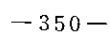


NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRIDO[2,1-b]-
BENZOTHAZOLES, PYRIMIDO[6,1-b]BENZOTHAZOLES AND PYRAZOLO[4,3-c]-
PYRIDAZINE DERIVATIVES

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Abstract- Novel synthesis of pyrido[2,1-b]benzothiazole, pyrimido-
[6,1-b]benzothiazole and pyrazolo[4,3-c]pyridazine derivatives util-
izing 2-cyanomethylbenzothiazole as starting component is reported.

The utilities of cyano compounds in organic synthesis are now receiving consider-
able interest¹⁻⁴. As a part of our program directed for development of new
simple and efficient procedures for the synthesis of fused heterocyclic nitrogen
compounds utilizing a readily obtainable nitrile containing intermediates⁵⁻⁹, we
have previously reported several new approaches for the synthesis of condensed
heterocycles utilizing 2-cyanomethylazolyl¹⁰⁻¹² and 2-cyanomethylbenzimidazole¹³
derivatives as starting material. In conjunction of this work we report a novel
synthesis of pyrido[2,1-b]benzothiazole and pyrimido[6,1-b]benzothiazole deriva-
tives utilizing 2-cyanomethylbenzothiazole 3 as starting material. Compound 3 can
be prepared by the reaction of 1 and 2 in EtOH/AcOH mixture at room temperature.
Compound 3 reacted with 4a,b in tetrahydrofuran and catalytic amount of triethyl-
amine in a 1:1 molar ratio to give 1-amino-2,4-dicyano-3-furyl or 3-thienyl-3H-
pyrido[2,1-b]benzothiazole 5a,b. The structure of 5a could be established for the
reaction product based on ¹H NMR which revealed a singlet at δ 4.42 ppm assigned
for H-3 proton, a broad band located at δ 6.48 ppm assignable to amino group and a
multiplet at δ 6.8-8.22 ppm assigned for furan and aromatic protons (cf. Table 2).
Compound 3 was easily condensed with 2-furancarboxyaldehyde and 2-thiophenecarboxy-
aldehyde to give 6 in high yields. Treatment of 6a,b with malononitrile in tetra-
hydrofuran at reflux temperature yielded 5. The reaction of 7 with 2-cyanomethyl-
benzothiazole 3 in boiling tetrahydrofuran gave 3-substituted 2,4-dicyano-1-oxo-1H-



pyrido[2,1-b]benzothiazoles 8a,b. Compounds 8a,b were also prepared by treating 2-(2-furfurylidene or 2-thiophenylidenecyanomethyl)benzothiazoles 6 with ethyl cyanoacetate, respectively. Compound 3 reacted with benzoylisothiocyanate in refluxing pyridine to yield 4-cyano-1-phenyl-3-thioxo-3H-pyrimido[6,1-b]benzothiazole 10. The formation of 10 in this reaction might be assumed to proceed via addition of benzoylisothiocyanate followed by water elimination under the reaction conditions to yield the finally isolated product 10. Compound 3 reacts with 2-benzoyl-3-(2-furyl)acrylonitrile (9a) and 2-benzoyl-3-(2-thienyl)acrylonitrile (9b) to form only the ylidene derivatives 6. Compound 3 also coupled with benzenediazonium chloride or with diazotized 4-amino-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one in ethanolic sodium acetate to yield the corresponding hydrazone 11a,b, respectively (or its possible tautomers). Compound 11b cyclized on reflux in ethanolic hydrochloric acid to give the pyrazolo[4,3-c]pyridazine derivative 12. The structure of 12 was supported by spectral data, thus the IR spectrum of the product revealed an absence of CN absorption and the ^1H NMR spectrum revealed two different methyl protons indicating that the methyl group at C-3 was not involved in the cyclization. Similar intramolecular cyclization of this type has been previously reported by us ¹⁴.

