

## 1,3-Disulfonic Acid Imidazolium Trifluoroacetate as a Highly Efficient and Dual-Functional Catalyst for the Pseudo Five-Component Reaction of Phenylhydrazine with Ethyl Acetoacetate and Arylaldehydes

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Ionic liquid 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) has been used as a highly efficient catalyst for the one-pot pseudo five-component reaction of phenylhydrazine (2 eq) with ethyl acetoacetate (2 eq) and arylaldehydes (1 eq) in ethanol (reflux conditions). In this reaction, 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s have been obtained in high yields and relatively short reaction times. High efficacy of [Dsim][TFA] can be attributed to dual-functionality (possessing three acidic and one basic sites). A plausible and attractive mechanism based on dual-functionality of the catalyst has been proposed.

**Keywords:** Phenylhydrazine, Ethyl acetoacetate, Arylaldehyde, 4,4'-(Arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol), 1,3-Disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]), Multi-component reaction

### INTRODUCTION

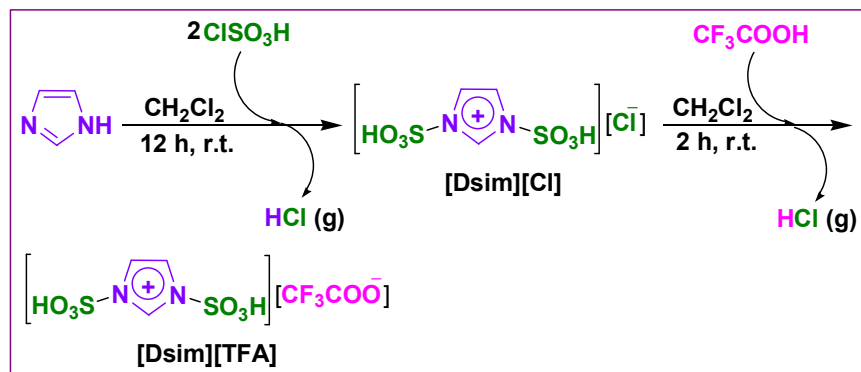
Heterocycles, especially nitrogen-containing ones, are among the fundamental components of many drugs and biological compounds [1-11]. For instance, pyrazole-containing heterocycles {e.g. 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s} represent a numerous biological and medicinal properties, such as antinociceptive [4], antiviral [5], analgesic [6], antimicrobial [7], antimalarial [8], anti-inflammatory [9], antitumor [10] and antifungal [11] activities. One of the best and practical procedures for production of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s is the one-pot pseudo five-component condensation of phenylhydrazine (2 eq) with ethyl acetoacetate (2 eq) and arylaldehydes (1 eq); for progressing this reaction, some catalysts have been employed [12-18]. Nevertheless, some drawbacks are accompanied with many of the reported methods, e.g. application of toxic organic solvents as reaction media,

harsh conditions, moderate yield, long reaction time and application of additional energy source (ultrasonic or microwave irradiation). So, discovery of catalysts to overcome the mentioned problems is still in demand.

It is noteworthy that we have previously applied pseudo three-component reaction of 1-phenyl-3-methylpyrazol-5-one (2 eq) with arylaldehydes (1 eq) using 1,3-disulfonic acid imidazolium tetrachloroaluminate ([Dsim][AlCl<sub>4</sub>]) to synthesize 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s [19]. There are many reports on the pseudo three-component production of these compounds; however, there are only a few reports, in the literature, on the pseudo five-component synthesis of this class of heterocycles. In this research, we introduce 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) as a highly effective catalyst for the pseudo five-component preparation of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s.

During the last decade, ionic liquids (ILs) have been broadly exerted in nearly all fields of chemistry (organic, inorganic, analytical, electrochemistry and catalysis). These

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Scheme 1. The synthesis of [Dsim][TFA]

extensive usages concern to the outstanding properties of ILs, *e.g.*, ability to exert as catalyst, reagent and solvent in organic reactions, very low vapor pressure, broad liquid range, high chemical, electrochemical and thermal stability, capacity to modify their physical and chemical properties by changing cation and anion structures, non-flammability and capability to dissolve numerous kinds of compounds [20-26]. Organic chemists have especially designed task-specific acidic ILs to use as catalysts (or reagents) in organic transformations [21-26].

