HETEROCYCLES, Vol. 71, No. 3, 2007, pp. 569 - 576. © The Japan Institute of Heterocyclic Chemistry
Received, 24th November, 2006, Accepted, 25th January, 2007, Published online, 26th January, 2007. COM-06-10958

A CONVENIENT K_2CO_3 CATALYSED REGIOSELECTIVE SYNTHESIS FOR BENZOPYRANO[4,3-*c*]PYRAZOLES IN AQUEOUS MEDIUM

Mazaahir Kidwai,* Priya, Kavita Singhal, and Shweta Rastogi

*Green Chemistry Research Laboratory, Department of Chemistry,
University of Delhi, Delhi-110007, India
Telefax : (91 11) 27666235; Email: kidwai.chemistry@gmail.com

Abstract – This synthetic approach features heterocondensation reaction between *in situ* generated 3-arylidene-2,4-chromanediones and *N*-substituted hydrazine moiety avoiding the use of organic solvents at any stage. Water as solvent is taken for the synthesis of selective benzopyranopyrazole derivatives under microwaves (MWs). Hydroxy coumarin moiety is employed for this ecofriendly strategy.

INTRODUCTION

The environment calls on the entire research edifice to define long term strategic goals for clean chemistry and to reduce the amount of pollutants produced including organic solvents whose recovery is mandated by evermore strict laws. To reduce the dependence on ecologically unsafe chemicals, it is advantageous to carryout reactions in aqueous media. Water is the abundantly available solvent, indeed a cheaper medium for many reactions but is often-appears as a nature's enemy to be kept away from the reaction mixture until work up. Reactions in aqueous media are environmentally benign, easy to handle and devoid of any corrosive or carcinogenic effects. Moreover, this leads to shorter reaction times with enhanced yield and greater ease of manipulation.[1,2] Therefore, the development of an efficient synthetic methodology to form carbon-nitrogen bond in aqueous media appears to be necessary. Being polar, water serves as an excellent solvent for microwave assisted reactions[3-4] too.

Coumarin (benzopyran) is one of the most interesting molecule as it exhibits diverse chemical[5-7] and biological[8-12] properties. In addition, pyrazole nucleus in fusion with benzopyrans confers pharmacological properties. [13-16]

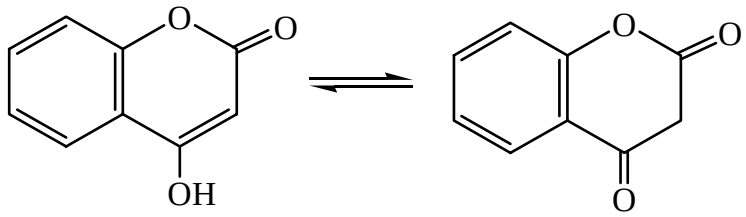
Keeping in view the medicinal importance of benzopyranopyrazoles and in continuation of our ongoing program[17] towards aqueous mediated ecofriendly green synthesis, it was thought worthwhile to regioselectively synthesize benzopyrano[4,3-*c*]pyrazoles under microwaves using water as solvent.

We herein report a regiocontrolled conversion of arylidene derivatives of benzopyran into substituted benzopyrano[4,3-*c*]pyrazoles **(4a-g)** by reaction with phenylhydrazine hydrochloride in refluxing water.

By help of ^{13}C NMR, it has been proved that cycloaddition would proceed in such a manner that union occurs between C_{9b} of coumarins and amino group of phenylhydrazine to give resulting product.

