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5-Iodo-3-Ethoxypyrazoles: An Entry Point to New Chemical Entities

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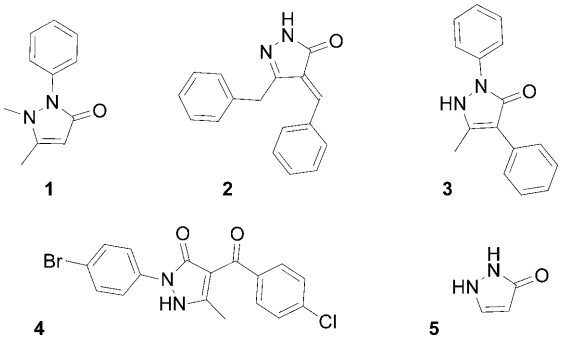
Abstract: Our program, which has focused on the preparation of new pyrazole derivatives, has led us to report here an original and simplified preparation of ethyl 3-ethoxy-1*H*-pyrazole-4-carboxylate. This is based on the reaction of hydrazine monohydrochloride and diethyl 2-(ethoxymethylene)malonate. Further transformations of this key compound allowed the preparation of the two possible iodinated isomers, namely, 3-ethoxy-4-iodo- and 3-ethoxy-5-iodo-1*H*-pyrazole. These compounds have opened the way to a quick access to many original pyrazole series. As an illustration, we report here on the selectivity of N-arylation, by using the Lam and Cham method, the C4- and C5-arylation of some of these 3-ethoxypyrazole derivatives by using the Suzuki–Miyaura reaction, and C5-benzylation reactions by means of the Negishi reaction. This was followed by hydrolysis of the ethoxy group, which led to the corresponding pyrazol-3-one derivatives. As a conclusion of this work, we conducted an investigation into the regiochemistry of the condensation between diethyl 2-(ethoxymethylene)malonate and the hydrochloride salts of methyl, benzyl, or phenyl hydrazine.

Keywords: arylation · heterocycles · organic synthesis · palladium · pyrazoles

Introduction

The pyrazole ring system and more precisely the 3- or 5-"oxo" derivatives cannot be considered as an original scaffold as many derivatives have been reported for their biological activities.[1] For instance, the analgesic N1-phenyl-pyrazol-5-one antipyrine (**1**) was first prepared as early as 1892.[2] More than one hundred years after, compound **2** and related structures were patented for their serine/threonine and tyrosine kinase inhibition properties.[3] Even more recently, derivatives such as **3** were reported as inhibitors of prion accumulation,[4] whereas 4-benzoyl analogues, such as **4**, are able to inhibit *Mycobacterium tuberculosis* growth.[5] Thus, the core pyrazol-3-one structure (**5**) with at least three potential nucleophilic centers (the two nitrogen atoms and one oxygen atom) and two carbon atoms is still an attractive heterocyclic entity. Many of its reactive centers may lend themselves to chemical transformations with a potential for "quick" chemical diversity attainable in few reaction steps. This number of reactive centers, although desirable for chemical diversity, does force protection and deprotection steps to ensure a reaction regioselectivity. In the case of the pyrazol-3-ones, this is a problem as the protection steps themselves also face this issue of regioselectivity, alkylation of such entities may[6] or may not[7] be selective. From *N*-aryl or *N*-alkyl hydrazines, the age-old Knorr reaction[8] provides a fairly selective access to many N1-subtituted pyrazol-5-ones. On the other hand, as we have recently reported,[9] the isomeric N1-subtituted pyrazol-3-ones are less easy to prepare. This aspect is illustrated by a chemical database survey. Out of the 76790 compounds featuring a pyrazolone moiety ever reported, some 66103 are N1-aryl (or alkyl) pyrazol-5-ones, but "only" 4563 are the isomeric N1-aryl (or alkyl) pyrazol-3-ones.



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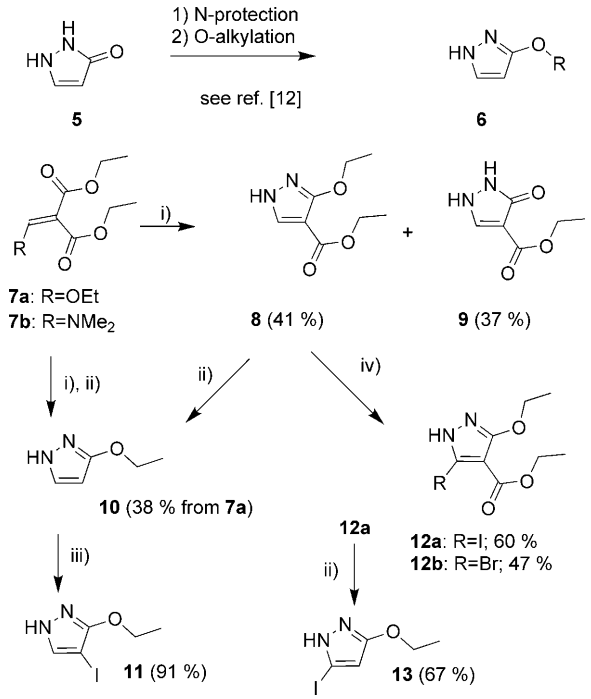
Results and Discussion

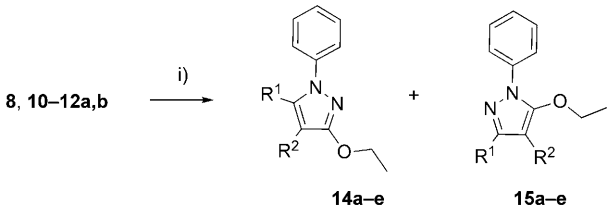
We have recently reported a study on the N-alkylation/-arylation selectivity of 5-substituted 3-alkoxypyrazoles.[9] However, an equivalent work on 5-unsubstituted 3-alkoxy pyrazoles, such as **6**, was not so easy to design as only two papers describe the direct O-alkylation of **5** or further chemical transformations.[10] It is only quite recently that the problem of selective oxygen protection of compound **5** was breached. As depicted in Scheme 1, a patent[11] describes the



Scheme 1. i) for **7a**: NH_2NH_2, HCl, EtOH, reflux; ii) HCl 6 N reflux or NaOH, ethanol 20%, 170 °C, MW; iii) I_2, NaI, K_2CO_3, EtOH, H_2O; iv) *N*-iodosuccinimide or *N*-bromosuccinimide, cyclohexane, reflux.

