SYNTHESIS OF HETEROCYCLES : SYNTHESIS OF NAPHTHO(4,5-b)-THIAZOLO(2,3-a)(1,2,4) TRIAZEPINES

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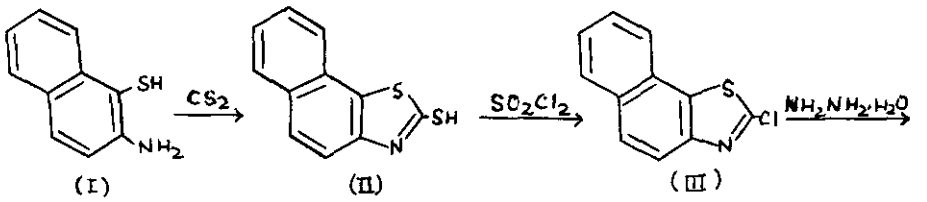
Some new fluorinated naphtho(4,5-b)thiazolo(2,3-c)-(1,2,4)triazepines have been synthesized by condensation of 2-hydrazinonaphtho(2,1-d)thiazoles with 1,3-diketones.

Introduction

In continuation of our earlier studies on synthesis of novel heterocycles[1], this paper reports the synthesis of hitherto unknown naphtho(4,5-b)thiazolo(2,3-c)(1,2,4)triazepine ring system (V). These have been synthesized in keeping view of their chemotherapeutic importance[2-5].

The scheme of synthesis of (V) is as follows:



(a) $R_1 = R_2 = CH_3$; (b) $R_1 = R_2 = CF_3$; (c) $R_1 = C_6H_5$; $R_2 = CF_3$
(d) $R_1 = C_6H_4F(P)$, $R_2 = C_2H_5$; (e) $R_1 = C_6H_4F(P)$, $R_2 = CF_3$

(III) was prepared by Hunter and Jones[6] directly from β-naphthyl isothiocyanate by heating with PCl_5 in a sealed tube. This method is impracticable because β-naphthyl isothiocyanate is always obtained in low yield. In the present investigation, (III) was obtained by the reaction of sulphuryl chloride on 2-mercaptonaphtho(2,1-d)-thiazole (II) in 70% yield. The already reported method of preparing

(II) made use of heating β-naphthylamine with CS_2 and S in a sealed tube and the yields were fairly low[7]. We made use of an alternate method which involved the reaction of 2-amino-1-thionaphthol (obtained by reduction of 2-amino-1-thiocyanatonaphthalene with Na_2S) with CS_2 in alcohol and gave (II) in 80% yield.

(III) was converted into its hydrazine analogue (IV) by treatment with hydrazine hydrate. The IR spectrum of the compound shows the characteristic $-NH_2$, $>C=N$, $-C=C-$ and $-N=N-$ vibrations at 3275, 1615 and 1575 cm^{-1} respectively. The structure is further supported by the NMR spectrum ($CDCl_3$) which shows signals for the aromatic protons as a multiplet at δ 6.8-7.9 and for $-NH-NH_2$ protons at δ 2.5-3.5.

Reaction of (IV) with 1,3-diketone[8] were seemed to afford (V) or (VI). However the structure (V) is more plausible due to the high nucleophilic reactivity of the enamino-ketone system[9]. In this reaction both carbonyl groups of 1,3-diketone are equally susceptible to the attack by the amino group of the hydrazine compound, but the diketone reacted only with one mole of the hydrazine compound to produce the final product (V). The structure of final product (Va) is supported by its NMR spectrum ($CDCl_3$) which shows a singlet at δ 2.35(3H) for $=C(CH_3)N-$, a singlet at δ 2.80(3H), for $-N=C-CH_3$, a singlet at δ 6.0(1H) for $-CH=C$ and a multiplet at δ 7.20-7.90 (6H). ^{19}F NMR spectra (TFA) shows signals at δ 3.9 due to $-CF_3$(vb).

Table - 1. Disubstituted naphtho(4,5-b)thiazolo(2,3-c)(1,2,4)triazepines.

S.No.	R_1	R_2	Molecular formula	M.P. °C	Analysis % Calcd.	Found
V.a.	CH_3	CH_3	$C_{16}H_{13}N_3S$	99-100	C,68.8 H, 4.6 N,15.0	68.6 4.5 14.9
b.	CF_3	CF_3	$C_{16}H_7N_3F_6S$	107	C,49.6 H, 1.8 N,10.8	49.5 1.7 10.6
c.	C_6H_5	CF_3	$C_{21}H_{12}N_3F_3S$	124	C,63.8 H, 3.0 N,10.6	63.7 2.8 10.5
d.	$C_6H_4F(p)$	C_2H_5	$C_{22}H_{16}N_3FS$	113	C,70.7 H, 4.2 N,11.2	70.6 4.0 11.1
e.	$C_6H_4F(p)$	CF_3	$C_{21}H_{11}N_3F_4S$	147	C,61.0 H, 2.6 N,10.1	60.8 2.3 9.8

Experimental

2-Mercaptonaphtho(2,1-d)thiazole (II):- 2-Amino-1-thiocyanonaphthalene (0.1 mole) was added in small portions to a boiling solution of Na_2S (0.15 mole) in H_2O (100 ml) during 30 minutes. The reaction mixture was further heated under reflux for 1 hour. After cooling the mixture was neutralized with acetic acid. The semisolid mass thus separated was extracted with ether, washed thoroughly with water and dried ($MgSO_4$). Ether was removed by distillation and the residual thiol (15 g) was heated under reflux with CS_2 (30 ml) and ethanol (10 ml). A yellow crystalline mass started separating after 3 hr . After 18 hrs the mixture was cooled and solid mass collected, washed with ether, dried and recrystallized from ethanol; yield 70%, m.p. 245°C (Lit,[10] m.p. 240°C).

2-Chloronaphtho(2,1-d)thiazole (III):- (II) (0.03 mole) was added to sulphuryl chloride (20 ml) and the mixture was kept at room temperature for 1 hr. The mixture was then heated to 50°C, cooled and then poured into crushed ice. The solid mass filtered, washed with water and dried. It was recrystallized from ethanol; yield 80%, m.p. 78°C (Lit,[10] m.p. 80°C).

2-Hydrazinonaphtho(2,1-d)thiazole (IV):- (III) (0.02 mole) was added in small portions to hydrazine hydrate (80%; 30 ml) at reflux during a period of 30 minutes. The mixture was further heated for 3 hr . On cooling a crystalline solid separated was filtered, washed with ether and dried. It was recrystallized from aq. alcohol; yield 75%, m.p. 220°C (Lit,[11] 222-223°C).

5,-7-Disubstituted naphtho(4,5-b)thiazolo(2,3-c)(1,2-4)triazepines (V):- A mixture of (IV) (0.01 mole) and 1,3-diketones (0.01 mole) in glacial acetic acid (10 ml) was heated under reflux for 2 hr . The solid obtained on cooling the mixture was recrystallized from light petroleum ether (60-80°C). The m.p., etc., are given in Table I.

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