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A highly effective and mild protocol for the production of 1-thioamidoalkyl-2-naphthols using 1,3-disulfonic acid imidazolium trifluoroacetate as a dual-functional catalyst

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Abstract: A solvent-free protocol for the production of 1-thioamidoalkyl-2-naphthols via a one-pot multi-component reaction of arylaldehydes with 2-naphthol and thioacetamide using the ionic liquid 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) is described. Furthermore, a plausible and attractive mechanism based on the dual functionality of the catalyst is proposed. Because of the dual functionality of [Dsim][TFA] (possessing acidic and basic sites), it is found to be generally highly effective, affording the products in high yields and short reaction times under mild conditions. We claim that this is one of the best protocols for the synthesis of 1-thioamidoalkyl-2-naphthols (in terms of yield, temperature, conditions, and/or the reaction time).

Keywords: 1-thioamidoalkyl-2-naphthol; 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]); dual-functional catalyst; ionic liquid; multi-component reaction; solvent-free reaction.

1 Introduction

1-Thioamidoalkyl-2-naphthol derivatives are of significance, as they can be readily hydrolyzed to the biologically important compounds 1,3-amino alcohols. Notch-sparing, secretase-inhibitory, antibacterial, antipain, bradycardiac, and hypotensive activities have been reported for 1,3-amino alcohols [1–4]. On the other hand, 1-thioamidoalkyl-2-naphthols contain *N*-alkyl thioamide or thioamide moieties, which are the bases for a variety of uses, including (i) luminescent activity when complexed with palladium [5], (ii) selective complexation of copper, silver, cadmium, and lead [6], (iii) application in peptide chemistry [7], (iv) quenching tryptophan and tyrosine fluorescence in a distance-dependent manner, and consequently used for monitoring the binding of thioamide-containing peptides to proteins [8], (v) utilization in medicinal chemistry [9], (vi) application as catalysts for organic transformations [10, 11], and others [12, 13]. The practical method for the synthesis of 1-thioamidoalkyl-2-naphthols involves the one-pot multi-component reaction of arylaldehydes with 2-naphthol and thioacetamide promoted by a catalyst [14–21]. However, the reported catalysts possess at least one of the following drawbacks: long reaction time, moderate yield, harsh conditions, utilization of volatile and toxic organic solvents as reaction media, nonsystematic approach to the synthesis (only a few 1-thioamidoalkyl-2-naphthols have been synthesized besides other products), and the use of large amounts of the catalyst. In addition, only a few catalysts have been reported for this synthesis in the literature. Hence, introducing a new catalyst for the reaction which does not have these disadvantages is of importance.

During the last decade, ionic liquids (ILs) have been introduced into nearly all fields of chemistry (organic, inorganic, analytical, electrochemistry, and catalysis). Their extensive use is based on the outstanding properties of ILs, e.g. high chemical, electrochemical, and thermal stability, broad liquid range, very low vapor pressure, capacity to modify their physical and chemical properties by changing the cation and anion structures, nonflammability, capability to dissolve numerous kinds of materials, and the ability to act as catalysts, reagents, and solvents in organic transformations. Organic chemists have designed a variety of acidic ILs to be utilized as catalysts (or reagents) in organic reactions [22–29]. 1,3-Disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) is an acidic IL that has been applied as catalyst for the preparation of 14*H*-dibenzo[*a*,*j*]xanthenes and 1,8-dioxo-decahydroacridines [25].

One-pot multi-component reactions are of importance in organic and pharmaceutical chemistry, where three or more starting materials are made to react in one pot and one step to afford a complex product that has the main elements of the all reactants. Consequently, this technique increases the yield, decreases the reaction time, saves energy and time, minimizes the use of volatile organic solvents, and reduces the generation of side products, which are in accordance with green chemistry protocols [30–32].

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Another important green technique in synthetic chemistry is carrying out reactions under solvent-free conditions. This technique has usually many advantages with respect to shorter reaction time, higher yield, easier work-up, safer reaction conditions, higher selectivity, preventing or decreasing byproducts/waste generation, and lower energy requirement [33–35].

Considering the above issues, we introduce here the ionic liquid [Dsim][TFA] as a highly effective, mild, and dual-functional catalyst for the synthesis of 1-thioamidoalkyl-2-naphthols by the one-pot multi-component reaction of arylaldehydes with 2-naphthol and thioacetamide under solvent-free conditions. Interestingly, this catalyst has none of the mentioned drawbacks.

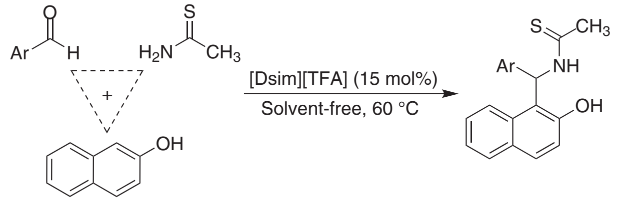
It should be mentioned that we had previously used [Dsim][HSO_4] and [Dsim][Cl] for the preparation of 1-carbamatoalkyl-2-naphthols and 1-amidoalkyl-2-naphthols at 80 and 120°C; however, during those investigations, we did not synthesize 1-thioamidoalkyl-2-naphthols [28, 29]. According to our experience, the production of 1-thioamidoalkyl-2-naphthols is more difficult than that of 1-carbamatoalkyl/amidoalkyl-2-naphthols.

