Regioselective Synthesis of Pyrazoles and Isoxazoles with Cyclopropanated Side-Chain

Franziska Bendrath,[a] Abiodun Falodun,[b] Zharylkasyn A. Abilov,[c] Alexander Villinger,[a] and Peter Langer[a,d]*

[a]Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin City, Nigeria
[c]Al-Farabi Kazakh National University, Al-Farabi ave. 71, 050040 Almaty, Kazakhstan
[d]Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
*E-mail: peter.langer@uni-rostock.de

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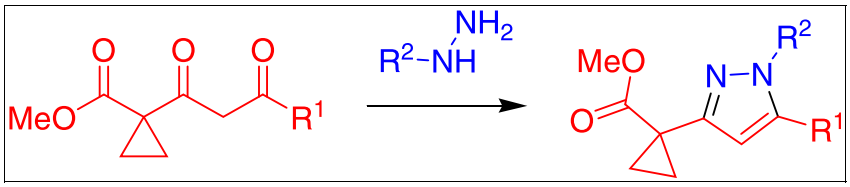

Pyrazoles and isoxazoles with cyclopropanated side-chain were prepared by cyclization of cyclopropanated 1,3,5-tricarbonyl compounds with hydrazine and hydroxylamine, respectively. The regioselectivity is influenced by the reaction conditions.

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INTRODUCTION

Pyrazoles are of considerable relevance in medicinal chemistry [1]. In particular, cyclopropanated pyrazoles show promising biological properties. For example, 1-(4-methoxybenzyl)-3-cyclopropyl-1*H*-pyrazol-5-amines exhibit antimicrobial activity; [2] 3-amino-5-cyclopropyl-pyrazoles have been used for the treatment of cancer and of Alzheimer's disease. [3] 3-Cyclopropyl-4-(3-amino-2-methylbenzoyl) pyrazoles, [4] *N*-cyclopropyl-1*H*-pyrazol-4-carboamides, [5] and pyrazol-substituted *O*-cyclopropylcarboxy-anilides [6] have been reported to act as herbicides and fungicides. Zoniporide is a selective inhibitor of sodium–hydrogen exchange in membranes and is used to reduce the risk of perioperative heart attacks (Scheme 1) [7].

Similar to pyrazoles, isoxazoles are also of considerable pharmacological relevance [8]. They are used as antibiotics and antiviral agents [9], and herbicides [10]. Isoxazolyl penicillins, such as dicloxacillin, are used for the fight against gram positive bacteria that are resistant against penicillin G [11].

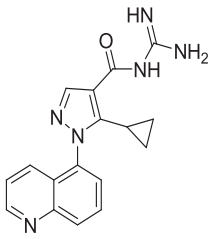
Herein, we report a convenient synthesis of novel pyrazoles and isoxazoles with cyclopropanated side-chain by regioselective cyclocondensation of readily available cyclopropanated 3,5-diketoesters with hydrazine and hydroxylamine, respectively.

RESULTS AND DISCUSSION

We have recently reported a convenient synthesis of cyclopropanated 3,5-diketoesters **1a–c** by the reaction of cyclopropanated dimethyl malonate with ketone enolates [12]. The reaction of aliphatic 3,5-diketoester **1a** with hydrazine hydrate (**2a**) afforded pyrazole **3a** in good yield (Scheme 2, Table 1). The reaction was carried out in EtOH at 50°C (method A). The reaction of **1a** with phenylhydrazine (**2b**) resulted, under identical conditions, in the formation of a mixture of regioisomers. In contrast, the reaction proceeded with excellent regioselectivity and the product **3b** was isolated in 79% yield when glacial acetic acid instead of ethanol was used (method B). Likewise, the application of method B was also allowed for the synthesis of products **3c–e** in good yields. In contrast, a regioisomeric mixture was obtained when method A was applied. The reaction of phenyl substituted 3,5-diketoester **1b** with parent hydrazine hydrate (**2a**) gave pyrazole **3f** in good yield (method A). The reaction of **1b** with methyl hydrazine afforded an unseparable 1:5 mixture of regioisomers **3g** and **4g** (method B). In contrast, the reaction of **1b** with (*p*-nitrophenyl)hydrazine afforded a separable mixture of **3h** (56%) and **4h** (10%). The reaction of *p*-methoxyphenyl substituted 3,5-diketoester **1c** with hydrazine hydrate (**2a**) gave pyrazole **3i** (method A). The reaction of **1c** with methyl hydrazine gave, similar to the corresponding reaction of **1b**, an unseparable 1:11 mixture of regioisomers **3j** and **4j** (method B). The reaction of **1c** with (*p*-nitrophenyl) hydrazine afforded pure **3k**, albeit, in low yield. The influence of the solvent on the regioselectivity of pyrazole formation has been previously reported [13].

