A Novel Synthesis of Fused Imidazo[5,1-*c*]-1,2,4-triazoles

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The new fused imidazo[5,1-*c*]-1,2,4-triazoles **4** were obtained by cyclization of the corresponding 2-imidazolidinone 4-phenylhydrazones **2** which were obtained by the action of phenylhydrazine on the arylmethylene derivatives of 4-thioxo-2-imidazolidinone **1**. The benzylimino derivatives **6** were obtained by the reaction of benzylamine with **1**. Alkylation of **1** with phenacyl bromide and/or ethyl bromoacetate afforded the *S*-alkyl derivatives **7**.

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The considerable biological activities of fused imidazoles reported in the past decade have stimulated considerable research in this field (1-7). In previous work, we have reported a new and efficient approach for the synthesis of fused thiazolotriazoles (8,9). In the present investigation, we report the synthesis of the new imidazo[5,1-*c*]-1,2,4-triazole system, of probable biological activity *via* the cyclization of the 2-imidazolidinone 4-phenylhydrazono derivatives **2a** and **2b**. Compounds **2a** or **2b** were obtained through the nucleophilic attack of phenylhydrazine on the arylmethylene derivatives of 4-thioxo-2-imidazolidinone **1a** or **1b**, together with 2-imidazolidinone 4-phenylhydrazone **3** which was obtained *via* arylmethylene cleavage of **1a** or **1b**. The structure of compound **2** is inferred from analytical and spectral data. The arylmethylene derivatives of 2-imidazolidinone 4-phenylhydrazone **2a** or **2b** when subjected to the action of ethanolic formaldehyde solution and/or ethanolic benzaldehyde solution effected cyclization with the formation of the fused imidazo[5,1-*c*]-1,2,4-triazole derivatives **4a-d**, respectively. The structure of compound **4** was established from both analytical and spectral data. In addition **4a** was obtained authentically by

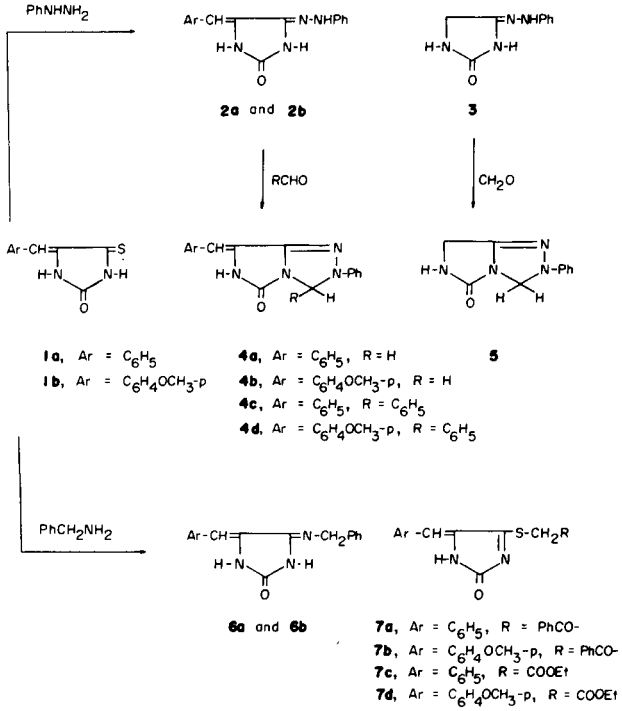

Table I

2,3,6,7-Tetrahydro-2-phenyl-7-(arylmethylene)-5*H*-imidazo[5,1-*c*]-1,2,4-triazol-5-ones (**4a-d**) and 1,5-Dihydro-4-(alkylthio)-5-(arylmethylene)-2*H*-imidazol-2-ones (**7a-d**)

Compound	Mp °C	Yield %	Formula	Analyses Calcd./Found C	H	N	S
4a	193	55	$C_{17}H_{14}N_4O$	70.33	4.86	19.30	—
				70.18	4.66	19.21	—
4b	202	40	$C_{18}H_{16}N_4O_2$	67.48	5.03	17.49	—
				67.38	4.98	17.36	—
4c	213	57	$C_{23}H_{18}N_4O$	75.39	4.95	15.29	—
				75.20	4.77	15.15	—
4d	254	55	$C_{24}H_{20}N_4O_2$	72.71	5.09	14.13	—
				72.60	4.90	14.01	—
7a	172	80	$C_{18}H_{14}N_2O_2S$	67.07	4.38	8.69	9.93
				66.85	4.25	8.51	9.81
7b	163	74	$C_{19}H_{16}N_2O_3S$	—	—	7.95	9.08
				—	—	7.90	8.98
7c	166	77	$C_{14}H_{14}N_2O_3S$	57.93	4.86	9.65	11.02
				57.82	4.68	9.49	10.82
7d	168	65	$C_{15}H_{16}N_2O_4S$	—	—	8.75	9.99
				—	—	8.66	9.75

