Asian Journal of Chemistry Vol. 13, No. 1 (2001), 226–230

Synthesis of Some Dimers of Substituted Oxazolin-5-ones

MANOJ D. PRABHAVAT*
Department of Chemistry, Institute of Science, Nagpur-440 001, India

Substituted 1,2-bis-(2-methyl/phenyl-4-arylidene-Δ 2-imidazolin-5-one-1-yl) ethane were synthesized from the reaction of diamino ethane with 2-methyl/phenyl-4-arylidene-oxazolin-5-ones in acidic ethanol.

INTRODUCTION

Research in oxazoles was greatly stimulated by Kondrateva's discussion[1] that these compounds function as dienes in the Diel's-Alder reaction and Huisgen's work[2] on 1,3-dipolar cyclo addition reaction of mesoionic derivatives. Oxazolones have been studied by protein chemists because of their close relationship to amino acids. Naturally occurring oxazoles are rare. Oxazoles are applied as scintillators, fluorescent whitening agents and drugs. During the past twenty years new alkaloids found have simple 2,5-disubstituted oxazoles.

Some macrocyclic antibiotics contain oxazole rings. Ostreogrycin-A is isolated from the soil organism, streptomyces. Ostreogriseus is a broad spectrum antibiotic. Most important application of oxazole is based on the scintillator properties of 2,5-diaryloxazoles[3]. Diaryl and aryl styryl oxazoles are fluorescent whitening agents. Medicinal properties derived from oxazole include antiepileptic drugs trimethadione and paramethadione[4]. It also possesses sedative and muscle relaxant[5] properties.

In continuation of our work on heterocyclic synthesis[6], we now discuss the synthesis of some substituted dimers of oxazolin. Reaction sequences leading to formation of different title compounds is outlined in Scheme I. Substituted oxazolin-5-one was synthesized in which an acetyl/acylglycine is condensed with aromatic aldehyde in presence of acetic anhydride and sodium acetate.

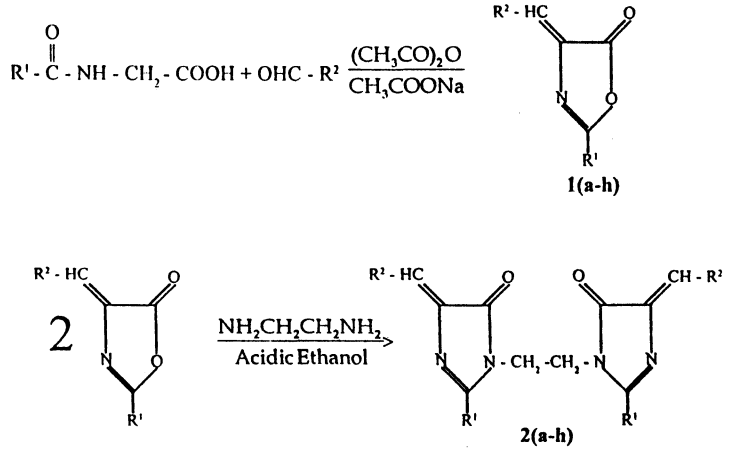
Two active oxygen atoms derived from each oxazolin tend to reacts with one molecule of ethylene diamine by the removal of water molecule resulting in the formation of 1, 2-bis-(2-methyl/phenyl-4-arylidene-Δ 2-imidazolin-1-yl) ethanes.

Erlenmeyer's azalactone synthesis (which is a valuable application of Perkin's reaction) has been used by various workers[7] for the synthesis of many substituted oxazolin-5-ones. Further we extended the work to form dimers by reacting oxazoline-5-ones with ethylene diamine in acidic ethanol.

---

*R&D Centre, Orchid Chemicals & Pharmaceuticals, 476/14, Sholinganallur, Chennai. E-mail: manoj_prabhavat@yahoo.com.

