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Layal Hariss, Kamal Bou Hadir, Mirvat El-Masri, Thierry Roisnel, René Grée, et al.. Preparation of imidazo[1,2-a]-N-heterocyclic derivatives with gem-difluorinated side chains. Beilstein Journal of Organic Chemistry, 2017, 13, pp.2115-2121. 10.3762/bjoc.13.208 . hal-01631917

**HAL Id: hal-01631917**

**<https://univ-rennes.hal.science/hal-01631917>**

Submitted on 3 May 2018

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## Preparation of imidazo[1,2-*a*]-*N*-heterocyclic derivatives with *gem*-difluorinated side chains

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### Full Research Paper

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**Keywords:**

aerobic oxidative coupling; imidazo[1,2-*a*]-*N*-heterocycles; *gem*-difluoroalkyl derivatives; propargylic fluorides

*Beilstein J. Org. Chem.* **2017**, *13*, 2115–2121.

doi:10.3762/bjoc.13.208

Received: 07 July 2017

Accepted: 27 September 2017

Published: 10 October 2017

This article is part of the Thematic Series "Organofluorine chemistry IV".

Guest Editor: D. O'Hagan

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## Abstract

Using an aerobic oxidative coupling, different new imidazo[1,2-*a*]-*N*-heterocycles with *gem*-difluoroalkyl side chains have been prepared in fair yields by the reaction of *gem*-difluoroenones with aminopyridines, -pyrimidines and -pyridazines. Condensed heterocycles of this type play an important role as key core structures of various bioactive compounds. Further, starting with a chloroimidazopyridazine derivative, Pd-catalyzed coupling reactions as well as nucleophilic substitutions have been performed successfully in order to increase the molecular diversity.

## Introduction

Nitrogen-containing heterocyclic compounds are frequently found in bioactive naturally occurring compounds, as well as in the synthetic pharmacopeia. Imidazo[1,2-*a*]pyridine is an important heterocyclic system present in many molecules featuring diverse biological activities, such as antiviral, antimicrobial, antitumor, anti-inflammatory, antiparasitic, hypnotic, etc. [1-5]. It is recognized as a key scaffold due to its broad occurrence in a number of drug candidates and drugs, such as

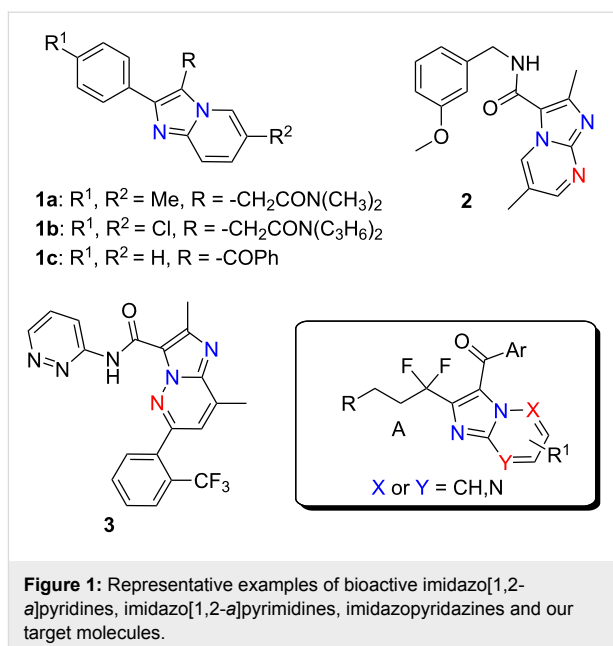
zolpidem [6] (**1a**, used in the treatment of insomnia), and alpidem [6] (**1b**, an anxiolytic agent). Some imidazopyridine derivatives also act as  $\beta$ -amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotonic agents [7-10]. Further, the biological activities of imidazo[1,2-*a*]pyridines proved to be strongly depending upon the nature of substituents at C2 and C3 positions. For instance, the 3-arylimidazo[1,2-*a*]pyridines **1c** demonstrated also good anticancer

properties [11,12], while imidazo[1,2-*a*]pyrimidines **2** are also known for their antituberculosis activity [13], and imidazopyridazine **3** acts as a sirtuin modulator [14].

