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GREENER PROTOCOL FOR THE SYNTHESIS OF SPIRO INDENO [1, 2-B]QUINOXALINES

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Abstract:A simple, efficient, and environmentally friendly synthesis of spiroindeno[1,2-b]quinoxalines has been achieved using basic bleaching earth as a naturally occurring cheap and ecofriendly catalyst. The low cost, easy availability of the catalyst, and simple reaction conditions are the important features of the present method.

Keywords: Quinoxalines, Spiro indeno, Ecofriendly

Introduction:

Multicomponent reactions (MCRs) offer unmatched opportunities for the expeditious increase of complexity and diversity in synthetic outcomes. The strategy offers noteworthy advantages over classical stepwise approaches, allowing the formation of several bonds and the construction of complex molecular scaffolds from simple precursors in a single synthetic operation without the need for the isolation of intermediates [1]. MCRs, particularly those performed in aqueous medium, have become increasingly useful tools for the synthesis of chemically and biologically important molecules because of their environmentally friendly, atom economic and green characteristics [2,3]. Important pharmaceuticals often possess heterocyclic scaffolds as their building blocks. Since pyrazoles and its derivatives acquire various biological activities, such as anti-inflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial, and antifilarial agents [4–7], the development of new methods for the synthesis of pyrazole derivatives, which will yield subsets of heterocycles having the potentiality to serve as templates for new biologically active compounds, is of great importance.

Experimental section:

General procedure for the synthesis of pyrazolone derivatives (3)

A solution containing 1,3-ketoester (1.0 mmole) and hydrazines (1.1 mmole) in ethanol (5 ml) was stirred at room temperature for 5 min. After the completion of reaction, the solution was diluted with ethanol (10 ml) and stirred in an ice bath for 30 min. The obtained solid was filtrated, washed with cold ethanol and recrystallized from ethanol to obtain pure pyrazolones.

General procedure for the synthesis of 11H-indeno [1, 2-b] quinoxalin-11-one derivatives (6)

A solution containing 1,2-phenylenediamines (1.0 mmole) and ninhydrine (1 mmole) in ethanol (5 ml) was stirred at 80^{o}C for 3h. After the completion of reaction, the solution was diluted with ethanol (10 ml) and stirred in an ice bath for 30 min. The resulting solid was filtrated, washed with cold ethanol, and recrystallized from ethanol to obtain pure 11H-indeno[1,2-b]quinoxalin-11-ones.

General procedure for the synthesis of spiroindeno[1,2- b]quinoxalines (8a–f)

To a neat solution containing 11H-indeno [1,2-b]qui- noxalin-11-one **6** (1 mmol), pyrazolone 3 (1 mmol), and malononitrile (1 mmol), 100mg of bleaching earth in ethanol (10 ml) was added. The reaction mixture was heated at 80 ^{o}C for 3h. After completion of the reaction as indicated by TLC, the reaction mass was extracted with dichloromethane, extract washed with brine solution, evaporation of solvent afford the pure product 8.

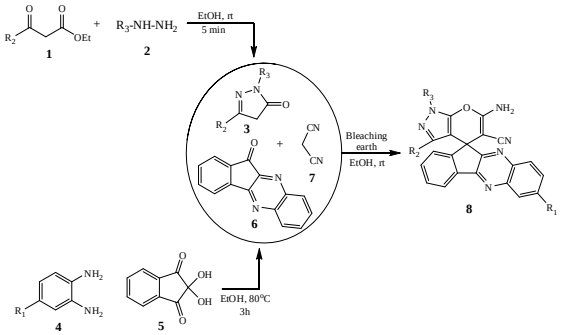
60-Amino-30-methyl-10H-spiro[indeno[1,2-b] quinoxaline-11, 40-pyrano[2,3-c]pyrazole]-50-carbonitrile

(8a)*:* Light green powder; MP 263–266 ^{o}C; IR (KBr, cm^{-1}): 3450, 3274, 3250, 3112, 2976, 2191, 1637, 1607, 1465, 1401; ^{1}H NMR

(250 MHz, DMSO-d_6): □H (ppm) 1.12 (3H, s, CH_3), 7.45–8.13 (10H, m, H–Ar and NH_2), 12.51 (1H, s, NH).

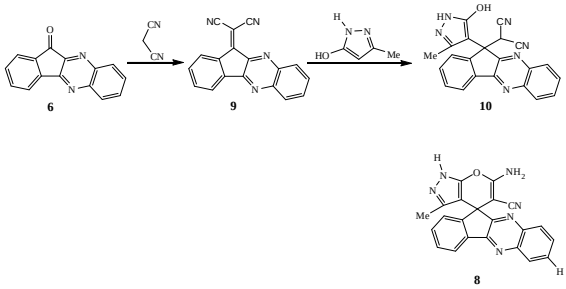
Results and discussion:

