Expeditious Solid-Phase Synthesis of Pyrazoledicarboxylic Acid Derivatives by Functionalization of Resin-Bound Cyanoformate

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Esterification of the Wang resin **5** with the monoamide of oxalic acid (oxamic acid, **7**) followed by dehydration of the amide function furnishes the resin-bound cyanoformate **9**, which can be elaborated by zinc-catalyzed reaction with β-keto esters. The obtained enamino keto diesters **10a–d** react with hydrazines affording, after removal from the solid support, fully substituted pyrazoledicarboxylic acids **12a–n**. Optimization of the above sequence and the solid-phase synthesis of a small test-library of 1,5-disubstituted pyrazole-3,4-dicarboxylic acid derivatives are described.

Introduction

Solid-phase organic synthesis, in conjunction with combinatorial strategies, represents a powerful tool for the rapid preparation of a large number of compounds.[1] In addition, the solid phase synthetic methods greatly speed up the achievement of a synthetic plan by simplifying the workup procedure after every synthetic step.[2,3]

Heterocyclic structures have received special attention in combinatorial chemistry.[4] They can be synthesized from easily available precursors to obtain a high degree of chemical diversity simply changing the subsitutents linked to a common heteroaromatic core.

The pyrazole nucleus is an especially interesting target due to the broad spectrum of biological activities of a number of its derivatives.[5] The solid-phase synthesis of libraries of tri- and tetrasubstituted pyrazole derivatives has attracted much attention, with the development of various synthetic strategies.[6]

A valuable solid-phase synthetic plan usually takes advantage of the use of readily available building blocks. Thus, the most widely used strategy to construct the pyrazole ring is the ring-forming reaction of a suitable electrophilic precursor, such as **3**, grafted to a polymeric support, with commercially available substituted hydrazines. Up to date the precursors used have been 1,3-dicarbonyl compounds[6g,6h,6m,6n] or their synthetic equivalents,[6b] enones[6c,6d,6i] or enoates,[6d] α,β-unsaturated carbonyl derivatives,[6j] and nitriles.[6k,6l] However, the solid-phase construction of a properly substituted precursor usually involves carbon–carbon bond-forming reactions which are not a minor task when carried out on solid phase.

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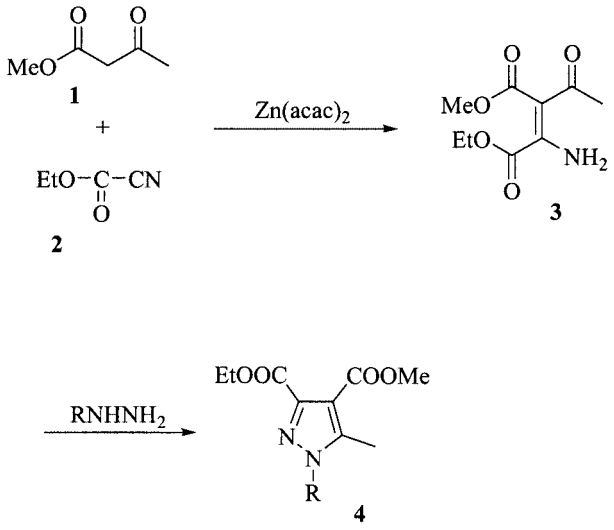
In recent years a new route to pyrazole, isoxazole and pyrimidine derivatives has been described,[7] in which the key step is the metal-catalyzed reaction between a β-keto ester **1** and an alkyl cyanoformate **2**.[8] The resulting intermediate, the enamino keto diester **3**, affords pyrazoledicarboxylic acids **4** by treatment with substituted hydrazines (Scheme 1). Usually one of the two possible regioisomeric pyrazoledicarboxylic acids, that corresponding to **4** in Scheme 1, is obtained as preponderant or as the only reaction product.[7,9]



Scheme 1. Synthesis of pyrazoledicarboxylic acid derivatives.

Due to the accessibility of the starting materials and the mild reaction conditions required, we have been persuaded that this approach could well be suited for the solid-phase synthesis of fully substituted and functionalized pyrazoledicarboxylic acid derivatives. The presence of two carboxylic

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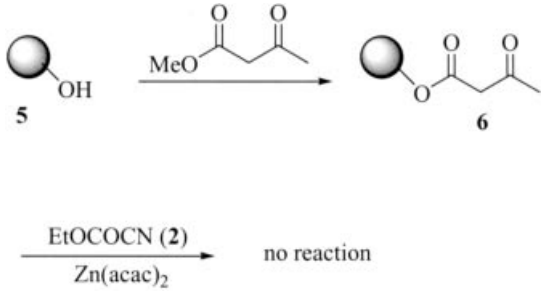
functions could also allow the choice of two possible ways to graft the starting material to the polymeric support.

