Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 15 Feb 2008.

To cite this article: Patrick Toto , Jacques Chenault , Ahmed El Hakmaoui , Mohamed Akssira & Gerald Guillaumet (2008): Synthesis of 3-Substituted-1-methyl-1H-thieno[2,3-c]pyrazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:5, 674-683

To link to this article: http://dx.doi.org/10.1080/00397910701818578

Synthetic Communications®, 38: 674–683, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701818578

Synthesis of 3-Substituted-1-methyl-1*H*-thieno[2,3-*c*]pyrazoles

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Abstract: We report a simple and practical six-step synthesis of new 1-methyl-1*H*-thieno[2,3-*c*]pyrazoles from 3-amino-1*H*-pyrazole-4-carboxylic acid ethyl ester.

Keywords: cyclization, pyrazoles, thienopyrazoles

INTRODUCTION

Thieno-fused heterocycles as thienopyridines,[1,2] thienopyrimidines,[3–5] and thienopyrroles[6,7] constitute a group of biologically active structures. Thienopyrazoles, the diazaanalogs of the corresponding thienopyrroles, are attractive targets for synthesis and activity studies.

Thienopyrroles are usually synthesized from the corresponding thiophene derivatives bearing the appropriate functionality at the ring.[8,9] We report herein the synthesis of the thienopyrazole derivatives **13** and **14** from functionalized pyrazoles, inspired by Fiesselmann's procedure,[10,11] widely used in thienofused heterocycle syntheses. Previously, and related to a study on the reactivity of pyrazoles,[12,13] we obtained the alkylsulfanylpyrazole hetrocyclic ring using Fiesselmann's procedure.

Received in Poland June 27, 2007
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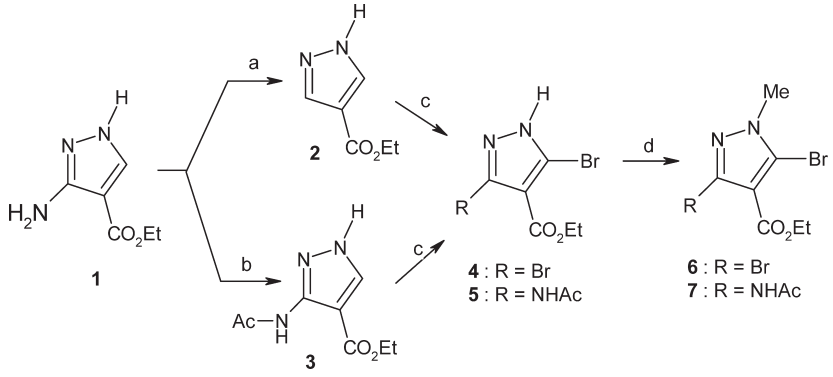
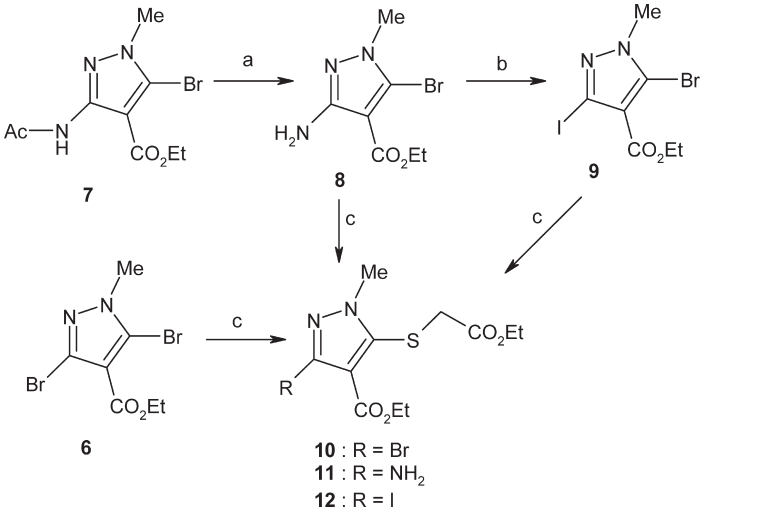


