"MICROWAVE ASSISTED SYNTHESIS OF SUBSTITUTED 3-ARYL-1H-PYRAZOL-5-AMINE, 3-PHENYLISOXAZOL-5-AMINE, AND 5-PHENYLISOXAZOL-3-AMINE."

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Abstract

A set of molecules of substituted 3-Aryl-1*H*-pyrazol-5-amine is synthesized from substituted benzoylacetonitrile under microwave irradiation in presence of catalytic $Ce(OTf)_3.SiO_2$. Also a set of compounds of substituted 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine and 5-phenylisoxazol-3-amine is synthesized from substituted 2-(2-phenyl-1, 3-dioxolan-2-yl)acetonitrile under microwave irradiation. Synthesized molecules characterized using spectroscopic techniques such as ^{1}H-NMR, MASS, ^{13}C and physical properties (Melting points). Synthesized molecules confirmed with their standard reported values. This methodology has advantages over classical-conventional method such as lower reaction time, green synthesis approach, high yield, low loading of heterogeneous $Ce(OTf)_3.SiO_2$ catalyst, recyclability of $Ce(OTf)_3.SiO_2$ catalyst and many more.

Keywords: 3-Aryl-1*H*-pyrazol-5-amine, 2-(2-phenyl-1, 3-dioxolan-2-yl)acetonitrile, 3-phenylisoxazol-5-amine, 5-phenylisoxazol-3-amine.

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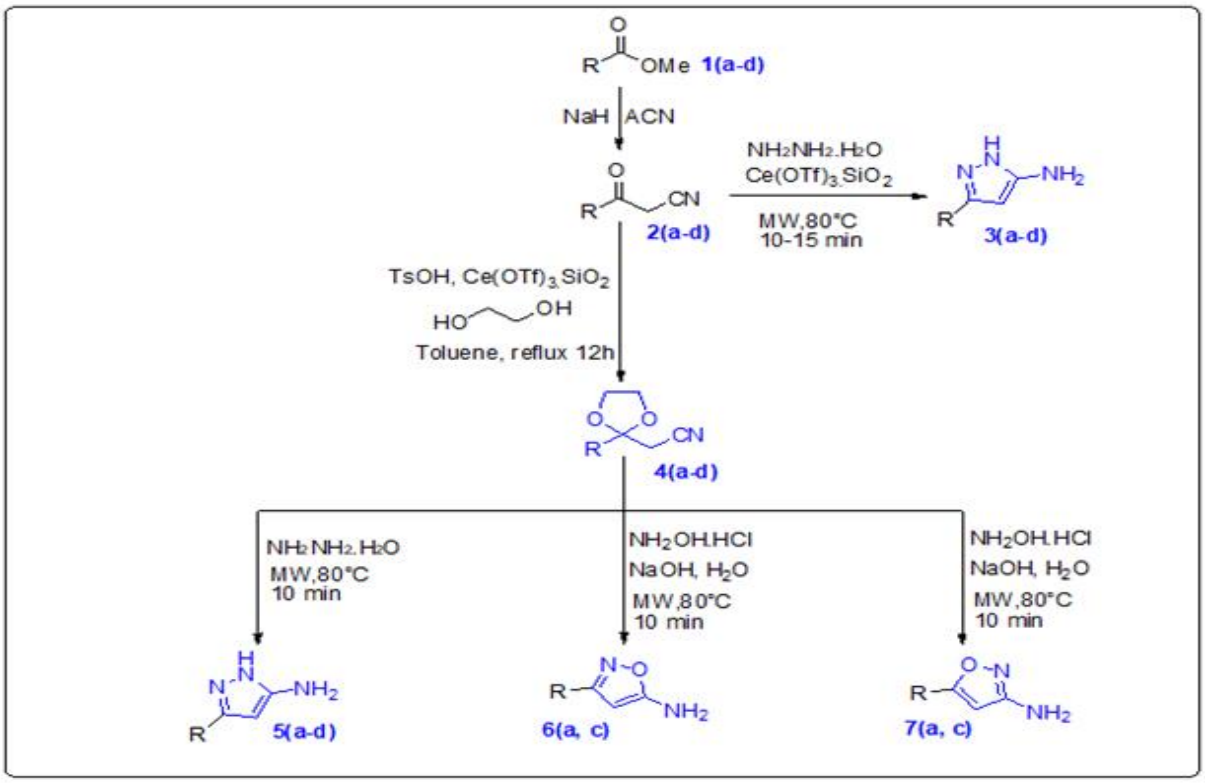
1. Introduction:

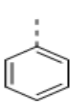
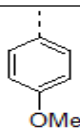
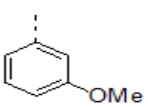
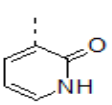
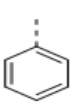
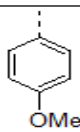
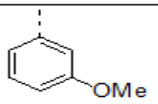
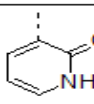
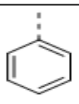
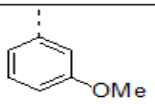
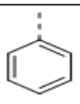
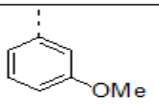
3-Aryl-1*H*-pyrazol-5-amine is a 5 membered-heterocyclic system in which 2 nitrogen present adjacent to each other. Substituted 3-Aryl-1*H*-Pyrazol-5-Amine and their derivatives exhibit high biological activities. Synthesis of 3-phenyl-1*H*-pyrazol-5-amines has been comprehensively investigated in the last few decades. Pyrazole and its derivatives are shows variable biological and pharmacological activities such as: anticancer[1,2], anti-inflammatory[3,4], antioxidant [5], antifungal [6], antibacterial [6,7,8], analgesic [9], antiviral [10,11], antimicrobial [12,13], antiglycemic[14], antiamoebic[15], and antidepressive [16,17]. Pyrazole is one of the most popular heterocycles in bioactive compounds, including drugs and agrochemicals [18-20]. By considering these substantial biological applications of pyrazole, it is one of the most widely studied nitrogen-containing heterocyclic nuclei. Pyrazole derivatives are composed of the pyrazole nucleus attached to other heterocyclic or aromatic moieties which facilitate them to exhibit improved pharmacological activities. Nazeri, et al. [21] , Marjani and group [22] , Everson et al [23] , Pires et al [24] , Bucha et al [25] , Liu and group [26] , Jismy et al [27] , Adachi et al [28] , Ahmad et al [29] , Cheng et al [30] , Emelina et al [31] , Liu and group [32] , Ma et al [33] , Becerra and group [34] , Nazeri and group [35] , Yijiaoa et al [36] , Panchal et al [37] , Sun et al [38] , Suryakiran et al [39] , Suryakiran et al [40] , Patil and group [41] , Uma et al [42] , Tandon et al [43] , Wenthur et al [44] describes variety of methods for the synthesis of 3-Aryl-1*H*-pyrazol-5-amine. 3-Phenylisoxazol-5-amine and 5-Phenylisoxazol-3-amine shows their enormous biological applications in organic synthesis.

2. Results & Discussion:

Scheme-1: *Synthesis of 3-Aryl-1H-pyrazol-5-amine, 3-phenylisoxazol-5-amine, 5-phenylisoxazol-3-amine*



Where R as follows,

3a	3b	3c	3d	5a	5b
					
5c	**5d**	**6a**	**6c**	**7a**	**7c**
					

In present work substituted 3-Aryl-1*H*-pyrazol-5-amine prepared from benzoylacetonitrile **2(a-d)** under microwave irradiation in presence of catalytic $Ce(OTf)_3.SiO_2$.

Also substituted 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine and 5-phenylisoxazol-3-amine prepared from substituted 2-(2-phenyl-1,3-dioxolan-2-yl)acetonitrile **3(a-d)** under microwave irradiation.

Reaction conditions of all steps were optimized with respect to stoichiometry of reagents, reaction temperature, Reaction time and reaction solvent. Optimized reaction condition was used during synthesis of all step intermediates.

As an effort to synthesis of 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine, 5-phenylisoxazol-3-amine from Benzoylacetonitrile is described herein the present article from benzoylacetonitrile. Several methods were reported for the synthesis of Benzoylacetonitrile followed by cyclizations to get desired 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine, 5-phenylisoxazol-3-amine.

Elimination of methoxy group of methyl benzoate ***1(a-d)*** with acetonitrile in presence of sodium hydride as a base in Acetonitrile resulted in the formation of Benzoylacetonitrile ***2(a-d)*** derivatives, respectively.[20] The compounds ***2(a-d)*** cyclocondensed with two equivalents of hydrazine hydrate and 5mole% $Ce(OTf)_3.SiO_2$ under microwave irradiation to give 3-aryl-1*H*-pyrazol-5-amines ***3(a-d)*** **(Scheme-1).** The structure of compounds ***3(a-d)*** was confirmed by their physical properties (melting point) and ^{1}H-NMR spectral data. Details of synthesized substituted 3-aryl-1*H*-pyrazol-5-amines were summarized in **Table-1**.