On the other hand, the incorporation of fluorine or fluorinated groups into organic molecules has been widely recognized as a general strategy toward drug development in pharmaceutical research. This is connected to fluorine's electronegativity, size, and lipophilicity [15,16], which can strongly improve the biological properties of molecules through, for instance, increase of metabolic stability and bioavailability for many drugs and pharmacological tools. So, the preparation of fluorinated molecules is a very attractive research area for organic and medicinal chemists [17–20].

Our research program aims to synthesize new fluorinated molecules based on the easy access and the versatility of fluorinated propargylic derivatives [21]. Thus, taking into account the known biological properties of the imidazo-fused *N*-heterocycles, we became interested in the preparation of new derivatives of this type possessing *gem*-difluorinated side chains as indicated in Figure 1. Such new fluorinated heterocycles could be of interest for bioorganic and medicinal chemistry studies.

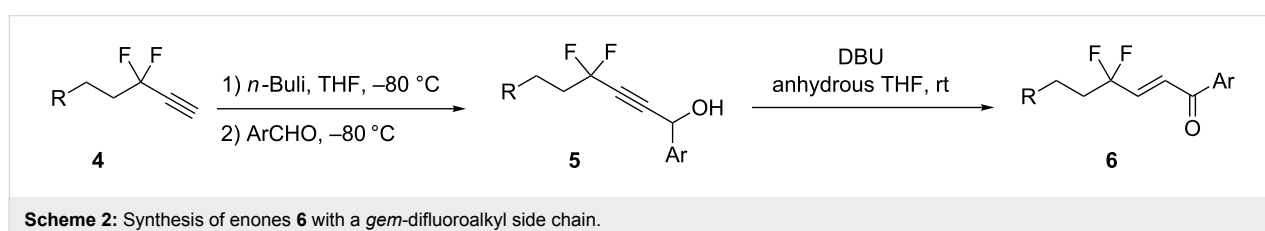
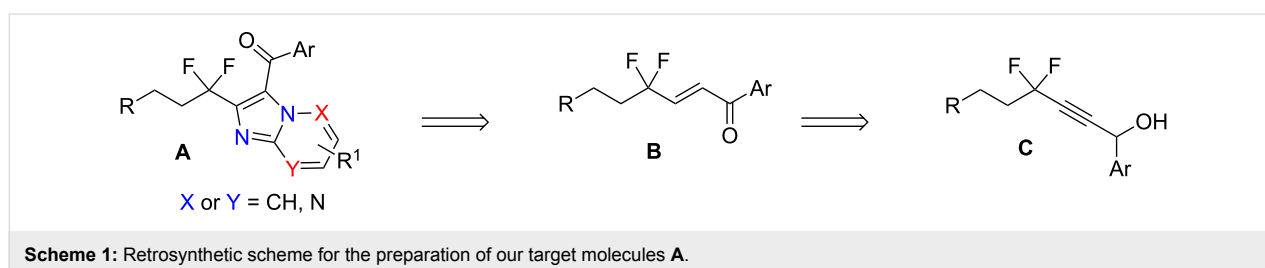
Several synthetic approaches for imidazopyridines are available, but only a few examples have been reported to date for the construction of this scaffold with introduction of fluorine [22], trifluoromethyl [23] or trifluoroethyl groups [24]. Herein, we report the synthesis of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, and imidazopyridazines with fluorinated side chains following an efficient strategy developed by Hajra et al. [25]. This methodology, developed for the synthesis of 3-aryl-imidazopyridines, involves a copper(II) acetate-catalyzed aerobic oxidative amination and it proceeds through a



tandem Michael addition followed by an intramolecular oxidative amination. Therefore, our target molecules **A** could be synthesized by the oxidative coupling of 2-aminopyridines with  $\alpha,\beta$ -unsaturated ketones **B**, themselves easily accessible from *gem*-difluoropropargylic alcohols **C** through a base-mediated isomerization process (Scheme 1) [26,27].

