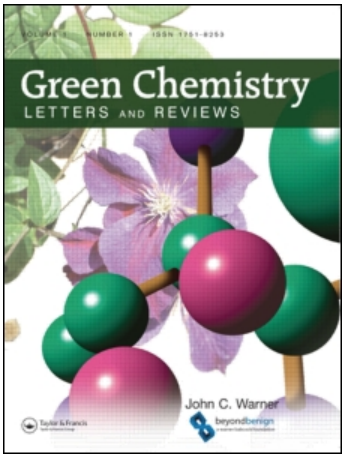

Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Eco-friendly synthesis of 2-azetidinone analogs of isonicotinic acid hydrazide

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Online publication date: 08 December 2010

To cite this Article Thomas, Asha Byju , Paradkar, Omkar , Nanda, Rabindra K. , Tupe, Preeti N. , Sharma, Piyoosh A. , Badhe, Ravi , Kothapalli, Lata , Banerjee, Anupam , Hamane, Sunil and Deshpande, Avinash(2010) 'Eco-friendly synthesis of 2-azetidinone analogs of isonicotinic acid hydrazide', Green Chemistry Letters and Reviews, 3: 4, 293 — 300
To link to this Article: DOI: 10.1080/17518253.2010.483601
URL: http://dx.doi.org/10.1080/17518253.2010.483601

Green Chemistry Letters and Reviews
Vol. 3, No. 4, December 2010, 293–300

Taylor & Francis
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RESEARCH ARTICLE

Eco-friendly synthesis of 2-azetidinone analogs of isonicotinic acid hydrazide

Asha Byju Thomas[a]*, Omkar Paradkar[a], Rabindra K. Nanda[a], Preeti N. Tupe[b], Piyoosh A. Sharma[a], Ravi Badhe[a], Lata Kothapalli[a], Anupam Banerjee[a], Sunil Hamane[a] and Avinash Deshpande[a]

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(Received 31 August 2009; final version received 31 March 2010)

2-Azetidinones possess broad and potent activity due to presence of β-lactam ring and has been established as one of the biologically important scaffolds. The synthesis of *N*-(4-aryl-2-oxoazetidinone)-isonicotinamide by novel methods of stirring and sonication are described. The conventional method for synthesis of 2-azetidinones involves use of Dean–Stark water separator for the removal of water from the reaction with long reaction time (12–16 h reflux) at a very low temperature (–70 to –90°C). The microwave method reported requires inert atmosphere of nitrogen gas for the synthesis of 2-azetidinones. We report herein the synthesis of 2-azetidinone analogs of isonicotinic acid hydrazide by novel green route methods of sonication and stirring using molecular sieves. Results indicate that higher yields and shorter reaction times can be achieved by employing novel green route methods of synthesis.

Keywords: green chemistry; 2-azetidinones; sonication; stirring

Introduction

Green Chemistry is designing chemical products and processes that reduce or eliminate the use and/or the generation of hazardous substances. Various green chemistry methods like microwave technology, sonochemistry, stirring, phase transfer catalyst, ionic liquid, and many more techniques include approaches for the creation of ''benign-by-design'' synthetic methods which are now accepted worldwide (*1,2*). Processes designed by green routes help in the promotion of resource and energy utilization efficiently. It involves low level of waste, and is inherently safe making the processes economically and environmentally beneficial.

The broad and potent activity of 2-azetidinone has been established as one of the biologically important scaffolds (*3*). 2-Azetidinone possesses a broad spectrum of activities, such as antibacterial (*4–8*), antihyperglycemic (*9*), antihyperlipidemic (*10–15*), CNS activity (*16*), tryptase inhibitory (*17,18*), human leukocyte elastase inhibitory (*19–21*), anti-inflammatory (*22,23*), vasopressin v1a antagonist (*24*), and anticancer activity (*25,26*). The Staudinger's ketene–imine cycloaddition reaction [2+2] is the most common method for the synthesis of azetidinones and has been reviewed till date by several researchers. The reactions are carried out thermally (*27*) or photochemically (*28–30*) using acid chlorides in the presence of triethylamine or α-diazoketones as ketene precursors. However, the conventional methods reported for the synthesis of 2-azetidinones requires longer reaction time (12–16 h reflux) (*31–37*) at very low temperature (–70 to –90°C) (*38–44*) with low yields (less than 70%) (*45–47*). The reactions also involve the use of a Dean–Stark water separator for the removal of water from the reaction. The previous decade has also seen the use of microwave radiation in the synthesis of azetidinones. However, the reported microwave methods also required inert atmosphere of nitrogen gas to enable the completion of the reaction (*48,49*).