Multi-component reactions (MCRs) are defined as reactions in which at least three starting materials react in a single pot to give a product which possesses the main moieties of all reactants. MCRs are associated with the following benefits: (i) they are economic, (ii) they are applicable for the synthesis of a wide range of organic, pharmaceutical and complex materials, and (iii) they supply an environmentally friendly protocol by diminishing the use of volatile organic solvents, waste making, process time, energy consumption and number of synthetic steps [27-32].

In view of the above topics, we introduce ionic liquid 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) as a highly effective catalyst for the one-pot pseudo five-component reaction of phenylhydrazine (2 eq) with ethyl acetoacetate (2 eq) and arylaldehydes (1 eq) in ethanol (under reflux conditions) to give 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s. It is noteworthy that our method has overcome the mentioned drawbacks.

## EXPERIMENTAL

### General

Starting materials and solvents were purchased from Merck, Aldrich or Fluka Chemical Companies. [Dsim][TFA] was prepared according to the reported protocol (Scheme 1) [21]. Structures of known compounds were recognized by comparison of their NMR data/melting points with those mentioned in the previous papers. Thin layer chromatography (TLC) was utilized for observation of the reactions progress. Bruker Avance DPX FT-NMR spectrometer was applied for running the <sup>1</sup>H NMR (500 MHz) and <sup>13</sup>C NMR (125 MHz) spectra. Büchi B-545 apparatus was employed for measuring the melting points in open capillary tubes.

### General Procedure for the Production of 4,4'-(Arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s

[Dsim][TFA] (0.07 mmol, 0.024 g) was added to a solution of phenylhydrazine (2 mmol, 0.217 g), ethyl acetoacetate (2 mmol, 0.260 g) and aldehyde (1 mmol) in absolute EtOH (2 ml), and the resulting solution was stirred at reflux conditions. After confirming the completion of reaction by TLC, the solvent was evaporated, and the resultant precipitate was recrystallized from EtOH (95%) to

afford the pure product.

### Selected Spectroscopic Data of the Products

**4,4'-(*p*-Tolylmethylene)-bis(3-methyl-1H-pyrazol-5-ol) (5).** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 2.24 (s, 3H, CH<sub>3</sub>, CH<sub>3</sub>-Ar), 2.30 (s, 6H, 2CH<sub>3</sub>), 4.90 (s, 1H, Ar-CH), 7.07 (d, *J* = 8.0 Hz, 2H, H<sub>Ar</sub>), 7.13 (d, *J* = 7.5 Hz, 2H, H<sub>Ar</sub>), 7.24 (m, 2H, H<sub>Ar</sub>), 7.43 (t, *J* = 7.0 Hz, 4H, H<sub>Ar</sub>), 7.70 (d, *J* = 8.0 Hz, 4H, H<sub>Ar</sub>); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 11.6, 20.5, 32.8, 105.0, 120.4, 125.5, 127.1, 128.6, 128.9, 134.8, 137.4, 139.1, 146.2.

**4,4'-(4-Chlororophenyl)methylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (10).** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 2.27 (s, 6H, 2CH<sub>3</sub>), 4.92 (s, 1H, Ar-CH), 7.17-7.22 (m, 4H, H<sub>Ar</sub>), 7.28 (d, *J* = 8.5 Hz, 2H, H<sub>Ar</sub>), 7.38 (t, *J* = 7.9 Hz, 4H, H<sub>Ar</sub>), 7.65 (d, *J* = 7.8 Hz, 4H, H<sub>Ar</sub>), 12.48 (br., 1H, OH), 13.84 (br., 1H, OH); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 12.2, 33.2, 121.2, 126.3, 128.7, 129.6, 129.77, 131.2, 136.3, 141.8, 146.9.