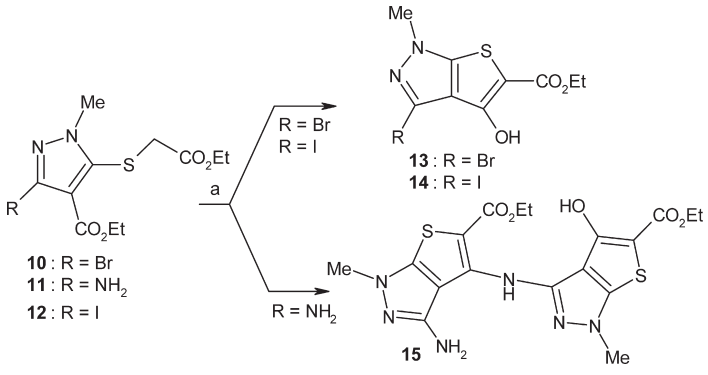
Scheme 1. Reagents and conditions: a) $NaNO_2$, AcOH/HCl, −5°C, EtOH reflux; b) AcCl reflux; c) Br_2, AcONa, EtOH/H_2O; and d) NaH, THF, MeI.

RESULTS AND DISCUSSION

The synthesis began by obtaining 5-bromopyrazole-4-carboxylic acid ethyl esters **4** and **5**. Condensation of hydrazine hydrate and ethyl 2-cyano-3-ethoxy-acrylate[14] gave the corresponding 3-amino-1*H*-pyrazole-4-carboxylic acid ethyl ester **1**, which was transformed in the derivatives **2** and **3** by reductive diazotation and acylation, respectively. Electrophilic bromination of these derivatives afforded the corresponding bromine derivatives **4** and **5** (Scheme 1).



Scheme 2. Reagents and conditions: a) EtOH/HCl reflux; b) $NaNO_2$, H_2SO_4, −5°C, KI; and c) Na_2S, DMF, 100°C, 2 h, then $BrCH_2CO_2Et$, 100°C, 2 h.



Scheme 3. Reagents and conditions: a) EtONa/EtOH, toluene 100°C, 1 h, then AcOH.

Methylation of bromine derivatives **4** and **5** gave the corresponding *N*-methylated derivatives **6** and **7** in very good yields.

The other brominated precursors **8** and **9** were easily prepared from **7** by simple selective *N*-deprotection and by the sequential deprotection–diazotation–substitution set of reactions shown in Scheme 2.

The alkylsulfanylpyrazoles **10**, **11**, and **12** were prepared from **6**, **8**, and **9**, respectively, following the method reported by Morimoto et al.[15] on the synthesis of 3,5-dichloropyrazole-4-carboxylic acids. Sodium sulfide nucleophilic substitution and homologation of the resulting thiolate by reaction with bromoacetic acid ethyl ester installed the required *S*-containing chain for the next ring-closing step.

Base-added cyclization of pyrazoles **10** and **12** was accomplished by the use of sodium ethanolate in toluene, affording the expected thieno[2,3-*c*]pyrazoles **13** and **14**.

Moreover, cyclization of the amine analog **11**, under the same conditions, yielded the imine derivative **15**, which probably comes from the self-condensation of the expected thienofused compound (Scheme 3).

CONCLUSION

We have accomplished the synthesis of novel 3-bromo- and 3-iodo-4-hydroxy-1-methyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl esters **13** and **14**. An interesting C-3 N-connected dimer homolog was also obtained in the cyclization of the amine derivative **11**. Different substitution patterns at positions C-3 and/or C-4 of these heterocyclic structures can be

easily accessed by standard palladocatalyzed couplings or regioselective alkylations. Studies are in progress in our laboratory.

EXPERIMENTAL

General

NMR spectra were recorded at 250 and 62.5 for ^{1}H and ^{13}C, respectively on a Bruker DPX250 spectrometer in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO). IR spectra were recorded on a Perkin-Elmer FT Paragon 1000 PC. Melting points were recorded on a Köfler apparatus and were uncorrected. Mass spectra were recorded on Perkin-Elmer Sciex API 3000. The chromatographic purifications were made using silica gel (Merck,, 40–63 μm) under nitrogen pressure. The reaction's evolution was monitored by thin-layer chromatography (TLC, Merck 60 F_{254}).

