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The synergistic effect of copper chromite spinel nanoparticles ($CuCr_2O_4$) and basic ionic liquid on the synthesis of cyclopropanecarboxylic acids

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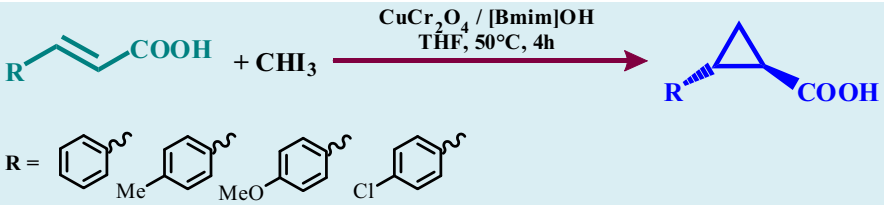
Abstract An efficient synthesis of cyclopropanecarboxylic acids using copper chromite spinel nanoparticles and basic ionic liquid is described. In this study, a relatively simple method starting with trans-cinnamic acid for the synthesis of (±)-trans-2-phenylcyclopropanecarboxylic acid, a key intermediate in the synthesis of tranylcypromine sulfate as an active pharmaceutical ingredient, was employed. Using a combination of basic ionic liquid [Bmim]OH and copper chromite spinel nanoparticles as a catalytic system, the best results were obtained in THF as a polar solvent. This method is a useful alternative to other approaches described in the literature. The use of commercially available chemicals, decreased environmental hazards, with no need for the separation of stereoisomers, and consequently a reduced number of overall steps, are the advantages of this approach that make it an appropriate choice at an increased scale.

Graphical Abstract



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Keywords Copper chromite spinel nanoparticles · Basic ionic liquid · (±)-Trans-2-phenylcyclopropanecarboxylic acid · Trans-cinnamic acid · Cyclopropanation

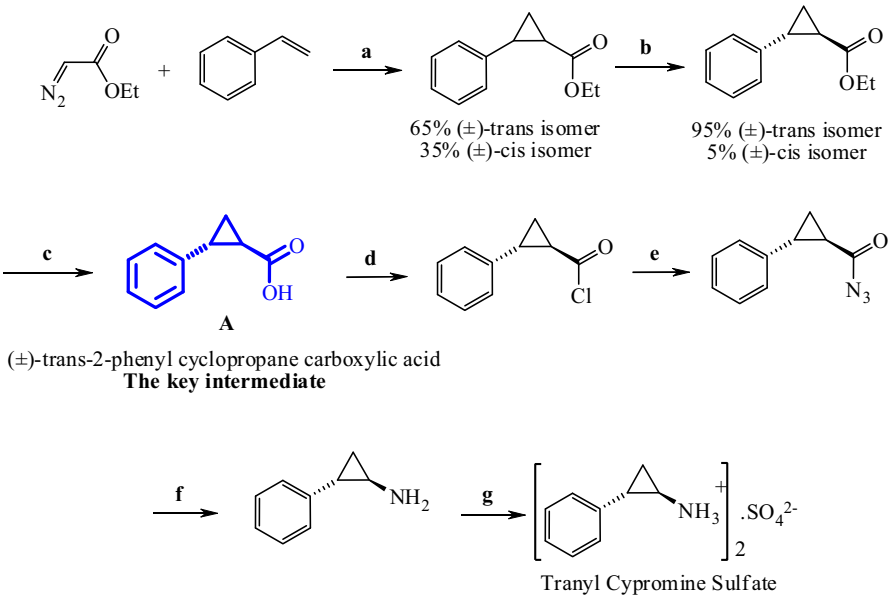
Introduction

Ionic liquids (ILs) are organic salts with low melting points and negligible vapor pressures [1]. Ionic liquids have polar characteristics and are excellent media to hold polar species such as transition-metal catalysts [2–5], and so they have been used for the immobilization of homogeneous catalysts [6, 7]. The application of ILs in catalysis has been increasing due to their ability as solvents for many transition metal-catalyzed reactions [8]. The IL phase efficiently induces catalyst immobilization and has a low miscibility with organic reaction products; as a consequence, liquid–liquid biphasic processes using ILs incorporating transition metal catalysts have been widely examined [9]. Functional nanoparticles have also been synthesized using ionic liquids [10, 11]. The use of metal nanocatalysts and the heterogenization of homogeneous catalysts in ILs are among attractive new concepts in the ILs area.