**4,4'-(2-Bromophenyl)methylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (12).** <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 2.23 (s, 6H, 2CH<sub>3</sub>), 5.05 (s, 1H, Ar-CH), 7.08 (t, *J* = 7.3 Hz, 1H, H<sub>Ar</sub>), 7.18 (t, *J* = 7.2 Hz, 2H, H<sub>Ar</sub>), 7.28 (t, *J* = 7.3 Hz, 1H, H<sub>Ar</sub>), 7.37 (t, *J* = 7.9 Hz, 4H, H<sub>Ar</sub>), 7.50 (d, *J* = 7.9 Hz, 1H, H<sub>Ar</sub>), 7.63 (d, *J* = 7.9 Hz, 4H, H<sub>Ar</sub>), 7.76 (s, 1H, H<sub>Ar</sub>), 12.41 (br., 1H, OH), 13.71 (br., 1H, OH); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 12.6, 34.9, 121.1, 123.4, 126.3, 128.1, 128.9, 129.6, 131.1, 133.4, 141.6, 146.6.

## RESULTS AND DISCUSSION

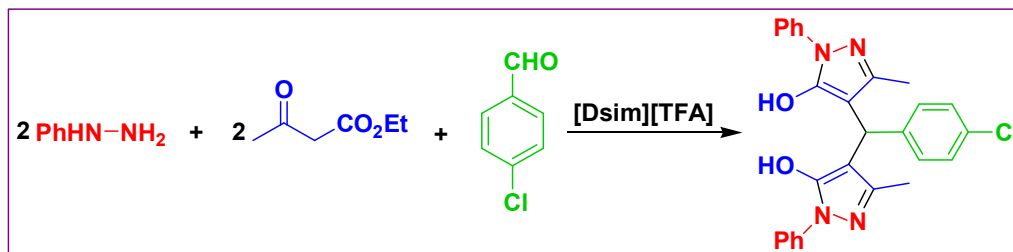
The reaction parameters (catalyst quantity, solvent and temperature) were optimized by studying the reaction of phenylhydrazine (2 mmol) with ethyl acetoacetate (2 mmol) and 4-chlorobenzaldehyde (1 mmol) in the presence of different molar ratios of [Dsim][TFA] in some solvents at range of 50 °C to reflux conditions (Scheme 2). Performing the reaction using 7 mol% of [Dsim][TFA] in EtOH under reflux conditions gave higher yield of the desired product and shorter reaction time (entry 2). The reaction was also

examined in solvent-free conditions in which the product was obtained in low yields (entries 4 and 5).

The generality and effectiveness of the protocol were appraised by investigating the influence of various substituents (electron-releasing, halogens and electron-attracting) on different positions of arylaldehydes, on the reaction. According to the data given in Table 2, [Dsim][TFA] was highly efficient and could be a general catalyst for the synthesis, because all aldehydes afforded the related products in high yields and in relatively short times.

A suggested mechanism, confirmed by the literature [13,15,35], is given in Scheme 3. Initially, trifluoroacetate anion of the catalyst assists phenylhydrazine for nucleophilic addition to the activated carbonyl group of ethyl acetoacetate (by acidic hydrogen of [Dsim][TFA]) to produce I. Intermediate I is converted to II by removal of a water molecule. Afterward, the IL activates the nucleophilic and electrophilic moieties of II for cyclization, to furnish III (after cyclization, a molecule of EtOH is eliminated). III is converted to its tautomer, and this tautomer (with helping the IL anion) is added to the carbonyl group of aldehyde (which was activated by the IL) to give IV. [Dsim][TFA] removes a water molecule from IV providing Michael-acceptor V. Then, Michael addition of another molecule of III tautomer (produced as mentioned above) to V provides VI; in this reaction, both Michael-donor and Michael-acceptor are activated by [Dsim][TFA]. In the last step, by a tautomerization reaction which is catalyzed by the IL, VI is converted to the product. The high catalytic effectuality of [Dsim][TFA] can be attributed to helping both acidic and basic moieties of it (cation and anion) for progressing all steps of the reaction; *i.e.* dual-functionality, as indicated in Scheme 3 and Fig. 1.

In another study, the results of [Dsim][TFA] to catalyze the reaction were compared with the results of the reported catalysts (Table 3). As the table indicates, [Dsim][TFA] gave better results in comparison with the other catalysts in terms of one or more of the factors: yield, temperature and time. Moreover, we have not used ultrasound irradiation to progress the reaction.



