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5 **1,3-Disulfonic Acid Imidazolium Trifluoroacetate as a Highly Efficient and**
6 **Dual-Functional Catalyst for the Pseudo Five-Component Reaction of**
7 **Phenylhydrazine with Ethyl Acetoacetate and Arylaldehydes**
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13 (Received 2 January 2018, Accepted 5 May 2018)

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15 Ionic liquid 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) has been used as a highly efficient catalyst for the one-pot
16 pseudo five-component reaction of phenylhydrazine (2 eq) with ethyl acetoacetate (2 eq) and arylaldehydes (1 eq) in ethanol (reflux
17 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
18 short reaction times. High efficacy of [Dsim][TFA] can be attributed to dual-functionality (possessing three acidic and one basic sites). A
19 plausible and attractive mechanism based on dual-functionality of the catalyst has been proposed.

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21 **Keywords:** Phenylhydrazine, Ethyl acetoacetate, Arylaldehyde, 4,4'-(Arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol),
22 1,3-Disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]), Multi-component reaction

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24 **INTRODUCTION**

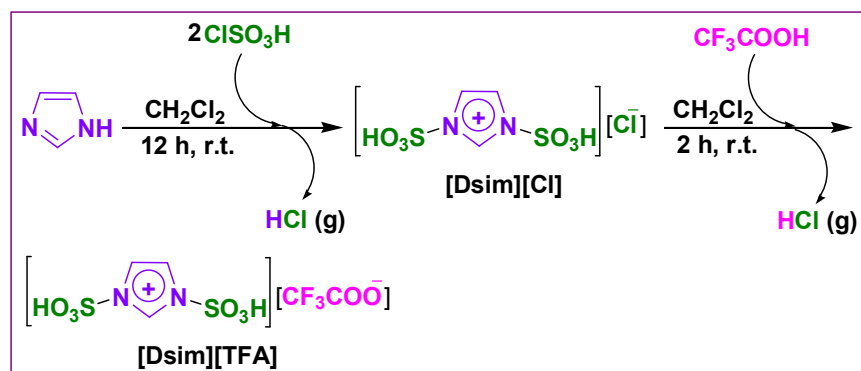
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26 Heterocycles, especially nitrogen-containing ones, are
27 among the fundamental components of many drugs and
28 biological compounds [1-11]. For instance, pyrazole-
29 containing heterocycles {e.g. 4,4'-(arylmethylene)-bis(3-
30 methyl-1-phenyl-1*H*-pyrazol-5-ol)s} represent a numerous
31 biological and medicinal properties, such as antinociceptive
32 [4], antiviral [5], analgesic [6], antimicrobial [7],
33 antimalarial [8], anti-inflammatory [9], antitumor [10] and
34 antifungal [11] activities. One of the best and practical
35 procedures for production of 4,4'-(arylmethylene)-bis(3-
36 methyl-1-phenyl-1*H*-pyrazol-5-ol)s is the one-pot pseudo
37 five-component condensation of phenylhydrazine (2 eq)
38 with ethyl acetoacetate (2 eq) and arylaldehydes (1 eq); for
39 progressing this reaction, some catalysts have been
40 employed [12-18]. Nevertheless, some drawbacks are
41 accompanied with many of the reported methods, e.g.
42 application of toxic organic solvents as reaction media,

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

49 It is noteworthy that we have previously applied pseudo
50 three-component reaction of 1-phenyl-3-methylpyrazol-5-
51 one (2 eq) with arylaldehydes (1 eq) using 1,3-disulfonic
52 acid imidazolium tetrachloroaluminate ([Dsim][AlCl₄]) to
53 synthesize 4,4'-(arylmethylene)- bis(3-methyl-1-phenyl-1*H*-
54 pyrazol-5-ol)s [19]. There are many reports on the pseudo
55 three-component production of these compounds; however,
56 there are only a few reports, in the literature, on the pseudo
57 five-component synthesis of this class of heterocycles. In
58 this research, we introduce 1,3-disulfonic acid imidazolium
59 trifluoroacetate ([Dsim][TFA]) as a highly effective
60 catalyst for the pseudo five-component preparation of
61 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-
62 ol)s.

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64 During the last decade, ionic liquids (ILs) have been
65 broadly exerted in nearly all fields of chemistry (organic,
66 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 ¹H NMR (500 MHz) and ¹³C 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-ols)

[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

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156 afford the pure product.

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158 Selected Spectroscopic Data of the Products

159 **4,4'-(*p*-Tolylmethylene)-bis(3-methyl-1-phenyl-1*H*-**
 160 **pyrazol-5-ol) (5).** ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm):
 161 2.24 (s, 3H, CH₃, CH₃-Ar), 2.30 (s, 6H, 2CH₃), 4.90 (s, 1H,
 162 Ar-CH), 7.07 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.13 (d, *J* = 7.5 Hz,
 163 2H, H_{Ar}), 7.24 (m, 2H, H_{Ar}), 7.43 (t, *J* = 7.0 Hz, 4H, H_{Ar}),
 164 7.70 (d, *J* = 8.0 Hz, 4H, H_{Ar}); ¹³C NMR (125 MHz, DMSO-*d*₆) δ (ppm): 11.6, 20.5, 32.8, 105.0, 120.4, 125.5, 127.1,
 166 128.6, 128.9, 134.8, 137.4, 139.1, 146.2.