Procedures and Characterizations

3-Amino-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**1**)

Hydrazine hydrate (l0 g, 0.17 mol) in ethanol (400 mL) was stirred with ethyl 2-cyano-3-ethoxyacrylate (29 g, 0.17 mol) at room temperature for 18 h. The ethanol was evaporated under reduced pressure, and the residue was crystallized at 0°C from isopropyl ether. Yield: 93%. Mp: 102°C;[14] IR (KBr): 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, $J = 7$ Hz, C**H**$_3$-CH$_2$-O), 4.32 (q, 2H, $J = 7$ Hz, CH$_3$-C**H**$_2$-O), 6.88 (s, 2H, N**H**$_2$), 7.78 (s, 1H, C$_5$-**H**); ^{13}C NMR ($CDCl_3$): δ 14.8 (**C**H$_3$-CH$_2$), 60.2 (CH$_3$-**C**H$_2$), 98.2 (**Cq**), 136.3 (**C**H), 154.3 (**Cq**), 164.9 (**C**═O); MS 156 $[M + H]^+$.

1*H*-Pyrazole-4-carboxylic Acid Ethyl Ester (**2**)

To a cooled solution (0°C) of 3-amino-1*H*-pyrazole-4-carboxylic acid ethyl ester **1** (5 g, 32.23 mmol, 1 eq) in dry acetic acid (30 mL), HCl 37% (9.9 mL, 3 eq) and aqueous $NaNO_2$ (2.34 g, 33.9 mmol, 1.05 eq) (10 ml) were sequentially added, keeping the temperature below 5°C. The reaction mixture was stirred at 0°C for 30 min. Ethanol (200) mL was added, and the mixture was allowed to reflux for 1 h. The ethanol was evaporated under reduced pressure, and the resulting residue was poured on water (150 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to afford **2** as a beige solid (4.47 g, 99%). Mp: 69°C;[16,17] IR (KBr): 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t. 3H, $J = 7.5$ Hz, C**H**$_3$-CH$_2$-O), 4.28 (q, 2H, $J = 7.5$ Hz, CH$_2$-O), 8.04 (s, 2H, C$_3$-**H** + C$_5$-**H**), 9.57

(s, 1H, N-**H**); ^{13}C NMR ($CDCI_3$): δ 14.8 (**C**H_3-CH_2-O), 60.9 (O-**C**H_2), 115.5 (**C**$_4$), 135 (C_3-H + C_5-H), 163.9 (**C**═O); MS 141 $[M + H]^+$.

3-Acetamido-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**3**)

3-Amino-1*H*-pyrazole-4-carboxylic acid ethyl ester **1** (10 g, 64.5 mmol, 1 eq) and acetyl chloride (40 mL) were mixed at 0°C and heated at reflux for 4 h. The excess of AcCl was evaporated off under reduced pressure, water (100 mL) was added, and the resulting mixture was stirred for 18 h. At this time, the white solid precipitate was filtered off and dried to give pure derivative **3** (l1.47 g, 90%). Mp: l30°C; IR (KBr): 1668 cm^{-1}, 1697 cm^{-1}; ^{1}H NMR ($CDCI_3$): δ 1.33 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 2.25 (s, 3H, C**H**$_3$-C═O), 4.29 (q, 2H, $J = 7.5$ Hz, O-C**H**$_2$), 7.74 (s, 1H, C_5-**H**), 9.56 (s, 1H, N-**H**), 11.75 (s, 1H, N-**H**); ^{13}C NMR ($CDCl_3$): δ 13.0 (**C**H_3-CH_2-O), 22.4 (**C**H_3-C═O), 59.1 (**C**H_2-O), 96.6 (**C**$_4$), 137.6 (**C**$_5$-H), 141.6 (**C**$_3$), 163.4 (**C**═O), 168.0 (**C**═O); MS 198 $[M + H]^+$. Anal. calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.78; H, 5.59; N, 21.34.

