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# Synthesis of Spiro Indanonepyran Compounds by Four-Component Reaction of CH-acids, Ninhydrin, and N-methyl-1-(methylthio)-2-nitroethenamine

Kochia Khudaidad[1*], Rasheedy Sheerazkhan[2], Shinwari Saifullah[3], Mirza Khil Ataullah[4], Mukhlis Sifatullah[5] , Hamdard Mohammed Nasir[6].
[*1]Chemistry Department, Faculty of Education, Faculty of Education, Nangarhar University, Jalalabad, Afghanistan.

*Corresponding author: khudaidadkochia@gmail.com

## ABSTRACT

Using primary amines, 1,1-bis(methylthio)-2-nitroethene, ninhydrin, an isatin derivative, and 1H-inden-1,3(3H)-dione as easily accessible starting materials, this study developed an effective and useful one-pot multicomponent synthetic strategy for the preparation of novel spiro-indenone-oxoindol-pyran derivatives. Without the use of a catalyst, the reaction proceeds by activating an enolizable C–H bond in ethanol under mild conditions, exhibiting a clear, eco-friendly, and operationally straightforward methodology. The method minimizes reaction steps, lowers waste production, and increases overall synthetic efficacy by simply requiring the mixing of the reaction components in a single vessel. This method has a number of important benefits, including as easy access to substrates, high product yields, mild reaction conditions, ease of process, and the use of ethanol as a reasonably environmentally friendly solvent. Additionally, the produced spiro compounds have a variety of hydrogen-bond donor and acceptor functions, such as carbonyl, amino, nitro, and oxygen-containing groups, which are useful structural features for molecular recognition and interactions with biological targets. Oxindole, indenone, and pyran moieties are uniquely incorporated into a single rigid spirocyclic framework, which improves structural variety and raises the possibility of advantageous pharmacological effects. As a result, these substances are attractive options for further biological research, such as enzyme inhibitory, antibacterial, anticancer, antioxidant, and anti-inflammatory studies. All things considered, the current study offers a straightforward, affordable, effective, and ecologically safe synthetic method for obtaining highly functionalized spiroheterocyclic molecules. This protocol's usefulness as a helpful platform for upcoming studies in heterocyclic, synthetic, and medicinal chemistry is highlighted by its operational convenience, high atom economy, excellent yields, and possible medicinal relevance.

**Keywords:** Ninhydrin, nitroketene dithioacetals, isatin, primary amines.

## INTRODUCTION

Spiro heterocycles form the core framework and constitute valuable scaffolds of numerous alkaloids and hold a distinguished position among heterocyclic compounds because of their diverse medicinal properties including antimicrobial, antitumor, antidiabetic, anticoagulant, and antiviral effects and therefore, act as highly vital and attractive targets in organic and medicinal chemistry. Also, pyrimidine is acore skeleton which exists in nature as substituted and ring-fused derivatives, including alloxan, which is known as a diabetogenic agent in some animal species, uracil, thymine, and cytosine as three essential structures of nucleic acids DNA and RNA. Pyrimidine ring is found in vitamins like thiamine, riboflavin, and folic acid. Barbitone as a pyrimidine derivative is the first barbiturate hypnotic sedative and anticonvulsant. Notable examples involve aldestrone commonly implicated in hypertension, nephrosis and toxemia of pregnancy, drospirenone implicating progestogen activity employed in oral contraceptives, spirotriprostatin, pteropodine, and isopetropodin (Prabhakar et al., 2006; Ziarani et al., 2015). Moreover, numerous spiro molecules have been purposefully designed and synthesized, with many demonstrating significant pharmacological potential (Elkalyoubi & Fayed, 2016). Spirocarboxylic and spiroheterocyclic structures are commonly present in natural products, such as sesquiterpene alkaloids,

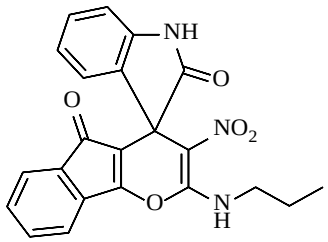
and a wide range of spiro derivatives are derivative of plants and other living organisms. Apart from their natural occurrence, these compounds serve as essential intermediates in drug synthesis (Dömling, 2006) and are present in marine products like pinaic acid, spiro (tetrahydroazepine-cyclohexene), and spirolidin, a seafood toxin. Among them, spiro heterocycles containing nitrogen and oxygen are considered especially valuable synthetic targets (Sun et al., 2001). During the last two decades, numerous inspiring, well-known drugs containing pyrimidine core have been introduced as chemotherapeutic agents with inclusive clinical applications. For example, antimicrobial agent Trimethoprim (Moffett et al., 2018). Phenobarbital which is commonly used to treat certain types of epilepsy and seizures (Catto et al., 2010). Many of these secondary metabolites are indane, indanone, indene, and indenol containing structures, such as phytoalexins, to fight infections produced by pathogens such as bacteria and fungi. The main structures have a bicyclic core in which a benzene ring is fused to a cyclopentane ring called benzocyclic compounds Mohammadi, A., Bayat, M., & Nasri, S. (2019). In addition, Kidder and Virginia have reported that the biological activity of pyrimidine changes with substitution Dömling, A. (2006).