The structures of the products were confirmed by H,[1]H-NOESY NMR spectroscopic studies. Relevant NOE correlations of **3b**,**h**,**k** and of **4j** are shown in Schemes 3 and 4, respectively.

Scheme 1. Structure of Zoniporide.



The structure of **3d** was independently confirmed by X-ray crystal structure analysis (Figure 1). The pyrazole and the *p*-nitrophenyl moiety are nearly in plane. This can be explained by the electronic *push–pull* interaction between the two rings.

The results can be explained as follows. In case of aliphatic 3,5-dioxoester **1a**, the lateral keto group is more electrophilic than the central one, because of steric reasons. In case of aryl substituted 3,5-dioxoesters **1b** and **1c**, the electrophilicity of the lateral keto group is decreased because of the mesomeric effect of the neighboring aryl group. The employment of glacial acetic acid results in complete and regioselective protonation of the more basic methyl substituted nitrogen atom of methyl hydrazine (**2c**). Therefore, the reaction of **2c** with **1a**, using method B, results in attack of the unprotonated NH_2 group at the sterically less hindered keto group located at carbon C-5 of **1a** and subsequent cyclization to give exclusively product **3c**. The cyclization of arylated hydrazines **2b** and **2e** with **1a**, using method B, gave products **3b** and **3e**. Their formation can be explained analogously. The reaction of methyl hydrazine with aryl substituted 3,5-dioxoesters **1b** and **1c** proceeded, as expected, by attack of the unprotonated NH_2 group to the more electrophilic keto group located at carbon C-3 of **1b** and **1c** and afforded products **4g** and **4j** as major components in the isomeric mixtures with **3g** and **3j**, respectively. The employment of *p*-nitrophenyl hydrazine (**2d**) is a special case. The application of method A in the reaction of **2d** with aliphatic 3,5-dioxoester **1a** mainly afforded **3d**. The product was isolated as a 5:1 mixture together with **4d** in moderate yield. This can be explained by the low nucleophilicity of the nitrogen atom attached to the electron withdrawing *p*-nitrophenyl group. The reaction of **2d** with **1a**, carried out by application of method B, resulted in selective formation of **3d** in very good yield. This can be explained again by protonation of the nitrogen atom attached to the aryl group. The cyclization of **2d** with arylated 3,5-dioxoesters afforded products **3h** and **3k**. The yields were relatively low, and the selectivity was not complete, which might be explained by the assumption that the nitrogen atom is not completely protonated, because of the electron withdrawing

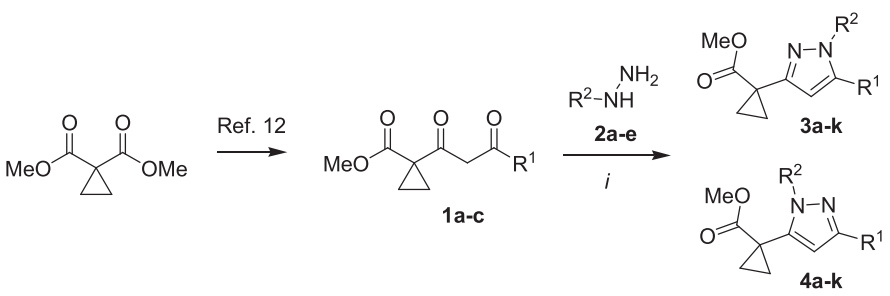
Table 1

Synthesis of pyrazoles **3** and **4**.

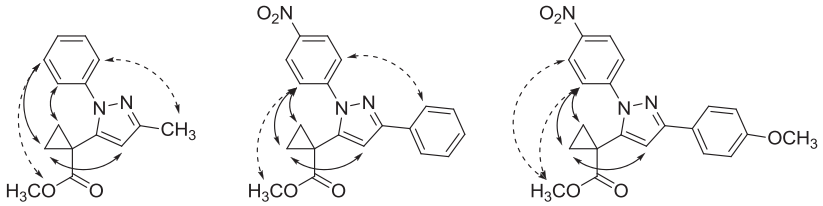
1	2	3, 4	R^1	R^2	Method [b]	% (**3**)[a]	% (**4**)[a]
a	**a**	**a**	Me	H	A	61	0
a	**b**	**b**	Me	Ph	B	79	0
a	**c**	**c**	Me	Me	B	83	0
a	**d**	**d**	Me	4-$NO_2C_6H_4$	A	57 (5:1)[c]	
a	**d**	**d**	Me	4-$NO_2C_6H_4$	B	84	0
a	**e**	**e**	Me	4-MeC_6H_4	B	62	0
b	**a**	**f**	Ph	H	A	76	0
b	**c**	**g**	Ph	Me	B	84 (1:5)[c]	
b	**d**	**h**	Ph	4-$NO_2C_6H_4$	B	56	10
c	**a**	**i**	4-(MeO)C_6H_4	H	A	54	0
c	**c**	**j**	4-(MeO)C_6H_4	Me	B	75 (1:11)[c]	
c	**d**	**k**	4-(MeO)C_6H_4	4-$NO_2C_6H_4$	B	22	0

