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N-arylation of 3-alkoxypyrazoles, the case of the pyridines

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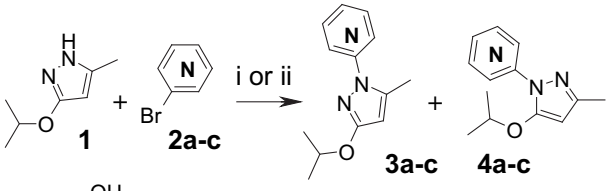
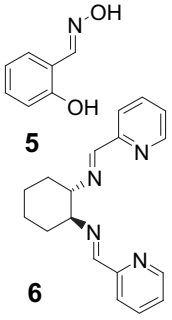
ABSTRACT

In the course of a research program focused on the preparation of libraries of new chemical entities derived from 3-alkoxypyrazoles, we studied their N-pyridylation using 2, 3 or 4-bromopyridines. This was achieved using Cristau and Taillefer copper-catalyzed arylation method and mostly led to the 3-alkoxy-1*H*-pyrazol-1-yl pyridine isomer along with lesser amount of the alternative 5-alkoxy-1*H*-pyrazol-1-yl pyridine. The structures of these isomers were often established via their chemical transformations and sometimes recourse to unambiguous synthetic routes for comparison purposes. The alternative use of 2-fluoropyridine-based arylation was also investigated and lifted some of the limitations encountered in the course of this study.

In the course of our preparation of new chemical entities,[1–3] we recently described[2] the regioselectivity of the N-arylations of readily available 3-alkoxypyrazoles[1] using Lam and Chan arylboronic-based reaction catalyzed by copper acetate.[4–8] We wish to report here investigations aiming at the introduction of a 2, 3 or 4 pyridyl moiety on various 3-alkoxypyrazoles. As only 3--pyridylboronates have been successfully used with the Lam and Chan approach, we focused here on the use of various halogenated pyridines under the optimized Ullmann-based N-arylation method[9–18] reported by Cristau and Taillefer.[19,20] Scheme 1 depicts such pyridylation from 3-isopropyloxypyrazole **1** and the three possible bromopyridines **2a–c**. The preparation of the isomeric pairs of *N*-pyridyl derivatives **3a–c** and **4a–c** was initially possible only if extensive heating was used, we thus resorted to the use of a microwave oven in an attempt to shorten this. Few control experiments with either 2- or 4-halogeno pyridines pointed out the need for copper in these reaction as of only traces amount of *N*-pyridyl derivatives were detected by LC/MS. In our experience with such reactions,[21] we suggest that deprotonation of the substrate is required. This is probably less easy for alkoxypyrazoles than for other pyrazole derivatives.[22–24] In the course of optimization trials, 2-pyridinyloxybenzonitriles occurrence was observed when using salicylaldoxime **5** as the copper ligand.[19,20] On the other hand, the use of the more elaborated [*N*,*N*′-bis-((2′-pyridine)-methylene)]-1,2-diaminocyclohexane (**6**)[25] avoided this bisaryl-ether occurrence and led to better yield of compounds **3a–c** and **4a–c**. Amongst the salient fact of this optimization work, we found





	2a-c	t (h)	% 3	% 4
a	2-BrC_5H_4N	2	53	25
b	3-BrC_5H_4N	2	13	5
b	"	6	30	2
c	4-BrC_5H_4N	2	8	26
c	"	6	17	10

Scheme 1. (i) or (ii): Cu_2O, Cs_2CO_3, ligand **6**, 4 Å molecular sieves, MeCN, MW 180 °C, 2 (or 6) hours.

that addition of small amount of 4 Å molecular sieves was essential for these reactions to proceed in dry acetonitrile. Aside from this, a most crucial feature in this reaction is a proper dissolution of the copper I oxide added. Upon the addition of this reagent, an insoluble pink foam is usually formed. It is only when this foam is dissolved that reproducible yield of N-pyridylation is obtained. This was routinely achieved by a very short (30 s) heating of the sealed vessel at 100 °C in a microwave reactor followed by a thorough shaking before heating at 180 °C for 2 h. The LC/MS monitoring of

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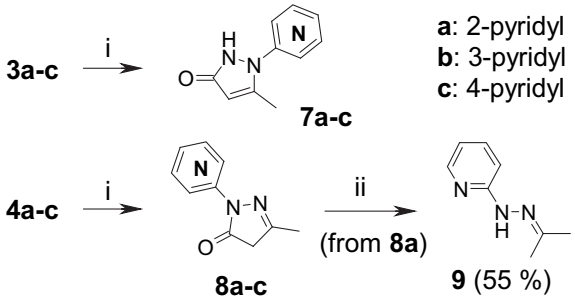
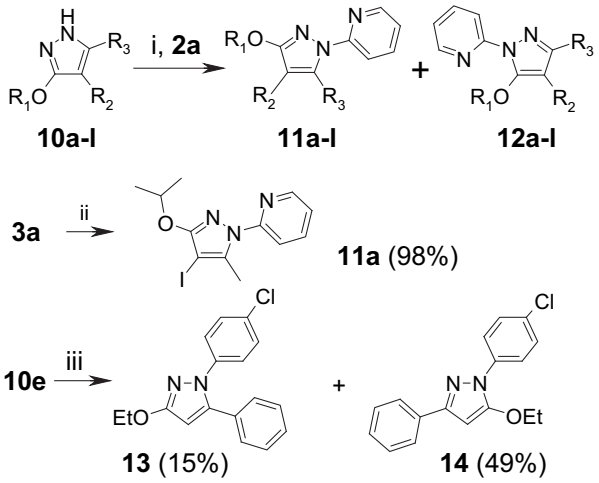
reaction trials using lower temperature or shorter reaction time proved that such parameters were necessary, in the case of 2-bromopyridine (**2a**). The use of acetonitrile was found to be the best as dimethylformamide led to the occurrence of small amount of dimethylaminopyridines. Interestingly, if the reaction could be brought to completion with 2-bromopyridine in 2 h at 180 °C, this was not the case when using 3 or 4-bromopyridine as much starting material could be recovered. An increase of the reaction duration led to the disappearance of the starting material **1** and lesser amount of isomers **4b**, and **4c**, which are probably not too stable under the reaction conditions. In effect this led to an apparent inversion of the N-arylation ratio. An improvement (up to 49% for **3c** along with 18% of compound **4c**) was obtained for the preparation of compounds **3c**/**4c** when using the readily available 4-iodopyridine[26] instead of 4-bromopyridine **2c**.

As depicted in Scheme 2, the structural assignments of the isomeric pairs **3a**–**c** and **4a**–**c** were made after an acidic cleavage of their isopropyloxy group to give compounds **7a**–**c** and **8a**–**c**. This was achieved in 60 mL sealed tubes with a small amount of 33% hydrogen bromide in acetic acid (1–2 mL) at 140 °C. It was quickly found that the exclusion of air was important to obtain the pyrazol-5-ones **8b** and **8c**. For the preparation of the isomer **8a**, as well as for **8c**, the reaction duration had to be shortened and its temperature had to be lowered to 100 °C. Indeed, isomer **8a** is fairly unstable and refluxing a sample in 2 N hydrochloric acid for 1 h led to an unreported pyrazole ring opening, followed by a decarboxylation, and thus to 55% of hydrazone **9**. The NMR study (in $CDCl_3$) of compounds **8b** and **8c** displayed ^1H NMR and ^{13}C NMR spectra featuring a methylene signal only compatible with the 1*H*-pyrazol-5(4*H*)-ones tautomers depicted in Scheme 1. From this, we could then determine the structure of the parent compounds **3b**–**c** and **4b**–**c**. In the case of **8a**, because of an internal hydrogen bond, the ^1H NMR and ^{13}C NMR spectra do not feature a methylene signal in any solvent tried.[27] A structural assignment could still be made as compound **8a** has been prepared in the past, from the condensation of 2-hydrazinopyridine and ethyl acetoacetate.[28] More thorough studies of the tautomeric forms of some pyrazol-3-ones adopted in solution have also been reported.[29,30]



Scheme 2. (i): HBr–AcOH 140 °C (or 100 °C). (ii): 2 N HCl, reflux.

As depicted in Scheme 3, further reactions were studied from 2-bromopyridine (**2a**) and the 3-ethoxypyrazoles **10a**–**k**, previously reported[1,2,31] or prepared as described in the Experimental part. Few remarkable facts were noticed in this study. Reaction with the 4-iododerivative **10a** led to the isolation of 45% of the reduced *N*-pyridyl compound **3a**. However, this difficulty was circumvented as 4-iodo isomer **11a** was obtained in an excellent 98% yield by iodination of **2a** using *N*-iodosuccinimide in cyclohexane in a microwave oven. Interestingly, this kind of reduction has been reported recently in the course of a copper-catalyzed arylation of pyrazole using 1,2-diiodobenzene.[32] Such phenomenon, along with a room temperature reduction we recently observed,[31] do provide insights in copper-catalyzed N-arylation mechanisms. From the labile 5-iodinated compound **11k** a similar reduction was seen although along with extensive decomposition and only traces of the reduced material **3a** were detected. Interestingly, extensive decomposition was the sole result seen when trying to arylate the trifluoromethyl derivative **10b**. From the ethoxy pyrazole **10c**, the proportion of the pyridyl isomers **11c** and **12c** obtained (55 and 26%) was fairly identical with the one obtained from the isopropyloxy derivative **1**. From the 4-fluoro derivative **10d**, no fluorine reduction was observed and isomers **11d** and **12d** were isolated in 67% and 9% yield, respectively. From the 5-phenyl derivative **10e**, a close to 1/1 ratio of the isomers **11e** and **12e** was observed. Such ratio from **10e** was unexpected. We previously observed that the N-arylation of **10e** using 4-chlorophenylboronic acid at room temperature leads to 2% of the isomer **13** as well as 83% of compound **14**.[2] On the other hand, as depicted, a control reaction between compound **10e** and 4-chloroiodobenzene under the present conditions led to a change in this ratio as compound **13** and its isomers **14** were isolated in 15% and 49% yield, respectively. Since one of the biggest difference in these reactions lies in the temperature (25 °C vs 180 °C), this suggests an increase of the freedom of rotation of the 5-phenyl bond.



