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TETRAHEDRON

Preparation of Lithium 5-Lithiomethyl-3-methylpyrazole-1-carboxylate and its Reaction with α-Oxoketene Dithioacetals: A New General Method for Substituted and Annelated Pyrazolo[1,5-*a*]pyridines

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Abstract: 5-Methylpyrazole derivative **1** is metallated at the C-5 methyl carbon atom to form lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate **3** which on reaction with α-oxoketene dithioacetals **4a-d, 12a-c** and **15a-b** yields substituted and annelated pyrazolo[1,5-*a*]pyridines **7a-d, 13a-c** and **16a-b.**

Metallation studies on *N*-methyl or *N*-benzylpyrazoles have revealed that the *N*-alkyl group preferentially undergoes deprotonation to yield kinetically favoured carbanions which, at higher temperatures, exchange protons from the pyrazole ring to give the thermodynamically more stable 5-lithiopyrazole anions in high yields [1,2]. Reactions of these anions with various electrophiles have been examined and their formation is fully established. Also, 1,5-dimethyl- and 1,3,5-trimethyl- pyrazoles have been shown to undergo exclusive *N*-methyl deprotonation in preference to any of the ring methyl protons [1,2,3]. Thus to our knowledge no studies are reported in the literature on deprotonation of pyrazole ring methyl groups through direct metallation. However, Katritzky and Akutagawa [4] have reported that 2-methylindole, when protected as its 1-lithium carboxylate, readily underwent lithiation at the α-methyl carbon to afford the corresponding lithium 2-lithiomethylindole-1-carboxylate in excellent yield. The anion reacted with various electrophiles to yield the corresponding 2-substituted methylindoles in high yields. This was the first example of the use of carbon dioxide for protection, activation and deprotonation sequence in a one-pot reaction. We have successfully reacted the same anion with various α-oxoketene dithioacetals to yield the corresponding carbinol thioacetals which were cyclized in the presence of H_3PO_4 to afford the corresponding carbazoles in excellent yields [5]. We therefore decided to attempt the deprotonation of less activated ring methyl protons situated adjacent to the NH group of heterocycles. For example, we have selected 3,5-dimethylpyrazole as a typical example to generate its lithium 5-lithiomethyl-3-methypyrazole-1-carboxylate **3** and study its reaction with various α-oxoketene dithioacetals [6] to afford the corresponding heteroaromatic products in accordance with our heteroaromatic annelation protocol [7]. We have indeed generated the anion **3** in high yield and reacted with α-oxoketene dithioacetals to afford pyrazolo[1,5-*a*]pyridines involving cyclization through ring nitrogen rather than ring carbon. We report these results in this paper.

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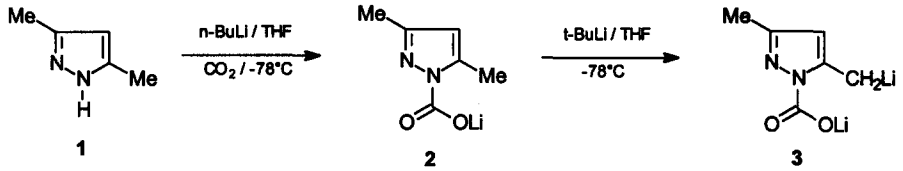
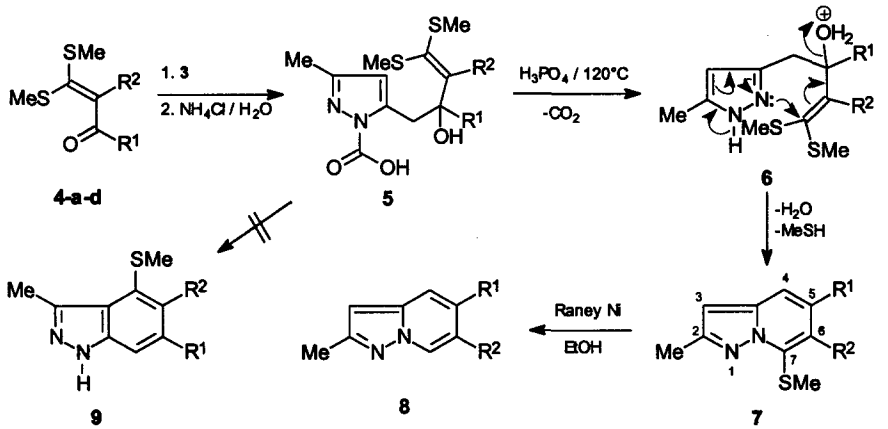
Results and Discussion

