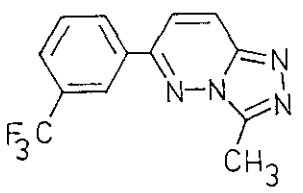
# SYNTHESIS OF NEW s-TRIAZOLO[4,3-b]PYRIDAZINES

Abdel Moneim El Massry and Adel Amer

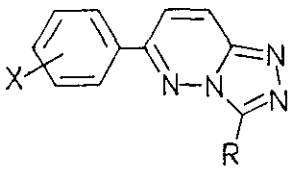
Department of Chemistry, Faculty of Science
Alexandria University, Alexandria, Egypt

Abstract— The 2,3-dihydropyridazin-3-ones **9** were synthesized via functionalized pyruvic acids **7** with hydrazine hydrate. Transformation of **9** to s-triazolo[4,3-b]pyridazines $10_{a-c}$ and $11_{a-c}$ has been achieved through the 3-chloropyridazines **4** by treatment with semicarbazide and phenylacetylhydrazine, respectively.

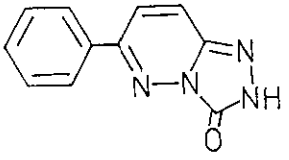
As part of a program in medicinal chemistry involved with the synthesis of novel heterocycles and their interaction with the benzodiazepine receptor complex, we noticed with interest several reports on triazolo[4,3-b]pyridazine derivatives such as 1[1] which has been a useful probe in labeling the benzodiazepine receptor in rat brain[2]. Some of these compounds **2** and **3** are also useful as anxiolytic agents[3] and antihypertensive[4,5]. These above reported findings promoted us to design a synthetic method to prepare s-triazolopyridazine ring system which contains substituents at C-6 and C-8 and to study their biological activity.



