SYNTHESIS OF SOME *N*-SUBSTITUTED HYDRAZIDES CONTAINING ISOXAZOLE HETEROCYCLE

NGUYEN TIEN CONG[*], NGUYEN DANG DAT[**], DUONG MINH TU[***]

ABSTRACT

*Ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate (**1**), ethyl 5-(4-nitrophenyl)isoxazole-3-carboxylate (**2**), 5-(4-nitrophenyl)isoxazole-3-carbohydrazide (**3**) and eight new N-substituted hydrazides (**4**$_{a-h}$) containing isoxazole heterocycle were synthesized. The structures of these compounds were confirmed by IR and ^{1}H-NMR spectral data.*

Keywords: Ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate, ethyl 5-(4-nitrophenyl)isoxazole-3-carboxylate, 5-(4-nitrophenyl)isoxazole-3-carbohydrazide, *N*-substituted hydrazide.

TÓM TẮT

Tổng hợp một số hyđrazit N-thế chứa dị vòng isoxazole

*Etyl 4-(4-nitrophenyl)-2,4-dioxobutanoat (**1**), etyl 5-(4-nitrophenyl)isoxazole-3-carboxylat (**2**), 5-(4-nitrophenyl)isoxazole-3-carbohyđrazit (**3**) và tám hợp chất mới là các hydrazit N-thế (**4**$_{a-h}$) chứa dị vòng isoxazole đã được tổng hợp. Cấu trúc của các chất đã được xác định qua phổ IR và phổ ^{1}H-NMR của chúng.*

Từ khóa: Etyl 4-(4-nitrophenyl)-2,4-dioxobutanoat, etyl 5-(4-nitrophenyl)isoxazole-3-carboxylat, 5-(4-nitrophenyl)isoxazole-3-carbohyđrazit, hyđrazit *N*-thế.

1. Introduction

Heterocyclic derivatives containing isoxazole were well known for their analgesic, antimicrobial, antifungal, antitubercular activities [7-9]. Some heterocyclic containing isoxazole compounds revealed the effect on increasing reactivity of cellobiase [2,4]. *N*-Substituted hydrazides have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities [6]. Recently, 5-(4-chlorophenyl)isoxazole-3-carbohydrazide and it's *N*-substituted hydrazide were synthesized [3]. These compounds were known as potential HSV-1 inhibitors. However, 5-(4-nitrophenyl)isoxazole-3-carbohydrazide and it's *N*-substituted hydrazides have not been found while searching by Scienfinder software in May 2015 at the Utah University, USA.

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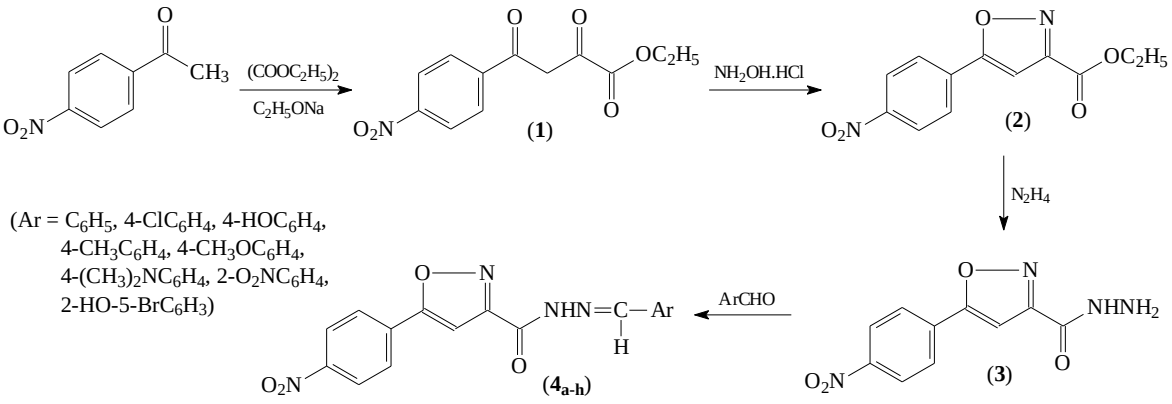
2. Results and discussion

Claisen condensation of 4-nitroacetophenone with diethyl oxalate in the presence of sodium ethoxide gave ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate (**1**). Cyclization of (**1**) with hydroxylamine hydrochloride afforded ethyl 5-(4-nitrophenyl)isoxazole-3-carboxylate (**2**). The compound (**2**), on further treatment with hydrazine hydrate in ethanol, afforded 5-(4-nitrophenyl)isoxazole-3-carbohydrazide (**3**) and finally, this hydrazide reacted with different aromatic aldehydes to yield a variety of *N*-substituted hydrazides derivatives (**4$_{a-h}$**) as shown in the Scheme 1.