Herein, we report the synthesis of Schiff's bases of isoniazid, which were further utilized for the synthesis of 2-azetidinone analogs by novel green routes of sonication and stirring.

Results and discussion

The synthetic strategies adopted to obtain the target compounds are outlined in Scheme 2 and 3. The key intermediate Schiff's bases (**2a**–**2e**) were prepared in excellent yields in a one step reaction (Scheme 1) by our previously reported synthesis using microwave (*50*).

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ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518253.2010.483601
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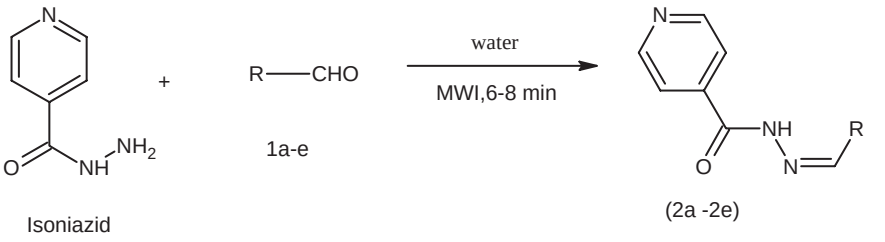


Scheme 1. Microwave assisted synthesis of Schiff's bases of isoniazid.

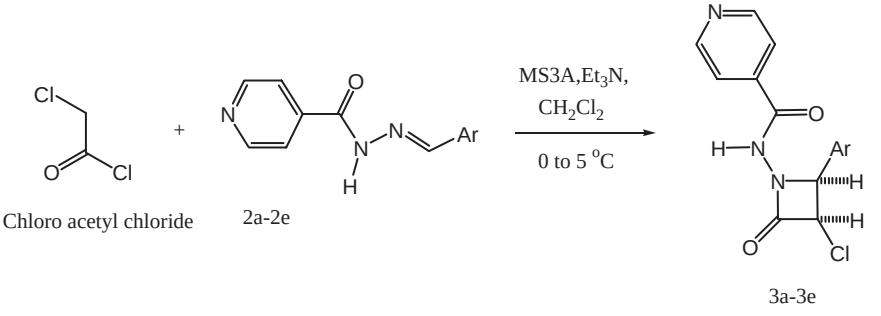
Furthermore, the intermediates which were synthesized represent versatile building blocks for the synthesis of new heterocycles incorporating azetidinone nucleus. The synthesized intermediates were characterized by the presence of a strong IR band at 1595–1625 cm^{-1}, ^1H NMR spectra also showed singlet signal equivalent to one proton for =CH group between 7.4 and 8.4, which confirms the formation of Schiff's bases.

The synthesized intermediates were further utilized for the synthesis of *N*-(4-aryl-2-oxoazetidinone)-isonicotinamide derivatives (**3a**–**3e**) containing 2-azetidinone nucleus by stirring and sonication (Scheme 2 and 3), which were characterized by the presence of a strong band at 1715–1780 cm^{-1} for the ring carbonyl group, which is considered a strong confirmation for the azetidinone nucleus formation. Another piece of evidence for cyclization is the appearance of a doublet signal equivalent to one proton in ^1H NMR spectrum between 5.2 and 5.6 ppm (C-3, CH) and doublet signal equivalent to 1 proton spectrum between 5.7 and 5.9 ppm (C-4, CH), which represents the formation of azetidinone nucleus.

