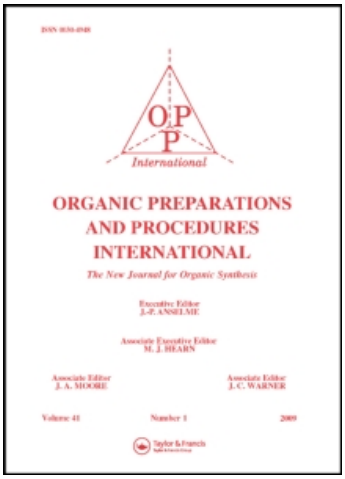


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 3-(2-ARYL-1H-INDOL-3-YL)-4-AROYL-5-ARYLISOXAZOLINES

Vijai N. Pathak[a]; Meenakshi Jain[a]; Anjali Tiwari[a]
[a] Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur, INDIA

To cite this Article Pathak, Vijai N. , Jain, Meenakshi and Tiwari, Anjali(2008) 'SYNTHESIS OF 3-(2-ARYL-1H-INDOL-3-YL)-4-AROYL-5-ARYLISOXAZOLINES', Organic Preparations and Procedures International, 40: 5, 493 — 498
To link to this Article: DOI: 10.1080/00304940809458114
URL: http://dx.doi.org/10.1080/00304940809458114

4. C. Ding, R. Batorsky, R. Bhide, H. J. Chao, Y. Cho, S. Chong, J. Gullo-Brown, P. Guo, S. H. Kim, F. Lee, K. Leftheris, A. Miller, T. Mitt, M. Patel, B. A. Penhallow, C. Ricca, W. C. Rose, R. Schmidt, W. A. Slusarchyk, G. Vite, N. Yan, V. Manne and J. T. Hunt, *J. Med. Chem.*, **42**, 5241 (1999).

5. Y. R. Rao, M. Mapuji and S. N. Mahapatra, *Org. Prep. Proc. Int.*, **14**, 199 (1982).

6. T. Nagasaka and Y. J. Koseki, *J. Org. Chem.*, **63**, 6797 (1998).

7. J.-M. Huang, H. Chen and R.-Y. Chen, *Synth. Commun.*, **32**, 2215 (2002).

8. O. Lack and R. E. Martin, *Tetrahedron Lett.*, **47**, 8207 (2005).

9. D. H. Kim, *J. Med. Chem.*, **20**, 209 (1977).

10. M. Uskoković, J. Iacobelli and W. Wenner, *J. Org. Chem.*, *27*, 3606 (1962).

11. D. H. Kim, *J. Heterocycl. Chem.*, **13**, 1187 (1976).

12. R. P. Tripathi, N. Saxena, V. K. Tiwari, S. S. Verma, V. Chaturvedi, Y. K. Manju, A. K. Srivastva, A. Gaikwad and S. Sinha, *Bioorg. Med. Chem.*, **14**, 8186 (2006).

****

SYNTHESIS OF 3-(2-ARYL-1H-INDOL-3-YL)-4-AROYL-5-ARYLISOXAZOLINES

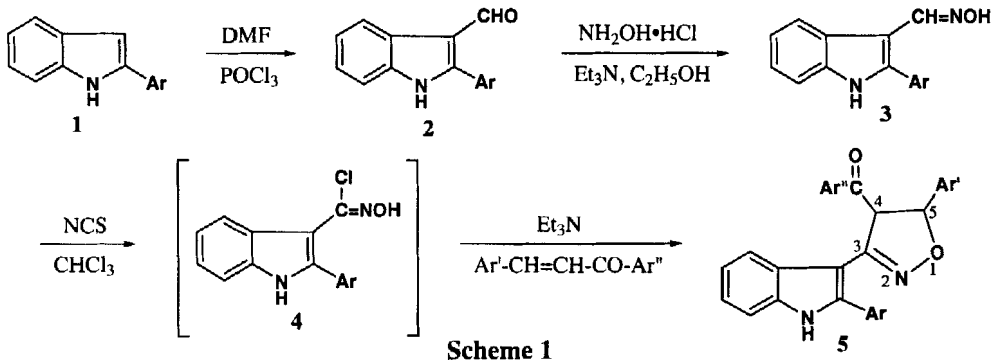
Submitted by (03/08/08)

