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Synthesis and Spectroscopic Study of Some New 1,2,4-Triazino[5,6-b]indole Derivatives

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ABSTRACT

The Scheme of this work included the synthesis and characterization of new two series of 1,2,4-triazino[5,6-b] indole and 8-bromo-1,2,4-triazino[5,6-b] indole derivatives according to the starting material used. Both, derivatives of 3-thione-1,2,4-triazino[5,6-b] indole and 8-bromo-3-thione-1,2,4-triazino[5,6-b] indole (3a & 3b) were prepared by using Isatin and 5-bromo isatin as a starting material, the new schiff`s bases (5a & 5b) were synthesized by the reaction of hydrazino indole derivatives (4a & 4b) with aromatic aldehydes. Tetracyclic derivatives (7a & 7b) were prepared by the reaction of hydrazino derivatives (4a & 4b) with carbon disulfide in the presence of pyridine. Also 3-(N-phenyl thiocarbamoyl hydrazino)-1,2,4-triazino-[5,6-b] indole, and 8-bromo-3-(N phenyl thiocarbamoyl hydrazino)-1,2,4-triazino-[5,6-b] indole (6a & 6b) were prepared by the reaction of the compound (4a & 4b) with phenyl thio isocyanate in the presence of DMF. Finally, new Mannich bases (9a & 9b) were prepared by the reaction of the new acetylenic indole derivatives (8a & 8b) with paraformaldehyde and secondary amine in the presence of coprous chloride as catalyst.

These compounds were identified by their melting points and spectral data (IR & UV), and elemental analysis (C,H,N) and thin layer chromatography (TLC) were used.

Keywords: Isatin, 5-bromo isatin, synthesis, derivatives & characterization.

INTRODUCTION

Indole derivatives are widely present in the unit of biologically active nature of products, and are very important heterocycles in the structure of many medicines [1]. The indole ring system is one of the most important heterocyclic ring generated by the fusion of a benzene ring to the 2,3-positions of a pyrrole. Therefore, the chemistry of indole ring is dominated

by its very easy electrophilic substitution, the heterocyclic ring is very electron rich, by comparison with a benzene ring, so the attack by the
electrophiles always takes place in the pyrrole ring; the β-position is preferred to yield β-indole derivatives [2].

Also, indoles underwent the Mannich reaction and Vilsmeier-Haack reaction to produce 3-(dimethyl amino methyl) indole (gramine) which is the natural component of wheat and indole-3-carboaldehyde, respectively [2]. The most widely used synthesis of indole derivatives is Fischer synthesis or Bischler`s synthesis [2,3].
Isatine (2,3-indolindione) is a very useful derivative for the synthesis of indoles and other heterocycles; it readily undergoes aromatic substitution reactions at C-5 and ketonic reactions at C-3 carbonyl group [4]. Recently, there has been a great deal of interest in the synthesis of derivatives possessing various functional groups. This research is concerned with the development of synthetic methods of indole derivatives by different routes. These derivatives were characterized by spectroscopic method (IR, UV), and their elemental analysis (C,H,N) and TLC.

EXPERIMENTAL

Instrument and Chemical

Melting points were determined on an electrothermal melting point apparatus. IR spectra were recorded using KBr disc on a pye-Unicam Sp3-1000 spectrophotometer. The UV-visible absorption were determined in ethanol 95% using Hitachi U 2000 spectrophotometer. Elemental analysis (C,H,N) were performed on an elemental analysis system. Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram SilG and the plates were developed with iodine vapour.
Preparation of compound (5-bromoindoline-2,3-dione) (1b)

To a solution of p-bromoaniline, (17.3 g, .01 mol) in concentrated hydrochloric acid with water (55 : 60) were added to a mixture of chloral hydrate (18.19 g, 0.11 mol) and aqueous solution of sodium sulfate (250 g). Then aqueous solution of hydroxyl amine hydrochloride (22 g, 0.33 mol) in water (100 ml) was added. The resulting mixture was refluxed for half hour. The yellow precipitate was formed on cooling, 4-bromo isonitroso acetainilide was collected and recrystallized from chloroform m.p. 142 °C (ref. 143°C) [17a].