In a typical experiment, pyrazole **1** reacted with *n*-BuLi in THF to afford the corresponding light yellow colored *N*-lithio-3,5-dimethylpyrazole to which carbon dioxide was bubbled at -78°C; during this time the light yellow colored solution turned into a colorless suspension of lithium pyrazole carboxylate **2**. The excess of carbon dioxide and the solvent were removed under vacuum to afford the corresponding colorless lithium salt **2** which was deprotonated with *t*-BuLi in hexane/THF at –78°C to yield light yellow colored dianion **3** (Scheme 1).

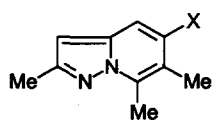


Scheme 1

The dianion **3** reacted with α-oxoketene dithioacetal **4a** and the corresponding carbinolthioacetal **5a** was obtained in good yield. Treatment of **5a** with H_3PO_4 at 120°C followed by work-up afforded a colorless solid which was characterized as 7-methylthio-2,5,6-trimethylpyrazolo[1,5-*a*]pyridine **7a** instead of indazole **9** ($R^1 = R^2 = Me$) on the basis of spectral and analytical data. Thus the IR spectrum of **7a** did not display any peak due to NH group between 3200-3400 cm^{-1}. Also its ^1H NMR spectrum (300 MHz) did not show any D_2O-exchangable signal between δ 8-14 characteristic of indazole and pyrazole ring N-H [8]. The pyrazolo[1,5-*a*]pyridine structure **7a** was further supported by the presence of a singlet at δ 6.08 due to H-3



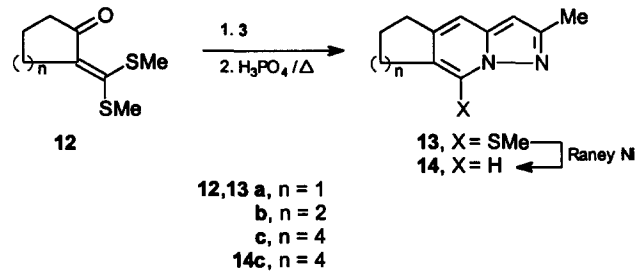
4-8 a, R^1 = Me, R^2 = Me
b, R^1 = Me, R^2 = H
c, R^1 = Ph, R^2 = H
d, R^1 = 4-$MeOC_6H_4$, R^2 = H



10a, X = SMe
11a, X = H

Scheme 2

in line with the earlier reported values [9]. In its ^{13}C NMR spectrum, **7a** displayed a characteristic C-3 signal at δ 95.54 confirming the structural assignment [10]. Dethiomethylation of **7a** with Raney Ni afforded sulfur-free **8a** in 94% yield. The ^1H NMR spectrum of **8a** established that the anion **3** has followed 1,2-addition mode to **4a** since the ring protons H-4 and H-7 in **8a** were observed as singlets. The other possible 5-methylthiopyrazolopyridine isomer **10a** would have yielded, after desulfurization, the corresponding 6,7-disubstituted pyrazolopyridine **11a** for which the resonances for H-4 and H-5 protons would have appeared as doublets through *o*-coupling. The presence of a low field singlet at δ 8.09 due to H-7 in the ^1H NMR spectrum of **8a** is also in agreement with the reported values for these compounds [9,11] while no proton of the aromatic ring of indazole appears at such a high δ value [8]. The other open chain ketene dithioacetals **4b-d** reacted similarly with **3** to afford the corresponding carbinol thioacetals **5b-d**, which were cyclized as described above to afford the corresponding 2-methyl-7-methylthio-5-substituted pyrazolo[1,5-*a*]pyridines **7b-d** in 72-82% overall yields. The probable mechanism for the formation of pyrazolo[1,5-*a*]pyridines **7** from **5** is shown in the Scheme 2. Apparently the decarboxylated carbinolthioacetal **6** cyclizes at the electron rich ring nitrogen instead of at C-4 to give pyrazolo[1,5-*a*]pyridines **7** rather than the indazoles. The cyclic oxoketene dithioacetals **12a-c** reacted similarly with **3** to afford the corresponding 5,6-cycloalkanopyrazolo[1,5-*a*]-pyridines **13a-c** in 67-70% overall yields (Scheme 2). The structures of all these products were established with the help of spectral and analytical data. The methylthiopyrazolo[1,5-*a*]pyridines **7b-d** and **13c** were also subjected to Raney Ni desulfurization when the corresponding sulfur-free **8b-d** and **14c** were obtained in 85-92% overall yields.