In this paper we describe the validation of the mentioned approach for the solid-phase synthesis of pyrazoledicarboxylic acid derivatives.

Results and Discussion

A polystyrenic resin containing 2% divinylbenzene as reticulating agent and functionalized with a benzyloxybenzyl linker (Wang resin, **5**) seemed to be suited for our purpose. This kind of resin has a good chemical stability, a high loading capacity (up to 1.5–2.0 mmol/g), good swelling properties in apolar solvents and the linked product can be removed from the solid support by treatment with a solution of trifluoroacetic acid in dichloromethane.

It is well known that the reactions of the Wang resin **5** with appropriate compounds give a resin-bound β-keto ester.[6i,10] So, methyl acetoacetate was allowed to react with that resin in *N*-methyl-2-pyrrolidone in the presence of DMAP,[6i] as a first attempt. The resulting polymer-bound β-keto ester **6** was subjected to metal-catalyzed functionalization with ethyl cyanoformate (10–100 equiv.) in the presence of 2–10 mol% of zinc acetylacetonate, under various experimental conditions. In all experiments, no appreciable amounts of the expected product were observed (Scheme 2). A plausible explanation could be that in the solid-phase reaction, differently from the liquid-phase approach, the starting dicarbonyl compound and the reaction product, both being bound to the solid support, cannot act as complexing agents able to ensure the mobility of the catalytic zinc within the reaction medium. Thus, the catalytic cycle is inhibited by sequestering the catalyst. On the base of these findings, our strategy was adapted to the use of resin-bound cyanoformate in order to have the complexing β-keto ester in solution, ensuring the exchange of the catalytically active zinc between the reaction product and the free β-keto ester reagent.



Scheme 2. First approach to the synthesis of resin-bound enamino keto diesters of type **3**.

Since the transesterification reaction between the Wang resin and an alkyl cyanoformate could be accompanied by polymer-bound carbonate ester formation, because of the leaving group ability of the cyano group, we decided to prepare the polymer-bound cyanoformate by modifying a precursor previously grafted to the solid support. To the best of our knowledge, polymer-supported cyanoformates were not known in the literature.

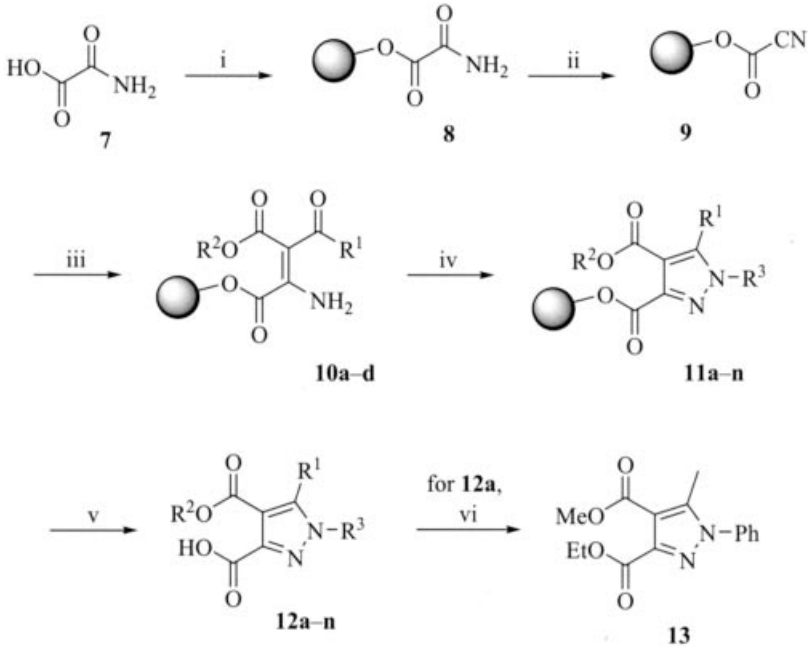
In a preliminary test, we used the monoamide of oxalic acid (oxamic acid) **7**, which was loaded onto the Wang resin **5** following the mixed anhydride method.[11] The amide functional group of intermediate **8** was then dehydrated[12] to give the resin-bound cyanoformate **9** (Scheme 3). All these steps were checked by FT-IR. In particular, the dehydration step showed the disappearance of the amide bond signals at 1714 and 1697 cm^{-1} and the appearance of a sharp peak of a carbon–nitrogen triple bond at 2244 cm^{-1}. Subsequent functionalization of **9** was accomplished using a 20-fold excess of methyl acetoacetate in dichloromethane solution in the presence of 5 mol% zinc acetylacetonate at room temperature for 24 hours affording **10a**. Reaction of **10a** with two equivalents of phenylhydrazine (room temperature, 12 hours) and removal of the product **11a** from the solid support with trifluoroacetic acid in dichloromethane gave the pyrazole acid **12a** in 70% overall yield. The pyrazole acid **12a** was finally esterified with thionyl chloride and ethanol to give the diester **13**, which was found to be identical in all respects to that previously described in the literature (Scheme 3).[7]

The metal-catalyzed formation of the intermediate enamino keto diester **10a** was then optimized with respect to the excess of β-keto ester required, the amount of the catalyst, and the reaction times.