The addition of 4-bromoisonitroso acetanilide (12.2 g, 0.05 mol) to concentrated hydrochloric acid portion twice, the mixture was heated at 30-40 °C for half an hour with stirring. Then it was heated at 80 °C for 15 min. the resulting mixture was poured in a beaker containing ice-water (about 10 times the volume of solution). The orange precipitate was formed, filtered off and recrystallized from glacial acetic acid m.p. 196 °C (ref. 198 °C) [17b].

Preparation of compound 2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione) & (8-bromo-2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione) (3a,b) [18]

A mixture of compound (1a or 1b) (7.3 g or 11.3 g, 0.05 mol), thiosemicarbazide (5 g, 0.005 mol) and solution of potassium carbonate (10.2 g, 0.075mol) in water (200 ml) was refluxed for 7-12 hrs. After cooling, the salt was filtered off; the filtrate was acidified with

glacial acetic acid. Finally, the product (3a or 3b) was collected and recrystalized from ethanol. See Physical properties (Table 1) and spectral data (Table 3).

Preparation of compound 3-hydrazinyl-5H-[1,2,4]triazino[5,6-b]indole & (8-bromo-3-hydrazinyl-5H-[1,2,4]triazino[5,6-b]indole) (4a,b) [19]

A solution of compound (3a or b) (4.04 g or 5.62 g, 0.02 mol) and hydrazine hydrate (20-30 ml) was refluxed (on water bath) for 5-8 hrs. After cooling, the hydrazide derivative (4a or 4b precipitated, filtered off, washed with ethanol, dried and recrystallized from DMF. See physical properties (Table 1).

Preparation of compound 5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazinyl)methyl) derivatives & ((2-(8-bromo-5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazinyl)methyl) derivatives (5a,b)

To the hydrazide derivatives (4a or 4b) (0.2 g, 0.001 mol), a solution of an appropriate aldehyde (0.001 mol) in DMF (15 ml) was added. The resulting mixture was refluxed as shown the refluxed time (Table 1). After cooling the precipitate 5a,b (Schiff`s bases) was filtered off and recrystalized from appropriate solvent (Table 1).

Preparation of compound 3(-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N-phenyltriazino-1-carbothioamide & (3-(8-bromo-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N-phenyltriazino-1-carbothioamide) (6a,b) [20]

A mixture of compound (4a or b) (0.0025 mol) and phenyl isothiocyanate (0.0025 mol) in DMF (15 ml), was refluxed (Table 1 as shown the refluxing time). After cooling, the precipitate was filtered off and recrystalized from appropriate solvent (Table 1). Preparation of compound 2,3-dihydro-1-thioxo-1,2,4-triazolo[3,4-c]-1,2,4-triazino[5,6-b] indole & 8-bromo2,3-dihydro-1-thioxo-1,2,4-triazolo[3,4-c]-1,2,4-triazino[5,6-b] indole (7a,b)

To the solution of hydrazide compound (4a or b) (2.02 g or 2.819g, 0.01 mol) in dry pyridine (30 ml), carbon disulfide (5 ml) was added. The resulting mixture was refluxed for the time mentioned in (Table 1). After cooling, the benzene (30 ml) was added with several drops of hydrochloric acid and diluted with water (30 ml), filtered off, dried and recrystalized from appropriate solvent (Table 1)

Preparation of compound 3-(prop-2-ynylthio)-5H-[1,2,4]triazino[5,6-b]indole) & (8-bromo-3-(prop-2-ynylthio)-5H-[1,2,4]triazino[5,6-b]indole) (8a,b)

A solution of compound (3a or b) (2.02 g, 0r 2.81 g) (0.01 mole) and triethyl amine (1.1 g, 0.01 mol) was heated gently; then propargyl bromide (1.2 g, 0.01 mol) was added. The mixture was heated under reflux for the time mentioned in (Table 1). After cooling and diluting with water, the solid was filtered off, dried and recrystalized from appropriate solvent (Table 1).

