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CONDENSATION REACTIONS OF 3-PHENACYLIDENE-2-INDOLINONE WITH 1,3-DINUCLEOPHILES SUCH AS GUANIDIN HYDROCHLORIDE AND HYDRAZINE HYDRATE TO PREPARE SPIRO COMPOUNDS

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Abstract- The condensation reaction of guanidine hydrochloride and hydrazine hydrate with 3-phenacylidene-2-indolinone, is extended to the formation of spiro[indole-3,4'-pyrimidin]-2(1*H*)-one and spiro[indol-3,3′-pyrazol]-2(1*H*)-one. These reactions occur in ethanol at reflux, in presence of sodium acetate. This method provides a new route to produce spiro pyrimidine and spiro pyrazoline in good yields.

KEYWORDS
Guanidine hydrochloride, hydrazine hydrate, 3-phenacylidene-2-indolinone, spiro pyrimidine and spiro pyrazoline.

INTRODUCTION

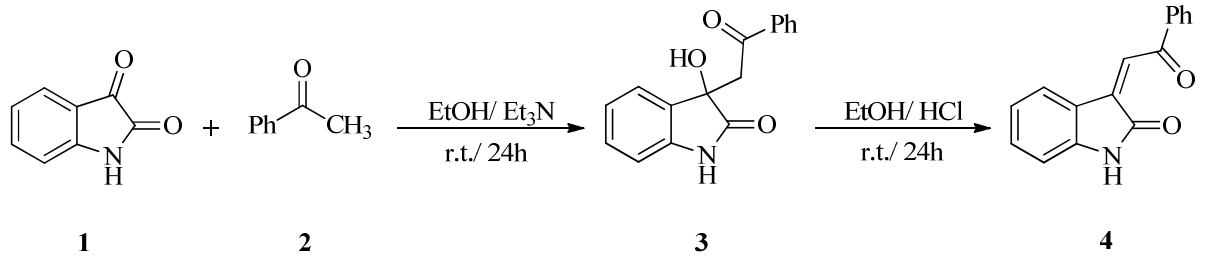
Heterocyclic molecules are of biological interest due to their potential physical and chemical properties.[I] Among these the pyrimidine derivatives have occupied an important position in natural and synthetic organic chemistry, because of their pharmacological properties including antiviral, antitumor, antibacterial, antihypertensive etc.[II-IV] Thus, pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties.[V] Moreover, some bioactive alkaloids such as batzelladine B, containing the dihydropyrimidine unit, have been isolated from marine sources and show anti-HIV activity.[VI] Also, pyrazolines can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular, antidepressant and insecticidal agents.[VII-IX] In addition, pyrazolines have played a critical part in the development of theory in heterocyclic chemistry and also used widely in organic synthesis.[X] After the pioneering work of Fischer and Knovenagel in the late nineteenth century,[XI] the reaction of α,β-unsaturated aldehydes and ketones with hydrazines became one of the most popular methods for the preparation of 2-pyrazolines.[XII-XIII]

Spirocyclic systems containing one carbon atom common to two rings are structurally interesting.[XIV] The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[XV] Spiro comp-pouunds represent an important class of naturally occurring substances characteristic by their highly pronounced biological properties.[XVI] Consequently, many synthetic methodologies have been developed for constructing these spirocycles, most of which were based on cyclo- addition

or condensation reactions.[XVII] In continuing our previous works on preparation hetrocyclic compounds by using condensation reactions of electrophiles with 1,3-dinucleo- philes,[XVIII-XX] we now wish to describe synthesis of spiro pyrimidin and pyrazolin derivativesin the presence of base catalysts.

RESULTS DISCUSSION

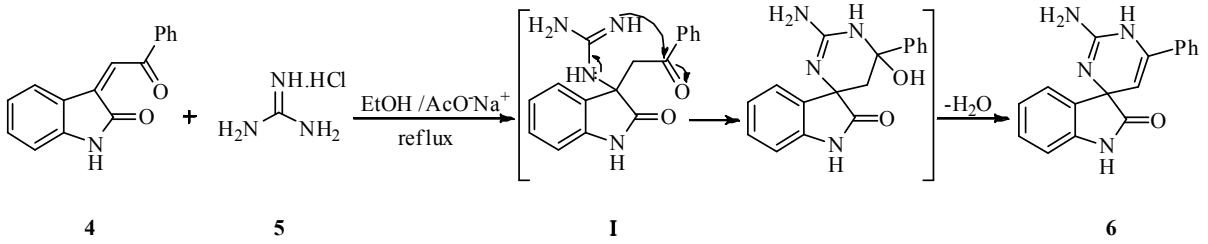
The reaction of isatin **1** with acetophenone **2** was carried out in the presence of triethyl amine as a basic catalyst giving rise to 3-hydroxy-3-phenacyl oxindole **3** in a good yield. Dehydration of this compound by dilute alcoholic hydrochloric acid gave 3-phenacylidene-2-indolinone **4** in quantitative yield **(Scheme 1).**