Scheme-1



	R^1	R^2		R^1	R^2
1a, 2a	CH_3	C_6H_5	**1e, 2e**	C_6H_5	C_6H_5
1b, 2b	CH_3	C_6H_4—OCH_3 (*p*)	**1f, 2f**	C_6H_5	C_6H_4—OCH_3 (*P*)
1c, 2c	CH_3	C_6H_4—NO_2 (*m*)	**1g, 2g**	C_6H_5	C_6H_4—NO_2 (*m*)
1d, 2d	CH_3	C_6H_4—$N(CH_3)_2$ (*m*)	**1h, 2h**	C_6H_5	C_6H_4—$N(CH_3)_2$ (*m*)

Antimicrobial activity: Synthesized compounds were screened for antibacterial[8] at 100 μg/mL concentration against *E. coli*, *Klebsiella* and *Psuedomonas*. Disc and plate dilution methods were used and ciprofloxacin was taken as a standard drug for comparison.

Compounds **2a, 2b, 2c, 2f** and **2h** show significant activity against *E. coli*, while compounds **2a, 2b** and **2c** show moderate to average activity against *Klebsiella* and *Psuedomonas*. **2e** and **2g** also show significant activity against *Klebsiella* and *Psuedomonas*. It was found that the substitution of groups like $-OCH_3$, $—NO_2$ and $—N(CH_3)_2$ showed significant antibacterial activity. The screening reports indicate that there is still scope for further improvement if the molecule is suitably modified.

Anticancer and anti-AIDS activities: Some of the synthesized compounds were screened for their anti-cancer and anti-AIDS activities. Compounds **2a, 2c, 2d, 2g** and **2e** were screened for anticancer activities. It was found active in preliminary stages against lung cancer and these compounds are now under screening in second stage for their anticancer activities.

Compounds **2b, 2c, 2f** and **2h** were screened for anti-AIDS activities. All the anticancer and anti-AIDS activities were screened at National Health Institute, Bethesda, Maryland, USA and their results are awaited.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra

(KBr) were recorded on a Perkin-Elmer spectrometer and ^1H NMR spectra on a Brucker AC 300 F NMR spectrometer at 300 MHz. The purity of the compound was checked by TLC using silica gel g (single spot recrystallization).

Preparation of 4-(4-methoxy) benzylidene-2-methyloxazol-5-one

Mixture of acetyl glycine (0.25 mol; 29 g), anisaldehyde (0.37 mol; 50,32 g), anhydrous sodium acetate (0.183 mol; 15 g) and acetic anhydride (0.62 mol; 59 ml; 63.5 g) was warmed on water bath with occasional stirring until solution was complete. Boiled the solution for 1 h, cool and left overnight. Stirred solid mass of yellow crystals with cold water, filtered, washed with cold water; recrystallised the product from CCl_4. Yield 76%, m.p. = 150–152°C.

IR (cm^{-1}): 2890 ν(Ar—CH), 2810 ν(—OCH_3), 1770 ν(C═N), 1580 ν(C═N)

^1H NMR (DMSO/d_6) = δ 3.5 (s, 3H, OCH_3), 6.9 (s, 1H, ═CH), 8–9.3 (m, 4H, Ar—H) Anal : calcd. for $C_{12}H_{11}O_3N$: C = 70.58; H = 4.81; N = 7.48; found: C = 70.50, H = 4.78, N = 7.40.

Compounds **1a, 1c** and **1d** were prepared similarly. Yields were 73, 79 and 72% respectively.

Preparation of 1,2-Bis (2-methyl-4-(4-methoxy) benzylidene-2-imidazolin-5-one-1-yl) ethane

A mixture containing 2-methyl-4-(4-methoxy)-benzylidene-oxazol-5-one (0.02 mol; 0.436 g) and ethylene diamine (0.01 mol; 0.6 mL) in ethanol (30 mL) containing traces of conc. HCl was refluxed for 10 min on water bath. After cooling, reaction mixture was diluted and a solid separated was filtered, washed with water, dried and crystallized from ethanol Yield 70%, m.p. = 172–174°C.

IR (cm^{-1}): 3350 ν(—OH); 2975 ν(Ar—CH); 2930 ν(—CH_2), 1795 ν(C═O).