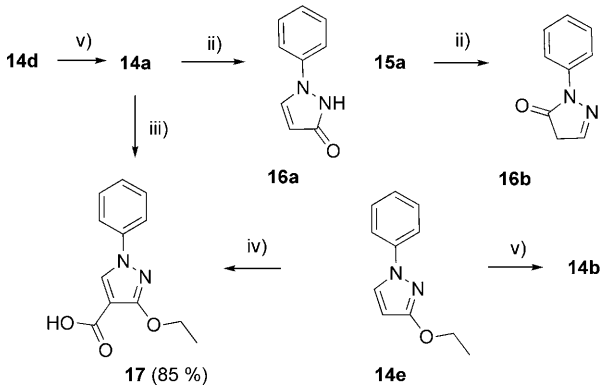
generalization of processes[12] involving either a transient N-carboxylation or -acetylation prior to a, then selective, O-alkylation. We wish to report here an alternative that shunts these three steps (the synthesis of the pyrazol-3-one, its transient N-protection, followed by its selective O-alkylation) as we prepared the readily O-protected ethyl 3-ethoxy-1*H*-pyrazole-4-carboxylate (**8**) in one step. This was achieved from diethyl 2-(ethoxymethylene)malonate (**7a**) in a 41% yield by means of its condensation with hydrazine hydrochloride in boiling ethanol. The alternative reaction product, the known ethyl 3-hydroxy-1*H*-pyrazole-4-carboxylate **9**, is also isolated in a 37% yield and is actually the sole compound obtained when using hydrazine hydrate.[12a,13] Surprisingly, this synthetic pathway has no precedent, although the reaction mechanism is likely to be related to the one-step synthesis of C5-substituted-3-alkoxypyrazoles from alkylacetoacetates that we improved recently.[7] This reaction turns out to proceed in a similar 42% yield from diethyl 2-[(dimethylamino)methylene]malonate (**7b**)[10b] and hydrazine dihydrochloride. On the other hand, a lesser amount of 3-ethoxypyrazole (**10**) was obtained from ethyl 3-(dimethylamino)acrylate (traces) or ethylpropiolate (7%). Moreover, under the same reaction conditions, a small quantity of the corresponding 3-methoxypyrazole was isolated when starting from methyl 3-methoxyacrylate. In any case, an acid hydrolysis of the ester moiety of compound **8** also leads to its decarboxylation and thus to compound **10** in a 38% yield from **7a**. From compounds **8** and **10**, further transformations allowed the preparation of the two iodo-bearing derivatives **11** and **12**. Although the synthesis of compound **11** could be said to be trouble-free, many attempts were made to prepare the 5-halogenated alkoxypyrazole **12**. This compound is of much interest as it avoids the nitrogen methylation required for a butyl lithium based halogenation strategy reported in a related case.[15] With this goal in mind we prepared compound **12a** from **8** in a 60% yield by using *N*-iodosuccinimide in boiling cyclohexane. The 5-brominated homologue **12b** was also prepared by using *N*-bromosuccinimide although in only a 47% yield. A related process (*N*-iodosuccinimide in hot DMF) was actually reported for the 5-iodination of two 3-carboxyethyl-bearing pyrazoles.[16] As heating is necessary for these reactions to proceed, we suggest a 1–2-migration reaction of a halogenated intermediate, from either C4 or N1, to C5 of the pyrazole nucleus. Such a mechanism suggests a stabilization effect of the ester moiety of **8**, which is in effect acting as a pyrazole C4 protecting group. This is all the more true as an acid (or a basic) hydrolysis of **12a** leads to a subsequent decarboxylation and thus to 67% (or 76%) of the stable 5-iodopyrazole **13**.

To illustrate the diversity attainable from compounds **8** and **10–13**, a few chemical transformations were studied. Scheme 2 depicts the copper-based N-phenylation of these compounds by using phenylboronic acid.[9,17] From **8**, a 92% yield of the N1-phenylation product **14a** along with 7% of its isomer **15a** were obtained. The latter isomer is actually the only one that had been partially reported previously.[18] The N-phenylation of the 4-iodo-bearing compound **11** gave 71% of the N1-phenylation product **14b** and only traces of **15b**. On the other hand, this reaction proceeded with a lesser selectivity from compound **12a** as the *N*-phenyl derivative **14c** was obtained in a 60% yield along with 26% of **15c**. A similar result was observed from **12b**, which led to compounds **14d** and **15d** in 54 and 13% yield, respectively. In addition, from compound **10**, isomers **14e** and **15e** are obtained in 56 and 20% yield, respectively. Arylation of compound **13** also proceeded well; however, we could not separate the 1:3 mixture of the corresponding isomeric products. A remarkable phenomenon took place if the arylation of **12a** was run under an inert atmosphere. The ^{1}H NMR spectra and the LCMS monitoring of the reaction mixture pointed out the occurrence of the expected derivative **14c** along with a substantial amount of the reduced derivative **14a**. As far as we know, such copper-caused halide reduction in an oxygen-deprived medium at room temperature has not been reported previously. The closest observation is proba-



	Starting material	R^1	R^2	**14** [%][a]	**15** [%][a]
a	**8**	H	CO_2Et	92	7
b	**11**	H	I	71	1.5
c	**12a**	I	CO_2Et	60	26
d	**12b**	Br	CO_2Et	54	13
e	**10**	H	H	56	20

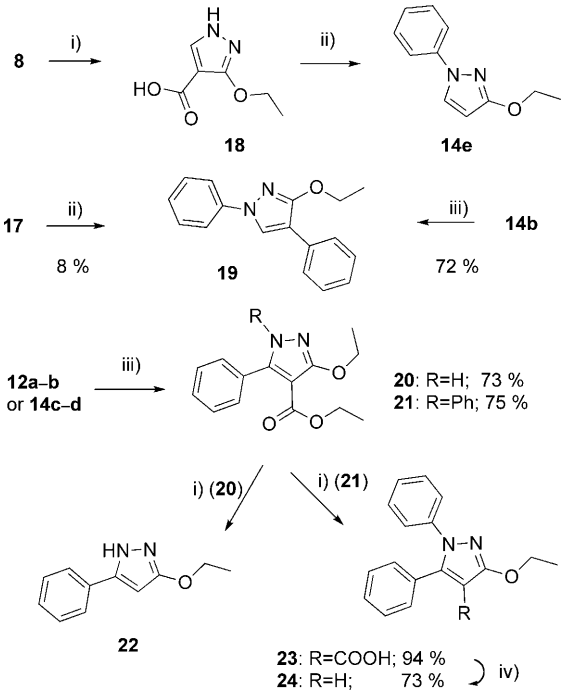
[a] Isolated yield.



Scheme 2. i) $PhB(OH)_2$, $Cu(OAc)_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2, air 25 °C; ii) HBr/AcOH 140 °C; iii) NaOH, EtOH, H_2O, reflux; iv) $MeSO_3H$, toluene reflux; v) NH_3, HCOOH, ethanol Pd/C reflux.

bly the Cu^I-mediated reductive cross-coupling of aromatic nitroso derivatives with arylboronates reported recently.[19] Of related interest is the copper-catalyzed reaction between O-acetylated oximes and arylboronates in the presence of copper that leads to a reductive amination yielding *N*-arylimines,[20] whereas the occurrence of *O*-aryloxime ethers is described when using free oximes.[21] In our case, this halogen reduction readily takes place on a large scale run if the reaction medium is insufficiently aired. Concerning the structure assignments of these products, as long distance correlation or NOE-based NMR spectroscopic experiments were of little use, they were ascertained beyond any doubt by further transformations of the separated isomers. As depicted in Scheme 2, an exhaustive acid hydrolysis of **14a** and **15a** led to compounds **16a** and **16b**. The ^1H and ^{13}C NMR spectra of **16b** in deuterated chloroform pointed out the occurrence of a methylene component only compatible with the mesomeric form **16b** drawn in Scheme 2. The saponification of the ester function of compound **14a** gave the acid **17**, which upon heating in the presence of an equivalent amount of methanesulfonic acid gave 56% of a decarboxylation product corresponding to the isomer **14e**. A partial (as the evolving hydrogen iodide poisons the catalyst) palladium-catalyzed reduction of compound **14b** also gave a small amount of the isomer **14e**. Under these reduction conditions, the bromine-bearing compound **14d** led to the isomer **14a**. Moreover, as is shown below, further chemistry by using compound **14c** and **14d** gave the same reaction product thus completing the structure assignment of all the *N*-phenyl derivatives described here.

