Pak. j. sci. ind. res., vol. 35, no. 7-8, July-August 1992

SYNTHESIS AND REACTIONS OF A 4-METHYL-3-(3'-THIOXO)-1', 2', 4'-TRIAZOL- 5'-YLCOUMARIN

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(Received February 25, 1992; revised July 14, 1992)

4-Methyl-3-(3-thioxo)-1`,2`,4`-triazol-5`-ylcoumarin (2) was prepared via condensation of ethyl 4-methylcoumarin-3-carboxylate (1) with thiosemicarbazide in boiling pyridine. Compound 2 reacts as a thione with nitrogen nucleophiles to yield the 4-methyl-3- (3`-hydrazinyl) -1`,2`,4`-triazol-5`-ylcoumarins (3a,b). Condensation of 3a with aromatic aldehydes gives the corresponding 4-methyl-3- (3`-arylidenehydrazonyl- 1`,2`,4`- triazol-5`-yl-coumarins (4a,b). Compound 2 reacts as a thiol with alkyl halides yielding 4- methyl-3 (1-alkyl-3-alkylthio)-1`,2`,4`-triazol-5`-ylcoumarins (5a,b). Treatment of 2 with acrylonitrile affords the corresponding 4-methyl-3`-[3`-(2`-cyanoethylthio)]-1`,2`,4`-triazol-5`- ylcoumarin (6). The antimicrobial activity of some new compounds has been screened.

Key words: Synthesis, Reaction, Coumarin.

Introduction

Various substituted triazoles have recently received significant importance because of their diverse pharmacological properties. These included analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, and anti-inflammatory properties [1-5].

The present work reports the synthesis of some heterocyclic compounds containing triazol thione and benzopyranone moieties because such compounds are expected to show pharmacological activity.

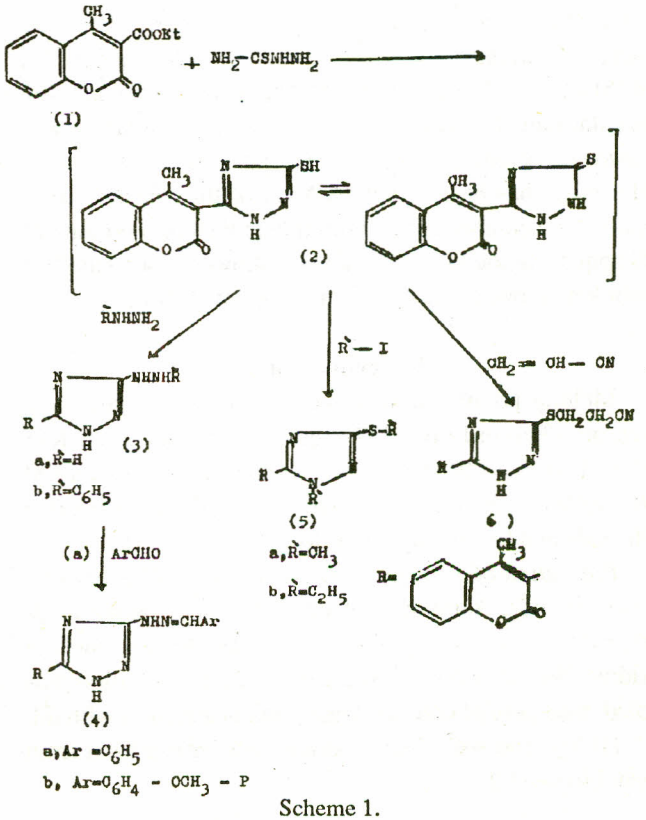
Results and Discussion

As extension of our studies on coumarin derivatives [6-10], we intended to prepare 4-methyl-3-(3'-thioxo)- 1`,2`,4`-triazol- 5`-ylcoumarin in order to establish the reactivity of the carbonyl groups of the α-pyrone and the thione group of the triazole rings toward some nitrogen nucleophiles and carbon electrophiles.