## Results and Discussion

The required propargylic alcohols **5a–e** (type **C**, Scheme 1) were obtained in 27–73% yields by reaction of the lithium salt of the easily accessible *gem*-difluoro propargylic derivatives **4** [28] with aromatic aldehydes. Then, the DBU-mediated isomerization afforded the desired enones **6a–e** in 21–66% yields (Scheme 2 and Table 1).



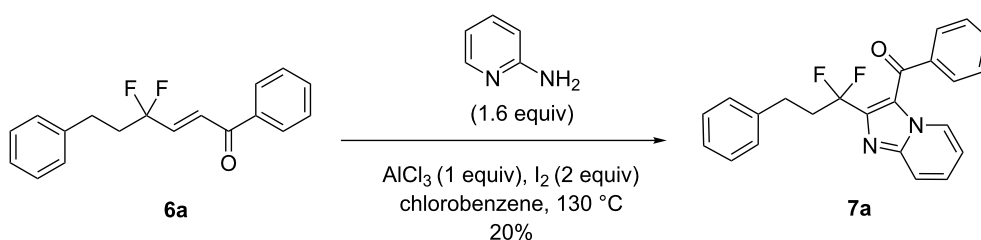
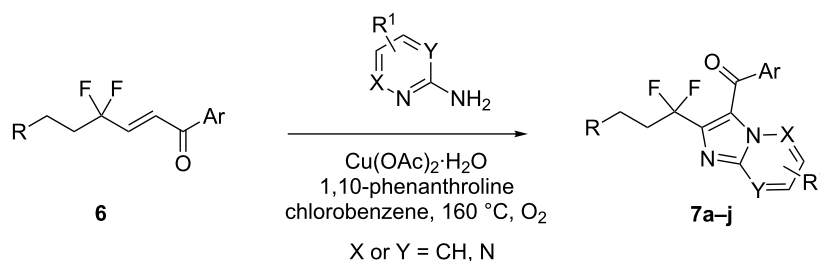
**Table 1:** Synthesis of enones **6a–e**.

| Entry | R                   | Ar                     | <b>5</b> : yield (%) | <b>6</b> : yield (%) |
|-------|---------------------|------------------------|----------------------|----------------------|
| 1     | Ph                  | Ph                     | <b>5a</b> (73%)      | <b>6a</b> (62%)      |
| 2     | Ph                  | <i>o</i> -PhBr         | <b>5b</b> (70%)      | <b>6b</b> (60%)      |
| 3     | Ph                  | 2-naphthaldehyde       | <b>5c</b> (71%)      | <b>6c</b> (50%)      |
| 4     | Ph                  | <i>p</i> -anisaldehyde | <b>5d</b> (27%)      | <b>6d</b> (21%)      |
| 5     | CH <sub>2</sub> OBn | Ph                     | <b>5e</b> (65%)      | <b>6e</b> (66%)      |

For the synthesis of the desired nitrogen heterocycles, we started our study by reacting **6a** with 2-aminopyridine in the presence of AlCl<sub>3</sub> and I<sub>2</sub> under an O<sub>2</sub> atmosphere [29]. However, only a poor yield was obtained (20%, Scheme 3).

Then, we found that Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (10 mol %) and 1,10-phenanthroline (10 mol %) in chlorobenzene at 160 °C under an

O<sub>2</sub> atmosphere, following the conditions recently reported by Hajra et al. [25], gave **7a** in 62% yield (Table 2, entry 1). Having these optimized conditions in hand, and to explore the substrate scope, different substituted 2-aminopyridines were successfully employed to afford the tandem oxidative cyclization products **7** in 32–65% yields. On the other hand, enones **6** with two different R groups (Table 2, entries 1, 2, 3, 6, 8, and 9)