Following this N-arylation study, we focused on pyrazoles C4 and C5-phenylation reactions. The recently reported palladium-catalyzed decarboxylative aryl–aryl coupling[22] led us to attempt such a reaction on 4-carboxylic acid bearing pyrazoles. We also put to good use a microwave (MW) oven, which greatly reduced the heating time. From acid **18**, readily obtained by the saponification of compound **8** (Scheme 3), the N-phenylated compound **14e**, resulting



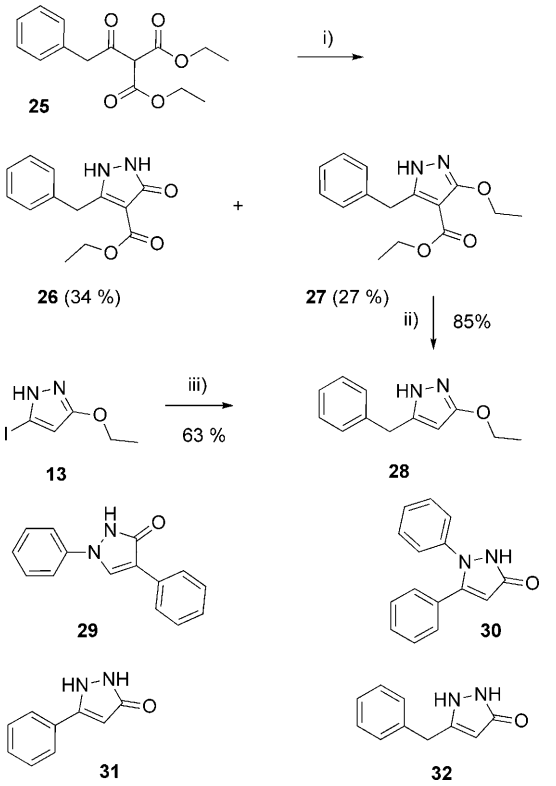
Scheme 3. i) KOH, EtOH, H_2O, reflux; ii) PhBr, $Pd(OAc)_2$, CuI, phenanthroline, K_2CO_3, 3 Å molecular sieves, *N*-methylpyrrolidone (NMP), 210 °C MW; iii) $PhB(OH)_2$, $[PdCl_2(dppf)]$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene), Cs_2CO_3, PrOH/H_2O 120 °C MW; iv) $MeSO_3H$, toluene reflux.

from an Ullmann/Buchwald–Hartwig reaction,[23] was the only product isolated (in a 41% yield). From acid **17**, the expected C4-arylation product **19** was isolated, although in only an 8% yield. On the other hand, a far better 72% yield of **19** was obtained from the 4-iodinated isomer **14b** by using the more conventional Suzuki–Miyaura aryl–aryl cross coupling reaction. The duration of this coupling reaction was greatly shortened by the use of the [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium as a precatalyst[24]

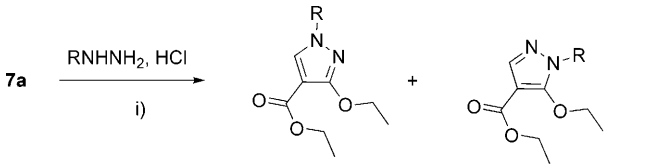
and a microwave oven. The use of these aryl–aryl coupling conditions successfully led to the C5 phenyl derivatives **20** and **21**, from compounds **12a** and **14c** in 75 and 74% yield, respectively. Very similar results were obtained from the 5-bromo homologues **12b** and **14d** (giving 73 or 62% yields of compounds **20** and **21**, respectively). However, attempts to achieve a direct C5-arylation of compound **13** led to an inseparable mixture of the arylation product, unreacted compound, and some reduced materials. A similar observation was made in the course of C4-arylation trials of compound **11** reminiscent of our earlier observations.[24a] Further work on these specific cases is underway and will be reported elsewhere. To complete this initial synthetic exploration, we undertook the removal of the carboxyl moiety of compounds **20** and **21**. In the case of **20**, this was achieved by using strongly basic conditions leading to the known compound **22** in 86% yield.[7] From ester **21**, a two-step sequence was used leading first to acid **23**, which then underwent an acid-catalyzed decarboxylation giving the known compound **24**[25] in a 68% overall yield.

Our attention was then drawn to a report claiming that the condensation between phenylacetylmalonate **25** and hydrazine hydrochloride gives exclusively the corresponding pyrazol-3-ones **26**.[26] In light of all our results with β-ketoesters,[7] we reinvestigated this work. Compound **25** (Scheme 4) was prepared by using the reported magnesium-based condensation between diethylmalonate and phenylacetyl chloride.[27] In our hands, from **25**, under the described reaction conditions, we could only isolate 34% of compound **26** (instead of the highly optimistic 81% reported[26]) along with 27% of the previously unreported 3-ethoxypyrazole derivative **27**. These results are thus in conformity with what we observed from the reaction of many β-ketoesters and hydrazine hydrochloride.[7] Decarboxylation of compound **27** led to the 5-benzyl derivative **28** and this compound could also be obtained in a more convergent fashion by means of the Negishi reaction between compound **13** and benzylzinc-bromide in a 63% yield. As mentioned above, the deprotection of these 3-alkoxypyrazoles derivatives to give the corresponding pyrazol-3-ones was usually performed in a sealed tube flushed with argon by using 33% hydrobromic acid in acetic acid at 140°C. The complete ether cleavage of compound **19** to give the 1,4-diphenylpyrazol-3-one **29** or the hydrolysis of the 1,5-diphenylderivatives **21** and **24** to give compound **30** were achieved in a maximum of 5 h at this temperature. A related heating time was required to fully hydrolyze the carboxyl-bearing compound **20** into 5-phenyl-pyrazol-3-one (**31**). On the other hand, hydrolysis of the ethoxy moieties of the 5-phenylpyrazole **22** or the 5-benzyl homologue **28**, leading to compounds **31** and **32**, respectively, took 23 h of heating time to be completed.

As a conclusion of this report, we also studied the regiochemistry of the condensation between the ethoxymethylenemalonate **7a** and phenyl, benzyl, or methyl hydrazine hydrochloride. Aside from the expected pyrazolones, this led to the separable pair of isomers of 3 and 5-ethoxypyrazoles derivatives. As depicted in Scheme 5, from phenyl hydrazine



Scheme 4. i) NH_2NH_2, HCl, EtOH, reflux; ii) NaOH, H_2O/EtOH, 110°C; iii) $PhCH_2ZnBr$, [$PdCl_2$(dppf)], THF, 85°C; iv) EtOH, reflux.



Scheme 5. i) NH_2NH_2, HCl, EtOH, reflux.

hydrochloride, a small 1.9% of the 1-phenyl-3-ethoxy pyrazole derivative **14a** could be isolated and 22% of the 1-phenyl-5-ethoxy pyrazole isomer **15a**. From benzyl hydrazine hydrochloride, the amount of 1-benzyl-3-ethoxy pyrazole isomer **33a** rose to 5.7%, whereas the 1-benzyl-5-ethoxy pyrazole derivative **34a** was isolated in a 22% yield. Interestingly, from methylhydrazine hydrochloride, no regioselectivity was observed as the isomers **33b** and **34b** were both isolated in 17% yields. Their structural assignments was fairly easy as ^1H–^{13}C NMR long distance correlations, from the methylenes of compounds **33a** and **34a** or from the methyls of compounds **33b** and **34b**, provided unambiguous evidence. Furthermore, we also searched for ethoxy-bearing isoxazoles arising from the reaction between **7a** and hydroxylamine hydrochloride. However, contrary to a previ-

ous case,[7] heating was necessary for any reaction to proceed and no 3- nor 5-ethoxyisoxazole derivatives could be detected in the reaction mixture.