167 **4,4'-((4-Chlororophenyl)methylene)-bis(3-methyl-1-**
 168 **phenyl-1*H*-pyrazol-5-ol) (10).** ¹H NMR (500 MHz,
 169 DMSO-*d*₆) δ (ppm): 2.27 (s, 6H, 2CH₃), 4.92 (s, 1H, Ar-
 170 CH), 7.17-7.22 (m, 4H, H_{Ar}), 7.28 (d, *J* = 8.5 Hz, 2H, H_{Ar}),
 171 7.38 (t, *J* = 7.9 Hz, 4H, H_{Ar}), 7.65 (d, *J* = 7.8 Hz, 4H, H_{Ar}),
 172 12.48 (br., 1H, OH), 13.84 (br., 1H, OH); ¹³C NMR (125
 173 MHz, DMSO-*d*₆) δ (ppm): 12.2, 33.2, 121.2, 126.3, 128.7,
 174 129.6, 129.77, 131.2, 136.3, 141.8, 146.9.

175 **4,4'-((2-Bromophenyl)methylene)-bis(3-methyl-1-**
 176 **phenyl-1*H*-pyrazol-5-ol) (12).** ¹H NMR (500 MHz,
 177 DMSO-*d*₆) δ (ppm): 2.23 (s, 6H, 2CH₃), 5.05 (s, 1H, Ar-
 178 CH), 7.08 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 7.18 (t, *J* = 7.2 Hz, 2H,
 179 H_{Ar}), 7.28 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 7.37 (t, *J* = 7.9 Hz, 4H,
 180 H_{Ar}), 7.50 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.63 (d, *J* = 7.9 Hz, 4H,
 181 H_{Ar}), 7.76 (s, 1H, H_{Ar}), 12.41 (br., 1H, OH), 13.71 (br., 1H,
 182 OH); ¹³C NMR (125 MHz, DMSO-*d*₆) δ (ppm): 12.6, 34.9,
 183 121.1, 123.4, 126.3, 128.1, 128.9, 129.6, 131.1, 133.4,
 184 141.6, 146.6.

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186 RESULTS AND DISCUSSION

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

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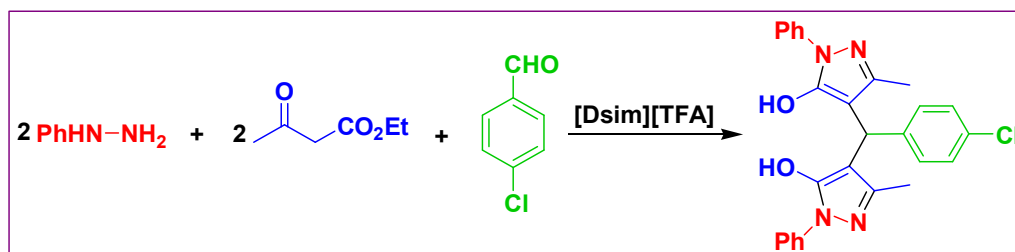
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199 examined in solvent-free conditions in which the product
 200 was obtained in low yields (entries 4 and 5).

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

209 A suggested mechanism, confirmed by the literature
 210 [13,15,35], is given in Scheme 3. Initially, trifluoroacetate
 211 anion of the catalyst assists phenylhydrazine for
 212 nucleophilic addition to the activated carbonyl group of
 213 ethyl acetoacetate (by acidic hydrogen of [Dsim][TFA]) to
 214 produce I. Intermediate I is converted to II by removal of a
 215 water molecule. Afterward, the IL activates the nucleophilic
 216 and electrophilic moieties of II for cyclization, to furnish III
 217 (after cyclization, a molecule of EtOH is eliminated). III is
 218 converted to its tautomer, and this tautomer (with helping
 219 the IL anion) is added to the carbonyl group of aldehyde
 220 (which was activated by the IL) to give IV. [Dsim][TFA]
 221 removes a water molecule from IV providing Michael-
 222 acceptor V. Then, Michael addition of another molecule of
 223 III tautomer (produced as mentioned above) to V provides
 224 VI; in this reaction, both Michael-donor and Michael-
 225 acceptor are activated by [Dsim][TFA]. In the last step, by a
 226 tautomerization reaction which is catalyzed by the IL, VI is
 227 converted to the product. The high catalytic effectuality of
 228 [Dsim][TFA] can be attributed to helping both acidic and
 229 basic moieties of it (cation and anion) for progressing all
 230 steps of the reaction; *i.e.* dual-functionality, as indicated in
 231 Scheme 3 and Fig. 1.

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

^aIsolated yield.