**Scheme 3:** Synthesis of **7a**.**Table 2:** Preparation of different imidazo[1,2-*a*]-*N*-heterocyclic derivatives.

| Entry | Product   | Ar               | R                    | R <sup>1</sup> | X  | Y  | Time  | Yield (%) |
|-------|-----------|------------------|----------------------|----------------|----|----|-------|-----------|
| 1     | <b>7a</b> | Ph               | Ph                   | H              | CH | CH | 25 h  | 62        |
| 2     | <b>7b</b> | Ph               | Ph                   | 7-Me           | CH | CH | 20 h  | 60        |
| 3     | <b>7c</b> | Ph               | Ph                   | 6-Br           | CH | CH | 46 h  | 60        |
| 4     | <b>7d</b> | Ph               | Ph                   | H              | CH | N  | 30 h  | 57        |
| 5     | <b>7e</b> | Ph               | Ph                   | 6-Cl           | N  | CH | 24 h  | 53        |
| 6     | <b>7f</b> | Ph               | -CH <sub>2</sub> OBn | H              | CH | CH | 33 h  | 55        |
| 7     | <b>7g</b> | Ph               | -CH <sub>2</sub> OBn | H              | CH | N  | 29 h  | 36        |
| 8     | <b>7h</b> | <i>o</i> -BrPh   | Ph                   | H              | CH | CH | 4 h   | 65        |
| 9     | <b>7i</b> | 2-naphthaldehyde | Ph                   | H              | CH | CH | 3.5 h | 59        |
| 10    | <b>7j</b> | <i>p</i> -MeOPh  | Ph                   | H              | CH | CH | 6 h   | 32        |

were well tolerated under the optimized conditions affording the tandem products **7** in fair to moderate yields, although lower yields were obtained in the cases of **7j** and **7g** (32% and 36%, respectively). Moreover, two other important heterocyclic frameworks, imidazo[1,2-*a*]pyrimidines **7d** and imidazo[1,2-*b*]pyridazines **7e**, have been synthesized by the same method albeit in slightly decreased yields (Table 2, entries 4 and 5).

The structures of molecules **7** are in full agreement with their spectroscopical (NMR) and analytical data (HRMS). For the imidazopyridines, the structure of **7a** was confirmed by X-ray analysis (Figure 2) [30] and the other derivatives were proposed by analogy. In the same way as for the imidazopyridazines, the structure of **7e** was established by X-ray analysis [30] and this was extended to the other derivatives. These results unambiguously demonstrate the regiochemistry of the reaction. These cascade reactions proceed first through a Michael addition of the primary amine on the enone, followed by an intramolecular cyclization by the pyridine/pyrimidine

nucleus. Unfortunately, no crystal structure could be obtained for the imidazopyrimidines and therefore the corresponding structures **7d** and **7g** were proposed by analogy.

These oxidative coupling conditions appeared compatible with the first isomerization step, therefore, the possibility of a "one-pot" reaction was considered. Indeed, by heating alcohol **5a** (Table 1, entry 1) with 2-aminopyridine and DBU (1,8-diazabicycloundec-7-ene) under the same conditions as mentioned above, the desired imidazopyridine derivative **7a** was isolated in 33% yield (Scheme 4). This one-pot process gives an overall yield very close to the two-step reaction (38%).

Further, the halogen-substituted substrate **7e** appeared as an attractive precursor to increase the molecular diversity around this scaffold. In order to explore this possibility, we performed two Suzuki–Miyaura reactions, as representative examples of Pd-catalyzed coupling processes (Table 3). They gave the target molecules **8** and **9** in 46% and 53% yields, respectively. On the other hand, two nucleophilic substitution reactions using phenol

