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NOVEL MAOS OF NOVEL CINNOLINE DERIVATIVES

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Abstract

An efficient and green novel microwave assisted organic synthesis (MAOS) method has been developed for dinitro cinnoline derivatives with better yields. The framework of these derivatives was constructed from dinitrophenyl arylethylidene hydrazines. Tetrabutylammonium bromide (TBAB) was used as a phase transfer catalyst (PTC), potassium carbonate as an inexpensive and efficient catalyst and water as solvent due to its polarity which helps to increase the temperature substantially. This methodology features a simple, environmentally friendly approach, employing water as a green solvent and using a one-pot reaction. The use of microwave increases the rate of reaction and it was observed that dinitro arylcinnolines can be synthesised in 8-12 min of microwave irradiation compared to conventional thermal heating protocol which requires more than 2 h. Spectral data confirms the identity of synthesized derivatives and satisfactory yields are obtained by this process.

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INTRODUCTION

Cinnoline 1,2-diazanaphtalene or benzo[c]-1,2-diazine (Hantsch-Widmann system)[1], $C_8H_6N_2$ is a nitrogenous organic base, obtained from certain complex diazo compounds, depicted in figure 1, is present in many compounds of considerable pharmacological and chemical importance[2]. It is six-membered ring system with two nitrogen atoms, an isosteric relative to either quinoline or isoquinoline and isomeric with phthalazine[3].

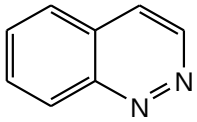


Figure 1. Structure of the cinnoline ring system

The cinnoline nucleus is a very important bicyclic heterocycle that is used as the structural subunit of many compounds with interesting pharmaceutical properties[4]. Cinnoline derivatives exhibit broad spectrum of pharmacological activities such as antibacterial, antifungal, antimalarial, anti-inflammatory, analgesic, anxiolytic and antitumor activities[5]. Some of them are under evaluation in clinical trials. Comprehensive and target oriented information clearly indicate that the development of cinnoline based molecules constitute a significant contribution to the identification of lead compounds with optimized pharmacodynamic and pharmacokinetic properties [6]. Synthesis of cinnoline and its derivatives has been extensively discussed in many papers. Until 2011, no compounds containing the cinnoline ring system were found in nature. The first natural cinnoline derivative 2-furanmethanol-(5′→11)-1,3-cyclopentadiene-[5,4-c]-1H-cinnoline 2 (figure 2) was isolated from *Cichorium endivia* when investigating the in vitro and in vivo hepatoprotective properties of *Cichorium endivia* L. extract (CEE) [2].

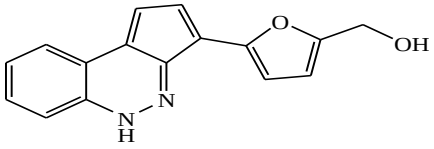


Figure 2. Structure of 2-furanmethanol-(50→11)-1,3-cyclopentadiene-[5,4-c]-1H-cinnoline

Synthetic molecules bearing a cinnoline framework are extensively studied due to their various biological activities depending on the nature and position of substituents but the time required for synthesis is higher and also they required hazardous chemicals which may spoils the environmental conditions and health of the researchers [7]. The nitro group and its location on aromatic rings influence the DNA binding and mutagenic profile of an aromatic compound. It has widely been suggested that nitro reduction plays a critical role in mutagenesis, as major DNA adducts formed with nitro aromatics have been isolated and characterized [8]. Keeping all these facts in mind it has been planned to synthesize dinitro arylcinnoline.

EXPERIMENTAL

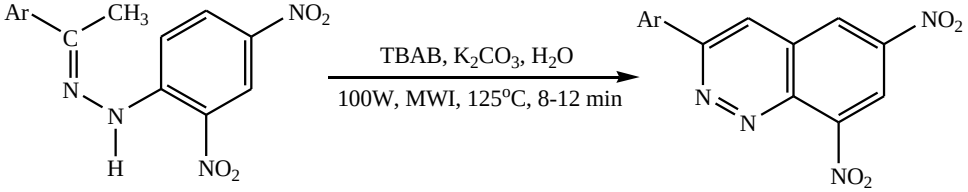
Materials and methods

Infra-red spectra was recorded on Jasco FT-IR 4100 type A model having TGS detector, ^{1}HNMR spectra was recorded on Bruker Advance Neo spectrophotometer at 500 MHz and DMSO as solvent, ^{13}CNMR spectra was on advance Neo spectrophotometer recorded at 600 in DMSO solvent. Melting points were determined on a digital melting point apparatus. High-resolution mass spectra were recorded using Bruker mass spectrophotometer with dlc-ms600mz_10min.m method. All microwave reactions (LabMate make) were carried out in sealed tube (5 mL) and maintenance of the reaction temperature was monitored by an external infrared sensor. The isolation of pure products was carried out via HPTLC which was performed on CAMAGE Lwin Server LABSERVER, version 3.1.21109.3 using Linomat IV applicator and Merck, TLC Al plates silica gel 60 F 254 using Chloroform:Methanol:Glacial Acetic Acid (7:2:1) solvent system. All other synthetic reagents were procured from commercial sources and used without further purification.

