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

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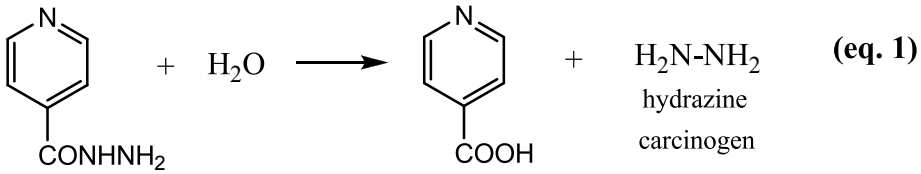
## Introduction

Isoniazid (isonicotinic acid hydrazide) **1a** is used as a veterinary antiactinomycotic agent [4a]; 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]. Iproniazid (isonicotinic acid 2-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 more toxic than isoniazid [1, 2, 4c]. Avery 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]".

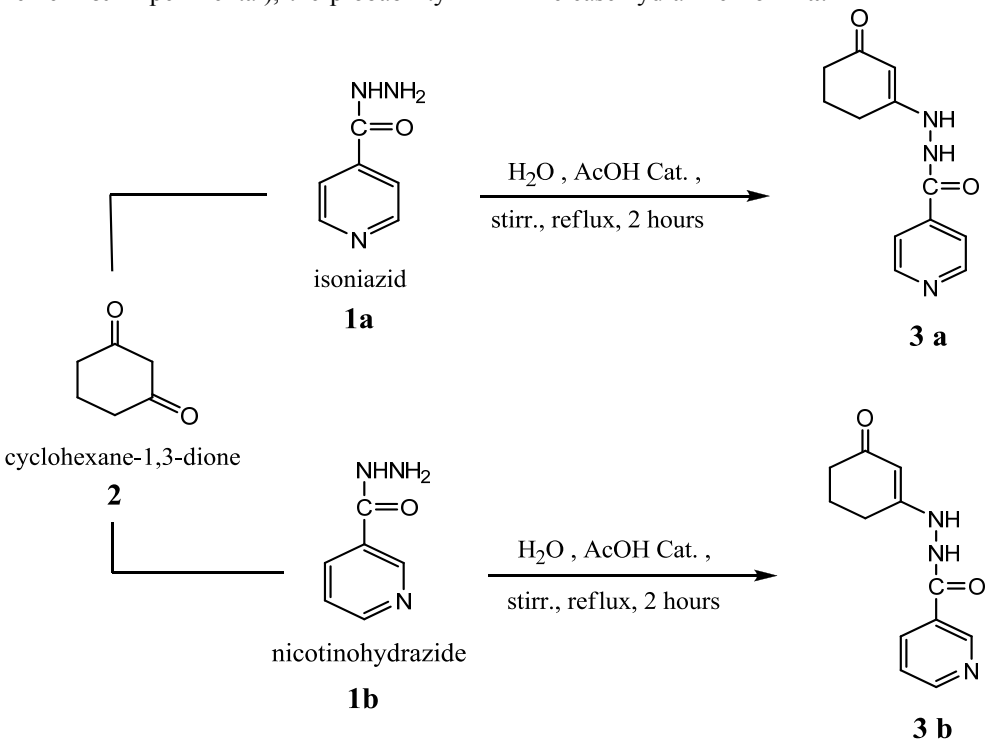



isoniazid **1a** isonicotinic acid **(eq. 1)**

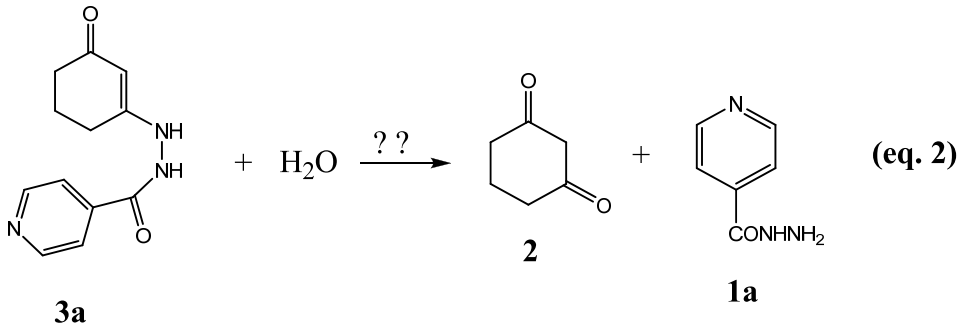
On the other hand, Enaminones have proven to be versatile synthons for the synthesis of various heterocycles and natural products [12-14]. They are involved in the synthesis of, for example, pyridines, pyrimidines, pyrroles, indolizidines, quinolizidines and perhydroindoles, many of which are common 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. 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 [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**