1



2

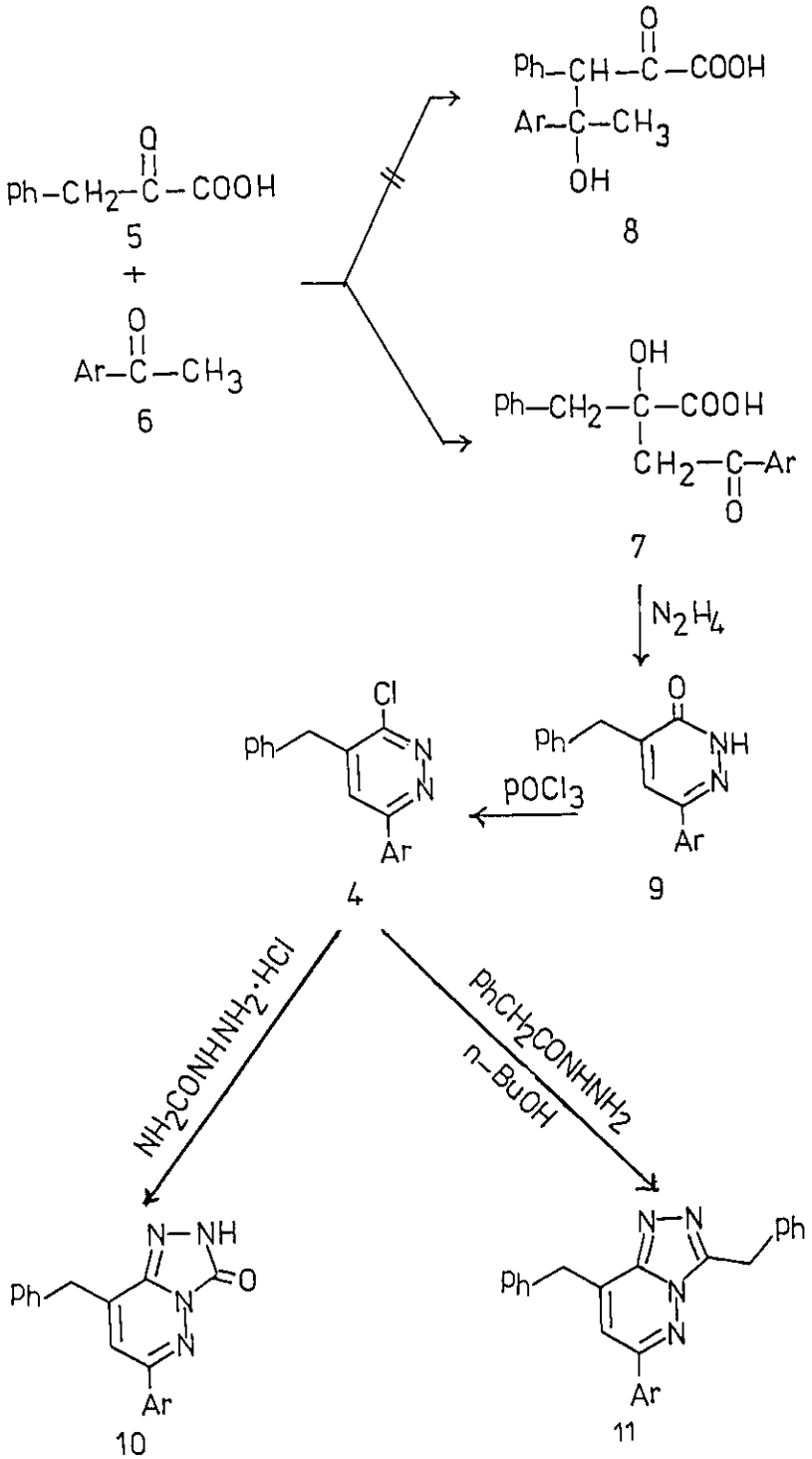


3

Our initial objective was an expeditious synthesis of substituted 3-chloropyridazines **4**, since 3-chloropyridazines react with semicarbazide or acylhydrazide to yield s-triazolo[4,3-b]pyridazin-3(2H)-*ones or* 3-*substituted* s-triazolo[4,3-b]pyridazines, respectively. A potential route to 6-aryl-4-benzyl-3-chloropyridazines **4** is acheived from phenylpyruvic acid **5**. Compounds **7** required for the present study were prepared by treatment of **5** with aryl methyl ketones **6** in aqueous ethanolic alkaline medium[6] at 0°C. Whereby colorless solids were obtained. On the basis of spectroscopic data, these products were confirmed to be compounds **7** rather than compounds **8**. Their $^1H$ nmr spectra (Table I) exhibited a characteristic two doublets in the region of $\delta$ 3.15-3.70 ppm of one proton intensity each, due to nonequivalent methylene protons adjacent to carbonyl group and the methylene protons adjacent to phenyl group caused a singlet of two proton intensity in the region of $\delta$ 2.80-3.03 ppm. Compounds **7** are existing in the open form in the solid state. Thus, absorptions in the regions 1670-1685, 1710-1745 and 3480-3500 $cm^{-1}$ in their infrared spectra indicated the presence of carbonyl, carboxyl and hydroxyl groups, respectively. When compounds **7** were refluxed with hydrazine hydrate in ethanol for three hours, coloress products were obtained whose elemental analysis indicated the loss of three molecules of water during the condensation process. Based on the spectroscopic data their structure were confirmed to be 6-aryl-4-benzyl-2,3-dihydropyridazin-3-ones **9** (Table II). The pyridazinones **9** were converted to the chloropyridazines **4** by treatment with phosphoryl chloride (Table III).

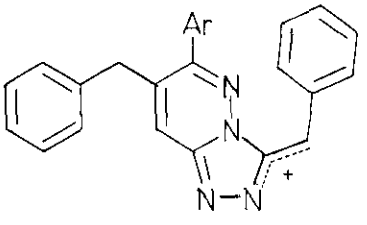
Treatment of compounds **4** with semicarbazide hydrochloride in boiling ethanol containing a small amount of mineral acid gave 6-aryl-8-benzyl-2,3-dihydro-s-triazolo[4,3-b]pyridazin-3-ones **10** in good yields (Table IV). However, it was claimed earlier[7] that the presence of an electron attracting group at the 6-position of 3-chloropyridazine was necessary for such cyclization reaction to take place.

