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Regiocontrolled Synthesis of Ring-Fused Thieno[2,3-*c*]pyrazoles through 1,3-Dipolar Cycloaddition of Nitrile Imines with Sulfur-Based Acetylenes

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Dedicated to Professor Pelajo Camps on the occasion of his 65th birthday

Keywords: Cycloaddition / Regioselectivity / Sulfur / Alkynes / Heterocycles / Fused-ring systems

1,3-Dipolar cycloadditions of *C*-carboxymethyl-*N*-arylnitrile imines with substituted acetylenes bearing thiol or sulfone groups were studied. The sulfur controls the regiochemistry of the reaction, and this protocol was applied to the synthesis of ring-fused thieno[2,3-*c*]pyrazoles.

Introduction

Pyrazole derivatives display a broad spectrum of biological activities[1] and represent an important structural class in pharmaceuticals[2] and agrochemicals.[3] They are present in leading drugs such as Viagra[2a] and Celebrex[2b] and, therefore, are considered very important for pharmaceutical industries.[4,5] Much work has been directed towards the design and the synthesis of complex pyrazoles giving particular relevance to the functionalization of the scaffold in different regions. Two general methods are known for the synthesis of pyrazoles. The first method involves the standard reaction of hydrazines with 1,3-difunctional substrates such as 1,3-dicarbonyl compounds,[6] ynones,[7] or β-aminoacrolein.[4] In addition, the 1,3-dipolar cycloaddition (1,3-DC) between alkynes and nitrile imines provides direct access to pyrazoles,[8] but regioisomeric mixtures of pyrazoles are frequently obtained. Moreover, during the last years new paths have emerged, like domino C–N coupling/hydroamination of enynes,[9] azacyclization of elaborated structures,[10] and direct *N*-arylation of a 1*H*-pyrazole.[11] However, the scope of these methods is still not general, in particular for the synthesis of ring-condensed structures. Indeed, the preparation of pyrazole-fused ring derivatives seems to be very important and challenging from a synthetic point of view.

Pyrazolo[3,4-*d*]pyrimidines of type **A** (Figure 1) show inhibition properties towards Src in a cell-free assay, as well as antiproliferative activity towards the epidermoid (A431) and breast cancer (BC-8701) cell line.[12] Pyrazolopyrimidines have also been tested in terms of inhibition of Abelson Kinase (Abl) enzymatic activity and antiproliferative properties towards human leukemic cells.[13] Huang recently reported that a novel class of indazol-4-ones of type **B** (now in multiple phase I clinical trials) exhibits low nanomolar antiproliferative potencies across multiple cancer cell lines.[14] 2,3-Dihydropyran[2,3-*c*]pyrazoles of type **C** have been recently obtained through multicomponent microwave-assisted organocatalytic domino Knoevenagel/hetero-Diels–Alder reaction and are potential antitubercular agents.[15] Pyrazolo[1,5-*C*]quinazolines[16] of type **D** are Gly/NMDA receptor antagonists, whereas pyrazolpiperidines **E** and pyrazolpyridines **F** are acorticotrophin-releasing-factor (CRF-1) receptor antagonists and are very promising for the treatment of depression and anxiety.[17]

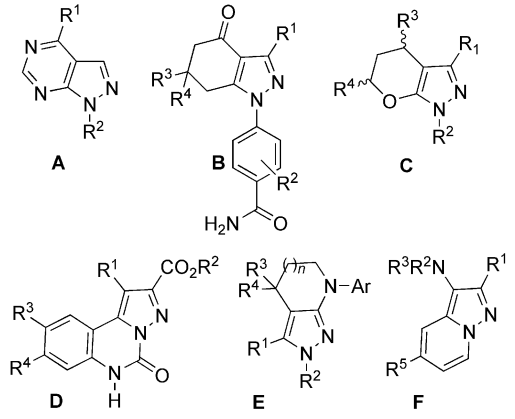

Figure 1. Ring-fused pyrazoles **A**–**F**.

Thieno[2,3-*c*]pyrazoles **G** (Figure 2) are an important class of potent kinase inhibitors.[18] Their synthesis can start from functionalized pyrazole derivatives, which through a

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multistep sequence is fused with the thiophene ring.[18a] On the other hand, in a recent patent,[18b] thieno[2,3-*c*]-pyrazoles were prepared starting from a suitable thiophene derivative in which the fusion with the pyrazole ring occurs in the final step of the synthetic sequence.

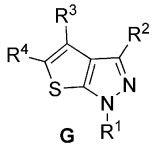


Figure 2. Structures **G** for thienopyrazoles.

We recently developed a method for the regiocontrolled synthesis of pyrazoles based on the 1,3-DC of nitrile imines with functionalized acetylenes.[19] As part of our group's ongoing effort[20] directed towards the preparation of pyrazoles as multikinases inhibitors we decided to investigate the application of our methodology to the regiocontrolled synthesis of thieno[2,3-*c*]-pyrazoles **G**, through 1,3-DC of nitrile imines and substituted acetylenes bearing thiol or sulfone groups.

Heteroatom-substituted acetylenes have been scarcely studied and reported in the 1,3-DC of nitrile imines as 1,3-dipoles. Only Zecchi reported the reaction of *N*-phenyl-*C*-phenylnitrile imine with alkynyl phenyl sulfones with yields of 15–71% and with the cycloadduct having the $PhSO_2$ group in the 4-position as the predominant or exclusive regioisomer,[21] whereas alkynyl phenyl sulfides have never been investigated in this 1,3-DC. On the other hand, these kinds of dipolarophiles, and the possible control of the regiochemistry, could play important roles in the installation of the S atom in the correct position of the pyrazole ring, allowing, after synthetic elaboration, the preparation of ring-fused thienopyrazoles.

Results and Discussion

We decided to investigate preliminarily mono- **1** and difunctional **2** sulfones containing a triple bond to extend Zecchi's result with the more versatile and unreported *C*-carboxymethyl-*N*-arylnitrile imines. Moreover, we present herein substituted acetylenes **3** and **4** bearing thiol groups and their general behavior in 1,3-DCs with nitrile imines derived from **5a**–**c** (Figure 3). Starting acetylenes **1**–**4** were readily prepared according to literature procedures (see the Experimental Section), whereas selected hydrazonoyl chlorides **5a**–**c** were obtained as reported by us.[19]

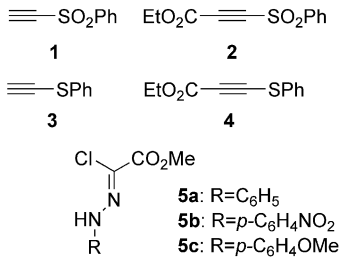
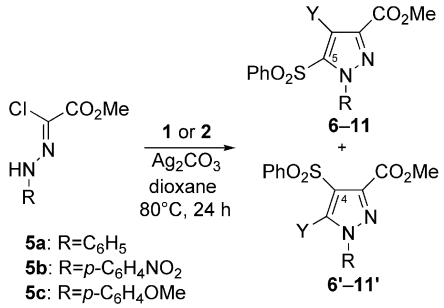


Figure 3. Dipolarophiles **1**–**4** and hydrazonoyl chlorides **5a**–**c**.