RESULTS AND DISCUSSION

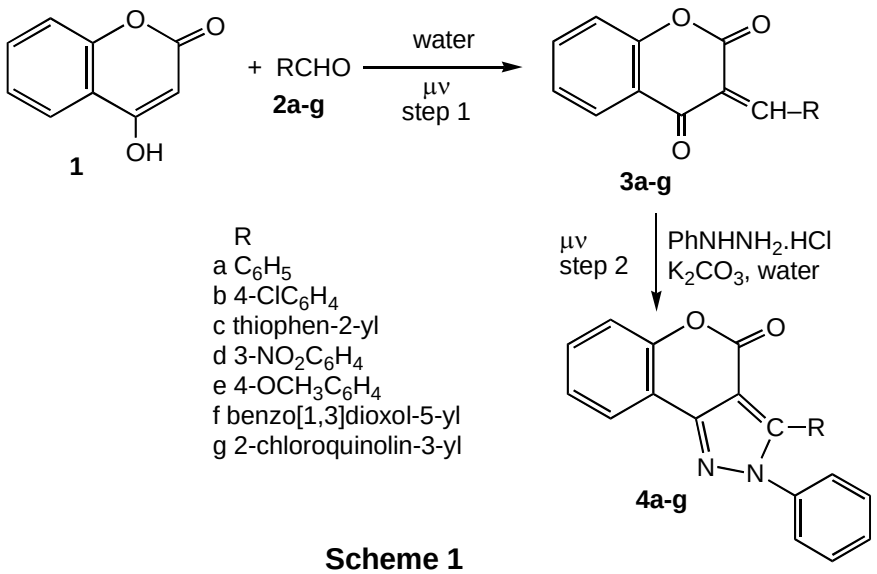
Various methods reported for Benzopyrano[4,3-*c*]pyrazole derivatives so far, employ the use of hazardous solvents like diphenylnitrilimine[18], acetic acid[19], pyridine[20], xylene[21], with harmful catalysts like HCl[22], triethylamine[23]. To greenify the above procedures for the synthesis of biologically active benzopyrano[4,3-*c*]pyrazoles using environmentally benign reagents, we explored a new route for the synthesis of regioselective benzopyrano[4,3-*c*]pyrazoles **4a-g** with K_2CO_3 as base and water as solvent. Firstly, 4-hydroxy-2*H*[1]benzopyran-2-one (4-hydroxycoumarin) **1** was taken with different aldehydes **2a-g** in water to yield 3-arylidenechromane-2,4-diones **3a-g**. In this preliminary study, we were pleased to find that in this Knoevenagel condensation reaction using water, base was not required. The arylidene derivatives thus obtained were in high yield. The structures of these known α,β-unsaturated carbonyls were found to be in consistency with the spectroscopic data.[25] Further these compounds were easily obtained as they precipitated out as an insoluble solid in water. Since 4-hydroxy-2*H*[1]benzopyran-2-one **1** exists in tautomeric form (Figure 1) with corresponding 2-hydroxy-4-pyrone[27] and is an active methylene reagent, thus the plausible mechanism of our protocol involves the condensation of one mole of aromatic aldehydes **2a-g** with one mole of 4-hydroxy-2*H*[1]benzopyran-2-one **1** in water to give arylidene derivatives **3a-g**.



1 (enol form) **1** (keto form)

Figure 1

Then these intermediates **3a-g** were reacted as an α,β-unsaturated carbonyl moiety with phenylhydrazine hydrochloride in the presence of catalytic amounts of K_2CO_3 in hot water. Here, the use of K_2CO_3 served as a mild water soluble inorganic base[26] which obviated the requirement of the removal of acidic components formed in the reaction medium and excess of K_2CO_3 gets easily washed off with water. Moreover, the use of K_2CO_3 is found to be necessary to solubilise the chalcones **3a-g** as well as to release phenylhydrazine from its hydrochloride salt. The product can be obtained after cooling in 10-15 minutes. The presence of K_2CO_3 makes easier the formation of pure phenylhydrazine from its hydrochloride and then the amino group of phenylhydrazine condensed with the carbonyl group of arylidene derivatives lead to cyclisation for benzopyrano[4,3-*c*]pyrazoles **(4a-g)**.