**(eq. 2)**

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** gather 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, b** (0.01mol) was dissolved, on hot, in 30 ml of 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-$CH_2$-, 3x m, 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: 202-4 $^{o}$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, t, aromatic hetryl), 4.97 (1H, s, -CO-CH=, enaminone), 2.41, 2.14, 1.87 (6H, 3x-$CH_2$-, 3x m, 3-oxocyclohex-1-enyl); **$^{13}$C NMR** (600 MHz, DMSO), δ, ppm = 195.27 (**C**O, ketone), 164.01 (**C**O, amidic), 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.

## References

[1] D. P. Elder, D. Snodin, A. Teasdale, Journal of Pharmaceutical and Biomedical Analysis 54, 900-910 (2011).
[2] A. Carlin, N. Gregory and J. Simmons, Journal of Pharmaceutical and Biomedical Analysis, 17, 885-890 (1998).
[3] G. L. Mandell, M. A. Sande, in: A. G. Gillman, T. W. Rall, A. S. Nies, P. Taylor (Eds.), The Pharmacological Basics of Therapeutics, 8th ed., Pergamon, New Yourk, 1146-1149 (1990).
[4] The Merck Index, Twelfth Edition, Susan Budavari, Editor, Merck Research Laboratories, Merck & CO., INC. Whitehouse Station, NJ

