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E. P. Coutant, Y. L. Janin

Paper

A Study of Negishi Cross-Coupling Reactions with Benzylzinc Halides To Prepare Original 3-Ethoxypyrazoles

Eloi P. Coutanta,b Yves L. Janin^{* a,b}

^a Unité de Chimie et Biocatalyse, Département de Biologie Structurale et Chimie, Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris Cedex 15, France yves.janin@pasteur.fr

- ^b Unité Mixte de Recherche 3523, Centre National de la Recherche Scientifique, 28 rue du Dr. Roux, 75724 Paris Cedex 15 France



Ar = Ph, 2-CIC₆H₄, 3-CIC₆H₄, 4-CIC₆H₄, 2,4-Cl₂C₆H₃, 3,4-Cl₂C₆H₃

Received: 01.10.2014 Accepted after revision: 24.10.2014 Published online: 21.11.2014 DOI: 10.1055/s-0034-1379458; Art ID: ss-2014-z0604-op

Abstract The Negishi palladium-catalyzed cross-coupling reaction between 3-ethoxy-4-iodo-1H-pyrazole and various benzylzinc halides was extensively studied. Using simplified, robust, and optimized reaction conditions, a series of electron-poor benzylzinc halides were prepared and used to synthesize 4-benzyl-3-ethoxy-1H-pyrazoles derivatives. From these, iodination on C5 of the pyrazole nucleus led to the corresponding 4-benzyl-3-ethoxy-5-iodo-1H-pyrazoles, these are original building blocks for the preparation of libraries of new chemical entities.

Key words cross-coupling, heterocycles, palladium, zinc, benzylation

Over the course of the past decade, we have worked on the design and optimization of synthetic accesses to new chemical entities featuring an alkoxypyrazole component. This has led us to report on many aspects of alkoxypyrazole chemistry,¹⁻⁹ and all the prepared compounds have been assayed in our research facilities during the course of screening campaigns against a number of infectious diseases. In a few cases, the results of these screenings led us to undertake additional iterations of synthesis and biological evaluation. We wish to report here our efforts to use the pathway depicted in Scheme 1 to prepare a set of 4-benzyl-3-ethoxy-5-iodo-1*H*-pyrazoles **5a**-**f** as building blocks for the synthesis of chemical libraries of potential biological interest.

The synthetic path chosen involved a Negishi^{10,11} carbon-carbon cross-coupling reaction between benzylzinc halides **2a**-**f**, prepared from the corresponding benzyl halides 1a-f, and the readily available 3-ethoxy-4-iodo-1Hpyrazole (**3**)⁵ to give the 4-benzyl derivatives **4a**–**f**. However, it quickly became apparent that full studies of the zinc insertion reaction as well as the Negishi cross-coupling step were required.



A major improvement in the achievement of a reproducible zinc insertion into a benzyl halide bond has been the combined use of zinc dust, a solution of dry lithium chloride in tetrahydrofuran, and two activation stages with the successive addition of small amount of 1,2-dibromoethane and chlorotrimethylsilane before the addition of the halogenated substrate.¹²⁻¹⁶ All these 'tricks', along with hydrochloric acid treatment of the zinc, have previously been used separately or in partial combination. Early reports pointed out the benefit of using 1,2-dibromoethane¹⁷⁻¹⁹ or chlorotrimethylsilane^{20,21} for improving various reactions and it has been reported that the latter reagent is not only instrumental in removing the zinc-passivating layer present on the surface of the metal but also in suppressing the effect of lead traces present in the zinc used.²² The successive addition of 1,2-dibromoethane and chlorotrimethylsilane to powdered zinc was then reported for its activation.^{23,24} Additionally, the generation of the highly active Rieke zinc^{25–28} by the reduction of zinc chloride with lithium is also an excellent method for the preparation of a

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tetrahydrofuran suspension of finely divided zinc containing two equivalents of lithium chloride. The importance of lithium chloride has been investigated and, based on mass spectroscopy and NMR, a recent report describes the occurrence of lithium organozincate complexes LiRZnX₂, which provides an explanation for the improvement in the preparation and reactivity of organozinc halides.²⁹