Preparation of compound 8-bromo-3-(but-2-ynylthio)-5H-[1,2,4]triazino[5,6-b]indole amine derivatives) (9a,b) (Mannich Bases).

A solution of compound (8a or b) (0.0026 mol) and paraformaldehyde (0.0026 mol) in dioxane (15 ml) was heated gently, then cuprous chloride (0.5 g) and secondary amine (0.0026 mol) were added. The resulting mixture was refluxed with stirring (on water bath) for the time mentioned in (Table 1). After cooling, the salt was filtered off. The filtrate was

diluted with ice water (25 ml). The precipitate was filtered off and recrystalized (Table 1 physical properties).

RESULTS AND DISCUSSION

The indole derivatives have a wide spread interest due to their key role in medically important species such as those displaying antiestrogen [5], analygcsic [6], antimicrobial [7], antiallergy, neuroleptic [8], and in cancer chemotherapy [9].

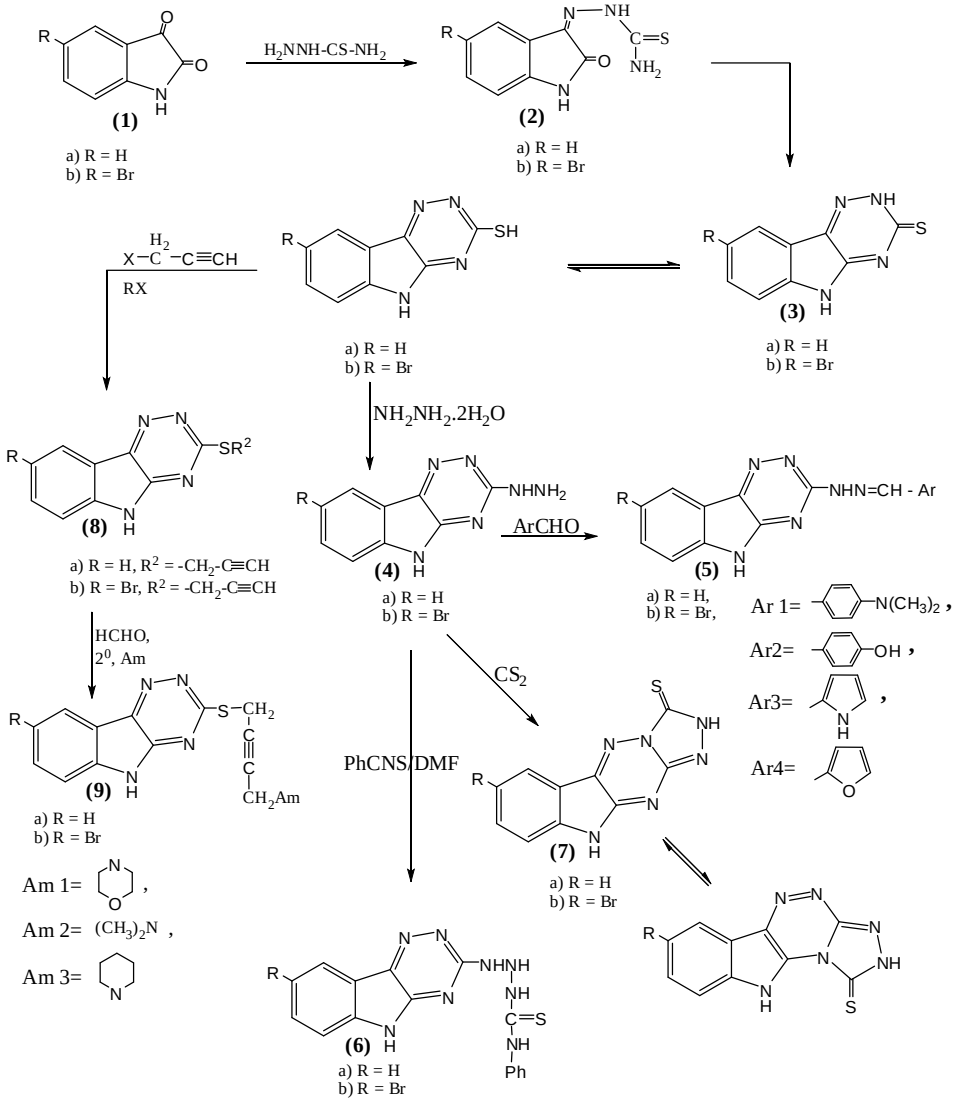
The synthesis and reaction of indoles have been a topic of research interests for over a century because a number of their derivatives occur in nature and the possess a variety of important biological activities [10]. Bromo indole alkaloids have been isolated as secondary metabolites of marine organism, which are promising sources of new biological active molecules [11], moreover, a bromo groups is a useful functional groups. In this paper, we have reported the synthesis of two series of 1,2,4-triazino[5,6-b] indole derivatives. Due to the importance of these compounds in organic chemistry research, the isatine (1a) and 5-bromo isatin (1b) were used as starting materials to prepare the two series of the derivatives. The reaction of (1a and 1b) with thiosemicarbazide in alkaline medium in the presence of potassium carbonate to give the corresponding thiosemicarbazone (2a and 2b) as a result of nucleophilic attack to the amino group of thiosemicarbazide to the β-carbonyl group in the (1a or 1b), followed, as it will undergo the internal cyclization in alkaline medium to give the corresponding 3-thione 1,2,4-triazino [5,6-b] indole derivatives (3a, 3b), which were in a tautomerism forms for thiol group (-SH to C=S), were isolated as yellow crystals as illustrated in scheme I; their structures were confirmed by physical properties (Table 1) and IR spectra (Table 3) showed the presence of C=N stretching absorption band at (1600 – 1630 cm^{-1}), S-H stretching absorption band at (2550 – 2600 cm^{-1}), C=S stretching absorption at (1050 – 1250 cm^{-1}) and disappearance of stretching absorption band of carbonyl group C=O at (1720 cm^{-1}), stretching band C-Br (600-750 cm^{-1}). Their UV spectrum showed λmax 371.5 nm (C=N, SH) (n $\rightarrow \pi^*$) and λmax 247.5 nm ($\pi \rightarrow \pi^*$) for aromatic ring [12].