The 4-methyl-3-(3`-thioxo)-1`,2`,4`-triazol-5` ylcoumarin (2) was prepared via condensation of ethyl 4-methylcoumarin-3- carboxylate (1) with thiosemicarbazide in boiling pyridine. The IR spectrum of 2 showed bands due to the α-pyrone CO (1695) and other bands at 3280-3175 (υNH), 1625 (υC=N), 1615 (υC=C) and 1180 cm^{-1} (υC=S). The PMR spectrum of 2 (CF_3COOD) showed signals at δ 2.2 (s, 3H, CH_3), 6.9-8.3 (m, 4H, Ar-H), 9.7 (br, 1H, SH ratio 44.6) and 10.1, 11.3 (br, 2H, NH and NHC=S ratio 55.4).

The formation of 2 may proceed by initial nucleophilic attack of the amino group at the ester carbonyl without attack at the carbonyl of the α pyrone ring followed by cyclization as shown in Scheme 1.

It has been reported [11,12] that the α, β-unsaturated α pyrone ring in coumarin derivatives is not opened by primary amines, while the action of hydrazines does cause the heterocylic ring opening of coumarin [13]. The reaction of compound 2 with hydrazine hydrate or phenylhydrazine gave the corresponding 4- methyl-3-(3'-hydrazinyl)-1',2',4'-triazol-5`-ylcoumarins (3a or 3b, Scheme 1). The IR spectra of 3 exhibited strong bands at 1690- 1696 (υ CO), 1615 (υ C=N) and 3390-3185 cm^{-1} (υ NH). The PMR spectrum of 3b ($CDCl_3$) showed signals at δ2.1 (s, 3H, CH_3), 5.2 (br, 2H, NHNH), 6.8-7.9 (m, 9H, Ar-H) and 10.5 (br,1H, NH cyclic).



Scheme 1.

The condensation of 3a with aromatic aldehydes, *viz.* benzaldehyde and anisaldehyde in boiling acetic acid yielded the corresponding 4-methyl -3(3`-arylidene hydrazonyl) 1`,2`,4`- triazol-5 `-ylcoumarins (4a,b). The IR spectra of 4 showed strong absorption bands at 3295-3240 (υ NH), 1690 (νCO) and 1625-1615 cm^{-1} (υC=N). The PMR spectrum of 4a (CF_3 COOD) showed signals at δ2.2 (s, 3H,CH_3), 6.7-8.7 (m, 11H, Ar-H, N=CH and NH) and 10.5 (br, 1H, NH cyclic).

Alkylation of compound 2 with alkyl halides, *viz* methyl iodide and ethyl iodide in the presence of sodium ethoxide solution, afforded the correspponding 4-methyl -3(1`-alkyl-3`-alkylthio)-1`,2`,4`-triazol-5`-ylcoumarins (5 a,b). Their IR spectra showed bands attributable to υ CO (1715), and υC=N (1625 cm^{-1}). The PMR spectrum of 5a (CF_3 COOD) showed signals at δ2.1 (s, 3H, CH_3), 2.9-3.2 (s, 6H, N-CH_3 and S -CH_3) and 6.9-8.0 (m, 4H, Ar-H).

The presence of a thione-thiol equilibrium in compound 2 promted us to study the behaviour of the active thiol group towards activated olefinic bonds. Treatment of 2 with acrylonitrile in the presence of anhydrous potassium carbonate under Michael reaction conditions gave 4-methyl -3-[3`-(2``- cyanoethylthio)]-1`,2`,4`-triazol-5-ylcoumarin (6). Its IR spectrum showed bands at 1695 (υCO), 1625 (υC=N), 2215 (υC=N) and 3205 cm^{-1} (υNH). The PMR (CF_3COOD) spectrum of 6 showed signals at δ 2.3 (s, 3H, CH_3), 3.2 and 4.4 (2xt, 4H, CH_2-CH_2), 7.0-8.2 (m, 4H, Ar-H) and 10.05 (s, 1H, NH).

