New Materials, Compounds and Applications
Vol.4, No.1, 2020, pp.16-19

SOME ISATIN BASED SYNTHESIS

Yegana V. Mamedova, Aynur E. Hasanova, Shargiyya Z. Gasimova, Rahila A. Huseynova, Ibrahim G. Mamedov*

Department of Oil Chemistry and Chemical Technology, Baku State University, Baku, Azerbaijan

Abstract. It was confirmed, that by condensation of isatin with a acetophenones in ethanol and in presence of catalitic amount of diethylamine, the corresponding hydroxyoxoethyl indolinone derivatives are formed. By the reaction of hydroxyoxoethyl indolinone derivatives with the acetic and hydrochloric acids, oxoethylidene indolinones were synthesized. By the two component reaction of oxyethylidene indolonones with hidrazine hydrate the spiroisatin derivatives were obtained. Structures of all synthesized compounds confirmed by NMR spectroscopy.

Keywords: *spiro, heterocycle, isatin, indolinone, NMR.*

Corresponding Author: *Ibrahim G. Mamedov, Department of Oil Chemistry and Chemical Technology, Baku State University, Z. Khalilov, 23, AZ1148, Baku, Azerbaijan, e-mail: bsu.nmrlab@mail.ru*

Received: *05 January 2020;* ***Accepted:*** *23 February 2020;* ***Published:*** *30 April 2020.*

1. Introduction

In nature, isatin (or its derivatives) is found in plants, as component of the secretion from the parotid gland and in humans as it is a metabolic derivative of adrenaline. Isatin has also been found to be a component of coal tar (Joaquim et al., 2001). In organic chemistry isatin and its derivatives are used as intermediates for different synthesis. Isatin has several biological and pharmacological properties, such as antibacterial, antifungal, antiviral, anti-HIV, antimycobacterial, anticancer, anti-inflammatory and anticonvulsant. Beside indicated, isatin is component of many alkaloids, drugs, dyes, pesticides, and analytical reagents (Da Silva *et al.*, 2001; Batanero *et al.*, 2006; Deng *et al.*, 2001; Jahng *et al.*, 2008; Aboul-Fadl *et al.*, 2010; Gupta *et al*., 2010; Shibinskaya *et al.*, 2010; Bandekar *et al;* 2010; Amal *et al.*, 2003; Bal *et al.*, 2005).

The reaction of isatin with various compounds have been under intensive studies by many authors and due to the importance of some derivatives, for example, pyrazoline, pyrimidinethione in different biological and practcial aspects and in these research works demonstrated obtaining of new molecules (Mohamed *et al.*, 2010; Bazhykova *et al.*, 2019; Naghiyev *et al.*, 2018; Magerramov *et al.*, 2018). Isatin based various heterocyclic and carbocyclic spirooxindoles are a particular class of compounds with both spiro-carbon in the molecule. These fascinating spiranic frameworks can serve building blocks in organic synthesis for the synthesis of large ring heterocycles (Qin *et al.*, 2013).

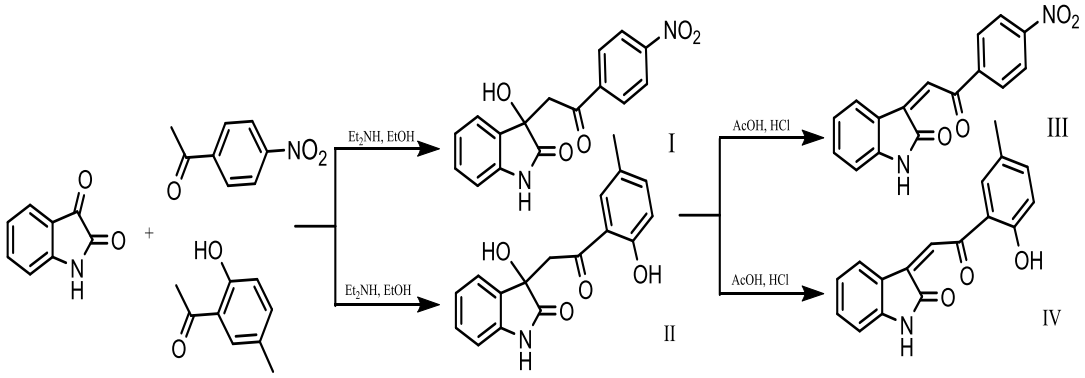
Multicomponent reactions at precense of isatin are an important class of chemical transformations for the efficient synthesis of natural products and screening compounds for the discovery of biological probes and drugs. Taking into account

above indicated, in this work some isatin based synthesis had been carried out.

