

Copper(I)-mediated preparation of new pyrano[3',4':4,5]imidazo[1,2-*a*]-pyridin-1-one compounds under mild palladium-free conditions†Zineb Bahlaouan,<sup>a</sup> Mohamed Abarbri,<sup>\*a</sup> Alain Duchêne,<sup>a</sup> Jérôme Thibonnet,<sup>a</sup> Nicolas Henry,<sup>b</sup> Cécile Enguehard-Gueiffier<sup>b</sup> and Alain Gueiffier<sup>b</sup>

Received 24th August 2010, Accepted 3rd November 2010

DOI: 10.1039/c0ob00622j

A general and efficient Cu(I)-mediated cross-coupling and heterocyclization reaction of 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylic acid, and terminal alkynes was developed under very mild conditions. This method allows the introduction in one pot of a third ring fused in positions 2 and 3 of the imidazo[1,2-*a*]pyridine core with reasonable yields and total regioselectivity. This procedure does not require the use of any expensive supplementary additives, and is palladium-free.

## 1. Introduction

The significant and potential biological activities of the imidazo[1,2-*a*]pyridine series have been widely studied in various pharmacological areas of medicinal chemistry: *e.g.* (i) in virology, in the treatment of hepatitis C virus infection,<sup>1</sup> herpes virus infection<sup>2</sup> and HIV infection;<sup>3</sup> (ii) in cancerology, as antagonists of the gonadotropin releasing hormone receptor,<sup>4</sup> PI3 kinase p110 $\alpha$  inhibitors,<sup>5</sup> histone deacetylase inhibitors,<sup>6</sup> receptor tyrosine kinase inhibitors<sup>7</sup> and ligands for peripheral benzodiazepine receptors;<sup>8</sup> and (iii) in neurology, as C3a receptor antagonists,<sup>9</sup> partial D4 agonist<sup>10</sup> and derivatives for imaging amyloid deposits in the brain to allow diagnosis of Alzheimer's disease.<sup>11</sup>

In the course of our studies evaluating the chemical and pharmacological properties of the imidazo[1,2-*a*]pyridine core, we have extensively investigated the metal-catalyzed methods of functionalization which allow the rapid preparation of a number of structural variants.<sup>12</sup> In particular we studied the Sonogashira cross-coupling reaction leading to alkyne derivatives.<sup>13</sup> Transition metal-catalyzed cyclization of alkynes possessing a nucleophile in close proximity to the triple bond is one of the most important processes in organic synthesis, which can construct various heterocycles in an efficient and atom economic way.<sup>14</sup> Over the past ten years, a wide range of transition metal-based catalysts (Ag, Hg, Rh, Pd, Zn, Au...) have been reported as effective catalysts to promote intramolecular addition of carboxylic acid to alkynes.<sup>15,16</sup> In addition to the formation of five membered lactones, six-

membered lactones have been obtained in some cases, resulting from the 6-*endo-dig* mode. However such synthesis suffered from lack of selectivity. In all cases described in the literature, the synthesis of oxygenated heterocycles such as butenolides, pyran-2-ones, phthalides, *etc.*, starting from 2-halobenzoic acid derivatives and alkynes using copper as catalyst has been performed in two separate steps: (1) coupling of 2-halobenzoic acid derivatives with terminal alkynes, typically by the Sonogashira reaction,<sup>17</sup> and (2) cyclization mediated by metal complexes,<sup>18</sup> bases,<sup>19</sup> and halogen.<sup>20</sup> The past few years have seen a resurgence of interest in copper(I)-catalyzed cross-coupling reactions.<sup>21</sup> Many synthesis protocols based on copper(I) catalysts for the formation of carbon-carbon and carbon-heteroatom bonds have been reported and they have been the subject of increasing attention.<sup>22,23</sup> In addition to being simple and mild, the newer copper-based methods have been shown to accommodate substrates that are difficult to couple by palladium reactions.<sup>24</sup> Copper catalysts still have the advantage of being of low cost for use in large-scale industrial applications.

In connection with our project to develop synthesis of new heterocycles *via* copper(I) mediated coupling heterocyclization reaction, we decided to develop a method to introduce a third ring fused in positions 2 and 3 of the imidazo[1,2-*a*]pyridine core, using copper(I) catalyzed-cross-coupling and a heterocyclization reaction sequence. This kind of tricyclic heterocycle has been little studied in the literature and could provide interesting pharmacological activities particularly as antitumoral agents.<sup>25</sup>

To the best of our knowledge, one pot non-palladium catalyzed synthesis of pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one from alkynes and 3-iodoimidazo[1,2-*a*]pyridin-2-carboxylic acid has never previously been reported. Only one synthesis of an unsubstituted compound of this type has been reported to date,<sup>26</sup> and synthesis of this tricyclic compound from 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylate required a three step sequence: Sonogashira coupling reaction, saponification of the ester group and copper catalyzed cyclization.

<sup>a</sup>Faculté des Sciences, Laboratoire de PhysicoChimie des Matériaux et Biomolécules EA 4244, Université François Rabelais, Parc de Grandmont, 37200 Tours, France. E-mail: mohamed.abarbri@univ-tours.fr; Fax: +33(0) 2 47.36.70.73

<sup>b</sup>Faculté de Pharmacie, Laboratoire de PhysicoChimie des Matériaux et Biomolécules EA 4244, Université François Rabelais, 31 Avenue Monge, 37200 Tours, France

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c0ob00622j

**Table 1** Optimization studies for the Cu-catalyzed coupling–heterocyclization sequence

Entry	CuX (100%)	Base	Solvent	Yield (%) <sup>a</sup>
1	CuI	none	DMF	0
2 <sup>b</sup>	CuI	K <sub>2</sub> CO <sub>3</sub>	"	0
3 <sup>c</sup>	CuI (20%)	"	"	9
4	CuI	K <sub>2</sub> CO <sub>3</sub>	DMF	40
5	CuCl	"	"	33
6	CuBr	"	"	35
7	CuCN	"	"	29
8	Cu <sub>2</sub> O	"	"	30
9	CuBr <sub>2</sub>	"	"	8
10	CuI	NaOH	"	10
11	"	CS <sub>2</sub> CO <sub>3</sub>	"	12
12	"	K <sub>3</sub> PO <sub>4</sub>	"	9
13	"	K <sub>2</sub> CO <sub>3</sub>	DMSO	39
14	"	"	Toluene	4
15	"	"	THF	6
16	"	"	MeCN	7

<sup>a</sup> Isolated yields. <sup>b</sup> Reaction performed at rt. <sup>c</sup> 20% CuI was used in this case.

