Construction of Some Pyridazine Derivatives and their Annelated Ring Systems from Keto Acids

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Abstract

2-Hydroxy-4-(4-methoxyphenyl)-2-(4-substituted phenacyl)butanoic acids **1** have been prepared from reaction of 4-methoxybenzylpyruvic acid with aryl methyl ketones. A new series of 2,3-dihydropyridazin-3-ones **2** were synthesized *via* condensation of **1** with hydrazine.The 1,2,4-triazolo[4,3-b]pyridazinones **4** and tetrazolo[1,5-b]pyridazines **6** were obtained from the 3-chloropyridazines **3** by treatment with semicarbazide and sodium azide, respectively. Attempted synthesis of 3-alloxypyridazines **7** by reacting **3** with sodium alloxide led instead to the N-allyl isomer **8** through Claisen rearrangement of **7**. The structural assignments for the new compounds were based on their elemental analysis and spectroscopic data.

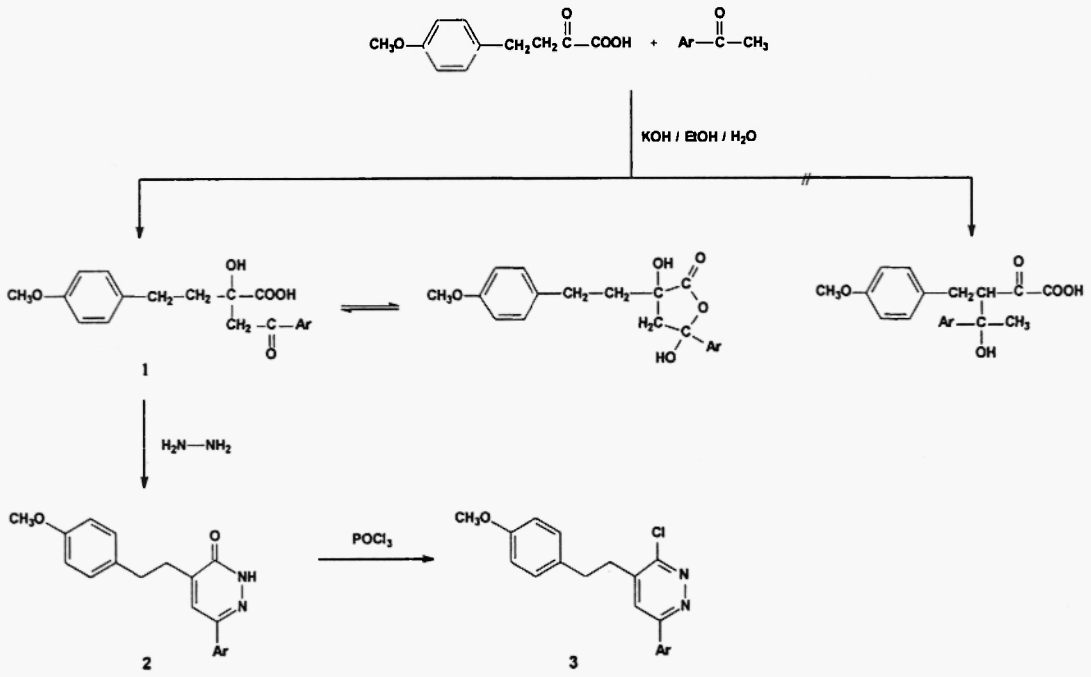
Introduction

The biological activities associated with the pyridazine ring derivatives (1-8) and its fused ring systems with phenylene and heterocyclic rings (9-14) attracted the attention towards the developing of synthetic approaches for their construction (2,3,16-19). Continuing our work on the role of keto acids and their functionalized analogues as precursors for the construction of heterocyclic compounds (15-22), the synthesis of some pyridazine derivatives and their conversion into triazolo- and tetrazolo-heterocycles is the subject of the present work.

