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SYNTHESIS OF SUBSTITUTED AZITIDINE DERIVATIVES VIA ONE POT THREE-COMPONENT (2II+2II) CYCLOADDITION REACTION UNDER ULTRASONIC IRRADIATION METHOD

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Abstract:

*We have efficient and ecofriendly synthesis of N-(7-R)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide derivatives (**IVa-n**) via one pot three-component (2π+2π) cycloaddition reaction using isoniazide(**I**), Aromatic Aldehydes (**IIa-n**), DHP (**III**) and a Lewis acid ($SnCl_2$) catalyst under Ultrasonic irradiation method. Advantages of this method are- one step reaction, mild conditions, short reaction time and good to excellent yields.*

Keywords: *Cycloaddition reaction; Substituted azitidine; Aromatic Aldehyde; Ultrasound irradiation.*

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INTRODUCTION:

In the recent organic synthesis, cycloaddition reactions are particularly important tools allowing the formation of two new bonds in single step by cyclization. Additionally, these modifications provide the assembly for complex molecular structures in an easy fashion, with high atom economy and consequently minimization of waste production1-2. Cycloaddition can be promoted by light, heat, high pressure, Ultrasonic irradiation.

Metal catalyzed cycloaddition reactions have been widely studied such as Rh(II)[3], Yb(OTf)3[4], TiCl2[5], InCl2[6], BF3.MeOH[7], Al(OTf)3[8], Sc(OTf)3[9] and Phosphoric acid [10] in the last decades. Substituted azitidine are one of the most important classes of natural products and exhibit a wide spectrum of biological and pharmaceutical properties including Antimicrobial [11-13], Antitubercular[14], Anticonvulsant[15], Anti-inflammatory[16] and Cardiovascular Activities17. An extensive literature survey revealed that the cycloaddition reaction has rarely explored under Ultrasonic irradiations method [18]. Thus, present study focuses on synthesis of N-(7-R)-2-oxa-8-azabicyclo [4.2.0]octan-8-yl)isonicotinamide derivatives(**IVa-n**) by Ultrasonic irradiation method and differ from reported work.

EXPERIMENTAL:

General information-

Ultrasonication was performed (230 V AC, 50 Hz, liquid holding capacity 5.5 L temperature 70°C. The 100 mL Round Bottom reaction flasks with condenser attached to stand and reaction flasks were suspended at center of the bath. ^{1}H NMR and ^{13}C NMR spectra were recorded at (Bruker) 400 MHz and 100 MHz in DMSO as solvent using TMS (internal standard). IR spectroscopy was performed on a (Perkin-Elmer) FT-IR Spectrometer. Melting points were measurements by manually. TLC was conducted on standard conversion aluminum sheets pre-coated with 0.2 mm layer of silica gel. All AR grade reagents were used.

General procedure for (2+2) cycloaddition reaction of the N-(7-R)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide derivatives-

In Ultrasound irradiation method, a mixture of ($SnCl_2$) (10%, mol), isoniazide (0.1 mol), aromatic aldehyde (0.1 mol) and DHP (0.1 mol) in THF as solvent (5 mL) was irradiated with Ultrasound (with a frequency of 50 Hz and power of 250 V AC) at 70 °C temperature for 2 hours. The reaction flasks were located at center of the bath with condensed assembly and the surface of the reactants was placed slightly lower than the water level in the Round Bottom flasks. The reaction progress was checked on TLC using ethyl acetate: hexane (3:7) as solvents. After the completion of reaction, the reaction mixtures cool at room temperature. A charged methanol (10 mL) was used for crystallization and then cools at 20°C temperature, stirred for15 minutes. Filter the product through G_1 sintered crucible with assembly and recrystallized by alcohol.