We recently reported the first one pot general and efficient regioselective palladium-free synthesis of 5-ylidene-5*H*-furan-2-ones and isocoumarins *via* the tandem cross-coupling heterocyclization reaction of terminal alkynes and (*Z*)-3-iodopropenoic acid derivatives under copper catalysis.<sup>27</sup> On the basis of the above, we now report the first efficient and regioselective one pot synthesis of pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one *via* the cross-coupling-heterocyclization reaction sequence of terminal alkynes and 3-iodoimidazo[1,2-*a*]pyridin-2-carboxylic acid mediated by a simple salt.

## 2. Results and discussion

To optimize the reaction conditions of this coupling–heterocyclization reaction, we examined a range of copper(I) salts, solvents and bases for the tandem C–C coupling–heterocyclization reaction using the coupling of **1a** with phenylacetylene as a test reaction (Table 1).

As shown in Table 1, all the copper(I) salts (CuBr, CuCl, CuBr<sub>2</sub>, Cu<sub>2</sub>O, CuCN...) tested provided moderate to poor yields of the tricyclic compound **2a**. Upon optimization, we found that CuI was the most effective catalyst for the coupling of **1a** with phenylacetylene (entries 4 and 13, Table 1). It should be noted that copper(II) salts were ineffective as catalysts for this reaction, and very low conversions were observed (<10%) (entry 9, Table 1). The effects of the amount of copper were investigated in the optimization process, and further experiments showed that the reaction was completed within 12 h at 100 °C with 40% yield using a stoichiometric amount of CuI (entry 4, Table 1). Lowering the amount of catalyst to 20 mol% of CuI provided very unsatisfactory yields of the desired product (<10%) (entry 3, Table 1). This result could be explained by the presence of nitrogen atoms in the starting material, such as the imidazo pyridine core **1a**, which is able to complex the copper(I) catalyst and prevent it reaching the reaction

site. The same report is observed in the case of other nitrogenized cycles undergoing the same type of reaction. This work is under development in our laboratory.

Several solvents were tested to evaluate their effects. As shown in Table 1, the use of DMF or DMSO as the solvent led to the formation of reasonable yields of heterocyclization product **2a** (entries 4 and 13, Table 1) whereas poor yields of the desired adducts were obtained in toluene, THF and CH<sub>3</sub>CN (<10%) (entries 14–16, Table 1). After screening of different bases, the use of K<sub>2</sub>CO<sub>3</sub>, an inexpensive base, provided the best results (entries 4 and 13, Table 1), while lower yields were observed with NaOH, Cs<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub> (entries 10–12, Table 1). In addition, no coupling–heterocyclization reaction was observed in the absence of base (entry 1, Table 1). Temperature was also a crucial parameter. The coupling reactions did not proceed at room temperature (the starting material was completely recovered) but required heating at 100 °C (entries 2 and 4, Table 1). After a careful analysis of our results, the optimum conditions used 1 equivalent of copper iodide, 1.5 equivalents of alkyne, and 2.0 equivalents of potassium carbonate in DMF at 100 °C for 12 h.

The reaction scope and limitations were then examined under the optimized conditions, and the results are summarized in Table 2.

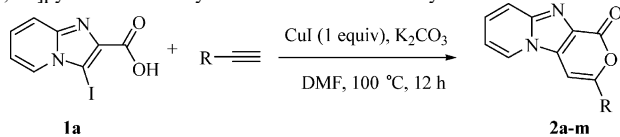
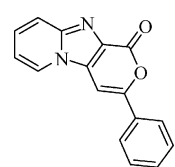
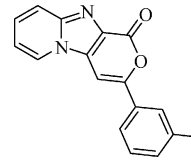
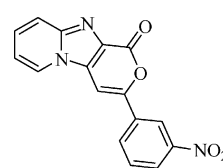
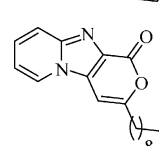
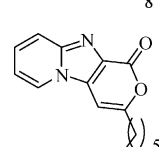
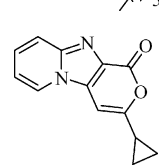
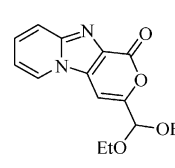
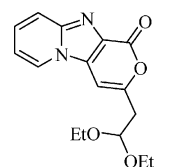
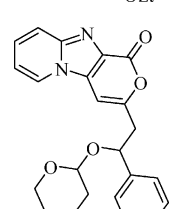
## 3. Scope of the method: preparation of **2**

To investigate the scope of the copper-mediated tandem coupling–heterocyclization reaction, a variety of available terminal alkynes were used to react with **1a**. This reaction showed very high regioselectivity. In each case, only the six-membered ring from 6-*endo-dig* cyclization was obtained, and no five-membered exocyclic products were detected by TLC monitoring. The six membered rings obtained could be differentiated from the corresponding five-membered rings on the basis of several spectroscopic findings, especially from IR spectra. Using a previously reported<sup>28</sup> comparison between the five- and six-membered lactone rings of butenolides [ $\nu_{\max}$  (C=O) 1770–1800 cm<sup>−1</sup>] and pyranones [ $\nu_{\max}$  (C=O) 1710–1740 cm<sup>−1</sup>], we found that our results were in full agreement with the spectral data reported for pyranones. The yields of isolated products **2** after purifying by column chromatography are presented in Table 2.