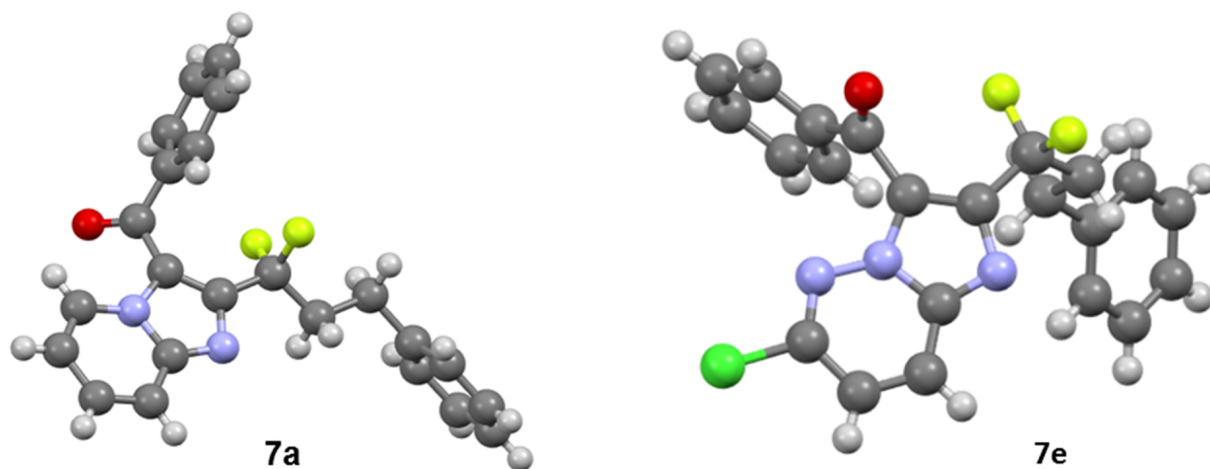
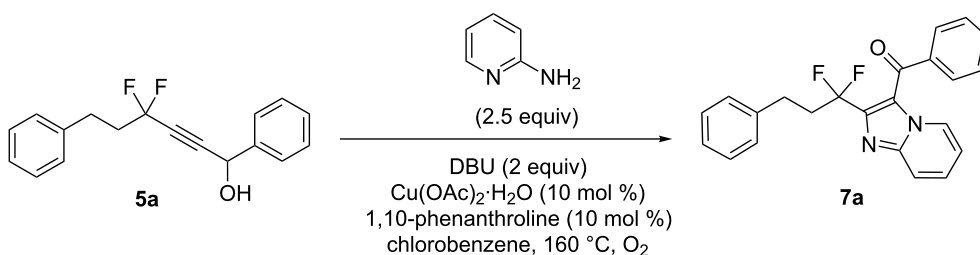


Figure 2: Structures of **7a** and **7e** by X-ray crystallography analysis.



Scheme 4: One-pot synthesis of **7a**.

**Table 3:** Coupling and substitution reactions.

**7e**

**8:** R = Ph

**9:** R =

**10:** R = OPh

**11:** R =

| Entry | Product   | R               | Conditions                                                                                                                        | Yield (%) |
|-------|-----------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1     | <b>8</b>  | Ph              | PhB(OH) <sub>2</sub><br>Na <sub>2</sub> CO <sub>3</sub> , PdCl <sub>2</sub> (dppf) <sub>2</sub><br>EtOH/H <sub>2</sub> O, 16 h    | 46        |
| 2     | <b>9</b>  | <i>p</i> -MeOPh | methoxyphenylboronic acid, Na <sub>2</sub> CO <sub>3</sub> , PdCl <sub>2</sub> (dppf) <sub>2</sub><br>EtOH/H <sub>2</sub> O, 16 h | 53        |
| 3     | <b>10</b> | PhO             | <br>K <sub>2</sub> CO <sub>3</sub> , DMF, 120 °C, 5 h                                                                             | 73        |
| 4     | <b>11</b> |                 | <br>NEt <sub>3</sub> , EtOH, reflux, 2 days                                                                                       | 23        |

and morpholine gave the expected heterocycles **10** and **11** in 73% and 23% yields, respectively.

## Conclusion

In summary, we developed a short and completely regioselective method for the synthesis of imidazo[1,2-*a*]-*N*-heterocycles with *gem*-fluorinated side chains starting from easily accessible propargylic fluorides. Although the yields are only moderate to fair, this short (1–2 steps) method offers significant flexibility to prepare focused libraries of molecules with this core structure. Such new fluorine-containing heteroaromatic frameworks would be of much interest for biological studies in different areas of life sciences.

## Experimental

### Representative procedure for the synthesis of imidazopyridine **7a**

The syntheses of propargylic fluorides **5** and enones **6** were performed in a similar way as described before [26].