***N*-(7-(2,5-dimethoxyphenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4a)-**

Creamy yellow powder, m.p. 182-184°C. FTIR (KBr cm^{-1}): 3212, 3058, 3001, 2842, 1650, 1169; ^{1}H NMR 400 MHz, DMSO) δ 11.8 (s, 1H, D_2O exchangeable NH), 8.66-8.77 (m, 2H,Ar), 7.50-7.80 (m, 2H,Ar), 6.86-6.88 (m, 1H,Ar), 6.85 (s, 1H,Ar), 6.80-6.82, (m, 1H,Ar), 4.98 (d, 1H,), 3.76 (d,1H), 3.73 (t, 2H), 3.62 (m, 1H), 3.0 (s, 6H), 2.48-2.58 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.28, 153.69, 152.83, 150.14, 140.84, 122.80, 121.81, 118.68, 112.70, 110.03, 78.77, 56.24, 41.00, 40.00, 39.01.

***N*-(7-(3,4-dihydroxyphenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4b)-**

Whitish yellow powder, m.p 240-242°C. FTIR (KBr cm^{-1}): 3211, 3001, 2843, 1654, 1170; ^{1}H NMR 400 MHz, DMSO) δ 11.7 (s, 1H, D_2O exchangeable NH), 8.67-8.70 (m, 2H,Ar), 7.20-7.81(m, 2H,Ar), 7.27-7.31 (s, 1H Ar), 6.96-6.72 (m, 2H,Ar), 5.0 (s, 2H, OH),4.96 (d, 1H,), 3.80 (d,1H), 3.70 (t, 2H), 3.58 (m, 1H), 2.48-2.50 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 161.63, 150.42, 149.91, 148.9, 145.74, 141.42, 128.00, 123.71, 121.95, 118.54, 113.06, 78.00, 77.10, 41.38, 40.30, 39.21.

***N*-(7-(3-hydroxyphenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4c)-**

White powder, m.p 240-242°C. FTIR (KBr cm^{-1}):3213, 3001, 2843, 1654, 1170; ^{1}H NMR 400 MHz, DMSO) δ 11.9 (s, 1H, D_2O exchangeable NH), 8.35-8.70 (m, 2H,Ar), 7.73-7.83(m, 2H,Ar), 7.00 (s, 1H Ar), 6.80-7.22 (m, 3H,Ar), 5.0 (s, 1H, OH),4.92 (d, 1H,), 3.80 (d,1H), 3.70 (t, 2H), 3.50 (m, 1H), 2.48-2.50 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.56, 150.13, 149.12, 147.51, 143.17, 140.46, 132.45, 124.10, 121.26, 115.62, 113.58, 78.00, 77.02, 41.08, 40.30, 39.70.

***N*-(7-(4-cynophenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4d)-**

yellow powder, m.p. 130-133°C. FTIR (KBr cm^{-1}): 3212, 3058, 3001, 2842, 1650, 1169; ^{1}H NMR 400 MHz, DMSO) δ 11.7 (s, 1H, D_2O exchangeable NH), 8.68-8.67 (m, 2H,Ar), 8.27 (m, 2H,Ar), 7.3-7.8 (m, 2H,Ar), 6.80-7.06 (m, 2H,Ar), 4.99 (d, 1H,), 3.61

(d,1H), 3.40 (t, 2H), 3.38 (m, 1H), 2.50 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.01, 150.20, 149.98, 146.97, 141.24, 127.15, 121.87, 120.85, 113.31, 111.30, 78.82, 77.00, 41.02, 40.00, 38.93.

***N*-(7-(3-hydroxy-4-methoxyphenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4e)-** Lemon yellow powder, m.p. 230-232ºC. FTIR (KBr cm^{-1}): 3213, 3001, 2843, 2223, 1655, 1170; ^{1}H NMR 400 MHz, DMSO) δ 12.1 (s, 1H, D_2O exchangeable NH), 8.4-8.72 (m, 2H,Ar), 8.1 (s, 1H,Ar), 7.81-7.82 (m, 2H,Ar), 7.59-7.7 (m, 2H,Ar), 5.0 (s, 1H, OH), 4.99 (d, 1H,), 3.61 (d,1H), 3.40 (t, 2H), 3.38 (m, 1H), 3.3 (s, 3H), 2.50 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.56, 150.13, 149.12, 147.51, 138, 132, 128.10, 127.59, 121.95, 118.54, 113.06, 110.03, 78.88, 77.00, 56.00, 41.00, 40.00, 39.01.