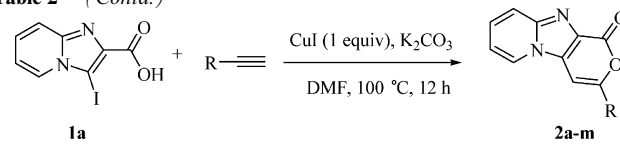
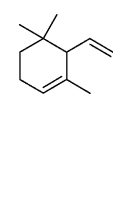
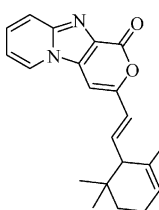
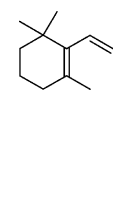
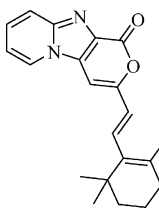
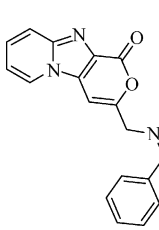
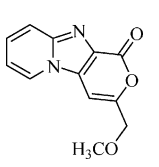
The reaction described is extremely versatile and provides a convenient method for the synthesis of various pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-ones with total regioselectivity, demonstrating that our strategy avoided the presence of any 1,3-di*H*-furan[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one derivatives.

Using this copper-mediated tandem coupling–cyclization process, a variety of functional groups (including alkyl, alkenyl, alkoxy, amino, phenyl, *etc.*) present in the acetylenic compounds employed so far were tolerated during the course of the reaction (Table 2). As shown in Table 2, phenylacetylene substituted with the methyl group on the aromatic ring give the coupling–heterocyclization product with reasonable yield (entry 2, Table 2). No significant electronic effects were observed for the electron-donating substituent methyl group at the *meta*-position of the terminal aromatic ring. Unfortunately, when the aromatic ring was substituted by an electron-withdrawing group such as NO<sub>2</sub>, only trace amounts of the coupling–heterocyclization product could be

**Table 2** Copper-mediated coupling–heterocyclization of 3-iodoimidazo[1,2-*a*]pyridin-2-carboxylic acid with terminal alkynes

				
Entry	R	Product	No.	Yield (%)
1	Ph		<b>2a</b>	40
2	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>		<b>2b</b>	41
3	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		<b>2c</b>	<2%
4	<i>n</i> -CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub>		<b>2d</b>	66
5	<i>n</i> -CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>		<b>2e</b>	50
6	Cyclopropyl		<b>2f</b>	62
7	CH(OEt) <sub>2</sub>		<b>2g</b>	43
8	CH <sub>2</sub> CH(OEt) <sub>2</sub>		<b>2h</b>	45
9	CH <sub>2</sub> CH(Ph)OTHP		<b>2i</b>	60

**Table 2** (Contd.)

				
Entry	R	Product	No.	Yield (%)
10			<b>2j</b>	60
11			<b>2k</b>	65
12	BnN(CH <sub>3</sub> )CH <sub>2</sub>		<b>2l</b>	40
13	CH <sub>3</sub> OCH <sub>2</sub>		<b>2m</b>	55

obtained (entry 3, Table 2). This result indicates that the electron-withdrawing groups on the aromatic ring must have an important role in the reaction, and the protocol did not tolerate electron-poor aryl acetylene, presumably due to the reduced electron density of the triple bond. Attempts to improve the yield by increasing the amount of copper catalyst (2.0 equiv) and alkyne (2.0 equiv) met with no success. We were pleased to find that the alkyne bearing a propargylic or a homopropargylic acetal reacted well with **1a**, affording reasonable isolated yields of the corresponding tricyclic compounds **2g–h** as sole products (entries 7–8, Table 2). Gratifyingly, the presence of a long-chain alkyl group in the terminal alkyne did not affect the regioselectivity of the coupling–cyclization process, and six-membered heterocycles **2d–f** were isolated exclusively with moderate yields (entries 4–6, Table 2), demonstrating again that the successful coupling–heterocyclization protocol is not specific to aryl acetylenes. The reason for the regioselectivity observed associated with the use of CuI (100 mol%) as catalyst system is not clear at this stage. Cu(I) salts are known to catalyze the intramolecular cyclization of 2-(alkynyl)benzoic acid or its derivative to the six-membered lactone ring.<sup>21b,d,e,24</sup>

In another case, the coupling–heterocyclization reaction of **1a** with (*E*)-6-(but-1-en-3-ynyl)-1,5,5-trimethylcyclohex-1-ene ( $\alpha$ )<sup>29</sup> (entry 10, Table 1) or (*E*)-2-(but-1-en-3-ynyl)-1,3,3-trimethylcyclohex-1-ene ( $\beta$ )<sup>29</sup> (entry 11, Table 1) under the same conditions as described above provided reasonable yields of the desired dienylypyranones **2j–k**. A NOESY NMR experiment on **2j–k** confirmed the retention of the double bond configuration of the starting materials. The structures of all products **2a–m** were confirmed by satisfactory spectroscopic data (MS, IR, <sup>1</sup>H and <sup>13</sup>C NMR). Extension of this tandem coupling–heterocyclization reaction using a copper-catalyst to other classes of functionalized imidazo[1,2-*a*]pyridine derivatives is currently being studied in our laboratory.

## 4. Conclusion

The aim of this research was to develop an efficient and cheap method for the synthesis of a new imidazo[1,2-*a*]pyridine library under mild and more environmentally friendly conditions. These issues were addressed by replacing the expensive palladium catalysts with less expensive 100 mol% CuI.

In summary, we have developed a practical and general copper mediated system [Cu(I) salts in DMF] for the efficient tandem coupling–heterocyclization reaction of 3-iodoimidazo[1,2-*a*]pyridin-2-carboxylic acid with terminal alkynes, leading to straightforward and easy access to an important range of pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-ones. The overall yields are reasonably good. The present methodology does not involve the use of an expensive, air-sensitive palladium(0) catalyst or any additive ligand. The process holds promise as a useful tool for the construction of complex heterocycles containing the imidazo[1,2-*a*]pyridine unit. Further applications of this catalytic system to generate new heterocycle-based chemical libraries of potential pharmacological interest are under investigation in our laboratory.

