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ORIGINAL ARTICLE

Green route synthesis of Schiff's bases of isonicotinic acid hydrazide

A.B. Thomas*, P.N. Tupe, R.V. Badhe, R.K. Nanda, L.P. Kothapalli, O.D. Paradkar,
P.A. Sharma and A.D. Deshpande

*Department of Pharmaceutical Chemistry, Padm. Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research,
Pimpri, Pune 411018, Maharashtra, India*

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Imines constitute a class of therapeutic agents that possess a broad spectrum of pharmacological activity. The conventional method for synthesis of imines by nucleophilic addition of amines to ketones or aldehydes requires long reaction times along with the use of organic solvents and a glacial acetic acid catalyst. We report the synthesis of Schiff's bases of isonicotinic acid hydrazide by novel, green routes using sonication, stirring, and microwave irradiation, respectively. Initial results are reported and indicate that by employing greener methods under aqueous conditions, high yields and shorter reaction times can be achieved.

Keywords: green chemistry; imines; sonication; stirring; microwave irradiation technique

Introduction

The goal of green chemistry is to develop environmentally friendly synthetic reactions and processes that avoid the use of reagents (reaction should be catalytic and reagent is reusable), avoid use of solvents if possible, and minimize formation of byproducts (1). Green chemistry (2) can be defined as carrying out chemical activities, including chemical design, manufacture, use, and disposal such that hazardous substances will not be used and generated. Green chemistry involves the use of microwave technology, sonochemistry, phase transfer catalysis, ionic liquids, and many more techniques.

Imines are functional groups or chemical compounds containing a carbon nitrogen double bond which have varied biological activities, such as anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, vasodilators, and antiviral activity (3–6). The preparation of imines has been carried out by refluxing the mixture of amines and the carbonyl compounds in organic solvent under azeotropic conditions in order to separate the water formed (7). An attempt was made to synthesize Schiff's bases of isonicotinic acid hydrazide by the green route techniques of stirring, microwave irradiation and sonication (8).

Results and discussion

The results of the spectral studies (UV, IR, ¹H NMR) of the synthesized Schiff's bases of isonicotinic acid hydrazide are as given below.

(1a) Benzylidene isonicotinoyl hydrazone

UV data – λ max–302 nm

IR-cm⁻¹ (KBR): 3199, 3026, 1689, 1598, 1552, 1355, 1411, 763, 686.

¹H NMR (DMSO) ppm: 9.44–9.53 (2H), 8.78–8.81 (2H), 8.37 (1H), 7.43–7.89 (5H), 7.43 (1H).

(1b) Salicylidene isonicotinoyl hydrazone

UV data – λ max–290 nm.

IR-cm⁻¹ (KBR): 3199, 3180, 3026, 1679, 1626, 1552, 1390, 1355, 1161, 999.

¹H NMR (DMSO) ppm: 11(1H), 8.6–8.9 (2H), 8.8 (1H), 7.8–8 (2H), 7.6 (1H), 7.4–7.8 (1H), 6.8–7 (2H), 7.3 (1H), 2.5.

(1c) *p*-anisalidene isonicotinoyl hydrazone

UV data – λ max–320 nm.

IR-cm⁻¹ (KBR): 3031, 2873, 1681, 1660, 1514, 1477, 1371, 1315, 740.

¹H NMR (DMSO) ppm: 8.8 (2H), 8.35 (1H), 7.63–7.70 (2H), 7.4 (1H), 6.84–6.89 (2H), 3.78 (3H), 2.5.

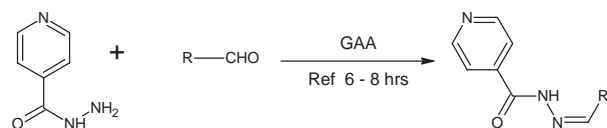
*Corresponding author. Email: dypharmachem@yahoo.co.in

(1d) Cinnamylidene isonicotinoyl hydrazonesUV data – λ max–326 nm.IR-cm⁻¹ (KBR): 3242, 3035, 1647, 1625, 1544, 1361, 910.¹H NMR studies (DMSO) ppm: 8.68 (2H), 8.16 (1H), 7.78 (2H), 7.28–7.4 (5H), 7.01 (1H), 6.92–6.97 (2H), 2.5.**(1e) 4-hydroxy benzylidene isonicotinoyl hydrazone**UV data – λ max–323 nm.IR spectra cm⁻¹(KBR): 3288, 3257, 3031, 1666, 1600, 1550, 1415, 1377, 1164.¹H NMR (DMSO) ppm: 11.5–12 (1H), 8.5–8.8 (2H), 8.3–8.4 (1H), 8 (1H), 7.7–7.9 (2H), 7.5 (2H), 6.8–7 (2H).

The comparative data with results of the synthesis of isonicotinoyl hydrazones by conventional and green route methods are given in Tables 1–5.

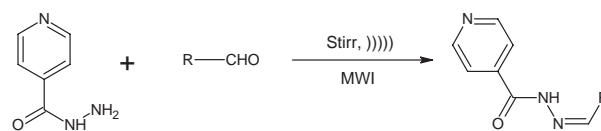
Experimental**Conventional method**

Synthesis of Schiff's bases of isoniazid by conventional method (9)

Reaction

Procedure. To a solution of isoniazid (0.01 M) in ethanol, various aldehydes (0.01 M) each in ethanol,

were added with intermittent shaking. To this mixture, glacial acetic acid (GAA) was added dropwise with shaking and then refluxed for 6–8 hrs. The completion of reaction was monitored by thin layer chromatography (TLC) (CHCl₃:Methanol 8:2). The reaction mixture was concentrated and the residue obtained washed with water and dried. The crude product obtained on re-crystallization from alcohol gave the pure hydrazones of isonicotinic acid hydrazine (INH) (1a–1e). The synthesized compounds were characterized by their melting point and by spectral data (UV, IR, ¹H NMR).

