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1-Bis(methoxy)-4-bis(methylthio)-3-buten-2-one: useful three carbon synthon for synthesis of five and six membered heterocycles with masked (or unmasked) aldehyde functionality

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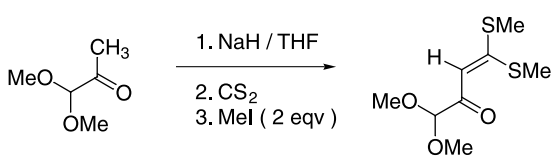
Abstract—1-Bis(methoxy)-4-bis(methylthio)-3-buten-2-one has been shown to be a useful three carbon synthon for efficient regiospecific synthesis of a variety of five (pyrazole and isoxazole) and six membered (pyrimidines, pyridone and pyridines) heterocycles with masked (or unmasked) aldehyde functionality by cyclocondensation with bifunctional heteronucleophiles such as hydrazine, hydroxylamine, guanidine, thiourea, cyanoacetamide and substituted β-lithioaminoacrylonitriles. Reaction of 1-bis(methoxy)-4-bis(methylthio)-3-buten-2-one with methylene iodide and Zn–Cu couple under Simmons–Smith reaction conditions afforded 2-(methylthio)thiophene-4-aldehyde in good yield, whereas cycloaromatization with thiophene-2- and 3-acetonitriles gave the corresponding substituted benzothiophene-4- and 7-aldehydes in good yields.

1. Introduction

The regiospecific introduction of a formyl group in five and six membered heterocycles is a useful synthetic operation since the formyl group is a versatile functionality for further elaboration of these heterocyclic compounds through C–C and C–heteroatom bond formation.[1] The usual methods for the synthesis of various heterocyclic aldehydes involve electrophilic substitution (Vilsmeier–Haack reaction),[2] formylation of metallated heterocycles,[1a,b,3] oxidation of methyl or hydroxymethyl groups[4] and reduction methods.[5] However, all these methods require preconstructed heterocyclic precursors and suffer from some limitations such as formation of inseparable regioisomeric mixtures of aldehydes, poor yields and drastic reaction conditions. On the other hand, there are only a few examples in the literature for the synthesis of heterocyclic aldehydes from acyclic two or three carbon synthons with masked aldehyde functionality (principal synthesis).[6] During the course of our continued interest in the development of new general synthetic methods for regiospecifically substituted and fused heterocycles based on α-oxoketene dithioacetals,[7] we now report the synthesis and heterocyclization of 1-bis(methoxy)-4-bis(methylthio)-3-buten-2-one (**2**) as a versatile multifunctional 1,3-bielectrophilic synthon for a variety of five and six membered heterocycles with masked (or unmasked) aldehyde functionality.

2. Results and discussion

The α-oxoketene dithioacetal **2** was obtained in 85% yield by treatment of pyruvaldehyde dimethylacetal **1** with sodium hydride and carbon disulfide in THF followed by alkylation with 2 equiv. of methyl iodide (Scheme 1). When **2** was reacted with hydrazine hydrate in refluxing ethanol, the corresponding 3(5)-[bis(methoxy)methyl]-5(3)-(methylthio)pyrazole **3** was obtained in 80% yield.[8] Hydrolysis of the dimethylacetal moiety of **3** with aqueous acetic acid (50%) yielded the corresponding pyrazole-3(5)-aldehyde **4** in 95% yield (Scheme 2). Similarly, treatment of **2** with hydroxylamine hydrochloride in ethanolic KOH under neutral conditions afforded 3-[bis(methoxy)methyl]-5-(methylthio)isoxazole **5** in 75% yield.[9] The corresponding 5(3)-cycloaminopyrazole derivatives **6** and **7** were also synthesized in a one pot sequence by prior displacement of one of the methylthio groups of **2** by the respective amines



1 **2** (85%)

Scheme 1.

Keywords: α-oxoketene dithioacetals; pyruvaldehye dimethylacetal; heterocyclization; heterocyclic aldehydes.

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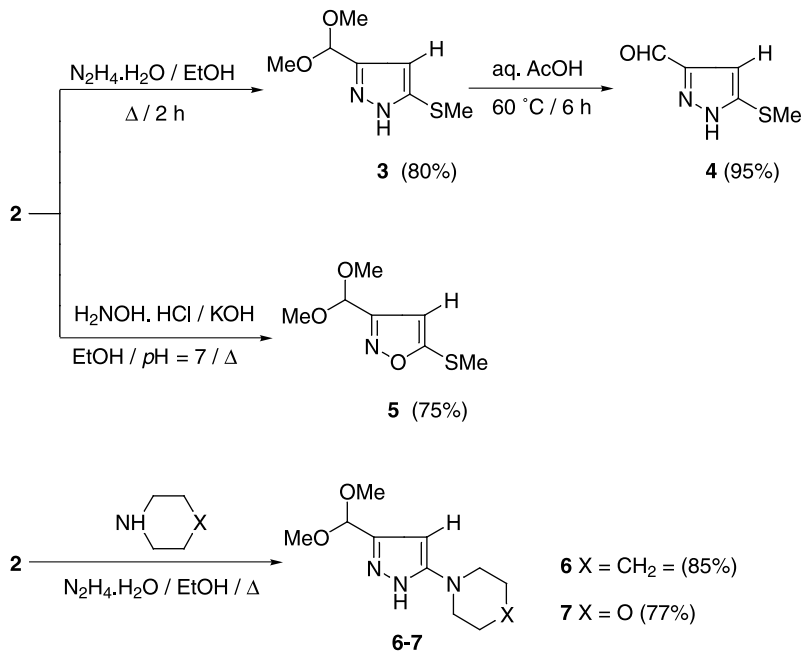
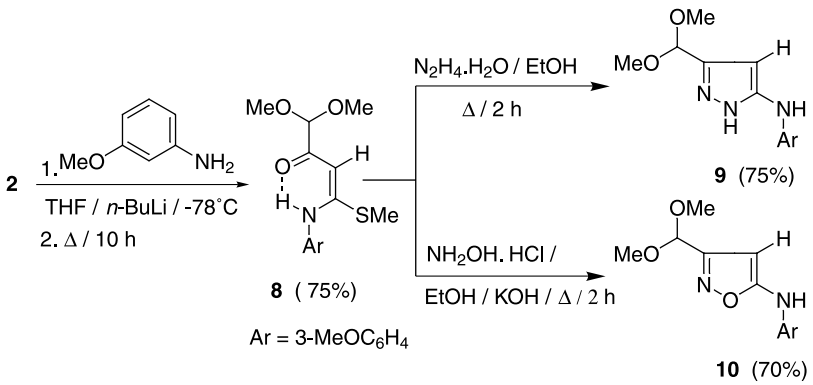


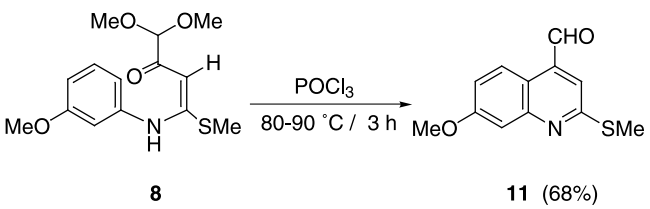
Scheme 2.