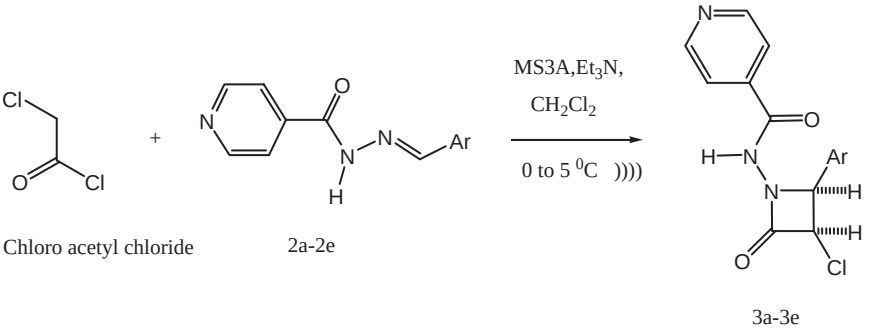
The Electron Impact Mass Spectrometry of selected compound **3b** displayed a molecular ion peak at m/z of 317 which confirmed its molecular weight. A base peak in the mass spectrum was obtained at $m/z = 241$ and is contributed to the loss of the (O = C–C–Cl) fragment from the molecule.

Experimental

Melting points (mp) were determined with Veego melting point apparatus (VMP PM, 32/1104) and are uncorrected. Thin layer chromatography (TLC) (*51*) was carried out using silica gel (G-60 mesh). R_f value for each compound was calculated using toulene:ethanol (4.5:0.5) as solvent and spots were located



Scheme 2. Synthesis of 2-azetidinones analogs using Schiff's bases by stirring.

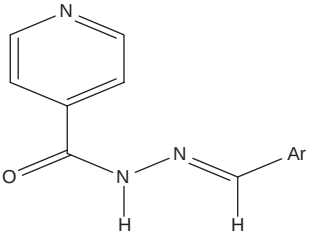


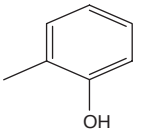
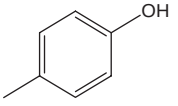
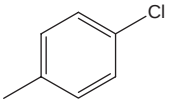
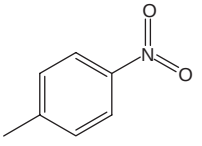
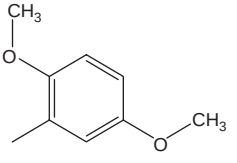
Scheme 3. Synthesis of 2-azetidinones analogs using Schiff's bases by sonication.

using iodine vapor. UV studies were carried out on UV–Visible Spectrophotometer (Shimadzu 1700) and the λ_{max} of the respective synthesized compounds were calculated using ethanol as the solvent. IR spectras (KBr) (*52*) were recorded on a FTIR Spectrophotometer with diffuse reflectance attachment (Shimadzu 8400S). ^{1}H NMR spectra (*53*) were obtained from NMR Spectrophotometer (Bruker Avance II 400 NMR) using dimethyl sulphoxide as the solvent. Chemical shifts were expressed in parts per million relative to $SiMe_4$ as internal standard.

Unless stated otherwise, all the materials were obtained from commercial suppliers and used without further purification.

Table 1. Chemical structures and properties of Schiff's bases of isoniazide by microwave (**2a**–**2e**).



Compound	–Ar	Yield (%)	Reaction time (min)	Melting point (°C)[a]	νC = O of amide[b]	νC = N of imines[b]
2a		95.6	6	262–264	1685	1616
2b		94.5	6	264–268	1662	1608
2c		98.1	8	218–221	1674	1593
2d		90.7	7	255–257	1685	1558
2e		95.2	6	185–188	1654	1600

[a]All melting points were uncorrected.
[b]Expressed in cm^{-1}; KBr.
Note: Ethanol was employed for recrystallization.