	R_1	R_2	R_3	%**11***	%**12***
a	iPr	I	Me	reduction of **10a**	
b	Et	H	CF3	decomposition	
c	Et	H	Me	55	26
d	Et	F	Me	67	9
e	Et	H	Ph	36	41
f	Et	H	CH_2Ph	41	25
g	Et	Ph	Me	79	5
h	Et	CH_2Ph	Me	66	7
i	Et	CO_2Et	H	72	traces
j	Et	H	H	70	traces
k	Et	H	I	decomposition	
l	Et	H	CH_2CO_2Et	7**	

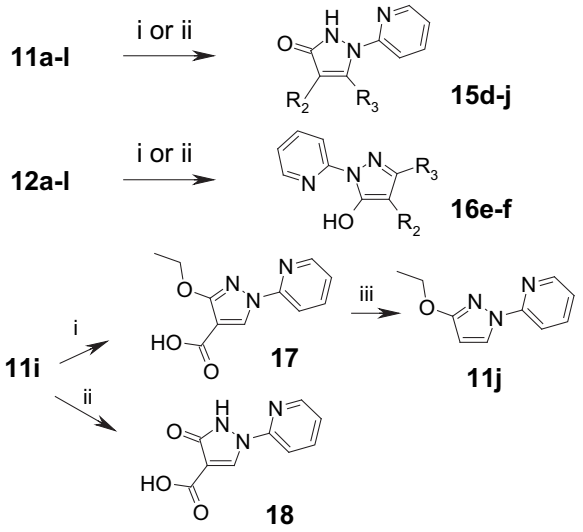
*: isolated yields. **: 17 % of **11c** were also isolated

Scheme 3. (i): Cu_2O, Cs_2CO_3, ligand **6**, 4 Å molecular sieves, MeCN, MW 180 °C, 2 h. (ii): NIS, cyclohexane, MW 140 °C, 45 min. (iii): conditions i, using 4-ClC_6H_4I.

This would lessen eventual hindrance and/or electronic effect, provided by conjugation, which could be precluding the arylation on the neighboring nitrogen at room temperature to give the isomer **13**. From the less hindered 5-benzyl pyrazole **10f**, a lesser amount of the pyridyl isomer **12f** was obtained. Moreover, from the 4-phenyl,

the 4-benzyl or the 4-ethoxycarbonyl derivatives **10g–i**, the N-pyridylation ratio is similar to the ones observed using arylboronic acids.[2,31]

As depicted in Scheme 4, when sufficient amount of the *N*-pyridyl derivatives was obtained, their ethyl ether cleavage was undertaken to give compounds **15c–j** or **16e–g**. In these instances,



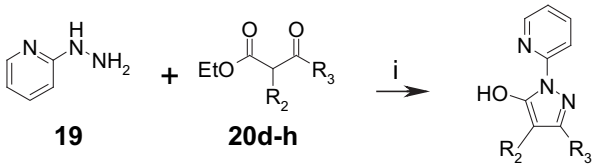
	R_2	R_3	%**15**	%**16**
c	H	Me	45 (**7a**)*	
d	F	Me	72	
e	H	Ph	64	29**
f	H	CH_2Ph	55	39
g	Ph	Me	69	-
h	CH_2Ph	Me	88	-
i	CO_2Et	H	see text	-
j	H	H	84	-

*: 7 days of reaction; 45 % of 11c were recovered.
**: 32 % of 12e were recovered.

Scheme 4. (i): HBr–AcOH, 140 °C. (ii): BBr_3, CH_2Cl_2, 25 °C, 48 h. (iii): Cu_2O, phenanthroline, Cs_2CO_3, DMF, MW, 200 °C 2 h.

1 M boron tribromide in dichloromethane at room temperature was used in an attempt to alleviate the decomposition trend observed when using hydrobromic acid in acetic acid at 140 °C. As seen from the yield of compounds **16e–g**, this met a limited success and we also observed the occurrence of strongly colored but intractable material. In few cases, 48 h at room temperature was not enough for a complete hydrolysis. Increasing the reaction time to 7 days, in the case of **11c**, only led to 45% of the hydrolysis product **7a** along with 45% of starting material. For this reason, we resorted to hydrogen bromide in acetic acid at 140 °C in the case of **11g**. Treatment of compound **11i** with hydrogen bromide in acetic acid at 140 °C only gave the 3-ethoxy acid **17**, which, as described in the experimental part, can also be obtained by saponification of **11i**. The use of boron tribromide on **11i**, allowed the isolation of the corresponding pyrazole-3-one **18** in 34% yield. The decarboxylation of acid **17** actually required rather harsh condition (200 °C) and led to compound **11j** in a 71% yield, this result establishing the structure of **11i**. Finally, upon saponification of ester **11l**, the corresponding acid was obtained. The ^1H NMR monitoring of a sample of this acid heated in a Kugelrohr at 240 °C for up to 15 min pointed out the occurrence of compound **11c**—and none of **12c**—along with unidentified material, thus establishing the structure of **11l**.

Aside for the previously described compound **15j**[33], which gave, directly or indirectly, the basis for the structures assignments of compounds **11i**, **11j** as well as **17** and **18**, the lack of precedent in the literature or easily obtained NMR NOE effects, led us to attempt unambiguous chemical synthesis. Accordingly as depicted in Scheme 5, we undertook the condensation of 2-hydrazinopyridine (**19**) and various β-ketoesters (**20d–h**) to obtain the 1-(pyridin-2-yl)-1*H*-pyrazol-5-ol isomers **16d–h**. From the β-ketoesters **20e**, **20g** or **20h**, the 1*H*-pyrazol-5-ols **16e**, **16g** or **16h** were prepared with little trouble although in the case of compound **16e**, the reaction



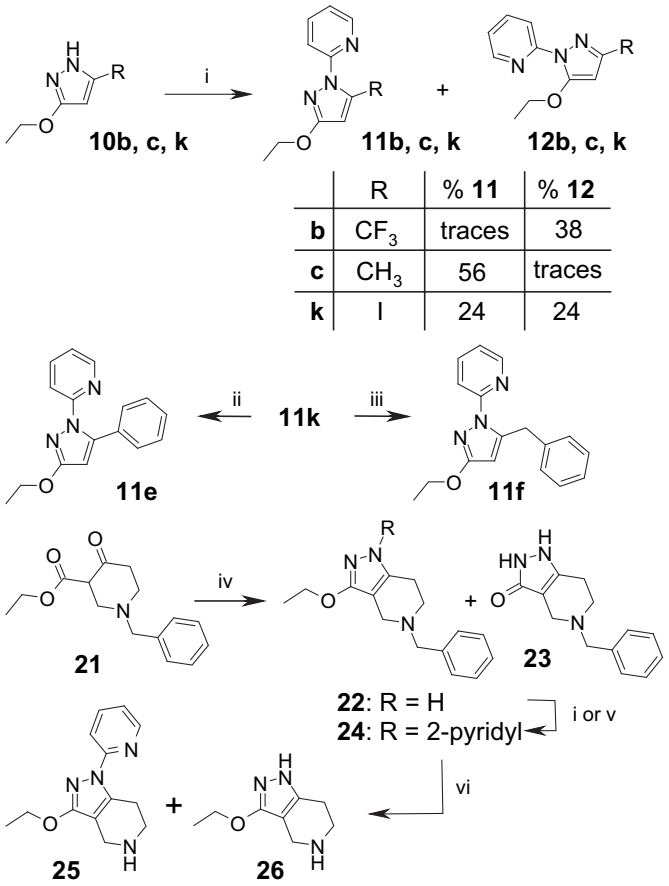
	R_2	R_3	% **16**
d	F	Me	0%, see text
e	H	Ph	90
g	Ph	Me	69
h	CH_2Ph	Me	70

Scheme 5. (i): AcOH, MW 100 °C or 25 °C (see text).

had to be made at room temperature to avoid an extensive decomposition. However, from ethyl 2-fluoroacetoacetate **20d**, many attempts only led to decomposition. The LC/MS monitoring of a trial at room temperature in ethanol pointed out the possible occurrence of uncyclized material (m/z=240) but, again, extensive decomposition was observed when further purification or heating was attempted in either neutral, basic or acidic conditions. Related difficulties have actually been reported in the past in other cases.[34–36] Moreover, attempts to fluorinate compound **11c** were surprisingly devoid of success. Further NMR studies pointed out the unexpectedly large values of the hydrogen's T1 (i.e., between 2 and 3 s for compound **11c**) for this type compounds and only led to useful NOESY spectra only at the frequency of 600 MHz. However, in recording the spectrum at 400 MHz, we found that the use of 1D measurement with degassed samples (by bubbling argon through the solution) led to good NOE effects. Thus, for isomers **11c** as for **11d**, the similar NOE seen between their methyl moieties and the 2-pyridyl protons H6 and H3 established the structure of **11d**.