Intermediate **10a** showed a complex FT-IR spectrum. A broad band between 1682 and 1745 cm^{-1} accounted for the conjugate system of two ester groups, and a ketone linked to the central ethylene unit. Therefore, the zinc-catalyzed reaction between the resin-bound cyanoformate **9** and methyl acetoacetate (**1**) was considered to be complete after the disappearance of the carbon–nitrogen triple-bond peak of the starting material **9** at 2244 cm^{-1}. The amount of the catalyst was determined by carrying out the reaction in the presence of 0.5, 1 and 2 mol% of zinc acetylacetonate, using 20 equiv. of β-keto ester. The short reaction times found for experiments carried out with 1 and 2 mol% zinc acetylacetonate (5 and 2 hours, respectively), prompted us to test whether a lower excess of the β-keto ester could be used. Indeed, we found that treatment of **9** with a 10-fold excess of methyl acetoacetate in the presence of 1 mol% zinc acetylacetonate gave complete reaction after 16 hours (FT-IR monitor).

Resin-bound enamino keto diester **10a** was then allowed to react with 2 equiv. of phenylhydrazine in dichloromethane at room temperature for 3 and 20 hours. The obtained products were cleaved from the resin and their yield and purity were checked by ^1H NMR spectroscopy. Interestingly, better yields of a purer product were obtained with the shorter reaction time.

To explore the breadth of applicability of such an optimized synthetic sequence, we performed the synthesis of a test library of representative pyrazole derivatives. The starting building blocks were selected on the basis of their electronic and steric requirements and are listed in Table 1. All the required β-keto esters **14a**–**c** were synthesized as ethyl



Scheme 3. Solid-phase synthesis of pyrazoledicarboxylic acid derivatives **12**. See Table 1 for R^1, R^2 and R^3. Reagents and conditions: i: 2,6-dichlorobenzoyl chloride, pyridine, Wang resin (**5**), DMF, 0 °C; ii: TFAA, pyridine, dichloromethane, 0 °C; iii: $R^1COCH_2COOR^2$ (**1** or **14a–c**), $Zn(acac)_2$, CH_2Cl_2, room temp.; iv: R^3NHNH_2, CH_2Cl_2, room temp.; v: TFA/CH_2Cl_2 (3:1 vol/vol), room temp.; vi: $SOCl_2$ followed by EtOH, 0 °C, then reflux.

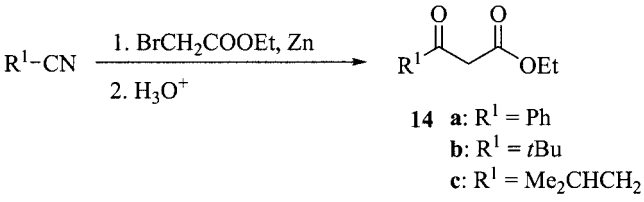
esters starting from commercially available nitriles by Blaise reaction with ethyl bromoacetate in the presence of zinc dust, followed by hydrolysis of the intermediate enamino ester (Scheme 4).[13]

Table 1. R^1, R^2 and R^3 residues for the test-library of the pyrazoles **12a–r**. See Scheme 3 for the synthetic plan.

12	R^1	R^2	R^3	Yield[a] [%]
a	Me	Me	Ph	82
b	Me	Me	Me	72
c	Me	Me	*p*-$MeOC_6H_4$	81
d	Me	Me	*p*-ClC_6H_4	40
e	Me	Me	*t*Bu	70
f	Ph	Et	Ph	55
g	Ph	Et	Me	80
h	Ph	Et	*p*-$MeOC_6H_4$	63
i	Ph	Et	*p*-ClC_6H_4	61
j	Ph	Et	*t*Bu	58
k	CH_2CHMe_2	Et	Ph	63
l	CH_2CHMe_2	Et	Me	74
m	CH_2CHMe_2	Et	*p*-$MeOC_6H_4$	50
n	CH_2CHMe_2	Et	*p*-ClC_6H_4	35
o	CH_2CHMe_2	Et	*t*Bu	–
p	*t*Bu	Et	Ph	–
q	*t*Bu	Et	Me	–
r	*t*Bu	Et	*t*Bu	–

[a] Isolated yields of compounds **12**. All compounds gave satisfactory elemental analyses.

