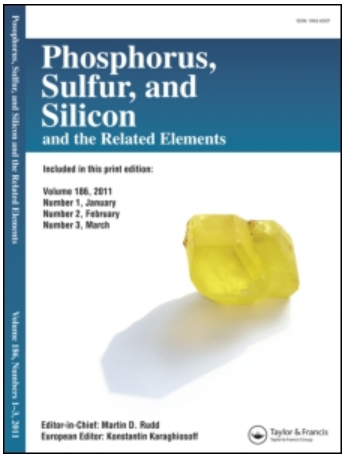

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A FACILE ONE POT CONVERSION OF CHALCONES TO PYRIMIDINE THIONE DERIVATIVES. RING OPENING REACTIONS OF OXIRANES DERIVED FROM CHALCONES

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Communication

A FACILE ONE POT CONVERSION OF CHALCONES TO PYRIMIDINE THIONE DERIVATIVES. RING OPENING REACTIONS OF OXIRANES DERIVED FROM CHALCONES

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Arylidene 2,5-dimethylacetophenones (**1**) reacted with thiourea and hydrogen peroxide to give pyrimidinethione (**2**) and oxirane derivatives (**7**), respectively. The behaviour of pyrimidinethione (**2**) towards hydrazine, acetylhydrazines, secondary amines under Michael reaction conditions, and phenylisocyanate has been investigated. The reaction of oxirane derivative (**7**) with aqueous sodium hydroxide, glacial acetic acid and *p*-xylene under Friedel Crafts reaction conditions is also described.

It has been reported that many homocyclic[1] and heterocyclic chalcones possess antimicrobial,[2] antiinflammatory[3] as well as carcinogenic[4] activities.

Consequently, the aim of the present work is to study the reactivity of homocyclic chalcones toward various nucleophilic reagents in an attempt to prepare new heterocycles incorporating the nitrogen bridgehead ring. This study was in part undertaken in view of the fact that pyrimidinethiones[5] have a wide spectrum of biological activity.

It was reported[6] when aroylarylacetylenes were allowed to react with thiourea in the presence of sodium ethoxide in ethanol they gave rise to the corresponding 4(6)-aryl-6(4)-phenylpyrimidine-2(1H)thiones.

In the present investigation the tetrahydropyrimidinethiones (**2**) are produced from the interaction of arylidene 2,5-dimethylacetophenones and thiourea in presence of sodium ethoxide in boiling ethanol. The reaction appears to proceed via Michael addition of the anion derived from thiourea, to arylidene 2,5-dimethylacetophenones followed by cyclisation of the intermediate (**2**) (cf. Scheme 1).

The structure of the thiones (**2**) was established by spectroscopic evidence. The i.r. data indicate that these compounds exist in (**2A**) thiolactam $\rightleftharpoons$ thiol (**2B**) dynamic equilibrium.

New publications appeared in the last decade[7–9] describing the synthesis and biological evaluation of new 6-(substituted phenyl)-1,2,4-triazolo[4,3-b]pyridazines, which show activity in tests predictive of anxiolytic activity. The present study deals with the behaviour of pyrimidinethione (**2**) towards hydrazine hydrate with the aim of finding convenient methods for the synthesis of hydrazinopyrimidines considered