General procedure for the synthesis

A 5 mL microwave reaction tube was charged with 1a-1e (0.3 mmol) along with tetrabutylammonium bromide TBAB (0.16g, 0.5 mmol), K_2CO_3 (0.415 g, 3.0 mmol), and H_2O (3 mL). After the tube was flushed with N_2 and capped, the reaction mixture was heated to 125ºC for 8-12 min by microwave

irradiation at 100 W initial power. Time required for compound 2a was 9 min. The mixture was then cooled to room temperature and filtered through a short silica gel column (ethyl acetate) to remove inorganic components. Removal of the solvent left a crude mixture to give 2a-2e.



2-(2,4-dinitrophenyl)-1-[1-arylethylidene)hydrazine **(1a-1e)**

6,8-dinitro-3-arylcinnoline **(2a-2e)**

Figure 3. Synthesis scheme

Ar = *p*-OH-C_6H_5, *p*-CH_3-C_6H_5, *p*-NH_2-C_6H_5, *p*-C_6H_5, *p*-OCH_3-C_6H_5

RESULT AND DISCUSSION

All products were characterized and confirmed by HPTLC, IR, ^{1}HNMR, ^{13}CNMR, and MS spectrometry. Spectroscopic data for all compounds were collected but graphical proofs were provided only for representative compound 2a.

6,8-dinitro-3-p-hydroxy phenylcinnoline (2a) ($C_{14}H_8N_4O_5$, 312.2417), Yellowish green (yield 67%), mp 93-94°C. HPTLC: single peak R_f=0.57.

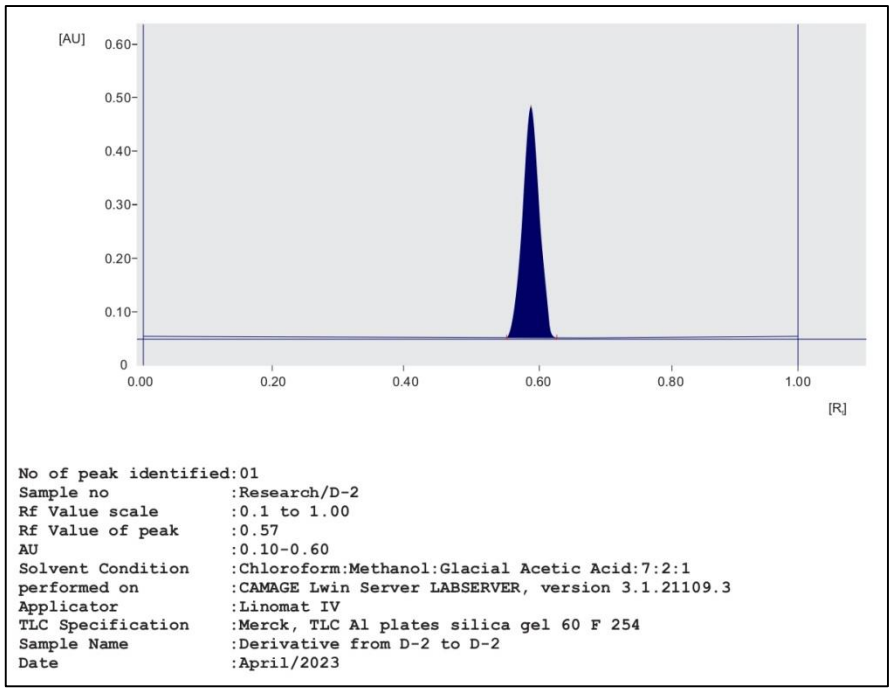


Figure 4. HPTLC of 2a

IR Spectra (cm^{-1}) (KBr): 3418 (O-H stretching), 2934 (C-H stretching), 2157 (N=N stretching), 1960 (C-H bending), 1901 (C=C=N stretching), 1490 (N-O stretching), 1450 (C-H bending), 1340 (O-H bending), 1263 (C-N stretching),