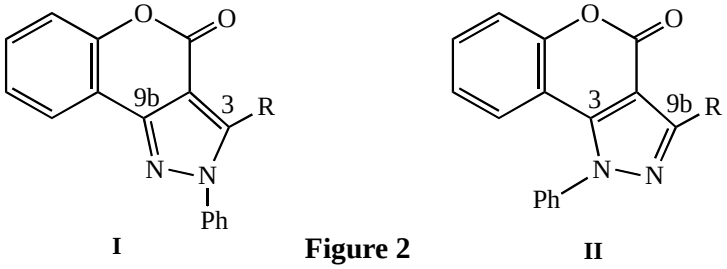
Scheme 1

Table 1. Reaction times and yields for 3-arylidene-chromane-2,4-diones (step 1) and benzopyrano-[4,3-*c*]pyrazoles (step 2)

R	Step 1			Step 2				
	Compound	mp/°C	Time (min) / Yield (%)	Compound	mp/°C	Method B time (hr) / yield (%)	Method C time (hr) / yield (%)	Method D time (min) / yield (%)
Ph	**3a**	234-236 [>230][24]	0.50/78	**4a**	130-135	6/50	5.5/68	2.0/77
4-ClC_6H_4	**3b**	220-225	0.75/80	**4b**	103-104	7/53	5.0/70	3.0/77
thiophen-2-yl	**3c**	202-206	1.0/85	**4c**	120-124	6.5/45	5.0/78	2.5/85
3-$NO_2C_6H_4$	**3d**	170-175	1.5/76	**4d**	105-108	7.0/40	5.5/70	3.5/75
4-$OCH_3C_6H_4$	**3e**	210-214 [212][24]	1.5/80	**4e**	98-102	5.5/45	4.0/72	2.5/78
benzo[1,3]dioxol-5-yl	**3f**	265-270	1.75/75	**4f**	270-273	7.0/52	4.5/68	2.5/75
2-chloroquinoline-3-yl	**3g**	246-248	2.0/75	**4g**	190-192	8.0/58	5.5/68	4.5/76

No minor reaction side products could be isolated from the reaction mixture.

The structures of the synthesized compounds **4a-g** were confirmed on the basis of their spectroscopic data. The infrared spectrum of products **4a-g** showed two bands at 1593-1608 cm^{-1} for C=N stretching and 1665-1677 cm^{-1} for C=O stretching. The significant ^1H NMR and mass spectrum further satisfied the proposed product of benzopyranopyrazoles. However, IR, mass and especially ^1H NMR spectra did not confirm the final product structure **4a-g.** Since the reaction pathway followed in the scheme resulted in two types of products i.e. structure I and II as shown in **Figure 2,** thus ^{13}C NMR was found to be informative.

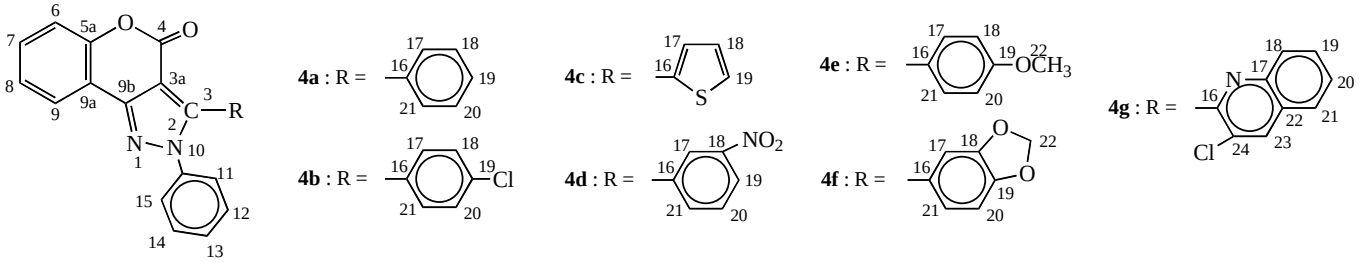


I **Figure 2** II

^{13}C NMR confirms the sole product **(I)** obtained in our protocol (**Table 2**). This can be explained simply. Had C-9b bonded with substituted nitrogen one side, this would have upfield its signal by 12-20 ppm and makes its appearance nearby the signal of C_3 carbon atom i.e. 143-145 (structure **II**, Figure 2). But our spectras does not consist of such type of signals. Whereas, the spectra shows the difference of C-9b and C-3 signals with range of 12-15 ppm apart which entirely eliminates the possibility of structure **II** and indicates that the unsubstituted nitrogen is attached to C_{9b} atom, which leads to the appearance of its signal ~ 153-160 ppm. The purity of compounds were determined by CHN data.

