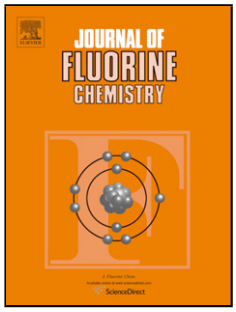

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New synthetic access to 3-fluoroalkyl-5-pyrazolecarboxylates and carboxylic acids

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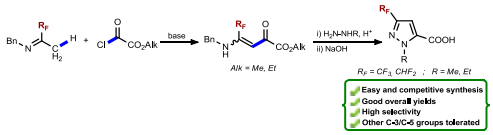
Graphical abstract



The synthesis of 3-fluoroalkyl-5-pyrazolecarboxylic acids was achieved by means of an optimised 3-step sequence from fluoroalkyl methylketones and alkyl oxalyl chlorides.

Highlights

- Convenient alternative to the scarce known methods to prepare 3-fluoroalkyl-5-pyrazolecarboxylates.
- Efficient and atom-economical synthesis of up to 18 compounds.
- Novel access to fluorinated and non-fluorinated vinamides with no precedents in the literature.
- Highly regioselective cyclization for the synthesis of 3,5-disubstituted pyrazoles.
- Easy setups, economical reagents and versatile tolerance to various functionalities.

Abstract

A novel process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates and carboxylic acids is hereby presented. Easily accesible α-fluorinated ketimines were condensed with oxalyl monochloride derivatives, and the obtained vinamides underwent acid-catalyzed cyclization with substituted hydrazines. This highly efficient protocol can also be used for non-fluorinated C-3 and C-5 substituents.

Keywords

• Fluorinated pyrazole • 3,5-disubstitution • Vinamide • Cyclization

1. Introduction

Pyrazoles conform a family of heterocyclic compounds with an important significance in chemistry, having been extensively reviewed by the scientific community [1]. Among the vast variety of related derivatives, (polyfluoroalkyl)pyrazolecarboxylic acids can certainly be highlighted as a group of molecules with high synthetic value as building blocks in the construction of bioactive molecules. This scaffold can be nowadays found in the structure of compounds with various roles, such as fungicides (Bixafen) [2], acaricides (Tebufenpyrad analogues) [3] or antivirals (AS-136A) [4]. The importance of this motif for the final properties of these and other active ingredients renders the study for new and more efficient synthetic methods highly interesting for the scientific community.

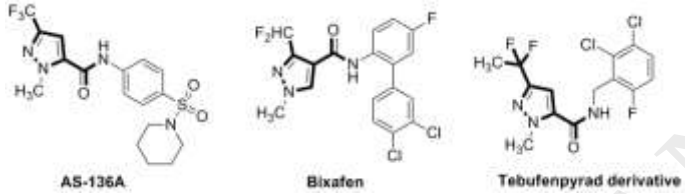
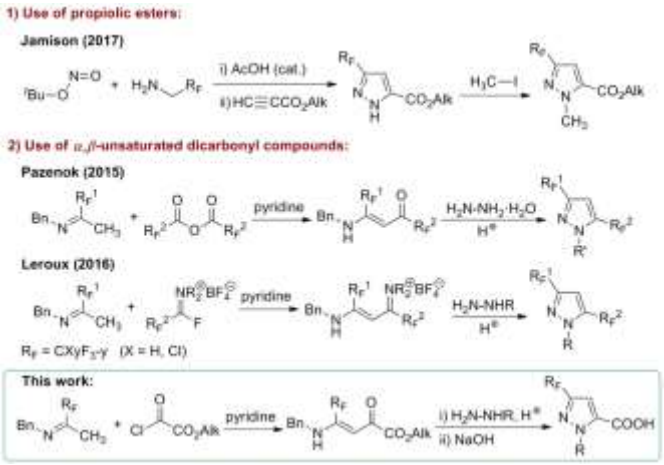


Figure 1. Examples of polyfluorinated pyrazolecarboxylic acid derivatives with bioactive properties.

Up to date, a variety of methods for the preparation of polyfluoroalkylated pyrazolecarboxylate species can be found in the literature, commonly proceeding through the reaction of appropriately substituted dicarbonyl compounds with hydrazine derivatives [5,6,7]. Among this vast literature, however, only a few reports for the preparation of 3-fluoroalkyl-5-pyrazolecarboxylates are available [7d,8], which is somehow surprising considering their outstanding nature and properties (common presence in biologically active chemicals [9], suitability for C-4 functionalisation...) [10]. These compounds are commonly prepared *via* the [3+2] cycloaddition of nitrilimines and propiolic esters [6m,8a,8d-f], or the cyclocondensation of *α,β*-unsaturated dicarbonyl compounds and hydrazines [8c]. The first strategy has been predominantly chosen for this synthesis, and even reports on flow synthesis conditions are available (Jamison and co-workers, **Scheme 1**) [8e]. However, the described methodologies still present inconveniences, such as long reaction times, moderate selectivities and a limited number of substrates due to their price and stability (*e.g. β*-fluoroamines).

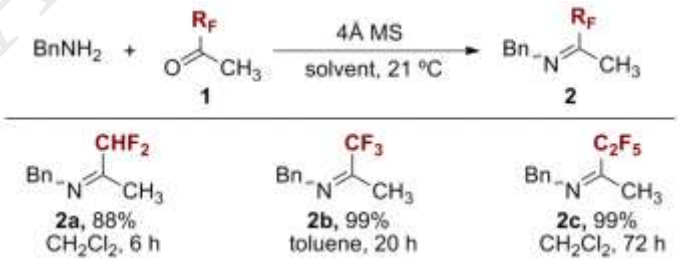


Scheme 1. Some methodologies for the synthesis of 3-fluoroalkyl-5-pyrazolecarboxylates and proposed approach.