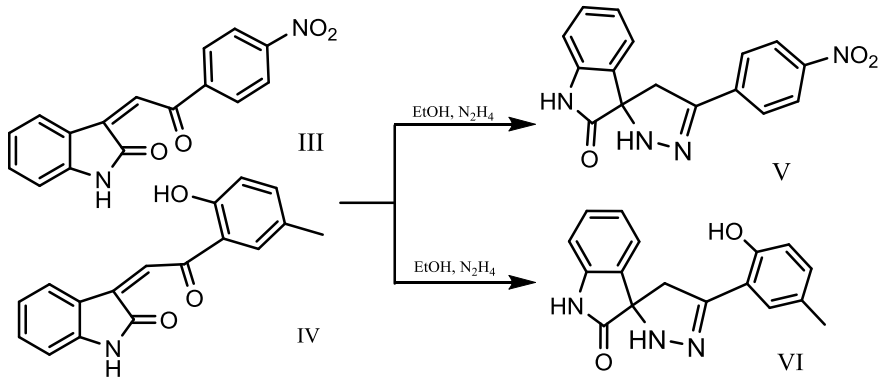
2. Results and discussions

In presented work, by the reaction of isatin with 4-nitroacetophenone (or 2-hydroxy-5-methylacetophenone) in the presence of catalytic amount of diethylamine, in ethanol solution, the corresponding 3-hydroxy-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one (I) and 3-hydroxy-3-(2-(2-hydroxy-5-methylphenyl)-2-oxoethyl)indolin-2-one (II) were formed.

(*Z*)-3-(2-(4-nitrophenyl)-2-oxoethylidene)indolin-2-one (III), (*Z*)-3-(2-(2-hydroxy-5-methylphenyl)-2-oxoethylidene)indolin-2-one (IV) were obtained by reaction of I (or II) with the acetic and hydrochloric acids.



As a result of reaction of III (or IV) with the hidrazine hydrate the corresponding spiroisatin derivatives were formed.



The structure of synthesized compounds were confirmed by using of NMR spectroscopy.

3. Experimental part. General remarks

All commercially available chemicals were obtained from Merck and Fluka (Sigma Aldrich) companies and used without further purification. Melting points were measured by Stuart SMP30 apparatus without correction. ^{1}H, ^{13}C NMR spectra were recorded on Bruker Avance 300-MHz spectrometer at 300 and 75 MHz, respectively. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the progress of reactions.

Experimental procedures:

Preparation of hydroxyoxyethyl indolinones (I and **II)**

A mixture of 0.01 mole isatin and 0.01 mole 4-nitroacetophenone (or 2-hydroxy-5-methylacetophenone) 0.01 mole dissolved in ethanol (30 mL) and diethyl amine (1 ml) was added. The mixture was allowed to stand overnight at room temperature, brown powder formed. The brown powder were filtered off, dried in air, and recrystallized from ethanol.

3-Hydroxy-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one (I):

^{1}H NMR spectrum (DMSO-d_6, δ): 4.0 and 4.2 (d, 2H, CH_2); 5.9 (s, 1H, OH); 6.7 (d, 1H, arom.); 6.9 (d, 1H, arom.); 7.1 (d, 1H, arom.); 7.2 (d, 1H, arom.); 7.9 (d, 2H, arom.); 8.1 (d, 2H, arom.); 10.5 (s, 1H, NH); ^{13}C NMR spectrum (DMSO-d_6, δ): 46.5, 79.9, 108.1, 122.5, 123.1, 124.7, 126.7, 127.5, 128.5, 141.3, 142.4, 153.3, 171.5, 201.3 (yield 73 %), m.p. = 185°C.

