The synthesis of novel ethyl 4-(substituted amino)isothiazolo[5,4-*b*]-pyridine-5-carboxylates

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The preparation of ethyl 4-(substituted amino)isothiazolo[5,4-*b*]pyridine-5-carboxylates via nucleophilic displacement of 4-chloroisothiazolo[5,4-*b*]pyridines by amino compounds is reported.

Keywords: fused pyrimidines, isothiazoles, hydrazides

Mononuclear isothiazole, a man-made molecule, was first reported by Adams and Slack in 1956. Since then, the synthesis, properties and applications of isothiazoles have been extensively reviewed.[1] Isothiazoles have been incorporated into a wide range of established drugs and are also known to serve as constituents of various physiologically active compounds.[1] In view of the multifarious applications of isothiazoles we became interested to develop methodologies for their preparation.

1a **1b**

X = heteroatom; Y = heteroatom or CH

Heterocyclic compounds of the types **1a** and **1b** having two heteroatoms in a five-membered ring fused to a pyridine ring have been reported.[2] The explosive growth in this field stems from the fact that many of these condensed systems exhibit fascinating biological, pharmacological and other interesting properties.

Isothiazolo[5,4-*b*]pyridines are known to exhibit analgesic,[2b] anorectic and antidepressant activities.[3] Some new derivatives of isothiazolo[5,4-*b*]pyridine of Mannich base type have been reported to exhibit high anorectic action in animal models as a result of stimulation of the seretoninergic system.[4] Isothiazole is reported to exhibit properties similar to pyridine,[5] and isothiazolo[5,4-*b*]pyridines may be expected to behave analogously to naphthyridines.

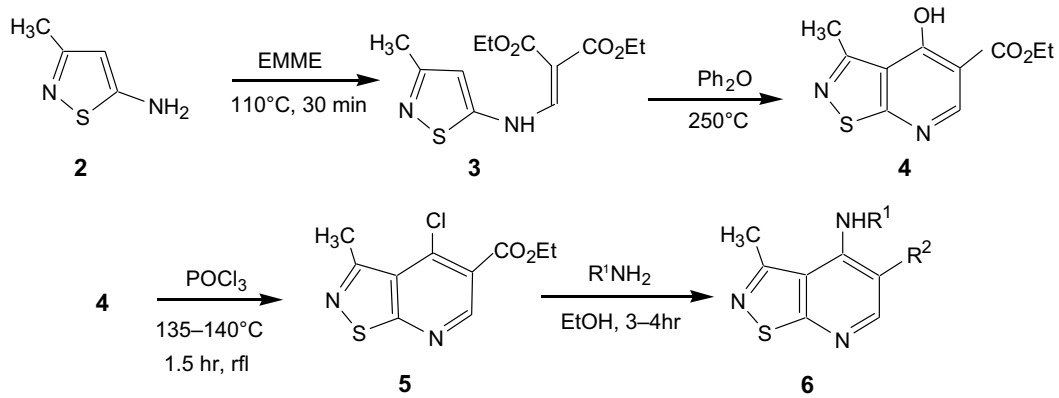
In an earlier communication[6] we reported a facile and high yielding synthesis of ethyl 4-hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylate (**4**). Compound **4**, when treated with phosphorus oxychloride for 1.5 h, afforded **5** in reasonable yield (65%). It may be mentioned here that compound **5** was previously prepared[7] in a much lower yield (35%). Herein, we report the preparation of novel ethyl 4-(substituted amino)isothiazolo [5,4-*b*]-pyridine-5-carboxylates (**6**) (Scheme 1) in good to excellent yields via nucleophilic displacement reactions of 4-chloroisothiazolo[5,4-*b*]pyridine-5-carboxylate (**5**).

The structures of all these compounds are secured by elemental and spectral analyses (Tables 2–4). Easy access to 4,5-disubstituted isothiazolo[5,4-b]pyridines has immense potential as their inbuilt functionality allows further chemical transformations of this class of compounds. Thus, the ester group at C-5 could easily be transformed to various other functional groups following conventional methodologies. In addition, the presence of the carboxylate group at C-5 in conjunction with a 4-(substituted amino) moiety leaves scope for further heterocyclisation and the preparation of novel isothiazolo-fused condensed systems.