The zinc-catalyzed reactions of methyl acetoacetate (**1**) and the keto esters **14a–c** with the resin-bound cyanoformate **9** were carried out in dichloromethane at room temperature with 10 equivalents of the dicarbonyl compounds and 1 mol% $Zn(acac)_2$ for 16 hours to give the compounds **10a–d** (Scheme 3 and Table 1). After this time the carbon–



14 **a**: R^1 = Ph
b: R^1 = *t*Bu
c: R^1 = Me_2CHCH_2

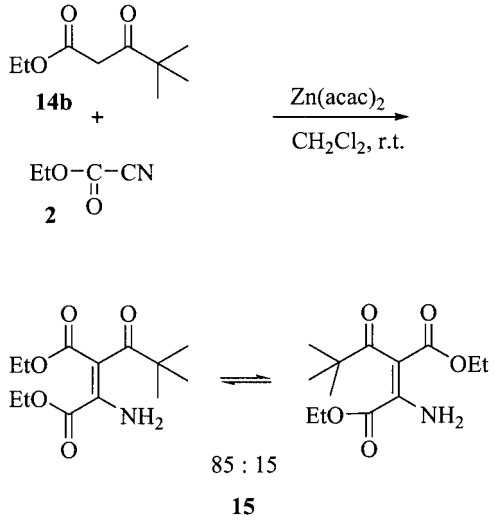
Scheme 4. Synthesis of the β-keto esters **14**.

nitrogen triple-bond signal of **9** in the FT-IR spectra was no longer detectable in all cases. The subsequent ring-forming reactions of intermediates **10a–d** (see Table 1 for hydrazine residues) occurred in the presence of two equivalents of the appropriate hydrazine at room temperature for 3.5 hours. Two equivalents of triethylamine were added to the reaction mixtures in the case of hydrazines in the form of their hydrochloride salts.

Cleavage of the resulting products **11a–n** from the solid support was accomplished with two consecutive treatments with trifluoroacetic acid in dichloromethane at room temperature for 30 min.

Pyrazoles **12a–n** were obtained in moderate to good chemical yields in all cases (Table 1). Considering what mentioned above,[7,9] we found that all the synthesized compounds consisted of only one regioisomer, as revealed by inspection of their ^1H and ^{13}C spectra. However, when the bulky *tert*-butyl group was linked as substituent at the ketonic carbonyl carbon (Entries p–r of Table 1), no appreciable amounts of the expected products were observed. To gain further insight on this point, ring-forming reactions of enamino keto diester **15** with various hydrazines were tested

in liquid phase. Compound **15** was prepared from **14b** and ethyl cyanoformate and was found to be present as an equilibrium mixture of geometric stereoisomers (Scheme 5) (cf. ref.[8a]). Reactions of compound **15** with methyl and phenylhydrazine gave intractable mixtures of rather unstable compounds. Treatment of enamino keto diester **15** with the sterically demanding *tert*-butylhydrazine resulted in no reaction at all. In this case, over 90% starting compound **15** was recovered unchanged even after 24 hours reaction time. Thus, steric hindrance of the substituent at the ketonic carbonyl carbon appears to be critical for the reaction, while the steric hindrance of the hydrazine is of minor importance. Steric bulkiness of the hydrazine substituent becomes critical only when a voluminous group is also present in the ketonic counterpart (see **12o** in Table 1).



Scheme 5. Synthesis of compound **15**.

Conclusions

A test-library of fully substituted pyrazoledicarboxylic acid derivatives was synthesized by addition of commercially available hydrazines to the easily prepared intermediates arising from the zinc-catalyzed reaction of the resin-bound cyanoformate with β-keto esters. The yields were satisfactory and the purity of the compounds obtained after minimal workup, was generally high enough to avoid further purification. The very mild experimental conditions and the high reproducibility of the reaction times make our approach potentially suitable for automation and for application to combinatorial synthetic strategies.

