J. Biol. Chem. Chron. **2018, 4***(2),* 65-69
ISSN (Print): 2454 – 7468
ISSN (Online): 2454 - 7476
www.eresearchco/jbcc/

Synthesis of Carbethoxycinnoline Derivatives and Antimicrobial Evaluation

Komal Jakhar

Department of Chemistry, M. D. University, Rohtak-124001, Haryana, INDIA

* *Correspondence: E-mail: komal.jakhar@rediffmail.com*

(Received 24 Oct, 2018; Accepted 17 Nov, 2018; Published 19 Nov 2018)

ABSTRACT: 3-Carbethoxy-6-substituted-4-methylcinnolines have been synthesized by cyclization of phenylhydrazonocarbethoxyacetones under microwave irradiations using polyphosphoric acid as condensing agent. The phenylhydrazonocarbethoxyacetones are prepared from benzenediazonium chloride and ethylacetoacetate. The antibacterial potential of the title compounds has been described against different bacteria's.

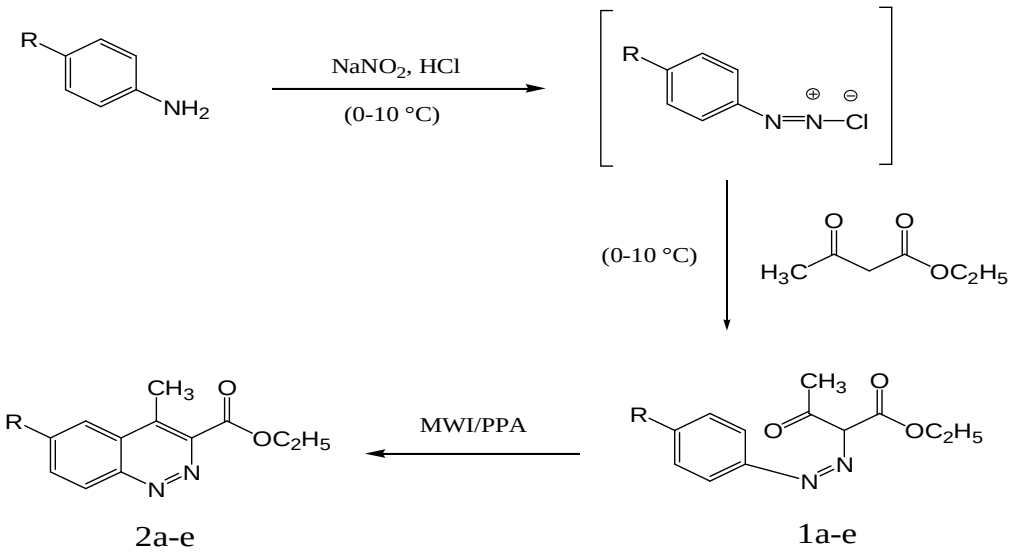
Keywords: 3-Carbethoxy-6-substituted-4-methylcinnolines; polyphosphoric acid; microwave irradiation and antibacterial activity.

INTRODUCTION: Cinnoline and its fused derivatives constitute a versatile class of nitrogen heterocyclics owning to its diverse pharmacodynamic properties such as anti-inflammatory[1], sedative[2], antimolluscicidal[3], LRRK2 kinase inhibitor[4], human neutrophil elastase inhibitors[5], antitumor[6], antithrombotic[7], antibacterial[8], insecticidal[9], antihypertensive[10], antileukemic[11] and antimalarial[12] activity. Cinnoline itself is a versatile organic compound and is reported to possess toxicity and antibacterial potential against *E.coli*[13]. Acyl derivatives of cinnoline possess remarkable biological activities like antifibrotic[14], antiallergic[15], antiulcer[16], sedative[17] and they are used as precursor for synthesis of diverse heterocyclic compounds with therapeutic importance. The cited methods for preparation of 3-acylcinnoline derivatives suffer from limitations of very poor yield, use of toxic chemicals and longer reaction times. In recent times, polyphosphoric acid has been used as an efficient and mild condensing agent in the synthesis of various heterocyclic compounds[18-20]. In an attempt towards synthesis of organic compounds using sustainable and greener methodologies[21-26], synthesis 3-carbethoxy-6-substituted-4-methylcinnolines has been explored under microwave irradiations using polyphosphoric acid.