In continuation of our interest in the synthesis of heterocyclic compounds based on in MCRs [8], we developed herein the synthesis of spiroindeno[1,2- b] quinoxalines 8 *via* a three-component condensation reaction of 11H-indeno[1,2-b]quinoxalin-11-one 6, pyrazolone 3 and malononitrile 7 in ethanol as green reaction medium by using basic bleaching earth catalyst (p^H-9.2) at 80 ^oC in high yield (Scheme 1). It should be noted that pyrazolone 3 was prepared by the condensation reaction of □-keto ester 1 and hydrazine 2 in ethanol after 5 min [9]. Also, 11H-indeno[1,2-b]quinoxalin-11-ones 6 was synthesized according to a method reported in literature [10] by means of a reaction between 1,2-phenylenediamines 4 and ninhydrine 5 (Scheme 1). In an initial endeavor, we first investigated the condensation of 11H-indeno [1,2-b]quinoxalin-11-one 6, 3-methyl-1H-pyrazol-5-ol 3 and malononitrile 7 under various conditions (Table 1). We first studied the reaction rate in different solvents by measuring the isolated yield using identical amounts of reactants in the presence of 100mg of basic bleaching earth catalyst for a fixed reaction time of 3 h at 80^{o}C (Table 1, entries 1–8). The desired product was obtained in polar solvents, such as water, ethanol, methanol, and acetonitrile, but ethanol can afford the product in good yield even better than other solvents (Table 1, entry 1). The desired product was not obtained in non-polar solvents, such as dichloromethane, toluene (Table 1, entries 4,5). Interestingly, the corresponding product was obtained in high yield when the reaction was performed in pure ethanol (entry 1). Next, we studied the model reaction in ethanol at different temperatures (entry 2 and entries 6-8). The reaction rate increased as the temperature was raised. The maximum yield (90%) was obtained at 80^{o}C in a reaction time of 3 h (entry 2).



Scheme1. Synthesis of spiroindeno[1,2-b]quinoxalines

With the optimized conditions we have synthesized some spiroindeno[1,2-b] quinoxaline (8a-d) derivatives. The results are summarized in Table 2. The structures of the synthesized compounds were established by IR, ^{1}H NMR and Mass spectroscopic methods. In all the cases, good yields were obtained. Mechanistically, it is plausible that the reaction involves the initial formation of the Michael acceptor 9 by the Knoevenagel condensation of the 11H-indeno[1,2-b]quinoxalin-11-one 6 with malononitrile 7. The active methylene of pyrazolone3 undergoes Michael addition with intermediate 9 to give the intermediate 10, which then undergoes a Thorpe–Ziegler intramolecular cyclization followed by a 1,3-sigmatropic shift into spiroindeno[1,2-b]quinoxalines 8. To clarify the proposed mechanism, the Michael acceptor 9 was synthesized by Knoevenagel condensation of the 11H-indeno [1,2- b]quinoxalin-11-one 6 with malononitrile 4. Subsequently, the reaction of compound 9 with pyrazolone 3 afforded the corresponding spiroindeno[1,2-b]quinoxaline 8 (Scheme 2).

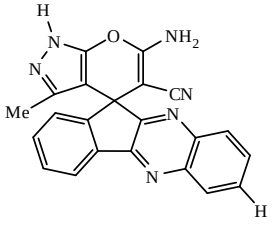
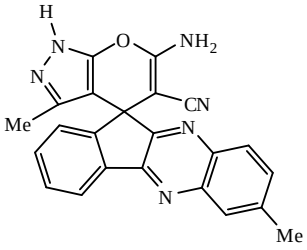
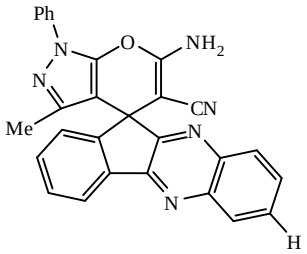
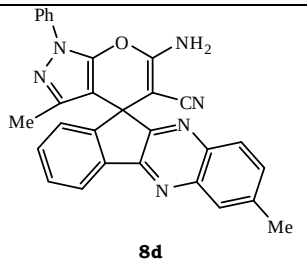


Scheme 2. Proposed mechanism

Table 1. Optimization of reaction conditions

Entry	Solvent	Temp (°C)	Yield (%)
1	Ethanol	80	90
2	Methanol	60	78
3	Acetonitrile	80	85
4	Toluene	80	Trace
5	Dichloromethane	60	Trace
6	Ethanol	25	45
7	Ethanol	50	70
8	Ethanol	100	90

Table 2. Synthesis of substituted spiroindeno[1,2-b]quinoxalines

Entry	Product	Yield (%)
1	 **8a**	90
2	 **8b**	88
3	 **8c**	85
4	 **8d**	82

Conclusion:

In conclusion, we have developed a simple and efficient approach for the synthesis of spiroindeno[1,2-b]quinoxaline derivatives from 11H-indeno[1, 2-b]quinoxalin-11-one, pyrazolone and malononitrile in ethanol by using basic bleaching earth in high yield. Simple reaction conditions, environmentally benign catalyst, high yields and easy product isolation areb the significant characteristics of the present method.

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