3-Hydroxy-3-(2-(2-hydroxy-5-methylphenyl)-2-oxoethyl)indolin-2-one (II):

^{1}H NMR spectrum (DMSO-d_6, δ): 2.3 (s, 3H, $CH_{3)}$; 4.1 and 4.3 (d, 2H, CH_2); 6.1 (s, 1H, OH); 6.7-7.3 (m, 6H, arom.); 7.5 (s, 1H, arom.); 10.5 (s, 1H, NH); 11.2 (s, 1H, OH); ^{13}C NMR spectrum (DMSO-d_6, δ): 22.5, 47.2, 78.9, 108.5, 117.5, 120.3, 122.3, 124.3, 125.7, 127.6, 129.5, 135.3, 141.3, 142.4, 154.5, 175.5, 199.7 (yield 68 %), m.p. = 170°C.

Preparation of oxoehylidene indolinones (III and **IV)**

A mixture of 0.01 mole of compound **I** (or **II**) in 20 ml ethanol, 8 ml of glacial acetic acid and 0.25 ml of concentrated hydrochloric acid was heated for 30 min at 95°C, allowed to stand overnight, the orange powder were formed. The orange powder were filtered off, dried in air, and recrystallized from ethanol.

(*Z*)-3-(2-(4-nitrophenyl)-2-oxoethylidene)indolin-2-one (III):

^{1}H NMR spectrum (DMSO-d_6, δ): 6.7 (d, 1H, arom.); 7.0 (d, 1H, arom.); 7.2 (d, 1H, arom.); 7.3 (d, 1H, arom.); 7.5 (s, 1H, =CH); 7.9 (d, 2H, arom.); 8.1 (d, 2H, arom.); 10.5 (s, 1H, NH); ^{13}C NMR spectrum (DMSO-d_6, δ): 109.1, 122.6, 123.7, 124.5, 127.1, 128.3, 129.4, 131.3, 141.2, 143.4, 149.3, 153.1, 691.5, 189.3 (yield 75 %), m.p. = 178°C

(*Z*)-3-(2-(2-hydroxy-5-methylphenyl)-2-oxoethylidene)indolin-2-one (IV):

^{1}H NMR spectrum (DMSO-d_6, δ): 2.4 (s, 3H, $CH_{3)}$; 6.9-7.4 (m, 7H, arom.); 7.6 (s, 1H, =CH); 10.5 (s, 1H, NH); 11.5 (s, 1H, OH); ^{13}C NMR spectrum (DMSO-d_6, δ): 23.1, 108.9, 118.5, 120.3, 121.1, 122.2, 123.7, 124.1, 125.6, 128.1, 129.3, 135.6, 141.3, 150.4, 161.5, 174.5, 198.8 (yield 63 %), m.p. = 162°C.

Preparation of spiroindilonones (V and **VI)**

A mixture of 0.01 mole of compound **IV** (**or V**) and hydrazine hydrate (80 %) in ethanol (30 mm) and diethyl amine (1 ml) was refluxed for 6-8 hours, then acetic acid (10 ml) was added to the cold solution. The precipitate formed after concentration was filtered and recrystallised from acetic acid ethanol.

5'-(4-Nitrophenyl)-2',4'-dihydrospiro[indole-3,3'-pyrazol]-2(*1H*)-one (V):

^{1}H NMR spectrum (DMSO-d_6, δ): 2.7 and 2.9 (d, 2H, CH_2); 7.0-7.4 (m, 4H, arom.); 7.9 (d, 2H, arom.), 8.1 (d, 2H, arom.); 9.3 (s, 1H, NH); 10.6 (s, 1H, NH); ^{13}C NMR spectrum (DMSO-d_6, δ): 44.5, 67.9, 114.1, 122.6, 126.5, 127.4, 129.4, 133.5, 141.3, 142.4, 148.3, 150.5, 151.2, 170.3 (yield 71 %), m.p. = 191°C.

5'-(2-Hydroxy-5-methylphenyl)-2',4'-dihydrospiro[indole-3,3'-pyrazol]-

2(*1H*)--one (VI):

^{1}H NMR spectrum (DMSO-d_6, δ): 2.4 (s, 3H, $CH_{3)}$; 2.7.1 and 2.9 (d, 2H, $CH_{2)}$; 6.8-7.4 (m, 6H, arom.); 7.5 (s, 1H, arom.); 9.1 (s, 1H, NH); 10.5 (s, 1H, NH); 11.7 (s, 1H, OH); ^{13}C NMR spectrum (DMSO-d_6, δ): 21.5, 45.2, 67.9, 116.5, 117.7, 121.3, 122.2, 124.1, 125.1, 127.3, 130.5, 135.3, 141.3, 149.4, 154.5, 159.5, 171.7 (yield 65 %), m.p. = 179°C.