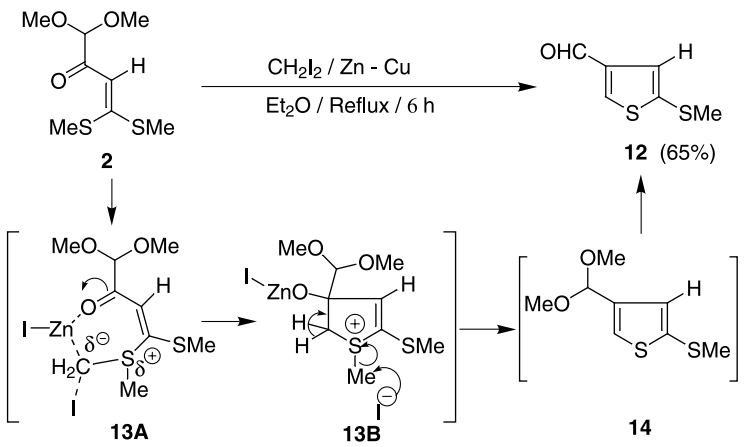
Scheme 3.

(i.e. piperidine and morpholine) in refluxing ethanol followed by in situ cyclization of the resulting *N*,*S*-acetals with hydrazine hydrate under similar reaction conditions (Scheme 2). The ketene dithioacetal **2** was also converted into the corresponding *N*,*S*-acetal **8** by treatment with *m*-methoxyaniline in the presence of *n*-BuLi.[10] Subsequent cyclization of **8** with either hydrazine hydrate or hydroxylamine hydrochloride afforded the corresponding 5(3)-(*m*-methoxyanilino)-pyrazole **9** and the corresponding isoxazole derivative **10** respectively in good yields (Scheme 3). The *N*,*S*-acetal **8** was also subjected to intramolecular cyclocondensation in the presence of $POCl_3$ to afford the corresponding 2-methylthio-7-methoxyquinoline-4-aldehyde **11** via Combes type synthesis (Scheme 4).[11]

The ketene dithioacetal **2** was next subjected to treatment with methylene iodide and Zn–Cu couple with a view to prepare the corresponding 2-methylthio-4-[bis(methoxy)-methyl]thiophene (**14**) in line with our earlier observations on Simmons–Smith reaction on α-oxoketene dithioacetals.[12] However the product isolated (65%) was characterized as 2-(methylthio)thiophene-4-aldehyde (**12**) which is apparently derived from the initially formed thiophene **14** through deacetylation under experimental conditions. The probable mechanism for the formation of **14** from **2** appears to be similar as suggested earlier[12] involving carbenoid methylene addition to one of the methylthio groups of **2** to give ylide **13A**, which on intramolecular aldol type condensation assisted by coordination of zinc with carbonyl oxygen lone pair followed by demethylation of *S*-methylthiophenium salt **13B** affords the thiophene **14** (Scheme 5). The reaction provides a facile entry to not



Scheme 4.

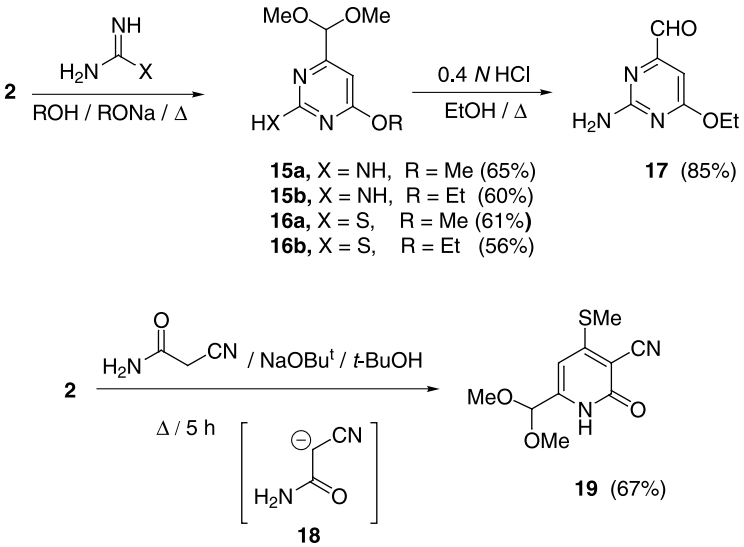


Scheme 5.

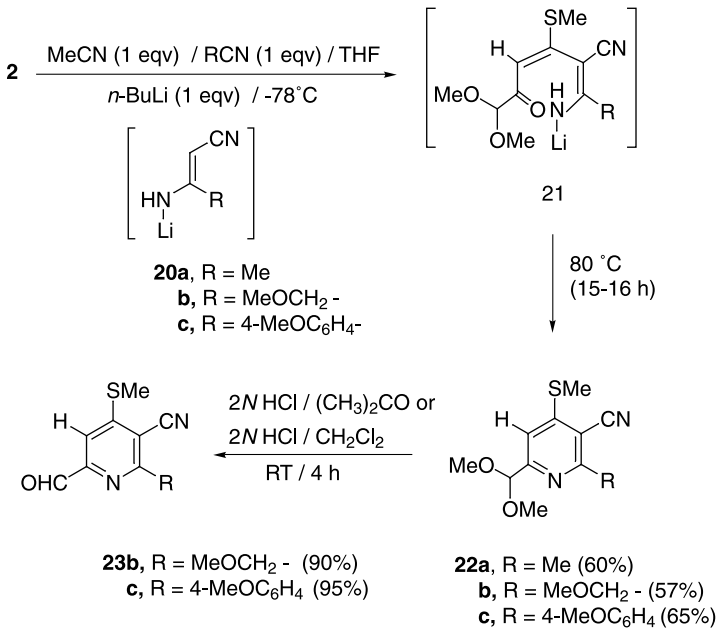
easily accessible thiophene-3-(or 4-) aldehyde since direct Vilsmeier formylation of thiophene affords only 2- (or 5-) formyl derivatives.[13]