2 Results and discussion

To obtain the appropriate amount of the catalyst and the suitable reaction temperature, the reaction of 3-nitrobenzaldehyde (1 mmol), 2-naphthol (1 mmol), and thioacetamide (1.3 mmol) for the production of compound **2** was examined using various amounts of [Dsim][TFA] (10–17 mol%) in the temperature range 50–65°C under solvent-free conditions (Scheme 1). Higher yields and shorter reaction times resulted when the reaction was carried out in the presence of 15 mol% of the IL at 60°C (yield = 97%, time = 25 min).

Then, the effectiveness and generality of use of [Dsim][TFA] was appraised by reacting miscellaneous aromatic aldehydes with 2-naphthol and thioacetamide under the optimized reaction conditions. The optimized reaction times and yields are displayed in Table 1. As the table shows, [Dsim][TFA] was highly effective and general for the synthesis. The corresponding 1-thioamidoalkyl-2-naphthols were produced in high to excellent yields and short reaction times when the arylaldehydes were bearing electron-withdrawing and electron-releasing substituents in the *ortho*, *meta*, or *para* positions. Furthermore, aldehydes possessing two substituents afforded the relevant products in high yields and relatively short times (products **5** and **12**).

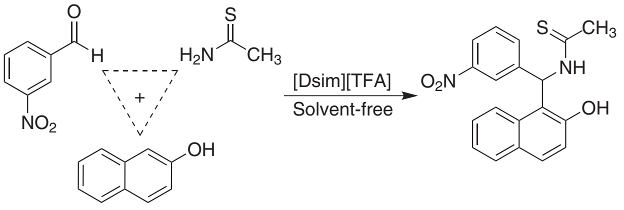
Table 1: Synthesis of 1-thioamidoalkyl-2-naphthols catalyzed by [Dsim][TFA].



Product no.	Ar	Time (min)	Yield (%)[a]	M.p. (°C)	
				Found	Reported [ref.]
1	C_6H_5	35	96	192–194	190–193 [19]
2	$3\text{-}O_2NC_6H_4$	25	97	231–233	234–236 [16]
3	$4\text{-}O_2NC_6H_4$	25	97	245–247	243–245 [15]
4	$2\text{-}O_2NC_6H_4$	75	88	228–231	229–231 [20]
5	$2,4\text{-}Cl_2C_6H_3$	55	95	222–224	219–221 [18]
6	$3\text{-}ClC_6H_4$	55	93	257–259	256–258 [18]
7	$4\text{-}ClC_6H_4$	35	95	244–246	243–245 [18]
8	$2\text{-}ClC_6H_4$	25	94	173–175	174–176 [20]
9	$4\text{-}FC_6H_4$	40	95	206–208	208–210 [16]
10	$3\text{-}CH_3OC_6H_4$	55	93	234–236	–
11	$4\text{-}CH_3OC_6H_4$	80	86	180–182	181–182 [18]
12	$2,5\text{-}(CH_3O)_2C_6H_3$	30	91	248–250	–
13	$4\text{-}CH_3C_6H_4$	25	94	183–185	180–183 [19]
14	$4\text{-}HOC_6H_4$	50	92	238–240	240–242 [16]

[a] Isolated yield.

The IL functions as a dual-functional catalyst, because it has both acidic and basic sites (SO_3H group as the acid, and trifluoroacetate as the base). Altogether, there are three acidic sites and one basic site in the catalyst (Fig. 1).



Scheme 1: Model reaction.

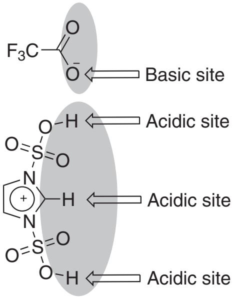
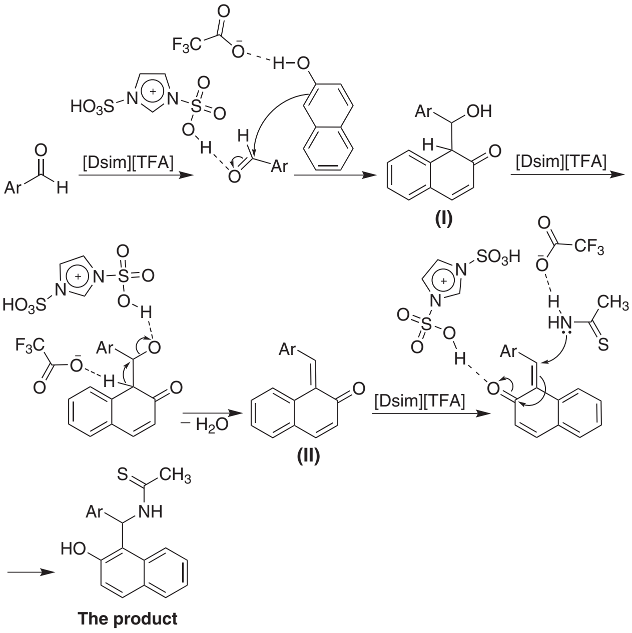


Fig. 1: Acidic and basic sites of [Dsim][TFA].