## 5. Experimental section

### 5.1 Materials

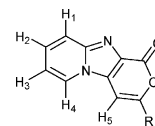
Et<sub>2</sub>O was dried and freshly distilled from sodium/benzophenone. CH<sub>2</sub>Cl<sub>2</sub> and DMF were dried by distillation over CaH<sub>2</sub> and stored under argon. Petroleum ether (PE) used was the fraction boiling in the range 40–60 °C. Flash chromatography was carried out with Merck silica gel (silica gel, 230–400 mesh). <sup>1</sup>H NMR spectra were recorded at 200 or 300 MHz using CDCl<sub>3</sub> as solvent. The findings, reported using the residual solvent proton resonance of CDCl<sub>3</sub> ( $\delta$ <sub>H</sub> = 7.25 ppm) as internal reference, were as follows (in order): chemical shift ( $\delta$  in ppm in relation to Me<sub>4</sub>Si), multiplicity (s, d, t, q, m, b for singlet, doublet, triplet, quartet, multiplet, broad) and coupling constants (*J* in Hz). <sup>13</sup>C NMR were recorded at 50.3 or 75 MHz using the CDCl<sub>3</sub> solvent peak at  $\delta$ <sub>C</sub> = 77.0 ppm as reference. Mass spectra were obtained in the GC-MS (70 eV) mode. IR spectra were recorded on a Perkin–Elmer 781 FT-IR spectrophotometer and are reported in cm<sup>-1</sup>. Melting points were uncorrected.

3-Iodoimidazo[1,2-*a*]pyridine-2-carboxylic acid **1a** was prepared from ethyl-3-iodoimidazo[1,2-*a*]pyridine-2-carboxylate according to a known procedure.<sup>30</sup>

### 5.2 General procedure for synthesis of compounds **2a–m**

A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with K<sub>2</sub>CO<sub>3</sub> (478 mg, 3.46 mmol, 2 equiv) and 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylic acid (500 mg, 1.73 mmol, 1 equiv). The mixture was evacuated and backfilled with argon. Anhydrous DMF (10 mL) was added and the suspension was stirred for 15 min. Then, the mixture was degassed at –80 °C for 10 min and backfilled with argon. After reaching room temperature, the alkyne (2.59 mmol, 1.5 equiv) was added and finally CuI (330 mg, 1.73 mmol, 1 equiv). The Schlenk tube was sealed, placed in a preheated oil bath at 100 °C and was stirred overnight. The reaction mixture was allowed to reach room temperature, was taken again with 50 mL of ethyl acetate and filtered over a Celite pad. The filtrate was partitioned between ethyl acetate (40 mL × 2) and saturated aqueous NH<sub>4</sub>Cl (30 mL). The organic portions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated by rotary evaporation. The material thus obtained was purified by flash chromatography on silica gel or by crystallization to give the desired pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one.

The numbering system of pyrano[3',4':4,5]imidazo[1,2-*a*]pyridinone shown below is used in the assignment of the chemical shifts.



#### 3-Phenylpyrano[3',4':4,5]imidazo[1,2-*a*]pyridinone (**2a**)

Yellow solid, 40% yield. Mp: 148–150 °C;  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3108, 1716, 1637, 1607 and 1120;  $\delta$ <sub>H</sub> (200 MHz; DMSO) 7.22 (1 H, t, *J* 6.6, H<sub>3</sub>), 7.51–7.58 (4 H, m, 3H<sub>Ph</sub> + H<sub>2</sub>), 7.75 (1 H, d, *J* 9.4, H<sub>1</sub>), 7.92 (2 H, d, *J* 7.4, H<sub>Ph</sub>), 8.26 (1 H, s, H<sub>5</sub>) and 8.87 (1 H, d, *J* 6.6, H<sub>4</sub>);  $\delta$ <sub>C</sub> (50 MHz; DMSO) 92, 114, 118.5, 124.8 (2C), 126.8, 127.2, 129.2 (2C), 129.6, 129.9, 131.8, 133.1, 147.0, 153.0 and 157.8; *m/z* (EI) 262 (M<sup>+</sup>, 100), 234 (23), 205 (62), 157 (10), 129 (14), 78 (42) and 51 (25); HRMS for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>): calcd. 262.0742, found 262.0750

#### 3-(3-Methylphenyl)pyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one (**2b**)

Yellow solid, 41% yield. Mp: 180–182 °C;  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3095, 1720, 1633, 1605 and 1125;  $\delta$ <sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 2.45 (3 H, s, CH<sub>3</sub>-Ph), 7.12 (1 H, t, *J* 6.0, H<sub>3</sub>), 7.24–7.32 (2H<sub>Ph</sub>, m), 7.35–7.45 (2H, m, H<sub>Ph</sub> + H<sub>2</sub>), 7.75 (1H, d, *J* 9.2, H<sub>1</sub>), 7.79 (1H, s, H<sub>5</sub>), 7.81 (1H, d, *J* 7.0, H<sub>Ph</sub>) and 8.27 (1H, d, *J* 6.0, H<sub>4</sub>);  $\delta$ <sub>C</sub> (50 MHz; CDCl<sub>3</sub>) 26.6, 97.0, 118.7, 123.5, 127.2, 130.4, 131.7, 132.6, 133.8, 134.1, 135.1, 135.4, 136.9, 142.1, 143.3, 158.7 and 163; MS (EI): 276 (M, 100), 248 (32), 205 (14), 91 (14), 78 (29); MS (EI) 276 (M, 100), 248 (32), 205 (14), 91 (14) and 78 (29); HRMS for C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>): calcd. 276.0899, found 276.0903.

#### 3-Nonylpyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one (**2d**)

Yellow solid, 66% yield. Mp: 136–138 °C;  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3106, 2917, 1714, 1627, 1469, 1146 and 1035;  $\delta$ <sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 0.82 (3H, t, *J* 7, CH<sub>3</sub>CH<sub>2</sub>), 1.20–1.24 (12H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.65 (2H, qt, *J* 7.0,



$\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.61 (2H, t,  $J$  7.2,  $\text{CH}_2\text{CH}_2$ ), 7.10 (1H, t,  $J$  6.6,  $\text{H}_3$ ), 7.33 (1H, s,  $\text{H}_5$ ), 7.48 (1H, dd,  $J$  9.2, 6.6,  $\text{H}_2$ ), 7.69 (1H, d,  $J$  9.2,  $\text{H}_1$ ), 8.78 (1H, d,  $J$  6.6,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 14.5, 23.0, 27.7, 29.4, 29.7 (2C), 29.8, 32.3, 34.5, 92.1, 114.1, 120.0, 125.0, 127.7, 128.2, 132.6, 147.5, 159.5 and 160.7; MS (EI) 312 (M, 100), 213 (39), 199 (51), 171 (33), 130 (27), 78 (40); HRMS for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): calcd. 312.1838, found 312.1845.