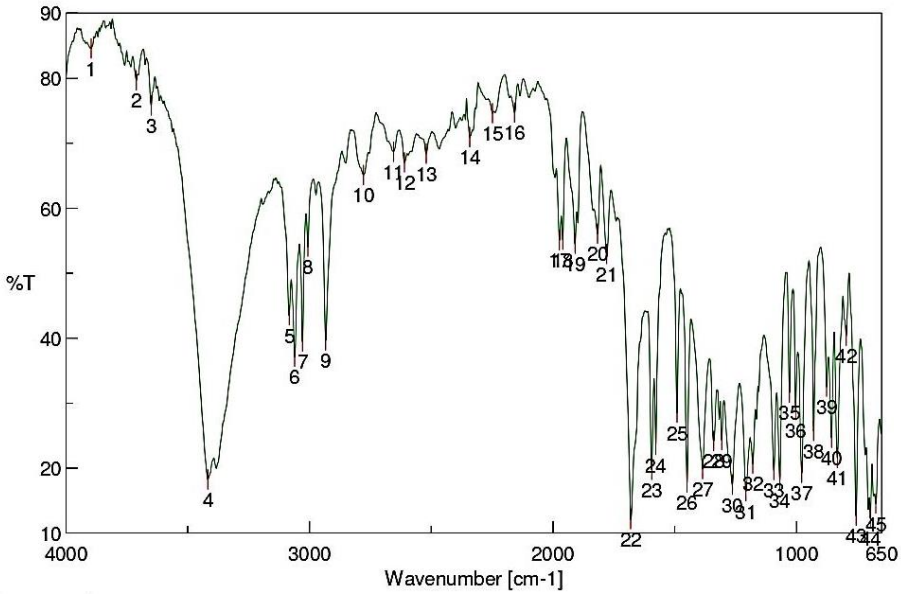


Figure 5. IR spectrum of 2a

[1]HNMR (500 MHz, DMSO): δ 7.11 (2H, ddd, *J* = 8.9, 1.5, 0.4 Hz), 7.83 (2H, ddd, *J* = 8.9, 1.7, 0.4 Hz), 8.55 (1H, d, *J* = 1.2 Hz), 8.83 (1H, d, *J* = 1.5 Hz), 9.01 (1H, dd, *J* = 1.5, 1.2 Hz).

