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Solvent-Free and Catalysis-Free Approach to the Solid State in Situ Growth of Crystalline Isoniazid Hydrazones

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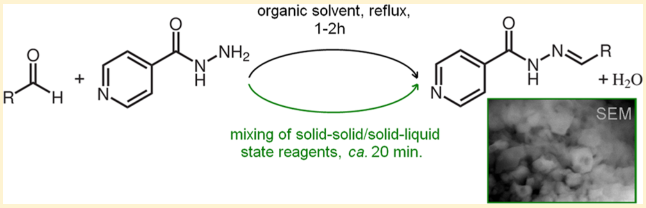
S *Supporting Information*

ABSTRACT: The isonicotinoylhydrazones and their coordination compounds have antibacterial, antifungal, antitubercular, antitumor, and anticonvulsant activities. A typical method employed in the preparation of isonicotinoylhydrazones involves the usage of the volatile organic solvents during the condensation reaction between isonicotinic acid hydrazide and carbonyl compounds. It has been shown that the solvent-free technique can be applied to obtain crystalline compounds. Reaction of isoniazid with carbonyl compound under solvent-free conditions results in microcrystalline solid state isonicotinoylhydrazones. The influence of solvent effect on the mechanism of condensation reaction was evaluated and the most significant intermediates and transition states, in the gas phase and in the presence of water and methanol were resolved. The solvent has positive effect on the reaction mechanism, but the organic solvent is unnecessary during the synthesis of crystalline isonicotinoylhydrazones derived from aldehydes. Mixing solid/liquid reactants together without additional solvent reduce the time of reaction and can be used to obtain microcrystalline compounds, which are synthesized for example to evaluate biological properties.



INTRODUCTION

Isoniazid-related hydrazones are very important group of imines. These derivatives are of great interest owing to their biological activities. The isonicotinoylhydrazones and their coordination compounds have potent antibacterial, antifungal, antitubercular, antitumor and anticonvulsant activities.[1−10]

A typical method employed in the preparation of isonicotinoylhydrazones involves the usage of the volatile organic solvents during the condensation reaction between isonicotinic acid hydrazide and carbonyl compounds, carried out by refluxing the mixture of substrates for several hours in the presence of an acidic catalyst. The solventless methods (including grinding, the usage of poly(propyleneglycol) (PPG) or water as an alternative reaction media and microwave irradiation as the nonpolluting method of activation) were successfully used in the synthesis of imines,[11−27] but the preparation of isonicotinoylhydrazones, considered as an effective pharmacophore, under solvent-free conditions was not confirmed. The mechanochemical syntheses[28−34] become more widely used as alternative to traditional solution phase methodology. The mechanochemistry has been successfully utilized to obtain nanoparticles of inorganic compounds.[35,36] Besides the absence of solvents or catalysts, which is a distinct advantage, the solventless reactions often lead to very pure products, allow shortening the synthesis time and minimizing the energy consumption. These factors are especially important in pharmaceutical industry. The active pharmaceutical ingredients are generally crystals of small organic molecules. The crystal size, shape, and crystal form of such compounds is crucial because it influence the physical and chemical properties of the solid such as solubility and bioavailability.[37,38] The application of solvent-free method reduces the number of unit operations and the amount of used solvents even if the purification or crystallization of the obtained product is required.

In this work, the experimental procedures and quantum-mechanical calculations have been used to check and explain the possibility of obtaining nicotinoylhydrazones in crystalline form via extremely simple solventless method, in which usage of microwave radiation, high pressure, etc., is unnecessary.

EXPERIMENTAL SECTION

Synthesis. Equimolar quantities of isonicotinohydrazide (mp 171 °C) (10 mmol) and the appropriate carbonyl compound (10 mmol of 2-nitrobenzaldehyde, furan-2-carbaldehyde, 4-dimethylaminobenzaldehyde, 2-hydroxybenzaldehyde, 2-acetylthiophene), existing in the liquid or solid state under normal conditions, were mixed. The mixtures were stirred and heated on an electric hot plate, in the absence of an addition of solvent and catalyst, until the initially watery mixtures (from water evolving during reaction) solidified to the products. The reaction times did not exceed 20 min (Table 1). The temperature of the samples was monitored by thermocouple connected to computer via Elmetron CX-505 device, and the reaction temperature was in range 56−60 °C (Table 1).

2-Nitrobenzaldehyde Isonicotinoylhydrazone (1): Orange solid; mp 232 °C; IR (KBr, cm^{-1}) 3650−2960 (νNH, νCH), 1680 (νC=O, δNH), 1600 (νC=N, νCC$_{\text{ring}}$), 1560 (νNO$_2$, νCC$_{\text{ring}}$), 1520 (δNH, δCH), 1415 (δCH), 1350 (δNO$_2$), 1290 (δCH, νCN), 1270 (δCH),

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Table 1. Experimental Details of Solvent-Free Syntheses

carbonyl compound	product	reaction temperature [°C]	reaction time [min.]	yield [%]
2-nitrobenzaldehyde (mp 45 °C)	1	57	15	99
furan-2-carbaldehyde (mp −37 °C)	2	60	15	99
4-dimethylaminobenzaldehyde (mp 74.5 °C)	3	60	20	99
2-hydroxybenzaldehyde (mp −7 °C)	4	56	20	99

790 (δCH, δNO_2), 740 (δNO_2); UV−vis (solid state, nm) 215 ($\pi \to \pi^*$), 270 ($\pi \to \pi^*$), 350 ($\pi \to \pi^*$); ^{1}H NMR (DMSO-d_6, δ, ppm) 12.40 (s, 1H, NH), 8.89 (s, 1H, HC=N), 8.81 (d, 2H), 8.13 (d, 2H), 7.85 (m, 3H), 7.72 (m, 1H); ^{12}C NMR (DMSO-d_6, δ, ppm) 153.2, 151.2, 147.2, 142.9, 136.6, 133.8, 131.3, 130.9, 127.6, 124.4; Anal. Calcd for $C_{13}H_{10}N_4O_3$ C, 57.77; Found C, 57.83.

