Enaminones in heterocyclic syntheses: part 5: isoniazid-enaminone a new organic synthon and tuberculostatic candidate.

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Abstract: condensation of nicotinic, isonicotinic acid hydrazides **1a,b** with1,3-cyclohexanedione **2**, in water, using acetic acid as catalyst, afforded enaminone derivatives **3a,b.**

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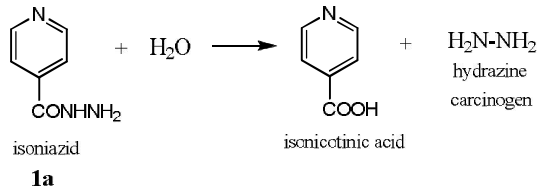
Introduction

Isoniazid (isonicotinic acid hydrazide) **1a** is used as a veterinary antiactinomycotic agent and, most important, as a primary drug for the treatment of all types of tuberculosis [1-4a] and is, normally, given in high doses over long periods of time [2, 5]. Also, iproniazid (isonicotinicacid2-isopropylhydrazide) is applied as antidepressant [4b, 6].

Isoniazid **1a** itself has been reported to be carcinogenic in mice [2, 7] but the carcinogenic activity is probably due to the release of free hydrazine (H_2NNH_2) by the hydrolysis of **1a** according to **equation 1** [1, 2, 7]. Hydrazine, one of isoniazid's principle degradation products (**equation 1**) is a known carcinogen [1-3] and considerably, is more toxic than isoniazid [1, 2, 4c]. A very recent review [1] reported that "hydrazines cause DNA damage and gene mutations [8, 9]; hydrazine, methylhydrazine and related hydrazides (isoniazid is a hydrazide derivative of hydrazine) are known human carcinogens [10]; and hydrazines, hydrazides and hydrazones all show conventional structural alerts for genotoxic potential [11]".

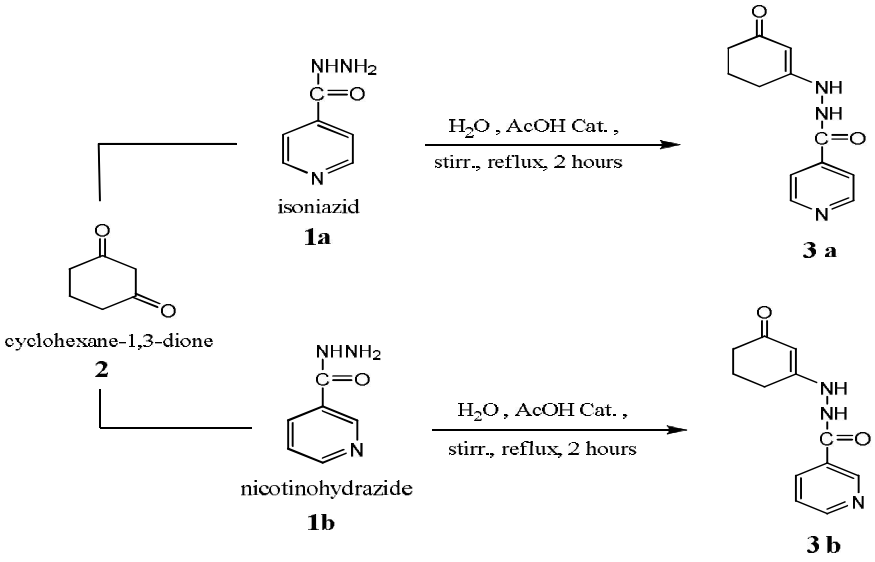
On the other hand, Enaminones have proven to be versatile synthons for the synthesis of various heterocycles and natural products [12-14]. They are involved in the synthesis of, for example, pyridines, pyrimidines, pyrroles, indolizidines, quinolizidines and perhydroindoles, many of which are common motifs in alkaloid structures [12, 13]. Enaminones are, also, frequently employed as building blocks for the preparation of highly functionalized mono-, bi- or larger- cyclic compounds of biological interest. In addition, some enaminones have been recognized as potential anticonvulsant [12, 15a-c] and analeptic [15d] compounds, with low toxicity.