Experimental Section

General Remarks: TLC was performed on silica gel F254 precoated aluminum sheets (0.2 mm layer, Merck, Darmstadt, Germany); components were detected by spraying a ceric sulfate ammonium molybdate solution, followed by heating to ca 150 °C. Silica gel (Merck, 40–63 μm) was used for flash chromatography (FC). ^{1}H and ^{13}C NMR spectra were recorded at 400.132 and 100.613 MHz, respectively with a Bruker AVANCE 400 Spectrometer using a Xwin-NMR software package; at 300.133 and 75.47 MHz with a Bruker AC 300 (Bruker, Karlsruhe, Germany), equipped with an ASPECT 3000 data system. Chemical shifts (δ) are given in ppm and were referenced to the signals of $CDCl_3$ (δ_H, 7.26 and δ_C 77.00 ppm). ^{13}C NMR signals multiplicities were based on APT spectra. FT-IR spectra were recorded with a Perkin–Elmer 1725 X spectrometer by triturating ca. 5 mg of resin with few drops of nujol. APCI mass spectra were recorded with a Termo Finnigan LCQ Advantage mass spectrometer. Wang resin (loading capacity 1.21 mmol g^{-1}, as specified by the supplier) was from Aldrich. Resin-bound cyanoformate **9** was prepared on 2.0 or 4.0 resin grams scale using standard glassware. Parallel synthesis of pyrazole derivatives was carried out by use of 12 mL fritted tubes by means of a home-modified Ika-vibrax-VXR orbital shaker. All reagents were of commercial quality. Ethyl 3-oxo-3-phenylpropanoate (**14a**),[14] ethyl 4,4-dimethyl-3-oxo-pentanoate (**14b**),[15] and ethyl 5-methyl-3-oxohexanoate (**14c**)[16] were prepared according to the literature.[13] Solvents were dried by standard methods prior to use.

Synthesis of the Resin-Bound Cyanoformate 9: To a solution of oxamic acid (862 mg, 9.68 mmol) in dry DMF (30 mL), cooled to 0 °C, pyridine was added (0.93 mL, 11.62 mmol) followed, after 5 min, by 2,6-dichlorobenzoyl chloride (2.10 mL, 14.52 mmol). After 5 min, the Wang resin was added (4.00 g, 4.84 mmol), and the suspension was stirred at 0 °C for 2 h. The resin was collected by filtration and washed consecutively with dry DMF (2 × 20 mL), AcOEt (3 × 20 mL) and dichloromethane (3 × 20 mL) and dried under reduced pressure. FT-IR (nujol mull): $\tilde{\nu}$ = 1737, 1714, 1697 cm^{-1}.

The resin obtained as described above was suspended in dry dichloromethane (40 mL) and the mixture was cooled to 0 °C. Pyridine was then added (1.90 mL, 24.20 mmol) and the suspension was stirred for 5 min. Trifluoroacetic anhydride (0.82 mL, 5.81 mmol) was added dropwise over 5 min and the resulting suspension was stirred at 0 °C for additional 30 min. The resin was collected by filtration, washed with dichloromethane (3 × 20 mL) and dried under reduced pressure. FT-IR (nujol mull): $\tilde{\nu}$ = 2244, 1746 cm^{-1}.

General Procedure for the Synthesis of the Polymer-Bound Enamino Keto Diesters 10a–d: Polymer-bound cyanoformate obtained as described above (1.0 g, ca 1.2 mmol) was suspended in CH_2Cl_2 (10 mL) in a 12-mL fritted tube. The appropriate β-keto ester (10 equiv.) and $Zn(acac)_2$ (32 mg, 0.12 mmol) were then added. The mixture was shaken at room temperature for 16 h, the liquid phase was removed by filtration, the resin was washed with DMF (10 mL), AcOEt (2 × 10 mL) and CH_2Cl_2 (2 × 10 mL) and dried under reduced pressure.

General Procedure for the Synthesis of the Polymer-Bound Pyrazole Derivatives 11a–n: Resin-bound enamino keto diester of type **10** (0.75 mmol) was suspended in CH_2Cl_2 (8 mL) in a 12-mL fritted tube. The appropriate hydrazine was then added (1.50 mmol). In the case of hydrazine hydrochlorides triethylamine (1.50 mmol) was also added. The mixture was shaken at room temperature for 3.5 h and filtered. The resin was washed with DMF (2 × 10 mL), AcOEt (2 × 10 mL) and CH_2Cl_2 (2 × 10 mL) and dried under reduced pressure.

General Procedure for the Cleavage of the Pyrazoledicarboxylic Acids from the Solid Support 12a–n: Resin-bound pyrazole derivative of type **11** (0.75 mmol) was shaken with a mixture of trifluoroacetic acid and CH_2Cl_2 (3:1 v/v, 8 mL) in a 12-mL fritted tube at room temperature for 1 h. The resin was filtered off and the liquid phase was collected. The procedure was repeated in order to ensure complete cleavage of the product from the solid support. The combined liquid phases were evaporated under reduced pressure; the

residue was taken up in ethyl acetate (10 mL) and washed with water (2 × 8 mL); the organic layer was extracted with half-saturated solution of $NaHCO_3$ (2 × 5 mL), the combined aqueous layers were acidified with concentrated HCl at pH ca 1 and extracted with AcOEt (3 × 8 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give pyrazole derivatives **12a**–**n**.