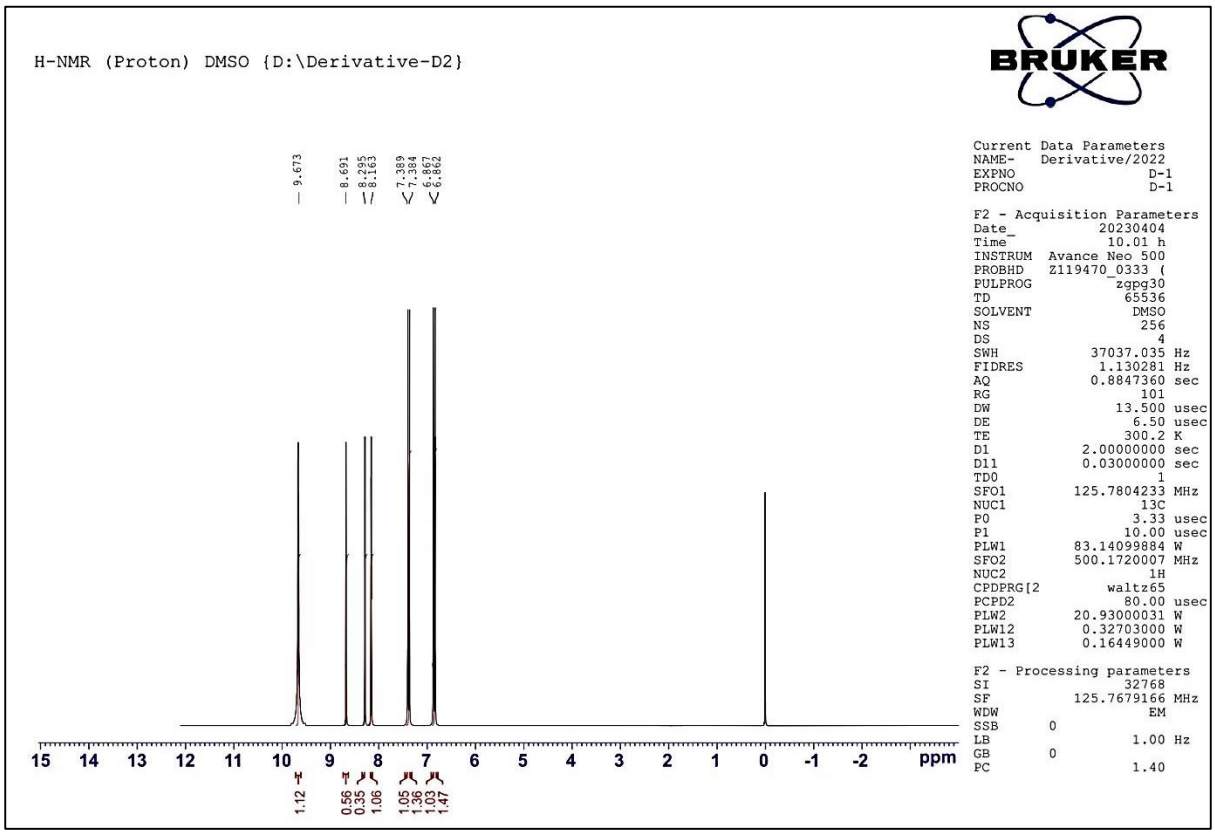


Figure 6. Proton NMR spectrum of 2a

[13]CNMR (600 MHz, DMSO): δ 115.0 (1C, s), 115.7-115.8 (3C, 115.7 (s), 115.8 (s)), 125.3 (1C, s), 128.1 (1C, s), 129.2 (2C, s), 137.5 (1C, s), 143.4 (1C, s), 143.7 (1C, s), 147.9 (1C, s), 151.5 (1C, s), 157.4 (1C, s).

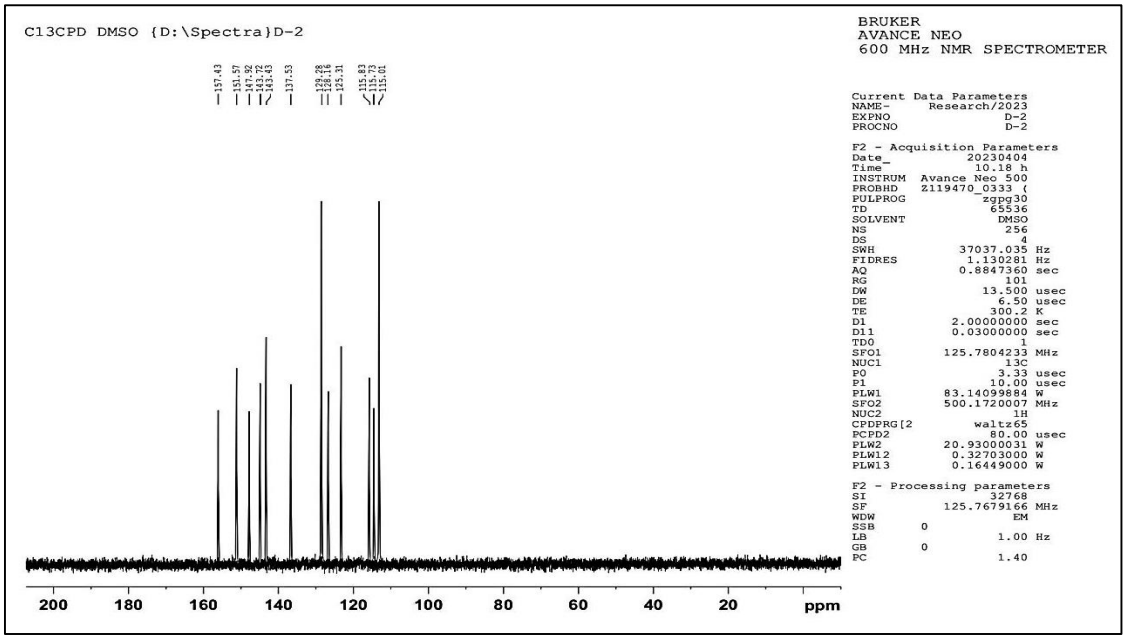


Figure 7. Carbon NMR spectrum of 2a

HRMS: (ESI$^+$): *m/z* calcd for $C_{14}H_8N_4O_5$ M^+ 385.2417, found 385.6571.