In our hands, the preparation of benzylzinc bromide (2a) was fairly permissive and robust (flame-dried inactivated technical powdered Zn and LiCl, anhydrous THF, stirring, 4 °C, 1 h). With a three-equivalent excess, this benzylzinc bromide solution, along with a 1:2 premixed mixture of palladium(II) acetate and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) as the pre-catalyst and heating at 50 °C for three hours, was used for the Negishi cross-coupling reaction with 3-ethoxy-4-iodo-1Hpyrazole (3). These conditions led to compound 4a in 70% isolated vield. Interestingly, the use of PdCl₂(dppf) at 50 °C was not efficient and at 80 °C, only a 49% yield of compound 4a could be isolated. However, when applied to the preparation of compound **4b-f**, these so far optimized conditions generally failed. Accordingly, in order to prepare the benzylzinc chlorides **2b-f** efficiently, we adapted previously reported conditions³⁰⁻³² to the specific cases of the electronpoor benzyl chlorides 1b-f, and compound 1c was selected as a model substrate. Since optimizing the consecutive reaction steps was a task with too many variables, first the preparation of 3-chlorobenzylzinc chloride (2c) was studied and extensive use was made of a reported³³ organozinc halide iodometric titration to establish the yield of 2c, next the ensuing Negishi cross-coupling step using 2c leading to compound 4c was studied (Scheme 2). We found that this titration method is impervious to the presence of zinc dust in suspension in the samples titrated, even if the zinc has undergone the various activation processes described below. It appears that the expected discoloration of the iodine solution by zinc alone is probably taking place so slowly that it does not interfere with the titration of the organozinc derivatives. After many experiments, we established that, in contrast to the preparation of **2a**, the preparation of **2c** required the use of zinc dust, with an average size smaller than 10 µm, in anhydrous tetrahydrofuran containing flame-dried lithium chloride, and the two-stage activation process (1,2-dibromoethane and chlorotrimethylsilane) followed by heating the suspension at 70 °C for one hour. Repeated titration of the resulting mixture indicated yields between 87-90% starting from benzyl chloride 1c. Interestingly, higher titers (96-100%) of 3-chlorobenzylzinc chloride (2c) were always obtained when the zinc powder was also flame-dried in the presence of the lithium chloride. Attempts to use coarser powdered zinc were less efficient. Omitting the lithium chloride gave a lower yield, whereas the two-stage activation process with chlorotrimethylsilane and 1,2-dibromoethane was mandatory. In the course of the study of the ensuing Negishi carbon-carbon crosscoupling step, few side compounds were observed. Along with volatile 3-chlorotoluene, the expected reduced pyrazole 6 occurred in varying amounts. This is either due to the acidic workup of the reaction in the presence of zinc, leading to a reduction of **3**, or to the fact that, in the presence of hydrochloric acid, such 4-iodopyrazoles are reduced, along with the occurrence of iodine and/or iodine monochloride, as we have previously reported.⁴ This observation was put to good use as such treatment allows the removal of the side products **3** and **6** from the reaction mixture prior to chromatography. The bibenzyl derivative 7 was also expected as a side product due to the excess of benzylzinc chloride added, ¹H NMR and LC/MS analysis of the crude reaction mixtures also showed the much less expected occurrence of polybenzylated materials such as compound 8 (m/z = 327/329) and **9** (*m*/*z* = 417/419), which we could not properly purify. Since such side compounds are due to a palladium insertion into a carbon-chlorine bond, we focused on limiting the amount of benzylzinc halide, altering the nature of the palladium ligands and/or the temperature of this reaction. Trials with varving amounts of 3-chlorobenzylzinc chloride (2c) indicated that two equivalents were optimum, as some unreacted compound 3 was observed below this amount. Higher quantities of 2c (3 equiv) led to more polybenzylated products. Of interest is the fact that adding more 3-chlorobenzyl chloride (1c) in a coupling trial did not result in an increase of the amount of polybenzylated material but led to a sharp increase in the quantity of the bibenzyl derivative 7. One of the most important observations, which came out of a rather long series of experiments, was that the palladium-catalyzed cross-coupling reactions leading to the polybenzylated products 8 and 9 took place even when some 4-iodopyrazole 3 was still present in the reaction mixture. During experiments with triphenylphosphine as the palladium ligand, it was necessarv to heat the reaction mixture to at least 50 °C for some carbon-carbon coupling to proceed. On the other hand, the use of XPhos as the ligand allowed us to lower the reaction temperature: the coupling reaction proceeded well with 2% of catalyst at 4 °C, but the reaction required three days. Even if this low temperature led to a slightly lower amount of the polybenzylated material, running the reaction at room temperature for 24 hours with a 2% catalyst loading was considered optimal and thus selected.