Reaction of compounds (3a,b) with hydrazine hydrate in ethanolic solution, due to the high reactivity of the amino group towards nucleophilic attack to thiol group, is normally to obtain hydrazino derivatives (4a & 4b) [13].Their structure was identified by physical properties (table 1), and IR spectra showed stretching absorption band (3200-3400 cm^{-1}) for NH2 & NH and disappearance of stretching absorption band of SH.

Treatment of compound (4a & 4b) with equimolar of selected aldehydes aromatic or heterocyclic (p-dimethylamino benzaldehyde, p-hydroxy benzaldehyde, α-pyrrol carboxyaldehyde and α-furfural) afforded the corresponding Schiff`s basses (5a & 5b) and their structures were confirmed by their physical properties (table 1), spectral data (table 3) & elemental analysis (C,H,N) (Table 2). TLC in mixture of hexane-ethylacetate in ratio (3:1) shows that the reaction occurred.

The importance of synthesizing hydrazine and triazole derivatives due to their potential biological activity [14], reaction of compounds (4a & 4b) with carbon disulfide in alkaline medium caused cyclization by internucleophilic attack to give the corresponding triazole derivatives (7a & 7b), either cyclization occur at N2 or N4. However, the cyclization at N4 was preferred because it is planar (planarity) the aromatic system of indole (10 πe). The products were confirmed by physical properties (Table 1), elemental analysis (Table 2). IR

spectra showed a stretching absorption band at (1250 cm^{-1} C=S) but the absorption band of (NH_2) disappeared; and UV spectra (Table 3) and TLC also showed that the reaction occurred.