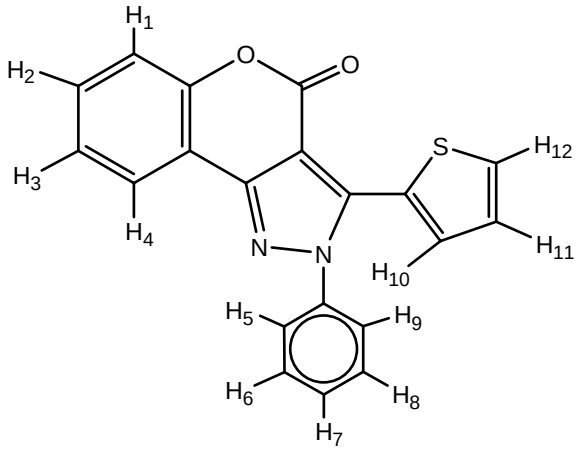
Knowing widespread application of benzopyrano[4,3-*c*]pyrazoles, their synthesis has been scaled up towards green chemistry domain by circumventing the use of any organic solvent and harmful catalysts. Water has been proved here as a suitable green solvent for the synthesis of benzopyranopyrazoles. In this protocol the products obtained in high yield, pure and easily isolable. Diversified point is the variation of the aryl group on the arylidene derivative which led to a library synthesis for wider role in pharmaceuticals. This is beneficial for synthetic chemist which involves only water as a solvent for the desired target synthesis.

Table 2. ^{13}C chemical shifts of compounds **(4a-g)**

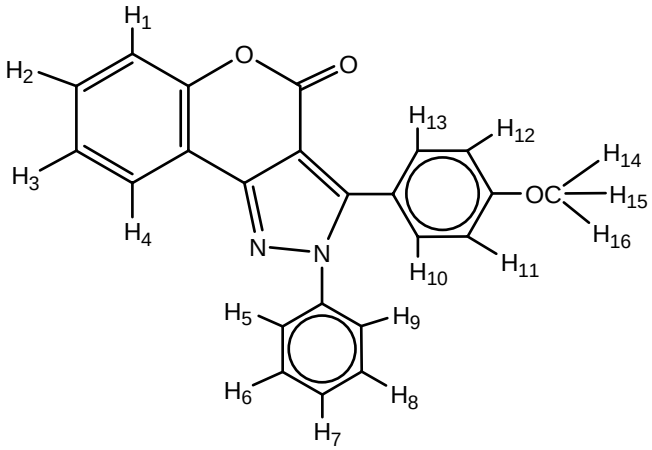


Carbon	4a	4b	4c	4d	4e	4f	4g
3	144.4	144.7	144.7	144.5	144.43	144.4	144.9
3a	105.3	105.8	105.6	105.6	105.2	105.3	105.7
4	162.0	162.4	162.3	162.6	162.2	162.4	162.7
5a	150.0	150.6	150.2	150.4	150.0	150.2	150.6
6	121.3	121.9	121.6	121.4	121.4	121.6	121.9
7	128.2	128.6	128.4	128.2	128.1	128.3	128.7
8	124.5	124.9	124.7	124.8	124.6	124.9	124.1
9a	129.1	129.4	129.2	129.5	129.2	129.5	130.1
9b	150.0	159.0	158.6	158.9	153.5	156.6	158.6
10	138.2	138.4	138.2	138.0	138.4	138.6	138.8
11	120.7	120.8	120.9	120.8	120.9	120.4	121.2
12	129.0	129.2	129.0	129.4	129.1	129.3	129.7
13	125.3	125.5	125.3	125.5	125.6	125.8	126.1
14	129.2	129.4	129.2	129.3	129.3	129.3	129.6
15	120.7	120.9	120.9	120.8	120.7	120.9	120.7
16	135.7	136.6	139.0	135.9	128.0	129.4	158.2