[a]Isolated yields.
[b]Method A: EtOH, 50°C; method B: conc. AcOH, 50°C.
[c]Unseparable mixture of regioisomers **3** and **4**; in brackets: ratio (by GC analysis).

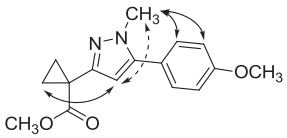
Scheme 2. Synthesis of pyrazoles **3** and **4**; *i*: method A: EtOH, 50°C, 4 h; method B: AcOH, 50°C, 4 h.



Scheme 3. Relevant ^{1}H,^{1}H-NOESY-correlations of **3b**,**h**,**k** (full line: strong; hyphenated: weak).



Scheme 4. Relevant ^{1}H,^{1}H-NOESY-correlations of **4j** (full line: strong; hyphenated: weak).



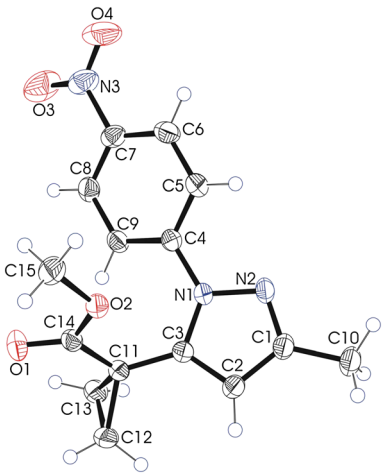
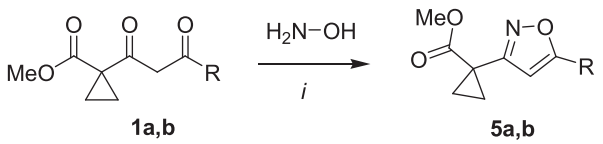


Figure 1. ORTEP plot of **3d** (50% probability level). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 5. Synthesis of isoxazoles **5a**,**b**; *i*: (1) pyridine, 20°C, 20 min; (2) 115°C, 1 h; (3) Et_2O, 10% HCl.



1a,b **5a,b**

Table 2

Synthesis of isoxazoles **5a**,**b**.

1	5	R	% (**5**)[a]
a	**a**	Me	63
b	**b**	Ph	62

[a]Isolated yields.

effect of the *p*-nitrophenyl group. A regiodirecting effect of the protonation of the 3,5-diketoesters **1a-c** by glacial acetic acid may also have an effect on the selectivity.

A classic approach to isoxazoles relies on the cyclization of hydroxylamine with 1,3-diketones [14]. The reaction of **1a**,**b** with hydroxylamine hydrochloride (1.1 equiv.), carried out in pyridine (20°C, the 115°C), afforded isoxazoles **5a**,**b** in good yields (Scheme 5, Table 2). The reactions proceed with very good regioselectivity by the attack of the amino group on the central keto group and subsequent cyclization via the oxygen atom.

In conclusion, we have reported a convenient and straightforward synthesis of novel pyrazoles and isoxazoles with cyclopropanated side-chain.

EXPERIMENTAL

General procedure for the synthesis of 3 and 4. To a solution of **1** (1.0 equiv.) in ethanol (2.5 mL per mmol of **1**) (method A) or in glacial acetic acid (2.5 mL per mmol of **1**) (method B) was added at 20°C the hydrazine derivative **2** (1.1 equiv.), and the mixture was stirred for 4 h at 50°C. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/EtOAc = 30/1).