2-Furfuryl Isonicotinoylhydrazone (**2**): Beige solid; mp 214 °C; IR (KBr, cm^{-1}) 3560−3040 (νNH, νCH), 1650 (νC=O, δNH), 1620 (νC=N), 1535 (νCC_{ring}), 1470 (νCC_{ring}, δNH), 1410 (δCC, δNH), 1360 (δNH, δCH), 1290 (δCH, νCN), 1160 (νCN), 1030 (νNN), 950 (νCO_{ring}), 770 (δCH), 680 (δCH); UV−vis (solid state, nm) 275 ($\pi \to \pi^*$); ^{1}H NMR (DMSO-d_6, δ, ppm) 11.98 (s, 1H, NH), 8.79 (d, 2H), 8.36 (s, 1H, HC=N), 7.88 (d, 1H), 7.81 (d, 2H), 6.99 (d, 1H), 6.66 (m, 1H); ^{12}C NMR (DMSO-d_6, δ, ppm) 164.3, 153.2, 152.0, 148.4, 143.2, 141.5, 125.9, 124.3, 117.1, 115.1; Anal. Calcd for $C_{11}H_9N_3O_2$ C, 61.39; Found C, 61.40.

p-(N,N-Dimethylamino)benzaldehyde Isonicotinylhydrazone Monohydrate (**3**): Pale green solid; mp 186 °C; IR (KBr, cm^{-1}) 3580−3130 (νNH, νCH, νOH), 1660 (νC=O, δNH, δOH), 1610 (νC=N), 1590 (νCC_{ring}), 1370 (δNH, δCH), 1315 (νCN), 1180 (νCN), 820 (δCH), 680 (δCH); UV−vis (solid state, nm) 275 ($\pi \to \pi^*$), 330 ($\pi \to \pi^*$), 400 ($n \to \pi^*$), 600 ($n \to \pi^*$); ^{1}H NMR (DMSO-d_6, δ, ppm) 11.76 (s, 1H, NH), 8.75 (d, 2H), 8.33 (s, 1H, HC=N), 7.81 (d, 2H), 7.57 (d, 2H), 6.77 (d, 2H), 2.99 (s, 6H); ^{12}C NMR (DMSO-d_6, δ, ppm) 163.9, 154.5, 153.1, 152.7, 152.3, 143.7, 131.5, 124.3, 124.0, 114.6; Anal. Calcd for $C_{15}H_{16}N_4O \cdot H_2O$ C, 62.92; Found C, 62.96.

Salicylaldehyde Isonicotinylhydrazone (**4**): Pale yellow solid; mp 243 °C; IR (KBr, cm^{-1}) 3600−2920 (νNH, νCH, νOH), 1680 (νC=O, δNH), 1620 (νC=N), 1600 (νC=N, νCC_{ring}), 1480 (νCC_{ring}, δNH), 1410 (δCC, δNH, δOH), 1290 (δCH, νCN), 1270 (δCH, νOH), 1160 (νCN), 1070 (δCH), 1000 (νNN), 850 (δCH, δCC_{ring}), 770 (δCH), 690 (δCH); UV−vis (solid state, nm) 270 ($\pi \to \pi^*$), 335 ($\pi \to \pi^*$); ^{1}H NMR (DMSO-d_6, δ, ppm) 12.29 (s, 1H, NH), 11.09 (s, 1H, OH), 8.81 (d, 2H), 8.69 (s, 1H, HC=N), 7.86 (d, 2H), 7.61 (d, 1H), 7.32 (m, 1H), 6.96 (m, 2H); ^{12}C NMR (DMSO-d_6, δ, ppm) 160.3, 153.2, 151.8, 142.8, 134.6, 132.1, 124.3, 122.3, 121.5, 119.3; Anal. Calcd for $C_{13}H_{11}N_3O_2$ C, 64.72; Found C, 64.65.

In the case of a reaction between isonicotinohydrazide and 2-acetylthiophene (mp 10 °C), for which the solventless method was unsuccessful, the traditional method involving the heating of substrates in the presence of a solvent was used. A 2-acetylthiophene (5 mmol) was added to a hot solution of an isonicotinohydrazide (5 mmol) in methanol (40 mL). The reaction mixture was heated under reflux for 2 h. The solution was then reduced by evaporation to a half-volume and allowed to cool. After 6 days, plate, yellow crystals of N′-(1-(2-thienyl)ethylidene)isonicotinohydrazide (**5**) were formed. Yield: 76%.

2-Acetylthiophene Isonicotinoylhydrazone, $C_{12}H_{11}N_3OS$ (**5**): mp 191−193 °C; IR (KBr, cm^{-1}) 3600−2930 (νNH, νCH), 1670 (νC=O, δNH), 1650 (νC=N), 1550 (νCC_{ring}), 1410 (δCC, δNH), 1390 (δNH, δCH), 750 (νCS), 705 (δCH); UV−vis (solid state, nm) 280 ($\pi \to \pi^*$), 330 ($\pi \to \pi^*$); ^{1}H NMR (DMSO-d_6, δ, ppm) 12.01 (s, 1H, NH), 8.78 (d, 2H), 7.79 (d, 2H), 7.65 (d, 1H), 7.56 (d, 1H), 7.10 (t, 1H), 2.31 (s, 3H); ^{12}C NMR (DMSO-d_6, δ, ppm): 161.4, 153.2, 151.8, 142.8, 140.9, 128.7, 128.0, 127.3, 124.3.

X-ray Crystallography. The crystal of compound **5** was mounted on a KM-4-CCD automatic diffractometer equipped with CCD detector, and used for data collection. X-ray intensity data were collected with graphite monochromated Cu$K\alpha$ radiation (λ = 1.54178 Å), with ω scan mode. The crystal used for data collection did not change its appearance during measurement. Lorentz, polarization and numerical absorption[39] corrections were applied. The structure was solved by direct methods and subsequently completed by difference Fourier recycling. All the non-hydrogen atoms were refined anisotropically using full-matrix, least-squares technique on F^2. The hydrogen atoms were found from difference Fourier syntheses and treated as "riding" on their parent non-hydrogen atoms, with assigned isotropic displacement parameters equal to 1.5 (methyl group) or 1.2 (other atoms) times the value of equivalent displacement parameters of the parent atoms. The geometry of hydrogen atoms attached to carbon atoms was idealized after each cycle of least-squares refinement. SHELXS97, SHELXL97, and SHELXTL[40] programs were used for all the calculations. Details concerning crystal data and refinement are summarized in Table 2.