Table II

The IR and ^{1}H-NMR Spectra for 2,3,6,7-Tetrahydro-2-phenyl-7-(arylmethylene)-5*H*-imidazo[5,1-*c*]-1,2,4-triazol-5-ones (**4a** and **4c**) and 1,5-Dihydro-4-(alkylthio)-5-(arylmethylene)-2*H*-imidazol-2-ones (**7a** and **7c**)

Compound	IR ν cm^{-1}	^{1}H-NMR δ ppm
4a	3280 cm^{-1} (NH) and 1720 cm^{-1} (C=O)	9.8 (s, 1H, N*H*), 7.9-7 (m, 10H, 2Ph), 5.9 (s, 1H, Ph-C*H*=C<) and 3.8 (s, 2H, N-CH_2-N)
4c	3290 cm^{-1} (NH) and 1710 cm^{-1} C=O)	9.9 (s, 1H, N*H*), 7.8-6.8 (m, 15H, 3Ph), 5.8 (s, 1H, Ph-C*H*=C<), and 3.6 (s, 1H, N-C*H*Ph-N)
7a	3300 cm^{-1} (NH) and 1720 cm^{-1} 1650 cm^{-1} (keto and ring C=O)	9.8 (s, 1H, N*H*), 7.9-7.4 (m, 10H, 2Ph), 6.0 (s, 1H, Ph-C*H*=C<) and 3.6 (s, 2H, S-CH_2-C=O)
7c	3320 cm^{-1} (NH) and 1725 cm^{-1} 1685 cm^{-1} (ester and ring C=O)	9.7 (s, 1H, N*H*), 7.8-7.5 (m, 5H, Ph), 5.9 (s, 1H, Ph-C*H*=C<), 3.95 (s, 2H, S-CH_2-COOEt), 3.8 (q, 2H, -CH_2-CH_3), and 1.2 (t, 3H, -CH_2-CH_3)

the action of benzaldehyde on the imidazo[5,1-*c*]-1,2,4-triazole derivative **5**, obtained by the action of ethanolic formaldehyde solution on 2-imidazolidinone 4-phenylhydrazone **3**.

Several potential tautomeric structures are possible for the alkyl derivatives (either *N*-alkyl or *S*-alkyl isomers) of 5-arylmethylene-4-thioxo-2-imidazolidinone **1a** or **1b**. Thus, subjecting **1a** or **1b**, in acetone solution containing potassium carbonate, to the action of phenacyl bromide and/or ethyl bromoacetate, effected *S*-alkylation rather than *N*-alkylation. The structure of the *S*-alkyl derivatives **7a-d** was established from both analytical and spectral data; moreover, hydrolysis of **7a** with ethanolic hydrochloric acid afforded 5-benzylidenehydantoin.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) using a Pye-Unicam IR 20. The ^{1}H-nmr were recorded on a Varian A-60 spectrometer in deuteriochloroform using TMS as an internal indicator and chemical shifts are expressed as δ ppm.

Action of Phenylhydrazine on **1a** or **1b**. Synthesis of 5-(Arylmethylene)-2,4-imidazolidinedione 4-(Phenylhydrazones) **2a** or **2b**.

Equimolecular amounts (0.01 mole) of each of 5-(arylmethylene)-4-thioxo-2-imidazolidinone **1a** or **1b** (11) and phenylhydrazine (0.01 mole) were mixed together at room temperature until the odour of hydrogen sulphide ceased. The reaction mixture was then triturated with ethanol and the solid, so obtained, was crystallised from ethanol to afford **2a** or **2b**, respectively. Compound **2a** formed orange crystals, yield 45%, mp 215°; ir: 3420, 3200 and 3050 cm^{-1} (NH) and 1685 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.87; H, 4.95; N, 20.01.

Compound **2b** formed red crystals, yield 50%, mp 190°; ir: 3340, 3180 and 3060 cm^{-1} (NH) and 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.00; H, 5.11; N, 18.01.

Cyclization of **2a** or **2b** with Formaldehyde and/or Benzaldehyde to Afford 2,3,6,7-Tetrahdyro-2-phenyl-7-(arylmethylene)-5*H*-imidazo[5,1-*c*]-1,2,4-triazol-5-ones **4a-d**.

