an addition of the metallated product to **1n** (Scheme 1, Table 2). As organozincs hardly react with ketones, the product **2n'** could rather result from an addition of 1-lithiofluorenone to **1n** more rapid than its trapping by the zinc species. These results suggest that the carbonyl direction in the metallated derivative coming from **1n** is less prone to stabilize a 1-lithio compound than that from **1m**.

Table 2 Substrates **1m** and **1n** and their calculated pK_a (THF) values, conditions used for the deprotonation-zincation, iodinated aryl ketones **2m** and **2n** obtained, and ORTEP diagram (30% probability) of compound **2n'**.

Entry	Substrate/n/temperature	Product/yield ^a (%)
1	 1m : 1.5 equiv, -55 °C	 2m : 72%
2	 1n : 1.5 equiv, -55 °C	 2n : 52%
		 2n' : 35%

^a Yield after purification by column chromatography.

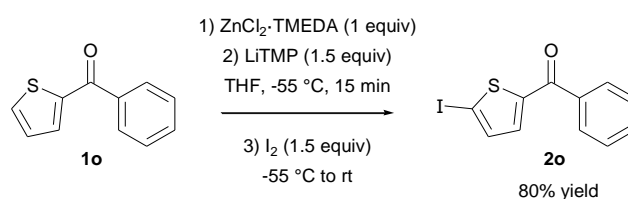
Interestingly, the deprotonation-*in situ* zincation could be combined with a subsequent Negishi cross-coupling reaction.²⁰ Thus, using catalytic amounts of PdCl₂ as palladium source and 1,1'-diphenylphosphinoferrrocene (dppf) as ligand with 2-chloropyridine^{12a} allowed **2'm** to be formed from 9-xanthone (**1m**) in 76% yield (Scheme 1).

CH acidities are in general useful data to better understand deprotonation outcomes, in particular regarding regioselectivity issues. We thus calculated selected pK_a values in THF solution by means of quantum chemistry at the DFT B3LYP level of theory.¹³ After geometry optimization and calculation of the vibrational frequencies by using the 6-31G(d) basis set, the single point energies were obtained using the 6-311+G(d,p) basis set. The solvent influence was treated through the polarized continuum model (PCM) with the default parameters for THF. Finally, the pK_a values were reached from the Gibbs energy of the homodesmotic reaction between the studied and probe heterocycles.

That both sets of CH acidity values for **1m** and **1n** are rather similar (Table 2) supports the role of the carbonyl direction on the course of the reaction through coordination.

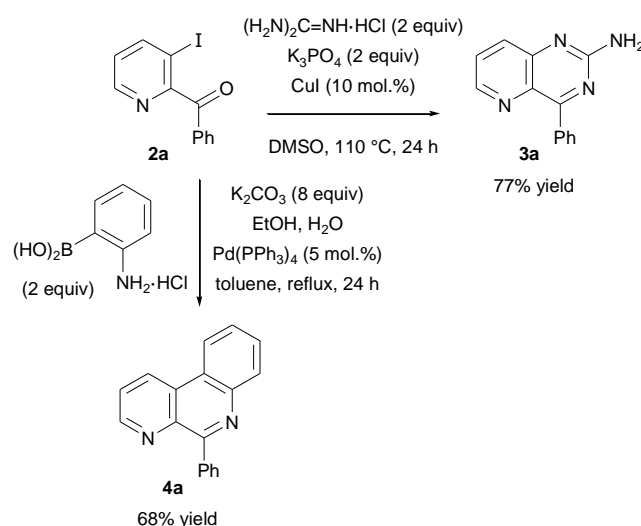
Analogously, the difference observed between the pK_a values of **1j** and **1k** is not significant enough to allow for a rationalization of the distinct yields noted, rather suggesting a more efficient stabilization of the metallated compound by the carbonyl group in the case of **1k** at the origin of the higher yield. Besides, the formation of dimetallated products from **1j** and **1k**, as demonstrated by isolation of **2j'** and **2k'** (Figure 1), could be favoured for the former by a nitrogen assistance and, for the latter, by a relatively low pK_a value (35.6) at the 6-position (Table 1).

Finally, when 2-benzoylthiophene (**1o**) was submitted to LiTMP in the presence of ZnCl₂-TMEDA as before, the reaction took place next to sulphur to afford after iodolysis the iodo derivative **2o** in 80% yield (Scheme 2).



Scheme 2 Zincation of phenyl 2-thienyl ketone (**1o**) using LiTMP in the presence of ZnCl₂-TMEDA followed by iodolysis to afford the iodinated 2-thienyl ketone **2o**.

To move towards nitrogen-containing derivatives of biological interest, 2-benzoyl-3-iodopyridine (**2a**) was involved in further reactions (Scheme 3). A catalyst-base system was first optimized to perform guanidine copper-catalysed *N*-arylation.²¹ Upon treatment with K₃PO₄ as base and CuI as catalyst source in the presence of DMSO, the iodide **2a** was converted to the pyrido[3,2-*d*]pyrimidine **3a** in 77% yield. Besides, cyclizing Suzuki coupling²² was performed from the ketone **2a** and 2-aminophenylboronic acid under palladium catalysis to provide 5-phenylbenzo[*f*][1,7]naphthyridine (**4a**)²³ in 68% yield.



Scheme 3 Conversion of 2-benzoyl-3-iodopyridine (**2a**) to derivatives of biological interest.

In summary, we have reported a short and simple access to iodinated aryl ketones. Additionally, transition metal-mediated reactions occurring with cyclization led to elaborated scaffolds. Applications towards the synthesis of libraries of compounds for biological evaluation are currently under investigation in our laboratory.

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