Methyl 1-(5-methyl-1H-pyrazol-3-yl)cyclopropane-carboxylate (3a). Starting with **1a** (1.0 mmol, 184 mg), hydrazine hydrate (**2a**) (80% aq. solution, 1.1 mmol, 0.07 mL) in 2.5 mL of ethanol, **3a** was isolated by chromatography (heptane/EtOAc = 15/1 → 1/1) as a yellow oil (109 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.30–1.33 (m, 2H, $J_{H,H}$ = 3.40 Hz, CH_2), 1.65–1.69 (m, 2H, $J_{H,H}$ = 3.40 Hz, CH_2), 2.27 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.89 (1H, CH), 6.18 (br, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.7 (CH_3), 18.0 (CH_2), 21.6 (C_q), 52.2 (OCH_2), 104.0 (CH), 143.0, 147.4 (CN), 173.8 (*C*$OOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3195 (m), 3138 (m), 3107 (m), 2952 (m), 2871 (w), 1720 (s), 1578 (m). MS (EI, 70 eV): *m*/*z* = 180 (M^+, 100), 148 (52), 120 (98), 91 (25), 79 (26). HRMS (EI, 70 eV) calcd for $C_9H_{12}N_2O_2$: 180.08933 (M^+); found: 180.08933.

Methyl 1-(5-methyl-2-phenyl-2H-pyrazol-3-yl)cyclopropane-carboxylate (3b). Starting with **1a** (1.0 mmol, 184 mg), phenylhydrazine (**2b**) (1.1 mmol, 120 mg) in 2.5 mL of ethanol, **3b** was isolated by chromatography (heptane/EtOAc = 30/1 → 10/1) as a red oil (202 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18–1.22 (m, 2H, CH_2), 1.59–1.62 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 6.08 (s, 1H, CH), 7.29–7.34 (m, 1H, Ph), 7.38–7.45 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.5 (CH_3), 18.9 (CH_2), 20.8 (C_q), 52.2 (OCH_3), 107.8 (CH), 124.3, 127.2, 128.8 (CH_{Ph}), 140.4, 142.0 (CN), 146.7 ($C_{q,Ph}$), 173.0 (*C*$OOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 3015 (w),

2950 (w), 2926 (w), 2871 (w), 2844 (w), 1720 (s), 1578 (m). MS (EI, 70 eV): $m/z = 256$ (M^+, 100), 241 (24), 197 (78), 182 (21), 154 (18), 77 (27). HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_2$: 256.12063 (M^+); found: 256.12066.

Methyl 1-(2,5-dimethyl-2H-pyrazol-3-yl)cyclopropane-carboxylate (3c). Starting with **1a** (1.0 mmol, 184 mg), methylhydrazine (**2c**) (1.1 mmol, 51 mg) in 2.5 mL of ethanol, **3c** was isolated by chromatography (heptane/EtOAc = 25/1 → 3/1) as a colorless oil (160 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18–1.22 (m, 2H, CH_2), 1.65–1.69 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, NCH_3), 5.86 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.4 (CH_3), 17.2 (CH_2), 19.8 (C_q), 36.3 (NCH_3), 52.6 (OCH_3), 105.9 (CH), 141.4, 146.9 (CN), 173.0 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097 (w), 3014 (w), 2951 (m), 2847 (w), 1722 (s), 1558 (m). MS (EI, 70 eV): $m/z = 194$ (M^+, 100), 179 (23), 162 (22), 135 (42), 133 (41), 94 (23). HRMS (EI, 70 eV) calcd for $C_{10}H_{14}N_2O_2$: 194.10498 (M^+); found: 194.10473.

Methyl 1-(5-methyl-2-(p-nitrophenyl)-2H-pyrazol-3-yl) cyclopropane-carboxylate (3d). Starting with **1a** (1.0 mmol, 184 mg), *p*-nitrophenylhydrazine (**2d**) (1.1 mmol, 168 mg) in 2.5 mL of ethanol, **3d** was isolated by chromatography (heptane/EtOAc = 50/1 → 7/1) as a colorless solid (254 mg, 84%), mp 139–141°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24–1.28 (m, 2H, CH_2), 1.69–1.73 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 6.13 (s, 1H, CH), 7.71–7.74 (dd, 2H, $^3J_{H,H}$ = 9.25 Hz, $^4J_{H,H}$ = 2.08 Hz), 8.24–8.27 (dd, 2H, $^3J_{H,H}$ = 9.25 Hz, $^4J_{H,H}$ = 2.08 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.4 (CH_3), 19.3 (CH_2), 21.1 (C_q), 52.4 (OCH_3), 110.1 (CH), 122.9, 124.4 (CH_{Ph}), 142.5 (CN), 145.4 ($C_{q,Ph}$), 145.4 (CN), 150.3 ($C_{q,Ph}$), 172.3 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3141 (w), 3111 (w), 2997 (w), 2949 (w), 2926 (m), 2853 (w), 1721 (s), 1681 (w), 1595 (s), 1568 (m), 1502 (m). MS (EI, 70 eV): $m/z = 301$ (M^+, 100), 242 (25), 196 (50), 195 (34), 154 (16). *Anal*. calcd for $C_{15}H_{15}N_3O_4$ (301.297): C, 59.79; H, 5.02; N, 13.95. Found: C, 59.74; H, 5.18; N, 13.85. For details of the X-ray crystal structure analysis, see ref. 15 [15].