Conclusion

These very few transformations utilizing the now available 5-iodo-bearing 3-ethoxypyrazoles pave the way to the synthesis of many original chemical libraries.[28] Most of them do have the great advantage of providing fairly elaborate structures in just a few synthetic steps. Amongst their potential interest, we can mention the reported antimicrobial activity of pyrazole-featuring compounds[13,25b,29] that fit our current interest in the design of original antimycobacterials.[30] The relatively easy synthesis of various analogues of many other pyrazoles of biological interest can also be envisioned. One could also mention analogues of HSP90 inhibitors,[31] HIV-1 protease inhibitors,[32] and pyrazoles useful for crop protection or with a potentially interesting biological effect.[1] We hope that, because of the flexibility of their chemistry, these alkoxypyrazoles may become useful in fragment-based approaches in drug discovery.[33]

Experimental Section

General: A Biotage initiator 2 microwave oven was used for reactions requiring microwave irradiations. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography was performed either with Merck silica gel 60 (0.035–0.070 mm) or neutral alumina containing a suitable proportion of water, by using a solvent pump operating at a pressure between 2 and 7 bar (25–50 mL min^{-1}) and an automated collecting system driven by a UV detector set to 254 nm unless stated 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 on the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LCMSD system by using an atmospheric electrospray ionization system and the HRMS were obtained by using a Waters Micromass Q-Tof with an electrospray ion source.

Preparation of compounds 8 and 9: Diethylethoxymethylenemalonate (37.4 g, 0.172 mol) and hydrazine hydrochloride (12.2 g, 0.178 mol) was refluxed in ethanol (500 mL) for 16 h. The solvent was removed under reduced pressure, then the residue was dispersed in water (500 mL) and slowly made basic by the addition of solid sodium hydrogencarbonate. The aqueous phase was extracted with dichloromethane; this organic phase was washed with a saturated solution of sodium hydrogencarbonate three times, dried over sodium sulfate, and concentrated to dryness to yield compound **8** as an oil that solidified very slowly (13.2 g, 41 %). The aqueous phase was cautiously made acidic with concentrated hydrochloric acid, then saturated with sodium chloride, and the resulting precipitate was filtered, washed with water, and dried under vacuum while heating at 60 °C to yield compound **9** (10 g, 37 %) as a white powder.

*Ethyl 3-ethoxy-1*H*-pyrazole-4-carboxylate (**8**)*: M.p. $<$50 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.35 (t, ^3J = 7.1 Hz, 3H), 1.46 (t, ^3J = 7.1 Hz, 3H), 4.30 (q, ^3J = 7.1 Hz, 2H), 4.36 (q, ^3J = 7.1 Hz, 2H), 7.89 (s, 1H), 11.4 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 14.3, 14.5, 60.1, 65.3, 99.0, 134.0, 162.3, 163.8 ppm; HRMS: m/z: calcd for $C_8H_{12}N_2O_3$+H: 185.0926; found: 185.0971.

*Ethyl 3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**9**)*: M.p. 185 °C (lit.:[34] 180 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 1.23 (t, ^3J = 7.1 Hz, 3H), 4.15 (q, ^3J = 7.1 Hz, 2H), 7.90 (brs, 1H), 10.20 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS, D1 set to 10 s): δ = 19.6, 64.1, 102.2, 139.5 (br), 165.2 (br), 168.0 ppm.

Preparation of 3-ethoxy-1*H*-pyrazole (10): By starting from diethylethoxymethylenemalonate (38.9 g, 0.179 mol), the protocol described above for the preparation of **8** was followed and the residue was dispersed in 6 N hydrochloric acid (100 mL). This mixture was heated to reflux until the end of the carbon dioxide evolution (4 h in the present case). The aqueous phase was diluted in water, slowly made basic by the addition of sodium hydrogencarbonate, saturated with sodium chloride, and then extracted with ethyl acetate four times. The organic phase was washed with a 1 N solution of sodium hydrogencarbonate once, with brine once, dried over sodium sulfate, and concentrated to dryness to yield compound **10** as an oil (7.77 g, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.43 (t, ^3J = 7.0 Hz, 3H), 4.23 (q, ^3J = 7.0 Hz, 2H), 5.74 (d, ^3J = 2.5 Hz, 1H), 7.37 (d, ^3J = 2.5 Hz, 1H), 9.40 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 14.9, 64.9, 90.3, 130.2, 167.7 ppm; HRMS: m/z: calcd for $C_5H_8N_2O$+H: 113.0715; found: 113.0788.

Preparation of 3-ethoxy-4-iodo-1*H*-pyrazole (11): Compound **10** (8.37 g, 0.074 mol), sodium iodide (11.2 g, 0.082 mol), and potassium carbonate (40 g, 0.289 mol) were dissolved in water (400 mL) and ethanol (100 mL). To this solution was added iodine (28.5 g, 0.112 mol). The resulting suspension was stirred for 90 min, decolorized (if necessary) with sodium bisulfate, and diluted with brine (400 mL). The resulting mixture was filtered, washed with water, and dried under vacuum while heating at 70 °C in a large Petri dish to sublimate the iodoform sometimes forming in this reaction to yield compound **11** as an off-white solid (16.2 g, 91 %). M.p. 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.44 (t, ^3J = 7.1 Hz, 3H), 4.31 (q, ^3J = 7.1 Hz, 2H), 7.42 (s, 1H), 9.35 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 14.8, 44.2, 65.5, 134.3, 163.2 ppm; HRMS: m/z: calcd for $C_5H_7N_2OI$+H: 238.9681; found: 238.9722.

Preparation of compounds 12a and 12b: Compound **8** (0.74 g, 4.02 mmol) and *N*-iodosuccinimide (0.94 g, 4.22 mmol) or *N*-bromosuccinimide (0.75 g, 4.22 mmol) were refluxed in cyclohexane (50 mL) for 24 h or 30 min. The resulting suspension was dissolved in ethyl acetate and then decolorized with a solution of sodium sulfite. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness. The residue was purified by chromatography over silica gel (dichloromethane/ethanol 98:2) to yield compound **12a** (0.75 g, 60 %) or **12b** (0.5 g, 47 %). On a small scale (3 g of compound **8**), the iodo-bearing derivative **12a** was also prepared in similar yield by using a microwave oven (45 min of heating at 150 °C).

*Ethyl 5-iodo-3-ethoxy-1*H*-pyrazole-4-carboxylate (**12a**)*: Obtained as an oil that slowly solidified; m.p. 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.36 (t, ^3J = 7.0 Hz, 3H), 1.39 (t, ^3J = 7.0 Hz, 3H), 4.31 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 14.2, 14.6, 60.4, 65.5, 87.0, 103.6, 161.9, 162.0 ppm; HRMS: m/z: calcd for $C_8H_{11}IN_2O_3$+H: 332.9712; found: 332.9722.