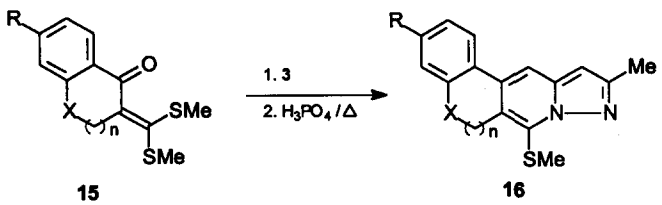


12 **13**, X = SMe
14, X = H

12,13 a, n = 1
b, n = 2
c, n = 4
14c, n = 4

Scheme 3

The reaction of α-oxoketene dithioacetals **15a** and **15b** derived from tetralone and 2,3,4,5-tetrahydro-benzo[*b*]thiepin-5-one with **3** under identical reaction conditions afforded novel tetracyclic pyrazolopyridines **16a** and **16b** in 63% and 64% yields respectively (Scheme 4).



15 **16**

15,16a : X = CH_2, R = H, n = 1
b : X = S, R = Me, n = 2

Scheme 4

In conclusion, we have successfully prepared lithium 5-lithiomethyl-3-methyl-pyrazole-1-carboxylate **3** and reacted it with various α-oxoketene dithioacetals to develop a new method for the synthesis of substituted and condensed pyrazolo[1,5-*a*]pyridines. Many pyrazolo[1,5-*a*]pyridines have been shown to be biologically important, exhibiting anti-inflammatory, antiallergic, bronchodilating and adenosine antagonist activity [12]. Most of the reported methods [13] for the synthesis of pyrazolo[1,5-*a*]pyridines utilize *N*-aminopyridinium salt precursors involving their reaction with 1,3-dicarbonyl compounds [14], acylating agents [11,15], activated acetylenic compounds [16], nitroolefins [17], dimethyl 1-chlorofumarate [18], alkoxymethylene carbonyl compounds [19] and activated acetonitrile derivatives [20]. Other syntheses involve reaction of 1-aminopyridine-2-thione with α-bromocarbonyl compounds [21], condensation of 1-amino-2-pyridones with active methylene ketones [22], base treatment of 1-[2-(substitutedmethylthio)methylene-amino]pyridinium halides [23], reaction of triazolopyridinium ylides with dimethyl acetylenedicarboxylate [24], reaction of 1-aminopyridin-2-imines with 1,3-dicarbonyl compounds [25] and thermal isomerization of allylidene dihydropyridine derivatives [26] or conjugated azines [27]. Most of these methods require substituted pyridine precursors for the synthesis of pyrazolo[1,5-*a*]pyridines. On the other hand, methods based on more easily accessible pyrazole derivatives are not described in the literature. One isolated example [28] involves thermolysis of Diels-Alder adduct of pyrazoline with tetraphenylcyclopentadienone to afford pentaphenylpyrazolo[1,5-*a*]pyridines. The reaction of cyanomethylpyrazole with 1,3-dicarbonyl compounds is also reported [29] to yield pyrazolo[1,5-*a*]pyridines which were not properly characterized. The present method utilizing lithiomethylpyrazole dianion **3** is therefore unique and efficient for the synthesis of novel pyrazolo[1,5-*a*]pyridines with diverse structural flexibility and full control of the substitution pattern in the pyridine ring.

Experimental Section

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were conducted in oven-dried (120°C) glass ware under a dry argon/nitrogen atmosphere. All reactions were monitored by TLC on glass plates coated with silica gel (Acme) containing 13% calcium sulfate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying with acidic potassium permanganate solution. Column chromatography was carried out using Acme silica gel (60-120 mesh). THF was distilled from sodium benzophenone ketyl prior to use. 3,5-Dimethylpyrazole was prepared according to the literature procedure [30]. *n*-BuLi and *t*-BuLi were purchased from Aldrich. The α-oxoketene dithioacetals were prepared according to the reported procedures [6].

