

Synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by one-pot cyclization of hydrazone dianions with diethyl oxalate

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Abstract

The one-pot cyclization of hydrazone dianions with diethyl oxalate allows a convenient synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates.

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1. Introduction

Pyrazole-3-carboxylic acid derivatives represent important building blocks in organic and medicinal chemistry. In addition, they are of interest in their own right, due to their pharmacological properties. For example, pyrazole-3-carboxylic acids and pyrazolo[1,5-*c*]quinazoline-2-carboxylates are nicotinic acid receptor agonists¹ and excitatory amino acid antagonists, respectively.² It was shown that related bis(benzo-[*g*]indazole-3-carboxamides) exhibit antiproliferative activity against various cancer cell lines.³ Ethyl 5-propyl-1*H*-pyrazole-3-carboxylate is a key intermediate for the synthesis of *viagra*.⁴ Celecoxib is the first-to-market drug of a number of selective cyclo-oxygenase 2 (COX-2) inhibitors which are promising anti-inflammatory and analgetic agents (without the undesirable side effects associated with other non-steroidal anti-inflammatories).⁵ Recently, Nicolaou et al.⁶ reported that a pyrazole-substituted epothilone derivative shows a strong antitumour activity through the stabilization of microtubules by binding with tubulin. In fact, it is considered to be the most potent epothilone derivative reported to date.

Pyrazoles are available by 1,3-dipolar cycloaddition reactions of diazoalkanes with alkynes and related transformations.⁷

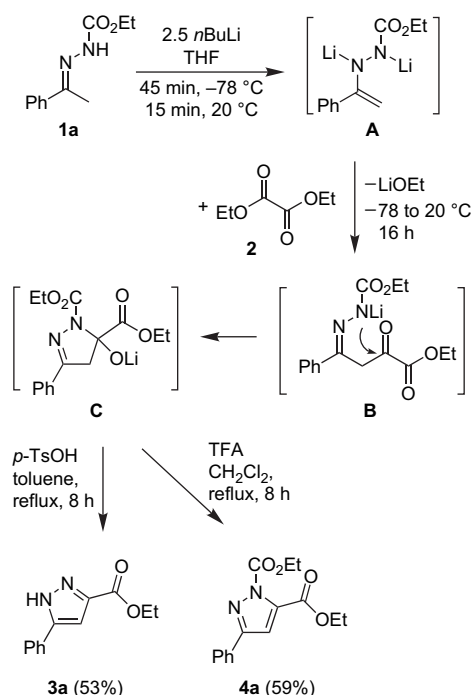
Other syntheses rely on cyclizations of 1,3-diketones with hydrazine⁸ and on Michael reactions of hydrazines with α,β -unsaturated ketones.⁹ An interesting approach to pyrazoles relies on the cyclization¹⁰ of hydrazone dianions, generated by means of *n*-BuLi, with esters,¹¹ acid chlorides¹² and nitriles.¹³ Pyrazolines have been prepared by cyclization of dilithiated hydrazones with α -haloketones.¹⁴ Recently, the synthesis of pyrazole-3-carboxylates by the reaction of hydrazines with propiolates and Weinreb amides has been reported.¹⁵ Ranatunge reported¹⁶ the synthesis of 5-arylpyrazole-3-carboxylates based on the condensation of hydrazines with 4-aryl-2,4-dioxoesters. The products were transformed into nitrate-substituted oximes which represent potent and selective COX-1 and COX-2 inhibitors. We reported the cyclization of oxime and hydrazone dianions with epibromohydrin to give 1,2-oxazines and oxazolo[3,4-*b*]pyridazin-7-ones, respectively.¹⁷ The cyclization of oxime dianions with diethyl oxalate, which provides a convenient access to isoxazole-5-carboxylates, has also been studied.¹⁸ Recently, we reported a new and convenient approach to pyrazole-3-carboxylates by one-pot cyclizations of hydrazone dianions with diethyl oxalate.¹⁹ Herein, we report full details of these studies. In addition to our preliminary communication,¹⁹ pyrazole-1,5-dicarboxylates (i.e., carbamate-protected pyrazole-3-carboxylates) have been prepared from the same starting materials.

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2. Results and discussion

The reaction of a THF solution of diethyl oxalate (**2**) with the dianion of acetophenone hydrazone **1a**, generated by *n*-butyllithium (2.5 equiv), and subsequent reflux of a toluene solution of the crude product in the presence of *p*-toluenesulfonic acid (PTSA) afforded pyrazole-3-carboxylate **3a** in up to 53% yield (Scheme 1). The best yields were obtained when the reaction mixture was allowed to slowly warm from -78 to 20 °C. The solvent was removed in vacuo without aqueous work-up and a toluene solution of the residue was simply refluxed in the presence of PTSA (4.0 equiv) for 8 h. Notably, the use of oxalyl chloride or ethyl oxalyl chloride resulted in polymerization. The employment of a tosyl- rather than carbamate-protected hydrazone was not successful (formation of complex mixtures).



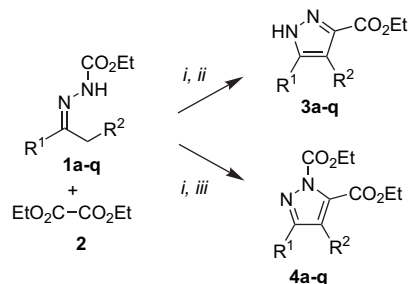
Scheme 1. Mechanism of the formation of pyrazole-3-carboxylate **3a** and of pyrazole-1,5-dicarboxylate **4a**.

The formation of **3a** can be explained by attack of the carbon atom of dianion **A** onto **2** to give intermediate **B**, subsequent cyclization by attack of the nitrogen atom onto the carbonyl group (intermediate **C**), aromatization upon addition of the acid and subsequent acid-mediated decarboxylation (Scheme 1). Reflux of a CH_2Cl_2 solution of the crude product in the presence of trifluoroacetic acid (TFA) afforded pyrazole-1,5-dicarboxylate **4a** in up to 59% yield. This result can be explained by the lower acidity of TFA compared to PTSA. Noteworthy, both the protected and the non-protected pyrazole-carboxylates were prepared from the same starting material.

The cyclization of the dianions of hydrazones **1a–i** with diethyl oxalate and subsequent dehydration with PTSA afforded the aryl-substituted pyrazole-3-carboxylates **3a–i**

(Scheme 2, Table 1). Likewise, the pyrazole-1,5-dicarboxylates **4a–i** were obtained when TFA was employed. The cyclization of diethyl oxalate with the dilithiated hydrazone of *p*-nitroacetophenone was unsuccessful. The cyclization of diethyl oxalate with the dianions of hydrazones **1j** and **1k**, prepared from 3-methylbutan-2-one and pentan-2-one, afforded the alkyl-substituted pyrazole-3-carboxylates **3j** and **3k** and pyrazole-1,5-dicarboxylates **4j** and **4k** in good yields, respectively. Pyrazoles **3l** and **4l**, containing a phenyl and a methyl substituent, were prepared based on the cyclization of diethyl oxalate with propiophenone-derived hydrazone **1l**. The cyclization of diethyl oxalate with the dianions of tetralone hydrazone **1m** and of cycloalkanone-derived hydrazones **1n–q** afforded, after dehydration and decarboxylation with PTSA, the annulated pyrazole-3-carboxylates **3m–q**. The pyrazole-1,5-dicarboxylates **4m–q** were isolated when the dehydration was carried out using TFA. The yields of pyrazole-1,5-dicarboxylates **4** were in most cases slightly better than those of pyrazole-3-carboxylates **3**.

