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THREE-COMPONENT ONE POT CYCLOADDITION REACTION USING PIPERIDINE CATALYST UNDER CONVENTIONAL / ULTRASONIC TECHNIQUES

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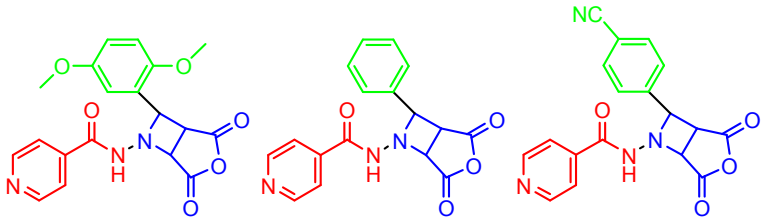
Abstract-New substituted N-(2,4-dioxo-3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives bearing isoniazid moieties have been successfully and conveniently synthesized through efficient three component one pot ($2\pi+2\pi$) cycloaddition reaction with isonicotinic acid hydrazide **(1)** as starting materials. Design and preparation of N-(2,4-dioxo-3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives **4(a-m)** was carried out by the condensation of isoniazid **(1)** with aromatic aldehyde 2**(a-m),** base catalyzed one pot cyclo-addition of isoniazid Schiff base with maleic anhydride **(3).** Piperidine plays the important role of base catalyst to carry out 2+2 cycloaddition to get moderate to significant yields under ultrasonic irradiation. In the present study a novel series of **4(a-m)** were synthesized and characterized by IR, 1HNMR, 13CNMR, spectral analysis. The synthetic details and characterization results are discussed.

Keywords: Piperidine, one pot, 2+2 Cycloaddition reaction, Ultra-sound irradiation

Introduction

One pot multicomponents reactions allow the construction of several new bonds. Multi-components reactions are very important role play in organic synthesis and their methods provide significant benefits over conventional synthesis [1]. Several benefits are- high degree of atom economy, easier reactions progress, reduced the reaction time, energy saving, environmental friendly, and less produces low waste are also most important [2,3]. With the conception in mind, our continuous research focuses on new strategies for nitrogen containing four member rings in moderate condition. Azitidine ring is one of the important class of heterocycles found in many natural products and thereby the structure can exhibit an array of biology and pharmaceutical activities [4].



(Some structure of Azitidine derivatives)

Azetidine derivatives are reported to show a variety of antimicrobial [5-7], antitubercular [8], anticonvulsant [9], anti-inflammatory [10] and cardiovascular Activities [11].

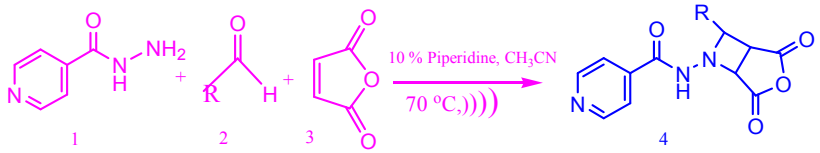
Cycloaddition reaction was carried out by different catalysts- mainly Lewis acids and very rare cases weak bases are used [12]. A carefully literature survey revealed that the cycloaddition reaction has rare explored under basic conditions [13]. This encouraged us to investigate a base catalyzed (2π+2π) cycloaddition reaction. Mainly, (cycloaddition) multicomponent one pot reaction was carried out in Reflux, Microwave [14] and very rarely ultrasonic methods are used.

Luche and Co-workers have written a number of studies that provided the fundamental of sonochemistry [15-17]. Recently, ultrasound irradiation has increasingly been used in organic synthesis [18-19].

In considering the factor discussed above and as part of our ongoing research on the chemical synthesis and biological properties of anti-tubercular [20]. We have selected the synthesized of base (Piperidine) catalyzed N-(2,4-dioxo-3-oxa-6-azabicyclo[3.2.0]-heptan-6-yl) isonicotinamide derivatives **4(a-m)** through (2π+2π) cycloaddition reaction under ultrasonic irradiation

Results and discussion

Although maleic anhydride have been extensively used in three component Aza-Diels-Alder reaction as a dienophiles and very rare examples of azetidine derivatives synthesized through (2π+2π) cycloaddition reaction.