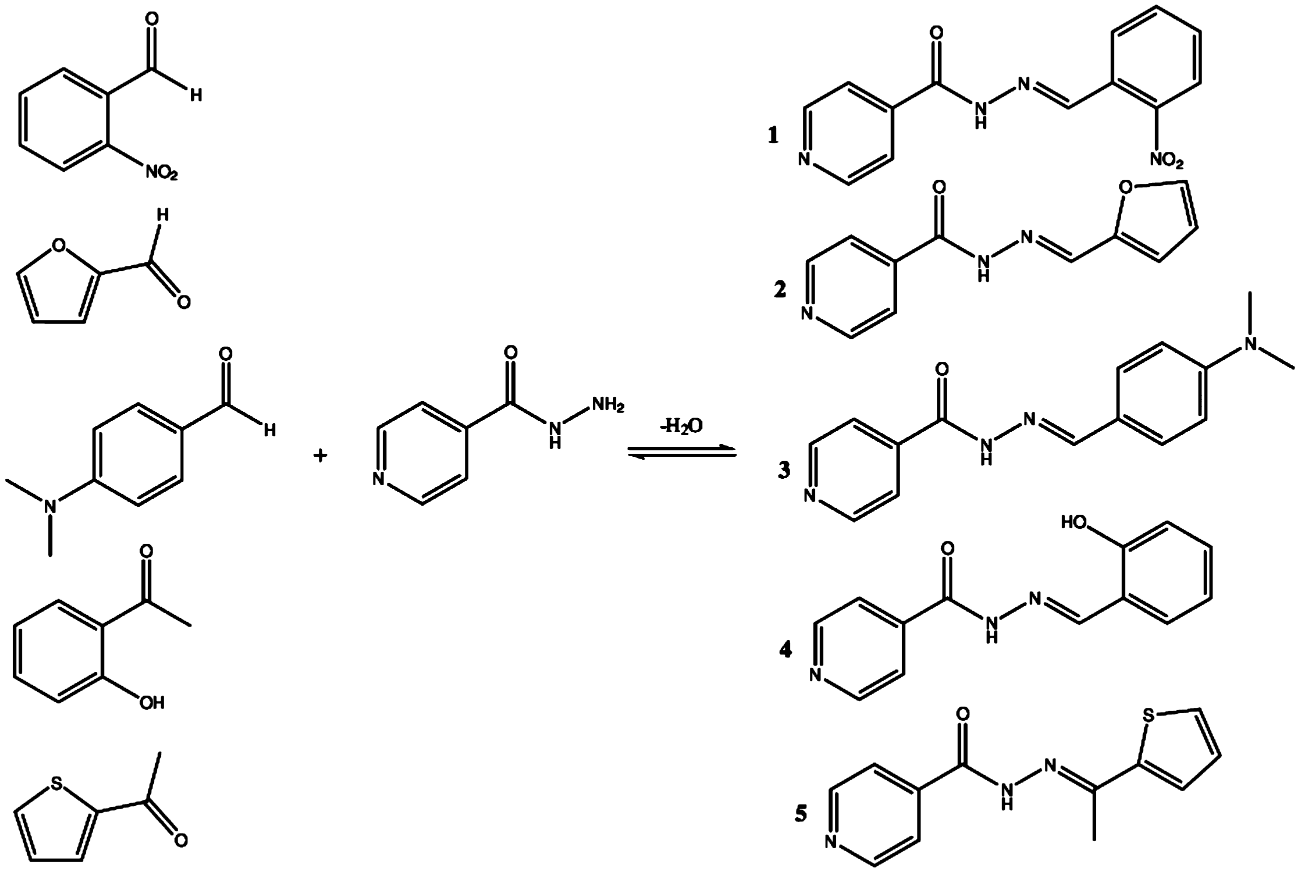
Table 2. Crystal Data and Refinement Details for 5

empirical formula	$C_{12}H_{11}N_3OS$
formula weight	245.30
crystal system	triclinic
space group	$P\bar{1}$
temperature [K]	291.0(3)
unit cell dimensions	
a [Å]	3.9533(2)
b [Å]	10.6197(4)
c [Å]	14.3961(6)
α [deg]	74.675(2)
β [deg]	82.622(3)
γ [deg]	79.443(2)
volume [Å^3]	570.99(4)
Z	2
absorption coefficient [mm^{-1}]	2.410
F (000)	256
θ range for data collection [deg]	3.19−69.56
index ranges	$-4 \le h \le 3$
	$-12 \le k \le 12$
	$-17 \le l \le 17$
goodness-of-fit on F^2	1.109
final R indices [$I > 2\sigma[I]$]	R_1 = 0.0349, R_2 = 0.0962
R indices [all data]	R_1 = 0.0353, R_2 = 0.0966
largest difference peak and hole [e Å^3]	0.214 and −0.278

Final products obtained by the solvent-free method were determined by X-ray powder diffraction analysis. The X-ray powder diffraction patterns were measured in reflection mode on an XPert PRO X-ray powder diffraction system equipped with Bragg−Brentano PW 3050/65 high resolution goniometer and PW 3011/20 proportional point detector. The Cu$K\alpha_1$ radiation was used. The patterns were measured at 298.0 K in the range 5−90° with the narrowest beam attenuator (0.017 mm). The 6 s per 0.01° step procedure was used. The thicknesses of the samples were no more than 0.01 mm. During the measurements each specimen was spun in the specimen plane to improve particle statistics.

Theoretical Calculations. The geometric parameters of substrates and products were employed from crystal structure data.[41−50] The gas phase and solution geometry optimization of reactants and intermediates was performed at the CBS-4 M (complete basis set[51,52]) level using the GAUSSIAN03[53] program package. CBS-4 M is a multistep method that involves a series of HF and MPn calculations. Since the relatively low method (HF/3-21G) is used by CBS-4 M in geometry optimization, the gas-phase geometry optimization of substrates and products was performed at the B3LYP/6-31++G(d,p) level of theory.