General Procedure for the Preparation of Lithium 5-Lithiomethyl-3-methylpyrazole-1-carboxylate and its Reaction with α-Oxoketene Dithioacetals: Synthesis of Substituted and Annelated Pyrazolo-[1,5-a]pyridines.

To a stirred solution of 3,5-dimethylpyrazole **1** (15 mmol) in THF (25 ml) at –78°C, *n*-BuLi in hexane (16 mmol) was added when the reaction mixture turned light yellow. After 30 min, analytical grade carbon dioxide was bubbled for 5 min at –78°C during which time the light yellow colored solution turned into a colorless suspension of lithium pyrazole-2-carboxylate **2**. The excess of carbon dioxide and the solvent were

removed under vacuum to afford the lithium salt **2** as colorless solid. Fresh THF (30 ml) was added to the reaction mixture, maintaining the temperature at –78°C, followed by dropwise addition of *t*-BuLi (16 mmol) in hexane when yellow colored dianion **3** was formed. After 1 h, the appropriate α-oxoketene dithioacetal (15 mmol) in THF (25 ml) was added dropwise whilst maintaining the temperature at –78C. The reaction mixture was further stirred for 1 hr at room temperature and then poured into saturated NH_4Cl solution (250 ml) and extracted with chloroform (3x60 ml). The combined organic extracts were washed with water, dried over sodium sulfate and the solvent distilled off to give the crude carbinolthioacetals which were used as such for further cyclization.

To the crude carbinolthioacetals, orthophosphoric acid (20 ml) was added and heated with stirring at 120°C for 2-3 h. It was then poured into ice cold water (250 ml), extracted with chloroform (3x50 ml), washed with water and dried over sodium sulfate. The solvent was distilled off and the crude products obtained were purified by column chromatography (silica gel) using hexane-ethyl acetate (97:3) as eluent.

7-Methylthio-2,5,6-trimethylpyrazolo[1,5-*a*]pyridine 7a:

Colorless crystals; Yield 78%; m.p. 75-76°C (ether); IR (KBr): 1479, 1529, 1626, 2916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.22 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2. 47 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.08 (s, 1H, H-3), 7.07 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 14.06, 15.70, 16.71, 20.76, 95.54, 115.71, 124.95, 131.79, 133.06, 139.74, 150.04; MS (*m/z*, %) 206 (M^+, 88.9), 172 (100); Anal. Calcd. for $C_{11}H_{14}N_2S$ (206.20): C, 64.02; H, 6.84; N, 13.59%. Found: C, 64.32; H, 6.63; N, 13.82%.

2,5-Dimethyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 7b:

Colorless crystals; Yield 72%; m.p. 98-99°C (ether); IR (KBr): 1289, 1497, 1621, 2986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.24 (s, 3H, CH_3), 2.47 (s, 6H, $(CH_3)_2$), 6.08 (s, 1H, H-3), 6.15 (brs, 1H, H-6), 6.88 (brs 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 13.87, 14.01, 21.17, 95.22, 108.12, 111.27, 133.23, 138.32, 141.19, 151.29; MS (*m/z*, %); 192 (M^+, 64.8), 159 (100): Anal. Calcd. for $C_{10}H_{12}N_2S$ (192.28): C, 62.46; H, 6.29; N, 14.57%. Found: C, 62.92; H, 6.53; N, 14.78%.

2-Methyl-5-phenyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 7c:

Colourless crystals; Yield 80%; m.p. 133-135°C (chloroform-hexane); IR (KBr): 1499, 1610, 2982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.31 (s, 1H, H-3), 6.65 (s, 1H, H-4), 7.30-7.45 (m, 4H, ArH), 7.56-7.59 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.19, 14.22, 97.07, 105.84, 110.04, 126.88, 127.95, 128.88, 136.40, 139.25, 139.40, 141.38, 152.28; MS (*m/z*, %): 254 (M^+, 93.7), 221 (100). Anal. Calcd. for $C_{15}H_{14}N_2S$ (254.36): C, 70.83; H, 5.55; N, 11.01%. Found: C, 71.02; H, 5.48; N, 11.12%.

