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A CONVENIENT SYNTHESIS AND ANTI-FUNGAL ACTIVITIES OF NEW IMIDAZO[1,2-A]-S-PYRIMIDIN-7-ONES

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ABSTRACT

Michael addition of nitrogen nucleophiles, 2-(arylamino)imidazolidines **3a-e** to 4– Arylidine-5(4H)oxazolones **4a-e** followed by ring transformation of the isolable Michael adducts **5a-l** yields new bicyclic compounds 5,8-diaryl-6-benzamido-2,3,5,6-tetrahydro-7H-imidazo[1,2-a]pyrimidin-7-ones **6a-l** in one pot procedure. The formation of Michael adducts **5a-l** and their ring transformation to **6a-l** are highly diastereoselective. Compounds **6e-f** exhibit 100% in vitro disease control (equivalent to Dithane M-45) against *Aspergillus niger* and *Fusarium oxysporum* at 1000 ppm concentration.

KEYWORDS: Imidazolidines, Diastereoselective, oxazolones, Aspergillus niger, Fusarium oxysporum, Pyrimidines.

INTRODUCTION

Imidazo[1,2-*a*]pyridines are an important class of fused nitrogen-bridged heterocyclic compounds due to the broad spectrum of biological activity profiles displayed, which strongly depend on the substitution pattern. Several representatives are clinically used, like the unsubstituted imidazole fragment cardiotonic agent olprinone, the 2-substituted analgesic miroprofen, the anticancer agent zolimidine, the 3-substituted antiosteoporosis drug minodronic acid, the 2,3-disubstituted derivatives with sedative and anxiolytic properties, alpidem, saripidem, and necopidem, and the agent for the treatment of insomnia and brain disorders, zolpidem. In consequence, several procedures for the synthesis of this fascinating framework are developed, mostly on the basis of metal catalyzed reactions and functionalizations, which are summarized in a series of review articles. The serious ecological problems nowadays provoke scientists to search environmentally benign synthetic strategies as much as possible. This Mini-Review summarizes the most effective recent protocols for the eco-friendly metal-free direct formation of derivatives with an imidazo[1,2-*a*]pyridine skeleton [1-3] with the hope that no significant contributions in the topic are unintentionally overlooked.

Owing to its presence in the essential biomolecule nucleic acids, pyrimidine nucleus has been widely used. Likewise, some fused ring systems, derived from the fusion of imidazole nucleus with other biolabile heterocycles, have been reported to display useful biological activities.[4-7] Thus, we have devised a one pot procedure for the pyrimidine and imidazole ring system fused together, because apart from their chemical interest, hitherto unreported fused ring compounds **6a-l** could also be a subject of studies as potential pharmacological agents and agrochemicals.[8]

The envisaged synthesis was successful via the route outlined in **Scheme – I**. Michael adduct 5a-l resulting from the Michael addition of nitrogen nucleophiles 2-(arylamino)imidazolidines **3a-e** to 4–Arylidine-5(4H)oxazolones **4a-e,** underwent intramolecular nucleophilic attack of nitrogen atom of arylamino function at the carbonyl carbon (C-5) of the oxazolone nucleus with the simultaneous cleavage of the oxazolone ring to yield **6a-l** (Table-1a) in one pot.

The structure assignment of the products were based on elemental analyses, IR and PMR spectral data. The IR spectra of **6a-l** exhibited significant bands around 1760 and 1640 cm^{-1}, respectively. The PMR spectra of the compounds exhibited significant singlet around δ 3.32 – 3.50 due to methylene protons of the imidazolidine ring, in the addition, the compound **6a-l** exhibited expected PMR signals for $–OCH_3$, CH_3 and Aryl protons.

MATERIAL AND METHODS

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr on

a Perkin-Elmer-157 infrared spectrophotometer (ν-max in Cm^{-1}). PMR spectra were recorded on an EM-360 (90 MHz) NMR spectrometer in $CDCl_3$ using TMS as internal reference (chemical shift in δ-ppm).

2-(arylamino)imidazolidines 3a-e: These compounds were prepared by the reaction of N-aryl-s-methylisothiourea hydroiodide **2a-e** and ethylenediamine in absolute ethanol.[9]

4-Arylidine-5(4H)oxazolones 4a-e: These compounds were prepared according to the literature procedure[10] by treating Hippuric acid with aromatic aldehydes in acetic anhydride.