Synthesis of Schiff's bases as intermediate

The synthesis of compounds (**2a**–**2e**) was performed according to our previously reported procedure (*50*) (Scheme 1). Isoniazid (0.01 M) and appropriate aromatic aldehydes (0.01 M) (**1a**–**1e**) in water were irradiated under microwave using a microwave synthesizer (Make-Raga's Scientific) at power level 3 (240 W, 35% irradiation) until the completion of the reaction. The reaction was monitored by TLC (acetone: ethanol = 4:1). The reaction mixture was filtered. The residue obtained was washed with water, followed by sodium thiosulphate ($Na_2S_2O_3$) solution, and then dried. The crude product was obtained upon recrystallization from alcohol to give the pure hydrazones of INH (**2a**–**2e**), Table 1. The synthesized compounds were characterized by their mp and spectral data (UV, IR, and ^{1}H NMR).

*Salicylidene isonicotinyl hydrazone (**2a**)*
White crystals; yield 95.6%; mp 262–264°C; IR (KBr): ν cm^{-1} = 3344 (–OH), 3178 (–NH), 3004 (–CH), 1685 (amide C = O), and 1616 (imine C = N); ^{1}H NMR (DMSO-d_6): δ ppm = 11 (s, OH), 8.8–8.9 (d, pyridine 2H), 8.6–8.8 (d, pyridine 2H), 8.7 (s, CH), 7.5–7.6 (d, aromatic 1H), 8.6 (s, NH), 6.8–7.0 (d, aromatic 2H), and 7.3–7.4 (m, aromatic 1H).

*4-Hydroxy benzylidene isonicotinyl hydrazone (**2b**)*
Yellow powder; yield 94.5%; mp 264–268°C; IR (KBr): ν cm^{-1} = 3340 (–OH), 3213 (–NH), 3055 (–CH), 1662 (amide C = O), and 1608 (imine C = N); ^{1}H NMR (DMSO-d_6): δ ppm = 11.5 (s, OH), 8.8–8.5 (d, pyridine 2H), 8.4–8.3 (d, pyridine 2H), 7.8 (s, CH), 8.0 (s, NH) 7.5–7.3 (d, aromatic 2H), and 7.0–6.8 (d, aromatic 2H).

*p-Cl benzylidene isonicotinyl hydrazone (**2c**)*
White crystals; yield 98.1%; mp 218–221°C; IR (KBr): ν cm^{-1} = 3166 (–NH), 3020 (–CH), 1674 (amide C = O), 1593 (imine C = N), and 784 (–Cl); ^{1}H NMR (DMSO-d_6): δ ppm = 8.88–8.91 (d, pyridine 2H), 7.99–8.05 (d, pyridine 2H), 8.32 (s, CH), 8.65 (s, NH) 7.79–7.80 (d, aromatic 2H), and 7.50–7.51 (d, aromatic 2H).

*p-NO_2 benzylidene isonicotinyl hydrazone (**2d**)*
Yellow powder; yield 90.7%; mp 255–257°C; IR (KBr): ν cm^{-1} = 3186 (–NH), 3001 (–CH), 1685 (amide C = O), 1558 (imine C = N), and 1280 ($–NO_2$); ^{1}H NMR (DMSO-d_6): δ ppm = 9.32–9.35 (d, pyridine 2H), 8.51–8.55 (d, pyridine 2H), 8.10 (s, CH), 8.34 (s, NH), 7.89–7.93 (d, aromatic 2H), and 7.60–7.62 (d, aromatic 2H).

*2,5-Di MeO benzylidene isonicotinyl hydrazone (**2e**)*
Yellow crystals; yield 95.2%; mp 185–188°C; IR (KBr): ν cm^{-1} = 3190 (–NH), 3061 (–CH), 1654 (amide C = O), 1600 (imine C = N), and 1218 (O–CH_3); ^{1}H NMR (DMSO-d_6): δ ppm = 8.89–8.92 (d, pyridine 2H), 8.11–8.15 (d, pyridine 2H), 8.22 (s, CH), 8.48 (s, NH), 7.5–7.8 (d of d, aromatic 2H), 6.92 (s, aromatic 1H), and 3.92–4.12 (m, O–CH_3).