The structures of compounds $\mathbf{10_{a-c}}$ were supported by ir, $^1H$ nmr and ms spectroscopy as well as elemental analysis. The ir spectra of $\mathbf{10_{a-c}}$ showed bands in the regions of 1700-1735 $cm^{-1}$ (CO) and 3000-3100 $cm^{-1}$ (NH). Their $^1H$ nmr spectra in dimethyl sulfoxide-$d_6$ solution (Table IV) showed only one exchangeable singlet in the region of $\delta$ 12.58-12.76 ppm (1H,NH) in addition to the methylene


Ph–CH2–C(=O)–COOH
5
+
Ar–C(=O)–CH3
6
Ph–CH(–C(=O)–COOH)–Ar–C(OH)–CH3
8
Ph–CH2–C(OH)(–CH2–C(=O)–Ar)–COOH
7
N2H4
Cl
Ph
N
N
Ar
4
POCl3
O
NH
9
NH2CONHNH2·HCl
PhCH2CONHNH2
n-BuOH
N–NH
O
10
N–N
11

and aromatic protons signals. Only a small number of intense fragment ions were observed in the mass spectra of all type **10** compounds. It was found that the molecular ion of $\mathbf{10_{a-c}}$ at m/z 302, 316 and 332 was the prominent ones (base peaks), this suggests a high stability of the dihydro-s-triazolo[4,3-b]-pyridazin-3-one ring.

Similarly, the condensation of $\mathbf{4_{a-c}}$ with phenylacetylhydrazine in butanol produced 6-aryl-3,8-dibenzyl-s-triazolo[4,3-b]pyradizines $\mathbf{11_{a-c}}$. The structure assignments of 11 were based on nmr, ir, and ms data (see Table V). The $^1$H nmr spectra of $\mathbf{11_{ac}}$ in deuteriochloroform showed a fine doublet at $\delta$ 4.43 of the methylene protons attached to **C-8** which is attributed to the allylic coupling with the proton at **C-7** of the triazolopyridazine ring. The ms spectra of $\mathbf{11_{a-c}}$ showed intense $[M]^+$ and $[M-1]^+$. Since the H radical is probably the most unfavourable leaving group in any fragmentation, the high intensity of the $[M-H]^+$ peak (the base peak in case of $\mathbf{11_b}$ and $\mathbf{11_c}$) indicated efficient stabilization of the resulting ion I.




I

Results of pharmacological screenings will be reported elsewhere.

**EXPERIMENTAL**

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Analytical tlc was performed using the ascending technique with EM silica gel 60 $F_{254}$ precoated on plastic sheets. Ir spectra were obtained on a Perkin Elmer model 599 spectrophotometer and were calibrated against the 1601 $cm^{-1}$ band of polystyrene. $^1$H Nmr spectra were obtained on an IBM NR-80 or varian EM-390 spectrometer. Chemical shifts are expressed in $\delta$ scale relative to tetramethylsilane as internal standard. A Hewlett-Packard 5995 gas chromatograph/mass spectrometer was used to record ms data at 70 ev. Elemental analyses were performed at Alexandria University, Faculty of Science Central Laboratory.

**2-Hydroxy-3-phenyl-2-(substituted phenacyl)propanoic acids $7_{a-c}$. General procedure.**

To a solution of 5 (3.28 g, 20 mmol) and **6** (20 mmol) in ethanol (15 ml) was added a solution of potassium hydroxide (2.24 g, 40 mmol) in water (15 ml) and the reaction mixture was kept at 0°C for three days. The mixture was then acidified with concentrated hydrochloric acid and the product which solidified[8] after two days was collected by filtration and crystallized from appropriate solvent. Yields and physical properties are summarized in Table I.

**6-Aryl-4-benzyl-2,3-dihydropyridazine-3-ones $9_{a-c}$. General procedure.**

A solution of **7** (1.7 mmol) in ethanol (10 ml) was refluxed with 99% hydrazine hydrate (1 ml) on a water-bath for three hours. The product which separated out on concentration was collected by filtration, dried, and crystallized from appropriate solvent. Yields and physical properties are summarized in Table II.