As shown in Table 1, we then used these conditions for the synthesis of compounds **4b** and **4d–f**. As for the preparation of **2c**, the benzylzinc chloride titer was always improved when both the lithium chloride, and then the mixture of zinc powder and lithium chloride were flamedried. From **2b** and **2d**, we then obtained acceptable yields of the 4-benzyl derivatives **4b** and **4d**. However, two additional difficulties arose in the case of the preparation of compounds **4e** and **4f**. First, despite initial experiments at various temperatures, the reaction never reached completion as 4-iodopyrazole **3** was observed in the crude reaction



Scheme 2 *Reagents and conditions:* (i) Zn powder (<10 μ m, 2 equiv), LiCl (2 equiv), THF, (activation by 1,2-dibromoethane and TMSCl), microwaves, 70 °C, 1 h; (ii) Pd(OAc)₂–XPhos (1:2, 0.02 equiv), THF, r.t., 24 h.

product in both cases. This led us to treat the reaction products with concentrated hydrochloric acid, to remove the unreacted 4-iodopyrazole **3**, before chromatography. Moreover, we observed the occurrence of greater quantities of polybenzylated material in these two cases and although we could isolate pure 4-benzyl derivative **4e** in 50% yield, all our purification attempts were unsuccessful in the case of compound **4f**.



^a Reaction conditions: **2a**: (i) Zn powder (2 equiv), LiCl (2.5 equiv), THF, 4 [°]C, 1 h; (ii) Pd(OAc)₂–XPhos (1:2, 0.02 equiv), THF, 50 [°]C, 3 h; **2b–**f: (i) Zn powder (<10 µm, 2 equiv), LiCl (2 equiv), THF, (activation by 1,2-dibromoethane and TMSCI), microwaves, 70 [°]C, 1 h; (ii) Pd(OAc)₂–XPhos (1:2, 0.02 equiv), THF, t.t., 24 h.

^b Determined by titration; no Zn drying.

- ^c Determined by titration; with Zn drying.
- ^d Using the flame-dried Zn for 2b-f.

e Not determined.

^f From BnZnBr (3 equiv).

^g Not isolated.

Accordingly, and as depicted in Scheme 3, in a final attempt to avoid the polybenzylation reaction in the case of the preparation of compound **4f**, we prepared the N-protected 4-iodopyrazole **10**. This compound was then coupled with a single equivalent of the 3,4-dichlorobenzylzinc chloride **2f** at 50 °C and, following treatment with hydrochloric acid to cleave the ethoxyethyl protecting group, this led to the isolation of compound **4f** in 63% yield containing less than 3% of polybenzylated material. This experiment also demonstrated that the free NH of the 4-iodopyrazole **3** is the reason behind the requirement for two equivalents of benzylzinc chloride in the Negishi reaction.



Scheme 3 Reagents and conditions: (i) $Pd(OAc)_2$ -XPhos (1:2, 0.02 equiv), THF, 50 °C, 3 h; (ii) 33% HCl; (iii) NIS (1.05 equiv), 1,2-dichloroethane, reflux.

Finally, compounds **4a–f** were treated with *N*-iodosuccinimide in refluxing dichloroethane to give smoothly, without unexpected difficulties, the 5-iodinated building blocks **5a–f** in 56–71% yields.

In conclusion, we hope that this unplanned, but necessary, study of the Negishi coupling reaction to access 4-benzvlpvrazoles 4a-f is of more general interest. especially since we avoided the use of a glove box or Schlenk apparatus when preparing the solutions of benzylzinc halides 2a**f**. In our experience, the iodometric titration was essential; it allowed the determination of the amount of benzylzinc chloride and thus reduced the multiplicity of factors involved in the optimization of these syntheses. Interestingly, an efficient palladium/ligand system was necessary for the 4-benzylation of 3-ethoxy-4-iodo-1H-pyrazole (3) to give the chlorinated derivatives **4a**-**f**, but this efficiency also resulted in the undesired palladium insertion reaction into the aryl chloride bond. To overcome this problem, we explored the lower limits of the reaction parameters, and a room temperature reaction over one day was selected in most cases. Following this study, we prepared the 5-iodin514

ated building blocks **5a**-**f** and we will report their transformations into chemical libraries of biological interest in due course.