Vijai N. Pathak†, Meenakshi Jain* and Anjali Tiwari

Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur-302 004, INDIA
e-mail: pathakvijain@yahoo.com

Isoxazolines are useful as intermediates in organic synthesis and possess a broad range of biological activities such as antibacterial and antifungal,[1] antiinflammatory,[2] antiviral,[3] herbicidal,[4] neurotropic and antitumor,[5] vasodilating, anticoagulant and cardio-protective activities,[6] glycoprotein IIb/ IIIa antagonistic,[7] anti-HIV and antidepressant activities.[8] They also act as novel inhibitors of cyclooxygenase-2 with analgesic activity[9] and inhibitors of human leukocyte elastase (HLE) and cathepsin G (Cath G).[10] Isoxazolines have been utilized as scaffolds for peptidominetics,[11] and core structures in medicinal chemistry. Indole derivatives also constitute an important class of therapeutic agents in medicinal chemistry including anticancer,[12] antioxi-

dant,[13] antirheumatoidal,[14] anti-HIV[15,16] and antimicrobial activities.[17,18] With these observations in mind, we coupled two pharmacophores, indole and isoxazoline, in the hope to achieve more potent pharmaceutical results and now report the synthesis of 3-(2-aryl-1H-indol-3-yl)-4-aroyl-5-arylisoxazolines by treatment of indolylnitriloxides with chalcones.



Scheme 1

2-Aryl-1H-indoles (**1**) were subjected to Vilsmeier-Haack formylation[19] with N,N-dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$) to give 2-aryl-1H-indole-3-carboxaldehydes (**2**), which on treatment with hydroxylamine hydrochloride and triethylamine (Et_3N) in ethyl alcohol gave indolylaldoximes (**3**); they were subsequently converted into the nitriloxides by treatment with N-chlorosuccinimide (NCS) in the presence of triethylamine *in situ* in the presence of chalcones to afford the title compounds (**5a-j**) regioselectively. The cycloaddition of nitriloxides to chalcones may lead to the formation of two isomeric intermediate species. However, the intermediate that consists anionic charge being conjugated to the carbonyl group is expected to be more stable, hence this intermediate will be formed preferentially and will afford the title compounds through intramolecular cyclization. The physical and analytical data of compounds (**5a-j**) are given in **Tables 1** and **2**.

Compounds (**5a-j**) were screened for their antimicrobial activity against the gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli* and fungi *Aspergillus flavus* and *Aspergillus niger* at different concentration by inhibition zone technique.[20] Streptomycin and betadine were used as reference compounds for evaluating the antibacterial and antifungal activities, respectively. Compounds (**5f-j**) showed enhanced antibacterial and antifungal activity which could be attributed to the presence of methoxy in the aroyl group and fluorine in the aryl group attached to the isoxazoline ring. The possible use of these compounds as drugs is being explored.

EXPERIMENTAL SECTION

All the melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 557 grating infrared spectrophotometer in KBr pellets. PMR spectra were recorded on Bruker spectrophotometer (300 MHz) using $CDCl_3$

as a solvent. TMS was used as internal standard (chemical shift in δ, ppm). Mass spectra were recorded on Jeol SX-102 (FAB) mass spectrometer. The purity of the compounds was checked by TLC using silica gel-G as adsorbent, UV light or iodine accomplished visualization. 2-Arylindoles (**1**) were prepared by the method of Joshi *et al.*[21] 2-Arylindole-3-carboxaldehydes (**2**) and chalcones were prepered by the literature method.[19,22]

Synthesis of Indolylaldoximes (3a-e).- A mixture of 2-aryl-1H-indole-3-carboxaldehyde (**2**) (2 mmol), hydroxylamine hydrochloride (2.2 mmol, 0.15 g) and triethylamine (2.2 mmol, 0.3 mL) in ethyl alcohol (25 mL) was refluxed on a steam bath for 1 hr. After completion of the reaction (checked by TLC), ethanol was removed by distillation on the steam bath. Addition of a small amount of water to the cooled residue followed by cooling and stirring in an ice bath gave the oxime as a crystalline solid, which was collected, washed with a little water and dried. Recrystallise from ethanol.