Methyl 1-(5-methyl-2-(p-tolyl)-2H-pyrazol-3-yl)cyclopropane-carboxylate (3e). Starting with **1a** (1.0 mmol, 184 mg), *p*-tolylhydrazine (**2e**) (1.1 mmol, 135 mL) in 2.0 mL glacial acetic acid, **3e** was isolated by chromatography (heptane/EtOAc = 16/1 → 3/1) as a brownish solid (165 , 62%), mp 89–90°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15–1.19 (m, 2H, C*H*$_2$CH$_2$), 1.55–1.59 (m, 2H, CH$_2$C*H*$_2$), 2.30 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.49 (s, 3H, OCH_3), 6.06 (s, 1H, CH), 7.19 (d, 2H, $^3J_{H,H}$ = 8.12 Hz, Ph), 7.31 (d, 2H, $^3J_{H,H}$ = 8.12 Hz, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.6 (CH_3), 18.9 (CH_2), 20.8 ($C_q[CH_2]_2$), 21.0 (CH_3), 52.3 (OCH_3), 107.6 (CH), 124.3, 129.4 (CH_{Ph}), 137.2, 138.0, 142.0, 148.5 (C_q), 173.2 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092 (w), 3045 (w), 2992 (w), 2951 (w), 2922 (m), 2851 (w), 1716 (s), 1612 (w), 1586 (w), 1556 (m), 1517 (s). MS (EI, 70 eV): $m/z = 270$ (M^+, 100), 255 (21), 211 (79), 195 (25), 154 (12), 91 (14). HRMS (ESI, 70 eV) calcd for $C_{16}H_{19}N_2NaO_2$: 293.0126 ($[M + Na]^+$); found: 293.1259.

Methyl 1-(5-phenyl-1H-pyrazol-3-yl)cyclopropane-carboxylate (3f). Starting with **1b** (1.0 mmol, 246 mg), hydrazine hydrate (**2a**) (80% aq. solution, 1.1 mmol, 0.07 mL) in 2.5 mL of ethanol, **3f** was isolated by chromatography (heptane/EtOAc = 15/1 → 1/1) as a slightly yellow solid (182 mg, 70%), mp 86–88°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.28–1.31 (m, 2H, $J_{H,H}$ = 3.40 Hz, CH_2), 1.61–1.65 (m, 2H, $J_{H,H}$ = 3.40 Hz, CH_2), 3.61 (s, 3H, OCH_3), 6.28 (s, 1H, CH), 7.17–7.31 (m, 3H, Ph), 7.61–7.64 (m, 2H, Ph), 9.61 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.1 (CH_2), 21.2 (C_q), 52.4 (OCH_3), 100.9 (CH), 125.5, 127.8, 128.6 (CH_{Ph}), 132.0 ($C_{q,Ph}$), 146.3, 128.9 (CN), 173.4 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3322 (s), 3088 (w), 3066 (w), 3041 (w), 3006 (w), 2955 (w), 2918 (w), 2848 (w), 1713 (s), 1605 (w), 1586 (w), 1560 (s), 1515 (m). HRMS (EI, 70 eV) calcd for $C_{14}H_{14}N_2O_2$ (242.10498, M^+): 242.10487. *Anal*. calcd for $C_{14}H_{14}N_2O_2$ (242.273): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.01; H, 6.09; N, 11.42.

