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Zinc Triflate induced synthesis of bisPyrazole derivatives

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Abstract: In the present protocol Zinc Triflate catalyst was utilized for the one-pot two-component reaction of various substituted Aromatic Aldehydes, with pyrazolone at 80oC temperature within 3-4 hours of reaction time in ethanol: water solvent system. The titled method has many major advantages like milder reaction conditions with easy operation simplicity, higher yields, by using a less toxic and lower costlier catalyst.

Keywords: Zinc Triflate, Substituted aromatic aldehydes, Pyrazolones, Ethanol, Water.

Introduction

There are many focussed approach towards synthesizing and developing novel protocols and greener strategies [1] towards potent and pharmaceutically valued drug candidates [2]. Although the literature is full of newer reported methods of synthesis towards bispyrazoles & its derivatives. Some methods offer advantages over reported ones while some approaches suffer from disadvantages like a costlier and toxic catalyst, lesser yield of product with isolation operational problems, higher temperature usability incorporating harsh reaction conditions. Thus owing to all these advantages along with disadvantages there is hope and scope for the utility of a new catalytic system that can offer novel applicability to overcome all the problems. Again nowadays due to the concern of environmental pollution [3-7]., there is a constant need for a greener synthetic protocol to save our mother earth by every single step that we put by any means.

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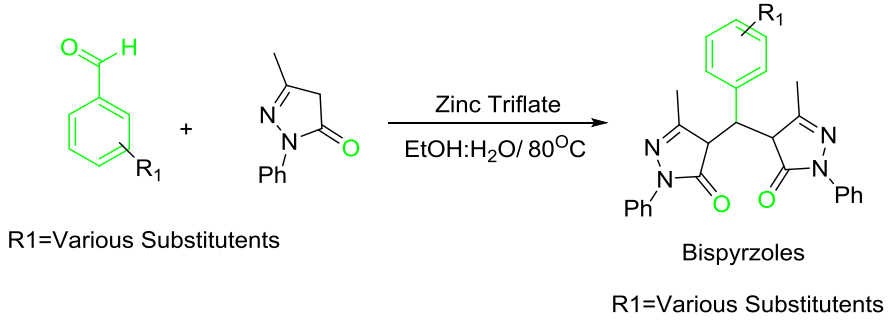
Anyhow, it is well known that the synthesis of heterocyclic compounds containing heteroatom possesses numerous values in heterocyclic chemistry and drug chemistry due to its medicinal, industrial, pharmaceutical properties in the current era. Further, literature survey has also revealed that compounds containing nitrogen-containing pyrazole, bispyrazole, and allied heterocyclic systems Figure **1**, have received surmount attention due to its worth mentioning diverse biological activities including bactericides, fungicides, anti-inflammatory, analgesic, gastric secretion stimulators', anti-filarial agents, pesticides, dyestuffs, chelating and extracting reagents for metal ions, antipyretic activities and inhibitory activity against monoamine oxidase for the treatment of Parkinson's and Alzheimer's disease [8-10]. Again, it is worth taking note that, a careful literature survey reveals that the said heterocyclic drug candidates have potential applications but to date, a handful of synthetic approaches have been reported across the globe. The reported methods include the use of piperidine in ethanolic solution, the tandem Knoevenagel–Michael reaction in benzene solutions,

use of sodium dodecyl sulphate in aqueous media, silica-bonded S-sulfonic acid, PEG-SO3H, PEG-400 at 110 OC, CAN, electro catalytic synthesis [11-15] etc. Although the reported methods have their own merits but, these protocols have some limitations like the use of toxic catalysts with toxic side products, costlier catalyst, tedious operational procedures, longer reaction time with low to the moderate yield of the products that too at the higher reaction temperature (Scheme **1**).