Treatment of chloro-compound **5** with hydrazine, on the other hand, afforded on usual work up a high-melting solid insoluble in most common organic solvents. However, analysis of IR (KBr) and mass spectrum showed this to be compound **6g**. In the mass spectrum (GC MS), peaks at *m/z* 239 [MH^+]; 277 [M + Na^+]; 499 [2M + Na^+] and 237 [M-H]$^-$ support its molecular formula being $C_8H_{10}N_6OS$.

Thus, formation of compound **6g** from **5** resulted from reaction of hydrazine not only with the chloro substituent at C-4 but also with the ester function at C-5. In spite of our best efforts, the reaction of hydrazine could not be confined to C-4 only. It is, however, noteworthy that reaction of phenylhydrazine takes place only at C-4.[7]

The preparation of carbohydrazide **6g** assumes importance in view of the reported biological activities of carbohydrazides.



Scheme 1 6 R^1 = (a) CH_2CH_2OH, (b) CH_2CO_2Me, (c) C_6H_5, (d) *p*-C_6H_4Me, (e) *p*-C_6H_4OMe, (f) *p*-C_6H_4Cl R^2 = CO_2Et throughout; (g) R^1 = NH_2, R^2 = $CONHNH_2$.

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Table 1 Preparation, and physical and analytical data of compounds **6a–6f**

Compd	R^1	R^2	M.p./°C	Yield/%	Mol. form.	Found/calc./%
6a	CH_2CH_2OH	CO_2Et	169–170	65	$C_{12}H_{15}N_3O_3S$	C, 51.42/51.25 H, 5.41/5.37 N, 14.79/14.94
6b	CH_2CO_2Me	CO_2Et	74–75	71	$C_{13}H_{15}N_3O_4S$	C, 49.68/50.49 H, 4.92/4.89 N, 13.63/13.59
6c	C_6H_5	CO_2Et	196–197	65	$C_{16}H_{15}N_3O_2S$	C, 61.56/61.34 H, 4.86/4.82 N, 13.29/13.41
6d	*p*-C_6H_4Me	CO_2Et	180–183	70	$C_{17}H_{17}N_3O_2S$	C, 62.43/62.38 H, 5.26/5.23 N, 12.69/12.83
6e	*p*-C_6H_4OMe	CO_2Et	170–172	72	$C_{17}H_{17}N_3O_3S$	C, 59.19/59.47 H, 5.02/4.99 N, 12.27/12.24
6f	*p*-C_6H_4Cl	CO_2Et	127–130	80	$C_{16}H_{14}ClN_3O_2S$	C, 55.47/55.26 H, 4.08/4.05 N, 12.03/12.08

Some heterocyclic carbohydrazides are useful as antifertility agents for rats and pigeons.[8] In addition, the 1,3,4-oxadiazole moiety, which shows antibacterial, fungicidal and insecticidal activity,[9] can also be introduced at C-5 of compound **6g** by a recently described procedure.[10] The ready availability of 4,5-disubstituted isothiazolo[5,4-*b*]pyridines **6** therefore not only provides an opportunity to study their properties, but also allows scope for elaboration of these functionality towards preparation of novel fused isothiazole derivatives.[7]

Experimental

Melting points were determined in open capillaries. All compounds were crystallised from ethyl acetate-pet ether (60–80°C). IR spectra (KBr) were taken on a Hitachi 270–30 spectrometer; UV spectra were taken on a Hitachi U-2000 spectrometer; ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on Bruker AV-300 and Spect-400 spectrometers with TMS as internal standard. Mass spectra were recorded by a Thermo Finnigan LCQ DUO. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyser.