Cyclocondensation of **2** with 1,3-heterobinucleophiles was next examined with a view to synthesize six membered heterocycles with a masked aldehyde group. Thus, cyclization of **2** with guanidine nitrate in the presence of the appropriate sodium alkoxides (NaOMe or NaOEt) in refluxing alkanols (methanol or ethanol) afforded the corresponding 2-amino-4-[bis(methoxy)methyl]-6-methoxy or ethoxypyrimidines **15a** and **15b** in 65 and 60% yields, respectively, in accordance with our earlier reported alkoxypyrimidine synthesis (Scheme 6).[14] Similarly, treatment of **2** with thiourea in the presence of either sodium methoxide or ethoxide under refluxing conditions furnished the respective 6-alkoxy-4-[bis(methoxy)methyl]-2-mercaptopyrimidines **16a**,**b** in good yields.[14] One of the alkoxypyrimidines **15b** was hydrolyzed with dilute HCl in ethanol to afford the corresponding 2-amino-6-ethoxypyrimidine-4-aldehyde **17** in 85% yield. (Scheme 6).[6c] Reaction of **2** with cyanoacetamide in the presence of sodium *t*-butoxide in *t*-butanol yielded the highly functionalized 6-[bis(methoxy)methyl]-3-cyano-4-(methylthio)-2(1*H*)-pyridone **19** in 67% yield (Scheme 6).[15]

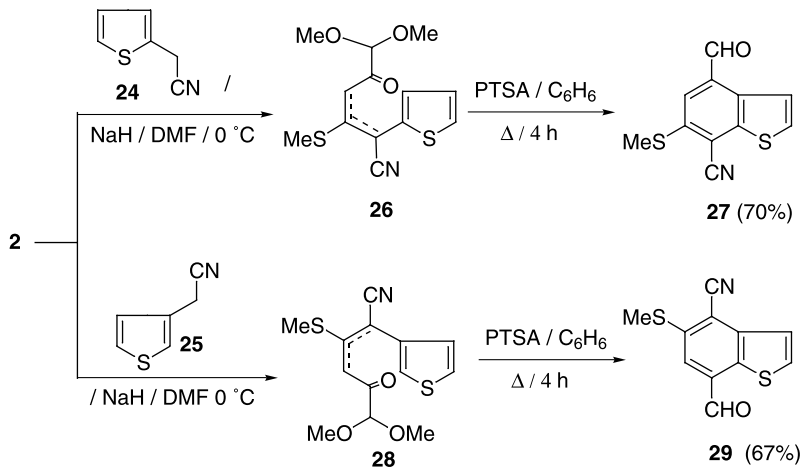
The oxoketene dithioacetal **2** was next subjected to cyclocondensation with β-lithioaminocrotononitrile **20a** and other β-substituted β-lithioaminoacrylonitriles **20b**,**c** according to our earlier reported method[7c,16] to afford the respective 6-[bis(methoxy)methyl]-2-substituted-4-(methylthio)nicotinonitriles **22a**–**c** with a masked 6-formyl group in 57–65% overall yields (Scheme 7). The nicotinonitriles **22b**,**c** were deprotected in the presence of dilute hydrochloric acid to give the corresponding 6-formyl derivatives **23b**,**c** in 90 and 95% yield, respectively. It should be noted that substituted pyridine-2-carbaldehydes are usually synthesized by long and circuitous routes, most commonly by oxidation of activated methyl group of the picolines[17] or their *N*-oxides[18] or by oxidative cleavage of 2-vinylpyridine derivatives.[19] Only recently, a short versatile route to 2-formyl nicotinates has been reported by cyclocondensation of methyl 3-amino-4-bis(methoxy)-but-2-enoate (bearing masked aldehyde group) with a variety of Mannich base hydrochlorides or β-aminovinyl ketones.[5b,20]



Scheme 6.



Scheme 7.



Scheme 8.

Finally, the versatility of **2** for regiospecific introduction of aldehyde functionality was demonstrated by its two step cycloaromatization with isomeric 2- and 3-thiophene acetonitriles **24** and **25** (Scheme 8).[7d] Thus compound **24** underwent base induced conjugate addition elimination with **2** to afford the conjugate adduct **26** in 78% yield. Acid induced intramolecular cyclocondensation of **26** in refluxing benzene directly afforded the multifunctional deprotected 7-cyano-6-(methylthio)benzothiophene-4-aldehyde **27** in 70% yield. The corresponding regioisomeric 4-cyano-5-(methylthio)benzothiophene-7-aldehyde **29** was similarly obtained in good yields by cyclocondensation of **2** with 3-cyanomethylthiophene **25** under identical conditions (Scheme 8).

In summary, cyclocondensation of readily accessible 1-bis(methoxy)-4-bis(methylthio)-3-buten-2-one (**2**) with various 1,2- and 1,3-binucleophiles provides efficient regiospecific routes to a variety of five and six membered heterocycles with masked aldehyde functionality which can be deprotected and utilized for further elaboration.

3. Experimental

3.1. General

^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6 and TMS was used as internal reference. Melting points are uncorrected. Chromatographic purification was done by column chromatography using 60–120 mesh silica gel obtained from Acme Synthetic Chemicals. All reactions were monitored by TLC on glass plate coated with silica gel (Acme) containing 13% calcium sulfate as binder and visualization was effected with short wavelength UV light (254 nm) or acidic $KMnO_4$ solution. All reagents were used directly as obtained commercially unless otherwise noted.

DMF was distilled over CaH_2 and stored over molecular sieves. THF was distilled over sodium benzophenone ketyl prior to use. *n*-BuLi (1.5 M) was purchased from Aldrich Chemical Co.

Pyruvaldehyde dimethylacetal (**1**), methoxyacetonitrile, thiophene-2- (**24**) and 3-acetonitriles (**25**) were purchased from Aldrich Chemical Co.

3.1.1. 1-Bis(methoxy)-4-bis(methylthio)-3-buten-2-one (2). To a suspension of NaH (0.96 g, 20 mmol, 50%) in THF (25 mL) under N_2 atmosphere at 0°C carbon disulfide (0.62 mL, 10 mmol) in THF (25 mL) was added followed by stirring for 20–30 min. A solution of pyruvaldehyde dimethylacetal (1.2 mL, 10 mmol) in THF (25 mL) was added over a period of 30 min at 0°C followed by stirring at room temperature for 7 h. The reaction mixture was then cooled at 0°C and a solution of methyl iodide (1.6 mL, 25 mmol) in THF (25 mL) was added and the reaction mixture was further stirred for 6 h. It was then poured into saturated ammonium chloride solution (50 mL), extracted with chloroform (3×50 mL), washed with water (3×50 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give the crude product which was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluent, to give the title compound **2** as dark red viscous liquid; R_f 0.40 (8.5:1.5 hexane–EtOAc). Yield 1.88 g, 85%; IR (CCl_4): 1642, 1102, 1069, 1013 cm^{-1}; δ_H (300 MHz, CCl_4) 6.29 (1H, s, =C*H*), 4.43 [1H, s, C*H*$(OMe)_2$], 3.38 (6H, s, OCH_3), 2.50 (3H, s, SCH_3), 2.47 (3H, s, SCH_3); δ_C (75 MHz, CCl_4) 187.5, 107.8, 104.0, 96.0, 53.9, 16.9, 14.5; MS: *m*/*z* (%): 222 (M^+, 14), 148 (100). Anal. calcd for $C_8H_{14}O_3S_2$ (222.32): C, 43.22; H, 6.35%. Found: C, 43.33; H, 6.25%.