Methyl 1-(1-methyl-5-phenyl-1H-pyrazol-3-yl)cyclopropane-carboxylate (3g) and methyl 1-(2-methyl-5-phenyl-2H-pyrazol-3-yl) cyclopropane-carboxylate (4g). Starting with **1b** (0.50 mmol, 124 mg), methylhydrazine (**2c**) (0.55 mmol, 26 mg) in 1.0 mL of glacial acetic acid, **3g** was isolated by chromatography (heptane/EtOAc = 15/1 → 5/1) as a colorless oil (107 mg) as an unseparable 1:5 mixture of **3g** and **4g** (ratio by GC). **3g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.39–1.43 (m, 2H, C*H*$_2$CH$_2$), 1.60–1.63 (m, 2H, CH$_2$C*H*$_2$), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, NCH_3), 6.39 (s, 1H, CH), 7.27–7.48 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.6 (CH_2), 22.5 (C_q), 37.3 (NCH_3), 52.2 (OCH_3), 106.7 (CH), 128.3, 128.6, 128.7 (CH_{Ph}), 130.6, 144.1, 149.4 (C_q), 174.2 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 3017 (w), 2950 (m), 2847 (w), 1721 (s), 1642 (w), 1605 (w), 1549 (m), 1500 (m). MS (EI, 70 eV): $m/z = 256$ (M^+, 100), 255 (48), 197 (46), 196 (70), 195 (58), 181 (14). HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_2$: 256.12063 (M^+); found: 256.12087. **4g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.27–1.31 (m, 2H, C*H*$_2$CH$_2$), 1.72–1.75 (m, 2H, CH$_2$C*H*$_2$), 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, NCH_3), 6.39 (s, 1H, CH), 7.27–7.48 (m, 3H, Ph), 7.74–7.77 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3 (CH_2), 19.9 (C_q), 36.7 (NCH_3), 52.7 (OCH_3), 103.7 (CH), 125.3, 127.5, 128.5 (CH_{Ph}), 133.2, 142.3, 149.4 (C_q), 172.8 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 3017 (w), 2950 (m), 2847 (w), 1721 (s), 1642 (w), 1605 (w), 1549 (m), 1500 (m). MS (EI, 70 eV): $m/z = 256$ (M^+, 100), 255 (48), 197 (46), 196 (70), 195 (58), 181 (14). HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_2$: 256.12063 (M^+); found: 256.12087.

Methyl 1-(2-(p-nitrophenyl)-5-phenyl-2H-pyrazol-3-yl) cyclopropane-carboxylate (3h) and methyl 1-(1-(p-nitrophenyl)-5-phenyl-1H-pyrazol-3-yl)cyclopropane-carboxylate (4h). Starting with **1b** (0.50 mmol, 124 mg), *p*-nitrophenylhydrazine (**2d**) (0.55 mmol, 84 mg) in 1 mL of glacial acetic acid, **3h** was isolated by chromatography (heptane/EtOAc = 30/1 → 5/1) as a yellow solid (100 mg, 56%). In addition, **4h** was isolated as a yellow solid (17 mg, 10%). **3h**: mp = 125–127°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.36–1.40 (m, 2H, C*H*$_2$CH$_2$), 1.79–1.82 (m, 2H, CH$_2$C*H*$_2$), 3.52 (s, 3H, OCH_3), 6.69 (s, 1H, CH), 7.36–7.46 (m, 3H, Ar), 7.84–7.89 (m, 4H, Ar), 8.33–8.36 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.6 (CH_2), 21.4 (C_q), 52.7 (OCH_3), 107.6 (CH), 123.5, 124.7, 125.8, 128.6, 128.7 (CH_{Ph}), 132.2, 143.4, 145.6, 145.9, 152.7 (C_q), 172.4 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3142 (w), 3088 (w), 2951 (w), 2920 (w), 2849 (w), 1725 (s), 1606 (w), 1592 (s), 1564 (m), 1505 (w), 1496 (s). MS (EI, 70 eV): $m/z = 363$ (M^+, 100), 304 (18), 258 (31), 257 (20), 154 (11). HRMS (ESI, 70 eV) calcd for $C_{20}H_{18}N_3O_4$ (364.12918, $[M + H]^+$): 364.12948. *Anal*. calcd for $C_{20}H_{17}N_3O_4$ (363.367): C, 66.11; H, 4.72; N, 11.56. Found: C, 66.12; H, 4.96; N, 11.50. **4h**: mp = 122–124°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.54–1.58 (m, 2H, C*H*$_2$CH$_2$), 1.68–1.71 (m, 2H, CH$_2$C*H*$_2$), 3.74 (s, 3H, OCH_3), 6.72 (s, 1H, CH), 7.24–7.28 (m, 2H, Ar), 7.34–7.46 (m, 5H, Ar), 8.13–8.16 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.2 (CH_2), 22.7 (C_q), 52.3 (OCH_3), 110.9 (CH), 124.3,

124.3, 128.5, 128.8, 128.9 (CH_{Ar}), 130.1, 144.8, 145.7, 145.9, 152.9 (C_q), 173.6 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3142 (w), 3116 (w), 3087 (w), 2952 (w), 2922 (w), 2849 (w), 1725 (s), 1607 (w), 1592 (s), 1565 (m), 1552 (w), 1497 (s). MS (EI, 70 eV): *m*/*z* = 363 (M^+, 100), 304 (15), 258 (28), 257 (20), 154 (10). HRMS (ESI, 70 eV) calcd for $C_{20}H_{18}N_3O_4$ (364.12918, $[M+H]^+$): 364.12914. *Anal*. calcd for $C_{20}H_{17}N_3O_4$ (363.367): C, 66.11; H, 4.72; N, 11.56. Found: C, 66.24; H, 5.18; N, 11.07.