Results and Discussion

The 4-methoxybenzylpyruvic acid was used as a precursor in this study for the synthesis of the target heterocycles. Thus its reaction with aryl methyl ketone in aqueous ethanolic alkaline medium at 0 °C led to the formation of **1**. Their structures were based on our previous studies (18,19, 23) and confirmed by studying their ^{1}H NMR spectra which indicated the absence of a resonance which can be due to a methyl group. Such data

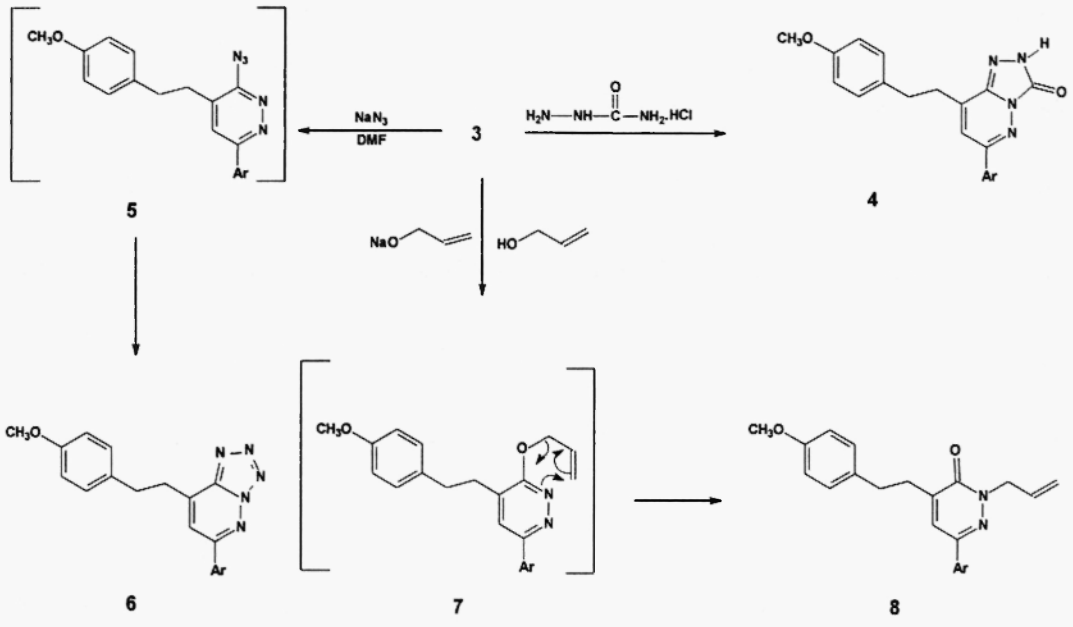
confirmed that a carbanion has been generated from the aryl methyl ketone which attacks 4-methoxybenzylpyruvic acid to give the 4-keto acid **1** and rules out the formation of a carbanion from the 4-methoxybenzylpyruvic acid which should then give a 2-keto acid. Compounds **1** may exist in equilibrium with the respective hemiacetals but this did not effect its efficiency towards the reaction with hydrazine.Thus, reaction of **1** with hydrazine hydrate in methanol gave the expected pyridazin-3-ones **2**. Transformation of **2** to their corresponding 3-chloropyridazines **3** could be achieved smoothly upon treatment with phosphoryl chloride. Nucleophilic substitution of the chlorine atom at position-3 with N-1 of semicarbazide was found to take place with subsequent ring closure to give the 1,2,4-triazolo[4,3-b]pyridazines **4** in a high yield. Reaction of **3** with sodium azide in N,N-dimethyl formamide led to the formation of tetrazolo[1,5-b]pyridazines **6** which is a result of the cyclization of the theoretically anticipated azido derivatives **5**. The structure of **6** was based on the IR spectroscopy which is lacking a band at 2200 cm^{-1} that should appear for azido groups in compounds **5**.



a, Ar = C_6H_5 ; b, Ar = $CH_3C_6H_4$; c, Ar = $CH_3OC_6H_4$

Treatment of **3** with sodium alloxide in allyl alcohol afforded a colorless product in each case. Their infrared spectra showed a band in the region 1649-1652 cm^{-1} which indicated that the product should be formulated as **8** rather than **7**. The formation of the N-allyl

compounds **8** may be explained to be due to a Claisen rearrangement of the presumably formed 3-alloxypyridazines **7**.