Scheme 2. The model reaction for optimizing the synthesis parameters

**Table 1.** Influence of Catalyst Quantity, Solvent and Temperature on the Model Reaction

Entry	Mol% of [Dsim][TFA]	Solvent	Temp. (°C)	Time (min)	Yield (%) <sup>a</sup>
1	5	EtOH	Reflux	70	71
2	7	EtOH	Reflux	30	93
3	10	EtOH	Reflux	30	91
4	10	Solvent-free	80	60	39
5	10	Solvent-free	90	60	47
6	10	MeOH	Reflux	45	90
7	10	MeCN	Reflux	30	85
8	10	EtOAc	Reflux	30	81
9	10	1,4-Dioxane	80	90	84
10	10	EtOH	50	40	57
11	10	EtOH	60	40	68
12	10	EtOH	70	30	76

<sup>a</sup>Isolated yield.

## CONCLUSIONS

Briefly, we showed that [Dsim][TFA] could successfully catalyze the one-pot pseudo five-component reaction of phenylhydrazine with ethyl acetoacetate to produce 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s. The merits of the protocol include: (i) providing the products in high yields and comparatively short times, (ii)

generality and efficacy of the catalyst, (iii) simple production of [Dsim][TFA] from easy available and inexpensive reactants, (iv) application of a few amount of the catalyst in the reaction (7 mol%), (v) performing the synthesis in a nontoxic solvent, (vi) usage of extremely beneficial technique in the synthesis; *i.e.*, MCRs, and (vii) straightforward workup and purification procedure. [Dsim][TFA] was not recoverable; nevertheless, we think

**Table 2.** The Production of 4,4'-(Arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s Using [Dsim][TFA]

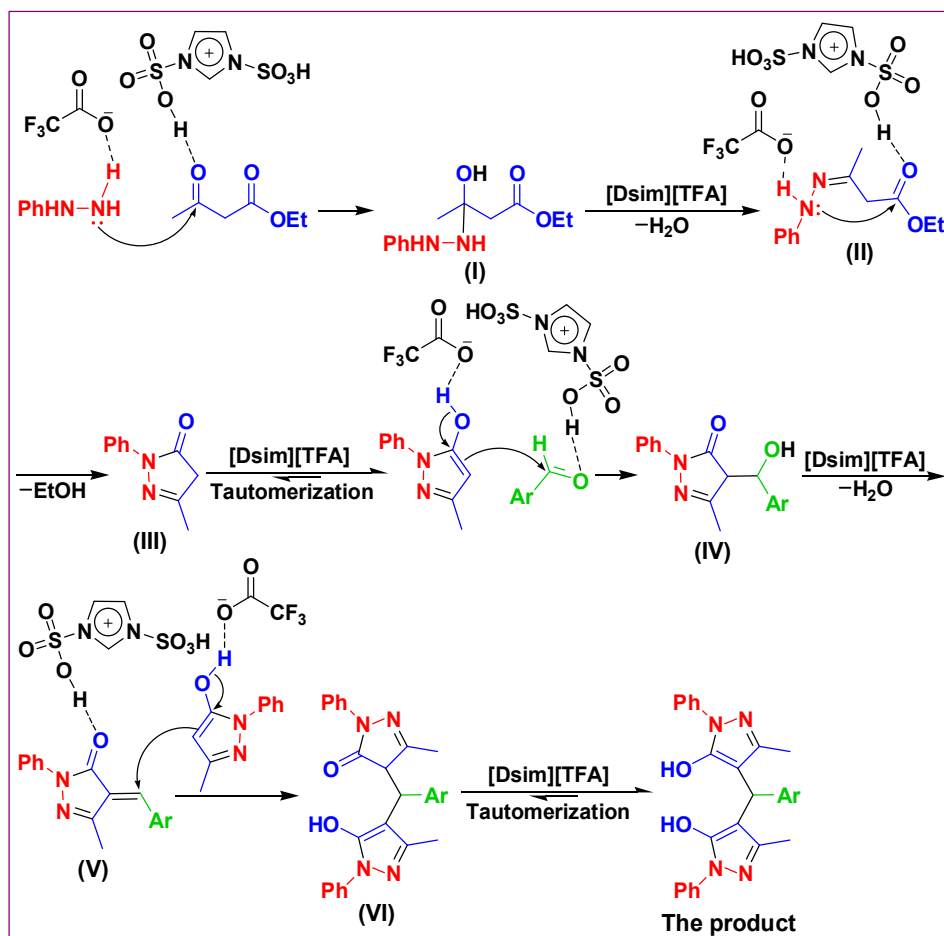
Com pd.	Ar	Time (min)	Yield (%) <sup>a</sup>	M.p. (°C)
1	C <sub>6</sub> H <sub>5</sub>	30	88	165-168 (166-169) [13]
2	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	30	90	192-194 (194-196) [33]
3	2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	45	93	135-137 (134-139) [13]
4	4-MeOC <sub>6</sub> H <sub>4</sub>	60	91	174-176 (173-175) [16]
5	4-MeC <sub>6</sub> H <sub>4</sub>	90	92	201-203 (200-202) [13]
6	4-HOC <sub>6</sub> H <sub>4</sub>	150	91	155-158 (153-155) [33]
7	2-FC <sub>6</sub> H <sub>4</sub>	60	79	154-156 (157-159) [25]
8	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	20	89	228-230 (227-229) [16]
9	2-ClC <sub>6</sub> H <sub>4</sub>	90	75	243-245 (237-239) [17]
10	4-ClC <sub>6</sub> H <sub>4</sub>	30	93	208-210 (209-210) [15]
11	4-FC <sub>6</sub> H <sub>4</sub>	30	92	183-185 (180-182) [34]
12	2-BrC <sub>6</sub> H <sub>4</sub>	45	85	250-252 (249-252) [13]
13	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	20	88	226-228 (227-230) [13]
14	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	15	85	156-158 (152-154) [34]