**6-Aryl-4-benzyl-3-chloropyridazines $4_{a-c}$. General procedure.**

A mixture of **9** (15 mmol) and phosphoryl chloride (49.35 g, 30 ml) was refluxed for two hours, cooled and cautiously poured into crushed ice. The mixture was neutralized with saturated solution of $NaHCO_3$ and the resulting precipitates were collected by filtration, washed with water, dried, and crystallized from ethanol. Yields and physical properties are summarized in Table III.

**6-Aryl-8-benzyl-2,3-dihydro-s-triazolo[4,3-b]pyridazin-3-ones $10_{a-c}$. General procedure.**

A mixture of **4** (3.6 mmol), semicarbazide hydrochloride (0.40 g, 3.6 mmol) and 75% ethanol (50 ml) in presence of several drops of hydrochloric acid was heated to boiling for eighteen hours. The yellow precipitates which were separated out after concentration and cooling were collected by filtration, dried, and crystallizd from appropriate solvent. Yields and physical properties are summarized in Table IV.

**6-Aryl-3,8-dibenzyl-s-triazolo[4,3-b]pyridazines $11_{a-c}$. General procedure.**

A mixture of **4** (4.0 mmol), phenylacetylhydrazine (0.60 g, 4.0 mmol) in butanol (10 ml) was refluxed for eight hours. Butanol was removed by distillation under reduced pressure, and the residue was treated with water. The solid products

were collected by filtration, dried, and crystallized from appropriate solvent. Yields and physical properties are summarized in Table V.

**Table I**

| Compound No. | Ar | Yield % | Mp °C (a) | Molecular Formula | Analyses Calcd&Found C | H | Ir($cm^{-1}$) CO | COO (KBr) | OH | $^1$H-Nmr (δ) ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|---|
| 7a | $C_6H_5$ | 46.8 | 142-144° $CCl_4$/Pet ether | $C_{17}H_{16}O_4$ | 71.82<br>71.60 | 5.67<br>5.70 | 1680 | 1730 | 3490 | 3.02(s,2H,$CH_2$-ph),3.30, 3.70(2d, J=16Hz,2H, $CH_2$-CO),7.28,7.78 (2m,10H,Aromatic H). |
| 7b | P-$CH_3C_6H_4$ | 40.3 | 145-147 EtOH | $C_{18}H_{18}O_4$ | 72.47<br>72.80 | 6.08<br>6.20 | 1670 | 1710 | 3480 | 2.70(s, 3H,$CH_3$),2.80 (s, 2H,$CH_2$-ph),3.15,3.55, (2d, J=18Hz,2H,$CH_2$CO), 6.98,7.53 (2m, 9H, Aromatic H) |
| 7c | P-$CH_3OC_6H_4$ | 27.5 | 166-167 $C_6H_6$ | $C_{18}H_{18}O_5$ | 68.78<br>68.50 | 5.77<br>6.80 | 1685 | 1745 | 3500 | 3.03(s, 2H,$CH_2$ph),3.16 3.66(2d,J=18Hz,2H $CH_2$CO),3.80(s,3H,$OCH_3$), 6.80,7.02,7.75(d,J=9Hz, m,d,J=9Hz,9H,Aromatic H). |