3.1.2. 3(5)-[Bis(methoxy)methyl]-5(3)-(methylthio)pyrazole (3). To a solution of **2** (1.1 g, 5 mmol) in ethanol (50 mL), hydrazine hydrate (0.36 mL, 7.5 mmol) was added and the reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in chloroform (100 mL), washed with water (3×100 mL), dried (Na_2SO_4) and concentrated to give crude product which was purified by column chromatography over silica gel using hexane–EtOAc (6:1) as eluent, to give the title compound **3** as light brown crystals ($CHCl_3$–hexane); R_f 0.35 (1:1 hexane–EtOAc); mp 135–136°C. Yield 0.75 g, 80%; IR (KBr): 3240, 1437, 1365, 1120, 1091 cm^{-1}; δ_H (300 MHz, CCl_4) 6.25 (1H, s, =C*H*), 5.54 [1H, s, C*H*$(OMe)_2$], 3.34 (6H, s, OCH_3), 2.49 (3H, s, SCH_3); δ_C (75 MHz, CCl_4) 144.3, 104.5, 97.3, 95.9, 51.8, 16.4; MS: *m*/*z* (%): 188 (M^+, 43), 157 (100). Anal. calcd for $C_7H_{12}N_2O_2S$ (188.25): C, 46.66; H, 6.42; N, 14.88%. Found: C, 46.51; H, 6.54; N, 14.90%.

3.1.3. 3(5)-(Methylthio)pyrazole-5(3)-aldehyde (4). The pyrazole (0.94 g, 5 mmol) was added at a time to 20 mL of ice cooled AcOH (50%) with stirring and the reaction mixture was heated at 60°C with continuous stirring for 4 h (monitored by TLC). It was then cooled, poured over ice-cooled saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3×50 mL). The combined extract was washed with water (1×50 mL), dried (Na_2SO_4) and evaporated to give crude aldehyde which was purified by column chromatography using hexane–EtOAc (5:1) as eluent, to give the title compound **4** as colorless crystals ($CHCl_3$–hexane); R_f 0.6 (8:2 hexane–EtOAc); mp 156–157°C. Yield 0.67 g, 95%; IR (KBr): 3154, 1696, 1535, 1468 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.80 (1H, s, C*H*O), 6.81 (1H, s, C*H*=), 2.49 (3H, s, SCH_3); δ_C (100 MHz, DMSO-d_6) 184.2, 138.8, 106.2, 103.8, 16.7; MS: *m*/*z* (%): 142 (M^+, 100). Anal. calcd for $C_5H_6N_2OS$ (142.18): C, 42.23; H, 4.25; N, 19.70%. Found: C, 42.35; H, 4.23; N, 9.51%.

3.1.4. 3-[Bis(methoxy)methyl]-5-(methylthio)isoxazole (5). A suspension of **2** (1.1 g, 5 mmol), hydroxylamine hydrochloride (0.52 g, 7.5 mmol) and potassium hydroxide (0.42 g, 7.5 mmol) were refluxed in ethanol (25 mL) for 3 h (monitored by TLC). The solvent was then removed under reduced pressure and the residue was diluted with water, extracted with chloroform. The combined extract was washed with water (2×50 mL), dried (Na_2SO_4) and evaporated to give the crude residue which was purified by column chromatography over silica gel using hexane–EtOAc as eluent, to give the title compound **5** as light brown crystals ($CHCl_3$–hexane); R_f 0.35 (1:1 hexane–EtOAc); mp 75–76°C. Yield 0.71 g, 75%; IR (KBr): 2994, 2934, 1544, 1194, 1115 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.07 (1H, s, C*H*=), 5.30 [1H, s, C*H*$(OMe)_2$], 3.35 (6H, s, OCH_3), 2.58 (3H, s, SCH_3); δ_C (75 MHz, CCl_4) 161.9, 99.8, 97.8, 96.2, 53.2, 15.1; MS: *m*/*z* (%): 187 (M−2, 43.3), 156 (62.5%). Anal. calcd for $C_7H_{11}NO_3S$ (189): C, 44.44; H, 5.82; N, 7.40%. Found: C, 44.56; H, 5.92; N, 7.51%.

3.2. 3(5)-[Bis(methoxy)methyl]-5(3)-aminopyrazoles 6 and 7: general procedure

To a solution of **2** (1.1 g, 5 mmol) in ethanol (25 mL), the respective amine (5.1 mmol) was added at a time and the reaction mixture was refluxed for 2 h. It was then brought to room temperature and hydrazine hydrate (0.36 mL, 7.5 mmol) in ethanol (10 mL) was added dropwise over a period of 10 min. Then the reaction mixture was refluxed for another 3–4 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was dissolved in chloroform (50 mL), washed with water (3×50 mL), dried (Na_2SO_4) and concentrated to give crude solid which on recrystallization from $CHCl_3$–hexane (1:3) yielded analytically pure compounds.

3.2.1. 3(5)-[Bis(methoxy)methyl]-5(3)-(1-*N*-piperidino)-pyrazole (6). Light brown crystals ($CHCl_3$–hexane); R_f 0.2 (7:3 hexane–EtOAc); mp 84–85°C. Yield 0.95 g, 85%; IR (KBr): 3191, 2928, 1568, 1362, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, brs, N*H*), 5.69 (1H, s, C*H*=), 5.45 [1H, s, C*H*$(OMe)_2$], 3.30 (6H, s, OCH_3), 3.13 [4H, t, J=5.4 Hz, N(CH_2)$_2$-], 1.61–1.67 (4H, m, CH_2), 1.50–1.55 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 159.7, 142.2, 97.5, 89.9, 52.4, 49.3, 25.3, 24.2; MS: *m*/*z* (%): 225 (M^+, 20). Anal. calcd for $C_{11}H_{19}N_3O_2$ (225.29): C, 58.64; H, 8.50; N, 18.65%. Found: C, 58.50; H, 8.56; N, 18.69%.