Green route methods

To a solution of isoniazid (0.01 M) in water, various aldehydes (0.01 M) were added. For reaction by stirring, the reaction mixture was stirred until the completion of the reaction (TLC, CHCl₃:Methanol 8:2). For the sonication method, the reaction mixture was sonicated (10) in an ultrasonic bath until the completion of the reaction (TLC, CHCl₃:Methanol 8:2). The microwave synthesis (11–13) was performed by irradiating the reaction mixture under microwave at the power level 3 (240 W, 35% irradiation) until the completion of the reaction (TLC, CHCl₃:Methanol 8:2). The reaction mixture was filtered and the residue

Table 1. Benzylidene isonicotinoyl hydrazone (1a).

Sr. No.	Method	Yield (%)	Time (min)	M.P. (°C)
a	Conventional	88.28	420	192–194
b	Green route			
1	Stirring	95	120	194–196
2	Sonication	95.60	60	194–196
3	Microwave Irradiation	96.88	8	196–198

Table 2. Salicylidene isonicotinoyl hydrazone (1b).

Sr. No.	Method	Yield (%)	Time (min)	M.P. (°C)
a	Conventional	82.98	420	262–264
b	Green route			
1	Stirring	89.28	60	260–264
2	Sonication	90.00	40	262–266
3	Microwave irradiation	91.28	8	262–266

Table 3. *p*-anisalidene isonicotinoyl hydrazone (1c).

Sr. No.	Method	Yield (%)	Time (min)	M.P. (°C)
a	Conventional	97.25	420	170–173
b	Green route			
1	Stirring	98.29	90	172–174
2	Sonication	98.82	70	170–173
3	Microwave irradiation	99.21	8	170–173

Table 4. Cinnamylidene isonicotinoyl hydrazones (1d).

Sr. No.	Method	Yield (%)	Time (min)	M.P. (°C)
a	Conventional	72.58	420	206–210
b	Green route			
1	Stirring	79.68	105	204–208
2	Sonication	87.64	80	202–205
3	Microwave irradiation	95.61	8	204–206

Table 5. 4-hydroxy benzylidene isonicotinoyl hydrazone (1e).

Sr. No.	Method	Yield (%)	Time (min)	M.P. (°C)
a	Conventional	82.98	420	262–265
b	Green route			
1	Stirring	88.82	120	262–265
2	Sonication	90.70	80	262–264
3	Microwave irradiation	91.28	8	262–266

obtained was washed with water and dried. The crude product obtained on re-crystallization from alcohol gave the pure hydrazones of INH shown in

Table 6 (1a–1e). The synthesized compounds were characterized by their melting point and by spectral data (UV, IR, ¹H NMR).

Table 6. Isonicotinoyl hydrazones (1a–1e).

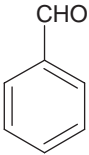
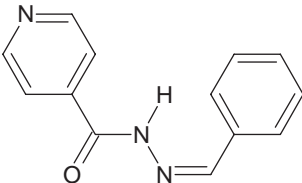
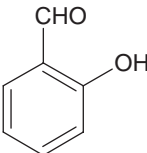
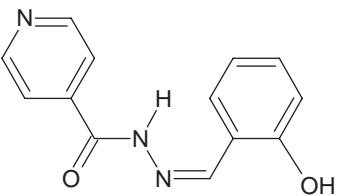
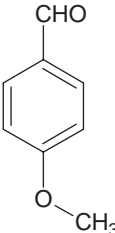
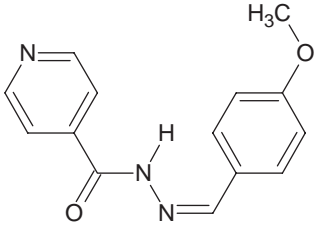
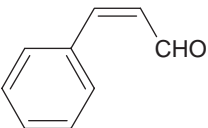
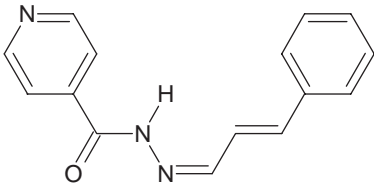
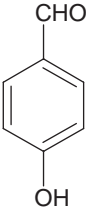
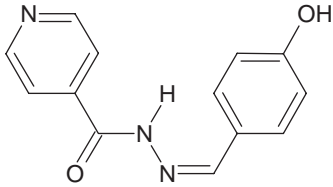
Sr. No.	R	Structure
1a		

Table 6. (Continued)

Sr. No.	R	Structure
1b		
1c		
1d		
1e		

Conclusion

The conventional reaction for the synthesis of Schiff's bases of isonicotinic acid hydrazone requires longer reaction times (360–420 min reflux) for the completion of the reaction. The reaction also involves the use of ethanol as solvent and GAA as a catalyst. On the other hand, the reactions carried out employing green route methods, such as sonication, microwave irradiation and by stirring using water as a solvent required no catalyst. In addition, the time span required for the completion of the

reaction is less than that of the conventional method. The reaction by the stirring method required 60–120 min while the sonication method required 40–80 min for the completion of reaction. The reaction involving microwave irradiation required very short reaction times (7–8 min for the completion of the reaction). The green route methods required simple workup procedures, i.e. simple filtration to isolate the products and also gave comparatively improved yields as compared to the conventional method.

The results of the physicochemical characterization of the synthesized products by chromatographic and spectroscopic studies suggested that the products obtained by both conventional and green route methods were comparable in chemical composition.

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