Antimicrobial activity. Antibacterial activity was measured by the following agar-diffusion teachnique [14] against *E.coli, P. aeruginosa* and *S. aureus*. Compounds (2), (3a), (4b) and (5) showed 80% activity at 500 ppm concentration level. Also, antifungal activity against *A. niger*, *P. digitatium* and *T. viride* using agar-plate diffusion technique [15] in 5% DMF and acetone has been screened. Most of the screened compounds showed about 65% inhibition at the concentration of 500 ppm. Compounds (2), (5) and (6) showed more than 75% inhibition at lower concentration (250ppm, Table 2).

Experimental

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer using KBr wafers. Proton NMR spectra were obtained on a Varian EM 360 spectrometer using solutions in hexadeuteriodimethyl sulfo-xide and tetramethylsilane as internal standard.

Formation of 4-methyl-3(3`-thioxo)-1`,2`,4`-triazol-5`-ylcoumarin (2). A mixture of ethyl 4-methylcoumarin -3-carboxylate (0.01 mol) and thiosemicarbazide (0.01 mol) in pyridine (50 ml) was refluxed for 15 hr. The solution was cooled, then poured onto ice-water, and neutralized with dil. HCl (10%). The solid that separated was crystallized from ethanol to yield 2.

TABLE 1. CHARACTERISATION DATA OF THE COMPOUNDS 2-6.

Compound	M.P(°C) (colour)	Crystalized (yield (%)	Mol. formula	Analysis(%) Calcd. (Found) C	H	N	S
2	170 (Pale yellow)	Ethanol (50)	$C_{12}H_9N_3O_2S$ (259)	55.59 (55.24	3.47 3.19	16.21 16.01	12.35 12.18)
3a	190 (Yellow)	Ethanol (55)	$C_{12}H_{11}N_5O_2$ (257)	56.03 (55.87	4.28 4.00	27.23 26.96	- -)
3b	85 (Orange)	Light petroleum (60-80) (35)	$C_{18}H_{15}N_5O_2$ (333)	64.86 (64.47	4.50 4.32	21.02 20.81	- -)
4a	260 (Yellow)	Acetic acid (60)	$C_{19}H_{15}N_5O_2$ (345)	66.08 (65.73	4.34 4.15	20.28 19.89	- -)
4b	285 (Yellow)	Acetic acid (65)	$C_{20}H_{17}N_5O_3$ (375)	64.00 (63.76	4.53 4.35	18.66 18.41	- -)
5a	230 (Pale yellow)	Ethanol (53)	$C_{14}H_{13}N_3O_2S$ (287)	58.53 (58.37	4.52 4.28	14.63 14.39	11.14 11.00)
5b	205 (Pale yellow)	Ethanol (55)	$C_{16}H_{17}N_3O_2S$ (315)	60.95 (60.64	5.39 5.08	13.33 13.01	10.15 9.87)
6	220 (Yellow)	Ethanol (60)	$C_{15}H_{12}N_4O_2S$ (312)	57.69 (57.28	3.84 3.56	17.94 17.59	10.25 10.01)

TABLE 2. ANTIMICROBIAL ACTIVITY.

Compd.	*E.coli*	*P.aeruginosa*	*S.aureus*	*A.niger*	*P.digitatium*	*T.viride*
2	+	+	+++	++	+	++
3a	+++	++	+	-	-	-
4b	++	+	++	+	-	-
5a	++	+	+++	+	++	+++
5b	++	++	+++	++	+	++
6	-	-	-	+++	-	+

- No antibacterial activity, + Mild activity,
++ Moderate activity, +++ Marked activity

Reaction of compound 2 with hydrazines: Formation of 4-methyl-3-(3`-substituted)-1`,2`,4`-triazol-5`-ylcoumarins (3 a,b). A solution of compound 2 (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in ethanol (50 ml) was refluxed for 6 hr. The hot mixture was filtered and then cooled. The solid which separated was filtered, dried and recrystallized from an appropriate solvent to give 3 a,b.