Methyl 1-(5-(p-methoxyphenyl)-1H-pyrazol-3-yl)cyclopropane-carboxylate (3i). Starting with **1c** (1.0 mmol, 276 mg), hydrazine hydrate (**2a**) (80% aq. solution, 1.1 mmol, 0.07 mL) in 2.5 mL of ethanol, **3i** was isolated by chromatography (heptane/EtOAc = 15/1 → 1/1) as a colorless oil (147 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.35–1.39 (m, 2H, CH_2), 1.69–1.72 (m, 2H, CH_2), 3.70, 3.81 (OCH_3), 6.29 (s, 1H, CH), 6.87–6.92 (dd, 2H, $^3J_{H,H}$ = 8.88 Hz, $^4J_{H,H}$ = 3.02 Hz, Ph), 7.59–7.64 (dd, 2H, $^3J_{H,H}$ = 8.88 Hz, $^4J_{H,H}$ = 3.02 Hz, Ph), 10.05 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.0 (CH_2), 21.3 (C_q), 52.4, 55.2 (OCH_3), 100.4 (CH), 114.0 (CH_{Ph}), 124.7 (C_q), 126.8 (CH_{Ph}), 146.4, 148.5 (CN), 159.4 (C_q), 173.4 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3312 (s), 3106 (w), 3092 (w), 3017 (w), 2957 (w), 2938 (w), 2916 (w), 2832 (w), 1721 (s), 1615 (m), 1562 (m), 1527 (s). MS (EI, 70 eV): *m*/*z* = 272 (M^+, 100), 213 (20), 212 (30), 211 (27), 184 (17), 169 (17). HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_3$ (272.11554, M^+): 272.11544.

Methyl 1-(1-methyl-5-(p-methoxyphenyl)-1H-pyrazol-3-yl) cyclopropane-carboxylate (4j) and methyl 1-(2-methyl-5-(p-methoxyphenyl)-2H-pyrazol-3-yl)cyclopropane-carboxylate (3j). Starting with **1c** (0.50 mmol, 138 mg), methylhydrazine (**2c**) (0.55 mmol, 26 mg) in 1.0 mL of glacial acetic acid, an unseparable 1:11 mixture of **3j** and **4j** (ratio by GC) was isolated by chromatography (heptane/EtOAc = 20/1 → 5/1) as a slightly yellow oil (107 mg, 75%). **4j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.38–1.42 (m, 2H, C*H*$_2$CH$_2$), 1.59–1.62 (m, 2H, CH$_2$C*H*$_2$), 3.69 (s, 3H, OCH_3), 3.80 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.33 (s, 1H, CH), 6.95–6.99 (m, 2H, Ph), 7.32–7.37 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.6 (CH_2), 22.5 (C_q), 37.2 (NCH_3), 52.3, 55.3 (OCH_3), 106.5 (CH), 114.0 (CH_{Ph}), 126.7 ($C_{q,Ph}$), 130.0 (CH_{Ph}), 143.3, 149.3, 159.7 (C_q), 174.3 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3002 (w), 2950 (m), 2840 (w), 1720 (s), 1612 (m), 1576 (w), 1508 (s). MS (EI, 70 eV): *m*/*z* = 286 (M^+, 100), 285 (50), 227 (38), 226 (55), 225 (46), 211 (13). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}N_2O_3$ (286.13119, M^+): 286.13129. **3j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.27–1.30 (m, 2H, C*H*$_2$CH$_2$), 1.70–1.74 (m, 2H, CH$_2$C*H*$_2$) 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.32 (s, 1H, CH), 6.90–6.91 (m, 2H, Ar), 7.66–7.69 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3 (CH_2), 19.9 (C_q), 36.6 (NCH_3), 52.7, 55.2 (OCH_3), 103.3 (CH), 114.0 (CH_{Ph}), 122.9 ($C_{q,Ph}$), 126.7 (CH_{Ph}), 142.3, 149.5, 159.3 (C_q), 172.8 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3002 (w), 2950 (m), 2840 (w), 1720 (s), 1612 (m), 1576 (w), 1508 (s). MS (EI, 70 eV): *m*/*z* = 286 (M^+, 100), 285 (50), 227 (38), 226 (55), 225 (46), 211 (13). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}N_2O_3$ (286.13119, M^+): 286.13129.