Reactions using microwave heating used a Biotage initiator 2 microwave oven. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively, referenced to TMS. Column chromatography was performed either on Merck silica gel 60 (0.035-0.070 mm) or neutral alumina using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition on the top of the column. LR-MS were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and HRMS were obtained using a Waters Micromass Q-Tof with an electrospray ion source. Anhyd THF used was purchased commercially. Note: some of the ¹H signals of the compounds described here are concentration dependent (not only the broad pyrazole NH signal but also the OCH₂CH₃ signals).

4-Benzyl-3-ethoxy-1H-pyrazole (4a)

LiCl (0.89 g, 21.0 mmol) was dried with a flame under high vacuum then technical grade Zn powder (1.10 g, 16.8 mmol) was added. The mixture was heated again under high vacuum then allowed to cool under an argon atmosphere. Anhyd THF (10 mL) was added and the suspension cooled to 0 °C with an ice bath. BnBr (1 mL, 8.4 mmol) was then added and the mixture stirred for 1 h at 4 °C. Titration showed 88% conversion of BnBr. 3-Ethoxy-4-iodo-1H-pyrazole (3, 0.45 g, 1.89 mmol) and premixed Pd(OAc)₂ and XPhos (1:2; 0.11 g, 0.093 mmol) were weighted into another flask and it was flushed with argon. The solution of 0.67 M BnZnBr (2a, 8.5 mL, 5.69 mmol) was added and the mixture was stirred for 3 h at 50 °C using an oil bath, and then diluted with EtOAc (100 mL). Excess 1 M HCl (50 mL) was added and the mixture was stirred for a few minutes. The organic layer was separated and washed with brine (30 mL), dried (MgSO₄), and concentrated in vacuo. The crude product was purified by chromatography (silica gel, CH₂Cl₂-EtOH, 99:1) to give 4a (0.27 g, 70%) as an oil.

¹H NMR (CDCl₃): δ = 7.37–7.24 (m, 5 H), 7.07 (s, 1 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.79 (s, 2 H), 1.44 (t, J = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 161.5, 141.2, 128.8, 128.5, 128.4, 125.9, 105.1, 64.7, 28.5, 15.0.

HRMS: *m*/*z* [M + H] calcd for C₁₂H₁₅N₂O: 203.1184; found: 203.1122.

3-Chlorobenzylzinc Chloride (2c); Typical Procedure for 2b-f

LiCl (1.00 g, 23.6 mmol, 2 equiv) was added to a microwave reaction vial, and dried with a flame for a few min in the open air. This vial was left to cool in a desiccator under high vacuum. Air was used to back pressurize the desiccator and Zn powder (size <10 µm) (1.54 g, 23.6 mmol, 2 equiv) was added. The vial was heated again with a flame for a few min in the open air, and left to cool in a desiccator under high vacuum; argon was used to back-pressurize the desiccator. A stirring bar was added and the vial was sealed, anhyd THF (10 mL) was injected via the septum, followed by 0.81 M 1,2-dibromoethane in dry THF (0.73 mL, 0.6 mmol, 0.05 equiv). This was heated in a microwave oven at 85 °C for 5 min. A solution of 0.2 M TMSCl in anhyd THF (0.59 mL, 0.12 mmol, 0.01 equiv) was then added and the suspension was heated once again at 85 °C for 5 min. 3-Chlorobenzyl chloride (1c, 2.05 mL, 16.1 mmol, 1 equiv) was added by syringe and the vial was heated with a microwave oven for 1 h at 70 °C. Iodometric titration³³ indicated a titer of 3-chlorobenzylzinc chloride (2c) of 0.89 M (0.92 M expected, 96% yield). Note: heating the reaction flask at 60 °C using an oil bath (under an inert atmosphere) instead of a microwave oven for the entire procedure did not lead to a significant change in the titer of the solution. By following this procedure (or the one omitting flamedrying the zinc) solutions of benzylzinc chloride **2b-f** were obtained with the titers listed in Table 1.