The compound (**1**) has been in our previous work [1] and the melting point of the compound is agreement with the one of the ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate [5]. The stretching bands at 1728 cm^{-1} and 1719 cm^{-1} in the FT-IR spectrum of (**1**) indicated that there was the presence of C=O bonds in a conjugational system. There was especially no significant change in the IR spectra of (**1**) and (**2**) in which the C=O absorption band was recognized at 1724 cm^{-1}. However, all protons in the ^{1}H-NMR spectrum of (**2**) were considered to be accordant with their expected chemical shift and integral values. The signals of protons in the ethyl group were assigned as *quartet* at 4.50 ppm (2H, *J*=7.0 Hz) and *triplet* at 1.46ppm (3H, *J*=7.0 Hz); the signals of aromatic protons on the benzene ring were determined at 8.37ppm (2H, *doublet*, *J*=9.0 Hz) and 8.00ppm (2H, *doublet*, *J*=9.0 Hz). Besides that, there was a singlet signal at 7.11 ppm with intensity of 1H. These signals correspond with the signal of the protons of ethyl 5-(4-nitrophenyl)isoxazol-3-carboxylate described in literatures. [10]

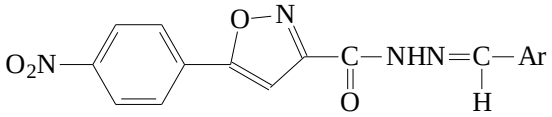


Scheme 1. *Pathway for synthesis*

Compound (**3**) was first confirmed via its IR spectral data in which the presence of a characteristic absorption band at 3339cm^{-1} and a strong one at 1684cm^{-1} was in turn represented for N-H bonds and C=O group. The absorption of carbonyl group in the hydrazide structure was considerably different from the corresponding ester due to a strong delocalization of the π electrons of the α-nitrogen atom in the hydrazino group (-$NHNH_2$), which would lead to the reduction of the electron density and the bond order of carbonyl group in its resonance structures. In the ^{1}H-NMR spectrum of (**3**), signals at 10.20ppm (1H, *broad*, N-H) and δ 4.70ppm (2H, *broad*, NH_2) which were evaluated for the hydrazino group (–$NHNH_2$), a signal of isoxazole ring at 7.60ppm (1H, *singlet*) and signals of benzene ring at 8.36ppm (2H, *doublet*, *J*=8.5 Hz) and 8.17ppm (2H, *doublet*, *J*=8.5 Hz) were also easily detected. The signals of protons at benzene and isoxazole rings in the (**3**) compound appear at the lower field than the corresponding signals in 5-(4-chlorophenyl)isoxazole-3-carbohydrazide compound [3] because of the electron-withdrawing of the nitro group.

In the IR spectrum of *N*-substituted hydrazides (or hydrazones) (**4$_{a-h}$**) obtained from hydrazide (**3**), there was not only a lack of broad stretching bands at around 3339cm^{-1}, but also a transfer of the absorption signal of carbonyl group up to a higher frequency (1682-1697 cm^{-1}). Yields, physical properties and IR spectral data of these hydrazones were shown in Table 1.

Table 1. *Physical and IR spectral data of the N-substituted hydrazides*

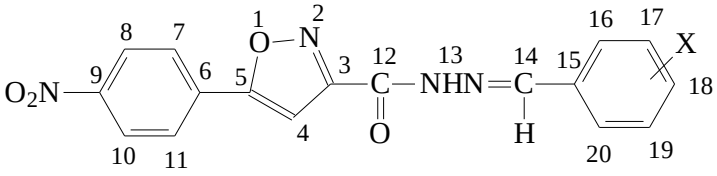


Comp. No.	Ar	M.p. (^{O}C)	Yield (%)	ν (cm^{-1})				
				Csp^2-H	N-H	C=O	C=N and C=C	NO_2
4$_a$	C_6H_5	178-180	58.8	3131	3287	1678	1607	1522
4$_b$	4-ClC_6H_4	200-202	61.4	3131	3289	1682	1609	1528
4$_c$	4-HOC_6H_4	180-182	60.5	3136	3291	1678	1604	1514
4$_d$	4-$CH_3C_6H_4$	199-200	60.3	3134	3306	1684	1605	1523
4$_e$	4-$CH_3OC_6H_4$	180-182	60.5	3134	3302	1680	1599	1522
4$_f$	4-$(CH_3)_2NC_6H_4$	206-208	56.7	3127	3285	1682	1597	1516
4$_g$	2-$O_2NC_6H_4$	194-195	57.4	3127	3260	1703	1667	1518
4$_h$	2-HO-5BrC_6H_3	203-205	65.4	3119	3331	1703	1620	1510