17	126.8	127.4	121.7	124.4	128.4	114.2	145.9
18	129.2	129.6	127.7	149.0	114.9	148.9	128.7
19	128.8	133.0	125.5	124.0	160.0	146.9	128.9
20	129.4	129.6	-	130.2	115.0	115.2	126.7
21	126.6	127.5	-	134.0	128.6	120.1	125.1
22	-	-	-	-	56.4	90.7	125.4
23	-	-	-	-	-	-	134.1
24	-	-	-	-	-	-	125.0



4c



4e

Figure 3

This is further confirmed with NOESY NMR spectra of compounds **4c** and **4e** in **Figure 3.** The cross correlation peaks due to coupling between aromatic protons ($\delta > 7$) and thienyl proton ($\delta < 7$) (H-9/H-10) in the case of **4c** and between aromatic proton of phenyl attached to N ($\delta > 7$) and aromatic proton of methoxyphenyl group ($\delta < 7$) (H-9/H-10) in the case of **4e** have been found. Hence, the synthetic method adopted in the work has been found to be regioselective favouring compound having structure I (shown in **Figure 2**).

EXPERIMENTAL

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. IR (in Nujol) were recorded on a model Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR was recorded on a Bruker Avance spectrospin 300 (300 MHz) and ^{13}C NMR was recorded on a Bruker Topspin 300 (300 MHz) spectrometer using TMS as internal standard. The purity of compounds were checked on silica gel coated aluminium plates (Merck). A Kenstar microwave oven, Model No. OM9925E at (2450 MHz, 800W) was used for MWI. Temperature of the reaction was measured through AZ, Mini Gun Type, Non-Contact IR Thermometer, Model No. 8868. Elemental analyses were performed using Heraeus CHN-Rapid Analyzer. EI mass spectra were recorded on a JEOL-JHS-DX 303 mass spectrometer.

General procedure for the synthesis of 3-Arylidene-chromane-2,4-diones 3a-g (STEP 1)

Method A

To the mixture of 4-hydroxycoumarin **1** (0.01 mol), aromatic/heteroaromatic aldehyde **2a-g** (0.01 mol), 3-4 mL of water was added. Irradiate the reaction mixture for appropriate time in microwave. Progress of the reaction was monitored by TLC examination. The solid obtained was filtered, washed with water and recrystallised with EtOH.

General procedure for the synthesis of 2-Phenyl-3-aryl[1]benzopyrano[4,3-c] pyrazol-4(2H)-ones 4a-g (STEP 2)

Method B (Conventional method)

To the mixture of 3-arylidenechromane-2,4-diones **3a-g** (0.01 mol), phenylhydrazine hydrochloride (0.015 mol) and K_2CO_3, 10 mL of EtOH was added. Refluxed the reaction mixture for appropriate time with constant stirring. Reaction was monitored by TLC examination. Upon completion of reaction, the solid obtained was filtered, washed with water. Then product was purified by column chromatography [column of silica gel, elution with Benzene:EtOAc 8:2 (v/v) preceded by recrystallisation with EtOH.

Method C (Conventional Method)

To the mixture of 3-arylidenechromane-2,4-diones **3a-g** (0.01 mol), phenylhydrazine hydrochloride (0.015 mol) and K_2CO_3, 10 ml of water was added. Refluxed the reaction mixture for appropriate time with constant stirring. Rest is same as above.

Method D (Microwave assisted synthesis)

In an Erlenmeyer flask, 3-arylidenechromane-2,4-diones **3a-g**, phenylhydrazine hydrochloride (0.015 mol) and K_2CO_3 with 2-3 mL of water were taken. The reaction mixture was subjected to microwave irradiation (MWI) for a specific time (Table 1) at low power (560 W). The progress of the reaction was monitored by TLC at an interval of every 30 sec. On completion, the reaction mixture was cooled and filtered, washed with cold water and dried. Rest is same as above.

2,3-Diphenyl[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4a**; IR ν (cm^{-1}) 1593 (C=N), 1666 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.09-7.52 (m, 14H, Ar-H). MS: m/z 338 (M^+). *Anal.* Calcd for $C_{22}H_{14}N_2O_2$: C, 78.1; H, 4.14; N, 8.28. Found: C, 78.23; H, 4.36; N, 8.36.