The structure of product **3b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).²⁰



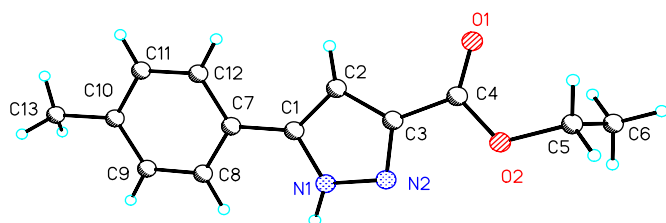
Scheme 2. Synthesis of pyrazole-3-carboxylates **3a–q** and pyrazole-1,5-dicarboxylates **4a–q**. (i) (1) *n*-BuLi (2.5 equiv), THF, 45 min, -78 °C; (2) 15 min, 20 °C; (3) **2**, $-78 \rightarrow 20$ °C, 16 h; (4) removal of THF; (ii) *p*-TsOH (4.0 equiv), toluene, reflux, 8 h; (iii) TFA, CH_2Cl_2 , reflux, 8 h.

Table 1
Synthesis of **3a–q** and **4a–q**

3	R ¹	R ²	3 ^a (%)	4 ^a (%)
a	C ₆ H ₅	H	53	59
b	4-MeC ₆ H ₄	H	57	61
c	3-MeC ₆ H ₄	H	61	48
d	4-(MeO)C ₆ H ₄	H	45	47
e	2-(MeO)C ₆ H ₄	H	— ^b	42
f	1-Naphthyl	H	45	— ^b
g	2-Naphthyl	H	38	— ^b
h	4-ClC ₆ H ₄	H	42	54
i	4-FC ₆ H ₄	H	47	41
j	<i>i</i> -Pr	H	69	72
k	<i>n</i> -Pr	H	72	70
l	C ₆ H ₅	Me	62	69
m	C ₆ H ₄ (CH ₂) ₂		54	49
n	(CH ₂) ₄		43	44
o	(CH ₂) ₅		40	47
p	(CH ₂) ₆		38	42
q	(CH ₂) ₁₀		31	65

^a Yields of isolated products.

^b Not carried out.

Figure 1. Crystal structure of **3b**.

In conclusion, we have reported a convenient and regioselective synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates based on cyclizations of hydrazone dianions with diethyl oxalate. Noteworthy, both protected and non-protected pyrazole-carboxylates are available from the same starting materials.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.2. Typical procedure for the synthesis of pyrazole-3-carboxylates **3a–q**

To a THF solution of hydrazones **1a–q** (2.0 mmol) was added *n*-butyllithium (2 mL, 2.5 M solution in hexane) at -78°C . After stirring for 45 min at -78°C , the mixture was stirred for 15 min at 20°C and, subsequently, diethyl oxalate (2.2 mmol) was added at -78°C . After warming of the reaction mixture to 20°C within 16 h, the solvent (THF) was removed in vacuo. To the residue were added *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene. The mixture was stirred under reflux for 8 h. After cooling to 20°C , a saturated aqueous solution (20 mL) of NaHCO_3 was added and the mixture was stirred for 15 min at 20°C . The organic layer was separated, dried (Na_2SO_4) and filtered. The solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc=10:1–2:1).

3.2.1. Ethyl 5-phenyl-1*H*-pyrazole-3-carboxylate (**3a**)

Starting with a THF solution (20 mL) of hydrazone **1a** (2.0 mmol, 0.412 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3a** (53%, 229 mg) was isolated as a colourless oil. ^1H NMR (300 MHz, CDCl_3): δ =1.21 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 4.21 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.12 (s, 1H, CH), 7.35 (m, 3H, ArH), 7.75 (d, 3J =8.2 Hz, 2H, ArH). ^{13}C NMR

(75 MHz, CDCl_3): δ =14.2 (CH_2CH_3), 61.2 (OCH_2CH_3), 116.5 (CH, pyrazole), 125.9, 128.7, 129.2 (CH, ArH), 132.0 (C, Ar), 141.1, 148.5 (C, pyrazole), 161.2 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3222 (m), 3200 (m), 3099 (m), 1802 (m), 1766 (m), 1745 (s), 1609 (s), 1600 (s), 1555 (s), 1432 (s), 1369 (m), 1253 (s), 1212 (s), 989 (s), 957 (m), 853 (s), 823 (m), 707 (m). MS (EI, 70 eV): m/z (%)=216 (M^+ , 79), 171 (19), 170 (20), 114 (100), 104 (7), 89 (5), 77 (11). HRMS (EI, 70 eV): calcd for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2$ (M^+): 216.0893, found: 216.0892.

3.2.2. Ethyl 5-(4-tolyl)-1*H*-pyrazole-3-carboxylate (**3b**)

Starting with a THF solution (20 mL) of hydrazone **1b** (2.0 mmol, 0.460 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3b** (57%, 262 mg) was isolated as a colourless solid, mp $145\text{--}147^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ =1.21 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.25 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.95 (s, 1H, CH), 7.18 (d, 3J =8.4 Hz, 2H, ArH), 7.59 (d, 3J =8.4 Hz, 2H, ArH). ^{13}C NMR (75 MHz, CDCl_3): δ =12.1 (OCH_2CH_3), 19.3 (CH_3), 58.8 (OCH_2CH_3), 102.7 (CH), 123.5, 127.5 (CH, ArH), 125.1, 136.5 (2C, Ar), 139.2, 145.1 (C, pyrazole), 159.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (w), 2985 (w), 1728 (s), 1447 (w), 1294 (s), 1248 (s), 1016 (w), 922 (w), 820 (s), 766 (m). MS (EI, 70 eV): m/z (%)=230 (M^+ , 100), 185 (13), 158 (9), 128 (86), 131 (8), 69 (21), 57 (8). HRMS (EI, 70 eV): calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}_2$ (M^+): 230.1139, found: 230.1134.

3.2.3. Ethyl 5-(3-tolyl)-1*H*-pyrazole-3-carboxylate (**3c**)

Starting with a THF solution (20 mL) of hydrazone **1c** (2.0 mmol, 0.460 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3c** (61%, 189 mg) was isolated as a yellow solid, mp $98\text{--}100^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ =1.22 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.26 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.05 (s, 1H, CH), 7.15 (d, 3J =8.2 Hz, 1H, ArH), 7.23 (m, 2H, ArH), 7.52 (s, 1H, ArH), 8.21 (br s, NH). ^{13}C NMR (75 MHz, CDCl_3): δ =14.2 (OCH_2CH_3), 21.5 (CH_3), 61.3 (OCH_2CH_3), 105.4 (CH), 122.9, 126.5, 128.9, 129.5 (CH, ArH), 130.3, 138.7 (2C, Ar), 139.0, 148.8 (C, pyrazole), 160.9 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3254 (s), 3146 (m), 3120 (m), 2983 (m), 2924 (m), 1716 (s), 1916 (m), 1567 (m), 1480 (s), 1464 (s), 1386 (s), 1281 (s), 1170 (s), 998 (m), 848 (m), 794 (s), 779 (s), 697 (m). MS (EI, 70 eV): m/z (%)=230.1 (M^+ , 43), 185 (20), 184 (19), 128 (100), 127 (14), 102 (9), 91 (10). HRMS (EI, 70 eV): calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}_2$ (M^+): 230.1260, found: 230.1261.