The ^{1}H-NMR spectral data of (**4$_{a-h}$**) as shown in Table 2 were in agreement with the formation of hydrazone compounds. All of these spectra showed three *singlets* signals with the same intensity of 1H. The first two signals at 12.04-12.73 ppm and 8.37-8.95 ppm were attributed to the NH and N=CH protons, respectively; and the last one at 7.74-7.81 ppm was assigned to the proton in the isoxazole ring.

Besides that, the resonance signals of four protons of the 4-nitrophenyl moiety were also observed as two doublets at 8.37-8.40 ppm and 8.22-8.26 ppm. Protons of the benzylidene moiety were in accordance with their expected chemical shift and integral values.

Table 2. *^{1}H-NMR spectral data (δ, ppm and J, Hz) of the N-substituted hydrazides*



Comp. No.	X	H^4	H^{7,11}	H^{8,10}	H^{13}	H^{14}	H^{17}	H^{18}	H^{20}
4$_a$	H	7.75*s*	8.38*d* *J*=9,0	8.23*d* *J*=8,5	12.33*s*	8.52*s*	7.46m	7.46*m*	7.73*m*
4$_b$	4-Cl	7.77*s*	8.37*d* *J*=9,0	8.22*d* *J*=8,5	12.41*s*	8.51*s*	7.52*d* *J*=8,0	-	7.74*d* *J*=8,5
4$_c$	4-HO	7.74*s*	8.39*d* *J*=8,5	8.24*d* *J*=8,5	12.12*s*	8.41*s*	6.85*d* *J*=8,0	-	7.57*d* *J*=8,0
4$_d$	4-CH_3	7.79*s*	8.40*d* *J*=9,0	8.26*d* *J*=9,0	12.32*s*	8.50*s*	7.29*d* *J*=8,0	-	7.64*d* *J*=8,0
4$_e$	4-CH_3O	7.79*s*	8.41*d* *J*=9,0	8.26*d* *J*=8,5	12.26*s*	8.47*s*	7.04*d* *J*=9,0	-	7.69*d* *J*=9,0
4$_f$	4-$(CH_3)_2N$	7.75*s*	8.40*d* *J*=9,0	8.25*d* *J*=9,0	12.04*s*	8.37*s*	6.77*d* *J*=9,0	-	7.55*d* *J*=9,0
4$_g$	2-NO_2	7.79*s*	8.38*d* *J*=9,0	8.24*d* *J*=9,0	12,73*s*	8.95*s*	8.10*m*	7.72*dd* J_1=J_2=7,5	8.10*m*
4$_h$	2-HO-5-Br	7.81*s*	8.40*d* *J*=9,0	8.25*d* *J*=9,0	12.67*s*	8.72*s*	6.91*d* *J*=9,0	7.45*dd* J_1=9,0 J_2=3,0	7.80*d* *J*=3,0

3. Experimental

Melting points were determined in open capillaries and the values are uncorrected. IR spectra of all synthesized compounds were recorded in KBr discs on a Shimadzu FTIR 8400S spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz) using DMSO-d_6 as solvent and TMS (0.00 ppm) as an internal standard.

Synthesis of ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate (**1**): Sodium (2.3 g, 0.1 mol) was dissolved in 40 ml of anhydrous ethanol. To this ice-cooled solution, a mixture of 4-nitroacetophenone (16.50 g, 0.1 mol) and diethyl oxalate (13.4 mL, 0.1 mmol) was slowly added while stirring. The mixture was magnetic stirred at 0 °C for 1 hour and for 24 hours more at room temperature. After standing overnight, the mixture was poured into ice water while stirring and the pH of the water phase was brought to 4 with 2 N HCl. The precipitate obtained was filtered off, washed with water and crystallized from ethanol to give (**1**) as dark red crystals in 52% yield. M.p. 72-74 ^{o}C.

Synthesis of ethyl 5-(4-nitrophenyl)isoxazole-3-carboxylate (**2**): A mixture of compound (**1**) (2.65 g, 0.01 mol) and hydroxylamin hydrochloride (0.7 g, 0.01 mol) in 20 mL ethanol was refluxed for 4 hours. The reaction mixture was cooled down to room temperature and the precipitate formed was filtered off and crystallized from dioxane to give (**2**) as yellow crystals in 44% yield. M.p. 141-142 ^{o}C.