^1H NMR (DMSO/d_6) = δ 3.7 (s, 3H, OCH_3), 6.7 (s, 1H, —CH_2); 7 (s, 1H, ═CH); 8.2–9.3 (m, 4H, Ar—H).

Anal.: Calcd. for $C_{26}H_{26}O_4N_4$: C = 70.29, H = 5.43, N = 20.08, found: C = 70.25, H = 5.40, N = 20.00.

Compounds **2a, 2c** and **2d** were prepared similarly; yields were 81, 65 and 72% respectively.

Preparation of 4-(4-methoxy) benzylidine-2-phenyloxazol-5-one

Benzoyl glycine (0.25 mol; 45g), anisaldehyde (0.25 mol; 34 mL) acetic anhydride (0.75 mol; 71.5 mL; 77 g) and sodium acetate (0.25 mol; 20.5 g) were heated on the hot plate with constant shaking; as soon as mixture got liquefied, it was transferred to water bath and heated for 2 h. Then ethanol (100 mL) was added slowly to the content of the flask and allowed the mixture to stand overnight. Filtered the crystallised product, washed with cold ethanol (100 mL) followed by boiling water. Yield = 78%, m.p. = 165–167°C.

IR (cm^{-1}): 3000 ν(Ar—CH), 2830 ν(—OCH_3), 1789 ν(C═O), 1596 ν(C═N).

^1H NMR (DMSO/d_6) = δ 3.4 (s, 3H, OCH_3), 7.1 (s, 1H, ═CH), 7.7–9.5 (m, 9H, Ar—H). Anal. Calcd. for $C_{17}H_{13}O_3N$: C = 73.11, H = 4.65, N = 5.01; found: C = 73.00, H = 4.50, N = 5.00.

Compounds **1e, 1g** and **1h** were prepared similarly, yields were 76, 75 and 70% respectively.

TABLE-1
YIELDS, MELTING POINTS, MOLECULAR FORMULA AND ELEMENTAL ANALYSIS OF THE COMPOUNDS 1 AND 2

Compd.	Yield (%)	m.p. (°C)	m.f.	Elemental analysis, calcd.(found)		
				C	H	N
1a	70	147–149	$C_{11}H_9NO_2$	70.58 (70.50)	4.81 (4.78)	7.48 (7.40)
1b	76	150–152	$C_{12}H_{11}NO_3$	66.35 (66.30)	5.06 (5.00)	6.45 (6.30)
1c	73	189–191	$C_{11}H_8N_2O_4$	56.89 (56.80)	3.44 (3.30)	12.06 (12.00)
1d	68	176–178	$C_{13}H_{14}N_2O_2$	67.82 (67.75)	6.08 (6.00)	12.17 (12.00)
1e	76	165–167	$C_{16}H_{11}NO_2$	77.10 (77.05)	4.41 (4.35)	5.02 (5.00)
1f	78	155–157	$C_{17}H_{13}NO_3$	73.11 (73.00)	4.65 (4.50)	5.01 (5.00)
1g	75	210–212	$C_{16}H_{10}N_2O_4$	65.30 (65.20)	3.40 (3.25)	9.52 (9.45)
1h	70	163–165	$C_{18}H_{16}O_2N_2$	73.97 (73.85)	5.47 (5.40)	9.58 (9.50)
2a	81	156–158	$C_{24}H_{22}N_4O_2$	72.36 (72.30)	5.52 (5.45)	14.07 (14.00)
2b	69	172–174	$C_{26}H_{26}N_4O_4$	68.12 (68.05)	5.67 (5.60)	12.22 (12.20)
2c	65	206–208	$C_{24}H_{20}N_6O_6$	70.29 (70.25)	5.43 (5.40)	20.05 (20.00)
2d	72	196–198	$C_{28}H_{32}N_6O_2$	69.42 (69.35)	6.61 (6.50)	17.35 (17.20)
2e	70	140–142	$C_{34}H_{26}N_4O_2$	78.16 (78.10)	4.98 (4.83)	10.72 (10.66)
2f	72	210–212	$C_{36}H_{30}N_4O_4$	74.22 (74.15)	5.15 (5.05)	9.62 (9.55)
2g	65	220–222	$C_{34}H_{24}N_6O_6$	66.66 (66.50)	3.92 (3.87)	13.72 (13.65)
2h	68	212–214	$C_{38}H_{36}N_6O_2$	75.32 (75.22)	5.92 (5.80)	13.81 (13.75)