Condensation of compound 3a with aromatic aldehydes: Formation of 4-methyl-3-(3' N-arylidenehydrazonyl) 1`,2`,4`-triazol-5`-ylcoumarins (4 a,b). A mixture of 3a (0.01 mol) and benzaldehyde or anisaldehyde (0.01 mol) in acetic acid (30 ml) was refluxed for 6 hr. The hot mixture was filtered, and then cooled. The solid which separated was filtered off, dried and crystallized from acetic acid to give 4 a,b.

Alkylation of compound 2 with alkyl halides: Formation of 4- methyl -3-(1`-alkyl-3`-alkylthio) 1`,2`,4`-triazol -5'-ylcoumarins (5 a,b). A mixture of 2 (0.01 mol) and methyl iodide or ethyl iodide (0.02 mol) in 30 ml sodium ethoxide

solution (0.005g atom sodium/25 ml abs. ethanol) was heated for 6 hr. Cooled, and poured into dil. HCl (1%). The solid which separated, was filtered, washed with water and crystallized from ethanol to give 5 a,b.

Reaction of compound 2 with acrylonitrile: Formation of 4-methyl-3-[3`(2``-cyanoethylthio)]-1`,2`,4`-triazol-5`-ylcoumarin (6). A mixture of compound 2 (0.01 mol) and acrylonitrile (0.01 mol) dissolved in ethanol (50 ml) and anhydrous potassium carbonate (2g, 0.02 mol) was heated for 6 hr. The mixture was poured into ice/10 % HCl mixture and the solid product was filtered off, dried, and crystallized from ethanol to give (6).

References

1. M. Yamamoto, S. Morooka, M. Koshiba, S. Inaba and H. Yamamoto, Japanes Patent 76, 100, 098 (1976); Chem. Abstr., **86,** P 121364 f (1977).
2. T. Denzel and H. Hoehn, U.S. Patent, 3, 971, 801 (1976), Chem. Abstr., **86,** P. 16675 K (1977).
3. C. Fauran, C. Douzon, G. Raynaud and B. Pourias, French Patent Application, **2,** 269, 938 (1975); Chem. Abstr., **84,** P. 164789 z (1976).
4. F. G. F. Eloy and R. W. Shanahan, U.S. Publ. Patent Application, **B,** 426, 493 (1976); Chem. Abstr., **84,** P. 164787x (1976).
5. T. George, D. Mehta, R. Tahilramani, J. David and P. Tolwalker, J. Med. Chem., **14,** 335 (1971).
6. M. M. Abdalla, M. El-Kady and A. F. El-Faragy, Egypt. J. Chem., **20,** 245 (1977).
7. A. F. El-Faragy, A. Y. Soliman, M. El-Mobayed and S. El- Esser, Egypt. J. Chem., **30,** 497 (1987).
8. A. F. El-Farargy, M. El-Mobayed and B. E. Bayoumy, Bull. Fac. Sci., Assiut, **18,** 71 (1989).
9. M. El-Kady, M. K. El-Deek, R. M. Saleh and G. El-Dein, Revue. Roum. De Chemie, **28,** 915 (1983).
10. A. Y. Soliman, N. B. El-Assy, F. El-Shahed, M. El-Kady and I. M. El-Deen, Indian J. Chem., **29B,** 326 (1990).
11. A. Sammour, A. Mari and S. El-Ashry, Egypt. J. Chem., **13,** 261 (1970).
12. A. Sammour, M. I. B. Selim and M. El-Kady, Egypt. J. Chem., **14,** 261 (1971).
13. S. H. Etaiw, M. About-Sekkina, G. B. El-Hefnawey and S. S. Assar, Can. J. Chem., **60,** 304 (1982).
14. J. G. Horstall, Bol. Rev., **11,** 857 (1945).
15. F. Cavangh, *Analytical Microbiology* (Academic Press, New York, 1963), pp.126.