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MAOS PROTOCOL FOR SYNTHESIS OF SOME BIOLOGICALLY ACTIVE N^1-CINNAMOYL -3, 5 –DIARYL- 2 -PYRAZOLINES

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ABSTRACT

A series of new N^1-cinnamoyl-3, 5-diaryl-2- pyrazolines (4) has been prepared by the condensation of cinnamoyl chloride with 3, 5-diaryl – 2 – pyrazolines (2) or by claisen – schmidt condensation of N-acetyl pyrazolines(3) with benzaldehyde using both conventional as well as MAOS protocol. The identity of products was established on the basis of their elemental analysis, spectral data, m.m.p. and Co-TLC. Newly prepared compounds were screened in vitro for their antibacterial activity.

Keywords: MAOS protocol, pyrazolines, claisen – schmidt condensation

INTRODUCTION

In past decade considerable attention has been paid to green chemistry[1-4], which involves the design, development and implementation of chemical processes and products that eliminates or reduce the use of hazardous pollutants in a feasible and economically viable manner. Among various Green Chemical techniques microwave irradiations has gained popularity due to several advantages associated with it. Microwave assisted organic synthesis (MAOS) has been used now a days as a powerful tool for rapid and efficient synthesis of a variety of compounds due to absorption of microwave energy by the polar molecules[5]. The utility[6-7] of MWI to provide enhanced reaction rates, higher yields with cleaner products and easy work up has been extended to modern drug discovery in complex multistep chemical synthesis and has been proving quite successful in formation of carbon – heteroatom bonds. The solvent free solid phase approach involving microwave exposure of neat reactants is applicable to rapid one pot assembly of heterocyclic compounds from in situ generated intermediates.

The chemistry of chalcones[8] has always attracted the attention of researchers due to their significance as natural biocides[9] and as versatile synthons for various chemical transformations[10]. A wide range of biological activities such as anti AIDS[11], cytotoxic[12], antimalarial[13], antiinflammatory[14], antitumor[15], antitubercular[16], and antihypertensive[17] activities are reported to be associated with chalcones.

Synthesis and characterization of pyrazoline derivatives[18, 19] is a developing field within the realm of heterocyclic chemistry. Due to their diverse chemical properties, fairly accessible path of synthesis and wide range of therapeutic and industrial applications, the pyrazoline derivatives had been centre of attractions for organic chemists. Pyrazoline derivatives have been reported to possess, antimicrobial[20], anticonvulsant[21], antiinflammatory[22], analgesic[23], antidepressent[24] antitubercular[25] and herbicidal[26] activities.

Keeping in mind above facts it was thought worthwhile to prepare some new chalcones containing pyrazoline moiety ,using MAOS protocol which may be act as potent biodynamic agents.

EXPERIMENTAL

All the melting points reported are uncorrected and were taken in open capillaries. The IR spectra (KBr, νcm^{-1}) were recorded on shimudzu – spectrometer, PMR spectra ($CDCl_3$, δppm) were taken on Bruker DRX-600 spectrometer using TMS as internal standard and Mass spectra (FAB) were recorded on Jeol

SX-DA600 mass spectrometer using m- nitro benzyl alcohol as matrix. The matrix peaks were observed at m/z 136, 137, 154, 289 and 307. The purity of compounds and progress of reaction was checked by TLC using silica Gel-G as adsorbent and ethyl acetate – benzene (1:1) as eluent. All the transformations were carried out in domestic microwave oven (samsung 1630 N, output 800 watt, 2450 Mhz).

General procedure for synthesis of N^1-Cinnamoyl-3,5- diaryl-2-pyrazolines (4a-g).