5-(4-Methoxyphenyl)-2-methyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 7d:

Colorless crystals; Yield 82%; m.p. 152-153°C (chloroform-hexane); IR (KBr): 1471, 1497, 1524, 1603, 2982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.63 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 6.31 (s, 1H, H-3), 6.64 (brs, 1H, H-6), 6.97 (d, J = 8.7 Hz, 2H, ArH), 7.34 (brs, 1H, H-4), 7.54 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR (75MHz, $CDCl_3$): δ 14.28, 15.27, 55.40, 95.39, 109.71, 110.67, 113.81, 125.67, 130.63, 134.98, 139.29, 142.45, 151.79, 160.52; MS (*m/z*, %); 284 (M^+, 81.8), 251 (100); Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.38): C, 67.58; H, 5.67; N, 9.85%. Found: C, 67.83; H, 5.81; N, 10.31%.

2-Methyl-8-(methylthio)cyclopenta[*d*]pyrazolo[1,5-*a*]pyridinė 13a:

Colourless crystals; Yield 67%; m.p. 87-88°C (chloroform-hexane); IR (KBr): 1539, 1588, 1629, 1683, 2926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.09-2.16 (m, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3),

2.93 (t, 2H, CH_2), 3.04 (t, 2H, CH_2), 6.16 (s, 1H, H-3), 7.16 (s, 1H, H-4); MS (*m/z*, %): 218 (M^+, 48.2), 185 (100); Anal. Calcd. for $C_{12}H_{14}N_2S$ (218.26): C, 66.04; H, 6.47; N, 12.83%. Found: C, 65.89; H, 6.51; N, 12.93%.

2-Methyl-9-methylthio-5,6,7,8-tetrahydropyrazolo[1,5-*b*]isoquinoline 13b:

Colorless crystals; Yield 70%; m.p. 97-98°C (ether); IR (KBr): 1425, 1529, 1622, 2932 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 1.80-2.00 (m, 4H, $(CH_2)_2$), 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.63 (brt, 2H, CH_2), 3.07 (brt, 2H, CH_2), 6.02 (s, 1H, H-3), 6.86 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 13.93, 14.37, 21.54, 22.34, 24.52, 24.87, 94.20, 106.70, 116.44, 134.95, 135.91, 139.56, 150.03; MS (*m/z*, %): 232 (M^+, 100), 217 (37.6); Anal. Calcd. for $C_{13}H_{16}N_2S$ (232.35): C,67.20; H, 6.94; N, 12.06%. Found: C, 67.52; H, 7.28; N, 12.41%.

2-Methyl-11-(methylthio)cycloocta[*d*]pyrazolo[1,5-*a*]pyridine 13c:

Light yellow crystals; Yield 67%; m.p. 81-82°C (chloroform-hexane); IR (KBr): 1473, 1682, 2921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 1.20-1.34 (brm, 2H, CH_2), 1.40-1.48 (brm, 2H, CH_2), 1.65-1.75 (brm, 4H, $(CH_2)_2$), 2.48 (s, 3H, CH_3), 2.57 (s, 3H, SCH_3), 2.75 (brt, 2H, CH_2), 3.09 (brt, 2H, CH_2), 6.11 (s, 1H, H-3), 7.11 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 14.08, 15.77, 25.36, 26.32, 28.06, 31.02, 32.72, 33.67, 95.56, 115.27, 128.96, 131.59, 138.40, 140.08, 150.08; MS (*m/z*,%): 260 (M^+,7.4). Anal. Calcd. for $C_{15}H_{20}N_2S$ (260.40): C, 69.19, H, 7.74, N, 10.76%. Found: C, 69.32; H, 7.70; N, 10.83%.

5,6-Dihydro-9-methyl-7-(methylthio)benzo[*f*]pyrazolo[5,1-*b*]isoquinoline 16a:

Light yellow crystals; Yield 63%; m.p. 107°C (chloroform-hexane); IR (KBr): 1445, 1496, 1614, 2921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.47 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.86 (s, 4H, $(CH_2)_2$), 6.17 (s, 1H, 10-H), 7.03 (s, 1H, 11-H), 7.24-7.40 (m, 3H, ArH), 9.29 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 14.14, 15.03, 24.06, 28.73, 94.68, 109.36, 119.93, 126.18, 126.97, 127.84, 128.46, 128.72, 132.80, 134.78, 138.26, 141.71, 150.37; MS (*m/z*, %): 280 (M^+, 100); Anal. Calcd. for $C_{17}H_{16}N_2S$ (280.39): C, 72.82, H, 5.75, N, 9.99%. Found: C, 72.69, H, 5.81, N, 9.93%.