a, Ar = C_6H_5 ; b, Ar = $CH_3C_6H_4$; c, Ar = $CH_3OC_6H_4$

Table I. 1H-NMR data

Compound No	Ar	^{1}H-NMR (δ)
2a	C_6H_5	2.95 (s, 4H, $2CH_2$), 3.78(s, 3H, OCH_3), 7.25 (m, 10H, Ar-H, HC=), 11.12 (bs, 1H, NH).
2b	4-$CH_3C_6H_4$	2.34 (s, 3H, CH_3), 2.83 (s, 4H, $2CH_2$), 3.70 (s, 3H, OCH_3), 6.84, 7.21, 7.70(d, 2d(overlapped), d & s (overlapped), 9H, Ar-H, HC=), 13.01 (s, 1H, NH).
3a	C_6H_5	2.96 (s, 4H, $2CH_2$), 3.73 (s, 3H, OCH_3), 7.00, 7.39, 7.84 (d, mm, 10H, Ar-H, HC=).
3b	4-$CH_3C_6H_4$	2.72 (s, 3H, CH_3), 2.96 (s, 4H, $2CH_2$), 3.68 (s, 3H, OCH_3), 6.81, 7.15, 7.35, 7.98, 8.12 (d, d, d, d, s, 9H, Ar-H, HC=).
4a	C_6H_5	2.84 (s, 4H, $2CH_2$), 3.71(s, 3H, OCH_3), 6.84, 7.17, 7.45, 7.79,7.82(d, d, t, d, s, 10H, Ar-H, HC=), 11.12 (s, 1H, NH).
4b	4-$CH_3C_6H_4$	2.42 (s, 3H, CH_3), 3.09 (s, 4H, $2CH_2$), 3.77(s, 3H, OCH_3), 6.84, 7.14, 7.49, 7.80 (s, d, s, d, 9H, Ar-H, HC=), 12.00 (s, 1H, NH).
4c	4-$CH_3OC_6H_4$	2.93 (s, 4H, $2CH_2$), 3.68, 3.80 (2s, 2x3H, 2 OCH_3), 6.81, 7.10, 8.05 (d, t, t, 9 H, Ar-H, HC=), 12.00 (bs, ~ 1H, NH)
6b	4-$CH_3C_6H_4$	2.35 (s, 3H, CH_3), 3.35 (s, 4H, $2CH_2$), 3.63 (s, 3H, OCH_3), 6.72, 7.09, 7.28 , 7.80, 8.02 (d, d, d, d, s, 9H, Ar-H, HC=).

Table II. Yields and Physical Properties.

Compound No.	Ar	Yield %	M.P °C	Molecular Formula	Analysis (%) Calcd./Found C H N	IR ν(cm^{-1})
2a	C_6H_5	70	174 -176	$C_{19}H_{18}N_2O_2$	74.49 5.92 9.15 74.50 5.50 9.20	3380 ,1663
2b	4-$CH_3C_6H_4$	74	174 –175	$C_{20}H_{20}N_2O_2$	74.97 6.29 8.74 75.00 6.40 8.70	3132 ,1653
2c	4-$CH_3OC_6H_4$	93	179-180	$C_{20}H_{20}N_2O_3$	71.41 5.99 8.33 71.20 5.98 8.00	3133 ,1650
3a	C_6H_5	71	84-85	$C_{19}H_{17}ClN_2O$	70.26 5.28 8.63 70.10 5.30 8.42	1612
3b	4-$CH_3C_6H_4$	77	119-120	$C_{20}H_{19}ClN_2O$	70.89 5.65 8.26 71.00 5.70 8.51	1612
3c	4-$CH_3OC_6H_4$	68	87	$C_{20}H_{19}ClN_2O_2$	67.70 5.40 7.90 68.00 5.32 8.00	1609
4a	C_6H_5	81	185	$C_{20}H_{18}N_4O_2$	69.35 5.24 16.18 69.21 5.20 16.10	3129 ,1656
4b	4-$CH_3C_6H_4$	71	180-182	$C_{21}H_{20}N_4O_2$	69.98 5.59 15.55 69.63 5.33 15.05	3131 ,1653
4c	4-$CH_3OC_6H_4$	75	166	$C_{21}H_{20}N_4O_3$	67.01 5.36 14.89 66.90 5.44 14.92	3133 ,1653
6a	C_6H_5	69	90	$C_{19}H_{17}N_5O$	68.86 5.17 21.16 69.00 5.30 21.50	1610
6b	4-$CH_3C_6H_4$	63	130	$C_{20}H_{19}N_5O$	69.54 5.54 20.28 69.72 5.60 20.44	1605
6c	4-$CH_3OC_6H_4$	68	160	$C_{20}H_{19}N_5O_2$	66.47 5.30 19.38 66.61 5.30 19.41	1611

Experimental

Melting points were determined with a Mel-Temp apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC-250 and/or Varian EM-390 spectrometers. Chemical shifts are expressed in δ scale in part per million relative to tetramethylsilane as internal standard. Tlc was performed using the ascending technique with EM silica gel 60 F_{254} precoated on plastic sheets. The IR spectra were obtained with Unicam SP 1025

spectrometer. A Hewlett-Packard 5995 Gas chromatograph/Mass spectrometer was used to record Mass spectral data at 70ev. Elemental analyses were performed in the Chemistry Department, Faculty of Science, Cairo and Mansoura Universities.