Most of the syntheses of enaminones [12, 13], (especially, *via* condensation of 1,3-dicarbonyl compounds with ammonia, primary or secondary amines [16-21]; or with hydrazines [22]) are, usually, carried out in dry organic solvents, with continuous removal of water as a reaction by-product. However, we, herein, present a synthesis- in water- of the new enaminones**3a, b** (Scheme 1, Experimental). This work is in continuation of our recent interest in the field of (*Green Chemistry*), especially, in the direction of applying water -the safest and most economic solvent- in place of hazardous and expensive solvents in synthetic organic reactions [23, 24]. It is, also, in continuation of the work of one of our team on enaminones [25-28].

When isoniazid **1a** was allowed to react with the highly enolisable 1,3-cyclohexanedione **2**, through two hours of reflux conditions in water, in

the presence of catalytic amount of acetic acid, the new enaminone derivative **3a** was obtained as a yellow fine crystalline matter in 80% yield of isolated product (Scheme 1, Experimental). In the light of forming and, hence, stability of the enaminone**3a** in the applied refluxed weak-acid catalyzed aqueous solution (Scheme 1 & Experimental), the probability of releasing free hydrazine -a carcinogen- from the enaminone**3a** should be eliminated under conditions comparable to, or softer than the applied synthetic conditions of **3a**. Moreover, a hypothetical assumption of splitting off free hydrazine from the enaminone derivative **3a** is -in our opinion- very much retarded since this splitting involves two consecutive reactions to occur. In the first assumed reaction, (**equation 2**), the enaminone**3a** has to be forced to be hydrolyzed -by water- into its building unites 1,3-cyclohexanedione **2** and isoniazid **1a**. In the second reaction, **equation 1** has to be applied to release hydrazine from **1a**.

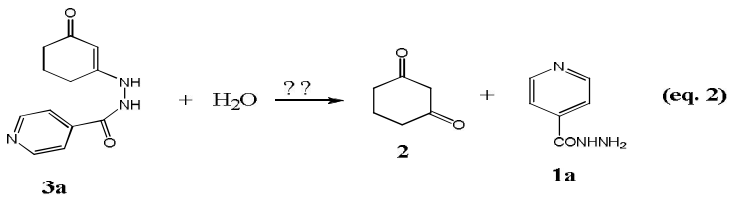


Scheme 1

Similar to **1a**, the nicotinic acid hydrazide **1b** was allowed to react with **2**, under the same experimental conditions to afford the new enaminone **3b** as yellow fine crystals (Scheme 1& Experimental).

The structures of **3a,b**were established on basis of satisfactory elemental and spectral (IR, ^{1}H NMR, ^{13}C NMR) analyses (Experimental). For example, the IR spectrum of **3a** showed stretching bands in the regions of 3229, 3170 and 1681 cm^{-1} for the –NH- and –CO- functional groups, respectively; its ^{1}H NMR (DMSO), showed singlet signal (s) in the regions of δ 10.83, 9.15 and 4.96 ppm for the proton (s) of the hydrazide nitrogen -CONH-, enaminone nitrogen (=C-NH-) and the ene (or vinylic) moiety(-CH=C-), respectively; and its ^{13}C NMR (DMSO) showed signal (s) in the regions of δ 195.30, 164.00 and 96.00 ppm for the ketonic carbonyl, hydrazide carbonyl carbon and the ene-methine (-CH=) carbon (i.e., C-2 in the 3-oxocyclohex-1-enyl moiety), respectively.

In the light of the above mentioned findings and results and as each of the new derivatives **3a,b**gathers or combines -in its chemical structure- between the functionality of cyclic enaminone and 2-substituted-hydrazide, it is worthy to suggest future studies to explore the potentiality of these new derivatives **3a, b** in both the fields of biological activity-especially, towards the different types of tuberculosis- and organic synthesis.