Diethyl 2-[(3-methylisothiazol-5-ylamino)methylene]malonate (**3**): a mixture of 3-methyl-5-aminoisothiazole[11] (**2**) (0.57 g; 5 mmol) and diethyl ethoxymethylenemalonate (EMME) (1.188 g; 5.5 mmol) was heated under N_2 atmosphere at 110°C for 30 min. This on cooling and followed by trituration with ether gave a pale yellow solid, which on crystallisation from ether-pet. ether (40–60°) furnished white needles (1.05 g, 74%) m.p. 70–72°C (lit.[6] m.p. 70–72°C).

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (**4**): a mixture of **3** (0.568 g, 2 mmol) and diphenyl ether (8.5 g) was refluxed for 10 min under N_2 atmosphere. The reaction mixture was then rapidly cooled to room temperature and diluted with *n*-hexane. The separated solid was filtered, washed (hexane) and crystallised from pyridine (lit.[6] m.p.273–274°C, yield 89%, 0.424 g).

Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (**5**): A mixture of **4** (0.238 g, 1 mmol) and distilled phosphorus oxychloride (1-2 ml) was heated to reflux in an oil bath at 135–140°C for 1.5–2 h. The reaction mixture was cooled to room temperature and excess $POCl_3$ was distilled off under reduced pressure. The remaining liquid was transferred to a beaker (25 ml) containing ice-cold water and was extracted with ethyl acetate (2 × 10 ml). The ethyl acetate extract was then shaken in turn with aqueous ammonia, saturated $NaHCO_3$, and finally with brine. Drying (anh. Na_2SO_4) and removal of solvent afforded the crude material which was purified by column chromatography (silica-gel 60–120 mesh, 3% ethyl acetate-pet ether) to yield **5** as a white crystalline solid, m.p. 77°C (lit.[7] m.p.77–78°C, yield 65%, 0.166 g). IR: 2930, 1726, 1559, 1520, 1418, 1367 cm^{-1}. UV: in EtOH, λ_{max} ($\varepsilon \times 10^{-3}$) 341 (3.4), 307 (8.6), 244 nm (24.6). ^{1}H NMR: δ 1.4 (t, 3H, CH_3CH_2), 2.9 (s, 1H, 3-CH_3), 4.4 (q, 2H, OCH_2CH_3), 8.9 (s, 1H, 6-H). ^{13}C NMR: δ 14.2, 23.3, 62.3, 123.0, 151.6, 162.8. MS: *m/z* 256/258 (M^+).

Ethyl 4-(substituted amino)-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (**6**): A mixture of **5** (0.256 g, 1 mmol) and the appropriate amine (1 mmol) in dry alcohol (4-5 ml) was refluxed on water bath for 3–4 h. The progress of the reaction was monitored from time to time by TLC (1: 3 ethyl acetate/pet. ether). After completion of the reaction, excess of alcohol was distilled off. The remaining solution was poured into water and extracted with ethyl acetate (2 × 10 ml) and the organic layer was washed with 2N HCl to remove excess of amine, followed by washing with brine and finally drying over anh. Na_2SO_4. Removal of the solvent afforded the expected products **6**, details of which are listed in Tables 1–4.

