

SYNTHESIS OF TRIAZOLO (4,3-b) PYRIDAZINES

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Eight new triazolo (4,3-b) pyridazine derivatives were synthesized by fusing 3-chloro-6-(1,4,6-substituted pyridazines with isonicotinic acid hydrazide or by reaction of 3-hydrazino-6-(bromophenyl)/(p-tolyl)/phenyl)/4,6-/5,6-diphenyl pyridazine with carbon disulfide. The structure of all obtained compounds was confirmed by microanalyses and spectral data.



Heterocyclic compounds, particularly those with six or five-membered rings such as pyridazine and 1,2, 4- triazole, have occupied the first place among various classes of organic compounds due to their diverse biological systems¹.

Fusion of the pyridazine and triazole nucleus is of great importance in biological activity particularly concerning usefulness as hypotensive agents².

This paper describes two methods of synthesis of triazolo (4,3-b) pyridazine derivatives.

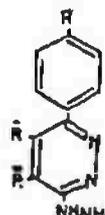
On fusion of 3-chloro- [(4,6-diphenyl / 6-(p-bromophenyl) / 6-(p-tolyl) / 5,6-diphenyl and 6-phenyl)] pyridazine 1, respectively, which were prepared according to Rao and Sattur 1979³ with isonicotinic acid hydrazide the corresponding triazolo- (4,3-b) pyridazine derivatives 3 were obtained.

The structure of these products was confirmed from their spectral data (see table 2), ir spectra of them revealed the absence of ν (C=O) and ν (NH, NH₂) and ν

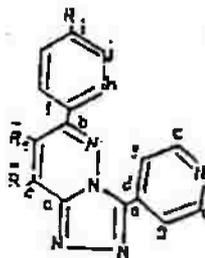
(C=N) stretching frequency appears at 1600-1640 cm^{-1} . The ¹Hnmr spectra of the products showed only multiple signals at 7.7-8.6 ppm which belong to the aromatic protons (compound 3c showed more single at 2.2 ppm belong, CH₃ protons), also ¹³C nmr spectra of 3e showed signals at Ca165.88, Cb 151.161, Cc 148.64, Cd142.19, Ce 133.25, Cf 131.24, Cg 129.58 Ch 127.68, Ci 123.70, Cj 123.07.



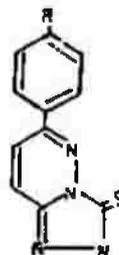
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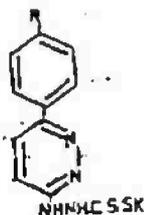
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On the other hand when the compound 2 was allowed to react with carbon disulfide and alcoholic potassium hydroxide, a cyclic product, namely 6-aryl-triazolo (4,3-b) pyridazine-3-thione 4 was obtained, via the cyclization of the intermediate 5 upon heating.



5

The ir and ^1H nmr spectra of 4 are in agreement with the proposed structure (see table 2). The ^1H nmr of these compounds showed only multiple signal at 6.7-8.7 ppm which belong the aromatic protons (except 4c showed more single at 6.22 ppm belong to CH_3 protons. The ν (NH) stretching frequency appears in the ir spectrum at 3340cm^{-1} and ν (C=S) at $1240\text{-}1290\text{cm}^{-1}$.

The microanalyses of products 3 and 4 were in satisfactory agreement (see table 1).

Table 1 : Analytical and Physical Data of the Products:

