SYNTHESIS OF 3-CARBOETHOXY-4-OXO-4H-PYRIMIDO[1',2':1,5][1,2,4]TRIAZOLO-[3,4-b]BENZOXAZOLE AND 5H-PYRIDO[3",2":5',6']PYRIMIDO[1',2':1,5][1,2,4]-TRIAZOLO[3,4-b]BENZOXAZOLE-5-ONE: NOVEL HETEROCYCLES+

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Abstract - Reaction of 3-amino-1,2,4-triazolo[3,4-b]benzoxazole 2 with diethyl ethoxymethylenemalonate and 2-chloropyridine-3-carboxylic acid chloride afforded 3-carboethoxy-4-oxo-4H-pyrido[1',2':1,5][1,2,4]triazolo[3,4-b]benzoxazole 4 and 5H-pyrido[3",2":5',6']pyrimido[1',2':1,5]-[1,2,4]triazolo[3,4-b]benzoxazole-5-one 6 respectively, new ring systems.

Derivatives of 1,2,4-triazoles[1], benzoxazoles[2] and pyrimidines[3] are of current interest in view of their broad spectrum biological activity exhibited by these compounds as drugs. Some times the fusion of heterocyclic nuclei enhances the biological profile many-fold more than its parent nucleus. In our program in the novel fused triazole series, we recently described the synthesis and promising biological activity of some 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles[4] and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines[5]. Potentiated by these findings and in continuation of our study in the condensed triazole series herein we report the synthesis of the title two novel ring systems which possess 1,2,4-triazole, benzoxazole and pyrimidine moieties in a single molecular frame work.

In literature the preparation of 3-amino-1,2,4-triazolo[3,4-b]benzoxazole 2 was reported as its hydrochloride in a German patent[6]. In the present work, compound 2 was synthesised as its hydrobromide by the reaction of 2-hydrazinobenzoxazole 1 with freshly prepared cyanogen bromide followed by neutralisation with aqueous potassium bicarbonate in 90% yield. 2 was reacted with diethyl ethoxymethylenemalonate (EMME) to obtain open chain compound 3. Subsequent ring closure was achieved in refluxing xylene to obtain 4. Alternatively, 4 was also obtained directly from 2 and EMME by refluxing in xylene for 8 h.

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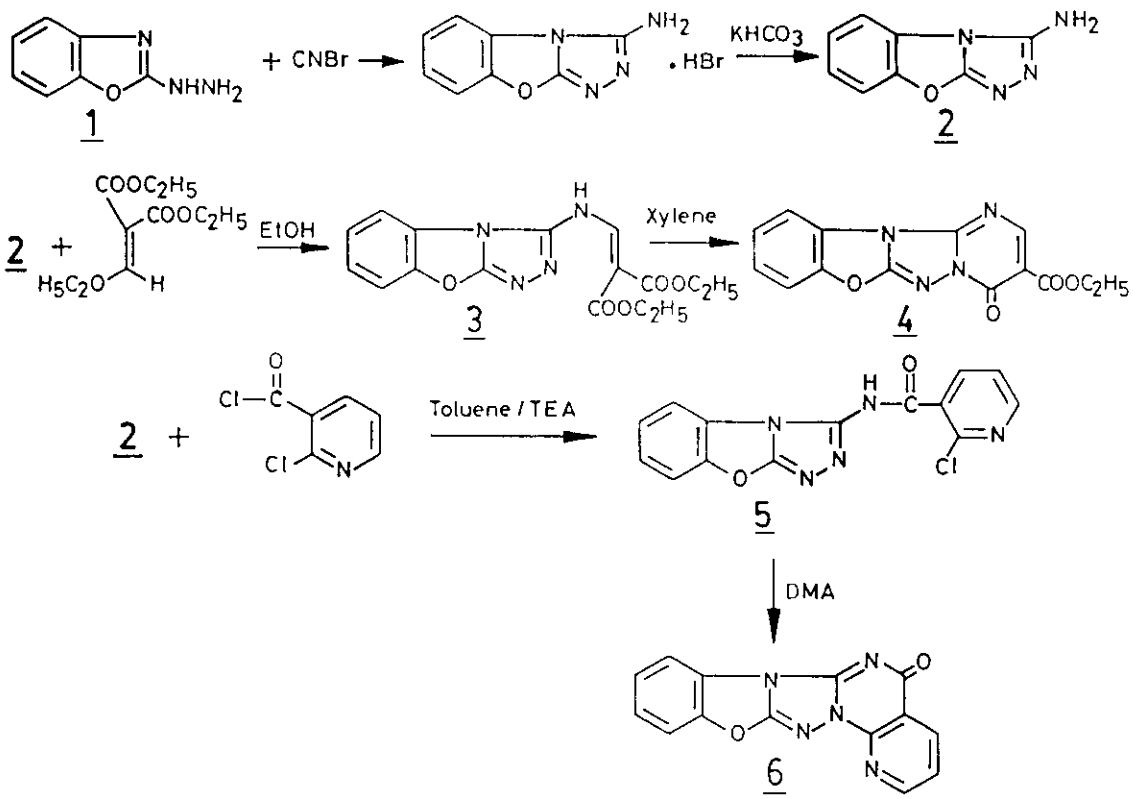
+ CNBr
• HBr
KHCO3
NHNH2
NH2
1
2
EtOH
Xylene
COOC2H5
H5C2O
H
3
4
Toluene / TEA
Cl
O
N
H
5
DMA
6

In our efforts to synthesise pentacyclic ring system by the reaction of 2-chloropyridine-3-carboxylic acid via its acid chloride with 2 in toluene and triethylamine gave N-(1,2,4-triazolo[3,4-b]benzoxazole-3-yl)-2-chloropyridine-3-carboxamide 5 which on cyclisation in dimethylacetamide (DMA) afforded 6.