4-(Methoxycarbonyl)-5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (12a): Obtained from **10a** and phenylhydrazine in 82% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, Me), 4.05 (s, 3 H, OMe), 7.41–7.46 (m, 2 H, aromatic H), 7.50–7.52 (m, 3 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.53 (Me), 53.61 (OMe), 110.47 (pyrazole C4), 126.19, 129.29, 129.89, 137.66 (aromatic C), 144.27 (pyrazole C3), 146.47 (pyrazole C5), 160.17 (COO), 168.17 (COO) ppm. MS-APCI: *m*/*z* = 261 [MH$^+$], 229 [M – MeOH].

4-(Methoxycarbonyl)-1,5-dimethyl-1*H*-pyrazole-3-carboxylic Acid (12b): Obtained from **10a** and methylhydrazine in 72% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, Me), 3.93 (s, 3 H, NMe), 4.02 (s, 3 H, OMe) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 12.64 (Me), 38.07 (NMe), 53.90 (OMe), 110.30 (pyrazole C4), 143.47 (pyrazole C3), 146.21 (pyrazole C5), 161.00 (COO), 168.45 (COO) ppm. MS-APCI: *m*/*z* = 199 [MH$^+$], 181 [M – H_2O], 167 [M – MeOH].

4-(Methoxycarbonyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxylic Acid (12c): Obtained from **10a** and (4-methoxyphenyl)-hydrazine hydrochloride in 81% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, Me), 3.83 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 6.95 (m, 2 H, aromatic H), 7.29 (m, 2 H, aromatic H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 13.52 (Me), 53.60 (OMe), 55.64 (OMe), 110.67 (pyrazole C4), 114.43, 127.49, 130.47 (aromatic C), 143.94 (pyrazole C3), 146.62 (pyrazole C5), 160.31 (COO or aromatic C), 160.32 (COO or aromatic C), 168.21 (COO) ppm. MS-APCI: *m*/*z* = 291 [MH$^+$], 259 [M – MeOH].

1-(4-Chlorophenyl)-4-(methoxycarbonyl)-5-methyl-1*H*-pyrazole-3-carboxylic Acid (12d): Obtained from **10a** and 4-chlorophenylhydrazine hydrochloride in 40% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, Me), 4.05 (s, 3 H, OMe), 7.38–7.41 (m, 2 H, aromatic H), 7.47–7.50 (m, 2 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.49 (Me), 53.70 (OMe), 110.71 (pyrazole C4), 127.46, 129.63, 135.98, 136.08 (aromatic C), 144.40 (pyrazole C3 or C5), 146.59 (pyrazole C3 or C5), 160.07 (COO), 168.01 (COO) ppm. MS-APCI: *m*/*z* = 295 [MH$^+$], 277 [M – H_2O], 263 [M – MeOH].

1-*tert*-Butyl-4-(methoxycarbonyl)-5-methyl-1*H*-pyrazole-3-carboxylic Acid (12e): Obtained from **10a** and *tert*-butylhydrazine hydrochloride in 70% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 9 H, *t*Bu), 2.58 (s, 3 H, Me), 4.01 (s, 3 H, OMe) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.95 (Me), 30.24 (C*Me*$_3$), 53.83 (OMe), 63.70 (*C*Me$_3$), 112.02 (pyrazole C4), 141.43 (pyrazole C3), 145.81 (pyrazole C5), 162.21 (COO), 168.87 (COO) ppm. MS-APCI: *m*/*z* = 241 [MH$^+$], 184 [MH$^+$ – isopropylidene].

4-(Ethoxycarbonyl)-1,5-diphenyl-1*H*-pyrazole-3-carboxylic Acid (12f): Obtained from **10b** and phenylhydrazine in 55% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 4.20 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.23–7.52 (m, 10 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.63 (CH_2CH_3), 63.14 (CH_2CH_3), 112.34 (pyrazole C4), 126.12, 128.61, 129.29, 129.40, 130.11, 130.62, 134.15, 138.57 (aromatic C), 144.68 (pyrazole C3), 148.67 (pyrazole C5), 160.96 (COO), 167.35 (COO) ppm. MS-APCI: *m*/*z* = 337 [MH$^+$], 291 [M – EtOH], 180 [M – EtOH – 111].

4-(Ethoxycarbonyl)-1-methyl-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (12g): Obtained from **10b** and methylhydrazine in 80% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.80 (s, 3 H, N-CH_3), 4.16 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.32–7.34 (m, 2 H, aromatic H), 7.52–7.55 (m, 3 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.51 (CH_2CH_3), 38.64 (N–CH_3), 63.14 (CH_2CH_3), 111.44 (pyrazole C4), 128.78, 129.05, 129.82, 130.58 (aromatic C), 143.53 (pyrazole C3), 149.34 (pyrazole C5), 161.85 (COO), 167.37 (COO) ppm. MS-APCI: *m*/*z* = 275 [MH$^+$], 229 [M – EtOH], 118 [M – EtOH – 111].