### 3-Hexylpyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2e)

Yellow solid, 50% yield. Mp: 141–143 °C;  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3109, 2954, 1722, 1624, 1269 and 1140;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 0.90 (3H, t,  $J$  7.0,  $\text{CH}_3\text{CH}_2$ ), 1.30–1.36 (6H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.73 (2H, qt,  $J$  7.0,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.66 (2H, t,  $J$  7.6,  $\text{CH}_2\text{CH}_2$ ), 6.61 (1H, s,  $\text{H}_5$ ), 6.96 (1H, t,  $J$  6.8,  $\text{H}_3$ ), 7.36 (1H, dd,  $J$  9.0, 6.8,  $\text{H}_2$ ), 7.72 (1H, d,  $J$  9.0,  $\text{H}_1$ ), and 8.11 (1H, d,  $J$  6.8,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 14.5, 23.0, 27.6, 29.0, 31.8, 34.4, 92.1, 114.1, 120.0, 125.0, 127.7, 128.3, 132.6, 147.5, 159.5 and 160.7; MS (EI) 270 (M, 100), 199 (65), 171 (50), 130 (40), 79 (26), and 78 (68); HRMS for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): calcd. 270.1368, found 270.1376.

### 3-[Cyclopropyl]pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2f)

Yellow solid: 62% yield. Mp: 150–152 °C;  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3091, 2918, 1739, 1621, 1516 and 1037;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 0.99–1.03 (2H, m,  $\text{CHCH}_2\text{CH}_2$ ), 1.14–1.18 (2H, m,  $\text{CHCH}_2\text{CH}_2$ ), 1.91–1.97 (1H, m,  $\text{CH}_2\text{CHCH}_2$ ), 6.68 (1H, s,  $\text{H}_5$ ), 6.96 (1H, t,  $J$  6.6,  $\text{H}_3$ ), 7.35 (1H, dd,  $J$  9.4, 6.6,  $\text{H}_2$ ), 7.71 (1H, d,  $J$  9.4,  $\text{H}_1$ ) and 8.12 (1H, d,  $J$  6.6,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 7.5, 14.2, 89.5, 113.2, 119.1, 124, 126.4, 127.4, 132.2, 146.4, 158.2 and 160; MS (EI) 226 (100), 197 (30), 184 (26), 169 (93), 155 (16), 129 (26), 78 (93), 51 (34) and 39 (14); HRMS for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): calcd. 226.0742, found 226.0747.

### 3-(Diethoxymethyl)pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2g)

Yellow solid: 43% yield. Mp: 168–170 °C;  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3059, 2974, 1734, 1685, 1636 and 1506;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.30 (6H, t,  $J$  7.0,  $2 \times \text{CH}_3\text{CH}_2\text{O}$ ), 3.66–3.79 (4H, m,  $2 \times \text{OCH}_2\text{CH}_3$ ), 5.36 (1H, s,  $\text{CH}(\text{OEt})_2$ ), 7.01 (1H, t,  $J$  6.6,  $\text{H}_3$ ), 7.16 (1H, s,  $\text{H}_5$ ), 7.40–7.43 (1H, m,  $\text{H}_2$ ), 7.74–7.76 (1H, m,  $\text{H}_1$ ) and 8.18–8.21 (1H, m,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 15.6 (2C), 63.0 (2C), 91.7, 98.0, 114.7, 120.3, 125.4, 128.8, 155.1 and 158.7; MS (EI) 288 (M, 70), 260 (54), 243 (62), 231 (39), 215 (100), 185 (46), 78 (72), 75 (49) and 47 (68); HRMS for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ): calcd. 288.1110, found 288.1119.

### 3-(2,2-Diethoxyethyl)pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2h)

Yellow solid: 45% yield. Mp: 164–166 °C.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3070, 2964, 1735, 1685, 1636 and 1507;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.17 (6H, t,  $J$  7.0,  $2 \times \text{CH}_3\text{CH}_2\text{O}$ ), 2.96 (2H, d,  $J$  5.6,  $\text{CH}_2\text{CH}$ ), 3.51–3.77 (4H, m,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.96 (1H, t,  $J$  = 5.8 Hz,  $\text{CH}_2\text{CH}(\text{OEt})_2$ ), 6.75 (1H, s,  $\text{H}_5$ ), 6.99 (1H, t,  $J$  6.7,  $\text{H}_3$ ), 7.38 (1H, dd,  $J$  9.4, 6.7,  $\text{H}_2$ ), 7.73 (1H, d,  $J$  9.4,  $\text{H}_1$ ) and 8.12 (1H, d,  $J$  6.7,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 14.8 (2C), 39.0, 62.2 (2C), 93.5, 100.0, 113.9, 118.7, 118.8, 124.4, 127.5, 128.5, 145.2, 155.4 and 158.2; MS (EI) 302 (M, 3),

229 (16), 228 (23), 200 (17), 103 (100), 78 (45), 75 (89) and 47 (64); HRMS for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ): calcd. 302.1267, found 302.1260.