In response to this need for more optimal routes, our most recent work in the assembly of fluorinated heterocycles was considered. Encouraged by the recent work of Pazenok and Lui with perfluoroalkyl anhydrides [8c], a new methodology employing Fluoroalkyl Amino Reagents (FARs) was developed and afforded access to 3,5-bis(fluoroalkyl)pyrazoles (**Scheme 1**) [11], resulting in a novel, efficient and industrially scalable alternative for the introduction of F-containing motifs in pyrazoles. However, the introduction of a C-5 carboxylate functionality was not investigated at the time. In order to explore this synthetic gap, and following an analogous approach to the aforementioned one, it is proposed that perfluoroalkyl vinamides appropriately substituted on the C-end by a carboxylate function, could afford the desired 3-polyfluoroalkyl-5-pyrazolecarboxylates after cyclisation in the presence of monosubstituted hydrazines (**Scheme 1**). These vinamides could be accessed through simple condensation of α-fluoroalkylated ketimines with oxalic acid derivatives under basic conditions. All reagents are commercially available and fairly economical, and the pretty straightforward reaction setups could prove being competitive for the preparation of these targets.

2. Results and discussion

To validate the proposed synthetic scheme, the accessibility to the required vinamides was first assessed. The preparation of the necessary *N*-benzylketimines was carried out by adapting a literature procedure which reacts fluorinated methyl ketones and amines in the presence of activated 4Å Molecular Sieves [12]. Using this protocol, three *N*-benzyl fluoroalkyl methylketones (**2a-c**) were successfully isolated as stable upon storage liquids in excellent yields (**Scheme 2**; for detailed experimental information, see the "Experimental" section).

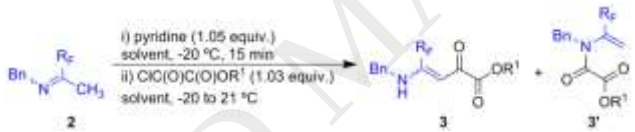


Reaction conditions: **1** (1.00-2.93 equiv.), Bn-NH_2 (1.00 equiv.), 4Å MS (1.00 g per mmol of **1**), 21 °C, 6-72 h.

Scheme 2. Synthesis of starting ketimines (**2**)

The reaction of the prepared ketimines with acyl electrophiles was next studied, employing an analogous procedure to that used in the case of FARs [11]. Substrates **2a-c** were reacted with alkyl oxalyl chlorides in the presence of pyridine as base; gratifyingly, under these conditions, **2a** and **2b** substrates could be successfully converted to their corresponding vinamides (**3**, **Table 1**). The main side product in the reaction was confirmed as the *N*-acylation species (**3'**, **Table 1**), with the ratio **3:3'** being strongly dependant on the substrate and reaction conditions (for the complete experimental optimisation, see the "Experimental" section). A pre-stirring time with pyridine of 15 minutes was generally employed for optimal results [13], while longer times led to higher percentages of **3'**. While CH_2Cl_2 was proven to be a suitable solvent for the reaction, the use of THF allowed for the two-fold reduction of the reaction times, thus increasing the selectivity towards **3**. Interestingly, during the solvent scope it was acknowledged that isopropyl acetate (lately included in a privileged selection of desirable green solvents for synthesis) [14], afforded similar reactivity and selectivity to THF, highlighting the interest of this route for its application in industrial scale. In the case of **2c**, despite many attempts towards the isolation of the major species observed by ^{19}F NMR monitoring, no expected product could be isolated [15].

Table 1. Synthesis of vinamides (**3**)[a]



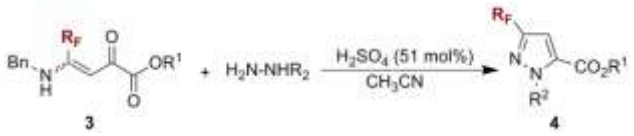
Entry	R_F	R^1	Solvent	*t* (h)	Product	3:3' [b]	Yield (%)[c]
1	CHF_2	Et	CH_2Cl_2	18	**3a**	61:39	64
2	CF_3	Me	CH_2Cl_2	18	**3b**	81:19	49
3	C_2F_5	Et	THF	72	**3c**	---	0[d]

[a] See the "Experimental" section for a detailed optimisation of reaction conditions. [b] Product ratio obtained in the crude reaction mixture according to ^1H NMR integration ratio. [c] Isolated yield of 3. [d] Decomposition observed.

Investigating the reaction conditions for the cyclisation of these vinamide intermediates was the next step of the present work. In a similar fashion to previous work [8c], the use of monosubstituted hydrazines under acidic conditions allowed the smooth conversion of substrates **3a** and **3b** into their corresponding 3-(polyfluoroalkyl)-5-pyrazolecarboxylates (**4**, **Table 2**). Both methyl- and phenylhydrazine were used as cyclization partners, and the products were cleanly isolated in yields of up to 81% (for the complete experimental information, see the "Experimental" section). In all tested examples, the 3-fluoroalkyl-5-carboxylate was the major isolated compound, thus highlighting the good selectivity of this method. While most compounds were directly obtained as pyrazoles, **4d** could only be isolated after dehydrating the 5-hydroxypyrazoline intermediate in the presence of a pyridine/$SOCl_2$ mixture, reflecting difficult OH elimination from the carbon attached to the strong electron

withdrawing CF_3-group. This species could not be detected in the other products, where spontaneous dehydration occurred either during the reaction or the silica gel purification.