Scheme 1:*General synthetic strategy*

In this work, we described a mild and efficient approach for the synthesis of azetidine derivatives (***scheme 1***) via (2π+2π) cycloaddition reaction using piperidine as the catalyst with moderate to good yields.

Scheme 2:

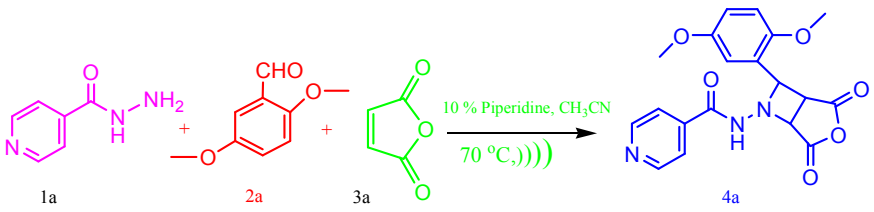


Table 1: Screening of solvents at different temperature and time conditions.

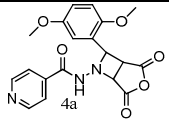
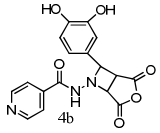
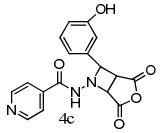
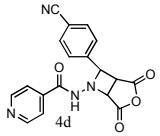
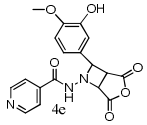
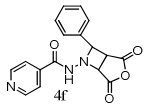
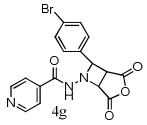
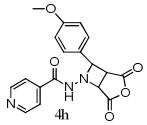
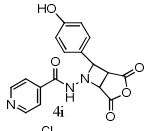
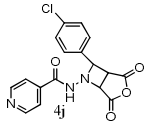
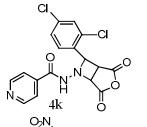
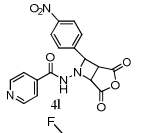
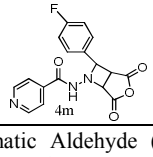
Entry	Solvent	Temp (^oC)	Time (h)	% Yield
1	CH_3CN	Rt	07	-
2	EtOH	Rt	07	-
3	DCE	Rt	07	-
4	DCM	Rt	07	-
5	DCM	Reflux (100^oC)	07	-
6	EtOH	Reflux (100^oC)	07	-
7	DCE	Reflux (100^oC)	07	-
8	CH_3CN	Reflux (100^oC)	07	50
9	DCM	Irradiation	1.5	-
10	EtOH	Irradiation	1.5	55
11	DCE	Irradiation	1.5	-
12	CH_3CN	Irradiation	1.5	83

(**Reaction conditions**: Isoniazide (0.1 mol), 2,5-methoxy benzaldehyde (0.1 mol), Maleic anhydride (0.1 mol), (10 mol%) Piperidine catalyst and each solvent (5 mL).

The reaction was first explored conveniently by stirring mixture of isoniazide, 2,5-methoxy benzaldehyde and maleic anhydride with 10% of piperidine at a room temperature in different solvents- DCM, EtOH, DCE and CH_3CN for 7 hours**,** Formation of N-arylimine (Schiff's base) was observed in ethanol by the interaction of isoniazide with 2,5- methoxy benzaldehyde which get desired product N-(7-2,5-dimethoxyphenyl)-2-4-dioxo-3oxa-6-azabicyclo[3.2.0] eptan-6-yl) isonicotinamide (**4a**) in acetonitrile. We had carried out the development study of tiltle compound with the help of different solvents such as acetonitrile, ethanol, dichloromethane and DCE etc. but generation of comp. (**4a**) was observed in ethanol and CH_3CN solvent, not DCM and DCE solvent. Screening of different solvents and temperature condition in conventional method is shown in (**Table 1**). Acetonitrile get significant results i.e. yield as compared to ethanol and other solvents so we have finalized acetonitrile as solvents for further derivatives.