Scheme (1)

In an extension of the results, we have studied further improvement of the reactions. In this paper, we report that the reaction of hydrazino derivatives (4a & 4b) with phenyl thiocyanate in DMF as solvent by nucleophilic attack to give the corresponding compound

(6a & 6b). Their structures were confirmed by elemental analysis (C,H,N) (Table 2) spectral data (Table 3).

Due to the importance of synthesizing new acetylenic derivatives arising from their potential biological activity [15], as well as their industrial and medical applications, there are many acetylenic derivatives which are found in the composition of plants. They do have medical effects since they are easily absorbed by the body and have minimal toxic effects. On refluxing compounds (3a & 3b) with propargyl bromide in the presence of trimethyl amine, the compounds (8a & 8b) were produced. The structures which were identified by physical properties (Table -1-), spectra data (table -3-) showed the presence of $\equiv C-H$ stretching absorption band at (3200 cm^{-1}) and $-C\equiv C-$ stretching absorption at (2100 cm^{-1}) and disappearance of the stretching band of (2250-2600 cm^{-1}) due to the SH, elemental analysis (Table -2-) and TLC (mixture) hexane: ethyl acetate (3:1) showed the Rf values for starting material and product.

Consequently, the compounds (8a & 8b) which were heated under reflux with paraformaldehyde and different secondary amines (dimethyl amine, morphine, piperidine) in the presence of coprous chloride CuCl as catalyst to increase the nucleophilicity of acetylenic carbon atom in the presence of dioxane were used as solvent to give the corresponding Mannich base (9a & 9b) [16]. The structures were confirmed by physical properties (Table -1-) spectra data (Table -3-) showing the presence of CH2 stretching absorption band at (2850-2900 cm^{-1}) (C-N aliphatic) (1020-1255 cm^{-1}) and absence of the stretching band at (3200 cm^{-1}) due to $\equiv C-H$. See Elemental analysis (Table -2-) and TLC (hexane & ethyl acetate).

Table (1): Characterization data of prepared compounds

Com. No.	Yield % (m.p.0C)	Formula	Color	Crystallization solvent	Refl. Time
5a,Ar1	30% 303-305)	C18H17N7	Deep yellow	DMF/water	3 hrs
5a,Ar2	33% (308-310)	C16H12N6O	Green-yellowish	DMF/water	3 hrs
5a,Ar3	36% (280-282)	C14H11N7	Pale yellow	DMF/water	3 hrs
5a,Ar4	36% (293-295)	C14H10N6O	Green-Yellowish	DMF/water	3 hrs
5b,Ar1	34% (240-243)	C18H16N7Br	Deep Red	DMF/Water	5 hrs
5b,Ar2	36% (270-272)	C16H11N6OBr	Orange	DMF/Water	5 hrs
5b,Ar3	39% (250-252)	C14H10N7Br	Red	DMF/Water	5 hrs
5b,Ar4	39% (249-250)	C14H9N6OBr	Pale green	DMF/water	5 hrs
6a	36% (240-243)	C16H13N7S	Gray	DMF/Water	2 hrs
6b	41% (250-252)	C16H12N7SBr	Brown	Ethanol/Water	5 hrs
7a	44% (>300)	C10H5N6S	Deep red	DMF/Water	5 hrs
7b	43% (229-230)	C10H4N6SBr	Orange	DMF/Water	10 hrs

8a	79% (110-112)	C12H8N4S	Pale yellow	Ethanol	3-4 hrs
8b	66% (143-145)	C12H7N4SBr	Brown	DMF	6-7 hrs
9a,Am1	57% (90-92)	C17H17N5SO	Black	Ethanol	3 hrs
9a,Am2	43% (70-72)	C15H16N5S	Black	Ethanol	3 hrs
9a,Am3	40% (85-86)	C18H20N5S	Brown	Ethanol	3 hrs
9b,Am1	60% (198-200)	C17H16N5SOBr	Brown	Ethanol	5 hrs
9b,Am2	45% (78-80)	C15H15N5SBr	Brown	Ethanol	5 hrs
9b,Am3	40% (158-160)	C18H19N5SBr	Brown	Ethanol	5 hrs