Table-1: *Synthesis of substituted 3-aryl-1H-pyrazol-5-amines-3(a-d).*

Sr. No.	**R**	**Comp.**	**Yields (%)**			**Melting points (°C)**	
			Microwave	Ultrasonic	Reference	Observed	Reference
1.	-C_6H_5	3a	95	91	92,[45]	121-125	126-127, [46]
2.	-4-OMe-C_6H_4	3b	94	95	95,[47]	141-143	141-142, [48]
3.	-3-OMe-C_6H_4	3c	84	88	83,[49]	128-132	-
4.	-2-OH-C_5H_3N	3d	72	74	61,[50]	178-182	-

The benzoylacetonitrile ***2(a-d)*** was taken as key intermediates to synthesize substituted 2-(2-aryl-1,3-dioxolan-2-yl)acetonitrile ***4(a-d)*** and their exploration to synthesis of 3-Aryl-1*H*-pyrazol-5-amine **5(a-d)**, 3-Arylisoxazol-5-amine **6(a, c)** and 5-arylisoxazol-3-amine **7(a, c).**

Table-2: *synthesis of* 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine and 5-phenylisoxazol-3-amine.

Sr. No.	**R**	**Comp.**	**Yields (%)**			**Melting points (°C)**	
			Microwave	Ultrasonic	Reference	Observed	Reference
1.	-C_6H_5	5a	93	95	92,[45]	121-125	126-127, [46]
2.	-4-OMe-C_6H_4	5b	96	94	95,[47]	141-143	141-142, [48]
3.	-3-OMe-C_6H_4	5c	88	84	83,[49]	128-132	-
4.	-2-OH-C_5H_3N	5d	76	72	61,[50]	178-182	-
5.	-C_6H_5	6a	73	78	65,[51]	113-15	111,[52]
6.	-3-OMe-C_6H_4	6c	79	73	72,[53]	85-87	83-85,[54]
7.	-C6H5	7a	85	81	68,[55]	138-140	136,[56]
8.	-3-OMe-C_6H_4	7c	83	75	traces,[57]	153-155	-

The structure of synthesized compounds confirmed by their physical properties (melting point) and ^{1}H-NMR spectral data. Details of synthesized compounds [5(a-d), 6(a, c) and 7(a, c)] are summarized in **Table -2.**