Copper chromite composite oxide ($CuCr_2O_4$) is an excellent catalyst for some chemical reactions such as alkylation, oxidation, hydrogenation, dehydrogenation, etc. [12]. Similar types of spinel ferrite materials have been prepared by microwave, and by conventional and plant extract-assisted combustion methods [13–18]. Due to the tetragonally distorted normal spinel structure and the arrangement of copper in its structure, copper chromite is a remarkably effective catalyst [19]. However, although this catalyst has been widely used in many chemical reactions, it has not been well investigated for the catalytic cyclopropanation of vinyl compounds as an interesting topic in chemical synthesis.

In recent years, many efforts have been made to synthesize (±)-trans-2-phenylcyclopropanecarboxylic acid (Scheme 1, **A**), a key intermediate in the synthesis of tranylcypromine sulfate as an active pharmaceutical ingredient [20–26]. The search for efficient synthesis methods of tranylcypromine sulfate under mild conditions is of continuing interest for pharmaceutical chemists. The most commonly used synthetic method to synthesize tranylcypromine sulfate is shown in Scheme 1. According to this method, tranylcypromine sulfate is synthesized in seven steps starting with styrene, in which the synthesis of (±)-trans-2-phenylcyclopropanecarboxylic acid **A** is of extreme importance.

As shown in Scheme 1, there are three successive steps for the synthesis of (±)-trans-2-phenylcyclopropanecarboxylic acid **A**. Firstly, the reaction of styrene with ethyldiazoacetate, a mixture of the (±)-cis and (±)-trans-2-phenylethyl esters of cyclopropane carboxylic acid, is prepared (Scheme 1, a). The isomerization of the (±)-cis isomer to the (±)-trans isomer is carried out by reacting the ester with metallic sodium in anhydrous ethyl alcohol (Scheme 1, b). The obtained ester is then hydrolyzed to a mixture of (±)-cis and (±)-trans-2-phenylcyclopropane carboxylic acid. Full separation of the (±)-trans isomers from the (±)-cis/trans mixture is carried out by recrystallization several times in hot water (Scheme 1, c).



Scheme 1 General method for the synthesis of tranylcypromine. Reagents and conditions: (a) *i* 125–140 °C/N_2/4 h, *ii* Distillation of styrene under vacuum; (b) *i* sodium metal in anhydrous ethanol/N_2/reflux/20 h, *ii* Extraction by benzene; (c) *i* NaOH/absolute ethanol:water/reflux/20 h, *ii* HCl (conc.); (d) $SOCl_2$/benzene/reflux/16 h; (e) NaN_3/toluene/80 °C/4 h; (f) *i* HCl (conc.)/reflux/15 h, *ii* KOH (60 %); (g) ethanolic solution of concentrated sulfuric acid