These compound were also prepared by A facile and effective approach for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones has been developed. Under solvent-assisted grinding in the presence of 2,4,6-trichloro-1,3,5-triazine, catalytic triphenylphosphine, and sodium carbonate, dehydration–condensation of hippuric acid with aromatic aldehydes proceeded rapidly within minutes at room temperature to afford the products in good to excellent yields.[11]

5,8-Diaryl-6-benzamido-2,3,5,6-tetrahydro-7H-imidazo[1,2-a]pyrimidin-ones 6a-l: An equimolar (0.2M) mixture of 4-arylidine-5-oxazolones **(4)** and 2-(arylamino)imidazolidines **(3)** were dissolve in a minimum amount of dioxin and the solution refluxed for 20 – 22 hours. The reaction mixture was concentrated, cooled and poured into water. The yellowish precipitate thus obtained was washed with water and successive crystallization from hot ethanol to get the product **(6)**. (**Table – 1a & 1b)**

Table 1a: Characterization data of 5,8-Diaryl-6-benzamido-2,3,5,6-tetrahydro-7H-imidazo [1,2-a]pyrimidin-7-ones (6).

Compd No.	R	R^1	m.p. ^0C	Yields %	Molecilar Formula	Found (Calculated) % C	H	N
6a	4-Cl	2-Cl	185	84	$C_{25}H_{20}N_4O_2Cl_2$	62.60 (62.93)	4.14 (4.18)	11.70 (11.68)
6b	4-Cl	2-Cl	205	80	$C_{25}H_{20}N_4O_2Cl_2$	62.60 (62.63)	4.14 (4.18)	11.72 (11.69)
6c	4-Cl	4-NO_2	172	79	$C_{25}H_{20}N_5O_4Cl$	61.27 (61.28)	4.10 (4.08)	14.28 (14.30)
6d	4-Cl	H	168	85	$C_{25}H_{21}N_4O_2Cl$	67.51 (67.49)	4.68 (4.72)	12.60 (12.59)
6e	4-Cl	2-OCH_3	178	76	$C_{26}H_{23}N_4O_3Cl$	65.75 (65.75)	4.83 (4.84)	11.70 (11.80)
6f	2-CH_3	4-Cl	140	82	$C_{26}H_{23}N_4O_2Cl$	68.10 (68.04)	5.08 (5.01)	12.20 (12.21)
6g	2-CH_3	2-OCH_3	180	72	$C_{27}H_{26}N_4O_3$	71.38 (71.36)	5.70 (5.72)	12.30 (12.33)
6h	2-CH_3	H	172	84	$C_{26}H_{24}N_4O_2$	73.56 (73.58)	5.66 (5.66)	13.20 (13.20)
6i	4-OCH_3	4-Cl	189	80	$C_{26}H_{23}N_4O_3Cl$	65.72 (65.75)	4.80 (4.84)	12.00 (11.90)
6j	4-OCH_3	4-OCH_3	186	77	$C_{27}H_{26}N_4O_4$	68.90 (68.930	5.51 (5.53)	11.90 (11.88)
6k	4-OCH_3	4-Cl	180	81	$C_{26}H_{23}N_4O_3Cl$	65.76 (65.75)	4.86 (4.840	12.00 (11.80)
6l	4-OCH_3	H	179	86	$C_{26}H_{24}N_4O_3$	73.60 (73.58)	5.64 (5.66)	13.20 (13.20)

Table 1b: IR and PMR spectra of 5,8-Diaryl-6-benzamido-2,3,5,6-tetrahydro-7H-imidazo [1,2-a]pyrimidin-7-ones (6).

Compd. No.	IR SPECTRA (ν-max in Cm^{-1})	PMR SPECTRA (chemical shift in δ-ppm)
5a 6a	1685(cyclic C=O), 3500(-NH) 1715(cyclic C=O), 1638(-CONH)	4.82(s,1H, -NH) 6.85(s,1H, -CONH), exhibited expected PMR signals for –OCH, CH_3 and Aryl protons in all compounds
5b 6b	1680(cyclic C=O), 3410(-NH) 1765(cyclic C=O), 1640(-CONH)	4.82(s,1H, -NH) 6.85(s,1H, -CONH)
5c 6c	1635(cyclic C=O), 3480(-NH) 1740(cyclic C=O), 1660(-CONH)	4.82(s,1H, -NH) 7.00(s,1H, -CONH)