The cycloadditions of **1** and **2** with the *C*-carboxymethyl-*N*-arylnitrile imines derived from **5a**–**c** were carried out in dry dioxane at 80 °C for 24 h by using Ag_2CO_3 (2.5 equiv.), and **1** or **2** was used in stoichiometric amount with respect to the dipoles with yields ranging from 35 to 63% (Scheme 1; Table 1, Entries 1–6).



Scheme 1. 1,3-DC of **1** or **2** with **5a**–**c**.

Cycloadducts **6**–**6′** were obtained in 35:65 ratio, **7**–**7′** were obtained in 40:60 ratio, and **8**–**8′** were isolated as balanced mixtures in a 54:46 ratio (Table 1, Entries 1–3). These results of regiochemistry fit with the data obtained for the *N*-phenyl-*C*-phenylnitrile imines[21] and are due to the strong electron-withdrawing effect of the sulfonyl group, which determines a large LUMO coefficient at the β-carbon of the acetylene with a consequent HOMO–(dipole) LUMO–(dipolarophile) interaction.

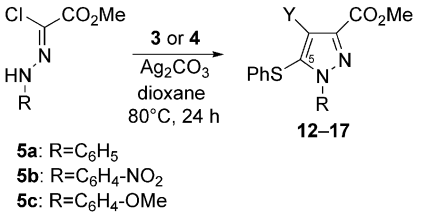
The same reactions were repeated in the presence of scandium triflate catalyst for a possible control of the regiochemistry.[19] As expected, the amount of the 4-isomer was higher under $Sc(OTf)_3$ catalysis (Table 1, Entries 1–3), and the 4-isomer increased to 12:88 for **6**–**6′** and to 14:86 for **7**–

Table 1. 1,3-DC of **1** or **2** with 1,3-dipoles derived from **5a**–**c**.

Entry	Dipolarophile	1,3-Dipole	Y	Cycloadducts	Yield [%][a]	Ratio[a]	Yield [%][b]	Ratio[b]
1	**1**	**5a**	H	**6**–**6′**	49	35:65	38	12:88
2	**1**	**5b**	H	**7**–**7′**	35	40:60	34	14:86
3	**1**	**5c**	H	**8**–**8′**	58	54:46	39	14:86
4	**2**	**5a**	CO_2Et	**9**–**9′**	63	11:89	72	8:92
5	**2**	**5b**	CO_2Et	**10**–**10′**	65	20:80	67	15:85
6	**2**	**5c**	CO_2Et	**11**–**11′**	60	10:90	64	9:91

[a] Without $Sc(OTf)_3$. [b] With 10% $Sc(OTf)_3$.

7′ and **8**–**8′** due to the possibility of a chelated transition state involving the CO_2Me group and the sulfonyl group with the scandium catalyst.[19] Disubstituted sulfone **2** gave good yields of cycloadducts (60–65%) with an higher quantity of the 4-isomer, ratio 11:89 for **9**–**9′**, 20:80 for **10**–**10′**, and 10:90 for **11**–**11′** (Table 1, Entries 4–6), but in this case no significant improvement was observed in the ratio under scandium catalysis in favor of the 4-isomer. Therefore, we believe that this kind of 1,3-DC is substrate-controlled and does not take place under the control of the catalyst. Moving to PhS dipolarophiles **3** and **4** a reversal in the regiochemistry in favor of the 5-substituted pyrazoles was observed. The *C*-carboxymethyl-*N*-arylnitrile imines derived from **5a**–**c** with **3** and **4** gave only regioisomers **12**–**17** with the PhS group in the 5-position with or without scandium catalysis (Scheme 2, Table 2). Satisfactory yields in the range 45–70% were achieved (Table 2, Entries 1–6). These results are in line with results obtained by us in 1,3-NED (normal electron demand) dipolar cycloadditions of nitrile imines with acetylene derivatives.[19]



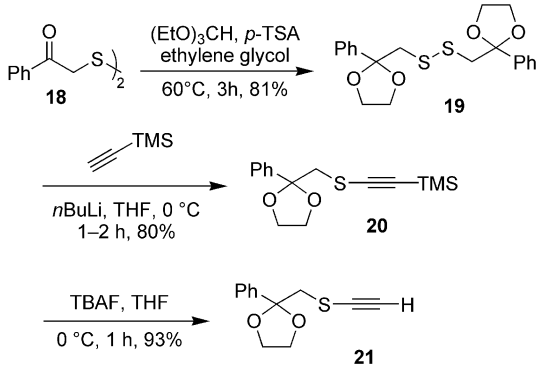
Scheme 2. 1,3-DC of **3** or **4** with **5a**–**c**.

The identification of the 5- and 4-pyrazoles in cycloadducts **6**–**8** and **12**–**14** was based on the ^1H NMR signals by taking advantage of the fact that it is known that the CH signal of C5 for the 4-substituted derivatives resonates at about 8.0 ppm. This signal was not found in our cycloadducts.[19] Furthermore, NOE experiments confirmed the formation of 5-pyrazole also for compounds **9**–**11** and **15**–**17**.

From these results we understood that different S-based functionalities control the regiochemistry of the cycloaddition. The electron-releasing properties of the S atom together with the electron-withdrawing CO_2Et group bring to a synergistic regiochemical effect that leads exclusively to one regioisomer, in contrast with the behavior of the SO_2-substituted triple bond. This regiochemistry is correct for the preparation of ring-fused thienopyrazoles of type **G**.

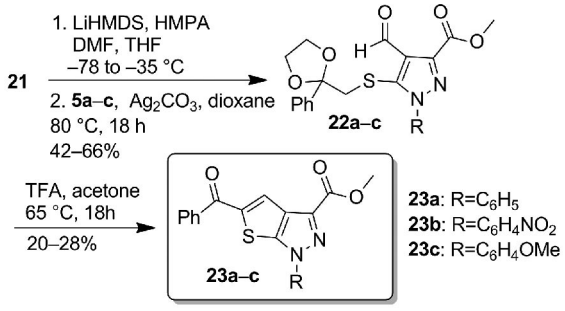
To apply this protocol to the synthesis of thieno[2,3-*c*]-pyrazoles we have "designed" a disubstituted acetylene with the S-substituent having a CH_2 in the α-position, and as the other substituent of the triple bond, a formyl group possessing electronic character similar to that of the ester used in the preliminary investigation and able to undergo intramolecular nucleophilic addition with subsequent aromatization to the thiophene ring.