6,7-Dihydro-3,10-dimethyl-8-(methylthio)benzo[*b*]pyrazolo[1',5'-1,6]pyrido[4,3-*d*]thiepin 16b:

Colourless crystals; Yield 64%; m.p. 190°C (chloroform-hexane); IR (KBr): 1467, 1524, 1621, 2917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.38 (s, 3H, CH_3), 2.51 (brs, 4H, CH_3 + H), 2.64 (s, 3H, CH_3), 2.91 (brm, 1H), 3.46 (brm, 1H), 3.80 (brm, 1H), 6.28 (s, 1H, 11-H), 7.14 (s, 1H, ArH), 7.27 (brs, 2H ArH), 7.38 (brs, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 14.07, 15.75, 20.76, 29.34, 37.42, 97.17, 115.42, 126.03, 128.42, 129.30, 130.91, 130.99, 135.51, 138.05, 138.11, 139.93, 142.07, 150.44; MS: (*m/z*, %): 326 (M^+, 100%). Anal. Calcd. for $C_{18}H_{18}N_2S_2$ (326.49): C, 66.22; H, 5.56; N, 8.58%. Found: C, 66.36; H, 5.67; N, 8.51%.

General Procedure for Dethiomethylation of 7a-d and 13c with Raney Nickel.

To a solution of corresponding methylthiopyrazolo[1,5-*a*]pyridine (2 mmol) in ethanol (30 ml), Raney nickel (W2, 6 times by weight) was added and the suspension was refluxed with stirring for 2-3 h (monitored by tlc). The reaction mixture was then cooled, filtered through sintered funnel and the residue was washed with ethanol. Ethanol was removed under vacuum and the residue was dissolved in chloroform (100 ml).The chloroform solution was then washed with water, dried over anhydrous sodium sulfate and concentrated to give crude products from which analytically pure compounds were obtained by passing through a small silica gel column using hexane as eluent.

2,5,6-Trimethylpyrazolo[1,5-*a*]pyridine 8a:

Colorless crystals; Yield 94%; m.p. 94-95°C (chloroform-hexane); IR (KBr): 1529, 1626, 2916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.07 (s, 1H, H-3), 7.10 (s, 1H,

H-4), 8.09 (s, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 16.68, 19.46, 94.33, 115.56, 120.67, 125.65, 134.45, 140.32, 150.88; MS (*m/z*, %); 160 (M^+, 100); Anal. Calcd. for $C_{10}H_{12}N_2$ (160.22): C, 74.97; H, 7.55; N, 17.48%. Found: C, 75.23; H, 7.79; N, 17.73%.

2,5-Dimethylpyrazolo[1,5-*a*]pyridine 8b:

Light yellow crystals; Yield 90%; m.p. 78-79°C (chloroform-hexane); IR (KBr): 1468, 1737, 2925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.11 (s, 1H, H-3), 6.44 (dd, *J* = 1.8, 7.1 Hz, 1H, H-6), 7.12 (brs, 1H, H-4), 8.22 (d, *J* = 7.1 Hz, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 21.12, 94.90, 113.32, 115.55, 127.29, 133.78, 141.37, 151.80; MS (*m/z*, %): 146 (M^+,100). Anal. Calcd. for $C_9H_{10}N_2$ (146.19): C, 73.94; H, 6.89; N, 19.16%. Found: C, 73.78; H, 6.92; N, 19.23%

2-Methyl-5-phenylpyrazolo[1,5-*a*]pyridine 8c:

Colorless crystals; Yield 85%; m.p. 120-121°C (chloroform-hexane); IR (KBr): 1522, 2919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/CCl_4$): δ 2.46 (s, 3H, CH_3), 6.21 (s, 1H, H-3), 6.86 (dd, *J* = 1.8, 7.2 Hz, 1H, H-6), 7.28-7.56 (m, 6H, ArH), 8.37 (d, *J* = 7.1 Hz, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$): δ 13.77, 96.24, 110.06, 113.78, 126.46, 127.63, 127.79, 128.61, 135.85, 138,93, 140.85, 151.68; MS (*m/z*, %): 208 (M^+, 100%), Anal. Calcd. for $C_{14}H_{12}N_2$ (208.26): C, 80.74, H, 5.81; N, 13.45%. Found: C, 81.07, H, 5.85, N, 13.39%.