3. **Plausible Mechanism:** Plausible mechanism represented as follows,

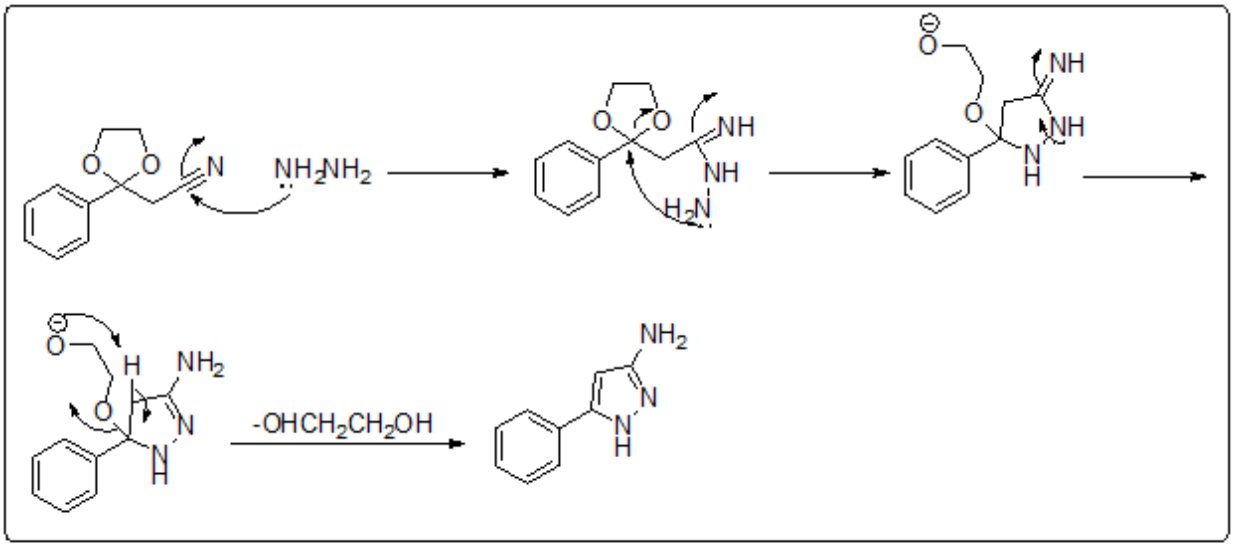


Figure-4.1.5.1: *Plausible mechanism of amino pyrazole*

4. Experimental Section:

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and Finar and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using Lab-India MR. Vis+ apparatus. The ^{1}H-NMR spectra were determined using Bruker 300 MHz instrument using TMS as the internal standard. Isolated compounds were purified using re-crystallization technique. All the synthesized products are reported in literature and were identified by comparison of their observed melting points and ^{1}H-NMR values with reported values.

4.1 Preparation of Benzoylacetonitrile 2(a-d)) [20].

Sodium hydride (60%, 15.08 g, 377.0 mmol) in a round bottom flask was cooled using an ice-water bath and kept under nitrogen atmosphere on a Schlenk line. Anhydrous acetonitrile (19.0 mL, 360 mmol) and 10.0 mL of anhydrous DMSO were added to the flask and the mixture was stirred for 20 minutes. Methyl benzoate (37.8 mL, 40.8 g, and 300 mmol) was added to the reaction mixture. After stirring for approximately 1.5 hours, the reaction mixture turned into a thick white solid. The excess NaH in the reaction mixture was quenched by slow addition of deionized water. HCl (62.3 mL 12.1 M, diluted to 600 mL) was added to fully protonate the product, which immediately gave a milky white suspension. The product was then extracted three times (150 ml each) with ethyl acetate. All organic layers were combined and washed with NaCl brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Solvent was evaporated under reduced pressure, giving a light orange oil, which, when triturated with a 1:1 mixture of hexane and diethyl ether, yielded 41.33 g (284.7 mmol, 95%) of 1a as a very light yellow solid. Synthesized compound identified by matching physical properties and ^{1}H-NMR with standard reported values.

4.2 Preparation of 3-aryl-1H-pyrazol-5-amines 3(a-d).

A mixture of benzoylacetonitrile **2(a)** (1.0eq.) and hydrazine hydrate (2.0eq.) was irradiated under microwave at 80°C for 10 min in presence of $Ce(OTf)_3.SiO_2$. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mass cooled to ambient temperature and solid catalyst removed by filtration. Then filtrate mL diluted with cold water and filtered out under vacuum to get crude material which was washed with water. The crude product purified with recrystalisation using ethanol solvent to afford 3-aryl-1*H*-pyrazol-5-amines **3(a)** as a pale yellow solid with excellent yield (Yield 95%). Synthesized compound characterized by their melting point and ^{1}H-NMR by comparing with reported values.

3a: 3-phenyl-1*H*-pyrazol-5-amine: ^{1}H-NMR (DMSO-d6, 300 MHz): d (ppm): 11.74 (Bs, 1H), 7.63-766 (d, 2H), 7.23-7.39 (m, 3H), 5.76 (s, 1H), 4.77 (s, 2H).

Same protocol employed for the synthesis of remaining targets 3(b-d) and synthesized compounds are confirmed by comparing Melting point and ^{1}H-NMR with reported ones.

4.3 Preparation of 2-(2-phenyl-1,3-dioxolan-2-yl)acetonitrile 4(a)

To a solution of benzoylacetonitrile (1.0eq.) and TsOH (0.02eq.) in toluene (120 mL) is added ethylene glycol (2.0eq.) and 5.0 mole% $Ce(OTf)_3.SiO_2$. The azeotropic mixture is heated at 120 °C for 12 h and collected water azeotropically. Progress of the reaction monitored by TLC. After completion of reaction, reaction mass cooled to ambient temperature and washed with 10% aqueous NaOH solution. The aqueous layer is extracted with Tert.butyl methyl ether (3 x 4vol). The combined organic layers are dried over sodium sulfate and evaporated to provide the crude compound. The crude material is purified using flash column chromatography to afford the title compound as an off-white solid (Yield 96%). Synthesized compound characterized by their melting point and ^{1}H-NMR by comparing with reported values.