2-Phenyl-3-(4-chlorophenyl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4b**; IR ν (cm^{-1}) 1608 (C=N), 1674 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.92 (m, 3H, Ar-H), 7.01 (d, 2H, Ar-H), 7.12 (d, 2H, Ar-H), 7.21-7.34 (m, 6H, Ar-H). MS: m/z 372 (M^+). *Anal.* Calcd for $C_{22}H_{13}N_2O_2Cl$: C, 70.96; H, 3.49; N, 7.52. Found: C, 70.99; H, 3.64; N, 7.72.

2-Phenyl-3-(thiophen-2-yl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4c**; IR ν (cm^{-1}) 1599 (C=N), 1663 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.76-6.81 (m, 1H, thienyl H), 6.94 (d, 2H, Ar-H), 7.00 (d, 2H, thienyl H), 7.16-7.21 (m, 5H, Ar-H), 7.34-7.44 (m, 2H, Ar-H). MS: m/z 344 (M^+). *Anal.* Calcd for

$C_{20}H_{12}N_2O_2S$: C, 69.76; H, 3.55; N, 8.14; S 9.75. Found: C, 69.99; H, 3.62; N, 8.37; S 9.70. NOE correlations: H-1/H-2, H-3/H-2, -4, H-5/H-6, H-7/H-6, -8, H-9/H-8, -10, H-11/H-10, -12.

2-phenyl-3-(3-nitrophenyl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4d**; IR ν (cm^{-1}) 1601 (C=N), 1665 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.23-7.41 (m, 8H, Ar-H), 7.67-7.8 (m, 4H, Ar-H), 8.23 (s, 1H, Ar-H). MS: m/z 383 (M^+). *Anal.* Calcd for $C_{22}H_{13}N_3O_4$: C, 68.92; H, 3.39; N, 10.96. Found: C, 70.12; H, 3.78; N, 10.99.

2-Phenyl-3-(4-methoxyphenyl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4e**; IR ν (cm^{-1}) 1605 (C=N), 1677 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.84 (s, 3H, OCH_3), 6.86-7.53 (m, 13H, Ar-H). MS: m/z 368 (M^+). *Anal.* Calcd for $C_{23}H_{16}N_2O_3$: C, 75.00; H, 4.34; N, 7.60. Found: C, 75.42; H, 4.73; N, 7.82. NOE correlations: H-1/H-2, H-3/H-2, -4, H-5/H-6, H-7/H-6, -8, H-9/H-8, -10, H-11/H-10, -OCH_3/H-11, -12, H-13/H-12.

2-Phenyl-3-(benzo[1,3]dioxol-5-yl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4f**; IR ν (cm^{-1}) 1599 (C=N), 1660 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.92 (s, 2H, O-CH_2-O), 6.72 (d, 2H, Ar-H), 7.14-7.39 (m, 10H, Ar-H). MS: m/z 382 (M^+). *Anal.* Calcd for $C_{23}H_{14}N_2O_4$: C, 72.25; H, 3.66; N, 7.32. Found: C, 72.47; H, 3.84; N, 7.46.

2-Phenyl-3-(2-chloroquinolin-3-yl)[1]benzopyrano[4,3-*c*]pyrazol-4[2*H*]-one **4g**; IR ν (cm^{-1}) 1608 (C=N), 1670 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.91-7.45 (m, 10H, Ar-H), 7.56-7.68 (m, 4H, Ar-H). MS: m/z 423 (M^+). *Anal.* Calcd for $C_{25}H_{14}N_3O_2Cl$: C, 70.84; H, 3.3; N, 9.91. Found: C, 70.96; H, 3.62; N, 10.09.

ACKNOWLEDGEMENTS

The authors are thankful to the Council of Scientific and Industrial Research, New Delhi for the financial assistance.