Since the trifluoromethyl-bearing derivative **10b**, or the iodine-bearing compounds **10k**, could not be successfully subjected to the 2-pyridylation conditions described above, we look for alternatives. Scheme 6 depicts our trials using the reported use of 2-fluoropyridine under basic condition and heating.[37,38] Initial optimization trials led us to heat compound **10c**, 2-fluoropyridine, and cesium carbonate without any solvent at 180 °C for 2 h and gave 56% of isomer **11c** along with only traces of isomer **12c**, which also appears to be unstable under these reaction conditions. From compound **10k**, 2 h of reaction turned out to lead to only small amount of the isomers **11k** and **12k** along with extensive decomposition. However, shortening the reaction time down to 15 min and lowering the reaction temperature to 160 °C improved the matter and isomers **11k** and **12k** were obtained in 24 and 24% yield, respectively. From the trifluoromethyl derivative **10b**, 180 °C for 15 min led to traces

amount of isomer **11b** along with 38% of the isomer **12b**. Its structural assignment was achieved by the observation of 1D NOE effects between its terminal methyl group (not from the ethylene) and the H2 and H6 of the 2-pyridyl moiety. To illustrate the



	R	% 11	% 12
b	CF_3	traces	38
c	CH_3	56	traces
k	I	24	24

Scheme 6. (i): 2-Fluoropyridine, Cs_2CO_3, MW, 180 °C, 15 min to 3 h (see text). (ii): $PheB(OH)_2$, Cs_2CO_3, *n*-PrOH–H_2O, MW 130 °C. (iii): $PhCH_2ZnBr$, THF, MW 110 °C. (iv): NH_2NH_2, HCl·EtOH, reflux. (v): **2a**, Cu_2O, Cs_2CO_3, ligand **6**, 4 Å molecular sieves, MeCN, MW 180 °C, 3 h. (vi): H_2, 25 bar, 10% Pd–C, AcOH, 65 °C, 3 h.

'diversity' potential of compound **11k**, a Suzuki reaction with phenylboronic acid gave to the 5-phenyl isomer **11e** along with the reduced material **11j** in 39 and 20%, respectively. Moreover, a Negishi reaction with benzylzincbromide gave the 5-benzyl isomer **11f** as well as the reduced compound **11j**, in 43 and 32%, respectively. These two transformations actually confirmed the structure assignment of compounds **11k** as well as **11f**. Finally, as an illustration of the quirk we encountered in this work, we also undertook the synthesis of *N*-pyridyl derivative **24** obtained via the pyrazolopyridine **22**; very simply prepared in one step from **21**. The reaction of compound **22** with 2-bromopyridine gave 42% of isomer **24** as seen by 1D NOE effects between the methylene on carbon 7 of the pyrazolopyridine ring and the H2 and H6 of the 2-pyridyl moiety. A trial with 2-fluoropyridine (at 180 °C for 3 h) gave an improved 55% yield along with traces amount of the other isomer (not depicted). However, the next step of our work called for the hydrogenolysis of the benzyl group to give compound **25**. This required rather strong conditions and gave 16% of **25** although along with substantial disappearance of the pyridine ring to give the pyrazolopyridine **26** in a 13% yield. A literature search pointed out that such chelation-assisted palladium-based hydrogenation of an aryl had been reported for another *N*-phenylpyrazole, which led to the corresponding *N*-cyclohexyl pyrazole.[39] Other interesting chelation-assisted reactions with *N*-arylpyrazoles and ruthenium salts were actually reported recently.[40,41] In our case, this hydrogenation gives rise to an unstable aminal, which undergoes an immediate hydrolysis to give compound **26**. On the NMR point of view, the methylenes ^1H NMR signals of compound **25** are a bit spread out because of the ring flexibility. On the other hand, this is far worse in the case of **26** as its 'visible' ^1H NMR as well as ^{13}C NMR signals can be summed up to one ethoxy signal. It is only the high-resolution mass spectrum of **26**, which provided a proof of structure in this case. This unexpected cleavage is currently leading us to redesign our strategy to prepare compounds featuring a pyrazolopyridine core structure.

In conclusion, this work provides some insights on the regioselectivity of copper-catalyzed N-arylation, hopefully useful beyond the alkoxypyrazoles. Our studies of the reaction conditions provided by the work of Cristau and Taillefer pointed out the importance of proper dissolution of the catalyst, the possible importance (in our cases) of adding small amount of molecular sieves as well as the interest of using a microwave oven to shorten the reaction duration. Further investigations on the alternative use of 2-fluoropyridine as a 2-pyridyl source provided a fairly simple alternative access to 2-pyridyl derivatives. As mentioned in a recent work,[32] this classic approach remains very useful, especially in the case of copper-sensitive substrates, such as iodinated substrates. Interestingly, one set of the pyridyl isomers obtained was usually found to be rather unstable either toward heat or acid treatment. In one instance, a previously unreported pyrazole ring acidic cleavage was observed. Moreover, our results also pointed out that a 2-pyridyl group can eventually be considered as a (rather expensive) protecting group of the nitrogen of the 3-alkoxypyrazoles.

1. Experimental part

A Biotage initiator 2 microwave oven was used for the reactions requiring microwaves irradiations. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometers at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in parts per million (ppm) with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed either Merck silica gel 60 (0.035–0.070 mm) or neutral alumina containing a suitable proportion of water, using a solvent pump operating at pressure between 2 and 7 bar (25–50 mL/min) and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise (i.e., if ethyl acetate was used then it would be set to 280 nm). Sample deposition was always carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low-resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high-resolution mass spectroscopy spectra (HRMS) was obtained using a Waters Micromass Q-Tof with an electrospray ion source.

1.1. General method for the copper-catalyzed arylation of alkoxypyrazoles with bromopyridines

In a 20 mL Biotage tube the 3-alkoxypyrazole (10 mmol), the bromopyridines **2a**–**c** (10.5 mmol), cesium carbonate (10.5 mmol, 3.42 g), 4 Å molecular sieves (0.5 g, 3.2 mm pellets) [*N*,*N*′-bis-((2′-pyridine)-methylene)]-1,2-diaminocyclohexane (**6**)[25] (0.1 mmol, 0.29 g) were dispersed in acetonitrile (14 mL, dried over 4 Å molecular sieves). The suspension was degassed using a slow stream of argon bubbling in the suspension. Copper oxide (0.05 mmol, 0.072 g) was then added and the tube was sealed. The tube was then shaken thoroughly, heated for 30 s in the microwave oven at 100 °C and shaken again. At this stage the pink copper oxide is well

dissolved in the reaction mixture; if not, another 30 s heating at 100 °C is required. The heating is then resumed at 180 °C for 2 h. An LC/MS monitoring of a sample usually points out the quasi disappearance of the starting alkoxypyrazole. As described in the text, further heating brought the reaction to an apparent completion in the case of 3- or 4-bromopyridines. The resulting suspension was dispersed in ethyl acetate, directly adsorbed over a small amount of the relevant solid phase and purified by a chromatography over that phase as described below.

*1.1.1. 2-(3-Isopropoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**3a**).* Obtained as an oil after a chromatography over silica gel (dichloromethane–ethanol 99/1) in a 53% yield. ^{1}H NMR ($CDCl_3$): 1.40 (d, 6H, *J*=6.1); 2.67 (s, 3H); 4.83 (sept, 1H, *J*=6.1); 5.66 (s, 1H); 7.07 (m, 1H); 7.73 (m, 1H); 7.82 (m, 1H); 8.37 (m, 1H). ^{13}C NMR ($CDCl_3$): 15.1; 22.1; 71.4; 96.1; 114.8; 119.7; 137.9; 142.5; 147.1; 153.8; 162.6. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1246.

*1.1.2. 2-(5-Isopropoxy-3-methyl-1H-pyrazol-1-yl)pyridine (**4a**).* Obtained as an oil in a 2% yield following a second chromatography of this fraction over neutral alumina containing 1.5% H_2O (cyclohexane–dichloromethane 3/1 to 1/4). ^{1}H NMR ($CDCl_3$): 1.42 (d, 6H, *J*=6.1); 2.30 (s, 3H); 4.48 (sept, 1H, *J*=6.1); 5.49 (s, 1H); 7.15 (m, 1H); 7.66 (m, 1H); 7.73 (m, 1H); 8.54 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.6; 21.8; 71.4; 87.8; 115.8; 120.8; 137.6; 148.8; 150.0; 150.8; 154.5. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1328.

Isomers **3b** and **4b**: these isomers were obtained after two chromatography (neutral alumina+1.5% H_2O; cyclohexane–dichloromethane 3/2 and then silica gel; dichloromethane–ethanol 99/1 to 98/2).

*1.1.3. 3-(3-Isopropoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**3b**).* Obtained as an oil in the yields mentioned in Scheme 1. ^{1}H NMR ($CDCl_3$): 1.38 (d, 6H, *J*=6.1); 2.35 (s, 3H); 4.83 (sept, 1H, *J*=6.1); 5.70 (s, 1H); 7.39 (m, 1H); 7.83 (m, 1H); 8.55 (m, 1H); 8.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.0; 22.1; 71.5; 95.0; 123.6; 131.2; 136.7; 140.5; 144.7; 147.2; 163.3. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1215.