Experimental

Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected; IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. ^{1}H-NMR and ^{13}C NMR spectra were performed on a BRUKER (600 and 150 MHz, respectively) ultra shield Avence III Spectrometer at the Faculty of Science, King Abd-Elaziz University, Jeddah, K.S.A, using (TMS) as an internal stander and DMSO as a solvent. Chemical shifts were expressed as δ ppm. Microanalytical data were performed on a PERKIN-ELMER 2400 C,H,N Elemental Analyzer at the Microanalytical Unit, Cairo University, EGYPT.

3.1. Synthesis of N'-(3-oxocyclohex-1-enyl)isonicotinohydrazide(3a)and N'-(3-oxocyclohex-1-enyl)nicotinohydrazide(3b) (Scheme 1).

General procedure:

The hydrazide **1a (or 1b)**(0.01mol) was dissolvedin 30 ml of hot distilled water, while stirring. 1,3-cyclohexanedione **2** (0.01 mol) was, then, added, in portions, in the presence of 2 drops glacial acetic acid as a catalyst. A after complete addition of **2,** heating, while stirring, continued for two additional hours. The reaction solvent -water- was, then, removed using a rotary evaporator system. The evaporation residue was cooled to room temperature and, next, triturated with petroleum ether (40-60 ^{o}C) till a solid was obtained. The solid product was, then, crystallized from ethanol: water (1: 4) mixture to give **3a, b**, respectively.

N'-(3-oxocyclohex-1-enyl)isonicotinohydrazide (3a).

Yellow fine crystals: Yield: 80%; m.p: 186-8 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3229,3170 (NH); 1681 (CO); **^{1}H NMR** (600 MHz, DMSO), δ, ppm = 10.83 (1H, s ,-CONH-, hydrazide), 9.15 (1H, s, =C-NH-, enaminone), 8.80 (2H, d, H-2, H-6, pyridyl), 7.78 (2H, d, H-3, H-5, pyridyl), 4.96 (1H, s, -CO-CH=, enaminone), 2.41, 2.14, 1.87 (6H, 3x m,3x-CH_2-, 3-oxocyclohex-1-enyl); **^{13}C NMR** (150 MHz, DMSO), δ, ppm = 195.30 (**C**O, ketone), 164.00 (**C**O, hydrazide), 150.46 139.23, 121.23, 96.00 (-CO-**C**H=, enaminone), 36.55 (**C**H_2-CO), 25.60 (**C**H_2), 21.56 (CH_2-**C**H_2-CH_2).

Anal.Calcd for $C_{12}H_{13}N_3O_2$ (Mol.Wt: 231.25): C, 62.3; H, 5.67; N, 18.17; Found: C, 62.22; H, 5.35; N, 17.93.

N'-(3-oxocyclohex-1-enyl) nicotinohydrazide (3b)

Yellow fine crystals: Yield: 75%; m.p: 202-204 ^{o}C; **IR** (KBr, cm^{-1}): γ = 3243, 3178 (NH); 1677 (CO); **^{1}H NMR** (600 MHz, DMSO), δ, ppm = 10.71 (1H, s ,-CONH-, hydrazide), 9.12 (1H, s, =C-NH-, enaminone), 9.03 (1H, s, pyridyl), 8.77 (1H, d, pyridyl), 8.23 (1H, d, pyridyl), 7.56 (1H, m,pyridyl), 4.97 (1H, s, -CO-CH=, enaminone), 2.41, 2.14, 1.87 (6H, 3x m, 3x-CH_2-, 3-oxocyclohex-1-enyl); **^{13}C NMR** (600 MHz, DMSO), δ, ppm = 195.27 (**C**O, ketone), 164.01 (**C**O, hydrazide), 152.6, 148.30, 135.19, 127.93, 123.72, 96.00 (-CO-**C**H-, enaminone), 36.56 (**C**H_2-CO), 25.69 (**C**H_2), 21.57 (CH_2-**C**H_2-CH_2).

Anal. Calcd for $C_{12}H_{13}N_3O_2$ (Mol.Wt: 231.25): C, 62.3; H, 5.67; N, 18.17; Found: C, 62.32; H, 5.55; N, 18.06.

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