*Ethyl 5-bromo-3-ethoxy-1*H*-pyrazole-4-carboxylate (**12b**)*: White crystals; m.p. 90 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.40 (t, ^3J = 7.0 Hz, 3H), 1.48 (t, ^3J = 7.0 Hz, 3H), 4.33 (m, 4H), 9.50 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS, D1 set to 10 s): δ = 14.2, 14.5, 60.4, 65.7, 99.0, 119.5 (br), 161.6 (br), 162.0 ppm; HRMS: m/z: calcd for $C_8H_{11}BrN_2O_3$+H: 263.0031; found: 263.0049.

Preparation of 3-ethoxy-5-iodo-1*H*-pyrazole (13): Compound **12a** (0.99 g, 3.2 mmol) was dispersed in 6 N hydrochloric acid (20 mL) and heated to reflux for 4 h. The aqueous phase was diluted in water, slowly made basic by the addition of concentrated ammonia, and extracted with ethyl acetate four times. The organic phase was washed with brine once, dried over sodium sulfate, and concentrated to dryness to yield compound **13** as an oil that crystallized very slowly (0.52 g, 67 %). M.p. $<$50 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.40 (t, ^3J = 7.0 Hz, 3H), 4.18 (q, ^3J = 7.0 Hz, 2H), 5.85 (s, 1H), 6.90 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 14.7, 65.7, 83.3, 98.4, 162.4 ppm; HRMS: m/z: calcd for $C_5H_7IN_2IO$+H: 238.9681; found: 238.9621. Alternatively, compound **12a** (1.27 g, 4.09 mmol), sodium hydroxide (0.70 g, 13.4 mmol) in ethanol

(8 mL), and water (2 mL) were heated in a microwave oven at 150 °C for 3 min. The resulting mixture was dispersed in water and extracted with ethyl acetate. The organic layer was then washed with brine, dried over magnesium sulfate, and concentrated to dryness with a high-vacuum pump to yield compound **13** (0.74 g, 76 %) as described above.

General procedure for the N-arylation of compounds 8, and 10–12a,b: The pyrazole derivative (5.43 mmol), benzeneboronic acid (0.73 g, 5.97 mmol), pyridine (0.88 mL, 10.9 mmol, dried over 4 Å molecular sieves), 4 Å molecular sieves (2 g), and copper(II) acetate hydrate (1.62 g, 8.15 mmol) were dispersed in dichloromethane (100 mL). The suspension was stirred in open air for 48 h. After concentration to dryness, the residue was absorbed on a small amount of silica gel and purified as described below for each pair of isomers.

Compounds 14a and 15a: From compound **8**, chromatography over silica gel (cyclohexane/ethyl acetate 8:1) led in this order to compound **15a** and then compound **14a** (92 %). The fraction containing **15a** had to be further purified by a second chromatography over neutral alumina containing 1.5 % water (cyclohexane/ethyl acetate 9:1) to yield pure **15a** (7 %).

*Ethyl 3-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**14a**)*: Solid; m.p. 78 °C (cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.38$ (t, $^3J = 7.1$ Hz, 3H), 1.51 (t, $^3J = 7.1$ Hz, 3H), 4.33 (q, $^3J = 7.1$ Hz, 2H), 4.46 (q, $^3J = 7.1$ Hz, 2H), 7.30 (m, 1H), 7.46 (m, 2H), 7.65 (m, 2H), 8.25 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.4$, 14.7, 60.1, 65.4, 102.2, 118.5, 126.6, 129.5, 131.1, 139.3, 162.5, 162.7 ppm; HRMS: *m/z*: calcd for $C_{14}H_{16}N_2O_3+H$: 261.1239; found: 261.1275.

*Ethyl 5-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**15a**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.31$ (t, $^3J = 7.1$ Hz, 3H), 1.37 (t, $^3J = 7.1$ Hz, 3H), 4.32 (q, $^3J = 7.1$ Hz, 2H), 4.42 (q, $^3J = 7.1$ Hz, 2H), 7.34 (m, 1H), 7.46 (m, 2H), 7.67 (m, 2H), 7.94 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 15.7$, 16.5, 61.4, 73.4, 102.3, 124.5, 128.8, 130.2, 139.2, 143.2, 156.1, 163.6 ppm; HRMS: *m/z*: calcd for $C_{14}H_{16}N_2O_3+H$: 261.1239; found: 261.1272.

Compounds 14b and 15b: From compound **11**, chromatography over silica gel (cyclohexane/dichloromethane 8:2) led, in this order, to compound **14b** (71 %) and its isomer **15b** (1.5 %).

*3-Ethoxy-4-iodo-1-phenyl-1*H*-pyrazole (**14b**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.48$ (t, $^3J = 7.0$ Hz, 3H), 4.42 (q, $^3J = 7.0$ Hz, 2H), 7.24 (m, 1H), 7.43 (m, 2H), 7.58 (m, 2H), 7.79 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.7$, 47.0, 65.6, 117.7, 125.7, 129.4, 131.8, 139.8, 163.7 ppm; HRMS: *m/z*: calcd for $C_{11}H_{11}N_2OI+H$: 314.9995; found: 315.0037.

*5-Ethoxy-4-iodo-1-phenyl-1*H*-pyrazole (**15b**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.32$ (t, $^3J = 7.0$ Hz, 3H), 4.21 (q, $^3J = 7.0$ Hz, 2H), 7.34 (m, 1H), 7.47 (m, 2H), 7.54 (s, 1H), 7.68 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 15.3$, 45.3, 71.2, 122.4, 127.2, 129.0, 138.4, 144.2, 153.2 ppm; HRMS: *m/z*: calcd for $C_{11}H_{11}N_2OI+H$: 314.9995; found: 315.0053.

Compounds 14c and 15c: From compound **12a**, chromatography over neutral alumina containing 1.5 % water (cyclohexane/ethyl acetate 96:4) led, in this order, to compound **15c** (26 %) and then compound **14c** (60 %).

*Ethyl 5-iodo-3-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**14c**)*: Solid; m.p. 80 °C; 1.40 (t, $^3J = 7.0$ Hz, 3H), 1.45 (t, $^3J = 7.0$ Hz, 3H), 4.37 (m, 4H), 7.48 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.2$, 14.6, 60.3, 65.1, 90.2, 105.4, 127.1, 128.9, 129.1, 140.1, 161.9, 163.8 ppm; HRMS: *m/z*: calcd for $C_{14}H_{15}N_2O_3I+Na$: 409.0025; found: 409.0036.

*Ethyl 3-iodo-5-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**15c**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.28$ (t, $^3J = 7.1$ Hz, 3H), 1.43 (t, $^3J = 7.1$ Hz, 3H), 4.27 (q, $^3J = 7.1$ Hz, 2H), 4.38 (q, $^3J = 7.1$ Hz, 2H), 7.39 (m, 1H), 7.46 (m, 2H), 7.65 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.3$, 15.2, 60.5, 72.7, 99.9, 104.7, 123.2, 128.3, 128.8, 137.1, 154.7, 161.2 ppm; HRMS: *m/z*: calcd for $C_{14}H_{15}N_2O_3I+Na$: 409.0025; found: 409.0026.

Compounds 14d and 15d: From compound **12b**, chromatography over neutral alumina containing 1.5 % water (cyclohexane/ethyl acetate 97:3) led, in this order, to compound **15d** (13 %) and then its isomer **14d** (54 %).

*Ethyl 5-bromo-3-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**14d**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.37$ (t, $^3J = 7.0$ Hz, 3H), 1.46 (t, $^3J = 7.0$ Hz, 3H), 4.37 (m, 4H), 7.46 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.3$, 14.6, 60.4, 65.0, 101.3, 118.4, 126.2, 128.9, 129.0, 138.5, 161.8, 162.7 ppm; HRMS: *m/z*: calcd for $C_{14}H_{15}N_2O_3{}^{79}Br+Na$: 361.0164; found: 361.0184.