Therefore, the starting material was diphenacyl disulfide **18**, prepared easily and in high yield through a modified literature method[22] from phenacyl mercaptan.[23] After protection of **18** as dioxolane **19**[24] in 81% yield, acetylene **20** was obtained by reaction of **19** with lithium trimethylsilyl acetylene in THF at 0 °C in 80% yield. Compound **21** was obtained through desilylation with TBAF at 0 °C, which occurred in 93% yield (Scheme 3).



Scheme 3. Synthesis of acetylene **21**.

In acetylene **21**, the formyl group was introduced by reaction with LiHMDS in THF at –78 °C followed by addition of a mixture of DMF and HMPA (Scheme 4). The disubstituted acetylene was not isolated but immediately treated with **5a**–**c** under the usual conditions. The corre-



Scheme 4. General method for the synthesis of ring-fused thieno-[2,3-*c*]pyrazoles **23a**–**c**.

Table 2. 1,3-DC of **3** or **4** with 1,3-dipoles derived from **5a**–**c**.

Entry	Dipolarophile	1,3-Dipole	Y	Cycloadduct	Yield [%][a]	Regioisomeric ratio
1	**3**	**5a**	H	**12**	70	>99:1
2	**3**	**5b**	H	**13**	57	>99:1
3	**3**	**5c**	H	**14**	67	>99:1
4	**4**	**5a**	CO_2Et	**15**	50	>99:1
5	**4**	**5b**	CO_2Et	**16**	45	>99:1
6	**4**	**5c**	CO_2Et	**17**	67	>99:1

[a] Without $Sc(OTf)_3$.

sponding cycloadducts were obtained with good overall yields, 66% for **22a**, 42% for **22b**, and 43% for **22c**, and fully characterized after chromatography on silica. Deprotection of the dioxolanes in **22a**–**c** and condensation[25] to thieno[2,3-*c*]pyrazoles **23a**–**c** took place in one step by reaction with trifluoroacetic acid in acetone in 20–28% overall yield (see the Experimental Section).

Conclusions

In summary, an efficient multistep synthetic sequence based on a 1,3-DC of *C*-carboxymethyl-*N*-arylnitrile imines with substituted acetylenes bearing thiol or sulfone groups has been developed, and this methodology appears suitable for the regiocontrolled synthesis of thieno[2,3-*c*]pyrazoles of type **G**. Of particular interest is the possible synthetic elaboration of the ester group that would allow the preparation of libraries of potentially active thieno[2,3-*c*]pyrazoles. Therefore, applications in medicinal chemistry call for other studies, which will be reported in due course.

Experimental Section

General Comments: ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$, CD_3OD, or [D_6]DMSO solutions at 300, 400, and 600 MHz for ^{1}H and 75.46, 100.6, and 150.92 MHz for ^{13}C. Chemical shifts are reported in ppm relative to $CHCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). ^{1}H and ^{13}C NMR spectral assignments were made by DEPT, gCOSY, and gHSQC experiments. IR spectra were recorded with a Perkin Elmer Spectrum RX I FT-IR System. Mass spectra (MS) were obtained with an electrospray ionization (ESI) source were recorded by using MeOH as the solvent. High-resolution mass spectra (HRMS) were recorded with a micromass LCT spectrometer by using electrospray (ESI+) ionization techniques. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under an atmosphere of Ar. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with b.p. 40–60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative TLC was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified as needed.

Ethynylsulfonylbenzene (1): To a stirred solution of trimethyl(phenylthioethynyl)silane (0.5 g, 2.4 mmol) in DCM (5 mL) was added a solution of *m*-CPBA (77%, 1.34 g, 6.4 mmol) in DCM (5 mL). The reaction was vigorously stirred for 1–2 h. After completion, the reaction was cooled to 0 °C and sat. $NaHCO_3$ solution (15 mL) was added with caution. Then, the reaction mixture was extracted with DCM (3 × 10 mL) and washed with water and brine. The DCM layer was dried with $MgSO_4$, and the solvents were evaporated. No purification was necessary as almost pure product was obtained as a yellow oil (0.55 g, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–8.09 (d, *J* = 6 Hz, 2 H), 7.55–7.75 (m, 3 H), 0.22–0.25 (s, 9 H) ppm. This oil (0.55 g, 2.3 mmol) was then dissolved in THF (10 mL) and cooled to –78 °C and then mixed with *n*Bu_4NF (1 M in THF, 0.7 mL, 0.7 mmol). The reaction mixture was stirred for 2–3 h at the same temperature. After completion of the reaction, sat. NH_4Cl solution (15 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL). The combined ether extracts were washed with water (2 × 10 mL) and brine and then dried with anhydrous Na_2SO_4. The ether layer was carefully evaporated in vacuo, and crude product **1** (0.33 g, 87% yield) was kept as a stock solution in diethyl ether (ca. 20% w/v) at –4 °C. The crude product was used as such for further reactions without purification.

Ethyl 3-(Phenylsulfonyl)propiolate (2): To a stirred solution of ethyl 3-(phenylthio)propiolate (**4**; 0.77 g, 3.7 mmol) in DCM (10 mL) was added a solution of *m*-CPBA (77%, 2.1 g, 9.3 mmol) in DCM (10 mL), and the mixture was left to react at room temperature for 2 h. Afterwards, the solution was washed with 10% aq. $Na_2S_2O_4$ solution (10 mL) and sat. aq. $NaHCO_3$ solution (2 × 10 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated, and the crude product was purified by chromatography on silica gel (EtOAc/light petroleum, 1:5) to yield compound **2** (0.59 g, 68%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 2 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.63 (t, *J* = 7.6 Hz, 2 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 139.6, 135.2, 129.6 (2 CH), 127.9 (2 CH), 79.7, 78.9, 63.5, 13.7 ppm. IR (CCl_4): $\tilde{\nu}$ = 3061, 2978, 2532, 1726, 1570, 1472, 1441, 1358, 1238, 1171, 1088 cm^{-1}. MS: *m*/*z* = 261 [M + Na]$^+$.