REFERENCES

1. M. Kidwai, S. Saxena, R. Mohan, and R. Venkataramanan, *J. Chem. Soc., Perkin Trans. I*, 2002, 1845.
2. M. Kidwai, *Pure Appl. Chem.*, 2001, **73**, 147.
3. N. E. Leadbeater, *Chem. Commun.*, 2005, 2881.
4. M. Kidwai, S. Rastogi, R. Thakur, and S. Saxena, *Z. Naturforsch*, 2004, **59B**, 606.
5. K. H. Drexhage, G. A. Reynold, Bio. Tech. Tap Int. Quantam Electron Conf. 8^{th}-9^{th}, 1974 (*Chem. Abstr.*, 1976, **90**, 114369n).
6. P. Czerney and H. Hartmann, *J. Liebscher, Germany*, 1981, **153**, 122 (*Chem. Abstr.*, 1982, **97**, 57).
7. K. H. Kaidbey and A. M. Kligman, *Arch. Dermatol.*, 1981, **117**, 258 (*Chem. Abstr.*, 1981, **95**, 19141e).
8. S. S. Misra and B. Nath, *Indian J. Appl. Chem.*, 1971, **34**, 260; R. Kuhn and H. R. Hensel, *Chem. Ber.*, 1953, **86**, 1333; S. S. Misra, *J. Indian Chem. Soc.*, 1973, **50**, 355; R. Aries, *Ger. Pat.*, 1974, **2**, 341514

(*Chem. Abstr.*, 1974, **80**, 146152).

9. T. O. Soine, *J. Pharm. Soc.*, 1964, **53**, 231.
10. T. R. Seshadri and S. Vishwapaul, *J. Scient. Ind. Res. India*, 1973, **32**, 227.
11. G. Furer, *Prog. Med. Chem.*, 1974, **10**, 85.
12. S. Tondon and R. Rastogi, *J. Scient. Ind. Res. India*, 1979, **38**, 428.
13. Y. Tarmura, M. Fujita, L. C. Chen, K. Uneo, and Y. Kita, *J. Heterocycl. Chem.*, 1982, **19**, 289.
14. N. K. Sangwan, B. S. Verma, O. P. Malik, and K. S. Dhindsa, *Indian J. Chem.*, 1990, **29B**, 294.
15. M. A. Stahman, C. F. Huebner, and K. P. Link, *J. Biol. Chem.*, 1941, **138**, 517.
16. S. S. Honmantgad, M. V. Kulkarni, and V. D. Patil, *Indian J. Chem.*, 1985, **24B**, 459.
17. M. Kidwai, S. Rastogi, and R. Venkataramanan, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 203; M. Kidwai, S. Saxena, M. K. R. Khan, and S. S. Thukral, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4295; M. Kidwai and K. Singhal, *Synth. Commun.*, 2006, **36**, 1887; B. S. Chikkara, A. K. Mishra, and V. Tandon, *Heterocycles*, 2004, **63**, 1057.
18. T. Fathi, N. Dinh An, G. Schmitt, E. Cerutti, and B. Laude, *Tetrahedron*, 1988, **44**, 4527.
19. B. Chantegrel, A. Nadi, and S. Gelin, *Tetrahedron Lett.*, 1983, **24**, 381.
20. A. Levai, *J. Heterocycl. Chem.*, 1998, **35**, 13.
21. A. S. Shawali, B. E. Elanadouli, and H. A. Albar, *Tetrahedron*, 1985, **41**, 1877.
22. G. Daidone, S. Plescia, and J. Fabra, *J. Heterocycl. Chem.*, 1980, **17**, 1409.
23. I. Strakova, M. Petrova, S. Belyakov, and A. Strakovs, *Chem. Heterocyclic Compds.*, 2003, **39**, 1608.
24. A. Cercek, B. Stanovnik, A. Stimac, and M. Tisler, *Heterocycles*, 1987, **26**, 2425.
25. B. Refouvelet, C. Guyon, Y. Jacquot, C. Girard, H. Fein, F. Bevalot, J. F. Robert, B. Heyd, G. Mantion, L. Richert, and A. Xicluna, *Europ. J. Med. Chem.*, 2004, **39**, 931.
26. M. Kidwai, R. Venkataramanan, and B. Dave, *Green Chem.*, 2001, **3**, 278.
27. A. P. Johnson and A. Petter, *J. Chem. Soc.*, 1966, 606.