Table 2. Acid-promoted cyclization of vinamides **3**.[a]

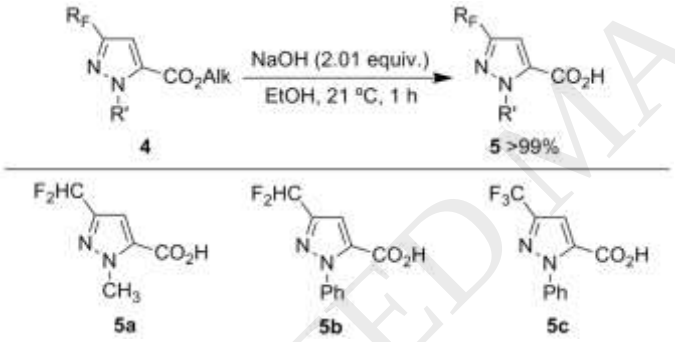


3 4

Entry	R_F	R^1	R^2	Product	*T* (°C)	*t* (h)	Yield (%)[b]
1	CHF_2	Et	Me	**4a**	21	1	63
2	CF_3	Me	Me	**4b**	85	1	(99)[c]
3	CHF_2	Et	Ph	**4c**	85	16	81
4	CF_3	Me	Ph	**4d**	85	16	64

[a] *Reaction conditions:* 3 (1.00 equiv.), substituted hydrazine (1.57 equiv.), H_2SO_4 (51 mol%), CH_3CN (0.4 M), 21-85 °C, 1-16 h. [b] Isolated yields. [c] ^{19}F NMR yield (using fluorobenzene as internal standard).

With these esters in hand, simple hydrolysis could be performed in order to obtain the related carboxylic acids. Although acidic conditions can also be used for this step, basic hydrolysis using NaOH in EtOH at 21 °C proved to be a suitable method for the quantitative conversion of all prepared esters into their corresponding pyrazolecarboxylic acids within 1 h (**5**, **Scheme 3**).

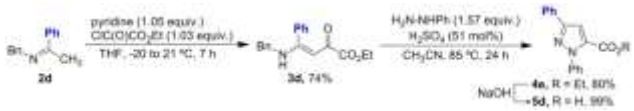


Reaction conditions: **4** (1.00 equiv.), NaOH (2.01 equiv.), EtOH, 21 °C, 1 h.

Scheme 3. Hydrolysis of 3-fluoroalkyl-5-pyrazolecarboxylates (**5**)

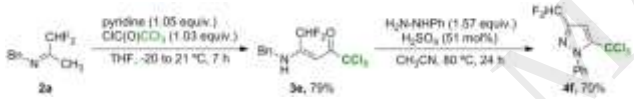
To further evaluate the utility of this synthetic route, it was suggested that variations of the employed reagents could allow the introduction of new C-3 and C-5 functionalities in the final pyrazoles, expanding its applicability. Two different examples were studied to assess this statement. First, the possibility to introduce other C-3 functionalities was tested by replacing polyfluorinated methyl ketones with acetophenone as starting material. After the isolation of the corresponding ketimine **2d** in 98% yield after 5 days at 21 °C in CH_2Cl_2 as solvent, this compound was further subjected to the optimised conditions for vinamide synthesis using THF as solvent. To our delight, the corresponding phenyl-substituted analogue **3d** was formed and could be isolated in 74% yield after standard workup techniques (**Scheme 4**). As with previous substrates, the main side species was the related *N*-acylation product (**3d'**), with all attempts to suppress its formation being unsuccessful. This compound was nevertheless isolated and fully characterised for further reference. Finally, the cyclisation of **3d** under acidic conditions was also possible, being complete after 24 h at 85 °C using phenylhydrazine, and obtaining the

corresponding product **4e** in 80% isolated yield (**Scheme 4**). This ester could be indeed quantitatively hydrolysed using the previously described conditions, and its related carboxylic acid **5d** could be cleanly isolated.



Scheme 4. Synthesis of non-fluorinated heterocycles: 3-phenyl-5-pyrazolecarboxylate **4e** and carboxylic acid **5d**.

Alternatively, exchanging the carbonyl electrophile employed in the condensation step was also evaluated as a way to provide access to a broader range of C-5 functionalities. Indeed, when the alkyl oxalyl monochloride derivatives were replaced with 2,2,2-trichloroacetyl chloride [16], the use of the optimised conditions for vinamide synthesis using THF as solvent proved being similarly effective. Full conversion of **2a** into a species identified as the corresponding vinamide **3e** was observed (**Scheme 5**), isolating this compound in 79% yield. Next, and upon treatment with phenyl hydrazine at 80 °C for 24 h, **3e** was successfully transformed into the CCl_3-functionalised pyrazole **4f** in 70% yield. Both steps proceeded efficiently in terms of reactivity, again with a significant preference for the 3-fluoroalkyl species. This provides an example of the exploitability of this approach, considering the significant variety of accessible acyl chloride derivatives in the market, and could definitely be a powerful synthetic tool for the preparation of 5-substituted pyrazoles.



Scheme 5. Synthesis of non-carboxylated pyrazoles: 3-fluoroalkyl-5-trichloromethyl pyrazole **4f**.

3. Conclusions

In conclusion, a new and facile methodology for the synthesis of 3-fluoroalkyl-5-pyrazolecarboxylates and carboxylic acids is hereby disclosed. This 3-step reaction sequence displays high efficiency using simple reagents and can be highlighted as a very convenient alternative to other known methods for the preparation of these scaffolds. Moreover, non-fluorinated substituents in either C-3 or C-5 position of the pyrazole ring are also well tolerated, increasing its applicability in organic synthesis.

4. Experimental

4.1. General methods

Solvents were purified and dried following standard procedures, and stored over 4Å Molecular Sieves upon convenience. Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, diethyl ether, toluene, and ethyl acetate) were used as received, without further purification. All reagents were purchased from standard commercial suppliers and used without further purification. All reactions were carried out in air, unless stated otherwise. Purification by flash column chromatography was performed

using silica gel 60 (40-63 μm, 230-400 mesh, ASTM). ^{1}H, ^{13}C-{^{1}H} and ^{19}F-{^{1}H} Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance 300 or 400 MHz spectrometers, using the residual solvent peak as reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm ; d6-DMSO: δ_H = 2.50 ppm, δ_C = 39.52 ppm). NOESY (Nuclear Overhauser Effect Spectroscopy) spectra were recorded on a Bruker Avance 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). The following abbreviations are used in the characterization details: s = singlet, s br = broad singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. High Resolution Mass Spectrometry (HRMS, accuracy ≤ 15 ppm) and elemental analyses were performed by the Analytical Facility at the University of Strasbourg.