2-Hydroxy-4-(4-methoxyphenyl)-2-(substituted phenacyl)butanoic acid (1).

General procedure.

A solution of 4-methoxybenzylpyruvic acid (2.00 g, 9.61 mmol) and aryl methyl ketone (9,61 mmol) in ethanol (7 ml) was treated with a solution of potassium hydroxide (1.07 g, 19.22 mmol) in water (4 ml). The reaction mixture was kept for 4 days at 0 °C. It was acidified with cold concentrated hydrochloric acid to give a sticky product, which was washed with water and dried.The products were crystallized from ethanol-water as colorless crystals.

2-Hydroxy-4-(4-methoxyphenyl)-2-phenacylbutanoic acid (1a).

This compound was obtained in 35% yield (1.11 g); mp 113-114 °C; ^{1}H NMR (90 MHz-DMSO-d_6): δ 1.93 (t, 2H, CH_2), 2.58 (m, 2H, CH_2), 3.48 (s, 2H, CH_2CO), 3.69 (s, 3H, OCH_3), 4.43 (s, ~1H, OH), 6.79, 7.06, 7.50, 7.93(d, d, pseudo-t, d, ~10H, Ar-H); IR(KBr): 3469, 1730, 1687 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 70.00; H, 5.90.

2-Hydroxy-4-(4-methoxyphenyl)-2-(4-methylphenacyl)butanoic acid (1b).

This compound was obtained in 43% yield (1.41 g); mp 94-95 °C;^{1}H NMR (90MHz, DMSO-d_6) : δ 2.03 (m, 4H, $2CH_2$), 2.31 (s, 3H, CH_3), 3.41 (d, 2H, CH_2CO), 3.67 (s, 3H, OCH_3), 5.06 (s, ~1H, OH), 6.64, 7.03, 7.68 (d, 2d overlapped, d, 9H, Ar-H); IR(KBr): 3526, 1713, 1681 cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}O_5$: C,70.16 ; H, 6.48. Found: C, 70.00; H, 6.26.

2-Hydroxy-2-(4-methoxyphenacyl)-4-(4-methoxyphenyl)butanoic acid (1c).

This compound was obtained in 51% yield (1.77 g); mp 156-158 °C; IR(KBr): 3436, 1730, 1693 cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C,66.89, H, 5.90.

6-Aryl-4-[2-(4-methoxyphenyl)ethyl]-2,3-dihydropyridazin-3-one (2).

General Procedure.

A mixture of 2-hydroxy-4-(4-methoxyphenyl)-2-(substituted phenacyl)butanoic acid (11.0 mmol) in ethanol (14 ml), hydrazine hydrate (3 ml) and few drops of glacial acetic acid, was heated under reflux for 3 hours and then left to cool. The colorless precipitate that separated out was filtered off, washed with ethanol and dried. Yields and physical properties are summarized in Table I and II.

6-Aryl-3-chloro-4-[2-(4-methoxyphenyl)ethyl]pyridazine (3).

General procedure.

A mixture of **2** (8.0 mmol) and phosphoryl chloride (10 ml) was heated under reflux for 2 hours. After cooling, the mixture was poured onto crushed ice. It was then neutralized with saturated aqueous sodium bicarbonate solution and the resulting precipitate was filtered off, washed with water and dried. Yields and physical properties are summarized in Table I and II.

6-Aryl-8-[2-(4-methoxyphenyl)ethyl]-2,3-dihydro-3-oxo-1,2,4-triazolo[4,3-b]pyridazine (4).

General Procedure.

A mixture of **3** (2.5 mmol), semicarbazide hydrochloride (2.5 mmol), 75% aqueous ethanol (40 ml) and few drops of hydrochloric acid was heated under reflux for 18 hours. The reaction mixture was concentrated and the product was filtered off, washed with ethanol and dried. Yields and physical properties are summarized in Table I and II.

6-Aryl-8-[2-(4-methoxyphenyl)ethyl]tetrazolo[1,5-b]pyridazine (6).

General procedure.

A solution of **3** (3.0 mmol) and sodium azide (3.3 mmol) in N,N-dimethylformamide (45 ml) was heated under reflux for 8 hours. It was then cooled, and poured onto water (200 ml). The product that separated out was filtered off, washed with water and dried. Yields and physical properties are summarized in Table I and II.

2-Allyl-6-aryl-4-[2 –(4-methoxyphenyl)ethyl]pyridazin-3-one (8).

General procedure.