3.2.2. 3(5)-[Bis(methoxy)methyl]-5(3)-(1-*N*-morpholino)-pyrazole (7). Colorless crystals ($CHCl_3$–hexane); R_f 0.15 (6.5:3.5 hexane–EtOAc); mp 98–99°C. Yield 0.87 g, 77%; IR (KBr): 3290, 2827, 1560, 1490, 1121 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, brs, N*H*), 5.73 (1H, s,

C*H*═), 5.52 [1H, s, C*H*(OMe)$_2$], 3.83 [4H, t, *J*=4.8 Hz, O(C*H*$_2$)$_2$–], 3.34 (6H, s, OC*H*$_3$), 3.20 [4H, t, *J*=4.8 Hz, N(C*H*$_2$)$_2$–]; δ_C (100 MHz, $CDCl_3$) 157.3, 143.7, 96.9, 89.4, 66.3, 52.6, 48.3; MS: *m*/*z* (%): 227 (M^+, 76), 196 (100). Anal. calcd for $C_{10}H_{17}N_3O_3$ (227.26): C, 52.85; H, 7.54; N, 18.45%. Found: C, 52.69; H, 7.42; N, 18.90%.

3.2.3. 1-Bis(methoxy)-4-(3-methoxyanilino)-4-(methylthio)-3-buten-2-one (8). To a solution of *m*-anisidine (1.23 g, 10 mmol) in dry THF (50 mL), *n*-BuLi (7.8 mL, 15 mmol) was added at −78°C under nitrogen atmosphere and stirred at the same temperature for 30 min. A solution of **2** (2.23 g, 10 mmol) in 25 mL dry THF was added over a period of 20 min at −78°C and the resulting suspension was allowed to warm to room temperature followed by refluxing for 10 h. It was then brought to room temperature, poured into ice cold saturated NH_4Cl solution (50 mL), extracted with $CHCl_3$ (3×50 mL), washed with water (3×50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude product which was further purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluent, to give the title compound **8** as deep red viscous liquid; R_f 0.45 (8.5:1.5 hexane–EtOAc). Yield 2.23 g, 75%; IR (DCM): 2952, 2839, 1554, 1477 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 13.04 (1H, brs, N*H*), 7.17 (1H, t, *J*=8.4 Hz, Ar*H*), 6.79 (1H, d, *J*=8.0 Hz, Ar*H*), 6.74 (1H, s, Ar*H*), 6.70 (1H, d, *J*=8.0 Hz, Ar*H*), 5.52 (1H, s, C*H*═), 4.57 [1H, s, C*H*(OMe)$_2$], 3.70 (3H, s, OC*H*$_3$), 3.36 (6H, s, OC*H*$_3$), 2.29 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 187.7, 168.9, 159.8, 138.6, 129.5, 117.0, 112.1, 110.3, 103.5, 87.4, 55.0, 53.8, 14.4. Anal. calcd for $C_{14}H_{19}N_2O_4S$ (297.38): C, 56.54; H, 6.43; N, 4.71%. Found: C, 56.49; H, 6.48; N, 4.76%.

3.2.4. 3(5)-[Bis(methoxy)methyl]-5(3)-(3-methoxy)anilinopyrazole (9). The pyrazole **9** was prepared following the earlier procedure for **3**, by refluxing a solution of **12** (1.45 g, 5 mmol) and hydrazine hydrate (0.36 g, 5 mmol) in 40 mL of ethanol. Workup and column chromatography of the reaction mixture using hexane–EtOAc (1:1) afforded the title compound **9** as red viscous liquid; R_f 0.2 (7:3 hexane–EtOAc). Yield 0.98 g, 75%; IR (DCM): 2943, 1603, 1491, 1341 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.62 (1H, brs, N*H*), 7.24 (1H, t, *J*=8.4 Hz, Ar*H*), 6.77–6.87 (2H, m, Ar*H*), 6.50 (1H, dd, *J*=8.4, 2.0 Hz, Ar*H*), 6.31 (1H, s, C*H*═), 5.74 [1H, s, C*H*(OMe)$_2$], 3.86 (3H, s, OC*H*$_3$), 3.49 (6H, s, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 160.6, 149.6, 144.6, 142.6, 130.0, 108.1, 104.6, 101.4, 97.6, 92.9, 55.1, 52.5; MS: *m*/*z* (%): 263 (M^+, 60), 188 (100). Anal. calcd for $C_{13}H_{17}N_3O_3$ (263.29): C, 59.30; H, 6.50; N, 15.96%. Found: C, 59.23; H, 6.66; N, 15.78%.

3.2.5. 3-[Bis(methoxy)methyl]-5-(3-methoxyanilino)-isoxazole (10). The isoxazole **10** was prepared following the similar procedure as for **5** by refluxing a suspension of **8** (1.45 g, 5 mmol), hydroxylamine hydrochloride (0.52 g, 7.5 mmol) and KOH (0.42 g, 7.5 mmol) in 25 mL of ethanol for 3 h. Workup and chromatography (hexane–EtOAc, 9:1) of the reaction mixture yielded the title compound **10** as red viscous liquid; R_f 0.48 (8.5:1.5 hexane–EtOAc). Yield 0.92 g, 70%; IR (DCM): 2926, 1600, 1493 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.21 (1H, t, *J*=7.8 Hz, Ar*H*), 6.77 (1H, brs, N*H*), 6.69 (1H, d, *J*=1.2 Hz, Ar*H*), 6.67 (1H, m, Ar*H*), 6.58 (1H, dd, *J*=8.2, 2.4 Hz, Ar*H*), 5.62 (1H, s, C*H*═), 5.35 [1H, s, C*H*(OMe)$_2$], 3.79 (3H, s, OC*H*$_3$), 3.41 (6H, s, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.4, 163.2, 160.7, 140.1, 130.4, 110.0, 108.0, 103.8, 98.3, 79.6, 55.3, 53.7; MS: *m*/*z* (%): 264 (M^+, 13). Anal. calcd for $C_{13}H_{16}N_2O_4$ (264.28): C, 59.08; H, 6.10; N, 10.60%. Found: C, 59.21; H, 6.05; N, 10.51%.

3.2.6. 7-Methoxy-2-(methylthio)quinoline-4-carbaldehyde (11). The *N*,*S*-acetal **8** (1.49 g, 5 mmol) was dissolved in $POCl_3$ (20 mL) at 0°C and was heated to 80–90°C with stirring for 3–4 h (monitored by TLC).The reaction mixture was cooled and poured into ice cold saturated $NaHCO_3$ solution. It was then extracted with chloroform, washed with water and dried over Na_2SO_4 to give the crude product which was further purified by column chromatography over silica gel using hexane–EtOAc as the eluent, to give the title compound **11** as yellow crystals ($CHCl_3$–hexane); R_f 0.70 (9:1 hexane–EtOAc); mp 93–94°C. Yield 0.79 g, 68%; IR (KBr): 2925, 1708, 1611, 1509 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.28 (1H, s, C*H*O), 8.75 (1H, d, *J*=9.1 Hz, ArH), 7.44 (1H, s, C*H*═), 7.37 (1H, d, *J*=2.4 Hz, ArH), 7.19 (1H, dd, *J*=9.1, 2.4 Hz, ArH), 3.95 (3H, s, OC*H*$_3$), 2.71 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 192.8, 161.2, 160.6, 151.3, 136.4, 125.7, 124.2, 119. 8, 116.2, 107.1, 55.5, 13.1; MS: *m*/*z* (%): 234 (M+1, 100). Anal. calcd for $C_{12}H_{11}NO_2S$ (233.30): C, 61.78; H, 4.75; N, 6.00%. Found: C, 61.62; H, 4.85; N, 6.18%.