Although this method also overcomes the isolation of stereoisomers, it has some disadvantages, as follows. First, this method uses styrene as a raw material. The use of styrene is limited due to its high polymerization potential. Styrene can be easily polymerized under the reaction conditions. So, before starting the reaction, the styrene should be purified by distillation under reduced pressure. Additionally, further purification of the polystyrene formed during the reaction must be carried out. On the other hand, ethyl diazoacetate, used in the first step of this method, is a hazardous chemical and considerations of safe industrial handling should be established. Since, in most cases, it is hard to access commercial ethyl diazoacetate, it must be synthesized in the laboratory, which involves the addition of one or two steps to the overall synthesis steps. The long reaction times, using metallic sodium in refluxing ethanol for a long period of time (20 h), which incurs considerable risks, and the use of toxic solvents such as benzene are among other disadvantages of this procedure which has made it laborious to scale up. In addition, the overall low yield of this process means that production on an industrial scale is not economically feasible. An alternative method to avoid the formation of a mixture of cis and trans isomers is the use of special chemical raw materials, which chemoselectively produce the desired isomer without any chiral catalyst. Trans-cinnamic acid is one such specific raw material that can be used to synthesize the key intermediate **A** in the cyclopropanation reaction. Therefore, our efforts have been particularly focused on the synthesis of compound **A** as the key intermediate using chromium (II) reagents in tranylcypromine synthesis.

We have developed a novel simple method for the synthesis of (±)-trans-2-phenylcyclopropane carboxylic acid **A** using copper chromite spinel nanoparticles ($CuCr_2O_4$) and basic ionic liquid by reducing the number of steps and improving the overall yield. In this paper, we suggest an excellent method for the synthesis of intermediate **A** which has many benefits without the disadvantages mentioned in the previous methods. The use of trans-cinnamic acid as commercial raw material is a possible alternative to prevent the formation of a mixture of cis/trans isomers. Our recommended method is briefly summarized in Scheme 2. In order to reduce costs, iodoform is effectively produced by the reaction of commercial acetone and iodine. The key intermediate **A** is readily synthesized by the reaction of trans-cinnamic acid and iodoform in dry THF in the presence of a catalytic system (Scheme 2).

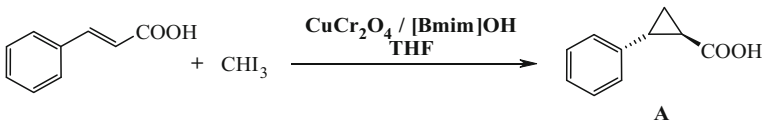
Experimental

Materials and general techniques

Chemicals were purchased from the Merck or Sigma-Aldrich. Progression of the reactions was monitored by TLC using silica-gel SIL G/UV 254 plates. Melting points were accurately recorded with an Electrothermal-9100 apparatus. Fourier transform infrared (FT-IR) spectra were achieved by a BRUKER EQUINOX 55 Fourier-transform spectrophotometer using the KBr pellet technique. NMR spectra were recorded on a Brucker Avance DPX instrument at 300 and 400 MHz, respectively; δ is reported in parts per million (ppm) and J in Hz. Transmission electron microscopy (TEM; Jeol JEM-1230, with an acceleration voltage of 100 kV) was carried out using to characterize the catalyst morphology. The X-ray diffraction (XRD) patterns were reported with a Philips X'Pert MPD diffractometer equipped with Cu Kα radiation ($\lambda = 0.154$ nm) in the range 10°–80° (2θ) at a speed of 0.05°/min to characterize the crystallographic nanoparticle structure. The qualitative analyses of products were conducted with a HP 6890/5973 GC–MS equipped with an FID detector.

Catalyst preparation

The $CuCr_2O_4$ spinel nanoparticles catalyst were prepared according to the literature [27]. $CuSO_4{\cdot}5H_2O$ (2.0 g) and $Cr_2(SO_4)_3{\cdot}12H_2O$ (10.0 g) were completely dissolved in a mixture of water (200 mL) and ethanol (20 mL). The pH of the clear dark blue solution was carefully adjusted to 8 by addition of an aqueous ammonia solution. Cetyltrimethylammonium bromide (1.50 g) was added to the



Scheme 2 Recommended synthesis of (±)-trans-2-phenylcyclopropane carboxylic acid **A**

solution and stirred for a few minutes. Hydrazine hydrate solution (0.6 g) was added gradually to the dark green gel to produce a brown gel. The resultant gel was aged under air at 40 °C for 1 h and properly sealed in an autoclave for 18 h at 180 °C. After cooling to room temperature, the precipitate was collected by centrifugation, washed with water (2 × 1000 mL) and ethanol (2 × 100 mL) and dried at 100 °C for 6 h. Finally, the powder was calcinated at 750 °C for 6 h to yield $CuCr_2O_4$ spinel nanoparticles.