3,5-Dibromo-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**4**)

Aqueous NaOAc (14 g in 120 mL) was added, to a solution of 1*H*-pyrazole-4-carboxylic acid ethyl ester **2** (3.5 g, 25 mmol, 1 eq) in ethanol (80 mL). Br_2 (5.25 mL, 100 mmol, 4 eq) was added, and the reaction mixture was stirred at room temperature 5 h and poured in water (200 mL). The aqueous phase was extracted with AcOEt (3 × 500 mL), and the combined organic phases were sequentially washed with a saturated solution of sodium thiosulfate (2 × 50 mL), dried on $MgSO_4$, filtered, and concentrated under reduced pressure to afford **4** as a yellow solid (7.37 g, 99%). Mp: 132°C; IR (KBr): 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 4.34 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O), 9.65 (s, 1H, N-**H**); ^{13}C NMR ($CDCl_3$): δ 14.5 (**C**H_3CH_2-O), 61.2 (O-**C**H_2), 113.0 (**C**$_4$), 124.5 (**C**$_3$ + **C**$_5$), 161.2 (**C**═O), MS 297, 299, 301 $[M + H]^+$. Anal. calcd. for $C_6H_6Br_2N_2O_2$: C, 24.19; H, 2.03; N, 9.40. Found: C, 24.17; H, 2.01; N, 9.46.

3-Acetylamino-5-bromo-l*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**5**)

3-Acetylamino-1-H-pyrazole-4-carboxylic acid ethyl ester **3** was brominated using the same procedure as in the case of compound **4**. Yield: 72%; mp: 199°C; IR (KBr): 1690 cm^{-1}, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 2.28 (s, 3H, C**H**$_3$-C═O), 4.31 (q, 2H, $J = 7.5$ Hz, O-C**H**$_2$), 9.77 (s, lH, N-**H**), 11.83 (s, 1H, N-**H**); ^{13}C NMR ($CDCl_3$): δ 14.0 (**C**H_3-CH_2O), 23.6 (**C**H_3-C═O), 60.8 (**C**H_2-O), 97.2 (**C**$_4$), 127.1 (**C**$_5$), 144.2 (**C**$_3$), 163.6, 169.7 (**C**═O); MS 276, 278. $[M + H]^+$. Anal. calcd. for $C_8H_{10}BrN_3O_3$: C, 34.80; H, 3.65; N, 15.22. Found: C, 34.85; H, 3.62; N, 15.28.

3,5-Dibromo-l-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**6**)

NaH (0.296 g, 7.38 mmol, 1.1 eq) was carefully added to a cooled (0°C) solution of 3-5-dibromo-1*H*-pyrazo1e-4-carboxylic acid ethyl ester **4** (2 g, 6.7 mmol, 1 eq) in dry THF (30 ml). The resulting mixture was stirred at room temperature for 30 min, and MeI (1.2 mL, 19.2 mmo1, 2.9 eq) was added. The new mixture was allowed to stir overnight at room temperature. Addition of water (150 mL) followed by organic extraction (CH_2Cl_2, 3×200 mL), drying on $MgSO_4$, filtration, and concentration under reduced pressure afforded **6** as a beige solid (1.99 g, 95%). Mp: 69°C; IR (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH$_2$-O), 3.86 (s, 3H, N-C**H**$_3$), 4.31 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O); ^{13}C NMR ($CDCl_3$): δ 14.5 (**C**H$_3$-CH$_2$-O), 38.9 (N-**C**H$_3$), 61.2 (CH$_3$-**C**H$_2$-O), 113.5 (**C**$_4$), 119.8 (**C**$_5$-Br), 128.6 (**C**$_3$-Br), 160.9 (**C**═O); MS 311, 313, 315 $[M + H]^+$. Anal. calcd. for $C_7H_8Br_2N_2O_2$: C, 26.95; H, 2.58; N, 8.98. Found: C, 26.83; H, 2.59; N, 9.02.

3-Acetylamino-5-bromo-l-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**7**)

3-Acetylamino-5-bromo-1*H*-pyrazole-4-carboxylic acid ethyl ester **5** was methylated using the same procedure as in the case of compound **6**. Yield: 82%; Mp: 150°C; IR (KBr): 1703 cm^{-1}, 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH$_2$-O), 2.25 (s, 3H, C**H**$_3$-C═O), 3.89 (s, 3H, N-C**H**$_3$), 4.33 (q, 2H, $J = 7.5$ Hz, O-C**H**$_2$), 9.29 (s, 1H, N-**H**); ^{13}C NMR ($CDCl_3$): δ 13.9 (**C**H$_3$-CH$_2$-O), 24.3 (**C**H$_3$-C═O), 38.0 (N-**C**H$_3$), 60.7 (**C**H$_2$-O), 100.6 (**C**$_4$), 117.2 (**C**$_5$), 148.9 (**C**$_3$), 163.2, 167.0 (**C**═O); MS 290, 292 $[M\text{-}H]^+$. Anal. calcd. for $C_9H_{12}BrN_3O_3$: C, 37.26: H, 4.17; N, 14.48. Found: C, 37.30; H, 4.15; N, 14.47.