## MATERIALS AND METHODS

Nitroketene dithioacetals, ninhydrin, various amines, isatin, and solvents were procured from Sigma Aldrich and Fluka Co. and used without further purification. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer, while NMR spectra were obtained on a Bruker DRX-300 Avance instrument using DMSO-d6 as the solvent (300 MHz for $^{1}H$ and 75.4 MHz for $^{13}C$). Chemical shifts are reported in parts per million (ppm), and coupling constants (J) are given in hertz (Hz). Mass spectra were measured on an Agilent 5975C VL MSD equipped with a Triple-Axis detector at an ionization potential of 70 eV. Elemental analyses were performed using a PerkinElmer 2004 series [II] CHN analyzer.

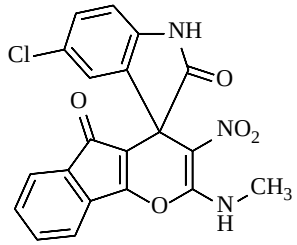
**General procedures for the formation of 123a-b:**

In a 50 mL round-bottom flask, amine (1 mmol), 1,1-bis(methylthio)-2-nitroethylene (0.165 g, 1 mmol), and ethanol (10 mL) were combined and stirred for 4 hours. Subsequently, ninhydrin (1 mmol) and isatin (1 mmol) were added to the reaction mixture, which was further stirred for the time specified in Figure 1. After completion, the mixture was cooled to room temperature, and the precipitate was collected by filtration. The crude solid was washed with 96% ethanol, dried at 150 °C, and subjected to $^{1}H$ and $^{13}C$ NMR analysis to characterize the products.




**123a**

**3-nitro-2-(propylamino)-5H-spiro[indeno[1,2-b]pyran-4,3'-indoline]-2',5-dione (123a):** Red powder, m.p.: 242-243 oC, yield 0.330 g (82%). $^{1}H$ NMR (300 MHz, DMSO): δ 0.97 (3H, t, 3JHH = 7.8 Hz, CH3), 1.71-1.76 (2H, m, CH2), 3.72-3.76 (2H, m, NCH2), 6.97-7.64 (8H, m, ArH), 10.28 (1H, br s, NH), 11.05 (1H, s, NH). 13C NMR (75.4 MHz, DMSO): δ 11.3 (CH3), 23.5 (CH2), 45.9 (NCH2), 48.5 (Cspiro), 99.6 (C-NO2), 113.6 (C=C-O), 118.1, 119.8, 120.6, 122.9, 124.9, 127.5, 129.2, 131.2, 131.9, 134.9, 136.3, 137.6 (Ar), 156.0 (O-C-N), 157.1 (C=C-O), 176.4 (NCO), 188.9 (CO); MS (EI, 70 eV): m/z (%) = 403 (0.5) [M]+, 398 (62), 356 (33), 313 (39), 271 (100), 231 (20).




**123b**

**2,5'-chloro-2-(methylamino)-3-nitro-5H-spiro[indeno[1,2-b]pyran-4,3'-indoline]-2',5-dione (123b):** Red powder, m.p.: 238-240 oC, yield 0.265 g (65%). $^{1}H$ NMR (300 MHz, DMSO): δ 3.39 (3H, d, 3JHH = 7.2 Hz, CH3), 7.11-7.63 (7H, m, ArH), 11.21-11.32 (1H, m, NH), 12.53 (1H, s, NH). 13C NMR (75.4 MHz, DMSO): δ 25.6 (CH3), 48.0 (Cspiro), 89.8 (C-NO2), 99.1 (C=C-O), 119.7, 120.2, 120.9, 127.9, 129.0, 131.5, 132.2, 134.5, 135.8, 136.3, 149.8 (Ar), 156.9 (O-C-N), 164.7 (C=C-O), 174.9 (NCO), 188.6 (CO); MS (EI, 70 eV): m/z (%) = 409 (0.3) [M]+, 376 (57), 291 (100), 265 (53), 236 (51), 201 (38), 146 (3).

## RESULTS

In this study, the target spiro-indenone-pyran compounds were synthesized through a one-pot,

four-component condensation reaction involving primary amines (81), 1,1-bis(methylthio)-2-nitroethene (17), isatin derivatives (19), and indenone (31). The reaction was carried out under mild conditions in ethanol solvent, without the use of a catalyst, and completed within 8–10 hours depending on the substituents present on the aryl isatin ring. This process afforded six-membered pyran rings, identified as 2-(alkylamino)-3-nitro-5H-spiro[indeno[1,2-b]pyran-4,3'-indoline]-2',5-diones (123), in good yields, as shown in Figure 1.