Thus, [Dsim][TFA] can act as a highly effective and general catalyst for reactions that need both acidic and basic sites simultaneously, e.g. the production 1-thioamidoalkyl-2-naphthols. This is shown in the reaction mechanism (Scheme 2).

At first, the basic anion (trifluoroacetate) assists 2-naphthol for the addition to the activated aldehyde (by the acidic hydrogen of [Dsim][TFA]) to produce the intermediate **I**. The removal of a H_2O molecule from **I** through the assistance of both the cation and the anion of the IL gives the intermediate **II**. Finally, a Michael-type addition of thioacetamide to **II** affords the product; this step is also accelerated by the acidic and basic sites of [Dsim][TFA]. The mechanism is supported by reports in the literature [14–16, 18].



Scheme 2: Proposed mechanism for the synthesis of 1-thioamidoalkyl-2-naphthols.

To highlight the merit of our catalyst in comparison with the reported catalysts, we have tabulated the results and the reaction conditions for the synthesis of compound **1** in the presence of these catalysts in Table 2. As can be seen in this table, [Dsim][TFA] afforded better results than the other catalysts (in terms of the reaction yield, time and temperature). Moreover, we have performed the synthesis under solvent-free conditions.

3 Conclusion

In summary, we have introduced an IL catalyst for the synthesis of 1-thioamidoalkyl-2-naphthols. The advantages of the presented protocol include high effectiveness, generality, high yields, short reaction times, cleaner reaction profile, simplicity, low cost, easy preparation of the catalyst, mild conditions, and good compliance with the green chemistry protocols. We claim that this is one of the best protocols for the synthesis of 1-thioamidoalkyl-2-naphthols.

4 Experimental

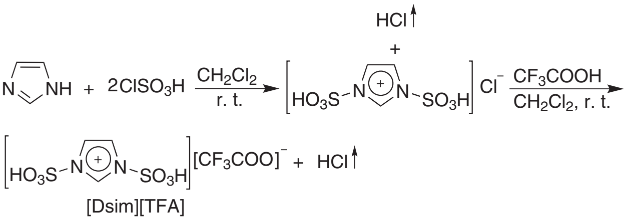
4.1 General

All starting materials and solvents were bought from Merck, Fluka, or Acros. [Dsim][TFA] was prepared according to the reported protocol (Scheme 3) [25]. Known compounds were identified by comparing their melting points/spectroscopic data with those reported in the literature.

Table 2: Comparison of the merit of [Dsim][TFA] with other reported catalysts for the synthesis of compound **1** in terms of the reaction yield, time, and temperature.

Catalyst	Conditions	Time (min)	Yield (%)	Ref.
[Dsim][TFA]	Solvent-free, 60°C	35	96	This work
Trichloro-1,3,5-triazinane-2,4,6-trione	Solvent-free, 120°C	25	80	[14]
1,3-Dichloro-5,5-dimethylhydantoin	Solvent-free, 120°C	35	73	[14]
$Fe(HSO_4)_3$	1,2-Dichloroethane, 60°C	390	88	[15]
1,3-Dibromo-5,5-dimethylhydantoin	Solvent-free, 130°C	200	93	[16]
Trityl chloride	Solvent-free, 70°C	12	78	[17]
DCDBTSD[a]	Solvent-free, 80°C	25	80	[18]
Saccharin sulfonic acid	Solvent-free, 70°C	50	80	[19]
p-Toluenesulfonic acid	1,2-Dichloroethane, reflux	60	95	[20]
$[Et_3N–SO_3H]Cl$	Solvent-free, 110°C	30	88	[21]

[a] *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide.



Scheme 3: Synthesis of [Dsim][TFA].

Progress of the reactions was monitored by thin-layer chromatography (TLC). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Spectra were recorded on the following apparatuses: ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) on Bruker Avance DPX, FT-NMR spectrometers, and the mass spectra on spectrometer 5975C VL MSD model with a triple axis detector.

4.2 General procedure for the synthesis of 1-thioamidoalkyl-2-naphthols

A mixture of arylaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), thioacetamide (1.3 mmol, 0.097 g) and [Dsim][TFA] (0.15 mmol, 0.051) was stirred at 60°C. Progress of the reaction was monitored by TLC. When the reaction was completed, the resulting precipitate was recrystallized from ethanol (95%) to afford the pure product.

5 Supporting information

Selected spectral data and spectra of the 1-thioamidoalkyl-2-naphthols have been given in the Supporting Information available online (https://doi.org/10.1515/znb-2018-0001).

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