4-(3-Chlorobenzyl)-3-ethoxy-1H-pyrazole (4c); Typical Procedure for 4b-e

3-Ethoxy-4-iodo-1*H*-pyrazole (3, 0.53 g, 2.23 mmol, 1 equiv) and premixed Pd(OAc)₂ and XPhos (1:2, 53 mg, 45 µmol, 0.02 equiv) were dissolved in anhyd THF (5 mL) in an argon-flushed microwave reaction vial. The mixture was allowed to stir for a few minutes and the (non-centrifuged) solution of 0.89 M 3-chlorobenzylzinc chloride (2c, 5 mL) was added with a syringe. The resulting mixture was allowed to stir for 24 h at r.t., and then diluted with EtOAc (100 mL). Excess 1 M HCl (50 mL) was added and the mixture was stirred for a few min. The organic layer was separated and washed with brine (30 mL), dried (MgSO₄), and concentrated in vacuo. The crude product was purified by chromatography (silica gel, CH_2Cl_2 -EtOH, 99:1) to give **4c** (0.43 g, 81%) as a white powder; mp 86 °C.

¹H NMR (CDCl₃): δ = 9.06 (s, 1 H), 7.27–7.12 (m, 4 H), 7.10 (s, 1 H), 4.28 (q, J = 7.0 Hz, 2 H), 3.71 (s, 2 H), 1.40 (t, J = 7.0 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 161.7, 143.1, 134.1, 129.5, 128.6, 128.5, 126.7, 126.1, 104.7, 64.5, 28.1, 14.9.

HRMS: m/z [M + H] calcd for C₁₂H₁₄ClN₂O: 237.0795; found: 237.0729.

4-(2-Chlorobenzyl)-3-ethoxy-1H-pyrazole (4b)

White crystals; yield: 0.73 g (67%); mp 68 °C.

¹H NMR (CDCl₃): 9.13 (s, 1 H), 7.38–7.34 (m, 1 H), 7.30–7.26 (m, 1 H), 7.22–7.15 (m, 2 H), 7.13 (s, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 3.84 (s, 2 H), 1.40 (t, J = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 161.8, 138.6, 133.8, 130.5, 129.3, 128.8, 127.4, 126.7, 103.6, 64.5, 26.2, 14.9.

HRMS: m/z [M + H] calcd for C₁₂H₁₄ClN₂O: 237.0795; found: 237.0722.

4-(4-Chlorobenzyl)-3-ethoxy-1H-pyrazole (4d)

White crystals; yield: 0.76 g (71%); mp 89 °C.

¹H NMR (CDCl₃): δ = 9.19 (s, 1 H), 7.28–7.22 (m, 2 H), 7.22–7.14 (m, 2 H), 7.07 (s, 1 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.69 (s, 2 H), 1.39 (t, J = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 161.7, 139.5, 131.7, 129.8, 128.4, 105.0, 64.5, 27.8, 14.9.

HRMS: m/z [M + H] calcd for C₁₂H₁₄ClN₂O: 237.0795; found: 237.0772.

4-(2,4-Dichlorobenzyl)-3-ethoxy-1*H*-pyrazole (4e)

In this case, prior to a chromatography, the crude reaction product was stirred in 12 M HCl for 1 h. The mixture was extracted with EtOAc $(2 \times 50 \text{ mL})$. The combined organic layers were washed with sat. NaHCO₃ (40 mL) and brine (30 mL), dried (MgSO₄), and concentrated to dryness. The residue was further purified as described in the typical procedure to give 4e (0.56 g, 50%) as a white solid; mp 107 °C.

¹H NMR (CDCl₃): δ = 8.81 (br s, 1 H), 7.38 (d, J = 1.9 Hz, 1 H), 7.24–7.12 (m, 3 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.79 (s, 2 H), 1.39 (t, J = 7.1 Hz, 3 H).

 ^{13}C NMR (CDCl_3): δ = 161.7, 137.1, 134.4, 132.4, 131.3, 129.1, 128.8, 127.0, 103.0, 64.6, 25.7, 14.9.

HRMS: m/z [M + H] calcd for $C_{12}H_{13}Cl_2N_2O$: 271.0405; found: 271.0347.