Table 1. Physical and Analytical Data of 3-(2-Aryl-1H-indol-3-yl)-4-aroyl-5-arylisoxazolines (**5a-j**)

Cmpd	Ar	Ar'	Ar''	mp. (°C)	(Found) Calcd C	H	N
5a	C_6H_5	C_6H_5	C_6H_5	88-90	(81.47) 81.44	(4.98) 4.97	(6.31) 6.33
5b	4-BrC_6H_4	C_6H_5	C_6H_5	106-108	(69.24) 69.23	(4.05) 4.03	(5.36) 5.38
5c	4-ClC_6H_4	C_6H_5	C_6H_5	98-100	(75.56) 75.55	(4.43) 4.40	(5.88) 5.87
5d	4-FC_6H_4	C_6H_5	C_6H_5	92-93	(78.29) 78.26	(4.54) 4.56	(6.07) 6.08
5e	3-$NO_2C_6H_4$	C_6H_5	C_6H_5	110-112	(73.91) 73.92	(4.33) 4.31	(8.61) 8.62
5f	C_6H_5	4-FC_6H_4	4-$CH_3OC_6H_4$	102-103	(75.90) 75.91	(4.71) 4.69	(5.70) 5.71
5g	4-BrC_6H_4	4-FC_6H_4	4-$CH_3OC_6H_4$	136-138	(65.47) 65.49	(3.89) 3.87	(4.90) 4.92
5h	4-ClC_6H_4	4-FC_6H_4	4-$CH_3OC_6H_4$	130-131	(70.91) 70.92	(4.20) 4.19	(5.31) 5.33
5i	4-FC_6H_4	4-FC_6H_4	4-$CH_3OC_6H_4$	124-126	(73.24) 73.22	(4.34) 4.33	(5.50) 5.51
5j	3-$NO_2C_6H_4$	4-FC_6H_4	4-$CH_3OC_6H_4$	142-144	(71.69) 71.67	(4.24) 4.23	(8.11) 8.09

Generation of Indolylhydroximoyl Chlorides (4a-e).- A mixture of indolylaldoxime (**3a-e**) (1 mmol) and NCS (1.1 mmol, 0.15 g) in chloroform (20 mL) was refluxed on a water bath for 1 hr.

Table 2. Spectral Data of 3-(2-Aryl-1H-indol-3-yl)-4-aroyl-5-arylisoxazolines (**5a-j**)