Path I:

(a) Conventional Method

2' – Hydroxy chalcone (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (50 ml) were refluxed on a water bath for 4-6 hours. After completion of reaction, the reaction mixture was left overnight at room temperature. The solid separated was filtered off, washed with water and crystallized from alcohol as colorless crystals of 3, 5-diaryl – 2 – pyrazolines (2a – g). Compounds (2), (0.01 mol) were dissolved in dry benzene (30ml). To it freshly prepared cinnamoyl chloride (0.012 mol) was added drop wise. After complete addition the resultant mixture was refluxed for 3-4-hours and left at room temperature. The separated solid was filtered off, washed with ice cold water and crystallized from benzene ethyl – acetate as colorless crystals of (4a-g).

(b)MAOS Method

2' – Hydroxy chalcone (0.01 mol) and hydrazine hydrate (0.015 mol) were mixed thoroughly to form a homogeneous paste. It was subjected to microwave irradiation at 180 watt for 3-5 minutes. After completion of reaction the reaction mixture was cooled to room temperature. It was washed with ice cooled water and crystallized from ethanol as colorless crystals of compounds (2 a- g) in 80-85% yield.

To the compounds 2, (0.01 mol) freshly prepared cinnamoyl chloride (0.012 mol) was added drop wise with continuous agitation. After complete addition the reaction mixture was subject to microwave irradiation at 180 watt for 2-3 minutes. After completion of reaction it was cooled to room temperature and washed with ice cold water. The resultant solid was crystallized from ethanol as colorless crystals of 4a – g

Path – II

(a)Conventional Method

2' – Hydroxychalcone (0.01 mol), hydrazine hydrate (0.015 mol) and glacial acetic acid (20 ml) were refluxed for 3-6 hours. After completion of reaction the mixture was left at room temperature. The separated solid was filtered, washed with ice cold water and crystallized from ethanol as colorless crystals of 3a – g in 60-70% yield. Compounds (0.01 mol) and KOH (4.0 gm) were taken in ethanol (50 ml) .To it benzaldehyde (0.012 mol) in ethanol (20 ml) was added slowly with continuous stirring. The stirring continued for 3 hours and reaction mixture was left overnight at room temperature. The residue obtained was neutralized with ice and dilute HCl. The separated solid was filtered, washed with ice cold water and crystallized from ethanol to get analytical sample of 4a– g.

(b)MAOS Method

2' – Hydroxychalcones (0.01 mol) and hydrazine hydrate (0.015 mol) were mixed thoroughly with glacial acetic acid (10 ml). The resultant paste was subjected to microwave irradiation at 300 watt for 4-6 minutes. After completion of reaction the residue was cooled to room temperature and washed with ice cold water. The separated solid was crystallized from ethanol to get analytical sample of compounds 3a – g. in 80-86% yield. Compounds 3a – g (0.01 mol) benzaldehyde (0.012 mol) and KOH (4.0 gm) were mixed thoroughly to form a homogeneous slurry. It was subjected to microwave irradiation at 300 watt for 3-5 minutes. After completion of reaction the residue obtained was washed with water and crystallized from ethanol to get analytical sample of 4a – g in 84-88% yield.