*Ethyl 3-bromo-5-ethoxy-1-phenyl-1 H-pyrazole-4-carboxylate (**15d**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.29$ (t, $^3J = 7.0$ Hz, 3H), 1.44 (t, $^3J = 7.0$ Hz, 3H), 4.28 (q, $^3J = 7.0$ Hz, 2H), 4.38 (q, $^3J = 7.0$ Hz, 2H), 7.37 (m, 1H), 7.46 (m, 2H), 7.66 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.3$, 15.2, 60.6, 72.8, 101.4, 123.2, 128.1, 128.8, 129.1, 137.1, 155.1, 161.2 ppm; HRMS: *m/z*: calcd for $C_{14}H_{15}N_2O_3{}^{79}Br+Na$: 361.0164; found: 361.0172.

Compounds 14e and 15e: From compound **10**, chromatography over neutral alumina containing 1.5 % water (cyclohexane/dichloromethane 9:1 and then 2:1) led, in this order, to compound **14e** (56 %) and its isomer **15e** (20 %).

*Ethyl 3-ethoxy-1-phenyl-1*H*-pyrazole (**14e**)*: Oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.46$ (t, $^3J = 7.0$ Hz, 3H), 4.33 (q, $^3J = 7.0$ Hz, 2H), 5.90 (d, $^3J = 2.5$ Hz, 1H), 7.23 (m, 1H), 7.42 (m, 2H), 7.63 (m, 2H), 7.74 ppm (d, $^3J = 2.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.8$, 64.9, 93.7, 117.8, 125.2, 125.5, 129.3, 140.2, 164.5 ppm; HRMS: *m/z*: calcd for $C_{11}H_{12}N_2O+H$: 189.1028; found: 189.1061.

*Ethyl 5-ethoxy-1-phenyl-1*H*-pyrazole (**15e**)*: Obtained as an oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.47$ (t, $^3J = 7.1$ Hz, 3H), 4.19 (q, $^3J = 7.1$ Hz, 2H), 5.67 (d, $^3J = 1.7$ Hz, 1H), 7.28 (m, 1H), 7.42 (m, 2H), 7.51 (d, $^3J = 1.7$ Hz, 1H), 7.77 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.6$, 67.9, 86.2, 122.0, 126.2, 128.8, 138.8, 139.6, 154.6 ppm; HRMS: *m/z*: calcd for $C_{11}H_{12}N_2O+H$: 189.1028; found: 189.0971.

Acid hydrolysis of compounds 14a and 15a: In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, the considered pyrazole (1 mmol) was degassed with argon and 33 % hydrogen bromide in acetic acid (1.5 mL) was then added. The tube was closed tightly and heated at 140 °C for 4 h. The resulting solution was cooled, diluted in water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness. The resulting residues were purified in both cases by chromatography over silica gel (dichloromethane/ethanol 97:3) to yield compounds **16a** or **16b** as described below.

*1-Phenyl-1*H*-pyrazol-3(2*H*)one (**16a**)*: White powder; yield: 81 %; m.p. 158 °C (lit.:[35] 156 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): $\delta = 5.80$ (d, $^3J = 2.5$ Hz, 1H), 7.18 (m, 1H), 7.47 (m, 2H), 7.67 (m, 2H), 8.20 (d, $^3J = 2.5$ Hz, 1H), 10.18 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): $\delta = 94.3$, 116.7, 124.5, 128.3, 129.3, 139.8, 162.6 ppm; HRMS: *m/z*: calcd for $C_9H_8N_2O+H$: 161.0715; found: 161.0793.

*1-Phenyl-1*H*-pyrazol-5(4*H*)one (**16b**)*: Obtained as an oil which solidified; yield: 71 %; m.p. 120 °C (dec., lit.:[36] 118 °C); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 3.51$ (d, $^3J = 1.2$ Hz, 1H), 7.21 (m, 1H), 7.43 (m, 2H), 7.49 (t, 1H, $J = 1.2$), 7.88 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 40.9$, 119.0, 125.4, 128.9, 137.9, 146.8, 169.9 ppm; HRMS: *m/z*: calcd for $C_9H_8N_2O+H$: 161.0715; found: 161.0799.

Preparation of 3-ethoxy-1-phenyl-1*H*-pyrazole-4-carboxylic acid (17): Ester **14a** (0.5 g, 1.92 mmol) was refluxed in a mixture of water/ethanol 1:1 (20 mL) containing sodium hydroxide (0.3 g, 7.5 mmol) for 1 h. The resulting solution was diluted in water, made acidic with 2 N hydrochloric acid, and the resulting precipitate was filtered, washed with water, and dried under vacuum to yield compound **17** as a white powder (0.38 g, 85 %). M.p. 172 °C (lit.:[37] 216 °C); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): $\delta = 1.37$ (t, $^3J = 7.1$ Hz, 3H), 4.33 (q, $^3J = 7.1$ Hz, 2H), 7.32 (m, 1H), 7.48 (m, 2H), 7.85 (m, 2H), 8.20 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): $\delta = 15.0$, 65.1, 102.6, 118.4, 126.8, 129.9, 133.2, 139.3, 162.4, 163.3 ppm; HRMS: *m/z*: calcd for $C_{12}H_{12}N_2O_3+H$: 233.0926; found: 233.0973.

Preparation of 3-ethoxy-1,5-diphenyl-1*H*-pyrazole-4-carboxylic acid (23): The protocol used for the preparation of compound **17** was used from **21**

to yield compound **23** as a white powder (94% yield). M.p. 211°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ=1.38 (t, ^3J=7.1 Hz, 3H), 4.32 (q, ^3J=7.1 Hz, 2H), 7.15 (m, 2H), 7.30 ppm (m, 8H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): δ=14.7, 64.3, 99.8, 125.4, 127.5, 127.8, 128.7, 128.8, 129.4, 130.3, 138.8, 146.3, 161.7, 163.0 ppm; HRMS: *m/z*: calcd for $C_{18}H_{16}N_2O_3$+H: 309.1239; found: 309.1239.

Preparation of 3-ethoxy-1*H*-pyrazole-4-carboxylic acid (18): Compound **8** (1 g, 5.43 mmol) was heated to reflux in 1 N sodium hydroxide solution (11 mL) for 1 h (a shorter time is likely to be better) and upon acidification the precipitate was filtered, washed with water, and dried under vacuum to yield **18** as a white powder (0.62 g, 58%). M.p. 250°C (dec.); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ=1.30 (t, ^3J=7.0 Hz, 3H), 4.20 (q, ^3J=7.0 Hz, 2H), 7.98 (s, 1H), 11.8 (brs, 1H), 12.5 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): δ=14.6, 64.0, 98.5, 134.3, 161.4, 163.4 ppm; HRMS: *m/z*: calcd for $C_6H_8N_2O_3$+H: 157.0613; found: 157.0600.