### 3-[2-(Phenyltetrahydro-2H-pyran-2-yloxy)ethyl]pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2i)

Yellow solid: 60% yield. Mp: 201–203 °C;  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3070, 2923, 1732, 1625, 1348 and 1124;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.41–1.68 (6H, m,  $3 \times \text{CH}_2\text{CH}_2$ ), 2.95 (1H, dd,  $J$  14.5 and  $J$  6.0,  $\text{CH}_2\text{CHO}$ ), 3.19 (1H, dd,  $J$  14.5 and  $J$  8.5,  $\text{CH}_2\text{CHO}$ ), 3.40–3.45 (1H, m,  $\text{OCH}_2\text{CH}_2$ ), 3.68–3.63 (1H, m,  $\text{OCH}_2\text{CH}_2$ ), 4.45 (1H, t,  $J$  6.0,  $\text{CH}_2\text{CHO}$ ), 5.27 (1H, dd,  $J$  8.6 and  $J$  5.0,  $\text{OCHCH}_2$ ), 6.76 (1H, s,  $\text{H}_5$ ), 6.97 (1H, t,  $J$  6.8,  $\text{H}_3$ ), 7.28–7.37 (6H, m,  $5\text{H}_{\text{Ph}} + \text{H}_2$ ), 7.72 (1H, d,  $J$  9.2,  $\text{H}_1$ ) and 8.07 (1H, d,  $J$  6.8,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 20.0, 25.7, 31.0, 43.2, 62.8, 74.6, 94.1, 96.0, 114.2, 120.1, 124.8, 126.7, 127.2 (2C), 128.4, 128.5, 129.1 (2C), 132.4, 141.1, 147.4, 156.8 and 159.3; MS (EI) 390 (M, 1), 200 (100), 182 (6), 154 (5), 129 (6), 85 (29), 78 (20), 57 (9) and 41 (9); HRMS for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ): calcd. 390.1580, found 390.1588.

### (E)-3-[2-(2,6,6-Trimethylcyclohex-2-enyl)vinyl]pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2j)

Yellow solid: 60% yield. Mp: 125–127 °C;  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3065, 2926, 1732, 1637, 1508, 1262 and 1035;  $\delta_{\text{H}}$  (200 MHz; DMSO) 0.85 (3H, s,  $\text{CH}_3$ ), 0.91 (3H, s,  $\text{CH}_3$ ), 1.50–1.53 (2H, m,  $\text{CH}_2\text{CH}_2$ ), 1.58 (3H, s,  $\text{CH}_3$ ), 1.99–2.02 (2H, m,  $\text{CH}_2\text{CH}_2$ ), 2.36–2.40 (1H, m,  $\text{CHCH}=\text{CH}$ ), 5.48 (1H, bs,  $\text{CH}_2\text{CH}=\text{C}$ ), 6.20–6.24 (2H, m,  $\text{CH}=\text{CH}$ ), 7.33 (1H, t,  $J$  6.4,  $\text{H}_3$ ), 7.46 (1H, s,  $\text{H}_5$ ), 7.53 (1H, dd,  $J$  9.0, 6.4,  $\text{H}_2$ ), 7.72 (1H, d,  $J$  9.0,  $\text{H}_1$ ) and 8.74 (1H, d,  $J$  6.4,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz; DMSO) 22.7, 26.6, 27.7, 30.8, 32.8, 53.5, 94.0, 113.8, 118.4, 121.6, 123.4, 126.7, 127.3, 129.3, 132.7, 132.8, 135.5, 135.7, 146.8, 152.2 and 157.6; MS (EI) 334 ( $\text{M}^+$ , 99), 278 (100), 249 (54), 213 (96), 149 (49) and 39 (34); HRMS for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): calcd. 334.1681, found 334.1687.

### (E)-3-[2-(2,6,6-Trimethylcyclohex-1-enyl)vinyl]pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2k)

Yellow solid: 65% yield. Mp: 119–121 °C.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3071, 2926, 1327, 1637, 1508, 1262 and 1035;  $\delta_{\text{H}}$  (200 MHz; DMSO) 1.08 (6H, s,  $2 \times \text{CH}_3$ ), 1.49–1.58 (4H, m,  $2 \times \text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.78 (3H, s,  $\text{CH}_3$ ), 2.07 (2H, t,  $J$  6.0,  $\text{CH}_2\text{CH}_2$ ), 6.28 (1H, d,  $J$  15.4,  $\text{CH}=\text{CH}$ ), 6.88 (1H, d,  $J$  15.0,  $\text{CH}=\text{CH}$ ), 7.14 (1H, t,  $J$  6.6,  $\text{H}_3$ ), 7.48 (1H, s,  $\text{H}_5$ ), 7.49 (1H, dd,  $J$  8.6, 6.6,  $\text{H}_2$ ), 7.70 (1H, d,  $J$  8.6,  $\text{H}_1$ ) and 8.72 (1H, d,  $J$  6.6,  $\text{H}_4$ );  $\delta_{\text{C}}$  (50 MHz; DMSO) 19.1, 21.8, 28.9 (2C), 33.3, 34.3, 39.6, 92.3, 113.9, 119.7, 123.4, 124.1, 124.8, 128.1, 131.9, 132.8, 133.4, 136.9, 152.9, 154.2 and 158.5; MS (EI) 334 ( $\text{M}^+$ , 50), 278 (58), 249 (39), 213 (40), 199 (39), 185 (37), 129 (25), 122 (32), 107 (24), 91 (17), 78 (72), 69 (23), 44 (86) and 36 (100); HRMS for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): calcd. 334.1681, found 334.1689.

### 3-[(N-Benzyl-N-methylamino)methyl]pyrano[3',4':4,5]imidazo[1,2-a]pyridin-1-one (2l)

Yellow solid: 40% yield. Mp: 175–176 °C.  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3094, 2925, 2852, 1731, 1616;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 2.39 (3H, s,  $\text{CH}_3\text{N}$ ), 3.58 (2H, s,  $\text{CH}_2\text{N}$ ), 3.71 (2H, s,  $\text{NCH}_2\text{Ph}$ ), 6.96 (1H, s,  $\text{H}_5$ ), 6.99

(1H, t, *J* 6.8, H<sub>3</sub>), 7.28–7.38 (6H, m, (5H<sub>ph</sub>+H<sub>2</sub>), 7.74 (1H, d, *J* 9.2, H<sub>1</sub>) and 8.17 (1H, d, *J* 6.8, H<sub>4</sub>);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 42.7, 58.0, 61.9, 92.6, 113.9, 119.7, 124.5, 127.3, 127.4, 128.0, 128.1, 128.2 (2C), 128.8, 131.4, 138.3, 147.0, 157.5 and 158.7; MS (EI). 319 (21), 275 (8), 228 (7), 199 (15), 184 (14), 134 (28), 120 (14), 91 (100) and 78 (20); HRMS for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> (M<sup>+</sup>): calcd. 319.1321, found 319.1329.