3.2.7. 2-(Methylthio)thiophene-4-carbaldehyde (12). To a well stirred suspension of Zn–Cu couple (3.0 g, 30 mmol) in dry Et_2O (25 mL), under nitrogen atmosphere, a small crystal of iodine and CH_2I_2 (1.34 g, 6.7 mmol) was added and the reaction mixture was refluxed for 45 min. A solution of **2** (1.5 g, 6.7 mmol) in dry THF (25 mL) was added to the reaction mixture followed by further refluxing for 6 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with $CHCl_3$ (150 mL), washed with water (100 mL) and the organic extract was filtered through sintered funnel to remove metal-based residue. The organic filtrate was washed with saturated NH_4Cl solution (100 mL), water (3×50 mL), dried (Na_2SO_4) and concentrated to give crude product which was purified by column chromatography over silica gel using hexane as eluent, to give the title compound **12** as pale yellow viscous liquid; R_f 0.7 (9.5:0.5 hexane–EtOAc). Yield 0.69 g, 65%; IR (CCl_4): 1682, 1506, 1387 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.74 (1H, s, C*H*O), 7.95 (1H, s, C*H*═), 7.38 (1H, s, C*H*═), 2.52 (3H, s, SC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 182.0, 143.2, 140.3, 136.6, 127.4, 20.9; MS: *m*/*z* (%): 158 (M^+, 48), 83 (100). Anal. calcd for $C_6H_6OS_2$ (158.25): C, 45.54; H, 3.82%. Found: C, 45.60; H, 3.78%.

3.3. 2-Amino-4-[bis(methoxy)methyl]-6-alkoxypyrimidines 15a,b: general procedure

Guanidine nitrate (0.61 g, 5 mmol) was added to a solution of sodium alkoxide (10 mmol, prepared in situ from 0.23 g of sodium metal and 5 mL of the corresponding alkanol) in alkanol (30 mL) and after 5 min of stirring at room temperature, a solution of **2** (1.1 g, 5 mmol) in corresponding alkanol (5 mL) was added. The reaction mixture was refluxed for 10–14 h with stirring (monitored by TLC). The solvent was removed under reduced pressure and the residue

was diluted with ice-cold water (50 mL). It was then extracted with $CHCl_3$ (3×50 mL), washed with water (3×50 mL), dried (Na_2SO_4) and evaporated to give crude product which was purified by column chromatography over silica gel using hexane–EtOAc (1:1) as eluent.

3.3.1. 2-Amino-4-[bis(methoxy)methyl]-6-methoxypyrimidine (15a). Colorless crystals ($CHCl_3$–hexane); R_f 0.15 (1:1 hexane–EtOAc); mp 105–106°C. Yield 0.65 g, 65%; IR (KBr): 3438, 3267, 1624, 1581, 1105, 1061 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.29 (1H, s, C*H*═), 5.51 (2H, brs, N*H*$_2$), 5.10 [1H, s, C*H*(OMe)$_2$], 3.88 (3H, s, OC*H*$_3$), 3.36 (6H, s, OC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 171.5, 166.2, 163.2, 102.0, 95.5, 53.5, 53.2; MS: *m*/*z* (%): 199 (M^+, 32), 153 (100). Anal. calcd for $C_8H_{13}N_3O_3$ (199.20): C, 48.24; H, 6.53; N, 21.10%. Found: C, 48.35; H, 6.69; N, 21.20%.

3.3.2. 2-Amino-4-[bis(methoxy)methyl]-6-ethoxypyrimidine (15b). Colorless crystals ($CHCl_3$–hexane); R_f 0.20 (1:1 hexane–EtOAc); mp 120–122°C. Yield 0.64 g, 60%; IR (KBr): 3301, 1632, 1575, 1169, 1057 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.27 (1H, s, C*H*═), 5.35 (2H, brs, N*H*$_2$), 5.08 [1H, s, C*H*(OMe)$_2$], 4.31 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 3.36 (6H, s, OC*H*$_3$), 1.36 (3H, t, *J*=7.0 Hz, C*H*$_3$CH$_2$); δ_C (75 MHz, $CDCl_3$) 171.1, 166.3, 163.1, 102.1, 95.7, 62.1, 53.2, 14.4; MS: *m*/*z* (%): 213 (M^+, 25), 181 (100). Anal. calcd for $C_9H_{15}N_3O_3$ (213.23): C, 50.69; H, 7.09; N, 19.70%. Found: C, 50.55; H, 7.12; N, 19.68%.

3.4. 6-Alkoxy-4-[bis(methoxy)methyl]-2-mercaptopyrimidines 16a,b: general procedure

The 2-mercaptopyrimidines **16a**,**b** were prepared following the similar procedure for 2-aminopyrimidines **15a**,**b** by refluxing a suspension of **2** (1.1 g, 5 mmol), thiourea (0.389 g, 5 mmol) and the corresponding sodium alkoxide (6 mmol) in the appropriate alkanol (60 mL) for 6–7 h. Workup and column chromatography (hexane–EtOAc 1:1) of the reaction mixture afforded the mercaptopyrimidines **16a**,**b**.

3.4.1. 4-[Bis(methoxy)methyl]-6-methoxy-2-mercaptopyrimidine (16a). Colorless crystals ($CHCl_3$–hexane); R_f 0.30 (6:4 hexane–EtOAc); mp 107–108°C. Yield 0.59 g, 55%; IR (KBr): 3143, 1631, 1567, 1186, 1049 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.26 (1H, s, C*H*═), 5.30 [1H, s, C*H*(OMe)$_2$], 3.40 (6H, s, OC*H*$_3$), 3.10 (3H, s, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 182.7, 168.9, 154.6, 97.9, 97.3, 55.6, 55.3; MS: *m*/*z* (%): 216 (M^+, 8). Anal. calcd for $C_8H_{12}N_2O_3S$ (216.35): C, 44.44; H, 5.55; N, 12.96%. Found: C, 44.53; H, 5.61; N, 12.72%.