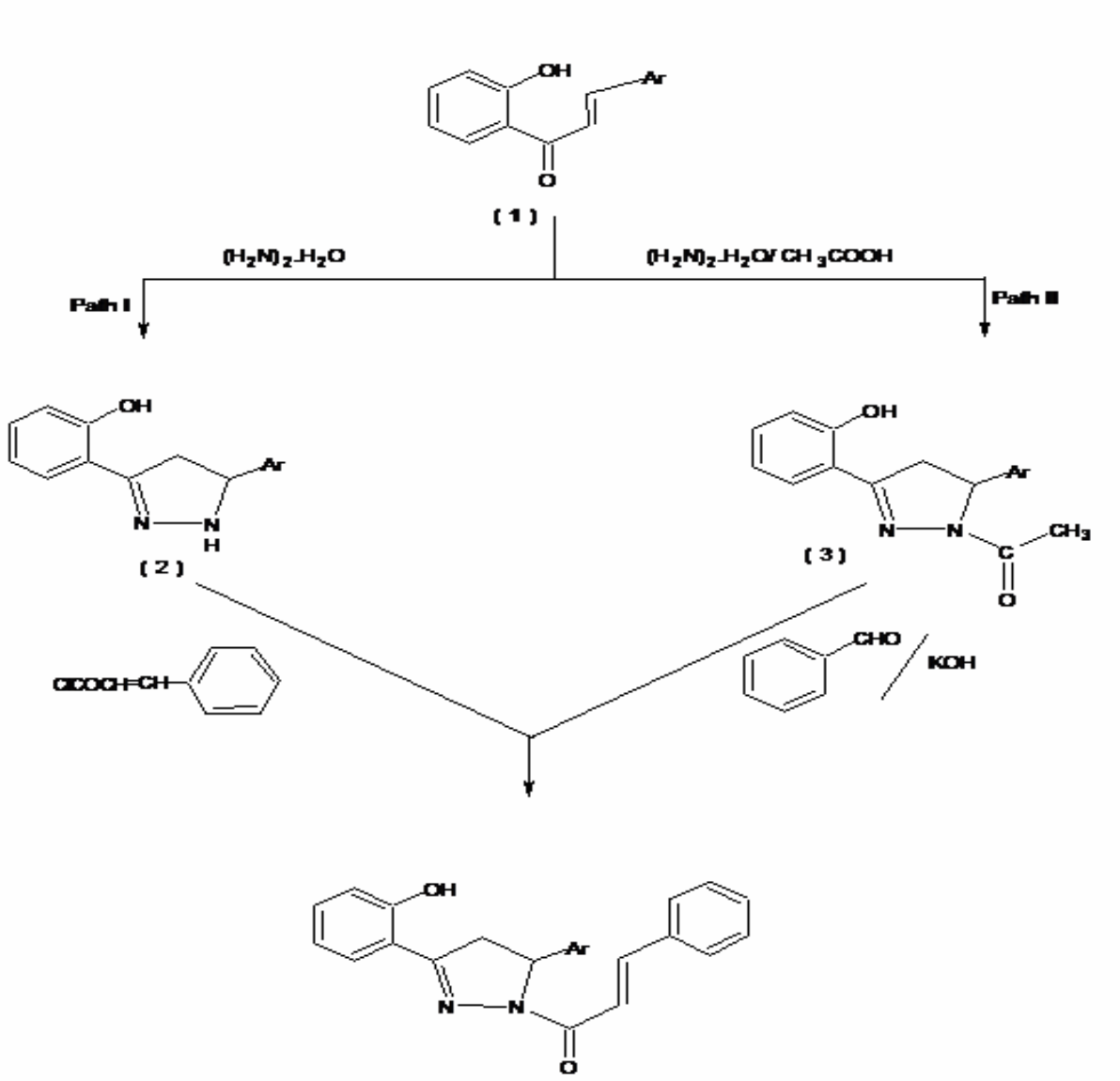
Biological Screening

Newly prepared chalcones (4) were screened for their antibacterial activity in vitro against *E. coli*, *S. aureus, S. albus, K. pneumonae* and *P. vulgaries* at a concentration of 250 µg/ml. The standard drug used

was ciprofloxange at a concentration 50 µg/ml. In comparison to ciprofloxange the sample were found to have moderate to good activity .

RESULTS AND DISCUSSION

2'– Hydroxy chalcones (1) were treated with hydrazine hydrate to afford 3, 5-diaryl– 2- pyrazolines (2) which on condensation, with freshly prepared cinnamoyl chloride gave desired N^1- cinnamoyl–3, 5-diaryl– 2 –pyrazolines (4) as colorless solid.(path-I). Alternatively 2'–hydroxy chalcones were treated with hydrazine hydrate in presence of glacial acetic acid to afford N^1-acetyl-3,5-diaryl–2- pyrazolines



(4)

Scheme-1

Compounds (3) were subjected to claisen- schmidt condensation with benzaldehyde in presence of base to get the desired product (4). (path II) However in this course of reaction a sticky mass was obtained which could be crystallized with difficulty to get analytical sample of (4), whereas using path I, clean product

was obtained in excellent yield. These transformations were carried out using both conventional heating as well as MAOS protocol.