### 3-Methoxymethylpyrano[3',4':4,5]imidazo[1,2-*a*]pyridin-1-one (2m)

Yellow solid: 55% yield. Mp: 155–157 °C.  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3091, 2918, 1739, 1621, 1516 and 1037;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 3.56 (3H, s, OCH<sub>3</sub>), 4.45 (2H, s, CH<sub>2</sub>OCH<sub>3</sub>), 6.94 (1H, s, H<sub>5</sub>), 7.02 (1H, t, *J* 7.2, H<sub>3</sub>), 7.42 (1H, dd, *J* 10.2, 7.2, H<sub>2</sub>), 7.78 (1H, d, *J* 10.2, H<sub>1</sub>) and 8.18 (1H, d, *J* 7.2, H<sub>4</sub>);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 59.2, 70.4, 91.9, 114.0, 119.6, 124.5, 128.5, 132.1, 147.2, 155.6 and 158.3; MS (EI) 230 (M, 100), 199 (29), 185 (40), 171 (50), 157 (19), 143 (18), 129 (39), 79 (15), 78 (91) and 51 (28); HRMS for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>): calcd. 230.0691, found 230.0686.

### Acknowledgements

We thank MESR for providing financial support and the “SAVIT, Tours (France)” for recording NMR and mass spectra.

### References

- 1 G. Bravi, A. G. Cheasty, J. A. Corfield, R. M. Grimes, D. Harrison, C. D. Hartley, P. D. Howes, K. J. Medhurst, M. L. Meeson, J. E. Mordaunt, P. Shah, M. J. Slater, G. V. White, WO 2007039146, 2007.
- 2 J. B. Veron, C. Enguehard-Gueffier, R. Snoeck, G. Andrei, E. De Clercq and A. Gueffier, *Bioorg. Med. Chem.*, 2008, **16**, 9536.
- 3 K. Gudmundsson, S. D. Boggs, WO 2007027999, 2007.
- 4 J. T. Lundquist, J. C. Pelletier, M. D. Vera, *US Pat.* 2006270848, 2006.
- 5 M. Hayakawa, H. Kaizawa, K. Kawaguchi, N. Ishikawa, T. Koizumi, T. Ohishi, M. Yamano, M. Okada, M. Ohta, S. Tsukamoto, F. I. Raynaud, M. D. Waterfield, P. Parker and P. Workman, *Bioorg. Med. Chem.*, 2007, **15**, 403.
- 6 K. C. L. Lee, E. Sun, H. Wang, WO 2008036046, 2008.
- 7 S. Allen, J. Greschuk, N. Kallan, F. Marmsäter, M. Munson, J. Rizzi, J. Robinson, S. Schlachter, G. Topalov, Q. Zhao, J. Lyssikatos, WO 2008124323, 2008; F. Marmsäter, M. Munson, J. Rizzi, J. Robinson, S. Schlachter, G. Topalov, Q. Zhao, J. Lyssikatos, WO 2008121687, 2008.
- 8 L. Murru, A. Latrofa, G. Trapani and E. Sanna, *J. Med. Chem.*, 2008, **51**, 6876.
- 9 M. M. Claffey, S. W. Goldstein, S. Jung, A. Nagel, V. Shulze, WO 2007034282, 2007.
- 10 C. Enguehard-Gueffier, H. Hubner, A. El Hakmaoui, H. Allouchi, H. P. Gmeiner, A. Argiolas, M. R. Melis and A. Gueffier, *J. Med. Chem.*, 2006, **49**, 3938.
- 11 M. Edin, J. Malmström, D. Pyring, C. Slivo, D. Wensbo, WO 2008091195, 2008.
- 12 N. Henry, C. Enguehard-Gueffier, I. Thery and A. Gueffier, *Eur. J. Org. Chem.*, 2008, **28**, 4824; C. Enguehard-Gueffier, I. Thery, A. Gueffier and S. L. Buchwald, *Tetrahedron*, 2006, **62**, 6042; C. Enguehard, H. Allouchi, A. Gueffier and S. L. Buchwald, *J. Org. Chem.*, 2003, **68**, 4367.
- 13 C. Enguehard-Gueffier, C. Croix, M. Hervet, J.-K. Kazock, A. Gueffier and M. Abarbri, *Helv. Chim. Acta*, 2007, **90**, 2349.
- 14 B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 2528; C. G. Bates, P. Saejueng, J. M. Murphy and D. Venkataraman, *Org. Lett.*, 2002, **4**, 4727; W. W. Cutchins and F. E. McDonald, *Org. Lett.*, 2002, **4**, 749; K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 86 and references therein; H. Zhang and R. C. Larock, *Tetrahedron Lett.*, 2002, **43**, 1359 and references therein; P. Aschwanden, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2000, **2**, 2331; F. E. McDonald, K. S. Reddy and Y. Diaz, *J. Am. Chem. Soc.*, 2000, **122**, 4304; C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu and J. M. Cook, *J. Org. Chem.*, 2001, **66**, 4525; T. Kondo, T. Okada, T. Suzuki and T.-A. Mitusudi, *J. Organomet. Chem.*, 2001, **622**, 149; T. E. Müller, M. Berger, M. Grosche, E. Herdtweck and F. P. Schmidtchen, *Organometallics*, 2001, **20**, 4384; L. Xu, I. R. Lewis, S. K. Davidsen and J. B. Summers, *Tetrahedron Lett.*, 1998, **39**, 5159.
- 15 For recent synthesis using Pd or Ag catalysts, see: V. Subramanian, V. R. Batchu, D. Barrange and M. Pal, *J. Org. Chem.*, 2005, **70**, 4778; C. Xu and E.-I. Negishi, *Tetrahedron Lett.*, 1999, **40**, 431; S. Ma and Z. Shi, *J. Org. Chem.*, 1998, **63**, 6387; R. Rossi, F. Bellina, M. Biagetti and L. Mannina, *Tetrahedron Lett.*, 1998, **39**, 7799; R. Rossi, F. Bellina, M. Biagetti and L. Mannina, *Tetrahedron Lett.*, 1998, **39**, 7599; R. Rossi, F. Bellina and L. Mannina, *Tetrahedron Lett.*, 1998, **39**, 3017; R. Rossi, F. Bellina, C. Bechini, L. Mannina and P. Vergamini, *Tetrahedron*, 1998, **54**, 135; J. A. Marshall, M. A. Wolf and E. M. Wallace, *J. Org. Chem.*, 1997, **62**, 367; J. A. Marshall, M. A. Wolf and E. M. Wallace, *J. Org. Chem.*, 1996, **61**, 3238; J. A. Marshall, M. A. Wolf and E. M. Wallace, *J. Org. Chem.*, 1995, **60**, 796.
- 16 Catalyzed by other metal complexes, see: T. Yao and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 5936; M. Biagetti, F. Bellina, A. Carpita, P. Stabile and R. Rossi, *Tetrahedron*, 2002, **58**, 5023; R. Mukhopadhyay and N. G. Kundu, *Tetrahedron*, 2001, **57**, 9475.
- 17 K. Sonogashira, in *Comprehensive Organic Synthesis* B. M. Trost, Ed.; Pergamon press, Oxford, UK, 1999; Vol. 3, p 521; K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.
- 18 S. Caachi, G. Fabrizi and P. Pace, *J. Org. Chem.*, 1998, **63**, 1001; S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro and P. Pace, *Synlett*, 1997, 1363; Y. Kondo, F. Shiga, N. Murata, T. Sakamoto and H. Yamanaka, *Tetrahedron*, 1994, **50**, 11803; K. Iritani, S. Matsubara and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1799.
- 19 A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488.
- 20 D. Yue and R. C. Larock, *Org. Lett.*, 2004, **6**, 1037.
- 21 (a) P. Saejueng, C. G. Bates and D. Venkataraman, *Synthesis*, 2005, 1706; (b) J.-X. Wang, Z. Liu, Y. Hu, B. Wei and L. Kang, *Synth. Commun.*, 2002, **32**, 1937; (c) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315; (d) K. Okuro, M. Furue, M. Enna, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 4716; (e) G. Batu and R. Stevenson, *J. Org. Chem.*, 1980, **45**, 1532.
- 22 For CuI-catalyzed C–N, see: B. Zou, Q. Yuan and D. Ma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2598; A. Shafir and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 8742 and references therein; Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen and B. Wan, *Tetrahedron*, 2006, **62**, 4435; Q. Cai, W. Zhu, H. Zhang, Y. Zhang and D. Ma, *Synthesis*, 2005, 496; H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164; B. M. Trost and D. T. Stiles, *Org. Lett.*, 2005, **7**, 2117; T. Hu and C. Li, *Org. Lett.*, 2005, **7**, 2035; Z. Wang, W. Bao and Y. Jiang, *Chem. Commun.*, 2005, 2849; Z. Lu and R. J. Twieg, *Tetrahedron Lett.*, 2005, **46**, 2997; H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem.–Eur. J.*, 2004, **10**, 5607 and references therein; D. Ma and Q. Cai, *Synlett*, 2004, 128.
- 23 Y. Fang and C. Li, *J. Org. Chem.*, 2006, **71**, 6427; X. Xie, Y. Chen and D. Ma, *J. Am. Chem. Soc.*, 2006, **128**, 16050; B. Lu and D. Ma, *Org. Lett.*, 2006, **8**, 6115; H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Chem.–Eur. J.*, 2006, **12**, 3636; Q. Cai, B. Zou and D. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 1276 and references therein; Q. Cai, G. He and D. Ma, *J. Org. Chem.*, 2006, **71**, 5268; X. Xie, G. Cai and D. Ma, *Org. Lett.*, 2005, **7**, 4693; W. Zhu and D. Ma, *J. Org. Chem.*, 2005, **70**, 2696; D. Ma, Q. Cai and X. Xie, *Synlett*, 2005, 1767; C. G. Bates, P. Saejueng and D. Venkataraman, *Org. Lett.*, 2004, **6**, 1441; H.-J. Cristau, P. P. Cellier, S. Hamada, J.-F. Spindler and M. Taillefer, *Org. Lett.*, 2004, **6**, 913; C. G. Bates, P. Saejueng, M. Q. Doherty and D. Venkataraman, *Org. Lett.*, 2004, **6**, 5005.
- 24 Y.-J. Chen and H. H. Chen, *Org. Lett.*, 2006, **8**, 5609; A. Y. Peng and Y.-X. Ding, *J. Am. Chem. Soc.*, 2003, **125**, 15006.
- 25 R. Cao, W. Yi, Q. Wu, X. Guan, M. Feng, C. Ma, Z. Chen, H. Song and W. Peng, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6558; R. Cao, W. Peng, Z. Wang and A. XU, *Curr. Med. Chem.*, 2007, **14**, 479.