***N*-(7-(2,4-dichloroyphenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4e)-** Luminary green powder, m.p. 220-223ºC. FTIR (KBr cm^{-1}): 3210, 3000, 2831, 2170, 1650, 1168; ^{1}H NMR 400 MHz, DMSO) δ 11.89 (s, 1H, D_2O exchangeable NH), 8.2-8.70 (m, 2H,Ar), 8.1-8.6 (s, 2H,Ar), 7.71-7.82 (m, 2H,Ar), 7.50-7.75 (s, 1H,Ar), 4.99 (d, 1H,), 3.61 (d,1H), 3.40 (t, 2H), 3.38 (m, 1H), 2.50 (m, 2H), 1.6-1.7 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.50, 150.03, 148.12, 145.67, 138.01, 132.02, 128.20, 126.48, 121.85, 118.44, 112.56, 110.00, 78.80, 77.00, 41.00, 40.00, 38.91.

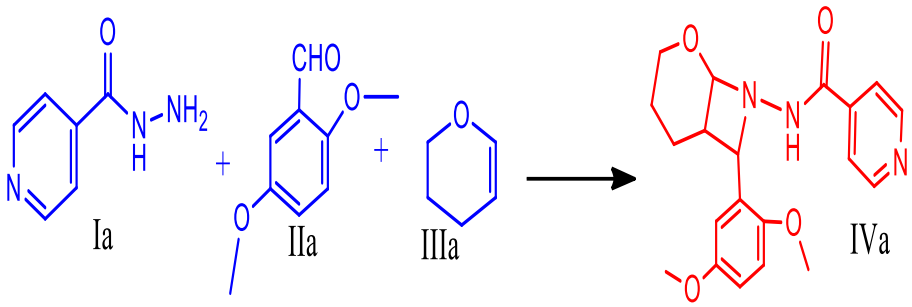
***N*-(7-(4-nitrophenyl)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide(4d)-** Creamy whitish powder, m.p. 130-133ºC. FTIR (KBr cm^{-1}): 3210, 3049, 3001, 2837, 1652, 1168; ^{1}H NMR 400 MHz, DMSO) δ 11.6 (s, 1H, D_2O exchangeable NH), 8.64-8.67(m, 2H,Ar), 8.19 (m, 2H,Ar), 7.1-7.78 (m, 2H,Ar), 6.79-7.00 (m, 2H,Ar), 4.89 (d, 1H,), 3.59 (d,1H), 3.37 (t, 2H), 3.25 (m, 1H), 2.48 (m, 2H), 1.5-1.68 (m, 2H); ^{13}C NMR (100 MHz, DMSO): 162.00, 150.23, 148.78, 146.64, 141.14, 127.05, 121.69, 119.95, 112.82, 111.35, 78.62, 77.00, 41.02, 40.00, 39.09.

RESULTS AND DISCUSSION:

The DHP(**III**) have been used extensively used in one pot multi- component (4π+2π) cycloaddition reaction but limited examples of synthesis of substituted azitidine derivatives.

In present work, we described a mild and efficient approach for the synthesis of azitidine derivatives (Table-**3**) via (2π+2π) cycloaddition reaction using $SnCl_2$ as a catalyst with moderate to good yields.

Initially, the reaction was explored by stirring mixture of isoniazide (**I**), 2,5-dimethoxybenzaldehyde(**IIa**), DHP(**III**) and (10 mol%) ($SnCl_2$) catalyst at a room temperature using different solvents like CH3CN, EtOH, DCE and THF (Table-**1, entries 1-4**) for 10 hours. But Product (**IVa**) was not obtained under these circumstances. So same reactions was carried out under reflux for 10 hours. Here Product (**IVa**) was observed in EtOH and THF solvents (Table **1,** entries **5,6**).