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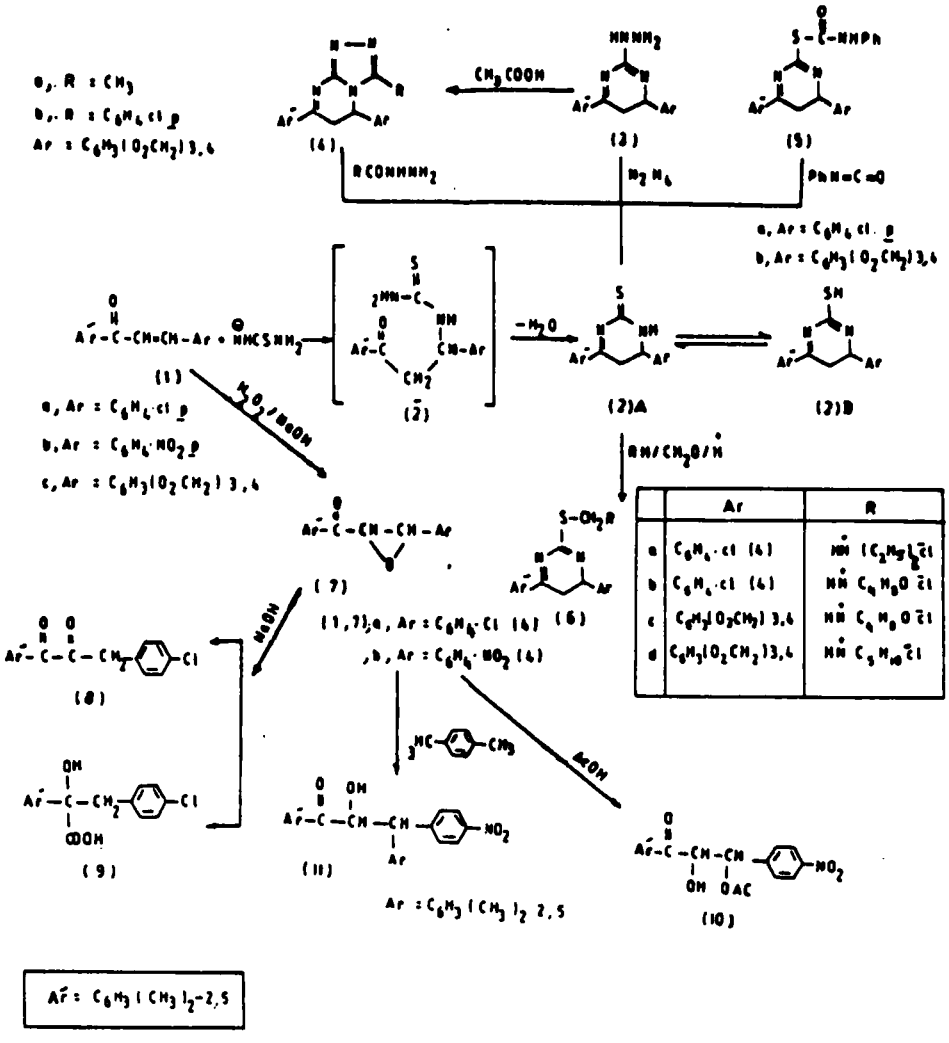

Scheme 1

as key starting materials for the synthesis of diverse triazolopyrimidine derivatives. Thus, when compound (**2**) was reacted with hydrazine hydrate in boiling ethanol, the hydrazinopyrimidine derivative (**3**) was formed.

Treatment of (**3**) with boiling acetic acid gave the triazolopyrimidine derivative (**4a**). Structure of compound (**4a**) was proved via its unambiguous synthesis by interaction of the thione (**2**) with acetylhydrazine in refluxing butanol.

Similarly, the thione (**2**) reacts with *p*-chlorobenzoylhydrazine in refluxing butanol to give the triazolopyrimidine derivative (**4b**).

Compounds **2a** and **c** reacted with phenylisocyanate to give the 5-N-phenylcarbamoyl derivative (**5**) with secondary amines (diethylamine, piperidine, and morpholine) and aqueous formaldehyde in boiling ethanol they yielded Mannich bases (**6**). The structure of the Mannich bases was inferred from their i.r. spectra.