5d 6d	1635(cyclic C=O), 3450(-NH) 1790(cyclic C=O), 1660(-CONH)	4.82(s,1H, -NH) 5.85(s,1H, -CONH)
5e 6e	1680(cyclic C=O), 3510(-NH) 1755(cyclic C=O), 1638(-CONH)	4.82(s,1H, -NH) 6.40(s,1H, -CONH)
5f 6f	1665(cyclic C=O), 3410(-NH) 1780(cyclic C=O), 1640(-CONH)	4.82(s,1H, -NH) 6.80(s,1H, -CONH)
6g 6g	1685(cyclic C=O), 3380(-NH) 1800(cyclic C=O), 1670(-CONH)	4.82(s,1H, -NH) 6.40(s,1H, -CONH)
6h 6h	1680(cyclic C=O), 34600(-NH) 1795(cyclic C=O), 1680(-CONH)	4.82(s,1H, -NH) 4.80(s,1H, -CONH)
5i 6i	1670(cyclic C=O), 3390(-NH) 1780(cyclic C=O), 1640(-CONH)	4.82(s,1H, -NH) 5.85(s,1H, -CONH)
5j 6j	1660(cyclic C=O), 3490(-NH) 1765(cyclic C=O), 1690(-CONH)	4.82(s,1H, -NH) 6.60(s,1H, -CONH)
5k 6k	1660(cyclic C=O), 3390(-NH) 1750(cyclic C=O), 1700(-CONH)	4.82(s,1H, -NH) 4.90(s,1H, -CONH)
5l 6l	1680(cyclic C=O), 3460(-NH) 1780(cyclic C=O), 1680(-CONH)	4.82(s,1H, -NH) 5.80(s,1H, -CONH)

