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SYNTHESIS AND PROPERTIES OF 1-(6-METHOXY)-2-BENZOTHIAZOLYL)-2-PYRIDONES

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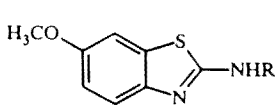
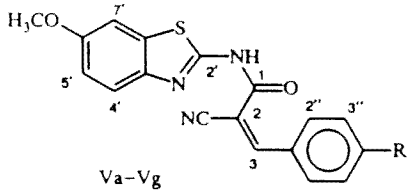
Substituted 1-(6-methoxy-2-benzothiazolyl)-2-pyridones were prepared from 2-amino-6-methoxybenzothiazole through N-(6-methoxy-2-benzothiazolyl) cyanoacetamide and 3-aryl-N-(6-methoxy-2-benzothiazolyl)-2-cyano-2-propenamides. The cyclization of the latter with malonodinitrile in the presence of piperidine gave the corresponding pyridones. The structures of the synthesized compounds were confirmed by ^1H NMR and mass spectral data.

Interesting biological properties and the availability of precursors motivated our entry into the chemistry of benzothiazoles [1-3]. In connection with our previous work [4] this contribution deals with the synthesis and study of properties of some substituted 1-(6-methoxy-2-benzothiazolyl)-2-pyridones (I). The 2-amino-6-methoxybenzothiazole (II) [5] served as appropriate starting material.

1-Cyanoacetyl-3,5-dimethylpyrazole (III) [6], an effective reagent for cyanoacetylation of amino derivatives [7], afforded with amine II the corresponding amide of cyanoacetic acid IV.



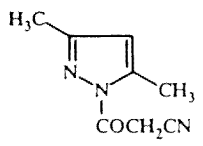
II R = H;
IV R = $COCH_2CN$



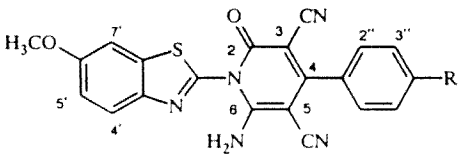
Va–Vg
R = H, CH_3, OCH_3, Cl, NO_2, CN, $N(CH_3)_2$

3-Aryl-N-(6-methoxy-2-benzothiazolyl)-2-cyano-2-propenamides (Va-g) were obtained in 80-95% yields by the Knoevenagel reaction of the C–H acid IV with 4-substituted benzaldehydes. The condensation was carried out in boiling ethanolic sodium hydroxide, or in a boiling solution of potassium acetate in acetic acid.

Propenamides of general formula V are in fact activated nitriles, which are suitable precursors for the synthesis of polysubstituted 2-pyridones I.



III



Ia–If
R = H, CH_3, OCH_3, Cl, NO_2, CN, $N(CH_3)_2$

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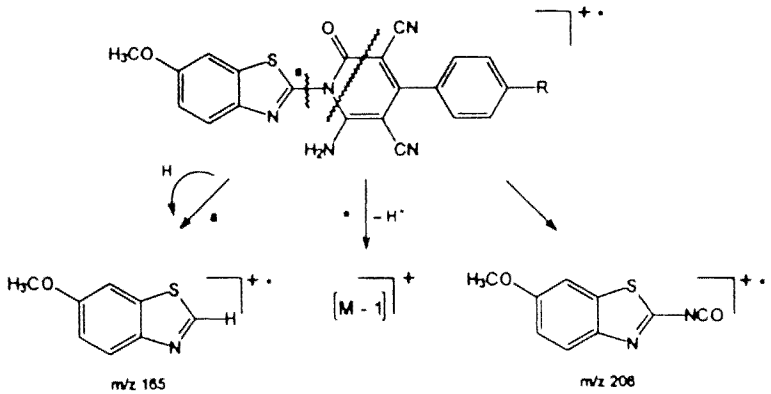
Although many authors prepared 2-pyridones I by various ways [8, 9], a synthesis starting from derivatives V has not been described so far. The desired 6-amino-4-aryl-1-(6-methoxy-2-benzothiazolyl)-3,5-dicyano-2-pyridones (Ia-f) were prepared by treating N-(6-methoxy-2-benzothiazolyl)-2-propenamides (Va-f) with malonodinitrile in boiling ethanol in the presence of piperidine (yields 24-34%). The reaction most probably starts as a Michael addition of the dinitrile to the α,β-unsaturated system, followed by cyclization and loss of hydrogen.

The ^{1}H NMR spectra of propenamides Va-g displayed a broad signal of the NH group at 13.22-13.33 ppm, and that of olefinic H-3 proton at 8.49-8.23 ppm as singlet. Doublets of H-7 and H-4 protons of the benzothiazole ring are found at 7.4-7.51 ppm ($J_{(7',5')}$ = 2.2-2.7 Hz) and 7.60-7.48; ($J_{(4',5')}$ = 9.3-8.1 Hz), respectively. The dd signal at 7.04-6.99 ppm belongs to the H-5. Substituent R affected chemical shifts of protons of the benzene ring.

The amino group arising by cyclization in pyridones Ia-f shows its singlet at 8.96-8.65 ppm. The signals of ring protons of the benzothiazole ring and that of methoxy group in position 6' in Ia-f are shifted downfield compared to those of amides Va-g, thus H-4' is found at 7.94-7.91, H-7' at 7.76-7.75, H-5' at 7.16-7.15, and OCH_3 at 3.82 ppm.

Scheme 1



R^1	M+•, m/z (%)	$[M-1]^+$, m/z (%)	m/z 165 (%)	m/z 206, (%)
H	399 (83)	398 (100)	29	4
CH_3	413 (78)	412 (100)	28	10
OCH_3	429 (55)	428 (100)	32	18
NO_2	444 (100)	443 (92)	59	35

Principal fragmentation patterns of molecular ions of pyridones I are depicted in Scheme 1. Fairly intense molecular ion peaks easily lose a hydrogen radical, giving rise in most cases to the base peak of the spectrum. Further fragmentation always generates ions with *m/z* 165 and *m/z* 206.

^{1}H NMR spectra were recorded on a Tesla BS 587 80 MHz spectrometer, mass spectra on an MS 902 S (A.E.I. Manchester) spectrometer, equipped with direct inlet, at electron energy 70 eV, trap current 100 μA, ion source temperature 220-240°C (compounds Va-g) or 150-200°C for compounds Ia-f.

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