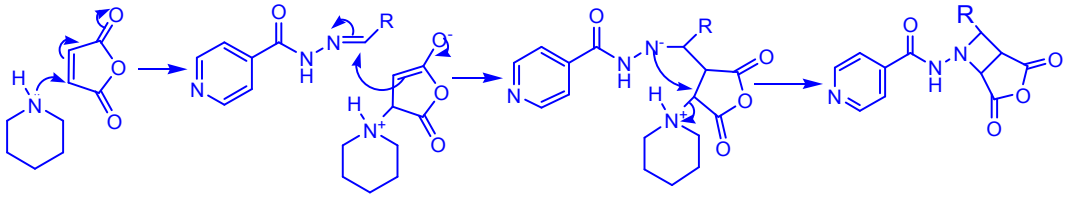
After finalization of solvent (ACN) and catalyst piperidine in convential method, we directly adopted same in ultrasonication method. So we also performed the same experiments under ultrasonic irradiation in order to observe the effect of ultrasonic irradiation. Isoniazide, 2,5-methoxy benzaldehyde and maleic anhydride with 10 mol% of piperidine at room temperature in CH_3CN for 07 hours did not give the corresponding the (**4a**) product. Then changing the temperature from room temperature to 70 ^oC gave the (**4a**) product in CH_3CN and EtOH solvent and the reaction was completed in 1.30 hours (Table 2).which indicate that sonication reduced the time cycle significantly during the reaction and also improve the yield of desired product because formation of biproduct and degredation of product is too less due to less time cycle at higher temperature.

Table 2: Synthesis of comp. 4(a-m) through ultrasonication

Entry	R	Compound	Time(min)	% Yield
1	2,5-Dimethoxyphenyl (2a)		49	83
2	3,4-Dihydroxyphenyl (2b)		60	80
3	3-Hydroxyphenyl (2c)		56	78
4	4-Cynophenyl (2d)		64	79
5	3-Hydroxy-4-methoxyphenyl (2e)		90	84
6	Phenyl (2f)		92	79
7	3-Bromophenyl (2g)		88	74
8	4-Methodyphenyl (2h)		57	82
9	4-Hydroxyphenyl (2i)		54	78
10	4-Chlorophenyl (2j)		84	81
11	2,4-Dichlorophenyl (2k)		75	76
12	4-Nitrophenyl (2l)		52	77
13	4-Flurobenzaldehyde (2m)		55	75

(**Reaction conditions**: Isoniazide (0.1 mol), Aromatic Aldehyde (0.1 mol), Maleic anhydride (0.1 mol) (10%,mol) piperidine, and CH_3CN (5 mL).at ultrasonic irradiation, 70^oC).

Reaction mechanisam of (2π+2π) cyclisation of Schiff's base and dienophile from piperidine base catalyst mechanism-



In order to observe the effect of the amount of piperidine on the reaction, we also performed the experiments using variable amount of catalyst like 5%, 10%, 15% and 20%, the yield (**Table 3**).

Table 3: development study of catalyst %

Entry	Catalyst	mol%	% Yield
1	Pipepidine	5	20
2	Pipepidine	10	83
3	Pipepidine	15	85
4	Piperidine	20	86

(All the reactions were carried out using (0.1 mol) of each 1a, 2a, 3a and 3 in 5 mL of CH_3CN solvent at 70^oC under ultrasonic irradiation 1.30 hours).

From the above results, it has been shows that Isoniazide, 2,5-methoxy benzaldehyde and maleic anhydride with 10 mol% of piperidine at 70 ^oC in CH_3CN under ultrasonic irradiation present an efficient procedure in the terms of high yields and less time consuming reaction.

With the optimal reaction condition, we then examined a variety of aromatic and hetero aromatic aldehydes in conventional and ultrasound promoted catalytic cycloaddition reactions several Schiff's base formed (formed in situ from aromatic aldehydes and isoniazide in CH_3CN as solvent) reacted smoothly with maleic anhydride under the conventional and ultrasonic techniques to afford the corresponding azitidine derivatives.

The products were purified by separation and recrystallization method and identified by FTIR, ^1H NMR, ^{13}C NMR and mass spectroscopic data.