The identity of the products obtained by both the routes was confirmed on the basis of their m.m.p., Co-TLC and super imposable IR spectra .The structure of compounds (4) was established by their elemental analysis and spectral data.

The IR spectra of these compounds gave prominent absorption bands at 3440-3400 cm^{-1} (-OH stretching) 1660-1640 cm^{-1} (>C=0), 1420-1340 cm^{-1} (N-N and C=N combined vibrations) and 1165=1080 cm^{-1} (>C=O out of plane) The PMR spectra of the compound 4a gave signals double doublets at δ3.01-3.11 (C_4-H_A) δ, 3.58-3.62 (C_4-H_B) and δ 4.98 – 5.02 (C_5-H_X) confirming the presence of ABX pattern of pyrazoline ring. A singlet at δ8.84 for –OH proton and a doublet at δ5.56-5.60 for CH=CH protons was also observed. The aromatic protons gave a multiplet at δ 7.60-8.10.

Table – 1:Physical Data of Compounds (2), (3) and (4)

Compd	Ar	Molecular Formula (M. wt.)	m.p. ˚C	% yield		Rxn Time	
				Conv.	MAOS	Conv. (Hrs.)	MAOS (Min.)
2a	Phenyl	$C_{15}H_{14}N_2O_4$ (238)	90	75	80	2.0	4.0
2b	4-OMe Phenyl	$C_{16}H_{16}N_2O_2$ (268)	108	70	75	3.0	3.0
2c	3,4- diOMe Phenyl	$C_{17}H_{18}N_2O_3$ (298)	110	75	85	3.5	3.0
2d	3,4,5 - triOMe Phenyl	$C_{18}H_{20}N_2O_4$ (328)	130	70	80	3.5	4.0
2e	4-Cl-Phenyl	$C_{15}H_{13}N_2OCl$ (272.5)	118	70	85	2.0	3.0
2f	4-NMe_2 Phenyl	$C_{17}H_{19}N_3O$ (281)	110	70	82	3.0	3.0
3a	Phenyl	$C_{17}H_{16}N_2O_2$ (280)	136	70	85	2.0	7.0
3b	4-OMe Phenyl	$C_{18}H_{18}N_2O_3$ (306)	140	75	85	2.5	7.0
3c	3,4- diOMe Phenyl	$C_{19}H_{20}N_2O_4$ (340)	122	75	80	2.5	8.0
3d	3,4,5 - triOMe Phenyl	$C_{20}H_{22}N_2O_5$ (370)	145	72	85	3.0	7.0
3e	4-Cl-Phenyl	$C_{17}H_{15}N_2O_2Cl$ (314.5)	110	70	80	2.5	7.0
3f	4-NMe_2 Phenyl	$C_{19}H_{21}N_3O_2$ (323)	115	75	85	3.0	8.0
4a	Phenyl	$C_{24}H_{20}N_2O_2$ (368)	160	67	82	5.0	3.0
4b	4-OMe Phenyl	$C_{25}H_{22}N_2O_3$ (398)	130	69	82	4.5	3.0
4c	3,4- diOMe Phenyl	$C_{26}H_{24}N_2O_4$ (428)	80	68	85	4.5	3.5
4d	3,4,5 - triOMe Phenyl	$C_{27}H_{26}N_2O_5$ (458)	145	66	83	5.0	3.0
4e	4-Cl-Phenyl	$C_{24}H_{19}N_2O_2Cl$ (402.5)	150	65	82	5.0	3.5
4f	4-NMe_2 Phenyl	$C_{26}H_{25}N_3O_2$ (411)	120	65	85	5.5	4.0

The mass spectra (FAB) of these compounds gave the molecular corresponding to their molecular masses. The physical Data of these compounds are tabulated in Table – 1.