3.4.2. 4-[Bis(methoxy)methyl]-6-ethoxy-2-mercaptopyrimidine (16b). Colorless crystals ($CHCl_3$–hexane); R_f 0.35 (6:4 hexane–EtOAc); mp 88–89°C. Yield 0.61 g, 53%; IR (KBr): 3562, 3113, 1844, 1794 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.22 (1H, s, C*H*═), 5.26 [1H, s, C*H*(OMe)$_2$], 4.54 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 3.39 (6H, s, OC*H*$_3$), 1.38 (3H, t, *J*=7.0 Hz, C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$) 182.7, 168.6, 154.3, 98.1, 97.2, 64.3, 53.4, 14.2; MS: *m*/*z* (%): 230 (M^+, 24). Anal. calcd for $C_9H_{14}N_2O_3S$ (230.29): C, 46.94; H, 6.12; N, 12.20%. Found: C, 47.00; H, 6.20; N, 12.01%.

3.4.3. 2-Amino-6-ethoxypyrimidine-4-carbaldehyde (17). A solution of alkoxypyrimidine dimethylacetal (**15b**) (1.06 g, 5 mmol) in 20 mL of ethanol and 40 mL of 0.4N HCl was refluxed for 1 h. It was then heated with animal charcoal, refluxed and filtered hot on a sintered funnel. The filtrate was adjusted to pH 9–10 with 5% NaOH solution. The resulting precipitate was dried in oven under reduced pressure for 1 h to give the title compound **17** as colorless crystals (ethanol). The aldehyde **17** was insoluble for recording ^1H NMR spectra in $CDCl_3$ or DMSO-d_6. Mp 390°C (decomposed). Yield 0.71 g, 85%; IR (KBr): 3475, 1697, 1456 cm^{-1}, MS: *m*/*z* (%): 167 (M^+, 100). Anal. calcd for $C_7H_9N_3O_2$ (167.16): C, 50.29; H, 5.42; N, 25.13%. Found: C, 50.12; H, 5.58; N, 25.21%.

3.4.4. 3-Cyano-6-[bis(methoxy)methyl]-4-(methylthio)-2(1*H*)-pyridone (19). To a stirring suspension of sodium *t*-butoxide [prepared by reacting molecular sodium (0.12 g, 5 mmol) in *t*-butanol (50 mL)], cyanoacetamide (0.42 g, 5 mmol) was added and the reaction mixture was further stirred for 10 min. A suspension of **2** (1.19 g, 5 mmol) in *t*-BuOH (5 mL) was then added followed by refluxing for 5 h. The solvent was removed under reduced pressure to give orange colored sodium salt of the pyridone **19** which was dissolved in water (30 mL) followed by acidification with dilute HCl (10 mL, 8%) to afford the title compound **19** as yellow crystals ($CHCl_3$); R_f 0.15 (1:1 hexane–EtOAc); mp 149–150°C. Yield 0.80 g, 67%; IR (KBr): 2213, 1656, 1602, 1468, 1353, 1205 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 6.37 (1H, s, C*H*═), 5.22 [1H, s, C*H*(OMe)$_2$], 3.34 (6H, s, OC*H*$_3$), 2.62 (3H, s, SC*H*$_3$); δ_C (75 MHz, DMSO-d_6) 164.2, 159.5, 153.7, 148.2, 114.8, 99.2, 98.8, 53.8, 13.9; MS: *m*/*z* (%): 240 (M^+, 33). Anal. calcd for $C_{10}H_{12}N_2O_3S$ (240.28): C, 49.99; H, 5.03; N, 11.66%. Found: C, 49.89; H, 5.10; N, 11.60%.

3.5. General procedure for synthesis of pyridines 22a–c

A solution of **2** (1.1 g, 5 mmol) in dry THF (25 mL) was added dropwise to a solution of either lithioaminocrotononitrile **20a** [7.5 mmol, generated[16] from acetonitrile (0.8 mL, 15.3 mmol) and *n*-BuLi (5.0 mL, 7.5 mmol)] or 2-substituted-2-lithioaminoacrylonitrile **20b**,**c** [generated[16] from acetonitrile (0.4 mL, 7.5 mmol), alkyl/aryl nitrile (7.5 mmol) and *n*-BuLi (5.0 mL, 7.5 mmol)] in THF (25 mL) at −78°C and the reaction mixture was brought to room temperature and refluxed for 2 days. It was then cooled and poured into saturated NH_4Cl (50 mL) solution, extracted with $CHCl_3$ (2×50 mL) and the combined organic layer was washed with water (2×50 mL), dried (Na_2SO_4) and concentrated to give crude product which was purified by column chromatography over silica gel using hexane–EtOAc (5:1) as eluent.

3.5.1. 3-Cyano-6-[bis(methoxy)methyl]-2-methyl-4-methylthiopyridine (22a). Colorless crystals ($CHCl_3$–hexane); R_f 0.40 (8.5:1.5 hexane–EtOAc); mp 78–79°C. Yield 0.73 g, 62%; IR (KBr): 2923, 2218, 1742, 1541 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27 (1H, s, C*H*═), 5.28 [1H, s, C*H*(OMe)$_2$], 3.42 (6H, s, OC*H*$_3$), 2.74 (3H, s, C*H*$_3$), 2.59 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 161.5, 159.0, 156.6, 115.1, 112.7, 106.1, 103.6, 54.1, 23.7, 14.1; MS: *m*/*z* (%): 236 (M-1, 15). Anal. calcd for $C_{11}H_{13}N_2O_2S$ (237.29): C,

55.44; H, 5.92; N, 11.78%. Found: C, 55.56; H, 5.83; N, 11.75%.

3.5.2. 3-Cyano-6-[bis(methoxy)methyl]-4-(methylthio)-2-(methoxymethyl)pyridine (22b). Colorless crystals ($CHCl_3$–hexane); R_f 0.40 (8:2 hexane–EtOAc); mp 77–79°C. Yield 0.76 g, 57%; IR (KBr): 2935, 2218, 1570, 1445 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 (1H, s, C*H*═), 5.33 [1H, s, C*H*$(OMe)_2$], 4.69 (2H, s, CH_2OCH_3), 3.50 (3H, s, OCH_3), 3.43 (6H, s, OCH_3), 2.60 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 160.1, 159.3, 157.4, 114.5, 114.1, 106.4, 103.8, 74.1, 59.3, 54.3, 14.3; MS: *m/z* (%): 268 (M^+, 10). Anal. calcd for $C_{12}H_{16}N_2O_3S$ (268.33): C, 53.70; H, 6.01; N, 10.44%. Found: C, 53.92; H, 5.81; N, 10.35%.