Table 1 : List of compounds 3, 5a,b, 6a,b, 8a,b, 10, 11a,b and 12

Compound*	Solvent of cryst.	Colour	Mp (°C)	Yield (%)	Mol. formula	M ⁺ m/z
<u>3</u>	EtOH	yellow	103	77	C ₉ H ₆ N ₂ S	174
<u>5a</u>	THF	yellow	130	75	C ₁₇ H ₁₀ N ₄ OS	
<u>5b</u>	THF	yellow	143	75	C ₁₇ H ₁₀ N ₄ S ₂	334
<u>6a</u>	MeOH	yellow	137	82	C ₁₄ H ₈ N ₂ OS	252
<u>6b</u>	MeOH	yellow	150	80	C ₁₄ H ₈ N ₂ S ₂	268
<u>8a</u>	MeOH-DMF	yellow	148	70	C ₁₇ H ₇ N ₃ O ₂ S	
<u>8b</u>	MeOH-DMF	yellow	165	72	C ₁₇ H ₇ N ₃ OS ₂	333
<u>10</u>	MeOH	yellow	> 275	85	C ₁₇ H ₉ N ₃ S ₂	
<u>11a</u>	EtOH	yellow	170	95	C ₁₅ H ₁₀ N ₄ S	278
<u>11b</u>	EtOH-DMF	orange	240	90	C ₂₀ H ₁₆ N ₆ OS	388
<u>12</u>	DMF	yellow	210	55	C ₂₀ H ₁₆ N ₆ OS	

* Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

Table 2: Spectroscopic data for compounds listed in Table 1

Compound	IR[cm ⁻¹] (Selected bands)	¹ H NMR [δ ppm]
<u>3</u>	2220 (CN)	4.77 (s, 2H, CH ₂); 6.82-7.66 (m, 2H, aromatic protons); 7.7-8.2 (m, 2H, aromatic protons)
<u>5a</u>	3400, 3300 (NH ₂); 2210 (CN)	4.42 (s, 1H, 3-H); 6.48 (s, 2H, NH ₂); 6.82 (dd, 1H, furan 3-H); 7.15 (m, 3H, 6, 7, 8-H); 7.62 (dd, 1H, furan 4-H); 7.80 (dd, 1H, furan 5-H); 8.22 (m, 1H, 9-H)
<u>5b</u>	3380, 3320 (NH ₂); 2215 (CN)	4.6 (s, 1H, 3-H); 6.56 (s, 2H, NH ₂); 7.12 (dd, 1H, thiophene 3-H); 7.22 (m, 3H, 6, 7, 8-H); 7.82 (m, 2H, thiophene 4, 5-H); 8.28 (m, 1H, 9-H)
<u>6a</u>	2215 (CN)	7.2-8.2 (m, 7H, furan and aromatic protons); 8.48 (s, 1H, ylidene CH proton)
<u>6b</u>	2220 (CN)	7.1-8.2 (m, 7H, thiophene and aromatic protons); 8.4 (s, 1H, ylidene CH proton)
<u>8a</u>	2220 (CN); 1680 (CO)	7.05-7.80 (m, 5H, furan and 7,8-H protons); 8.20-8.30 (m, 1H, 6-H proton); 9.0-9.2 (m, 1H, 9-H)
<u>8b</u>	2222 (CN); 1685 (CO)	7.23-7.95 (m, 5H, thiophene and 7,8-H protons); 8.2-8.84 (m, 1H, 6-H); 9.00-9.2 (m, 1H, 6-H); 9.00-9.2 (m, 1H, 9-H)
<u>10</u>	2210 (CN)	7.2-7.9 (m, 8H, aromatic protons); 8.00 (m, 1H, 9-H)
<u>11a</u>	3400, 3330 (NH); 2210 (CN)	7.18-7.8 (m, 9H, aromatic protons); 12.2 (s, br, 1H, NH)
<u>11b</u>	3450, 3320 (NH); 2215 (CN); 1680 (CO)	2.6 (s, 3H, 3-CH ₃); 3.2 (s, 3H, 2-CH ₃); 7.3-7.9 (m, 9H, aromatic protons); 12.8 (s, br, 1H, NH)
<u>12</u>	3250 (NH); 1660 (CO)	2.4 (s, 3H, 3-CH ₃); 3.24 (s, 3H, 2-CH ₃); 4.6 (s, br, 1H, NH); 7.2-7.9 (m, 9H, aromatic protons)

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