Methyl 1-(5-(p-methoxyphenyl)-2-(p-nitrophenyl)-2H-pyrazol-3-yl)cyclopropane-carboxylate (3k). Starting with **1c** (0.50 mmol, 138 mg), *p*-nitrophenylhydrazine (**2d**) (0.55 mmol, 84 mg) in 1.0 mL of glacial acetic acid, **3k** was isolated by chromatography (heptane/EtOAc = 40/1 → 8/1) as a yellow solid (43 mg, 22%), mp = 136–138°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.35–1.39 (m, 2H, C*H*$_2$CH$_2$), 1.77–1.82 (m, 2H, CH$_2$C*H*$_2$), 3.50 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.61 (s, 1H, CH), 6.92–6.98 (m, 2H, Ar), 7.76–7.88 (m, 4H, Ar), 8.29–8.35 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.6 (CH_2), 21.4 (C_q), 52.7, 55.3 (OCH_3), 107.3 (CH), 114.1, 123.3, 124.7 (CH_{Ar}), 124.9 (C_q), 127.1 (CH_{Ar}), 143.3, 145.7, 145.7, 152.5, 160.0 (C_q), 172.5 (*C*OOCH$_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3115 (w), 3090 (w), 3020 (w), 2996 (w), 2947 (w), 2918 (m), 2848 (m), 1725 (s), 1683 (w), 1611 (w), 1594 (s), 1564 (w), 1511 (s). MS (EI, 70 eV): *m*/*z* = 394 (M^+, ^{15}N, 24), 393 (M^+, ^{14}N, 100), 378 (5), 334 (6), 332 (5), 288 (10). HRMS (EI, 70 eV) calcd for $C_{21}H_{19}N_3O_5$: 393.13192 (M^+): found: 393.13246.

General procedure for the synthesis of isoxazoles 5a,b. To a solution of pyridine (2 mL per mmol of **1**) was added hydroxylamine hydrochloride (1.1 equiv.) and **1** (1.0 equiv.). After stirring for 20 min at 20°C, the mixture was heated under reflux for 1 h. The solvent was removed *in vacuo* and to the residue were added diethyl ether and hydrochloric acid (10%). The layers were separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel).

1-(5-Methylisoxazol-3-yl)cyclopropane-carboxylate (5a). Starting with **1a** (1.0 mmol, 184 mg), hydroxylamine hydrochloride (1.1 mmol, 77 mg) in 2.0 mL of pyridine, **5a** was isolated by chromatography (heptane/EtOAc = 15/1) as a colorless oil (113 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49–1.53 (m, 2H, C*H*$_2$CH$_2$), 1.69–1.73 (m, 2H, CH$_2$C*H*$_2$), 2.26 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.25 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.2 (CH_3), 18.3 (CH_2), 21.5 (C_q), 52.4 (OCH_3), 103.9 (CH), 159.8 (CN), 169.0, 171.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129 (w), 3003 (w), 2956 (w), 2849 (w), 1728 (s), 1604 (s), 1500 (w). MS (EI, 70 eV): *m*/*z* = 181 (M^+, 100), 149 (17), 82 (44), 59 (30), 53 (42), 39 (21). *Anal*. calcd for $C_9H_{11}NO_3$ (181.189): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.57; H, 6.38; N, 7.52.

Methyl 1-(5-phenylisoxazol-3-yl)cyclopropane-carboxylate (5b). Starting with **1b** (0.50 mmol, 123 mg), hydroxylamine hydrochloride (0.55 mmol, 39 mg) in 2.0 mL of pyridine, **5b** was isolated by chromatography (heptane/EtOAc = 30/1 → 15/1) as a colorless oil (74 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.61–1.65 (m, 2H, C*H*$_2$CH$_2$), 1.77–1.81 (m, 2H, CH$_2$C*H*$_2$), 3.77 (s, 3H, OCH_3), 6.77 (s, 1H,. CH), 7.44–7.46 (m, 3H, Ph), 7.79–7.82 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.8 (CH_2), 21.9 (C_q), 52.6 (OCH_3), 101.5 (CH), 126.7, 128.8 (CH_{Ph}), 129.1 ($C_{q,Ph}$), 129.9 (CH_{Ph}), 162.6 (CN), 169.9, 171.3 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3125 (s), 3053 (w), 3022 (w), 2953 (m), 2916 (m), 2847 (m), 1724 (s), 1611 (s), 1581 (m), 1504 (w). MS (EI, 70 eV): *m*/*z* = 244 (M^+, ^{15}N, 16), 243 (M^+, ^{14}N, 100), 144 (57), 127 (12), 117 (36), 77 (35). HRMS (EI, 70 eV) calcd for $C_{14}H_{13}NO_3$: 243.08899 (M^+); found: 243.08968.

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