Table (2): Elemental analysis of prepared compounds

Comp. No.	Elemental analysis C,H,N calculated (C,H,Nfound)		
	C	H	N
5a,Ar1	65.45 (65.15)	4.84 (4.28)	29.09 (29.15)
5b,Ar1	49.87 (49.57)	3.89 (3.59)	25.45 (25.09)
6a	57.31 (57.08)	3.88 (3.49)	29.25 (29.12)
6b	46.37 (46.20)	2.89 (2.60)	23.67 (23.27)
7a	49.79 (49.83)	2.07 (2.12)	34.8 (34.41)
7b	37.5 (37.0)	1.25 (1.05)	26.25 (26.15)
8a	60.0 (59.52)	3.33 (3.12)	23.3 (23.0)
8b	45.14 (45.14)	2.19 (2.09)	17.55 (17.05)
9aAm1	60.17 (60.40)	5.01 (5.22)	20.60 (20.16)
9aAm3	64.09 (64.15)	5.63 (5.50)	20.77 (20.52)
9bAm1	48.80 (48.35)	3.80 (3.50)	16.74 (16.34)
9bAm3	51.92 (51.72)	4.32 (4.12)	16.81 (16.51)

Table (3): The spectra data of the prepared compounds (IR & UV)

Comp. No.	IR spectra*							UV. Visible**
	ν =C-H	ν CH3	ν C=N arom.	ν -C-N	ν C=C arom.	=C-H out of plane	Others	λ max (nm) (ε max)
3a	3000-3100	-	1600-1630	-	1400-1600	690-950	C=S (1050-1250), SH (2550-2600), N=N (1450), NH (3200)	247.5 (632), 371.5 (1627)
3b	3000-3100	-	1630	-	1400-1600	690-950	C=S (1050-1250), N=N (1450), C-Br (600-700), SH (2550-2600)	244 (1533), 298.0 (1505), 372 (1297)
4a	3100	-	1630	-	1400-1470	-	NHNH2 (3200-3400)	322 (1449), 401 (2418)
4b	3080	-	1630	-	1400-1460	-	NHNH2 (3200)	344 (1364), 454 (2977)
5a1	3100	2900-2840	1630	1070-1030	1490-1450	755	NH (3200-3400)	231 (1184), 252 (1322), 300 (1457)
5a2	3070	-	1630	1070-1020	1490, 1400	830	NH (3400-3200) & OH (3600)	250 (1390), 298 (1430), 372 (661), 382 (659)
5a3	3060	-	1630	1050 1020	1490, 1450	840	NH (3200-3400)	250 (1165), 307 (1197), 372 (621)
5a4	3080	-	1600	1120, 1060	1590, 1500	870	NH (3400-3200)	248.5 (1554), 300 (1563), 373 (1588), 384 (1667)
5b1	3080-3040	2940 2830	1630	1260, 1060	1470, 1400	840	NH (3200), OH (3600), C-Br (600-750)	244 (1238), 307 (1427)
5b2	3100	-	1630	1070 1030	1600, 1460	750	NH (3200), OH (3600), C-Br (600-750)	234 (1066), 257 (1146), 301 (1480)
5b3	3100	-	1600	1520 1080	1500, 1450, 1400	700	NH (3200), C-Br (600-750)	205 (103), 231 (654), 303 (1394)
5b4	3080	-	1600	1100, 1030	1480, 1400	680	NH (3200), C-Br (600-750)	245 (1129), 295 (1373), 372 (716)
6a	3100	-	1620	1070, 1030	1490, 1450	755	C=S (1250), NH (3400-3200)	254 (541), 316 (883), 414 (199.8)
6b	3100	-	1630	1060-1020	1490-1440	740	C=S (1250), NH (3200), C-Br (600-700)	246 (1372), 300(1521), 312 (1508), 372 (1379)
7a	3100	-	1630	1080, 1030	1500, 1460, 1400	750	C=S (1250), NH (3200)	246 (1562), 301 (1552), 372 (1018), 467 (710)
7b	3080	-	1630	1020-1250	1600, 1400	760	C=S (1250)	264 (354), 306 (751)
8a	3000-3100	2900-2960	1630-1600	1070-1030	1640-1600	755	$-C\equiv CH$ (2100), NH (3200), CHbend (3200)	244 (1562), 300 (1519), 372 (1582)
8b	3070	2900-2840	1630	1060-1020	1490-1400	830	CHbend (3200), $-C\equiv CH$ (2100), C-Br (760)	244 (1463), 295 (1580), 303 (1575), 372 (1359)