3.2.4. Ethyl 3-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (**3d**)

Starting with a THF solution (20 mL) of hydrazone **1d** (2.0 mmol, 0.472 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3d** (45%,

221 mg) was isolated as a colourless solid, mp 130–132 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.61 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 3.71 (s, 3H, OCH_3), 4.12 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.79 (s, 1H, CH), 6.81 (d, 3J =8.4 Hz, 2H, ArH), 7.51 (d, 3J =8.4 Hz, 2H, ArH), 10.55 (br, 1H, NH). ^{13}C NMR (75 MHz, CDCl_3): δ =14.0 (OCH_2CH_3), 55.2 (OCH_3), 60.9, 62.2 (OCH_2CH_3), 104.2 (CH), 114.2, 127.0 (4CH, ArH), 122.52, 159.81 (2C, Ar), 148.89, 158.65 (C, pyrazole), 161.47 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3241 (m), 3191 (m), 3142 (m), 2990 (m), 1752 (m), 1723 (s), 1699 (s), 1615 (s), 1511 (s), 1456 (s), 1309 (m), 1279 (s), 1243 (s), 995 (s), 964 (m), 832 (s), 811 (m), 722 (m). MS (EI, 70 eV): m/z (%)=246 (M^+ , 83), 200 (22), 144 (100), 101 (11), 201 (11), 146 (6). HRMS (EI, 70 eV): calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{N}_2$ (M^+): 246.0995, found: 246.0998.

3.2.5. Ethyl 5-(naphth-1-yl)-1H-pyrazole-3-carboxylate (**3f**)

Starting with a THF solution (20 mL) of hydrazone **1f** (2.0 mmol, 0.568 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3f** (45%, 239 mg) was isolated as a yellow solid, mp 172–174 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.20 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 4.39 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.17 (s, 1H, CH), 7.57 (m, 3H, NaphH), 7.72 (d, 1H, NaphH), 7.96 (d, 2H, NaphH), 8.02 (s, 1H, NaphH). ^{13}C NMR (75 MHz, CDCl_3): δ =18.9 (OCH_2CH_3), 65.6 (OCH_2CH_3), 114.0 (CH), 130.5, 130.6, 131.2, 131.8, 132.4, 133.5, 134.1 (CH), 135.0, 148.6, 149.1 (3C), 150.3, 159.0 (C, pyrazole), 160.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3138 (m), 3058 (m), 2979 (m), 1732 (s), 1560 (m), 1382 (s), 1262 (s), 1244 (s), 1144 (s), 1100 (s), 1024 (s), 802 (s), 777 (s), 659 (m), 570 (m). MS (EI, 70 eV): m/z (%)=266 (M^+ , 19), 221 (100), 193 (26), 139 (25), 127 (56), 73 (35), 45 (16). HRMS (EI, 70 eV): calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_2$ (M^+): 266.1055, found: 266.1048.

3.2.6. Ethyl 3-(naphth-2-yl)-1H-pyrazole-3-carboxylate (**3g**)

Starting with a THF solution (20 mL) of hydrazone **1g** (2.0 mmol, 0.568 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3g** (38%, 202 mg) was isolated as a yellow solid, mp 172–174 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.35 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 4.37 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.41 (s, 1H, CH), 7.57 (m, 2H, NaphH), 7.83–8.02 (m, 4H, NaphH), 8.49 (s, 1H, NaphH). ^{13}C NMR (75 MHz, CDCl_3): δ =14.4 (OCH_2CH_3), 60.2 (OCH_2CH_3), 105.4 (CH), 123.5, 124.2, 126.6, 127.0, 127.0, 128.2, 128.8 (CH), 135.0, 148.6, 149.1 (3C), 150.3, 159.0 (C, pyrazole), 160.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3445 (m), 3433 (m), 3264 (s), 3137 (m), 2986 (m), 2926 (m), 1712 (s), 1559 (w), 1511 (s), 1481 (m), 1419 (m), 1384 (m), 1259 (s), 1184 (s), 1162 (s), 913 (w), 827 (m), 779 (m), 759 (m). MS (EI, 70 eV): m/z (%)=266 (M^+ , 15), 220 (11), 165 (18), 164 (100), 163 (32), 127 (12), 126 (6). HRMS (EI, 70 eV): calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_2$ (M^+): 266.1018, found: 266.1048.

3.2.7. Ethyl 5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate (**3h**)

Starting with a THF solution (20 mL) of hydrazone **1h** (2.0 mmol, 0.480 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3h** (42%, 211 mg) was isolated as a yellow solid, mp 179–181 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.19 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 4.18 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.90 (s, 1H, CH), 7.15 (d, 3J =8.4 Hz, 2H, ArH), 7.55 (d, 3J =8.4 Hz, 2H, ArH), 10.6 (br s, 1H, NH). ^{13}C NMR (75 MHz, CDCl_3): δ =14.2 (OCH_2CH_3), 61.4 (OCH_2CH_3), 105.3 (CH), 127.00, 129.14 (CH, ArH), 129.6, 134.5 (2C, Ar), 139.1, 147.9 (C, pyrazole), 160.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3132 (m), 2965 (s), 2939 (m), 2901 (m), 2873 (w), 1769 (s), 1734 (m), 1621 (m), 1444 (s), 1422 (s), 1331 (s), 1248 (s), 1182 (s), 942 (s), 865 (m), 824 (s), 773 (s), 728 (m). MS (EI, 70 eV): m/z (%)=252 [M^+ , ^{37}Cl] (28), 250 [M^+ , ^{35}Cl] (83), 206 (11), 204 (27), 148 (100), 113 (23), 75 (9). HRMS (EI, 70 eV): calcd for $\text{C}_{15}\text{H}_{15}\text{O}_4\text{N}_2\text{Cl}$ [M^+ , ^{35}Cl]: 250.0503, found: 250.0502.

3.2.8. Ethyl 5-(4-fluorophenyl)-1H-pyrazole-3-carboxylate (**3i**)

Starting with a THF solution (20 mL) of hydrazone **1i** (2.0 mmol, 0.448 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3i** (47%, 228 mg) was isolated as a yellow solid, mp 188–189 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.19 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 4.18 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.86 (s, 1H, CH), 7.00 (t, 3J =8.4 Hz, 2H, ArH), 7.60 (t, 3J =8.4 Hz, 2H, ArH), 9.50 (br s, 1H, NH). ^{13}C NMR (75 MHz, CDCl_3): δ =14.1 (OCH_2CH_3), 61.3 (OCH_2CH_3), 105.1 (CH), 115.7, 116.1 (d, $^3J_{\text{CF}}$ =95 Hz, CH, Ar), 127.5, 127.6 (d, $^2J_{\text{CF}}$ =109 Hz, CH, Ar), 126.6 (C, Ar), 160.7, (d, $^1J_{\text{CF}}$ =240 Hz, CF, Ar), 140.0, 137.6 (C, pyrazole), 164.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437 (w), 3193 (m), 3133 (m), 3058 (m), 2985 (w), 1727 (s), 1612 (w), 1508 (s), 1449 (w), 1411 (m), 1275 (s), 1246 (s), 1197 (s), 994 (s), 840 (s), 824 (s), 779 (s), 615 (m). MS (EI, 70 eV): m/z (%)=234 [M^+ , (73)], 189 (15), 188 (18), 134 (9), 133 (16), 132 (100). HRMS (EI, 70 eV): calcd for $\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_2\text{F}$ (M^+): 234.0799, found: 234.0797.