- 26 M. Hellal, J.-J. Bourguignon and F. J.-J. Bihel, *Tetrahedron Lett.*, 2008, **49**, 62.
- 27 S. Inack-Ngi, R. Rahmani, L. Commeiras, G. Chouraqui, J. Thibonnet, A. Duchêne, J.-L. Parrain and M. Abarbri, *Adv. Synth. Catal.*, 2009, **351**, 779.
- 28 K. Cherry, J.-L. Parrain, J. Thibonnet, A. Duchêne and M. Abarbri, *J. Org. Chem.*, 2005, **70**, 6669; R. Rossi, F. Bellina, M. Biagetti, A. Catanese and L. Mannina, *Tetrahedron Lett.*, 2000, **41**, 5281; R. Rossi, A. Carpita, F. Bellina, P. Stabile and L. Mannina, *Tetrahedron*, 2003, **59**, 2067.
- 29 The dienyne ( $\alpha$ ) and ( $\beta$ ) were obtained from  $\alpha$ - or  $\beta$ -ionone according to the procedure described by E.-I. Negishi, A. O. King and W. L. Klima, *J. Org. Chem.*, 1980, **45**, 2526.
- 30 J. A. Kaizerman, M. I. Gross, Y. Ge, S. White, W. Hu, J.-X. Duan, E. E. Baird, K. W. Johnson, R. D. Tanaka, H. E. Moser and R. W. Bürl, *J. Med. Chem.*, 2003, **46**, 3914.