Scheme 1: Synthesis of Bispyrazoles

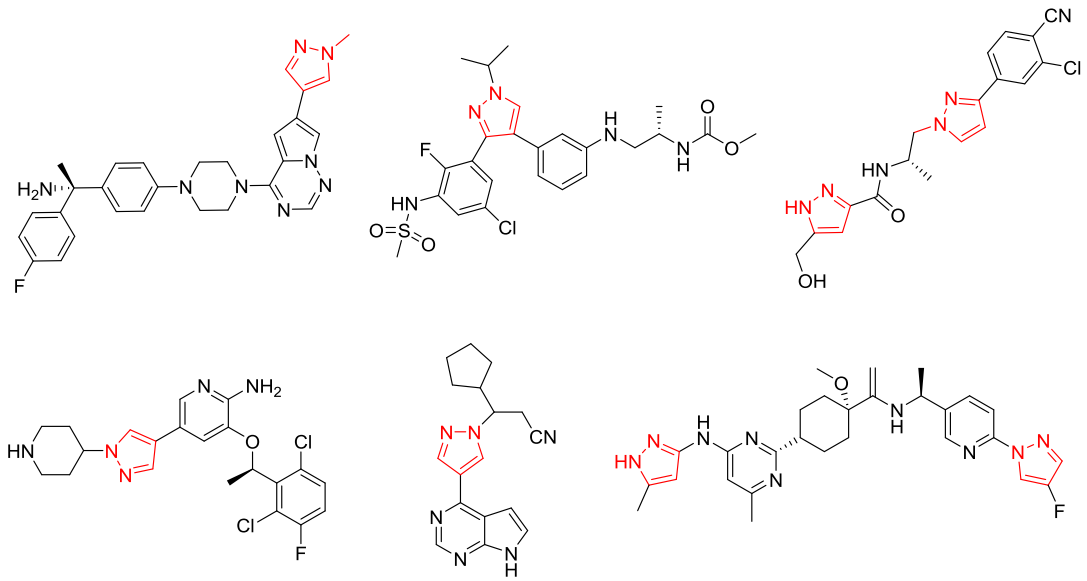


Figure 1: Representative examples of drug molecules containing Pyrazole moieties

All these compiled demerits motivated us to take up the synthesis of bispyrazoles utilizing a catalyst that can bypass all these demerits nicely and we are successful the same with the utilization of Zinc Triflate as a newer and novel catalyst for carrying out the organic transformation of 4,4,9-(arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)s. To the best of our knowledge Zinc triflate [16-18] has not been utilized for its catalytic activity for the synthesis of said heterocyclic compound.

Results and discussion

To formulate and standardize the reaction conditions we have performed various set of optimization protocols on different parameters that include the amount of Zinc Triflate (10 % mole) utilized, time of reaction, the solvent used and temperature. Further, the set the reaction condition on a primary basis, a model reaction of between benzaldehyde (1 mmol) with Pyrazolone (2.0 mmol) was selected first. At the start when the reaction was performed without the aid of any catalyst in water, ethanol as a starting solvent we yielded trace amount of product but when we recruited our catalyst in 10 mole % of Zinc triflate catalyst we able to receive around 68 % & 65 % yield of the product respectively at room temperature taking the reaction time of around 10 hours in both solvents (Table **1**). Owing to the solid nature of the starting

material we have not performed the reaction under solvent-free conditions as we thought heating the starting material at a higher temperature may decompose the starting products or form a complex product. We have studied various solvent systems and after studying various reactions on the different solvent systems, Dichloromethane, Chloroform, water, ethanol, and ethanol: water system, but we are happy to note that we ended the reaction giving the product in 41%, 44%, 68%, 65%, and 88 % yield respectively, proving that ethanol: water (1:1) system will be more efficient to yield the product in 8 hrs at room temperature. Further, we have checked and examined the effect of mole % Zinc Triflate catalyst in aforesaid reaction protocol and as expected we ended the reaction yielding trace, 52 %, 90 %, 91 % of the product when 0%, 5 %, 10 %, and 20 % of catalyst was utilized (Table **2**). Further, we have carried out standardization of reaction on the temperature of the reaction and as per expectation at room temperature, 50OC, 80OC, and 100OC it yielded 68%, 90% and 91% of the product within 8 hrs. Thus from the above observation, it is clear that a 10% mole of the catalyst was sufficient to carry out the reaction at 80OC utilizing ethanol: water as a solvent system. Finally, to set reaction time, we have performed the reaction under the set reaction conditions for 30 min, 120 min, 180 min, and 240 min. To our surprise, the reaction was good enough to give the expected product in 240 minutes of reaction time in 90% yield. Extended reaction time doesn't yield a major amount of product which indicated that to obtain the maximum amount of product yield only 240 minutes of reaction time was sufficient (Table **3**).

Table 1. Screening of solvents (Room temperature).

Entry	**Solvent**	**Time**	**Yield**
1	No Solvent	10 Hrs	No reaction
2	No Catalyst	12 Hrs	Trace
3	Dichloromethane	8 Hrs	41 %
4	$CHCl_3$	8 Hrs	44 %
5	Water	8 Hrs	68 %
6	Ethanol	3-4 Hrs	65%
7	Ethanol: Water	8 Hrs	88%

Table 2. Mole % of Catalyst.

Entry	**Catalyst**	**Time**	**Yield**
1	No Catalyst	20 Hrs	Trace
2	5 %	6-8 Hrs	52%
3	10%	3-4 Hrs	90 %
4	20%	3-4 Hrs	91 %

Table 3. Screening of temperature in solvent system.

Entry	**Solvent**	**Time**	**Yield**
1	Ethanol: Water	10 Hrs, RT	88%
2	Ethanol: Water	3-4 Hrs/ $50^{O}C$	68%
3	Ethanol: Water	3-4 Hrs/ $80^{O}C$	90%

4	Ethanol: Water	3-4 Hrs/ 100^{O}C	91%

Conclusion

Thus to conclude, we are successful in synthesizing, and developing a newer approach towards performing a two component synthesis of pharmaceutically valued bispyrazoles and its derivatives by the recruitment of Zinc Triflate. Further we are also successful in exploring catalytic activity of Zinc Triflate which is a cheap, mild, environmental benign, nontoxic catalyst. Further the present protocol has many advantages over the existing approaches that include mainly use of cheap and non-toxic catalyst, operational simplicity, higher yield of products with shorter reaction time in ethanol: water system.