MATERIAL AND METHODS: The required chemicals and reagents were procured from Sigma-Aldrich. The IR spectra were measured on Perkin-Elmer Spectrophotometer, proton NMR on BrukerAvance II 400 MHz Spectrometer and Perkin-Elmer 2400 CHN Elemental analyzer was used for micro-analysis. The microwave stimulated reactions were carried on Samsung microwave oven (Model No. CE745G) at 400W power.

General procedure for synthesis of phenylhydrazonocarbethoxyacetones: Aniline (0.1025 mol) was dissolved in IN HCl (200 ml) and cooled up to 0-5°C. A cooled solution of sodium nitrite (0.1072 mol) in water (26 ml) was added dropwise to aniline solution with constant stirring keeping the temperature below 5 °C. Benzenediazonium chloride thus prepared was added to a precooled solution of ethanol (30 ml), water (500 ml) and ethylacetoacetate (0.129 mol) slowly with stirring maintaining the temperature below 5 °C. After this, sodium acetate was added to make the reaction mixture alkaline and stirring was continued for next 20 minutes. The crude product was filtered, dried and recrystallized with ethanol.

General procedure for synthesis of 3-carbethoxy-6-substituted-4-methylcinnolines: Phenylhydrazonocarbethoxyacetones (0.01 mol) intimately mixed with polyphosphoric acid (2g) was subjected to microwave irradiation at 400W. The reaction was completed in 15 sec as checked on silica coated TLC plates. The mixture was poured over crushed ice, the crude product was filtered, dried and recrystallized by ethanol.



2a-e 1a-e

R = H, CH_3, OCH_3, Cl, Br

[Reaction Scheme]

RESULTS AND DISCUSSION: The carbon based organic solvents are highly volatile, noxious in nature and leads to a number of physiological impairments in living beings. For sustainable future and environmentally benign technological developments, a shift should be made from classical methods of organic synthesis to greener alternatives. In the present study, differently substituted phenylhydrazonocarbethoxyacetones have been cyclized using polyphosphoric acid under microwave irradiations to form 3-carbethoxy-6-substituted-4-methylcinnolines (Reaction scheme). Simplified procedures, high yields in short reaction time and solvent free conditions are the remarkable features of this procedure. The IR, ^{1}H NMR and elemental analysis data have been used for characterization of compounds. The results are compiled in Table 1 and 2.

Table 1: Synthesis of phenylhydrazonocarbethoxyacetones and carbethoxycinnolines.

Comp. Code	M. P. (°C)	Yield (%)	Mol. Formula	C %		H %		N %	
				Calc.	Found	Calc.	Found	Calc.	Found
1a	71-72	82	$C_{12}H_{14}N_2O_3$	61.54	61.42	5.98	5.83	11.97	11.86
1b	60-61	80	$C_{13}H_{16}N_2O_3$	62.90	62.79	6.45	6.31	11.29	11.12
1c	80-81	83	$C_{12}H_{13}N_2O_3Cl$	53.63	53.48	4.84	4.77	10.43	10.35
1d	85-86	85	$C_{13}H_{16}N_2O_4$	59.09	59.20	6.06	6.01	10.60	10.48
1e	87-88	82	$C_{12}H_{13}N_2O_3Br$	46.02	45.95	4.15	4.04	8.95	8.81
2a	73-74	81	$C_{12}H_{12}N_2O_2$	66.66	66.53	5.55	5.37	12.96	12.79
2b	64-65	78	$C_{13}H_{14}N_2O_2$	67.83	67.95	6.08	6.15	12.17	12.04
2c	88-89	85	$C_{12}H_{11}N_2O_2Cl$	57.48	57.61	4.39	4.50	11.17	11.05
2d	85-86	80	$C_{13}H_{14}N_2O_3$	63.41	63.27	5.69	5.60	11.38	11.20
2e	90-91	84	$C_{12}H_{11}N_2O_2Br$	48.83	48.95	3.73	3.90	9.49	9.36