Scheme 1. Studied Reactions of Carbonyl Compounds with Isonicotinohydrazide



The optimized geometrical parameters obtained by both methods differ by ~0.03 Å. Local minima and transition states were identified by the number of imaginary frequencies. The solvent effect was included by usage of the polarizable continuum model.[54,55] The optimized geometrical parameters were similar to those found from X-ray measurement except 2-acetylthiophene isonicotinoylhydrazone (Supporting Information Figure S1). The gas-phase geometry optimized molecule is almost planar (the N−C(O)−$C_{pyridine}$−$C_{pyridine}$ angle is 0.02°), whereas in the crystal structure as well as in the implicit-solvent optimized molecule the pyridine ring is twisted (the N−C(O)−$C_{pyridine}$−$C_{pyridine}$ angle is −49.08° (in crystal), −31.00° (in methanol as a continuous medium) and −31.67° (in water as a continuous medium)). In general, the optimized imine bond length is shorter than this observed in the solid state.

Other measurements. The IR spectra (400−4000 cm^{-1}) of the samples prepared as KBr disks were recorded with a Jasco FT/IR-6200 spectrophotometer. The UV−vis spectra were recorded with a Jasco V-660 spectrophotometer, in transmission mode, for the solid-state samples pressed between two quartz plates. The differential scanning calorimeter (DSC 200 F3 *Maia*, Netzsch) was used to measure the melting points. The elemental analyses were performed using the total organic carbon analyzer (SSM-5000A, Shimadzu). The SEM measurements were performed using S-4700 scanning electron microscope (HITACHI S-4700) equipped with energy dispersive spectrometer (ThermoNoran). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II Plus spectrometer at 700 MHz (^{1}H) and 176 (^{13}C) in DMSO-d_6 as solvent using TMS as the internal standard.

RESULTS AND DISCUSSION

Since the synthesis of isonicotinoylhydrazones was performed under solvent-free conditions, the analysis methods can not involve any dissolution of the obtained products (dissolving of the unreacted samples may lead to reaction within a solution and can give the ambiguous results). The reaction products were characterized by X-ray powder diffraction technique (XRD), IR, and UV−vis spectroscopy, differential scanning calorimetry (DCS), and elemental analysis.

The results of heating on a hot plate of solid−solid/solid−liquid state reactants show that nicotinoylhydrazones can be obtained by the solventless methods. In the absence of an organic solvent, a liquid reactant acts both as a reactant and as an organic phase. The following reactants have been used: the isoniazid (as a source of NH_2 group) and various carbonyl compounds: 2-nitrobenzaldehyde, furan-2-carbaldehyde, 4-dimethylaminobenzaldehyde, 2-hydroxybenzaldehyde, 2-acetylthiophene (Scheme 1). The carbonyl compounds have been selected to exhibit different states of matter, and to possess different chemical properties related to the structure. Generally, the known, previously synthesized by traditional method and structurally characterized compounds were obtained to allow the comparisons of results with literature data.[41−44] In all cases, the heating process was carried out no longer than 20 min, and the heating did not exceed the 60 °C. Four of five studied compounds have been successfully obtained. The nicotinoylhydrazones are formed in near-quantitative yield (small amount of products remains on reaction vessels). Only one compound, the one derived from 2-acetylthiophene, could not be obtained under the above-mentioned conditions. An increase of the reaction time to 1 h has not led to formation of the hydrazone, and the sample did not become solid. In general, ketones are less reactive in the nucleophilic addition reaction and the methyl group of acetylthiophene sterically hinders the approach of the nucleophile, and this can explain the observed lack of reactivity in the solid state.