*1.1.4. 3-(5-Isopropoxy-3-methyl-1H-pyrazol-1-yl)pyridine (**4b**).* Obtained as an oil in the yields mentioned in Scheme 1. ^{1}H NMR ($CDCl_3$): 1.42 (d, 6H, *J*=6.1); 2.28 (s, 3H); 4.48 (sept, 1H, *J*=6.1); 5.49 (s, 1H); 7.36 (m, 1H); 8.08 (m, 1H); 8.47 (m, 1H); 9.07 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.6; 21.9; 76.1; 87.1; 123.5; 128.6; 135.8; 142.5; 146.1; 150.1; 154.4. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1212.

*1.1.5. 4-(3-Isopropoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**3c**).* The reaction was undertaken from 4-bromopyridine hydrochloride. This forced the use of twice the amount of cesium carbonate. For this reason, the reaction was usually run on a smaller scale (i.e., 5 mmol). Compound **3c** was obtained as an oil in the yield mentioned in Scheme 1 after two chromatography (silica gel; dichloromethane–ethanol 98/2 and then neutral alumina+1.5% H_2O; cyclohexane–dichloromethane 1/2). ^{1}H NMR ($CDCl_3$): 1.40 (d, 6H, *J*=6.1); 2.48 (s, 3H); 4.85 (sept, 1H, *J*=6.1); 5.73 (s, 1H); 7.49 (m, 2H); 8.63 (s (br), 2H). ^{13}C NMR ($CDCl_3$): 14.1; 28.1; 71.6; 97.1; 115.9; 140.9; 146.7; 150.6; 163.2. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1230.

*1.1.6. 4-(5-Isopropoxy-3-methyl-1H-pyrazol-1-yl)pyridine (**4c**).* The reaction was undertaken from 4-bromopyridine hydrochloride. This forced the use of twice the amount of cesium carbonate. For this reason, the reaction was usually run on a smaller scale (i.e., 5 mmol). Compound **4c** was obtained as an oil in the yield mentioned in Scheme 1 after two chromatography (silica gel; dichloromethane–ethanol 98/2 and then neutral alumina+1.5% H_2O; cyclohexane–dichloromethane 1/2). ^{1}H NMR ($CDCl_3$): 1.46 (d, 6H, *J*=6.1); 2.27 (s, 3H); 4.50 (sept, 1H, *J*=6.1); 5.48 (s, 1H); 7.79 (m, 2H); 8.58 (s (br), 2H); nota: the 7.79 signal is dependent on the acidity of the solvent; and is sometimes seen at 7.93. ^{13}C NMR ($CDCl_3$): 11.6; 21.9; 76.3; 87.2; 113.8; 145.5; 150.5; 150.6; 155.3. HRMS: calcd for $C_{12}H_{15}N_3O$+H: 218.1293; exp: 218.1200.

1.2. Deprotection using hydrobromic acid in acetic acid

The alkoxypyrazole (1 mmol) was placed in a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap. The tube was degassed with argon and then 33% hydrogen bromide in acetic acid (1.5 mL) was added. The tube was tightly closed and was heated at 140 °C for 3 h. The resulting suspension was cooled, dissolved in ethanol, concentrated to dryness made basic with ethanolic ammonia and concentrated to dryness again. The residues were further purified as described below.

*1.2.1. 5-Methyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**7a**).* Obtained as a solid in a 46% yield after a chromatography over silica gel (dichloromethane–ethanol 9/1). Mp=185 °C. ^{1}H NMR ($CDCl_3$): 2.62 (s, 3H); 5.70 (s, 1H); 7.17 (m, 1H); 7.61 (m, 1H); 7.84 (m, 1H); 8.43 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 95.9; 115.3; 120.6; 138.6; 143.4; 147.6; 152.5; 162.8. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0864.

*1.2.2. 3-Methyl-1-(pyridin-2-yl)-1H-pyrazol-5-ol (**8a**)*[28]. This compound was obtained in a better 53% yield as a solid if the heating was shortened to 1 h and the temperature kept to 100 °C. Obtained as a solid after a chromatography over silica gel (dichloromethane–ethanol 9/1). Mp=111 °C. ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H); 5.44 (s, 1H); 7.12–7.18 (m, 1H); 7.80–7.86 (m, 1H); 7.89–7.97 (m, 1H); 8.20–8.30 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.5; 88.7; 111.9; 119.5, 139.8; 145.1; 151.5; 154.1; 157.3. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0790.

*1.2.3. 5-Methyl-1-(pyridin-3-yl)-1H-pyrazol-3(2H)-one (**7b**).* Obtained in a 65% yield as a solid after a chromatography over silica gel (dichloromethane–ethanol 95/5). Mp=190 °C. ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H); 5.70 (s, 2H); 7.47 (m, 1H); 7.82 (m, 1H); 8.60 (m, 1H); 8.93 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.7; 94.8; 123.8; 131.0; 135.8; 141.2; 145.3; 147.4; 163.3. HRMS calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0764.

*1.2.4. 3-Methyl-1-(pyridin-3-yl)-1H-pyrazol-5(4H)-one (**8b**).* Obtained in a 69% yield as a solid after a chromatography over silica gel (dichloromethane–ethanol 95/5). Mp=129 °C. ^{1}H NMR ($CDCl_3$): 2.23 (s, 3H); 3.46 (s, 2H); 7.34 (m, 1H); 8.29 (m, 1H); 8.45 (m, 1H); 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$): 17.1; 42.7; 123.7; 125.6; 134.9; 139.9; 145.3; 157.3; 170.8. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0788.

*1.2.5. 5-Methyl-1-(pyridin-4-yl)-1H-pyrazol-3(2H)-one (**7c**).* Obtained in a 82% yield as a solid after a chromatography over silica gel (dichloromethane–ethanol 94/6). Mp=204 °C. ^{1}H NMR ($CDCl_3$): 2.48 (s, 3H); 5.78 (s, 1H); 7.43 (m, 2H); 8.71 (m, 2H). ^{1}H NMR (DMSO-d_6): 2.44 (s, 3H); 5.73 (s, 1H); 7.54 (m, 2H); 8.58 (m (br), 2H); 10.28 (s, 1H). ^{13}C NMR (DMSO-d_6): 13.5; 96.9; 115.5 (br); 141.2; 146.1; 150.5; 162.2. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0866.

*1.2.6. 3-Methyl-1-(pyridin-4-yl)-1H-pyrazol-5(4H)-one (**8c**).* Obtained in a 52% yield as a yellow solid after a chromatography over silica gel (dichloromethane–ethanol 96/4) if, as for compound **8a**, the heating was shortened to 1 h and the

temperature kept to 100 °C. Mp=206 °C. ^{1}H NMR ($CDCl_3$): 2.23 (s, 3H); 3.47 (s, 2H); 7.88 (m, 2H); 8.57 (m, 2H). ^{1}H NMR (DMSO-d_6): 2.13 (s, 3H); 5.36 (s (br), 1H); 7.81 (m, 2H); 8.53 (m, 2H). ^{13}C NMR (DMSO-d_6): much dispersed signals 14.0; 89.5; 112.4; 145.0; 150.0; 151.1; 157.4. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; exp: 176.0771.

*1.2.7. 2-(2-(Propan-2-ylidene)hydrazinyl)pyridine (**9**).* Compound **4a** (0.17 g, 0.97 mmol) was boiled in 2 N hydrochloric acid (15 mL) for 1 h. The resulting suspension was made basic with sodium hydrogencarbonate, and extracted with ethyl acetate. The organic phase was washed with brine dried over magnesium sulfate and concentrated to dryness to yield compound **9** (0.08 g, 55%) as an off-white solid. Mp=73 °C (lit.[42]=69–70 °C). ^{1}H NMR ($CDCl_3$): 1.92 (s, 3H); 2.07 (s, 3H); 6.73 (m, 1H); 7.24 (m, 1H); 7.57 (m, 1H); 7.80 (s (br), 1H); 8.09 (m, 1H). ^{13}C NMR ($CDCl_3$): 15.9; 25.2; 107.4; 115.1; 138.3; 146.0; 146.9; 157.2. HRMS: calcd for $C_8H_{11}N_3$+H: 150.1031; exp: 150.1050.

1.3. Preparation of 3-ethoxypyrazoles 10g, 10i, 22, and 23

As previously described,[1] the relevant ethyl β-ketoesters (0.01 mmol) and hydrazine hydrochloride (0.89 g, 0.0103 mmol) were refluxed in ethanol (20 mL) for 8 h. The solvent was removed under reduced pressure, the residue was dispersed in dichloromethane and an excess of a saturated solution of sodium hydrogencarbonate. The organic phase was washed three times with sodium hydrogencarbonate, dried over magnesium sulfate, and concentrated to dryness to yield compounds **10g**, **10i**, **22**, and **23**as described below.