TABLE I

Characterisation and Physical Data of Compounds

M.p. C colour	Solvent yield (%)	Mol. formula (M. wt)	Analysis % (Calcd/Found) C	H	N	IR spectra NH, OH	CO	C=N,	C
180	M 73	$C_{18}H_{17}ClN_2S$ (328.5)	(65.75) 65.71	(5.18) 5.68	(8.52) 8.51	3250–3300		1600–1615	1400
171	M 68	$C_{18}H_{17}N_3SO_2$ (339)	(63.72) 63.66	(5.01) 4.92	(12.39) 12.30	3255–3300		1600–1615	1400
161	E 82	$C_{19}H_{18}N_2SO_2$ (338)	(67.46) 67.39	(5.33) 5.25	(8.28) 8.17	3250–3310		1590–1620	1400
172	E 65	$C_{19}H_{20}N_4O_2$ (336)	(67.88) 67.77	(5.95) 5.86	(16.67) 16.63	3200–3100		1590–1610	
187	M 52	$C_{21}H_{20}N_4O_2$ (360)	(70.00) 69.87	(5.56) 5.46	(15.56) 15.49				
295	E 55	$C_{26}H_{21}ClN_4O_2$ (456.5)	(68.35) 68.25	(4.60) 4.49	(12.27) 12.23				
201	B 62	$C_{25}H_{22}ClN_3SO$ (447.5)	(67.04) 66.75	(4.92) 4.86	(9.39) 9.27		1650–1665		
220	B 65	$C_{26}H_{23}N_3SO_3$ (457)	(68.27) 68.15	(5.03) 4.79	(9.19) 9.07		1655–1670		
205	E 72	$C_{23}H_{29}Cl_2N_3S$ (450)	(61.33) 61.23	(6.44) 6.38	(9.33) 9.34			1600–1620	
223	E 65	$C_{23}H_{27}Cl_2N_3SO$ (464)	(59.48) 60.91	(5.82) 5.66	(9.05) 9.21			1610–1620	
211	M 68	$C_{24}H_{28}ClN_3SO_3$ (473.5)	(60.82) 60.61	(5.91) 5.88	(8.87) 8.82			1595–1610	
209	M 71	$C_{25}H_{30}ClN_3SO_2$ (471.5)	(63.63) 63.46	(6.36) 6.13	(8.91) 8.71			1590–1615	
117	P 75	$C_{17}H_{15}ClO_2$ (286.5)	(71.20) 70.97	(5.23) 5.15				1675–1690	
129	P 70	$C_{17}H_{15}NO_4$ (297)	(68.68) 68.63	(5.05) 4.89	(4.71) 4.66			1650–1660	
127	P 25	$C_{17}H_{15}ClO_2$ (286.5)	(71.20) 70.58	(5.23) 5.17					
140	E 17	$C_{17}H_{17}ClO_3$ (304.5)	(66.99) 66.25	(5.58) 5.22					
102	P 72	$C_{19}H_{19}NO_6$ (357)	(63.86) 63.55	(5.32) 5.12	(3.92) 3.85				
140	M 42	$C_{25}H_{25}NO_4$ (403)	(74.44) 73.92	(6.20) 6.01	(3.47) 3.35			3250	1670

Methanol; E = ethanol; B = benzene; P = petroleum ether (80–100°).

ound (2) shows ν_{SH} at 2100–2150.

ound (11) shows stretching frequency characteristic of epoxide linkage at 1250–1260.

spectrum of 2c showed peaks at 338 (M + 2) at 340 and 304 (M—M_2S) for mercaptans.

MR of 7b showed signals at δ 2.5 (s, 6H, $2CH_3$), 4.2 (d, 2H, methine protons) and 7.6–8.7 (m, 7H, aromatic protons).

The present investigation also deals with the behaviour of arylidine 2,5-dimethylacetophenones toward oxygen nucleophile. Thus, treatment of **1a** and **1b** with H_2O_2 in alkaline medium, give the oxirane derivatives **7a** and **7b**, respectively.

The structure of the oxirane derivatives (**7**) was established by spectroscopic evidence. Compound **7a** reacted with aqueous sodium hydroxide to give a mixture of two products, the diketone derivative (**8**) and the glycolic acid derivative (**9**).

Treatment of **1b** by acetic acid at room temperature afforded the acetate derivative (**10**).

The reaction of the oxirane derivative (**7b**) with *p*-xylene in the presence of anhydrous aluminium chloride yielded α-(2,5-dimethylbenzoyl)-β-(2,5-dimethylphenyl)-β-(4-nitrophenyl)ethanol 11. The reaction proceeds by opening of the oxirane ring with formation of a carbonium ion which alkylates the aromatic hydrocarbon.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (KBr) were measured on a Perkin Elmer 137 spectrophotometer. The ^{1}H-NMR spectra on a Varian A 60 equipment using TMS as an internal standard and $CDCl_3$ as a solvent. The mass spectra were run at 70 eV on a Varian Mat 711 mass spectrometer. Characterisation and physical data are listed in Table I.

Synthesis of tetrahydropyrimidinethione (**2a–c3**). A mixture of compounds (**1a–c**) (0.01 mole), thiourea (0.011 mole) and sodium ethoxide (0.25 mole) in ethanol (30 ml) was refluxed for 4 hrs. On concentration and cooling the separated products were filtered and recrystallized from the proper solvent to give pyrimidinethiones (**2a–c**).

Reaction of tetrahydropyrimidinethione (**2c**) *with hydrazine hydrate; Formation of* **3**. A mixture of compound (**2c**) (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (20 ml) was refluxed for 5 hrs. The reaction mixture was cooled, the solid that separated was collected and recrystallized from the proper solvent to give the hydrazino derivative (**3**).

Reaction of tetrahydropyrimidinethione (**2**) *with acylhydrazine; Formation of triazolo-derivatives* (**4**). A mixture of compound (**2c**) (0.01 mole) and acylhydrazine (0.01 mole) in *n*-butanol (30 ml) was refluxed for 6 hrs. The reaction mixture was cooled, the solid product recrystallized from the proper solvent to give triazolopyrimidine (**4a** and **b**).