Phenylthioacetylene (3): Trimethylsilylethyne (1 g, 10.2 mmol) was dissolved in dry THF (15 mL) at 0 °C. A solution of *n*BuLi (1.6 M in hexane, 6.4 mL, 10.2 mmol) was then added dropwise with stirring under an atmosphere of argon at 0 °C. After 45 min. a solution of *S*-phenyl benzenethiosulfonate (2.3 g, 9.2 mmol) in THF (10 mL) was introduced at 0 °C and stirring was continued for 2 h. The reaction mixture was then quenched with sat. NH_4Cl solution (20 mL). The reaction mixture was extracted with diethyl ether (3 × 15 mL), and the organic layer was washed with water (2 × 15 mL) and brine. The ether layer was then dried with anhydrous Na_2SO_4 and the solvents were evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane) to afford a yellow oil (1.48 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.55 (m, 2 H), 7.42–7.49 (t, *J* = 7.5 Hz, 2 H), 7.29–7.38 (tt, *J* = 7.5, 1.5 Hz, 1 H), 0.36–0.38 (s, 9 H) ppm. This oil, trimethyl(phenylthioethynyl)silane (1 g, 4.8 mmol), was then dissolved in THF (20 mL), cooled to –78 °C, and then mixed with *n*Bu_4NF (1 M in THF, 1.45 mL, 1.4 mmol). The reaction mixture was stirred for 2–3 h at the same temperature. After completion, sat. NH_4Cl (20 mL) was added, and the reaction mixture was extracted with diethyl ether (3 × 15 mL). The combined ether extracts were washed with water (2 × 15 mL) and brine and then dried with anhydrous Na_2SO_4. The ether layer was carefully evaporated in vacuo and crude product **3** (0.63 g, 97% yield) was kept as a stock solution in diethyl ether (ca. 20%w/v) at –4 °C. The crude product was used as such for further reactions without purification.

Ethyl 3-(Phenylthio)propiolate (4): To a stirred solution of ethyl propiolate (0.4 mL, 4 mmol) in THF (8 mL) at –78 °C was added slowly a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 4 mL, 4 mmol). After 30 min, a solution of *S*-phenyl benzenethiosulfonate (1.0 g, 4 mmol) in THF (6 mL) was added at –78 °C, and the mixture was left to react at room temperature for 2 h. After completion of the reaction, a sat. NH_4Cl solution (10 mL) was added, and the reaction mixture was extracted with diethyl ether (2 × 10 mL). The combined organic layers were then dried with an-

hydrous Na_2SO_4, filtered, and concentrated in vacuo to afford product **4** as a yellow oil (0.77 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.9 Hz, 2 H), 7.39 (t, J = 7.9 Hz, 2 H), 7.30 (t, J = 7.3 Hz, 1 H), 4.27 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 129.6 (2 CH), 129.5, 127.9, 127.4 (2 CH), 91.6, 79.8, 62.0, 14.1 ppm. IR (CCl_4): $\tilde{\nu}$ = 3066, 2984, 2153, 1709, 1583, 1479, 1444, 1366, 1232, 1037 cm^{-1}. MS: m/z = 229 $[M + Na]^+$.

General Procedure for the 1,3 Dipolar Cycloaddition: To a stirred solution of phenylthioacetylene (1 equiv.) and the 1,3-dipole (1 equiv.) in freshly distilled dioxane (5 mL) was added silver carbonate (2.5 equiv.) under an argon atmosphere. The reaction was heated at reflux overnight. After completion, the reaction mixture was allowed to cool and filtered through a bed of Celite and washed with DCM (5 mL). The filtrate was then evaporated in vacuo to give a dark-red crude oil. The crude product was purified by column chromatography to give the corresponding title compounds.

Methyl 1-Phenyl-5-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (6) and Methyl 1-Phenyl-4-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (6′): Compounds **6** and **6′** were obtained as off-white solids by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel (EtOAc/hexane, 2:8). Data for **6**: M.p. 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.60 (s, 1 H), 7.44–7.57 (m, 4 H), 7.32–7.42 (q, J = 7.9 Hz, 4 H), 7.22–7.28 (m, 2 H), 3.92–3.98 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 144.0, 142.7, 138.7, 137.6, 134.1, 130.2, 129.0 (2 C), 128.6 (2 C), 128.1 (2 C), 127.1 (2 C), 114.6, 52.6 ppm. IR (CCl_4): $\tilde{\nu}$ = 2955, 1737, 1509, 1328, 1236, 1151, 1067, 816 cm^{-1}. MS: m/z = 343 $[M + H]^+$. Data for **6′**: M.p. 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64–8.66 (s, 1 H), 8.08–8.14 (d, J = 6 Hz, 2 H), 7.70–7.77 (d, J = 6 Hz, 2 H), 7.40–7.65 (m, 6 H), 3.88–3.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 141.1, 140.8, 138.2, 133.3, 133.2, 129.7 (2 C), 128.8, 128.6 (2 C), 128.1 (2 C), 128.3, 120.2 (2 C), 52.6 ppm. IR (CCl_4): $\tilde{\nu}$ = 2955, 1737, 1509, 1328, 1236, 1151, 1067, 816 cm^{-1}. MS: m/z = 343 $[M + H]^+$.

Methyl 1-(4-Nitrophenyl)-5-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (7) and Methyl 1-(4-nitrophenyl)-4-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (7′): Compounds **7** and **7′** were obtained as off-white solids by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel (EtOAc/hexane, 2:8). Data for **7**: M.p. 192–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28–8.35 (d, J = 9 Hz, 2 H), 7.59–7.71 (m, 4 H), 7.42–7.53 (m, 3 H), 7.25–7.28 (s, 1 H), 3.96–3.99 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 148.2, 144.4, 143.8, 142.5, 138.6, 134.7, 129.4 (2 C), 128.0 (2 C), 127.8 (2 C), 124.1 (2 C), 115.3, 52.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3970, 2985, 1737, 1531, 1346, 1236 cm^{-1}. MS: m/z = 388 $[M + H]^+$. Data for **7′**: M.p. 218–219 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75–8.79 (s, 1 H), 8.39–8.46 (d, J = 9 Hz, 2 H), 8.09–8.15 (d, J = 6 Hz, 2 H), 7.96–8.03 (d, J = 9 Hz, 2 H), 7.52–7.69 (m, 3 H), 3.90–3.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.5, 142.6, 140.7, 133.9, 133.8, 129.1, 129.0, 128.6 (2 C), 125.7 (2 C), 120.5 (2 C), 53.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3070, 2985, 1737, 1531, 1346, 1236, 1068 cm^{-1}. MS: m/z = 388 $[M + H]^+$.