4.2. General procedure for the synthesis of imines 2a-d

To a mixture of the corresponding fluoroalkyl methylketone (1.00 mol, 1.00 equiv.) in CH_2Cl_2 or toluene (0.5 mL), benzylamine (107 g, 1.00 mol, 1.00 equiv.) was slowly added at 10 °C, and the reaction mixture was stirred at the corresponding temperature and time. The solvent was removed under vacuum to yield the corresponding (fluoroalkyl-2-ylidene)benzylamines.

***N*-(1,1-difluoropropan-2-ylidene)benzylamine (2a)**
Pale oil (88% yield).
^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.41-7.29 (m, 5H, CH_{Ar}), 5.99 (t, 1H, $^{2}J_{H-H}$ = 55.6 Hz, CHF$_2$), 4.60 (s, 2H, CH_2N) , 2.00 (s, 3H, CH_3).
^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 163.1 (t, 1C, $^{2}J_{C-F}$ = 28.5 Hz, *C*=N), 138.7 (s, 1C, *C*CH$_2$), 128.7 (s, 2C, *C*H$_{Ar}$), 127.8 (s, 2C, *C*H$_{Ar}$), 127.2 (s, 1C, *C*H$_{Ar}$), 115.7 (t, $^{1}J_{C-F}$ = 243 Hz, CHF$_2$), 55.2 (s, 1C, CH$_2$), 11.3 (s, 1C, CH$_3$).
^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) **=** -120.6 (tt, 2F, $^{2}J_{F-H}$ = 56 Hz, $^{4}J_{F-H}$ = 3 Hz, CHF_2).

***N*-(1,1,1-Trifluoropropan-2-ylidene)benzylamine (2b)**
Colourless oil (99% yield).
^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.37-7.30 (m, 5H, CH_{Ar}), 4.67 (s, 2H, CH_2N), 2.12 (s, 3H, CH_3).
^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 157.1 (q, 1C, $^{2}J_{C-F}$ = 33.5 Hz, *C*=N), 138.0 (s, 1C, C_{Ar}), 128.7 (s, 2C, *C*H$_{Ar}$), 127.7 (s, 2C, *C*H$_{Ar}$), 127.3 (s, 2C, *C*H$_{Ar}$), 119.9 (q, 1C, $^{1}J_{C-F}$ = 278 Hz, CF_3), 55.2 (s, 1C, NCH$_2$), 13.0 (s, 1C, CH$_3$).
^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) **=** -74.6 (t, 3F, $^{4}J_{F-H}$ = 1.6 Hz, CF_3).

***N*-(3,3,4,4,4-Pentafluorobutan-2-ylidene)benzylamine (2c)**
Pale yellow oil (99% yield) (1:99, *Z*:*E*).
^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.29-7.26 (m, 2H, CH_{Ar}), 7.25-7.18 (m, 3H, CH_{Ar}) 4.61 (s, 2H, CH_2), 2.03 (s, 3H, CH_3).
^{13}C-{^{1}H} NMR (125 MHz, $CDCl_3$, 298K): δ (ppm) = 158.3 (t, 1C, $^{2}J_{C-F}$ = 26.7 Hz, *C*=N), 138.2 (s, 1C, C_{Ar}), 128.7 (s, 2C, *C*H$_{Ar}$), 127.4 (s, 2C, *C*H$_{Ar}$), 127.2 (s, 1C, C_{Ar}), 118.9 (qt, 1C, $^{1}J_{C-F}$ = 286.4 Hz, $^{2}J_{C-F}$ = 35 Hz, CF_2CF_3), 110.4 (tq, 1C, $^{1}J_{C-F}$ = 255.5 Hz, $^{2}J_{C-F}$ = 36.3 Hz, CF_2CF_3), 55.6 (s, 1C, *C*H$_2$N), 13.3 (s, 1C, *C*H$_3$).
^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) **=** -81.3 (s, 3F, CF_3), -118.2 (s, 2F, CF_2).

***N*- (1-Phenylethylidene)benzylamine (2d)**

Brown oil (98% yield) (8:92, *Z:E*).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.90-7.85 (m, 2H, CH_{Ar}), 7.52-7.33 (m, 8H, CH_{Ar}), 4.75 (s, 2H, CH_2), 2.34 (s, 3H, CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 166.1 (s, 1C, *C*=N), 141.2 (s, 1C, C(N)C_{Ar}), 140.7 (s, 1C, CCH_2), 129.7 (s, 1C, CH_{Ar}), 128.5 (s, 2C, CH_{Ar}), 128.3 (s, 2C, CH_{Ar}), 127.8 (s, 2C, CH_{Ar}), 126.9 (s, 2C, CH_{Ar}), 126.7 (s, 1C, CH_{Ar}), 55.82 (s, 1C, CH_2), 16.0, (s, 1C, CH_3).

4.3. General procedure for the synthesis of vinamides 3a-d

A solution of the ketimine (1.00 equiv.) in the appropriate solvent (approx. 2M) was cooled to -20 °C. Pyridine (1.05 equiv.) was then added, and the mixture was stirred at -20 °C for 15 minutes (in the case of the use of THF as solvent, no additional stirring time was required at this stage). A solution of ethyl oxalyl chloride (1.03 equiv.) in the solvent (1.00-1.50 M) was then added dropwise. The mixture was left to evolve from -20 °C to 21 °C under stirring over a period of 7-18 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through cotton, and the resulting filtrate was concentrated to dryness under vacuum. The crude residue was purified by flash chromatography to yield the desired compound.

Ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (3a)

CH_2Cl_2 as solvent, 18 h. Purification by flash chromatography (Cyclohexane:AcOEt, 100:0 to 85:15). Orange oil (61% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 10.91 (s br, N*H*), 7.39-7.28 (m, 5*H*, Phenyl), 6.18 (t, C*H*F_2, $^{4}J_{H\text{-}H}$ = 53 Hz), 6.17 (s, C*H*CO), 4.66 (d, CH_2NH), 4.31 (q, OCH_2), 1.36 (t, OCH_2CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 180.2 (s, 1C, *C*(O)COOEt), 162.6 (s, 1C, *C*(O)OEt), 156.8 (t, 1C, $^{2}J_{H\text{-}F}$ = 22 Hz, *C*CHF_2), 136.2 (s, 1C, C_{Ph}), 129.2(s, 2C, CH_{Ph}), 128.3(s, 2C, CH_{Ph}), 127.3 (s, 1C, CH_{Ph}), 111.4 (t, $^{1}J_{H\text{-}F}$ = 245 Hz, *C*HF_2), 91.4 (t, 1C, $^{3}J_{C\text{-}F}$ = 7 Hz, *C*HCO), 62.2 (s, 1C, OCH_2), 48.2 10 (s, 1C, CH_2NH), 14.1 (s, 1C, OCH_2CH_3).

^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) **=** -118.9 (d, 2F, $^{2}J_{H\text{-}F}$ = 53 Hz, CHF_2).

Anal. calcd for $C_{14}H_{15}F_2NO_3$: C, 59.36; H, 5.34; F, 13.41; N, 4.94; O, 16.94. Found: C, 59.16; H, 5.36; N, 4.95.

Methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (3b)

CH_2Cl_2 as solvent, 18 h. Purification by flash chromatography (Cyclohexane:AcOEt, 100:0 to 90:10). Colourless oil (49% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 11.02 (s br, N*H*), 7.40-7.28 (m, 5*H*, Ph), 6.40 (s, 1H, C*H*CO), 4.64 (d, 2H, CH_2NH), 3.87 (s, 3H, COOCH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 180.3 (s, 1C, CH*C*O), 162.7 (s, 1C, *C*OOMe), 152.6 (q, 1C, $^{2}J_{C\text{-}F}$ = 32.5 Hz, *C*CF_3), 135.8 (s, 1C, C_{Ph}), 129.3 (s, 2C, CH_{Ph}), 128.5 (s, 2C, CH_{Ph}), 127.4 (s, 1C, CH_{Ph}), 119.6 (q, 1C, $^{1}J_{C\text{-}F}$ = 278 Hz, *C*F_3), 90.4 (q, 1C, $^{3}J_{C\text{-}F}$ = 5 Hz, *C*HCO), 53.1 (s, 1C, COOCH_3), 49.0 (s, 1C, CH_2NH).

^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) **=** -66.6 (s, 3F, CF_3).

HRMS (ESI) - calcd for $C_{13}H_{12}F_3NNaO_3$ [M+Na]: 310.0661. Found: 310.0635.

Ethyl 4-(benzylamino)-2-oxo-4-phenylbut-3-enoate (3d)

THF as solvent, 7 h. Purification by column chromatography (pentane:AcOEt, 80:20 to 70:30). Orange oil (86% yield) (mixture of *Z:E* isomers, ratio not determined).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 11.83 (s br, 1H, N*H*), 7.54-7.07 (m, 10*H*, CH_{Ar}), 5.98 (s, 1H, C*H*CO), 4.48 (d, 2H, $^{3}J_{H\text{-}H}$ = 6.4 Hz, CH_2NH), 4.30 (q, 2H, $^{3}J_{H\text{-}H}$ = 7.1 Hz, OCH_2), 1.36 (t, 3H, $^{3}J_{H\text{-}H}$ = 7.1 Hz, OCH_2CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 177.3 (s, 1C, *C*=O), 169.7 (s, 1C, *C*(O)OEt), 164.1 *C*Ph_{vinyl}), 137.3 (s, 1C, *C*$_{Ph}$), 134.2 (s, 1C, *C*$_{Ph}$), 130.4 (s, 1C, *C*H$_{Ph}$), 129.0 (s, 2C, *C*H$_{Ph}$), 128.9 (s, 2C, *C*H$_{Ph}$), 127.9 (s, 1C, *C*H$_{Ph}$) , 127.7 (s, 2C, *C*H$_{Ph}$), 127.0 (s, 2C, *C*H$_{Ph}$), 95.0 (s, 1C, *C*HCO), 61.8 (s, 1C, O*C*H_2), 49.0 (s, 1C, *C*H_2NH), 14.3 (s, 1C, OCH_2CH_3).

HRMS (ESI) - calcd for $C_{19}H_{19}NO_3Na$ [M+Na]: 332.1257. Found: 332.1232.

Ethyl 2-(benzyl(1-phenylvinyl)amino)-2-oxoacetate (3d')

Isolated as a side species from the synthesis of **3d**. Viscous orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.48-7.40 (m, 5H, CH_{Ar}), 7.30-7.27 (m, 3*H*, CH_{Ar}), 7.19-7.17 (m, 2H, CH_{Ar}), 5.32 (s, 1H, C$H_{2,vinyl}$), 4.90 (s, 1H, C$H_{2,vinyl}$), 4.61 (s, 2H, CH_2Ph), 4.19 (q, 2H, $^{3}J_{H\text{-}H}$ = 7.2 Hz, CH_2CH_3), 1.17 (t, 3H, $^{3}J_{H\text{-}H}$ = 7.1 Hz, CH_2CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 162.8 (s, 1C, *C*=O), 162.3 (s, 1C, *C*OOMe), 145.5 (s, 1C, N*C*CH_2), 135.8 (s, 1C, *C*$_{Ar}$), 134.6 (s, 1C, *C*$_{Ar}$), 129.7 (s, 1C, *C*H$_{Ar}$), 129.3 (s, 2C, *C*H$_{Ar}$) 128.9 (s, 2C, *C*H$_{Ar}$), 128.6 (s, 2C, *C*H$_{Ar}$), 127.9 (s, 1C, *C*H$_{Ar}$), 127.5 (s, 2C, *C*H$_{Ar}$), 114.7 (s, 1C, *C*$H_{2,vinyl}$), 62.0 (s, 1C, *C*H_2CH_3), 48.4 (s, 1C, *C*H_2N), 13.8 (s, 1C, CH_2CH_3).