The basic ionic liquid was prepared and purified according to the procedure described previously [28]. The $CuCr_2O_4$ spinel nanoparticles catalyst (2.0 g) and the [Bmim]OH (10 mL) were added to methanol (50 mL), and the resulted mixture was stirred for 6 h at 50 °C. The solvent was removed by evaporation under reduced pressure to produce an ionic liquid incorporating copper chromite nanoparticles.

The synthesis of A starting with trans-cinnamic acid

A mixture of trans-cinnamic acid (0.3 g, 2 mmol) and 1.18 g iodoform (3 mmol) in dried THF (5 mL) was stirred at room temperature. The ionic liquid prepared in the previous step (1 mL), was added to the stirring mixture and the resultant liquid–liquid biphasic system was vigorously stirred at 50 °C for 4 h. Then, the reaction mixture was poured into an aqueous hydrochloric acid (1 M, 10 mL) and stirred for 60 min at room temperature. The mixture was extracted with dried THF (3 × 10 mL). The aqueous phase was stored in order to recycle the IL catalyst for subsequent reactions. The combined organic phases were then evaporated under reduced pressures. The residue was added to sodium hydroxide (33 %, 5 mL) and then acidified with concentrated hydrochloric acid to pH = 2. The precipitate was filtered, recrystallized in boiling water and dried to yield 0.3 g (93 %) (±)-trans-2-phenylcyclopropanecarboxylic acid **A**. ^{1}H NMR, ^{13}C NMR and IR spectra of **A** as a key intermediate in the tranylcypromine synthesis are indicated in the supplementary material.

(±)-Trans-2-phenylcyclopropanecarboxylic acid (A)

$C_{10}H_{10}O_2$; m.p.: 93–98 °C; MW: 162.2; ^{1}HNMR (300 MHz, $CDCl_3$) δ(ppm): 1.42 (ddd, J = 8.1, 6.5, 4.8 Hz, 1 H), 1.67 (dt, J = 14.4, 5.1 Hz, 1 H), 1.91 (dt, J = 12.9, 4.8 Hz, 1 H), 2.61 (ddd, J = 8.8, 6.2, 4. 5 Hz, 1 H), 7.11–7.33 (m, 5 H); ^{13}CNMR (75 MHz, $CDCl_3$) δ(ppm): 17.5, 23.9, 27.1, 126.3, 126,7, 128.5, 139.5, 179.4; IR (KBr) $\bar{\nu}$ (cm^{-1}): 754, 934, 1232, 1331, 1443, 1603, 1683, 2862, 3050, 3381; R_f = 0.40 (hexane:ethyl acetate 4:1)

Results and discussion

Catalyst characterization

The X-ray diffraction (XRD) patterns were analyzed to confirm the catalyst structure using reference standards [27]. The XRD profiles of the copper chromite catalyst are shown in Fig. 1 with the maximum intensity peak at $2\theta = 35.7°$.