Methyl 1-(4-Methoxyphenyl)-5-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (8) and Methyl 1-(4-Methoxyphenyl)-4-(phenylsulfonyl)-1*H*-pyrazole-3-carboxylate (8′): Compounds **8** and **8′** were obtained as off-white solids by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel (EtOAc/hexane, 2:8). Data for **8**: M.p. 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.61 (m, 2 H), 7.47–7.53 (m, 2 H), 7.34–7.43 (t, J = 7.5 Hz, 2 H), 7.12–7.18 (d, J = 9 Hz, 2 H), 6.83–6.89 (d, J = 9 Hz, 2 H), 3.94–3.97 (s, 3 H), 3.86–3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 160.6, 144.0, 142.5, 138.8, 134.0, 130.4, 128.9 (2 C), 128.4 (2 C), 128.0 (2 C), 114.3, 113.6 (2 C), 55.6, 52.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 2919, 1740, 1550, 1520, 1464, 1330, 1251, 1172, 1069 cm^{-1}. MS: m/z = 373 $[M + H]^+$. Data for **8′**: M.p. 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51–8.55 (s, 1 H), 8.07–8.14 (d, J = 6 Hz, 2 H), 7.51–7.67 (m, 5 H), 6.97–7.05 (m, 2 H), 3.89–3.90 (s, 3 H), 3.86–3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 141.0, 140.8, 133.2, 133.1, 131.7, 128.6 (2 C), 128.3, 128.1 (2 C), 126.9, 121.9 (2 C), 114.7 (2 C), 55.7, 52.6 ppm. IR (CCl_4): $\tilde{\nu}$ = 2919, 1740, 1550, 1520, 1464, 1330, 1251, 1172, 1069 cm^{-1}. MS: m/z = 373 $[M + H]^+$.

4-Ethyl 3-Methyl 1-Phenyl-5-(phenylsulfonyl)-1*H*-pyrazole-3,4-dicarboxylate and 5-Ethyl 3-Methyl 1-Phenyl-4-(phenylsulfonyl)-1*H*-pyrazole-3,5-dicarboxylate (9 and 9′): Compounds **9** and **9′** were obtained as white solids by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel (EtOAc/light petroleum, 3:7). The two regioisomers were further separated by preparative TLC (EtOAc/light petroleum, 2:3) as yellow oils. Data for **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.49 (m, 4 H), 7.43–7.35 (m, 4 H), 7.14 (d, J = 7.8 Hz, 2 H), 4.56 (q, J = 7.2 Hz, 2 H), 3.94 (s, 3 H), 1.49 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.1, 160.4, 141.0, 139.8, 138.8, 137.2, 134.4, 130.6, 129.1 (2 CH), 128.7 (2 CH), 128.4 (2 CH), 127.6 (2 CH), 122.7, 62.8, 52.7, 14.0 ppm. IR (CCl_4): $\tilde{\nu}$ = 2957, 2931, 1745, 1504, 1450, 1331, 1222, 1159 cm^{-1}. MS: m/z = 437 $[M + Na]^+$. Data for **9′**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.6 Hz, 2 H), 7.67–7.44 (m, 8 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.8, 158.9, 141.6, 140.7, 139.5, 137.8, 133.5, 130.0, 129.4 (2 CH), 128.7 (2 CH), 128.5 (2 CH), 124.7, 124.4 (2 CH), 63.7, 52.9, 13.7 ppm. IR (CCl_4): $\tilde{\nu}$ = 2955, 2928, 1746, 1501, 1447, 1336, 1219, 1163 cm^{-1}. MS: m/z = 437 $[M + Na]^+$.

4-Ethyl 3-Methyl 1-(4-Nitrophenyl)-5-(phenylsulfonyl)-1*H*-pyrazole-3,4-dicarboxylate and 5-Ethyl 3-Methyl 1-(4-Nitrophenyl)-4-(phenylsulfonyl)-1*H*-pyrazole-3,5-dicarboxylate (10 and 10′): Compounds **10** and **10′** were obtained by following the general procedure for the 1,3-DC and were separated by preparative TLC (EtOAc/light petroleum, 2:3). Data for **10**: M.p. 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 8.9 Hz, 2 H), 7.68–7.61 (m, 3 H), 7.50–7.40 (m, 4 H), 4.54 (q, J = 7.2 Hz, 2 H), 3.95 (s, 3 H), 1.48 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.5, 159.8, 148.6, 141.9, 141.2, 140.9, 138.6, 134.9, 129.4 (2 CH), 128.6 (2 CH), 128.1 (2 CH), 124.0 (2 CH), 123.3, 63.0, 53.0, 14.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2930, 1745, 1615, 1600, 1539, 1505, 1439, 1347, 1223, 1164 cm^{-1}. MS: m/z = 482 $[M + Na]^+$. Data for **10′**: M.p. 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 9.1 Hz, 2 H), 8.23 (d, J = 7.7 Hz, 2 H), 7.75 (d, J = 9.1 Hz, 2 H), 7.68–7.56 (m, 3 H), 4.46 (q, J = 7.2 Hz, 2 H), 3.95 (s, 3 H), 1.34 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.6, 158.8, 148.1, 142.8, 142.4, 140.4, 139.5, 133.8, 128.9 (2 CH), 128.6 (2 CH), 126.1, 125.0 (2 CH), 124.9 (2 CH), 64.2, 53.0, 13.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2928, 1747, 1615, 1600, 1537, 1505, 1436, 1345, 1221, 1164 cm^{-1}. MS: m/z = 482 $[M + Na]^+$.

4-Ethyl 3-Methyl 1-(4-Methoxyphenyl)-5-(phenylsulfonyl)-1*H*-pyrazole-3,4-dicarboxylate and 5-Ethyl 3-Methyl 1-(4-Methoxyphenyl)-4-(phenylsulfonyl)-1*H*-pyrazole-3,5-dicarboxylate (11 and 11′): Compounds **11** and **11′** were obtained as yellow oils by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel (EtOAc/light petroleum, 3:7). The two regioisomers were further separated by preparative TLC (EtOAc/

light petroleum, 2:8). Data for **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (t, J = 8.5 Hz, 3 H), 7.40 (t, J = 8.0 Hz, 2 H), 7.04 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.55 (q, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 1.48 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.2, 161.1, 160.4, 146.1, 134.4, 131.9, 129.9, 129.1 (2 CH), 128.8 (2 CH), 128.6, 128.4 (2 CH), 114.7, 113.7 (2 CH), 62.7, 55.6, 52.7, 14.1 ppm. IR (CCl_4): $\tilde{\nu}$ = 2955, 1745, 1510, 1460, 1441, 1340, 1219, 1163 cm^{-1}. MS: m/z = 467 [M + Na]$^+$. Data for **11′**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 7.8 Hz, 2 H), 7.67–7.54 (m, 3 H), 7.42 (d, J = 8.6 Hz, 2 H), 6.95 (d, J = 8.6 Hz, 2 H), 4.38 (q, J = 7.2 Hz, 2 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.6, 159.8, 159.0, 141.2, 140.7, 139.7, 133.5, 130.7, 128.6 (2 CH), 128.5 (2 CH), 126.0 (2 CH), 124.4, 114.4 (2 CH), 63.6, 55.6, 52.8, 13.8 ppm. IR (CCl_4): $\tilde{\nu}$ = 2953, 1743, 1515, 1463, 1444, 1337, 1219, 1163 cm^{-1}. MS: m/z = 467 [M + Na]$^+$.