HRMS (ESI) - calcd for $C_{19}H_{19}NO_3Na$ [M+Na]: 332.1257. Found: 332.1255.

4.4. Procedures for the synthesis of pyrazoles 4a-f.

Ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (4a): To a solution of ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (3a, 363 mg, 1.78 mmol, 1.00 equiv.) in CH_3CN (4.00 mL) was added methylhydrazine (129 mg, 2.79 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (0.05 mL, 0.91 mmol, 0.51 equiv.) under argon. The reaction mixture was stirred at 21 °C for 1 h and was then diluted with CH_2Cl_2 (5.00 mL), filtered through cotton and concentrated to dryness under vacuum. The crude product was purified by flash chromatography (pentane:Et_2O, 100:0 to 60:40), and afforded ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (**4a**) as a colourless oil (230 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.04 (t, 1H, $^{4}J_{H\text{-}H}$ = 1 Hz, 4-C*H*), 6.66 (t, 1H, $^{2}J_{H\text{-}F}$ = 55 Hz, C*H*F_2), 4.36 (q, 2H, O*C*H_2), 4.19 (s, 3H, CH_3), 1.38 (t, 3H, OCH_2CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 159.4 (s, 1C, *C*=O), 145.1 (t, 1C, $^{2}J_{C\text{-}F}$ = 29.8 Hz, *C*CHF_2), 134.0 (s, 1C, *C*COOEt), 110.8 (t, 1C, $^{1}J_{C\text{-}F}$ = 234 Hz, *C*HF_2), 108.7 (s, 1C, 4-*C*H), 61.5 (s, 1C, O*C*H_2), 40.1 (s, 1C, N*C*H_3), 14.3 (s, 1C, OCH_2CH_3).

^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) = -112.1 (d, 2F, $^{2}J_{H\text{-}F}$ = 55 Hz, CH*F*$_2$).

HRMS (ESI) - calcd for $C_8H_{11}F_2N_2O_2$ [M+H]: 205.0783. Found: 205.0782.

Methyl 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (4b): To a solution of methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (3b, 150 mg, 0.47 mmol, 1.00 equiv.) in CH_3CN (1.00 mL) was added methylhydrazine (34.2 mg, 0.74 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (13.0 µL, 0.24 mmol, 0.51 equiv.) under argon. The reaction mixture was stirred at 90 °C for 1 h and was then removed from the oil bath for 5 min. Pyridine (305 µL, 3.77 mmol, 8.02 equiv.) was added, followed by $SOCl_2$ (70.0 µL, 0.97 mmol, 2.05 equiv.). The mixture was stirred for 30 minutes, and analyzed by NMR using fluorobenzene as an internal standard. Methyl 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (**4b**) was detected but not isolated. ^{19}F NMR yield >99%.

Ethyl 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (4c): To a solution of ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (3a, 420 mg, 1.44 mmol, 1 equiv.) in CH_3CN (3.00 mL) was added phenylhydrazine (0.22 mL, 2.26 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (40.2 µL, 0.73 mmol, 0.51 equiv.) under argon. The reaction mixture was refluxed for 16 h. CH_2Cl_2 (15.0 mL) was added, the mixture filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (cyclohexane:AcOEt, 100:0 to 98:2) to give ethyl 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (**4c**) as an orange oil (310 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.50-7.41 (m, 5*H*, C*H*$_{Ph}$), 7.24 (s, 1H, 4-C*H*), 6.76 (t, 1H, $^2J_{H\text{-}F}$ = 54.9 Hz, C*H*F_2), 4.26 (q, 2H, OC*H*$_2$), 1.26 (t, 3H, OCH_2CH_3).

^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 158.4 (s, 1C, *C*=O), 146.8 (t, 1C, $^2J_{C\text{-}F}$ = 30 Hz, *C*CHF_2), 139.8 (s, 1C, N*C*$_{Ph}$), 135.0 (s, 1C, *C*COOEt), 129.2 (s, 2C, *C*H$_{Ph}$), 128.7 (s, 1C, *C*H$_{Ph}$), 126.0 (s, 2C, *C*$_{Ph}$), 110.7 (t, 1C, $^1J_{C\text{-}F}$ = 234 Hz, *C*HF_2), 109.6 (s, 1C, 4-*C*H), 61.6 (s, 1C, O*C*H_2), 13.9 (s, 1C, OCH_2CH_3).

^{19}F NMR (376 MHz, $CDCl_3$, 298K): δ (ppm) = -112.2 (d, 2F, $^2J_{F\text{-}H}$ = 54.6 Hz, CHF_2,).

HRMS (ESI) - calcd for $C_{13}H_{13}F_2N_2O_2$ [M+H]: 267.0940. Found: 267.0918.

Methyl 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (4d): To a solution of methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (3b, 500 mg, 1.74 mmol, 1 equiv.) in CH_3CN (5.00 mL) was added phenylhydrazine (0.27 mL, 2.73 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (49.0 µL, 0.89 mmol, 0.51 equiv.) under argon. The reaction mixture was refluxed for 16 h. CH_2Cl_2 (20.0 mL) was added, the mixture was refluxed for 2 days and cooled to room temperature. Pyridine (1.10 mL, 13.6 mmol, 7.81 equiv.) was added, followed by slow addition of $SOCl_2$ (410 mg, 0.25 mL, 3.45 mmol, 1.98 equiv.) via syringe. The mixture was stirred for 30 min, then filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (pentane:Et_2O, 100:0 to 95:5), to give methyl 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (**4d**) as a red solid (370 mg, ca. 80wt.% = 300 mg, 64% yield), which was not further purified.