3.2.9. Ethyl 5-isopropyl-1H-pyrazole-3-carboxylate (**3j**)

Starting with a THF solution (20 mL) of hydrazone **1j** (2.0 mmol, 0.334 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3j** (72%, 262 mg) was isolated as a yellow solid, mp 61–63 °C. ^1H NMR (300 MHz, CDCl_3): δ =1.40 (m, 3J =7.2 Hz, 9H, 3 CH_3), 3.27 (m, 3J =7.2 Hz, 1H, $(\text{CH}_3)_2\text{CH}$), 4.48 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.70 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ =13.5, 22.3 ($(\text{CH}_3)_2\text{CH}$), 32.2 (OCH_2CH_3), 61.0 (OCH_2CH_3), 104.6, 105.9 (CH), 142.0, 153.4 (C, pyrazole), 162.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (m), 2968 (m), 2835 (m), 1809 (s), 1759 (s), 1534 (w), 1468 (s), 1386 (s), 1231

(s), 1219 (s), 1011 (s), 1000 (m), 969 (m), 778 (m). MS (EI, 70 eV): m/z (%)=182 (M^+ , 27), 121 (100), 107 (23), 79 (24), 67 (17), 29 (21). HRMS (EI, 70 eV): calcd for $C_9H_{14}O_2N_2$ (M^+): 182.1055, found: 182.1052.

3.2.10. Ethyl 5-*n*-propyl-1*H*-pyrazole-3-carboxylate (**3k**)

Starting with a THF solution (20 mL) of hydrazone **1k** (2.0 mmol, 0.334 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3k** (63%, 228 mg) was isolated as a yellow solid, mp 67–69 °C. 1H NMR (300 MHz, $CDCl_3$): δ =0.79 (t, 3J =7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.19 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 1.52 (m, 3J =7.2 Hz, 2H, $CH_2CH_2CH_3$), 2.54 (t, 3J =7.2 Hz, 2H, $CH_2CH_2CH_3$), 4.20 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.45 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.9 ($CH_2CH_2CH_3$), 14.5 (OCH_2CH_3), 22.7, 29.4 (2 CH_2), 62.4 (OCH_2CH_3), 106.4 (CH), 142.4, 147.3 (C, pyrazole), 162.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2999 (m), 2964 (m), 2831 (m), 1803 (s), 1765 (s), 1523 (w), 1478 (s), 1389 (s), 1236 (s), 1212 (s), 1019 (s), 1003 (m), 969 (m), 778 (m). MS (EI, 70 eV): m/z (%)=182 (M^+ , 18), 121 (100), 108 (51), 107 (23), 79 (14), 43 (15), 29 (11). HRMS (EI, 70 eV): calcd for $C_9H_{14}O_2N_2$ (M^+): 182.1055, found: 182.1051.

3.2.11. Ethyl 4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (**3l**)

Starting with a THF solution (20 mL) of hydrazone **1l** (2.0 mmol, 0.438 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3l** (62%, 251 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.22 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 2.54 (s, 3H, CH_3), 4.25 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.48 (m, 3H, ArH), 7.63 (d, 3J =8.2 Hz, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =10.1 (CH_2CH_3), 14.5 (CH_3), 60.8 (OCH_2CH_3), 128.0, 128.4, 129.0, 130.2, 130.8 (CH, ArH), 133.7 (C, Ar), 117.4, 138.3, 145.0 (C, pyrazole), 161.21 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3221 (w), 3123 (m), 3099 (m), 3025 (m), 2956 (w), 1861 (s), 1821 (s), 1399 (s), 1365 (s), 1332 (s), 1299 (s), 1251 (s), 1989 (s), 1005 (s), 986 (s), 865 (m), 779 (m), 763 (m), 699 (m). MS (EI, 70 eV): m/z (%)=231 (M^+ , 13), 230 (90), 185 (18), 184 (26), 183 (29), 129 (13), 128 (100), 77 (18). HRMS (EI, 70 eV): calcd for $C_{13}H_{14}O_2N_2$ (M^+): 203.1055, found: 203.1057.

3.2.12. Ethyl 4,5-dihydro-1*H*-benzo[*g*]indazole-3-carboxylate (**3m**)

Starting with a THF solution (20 mL) of hydrazone **1m** (2.0 mmol, 0.464 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3m** (54%, 261 mg) was isolated as a yellow solid, mp 153–156 °C. 1H NMR (300 MHz, $CDCl_3$): δ =1.21 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 2.91 (m, 4H, CH_2), 4.14 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 7.17 (m, 3H, ArH), 7.72 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.7 (OCH_2CH_3), 19.9, 29.4

(CH_2), 61.1 (OCH_2CH_3), 122.6, 127.2, 128.6, 129.4 (CH), 120.1, 137.0 (2C), 128.3, 133.9, 145.8 (3C, pyrazole), 161.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (w), 2985 (m), 2963 (m), 1724 (s), 1443 (w), 1294 (s), 1248 (s), 1016 (w), 928 (w), 820 (s), 761 (m). MS (EI, 70 eV): m/z (%)=242 (M^+ , 16), 240 (100), 212 (6), 195 (24), 194 (31), 168 (43), 140 (43), 139 (22), 138 (95), 113 (8). HRMS (EI, 70 eV): calcd for $C_{14}H_{14}O_2N_2$ (M^+): 242.1049, found: 242.1047.

3.2.13. Ethyl 4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (**3n**)

Starting with a THF solution (20 mL) of hydrazone **1n** (2.0 mmol, 0.368 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3n** (43%, 167 mg) was isolated as a yellow oil, mp 116–118 °C. 1H NMR (300 MHz, $CDCl_3$): δ =1.27 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 1.62–1.85 (m, 4H, CH_2), 2.53–2.67 (m, 4H, CH_2), 4.27 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 9.00 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.4 (OCH_2CH_3), 21.7, 22.1, 22.3, 22.5 (CH_2), 60.9 (OCH_2CH_3), 120.3, 136.2, 145.6 (3C), 161.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3240 (s), 3216 (s), 147 (s), 3130 (s), 2986 (m), 2938 (s), 2859 (s), 2768 (m), 1727 (s), 1719 (s), 1446 (s), 1328 (s), 1262 (s), 1228 (s), 1176 (s), 1156 (s), 933 (s), 863 (s), 778 (s), 623 (s), 582 (s). MS (EI, 70 eV): m/z (%)=194 (M^+ , 37), 165 (100), 149 (20), 121 (32), 94 (7), 67 (9). HRMS (EI, 70 eV): calcd for $C_{11}H_{18}O_2N_2$ (M^+): 194.1049, found: 194.1046.

3.2.14. Ethyl 1,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-3-carboxylate (**3o**)

Starting with a THF solution (20 mL) of hydrazone **1o** (2.0 mmol, 0.396 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol), **3o** (40%, 167 mg) was isolated as a yellow solid, mp 60–63 °C. 1H NMR (300 MHz, $CDCl_3$): δ =1.24 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 1.58 (m, 4H, CH_2), 1.73 (m, 2H, CH_2), 2.67, 2.83 (mm, 4H, CH_2), 4.28 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 9.41 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.2 (OCH_2CH_3), 23.2, 26.1, 27.1, 28.7, 31.1 (CH_2), 59.8 (OCH_2CH_3), 123.5, 133.6, 149.7 (3C), 160.6 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3179 (s), 3122 (s), 3074 (s), 2923 (s), 2850 (m), 1716 (s), 1581 (w), 1514 (w), 1443 (s), 1414 (s), 1259 (s), 1243 (s), 1158 (s), 1132 (s), 1044 (s), 956 (m), 886 (m), 791 (m), 722 (w). MS (EI, 70 eV): m/z (%)=208 (M^+ , 33), 179 (100), 161 (52), 135 (13), 133 (16). HRMS (EI, 70 eV): calcd for $C_{11}H_{16}O_2N_2$ (M^+): 208.1206, found: 208.1201.