Methyl 1-Phenyl-5-(phenylthio)-1*H*-pyrazole-3-carboxylate (12): Compound **12** was obtained as a light-yellow oil by following the general procedure for the 1,3-DC and was separated by chromatography on silica gel (EtOAc/hexane, 1:9). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.60 (m, 5 H), 7.30–7.40 (m 4 H), 7.22–7.29 (m, 1 H), 7.12–7.17 (m, 1 H), 4.03–4.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 143.3, 137.9, 134.9, 132.8, 128.9 (2 C), 128.7 (2 C), 128.2, 128.1 (2 C), 126.9, 124.9 (2 C), 115.2, 51.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 2919, 1726, 1229, 1011 cm^{-1}. MS: m/z = 311 [M + H]$^+$.

Methyl 1-(4-Nitrophenyl)-5-(phenylthio)-1*H*-pyrazole-3-carboxylate (13): Compound **13** was obtained as a light-yellow solid by following the general procedure for the 1,3-DC and was separated by chromatography on silica gel (EtOAc/hexane, 1:9). M.p. 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.44 (m, 2 H), 7.85–7.92 (m, 2 H), 7.36–7.42 (m, 3 H), 7.24–7.30 (m, 2 H), 7.19–7.20 (s, 1 H), 4.06–4.09 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 147.0, 145.0, 143.2, 136.0, 132.5, 129.6 (2 C), 129.5 (2 C), 127.9, 125.8 (2 C), 124.2 (2 C), 117.0, 52.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 2919, 1730, 1531, 1345, 1233, 1125, 1009, 854 cm^{-1}. MS: m/z = 356 [M + H]$^+$.

Methyl 1-(4-Methoxyphenyl)-5-(phenylthio)-1*H*-pyrazole-3-carboxylate (14): Compound **14** was obtained as a light-yellow solid by following the general procedure for the 1,3-DC and was separated by column chromatography on silica gel (EtOAc/light petroleum, 1:9). M.p. 83–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.47 (m, 2 H), 7.32–7.40 (m, 3 H), 7.23–7.27 (m, 2 H), 7.14–7.15 (s, 1 H), 6.98–7.04 (m, 2 H), 4.04–4.06 (s, 3 H), 3.94–3.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 160.1, 143.9, 136.0, 133.9, 131.9, 129.8 (2 C), 129.6 (2 C), 127.7, 127.3 (2 C), 115.9, 114.1 (2 C), 55.7, 52.3 ppm. IR (CCl_4): $\tilde{\nu}$ = 2956, 1745, 1726, 1512, 1247, 1225, 1126, 1011 cm^{-1}. MS: m/z = 341 [M + H]$^+$.

4-Ethyl 3-Methyl 1-Phenyl-5-(phenylthio)-1*H*-pyrazole-3,4-dicarboxylate (15): Compound **15** was obtained as a light-yellow oil by following the general procedure for the 1,3-DC and was separated by chromatography on silica gel (EtOAc/light petroleum, 1:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 7.15–7.09 (m, 3 H), 7.04–6.99 (m, 2 H), 4.31 (q, J = 7.2 Hz, 2 H), 3.92 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.3, 161.5, 142.5, 138.0, 135.7, 133.0, 129.4 (2 CH), 129.3, 129.0 (2 CH), 128.7 (2 CH), 127.3, 126.0 (2 CH), 122.3, 61.5, 52.4, 13.8 ppm. IR (CCl_4): $\tilde{\nu}$ = 3065, 2928, 2843, 1731, 1586, 1498, 1472, 1363, 1285, 1212, 1186 cm^{-1}. MS: m/z = 405 [M + Na]$^+$.

4-Ethyl 3-Methyl 1-(4-Nitrophenyl)-5-(phenylthio)-1*H*-pyrazole-3,4-dicarboxylate (16): Compound **16** was obtained as a yellow oil by following the general procedure for the 1,3-DC and was separated by chromatography on silica gel (EtOAc/light petroleum, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 9.1 Hz, 2 H), 7.64 (d, J = 9.1 Hz, 2 H), 7.20–7.16 (m, 3 H), 7.06–7.03 (m, 2 H), 4.36 (q, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 1.31 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.8, 161.1, 147.5, 143.6, 142.7, 136.0, 132.3, 129.4 (2 CH), 129.2 (2 CH), 127.7 (2 CH), 126.6 (2 CH), 124.1, 123.5, 61.7, 52.7, 13.9 ppm. IR (CCl_4): $\tilde{\nu}$ = 3065, 2954, 1734, 1653, 1533, 1347, 1203, 1127, 1079 cm^{-1}. MS: m/z = 450 [M + Na]$^+$.

4-Ethyl 3-Methyl 1-(4-Methoxyphenyl)-5-(phenylthio)-1*H*-pyrazole-3,4-dicarboxylate (17): Compound **14c** was obtained as a white oil by following the general procedure for the 1,3-DC and was separated by chromatography on silica gel (EtOAc/light petroleum, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.14 (m, 5 H), 7.06–7.02 (m, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 4.31 (q, J = 7.2 Hz, 2 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.3, 161.5, 160.0, 142.3, 135.7, 133.2, 130.9, 129.3 (2 CH), 129.0 (2 CH), 127.4 (2 CH), 127.2, 122.1, 113.7 (2 CH), 61.5, 55.4, 52.4, 13.9 ppm. IR (CCl_4): $\tilde{\nu}$ = 3063, 2955, 2839, 1734, 1515, 1478, 1365, 1287, 1253, 1212, 1183 cm^{-1}. MS: m/z = 435 [M + Na]$^+$.