Synthesis of 5-(4-nitrophenyl)isoxazole-3-carbohydrazide (**3**): A mixture of compound (**2**) (1.31 g, 5.0 mmol) and hydrazine hydrate 50% (2.5 mL, 0.03 mol) in ethanol-dioxane was refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature and the precipitate obtained was filtered off and crystallized from dioxane to give (**3**) as yellow crystals in 47% yield. M.p. 171-172 ^{o}C.

General procedure for the synthesis of *N*-substituted hydrazides ($\mathbf{4_{a-h}}$): Equimolar quantity of hydrazide (**3**) and a definite aldehyde was refluxed in dioxane for 4 hours. The reaction mixture was cooled down to room temperature and the precipitate obtained was filtered off and crystallized from DMF to give the corresponding products.

4. Conclusion

Ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate (**1**), ethyl 5-(4-nitrophenyl)isoxazole-3-carboxylate (**2**), 5-(4-nitrophenyl)isoxazole-3-carbohydrazide (**3**) and eight novel *N*-substituted hydrazides ($\mathbf{4_{a-h}}$) have been synthesized. Structures of all new compounds were determined by their IR and ^{1}H-NMR spectra.

REFERENCES

1. Nguyen Tien Cong, Duong Minh Tu (2012), "Synthesis of the compounds containing pyrazole heterocycle starting from 4-nitroacetophenone", *Journal of Science of Ho Chi Minh University of Pedagogy*, 74, pp. 70-76.
2. Mohamed Abdel Hamid Abd, Gawaad Awas (2008), "Synthesis and Cyclization Reactions with pyrazolopyrimidinyl keto-esters and their enzymaic activity", *Acta Chimica Slovenica*, 55, pp. 492-501.
3. Kamal M. Dawood, Hassan Abdel-Gawad, Hanan A. Mohamed, Farid A. Badria (2011), "Synthesis, anti-HSV-1, and cytotoxic activities of some new pyrazole and isoxazole based heterocycles", *Medicinal Chemistry Research*, 20(4), pp. 408-420.
4. M. M. Ismail, H. M. Mohamed (2005), "Synthesis and Cyclization Reactions with Quinolinyl keto esters. II. Synthesis of novel 3-diazolylquinolinones and their enzymic activity", *Chemical Papers*, 59(2), pp. 127-138.
5. Lingaiah Nagarapu, Hanmant K. Gaikwad, Kartheeka Sarikonda, Jhansi Mateti, Rajashaker Bantu, P.S. Raghu, Krishna Madhuri Manda, Shasi Vardhan Kalvendi (2010), "Synthesis and cytotoxicity evaluation of 1-[3-(9H-carbazol-4-yloxy)-2-hydroxypropyl]-3-aryl-1H-pyrazole-5-carboxylic acid derivatives", *European Journal of Medicinal Chemistry*, 45, pp. 4720-4725.
6. Sevim Rollas, S. Guniz Kucukguzel (2007), "Biological activities of hydrazone derivatives", *Molecules*, 12, pp. 1910-1939.
7. S.K. Sahu, M. Banerjee, D. Sahu, C.C. Behera, G.C. Pradhan, Md. Afzal Azam (2008), "Synthesis, analgesic and antimicrobial activities of some novel isoxazole derivatives", *Journal of Pharmaceutical Sciences*, **7**(2), pp. 113-118.
8. B. Shafii, M. Amini, T. Akbarzadeh, A. Shafiee (2008), "Synthesis and Antitubercular Activity of N^3, N^5-Diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide", *Journal of Sciences, Islamic Republic of Iran*, 19(4), pp. 323-328.
9. Tejaskumar Shah and Vikas Desai (2007), "Synthesis and antibacterial studies of some novel isoxazoline derivatives", *J. Serb. Chem. Soc*, 72(5), pp. 443-449.
10. Juntao Zhao, Wei Tian, Jingjing Qi, Diya Lv, Yang Liu, Yan Jiang, Guoqiang Dong, Qianqian Chen, Youjun Zhou, Ju Zhu, Heling Wang, Chunquan Sheng, Jiaguo Lv (2014), "Design and synthesis of phenylisoxazole derivatives as novel human acrosin inhibitors", *Bioorganic & Medicinal Chemistry Letters*, 24, pp. 2802-2806.

(*Received: 30/3/2015; Revised: 16/5/2015; Accepted: 18/5/2015)*