Scheme-1.

Table 1: Optimization reaction conditions for solvents using stannous chloride (10 mol%) Catalyzed (2π+2π) cycloaddition reaction

Entry	Solvent	Method	Temp (°C)	Time (h)	Isolated Yield (%)
1.	CH_3CN	Stir	Rt	10	-
2.	EtOH	Stir	Rt	10	-
3.	DCE	Stir	Rt	10	-
4.	THF	Stir	Rt	10	-
5.	THF	Reflux	(110°C)	10	70
6.	EtOH	Reflux	(110°C)	10	63
7.	DCE	Reflux	(110°C)	10	-
8.	CH_3CN	Reflux	(110°C)	10	-
9.	THF	U.S. irradiation	(70°C)	1.5	83
10.	EtOH	U.S. irradiation	(70°C)	02	60
11.	DCE	U.S. irradiation	(70°C)	02	-
12.	CH_3CN	U.S. irradiation	(70°C)	02	68
13.	THF	U.S. irradiation	Rt	02	-
14.	EtOH	U.S. irradiation	Rt	02	-
15.	CH_3CN	U.S. irradiation	Rt	02	-

Reaction conditions- Isoniazide (0.1 mol), 2,5-dimethoxybenzaldehyde (0.1 mol), DHP (0.1 mol) and stannous chloride ($SnCl_2$) (10 mol%) catalyst and each 5 mL solvent).

Thus, we have performed these reactions under Ultrasonic irradiation and observed effect. The product **(IVa)** was obtained within 2 hours at 70 °C using EtOH and CH_3CN solvent but same product **(IVa)** was obtained at 70 °C within 1.5 hours using THF as solvent (Table **1**, entries **9,10 and 12**).

Further, varying the temperature from 70 °C to room temperature using same solvent, product **(IVa)** was not obtained (Table **1**, entries **13-15**).

From above experimental results, we have choose THF solvent and irradiation method for synthesis of substituted azitidine derivatives(Table **1**, entry **9**).

Fig. 1: Ultrasonic irradiator with condense unit

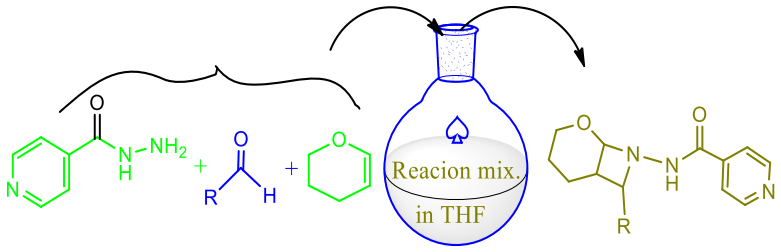


Fig. 2: One pot containing three components

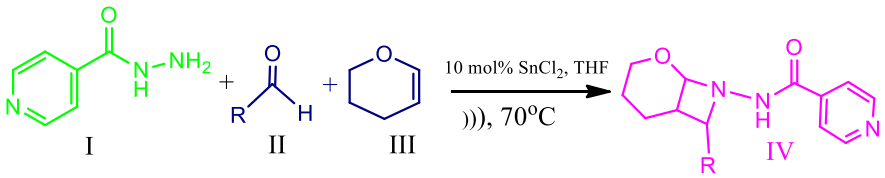
In order to observe the effect of ($SnCl_2$) on the reaction, variable amount of catalyst (Table **2**) was experimented.

Table 2: Optimization of reaction conditions for stannous chloride catalyzed (2π+2π) cycloaddition reaction.

Entry	(mol %)	Time(h)	Isolated Yield (%)
1.	5	1.5	40
2.	10	1.5	83
3.	15	1.5	83
4.	20	1.5	84

Reaction conditions-(Isoniazide (0.1 mol), 2,5-dimethoxybenzaldehyde (0.1 mol) and dihydropyran (0.1 mol) in THF solvent under Ultrasound irradiation at 70°C temperature).