To a solution of each of **2a** or **2b** (0.01 mole) in 20 ml of ethanol was added 5 ml of formaldehyde solution (40%) and/or benzaldehyde (2.0 g), the reaction mixture was boiled under reflux for 30 minutes then left to cool. The solid that separated was filtered off, washed with water and crystallised from ethanol. The yellow coloured products **4a-d** are listed in Table I. The ir and ^{1}H-nmr data are listed in Table II.

Action of Phenylhydrazine on 4-Thioxo-2-imidazolidinone to Afford 2-Imidazolidinone 4-Phenylhydrazone **3**.

Equimolecular amounts of 4-thioxo-2-imidazolidinone (11) and phenylhydrazine (0.01 mole) in 20 ml of ethanol were mixed until the odour of hydrogen sulphide ceased. The solid so obtained was filtered off and crystallised from ethanol to give **3** as colourless crystals, mp 133°, yield 50%; ir: 3340, 3200 and 3050 cm^{-1} (NH) and 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H,5 .30; N, 29.46. Found: C, 56.68; H, 5.11; N, 29.32.

Cyclization of Compound **3** With Formaldehyde to Give 5*H*-Imidazo-[5,1-*c*]-1,2,4-triazol-5-one Derivative **5**.

To a solution of **3** (1.0 g) in 20 ml of ethanol was added 5 ml of formaldehyde solution (40%) and the reaction mixture was refluxed for 30 minutes then allowed to cool. The solid that separated was filtered off, washed with water and crystallised from ethanol to yield **5** as colourless crystals, mp 194°, yield 50%. The ir spectrum of **5** showed absorption at 3200 cm^{-1} (NH) and 1680 cm^{-1} (C=O); ^{1}H-nmr: 9.9 (br, 1H, N*H*), 7.8-6.9 (m, 5H, Ph), 6.2 (d, 2H, N-CH_2-N) and 6 (d, 2H, -CH_2-C=).

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.15; H, 4.77; N, 27.52.

Action of Benzaldehyde on 5*H*-Imidazo[5,1-*c*]-1,2,4-triazol-5-one Derivative **5** to Give **4a**.

A mixture of **5** (1.0 g), benzaldehyde (1.0 g) and sodium acetate (2.0 g) in acetic acid (15 ml) was heated on a water bath for two hours then allowed to cool. The solid so obtained was crystallised from ethanol to afford yellow crystals mp 193°, which proved to be identical (mp and mixed mp) with **4a**.

Action of Benzylamine on **1a** or **1b** to Give 5-(Arylmethylene)-4-(phenylmethyl)imino-2-imidazolidinones **6a** or **6b**.

Equimolecular amounts of each of **1a** or **1b** (0.01 mole) and benzylamine (0.01 mole) in 30 ml of ethanol were heated under reflux on a water bath for one hour and the reaction mixture was allowed to cool. The solid so obtained was crystallised from ethanol as yellow crystals of **6a** or **6b** respectively. Compound **6a** formed yellow crystals, mp 176°, yield 50%; ir: 3250 and 3050 cm^{-1} (NH) and 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.41; H, 5.44; N, 14.92.

Compound **6b** formed yellow crystals, mp 235°, yield 65%, ir: 3220 and 3050 cm^{-1} (NH) and 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.21; H, 5.44; N, 13.52.

1,5-Dihydro-4-(alkylthio)-5-(arylmethylene)-2*H*-imidazol-2-ones **7a-d**.

General Procedure.

To a solution of each of **1a** or **1b** (1.0 g) in 20 ml of acetone was added 1.0 g of either phenacyl bromide or ethyl bromoacetate and 1.0 g of potassium carbonate. The reaction mixture was heated for one hour on a water bath then allowed to cool. The crystals that separated were filtered off, washed with water and then recrystallised from ethanol. 1,5-Dihydro-4-[(2-oxo-2-phenylethyl)thio]-5-(arylmethylene)-2*H*-imidazol-2-ones **7a** and **7b** are yellow in colour and are listed in Table I.

1,5-Dihydro-4-(ethylthioacetate)-5-(arylmethylene)-2*H*-imidazol-2-ones **7c** and **7d** are yellow in colour and are listed in Table I.

The spectral data of compounds **7a-d** are listed in Table II.

Action of Ethanolic Hydrochloric Solution on Each of **6a** and/or **7a** to Give 5-Benzylidenehydantoin.

A suspension of each of **6a** and/or **7a** (1.0 g) in a solution of ethanol (10 ml) and hydrochloric acid (2.0 ml) was heated under reflux for one hour, then allowed to cool. The reaction mixture was diluted with water and the solid product that separated was filtered off and crystallised from acetic acid to afford crystals of mp 220°, which proved to be identical (mp and mixed mp) with 5-benzylidenehydantoin (10).

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