3.2.15. Ethyl 4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*c*]pyrazole-3-carboxylate (**3p**)

Starting with a THF solution (20 mL) of hydrazone **1p** (2.0 mmol, 0.426 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3p** (38%, 168 mg) was isolated as a yellow solid, mp 121–123 °C. 1H NMR (300 MHz, $CDCl_3$): δ =1.20 (t, 3J =7.2 Hz, 3H,

OCH₂CH₃), 1.25–1.40 (m, 4H, 2CH₂), 1.50–1.60 (m, 4H, CH₂), 2.68, 2.75 (mm, 4H, 2CH₂), 4.19, 4.30 (q, ³J=7.2 Hz, 2H, OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ=12.9 (OCH₂CH₃), 20.4, 23.7, 24.5, 24.6, 27.4, 28.9 (6CH₂), 59.6 (OCH₂CH₃), 121.9, 134.6, 146.9 (3C), 160.9 (CO). IR (KBr, cm⁻¹): $\tilde{\nu}$ = 3183 (m), 3125 (m), 2928 (m), 2853 (m), 1717 (s), 1456 (s), 1445 (s), 1270 (s), 1245 (s), 1151 (s), 1095 (s), 1043 (s), 948 (m), 865 (m), 779 (m), 732 (m). MS (EI, 70 eV): *m/z* (%)=222 (M⁺, 46), 194 (14), 193 (86), 177 (12), 176 (25), 175 (100), 149 (13), 147 (12), 121 (12), 120 (12). HRMS (EI, 70 eV): calcd for C₁₂H₁₈O₂N₂ (M⁺): 222.1362, found: 222.1358.

3.2.16. Ethyl 4,5,6,7,8,9,10,11,12,13-decahydro-1H-cyclo-dodeca[c]pyrazole-3-carboxylate (**3q**)

Starting with a THF solution (20 mL) of hydrazone **1q** (2.0 mmol, 0.536 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene, **3q** (34%, 189 mg) was isolated as a yellow solid, mp 121–123 °C. ¹H NMR (300 MHz, CDCl₃): δ=1.09 (t, ³J=7.2 Hz, 3H, OCH₂CH₃), 1.05–1.42 (m, 12H, CH₂), 1.63 (m, 4H, CH₂), 2.59 (m, 4H, CH₂), 4.15 (q, ³J=7.2 Hz, 2H, OCH₂CH₃), 9.92 (br s, 1H, NH). ¹³C NMR (75 MHz, CDCl₃): δ=14.0 (OCH₂CH₃), 20.5, 21.0, 22.1, 22.9, 24.0, 25.1, 25.2, 25.2, 27.3, 28.1 (CH₂), 60.3 (OCH₂CH₃), 121.9, 137.4, 145.9 (3C), 162.0 (CO). IR (KBr, cm⁻¹): $\tilde{\nu}$ = 3419 (w), 3178 (m), 3120 (m), 2957 (s), 2930 (s), 2848 (m), 1720 (s), 1577 (w), 1470 (m), 1440 (m), 1410 (m), 1296 (m), 1260 (m), 1161 (s), 1182 (s), 1094 (m), 964 (w), 793 (w), 728 (w). MS (EI, 70 eV): *m/z* (%)=278 (M⁺, 69), 235 (23), 232 (37), 205 (100), 168 (28), 149 (21), 122 (39), 121 (20). HRMS (EI, 70 eV): calcd for C₁₆H₂₆O₂N₂ (M⁺): 278.2115, found: 278.2113.

3.3. Typical procedure for the synthesis of pyrazole-1,5-carboxylates **4a–q**

To a THF solution of hydrazones **1a–q** (2.0 mmol) was added *n*-butyllithium (2 mL, 2.5 M solution in hexane) at –78 °C. After stirring for 45 min at –78 °C, the mixture was stirred for 15 min at 20 °C and, subsequently, diethyl oxalate (2.2 mmol) was added at –78 °C. After warming of the reaction mixture to 20 °C within 16 h, the solvent (THF) was removed in vacuo. To the residue were added TFA (1 mL) and 30 mL of CH₂Cl₂. The mixture was stirred under reflux for 8 h. After cooling to 20 °C, a saturated solution (20 mL) of NaHCO₃ was added and the mixture was stirred for 15 min at 20 °C. The combined organic layers were dried (Na₂SO₄), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc=10:1–2:1).

3.3.1. Diethyl phenylpyrazole-1,5-dicarboxylate (**4a**)

Starting with a THF solution (20 mL) of hydrazone **1a** (2.0 mmol, 0.412 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol),

TFA (1 mL) and 30 mL of CH₂Cl₂, **4a** (59%, 339 mg) was isolated as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ=1.28–1.39 (tt, ³J=7.2 Hz, 6H, 2OCH₂CH₃), 4.29–4.59 (qq, ³J=7.2 Hz, 4H, 2OCH₂CH₃), 7.06 (s, 1H, CH), 7.39 (m, 3H, ArH), 7.87 (d, ³J=8.2 Hz, 2H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ=14.4, 14.7 (2CH₂CH₃), 62.0, 65.6 (2OCH₂CH₃), 110.4 (CH, pyrazole), 126.8, 127.1, 128.4, 129.1, 129.8 (CH, ArH), 130.9 (C, Ar), 138.8, 149.4 (C, pyrazole), 154.4, 160.6 (2CO). IR (KBr, cm⁻¹): $\tilde{\nu}$ = 3201 (m), 3012 (s), 2956 (m), 2931 (w), 1798 (s), 1731 (s), 1615 (m), 1565 (m), 1538 (m), 1465 (s), 1321 (s), 1254 (s), 935 (s), 865 (m), 732 (m). MS (EI, 70 eV): *m/z* (%)=288 (M⁺, 56), 171 (100), 170 (15), 142 (23), 114 (29), 104 (8), 89 (29), 77 (18). HRMS (EI, 70 eV): calcd for C₁₅H₁₆O₄N₂ (M⁺): 288.1110, found: 288.1115.