Compound **3** (3.4 mmol) was added to a solution of sodium (10 mmol) in allyl alcohol (30 ml). The mixture was heated under reflux for 18 hours. The reaction mixture was poured onto water (50 ml), and the precipitate was filtered off, washed with water and dried.

2-Allyl-4-[2-(4-methoxyphenyl)ethyl]-6-phenylpyridazin-3-one (8a).

This compound was obtained in 52% yield; mp 95 °C; IR (KBr): 1649 cm^{-1}; MS,m/z(%): 346($M^{+\cdot}$, 44), 345 (5), 317 (5), 305 (6), 128 (8), 122(19), 121 (100), 91 (8), 87 (8), 77 (13). Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C,76.27 ; H, 6.40; N, 8.09. Found: C,76.40; H,6.60; N, 8.10.

2-Allyl-4-[2 -(4-methoxyphenyl)ethyl]-6-(4-methylphenyl)pyridazin-3-one (8b).

This compound was obtained in 47% yield; mp 96 °C; IR (KBr): 1650 cm^{-1}; MS, m/z(%): 360 ($M^{+\cdot}$,44), 331(5), 319(7), 141(5), 122(10), 121(100), 115(5), 91(8).
Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H,6.71; N, 7.77. Found: C, 76.80; H,6.60; N, 7.70.

References

1. J. A. M. Guard and P. J. Steel, *Aust. J. Chem.*, **48**, 1601 (1995)..
2. M. Tisler and B. Stanovnik, *Adv. Heterocycl. Chem.*, **9**, 211 (1968).
3. F. W. Mason and D. L. Aldous in R. N. Castle (Ed.), Heterocyclic Compounds, Vol. **28**, Interscience, New York, p. 23 (1973).
4. Mitsui Toatsu Chemicals, Inc. Jpn. Kokai Tokkyo Koho Jap. Pat. 59 53,482; Chem.Abstr., **101**, 90955w (1984).
5. S. P. Breukelman, G. Meakins and A. M. Roe, *J. Chem. Soc. Perkin Trans. I,* 1627 (1985).
6. I. Sircar, B. Duell, G. Robowski, J. A. Bristol and D. B. Evans, *J. Med. Chem.*, **28**, 1405 (1985).
7. M. Takaya, M. Sato, K. Terashima and H. Tanizawa, *J. Med. Chem.*, **22**, 53 (1979).
8. G. Y. Lesher, U. S. Pat. 4,305,943 (1981).

9. Occelli, D. Barone, G.Tarzia and A. Giunta, Eur. Pat. Application 85,840 (1983).
10. H. Zimmer, J. M. Kakosa and K. J. Shah, *J. Org. Chem.*, **40**, 2901 (1975).
11. H. Zimmer and A. Amer, *Heterocycles,* **26**, 1177 (1987).
12. A. Amer and H. Zimmer, *J. Heterocyclic Chem.*, **20**, 1231 (1983).
13. G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, L. Betti, G. Giannaccini, and A. Lucacchini, *Farmaco*, **54**, 615(1999).
14. A. A. Katrusiak, S. S. Baloniak, and A. A. S. Katrusiak, *Pol. J. Chem.*, **70**, 1279 (1996).
15. A. M. El Massry, *Heterocycl. Commun.*, **5**, 555 (1999).
16. E. S. H. El Ashry, Y. El Kilany and A. Amer, *Heterocycles*, **26**, 2101 (1987).
17. A. Amer, A. M. El Massry, M. Badawi, M. M. A. Rahaman, S. A. F. El Sayed, and E. S. H. El Ashry, *J. Prakt. Chem.*, **339**, 20 (1997).
18. A. M. El Massry, and A. Amer , *Heterocycles,* **29**, 1907 (1989).
19. E. S. H. El Ashry, A. Amer, G. H. Labib, M. M. A. Rahman, and A. M. El Massry, *J. Heterocycl. Chem.*, **24**, 63 (1987).
20. E. S. H. El Ashry and N. Rashed, *Current Org. Chem.*, **6**, 609 (2000).
21. E. S. H. El Ashry, A. Mousad and N. Rashed, *Adv. Heterocycl. Chem.*, **53**, 233 (1992).
22. E. S. H. El Ashry, *Adv. Chem. Se13r. Amer. Chem. Soc.*, **200**, 179 (1982).
23. G. H. Labib, M. M. A. Rahman, H. A. Hamid, A. M. El Massry, and E. S. H. El Ashry, A*lex. J. Pharm. Sci.*, **6**, 155 (1992).

Received on March 5, 2001