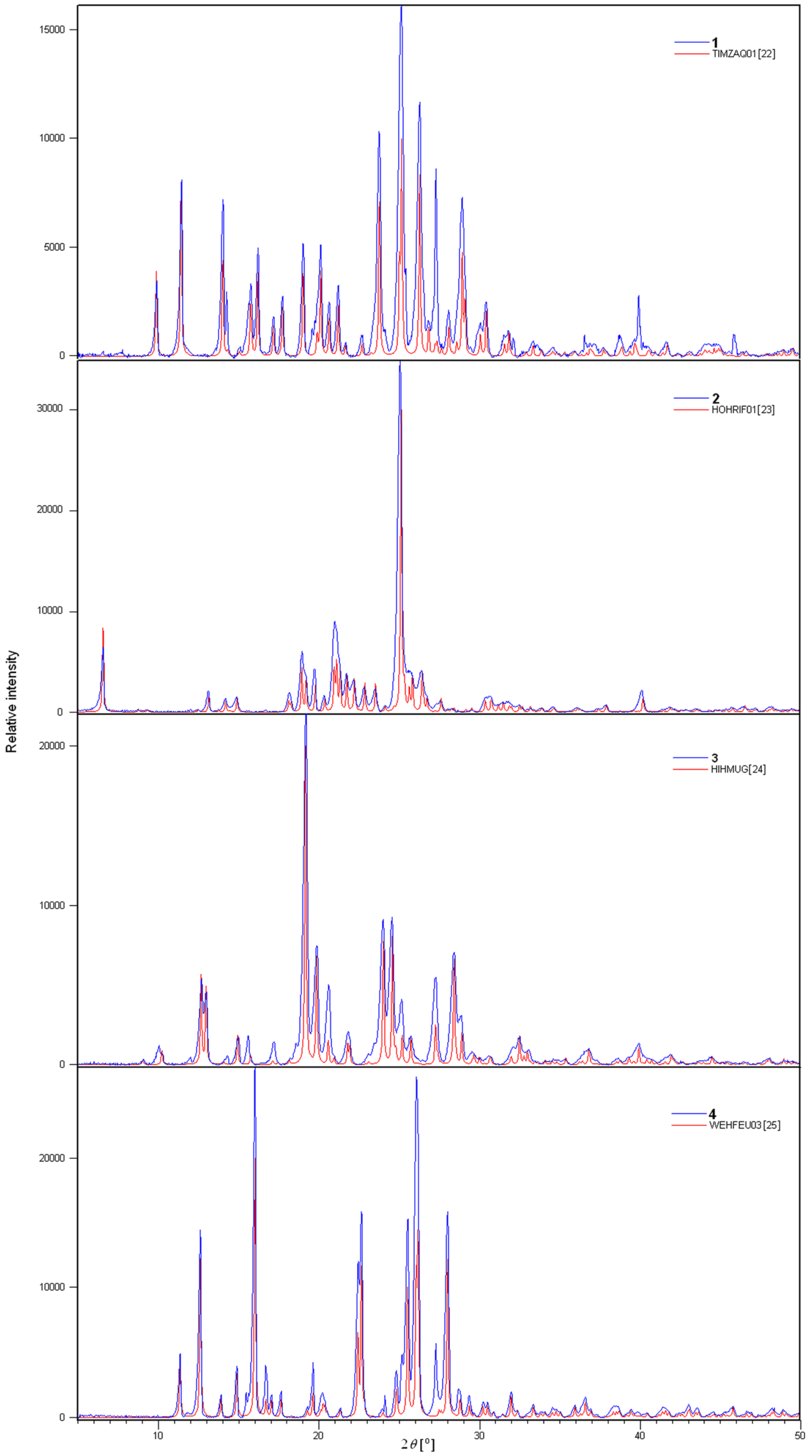


Figure 1. The X-ray powder diffraction patterns of compounds **1**−**4** obtained by solventless method compared with the reference X-ray powder diffraction patterns calculated on the basis of the single crystal structures.[41−44].

The phase homogeneity of obtained solid-state products was confirmed by X-ray powder diffraction technique by comparison of obtained reflection positions with the reference X-ray powder diffraction patterns calculated on the basis of the single crystal structures[41−44] (Figure 1), although the presence of traces of unreacted substrates cannot be excluded by this method. The lack of the substrates in the final products was confirmed by the absence of the band corresponding to N−H stretching vibrations of NH_2 group in the IR spectra. The lattice constants calculated for polycrystalline products are in agreement with those determined for single crystals from X-ray diffraction measurements.

Although it could be expected that water molecules would be evolved during the solventless synthesis process, the 4-dimethylaminobenzaldehyde isonicotinoylhydrazone was obtained in a monohydrate form similarly to the previously reported crystal structure of this compound.[31] The 2-furaldehyde isonicotinoylhydrazone, obtained by the traditional method including the usage of an organic solvent, crystallizes with one or two independent molecules in the asymmetric unit (the space group Cc[56] and $P2_1/c$,[42] respectively). The analysis of the experimental X-ray powder pattern proves that the solvent-free synthesis leads to formation of only one crystal form, that one with two independent molecules in the asymmetric unit, crystallizing in the $P2_1/c$ space group.[42] The morphology of crystalline samples of **1**−**4**, was evaluated using scanning electron microscopy (SEM). The solid-state samples are composed of aggregated irregular microparticles (Figure 2). The average size of the crystallites was determined by Scherrer equation after correction of the deconvoluted reflections fwhm on the instrumental broadening (with usage of the highly crystalline standard). For each sample the reported value was based on 10 reflections. The average size of the crystallites is 102(3) nm for **1**, 72(5) nm for **2**, 177(3) nm for **3**, and 133(2) for **4**.

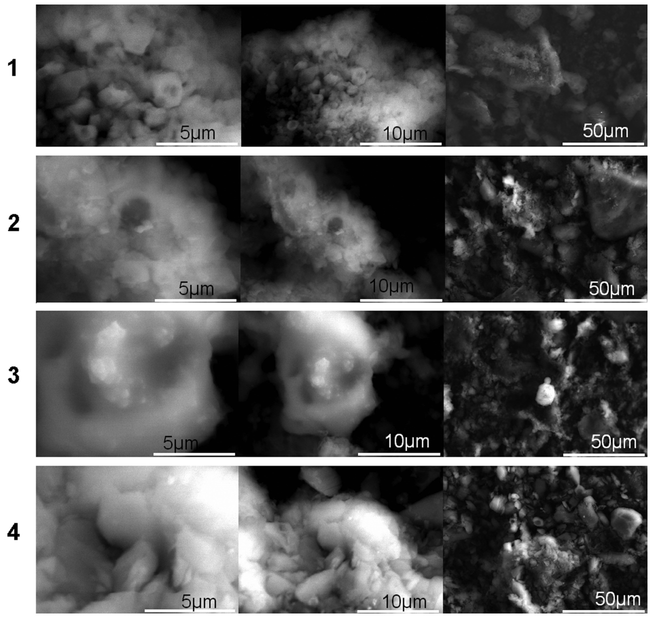


Figure 2. SEM images of compounds **1**−**4**.

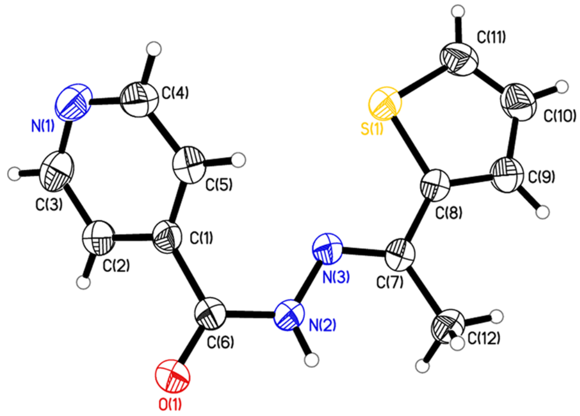


Figure 3. Molecular structure of **5** showing the atom numbering scheme. The displacement ellipsoids are drawn at 50% probability level and H atoms are shown as spheres of arbitrary radii.