(a) solvent of crystallization

**Table II**

| Compound No. | Ar | Yield % | Mp °C (a) | Molecular Formula | Analyses Calcd&Found C | H | N | Ir($cm^{-1}$) CON (KBr) | $^1$H-Nmr (δ) ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|
| 9a | $C_6H_5$ | 70.9 | 179-181 EtOH | $C_{17}H_{14}N_2O$ | 77.84<br>77.40 | 5.38<br>5.70 | 10.68<br>10.70 | 1635 | 3.96(s, 2H,$CH_2$),7.45, 7.75(2m,11H,Aromatic H,=CH) 12.32(s,1H,NH is deuterium oxide exchangeable) |
| 9b | P-$CH_3C_6H_4$ | 70.9 | 216-218 EtOH | $C_{18}H_{16}N_2O$ | 78.23<br>77.90 | 5.84<br>6.10 | 10.14<br>10.30 | 1655 | 2.37(s,3H,$CH_3$),3.97 (s,2H,$CH_2$),7.18,7.51 (m,d,J=9Hz,10H,Aromatic H,=CH), 12.05(s,1H,NH is deuterium oxide exchangeable). |
| 9c | P-$CH_3OC_6H_4$ | 82.1 | 201-203 $C_6H_6$ | $C_{18}H_{16}N_2O_2$ | 73.95<br>73.80 | 5.52<br>5.50 | 9.59<br>9.60 | 1650 | 3.78(s,3H,$OCH_3$),3.94 (s,2H,$CH_2$),6.87,7.24, 7.55(d,J=9Hz,m,d,J=9Hz, 10H,Aromatic H,=CH), 11.31(s,1H,NH is deuterium oxide exchangeable). |

(a) solvent of crystallization

**Table III**

| Compound No. | Ar | Yield % | Mp °C | Molecular Formula | Analyses Calcd&Found C | H | N | $^1$H-Nmr (δ) ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|
| 4a | $C_6H_5$ | 87.2 | 114-116 | $C_{17}H_{13}ClN_2$ | 72.73<br>72.40 | 4.67<br>5.00 | 9.98<br>10.20 | 4.10(s,2H,$CH_2$),7.23,7.87 (2m,11H,Aromatic H,=CH). |
| 4b | P-$CH_3C_6H_4$ | 96.6 | 113-115 | $C_{18}H_{15}ClN_2$ | 73.34<br>73.10 | 5.13<br>6.30 | 9.51<br>9.30 | 2.47(s,3H,$CH_3$),4.14 (s,2H,$CH_2$),7.30,7.83 (m,d,J=9Hz,10H,Aromatic H,=CH). |
| 4c | P-$CH_3OC_6H_4$ | 95.4 | 133-135 | $C_{18}H_{15}ClN_2O$ | 69.56<br>69.90 | 4.87<br>5.20 | 9.02<br>9.20 | 3.82(s,3H,$OCH_3$),4.08 (s,2H,$CH_2$),6.90,7.20, 7.83(d,J=9Hz,m,d,J=9Hz, 10H,Aromatic H,=CH). |

**Table IV**

| Compound No. | Ar | Yield % | Mp °C (a) | Molecular Formula | Analyses Calcd&Found C | H | N | Ir($cm^{-1}$) CO | NH (KBr) | 1H-Nmr (δ) (DMSO -$d_6$) | Ms (m/z) (Relative intensity) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10a | $C_6H_5$ | 55.2 | 230-231 EtOH | $C_{18}H_{14}N_4O$ | 71.51<br>71.60 | 4.67<br>4.50 | 18.53<br>18.20 | 1735 | 3100 | 4.13(s, 2H,$CH_2$-Ph), 7.43,7.98(2m, 11H, Aromatic H,=CH), 12.76 (s,1H,NH). | 302 (100)<br>230 (14) | 301 (17)<br>115 (11) | 245 (14)<br>91 (10) |
| 10b | P-$CH_3C_6H_4$ | 65.2 | 251-252 MeOH | $C_{19}H_{16}N_4O$ | 72.13<br>72.50 | 5.10<br>4.80 | 17.71<br>17.40 | 1720 | 3100 | 2.37(s,3H,$CH_3$),4.11 (s,2H,$CH_2$-Ph),7.31, 7.68(m,d,J=9Hz,10H, Aromatic H,=CH),12.71 (s,1H, NH). | 316 (100)<br>259 (7) | 315 (15)<br>115 (5) | 244 (5)<br>91 (7) |
| 10c | P-$CH_3OC_6H_4$ | 75.3 | 225-226 EtOH | $C_{19}H_{16}N_4O_2$ | 68.66<br>68.40 | 4.85<br>4.40 | 16.86<br>16.50 | 1700 | 3000 | 3.84(s,3H,$OCH_3$), 4.12 (s,2H,$CH_2$-Ph),6.97, 7.28,7.86(d,J=9Hz,m,d, J=9Hz,10H,Aromatic H, =CH), 12.58 (s,1H,NH). | 332 (100)<br>115 (2) | 331 (12)<br>91 (2) | 275 (6) |