Preparation of 1,2-bis (2-phenyl-4-(4-methoxy)-benzylidene-Δ 2-imidazolin-5-one-1-yl) ethane

A mixture containing 2-phenyl-4-(4-methoxy) benzylidene-oxazol-5-one (0.02 mol; 0.528 g) and ethylene diamine (0.01 mol; 0.6 mL) containing traces of conc. HCl was refluxed for 10 min on water bath. After cooling, reaction mixture was diluted and the solid separated was filtered, washed with water, dried and crystallized from ethanol. Yield 72%, m.p. = 210–212°C.

IR (cm^{-1}): 3369 ν(OH), 3063 ν((=CH), 2940 ν(—CH_2), 2845 ν(—OCH_3), 1603 ν(C=N), 1513 ν(amide)

^{1}H NMR (DMSO/d_6) = δ 3.8 (s, 3H, OCH_3), 6.9 (s, 2H, CH_2), 7.2 (s, 1H, =CH), 7.5–9.9 (m, 9H, Ar—H).

Anal: Calcd. for $C_{36}H_{30}O_4N_4$: C = 74.22, H = 5.15, N = 9.62 found: C = 74.10, H = 5.00, N = 9.50.

Compounds **2e, 2g** and **2h** were prepared similarly; yields were 70, 65 and 68% respectively.

TABLE-2
DATA FOR ANTIMICROBIAL ACTIVITY (IN mm.)

Compounds	*E. coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
1a	8	11	10
1b	10	17	9
1c	8	12	12
1d	15	7	11
1e	9	13	7
1f	11	14	5
1g	8	11	10
1h	12	15	9
2a	18	19	18
2b	18	12	10
2c	13	19	20
2d	20	14	11
2e	17	11	8
2f	19	13	10
2g	21	9	13
2h	7	10	10
Std Cipro-floxacin			

ACKNOWLEDGEMENTS

Author is thankful to Prof. B.J. Ghiya, Emeritus Scientist, and Prof. A.R. Vyawahare, Reader, Institute of Science, Nagpur, for their inspiring guidance; to UGC, New Delhi for major project grant; to RSIC (Nagpur) and Chandigarh for IR, NMR and elemental analysis. Also thankful to Microbiology Department of Nagpur University for antimicrobial activity and "AASCON-TISCO" for award of research scholarship.

REFERENCES

1. G.Ya. Kondra'eva, *Khim. Nauka Prom.*, **2**, 666 (1967); *Chem. Abstr.*, **52**, 6345 (1958).
2. R. Huisgen, in Aromaticity, Chemical Society Special Publication, Chemical Society, London, 21, S 1 (1967).
3. E.D. Bransome (Ed.), The Current Status of Liquid Scintillatron Countina, Graune and Stratton, New York (1970).
4. C.D. Withrow, *Adv. Neuro.*, **27**, 577 (1980).
5. E. Tubaro, *Bull. Chim. Farm.*, **104**, 602 (1965).
6. Manoj D. Prabhavat, A.R. Vyawahare and B.J. Ghiya, *Asian J. Chem.*, **11**, 1123 (1999).
7. Bir Sain, Satyendrapal Singh and Jagir S. Sandhu, *Chem. Band.*, **15**, 497 (1990).
8. R. Cruickshank, J.P. Duguid, B.P. Manmion and R.H.A. Swain, Med. Microbial, 12th Edn., Churchill-Livingstone, Edinburg-London, p. 2 (1975).

(*Received:* 25 August 2000; *Accepted:* 7 November 2000) AJC-2156