3.5.3. 3-Cyano-6-[bis(methoxy)methyl]-2-(4-methoxyphenyl)-4-(methylthio)pyridine (22c). Colorless crystals ($CHCl_3$–hexane); R_f 0.30 (9.5:0.5 hexane–EtOAc); mp 107–108°C. Yield 1.07 g, 65%; IR (KBr): 3447, 2926, 2852, 2217, 1607, 1512 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, dd, *J*=9.6, 2.9 Hz, Ar*H*), 7.33 (1H, s, C*H*═), 7.01 (2H, dd, *J*=9.6, 2.9 Hz, Ar*H*), 5.33 [1H, s, C*H*$(OMe)_2$], 3.87 (3H, s, OCH_3), 3.47 (6H, s, OCH_3), 2.62 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 161.2, 160.5, 159.3, 157.9, 130.6, 129.4, 115.9, 113.9, 112.5, 104.3, 103.9, 55.4, 54.5, 14.4; MS: *m/z* (%): 330 (M^+, 10). Anal. calcd for $C_{17}H_{18}N_2O_3S$ (330.39): C, 61.79; H, 5.40; N, 8.48%. Found: C, 61.52; H, 5.62; N, 8.59%.

3.6. Acid induced hydrolysis of 22b,c to 23b,c

To an ice cold solution of dimethylacetal **22b**,**c** (1 mmol) in $(CH_3)_2CO$ (**22b**) or CH_2Cl_2 (**22c**), 5 mL of 2N HCl was added and the reaction mixture was stirred at room temperature for 1 h. It was then neutralized with ice cooled saturated $NaHCO_3$ solution and the precipitated aldehydes were filtered, dried and crystallized from hexane–$CHCl_3$ to give analytically pure products.

3.6.1. 3-Cyano-2-methoxymethyl-4-(methylthio)pyridine-6-carbaldehyde (23b). Orange crystals ($CHCl_3$–hexane); R_f 0.5 (1:1 hexane–EtOAc); mp 114–115°C. Yield 0.21 g, 95%; IR (KBr): 3158, 2274, 1651, 1438 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.08 (1H, s, C*H*O), 8.02 (1H, s, C*H*═), 4.78 (2H, s, CH_2OCH_3), 3.56 (3H, s, OCH_3), 2.66 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 192.3, 161.2, 158.8, 152.0, 114.1, 113.4, 109.5, 73.7, 59.5, 14.3; MS: *m/z* (%): 224 (M+2, 15). Anal. calcd for $C_{10}H_{10}N_2O_2S$ (222.26): C, 54.03; H, 4.50; N, 12.60%. Found: C, 54.20; H, 4.45; N, 12.81%.

3.6.2. 3-Cyano-4-(methylthio)-2-(4-methoxyphenyl)pyridine-6-carbaldehyde (23c). Pale yellow crystals ($CHCl_3$–hexane); R_f 0.65 (8.5:1.5 hexane–EtOAc); mp 203–204°C. Yield 0.27 g, 95%; IR (KBr): 3099, 2360, 2338, 1711 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.10 (1H, s, C*H*O), 7.95 (2H, dd, *J*=6.8, 1.9 Hz, Ar*H*), 7.66 (1H, s, C*H*═), 7.06 (2H, dd, *J*=6.8, 1.9 Hz, Ar*H*), 3.89 (3H, s, OCH_3), 2.68 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 192.7, 161.7, 161.5, 159.4, 152.1, 130.7, 128.6, 115.3, 114.2, 112.2, 107.2, 55.5, 14.5; MS: *m/z* (%): 284 (M^+, 76.6). Anal. calcd for $C_{15}H_{12}N_2O_2S$ (284.33): C, 63.35; H, 4.20; N, 9.85%. Found: C, 63.26; H, 4.35; N, 9.95%.

3.7. 7-Cyano-6-(methylthio)benzothiophene-4-carbaldehyde (27) and 4-cyano-5-(methylthio)-benzothiophene-7-carbaldehyde (28): general procedure

To a stirred suspension of NaH (0.60 g, 40%, 10 mmol) in DMF (10 mL) at 0°C, a solution of 2- or 3-thiopheneacetonitrile (5 mmol) in DMF (5 mL) was added dropwise during 15 min and the reaction mixture was stirred at 0°C for 45 min. A solution of **2** (1.1 g, 5 mmol) in DMF (10 mL) was slowly added and the reaction mixture was allowed to warm to room temperature with stirring during 8–10 h. It was then poured into saturated NH_4Cl solution (200 mL) and extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with water (3×50 mL), dried (Na_2SO_4) and evaporated to give the crude adducts (**26**, **28**) which were used as such for further cyclization. The crude adduct (~5 mmol) dissolved in dry C_6H_6 (20 mL) was refluxed with PTSA (1.9 g, 10 mmol) for 3–4 h (monitored by TLC). It was then cooled, poured into ice-cold water (150 mL), extracted with $CHCl_3$ (3×50 mL), the combined organic layer was washed with water (3×50 mL) and dried over Na_2SO_4. The solvent was distilled under reduced pressure to give crude product, which was purified by column chromatography over silica gel using hexane–EtOAc (97:3) as eluent.

3.7.1. 7-Cyano-6-(methylthio)benzothiophene-4-carbaldehyde (27). Yellow crystals ($CHCl_3$–hexane); R_f 0.75 (9.5:0.5 hexane–EtOAc); mp 197–199°C. Yield 0.82 g, 70%; IR (KBr): 3123, 2919, 2218, 1681 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.32 (1H, s, C*H*O), 8.27 (1H, d, *J*=5.6 Hz, C*H*═), 7.83 (1H, s, ArH), 7.76 (1H, d, *J*=5.6 Hz, C*H*═), 2.73 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 190.1, 143.3, 141.1, 135.0, 134.0, 132.4, 128.4, 121.1, 115.4, 111.0, 17.1; MS: *m/z* (%): 233 (M^+, 100). Anal. calcd for $C_{11}H_7NOS_2$ (233.32): C, 56.63; H, 3.02; N, 6.00%. Found: C, 56.68; H, 3.01; N, 5.90%.

3.7.2. 4-Cyano-5-(methylthio)benzothiophene-7-carbaldehyde (29). Yellow crystals ($CHCl_3$–hexane); R_f 0.75 (9.5:0.5 hexane–EtOAc); mp 199–200°C. Yield 0.78 g, 67%; IR (KBr): 3113, 2208, 1688, 1308 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.28 (1H, s, C*H*O), 7.88 (1H, d, *J*=5.6 Hz, C*H*═), 7.84 (1H, s, ArH), 7.61 (1H, d, *J*=5.6 Hz, C*H*═), 2.73 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 190.1, 143.4, 141.1, 135.0, 134.2, 132.4, 128.5, 121.1, 115.4, 111.0, 17.1; MS: *m/z* (%): 233 (M^+, 100). Anal. calcd for $C_{11}H_7NOS_2$ (233.32): C, 56.63; H, 3.02; N, 6.00%. Found: C, 56.42; H, 3.10; N, 6.24%.

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