Cmpd	IR (KBr)(cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm)	MS (FAB) m/z
5a	3320 (NH str.), 3050 (aromatic C-H str.), 2875 (aliphatic C-H str.), 1710 (C=O str.), 1575 (C=N str.)	8.5 (s, NH, 1H), 7 – 7.7 (m, Ar-H, 19H), 3.44 (d, H-5, 1H, J=6 Hz), 3.39 (d, H-4, 1H, J=6 Hz)	443 (M^+ + 1)
5b	3263 (NH str.), 3050 (aromatic C-H str.), 2838 (aliphatic C-H str.), 1663 (C=O str.), 1562 (C=N str.), 525 (C-Br)	8 (s, NH, 1H), 7.2 – 7.7 (m, Ar-H, 18H), 3.74 (d, H-5,1H, J=6.9 Hz), 3.70 (d, H-4, 1H, J=6.9 Hz)	520 / 522* (M^++ 1)
5c	3240 (NH str.), 3040 (aromatic C-H str.), 2840 (aliphatic C-H str.), 1710 (C=O str.), 1580 (C=N str.), 735 (C-Cl)	8.3 (s, NH, 1H), 7.1 – 8.2 (m, Ar-H, 18H), 3.42 (d, H-5, 1H, J=6.9 Hz), 3.37 (d, H-4, 1H, J=6.9 Hz)	477 / 479* (M^++ 1)
5d	3263 (NH str.), 3050 (aromatic C-H str.), 2840 (aliphatic C-H str.), 1663 (C=O str.), 1600 (C=N str.), 1100 (C-F)	8.4 (s, NH, 1H), 8 – 8.3 (m, Ar-H, 18H), 4.25 (d, H-5, 1H, J=6.9 Hz), 4.21 (d, H-4, 1H, J=6.9 Hz)	461 (M^+ + 1)
5e	3313 (NH str.), 3050 (aromatic C-H str.), 2856 (aliphatic C-H str.), 1583 (C=O str.), 1609 (C=N str.),1338(-NO_2)	8.3 (s, NH, 1H), 7.1 – 8.2 (m, Ar-H, 18H), 3.43 (d, H-5, 1H, J=6.9 Hz), 3.38 (d, H-4, 1H, J=6.9 Hz)	488 (M^+ + 1)
5f	3175 (NH str.), 3050 (aromatic C-H str.), 2850 (aliphatic C-H str.), 1713 (C=O str.), 1563 (C=N str.), 1083 (C-F)	8.5 (s, NH, 1H), 7.1 – 7.3 (m, Ar-H, 17H), 3.50 (d, H-5, 1H, J=6.9 Hz), 3.46(d, H-4, 1H, J=6.9 Hz), 3.6 (s, OCH_3, 3H)	491 (M^+ + 1)
5g	3263 (NH str.), 3025 (aromatic C-H str.), 2838 (aliphatic C-H str.), 1663 (C=O str.), 1609 (C=N str.),1100 (C-F), 525 (C-Br)	8.2 (s, NH, 1H), 7 – 7.5 (m, Ar-H, 16H), 3.43 (d, H-5, 1H, J=6.9 Hz), 3.38 (d, H-4, 1H, J=6.9 Hz), 3.5 (s, OCH_3, 3H)	568 / 570* (M^++ 1)
5h	3175 (NH str.), 3050 (aromatic C-H str.), 2836 (aliphatic C-H str.), 1706 (C=O str.), 1575 (C=N str.),1106 (C-F), 745 (C-Cl)	8.8 (s, NH, 1H), 7.1 – 7.8 (m, Ar-H, 16H), 3.43 (d, H-5, 1H, J=6 Hz), 3.39 (d, H-4, 1H, J=6 Hz), 3.5 (s, OCH_3, 3H)	525 / 527* (M^++ 1)
5i	3312 (NH str.), 3038 (aromatic C-H str.), 2838 (aliphatic C-H str.), 1656 (C=O str.), 1588 (C=N str.), 1100 (C-F)	8.2 (s, NH, 1H), 7 – 7.5 (m, Ar-H, 16H), 3.43 (d, H-5, 1H, J=6.9 Hz), 3.38 (d, H-4, 1H, J=6.9 Hz), 3.5 (s, OCH_3, 3H)	509 (M^+ + 1)
5j	3263 (NH str.), 3050 (aromatic C-H str.), 2838 (aliphatic C-H str.), 1706 (C=O str.), 1603 (C=N str.),1086 (C-F), 1338 (-NO_2)	8.2 (s, NH, 1H), 7 – 7.5 (m, Ar-H, 16H), 3.43 (d, H-5, 1H, J=6.9 Hz), 3.38 (d, H-4, 1H, J=6.9 Hz), 3.5 (s, OCH_3, 3H)	520 (M^+ + 1)

After completion of the reaction (checked by TLC), the solution of the indolylhydroximoyl chloride was cooled and used for further reaction without isolation. The end point of the chlorination is reached when the solid has dissolved and color of solution changes yellow to dark red. Since the lifetime of the nitriloxides is too short for isolation, the solution must be used immediately in the reaction with the chalcones.

Synthesis of 3-(2-Aryl-1H-indol-3-yl)-4-aroyl-5-arylisoxazolines (5a-j).- To a stirred solution of (**4**) (1 mmol in 15 mL chloroform) was added the chalcone (1 mmol in 10 mL chloroform), followed by the dropwise addition of triethylamine (1 mmol in 5 mL chloroform) over 30 minutes at room temperature. Stirring was continued for 45 minutes until the completion of the reaction (checked by TLC). The solution was washed with 2N NaOH solution (3 x 25 mL) followed by water (3 x 25 mL). After drying over magnesium sulfate, the solvent was evaporated *in vacuo* to give products which were purified by column chromatography over silica gel-G using the benzene, petroleum ether solvent system.