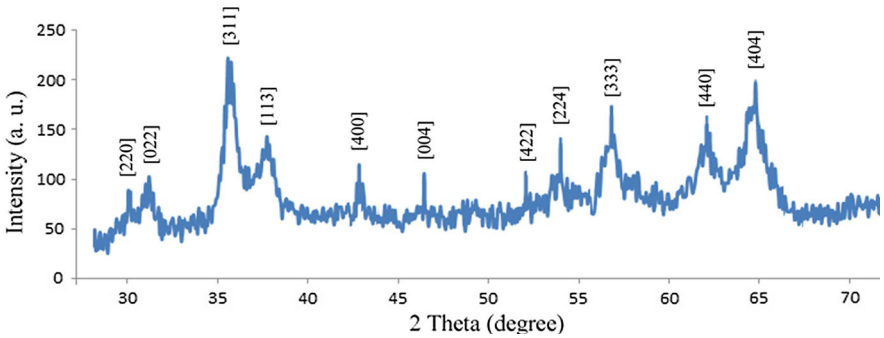


Fig. 1 XRD pattern of copper chromite spinel nanoparticles ($CuCr_2O_4$); 2θ (°): 30.0, 31.0, 35.7, 37.7, 42.7, 46.4, 53.8, 56.8, 58.1, 62.3, 64.8

For further understanding the catalyst structure, the TEM images of $CuCr_2O_4$ catalysts are shown in Fig. 2.

Synergistic effect of the copper chromite nanoparticles and ionic liquid on the cyclopropanation reaction

In this study, we have successfully employed a simple and efficient procedure for the synthesis of intermediate **A** without using any extremely unsafe conditions. For this special purpose, some experiments were performed to determine the best conditions, beginning with trans-cinnamic acid as the starting raw material. In this study, different conditions including various solvents were assessed and the results are briefly described in Table 1. Furthermore, to evaluate the catalyst repeatability, further experiments using other functionalized trans-cinnamic acids were performed, with the results given in Table 2.

Initially, we performed the reaction in water as the solvent without any catalyst and stirred up to 24 h at 50 °C without any progress in the reaction (Table 1, entry 1). The reaction progress was continuously monitored by TLC. The reaction was also carried out using aqueous solution of sodium carbonate and sodium hydroxide, and the cyclopropanation reaction was performed with low yield (Table 1, entries 2, 3). The use of basic ionic liquid [Bmim]OH was also accompanied with poor results (Table 1, entries 4, 5). The reaction efficiency was significantly improved using copper chromite spinel nanoparticles ($CuCr_2O_4$) in tetrahydrofuran as the solvent (Table 1, entry 6). When [Bmim]OH was used without any catalyst, the product yield was comparable to that of alkali aqueous solutions. As a consequence, the use of [Bmim]OH incorporating nanoparticles as an immiscible heterogeneous catalytic system was preferred.

To investigate the synergistic effect of copper chromite spinel nanoparticles and basic ionic liquid in the cyclopropanation reaction, the reaction was also performed in some more immiscible solvents with water such as dichloromethane, diethylether, ethylacetate and toluene (Table 1, entries 7–12). It was clearly confirmed that using a combination of ionic liquid [Bmim]OH and $CuCr_2O_4$ spinel nanoparticles as a catalytic system, the best results were obtained in THF as a polar solvent (Table 1,