3-Amino-5-bromo-1-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**8**)

Acetylaminopyrazole **7** (2.5 g, 8.62 mmol, 1 eq) was dissolved in a cooled (0°C) solution of HCl (1 ml) in ethanol (50 mL), and the solution was refluxed for 30 min. The ethanol was evaporated off under reduced pressure, and a solution of aqueous $NaHCO_3$ (5%, 150 ml) was added, to neutralize the residue. The aqueous phase was extracted with AcOEt (3×100 mL), and the combined organic phases were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to afford **8** as a crystalline solid (1.6 g, 75%). Mp: 68°C; IR (KBr): 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, $J = 7$ Hz, C**H**$_3$-CH$_2$-O), 3.65 (s, 3H, N-C**H**$_3$), 4.25 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O), 4.76 (s, 2H, N**H**$_2$); ^{13}C NMR ($CDCl_3$): δ 14.4 (**C**H$_3$-CH$_2$-O), 37.5 (N-**C**H$_3$), 60.2 (**C**H$_2$-O), 98.7 (**C**$_4$), 116.8 (**C**$_5$), 156.7 (**C**$_3$), 170.9 (**C**═O). MS 248, 250

$[M + H]^+$. Anal. calcd. for $C_7H_{10}BrN_3O_2$: C, 33.89; H, 4.06; N, 16.94. Found: C, 34.01; H, 4.08; N, 16.89.

5-Bromo-3-iodo-1-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**9**)

An aqueous solution of $NaNO_2$ (1.58 g, 22.84 mmol, 1.1 eq) (10 mL) was dropwise added to a cooled (-10°C) solution of aminopyrazole **8** (5.15 g, 20.77 mmol, 1 eq) in H_2SO_4 (50%, 100 mL), keeping the temperature below 0°C. The reaction mixture was stirred for 30 min, at 0°C, and then an aqueous solution of KI (10.35 g, 62.3 mmol, 3 eq) (10 mL) was added. The aqueous mixture was allowed to stir for 10 min, and water (200 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were sequentially washed with $NaHCO_3$ (5%, 2 × 50 mL) and a saturated solution of sodium thiosulfate (2 × 100 mL), dried on $MgSO_4$, filtered, and concentrated under reduced pressure to give a solid residue. Column chromatography (7/3, petroleum ether/AcOEt) afforded pure compound **9** (4 g, 53%) of a white solid. Mp: 134°C, IR (KBr): 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 3.93 (s, 3H, N-C**H**$_3$), 4.32 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O); ^{13}C NMR ($CDCl_3$): δ 14.5 (**C**H_3-CH_2-O), 39.0 (N-**C**H_3), 61.2 (O-**C**H_2), 98.8 (**C**$_4$), 116.9 (**Cq**), 118.9 (**Cq**), 161.0 (**C**═O); MS 359, 361 $[M + H]^+$. Anal. calcd. for $C_7H_8BrIN_2O_2$: C, 23.42; H, 2.25; N, 7.80. Found: C, 23.47; H, 2.30; N, 7.82.

3-Bromo-5-ethoxycarbonylmethylsulfanyl-1-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**10**)