Synthesis of N-(4-aryl-2-oxoazetidinone)-isonicotinamide analogs using Schiff's bases

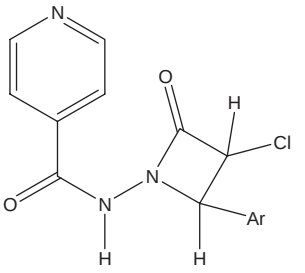
The appropriate Schiff's base (0.0025 M) was dissolved in 10 ml of dichloromethane. Molecular sieves [MS (1–2 g, 3A × 1.5 mm)] were added to the reaction mixture. The reaction mixture was then stirred in an ice bath at 0–5°C. Chloroacetyl chloride (0.0037 M) followed by triethyl amine (0.0075 M) were then added drop wise to the reaction mixture with constant stirring at low temperature (0–5°C). The reaction mixture was further stirred at room temperature until the completion of reaction [TLC (toulene:ethanol = 4.5:0.5)]. For the sonication method, the reaction mixture was sonicated on an ultrasonic bath (local make) until the completion of reaction [TLC (toulene:ethanol = 4.5:0.5)].

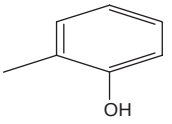
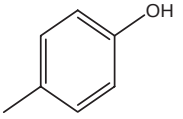
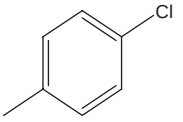
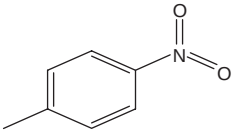
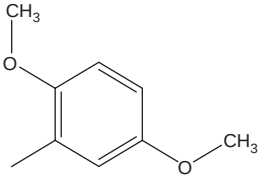
The reaction mixture was added into crushed ice and stirred to obtain the crude product. The product obtained was washed with concentrated brine and sodium bicarbonate solution and then dried. The crude product was obtained upon recrystallization from alcohol to give the pure 2-azetidinones of isonicotinoyl hydrazones (**3a**–**3e**) (Table 2). The synthesized compounds were characterized by their mp and spectral data (UV, IR, ^{1}H NMR, and MS).

Table 3 represents structures of aldehydes and their respective synthesized Schiff's bases and 2-azetidinone analogs.

*N-(4-salicylidene-2-oxoazetidinone)-isonicotinamide (**3a**)*
Yellow powder; yield 91.1%; mp 98–105°C; IR (KBr): ν cm^{-1} = 3467 (–OH), 3193 (–NH), 3043 (–CH), 1774 (ring C = O), and 1677 (amide C = O); ^{1}H NMR (DMSO-d_6): δ ppm = 8.89–8.83 (d, pyridine 2H), 7.77–7.75 (d, pyridine 2H), 4.91 (s, –NH), 7.36–6.97 (m, aromatic, 4H), 4.51–4.42 (d, CH Aze ring

Table 2. Chemical structures and properties of 2-azetidinones (**3a**–**3e**).



Compound	–Ar	Method of reaction	Yield (%)	Reaction time (min)	Melting point (°C[a])	νC = O stretch of amide and azetidinone nucleus[b]
3a		Stirring	89.8	120	95–108	1778, 1685
		Sonication	91.1	20	98–105	1774, 1677
3b		Stirring	82.2	125	98–110	1766, 1685
		Sonication	86.0	20	102–110	1762, 1662
3c		Stirring	79.5	120	90–96	1728, 1677
		Sonication	81.9	20	92–100	1720, 1666
3d		Stirring	83.5	120	110–118	1731, 1685
		Sonication	85.8	20	112–116	1735, 1685
3e		Stirring	89.4	115	140–148	1736, 1685
		Sonication	92.2	20	150–152	1735, 1681