Preparation of 3-ethoxy-1,4-diphenyl-1*H*-pyrazole (19): In a 10 mL Biotage-adapted tube, compound **17** (0.11 g, 0.47 mmol), bromobenzene (0.068 mL, 0.64 mmol), potassium carbonate (0.078 g, 0.57 mmol), copper iodide (0.009 g, 0.047 mmol), phenanthroline (0.013 mg, 0.071 mmol), and 4 A molecular sieves (0.02 g) were dispersed in *N*-methylpyrolidinone (4 mL). The oxygen was removed by a slow stream of argon and palladium acetate (5 mg, 0.023 mmol) was then added before sealing the tube. This tube was heated in the microwave oven for 40 min at 210°C. The resulting suspension was concentrated to dryness under high vacuum. The residue was dispersed in water and extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was purified by chromatography over silica gel (cyclohexane/dichloromethane 95:5) to yield compound **19** as a solid (0.010 g, 8%). M.p. 61°C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.58 (t, ^3J=7.0 Hz, 3H), 4.55 (q, ^3J=7.0 Hz, 2H), 7.27 (m, 2H), 7.48 (m, 4H), 7.70 (m, 2H), 7.81 (m, 2H), 8.04 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=15.0, 65.0, 109.9, 117.7, 124.4, 125.2, 126.1 (two signals), 128.6, 129.4, 131.8, 140.1, 161.4 ppm; HRMS: *m/z*: calcd for $C_{17}H_{16}N_2O$+H: 265.1341; found: 265.1365.

Note: As mentioned in the text, under these reaction conditions, the N-phenylated derivative **14a** described above was obtained in a 41% yield from acid **18**.

Preparation of 3-ethoxy-5-phenyl-1*H*-pyrazole (22): Compound **20** (0.08 g, 0.30 mmol) and sodium hydroxide (1 g, 25 mmol) were heated to reflux in a mixture of water (4 mL) and ethanol (2 mL) for 12 h. The solution was extracted with ethyl acetate, dried over sodium sulfate, and concentrated to dryness to yield **22** (0.05 g, 86%). This compound was identical to a sample we have previously prepared.[7]

Preparation of 3-ethoxy-1,5-diphenyl-1*H*-pyrazole (24): Acid **23** (0.08 g, 0.25 mmol) and methanesulfonic acid (0.016 mL, 0.25 mmol) were refluxed in toluene (20 mL) for 2 h. The solution was washed with a saturated sodium hydrogencarbonate solution, dried over sodium sulfate, and concentrated to dryness to yield compound **24** as an oil (0.05 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.46 (t, ^3J=7.1 Hz, 3H), 4.34 (q, ^3J=7.1 Hz, 2H), 5.97 (s, 1H), 7.27 ppm (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.9, 64.7, 93.7, 124.9, 126.7, 128.3, 128.4, 128.7, 128.8, 130.7, 140.1, 144.1, 163.5 ppm; HRMS: *m/z*: calcd for $C_{17}H_{16}N_2O$+H: 265.1341; found: 265.1286.

Representative aryl–aryl coupling procedure, preparation of ethyl 3-ethoxy-5-phenyl-1*H*-pyrazole-4-carboxylate (20): In a 10 mL biotage-adapted tube, compound **13** (0.10 g, 0.34 mmol), phenyl boronic acid (0.054 g, 0.442 mmol), and cesium carbonate (0.28 g, 0.847 mmol) were dispersed in a mixture of propanol (3 mL) and water (2 mL). The oxygen was removed by a slow stream of argon and [1,1′-bis(diphenylphosphino)-ferrocene] dichloropalladium complexed with dichloromethane (0.057 mmol) was then added before sealing the tube. This was heated in the microwave oven for 30 min at 120°C. The resulting suspension was diluted in water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane/ethanol 99:1) to yield compound **20** as an oil that slowly solidified (0.065 g, 73%). M.p. 95°C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.17 (t, ^3J=7.0 Hz, 3H), 1.36 (t, ^3J=7.0 Hz, 3H), 4.16 (q, ^3J=7.0 Hz, 2H), 4.21 (q, ^3J=7.0 Hz, 2H), 7.38 (m, 3H), 7.51 (m, 2H), 10.74 ppm (brs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.0, 14.6, 59.8, 65.0, 96.8, 128.1, 129.0, 129.3, 129.5, 147.3, 163.2, 163.3 ppm; HRMS: *m/z*: calcd for $C_{14}H_{16}N_2O_3$+H: 261.1239; found: 261.1228.

Preparation of ethyl 3-ethoxy-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (21): This compound was obtained from compound **14c**, by using the procedure described for **20**, as an oil that slowly solidified in 75% yield after a purification by chromatography over silica gel (dichloromethane/ethanol 99:1). M.p. 111°C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.22 (t, ^3J=7.0 Hz, 3H), 1.31 (t, ^3J=7.0 Hz, 3H), 4.15 (q, ^3J=7.0 Hz, 2H), 4.48 (q, ^3J=7.0 Hz, 2H), 7.28 ppm (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=13.9, 14.8, 59.7, 65.1, 100.1, 125.1, 127.2, 127.9, 128.7, 128.9, 129.8, 130.4, 139.2, 144.4, 162.7, 162.8 ppm; HRMS: *m/z*: calcd for $C_{20}H_{20}N_2O_3$+H: 337.1552; found: 337.1545.

Preparation of compounds 26 and 27: Compound **25** was prepared as described from diethylmalonate (5 g, 0.312 mol).[26] However, despite repeated trials, in our hands, the batches prepared still contained 12 mol% of ethyl phenylacetate and 12 mol% of unreacted diethyl malonate. The batches were used without further purification. Thus, such a batch and hydrazine hydrochloride (0.032 mol, 2.2 g) were dissolved in ethanol (150 mL) and heated to reflux for 6 h. The resulting suspension was concentrated to dryness, dispersed in water, made basic with solid sodium hydrogenocarbonate, and extracted with ethyl acetate (400 mL). The organic layer was washed with a saturated solution of sodium hydrogenocarbonate, washed with brine, and then dried over sodium sulfate. The mixture was then concentrated to dryness and the residue purified by chromatography (dichloromethane/ethanol 97.5:2.5 to 95:5) to yield, in this order, compound **27** (2.30 g, 27% from the starting diethyl malonate) and then the known[26] compound **26** (1.08 g, 13.8% from the starting diethyl malonate). An additional amount of compound **26** (1.5 g, 20.2% from the starting diethyl malonate) was obtained by acidification of the aqueous phase with concentrated hydrochloric acid and then filtration of the resulting precipitate, which was washed with water and dried under vacuum.

*Ethyl 5-benzyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**26**)*: Analytical data are identical with those reported.[26]

*Ethyl 3-ethoxy-5-benzyl-1*H*-pyrazole-4-carboxylate (**27**)*: M.p. 103°C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.22 (t, ^3J=7.0 Hz, 3H), 1.31 (t, ^3J=7.0 Hz, 3H), 4.18 (m, 6H), 7.20 (m, 5H), 8.70 ppm (brs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.3, 14.6, 32.7, 59.8, 64.9, 97.0, 127.2, 128.9, 129.0, 135.9, 147.6, 163.1, 163.4 ppm; HRMS: *m/z*: calcd for $C_{15}H_{18}N_2O_3$+H: 275.1396; found: 275.1360.

Preparation of 5-benzyl-3-ethoxy-1*H*-pyrazole (28)

*By decarboxylation of **27***: In a Teflon flask, compound **27** (1.32 g, 4.81 mol) was dispersed in a mixture of water/ethanol 1:2 (45 mL) containing sodium hydroxide (5 g, 0.12 mol). This was heated at 110°C under an inert atmosphere for 16 h and then diluted in water. The aqueous phase was extracted with dichloromethane, the organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness to yield compound **28** as described below (0.83 g, 85%).