5-(4-Methoxyphenyl)-2-methyl-pyrazolo[1,5-*a*]pyridine 8d:

Colorless crystals; Yield 92%; m.p. 144-145°C (chloroform-hexane); IR (KBr): 1487, 1514, 1639, 2901 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/ CCl_4): δ 2.49 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.26 (s,1H, H-3), 6.88 (dd, 1H, *J* = 2, 7.3 Hz, H-6), 6.97 (d, 2H, *J* = 8.8 Hz, ArH), 7.51 (m, 1H, H-4), 7.55 (d, 2H, *J* = 8.9 Hz, ArH), 8.36 (d, 1H, *J* = 7.2 Hz, H-7); MS (*m/z*, %): 238 (M^+, 100); 223 (82). Anal. Calcd. for $C_{15}H_{14}N_2O$ (238.29): C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.96; H, 6.19; N, 12.03%.

2-Methylcycloocta[*d*]pyrazolo[1,5-*a*]pyridine 14c:

Colorless crystals, Yield 91%; m.p. 75-76°C (chloroform-hexane); IR (KBr): 1441, 1528, 1602, 2952, cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.00-2.00 (brm, 8H), 2.36 (s, 3H, CH_3), 2.60-2.90 (m, 4H), 6.00 (s, 1H, H-3), 7.10 (s, 1H, H-4), 8.12 (s, 1H, H-11); MS (*m/z*, %): 214 (M^+, 100%). Anal. Calcd. for $C_{14}H_{18}N_2$ (214.31): C, 78.46; H, 8.47; N, 13.07%. Found: C, 78.63; H, 8.41; N, 13.12%.

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References

[1] Katritzky AR, Jayaram C, Vassilatos SN. Tetrahedron 1983; 39: 2023 and references therein.

[2] Butler DE, Alexander SM. J. Org.Chem. 1972; 37: 215.

[3] Micetich RG. Can. J. Chem. 1970; 48: 2006.

[4] Katritzky AR, Akutagawa K. J. Am. Chem. Soc. 1986; 108: 6808.

[5] Syamkumar UK, Patra PK, Ila H, Junjappa H. Tetrahedron Lett. 1998; *39*: 2029.

[6] Review: Junjappa H, Ila H, Asokan CV. Tetrahedron 1990; 46: 5423.

[7] Patra PK, Suresh JR, Ila H, Junjappa H. Tetrahedron 1998; 54: 10167 and references therein.

[8] Elguero J. Pyrazole and their Benzo Derivatives. In: Katritzky AR, Rees CW, Potts KT, editors. Comprehensive Heterocyclic Chemistry, Oxford: Pergamon Press, 1984;5:186 and 184.

[9] Greenhill JV. Pyrazoles with fused Six-membered Heterocyclic Rings. In: Katritzky AR, Rees CW, editors. Comprehensive Heterocyclic Chemistry. Oxford: Pergamon Press, 1984; 5:307.