Conversion of hydrazino-derivative (**3**) *to triazolopyrimidine* (**4a**). A solution of hydrazinopyrimidine (**3**) (0.01 mole) in glacial acetic acid (30 ml) was heated under reflux for 5 hrs. After cooling the precipitate was recrystallized from the proper solvent to give (**4a**) which was identified via melting point and mixed melting point determinations.

Reaction of **2a** *and* **c** *with phenylisocyanate; Formation of* **5a** *and* **b**. A solution of 2 (0.01 mole) and phenylisocyanate (0.01 mole) in dry benzene (20 ml) was heated under reflux for 1 hr. The reaction was then cooled, the solid product that separated was collected and recrystallized from the proper solvent to give (5a and b).

Synthesis of Mannich bases (**6**). A mixture of compound (**2a** and/or **2c**) (0.01 mole), 40% aqueous formaldehyde (0.01 mole) and secondary amine, (diethylamine, morpholine and piperidine) (0.01 mole), hydrochloric acid (1 ml) in ethanol (30 ml) was refluxed for 3 hrs. The reaction mixture was cooled and diluted with water, the solids separated were recrystallized from the proper solvent to give the Mannich bases (**6a–d**).

Synthesis of oxirane derivatives (**7a** *and* **b**). A solution of chalcone (**1a** or **b**) in acetone/methanol (40:15 ml), was treated with aqueous sodium hydroxide (8%; 12 ml) and hydrogen peroxide (30%; 5 ml). The solution was left overnight at room temperature. After evaporating most of the solvent a white crystalline product deposited and was recrystallized from the proper solvent giving oxirane derivative (**7a** and **b**).

Action of sodium hydroxide on the oxirane (**7a**)*; Formation of diketone* (**8**) *and glycolic acid derivative* (**9**). A solution of oxirane **7a** (0.01 mole) in ethanol (20 ml) was treated with aqueous sodium hydroxide (10%; 15 ml) and heated under reflux for 3 hrs. The reaction mixture was concentrated in vacuo and water was added (20 ml). The solution was extracted by ether; the ethereal layer was separated. Evaporation of the solvent left the diketone (**8**). Acidification of the aqueous layer gave a solid product which recrystallized from the proper solvent to give glycolic acid derivative (**9**).

Action of glacial acetic acid on oxirane (**7b**)*; Formation of acetate* (**10**). A solution of **7b** (0.01 mole) in glacial acetic acid (20 ml) was heated under reflux for 3 hrs. The white solid obtained after concentrating and cooling was recrystallised from the proper solvent to give the acetate (**10**).

Action of p-xylene on oxirane (**7b**)*; Formation of* **11**. To a cooled stirred mixture of anhydrous aluminium chloride (0.03 mole) in dry xylene (30 ml), a solution of **7b** (0.01 mole) in dry xylene (20 ml) was added, stirring was continued for an additional 3 hrs at room temperature. The reaction mixture was decomposed with 250 ml dilute hydrochloric acid, and the organic material extracted with ether, the ethereal layer was washed with water and dried under anhydrous sodium sulphate. The residue left after evaporation of the ether, was crystallized from the proper solvent to give compound (**11**).

REFERENCES

1. S. S. Misra and B. Nath, *Ind. J. Appl. Chem.*, 35 (1972).
2. S. S. Misra, *J. Ind. Chem. Soc.*, **50,** 335 (1973).
3. K. K. Hsu and F. G. Chen, *Tai-wan Hsueh, K O*, **27,** 236 (1973).
4. H. J. Kanoda, *Agr. Chem. Soc. Jap.*, **28,** 891 (1954).
5. M. P. V. Boarland, J. F. W. Mcomie and R. N. Timmis, *J. Chem. Soc.*, **4691 (1972).**
6. F. G. Baddar, F. H. Al-Hajjar and N. R. El-Rayyes, *J. Heterocyclic Chem.*, **15,** 105 (1978).
7. M. A. El-Hashash, S. I. El-Nagdy and R. M. Saleh, *J. of Chemical and Engineering Data,* **361,** 29 (1983).
8. G. Nannini, G. Biasoli, E. Perrone, A. Forgione, A. Buttinani, and M. Ferrari, *Eur. J. Med. Chem.*, **14,** 53 (1979).
9. J. D. Albright, D. B. Moran, W. B. Wright, J. B. Collins, B. Beer, A. C. Lippa, and E. N. Greenblat, *J. Med. Chem.*, **24,** 592 (1981).