Antibacterial evaluation: The antibacterial activity of cinnoline derivatives were determined against *S. aureus*, *E. coli*, *S. typhii*, *P. aeruginosa* and *K. pneumonia* using ditch diffusion method[27]. Antibacterial activity was evaluated at 10 and 100 ppm concentrations by measuring the diameter of the inhibition zone. Dimethylformamide was used as a solvent control. Ciprofloxacin was used as standard antibacterial drug. The optimum results were obtained at 10 ppm concentration for all the compounds. Antibacterial screening data indicate that all carbethoxycinnolines showed moderate to good activity against *E. coli*, *S. typhii*, *P. aeruginosa* and *K. pneumonia.* The Compounds 2a, 2d and 2e showed moderate activity against *S. aureus*. The antimicrobial results are illustrated in Table 3.

Table 2: Spectral data of compounds 1a-e and 2a-e.

Comp. Code	IR (KBr) (in cm^{-1})				^1H NMR ($CDCl_3$, 400MHz): δ
	CH_3str	C=O str	-N=N- str	-C-N= N- str	
1a	2982	1708	1510	1170	14.80 (s, 1H, enolic OH), 7.38-7.15 (m, 5H, Ar-H), 4.39-4.30 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 1.77 (s, 1H, -CH), 1.42-1.38 (t, 3H, CH_3).
1b	2985	1693	1515	1183	14.89 (s, 1H, enolic OH), 7.32-7.14 (m, 4H, Ar-H), 4.38-4.30 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 1.94 (s, 1H, -CH), 1.41-1.37 (t, 3H, CH_3).
1c	2983	1702	1526	1203	14.74 (s, 1H, enolic OH), 7.36-7.33 (m, 4H, Ar-H), 4.38-4.31 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 1.67 (s, 1H, -CH), 1.41-1.38 (t, 3H, CH_3).
1d	2986	1689	1517	1190	14.85 (s, 1H, enolic OH), 7.40-7.17 (m, 4H, Ar-H), 4.37-4.33 (q, 2H, CH_2), 3.84 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3), 1.80 (s, 1H, -CH), 1.40-1.36 (t, 3H, CH_3).
1e	2980	1695	1528	1196	14.72 (s, 1H, enolic OH), 7.41-7.30 (m, 4H, Ar-H), 4.40-4.32 (q, 2H, CH_2), 2.55 (s, 3H, CH_3), 1.78 (s, 1H, -CH), 1.41-1.37 (t, 3H, CH_3).
2a	2984	1710	1510	1163	7.41-7.34 (m, 4H, Ar-H), 4.35-4.29 (q, 2H, CH_2), 2.57 (s, 3H, CH_3), 1.41-1.37 (t, 3H, CH_3).
2b	2982	1695	1512	1185	7.32-7.16 (m, 3H, Ar-H), 4.38-4.30 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.38 (s, 3H, CH_3),1.41-1.37 (t, 3H, CH_3).
2c	2986	1702	1527	1204	7.42-7.35 (m, 3H, Ar-H), 4.36-4.31 (q, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.42-1.38 (t, 3H, CH_3).
2d	2988	1705	1520	1190	7.40-7.21 (m, 3H, Ar-H), 4.39-4.31 (q, 2H, CH_2), 3.75 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3), 1.40-1.35 (t, 3H, CH_3).
2e	2985	1710	1514	1180	7.45-7.32 (m, 3H, Ar-H), 4.37-4.30 (q, 2H, CH_2), 2.55 (s, 3H, CH_3), 1.40-1.37 (t, 3H, CH_3).

Table 3: Antibacterial activity of carbethoxycinnolines.