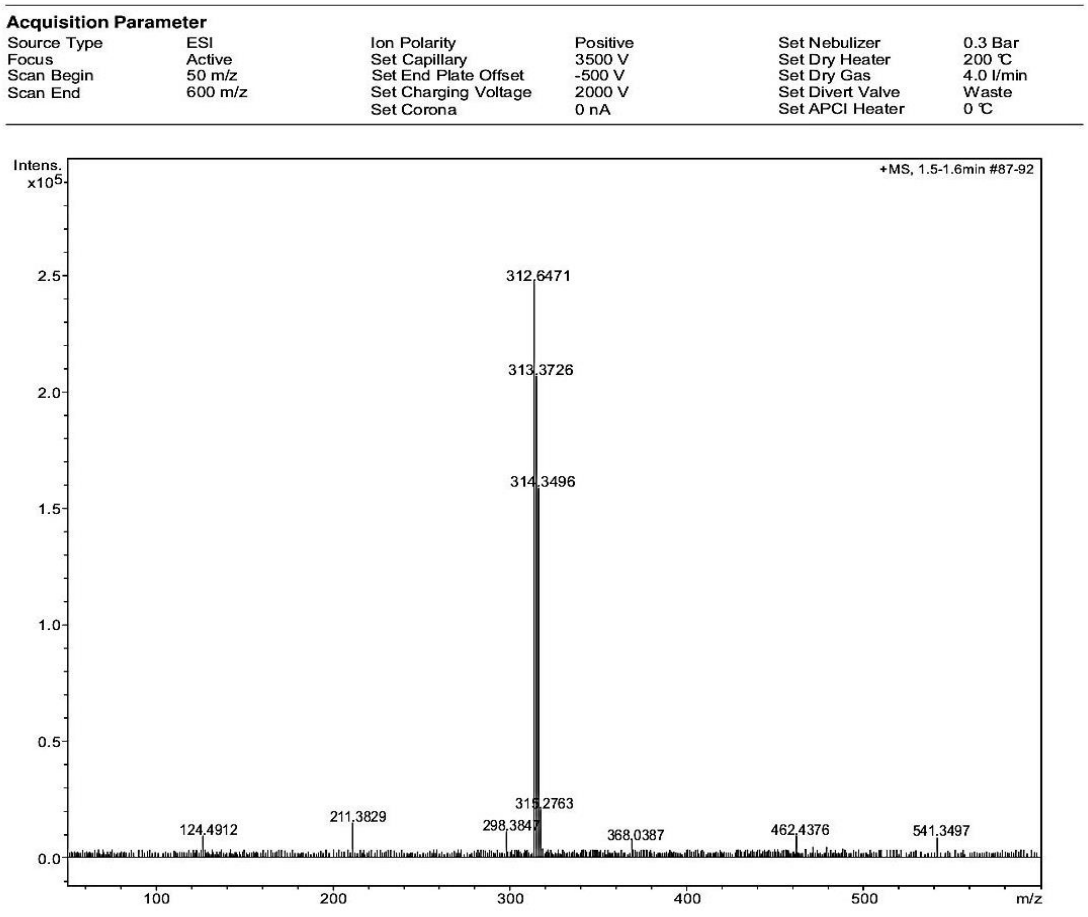


Figure 8. High resolution mass spectrum of 2a

Table 1- Technical data of other derivatives

Code	Functional group	Mol formula	Mol weight	MWI Time	MP (ºC)	R_f	% yield	m/z
2b	*p*-CH_3-C_6H_5	$C_{14}H_9N_5O_4$	311.24	9 min	110-111	0.56	68	311.33
2c	*p*-NH_2-C_6H_5	$C_{14}H_{10}N_4O_4$	310.26	8 min	97-99	0.69	71	310.15
2d	*p*-C_6H_5	$C_{14}H_8N_4O_4$	296.24	10 min	120-121	0.63	66	296.32
2e	*p*-OCH_3-C_6H_5	$C_{15}H_{10}N_4O_5$	326.26	12 min	122-113	0.58	81	325.41

CONCLUSION

A competent novel one pot synthesis method was successfully developed for synthesis of dinitro cinnoline derivatives. All the synthesized derivatives (2a–2e) were subjected to the identification and confirmation by HPTLC, and by spectral analysis including IR, ^{1}HNMR, ^{13}CNMR and HRMS after purification by recrystallization (solvent used was ethyl alcohol) or by column chromatography as per the need and showed better correlation. Compound 2c showed better yield of 71 % while compound 2c required minimum time of 8 min for MW reaction. As compared to conventional method which required more than 2 h for synthesis of these derivatives, MAOS has reduced time of synthesis by 6 times which can save the time of reaction. Solvent used is water and other chemicals are also non-hazardous which offers another advantage. The developed synthetic method can be successfully employed for further synthesis of dinitro derivatives. Large scale synthesis of these derivatives may require trial and errors. Synthesized derivatives can be evaluated pharmacologically for different biological activities in future.

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