[10] (a) Ref. 9, p. 308; (b) Pugmire RJ, Smith JC, Grant DM, Stanovnik B, Tisler M, Vercek B, J. Heterocycl. Chem. 1987;24:805.
[11] Potts KT, Singh UP, Bhattacharyya J. J. Org. Chem. 1968;33:3766.
[12] (a) Kuroda S, Itani H, Akabane A. Japan Kokai, 1997:216,883; Chem. Abstr. 1997;127:262667j. (b) Ogata T, Amada J, Okamura H, Oohashi M, Matsuzawa K. Japan Kokai, 1996:12,673; Chem. Abstr. 1996;124:317153j. (c) Tanaka Y, Uno T, Ju T, Oohashi M. Japan Kokai, 1995:215,974; Chem. Abstr. 1996;124:55944v. (d) Ogata T, Amada J, Oohashi M, Matsuzawa K. Japan Kokai, 1995:33,769; Chem. Abstr. 1995;123:55871y. (e) Tanaka Y, Uno T, Ju T, Oohashi M. Japan Kokai, 1995:33,768; Chem. Abstr. 1995;123:33062h. (f) Shiokawa Y, Akahane A, Katayama H, Mitsunaga T. Eur. Pat. 1990:379,979; Chem. Abstr. 1991;114:62080g. (g) Nishino K, Ohkubo H, Ohashi M, Hara S, Kito J, Irikura T. Jpn. J. Pharmacol. 1983;33:267.
[13] (a) Ref. 9, p 316. (b) Hardy CR. The Chemistry of Pyrazolopyridines. In: Katritzky AR, editor. Advances in Heterocyclic Chemistry, Orlando: Academic Press, 1984; 36: 381.
[14] (a) Tamura Y, Yamakami A, Ikeda M. J. Pharm. Soc. Jpn. 1971;91:1154. (b) Potts KT, Dugas R, Surapaneni CR. J. Heterocyclic Chem. 1973;10:821. (c) Molina P, Arques A, Hernandez H. Synthesis, 1983:1021.
[15] (a) Suzne S, Hirobe M, Okamoto T. Chem. Pharm. Bull. 1973;21:2146. (b) Kato T, Masuda S. Chem. Pharm. Bull. 1975; 23:452.
[16] (a) Huisgen R. Angew. Chem. 1963;75:621. (b) Boekelheide V, Fedoruk NA. J. Org. Chem. 1968;33:2062. (c) Huisgen R, Grashey R, Krischke R. Tetrahedron Lett. 1962:387. (d) Sasaki T, Kanematsu Y, Yukimoto Y. J. Chem. Soc. C 1970:481. (e) Tsuchiya T, Sashida H. J. Chem. Soc. Chem. Commun. 1970:481. (f) Krischke R, Grashey R, Huisgen R. Justus Leibigs Ann. Chem. 1977:498. (f) Miki Y, Nakamura N, Hachiken H, Takemura S. J. Heterocycl. Chem. 1989;26:1739.
[17] (a) Fujito H, Tominaga Y, Matsuda Y, Kobayashi G. Heterocycles, 1977;6:379. (b) Tominaga Y, Ichihara Y, Hosomi A. Heterocycles 1988, 27, 2345.
[18] Sasaki T, Kanematsu K, Kakehi A. J. Org. Chem. 1972;37:3106.
[19] (a) Tamura Y, Miki Y, Sumida Y, Ikeda M. J. Chem. Soc. Perkin Trans.1, 1973:2580. (b) Tominaga Y, Ichihara Y, Mori T, Kamio C, Hosomi A. J. Heterocycl. Chem. 1990;27:263.
[20] Arques A, Hernandez H, Molina P, Vilaplana MJ. Synthesis 1981:910.
[21] Molina P, Arques A, Ferao A. Synthesis 1982:645.
[22] Phadke RC, Rangnekar DW. Synthesis 1987:484.
[23] (a) Kakehi A, Ito S, Ito M, Yotsuya T. Heterocycles 1984;22:2237. (b) Kakehi A, Ito S, Kinoshita N, Abaka Y. Bull. Chem. Soc. Jpn. 1988;61:2055. (c) Kakehi A, Ito S, Isawa H, Takashima T. Chem. Pharm. Bull. 1990;38:2662.
[24] Abarca B, Ballesteros R, Metni MR, Jones G, Ando DJ, Hursthouse MB. Tetrahedron Lett. 1991;32:4977.
[25] Kockritz P, Riemer B, Michler A, Hassoun A, Liebscher J. J. Heterocycl.Chem. 1994;31:1157.
[26] (a) Kakehi A, Ito S, Uchiyama K, Hondo K. Chem. Lett. 1977:545. (b) Kakehi A, Ito S, Watanabe K, Ono T, Miyazima T. Chem. Lett. 1979:205. (c) Kakehi A, Ito S, Uchiyama K, Hondo K. J. Org. Chem. 1978;43:2896.
[27] Schweizer EE, Hayes JE, Hirwe SN, Rheingold AL. J. Org. Chem. 1987;52:1319.
[28] Rees CW, Yelland MJ. J. Chem. Soc. Perkin Trans.1 1973:221.
[29] Taylor EC, Hartke KS. J. Am. Chem. Soc. 1959;81:2452.
[30] Vogel's Textbook of Practical Organic Chemistry, 5th ed., London: ELBS, 1989:1149.