2-Mercapto-1-phenylethanone: A solution of thiolacetic acid (5.6 g, 73.6 mmol) in dry pyridine (40 mL) was added to a solution of phenacyl chloride (10 g, 65.0 mmol), and resultant reaction mixture was maintained at 85 °C for 1.5–2 h. After cooling to room temperature, chloroform (200 mL) was added to the orange reaction mixture, which was washed with 10% HCl (150 mL) and extracted with 10% NaOH (150 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography (1–2% EtOAc/hexane) to afford phenacyl thiolacetate (10.2 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–8.02 (m, 2 H), 7.58–7.64 (tt, J = 6, 1.5 Hz, 1 H), 7.47–7.53 (m, 2 H), 4.41 (s, 2 H), 2.42 (s, 3 H) ppm. A solution of phenacyl thiolacetate (10.2 g, 52.5 mmol) in diethyl ether (60 mL) was stirred vigorously while aq. 2 N NaOH solution (58 mL, 120 mmol) was added. This mixture was stirred for 2 h and then separated. The aqueous layer was cooled to 0 °C and acidified. This was extracted with DCM (2 × 100 mL). The combined organic layers were dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude product 2-mercapto-1-phenylethanone was purified by flash column chromatography (5% EtOAc/hexane) to afford the pure product as a yellow oil (7.3 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.99 (m, 2 H), 7.56–7.63 (m, 1 H), 7.45–7.52 (m, 2 H), 3.94–3.98 (d, J = 8 Hz, 2 H), 2.11–2.15 (t, J = 8 Hz, 1 H) ppm.

2,2′-Disulfanediylbis(1-phenylethanone) (18): To a stirred solution of 2-mercapto-1-phenylethanone (5 g, 32.9 mmol) in EtOAc (30 mL) was added NaI (49.5 mg, 0.33 mmol) and 30% H_2O_2 (3.38 mL, 32.9 mmol), and the mixture was stirred at room temperature for 1 h. Sat. aq. $Na_2S_2O_3$ (100 mL) was then added, and resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo. The crude product was purified with flash column chromatography (5% EtOAc/hexane) to obtain a white solid (4.65 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.99 (d, J = 6 Hz, 4 H), 7.55–7.63 (tt, J = 7.5, 1.5 Hz, 2 H), 7.42–7.51 (t, J = 7.5 Hz, 4 H), 4.20 (s, 4 H) ppm.

1,2-Bis[(2-phenyl-1,3-dioxolan-2-yl)methyl]disulfane (19): A solution of **18** (4.65 g, 15.4 mmol), ethylene glycol (5.9 g, 92.4 mmol), triethyl orthoformate (11.58 mL, 61.6 mmol), and PTSA (0.3 g, 1.57 mmol) in toluene was heated to 60 °C for 3 h. After comple-

tion, the reaction mixture was cooled and diluted with EtOAc (30 mL) and then washed with aq. K_2CO_3 and brine. The organic layer was then dried with anhydrous $MgSO_4$ and the solvents were evaporated. The crude solid product was purified by column chromatography (1–5% EtOAc/hexane) to give a light-yellow solid (4.9 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.53 (m, 4 H), 7.25–7.38 (m, 6 H), 4.03–4.18 (m, 4 H), 3.77–3.89 (m, 4 H), 3.33 (s, 4 H) ppm.

Trimethyl{[(2-phenyl-1,3-dioxolan-2-yl)methylthio]ethynyl}silane (20): Trimethylsilylethyne (0.5 g, 5.1 mmol) was dissolved in dry THF (10 mL) at 0 °C. A solution of *n*BuLi (1.6 M in hexane, 3.8 mL, 6.1 mmol) was then added dropwise with stirring under an atmosphere of argon. After 45 min a solution of 1,2-bis[(2-phenyl-1,3-dioxolan-2-yl)methyl]disulfane (2 g, 6.6 mmol) in THF (20 mL) was introduced at 0 °C and stirring was continued for 1–2 h. Then reaction mixture was quenched with sat. NH_4Cl solution (15 mL). The mixture was then extracted with diethyl ether (3 × 15 mL), and the organic layer was washed with water (2 × 15 mL) and brine. The ether layer was then dried with anhydrous $MgSO_4$ and the solvents were evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane) to give a colorless oil (1.2 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.55 (m, 2 H), 7.30–7.44 (m, 3 H), 4.02–4.22 (m, 2 H), 3.78–3.93 (m, 2 H), 3.34 (s, 2 H), 0.14 (s, 9 H) ppm.

2-(Ethynylthiomethyl)-2-phenyl-1,3-dioxolane (21): To a stirred solution of **20** (0.5 g, 1.71 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of TBAF-hydrate (0.5 g, 1.91 mmol) dissolved in THF (5 mL). The reaction mixture was then vigorously stirred at 0 °C for 1–2 h. After completion, sat. NH_4Cl (15 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL). The combined ether extracts were washed with water (2 × 15 mL) and brine. The ether layer was then dried with anhydrous $MgSO_4$, and the solvents were evaporated in vacuo to give **21** as a brown solid (351 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.57 (m, 2 H), 7.32–7.44 (m, 3 H), 4.17–4.25 (m, 2 H), 3.88–3.94 (m, 2 H), 3.34 (s, 2 H), 2.70 (s, 1 H) ppm.

General Procedure for the Preparation of Compounds 22: To a solution of **21** (0.1 g, 0.43 mmol) in dry THF (5 mL) at –78 °C was added dropwise a solution of LiHMDS (1 M in THF, 0.47 mL, 0.47 mmol), and the resulting mixture was stirred for 20 min at the same temperature. After 20 min freshly distilled HMPA (0.37 mL, 2.15 mmol) was added to the reaction, and the mixture was warmed slowly to –35 °C over 2 h. The reaction was again cooled to –78 °C and dry DMF (0.06 mL, 0.86 mmol) was added. The reaction was warmed to –35 °C over 2 h and kept at the same temperature for a further 1.5 h, then quenched at –35 °C with sat. NH_4Cl (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were washed with water (2 × 10 mL) and brine. The organic layer was then dried with anhydrous $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was used as such for further reactions without purification. Compounds **22a**–**c** were then obtained as a light-yellow oils by following the general procedure for the 1,3-DC and were separated by chromatography on silica gel.

Methyl 4-Formyl-1-phenyl-5-[(2-phenyl-1,3-dioxolan-2-yl)methylthio]-1*H*-pyrazole-3-carboxylate (22a): Eluent: 10–20% EtOAc/hexane. Yield: 126 mg (66% overall). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.54 (s, 1H), 7.41–7.66 (m, 5 H), 7.16–7.33 (m, 5 H), 4.00 (s, 3 H), 3.58–3.68 (m, 4 H), 3.38 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 162.1, 144.9, 142.5, 140.8, 138.4, 129.7, 129.1, 128.6, 128.4, 126.7, 125.8, 124.8,108.9, 65.4, 52.9, 45.3 ppm. IR (CCl_4): $\tilde{\nu}$ = 3003, 2960, 1728, 1690 cm^{-1}. MS: *m*/*z* = 447 [M + Na]$^+$.