### Synthesis of 4,4-difluoro-1,6-diphenylhex-2-yn-1-ol (**5a**)

To a solution of *gem*-difluoro intermediate **4** [28] (500 mg, 2.77 mmol, 1 equiv) in anhydrous THF (6 mL) cooled at –80 °C was added dropwise under nitrogen a 2.5 M solution of *n*-BuLi in hexanes (1.3 mL, 3.30 mmol, 1.2 equiv). The mixture was stirred for 1 h at a temperature below –80 °C before dropwise addition of the aldehyde (0.35 mL, 3.33 mmol,

1.2 equiv) in anhydrous THF (4 mL). The reaction mixture was stirred for additional 45 min at *t* < –80 °C and then allowed to warm to rt for 2 h. The mixture was then treated with a saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic phases were washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was purified by chromatography on silica gel, using a mixture of petroleum ether/ethyl acetate as eluent. After purification by chromatography on silica gel, propargylic alcohol **5a** was obtained as a colorless oil (580 g, 73% yield); *R*<sub>f</sub> 0.46 (petroleum ether/AcOEt 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.59–7.25 (m, 10H), 5.54 (t, *J*<sub>HF</sub> = 3.9 Hz, 1H), 2.99–2.93 (m, 2H), 2.54–2.38 (m, 2H), 2.83 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 139.7, 138.9 (t, <sup>4</sup>*J* = 1.1 Hz), 128.8, 128.7 (2C), 128.5 (2C), 128.3 (2C), 126.5, 126.3, 125.9, 114.1 (t, <sup>1</sup>*J* = 233.4 Hz), 87.0 (t, <sup>3</sup>*J* = 6.8 Hz), 79.1 (t, <sup>2</sup>*J* = 40.9 Hz), 64.0 (t, <sup>4</sup>*J* = 1.8 Hz), 40.8 (t, <sup>2</sup>*J* = 26.1 Hz), 28.9 (t, <sup>3</sup>*J* = 4.0 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –83.45 (td, *J*<sub>FH</sub> = 14.6, 3.9 Hz); HRMS (ESI) *m/z* [M + Na]<sup>+</sup>: calcd. for C<sub>18</sub>H<sub>16</sub>OF<sub>2</sub>Na, 309.10614; found, 309.1060 (0 ppm); *m/z* [M – HF + Na]<sup>+</sup>: calcd. for C<sub>18</sub>H<sub>15</sub>OFNa, 289.09991; found, 289.0992 (2 ppm).

### Synthesis of (*E*)-4,4-difluoro-1,6-diphenylhex-2-en-1-one (**6a**)

The previous difluoropropargylic alcohol **5a** (540 mg, 1.88 mmol, 1 equiv) was dissolved in THF (4 mL), then DBU (0.42 mL, 2.82 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature. After 2 h, <sup>19</sup>F NMR

showed 100% conversion and the reaction mixture was neutralized with a saturated solution of  $\text{NH}_4\text{Cl}$ . After extraction with ethyl acetate, the organic phases were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude product was purified by chromatography on silica gel, using a mixture of petroleum ether/ethyl acetate as eluent. Enone **6a** was isolated as a colorless oil (335 mg, 62% yield);  $R_f$  0.43 (petroleum ether/AcOEt 9:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.04 (m, 2H), 7.66–7.64 (m, 1H), 7.57–7.52 (m, 2H), 7.35–7.28 (m, 6H), 6.97 (m, 1H), 2.93–2.92 (m, 2H), 2.41–2.35 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  188.93, 139.8, 138.3 (t,  $^2J = 27.1$  Hz), 136.7, 133.5, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 127.6 (t,  $^3J = 7.5$  Hz), 126.3, 120.6 (t,  $^1J = 240.4$  Hz), 38.9 (t,  $^2J = 25.9$  Hz), 28.2 (t,  $^3J = 4.3$  Hz);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –98.84 (m); HRMS (ESI)  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$ : calcd. for  $\text{C}_{18}\text{H}_{16}\text{OF}_2\text{Na}$ , 309.10614; found, 309.1059 (1 ppm).