A mixture of dibromopyrazole **6** (l.83 g, 5.8 mmol, 1 eq) and Na_2S (60%, 920 mg, 7.08 mmol, 1.2 eq) in dry DMF (20 mL) was heated at l00°C for 2 h. The mixture was allowed to cool at room temperature, and bromoacetic acid ethyl ester (0.72 mL, 6.38 mmol, 1.1 eq) was added. After 2 h, the DMF was removed under reduced pressure, and the residue was poured on water (50 mL). The aqueous phase was extracted with AcOEt (3 × 100 mL), and the combined organic phases were washed with brine (2 × 50 mL), dried on $MgSO_4$, filtered, and concentrated. Yield: 76%; Mp: 67°C; IR (KBr): 1744 cm^{-1}; 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 1.37 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 3.74 (s, 2H, S-C**H**$_2$), 3.98 (s, 3H, N-C**H**$_3$), 4.08 (q, 2H, $J = 7.5$ Hz, CH_3-C**H**$_2$-O), 4.33 (q, 2H, $J = 7.5$ Hz, CH_3-C**H**$_2$-O); ^{13}C NMR ($CDCl_3$): δ 15.1 (CHrCH2-O), 15.2 (**C**H_3-CH_2-O), 38.3 (S-**C**H_2), 38.9 (N-**C**H_3), 61.9 (CH_3-**C**H_2-O), 62.9 (CH_3-**C**H_2-O), 117.7 (**C**$_4$), 128.9 (**C**$_5$), 139.4 (**C**$_3$), 162.5 (**C**═O), 169.9 (**C**═O); MS 351, 353 $[M + H]^+$. Anal. calcd. for $C_{ll}H_{15}BrN_2O_4S$: C, 37.62; H, 4.30; N, 7.98. Found: C, 37.60; H, 4.32; N, 7.99.

3-Amino-5-ethoxycarbonylmethylsulfanyl-1-methyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**11**)

Aminopyrazole **8** was alkylated using the same procedure as in the case of compound **10**. Yield: 60%; Mp: 56°C; IR (KBr): 1750 cm^{-1}; 1696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 1.38 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 3.7 (s, 2H, S-C**H**$_2$), 3.84 (s, 3H, N-C**H**$_3$), 4.11 (q, 2H, $J = 7.5$ Hz, O-C**H**$_2$), 4.34 (q, 2H, $J = 7.5$ Hz, O-C**H**$_2$), 4.75 (s, 2H, N**H**$_2$); ^{13}C NMR ($COCl_3$): δ 13.2 (**C**H_3-CH_2-O), 13.6 (**C**H_3-CH_2-O), 35.9 (N-**C**H_3), 36.3 (S-**C**H_2), 59.2 (CH_3-**C**H_2-O), 60.8 (CH_3-**C**H_2-O), 100.0 (**C**$_4$), 134.5 (**C**$_5$), 155.6 (**C**$_3$), 162.7 (**C**═O), 168.2 (**C**═O); MS 288 $[M + H]^+$. Anal. calcd. for $C_{11}H_{17}N_3O_4S$: C, 45.98; H, 5.96; N, 14.62. Found: C, 45.89; H, 5.97; N, 14.68.

5-Ethoxycarbonylmethylsulfanyl-3-iodo-1-methyl-1*H*-pyrazole-4-carboxyl Carboxylic Acid Ethyl Ester (**12**)

Iodopyrazole **9** was alkylated using the same procedure as in the case of compound **10**. Yield: 80%; Mp: 76°C, IR (KBr): 1740 cm^{-1}, 1692 cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 1.40 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 3.74 (s, 2H, S-C**H**$_2$), 4.02 (s, 3H, N-C**H**$_3$), 4.05 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O), 4.35 (q, 2H, $J = 7.5$ Hz, CH_2-O); ^{13}C NMR ($CDCl_3$): δ 14.1 (**C**H_3-CH_2-O), 14.3 (**C**H_3-CH_2-O), 37.4 (S-**C**H_2), 38.0 (N-**C**H_3), 61.0 (**C**H_2-O), 61.9 (**C**H_2-O), 98.5 (**C**$_4$), 120.7 (**C**$_5$), 137.5 (**C**$_3$), 161.5 (**C**═O), 169.0 (**C**═O); MS 399 $[M + H]^+$. Anal. calcd. for $C_{ll}H_{15}IN_2O_4S$: C, 33.18; H, 3.80; N, 7.03. Found: C, 33.09; H, 3.81; N, 7.06.