Comp. Code	Diameter of zone of inhibition (mm)									
	E. coli		*S. typhii*		*P. aeruginosa*		*K. pneumonia*		*S. aureus*	
Conc.(ppm)	10	100	10	100	10	100	10	100	10	100
2a	15	13	13	11	15	13	15	13	12	10
2b	14	12	12	10	13	10	16	14	-	-
2c	14	11	12	10	12	11	16	13	-	-
2d	15	13	14	12	15	13	17	15	12	11
2e	14	13	13	11	13	11	15	14	13	11
Ciprofloxacin	20	20	20	20	20	20	20	20	20	20

CONCLUSION: A series of differently substituted 3-carbethoxy-6-substituted-4-methycinnolines have been synthesized under greener conditions. Some carbethoxycinnolines shows remarkable antibacterial strength and can be further used in synthetic and pharmaceutical research.

ACKNOWLEDGEMENT: The author is thankful to M. D. University, Rohtak, India for providing research facilities.

REFERENCES:

1. Tonk R. K., Bawa S., Chawala G., Deora G. S., Kumar S., Rathore V., Mulakayala N., Rajaram A., Kalle A. M and Afzal O. (2012) Synthesis and pharmacological evaluation of pyrazolo[4,3-c]cinnoline derivatives as potential anti-inflammatory and antibacterial agents, *Eur. J. Med. Chem.*, 57, 176-184.
2. Stanczak A., Lewgowd W. and Pakulska W. (1998) Synthesis and biological activity of some 4-amino-3-cinnoline carboxylic acid derivatives. Part 4: 2,4-Dioxo-1,2,3,4-tetrahydropyrimido[5,4-c]cinnolines, *Pharmazie*, 53(3), 156-161.
3. Abdelrazek F. M., Metz P., Metwally N. H. and El-Mahrouky S. F. (2006) Synthesis and molluscicidal activity of new cinnoline and pyrano[2,3-c]pyrazole derivatives, *Arch. Pharm.*, 339(8), 456-460.
4. Garofalo A. W., Adler M., Aubele D. L., Bowers S., Franzini M., Goldbach E., Lorentzen C., Neitz R. J., Probst G. D., Quinn K. P., Santiago P., Sham H. L., Tam D., Truong A. P., Ye X. M. and Ren Z. (2014) Novel cinnoline-based inhibitors of LRRK2 kinase activity, *Bioorg. Med. Chem. Lett.*, 23(1), 71-74.
5. Giovannoni M. P., Schepetkin I. A., Crocetti L., Ciciani G., Cilibrizzi A., Guerrini G., Khlebnikov A. I., Quinn M. T. and Vergelli C. (2016) Cinnoline derivatives as human neutrophil elastase inhibitors, *J. Enzyme inhib. Med. Chem.*, 31(4), 628-639.
6. Awad E. D., El-Abadelah M. M., Matar S., Zihlif M. A., Naffa R. G., Al-Momani E. Q. and Mubarak M. S. (2012) Synthesis and biological activity of some 3-(4-(substituted)-piperazin-1-yl)cinnolines, *Molecules*, 17, 227-239.
7. Cignarella G., Barlocco D., Pinna G. A., Loriga M., Curzu M. M., Tofanetti O., Germini M., Cazzulani P. and Cacalletti E. (1989) Synthesis and biological evaluation of substituted benzo[h]cinnolinones and 3H-benzo[6,7]cyclohepta[1,2-c]pyridazinones: higher homologs of the antihypertensive and antithrombotic 5H-indeno[1,2-c]pyridazinones, *J. Med. Chem.*, 32(10), 2277-2282.
8. Barraja P., Diana P., Lauria A., Passannanti A., Almerico A. M., Minnei C., Longu S., Congiu D., Musiu C. and Colla P. L. (1999) Indolo[3,2-b] cinnolines with antiproliferative, antifungal and antibacterial activity, *Bioorg. Med. Chem.*, 7(8), 1591-1596.
9. Gautam N. and Chourasia O. P. (2010) Synthesis, antimicrobial and insecticidal activity of some new cinnoline based chalcones and cinnoline based pyrazoline derivatives, *Indian J. Chem.*, 49B, 830-835.
10. Curran W. V. and Ross A. (1974) 6-Phenyl-4,5-dihydro-3(2H)-pyridazinones. Series of hypotensive agents, *J. Med. Chem.*, 17(3), 273-281.
11. Cirrincione G., Almerico A. M., Diana P., Grimaudo S., Daltolo G., Aiello E., Barraja P. and Mingoia F. (1995) Polycondensed nitrogen heterocycles. Part 27. Indolo[3,2-c]cinnolines. Synthesis and antileukemic activity, *Farmaco*, 50(12), 849-852.
12. Keneford J. R. and Simpson J. C. E. (1947) Synthetic antimalarials. Part XX. Cinnolines. Part XIII. Synthesis and antimalarial action of 4-aminoalkylaminocinnolines, *J. Chem. Soc.*, 917-920.
13. Bekhit A. A. (2001) Fused cinnolines: synthesis and biological activity, *Boll Chim.Farm.*, 140(4), 243-253.
14. Franklin T. J., Hales N. J., Johnstone D., Morris W. B., Cunliffe C. J., Millest A. J. and Hill G. B. (1991) Approaches to the design of anti-fibrotic drugs, *Biochem. Soc. Trans.*, 19(4), 812-815.
15. Holland D., Jones G., Marshall P. W. and Tringham G. D. (1976) Cinnoline-3-propionic acids, a new series of orally active antiallergic substances, *J. Med. Chem.*, 19(10), 1225-1228.
16. Lowrie H. S. (1966) 3-Phenylcinnolines. 1. Some reactions and derivatives of 3-phenylcinnoline-4-carboxylic acids, *J. Med. Chem.*, 9(5), 664-669.
17. Stanczak A., Kwapiszewski W., Szadowska A. and Pakulska W. (1994) Synthesis and action on the central nervous system of some N2-substituted cinnoline dreivatives, *Pharmazie*, 49(6), 406-412.
18. Dubey R. and Moorthy N. S. H. N. (2007) Comparative study on conventional and microwave assisted synthesis of benzimidazole and their 2-substituted derivatives with the effect of salt form of reactant, *Chem. Pharm. Bull.*, 55(1), 115-117.
19. Moghaddam F. M., Bardajee G. R. and Ismaili H. (2007) Microwave-assisted one pot synthesis of