A comparison of conventional heating method with MAOS method clearly indicates the superiority of the latter due to advantages like cleaner products, selectivity of the reaction, higher yields, lesser reaction time and easy work up. Furthermore the reaction under MAOS was carried out in solvent less solid phase, avoiding the use of hazardous solvent, thus whole process becomes eco-friendly and economic falling in domain of Green chemistry.

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REFRENCES

1. P.T. Anastas, and J.C. Warner, *Green chemistry, Theory and Practice,* Oxford University press, New York. (1998)
2. R.S, Varma, *ACS Symposium series no. 767; Green chemical synthesis and processes*, Chapter 23, 290, Washington, D.C. (2001).
3. R.S Varma, *Green Chemistry: Challenging Perspective,* Oxford University press, New York 221,(2000)
4. R.S Varma, *Microwaves in organic synthesis,* Chapapter 6, 181, Wiley-VCH Weinheim,(2002).
5. R.S. Varma, *Microwave, Theory and Application in material processing,* IV, 357, ACS, Westerville, (1997).
6. S.K. Dewan, *Indian J. Chem,* **45B**, 2537, (2004).
7. C.O. Kappe, *Angew. Chem Int.* Ed., **43**, 6256, (2004).
8. D.N. Dhar, *Chemistry of Chalcones,* Wiley New York (1981).
9. D.W. Dommock, M.A. Etias, Beazley and N.H. Kendeque, *Curr. Med. Chem.* 112, (1999).
10. N.H.New, Y. Kim, Y.J. Yu, D.H.Heng, H.M. Kim, and B.Z. Ahm, *Eur. J. Med. Chem,* **38**,139,(2003).
11. J.H. Nu, X.D. Wang, Y.H. Yi, and K.H. Lee, *Bioorg. Med. Chem.* Lett. **13**, 1813,(2003).
12. X. Wu, P. Wiliarat, and M.L. Go, *Bioorg Med. Chem*., Lett., **12**, 2299,(2002).
13. H.K. Hsein, I.T. Tisao, J.P Wang, and C.P. Lin. *J. Pharm Pharmacol* . ,**52**, 163,(2000).
14. P.Tuchinda, V.Reutrakel, P.Claison, P.Pargoroypron, T .Sematong and W.C Taylor, *Phytochem.* **59**, 169,(2002).
15. Y. XIa, Z.Y.Y.Yang, P.XIa., K. F. Bestow, Y. Nakamishi and K.H. Lee, *Bioorg Med. Chem*.Lett., **10**, 699,(2000).
16. E.D.J. Barton, and F.H.P. Freeman, *Chem. Abstr.,* **74**, 99891d,(1971).
17. J.J. Baldwin, A. Scriabine, G.S. Ponticella, E.L. Enzelhardt and C.S. Sweeti*, J. Helerocyclic Chem.,* **17(3)** 425,(1980).
18. M.Singhal, B.L.Verma ,Y.S.Jhala,and S.S . Dulawat, *Indian J. Heterocyclic Chem.* ,**12**, 343,(2005).
19. A.P. Prajapati, R .Bardia, J.T.Rao,and V. Verma *, J. Inst. Chemists (India),* **79**, 7, (2007).
20. A.Solankee, and I. Thakor, *Indian J. Chem.* ,**45B**, 51,(2006).
21. A. Solankee, K. Kapadia, H. Patel, H. Prajapati, P. Solankee, and S.Solankee*, Indian J. Helterdeyclic Chem.* ,**16**, 287,(2007).
22. E. Bansal, T. Ram, V.K. Srivastava, and . A Kumar, Indian *J. Pharm Sci,* **61B**, 385,(1999).
23. M. Kumar, P. Manoj, A.R. Kumar, and T.K. Ravi, Indian *J. Pharm. Sci*, **67(6),** 755,(2005).
24. B.L. Verma, M. Singhal*, Indian J. Heterocyclic Chem.* ,**14**, 343,(2007).
25. A.A. Bilgin, E. Palaska, R. Sunal, and B.Gunnesel, *Pharmazie,* **49(1**), 67,(1994).

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