(1996), (a) Item No. 5203, p. 885., (b) Item No. 5094, p. 871., (c) Item No. 4809, p. 816.
[5] The Merck Manual of Diagnosis and Therapy, 16th ed., Merck, Rahway, NJ, (1992) 139-140., (through ref. 2).
[6] J. Clayden, N. Greeves, S. Warren and P. Wothers, (Organic Chemistry), OXFORD University press INC, New Yourk, p. 29 (2008).
[7] J. C. Arcos, Y. T. Woo, M. F. Argus, D. Y. Lai, Chemical Induction of Cancer, Academic Press, New York, p. 363, (1982).
[8] S. Parodi, S. Deflora, M. Cavanna, DNA-damaging activity in vivo and bacterial mutagenicity of sixteen hydrazine derivatives as related quantitatively to their carcinogenicity, Cancer Res. 41 (1981) 1469–1482.
[9] M. J. Zeilmaker, M.J. Horsfall, J.B. van Helten, Mutational specificities of environmental carcinogens in the lacl gene of Escherichia coli H. V: DNA sequence analysis of mutations in bacteria recovered from the liver of Swiss mice exposed to 1,2-dimethylhydrazine, azoxymethane, and methyl azoxymethanol acetate, Mol. Carcinog. 4,180-188 (1991).
[10] J. A. Knottnerus, N-Methylhydrazine, Evaluation of the Carcinogenicity and Genotoxicity, Dutch Expert Committee on Occupational Standards, A Committee of the Health Council of the Netherlands, Nr 2002/07OSH, The Hague, 16th April 2002.
[11] K. Sawatari, Y. Nakanishi, T. Matsushimi, Relationships between chemical structures and mutagenicity: a preliminary survey for a database of mutagenicity test results of new work place chemicals, Ind. Health 39, 341–345 (2001).
[12] G. Negri, C. Kascheres and A. J. Kascheres, J. Heterocyclic Chem. 41, 461-491 (2004).
[13] B. Stanovnik and J. Svete, Chem. Rev., 104, 2433-2480 (2004).
[14] B. Stefane and S. Polanc, New J. Chem., 26, 28-32 (2002).
[15] (a) I. O. Edafiogho, C. N. Hinko, H. Chang, J. A. Moore, D. Mulzac, J. M. Nicholson and K. Scott, J. Med. Chem. 35, 2798 (1992); (b) K. R. Scott, I. O. Edafiogho, E. L. Richardson, V. A. Farrar, J. A. Moor, E. I. Tietz, C. N. Hinko, H. Chang, A. El-Assadi and J. M. Nicholson, J. Med. Chem., 36, 1974 (1993); (c) K. R. Scott, G. O. Rankin, J. P. Stables, M. S. Alexander, I. O. Edafiogho, V. A. Farrar, K. R. Kolen, J. A. Moor, L. D. Smis and A. D. Tonnu, J. Med. Chem. 38 (1995) 4033; (d) Hoffimann-La Roche, Ger. Pat. (DRP), 614, 195 (1935); Chem. Abstr., 29, 5995 (1935).
[16] K. R. Scott, G. O. Rankin, J. P. Stables, M. S. Alexander, I. O. Edafiogho, V. A. Farrar, K. R. Kolen, J. A. Moore, L. D. Sims and A. D. Tonnu, J. Med. Chem., **38**, 4033 (1995). Chem. Abstr., **123**, 313499h (1995).
[17] I. O. Edafiogho, J. A. Moore, V. A. Farrar, J. M. Nicholson and K. R. Scott, J. Pharm. Sci., **83**, 79 (1994).
[18] K. R. Scott, I. O. Edafiogho, E. L. Richardson, V. A. Farrar, J. A. Moore, E. I. Tietz, C. N. Hinko, H. Chang, A. El-Assadi and J. M. Nicholson, J. Med. Chem., **36**, 1947 (1993); Chem. Abstr., **119**, 116884w (1993).
[19] I. O. Edafiogho, C. N. Hinko, H. Chang, J. A. Moore, D. Mulzac, J. M. Nicholson and K. R. Scott, J. Med. Chem., **35**, 2798 (1992). Chem. Abstr., **117**, 69477n (1992).
[20] J. V. Greenhill, I. Chaaban and P. J. Steel, J. Heterocyclic Chem., **29**, 1375 (1992).
[21] B. V. Lichitsky, S. N. Ivanov, A. A. Dudinov, S. A. Woznesensky and M. M. Krayushkin, Russ. Chem. Bull., Int. Ed., **50**, 2428 (2001).
[22] B. V. Lichitsky, V. N. Yarovenko, I. V. Zavarzin and M. M. Krayushkin, Russ. Chem. Bull., Int. Ed., **49**, 1251 (2000).
[23] F. H. A. Bamanie, A. S. Shehata, M. A. Moustafa and M. M. Mashaly, Journal of American Science, 8, 481-485 (2012).
[24] A. S. Shehata, F. H. A. Bamanie, M. A. Moustafa and M. M. Mashaly, Journal of American Science, 7, 240-242 (2011).
[25] M. M. Mashaly and M. Hammouda, Z. Naturforsch., 54b, 1205-1209 (1999).
[26] M. Hammouda, M. M. Mashaly and A. A. Fadda, Arch. Pharm. Res., 18, 213-214 (1995).
[27] M. Hammouda, M. M. Mashaly and E. M. Afsah, Pharmazie 49, 365-366 (1994).
[28] S. R. El-Gogary, M. M. Mashaly and T. R. Kosbar, "Enaminones in heterocyclic syntheses: part 4: a new one step synthetic route to pyrrolo[3,4-b]pyridine and convenient syntheses of 1,4-dihydropyridines and 1,1'-(1,4-phenylene)bis(1,4-dihydropyridine)s., accepted on 23-Dec.-2011 by J. Heterocyclic Chem.

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