(a) solvent of crystallization

**Table V**

| Compound No. | Ar | Yield % | Mp °C (a) | Molecular Formula | Analyses Calcd&Found C | H | N | $^1$H-Nmr (δ) ($CDCl_3$) | Ms (m/z) (Relative intensity) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11a | $C_6H_5$ | 75.2 | 179-181 EtOH | $C_{25}H_{20}N_4$ | 79.76<br>79.70 | 5.36<br>5.30 | 14.88<br>14.90 | 4.45(d,J=0.4Hz,2H,$CH_2$-Ph), 4.62(s,2H,$CH_2$-C=N), 7.47(m,16H,Aromatic H,=CH) | 376 (35)<br>91 (16) | 375 (35)<br>83 (100) | 273 (16)<br>77 (15) |

**Table V (continued)**

| Compound No. | Ar | Yield % | Mp °C (a) | Molecular Formula | Analyses Calcd&Found C | H | N | $^1$H-Nmr (δ) ($CDCl_3$) | Ms (m/z) (Relative intensity) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11b | P-$CH_3C_6H_4$ | 67.9 | 147-149 MeOH | $C_{26}H_{22}N_4$ | 79.97<br>79.80 | 5.68<br>5.30 | 14.35<br>14.00 | 2.40(s,3H,$CH_3$),<br>4.43(d,J=0.4Hz,2H,$CH_2$-Ph),4.61<br>(s,2H,$CH_2$-C=N),7.40(m,<br>15H,Aromatic H,=CH), | 390 (91)<br>274 (10)<br>116 (21) | 389 (100)<br>273 (50)<br>115 (23) | 299 (24)<br>272 (20)<br>91 (50) |
| 11c | P-$CH_3OC_6H_4$ | 82.1 | 150-152 EtOH | $C_{26}H_{22}N_4O$ | 76.82<br>76.80 | 5.46<br>5.50 | 13.79<br>13.80 | 3.85(s,3H,$OCH_3$),4.44<br>(d,J=0.4Hz,2H,$CH_2$-Ph),4.62<br>(s,2H,$CH_2$-C=N),7.38<br>(m,15H,Aromatic H,=CH). | 406 (88)<br>273 (57)<br>140 (11) | 405 (100)<br>272 (16)<br>91 (31) | 299 (17)<br>141 (11) |

(a) solvent of crystallization

**ACKNOWLEDGEMENT**

The authors are indebted to Prof. G.H. Labib for his encouragement. They also thank Professor Hans Zimmer (Department of Chemistry, University of Cincinnati, USA) for the mass spectra of compounds $10_{a-c}$ and $11_{a-c}$.

**REFERENCES AND NOTES**

1. J.D. Albright, D.B. Moran, W.B. Wright, Jr., J.B. Collins, B. Bear, A.S. Lhppa, and E.N. Greenblatt, J. Med. Chem., 1981, 24, 592.

1. H.I. Yamamura, T. Mimaki, S.H. Yamamura, W.D. Horst, M. Morelli, G. Bantz, and R.A.O. Brien, Eur. J. Pharm., 1982, 77, 351.

3. D.B. Moran, J.P. Dusza, and J.D. Albright, US Patent 4, 260, 765 (1981) (Chem. Abst., 1973, 78, 43468m).

4. G. Szilagyi, E. Kasztreiner, P. Matyus, and K. Czako, Synth. Commun., 1981, 11, 835.

5. J. Kosary, E. Kasztreiner, A. Lazar, and M. Soti, Acta Pharm. Hung., 1982, 52, 217.

6. P. Cordier, Ann. Pharm. Fr., 1964, 22, 229.

7. P. Francavilla and F. Lanria, J. Heterocyclic Chem., 1971, 8, 415.

8. $7_c$ was left at room temperature for 4 days and the oily product produced after acidification was triturated with benzene to give colourless crystals.

Received, 8th May, 1989