Table no.**2** shows the effect of amount of catalyst on the yield of product. So, (10 mol%) of catalyst is suitable for present work.



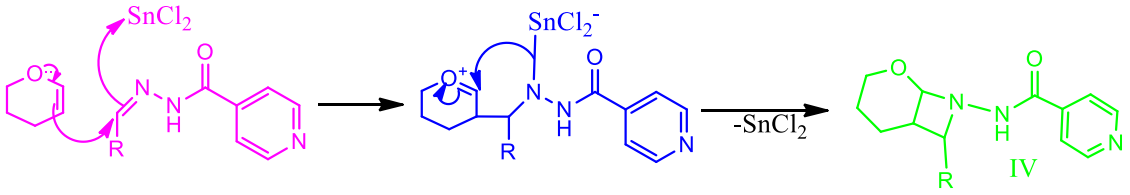
Scheme-2.

Table 3. Synthesis of N-(7-R)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide derivatives(**IVa-n**)

Entry	R	Prod.	Time(min)	Isolated Yield (%)
1	2,5- $(MeO)_2C_6H_3$	IVa	90	83
2	3,4-$(HO)_2C_6H_3$	IVb	96	80
3	3- HOC_6H_4	IVc	80	79
4	4- CNC_6H_4	IVd	99	76
5	4-HO-3-$MeOC_6H_3$	IVe	94	81
6	ph	IVf	65	79
7	3-BrC_6H_4	IVg	79	75
8	4-$MeOC_6H_4$	IVh	97	80
9	4- HOC_6H_4	IVi	63	77
10	4- ClC_6H_4	IVj	91	76
11	2,4- $(Cl)_2C_6H_3$	IVk	88	78
12	4- $NO_2C_6H_4$	IVl	108	75
13	4- FC_6H_4	IVm	74	77
14	2,3- $(HO)_2C_6H_3$	IVn	65	81

Reaction conditions-(Isoniazide (0.1 mol), Aromatic aldehydes (0.1 mol), dihydropyran (0.1 mol) and (10 mol%) stannous chloride ($SnCl_2$) catalyst in THF solvent (5 mL) at temperature 70°C under irradiation).

Scheme 3. The proposed mechanism of ($SnCl_2$) catalyzed (2π+2π) cycloaddition reaction.



The above result exhibit, synthesis of substituted azitidine derivatives using (10 mol%) $SnCl_2$ at 70°C in THF solvent under ultrasonic irradiation evolves an efficient procedure in terms of high yields and less time. With the optimal reaction condition, we then checked a variety of aromatic aldehydes in conventional and Ultrasound

promoted catalytic in cycloaddition reactions several imines intermediate were formed (in situ from aromatic aldehydes and isoniazide in THF as solvent). These intermediate smoothly cyclize with DHP (**III**) under the Ultrasonic irradiation to afford N-(7-R)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide derivatives (**IVa-n**).

The excellent yields of products(**IVa,b,c,e,f,h,i,j,k,m** and **n**) were obtained (Table **3**, entries **1 to 6, 8 to 11** and **13,14**)and good yields of (**IVl** and **g**) were obtained (Table **3,** entries **7** and **11**).

The products were purified by methanol separation and were recrystallized by alcohol; and they were identified by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopic data.

CONCLUSION:

We have discovered highly efficient synthesis of N-(7-R)-2-oxa-8-azabicyclo[4.2.0]octan-8-yl)isonicotinamide derivatives (**IVa-n**) through one pot multi-component ($2\pi+2\pi$) cycloaddition reaction (isoniazide(**I**), aromatic aldehyde(**IIa-n**), and DHP(**III**) catalyst $SnCl_2$) under Ultrasonic irradiation method. This cycloaddition reaction is mild, environmental friendly and operationally simple and less time consuming.

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