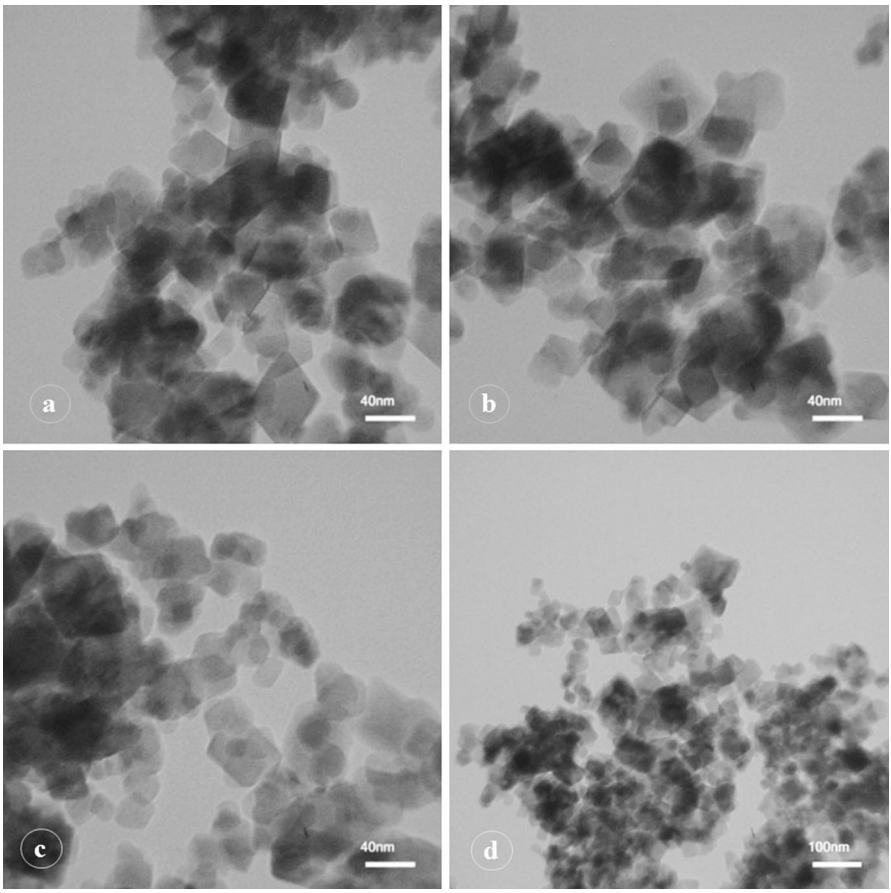
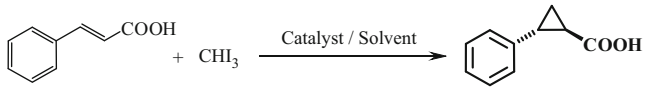


Fig. 2 TEM images of copper chromite spinel nanoparticles ($CuCr_2O_4$)

entry 13). The reaction was performed at room temperature; as a consequence, the reaction yield was dramatically decreased (Table 1, entry 14). In order to replace sensitive basic ionic liquid [Bmim]OH in the reaction media, in a further experiment, we used commercially ionic liquid [Bmim]Cl and an alkali solution of sodium hydroxide (NaOH, 10 %) together with copper chromite spinel nanoparticles (Table 1, entry 15). The main advantage of this reaction is the generation of ionic liquid [Bmim]OH in situ. Therefore, there is no need for the separately synthesis of [Bmim]OH. On the other hand, despite a slight decrease in the reaction yield, the use of basic ionic liquid is significantly reduced. The results in Table 1 indicate that the present method is applicable for the cyclopropanation of trans-cinnamic acid under mild conditions. Impurities were eliminated by recrystallization of the solid product in boiling water. Simple filtration was needed to collect the product.

To evaluate the repeatability of the catalyst efficiency on the cyclopropanation reaction, this reaction was performed with some more functionalized trans-cinnamic acids. The reaction condition is similar to the procedure described above for the trans-

Table 1 The one-pot reaction of trans-cinnamic acid with iodoform under various conditions



i trans-cinnamic acid | *ii* iodo form | **A** trans-(±)-2-phenyl-cyclopropanecarboxylic acid

Entry	Molar ratio (i:ii)	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	1:1	–	H_2O	24	Trace
2	1:1	–	H_2O (Na_2CO_3, 10 %)	24	25
3	1:1	–	H_2O (NaOH, 10 %)	24	22
4	1:1	[Bmim]OH	H_2O	24	26
5	1:1	[Bmim]Cl	H_2O (NaOH, 10 %)	24	25
6	1:1	$CuCr_2O_4$	THF	24	47
7	1:1	[Bmim]OH/$CuCr_2O_4$	THF	24	73
8	1:1	[Bmim]OH/$CuCr_2O_4$	THF	4	68
9	1:1	[Bmim]OH/$CuCr_2O_4$	CH_2Cl_2	4	61
10	1:1	[Bmim]OH/$CuCr_2O_4$	Et_2O	4	59
11	1:1	[Bmim]OH/$CuCr_2O_4$	EtOAc	4	55
12	1:1	[Bmim]OH/$CuCr_2O_4$	Toluene	4	47
13	1:1.5	[Bmim]OH/$CuCr_2O_4$	THF	4	93
14	1:1.5	[Bmim]OH/$CuCr_2O_4$	THF	4	65[b]
15	1:1.5	[Bmim]Cl/$CuCr_2O_4$	THF/H_2O (NaOH, 10 %)	4	90[c]