References

Aboul-Fadl, T., Bin-Jubair, F.A.S., Aboul-Wafa, O. (2010). Schiff bases of indoline-2,3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building, *Eur. J. Med. Chem*., 45, 4578–4586.

Amal Raj, A., Raghunathan, R., Sridevi Kumari, M.R., Raman, N. (2003). Synthesis, antimicrobial and antifungal activity of a new class of spiro pyrrolidines, *J. Bioorg. Med. Chem*., 11, 407–419.

Bal, T.R., Anand, B., Yogeeswari, P., Sriram, D. (2005). Synthesis and evaluation of anti-HIV activity of isatin beta-thiosemicarbazone derivatives, *J. Bioorg. Med. Chem. Lett*. 2005, 15, 4451–4455.

Bandekar, P.P., Roopnarine, K.A., Parekh, V.J., Mitchell, T.R., Novak, M.J., Sinden, R.R.J. (2010). Antimicrobial activity of tryptanthrins in Escherichia coli, *J. Med. Chem*., 53, 3558–3565.

Batanero, B., Barba, F. (2006). Electrosynthesis of tryptanthrin, *Tetrahedron Lett*., 47, 8201–8203.

Bazhykova, K.B., Yergaliyeva, E.M., Abduali, G.A., Mukhan, D.N., Abik N.A., Otynshiyev, Eldar B. (2019). Synthesis of new heterocyclic compounds from a number of substituted tetrahydropyranones, *New Mat. Compd. Appl., 3*(1), 47-51.

Da Silva, J.F.M., Garden, S.J., Pinto, A.C.J. (2001). The chemistry of isatins: a review from 1975 to 1999, *J. Braz. Chem. Soc*., *12*(3), 273-324.

Deng, H., Konopelski, J. P. (2001). Aryllead (IV) reagents in synthesis: Formation of the C11 quaternary center of *N*-methylwelwitindolinone isothiocyanate, *J. Org. Lett*., 3, 3001-3004.

Gupta, L., Sunduru, N., Verma, A., Srivastava, S., Gupta, S., Goyal, N., Chauhan, P.M.S. (2010). Synthesis and biological evaluation of new [1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines against Leishmania donovani, *Eur. J. Med. Chem*., 45, 2359–2365.

Jahng, K.C., Kim, S.I., Kim, D.H., Seo, C.S., Son, J.K., Lee, S.H., Lee, E.S., Jahng, Y. (2008). One-pot synthesis of simple alkaloids: 2,3-polymethylene-4(3H)-quinazolinones, luotonin A, tryptanthrin, and rutaecarpine, *Chem. Pharm. Bull*., 56, 607–609.

Qin, F., Chao, G.Y. (2013). Facile synthesis of functionalized spiro[indoline-3,2'-oxiran]-2-ones by Darzens reaction, *Beilstein J. Org. Chem., 9*, 918–924.

Magerramov, A.M., Naghiyev, F.N., Mamedova, G.Z., Asadov, Kh.A., Mamedov, I.G. (2018). Synthesis of spiroindolines on the basis of isatylidene malononitrile, *Russian Journal of Organic Chemistry*., 54 (11), 1713–1715.

Mohamed, N.I.,, Mohamed, F.E., Mohamed G.A.EL. (2010). Synthesis of spiro heterocyclic compounds, *E-Journal of Chemistry*, 7 (1), 55-58.

Naghiyev, F.N., Asgarova, A.R., Shikhaliev, N.G., Mammadova, G.Z., Guseynov, E.Z., Mamedov, I.G. (2018). Synthesis of the polar double bonded compounds, *New Materials, Compounds and Applications*, *2*(3), 243-246.

Shibinskaya, M.O., Lyakhov, S.A., Mazepa, A.V., Andronati, S.A., Turov, A.V., Zholobak, N.M., Spivak, N.Y. (2010). Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6-(2-aminoethyl) 6H-indolo[2,3-b]quinoxalines, *Eur. J. Med.*

Chem., 45, 1237–1243.