9a1	3100-3040	2960-2800	1630	1240, 1070	1586-1450	830	C-O-C (1100), NH (3300)	208 (370), 244 (1464), 301 (1595), 389 (2311)
9a2	3090	2960-2800	1630	1170, 1080	1480, 1400	840	NH (3300)	
9a3	3080	2950, 2910 2840	1600	1240	1490, 1450, 1400	750-850	NH (3300)	244 (1450), 307 (1575), 319 (1544), 396 (2404)
9b1	3100	2900, 2800	1600	1210-1080	1480, 1400	770	C-O-C (1100-1120), NH (3300)	
9b2	3080	2820, 2700	1600	1100-1030	1480 1400	680	NH (3300)	
9b3	3100	2980 2940 2840	1630	1250, 1080	1500 1450	770	NH (3300)	208 (172), 242 (1315), 296 (1295).

* KBr disc, **conc. 10-3, solvent ethanol 95%.

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تحضير ودراسة طيفية لمشتقات جديدة من 4,2,1-ترايزينو[6,5-بي] اندول

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ملخص

يتضمن هذا البحث تحضير و والتعرف على سلسلتين جديتين من 4,2,1-ترايازينو[6,5-بي] اندول و 8-بروميد-4,2,1-ترايزينو[6,5-بي] اندول ومشتقاتها وفقا للمادة المتفاعلة المستعملة. تم تحضير كل من مشتق 3-ثيون-4,2,1-ترايزينو[6,5-بي] اندول و 8-بروميد-3-ثيون-4,2,1-ترايزينو[6,5-بي] اندول (a3 & b3) من الايساتين و 5-بروميد ايساتين. كما تم تحضير قواعد شيف (5b&5a) بتفاعل مشتقات هيدرازينو اندول (4b&4a) مع الالدهيدات الاروماتية. كذلك تم تحضير المشتقات رباعية الحلقة (7b&7a) بتفاعل مشتقات هيدرازينو اندول (4b&4a) مع ثاني كبريتيد الكربون في وجود البريدين. كما حضر 3-(ن-فينيل ثيوكارباموبل هيدرازينو) -4,2,1- ترايزينو[6,5-بي] اندول و8-بروميد-3-(ن-فينيل ثيوكارباموبل هيدرازينو) -4,2,1- ترايزينو[6,5-بي] اندول (6b&6a) من تفاعل المركبات (4b&4a) مع فينيل ايزوثيوسيانات في وجود ثنائي ميثيل فورمامايد (DMF). وفي الاخير تم تحضير قواعد مانيش (9b&9a) من تفاعل المشتقات الجديدة للاندول الاسيتيلينية مع بارافورمالدهيد وامين ثانوي في وجود كلوريد النحاسوز كحفاز. تم التعرف على هذه المركبات عن طريق قياس نقط الانصهار، واطياف الاشعة تحت الحمراء وفوق البنفسجية، والتحليل العنصري للكربون والهيدروجين والنيتروجين، كما تم استعمال طرق الفصل الكروماتوجرافي (TLC).