Table 2 ^{1}H NMR spectra of compounds **6a–6f**

Compd	PMR ($CDCl_3$/TMS, δ in ppm)
6a	1.45 (t, 3H, CH_2CH_3), 2.85 (s, 3H, 3-CH_3), 3.60 (q, 2H, CH_2), 3.80 (q, 2H, CH_2), 4.45 (q, 2H, CH_2CH_3), 8.30 (bt, 1H, NH), 8.95 (s, 1H, C_6-H)
6b	1.45 (t, 3H, CH_2CH_3), 2.90 (s, 3H, 3-CH_3), 3.85 (s, 3H, OCH_3), 4.15 (d, 2H, $NHCH_2$), 4.45 (q, 2H, CH_2CH_3), 7.90 (t, 1H, NH), 8.35(s, 1H, C_6-H)
6c	1.44 (t, *J* = 7.2, 3H, CH_2CH_3), 2.04 (s, 3H, 3-CH_3), 4.42 (q, *J* = 7.1, 2H, CH_2CH_3,), 6.97-7.31 (m, 5H, Ar-H), 9.13 (s, 1H, C_6-H), 10.27 (s, 1H, NH)
6d	1.47 (t, J = 6.66, 3H, CH_2CH_3), 1.84 (s, 3H, 3-CH_3), 2.40 (s, 3H, CH_3), 4.49 (q, J = 6.49, 2H, CH_2CH_3), 7.09 (d, *J* = 7.47, 1H), 7.24 (d, J = 7.11, 1H) 9.08 (s, 1H, s, C_6-H), 11.67 (s, 1H, NH)
6e	1.47 (t, *J* = 7.11, 3H, CH_2CH_3), 1.87 (s, 3H, 3-CH_3), 3.85 (s, 3H, OCH_3), 4.49 (q, *J* = 7.11, 2H, CH_2CH_3,), 6.95 (d, *J* = 8.82, 2H), 7.16 (d, *J* = 8.82, 2H), 9.04 (s, 1H, C_6-H), 11.68 (s, 1H, NH)
6f	1.45 (t, *J* = 7.05, 3H, CH_2CH_3), 2.07 (s, 3H, 3-CH_3), 4.43 (q, *J* = 7.00, 2H, CH_2CH_3,), 6.94 (d, *J* = 8.1, 1H), 7.26 (d, J = 7.8, 1H), 9.14 (s, 1H, C_6-H), 10.38 (s, 1H, NH)

Table 3 ^{13}C NMR and MS of compounds **6a–6g**

Compd	CMR (δ, $CDCl_3$)	MS (*m/z*)
6a	14.2, 22.5, 53.1, 61.3, 62.2, 107.2, 118.7, 152.5, 157.3, 161.0, 168.0, 179.1	282 (MH^+) 236 (M^+ - OEt)
6b	14.3, 22.6, 50.25, 52.8, 61.5, 107.85, 118.5, 143.0, 153.7, 160.8, 167.0, 171.7, 178.3	310 (MH^+)
6c	14.0, 22.0, 62.3, 107.8, 119.6, 121.25, 126.1, 130.0, 141.7, 148.1, 153.2, 161.8, 166.8, 172.9	314 (MH^+)
6d	14.0, 21.0, 22.2, 63.1, 106.7, 119.6, 122.3, 130.9, 137.5, 138.1, 143.9, 154.9, 161.5, 166.0, 167.4	328 (MH^+)
6e	14.0, 22.25, 55.6, 63.1, 106.3, 115.5, 119.3, 124.1, 132.7, 143.4, 155.1, 159.0, 161.35, 166.0, 167.0	344 (MH^+)
6f	14.6, 22.75, 62.2, 121.8, 130.1, 130.3, 142.7, 152.0, 152.6, 162.4, 168.2, 179.0	348 (MH^+) 350 (MH^+ + 2)
6g	____	239 (MH^+) 237 $(M-H)^-$

Table 4 UV and IR spectra of compounds **6a–6g**

Compd	UV[a]	IR [b]
6a	305 (5.31), 231 (12.7)	3242, 1678, 1565, 1553, 1461, 1369, 1322
6b	314 (17.0), 241 (32.1)	3418, 1694, 1564, 1370, 1306, 1195, 1122
6c	341 (14.6), 333 (14.5), 243 (20.8)	2932, 1675, 1573, 1546, 1538,1492, 1441, 1367, 1312
6d	331 (16.1), 239 (26.7)	2984, 1719, 1600, 1503, 1459, 1424, 1372, 1346
6e	336 (28.2), 273 (23.9), 243 (38.3)	3250, 1718, 1574, 1498, 1456, 1372, 1349
6f	334 (12.5), 241 (22.3)	2986, 1681, 1588, 1539, 1487, 1439, 1372, 1314
6g	____	2998, 1691, 1583, 1529, 1441, 1414, 1370, 1347

[a]in EtOH, λ_{max}, nm ($\varepsilon \times 10^{-3}$) [b] ν_{max}, cm^{-1}, KBr

Received 11 July 2005; accepted 19 January 2006
Paper 05/3353

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