For compound **5**, the composition of the reaction product was confirmed by single crystal X-ray diffraction study. The hydrazone molecule of **5** exists as the keto-amine tautomer with the configuration E toward azomethine bond (Figure 3). In contrast to previously reported crystal structures of *N*′-thienylidene-isonicotinohydrazide,[57−59] the hydrazone molecule of **5** shows uncommonly large deviation from planarity, with the dihedral angle between the weighted least-squares planes calculated through all non-H atoms of the pyridine and thiophene rings equal to 46.65(13)°. These two rings make angles of 47.42(12)° and 2.93(13)°, respectively, with the central aliphatic hydrazone moiety (O1−C6−N2−N3−C7). Because of the steric hindrance, resulting from the presence of the methyl group at the imine carbon atom, the NH group of a hydrazone moiety is able to form strongly limited number of hydrogen bonds. Molecules of **5** are assembled by the intermolecular $N_2{-}H_2N\cdots O1^{i}$ hydrogen bonds (symmetry transformation: (i) $-x - 1, -y + 1, -z + 2$, N−H distance is 0.85 Å, N···O distance is 2.9633(17) Å and N−H···O angle is 168.1°) and create a dimer forming $N_1R^2_2(8)$ motif[60] (Figure 4). The close inspection of the short contacts existing in the crystal structure shows that only one additional interaction can be classified as the hydrogen bond (weak intramolecular C5−H5···N3 interaction, with C−H distance of 0.93 Å, C···N distance of 2.944(2) Å and C−H···N angle of 101.6°). The possibility of the $\pi\cdots\pi$ interactions between the rings containing double and delocalized bonds were excluded on the basis of the shortest distance between ring centroids equal to 5.759(2) Å.

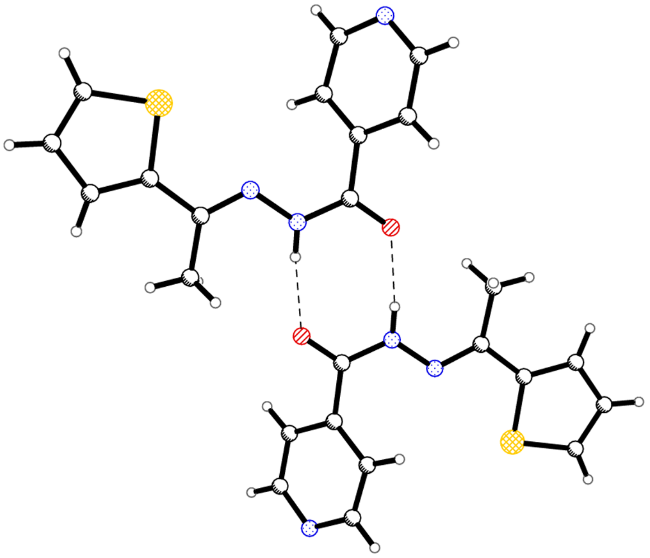


Figure 4. Dimer of **5**. Dashed lines indicate hydrogen bonds.

In most cases, the solvent molecules do not participate in chemical reaction, they are used as a heat transfer and a transport medium. The solvent in which the reaction is carried out can stabilize or destabilize the transition state, changing the electron distributions of the solutes because of its dielectric properties. The results of experiments involving heating and mixing of

Table 3. Calculated Gibbs Free Energies (G Obtained by the Extrapolation to the CBS) and Gibbs Free Energy Changes of a Reaction ($\Delta_r G^0$) (1 a.u. = 627.5095 kcal mol^{-1})

		G [a.u.]				
compound	medium	isonicotinohydrazide	aldehyde/ketone	hydrazone	water	ΔG^0 [kcal mol^{-1}]
1	gas-phase	−471.663607	−549.365061	−944.669624	−76.368248	−5.78
	methanol	−471.689526	−549.380495	−944.702794	−76.382222	−9.41
	water	−471.690825	−549.381401	−944.706409	−76.382688	−10.59
2	gas-phase	−471.663607	−342.905288	−738.205581	−76.368248	−3.10
	methanol	−471.689526	−342.91687	−738.240192	−76.382222	−10.05
	water	−471.690825	−342.917279	−738.242351	−76.382688	−10.63
3	gas-phase	−471.663607	−478.822154	−874.12277	−76.368248	−3.30
	methanol	−471.689526	−478.835175	−874.154801	−76.382222	−7.73
	water	−471.690825	−478.835748	−874.15692	−76.382688	−8.18
4	gas-phase	−471.663607	−420.222308	−815.534262	−76.368248	−10.41
	methanol	−471.689526	−420.243417	−815.56706	−76.382222	−10.25
	water	−471.690825	−420.244403	−815.568991	−76.382688	−10.32
5	gas-phase	−471.663607	−704.777915	−1100.078351	−76.368248	−3.19
	methanol	−471.689526	−704.787952	−1100.103423	−76.382222	−5.12
	water	−471.690825	−704.78839	−1100.105043	−76.382688	−5.34

reactants showed that an organic solvent and a catalyst are not required for the formation of various imines. In the synthesis reaction of these compounds under solvent-free conditions, the microwave radiation, ultrasounds or grinding can be used as a source of energy required to overcome activation barriers. In the case of microwave-assisted organic synthesis, the reaction rate is accelerated due to high reaction temperature, which quickly can be achieved during process. Grinding or simple stirring of reactants causes their molecular motions, friction, reduction of particle size, and heating.

In general, the synthesis of imines from carbonyl compounds and primary amines includes formation of a carbinolamine intermediate, which next undergoes rearrangement, and finally dehydrates, forming the corresponding imine. The imine formation requires a hydrogen transfer step and the reaction proceeds much faster in a polar solvent. According to the results of quantum-mechanical calculations,[61−63] the relatively high energy barrier of imine formation can be reduced by the presence of a water molecule or molecules acting as catalyst, which facilitate the proton transfer processes, because of their hydrogen bonding ability. Incorporation of one or two water molecules can decrease the strain within the cyclic transition state (the four-membered ring becomes more stable six- or eight-membered ring). These findings suggest that the water formation during the reaction lowers the energy barrier, since water molecules can participate in relaying of a proton, can increase the contact of the substrates and thus the additional solvent is not required. Moreover, formation of small amount of water continuously removed during the reaction prevents the reaction from reversing and thus the formation of the reactants from the products.

The condensation reaction mechanism has several steps. In the reaction environment, the molecules of reactants, products, and intermediates can be present at the same time. These molecules can interact with each other. In the studied reaction two solid−solid or liquid−solid reactants give the solid and liquid products, of which the second one evaporates in the reactions conditions (the provided energy is sufficient to remove the gradually produced water from the reaction environment), but before the water molecules are removed from the reaction system, they may influence the reaction mechanism. Water is present even during studied solid−solid reaction under solventless conditions. Because of complexity, such systems cannot be directly reproduced by theoretical calculation and only an approximate approach can be used.