HRMS (ESI) - calcd for $C_{12}H_{10}F_3N_2O_2$ [M+H]: 271.0689. Found: 271.0697.

Ethyl 1,3-diphenyl-1*H*-pyrazole-5-carboxylate (4e): To a solution of ethyl 4-(benzylamino)-2-oxo-4-phenylbut-3-enoate (3d, 250 mg, 0.81 mmol, 1.00 equiv.) in CH_3CN (2.00 mL) was added phenylhydrazine (0.13 mL, 1.27 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (23.0 μL, 0.41 mmol, 0.51 equiv.) under argon. The reaction mixture was stirred at 80 for 24 h, and was then diluted with CH_2Cl_2 (5.00 mL), filtered through Celite® (washing the Celite® pad with 2 x 3 mL CH_2Cl_2). The filtrate was then evaporated under vacuum. The crude was purified by flash chromatography (pentane:AcOEt, 9:1 to 8:2), to give ethyl 1,3-diphenyl-1*H*-pyrazole-5-carboxylate (**4d**) as a pale orange oil (191 mg, 81% yield).
^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.36-7.28 (m, 8*H*, CH_{Ph}), 7.23-7.20 (m, 2H, CH_{Ar}), 7.04 (s, 1H, CH_{pyr}), 4.46 (q, 2H, $^3J_{H-H}$ = 7.1 Hz, OCH_2), 1.42 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, OCH_2CH_3).
^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 162.6 (s, 1C, *C*=O), 144.8 (s, 1C, 3-C), 144.5 (s, 1C, C_{pyr}*C*(Ph)), 139.7 (s, 1C, NC_{Ph}), 129.7 (s, 1C, *C*COOEt), 129.1 (s, 2C, *C*H_{Ph}), 128.9 (s, 2C, *C*H_{Ph}), 128.8 (s, 1C, *C*H_{Ph}), 128.7 (s, 2C, *C*H_{Ph}), 128.5 (s, 1C, *C*H_{Ph}), 125.9 (s, 2C, *C*H_{Ph}), 110.1 (s, 1C, 4-*C*H), 61.3 (s, 1C, OCH_2), 14.6 (s, 1C, OCH_2CH_3).

3-(Difluoromethyl)-1-phenyl-5-(trichloromethyl)-1*H*-pyrazole (4f): To a solution of 4-(benzylamino)-1,1,1-trichloro-5,5-difluoropent-3-ene-2-one (3ab, 154 mg, 0.47 mmol, 1.00 equiv.) in CH_3CN (1.50 mL) was added phenylhydrazine (75.0 μL, 0.74 mmol, 1.57 equiv.), followed by concentrated H_2SO_4 (13.0 μL, 0.24 mmol, 0.50 equiv.) under argon and under vigorous stirring. The reaction mixture was stirred at 80 °C for 24 h and was then diluted with CH_2Cl_2 (5.00 mL), filtered through Celite® and evaporated under vacuum. The crude product was purified by flash chromatography (pentane:AcOEt, 98:2 to 96:4), to give 3-(difluoromethyl)-1-phenyl-5-(trichloromethyl)-1*H*-pyrazole (**4f**) as an orange solid (102 mg, 70%).
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.56-7.47 (m, 5H, CH_{Ar}), 7.11 (br s, 1H, CH_{pyr}), 6.70 (t, 1H, $^2J_{H-F}$ = 54.4 MHz, CHF_2).
^{13}C-{^{1}H} NMR (100 MHz, CDCl3, 298K, TMS): δ (ppm) = 146.2 (s, 1C, *C*-CCl_3), 145.3 (t, 1C, $^2J_{C-F}$ = 30.0 MHz, C_{pyr}), 139.4 (s, 1C, NC_{Ph}), 130.3 (s, 1C, *C*H_{Ar}), 128.9 (s, 2C, *C*H_{Ar}), 128.4 (s, 2C, *C*H_{Ar}), 110.7 (t, 1C, $^2J_{C-F}$ = 234 MHz, *C*HF_2), 106.3 (s, 1C, *C*H_{pyr}), 86.2 (s, 1C, C-*C*Cl_3).
^{19}F NMR (376 MHz, $CDCl_3$, 298K, TMS): δ (ppm) **=** -112.3 (d, 2F, $^2J_{F-H}$ = 54.4 MHz, CHF_2).
HRMS (ESI) - calcd for $C_{11}H_8Cl_3F_2O_2$ [M+H]: 310.9716. Found: 310.9710.

4.5. General procedure for the synthesis of pyrazoles 5a-d.

A mixture of the corresponding pyrazolecarboxylate (**4**, 1.00 equiv., 0.6-0.8 M) and NaOH (2.01 equiv., 2N) in EtOH was stirred at 21 °C for 1 h. The mixture was treated with 1N HCl until pH 2-3, and was then extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*, to yield the desired product after trituration with the appropriate solvent.

3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (5a)
Following the general procedure, ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (**4a**, 185 mg, 0.906 mmol, 1.00 equiv.) afforded 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (**5a**) after trituration with pentane, as a white solid (160 mg, >99% yield).
M.p: 179.8 to 180.2 °C.