*Alternative preparation of **28** by a Negishi reaction*: In a glass tube sealable with a teflon-coated joint, compound **13** (0.35 g, 1.49 mmol) was degassed with argon. A 0.5 M solution of benzylzincbromide in THF (4.47 mmol, 9 mL) was added, followed by [1,1′-bis(diphenylphosphino)-ferrocene] dichloropalladium complexed with dichloromethane (0.06 g, 0.074 mmol). This mixture was sealed and heated at 85°C for 6 h by using an oil bath. After cooling to room temperature, the resulting mixture was diluted in ethyl acetate, washed with a 0.25 N solution of potassium sodium tartrate twice and water once, dried over sodium sulfate, and concentrated to dryness. The residue was purified by chromatography over silica gel (dichloromethane/ethanol 99:1) to yield compound **28** (0.19 g, 63%) as colorless crystals. M.p. 96°C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.38 (t, ^3J=7.1 Hz, 3H), 3.96 (s, 2H), 4.17 (q, ^3J=7.1 Hz, 2H), 5.54 (s, 1H), 7.28 ppm (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.8, 32.8, 65.0, 89.6, 126.9, 128.7, 128.8, 137.2, 144.5, 163.2 ppm; HRMS: *m/z*: calcd for $C_{12}H_{14}N_2O$+H: 203.1184; found: 203.1135.

Preparation of 1,4-diphenyl-1*H*-pyrazol-3(*2H*)one (29): In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, the ethoxypyrazole **19** (0.1 g, 1 mmol) was degassed with argon. Following this, 33% hydrogen bromide in acetic acid (1.0 mL) was added, the tube was tightly closed and was heated at 140°C for 4 h. The resulting reaction mixture then precipitated in water to give compound **29** (0.074 g, 83%) as a white powder. M.p. 195°C (lit.: 202[38] or 205°C[39]); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ=7.17 (m, 2H), 7.43 (m, 2H), 7.39 (m, 2H), 7.47 (m, 2H), 7.77 (m, 4H), 8.76 (s, 1H), 10.93 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): δ=109.0, 117.2, 125.3, 125.9, 126.0, 126.1, 128.9, 129.9, 132.4, 140.0, 160.4 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{12}N_2O$+H: 237.1028; found: 237.1043.

Preparation of 1,5-diphenyl-1*H*-pyrazol-3(*2H*)one (30): In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, a mixture of compound **21** (0.062 g, 0.23 mmol) was degassed with argon. Following this, 33% hydrogen bromide in acetic acid (1.0 mL) was added, the tube was tightly closed and was heated at 140°C for 5 h. The resulting suspension was dissolved in ethanol, concentrated to dryness, made basic with ethanolic ammonia, and concentrated to dryness again. The residue was purified by chromatography over silica gel (dichloromethane/ethanol 97:3) to yield compound **30** (0.045 g, 81%) as a white powder. M.p. >250°C (lit.:[40] 257°C); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ=5.94 (s, 1H), 7.15–7.42 (m, 10H), 10.19 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): δ=94.3, 124.5, 126.5, 128.28, 128.31, 128.5, 128.8, 130.4, 139.9, 143.1, 161.7 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{12}N_2O$+H: 237.1028; found: 237.0966.

Preparation of 5-phenyl-1*H*-pyrazol-3(*2H*)one (31): By using the procedure described above for the preparation of **30**, compound **31** was obtained from compound **20** in a 76% yield as a white powder that displayed analytical data identical with that reported.[41] When starting from compound **22**, the heating had to be increased to 23 h to yield compound **31** in a similar 72% yield.

Preparation of 5-benzyl-1*H*-pyrazol-3(*2H*)one (32): The procedure described for compound **30** was used to prepare **32**, although the heating time had to be extended to 23 h for complete conversion. Compound **32** was thus obtained as a solid in a 60% yield after chromatography over silica gel (dichloromethane/ethanol 95:5 to 9:1). M.p. 184°C (lit.:[42] 192°C); ^{1}H NMR (400 MHz, [D$_6$]DMSO, TMS): δ=3.79 (s, 2H), 5.21 (s, 2H), 7.20 (m, 3H), 7.30 ppm (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, TMS): δ=30.7, 88.6, 119.5, 128.3, 139.3, 143.1, 160.6 ppm; HRMS: *m*/*z*: calcd for $C_{10}H_{10}N_2O$+H: 175.0871; found: 175.0856.

Preparation of compounds 33a,b and 34a,b: The protocol described for the preparation of compound **8** was used. The resulting organic extract was further purified by chromatography as described below.

*Ethyl 1-benzyl-3-ethoxy-1*H*-pyrazole-4-carboxylate (**33a**)*: Oil; yield: 5.7% after chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 97.5:2.5 to 95:5); ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.31 (t, ^3J=7.1 Hz, 3H), 1.44 (t, ^3J=7.1 Hz, 3H), 4.23 (q, ^3J=7.1 Hz, 2H), 4.33 (q, ^3J=7.1 Hz, 2H), 5.11 (s, 2H), 7.23 (m, 1H), 7.35 (m, 3H), 7.64 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.4, 14.7, 56.2, 59.8, 65.2, 99.9, 127.9, 128.3, 128.9, 134.2, 135.3, 162.1, 162.6 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{18}N_2O_3$+Na: 297.1215; found: 297.1219.

*Ethyl 1-benzyl-5-ethoxy-1*H*-pyrazole-4-carboxylate (**34a**)*: Oil; yield: 22% after chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 97.5:2.5 to 95:5); ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.24 (m, 6H), 4.18 (q, ^3J=7.1 Hz, 2H), 4.31 (q, ^3J=7.1 Hz, 2H), 5.09 (s, 2H), 7.22 (m, 5H), 7.72 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.4, 15.3, 51.1, 59.9, 71.7, 99.4, 127.5, 127.9, 128.7, 136.3, 141.2, 154.7, 162.4 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{18}N_2O_3$+H: 275.1396; found: 275.1345.

*Ethyl 3-ethoxy-1-methyl-1*H*-pyrazole-4-carboxylate (**33b**)*: Oil; yield: 17%; crystallizes after a chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 95:5 to 4:1); ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.27 (t, ^3J=7.1 Hz, 3H), 1.41 (t, ^3J=7.1 Hz, 3H), 3.72 (s, 3H), 4.24 (q, ^3J=7.1 Hz, 2H), 4.28 (q, ^3J=7.1 Hz, 2H), 7.63 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.4, 14.7, 39.3, 59.7, 65.1, 99.3, 134.9, 162.1, 162.5 ppm; HRMS: *m*/*z*: calcd for $C_9H_{14}N_2O_3$+H: 199.1083; found: 199.1046.

*Ethyl 5-ethoxy-1-methyl-1*H*-pyrazole-4-carboxylate (**34b**)*: Oil; yield: 17% after chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 95:5 to 4:1); ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=1.35 (t, ^3J=7.1 Hz, 3H), 1.41 (t, ^3J=7.0 Hz, 3H), 3.68 (s, 3H), 4.27 (q, ^3J=7.1 Hz, 2H), 4.48 (q, ^3J=7.0 Hz, 2H), 7.76 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ=14.4, 15.4, 34.1, 59.9, 71.6, 99.3, 140.7, 154.7, 162.4 ppm; HRMS: *m*/*z*: calcd for $C_9H_{14}N_2O_3$+H: 199.1083; found: 199.1001.

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