Reactions conditions: solvent (5 mL), catalyst (5 mL), 50 °C

[a] GC yield of **A** including trans-cinnamic acid as the starting material

[b] The reaction was carried out room temperature

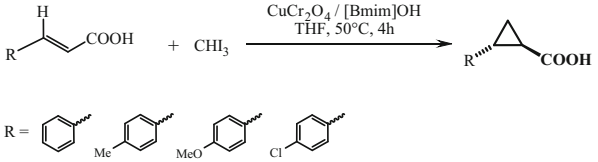
[c] Reaction conditions: [Bmim]Cl (1 mL), $CuCr_2O_4$ (5 mol%), dried THF (5 mL), H_2O (NaOH, 10 %, 5 mL), 50 °C

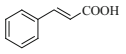
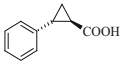
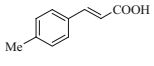
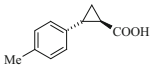
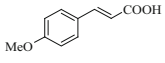
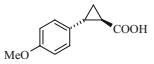
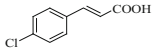
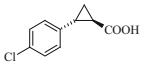
cinnamic acid. (*E*)-3-*p*-tolylacrylic acid, (*E*)-3-(4-methoxyphenyl)acrylic acid and (*E*)-3-(4-chlorophenyl)acrylic acid were used to produce (±)-trans-2-*p*-tolylcyclopropanecarboxylic acid **B**, (±)-trans-2-(4-methoxyphenyl)cyclopropanecarboxylic acid **C** and (±)-trans-2-(4-chlorophenyl)cyclopropanecarboxylic acid **D**, respectively (Table 2). TLC analysis, FT-IR, melting point analysis, ^{1}HNMR and ^{13}CNMR indicated elevated yields and high purity. Tranyl cypromine sulfate as an API is also synthesized and the results of this part of the research are provided in the supplementary material.

Synthesis of tranylcypromine sulfate starting with (±)-trans-2-phenylcyclopropanecarboxylic acid (A)

A mixture of 1.62 g (±)-trans-2-phenylcyclopropanecarboxylic acid **A** (10 mmol), 1.63 g of ethylchloroformate (15 mmol) and 1.5 ml of triethylamine in 10 ml of toluene in an ice-bath was continuously stirred for 4 h. A suspension of 0.975 g sodium azide (15 mmol) in 5 ml of toluene was added dropwise over 1 h at 80 °C.

Table 2 The cyclopropanation reaction of functionalized trans-cinnamic acids



Entry	Reagent	Product		Yield (%)[a]	dr[b]	Reference
1			**A**	93	>98/2	[29]
2			**B**	90	>98/2	[29]
3			**C**	95	>98/2	[29]
4			**D**	81	>98/2	[29]

Reaction conditions: functionalized trans-cinnamic acid (2 mmol, 1 equiv.), iodoform (3 mmol, 1.5 equiv.), [Bmim]Cl (1 mL), $CuCr_2O_4$ (5 mol%), dried THF (5 mL), H_2O (NaOH, 10 %, 5 mL), 50 °C, 4 h