To investigate the solvent effect on the mechanism of condensation reaction of the studied isonicotinohydrazide with carbonyl compounds the quantum−mechanical calculations were performed for the single molecules of reactants, products, the most significant intermediates, and transition states in the gas phase and in the presence of water and methanol using continuum solvation model. These polar solvents were used because the methanol is the most popular solvent used in the traditional imine synthesis process and the water is the constant product of imine formation reaction. Thus the combined approach based on calculation results performed for the gas phase and for the water polarizable continuum model can reasonably approximate the solvent-free reaction conditions in studied systems. The comparison of single molecule energy values of studied compounds can provide the useful information about the reaction pathway, allows a validation of the most popular reaction conditions (methanolic ones). The disadvantage of such theoretical approach is the exclusion the noncovalent intermolecular interactions of the reaction species with the neighboring molecules. However, it was shown for the reaction of reversible disulfide metathesis that the inclusion of the crystal lattice energy and the molecular conformation-related energy in the solid state only slightly influences the energetic effect of the reaction. These factors allow explaining the differences in reactivity of compounds in solution and during the solvent-free reactions, but only for metathesis reactions in which purely solid products were formed.[31] In studied reactions, the formation and evolving of water affects the reaction state of matter and additionally the energetic effects are distinctly larger than in mentioned metathesis reactions.

The solvent effect was incorporated using the polarizable continuum model, which includes global electrostatic solute−solvent interactions. The initial geometric parameters of reactants and products were employed from crystal structure data,[41−50] except the parameters of 2-furfural and salicylaldehyde, which were obtained from their cocrystal structures, and 2-acetylthiophene, which were obtained from the bromo-derivative.

The calculated CBS-4 M Gibbs free energies of reaction ($\Delta_r G^0$) at room temperature are reported in Table 3. All the

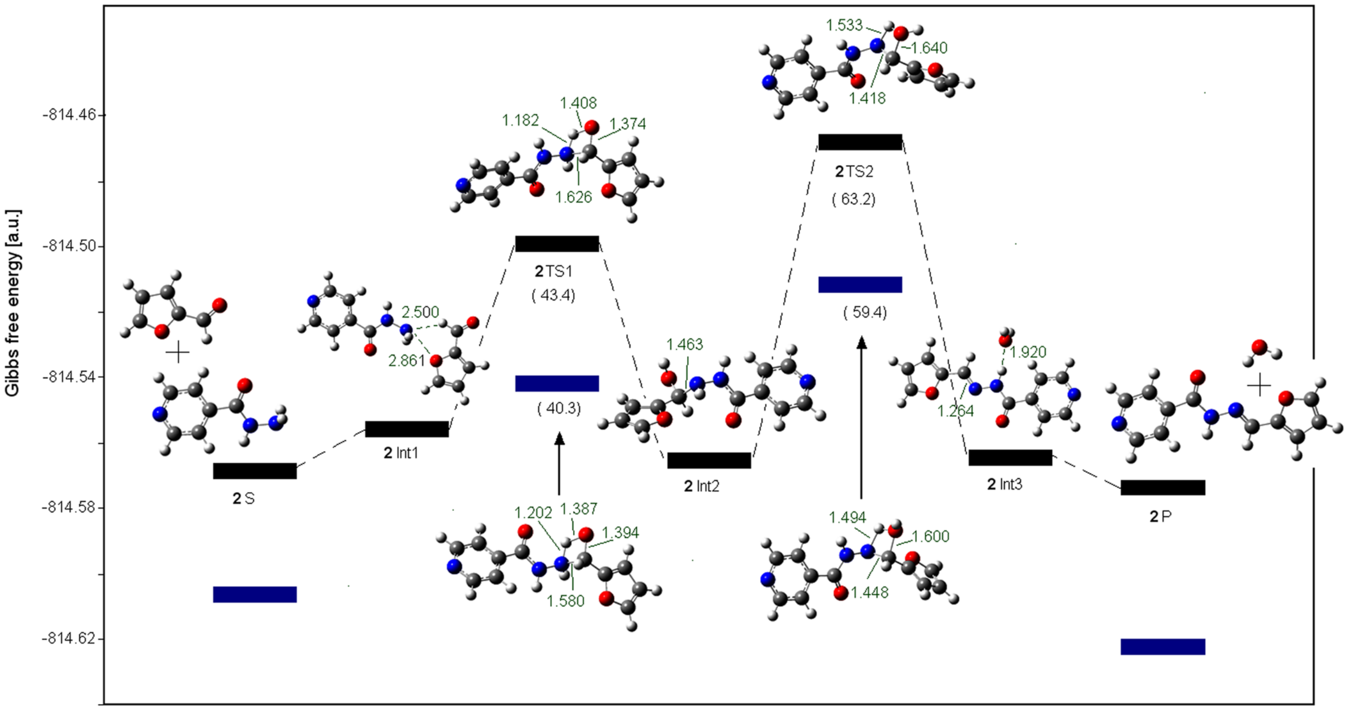


Figure 5. Gibbs free-energy profile (298 K) for the formation of 2-furfuryl isonicotinoylhydrazone **2** in the gas phase (black dash) and in the presence of the methanol (solvent) treated as a polarizable continuum (blue dash). This figure includes significant geometric parameters of the reaction (distances, Å). The values in parentheses are the energy (kcal mol^{-1}) difference between the Gibbs free energy of transition state (TS) and a sum of isolated substrate molecules Gibbs free energy.

calculated reaction paths were found to be exergonic. The change of the Gibbs free energy ($\Delta_r G^0$) for reaction was determined from the standard Gibbs free energy of the individual reactants and products. In general, the inclusion of continuum solvent–solute interactions makes the reactions thermodynamically more favored. The solvation effects reduce the values of Gibbs free energy change, but do not reverse the general reactivity trend. The exception is the 2-hydroxybenzaldehyde isonicotinohydrazone (**4**), for which the presence of solvent seems to have negative influence on reaction equilibrium. The changes of the Gibbs free energy ($\Delta_r G^0$) for reaction in methanol and water are very similar. The change of the Gibbs free energy of reaction does not depend on simple molecular properties (such as dipole moment), but it originates from the whole distribution of the electrostatic potential of the molecule. The 2-hydroxybenzaldehyde isonicotinylhydrazone (**4**) creates the O–H···N intramolecular hydrogen bond (the six-membered supramolecular ring) and such interaction can also stabilize the transition state in the absence of the solvent. The lack of possibility of such interaction formation among other compounds leads to more preferred reaction in solvents than in the gas phase. In terms of Gibbs free energy, the condensation reaction of amines and carbonyl compounds should occur even without the presence of additional organic solvent, also for *N*′-(1-(2-thienyl)ethylidene)-isonicotinohydrazide.