3-Bromo-4-hydroxy-1-methyl-1*H*-thieno[2,3-c]pyrazole-5-carboxylic Acid Ethyl Ester (**13**)

To a solution of sodium (23.5 mg, 1.03 mmol, 1.2 eq) in dry ethanol (0.5 mL), a solution of **10** (300 mg, 0,86 mmol, 1 eq) in dry toluene (10 mL) was added, and the reaction mixture was heated under reflux for 1 h. Acetic acid (0.2 ml) was then added to destroy the excess of base, and the resulting mixture was diluted with AcOEt (200 ml), washed with water (30 mL), dried on $MgSO_4$, filtered, and concentrated under reduced pressure to afford **13** (251 mg, 96%); Mp: 133°C; IR (KBr): 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH_2-O), 3.88 (s, 3H, N-C**H**$_3$), 4.36 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O), 10.39 (s, 1H, O-**H**); ^{13}C NMR ($CDCl_3$): δ 14.7 (**C**H_3-CH_2-O), 38.6 (N-**C**H_3), 61.7 (0-**C**H_2), 117.7 (**C**$_4$), 120.9 (**C**$_5$), 155.0 (**C**-OH), 168.3 (**C**═O); MS 305, 307 $[M + H]^+$. Anal. calcd. for $C_9H_9BrN_2O_3S$: C, 35.43; H, 2.97; N, 9.18. Found: C, 35.48; H, 2.98; N, 9.19.

4-Hydroxy-3-iodo-1-methyl-1*H*-thieno[2,3-*c*]-pyrazole-5-carboxylic Acid Ethyl Ester (**14**)

Thieno[2,3-*c*]pyrazole **14** was obtained from **12** using the same procedure as in the case of compound **13**. Yield: 92%; Mp: 140°C; IR (KBr): 1651 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (t, 3H, $J = 7.5$ Hz, C**H**$_3$-CH$_2$-O), 3.90 (s, 3H, N-C**H**$_3$), 4.28 (q, 2H, $J = 7.5$ Hz, C**H**$_2$-O), 10.45 (s, 1H, O-**H**); ^{13}C NMR (DMSO-d_6): δ 15.1 (**C**H$_3$CH$_2$-O), 38.7 (N-**C**H$_3$), 61.5 (O-**C**H$_2$), 87.9 (**Cq**), 101.9 (**Cq**), 145.0 (**Cq**), 153.2 (**Cq**), 165.2 (**C**═O); MS 353 $[M + H]^+$. Anal. calcd. for $C_{11}H_{15}IN_2O_4S$: C, 30.70; H, 2.58; N, 7.95. Found: C, 30.76; H, 2.60; N, 7.89.

Imine of the 3-Amino-4-hydroxy-1-methyl-1*H*-thieno[2,3-*c*]-pyrazole-5-carboxylic Acid Ethyl Ester (**15**)

Compound **15** was obtained from aminopyrazole **11** using the same procedure as in the case of compound **13**. Yield: 90%; mp: 205°C; IR (KBr): 1698 cm^{-1}, 1732 cm^{-1}, 1741 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25 (t, 3H, $J = 6.9$ Hz, C**H**$_3$-CH$_2$-O), 1.26 (t, 3H, $J = 6.9$ Hz, C**H**$_3$-CH$_2$-O), 3.66 (s, 3H, N-C**H**$_3$), 3.80 (s, 3H, N-C**H**$_3$), 3.86 (s, 2H, N-**H** + O-**H**), 4.18 (q, 2H, $J = 6.9$ Hz, C**H**$_2$-O), 4.20 (q, 2H, $J = 6.9$ Hz, C**H**$_2$-O), 5.50 (s, 2H, N**H**$_2$). ^{13}C NMR (DMSO-d_6): δ 12.9 (**C**H$_3$-CH$_2$-O), 13.2 (**C**H$_3$-CH$_2$-O), 35.1 (N-**C**H$_3$), 36.1 (N-**C**H$_3$), 58.2 (O-**C**H$_2$), 58.7 (O-**C**H$_2$), 98.6 (**Cq**), 109.5 (**Cq**), 124.2 (**Cq**), 135.0 (**Cq**), 142.9 (**Cq**), 149.2 (**Cq**), 155.5 (**Cq**), 161.1 (**C**═O), 161.9 (**C**═O), 167.0 (**C**═N); MS 465 $[M + H]^+$. Anal. calcd. for $C_{18}H_{20}N_6O_5S_2$: C, 46.54; H, 4.34; N, 18.09. Found: C, 46.62; H, 4.38; N, 17.98.

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