3-Ethoxy-1-(1-ethoxyethyl)-4-iodo-1H-pyrazole (10)

Under a CaCl₂-protected atmosphere, 3-ethoxy-4-iodo-1*H*-pyrazole (**3**, 1.50 g, 6.3 mmol, 1 equiv), ethyl vinyl ether (0.73 mL, 7.6 mmol, 1.2 equiv), and TsOH (32 mg, 0.13 mmol, 0.02 equiv) were dissolved in CH₂Cl₂ (stabilized with 2-methylbut-2-ene, 50 mL), After 3 h, the mixture was concentrated in vacuo and the resulting oil was used without further purification.

¹H NMR (DMSO- d_6): δ = 7.90 (s, 1 H), 5.32 (q, *J* = 6.0 Hz, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 3.39 (dq, *J* = 9.6, 7.0 Hz, 1 H), 3.22 (dq, *J* = 9.6, 7.0 Hz, 1 H), 1.52 (d, *J* = 6.0 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.03 (t, *J* = 7.0 Hz, 3 H).

¹³C NMR (DMSO- d_6): δ = 162.1, 134.6, 86.8, 65.1, 63.4, 45.0, 21.1, 15.2, 15.1.

4-(3,4-Dichlorobenzyl)-3-ethoxy-1H-pyrazole (4f)

Under an argon atmosphere, in a microwave reaction vial, compound **10** (0.80 g, 2.6 mmol, 1 equiv) and premixed Pd(OAc)₂ and XPhos (1:2, 61 mg, 51 µmol, 0.02 equiv) were dissolved in anhyd THF (5 mL). A solution of 0.32 M 3,4-dichlorobenzylzinc chloride (**2f**) in THF (8.0 mL, 2.6 mmol, 1 equiv) was added and the mixture was heated at 50 °C for 1 h. Concd HCl (2 mL, 37%) was added and the solution was stirred for a further 5 min, and then diluted with EtOAc (100 mL). The organic layer was separated and washed with brine (30 mL), dried (MgSO₄), and concentrated in vacuo. The crude product was purified by chromatography (silica gel, CH₂Cl₂–EtOH, 99:1) to give **4f** (0.44 g, 63%) as a yellowish solid; mp 87 °C.

¹H NMR (CDCl₃): δ = 7.38–7.31 (m, 2 H), 7.12 (s, 1 H), 7.08 (dd, J = 8.1, 2.1 Hz, 1 H), 4.28 (q, J = 7.0 Hz, 2 H), 3.68 (s, 2 H), 1.39 (t, J = 7.0 Hz, 3 H).

 ^{13}C NMR (CDCl_3): δ = 161.5, 141.3, 132.2, 130.4, 130.2, 129.9, 128.5, 127.9, 104.2, 64.6, 27.6, 14.9.

HRMS: m/z [M + H] calcd for $C_{12}H_{13}Cl_2N_2O$: 271.0405; found: 271.0350.

4-(3-Chlorobenzyl)-3-ethoxy-5-iodo-1*H*-pyrazole (5c); Typical Procedure for 5a–f

4-(3-Chlorobenzyl)-3-ethoxy-1*H*-pyrazole (**4c**, 0.41 g, 1.73 mmol, 1 equiv) and NIS (0.41 g, 1.82 mmol, 1.05 equiv) were heated to reflux in 1,2-dichloroethane (25 mL) for 10 h. The solution was diluted with EtOAc (100 mL), the organic layer was separated and discolored with Na₂SO₃ solution (0.5 g in 50 mL of H₂O), washed with H₂O (30 mL) and brine (30 mL), and dried (MgSO₄), and then concentrated in vacuo. The crude product was purified by chromatography (silica gel, CH₂Cl₂-EtOH, 99:1) to give **5c** (0.45 g, 1.24 mmol, 71%) as a yellowish oil.

¹H NMR (CDCl₃): δ = 7.27 (s, 1 H), 7.24–7.11 (m, 3 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 3.64 (s, 2 H), 1.38 (t, *J* = 7.0 Hz, 3 H).

 ^{13}C NMR (CDCl_3): δ = 161.2, 142.1, 134.0, 129.5, 128.7, 126.7, 126.2, 109.6, 82.8, 64.8, 29.1, 14.8.

HRMS: m/z [M + H] calcd for C₁₂H₁₃ClIN₂O: 362.9761; found: 362.9756.