<sup>a</sup>Isolated yield.

application of the catalyst for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s was economic because of possessing various advantages mentioned above.

## ACKNOWLEDGEMENTS

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Scheme 3. The proposed mechanism

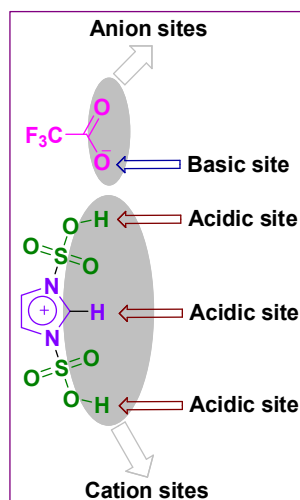


Fig. 1. The acidic and basic sites of [Dsim][TFA].

**Table 3.** Comparing the Results of [Dsim][TFA] with the Reported Catalysts

Catalyst	Conditions	Time range (min)	Yield range (%)	Ref.
[Dsim][TFA]	EtOH, reflux	15-150	75-93	This work
La(OTf) <sub>2</sub> -grafted-GO <sup>a</sup>	Solvent-free, 100 °C	10-45	70-98	[12]
[cmpy]Cl <sup>b</sup>	Solvent-free, 110 °C	5-20	73-92	[13]
DCDBTSD <sup>c</sup>	Solvent-free, 80 °C	35-100	71-85	[15]
Ce(SO <sub>4</sub> ) <sub>2</sub> .4H <sub>2</sub> O	Solvent-free, 125 °C	5-12	81-98	[16]
Catalyst-free	H <sub>2</sub> O-EtOH, r.t., ultrasound	12-20	83-98	[17]
Catalyst-free	H <sub>2</sub> O-EtOH, r.t.	180	Trace-20	[17]
Pyridine trifluoroacetate	H <sub>2</sub> O, 70 °C	300-900	75-95	[18]
Na <sup>+</sup> -MMT-[pmim]HSO <sub>4</sub> <sup>d</sup>	Solvent-free, 100 °C	10-70	84-92	[36]
2-HEAP <sup>e</sup>	Solvent-free, 90 °C	10-50	77-96	[37]

<sup>a</sup>Immobilized La(OTf)<sub>2</sub> on graphene oxide. <sup>b</sup>1-(Carboxymethyl)pyridinium chloride. <sup>c</sup>N<sub>2</sub>-dibromo-6-chloro-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide-1,1-dioxide. <sup>d</sup>1-Methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate ionic liquid supported on nanoporous Na<sup>+</sup>-montmorillonite. <sup>e</sup>2-Hydroxy ethylammonium propionate.

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