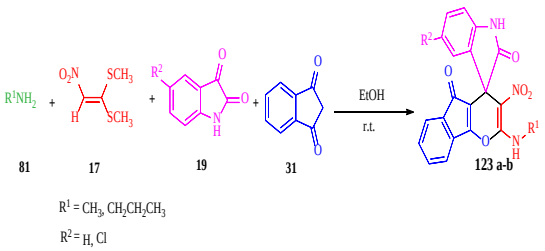



*Figure 1: Synthesis of spiro indenone oxoindole pyran products*

## DISCUSSION

Given the biological significance of pyran derivatives and indanone-containing drugs in organic synthesis, along with the diverse reactivity of ninhydrin and isatin in the construction of heterocyclic frameworks, this study reports the synthesis of a new series of compounds (23a–b) as valuable enamines (Mohammadi et al., 2019). As noted by Kohl-Landgraf et al. (2012), the reaction employs ethanol as an inexpensive, environmentally friendly, and water-soluble solvent. The condensation of primary amines (81) with 1,1-bis(methylthio)-2-nitroethene (17) affords N-methyl-1-(methylthio)-2-nitroethenamine (86), where the nitrogen and sulfur atoms enhance the electron density on carbon. Isatin, a highly reactive cyclic asymmetric ketone, plays a key role in organic synthesis as a versatile precursor for constructing diverse spiro-oxoindole scaffolds. Its carbonyl functionality readily promotes the formation of spiro compounds, making it one of the most common starting materials for spiro-oxoindole derivatives. Ninhydrin or acenaphthoquinone, which equally produce spiro-oxoindole heterocyclic arrangements, can be used in place of isatin in these combinations. Pharmacologically active materials, such as progesterone receptor ligands, anti-HIV drugs, anticancer and antimalarial substances, and enzyme inhibitors, include certain structural patterns. (Catto et al., 2010; Moffett et al., 2018).

Since the target compounds are insoluble in ethanol, column chromatography or TLC-based purification methods are not required, and the last products can be easily filtered by washing with 96% ethanol.

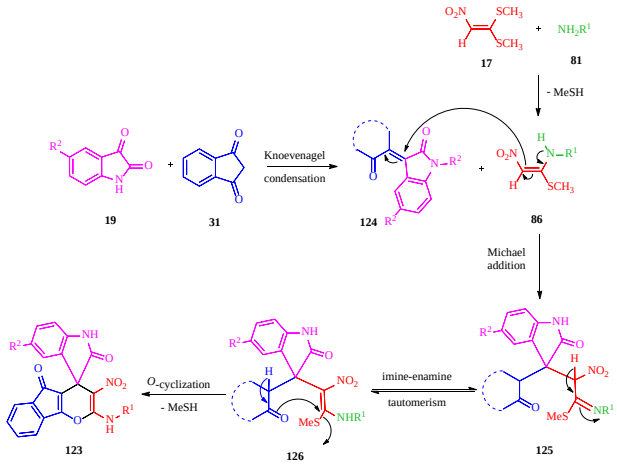
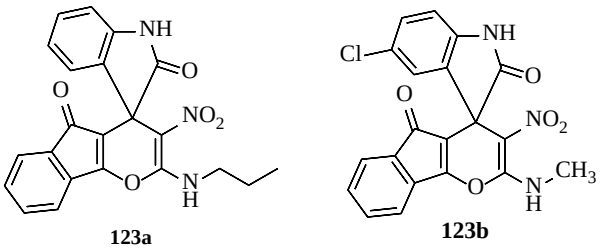



*Figure 2: Acceptable mechanism for the formation of compound 123*




## CONCLUSIONS

The synthetic utility of isatin and 3-methyl-1-phenyl-2-pyrazolin-5-one, which function as pliable intermediates and precursors for the creation of physiologically vigorous molecules, motivated this study. In this work, we describe the synthesis of spiro-indanone-pyran derivatives to produce spiro-indanone-oxindole-pyran scaffolds with possible biological and pharmacological uses, especially as prospective solutions to the increasing problem of drug resistance in pharmaceutical research. Isatin is significant since it is found in numerous biologically important compounds and is widely used in medicinal chemistry. The specified reactions are simple and can be performed by simply combining the initial ingredients with ethanol. Mild reaction conditions, a simple checkup procedure, the creation of highly functionalized, drug-like molecules, and the ability to continue without the requirement for a catalyst are just a few benefits of this synthetic technique.

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**Conflict of interest**

There are no conflicts of interest in the research, manuscript, or submission to the journal, as stated by any author.

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