4-Benzyl-3-ethoxy-5-iodo-1H-pyrazole (5a)

Chromatography (silica gel, cyclohexane–EtOAc, 5:1) gave the product (0.25 g, 61%) as a white solid; mp 113 $^\circ C.$

¹H NMR (CDCl₃): δ = 7.34–7.20 (m, 5 H), 6.10 (s, 1 H), 4.25 (q, J = 7.0 Hz, 2 H), 3.68 (s, 2 H), 1.38 (t, J = 7.0 Hz, 3 H).

 ^{13}C NMR (CDCl₃): δ = 161.1, 140.3, 128.6, 128.3, 127.2, 126.0, 110.1, 83.2, 64.9, 29.4, 14.9.

HRMS: *m*/*z* [M + H] calcd for C₁₂H₁₄IN₂O: 329.0151; found: 329.0152.

4-(2-Chlorobenzyl)-3-ethoxy-5-iodo-1*H*-pyrazole (5b)

Yellowish oil; yield: 0.49 g (68%).

¹H NMR (CDCl₃): δ = 11.14 (s, 1 H), 7.42–7.35 (m, 1 H), 7.21–7.12 (m, 2 H), 7.12–7.00 (m, 1 H), 4.26 (q, *J* = 7.0 Hz, 2 H), 3.83 (s, 2 H), 1.34 (t, *J* = 7.0 Hz, 3 H).

 ^{13}C NMR (CDCl₃): δ = 161.4, 137.0, 134.0, 130.1, 129.2, 127.4, 126.5, 108.0, 83.8, 65.0, 27.0, 14.9.

HRMS: m/z [M + H] calcd for $C_{12}H_{13}CIIN_2O$: 362.9761; found: 362.9783.

4-(4-Chlorobenzyl)-3-ethoxy-5-iodo-1*H*-pyrazole (5d)

White solid; yield: 0.66 g (71%); mp 116 °C.

¹H NMR (CDCl₃): δ = 7.22 (m, 4 H), 4.24 (q, *J* = 7.0 Hz, 2 H), 3.64 (s, 2 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

 ^{13}C NMR (CDCl_3): δ = 161.1, 138.6, 131.8, 129.8 (2 C), 128.4 (2 C), 109.9, 82.7, 64.7, 28.8, 14.8.

HRMS: m/z [M + H] calcd for C₁₂H₁₃ClIN₂O: 362.9761; found: 362.9820.

4-(2,4-Dichlorobenzyl)-3-ethoxy-5-iodo-1H-pyrazole (5e)

Yellowish solid; yield: 0.23 g (56%); mp 146 °C.

¹H NMR (DMSO- d_6): δ = 12.37 (s, 1 H), 7.55 (d, J = 2.2 Hz, 1 H), 7.33 (dd, J = 8.4, 2.2 Hz, 1 H), 7.02 (d, J = 8.4 Hz, 1 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.61 (s, 2 H), 1.20 (t, J = 7.0 Hz, 3 H).

 $^{13}\mathsf{C}$ NMR (DMSO- d_6): δ = 161.2, 136.6, 134.1, 131.9, 131.8, 128.9, 127.6, 105.8, 85.4, 64.3, 26.5, 15.1.

HRMS: m/z [M + H] calcd for $C_{12}H_{12}Cl_2IN_2O$: 396.9371; found: 396.9361.

4-(3,4-Dichlorobenzyl)-3-ethoxy-5-iodo-1*H*-pyrazole (5f)

Yellowish wax; yield: 0.26 g (57%).

¹H NMR (CDCl₃): δ = 7.36 (d, *J* = 2.1 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.09 (dd, *J* = 8.2, 2.1 Hz, 1 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 3.63 (s, 2 H), 1.38 (t, *J* = 7.0 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 161.1, 140.3, 132.1, 130.5, 130.1, 130.0, 127.9, 109.2, 82.8, 64.8, 28.6, 14.8.

HRMS: m/z [M + H] calcd for $C_{12}H_{12}Cl_2IN_2O$: 396.9371; found: 396.9404.

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Acknowledgment

This work was supported by the Agence Nationale de la Recherche (ANR), grant ANR-11-CRNT-0004, in the context of the investment program 'GLOBAL CARE', an association of the Instituts Carnot 'Pasteur-Maladies Infectieuses', 'Curie-Cancer', 'Voir et Entendre', 'Institut du Cerveau et de la moelle Épinière' and the 'Consortium pour l'Accélération de l'Innovation et de son Transfert dans le domaine du Lymphome' (CALYM).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379458.

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