3.3.2. Diethyl 3-(4-tolyl)-1H-pyrazole-1,5-dicarboxylate (**4b**)

Starting with a THF solution (20 mL) of hydrazone **1b** (2.0 mmol, 0.46 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH₂Cl₂, **4b** (61%, 368 mg) was isolated as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ=1.31, 1.39 (tt, ³J=7.2 Hz, 6H, 2OCH₂CH₃), 2.31 (s, 3H, CH₃), 4.25, 4.47 (qq, ³J=7.2 Hz, 4H, 2OCH₂CH₃), 6.94 (s, 1H, CH), 7.17 (d, ³J=8.3 Hz, 2H, ArH), 7.67 (d, ³J=8.3 Hz, 2H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ=14.1, 14.2 (OCH₂CH₃), 21.4 (CH₃), 62.4, 65.3 (OCH₂CH₃), 110.0 (CH), 126.4, 129.6 (CH, ArH), 128.1, 139.6 (2C, Ar), 138.1, 147.9 (C, pyrazole), 154.2, 160.0 (CO). IR (KBr, cm⁻¹): $\tilde{\nu}$ = 3140 (m), 2984 (s), 2939 (m), 2871 (w), 1770 (s), 1739 (s), 1616 (m), 1558 (m), 1522 (m), 1403 (s), 1371 (s), 1293 (s), 947 (s), 861 (m), 720 (m). MS (EI, 70 eV): *m/z* (%)=302 (M⁺, 60), 229 (19), 203.1 (56), 185 (29), 184 (25), 158 (21), 128 (100), 29.2 (15), 91.1 (10). HRMS (EI, 70 eV): calcd for C₁₆H₁₈O₄N₂ (M⁺): 302.1260, found: 302.1261.

3.3.3. Diethyl 3-(3-tolyl)-1H-pyrazole-1,5-dicarboxylate (**4c**)

Starting with a THF solution (20 mL) of hydrazone **1c** (2.0 mmol, 0.461 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH₂Cl₂, **4c** (48%, 289 mg) was isolated as a colourless oil. ¹H NMR (300 MHz, CDCl₃): δ=1.35, 1.40 (tt, ³J=7.2 Hz, 3H, OCH₂CH₃), 2.35 (s, 3H, CH₃), 4.35, 4.47 (qq, ³J=7.2 Hz, 2H, OCH₂CH₃), 6.97 (s, 1H, CH), 7.13, 7.53 (dd, ³J=8.2 Hz, 2H, ArH), 7.20 (m, 1H, ArH), 7.61 (s, 1H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ=14.2, 14.3 (OCH₂CH₃), 21.5 (CH₃), 62.5, 65.4 (OCH₂CH₃), 110.3 (CH), 123.8, 127.2, 128.8, 130.4 (CH, ArH), 130.9, 138.7 (2C, Ar), 138.1, 149.6 (C, pyrazole), 154.9, 160.4 (CO). IR (KBr, cm⁻¹): $\tilde{\nu}$ = 3138 (w), 3053 (w), 2983 (m), 2938 (m), 2872 (w), 1767 (s), 1739 (s), 1558 (m), 1466 (s), 1446 (s), 1338 (s), 1293 (s), 1155 (s), 963 (s), 862 (s), 791 (s), 771 (s), 705 (m). MS (EI, 70 eV): *m/z* (%)=302 (M⁺, 76), 229 (21), 185 (13), 184 (12), 129 (14), 128 (100), 102 (6).

HRMS (EI, 70 eV): calcd for $C_{16}H_{18}O_4N_2$ (M^+): 302.1260, found: 302.1262.

3.3.4. Diethyl 3-(4-methoxyphenyl)-1H-pyrazole-1,5-dicarboxylate (**4d**)

Starting with a THF solution (20 mL) of hydrazone **1d** (2.0 mmol, 0.472 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4d** (47%, 302 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.31, 1.40 (t, 3J =7.2 Hz, 3H, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 4.33, 4.47 (q, 3J =7.2 Hz, 2H, OCH_2CH_3), 6.85 (s, 1H, *CH*), 6.90 (d, 2H, *ArH*), 7.67 (d, 2H, *ArH*). ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.9, 14.0 (OCH_2CH_3), 55.2 (OCH_3), 62.1, 65.0 (OCH_2CH_3), 109.6 (*CH*), 114.0, 127.7 (*CH*, *ArH*), 123.6, 154.6 (2C, *Ar*), 138.7, 148.7 (C, pyrazole), 157.9, 162.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3138 (w), 2983 (m), 2938 (m), 2838 (w), 1761 (s), 1739 (s), 1613 (s), 1524 (m), 1456 (m), 1433 (s), 1371 (s), 1293 (s), 948 (m), 861 (m), 770 (m). MS (EI, 70 eV): m/z (%)=318 (M^+ , 75), 246 (45), 231 (10), 200 (33), 200 (22), 144 (100), 174 (14), 146 (10), 29 (16). HRMS (EI, 70 eV): calcd for $C_{16}H_{18}O_5N_2$ (M^+): 318.1210, found: 318.1216.

3.3.5. Diethyl 3-(3-methoxyphenyl)-1H-pyrazole-1,5-dicarboxylate (**4e**)

Starting with a THF solution (20 mL) of hydrazone **1e** (2.0 mmol, 0.472 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4e** (42%, 254 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.27, 1.38 (t, 3J =7.2 Hz, 3H, $2OCH_2CH_3$), 3.82 (s, 3H, OCH_3), 4.32, 4.45 (q, 3J =7.2 Hz, 2H, $2OCH_2CH_3$), 7.20 (s, 1H, *CH*), 6.81–6.96 (m, 2H, *ArH*), 7.92 (m, 1H, *ArH*). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.2, 14.2 ($2OCH_2CH_3$), 55.3 (OCH_3), 62.0, 64.9 (OCH_2CH_3), 111.1 (*CH*), 114.0, 120.7, 129.2, 130.5 (*CH*, *ArH*), 119.9, 151.7 (2C, *Ar*), 136.5, 148.3 (C, pyrazole), 157.5, 162.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2983 (m), 2939 (s), 2909 (m), 2839 (w), 1761 (s), 1736 (s), 1604 (m), 1586 (m), 1504 (m), 1470 (s), 1439 (s), 1342 (s), 1294 (s), 948 (s), 861 (m), 829 (m), 758 (m). MS (EI, 70 eV): m/z (%)=318 (M^+ , 100), 201 (35), 145 (30), 144 (32), 134 (18), 132.1 (37), 114 (28), 29 (32). HRMS (EI, 70 eV): calcd for $C_{16}H_{18}O_4N_2$ (M^+): 318.1210, found: 318.1217.

3.3.6. Diethyl 3-(4-chlorophenyl)-1H-pyrazole-1,5-dicarboxylate (**4h**)

Starting with a THF solution (20 mL) of hydrazone **1h** (2.0 mmol, 0.481 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4h** (54%, 347 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.23, 1.32 (tt, 3J =7.2 Hz, 6H, $2OCH_2CH_3$), 4.27, 4.39 (qq, 3J =7.2 Hz, 4H, $2OCH_2CH_3$), 6.88 (s, 1H, *CH*), 7.24 (d, 3J =8.3 Hz, 2H, *ArH*), 7.68 (d, 3J =8.3 Hz, 2H, *ArH*). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.1 ($2CH_3$), 62.4, 65.4 ($2CH_2$), 109.8 (*CH*), 127.8, 129.0 (*CH*, *ArH*), 135.4, 138.6 (2C, *Ar*),

138.6, 148.9 (C, pyrazole), 152.9, 160.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3139 (m), 2984 (s), 2939 (m), 2907 (m), 2873 (w), 1763 (s), 1739 (m), 1602 (m), 1449 (s), 1427 (s), 1337 (s), 1244 (s), 1180 (s), 948 (s), 861 (m), 827 (s), 770 (s), 738 (m). MS (EI, 70 eV): m/z (%)=324 [M^+ , ^{37}Cl] (30), 322 [M^+ , ^{35}Cl] (54), 250 (74), 205 (37), 148 (100), 113 (33), 75 (9). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}O_4N_2Cl$ [M^+ , ^{35}Cl]: 322.0720, found: 322.0724.