^{1}H NMR (400 MHz, d6-DMSO, 298K): δ (ppm) = 13.7 (s br, COO*H*), 7.02 (s, 1H, 4-C*H*), 7.01 (t, $^{2}J_{H-F}$ = 54.4 Hz, C*H*F_2), 4.11 (s, 3H, NC*H*$_3$).
^{13}C-{^{1}H} NMR (100 MHz, d6-DMSO, 298K): δ (ppm) = 160.1 (s, 1C, *C*=O), 144.0 (t, 1C, $^{2}J_{C-F}$ = 28.5 Hz, *C*CHF$_2$), 134.6 (s, 1C, *C*COOH), 110.9 (t, 1C, $^{1}J_{C-F}$ = 232 Hz, *C*HF$_2$), 108.4 (s, 1C, 4-*C*H), 39.7 (s, 1C, N*C*H$_3$).
^{19}F NMR (376 MHz, d6-DMSO, 298K): δ (ppm) **=** -111.6 (d, 2F, $^{2}J_{F-H}$ = 54.5 Hz, CH*F*$_2$).
HRMS (ESI) - calcd for $C_8H_{11}F_2N_2O_2$ [M+H]**:** 205.0783. Found: 205.0782.

3-(Difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylic acid (5b):
Following the general procedure, ethyl 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (**4a**, 160 mg, 0.601 mmol, 1 equiv.) was hydrolyzed for 1 h, affording 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylic acid (**5e**) after trituration in pentane, as a brown solid (142 mg, >99% yield).
M.p: 132.7 to 133.5 °C.
^{1}H NMR (400 MHz, d6-DMSO, 298K): δ (ppm) = 13.6 (s, 1H, *C*OOH), 7.50 (m, 5*H*, C*H*$_{Ph}$), 7.25 (s, 1H, 4-C*H*), 7.13 (t, 1H, $^{2}J_{H-F}$ = 54 Hz, C*H*F_2).
^{13}C-{^{1}H} NMR (100 MHz, d6-DMSO, 298K): δ (ppm) = 159.3 (s, 1C, *C*OOH), 146.0 (t, 1C, $^{2}J_{C-F}$ = 29 Hz, *C*CHF$_2$), 139.7 (s, 1C, N*C*$_{Ph}$), 135.9 (s, 1C, *C*COOH), 128.9 (s, 2C, *C*H$_{Ph}$), 128.7 (s, 1C, *C*H$_{Ph}$), 125.9 (s, 2C, *C*H$_{Ph}$), 110.9 (t, 1C, $^{1}J_{C-F}$ = 233 Hz, *C*HF$_2$), 109.5 (s, 1C, 4-*C*H).
^{19}F NMR (376 MHz, d6-DMSO, 298K): δ (ppm) **=** -112.2 (d, 2F, $^{2}J_{F-H}$ = 53.7 Hz, CH*F*$_2$) ppm.
Anal. calcd for $C_{11}H_8F_2N_2O_2$: C, 55.47; H, 3.39; F, 15.95; N, 11.76; O, 13.43. Found: C, 55.97; H, 3.54; N, 11.61.

1-Phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid (5c): Following the general procedure, methyl 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (**4b**, 170 mg, 0.503 mmol, 1 equiv.) afforded 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid (**5f**) as a brown solid (128 mg, >99% yield).
M.p: 155 - 165 °C (degradation observed).
^{1}H NMR (400 MHz, d6-DMSO, 298K): δ (ppm) = 13.8 (s br, COO*H*), 7.55-7.53 (m, 5H, C*H*$_{Ph}$), 7.50 (s, 1H, 4-C*H*).
^{13}C-{^{1}H} NMR (100 MHz, *d6*-DMSO, 298K): δ (ppm) = 158.9 (s, 1C, *C*OOH), 141.0 (q, 1C, $^{2}J_{C-F}$ = 38 Hz, *C*CF$_3$), 139.4 (s, 1C, N*C*$_{Ph}$), 136.4 10 (s, 1C, *C*COOH), 129.3 (s, 2C, *C*H$_{Ph}$), 128.7 (s, 1C, *C*H$_{Ph}$), 126.0 (s, 2C, *C*H$_{Ph}$), 120.9 (q, 1C, $^{1}J_{C-F}$ = 269 Hz, *C*F$_3$), 110.1 (s, 1C, 4-*C*H).
^{19}F NMR (376 MHz, *d6*-DMSO, 298K): δ (ppm) **=** -60.9 (s, 3F, C*F*$_3$).
HRMS (ESI) - calcd for $C_{11}H_8F_3N_2O_2$ [M+H]: 257.0532. Found: 257.0536.

1,3-Diphenyl-1*H*-pyrazole-5-carboxylic acid (5d): Following the general procedure, ethyl 1,3-diphenyl-1*H*-pyrazole-5-carboxylate (**4d**, 116 mg, 0.397 mmol, 1.00 equiv.) afforded 1,3-diphenyl-1*H*-pyrazole-5-carboxylic acid (**5d**) after trituration with pentane, as an orange solid (103 mg, >99% yield).
^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ (ppm) = 7.37-7.29 (m, 8*H*, C*H*$_{Ph}$), 7.23-7.21 (m, 2H, C*H*$_{Ar}$), 7.09 (s, 1H, C*H*$_{pyr}$).
^{13}C-{^{1}H} NMR (100 MHz, $CDCl_3$, 298K): δ (ppm) = 165.3 (s, 1C, *C*=O), 145.4 (s, 1C, 3-C), 143.4 (s, 1C, C$_{pyr}$*C*(Ph)), 139.4 (s, 1C, N*C*$_{Ph}$), 129.4 (s, 1C, *C*COOEt), 129.2 (s, 2C, *C*H$_{Ph}$), 129.1 (s, 2C, *C*H$_{Ph}$), 128.9 (s, 1C, *C*H$_{Ph}$), 128.8 (s, 2C, *C*H$_{Ph}$), 128.7 (s, 1C, *C*$_{Ph}$), 125.7 (s, 2C, *C*H$_{Ph}$), 110.3 (s, 1C, 4-*C*H).

HRMS (ESI) - calcd for $C_{16}H_{12}N_2NaO_2$ [M+Na]**:** 287.0791. Found: 287.0793.

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