AN EFFICIENT METHOD FOR ONE-POT SYNTHESIS OF BISPYRAZOLYL METHANE DERIVATIVES

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Abstract : An effective approach has been developed for the synthesis of bispyrazolyl methane derivatives by the reaction of aromatic aldehydes, phenyl hydrazine and ethyl acetoacetate in presence of phenylboronic acid as catalyst at room temperature. The mild reaction condition and excellent yield are the notable features of this method.

Keywords: Bispyrazolyl methane, one-pot synthesis, phenylboronic acid, ethyl acetoacetate, phenyl hydrazine

I. INTRODUCTION

Combinatorial chemistry is widely helpful for the sighting of novel biologically active compounds [1]. In this scaffold, multicomponent reactions (MCRs) are an efficient tool in the modern drug discovery process in terms of lead finding and optimization, but the variety of easily accessible and functionalized small heterocycles is rather limited [2]. These strategies have emerged as flexible approaches in organic synthesis due to their advantages over the conventional multistep synthesis. In addition, they are eco-friendly, have superior atom economy, require less time and low-cost purification processes and without protection-deprotection steps. Therefore, the design and development of novel, efficient and green MCRs focused on a target product is one of the most important challenges in organic synthesis.

Pyrazole and its derivatives have drawn considerable attention of the researchers in the past few decades owing to their high therapeutic values. Some of the drugs, possessing pyrazole as basic moiety, like celecoxib, deracoxib, etoricoxiband atorivodine are already booming in the market. As pyrazole derivatives do not exist in nature, probably, due to the difficulty in the construction of N-N bond by living organisms, their availability depends on the synthetic methods. Pyrazole derivatives proved to possess different bioactivities such as, anti-inflammatory [3], p56 Lck inhibitor [4], anticancer [5], antidepressant [6], corticotrophin releasing factor-1 (CRF-1) receptor antagonist [7], antimalarial [8], GABA inhibitor with selectivity towards insect versus mammalian receptors [9], antifungal [10], antibacterial [11] and NPY5 antagonist [12]. Nowadays, the pyrazolone derivatives paid much attention for their various biological activities such as antitumor [13], selective COX-2 inhibitor [14], cytokine inhibitors [15], agrochemicals, dyes and pigments. Moreover, they are capable of prototropic tautomerism [16]. Compounds that contain two pyrazolone rings can be used as extractant for some metal ions [17] and ligands [18]. 2,4-Dihydro-3H-pyrazol-3-one derivatives including 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) are being used as gastric secretion stimulatory [19], antidepressant [20], antibacterial [21] and antifilarial agents [22]. Moreover, the corresponding 4, 4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) are applied as fungicides [23], pesticides [24], insecticides [25] and dyestuffs [26].

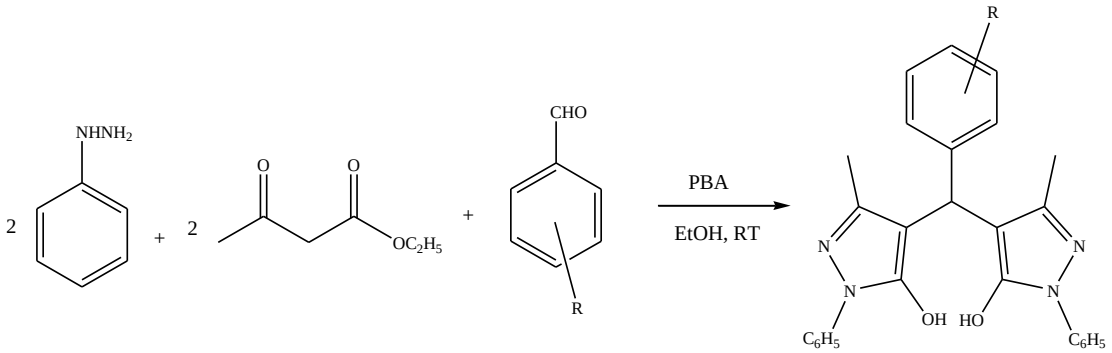
Recently in synthetic organic chemistry, boronic acid has been effectively used as catalyst in several organic transformations as an efficient Lewis acid catalyst [27-34]. Hence in continuation on the application of eco-friendly materials as catalyst and atom economic method for developing of new synthetic methodology, herein we describe a one-pot three-component synthesis of bispyrazolyl methanes starting from aromatic aldehyde, phenyl hydrazine and ethyl acetoacetate using phenylboronic acid as an efficient catalyst under ambient condition.

II. EXPERIMENTAL SECTION

All solvents were utilized as commercial anhydrous grade without further purification. Melting points were determined in open capillary tube and are uncorrected.

Typical procedure for synthesis of bispyrazolyl methane derivatives (4a-e):

A mixture of phenyl hydrazine (2 mmol), ethyl acetoacetate (2 mmol) was stirred in ethanol (10 ml) in presence of catalytic amount of phenylboronic acid (0.2 mmol) for 10 min. Then the aromatic aldehyde (1 mmol) was added to reaction mixture and stirred at room temperature for the required time as mentioned in Table 1. Progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and then obtained precipitate was filtered and dried and melting points were recorded.



1 **2** **3a-e** **4a-e**

Scheme 1

III. RESULTS AND DISCUSSION

In literature there are some methods for the synthesis of bispyrazolyl methanes derivatives, but in all, we have to make selection for either excellent yields or good reaction conditions. Most of the methods offered product in good yield but they make use of expensive catalyst or harsh reaction condition like use of very toxic solvent and long reaction time. There are also methods in which reaction conditions and catalyst cost are taken care of, but yields very poor or no product.

In search of efficient method for synthesis of bispyrazolyl methane derivatives we used phenylboronic acid which is non toxic and very effective catalyst. Reactions need no special set up.

A mixture of aromatic aldehyde, phenyl hydrazine and ethyl acetoacetate were taken in ethanol solvent with phenylboronic acid as a catalyst. Results obtained are given in table-1. In results, phenylboronic acid is demonstrated to be mild and efficient catalyst for synthesis of bispyrazolyl methane derivatives.

Table1: Synthesis of bispyrazolyl methane derivatives

Entry	R	Product	Reaction time. (hrs)	M. P. (ºC)	Yield (%)
A	H	**4a**	5.00	171	84
B	4-Cl	**4b**	4.00	214	89
C	4-NO_2	**4c**	4.00	223	90
D	4-OH	**4d**	4.30	153	87
E	3-OCH_3, 4-OH	**4e**	5 .00	203	88

IV. CONCLUSION:

In conclusion, our results show that Phenylboronic acid is an efficient catalyst for the excellent yield of corresponding bispyrazolyl methane derivatives. This protocol offer several advantages such as high yield, short reaction time and mild reaction conditions.

V. ACKNOWLEDGEMENT

We are grateful to Dr. S. S. Kadam, Principal and Dr. B. C. Khade, Head, Dnyanopasak College, Parbhani for offering required facilities to research work.

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