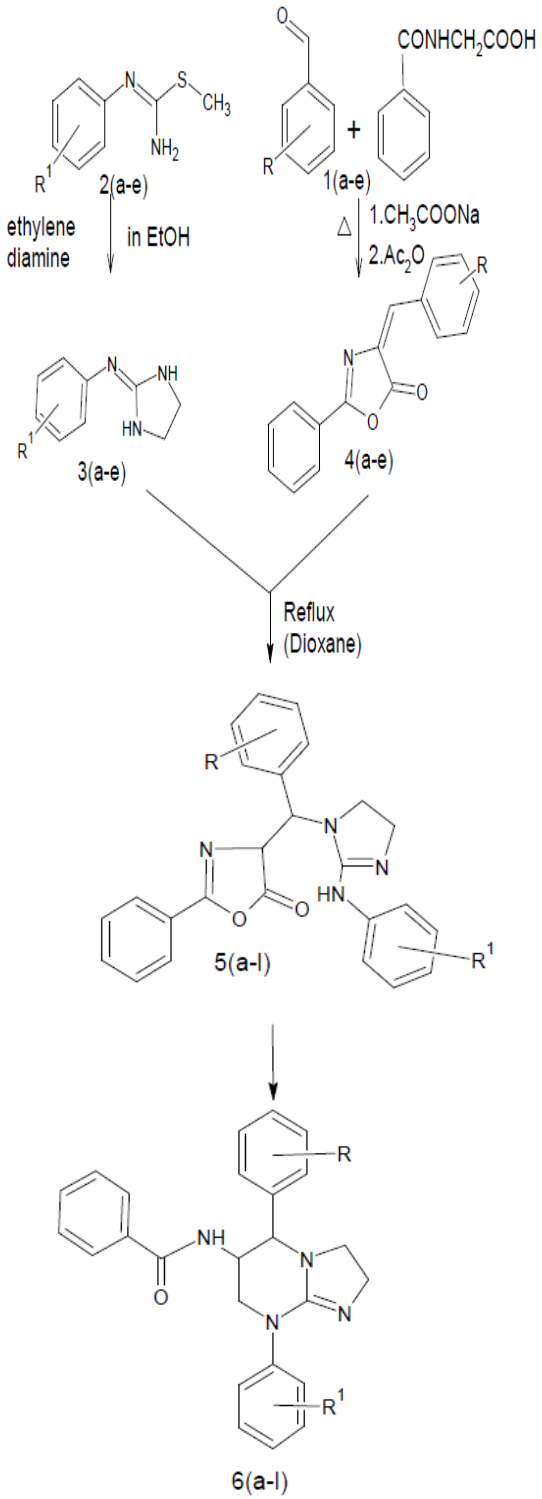
RESULTS AND DISCUSSIONS

Fungicidal screening: Compound **6a-l** were evaluated for their in vitro fungicidal activity against *Aspergillus niger* and *Fusarium oxysporum* by poisoned food technique[12] at 100 and 1000 ppm concentrations using Czapek's agar medium as described earlier.[13,14] The fungus *Aspergillus niger* is **a type of mould, which can sometimes be attributed to the cause of some cases of pneumonia**. It is also the causative agent of 'black mould' on the outsides of certain foods, such as apricots, onions, grapes, etc., therefore making *Aspergillus niger* a food 'spoilage' organism. **Fusarium wilt**, widespread plant disease caused by many forms of the soil-inhabiting fungus *Fusarium oxysporum*. Several hundred plant species are susceptible, including economically important food crops such as sweet potatoes, tomatoes, legumes, melons, and bananas.

The compounds **6e, 6g**, and **6j** displayed fungitoxicity equivalent to that of a commercial fungicide Mancozeb M-45 at 1000 ppm against both the fungi. Due to presence of 4-Cl, 4-CH_3 and 4-OCH_3 groups. (**Table – 2)**

Table 2: Fungicidal Screening data for 5,8-Diaryl-6-benzamido-2,3,5,6-tetrahydro-7H-imidazo [1,2-a]pyrimidin-7-ones (6).

Compd.	% Inhibition after 96 Hours			
	Aspergillus niger		Fusarium oxysporum	
	100 pmm	1000 ppm	100 ppm	1000 ppm
6a	66	81	56	70
6b	72	87	67	72
6c	64	92	58	86
6d	61	78	72	71
6e	79	98	68	96
6f	59	72	76	78
6g	71	92	60	98
6h	67	78	58	72
6i	69	81	78	78
6j	74	96	52	95
6k	44	68	51	71
6l	48	70	55	78
Mancozeb M-45	80	100	82	100



CONCLUSIONS

The compounds **6e, 6g**, and **6j** displayed fungitoxicity equivalent to that of a commercial fungicide Mancozeb M-45 at 1000 ppm against both the fungi. Due to presence of 4-Cl, 4-CH_3 and 4-OCH_3 groups.

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REFERENCES

1. Javeed A T, Davinder S, Gulshan K, Ravi S. Regioselective Base-controlled Pd-catalyzed Arylation of Imidazo[1,2-a]pyridines: leading selectivity at C8 position by N-chelation over O-chelation. Asian Journal of Organic Chemistry, 2021; *10*(7): 1655-1659.
2. Prashant P T, Sagar D, Abdullatif N S, Manisha M, Ashiwini P, Vivek D B, Pravin C M. Design, Synthesis, Antimicrobial and Ergosterol Inhibition Activity of New 4-(Imidazo[1,2-a]Pyridin-2-yl)Quinoline Derivatives. Polycyclic Aromatic Compound**s,** 2002; *27*: 1-18.
3. Tber Z, Hiebel M A, El Hakmaoui A, Akssira M, Guillaumet G, Berteina-Raboin S. Metal Free Formation of Various 3-Iodo-1H-pyrrolo[3′,2′:4,5]imidazo-[1,2-a]pyridines and [1,2-b]Pyridazines and Their Further Functionalization. J. Org. Chem, 2015; 80: 6564– 6573.
4. Vince R & Daluge S, J. Med. Chem, 1977; 20: 612.
5. Schaeffer H J, Ger. Offen, 2, 708,825, 1976; Chem. Abstr, 1978; 88: 694.
6. Bread C C, U S Pat., 4,009, 1977; Chem. Abstr, 1977; 86: 189943.
7. Mohan J & Ajaneyutu G S R, Indian J. Chem, 1989; 28B: 631.
8. Abdelhemid A O, Abdelall E K A, zaki Y H, J. Heterocyclic Chem, 2010; 47: 477-482.
9. Singh H, L D S Yadav, Bull.Soc. Chem. Belg, 1977; 86: 393.
10. Yadav L D S, Mishra A R, Singh H, J.Agric. Food Chem, 1988; 36: 633.
11. Patterawarapan M, Jaita S, Phakhode W, Tetrahedron Letter, 2016; 57: 3171 – 3174.
12. Vogel A I, Vogel's text Book of Practical Chemistry, (Longman Harlow, England), 1975; 884.
13. Matsuo M, Taniguchi K, Karsura Y, Kamitani T & Veda I, Pharm. Bull, 1985; 33: 4409.
14. Harsfall J G, Bot. Rev, 1945; 11: 357.