1 **2** **3** **4**

Scheme 1

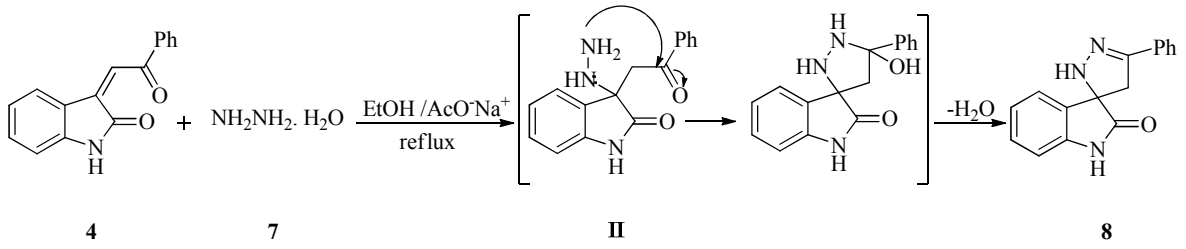
In order to develop further the methods for the synthesis of analogous spiro compounds, the first step, we have investigated the Michael addition of guanidine hydrochloride **5** to the 3-phenacylidene-2-indolinone **4** in presence of sodium acetate as a base at reflux in ethanol led to 2'-amino-6'-phenyl-1'*H*-spiro[indole-3,4'-pyrimidin]-2(1*H*)-one **6** in a good yield **(Scheme 2).** This product was prepared by intramolecular nucleophilic addition of amino group intermediate (**I**) on carbonyl followed by the loss of water.



4 **5** **I** **6**

Scheme 2

Accordingly the reaction of hydrazine hydrate **7** with 3-phenacylidene-2-indolinone **4**, was carried out in presence of sodium acetate released to spiropyrazoline **8**. The formation of this compound can be considered to proceed by an initial Michael addition of a hydrazine hydrate **7**, to the substituted 3-phenacylidene-2-indolinone **4**, afforded the intermediate (**II**). The last step is intramolecular nucleophilic addition amino group of intermediate (**II**) on carbonyl group, along with elimination of water from intermediate (**II**) and then formation of 5′-phenyl-2′,4′-dihydro-spiro[indol-3,3′-pyrazol]-2(1*H*)-one **8 (Scheme 3).**



4 **7** **II** **8**

Scheme 3

CONCLUSIONS

In summary, we have developed a simple method for the preparation of spiro heterocyclic compounds via reaction of 3-phenacylidene-2-indolinone with guanidine hydrochloride or hydrazine hydrate. The products were obtained with up to 80% yields in ethanol at reflux. Synthesis of spiro pyrimidine or pyrazoline derivatives are very important because these heterocyclic compounds have occupied an important position in natural and synthetic organic chemistry, due mainly to their wide range of biological activities.

EXPERIMENTAL SECTION

General Procedures. Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Avance III 400 Bruker spectrometer at 400 and 100 MHz, respectively.3-phenacylidene-2-indolinone **4** was prepared according to a literature procedure.[XXI]

General procedure for the preparation of spiro compounds 6 and 8:

A mixture of 3-phenacylidene-2-indolinone **4** (2 mmol) guanidine hydrochloride **5** (2 mmol) or hydrazine hydrate **7** (2 mmol) and sodium acetate (0.2 g) in ethanol (20 mL) was refluxed with stirring for 12 h. When the reaction was completed as indicated by TLC, the crude products **6** and **8** were precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized with ethanol to get pure product.

2'-Amino-6'-phenyl-1'*H*-spiro-[indole-3,4'-pyrimidin]-2-(1*H*)-one (6): Orange crystals; yield: 80%. mp=180 ˚C. IR (KBr, νmax/cm^{-1}): 3478, 3344, 3304 (NH, NH_2), 3100 (NH-C=O), 1711 (C=O), 1681 (C=N), 1542 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): 10.84 (s, 1H, NH-C=O), 8.05-6.94 (m, 9H, Ar), 7.37 (s,1H, NH), 6.87 (s, 1H, H5'), 6.39 (s, 2H, NH_2). ^{13}C NMR (100MHz, DMSO-d_6): 168.58 (C=O), 158.27 (C=N), 145.43, 137.47, 136.88, 134.51, 133.37, 129.60, 129.00, 127.13, 126.36, 122.17, 120.37, 110.88, 64.20 (spiro carbon).

5′-Phenyl-2′,4′-dihydrospiro[indol-3,3′-pyrazol]-2(1*H*)-one (8): Colorless crystals; yield: 89%; mp=200-202 ˚C. IR (KBr, νmax/cm^{-1}): 3479 (NH), 3272 (NH), 1701 (C=O), 1613 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 9.06 (s, 1H, NH-C=O), 8.02-6.90 (m, 9H, Ar), 6.20 (s, 1H, NH), 3.72 (s, 2H, CH_2). ^{13}C NMR (100MHz, DMSO-d_6): 180.30 (C=O), 151.10 (C=N), 140.41,

132.53, 132.27, 130.22, 129.64, 129.12, 129.01, 128.45, 128.28, 126.78, 123.63, 70.26 (spiro carbon), 44.12 (CH_2).

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