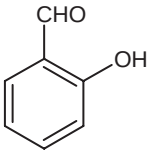
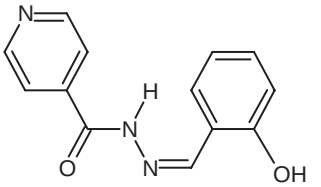
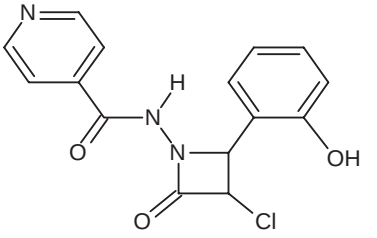
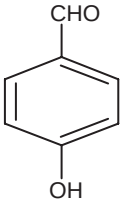
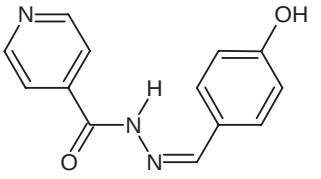
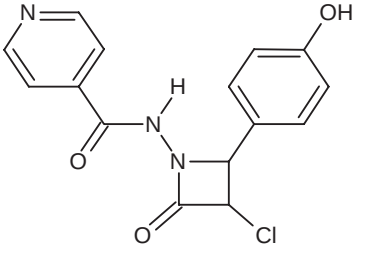
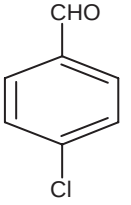
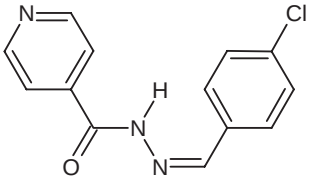
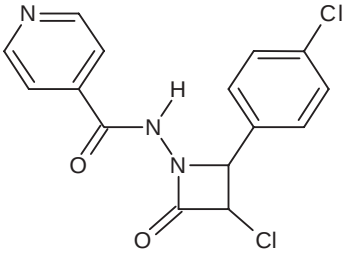
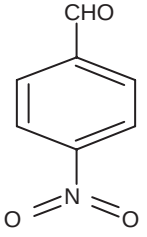
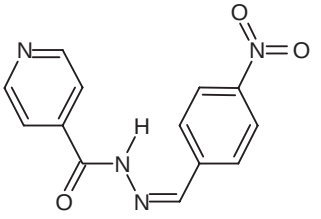
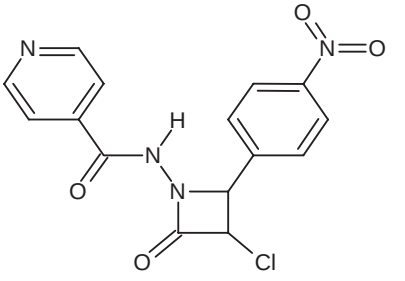
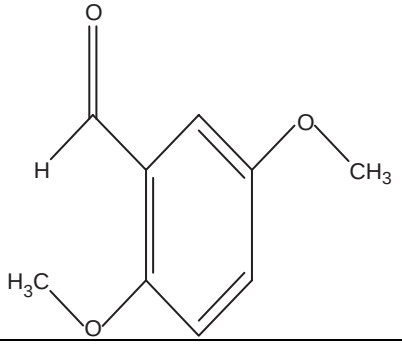
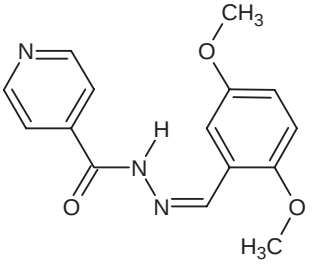
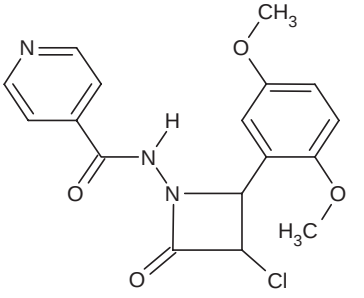
[a]All melting points were uncorrected.
[b]Expressed in cm^{-1}; KBr.
Note: Ethanol was employed for recrystallization.

(C-4), 1H), 5.75–5.71 (d, CH Aze ring (C-3), 1H), and 8.22 (s, OH).

*N-[4-(4-hydroxy benzylidene)-2-oxoazetidinone]-isonicotinamide (**3b**)*

Yellow powder; yield 86%; mp 102–110°C; IR (KBr): ν cm^{-1} = 3556 (–OH), 3186 (–NH), 3012 (–CH), 1762 (ring C = O), and 1662 (amide C = O); ^{1}H NMR (DMSO-d_6): δ ppm = 8.77–8.79 (d, pyridine 2H), 7.96–7.93 (d, pyridine 2H), 4.21 (s, –NH), 7.24–7.23 (d, aromatic, 2H), 6.86–6.84 (d, aromatic, 2H), 4.56–4.54 (d, CH Aze ring (C-4), 1H), and 5.71–5.68 (d, CH Aze ring (C-3), 1H); EIMS (70 eV, *m*/*z*): 317 (M^+), 241 (base peak).