4-(Ethoxycarbonyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (12h): Obtained from **10b** and (4-methoxyphenyl) hydrazine hydrochloride in 63% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.78 (s, 3 H, OCH_3), 4.20 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 6.77–6.79 (m, 2 H, aromatic H), 7.15–7.17 (m, 2 H, aromatic H), 7.22–7.25 (m, 2 H, aromatic H), 7.35–7.49 (m, 3 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.23 (CH_2CH_3), 55.46 (O–CH_3), 62.72 (CH_2CH_3), 110.21 (pyrazole C4), 113.97, 127.00, 128.19, 128.48, 129.61, 130.21, 131.15 (aromatic C), 144.04 (pyrazole C3), 148.28 (pyrazole C5), 159.73 (aromatic C), 160.63 (COO), 166.85 (COO) ppm. MS-APCI: *m*/*z* = 367 [MH$^+$], 321 [M – EtOH], 210 [M – EtOH – 111].

1-(4-Chlorophenyl)-4-(ethoxycarbonyl)-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (12i): Obtained from **10b** and 4-chlorophenylhydrazine hydrochloride in 61% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 4.21 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.19–7.29 (m, 6 H, aromatic H), 7.39–7.42 (m, 3 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.62 (CH_2CH_3), 63.24 (CH_2CH_3), 112.00 (pyrazole C4), 127.22, 127.98, 128.82, 129.55, 130.35, 130.55, 135.43, 137.07 (aromatic C), 145.01 (pyrazole C3), 148.71 (pyrazole C5), 160.51 (COO), 167.26 (COO) ppm. MS-APCI: *m*/*z* = 371 [MH$^+$], 325 [M – EtOH], 214 [M – EtOH – 111].

1-*tert*-Butyl-4-(ethoxycarbonyl)-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (12j): Obtained from **10b** and *tert*-butylhydrazine hydrochloride in 58% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.47 (s, 9 H, *t*Bu), 3.99 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.27–7.28 (m, 2 H, aromatic H), 7.39–7.42 (m, 3 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.31 (CH_2CH_3), 31.72 [C(*C*H$_3$)$_3$], 62.59 (CH_2CH_3), 63.46 (*C*Me$_3$), 112.95 (pyrazole C4), 128.33, 129.85, 130.65, 131.77 (aromatic C), 141.84 (pyrazole C3), 148.53 (pyrazole C5), 161.46 (COO), 167.71 (COO) ppm. MS-APCI: *m*/*z* = 317 [MH$^+$], 260 [MH$^+$ – isopropylidene].

4-(Ethoxycarbonyl)-5-isobutyl-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (12k): Obtained from **10c** and phenylhydrazine in 63% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 = [d, *J* = 6.8 Hz, 6 H, $CH_2CH(CH_3)_2$], 1.44 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.80 [m, 1 H, $CH_2CH(CH_3)_2$], 2.86 [d, *J* = 7.0 Hz, 2 H, $CH_2CH(CH_3)_2$], 4.48 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.35–7.37 (m, 2 H, aromatic H), 7.45–7.49 (m, 3 H, aromatic H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 14.03 (CH_2CH_3), 22.23 [$CH_2CH(CH_3)_2$], 29.36 [$CH_2CH(CH_3)_2$], 34.57 [$CH_2CH(CH_3)_2$], 63.14 (CH_2CH_3), 109.90 (pyrazole C4), 126.91, 129.39, 130.01, 138.07 (aromatic C), 144.42 (pyrazole C3), 150.25 (pyrazole C5), 165.59 (COO), 167.70 (COO) ppm. MS-APCI: *m*/*z* = 317 [MH$^+$], 271 [M$^+$ – EtOH], 253 [M$^+$ – EtOH – H_2O].

4-(Ethoxycarbonyl)-5-isobutyl-1-methyl-1*H*-pyrazole-3-carboxylic Acid (12l): Obtained from **10c** and methylhydrazine in 74% overall

yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 [d, J = 6.8 Hz, 6 H, $CH_2CH(CH_3)_2$], 1.45 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.00 [m, 1 H, $CH_2CH(CH_3)_2$], 2.85 [d, J = 7.6 Hz, 2 H, $CH_2CH(CH_3)_2$], 3.94 (s, 3 H, N–CH_3), 4.46 (q, 2 H, J = 7.2 Hz, CH_2CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.37 (CH_2CH_3), 22.68 [$CH_2CH(CH_3)_2$], 29.67 [$CH_2CH(CH_3)_2$], 34.91 [$CH_2CH(CH_3)_2$], 38.35 (N–CH_3), 63.40 (CH_2CH_3), 110.36 (pyrazole C4), 143.82 (pyrazole C3), 149.67 (pyrazole C5), 161.18 (COO), 167.94 (COO) ppm. MS-APCI: m/z = 255 [MH^+], 209 [M^+ – EtOH], 191 [M^+ – EtOH – H_2O].