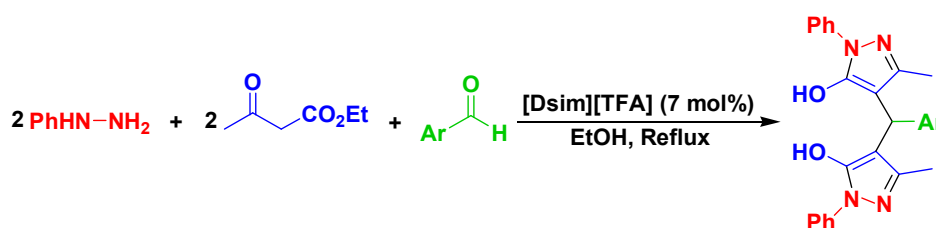
CONCLUSIONS

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)

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

^aIsolated yield.

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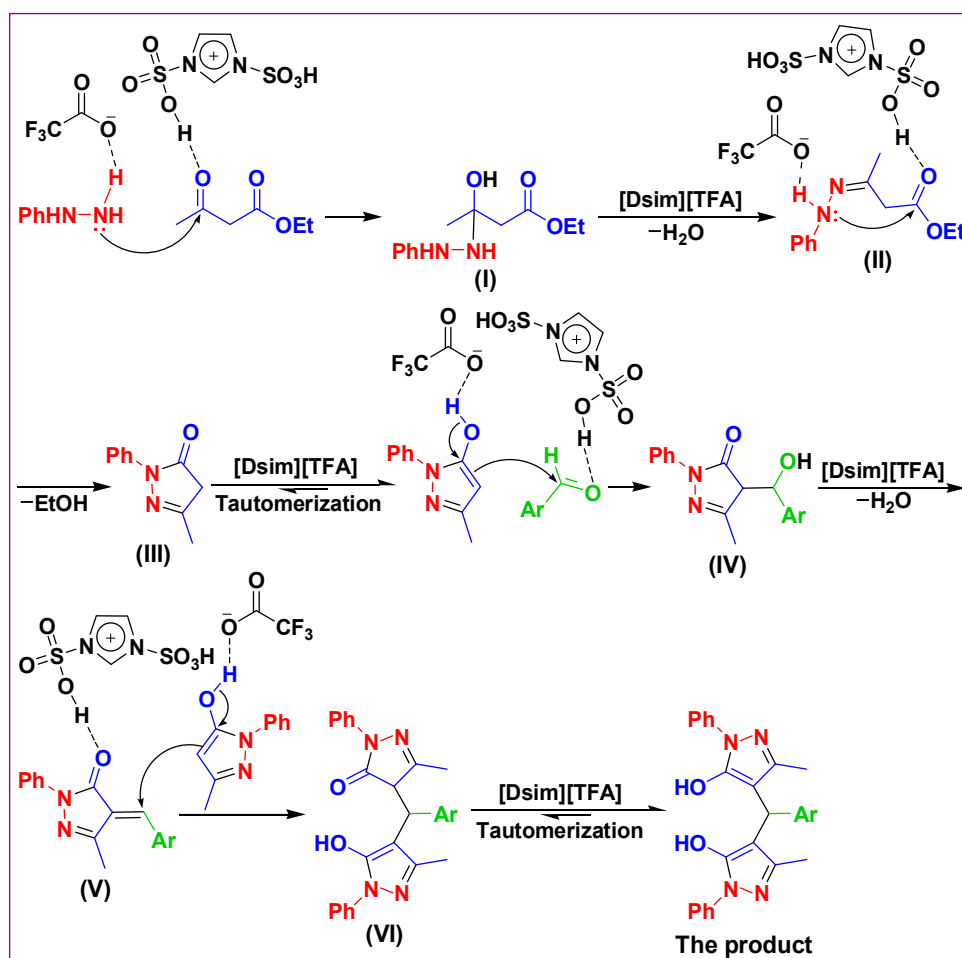
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370 application of the catalyst for the synthesis of
 371 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-
 372 ol)s was economic because of possessing various
 373 advantages mentioned above.

ACKNOWLEDGEMENTS

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417 Providing the necessary equipments by Payame Noor
 418 University, to achieve this research, is acknowledged.



Scheme 3. The proposed mechanism

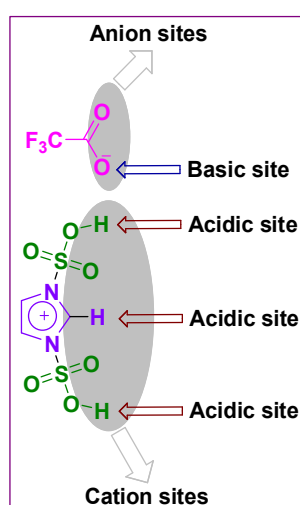


Fig. 1. The acidic and basic sites of [Dsim][TFA].

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

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

^aImmobilized La(OTf)₂ on graphene oxide. ^b1-(Carboxymethyl)pyridinium chloride. ^cN,2-dibromo-6-chloro-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide-1,1-dioxide. ^d1-Methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate ionic liquid supported on nanoporous Na⁺-montmorillonite. ^e2-Hydroxy ethylammonium propionate.

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