Comp. No.	R	R	R	Mol. Formula Mol. Weight	Yield %	M.p.	Solvent of Cryst.	Microanalysis		
								C	H	N
3a	H	H	Ph	$\text{C}_{22}\text{H}_{15}\text{N}_5$	86	>310	Ethanol	75.63	4.33	20.04
				349.4				75.57	4.28	20.01
3b	Br	H	H	$\text{C}_{16}\text{H}_{10}\text{BrN}_5$	90	>310	DMF	54.57	2.86	19.88
				352.2				54.70	2.86	19.93
3c	CH_3	H	H	$\text{C}_{17}\text{H}_{13}\text{N}_5$	90	209	Ethanol	71.02	4.56	24.37
				287.3				70.92	4.60	24.30
3d	H	Ph	H	$\text{C}_{22}\text{H}_{15}\text{N}_5$	89	305	DMF	75.63	4.33	20.04
				349.4				75.54	4.25	20.00
3e	H	H	H	$\text{C}_{16}\text{H}_{11}\text{N}_5$	55	300	DMF	70.32	4.06	25.63
				273.3				70.32	4.04	25.64
4b	Br	H	H	$\text{C}_{11}\text{H}_7\text{N}_4\text{S}_2\text{r}$	57	270	Methanol	43.01	2.30	18.24
				307.2				41.95	2.25	18.21
4c	CH_3	H	H	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{S}$	53	253	Methanol	59.49	4.16	23.12
				242.3				59.53	4.10	23.12
4d	H	H	H	$\text{C}_{11}\text{H}_8\text{N}_4\text{S}$	73	255	Methanol	57.88	3.53	24.54
				228.3				57.80	3.50	24.49

Table 2 . Spectral Data of Compounds 3 & 4

Comp. No.	IR (KBr) v(cm ⁻¹)	¹ H-NMR (DMSO/TMS) δ (ppm)
3a	str.C-H(3100),C=N(1600-1640)	8.3(m, 11H arom)
3b	str.C-H(3050),C=N(1600)	8.2-8.4 (m, 15H arom.)
3c	str.C-H(3050),C=N(1600)	2.2 (s,CH ₃), 7.5-8.0 (m, 10H arom)
3d	str.C-H(3090),C=N(1600-1640)	8.0-8.6 (m, 15H arom)
3e	str.C-H(3030),C=N(1600)	7.7-8.0 (m, 10H arom)
4b	str.C-H(3070) str.N-H (3150) C=N(1590-1610)	8.0-8.6 (6H, arom)
4c	str.C-H(3050),N-H(3130) C=N(1600)	2.2(s,CH ₃),8.0. (m, 6H arom)
4e	str.C-H(3090),NH(3150) C=N(1600-1620)	7.5-8.4 (m, 7H arom.)

Antimicrobial activity

The purified compounds 3 and 4 were screened for antimicrobial activity using cup-plate method⁴. The compounds were tested against a variety of bacteria and fungi; *Staphylococcus*, *Pseudomonas aerogenes*, *Escherichia Coli*, *Bacillus subtilis*, *Aspergillus niger*, *Penicillium sp* and *Micrococcus sp*.

From the experimental data, it was observed that all compounds showed good activity (inhibition zone 12-25-mm), except 3b and 3c were less active against *Pseudomonas aerogenes* and *Bacillus subtilis subtilis*, also 3e was less active against *Pseudomonas aerogenes*.

Experimental:

All melting points were recorded on an electrothermal melting point apparatus and are uncorrected. ¹H nmr spectra were recorded on EM-39090 NM NMR spectrometer, infrared spectra (KBr) on Beckman IR 4240.

3-Pyridyl-6-/4,6-/5,6-substituted-triazolo (4,3-b) pyridazines. (3a-e).

A mixture of 3-chloro-substituted pyridazine (1a-e) (0.01 mol.) isonicotinic acid hydrazide (0.01 mol) was heated in an oil-bath for 3h, at 170-180°C. Afterwards, the products 3a-e were recrystallized from proper solvents.

6-Substituted-triazolo (4,3-b) pyridazine-3-thiones.

1) To a solution of 3-chloro-substituted-pyridazine (1b,c,e) (0.01 mol) in absolute ethanol (30ml) hydrazine hydrate (0.01 mol) was added. The reaction mixture was refluxed for 4h. The products (2b,c,e) obtained were recrystallized from proper solvents.

2) 3ml of CS₂ was added dropwise to a solution of potassium hydroxide (0.012 mol) in absolute ethanol (100 ml) and (0.01 mol) of (2a,c,e) with stirring at room temperature. After the addition was complete, the mixture was heated in an oil-bath at 120°C for 6h. with continuous stirring. Precipitate filtered, dissolved in water and acidified with HCl then filtered, washed with water and recrystallized from proper solvent.

Acknowledgement:

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تخليق ترايازولو (٣ر٤ ب) بيوريازينات

العكثرة لجازي ابراهيم العفالق

طرس بقسم الكيمياء

كلية علوم النبات - الحمام

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