Acknowledgements.- The authors are thankful to Dr. K. P. Madhusudanan, Deputy Director and Head, Saif, Central Drug Research Institute (CDRI), Lucknow and Head, Department of Chemistry, University of Rajasthan, Jaipur (India) for elemental analysis and spectral (IR, ^{1}H NMR and FAB Mass) data. We are also thankful to Ms. S. Rupadevi, Lecturer, Department of Biotechnology, JECRC, Jaipur (India) for biological screening of these compounds.

REFERENCES

† Deceased

1. T. K. Shah and V. Desai, *J. Serb. Chem. Soc.*, **72**, 443 (2007).
2. K. K. Park, D. H. Ko, Z. You, M. O. F. Khan and H. J. Lee, *Steroids*, **71**, 183 (2006).
3. S. D. Sokolov, S. M. Vinogradova, V. S. Ignatov, V. V. Paramonova, I. S. Nikolaeva, N. S. Bogdanova and G. N. Pershin, *Pharma. J. Chem.*, **15**, 854 (1981).
4. I. T. Hwang, H. R. Kim, J. S. Choi, D. J. Jeon, K. S. Hong, J. H. Song and K. Y. Cho, *Weed biology and Management*, **6**, 102 (2006).
5. E. Lukevics, P. Arsenyan, S. Germane and I. Shestakova, *Appl. Org. Chem.*, **13**, 795 (1999).
6. E. Lukevics, P. Arsenyan and M. Veveris, *Metal-based drugs*, **5**, 251 (1998).
7. S. A. Mousa and J. Wityak, *Cardiovascular Drug Reviews*, **16**, 48 (1998).
8. M. Imran, S. A. Khan and N. Siddiqui, *Indian J. Pharm. Sci.*, **66**, 377 (2004).
9. A. G. Habeeb, P. N. Praveen Rao and E. E. Knaus, *J. Med. Chem.*, **44**, 2921 (2001).
10. W. C. Groutas, R. Venkataraman, L. S. Chong, J. E. Yoder, J. B. Epp, M. A. Stanga and E. H. Kim, *Bioorg. Med. Chem.*, **3**, 125 (1995).

11. Y. J. Chung, E. J. Ryu, G. Keum and B. H. Kim, *Bioorg. Med. Chem.*, **4**, 209 (1996).

12. I. Chen, S. Safe and L. Bjoldanes, *Biochem. Pharmacol.*, **51**, 1069 (1996).

13. S. Suzen and E. Buyukbingol, *Il Farmaco.*, **55**, 246 (2000).

14. G. Giagoudakis and S. L Markantonis, *Pharmacotherapy*, **25**, 18 (2005).

15. E. Buyukbingol, S. Suzen and G. Klopan, *Il Farmaco.*, **49**, 443 (1994).

16. S. Suzen and E. Buyukbingol, *Il Farmaco.*, **53**, 525 (1998).

17. H. H Hoppe, A. Kerkenaar and A. Kaars Sijpesteijn, *Pestic. Biochem. Physiol.*, **6**, 413 (1976).

18. S. K. Sridhar, S. N. Pandeya, S. K Bajpai and H. Manjula, *Indian Drugs*, **36**, 412 (1999); *Chem. Abstr.*, **132**, 166091z (2000).

19. K. C. Joshi, V. N. Pathak and R. K. Chaturvedi, *Pharmazie*, **41**, 634 (1986).

20. M. C. Bryant, *Antibiotics and their Laboratory Control*, Butterworth, London (1968).

21. K. C. Joshi, V. N. Pathak and P. Chand, *J. prakt. Chem.*, **320**, 701 (1978).

22. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry* (5th ed.), Pearson Education: Singapore, pp.1033 (**2005**).

****