3.3.7. Diethyl 3-(4-fluorophenyl)pyrazole-1,5-dicarboxylate (**4i**)

Starting with a THF solution (20 mL) of hydrazone **1i** (2.0 mmol, 0.448 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4i** (41%, 250 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.22–1.38 (tt, 3J =7.2 Hz, 6H, $2OCH_2CH_3$), 4.26–4.49 (qq, 3J =7.2 Hz, 4H, $2OCH_2CH_3$), 6.89 (s, 1H, *CH*), 7.00 (t, 3J =8.3 Hz, 2H, *ArH*), 7.70 (t, 3J =8.3 Hz, 2H, *ArH*). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.4, 14.4 ($2CH_3$), 62.7, 65.4 ($2CH_2$), 110.1 (*CH*), 116.1, 116.3 (d, $^3J_{CF}$ =95 Hz, *CH*, *Ar*), 127.5, 127.8 (d, $^2J_{CF}$ =109 Hz, *CH*, *Ar*), 127.5 (C, *Ar*), 153.4, 160.4 (d, 1J =240 Hz, CF, *Ar*), 138.9, 149.3 (C, pyrazole), 162.2, 165.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3139 (w), 3067 (w), 2985 (s), 2940 (m), 2908 (w), 1763 (s), 1739 (s), 1608 (s), 1455 (s), 1433 (s), 1371 (s), 1244 (s), 1159 (s), 949 (s), 831 (s), 770 (s). MS (EI, 70 eV): m/z (%)=306 [M^+ , (45)], 235 (10), 234 (75), 233 (26), 189 (47), 188 (39), 162 (23), 134 (16), 133 (25), 132 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}O_4N_2F$ (M^+): 306.1016, found: 306.1011.

3.3.8. Diethyl isopropylpyrazole-1,5-dicarboxylate (**4j**)

Starting with a THF solution (20 mL) of hydrazone **1j** (2.0 mmol, 0.344 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4j** (72%, 365 mg) was isolated as a yellow oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.15 (d, 3J =7.2 Hz, 6H, $(CH_3)_2CH$), 1.22–1.34 (tt, 3J =7.2 Hz, 6H, $2OCH_2CH_3$), 2.95 (m, 3J =7.2 Hz, 1H, $(CH_3)_2CH$), 4.19–4.43 (qq, 3J =7.2 Hz, 4H, $2OCH_2CH_3$), 6.49 (s, 1H, *CH*). ^{13}C NMR (75 MHz, $CDCl_3$): δ =14.2, 28.0 ($2OCH_2CH_3$), 22.2 ($(CH_3)_2CH$), 62.4, 65.7 ($2CH_2$), 110.1, 110.2 (*CH*), 149.3, 160.8 (C, pyrazole), 138.2, 162.1 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2973 (m), 2938 (w), 2876 (w), 1776 (s), 1739 (s), 1657 (s), 1479 (s), 1373 (s), 1292 (s), 1235 (s), 1064 (s), 1017 (m), 981 (m), 771 (m). MS (EI, 70 eV): m/z (%)=254 (M^+ , 38), 209 (12), 182 (16), 181 (62), 167 (30), 137 (38), 136 (26), 135 (70), 121 (100), 67 (12), 29 (31). HRMS (EI, 70 eV): calcd for $C_{12}H_{18}O_4N_2$ (M^+): 254.1261, found: 254.1258.

3.3.9. Diethyl *n*-propylpyrazole-1,5-dicarboxylate (**4k**)

Starting with a THF solution (20 mL) of hydrazone **1k** (2.0 mmol, 0.344 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4k** (70%, 365 mg) was isolated as a yellow oil. 1H NMR (300 MHz, $CDCl_3$):

$\delta=0.85$ (t, $^3J=7.2$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.24–1.40 (tt, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 1.61 (m, $^3J=7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.55 (t, $^3J=7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.24–4.48 (qq, $^3J=7.2$ Hz, 4H, $2\text{OCH}_2\text{CH}_3$), 6.49 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): $\delta=14.5$ ($\text{CH}_2\text{CH}_2\text{CH}_3$), 22.6, 30.7 ($2\text{OCH}_2\text{CH}_3$), 62.5, 65.3 (2CH_2), 111.7 (CH), 149.2, 160.8 (C, pyrazole), 132.9, 158.3 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}=2964$ (m), 2936 (m), 2874 (m), 1775 (s), 1739 (s), 1558 (w), 1471 (s), 1374 (s), 1297 (s), 1237 (s), 1064 (s), 1018 (m), 986 (m), 770 (m). MS (EI, 70 eV): m/z (%) = 254 (M^+ , 4), 226 (27), 209 (10), 182 (21), 154 (83), 137 (42), 136 (17), 121 (24), 108 (100), 107 (14), 79 (21). HRMS (EI, 70 eV): calcd for $\text{C}_{12}\text{H}_{18}\text{O}_4\text{N}_2$ (M^+): 254.1261, found: 254.1264.

3.3.10. Diethyl 4-methyl-5-phenylpyrazole-1,5-dicarboxylate (**4l**)

Starting with a THF solution (20 mL) of hydrazone **1l** (2.0 mmol, 0.412 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4l** (69%, 416 mg) was isolated as a yellow oil. ^1H NMR (300 MHz, CDCl_3): $\delta=1.30$ – 1.40 (tt, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 2.20 (s, 3H, CH_3), 4.30–4.59 (qq, $^3J=7.2$ Hz, 4H, $2\text{OCH}_2\text{CH}_3$), 7.30 (m, 3H, ArH), 7.59 (d, $^3J=8.2$ Hz, 2H, ArH). ^{13}C NMR (75 MHz, CDCl_3): $\delta=9.8$, 14.5 ($2\text{CH}_2\text{CH}_3$), 15.6 (CH_3), 62.9, 65.4 ($2\text{OCH}_2\text{CH}_3$), 128.7, 128.9, 129.3 (CH, ArH), 131.9 (C, Ar), 120.8, 136.1, 149.5 (C, pyrazole), 155.0, 161.6 (2CO). IR (KBr, cm^{-1}): $\tilde{\nu}=3063$ (w), 2982 (m), 2964 (m), 2953 (m), 2873 (w), 1771 (s), 1758 (s), 1444 (s), 1371 (s), 1345 (s), 1302 (s), 1244 (s), 1216 (s), 1083 (s), 1047 (s), 860 (m), 774 (m), 763 (m), 700 (m). MS (EI, 70 eV): m/z (%) = 302 (M^+ , 60), 230 (47), 229 (23), 207 (13), 185 (47), 184 (45), 128 (100), 104 (22), 77 (22), 29 (26). HRMS (EI, 70 eV): calcd for $\text{C}_{16}\text{H}_{18}\text{O}_4\text{N}_2$ (M^+): 302.1261, found: 302.1263.