Methyl 4-Formyl-1-(4-nitrophenyl)-5-[(2-phenyl-1,3-dioxolan-2-yl)methylthio]-1*H*-pyrazole-3-carboxylate (22b): Eluent: 10–20% EtOAc/hexane. Yield: 60 mg, 42%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.54 (s, 1 H), 8.35–8.41 (d, *J* = 9 Hz, 2 H), 7.82–7.87 (d, *J* = 9 Hz, 2 H), 7.18–7.28 (m, 5 H), 4.02–4.05 (s, 3 H), 3.65–3.75 (m, 4 H), 3.46–3.50 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.0, 161.6, 147.9, 145.6, 143.0, 142.8, 140.3, 128.9, 128.5 (2 C), 127.4 (2 C), 125.8 (2 C), 125.6, 124.4 (2 C), 108.8, 65.3 (2 C), 53.1, 45.6 ppm. IR (CCl_4): $\tilde{\nu}$ = 2956, 1729, 1686, 1598, 1541, 1533, 1347, 1254, 1141, 1011 cm^{-1}. MS: *m*/*z* = 492 [M + Na]$^+$.

Methyl 4-Formyl-1-(4-methoxyphenyl)-5-[(2-phenyl-1,3-dioxolan-2-yl)methylthio]-1*H*-pyrazole-3-carboxylate (22c): Eluent: 10–20% EtOAc/hexane. Yield: 58 mg, 43%.^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.53 (s, 1 H), 7.44–7.48 (d, *J* = 6 Hz, 2 H), 7.21–7.25 (m, 5 H), 6.97–7.02 (d, *J* = 6 Hz, 2 H), 3.99–4.02 (s, 3 H), 3.87–3.89 (s, 3 H), 3.62–3.72 (m, 4 H), 3.36–3.39 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.4, 162.3, 160.5, 144.7, 142.5, 140.8, 131.4, 128.6, 128.4 (2 C), 127.9 (2 C), 127.3, 125.8 (2 C), 114.2 (2 C), 108.8, 65.4 (2 C), 55.9, 52.9, 45.1 ppm. IR (CCl_4): $\tilde{\nu}$ = 3065, 2955, 2892, 1726, 1682, 1612, 1515, 1475, 1253, 1172, 1142, 1040 cm^{-1}. MS: *m*/*z* = 477 [M + Na]$^+$.

Methyl 5-Benzoyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-3-carboxylate (23a): To a stirred solution of **22a** (100 mg, 0.23 mmol) in acetone (10 mL) was added 50% TFA in water (10 mL). The resulting mixture was then heated at 65 °C overnight. After completion, the reaction was cooled to room temperature and then acetone was removed carefully under reduced pressure. The aqueous layer was then extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water till neutral and then with brine. The organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated in vacuo to give the crude product. This crude product was then purified by preparative TLC (DCM) to give **23a** as a white solid. Yield: 17 mg, 20%. M.p. 212–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.97 (m, 4 H), 7.87 (s, 1 H), 7.62–7.69 (t, *J* = 16 Hz, 1 H), 7.51–7.62 (q, *J* = 12 Hz, 4 H), 7.37–7.46 (t, *J* = 16 Hz, 1 H), 4.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 162.0, 145.6, 144.8, 138.9, 138.0, 137.4, 132.9, 132.1, 130.0, 129.3, 128.9, 127.9, 125.5, 119.3, 52.8 ppm. IR (CCl_4): $\tilde{\nu}$ = 3005, 2950, 1750, 1725 cm^{-1}. MS: *m*/*z* = 385 [M + Na]$^+$.

Methyl 5-Benzoyl-1-(4-nitrophenyl)-1*H*-thieno[2,3-*c*]pyrazole-3-carboxylate (23b): To a stirred solution of **22b** (80 mg, 0.16 mmol) in acetone (6 mL) was added 50% TFA in water (6 mL). Isolation of **23b** as a yellow solid was carried out as for **23a**. Eluent: 25% EtOAc/hexane. Yellow solid. Yield: 18 mg, 28%. M.p. 223–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45–8.49 (d, *J* = 9 Hz, 2 H), 8.09–8.13 (d, *J* = 9 Hz, 2 H), 7.90–7.96 (dt, *J* = 9, 1.5 Hz, 2 H), 7.88–7.90 (s, 1 H), 7.64–7.72 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.53–7.62 (tt, *J* = 7.5, 1.5 Hz, 2 H), 4.05–4.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3, 161.5, 146.3, 145.9, 145.7, 143.2, 139.5, 137.0, 133.2, 132.8, 129.3 (2 C), 129.0 (2 C), 125.9 (2 C), 125.1, 119.3 (2 C), 53.1 ppm. IR (CCl_4): $\tilde{\nu}$ = 2927, 1752, 1727, 1640, 1532, 1508, 1341, 1285 cm^{-1}. MS: *m*/*z* = 430 [M + Na]$^+$.

Methyl 5-Benzoyl-1-(4-methoxyphenyl)-1*H*-thieno[2,3-*c*]pyrazole-3-carboxylate (23c): To a stirred solution of **22c** (100 mg, 0.22 mmol) in acetone (6 mL) was added 50% TFA in water (6 mL). Isolation of **23c** as an off-white solid was carried out as for **23a**. Eluent: 25% EtOAc/hexane. Yield: 20 mg, 23%. M.p. 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.93 (d, *J* = 6 Hz, 2 H), 7.84–7.86 (s, 1 H), 7.80–7.84 (d, *J* = 6 Hz, 2 H), 7.62–7.68 (tt, *J* = 6, 1.5 Hz, 1 H), 7.52–7.58 (t, *J* = 6 Hz, 2 H), 7.05–7.09 (d, *J* = 9 Hz, 2 H), 4.00–4.03 (s, 3 H), 3.87–3.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 162.1, 159.3, 145.4, 144.7, 137.5, 132.8, 132.4, 132.0,

129.3 (2 C), 128.9 (2 C), 125.6, 123.0, 121.0 (2 C), 115.1 (2 C), 55.9, 52.7 ppm. IR (CCl_4): $\tilde{\nu}$ = 3005, 2954, 1748, 1723, 1543, 1518, 1287, 1252 cm^{-1}. MS: *m*/*z* = 415 $[M + Na]^+$.

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[25] One of the referee suggested for the ring-closure of **22a**–**c** the use of sodium ethoxide in refluxing toluene according to P. Toto, J. Chenault, A. El Hakmaooui, M. Akssira, G. Guillament, *Synth. Commun.* **2008**, *38*, 674–683 but in our hands this protocol failed. It is likely due to the high acidity of the CH_2 α to sulfur, where several undesired side reactions took place.

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