The inclusion of explicit water molecules have been previously considered only for the proton transfer steps of reactions between methylamine with formaldehyde (G2(MP2,SVP) level of theory),[63] acetaldehyde (B3LYP/6-31g(d,p) level),[61] and acetone (B3LYP/6-31g(d,p) and B3LYP/6-311+G(2d,p) levels),[62] and thus only the decreasing of the energies of transition states were observed, while the presence of water molecules possessing the ability to form hydrogen bonds can also change the energies of substrates and products. The inclusion of one water molecules decreases the activation energy by about 19 kcal mol^{-1}.[61−63]

For the studied reactions, the calculated Gibbs free energy values of reactant and product molecules, as well as of the most significant intermediates and transition states, are lowered when the methanol solvent as a polarizable continuum is included, but the barrier heights do not change significantly (for **2** and **3**) if the sum of Gibbs free energies of substrate molecules is included (Supporting Information Figure S2 and Table S1). In case of compound **4**, for which the geometry of transition structures (TS2) is different, the barrier height in methanol is higher in comparison to this one existing in the gas-phase. The energy profile of the studied path for compound **2** synthesis reaction is given as example in Figure 5. Solvation effect is associated with change of the electrostatic properties of a solute and polarization of its electron density by the solvent. Since the studied compounds are polar, they undergo larger stabilization in solution. The solvation alters the charge of carbonyl group atoms of aldehyde/ketone, the carbon atom becomes more positive, and hence more reactive, whereas the oxygen atom becomes more negative, on the basis of Breneman[64] and atomic polar tensor (APT[65]) derived charge values (Table 4). In general, the imine formation proceeding via a four-membered ring transition state (TS2) requires more energy than the carbinolamine formation (TS1), which is consistent with the results of previous computational studies concerning the imine formation mechanism in the gas phase and in the presence of explicit solvent molecules.[61−63] In case of 2-acetylthiophene isonicotinoylhydrazone (**5**), the proton transfer to the hydroxyl group, resulting in the elimination of a water molecule, requires less energy in the presence of methanol than in the gas-phase. The geometry of transition structures is different, as for **2** and **4** (Supportign Information Figure S2), and all these differences

Table 4. Atomic Charges [a.u.]

		ATP charge		Breneman charge	
compound	atom	gas-phase	methanol	gas-phase	methanol
1	C	0.784	1.056	0.449	0.512
	O	−0.662	−0.891	−0.518	−0.609
2	C	0.963	1.253	0.530	0.584
	O	−0.705	−0.949	−0.556	−0.664
3	C	1.085	1.454	0.454	0.492
	O	−0.807	−1.106	−0.554	−0.670
4	C	0.902	1.214	0.521	0.588
	O	−0.728	−0.994	−0.572	−0.681
5	C	1.002	1.334	0.672	0.729
	O	−0.754	−1.003	−0.602	−0.700

originate from possibility of solute−solvent interactions. The solvent modifies the electron distribution in the solute structure and thereby its geometry. It is worth mentioning that the molecular geometry of the hydrazone **1**−**4**, changes only marginally in a solvent. The presence of solvent−solute interactions plays an important role in the hydrazone synthesis from a ketone. The electrostatic interactions reduce the reaction barrier by changing the geometry of transition structure, possessing the methyl group responsible for sterical hindrance. In the synthesis of hydrazones derived from ketones the solvent has significantly more positive effect on the reaction mechanism in comparison to these ones derived from aldehydes.

CONCLUSIONS

The experimental and quantum-mechanical results suggest that the additional solvent is the unnecessary component in the synthesis of nicotinoylhydrazones, especially these ones derived from aldehydes. The experimental procedure is not complicated and it does not require any sophisticated laboratory equipment. The simple heating on a hot plate of solid−solid/solid−liquid state reactants can be routinely used to obtain new nicotinoylhydrazones on laboratory scale. The energy delivered in this way is enough to overcome activation barriers. The results of XRD and SEM measurements showed that obtained under solvent-free conditions isonicotinoylhydrazones form crystalline microparticles. It is important since these compounds are synthesized as target structures for evaluation of biological activities, and the size and shape of particles influences the compound properties such as bioavailability. The one-step solvent-free method of synthesis can be used to obtain crystalline compounds.

The water formation during the reaction lowers the energy barrier significantly in comparison to gas phase[61−63] since the water molecules can participate in relaying a proton, increase the contact of the substrates and thus the additional solvent is not required. Thermochemical parameter of the formation of isonicotinoylhydrazones, the free Gibbs energy change, indicated that all studied compound can be obtained. Although the solvent has positive effect on the reaction mechanism (the energy of transition states is lowered by about 26 kcal mol^{-1} for **1**−**4**), the organic solvent is unnecessary during the synthesis of isonicotinoylhydrazones derived from aldehydes. Only one compound, this one derived from 2-acetylthiophene, could not be obtained under solventless conditions. In this case, the solvent effects are considerable in reducing the energy barriers due to the stabilization of the transition state. In general, ketones are less reactive in the nucleophilic addition reaction and the methyl group of acetylthiophene sterically hinders the approach of the nucleophile.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The selected bond lengths of reactant molecules from the crystal structures for the gas-phase optimized structures and implicit-solvent optimized molecule−methanol and water, the optimized structures of intermediates (Int), transition structures (TS), substrate and product molecules for **1** and **3**, the calculated Gibbs free energy values for reactant and product molecules, as well as for transition states and intermediates in the gas phase and in the presence of the methanol solvent as a polarizable continuum. This information is available free of charge via the Internet at http://pubs.acs.org/. CCDC-892705 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, U.K.; fax +44(0)1223−336033; e-mail deposit@ccdc.cam.ac.uk].

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Notes

The authors declare no competing financial interest.

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