4a: 2-(2-phenyl-1,3-dioxolan-2-yl)acetonitrile: ^{1}H-NMR ($CDCl_3$, 300 MHz): d (ppm): 7.635-754 (m, 5H), 4.13-4.30 (t, 4H), 2.96 (s, 2H)., ^{13}C:(139,128,125,115,106,60,30).

Same protocol employed for the synthesis of remaining targets 4(b-d) and synthesized compounds are confirmed by comparing Melting point and ^{1}H-NMR with reported ones.

4.4 Preparation of 3-phenyl-1*H*-pyrazol-5-amine (5a) under microwave irradiation.

A mixture of 2-(2-phenyl-1, 3-dioxolan-2-yl)acetonitrile **4(a)** (1.0eq.) and hydrazine hydrate (2.0eq.) was irradiated under microwave at 80°C for 10 min. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mass cooled to ambient temperature diluted with cold water and filtered out under vacuum to get crude material which was washed with water. The crude product purified with recrystalisation using ethanol solvent to afford 3-aryl-1*H*-pyrazol-5-amines **5(a)** as a pale yellow solid with excellent yield (Yield 93%). Synthesized compound characterized by their melting point and ^{1}H-NMR by comparing with reported values.

Same protocol employed for the synthesis of remaining targets 5(b-d) and synthesized compounds are confirmed by comparing Melting point and ^{1}H-NMR with reported ones.

4.5Preparation of 3-(3-methoxyphenyl) isoxazol-5-amine (6c) under microwave irradiation.

A solution of 2-(2-phenyl-1, 3-dioxolan-2-yl)acetonitrile **4(a)** (1.0eq.), $NH_2OH{\cdot}HCl$ (1.05 eq.) & NaOH (2.05 eq.) in 10 volume water is irradiated under microwave for 10 min. at 80 °C. Progress of the reaction monitored by TLC. After completion of reaction, reaction mass cooled to ambient temperature and extracted with dichloromethane. Combined dichloromethane layer washed with brine solution. Organic layer concentrated under reduced pressure to get crude product which was purified using flash column chromatography to afford as a white solid compound 8a with 79% yield.

3-(3-methoxyphenyl)isoxazol-5-amine 6(c) : yield 79%; mp: 85–87 °C, ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 7.35-7.38 (t, 1H), 7.22–7.29 (m, 2H), 6.99–7.01 (d, 1H); 5.42 (s, 1H); 3.78 (s, 2H; LC-MS (ESI) m/z 190.9 [M+H].

Same protocol employed for the synthesis of remaining targets 6(a) and synthesized compounds are confirmed by comparing Melting point and ^{1}H-NMR with reported ones.

4.6Preparation of 5-(3-methoxyphenyl) isoxazol-3-amine (7c) under microwave irradiation.

To a stirred solution of 2-(2-phenyl-1, 3-dioxolan-2-yl)acetonitrile **4(a)** (1.0eq.) and NaOH (1.1eq.) in water (5 vol): EtOH (5 vol) was added hydroxylamine hydrochloride (1.1eq.). The mixture was stirred at 80°C for 10 min under microwave irradiation. Progress of the reaction monitored with the help of TLC. After completion of reaction, conc. HCl (1.5eq.) was added and the resulting mixture was irradiated at 80°C further 10 min. pH was adjusted 10 using Aq. NaOH and product extracted with ethyl acetate. The combined extract was concentrated under reduced pressure and the residue was purified by flash column chromatography to afford titled compound as a yellow solid.

Same protocol employed for the synthesis of remaining targets 7(a) and synthesized compounds are confirmed by comparing Melting point and ^{1}H-NMR with reported ones.

5. Conclusion:

An efficient, mild, and green methodology has been developed for the synthesis of 3-Aryl-1*H*-pyrazol-5-amine, 3-phenylisoxazol-5-amine and 5-phenylisoxazol-3-amine under microwave irradiation. The developed methodology has a simple isolation process with good to excellent yields; relatively short reaction times are of some advantages of this protocol. This improved reaction condition allows the preparation of a wide variety of substituted 3-Aryl-1*H*-pyrazol-5-

amine, 3-phenylisoxazol-5-amine and 5-phenylisoxazol-3-amine in high to good yields and excellent purity under mild reaction conditions. We believe the applicability of this methodology with the mentioned advantages makes our method superior among other reported methods

6. ACKNOWLEDGMENT

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