*1.3.1. 3-Ethoxy-5-methyl-4-phenyl-1H-pyrazole (**10g**).* Obtained as a solid in a 39% yield after a chromatography over silica gel (dichloromethane–ethanol 99/1). Mp=141 °C. ^{1}H NMR ($CDCl_3$): 1.43 (t, 3H, *J*=7.1); 2.38 (s, 3H); 4.34 (q, *J*=7.1 Hz, 2H); 7.23 (m, 1H); 7.39 (m, 2H); 7.50 (m, 2H); 7.70 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 11.6; 14.9; 64.6; 104.8; 125.8; 128.2; 128.3; 132.3; 137.6; 161.0. HRMS: calcd for $C_{12}H_{14}N_2O$+H: 203.1184; exp: 203.1149.

*1.3.2. Ethyl 2-(3-ethoxy-1H-pyrazol-5-yl)acetate (**10i**).* Obtained as an oil in a 43% yield. ^{1}H NMR ($CDCl_3$): 1.30 (t, 3H, *J*=7.0); 1.40 (t, 3H, *J*=7.0); 3.69 (s, 2H); 4.21 (m, 4H); 5.62 (s, 1H); 9.00 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 14.1; 14.8; 32.1; 61.5; 64.9; 90.2; 137.3; 163.1; 169.6. HRMS: calcd for $C_9H_{14}N_2O_3$+H: 199.1083; exp: 199.1039.

*1.3.3. 5-Benzyl-3-ethoxy-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (**22**) and 5-benzyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3(2H)-one (**23**).* Compound **22** was obtained as a glass in a 38% yield, from the commercially available hydrochloride salt of **21**, after an extraction as described above, using ethyl acetate. Whereas the hydrochloride salt of **23** was filtered off from the initial ethanolic solution (isolated as a white powder in a 52% yield).

Compound **22**: mp=105 °C. ^{1}H NMR ($CDCl_3$): 1.37 (t, 3H, *J*=7.0); 2.65 (q, 2H); 2.76 (q, 2H); 3.42 (s, 2H); 3.73 (d, 2H); 4.23 (q, 2H, *J*=7.0); 7.2–7.4 (m, 5H); 8.9 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.9; 22.3; 47.8; 62.0; 64.1; 99.9; 127.1; 128.3; 129.0; 138.4; 139.0; 159.6. HRMS: calcd for $C_{15}H_{19}N_3O$+Na: 280.1426; exp: *m*/*z*, 280.1442.

Hydrochloride salt of **23**: mp>240 °C (dec). ^{1}H NMR (DMSO-d_6): 2.99 (s (br), 1H); 3.15 (s (br), 1H); 3.37 (s (br), 1H); 3.64 (s (br), 1H); 4.01 (s (br), 2H); 4.45 (m, 2H); 7.50 (m, 3H); 7.71 (m, 2H); 11.87 (s (br), 1H); 13.46 (s (br), 3H). ^{13}C NMR (DMSO-d_6): 18.8; 45.2; 47.9; 57.7; 92.8; 128.7; 129.4; 129.8; 131.4; 139.8; 153.7. HRMS: calcd for $C_{13}H_{15}N_3O$+H: 230.1293; exp: *m*/*z*, 230.1229.

*1.3.4. 2-(4-Iodo-3-isopropoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**11a**).* In a Biotage vial, compound **2a** (0.18 g, 0.83 mmol) and *N*-iodosuccinimide (0.22 g, 0.91 mmol) were dispersed in cyclohexane (4 mL). The tube was heated in a microwave oven at 140 °C for 45 min. The resulting purple solution was dissolved in ethyl acetate and water, the mixture was decolorized with sodium sulfite, the organic layer was washed with water, brine, dried over magnesium sulfate, and concentrated to dryness under high vacuum to yield pure compound **11a** as an oil (0.28 g, 98%). ^{1}H NMR ($CDCl_3$): 1.44 (d, 3H, *J*=6.1); 2.72 (s, 3H); 5.03 (sept, 1H, *J*=6.1); 7.13 (m, 1H); 7.78 (m, 2H); 8.40 (m, 1H). ^{13}C NMR ($CDCl_3$): 15.6; 22.1; 54.9; 117.4; 120.3; 138.3; 143.3; 147.2; 153.4; 162.0. HRMS: calcd for $C_{12}H_{14}IN_3O$+H: 344.0260; exp: 344.0269.

By using the copper-based N-arylation protocol described above, the following compounds were also obtained.

*1.3.5. 2-(3-Ethoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**11c**).* Obtained as an oil that slowly crystallized after a chromatography over silica gel (cyclohexane–ethyl acetate 95/5 to 1/1) in a 55% yield. Mp<50 °C. ^{1}H NMR ($CDCl_3$): 1.43 (t, 3H, *J*=7.1); 2.66 (s, 3H); 4.28 (q, 2H, *J*=7.1); 5.68 (s, 1H); 7.08 (m, 1H); 7.73 (m, 1H); 7.82 (m, 1H); 8.38 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 15.1; 64.5; 95.6; 114.9; 119.8; 138.1; 142.7; 147.1; 153.7; 163.3. HRMS: calcd for $C_{11}H_{13}N_3O$+H: 204.1137; exp: 204.1083.

*1.3.6. 2-(5-Ethoxy-3-methyl-1H-pyrazol-1-yl)pyridine (**12c**).* This compound was obtained as an oil in a 26% yield after a second chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 7/3). ^{1}H NMR ($CDCl_3$): 1.44 (t, 3H, *J*=7.0); 2.28 (s, 3H); 4.16 (q, 2H, *J*=7.0); 5.48 (s, 1H); 7.13 (m, 1H); 7.67 (m, 1H); 7.74 (m, 1H); 8.52 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.5; 14.6; 68.1; 87.0; 115.8; 120.9; 137.8; 148.7; 150.0; 150.9; 155.5. HRMS: calcd for $C_{11}H_{13}N_3O$+H: 204.1137; exp: 204.1113.

*1.3.7. 2-(3-Ethoxy-4-fluoro-5-methyl-1H-pyrazol-1-yl)pyridine (**11d**).* This compound was obtained as an oil that slowly solidified in a 67% yield after a chromatography over silica gel (dichloromethane and then dichloromethane–ethanol 99/1). Mp<50 °C. ^{1}H NMR ($CDCl_3$): 1.47 (t, 3H, *J*=7.2); 2.65 (s, 3H); 4.40 (q, 2H, *J*=7.2); 7.08 (m, 1H); 7.75 (m, 2H); 8.36 (m, 1H). ^{13}C NMR ($CDCl_3$): 11.5; 14.7; 65.0; 113.9; 119.8; 127.4 (*J*=24 Hz); 136.2 (*J*=243 Hz); 138.2; 147.1; 150.9; 153.9. HRMS: calcd for $C_{11}H_{12}N_3OF$+H: 222.1043; exp: 222.0974.

*1.3.8. 2-(5-Ethoxy-4-fluoro-3-methyl-1H-pyrazol-1-yl)pyridine (**12d**).* This compound was obtained as an oil in a 9% yield after a second chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, *J*=7.1); 2.29 (s, 3H); 4.41 (m, 2H); 7.19 (m, 1H); 7.66 (m, 1H); 7.77 (m, 1H); 8.55 (m, 1H). ^{13}C NMR ($CDCl_3$): 10.9; 15.3; 69.6; 115.6; 121.4; 134.2 (*J*=240 Hz); 138.0 (*J*=10 Hz); 138.1; 139.2 (*J*=20 Hz); 148.7; 150.9. HRMS: calcd for $C_{11}H_{12}N_3OF$+H: 222.1043; exp: 222.0979.

*1.3.9. 2-(3-Ethoxy-5-phenyl-1H-pyrazol-1-yl)pyridine (**11e**).* This compound was obtained as a wax in a 36% yield after a chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 95/5 to 9/1). ^{1}H NMR ($CDCl_3$): 1.45 (t, 3H, *J*=7.1); 4.38 (q, 2H, *J*=7.1); 5.99 (s, 1H); 7.13 (m, 1H); 7.31 (m, 5H); 7.42 (m, 1H); 7.69 (m, 1H); 8.31 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 64.7; 95.9; 118.0; 121.4; 128.1; 128.2; 128.7; 131.3; 138.0; 145.1; 148.2; 152.4; 163.9. HRMS: calcd for $C_{16}H_{15}N_3O$+H: 266.1293; exp: 266.1242.

*1.3.10. 2-(5-Ethoxy-3-phenyl-1H-pyrazol-1-yl)pyridine (**12e**).* This compound was obtained as an oil in a 41% yield after a chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 95/5 to 9/1). ^{1}H NMR ($CDCl_3$): 1.51 (t, 3H, *J*=7.1); 4.30 (q, 2H, *J*=7.1); 6.04 (s, 1H); 7.22 (m, 1H); 7.35 (m, 1H); 7.44 (m, 2H); 7.80 (m, 1H); 7.82 (m, 1H); 7.91 (m, 2H); 8.62 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.6; 68.5; 84.6; 116.8; 121.4; 125.8; 128.3; 128.4; 133.1;

138.2; 148.6; 151.2; 151.7; 156.0. HRMS: calcd for $C_{16}H_{15}N_3O$+H: 266.1293; exp: 266.1216.