EXPERIMENTAL

Melting points were determined on Büchi 510 apparatus and are uncorrected, ir spectra were recorded with a Perkin-Elmer 221 spectrophotometer in KBr. ^{1}H-Nmr spectra have been obtained with a Varian FT-80A spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a VG micromass 70-70H mass spectrometer at 70 eV.

3-Amino-1,2,4-triazolo[3,4-b]benzoxazole (2)

A solution of 7.45 g (0.05 mol) of 2-hydrazinobenzoxazole in 60 ml of absolute ethanol and 5.83 g (0.055 mol) of freshly prepared cyanogen bromide was stirred for 4 h at room temperature. The hydrobromide formed was filtered, mp 220-223°C; ir : 3360-3120 cm^{-1}. After neutralisation of the hydrobromide with 10% aqueous $KHCO_3$, the resulting solid was filtered which on crystallisation from ethanol gave 2 (7.83 g, 90%), mp 270°C; ir : 3320-3130 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ : 7.3-7.9 (4H,m,aromatic protons), 6.5 (2H,s,NH_2,D_2O exchangeable); ms : m/z 174 (M^+). Anal. Calcd for $C_8H_6N_4O$:C,55.17; H,3.47; N,32.17. Found:C,55.10; H,3.40; N,32.01.

Diethyl (3-amino-1,2,4-triazolo[3,4-b]benzoxazole)methylenemalonate (3)

A solution of 1.74 g (0.01 mol) of 2 and 2.16 g (0.01 mol) of EMME in ethanol (20 ml) was refluxed for 2 h. The solution was kept at 0°C overnight and the crystalline product was filtered to give 3 (2.87 g) in 84% yield, mp 178°C; ir:3160 and 1730 cm^{-1}; ^{1}H-nmr($CDCl_3$) δ :10.8 (1H,d, J=11Hz,NH,D_2O exchangeable), 8.6 (1H,d,J=11Hz,N-CH, collapses to s with D_2O), 7.2-7.6 (4H,m, aromatic protons), 4.3 (4H,q,J=7Hz,2xCH_2), 1.3 (6H,t,J=7Hz,2xCH_3); ms:m/z 344 (M^+). Anal. Calcd for $C_{16}H_{16}N_4O_5$:C,55.81; H,4.68; N,16.27. Found: C,55.69; H,4.58; N,16.40.

3-Carboethoxy-4-oxo-4H-pyrimido[1',2':1,5][1,2,4]triazolo[3,4-b]benzoxazole (4)

A solution of 1 g of 3 in xylene (10 ml) was refluxed for 4 h. After cooling, n-hexane was added and the solid obtained was filtered, recrystallised from chloroform-ethanol to give 4 (0.606 g) in 70% yield, mp 130°C; ir : 1730 and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ : 8.8 (1H,s,N-CH), 7.3-7.6 (4H,m,aromatic protons), 4.4 (2H,q,J=7Hz,CH_2), 1.3 (3H,t,J=7Hz,CH_3); ms:m/z 298 (M^+). Anal. Calcd for $C_{14}H_{10}N_4O_4$: C,56.38; H,3.38; N,18.78. Found:C,56.29; H,3.40; N,18.88.

3-Carboethoxy-4-oxo-4H-pyrimido[1',2':1,5][1,2,4]triazolo[3,4-b]benzoxazole (4)

A mixture of 1.74 g (0.01 mol) of 2, 2.16 g (0.01 mol) of EMME and xylene (20 ml) was refluxed for 8 h. After cooling, n-hexane was added and the product obtained was filtered. It was recrystallised from chloroform-ethanol to give 4 (2.03 g, 68% yield), mp 130°C and identical in all respects with 4 obtained by above two step method as evidenced by elemental anlysis, ir and ^{1}H-nmr.

N-(1,2,4-Triazolo[3,4-b]benzoxazole-3-yl)-2-chloropyridine-3-carboxamide (5)

2-Chloropyridine-3-carboxylic acid 1.57 g (0.01 mol) and thionyl chloride (8 ml) were refluxed in benzene (20 ml) for 4 h. The excess thionyl chloride was distilled off, benzene (10 ml) was added and was also distilled off so as to remove the traces of thionyl chloride. The resulting crude 2-chloropyridine-3-carboxyl chloride was dissolved in toluene (15 ml) and added dropwise while stirring to a mixture of 1.74 g (0.01 mol) of 2 in toluene (20 ml) and triethylamine (1 ml). After the addition, the mixture was refluxed for 4 h. The solid obtained was filtered off and the filtrate was concentrated to give 5 (2.38 g) in 76% yield, mp 176°C; ir : 3120 and 1700 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ : 7.3-8.0 (7H,m,aromatic protons), 8.6 (1H,br,NH,D_2O exchangeable); ms:m/z 313 (M^+). Anal. Calcd for $C_{14}H_8ClN_5O_2$:C,53.61; H,2.57; Cl,11.30; N,22.32. Found : C,53.70; H,2.55; Cl,11.40; N,22.41.

5H-Pyrido[3",2":5',6']pyrimido[1',2':1,5][1,2,4]triazolo[3,4-b]benzoxazole-5-one (6)

A solution of 1 g (0.0032 mol) of 5 in DMA (10 ml) was refluxed for 24 h. After cooling, the solution was poured into ice cold water. The precipitate formed was filtered and recrystallised from ethanol to give 6 (0.54 g) in 61% yield, mp 248°C; ir : 1640 and 1620 cm^{-1}; ms:m/z 277 (M^+). Anal. Calcd for $C_{14}H_7N_5O_2$: C,60.65; H,2.54; N,25.26. Found : C,60.56; H,2.56; N,25.34.

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