Materials and methods:

General methods

Ultrasonication was performed 230 V AC, 50 Hz, liquid holding capacity 5.5 L and temperature 70^oC. The 100 mL Round bottom reaction flasks with condenser attached to stand and reaction flasks were suspended at center of the bath. ^{1}NMR spectra were determined on a Bruker 400 MHz NMR.^{13}C NMR spectra were determined on 100.61 MHz ^{13}C. The FTIR spectra were reported on a Perkin-Elmer FT-IR Spectrometer and absorption frequency were reported in cm^{-1}. Melting points were measured by manually. TLC was conducted on standard conversion aluminum sheets pre-coated with 0.2 mm layer of silica gel. All reagents were commercially available.

General procedure for synthesis of the N-(2,4-dioxo-3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives under ultrasonic irradiation:

For the ultrasound-assisted method, a mixture of piperidine (10%,mol), isoniazide (0.1 mol), aldehyde (0.1 mol), maleic anhydride (0.1 mol) in acetonitrile as solvent (5 ml) was irradiated with ultrasound (with a frequency of 50Hz and power of 250 V AC) at 70 ^oC for

1.5 hours. The reaction flask was located at center of the bath with condensed assembly and the surface of the reactants was placed slightly lower than the water level. The reaction progress check on TLC using ethyl acetate: hexane (7:3) as solvents. After the completion of reaction, the reaction mixture cool at room temperature, charged methanol (7 mL) for crystallization then cool at 20^{o}C stir for 20 minutes, filter the product through G_1 sintered crucible with assembly and recrystallized by alcohol.

N-(2,5-dimethoxyphenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4a): Yellowpowder, m.p. 180-184^{o}C. FTIR (KBr cm^{-1}): 3197, 3029, 1645, 1603, 1549, 1508; ^{1}H NMR 400 MHz, DMSO) δ 11.89 (s, 1H, D_2O exchangeable NH), 8.67-8.77 (m, 2H,Ar), 7.80 (m, 2H,Ar), 7.48 (s, 1H,Ar), 6.86-7.10 (m, 2H,Ar), 3.74 (d, 1H,), 3.77 (d 1H), 3.60 (m, 1H), 3.2 (s, 6H),^{13}C NMR (100 MHz, DMSO): 170.0, 162.14, 153.67, 152.82, 150.25, 149.40, 145.53, 140.88, 140.74, 122.87, 121.78, 118.48, 112.82, 110.06, 77.06, 56.27, 55.81.

N-(3,4-dihydroxyphenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4b): White powder, m.p. 248-250 ^{o}C. FTIR (KBr cm^{-1}): 3029, 1644, 1602, 1566, 1549,1508, 1456; ^{1}H NMR 400 MHz, DMSO) δ 11.72 (s, 1H, D_2O exchangeable NH), 8.98-8.2 (m, 2H,Ar), 7.8-7.6 (m, 2H,Ar), 7.3 (s, 1H,Ar), 7-6.8 (m, 2H,Ar), 4.7-5.3 (s, 2H)3.8 (d, 1H,), 3.2 (d 1H), 2.5 (m, 1H),^{13}C NMR (100 MHz, DMSO): 170.0, 162.00, 150.27-149.54, 147.03, 145.37, 141.06, 127.20, 123.70, 121.77, 120.82, 120.55, 113.26, 112.46, 111.41, 77.02, 56.20, 55.88.

N-(3-hydroxyphenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4c): Greenish yellow powder, m.p. 142-144 ^{o}C. FTIR (KBr cm^{-1}): 3276, 3028, 1651, 1599, 1551, 1550, 1526, 1456; ^{1}H NMR 400 MHz, DMSO) δ 11.72 (s, 1H, D_2O exchangeable NH), 9.1-9 (m, 2H,Ar), 8.6-8.2 (m, 2H,Ar), 7.7 (s, 1H,Ar), 7.2-6.7 (m, 3H,Ar), 5.3 (s, 1H), 3.8 (d, 1H,), 3.77 (d 1H), 3.5 (d, 1H), 2.5 (d, 1H),^{13}C NMR (100 MHz, DMSO): 170.0, 161.79, 150.31-149.54, 148.53, 145.92, 141.09, 125.82, 121.80, 121.20, 115.70, 113.47, 77.07, 55.95, 55.27.