Experimental

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were obtained on an FT-IR Hartman- Bomen spectrophotometer as KBr disks, or neat. The ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates. All products are identified by their spectral characterization and also compared with the reported ones.

General procedure

A mixture of various aldehyde (1 mmol), pyrazolones (2 mmol) was taken in a round bottom flask which was dissolved in ethanol: water (10 ml). After adding 10 mole % of Zinc Triflate catalyst, the reaction was vigorously stirred at room temperature for 10 min. Further, the reaction was subjected to heating in an ethanol: water system at 80 °C for 3-4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. Further, it was filtered off and washed with cold H_2O (3×10 mL). Finally, the crude product was recrystallized from hot ethanol to give the pure product in 84 to 94 % yield which is characterized by comparing their physical and spectral data with those of the authentic samples (Table **4**).

Table 4. Synthesis of various bispyrazole derivatives.

Entry	Compound	Ar	Time (Hrs)	Yield (%)	M.P. (°C)
1	1a	Ph	**4**	**90**	170-172[11]
2	1b	3-NO_2-Ph	**3**	**95**	233-235[11]
3	1c	4-Me-Ph	**3**	**94**	202-204[11]
4	1d	4-Cl-Ph	**3**	**94**	215-217[11]
5	1e	4-MeO-Ph	**2.5**	**95**	173-175[11]
6	1f	4-OH-Ph	**3.5**	**95**	151-153[11]
7	1g	3,4-OMe-Ph	**4**	**84**	202-204[11]
8	1h	3-Br-Ph	**3**	**90**	143-145[11]

4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) **(1a):**

M.P.=170-172 ºC; ^{1}H NMR (Avance Neo, DMSO-d6, 500 MHz): δ (ppm) 2.33 (s, 6H, CH3), 4.87 (s, 1H), 7.08 (m, 1H), 7.19 (m, 6H), 7.43 (t, J = 7.5 Hz, 4H), 7.59 (d, J = 7.8 Hz, 4H); ^{13}C NMR (Avance Neo, DMSO-d6, 500 MHz): δ (ppm) 12.0, 33.4, 121.5, 126.1, 126.9, 127.7, 128.3, 129.2, 137.4, 143, 146.2, ESI/MS= 436.

4, 4'-((3-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)(1b):

M.P.= 233-235ºC; ^{1}H NMR (Avance Neo, DMSO-d6, 500 MHz): δ: 2.26 (s, 3H), 2.50 (s, 3H), 5.15(s,1 H), 7.24-7.27 (m, 2H), 7.43-7.46 (d, J =8.0 Hz, 4H), 7.59-7.62 (m, 1H), 7.7=7.75 (m, 5H), 8.07-8.09 (m, 2H), 12.5 (bs, 1H), 13.87(bs, 1H), ; ^{13}C NMR (Avance Neo, DMSO-d6, 500 MHz) δ: 33.6, 121.12, 121.67, 122.21, 126.23. 129.44, 130.17, 134.80, 145.10,146.79,148.26; ESI/MS=482.

***4, 4'-(p-tolylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)*(1c):**

M.P.= 202-204ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.36 (s, 1H), 7.24-7.35 (m, 10H), 7.49-7.54, (t, J =8.0 Hz, 6H), 7.64-7.70 (m, 2H), 7.84 (d, J =8.0 Hz, 4H), 8.0 (s, 1H), 8.14 (d, J =7.9 Hz, 1H), 14.47 (s, 1H); ^{13}C NMR (Avance Neo, DMSO-d6, 500 MHz) δ: 33.9, 121.4, 121.6, 121.9, 122.0, 126.1, 126.6, 126.9, 128.6, 129.3, 129.5, 130.6, 134.4, 144.5, 148.5, 149.3. ESI/MS=605.

***4, 4'-((4-chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)* (1d):**

M.P.= 233-235ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.36 (s, 1H), 7.24-7.35 (m, 10H), 7.49-7.54, (t, J =8.0 Hz, 6H), 7.64-7.70 (m, 2H), 7.84 (d, J =8.0 Hz, 4H), 8.0 (s, 1H), 8.14 (d, J =7.9 Hz, 1H), 14.47 (s, 1H); ^{13}C NMR (Avance Neo, DMSO-d6, 500 MHz) δ: 33.9, 121.4, 121.6, 121.9, 122.0, 126.1, 126.6, 126.9, 128.6, 129.3, 129.5, 130.6, 134.4, 144.5, 148.5, 149.3. ESI/MS=605.

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