*1.3.11. 2-(5-Benzyl-3-ethoxy-1H-pyrazol-1-yl)pyridine (**11f**).* This compound was obtained as an oil in a 41% yield after a chromatography over silica gel (dichloromethane and then dichloromethane–ethanol 99/1). ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, *J*=7.1); 4.27 (q, 2H, *J*=7.1); 4.55 (s, 2H); 5.51 (s, 1H); 7.08 (m, 1H); 7.28 (m, 5H); 7.74 (m, 1H); 7.81 (m, 1H); 8.36 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 34.9; 64.5; 96.2; 115.0; 120.0; 126.3; 128.3; 129.1; 138.1; 138.8; 146.1; 147.1; 153.6; 163.3. HRMS: calcd for $C_{17}H_{17}N_3O$+H: 280.1450; exp: 280.1378.

*1.3.12. 2-(3-Benzyl-5-ethoxy-1H-pyrazol-1-yl)pyridine (**12f**).* This compound was obtained as an oil that slowly solidified in a 25% yield after a second chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 9/1). Mp<50 °C. ^{1}H NMR ($CDCl_3$; solution becomes bright red over time): 1.43 (t, 3H, *J*=7.1); 4.02 (s, 2H); 4.13 (q, 2H, *J*=7.1); 5.40 (s, 1H); 7.19 (m, 1H); 7.24 (m, 1H); 7.32 (m, 4H); 7.72 (m, 1H); 7.79 (m, 1H); 8.61 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.5; 35.8; 68.2; 86.4; 116.0; 121.1; 126.3; 128.5; 128.9; 138.2; 139.4; 148.7; 150.7; 153.4; 155.6. HRMS: calcd for $C_{17}H_{17}N_3O$+H: 280.1450; exp: 280.1405.

*1.3.13. 2-(3-Ethoxy-5-methyl-4-phenyl-1H-pyrazol-1-yl)pyridine (**11g**).* Obtained as an oil that slowly crystallized in a 79% yield after a chromatography over silica gel (cyclohexane–ethyl acetate 95/5 to 1/1). Mp=78 °C. ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, *J*=7.1); 2.62 (s, 3H); 4.31 (q, 2H, *J*=7.1); 7.13 (m, 1H); 7.31 (m, 1H); 7.42 (m, 2H); 7.50 (m, 2H); 7.79 (m, 1H); 7.85 (m, 1H); 8.44 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.0; 14.8; 64.5; 109.9; 115.6; 120.1; 126.3; 128.3; 129.3; 131.7; 138.2; 138.9; 147.3; 153.7; 161.2. HRMS: calcd for $C_{17}H_{17}N_3O$+H: 280.1450; exp: 280.1370.

*1.3.14. 2-(5-Ethoxy-3-methyl-4-phenyl-1H-pyrazol-1-yl)pyridine (**12g**).* Obtained as an oil in a 5% yield after a second chromatography over alumina containing 1.5% of water (cyclohexane–ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$): 1.18 (t, 3H, *J*=7.0); 2.38 (s, 3H); 3.96 (q, 2H, *J*=7.0); 7.22 (m, 1H); 7.32 (m, 1H); 7.44 (m, 2H); 7.51 (m, 2H); 7.76 (m, 1H); 7.80 (m, 1H); 8.59 (m, 1H). ^{13}C NMR ($CDCl_3$): 10.0; 15.1; 70.7; 108.5; 116.3; 121.4; 126.6; 128.4; 128.9; 132.1; 138.1; 148.5; 148.7; 151.0; 151.2. HRMS: calcd for $C_{17}H_{17}N_3O$+H: 280.1450; exp: 280.1404.

*1.3.15. 2-(4-Benzyl-3-ethoxy-5-methyl-1H-pyrazol-1-yl)pyridine (**11h**).* This compound was obtained as an oil in a 66% yield after a chromatography over silica gel (dichloromethane and then dichloromethane–ethanol 99/1). ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, *J*=7.2); 2.59 (s, 3H); 3.76 (s, 2H); 4.36 (q, 2H, *J*=7.2); 7.07 (m, 1H); 7.19 (m, 1H); 7.29 (m, 4H); 7.74 (m, 1H); 7.79 (m, 1H); 8.38 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.2; 14.8; 27.7; 64.2; 107.1; 115.0; 119.5; 125.7; 128.2; 128.3; 138.2; 139.5; 140.8; 147.1; 153.8; 162.4. HRMS: calcd for $C_{18}H_{20}N_3O$+H: 294.1606; exp: 294.1579.

*1.3.16. 2-(4-Benzyl-5-ethoxy-3-methyl-1H-pyrazol-1-yl)pyridine (**12h**).* This compound was obtained as an oil in a 7% yield after a second chromatography over neutral alumina containing 1.5% H_2O (cyclohexane–ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$): 1.29 (t, 3H, *J*=7.1); 2.17 (s, 3H); 3.81 (s, 2H); 4.05 (q, 2H, *J*=7.1); 7.19 (m, 1H); 7.23 (m, 3H); 7.29 (m, 2H); 7.75 (m, 1H); 7.80 (m, 1H); 8.56 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.2; 15.2; 28.3; 71.3; 106.1; 115.7; 121.1; 126.0; 128.1; 128.4; 138.2; 140.1; 148.5; 149.8; 151.3; 152.0. HRMS: calcd for $C_{18}H_{19}N_3O$+H: 294.1606; exp: 294.1602.

*1.3.17. Ethyl 3-ethoxy-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate (**11i**).* This compound was obtained as a solid in a 67% yield after a chromatography over silica gel (dichloromethane and then dichloromethane–ethanol 99/1) followed by drying it under high vacuum to remove traces of the decarboxylated material. Mp=60 °C. ^{1}H NMR ($CDCl_3$): 1.36 (t, 3H, *J*=7.1); 1.52 (t, 3H, *J*=7.1); 4.32 (q, 2H, *J*=7.1); 4.47 (q, 2H, *J*=7.1); 7.20 (m, 1H); 7.83 (m, 1H); 7.86 (m, 1H); 8.41 (m, 1H); 8.89 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.3; 14.6; 60.0; 65.4; 103.0; 112.1; 121.4; 131.6; 138.7; 148.1; 150.1; 162.3; 163.0. HRMS: calcd for $C_{13}H_{15}N_3O_3$+H: 262.1192; exp: 262.1114.

*1.3.18. 2-(3-Ethoxy-1H-pyrazol-1-yl)pyridine (**11j**).* This compound was obtained as an oil in a 70% yield after a chromatography over silica gel (cyclohexane–ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 1.44 (t, 3H, *J*=7.0); 4.33 (q, 2H, *J*=7.0); 5.92 (d, 1H, *J*=2.7); 7.09 (m, 1H); 7.75 (m, 1H); 7.82 (m, 1H); 8.34 (m, 1H); 8.38 (d, 1H, *J*=2.7). ^{13}C NMR ($CDCl_3$): 14.8; 64.9; 94.8; 115.5; 120.1; 128.2; 138.5; 147.7; 151.5; 165.0. HRMS: calcd for $C_{10}H_{11}N_3O$+H: 190.0980; exp: 190.0919.

*1.3.19. Ethyl 2-(3-ethoxy-1-(pyridin-2-yl)-1H-pyrazol-5-yl)acetate (**11l**).* Obtained as an oil after a chromatography over silica gel (cyclohexane–ethyl acetate 95/5 then 9/1). This chromatography first gave 17% of compound **11c** followed by 5% of compound **11l**. ^{1}H NMR ($CDCl_3$): 1.17 (t, 3H, *J*=7.0); 1.44 (t, 3H, *J*=7.0); 4.12 (q, 2H, *J*=7.0); 4.31 (q, 2H, *J*=7.0); 5.84 (s, 1H); 7.06 (m, 1H); 7.75 (m, 1H); 7.87 (m, 1H); 8.28 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.1; 14.8; 35.2; 60.7; 64.6; 97.4; 113.8; 119.8; 138.3; 138.4; 146.6; 153.2; 163.2; 169.7. HRMS: calcd for $C_{14}H_{17}N_3O_3$+H: 276.1348; exp: 276.1265.

*1.3.20. Preparation of 1-(4-chlorophenyl)-3-ethoxy-5-phenyl-1H-pyrazole (**13**) and 1-(4-chlorophenyl)-5-ethoxy-3-phenyl-1H-pyrazole (**14**).* As mentioned in the text, this pair of isomers were obtained in 15 and 49% yield, respectively using the protocol described above from compound **10e** and 4-chloroiodobenzene after a initial chromatography over silica gel (cyclohexane–ethyl acetate 97/3) followed by second chromatography over silica gel (cyclohexane–dichloromethane 4/1). Their analytical data were identical to the previously reported one.[2]

1.3.21. Deprotection using boron tribromide in dichloromethane. The alkoxypyrazole (1 mmol) was placed in a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap. A 1 N solution of boron tribromide in dichloromethane (1.5 mL) was then added. The tube was tightly closed and stirred at 25 °C for 48 h. The tube was then cooled to 0 °C, opened, and cautiously quenched with 90% ethanol. The resulting solution was concentrated to dryness, made basic with ethanolic ammonia, and concentrated to dryness again. The residues were further purified as described below.

*1.3.22. 4-Fluoro-5-methyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**15d**).* This compound was obtained in a 72% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol 99/1 to 95/5). Mp=216 °C (toluene). ^{1}H NMR (DMSO-d_6): 2.55 (d, 3H, *J*=2.0); 7.22 (m, 1H); 7.66 (m, 1H); 7.89 (m, 1H); 8.37 (m, 1H); 10.98 (s (br), 1H). ^{13}C NMR (DMSO-d_6): 11.9; 113.7; 120.7; 126.7 (d, *J*=24); 136.2 (d, *J*=241); 139.3; 147.9; 149.8; (d, *J*=9.5); 153.7. HRMS: calcd for $C_9H_8N_3OF$+H: 194.0730; exp: 194.0676.