4-(Ethoxycarbonyl)-5-isobutyl-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic Acid (12m): Obtained from **10c** and (4-methoxyphenyl)-hydrazine hydrochloride in 50% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 [d, J = 6.6 Hz, 6 H, $CH_2CH(CH_3)_2$], 1.48 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.85 [m, 1 H, $CH_2CH(CH_3)_2$], 2.85 [d, J = 7.2 Hz, 2 H, $CH_2CH(CH_3)_2$], 3.89 (s, 3 H, OMe), 4.51 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 7.00 (m, 2 H, aromatic H), 7.30 (m, 2 H, aromatic H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.41 (CH_2CH_3), 22.57 [$CH_2CH(CH_3)_2$], 29.66 [$CH_2CH(CH_3)_2$], 34.99 [$CH_2CH(CH_3)_2$], 55.01 (OMe), 63.42 (CH_2CH_3), 110.54 (pyrazole C4), 114.74, 128.58, 131.31 (aromatic C), 144.65 (pyrazole C3), 150.75 (pyrazole C5), 160.89 (aromatic C or COO), 160.91 (aromatic C or COO), 168.10 (COO) ppm. MS-APCI: m/z = 347 [MH^+], 301 [M^+ – EtOH], 283 [M^+ – EtOH – H_2O].

1-(4-Chlorophenyl)-4-(ethoxycarbonyl)-5-isobutyl-1*H*-pyrazole-3-carboxylic Acid (12n): Obtained from **10c** and 4-chlorophenylhydrazine hydrochloride in 35% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 [d, J = 6.4 Hz, 6 H, $CH_2CH(CH_3)_2$], 1.44 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.80 [m, 1 H, $CH_2CH(CH_3)_2$], 2.83 [d, J = 7.2 Hz, 2 H, $CH_2CH(CH_3)_2$], 4.48 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 7.31 (m, 2 H, aromatic H), 7.46 (m, 2 H, aromatic H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 13.97 (CH_2CH_3), 22.18 [$CH_2CH(CH_3)_2$], 29.40 [$CH_2CH(CH_3)_2$], 34.53 [$CH_2CH(CH_3)_2$], 63.25 (CH_2CH_3), 110.32 (pyrazole C4), 128.18, 129.65, 136.50, 138.07 (aromatic C), 145.40 (pyrazole C3), 150.36 (pyrazole C5), 160.53 (COO), 167.18 (COO) ppm. MS-APCI: m/z = 351 [MH^+], 305 [M^+ – EtOH], 287 [M^+ – EtOH – H_2O].

Synthesis of Diethyl 2-Amino-3-(2,2-dimethylpropanoyl)-2-butenedioate (15): To a solution of ethyl 4,4-dimethyl-3-oxo-pentanoate (**14b**) (1.11 g, 6.45 mmol) and ethyl cyanoformate (**2**) (0.70 mL, 7.10 mmol) in dry dichloromethane (1.5 mL), zinc acetylacetonate (34 mg, 0.13 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with ethyl acetate (10 mL) and filtered through celite. The filtrate was evaporated under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate/hexane, 2:8) to give the title compound. White powder, 1.57 g, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): two inseparable geometric isomers were present in solution (see ref.[8a]). Major isomer (85%) showed resonances at δ = 1.21 (s, 9 H, CMe_3), 1.28 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.35 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.20 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.32 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.75 (br. s, 2 H, NH_2) ppm. The minor isomer (15%) showed distinguishable resonances at δ = 1.22 (s, 9 H, CMe_3), 7.75 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): two inseparable geometric isomers were present in solution. Major isomer showed resonances at δ = 13.71 (CH_2CH_3), 13.99 (CH_2CH_3), 28.31 (CMe_3), 45.29 (CMe_3), 60.19 (CH_2CH_3), 62.71 (CH_2CH_3), 104.48 (C3), 145.77 (C2), 162.64 (COO), 167.32 (COO), 210.29 (CO) ppm. The minor isomer showed distinguishable resonances at δ = 27.25 (CMe_3), 43.77 (CMe_3), 60.60 (CH_2CH_3), 63.03 (CH_2CH_3) ppm. $C_{13}H_{21}NO_5$ (271.14): calcd. C 57.55, H 7.80, N 5.16; found C 57.81, H 8.00, N 4.97.

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