### Synthesis of (2-(1,1-difluoro-3-phenylpropyl)imidazo[1,2-a]pyridin-3-yl)(phenyl)methanone (**7a**)

A mixture of 2-aminopyridine (20 mg, 0.21 mmol, 1.2 equiv), enone **6a** (51 mg, 0.17 mmol, 1 equiv),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (3.6 mg, 0.02 mmol, 10 mol %), and 1,10-phenanthroline (2.5  $\mu\text{L}$ , 0.02 mmol, 10 mol %) in chlorobenzene (1 mL) was stirred in a reaction tube at 160 °C under an  $\text{O}_2$  atmosphere. After 25 h,  $^{19}\text{F}$  NMR monitoring indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature, filtered and extracted with dichloromethane. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate as eluent. **7a** was isolated as white crystals (32 mg, 62% yield);  $R_f$  0.46 (petroleum ether/EtOAc 7:3); Mp: 117 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  8.76 (d,  $J = 6.9$  Hz, 1H), 7.89 (s, 1H), 7.86 (s, 1H), 7.75 (d,  $J = 9.0$  Hz, 1H), 7.64 (t,  $J = 7.3$  Hz, 1H), 7.53–7.43 (m, 3H), 7.26–7.13 (m, 5H), 7.02 (t,  $J = 6.7$  Hz, 1H), 2.72–2.65 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  187.9, 146.1, 145.1, 140.4, 139.5 (t,  $^3J = 2.1$  Hz), 133.3 (2C), 129.5, 128.4 (2C), 128.3 (3C), 128.2 (2C), 127.3, 126.0, 120.6, 120.3 (t,  $^1J = 239.8$  Hz), 118.2, 114.7, 39.3 (t,  $^2J = 25.1$  Hz), 28.3 (t,  $^3J = 4.4$  Hz);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –90.93 (t,  $J = 15.7$  Hz); HRMS (ESI)  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$ : calcd. for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{OF}_2\text{Na}$ , 399.12794; found, 399.1279 (0 ppm);  $m/z$  [ $\text{M} + \text{H}$ ] $^+$ : calcd. for  $\text{C}_{23}\text{H}_{19}\text{N}_2\text{OF}_2$ , 377.14599; found, 377.1454 (2 ppm);  $m/z$  [ $\text{M} - \text{HF} + \text{Na}$ ] $^+$ : calcd. for  $\text{C}_{23}\text{H}_{17}\text{N}_2\text{OFNa}$ , 379.12171; found, 379.1216 (0 ppm).

### One pot synthesis of (2-(1,1-difluoro-3-phenylpropyl)imidazo[1,2-a]pyridin-3-yl)(phenyl)methanone (**7a**)

A mixture of 2-aminopyridine (25 mg, 0.26 mmol, 2.5 equiv), alcohol **5a** (30 mg, 0.10 mmol, 1 equiv), DBU (0.03 mL,

0.20 mmol, 2 equiv),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (2.1 mg, 0.01 mmol, 10 mol %), and 1,10-phenanthroline (1.4  $\mu\text{L}$ , 0.01 mmol, 10 mol %) in chlorobenzene (1 mL) was stirred in a reaction tube at 160 °C under an  $\text{O}_2$  atmosphere. After 4 h monitoring by  $^{19}\text{F}$  NMR indicated the disappearance of the starting material. Thus the mixture was cooled to room temperature, filtered, washed and extracted with dichloromethane. The organic phase was concentrated and the crude product was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate as eluent. Imidazopyridine **7a** was isolated in 33% yield.

## Supporting Information

### Supporting Information File 1

Experimental details and characterization data of new compounds with copies of  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra. [<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-208-S1.pdf>]

## Acknowledgements

This work was financially supported by the Research Grant Program at Lebanese University (Lebanon). We thank all members of the two teams (Beirut and Rennes) for fruitful discussion and kind help. We thank CRMPO (Rennes) for the mass spectral analysis.

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30. CCDC 1549632 (for compound **7a**) and CCDC 1549633 (for compound **7e**) contain the supplementary crystallographical data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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doi:10.3762/bjoc.13.208