*1.3.23. 5-Phenyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**15e**).* This compound was obtained in a 64% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol 100/0 to 97/3). Mp=186 °C. ^{1}H NMR (DMSO-d_6): 6.17 (s, 1H); 7.22 (m, 3H); 7.31 (m, 3H); 7.56 (m, 1H); 7.92 (m, 1H); 8.16 (m, 1H); 10.32 (s, 1H). ^{13}C NMR (DMSO-d_6): 96.5; 118.0; 122.2; 128.3; 128.4; 128.7; 131.7; 139.2; 144.6; 148.0; 152.7; 162.4. HRMS: calcd for $C_{14}H_{11}N_3O$+H: 238.0980; exp: 238.0937.

*1.3.24. 3-Phenyl-1-(pyridin-2-yl)-1H-pyrazol-5-ol (**16e**).* This compound was obtained in a 29% yield as a white powder after a chromatography over silica gel (dichloromethane). *Nota*: the

more polar (!) starting material **12e** was also recovered in the course of this chromatography in a 32% yield. Alternatively, this compound was prepared by stirring overnight ethyl 3-oxo-3-phenylpropanoate (0.17 g, 0.91 mmol) and 2-pyridylhydrazine (**19**) (0.1 g, 0.91 mmol) in acetic (1 mL) at room temperature. The solution was concentrated to dryness in a high vacuum. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, and dried over magnesium sulfate. The slowly crystallizing solid obtained after concentration (0.19 g, 90%) featured spectral characteristics identical with the one described below. Mp=118 °C. ^{1}H NMR (DMSO-d_6): 6.17 (s, 1H); 7.38 (m, 2H); 7.46 (m, 2H); 7.91 (m, 3H); 8.08 (m, 1H); 8.48 (m, 1H); 12.5 (s, 1H). ^{13}C NMR (DMSO-d_6): 86.0; 113.2; 121.4; 126.0; 129.1 (two signals); 133.2; 140.9; 147.0; 151.7; 153.4; 156.6. HRMS: calcd for $C_{14}H_{11}N_3O$+H: 238.0980; exp: 238.0893.

*1.3.25. 5-Benzyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**15f**).* This compound was obtained in a 55% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol 100/0 to 99/1). Mp=152 °C. ^{1}H NMR (DMSO-d_6): 4.47 (s, 2H); 5.47 (s, 1H); 7.24 (m, 6H); 7.63 (m, 1H); 7.86 (m, 1H); 8.38 (m, 1H); 10.18 (s, 1H). ^{13}C NMR (DMSO-d_6): 34.3; 97.2; 114.7; 120.7; 126.6; 128.7; 129.2; 139.2; 139.3; 145.5; 147.8; 153.5; 162.0. HRMS: calcd for $C_{15}H_{13}N_3O$+H: 252.1137; exp: 252.1082.

*1.3.26. 3-Benzyl-1-(pyridin-2-yl)-1H-pyrazol-5-ol (**16f**).* This compound was obtained in a 39% yield as an oil after a chromatography over silica gel (dichloromethane). ^{1}H NMR ($CDCl_3$): 3.96 (s, 2H); 5.39 (s, 1H); 7.12 (m, 1H); 7.25 (m, 1H); 7.33 (m, 4H); 7.86 (m, 1H); 7.96 (m, 1H); 8.26 (m, 1H). ^{13}C NMR ($CDCl_3$): 35.6; 88.2; 112.1; 119.7; 126.4; 128.5; 128.8; 138.9; 139.9; 145.1; 154.2; 154.5; 157.2. HRMS: calcd for $C_{15}H_{13}N_3O$+H: 252.1137; exp: 252.1077.

*1.3.27. 5-Methyl-4-phenyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**15g**).* This compound was obtained in a 69% yield when using the hydrobromic acid in acetic acid deprotection method described above, as a white powder after a chromatography over silica gel (dichloromethane the dichloromethane–ethanol 94/6). Mp=216 °C. ^{1}H NMR (DMSO-d_6): 2.64 (s, 3H); 7.25 (m, 2H); 7.43 (m, 4H); 7.71 (d, 1H, J=8.3); 7.93 (m, 1H); 8.44 (m, 1H); 10.61 (s, 1H). ^{13}C NMR (DMSO-d_6): 14.4; 109.6; 115.4; 120.9; 126.6; 128.7; 129.4; 132.2; 138.3; 139.3; 147.9; 153.5; 160.1. HRMS: calcd for $C_{15}H_{13}N_3O$+H: 252.1137; exp: 252.1146.

*1.3.28. 4-Benzyl-5-methyl-1-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**16h**).* This compound was obtained in a 88% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol 100/0 to 97/3). Mp=163 °C. ^{1}H NMR (DMSO-d_6): 2.53 (s, 3H); 3.66 (s, 2H); 7.22 (m, 6H); 7.65 (d, 1H, J=8.1); 7.87 (m, 1H); 8.37 (m, 1H); 10.36 (s, 1H). ^{13}C NMR (DMSO-d_6): 13.2; 27.1; 106.7; 114.1; 119.8; 125.7; 127.9; 128.2; 138.4; 138.6; 140.9; 147.3; 153.3; 160.8. HRMS: calcd for $C_{16}H_{15}N_3O$+H: 266.1293; exp: 266.1241.

*1.3.29. 3-Ethoxy-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylic acid (**17**).* By treating **11i** with hydrogen bromide in acetic acid at 140 °C as described above, compound **17** was obtained in a 63% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol 100/0 to 96/4). Alternatively, this compound was obtained by heating in a microwave oven compound **11i** (0.25 g; 0.95 mmol) and sodium hydroxide (0.86 g, 21.5 mmol) in a 3/1 water–ethanol mixture (2 mL) for 15 min at 140 °C. Upon acidification of the diluted reaction mixture and extraction with ethyl acetate, compound **17** was also obtained (0.19 g, 85%). Mp=190 °C. ^{1}H NMR (DMSO-d_6): 1.38 (t, 3H, J=7.1); 4.36 (q, 2H, J=7.0); 7.36 (m, 1H); 7.78 (d, 1H, J=8.2); 7.99 (m, 1H); 8.45 (m, 1H); 8.73 (s, 1H); 12.43 (s (br), 1H). ^{13}C NMR (DMSO-d_6): 15.0; 65.2; 103.5; 112.1; 122.6; 131.8; 140.1; 148.9; 150.2; 162.7; 163.0. HRMS: calcd for $C_{11}H_{11}N_3O_3$+H: 234.0879; exp: 234.0828.

*1.3.30. 3-Oxo-1-(pyridin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid (**18**).* Compound **11i**, was treated with boron tribromide in dichloromethane as described above, the corresponding acid **18** was obtained in a 34% yield as a white powder after a chromatography over silica gel (dichloromethane–ethanol–acetic acid 90/9/1) followed by dispersion of the corresponding fraction in boiling toluene. Mp>250 °C (dec). ^{1}H NMR (DMSO-d_6): 7.34 (m, 1H); 7.70 (m, 1H); 7.98 (m, 1H); 8.46 (m, 1H); 8.67 (s, 1H). ^{13}C NMR (DMSO-d_6): 102.7; 111.5; 121.9; 130.4; 139.6; 148.4; 149.8; 162.1; 163.3. HRMS: calcd for $C_9H_7N_3O_3$−H: 204.0409; exp: 204.0381.

*1.3.31. 1-(Pyridin-2-yl)-1H-pyrazol-3(2H)-one (**15j**).* This compound was obtained from **11j** by treatment with boron tribromide in a 84% yield as described above as a white powder after a chromatography over silica gel (dichloromethane–ethanol 100/0 to 97/3). Mp=157 °C. ^{1}H NMR ($CDCl_3$): 5.98 (d, 1H, J=2.8); 7.15 (m, 1H); 7.63 (m, 1H); 7.85 (m, 1H); 8.40 (m, 2H); identical with the reported[33] data. ^{1}H NMR (DMSO-d_6): 5.88 (d, J=2.7); 7.22 (m, 1H); 7.66 (m, 1H); 7.90 (m, 1H); 8.38 (m, 2H); 10.45 (s, 1H). ^{13}C NMR (DMSO-d_6): 96.1; 111.1; 120.8; 128.3; 139.7; 148.5; 151.2; 163.8. HRMS: calcd for $C_8H_7N_3O$+H: 162.0667; exp: 162.0663.

1.4. Compounds only obtained from 2-pyridylhydrazine (19), general protocol

The appropriate β-ketoester (0.91 mmol) and 2-pyridylhydrazine (0.1 g, 0.91 mmol) were heated at 130 °C in acetic acid (1 mL) for 5 min using a microwave oven. The solution was concentrated to dryness under high vacuum and the residue further purified as described below.