symmetrical 4H-pyran-4-ones, *J. Braz. Chem. Soc.*, 18(5), 1024-1027.

20. Khojastehnezhad A., Moeinpour F. and Davoodnia A. (2011) PPA-SiO_2catalysed efficient synthesis of polyhydroquinoline derivatives through Hantzsch multicomponent condensation under solvent-free conditions, *Chin. Chem. Lett.*, 22(7), 807-810.

21. Jakhar K. and Makrandi J. K. (2008) An eco-friendly oxidative bromination of alkanones by an aqueous grinding technique, *Green Chem. Lett. Rev.*, 1, 219-221.

22. Jakhar K. and Makrandi J. K. (2012) Synthesis of 2-aryl-5-(benzofuran-2-yl)-thiazolo[3,2-b][1,2,4] triazoles using green procedures and their antibacterial activity, *Indian J. Chem.*, 51B, 531-536.

23. Singh R. and Jakhar K. (2016) Green synthesis of saccharin substituted urea and thiourea derivatives and their antimicrobial evaluation, *Der Pharma Chem.*, 8(20), 175-181.

24. Singh R., Jakhar K. and Sharma P. (2017) $ZrOCl_2.8H_2O$: An efficient catalyst for synthesis of N,N'-disubstituted ureas from biuret under solvent free conditions, *Chem. Sci. Trans.*, 6(1), 135-140.

25. Lima R. N. and Porto A. L. M. (2017) Facile synthesis of new quinoxalines from ethyl gallate by green chemistry protocol, *Tetrahedron Lett.*, 58(9), 825-828.

26. Maryamabadi A., Hasaninejad A., Nowrouzi N. and Mohebbi G. (2017), Green synthesis of novel spiroindenoquinoxaline derivatives and their cholinesterases inhibition activity, *Bioorg. Med. Chem.*, 25(7), 2057-2064.

27. Nair R., Kalariya T. and Chanda S. (2005) Antibacterial activity of some selected Indian medicinal flora, *Turk J. Biol.*, 29, 41-47.