Table 3. Isonicotinyl hydrazones and their 2-azetidinone analogs.

Sr. No.	Aldehydes (**1**)	Isonicotinyl hydrazone (**2**)	2-Azetidinone (**3**)
a			
b			
c			
d			
e			

*N-(4-p-Cl benzylidene-2-oxoazetidinone)-isonicotinamide (**3c**)*

Brown crystals; yield 81.9%; mp 92–100°C; IR (KBr): ν cm^{-1} = 3193 (–NH), 3024 (–CH), 1720 (ring C = O), 1666 (amide C = O), and 829 (–Cl); ^{1}H NMR (DMSO-d_6): δ ppm = 9.38–9.36 (d, pyridine 2H), 8.30–8.28 (d, pyridine 2H), 4.78 (s, –NH), 7.70–7.76 (d, aromatic, 2H), 7.35–7.33 (d, aromatic, 2H), 5.43–5.42 (d, CH Aze ring (C-4), 1H), and 5.81–5.80 (d, CH Aze ring (C-3), 1H).

*N-(4-p-NO_2 benzylidene-2-oxoazetidinone)-isonicotinamide (**3d**)*

Brown crystals; yield 85.8%; mp 112–116°C; IR (KBr): ν cm^{-1} = 3035 (–NH), 2974 (–CH), 1735 (ring C = O), 1685 (amide C = O), and 1172 (–NO_2); ^{1}H NMR (DMSO-d_6): δ ppm = 9.38–9.36 (d, pyridine 2H), 7.97–7.95 (d, pyridine 2H), 4.91 (s, –NH), 8.30–8.28 (d, aromatic, 2H), 7.19–7.17 (d, aromatic, 2H), 5.43–5.42 (d, CH Aze ring (C-4), 1H), and 5.81–5.80 (d, CH Aze ring (C-3), 1H).

*N-(4-2,5-di MeO benzylidene-2-oxoazetidinone)-isonicotinamide (**3e**)*

Brown crystals; yield 92.2%; mp 150–152°C; IR (KBr): ν cm^{-1} = 3195 (–NH), 2974 (–CH), 1735 (ring C = O), 1681 (amide C = O), and 1073 (O–CH_3); ^{1}H NMR (DMSO-d_6): δ ppm = 9.38–9.36 (d, pyridine 2H), 7.97–7.84 (d, pyridine 2H), 4.42 (s, –NH), 6.83–6.86 (d, aromatic 1H), 6.19 (s, aromatic 1H), 6.21 (doublet, aromatic, 1H), 5.42–5.43 (d, CH Aze ring (C-4), 1H), 4.78–4.90 (d, CH Aze ring (C-3), 1H), and 3.77–3.60 (m, o–CH_3, 6H).

Conclusion

The synthesis of 2-azetidinones by novel green route methods of sonication and stirring are described. The reactions were carried out in the presence of molecular sieves for removal of water generated during the reaction. The time span required for the completion of reaction is less than that of conventional methods. The reaction by stirring method requires 110–130 min, while the sonication method requires 20–30 min for the completion of the reaction. Furthermore, the present investigation offers rapid and effective new procedures for the synthesis of 2-azetidinone analogs with improved yield (81–93%).

The results of physiochemical characterization of the synthesized products by chromatographic and spectroscopic studies suggested that the product obtained by both stirring and sonication methods were comparable in chemical composition.

Acknowledgements

This work was financially supported by University of Pune, Pune, India. The authors wish to thank the Principal, Padm. Dr. D.Y. Patil Institute of Pharmaceutical Science and Research, Pune, India, for providing the necessary infrastructural facilities to carry out this work. NMR characterization was carried out by SAIF/CIL, Punjab University, Chandigarh, India.

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