*1.4.1. 3-Methyl-4-phenyl-1-(pyridin-2-yl)-1H-pyrazol-5-ol (**16g**).* A recrystallisation in cyclohexane led to compound **16g** (0.16 g, 69%). Mp=118 °C. ^{1}H NMR (DMSO-d_6): 2.38 (s, 3H); 7.23 (m, 2H); 7.40 (m, 2H); 7.60 (m, 2H); 7.97 (m, 1H); 8.41 (s (br), 1H); 8.46 (m, 1H). ^{13}C NMR (DMSO-d_6): spectra features broad peaks 12.8 (br); 104.3(br); 112.0 (br); 120.7; 125.9; 127.8; 128.6; 132.7; 139.4 (br); 146.2 (br); 147.8 (br); 148.8 (br); 161.2 (br). HRMS: calcd for $C_{15}H_{13}N_3O$+H: 252.1137; exp: 252.1111.

*1.4.2. 4-Benzyl-3-methyl-1-(pyridin-2-yl)-1H-pyrazol-5-ol (**16h**).* A chromatography over silica gel (dichloromethane–ethanol 100/0 to 98/2) led to compound **16h** as an oil (0.17 g, 70%). ^{1}H NMR (DMSO-d_6): 2.12 (s, 3H); 3.54 (s, 2H); 7.14 (m, 1H); 7.24 (m, 5H); 7.89 (m, 1H); 8.40 (m, 2H). ^{1}H NMR ($CDCl_3$): 2.17 (s, 3H); 3.74 (s, 2H); 7.09 (m, 1H); 7.20 (m, 1H); 7.29 (m, 4H); 7.83 (m, 1H); 7.96 (m, 1H); 8.25 (m, 1H). ^{13}C NMR ($CDCl_3$): 12.9; 27.6; 99.0; 111.8; 119.4; 125.9; 128.2; 128.3; 139.8; 140.7; 145.2; 150.8; 153.8; 155.8. HRMS: calcd for $C_{16}H_{15}N_3O$+H: 266.1293; exp: 266.1247.

1.5. General preparation of 2-pyridyl derivatives using 2-fluoropyridine

In a 0.5–2 mL Biotage tube, the alkoxypyrazoles (3.9 mmol), cesium carbonate (1.42 g, 4.3 mmol) were dispersed 2-fluoropyridine (1.1 mL). The suspension was heated as described in the text, and diluted in ethyl acetate. The organic layer was washed with water, with brine, dried over magnesium sulfate, and concentrated to dryness. The residue was purified as described below.

*1.5.1. 2-(5-Ethoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyridine (**12b**).* A chromatography over silica gel (dichloromethane–cyclohexane 1/1 to 3/1) led to compound **12b** as an oil in a 38% yield. ^{1}H

NMR ($CDCl_3$): 1.48 (t, 3H, J=7.1); 4.26 (q, 2H, J=7.1); 5.94 (s, 1H); 7.30 (m, 1H); 7.70 (m, 1H); 7.84 (m, 1H); 8.60 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.4; 69.0; 85.1; 117.5; 120.8 (q, J=268); 122.7; 138.3; 142.8 (q, J=38); 148.9; 150.4; 155.5. HRMS: calcd for $C_{11}H_{10}F_3N_3O$+H: 258.0854; exp: 258.0826.

*1.5.2. 2-(3-Ethoxy-5-iodo-1H-pyrazol-1-yl)pyridine (**11k**).* A chromatography over alumina containing 1.5% of water (dichloromethane–cyclohexane 1/2) led to compound **11k** as a solid. Mp=76 °C. ^1H NMR ($CDCl_3$): 1.43 (t, 3H, J=7.1); 4.29 (q, 2H, J=7.1); 6.17 (s, 1H); 7.25 (m, 1H); 7.74 (m, 1H); 7.82 (m, 1H); 8.50 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 64.8; 106.3; 116.9; 120.0; 121.9; 138.3; 147.4; 152.3; 165.6. HRMS: calcd for $C_{10}H_{10}IN_3O$+H: 315.9947; exp: 315.9933.

*1.5.3. 2-(5-Ethoxy-3-iodo-1H-pyrazol-1-yl)pyridine (**12k**).* A second chromatography of the corresponding fraction over silica gel (ethyl acetate–cyclohexane 1/4).led to compound **12k** as a solid. Mp=71 °C. ^1H NMR ($CDCl_3$): 1.46 (t, 3H, J=7.0); 4.21 (q, 2H, J=7.0); 5.86 (s, 1H); 7.24 (m, 1H); 7.76 (m, 1H); 7.80 (m, 1H); 8.56 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.5; 68.7; 95.8; 98.3; 116.5; 122.0; 138.2; 148.8; 150.2; 155.5. HRMS: calcd for $C_{10}H_{10}IN_3O$+H: 315.9947; exp: 316.0002.

1.6. Suzuki reaction between 11k and phenylboronic acid, alternative preparation of 11e

In a 10 mL Biotage tube, compound **11k** (0.24 g, 0.76 mmol), phenylboronic acid (0.11 g, 0.91 mmol), cesium carbonate (0.62 g, 1.9 mmol) were dispersed in a 1/1 mixture of propanol and water (4 mL). The suspension was degassed by a slow stream of argon and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.03 g, 0.038 mmol) was added. The tube was sealed and heated in a microwave oven for 90 min at 130 °C. The resulting mixture was diluted in ethyl acetate, washed with brine, dried over magnesium sulfate, and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane–ethyl acetate 98/2 to 9/1) to yield compound **11j** (0.03 g, 20%) and then compound **11e** (0.08 g, 39%) as described above.

1.7. Negishi reaction between 11k and benzylzincbromide, alternative preparation of 11f

In a 10 mL Biotage tube, under an argon atmosphere, compound **11k** (0.21 g, 0.66 mmol) and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.027 g, 0.033 mmol) were dissolved in a 0.5 M solution of benzylzincbromide in THF (4 mL, 2 mmol). The tube was sealed and heated in a microwave oven for 30 min at 110 °C. The solution was diluted in ethyl acetate, washed with brine, dried over magnesium sulfate, and concentrated to dryness. The resulting residue was purified by a chromatography over alumina containing 1.5% of water (cyclohexane–ethyl acetate 98/2) to yield, as seen by ^1H NMR, a 'pure' 1/2.8 mixture of compound **11j** and **11f** (0.12 g) from which the more volatile compound **11j** (0.04 g, 32%) could be completely removed under high vacuum in a few days to give clean compound **11f** (0.08 g, 43%) as described above.

*1.7.1. 5-Benzyl-3-ethoxy-1-(pyridin-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (**24**).* This compound was obtained as a solid in either a 42% or in a 55% yield after a chromatography over silica gel (dichloromethane–ethanol 98/2) from compound **22** by following either the copper-catalyzed arylation of alkoxypyrazoles with bromopyridines described above (heating for 3 h) or the 2-fluoropyridine method also described above (same heating time). Mp=93 °C. ^1H NMR ($CDCl_3$): 1.41 (t, 3H, J=7.0); 2.81 (m, 2H); 3.31 (s, 2H); 3.46 (s, 2H); 3.77 (s, 2H); 4.34 (q, 2H, J=7.0); 7.00 (m, 1H); 7.28–7.43 (m, 5H); 7.70 (m, 1H); 7.78 (m, 1H); 8.31 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 26.7; 47.8; 50.0; 62.0; 64.3; 104.5; 112.9; 119.1; 127.2; 128.3; 129.0; 138.0; 138.4; 140.1; 147.4; 153.6; 160.2. HRMS: calcd for $C_{20}H_{22}N_4O$+H: 335.1872; exp.: 335.1870.

1.8. Reduction of compound 24, isolation of 25 and 26

In a 22 mL steel reactor, compound **24** (0,29 g 0,87 mmol) and 10% palladium over charcoal (0.09 g, 0.087 mmol) were dispersed in acetic acid (10 mL). Hydrogen was charged into the reactor (25 bar) and then heated at 65 °C for 3 h. The reactor was cooled, hydrogen was removed under vacuum, and the resulting solution filtrated and concentrated to dryness. The residue was dissolved in dichloromethane; this solution was washed with a saturated solution of sodium hydrogencarbonate, with brine, dried over magnesium sulfate, and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane–ethanol 9/1) to yield compounds **25** and **26** as described below.

*1.8.1. 3-Ethoxy-1-(pyridin-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (**25**).* This compound was obtained as a solid in a 16% yield. Mp=99 °C. ^1H NMR (DMSO-d_6): 1.35 (t, 3H, J=7.0); 2.92 (s (br), 2H); 3.05 (s (br), 2H); 3.58 (s (br), 2H); 4.28 (q, 2H, J=7.0); 7.18 (m, 1H); 7.69 (m, 1H); 7.88 (m, 1H); 8.36 (m, 1H). ^{13}C NMR (DMSO-d_6): 14.7; 26.9; 30.7; 42.3; 63.8; 104.4; 112.6; 119.7; 138.8; 140.1; 147.5; 152.8; 159.6. HRMS: calcd for $C_{18}H_{16}N_4O$+H: calcd 245.1333; exp: 245.1402.

*1.8.2. 3-Ethoxy-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (**26**).* This compound was obtained as a solid in a 13% yield. Mp=78 °C (dec). ^1H NMR ($CDCl_3$): 1.36 (m, 3H); 2.64 (s (br), 2H); 2.00–5.00 (large 'bump', 4H); 4.35 (m, 2H). ^{13}C NMR ($CDCl_3$): 14.9; 64.2; with our reverse ^{13}C NMR probe no other carbon signals could be seen. HRMS: calcd for $C_8H_{13}N_3O$+H: calcd 168.1137; exp: 168.1115.

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