3.3.11. Diethyl 4,5-dihydrobenzo[g]indazole-1,5-carboxylate (**4m**)

Starting with a THF solution (20 mL) of hydrazone **1m** (2.0 mmol, 0.464 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4m** (49%, 339 mg) was isolated as a yellow solid, mp 131–133 °C. ^1H NMR (300 MHz, CDCl_3): $\delta=1.36$ – 1.51 (tt, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 2.94 (m, 4H, CH_2), 4.20–4.58 (qq, $^3J=7.2$ Hz, 4H, $2\text{OCH}_2\text{CH}_3$), 7.29 (m, 3H, ArH), 8.03 (m, 1H, ArH). ^{13}C NMR (75 MHz, CDCl_3): $\delta=14.2$, 19.152 ($2\text{OCH}_2\text{CH}_3$), 29.4, 31.9 (2CH_2), 62.0, 64.9 ($2\text{OCH}_2\text{CH}_3$), 124.0, 127.1, 128.5, 129.5 (CH), 127.4, 137.6 (2C), 127.4, 129.5, 151.4 (3C, pyrazole), 149.5, 160.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}=3434$ (w), 3412 (m), 3142 (m), 2956 (m), 1856 (s), 1567 (w), 1354 (s), 1198 (s), 1101 (w), 899 (w), 856 (s), 785 (m). MS (EI, 70 eV): m/z (%) = 314 (M^+ , 100), 242 (36), 241 (20), 213 (37), 196 (49), 195 (65), 169 (80), 168 (59), 140 (88), 139 (63), 115 (35). HRMS (EI, 70 eV): calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{N}_2$ (M^+): 314.1261, found: 314.1262.

3.3.12. Diethyl 4,5,6,7-tetrahydroindazole-1,5-dicarboxylate (**4n**)

Starting with a THF solution (20 mL) of hydrazone **1n** (2.0 mmol, 0.481 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4n** (44%, 234 mg) was isolated as a colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta=1.35$, 1.41 (t, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 1.63–1.84 (m, 4H, CH_2), 2.66, 2.72 (tt, $^3J=6.8$ Hz, 4H, 2CH_2), 4.35, 4.49 (q, $^3J=7.2$ Hz, 4H, $2\text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3): $\delta=12.8$, 12.9 (OCH_2CH_3), 19.3, 21.0, 21.2, 22.9 (CH_2), 60.4, 63.2 (OCH_2CH_3), 120.0, 136.9, 146.5 (3C), 152.3, 160.4 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}=2967$ (m), 2935 (s), 2857 (s), 2763 (m), 1725 (s), 1718 (s), 1444 (s), 1326 (s), 1176 (s), 933 (s), 868 (s), 774 (s), 622 (s), 587 (s). MS (EI, 70 eV): m/z (%) = 266 (M^+ , 24), 221 (15), 193 (54), 165 (100), 149 (53), 121 (48), 91 (17), 79 (14), 67 (15). HRMS (EI, 70 eV): calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4\text{N}_2$ (M^+): 266.1267, found: 266.1269.

3.3.13. Diethyl 4,5,6,7,8-pentahydrocyclohepta[c]pyrazole-1,5-dicarboxylate (**4o**)

Starting with a THF solution (20 mL) of hydrazone **1o** (2.0 mmol, 0.396 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4o** (47%, 263 mg) was isolated as a colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta=1.35$, 1.41 (tt, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 1.53–1.77 (m, 4H, CH_2), 1.76–1.91 (m, 2H, CH_2), 2.59, 2.81 (2×m, 4H, 2CH_2), 4.37, 4.44 (2×q, $^3J=7.2$ Hz, 2H, OCH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3): $\delta=12.0$, 12.2 ($2\text{OCH}_2\text{CH}_3$), 22.2, 25.0, 27.6, 28.2, 30.0 (CH_2), 62.6, 63.9 ($2\text{OCH}_2\text{CH}_3$), 125.3, 131.8, 147.0 (3C), 156.8, 159.4 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}=2923$ (s), 2850 (m), 1716 (s), 1581 (w), 1514 (w), 1443 (s), 1414 (s), 1259 (s), 1243 (s), 1158 (s), 1132 (s), 1044 (s), 956 (m), 886 (m), 791 (m), 722 (w). MS (EI, 70 eV): m/z (%) = 280 (M^+ , 35), 234 (43), 207 (53), 179 (78), 161 (100), 91 (12), 79 (17), 67 (17). HRMS (EI, 70 eV): calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{N}_2$ (M^+): 280.1417, found: 280.1418.

3.3.14. Diethyl 4,5,6,7,8,9-hexahydrocycloocta[c]pyrazole-1,5-dicarboxylate (**4p**)

Starting with a THF solution (20 mL) of hydrazone **1p** (2.0 mmol, 0.424 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4p** (42%, 247 mg) was isolated as a colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta=1.36$, 1.37 (t, $^3J=7.2$ Hz, 6H, $2\text{OCH}_2\text{CH}_3$), 1.32–1.54 (m, 4H, 2CH_2), 1.63–1.79 (m, 4H, CH_2), 2.59, 2.82 (mm, 4H, 2CH_2), 4.39, 4.49 (q, $^3J=7.2$ Hz, 4H, $2\text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3): $\delta=14.4$, 14.52 ($2\text{OCH}_2\text{CH}_3$), 21.6, 25.5, 25.7, 25.8, 30.0, 30.0 (6CH_2), 62.4, 65.0 ($2\text{OCH}_2\text{CH}_3$), 126.5, 134.1, 149.4 (3C), 158.3, 161.6 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}=3481$ (w), 2982 (m), 2930 (s), 2855 (m), 1753 (s), 1732 (s), 1482 (s), 1459 (s), 1384 (s), 1374 (s), 1235 (s), 1157 (s), 1051 (s), 969 (w), 862 (m), 831 (m), 765 (m). MS (EI, 70 eV): m/z (%) = 294 (M^+ , 22), 248 (31), 221 (33), 193

(29), 193 (29), 177 (23), 176 (53), 175 (100), 161 (20), 122 (23). HRMS (EI, 70 eV): calcd for $C_{15}H_{22}O_4N_2$ (M^+): 294.0118, found: 294.0116.

3.3.15. Diethyl 4,5,6,7,8,9,10,11,12,13-decahydro-cyclododeca[c]pyrazole-1,5-dicarboxylate (**4q**)

Starting with a THF solution (20 mL) of hydrazone **1q** (2.0 mmol, 0.536 g), *n*-butyllithium (2.0 mL, 2.0 M solution in hexane, 2.5 mmol), diethyl oxalate (0.3 mL, 2.2 mmol), TFA (1 mL) and 30 mL of CH_2Cl_2 , **4q** (65%, 227.5 mg) was isolated as a colourless oil. 1H NMR (300 MHz, $CDCl_3$): δ =1.36, 1.37 (t, 3J =7.2 Hz, 6H, $2OCH_2CH_3$), 1.32–1.54 (m, 12H, $6CH_2$), 1.63, 1.79 (m, 4H, CH_2), 2.51, 2.68 (t, 4H, $2CH_2$), 4.39, 4.49 (q, 3J =7.2 Hz, 4H, $2OCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ =13.7, 13.9 ($2OCH_2CH_3$), 20.1, 22.7, 22.8, 23.0, 24.7, 24.9, 25.5, 25.6, 27.4, 27.9 ($10CH_2$), 61.68, 64.39 ($2OCH_2CH_3$), 125.9, 134.61, 149.0 (3C), 156.8, 161.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3485 (w), 2989 (m), 2927 (s), 2855 (m), 1749 (s), 1736 (s), 1485 (s), 1459 (s), 1381 (s), 1374 (s), 1235 (s), 1157 (s), 1049 (s), 969 (w), 862 (m), 831 (m), 765 (m). MS (EI, 70 eV): m/z (%)=350 (M^+ , 22), 278 (19), 277 (100), 240 (17), 231 (21), 205 (11), 121 (10). HRMS (EI, 70 eV): calcd for $C_{15}H_{22}O_4N_2$ (M^+): 350.2200, found: 350.2195.

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