N-(4-cynophenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4d): White powder, m.p. 240-242 ^{o}C. FTIR (KBr cm^{-1}): 3029, 2224, 1652, 1599, 1551, 1508, 1450; ^{1}H NMR 400 MHz, DMSO) δ 11.72 (s, 1H, D_2O exchangeable NH), 8.9-8.6 (m, 2H,Ar), 8.2 (m, 2H,Ar), 7.8-7.3 (m, 2H,Ar), 7.6-6.8-7 (m, 2H,Ar), 3.8 (d, 1H,), 3.4 (d 1H), 2.5 (m, 1H), ^{13}C NMR (100 MHz, DMSO): 170.0, 161.94, 150.29-149.55, 147.07, 145.92, 141.05, 127.21, 123.68, 121.77, 120.82, 113.22, 112.44, 111.41, 76.98, 56.15, 55.88.

N-(3-hydroxy-4-methoxyphenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4e): Powderpowder, m.p. 258-260 ^{o}C. FTIR (KBr cm^{-1}): 3057, 1655, 1598, 1552, 1512, 1449; ^{1}H NMR 400 MHz, DMSO) δ 12.1 (s, 1H, D_2O exchangeable NH), 8.7-8.5 (m, 2H,Ar), 7.9-7.7 (m, 2H,Ar), 7.7 (m, 2H,Ar), 7.6 (s, 1H,Ar), 4.6 (s, 1H), 3.7 (d, 1H,), 3.5 (s 1H), 2.6 (s, 6H), 2.5 (d, 1H), ^{13}C NMR (100 MHz, DMSO): 170.03, 162.46, 150.44-149.68, 147.36, 140.52, 138.67, 132.59, 128.11-127.63, 123.68, 123.48, 121.82,118.58, 113.00, 77.08, 56.00, 55.79.

N-(4-chlorophenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4j): Whitepowder, m.p. 169-172 ^{o}C. FTIR (KBr cm^{-1}): 3059, 1658, 1600, 1551, 1509, 1450; ^{1}H

NMR 400 MHz, DMSO) δ 11.78 (s, 1H, D_2O exchangeable NH), 8.92-8.87 (m, 2H,Ar), 7.84 (m, 2H,Ar), 7.50-7.61 (m, 2H,Ar), 7.42 (m, 2H,Ar), 3.93 (d, 1H,), 3.89 (d 1H), 3.70 (m, 1H),^{13}C NMR (100 MHz, DMSO): 171.0, 162.96, 150.29-149.70, 140.07, 140.05, 131.02, 129.3, 127.57, 77.00, 55.88, 40.88.

N-(3-bromophenyl)-2,4-dioxo-3oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4g): Greenish yellow powder, m.p. 110-113 ^{o}C. FTIR (KBr cm^{-1}): 3063, 1658, 1615, 1559, 1507, 1453; ^{1}H NMR 400 MHz, DMSO) δ 11.7 (s, 1H, D_2O exchangeable NH), 8.9-8.8 (m, 2H,Ar), 7.8 (m, 2H,Ar), 7.2-7.3 (m, 3H,Ar), 7.2 (s, 1H,Ar), 3.8 (d 1H), 3.90 (m, 1H), 2.5 (m, 1H)^{13}C NMR (100 MHz, DMSO): 170.52, 163.03,158.00, 140.2, 140.07, 132.12, 131.21, 114.19, 113.57, 77.40, 57.89, 48.38.

Conclusion: In the present investigation we have designed and synthesized novel N-(2,4-dioxo-3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives through efficient (2π+2π) cycloaddition reaction of Schiff's base (aromatic aldehyde and isoniazide) with maleic anhydride catalyzed by piperidine under conventional method and ultrasonic irradiation. From experimental and characterization details we conclude that ultrasonication is quite superior to conventional method for the development of title compound.

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