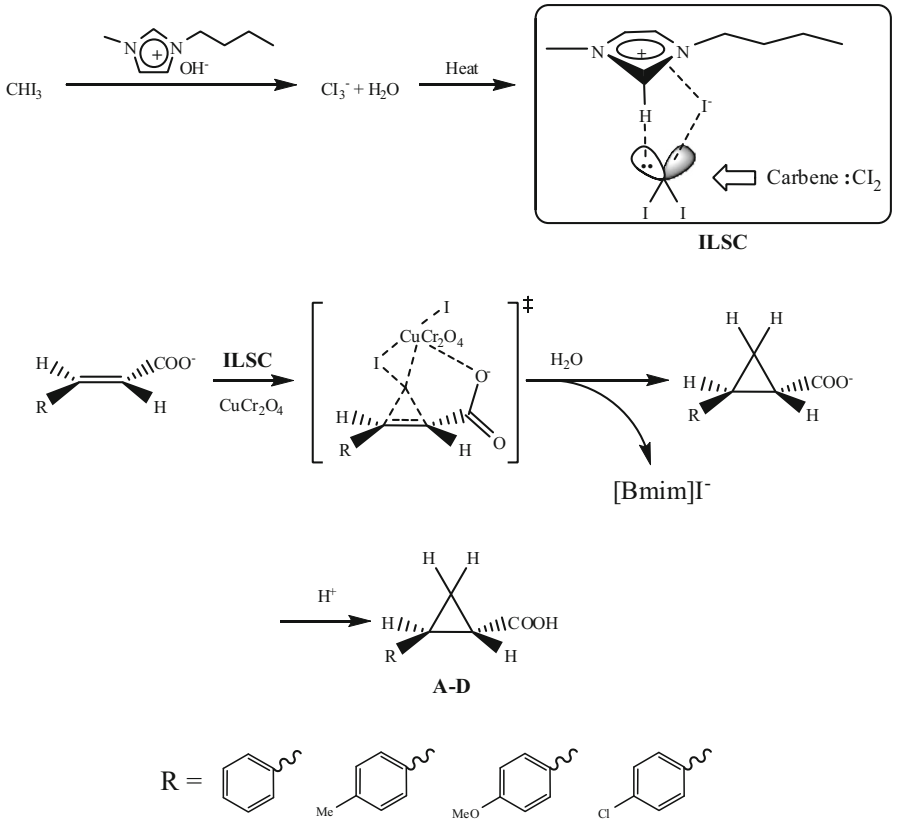
[a] GC yield

[b] Diastereoisomeric ratio (dr) was determined by GC and ^{1}H NMR analysis of the crude products

Slow evolution of nitrogen was observed during the addition. Then, the reaction mixture was refluxed for 4 h. The completion of the reaction was regularly checked by TLC. The mixture was cooled and the precipitate was filtered and washed with 2 × 5 ml toluene. The organic phases were combined and concentrated. The obtained azide intermediate as a viscous oil was used directly in the next step in which 10 ml of hydrochloric acid (37 %) was gently added to the cooled oil in an ice-bath. Gradual evolution of carbon dioxide gas was observed. After the loss of gas evolution, the reaction mixture was refluxed overnight. Then, the mixture was concentrated under reduced pressure. The residue was made strongly basic with 33 % sodium hydroxide to pH ≥ 12 and extracted with 2 × 10 ml dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate, and concentrated at reduced pressures to obtain a yellowish viscous oil of (±)-trans-2-phenylcyclopropylamine. This viscous oil was completely dissolved in 5 ml of 2-propanole in an ice-bath. An ethanolic solution of concentrated sulfuric acid was added gradually to the solution until pH = 2. The white precipitate was filtered, washed with absolute ethanol and dried in an oven at 60°C for 6 h. Finally, 2.66 g (±)-trans-2-phenylcyclopropylamine sulfate (tranylcypromine sulfate) as an API was obtained (Ra = 73 %).

(±)-Trans-2-phenylcyclopropylamine sulfate

$C_{18}H_{24}N_2O_4S$; m.p.: 242–243 °C; MW: 364.4; ^{1}HNMR (400 MHz, $CDCl_3$) δ(ppm): 1.54 (ddd, J = 8.5, 6.3, 4.9 Hz, 1 H), 1.78 (dt, J = 12.9, 5.3 Hz, 1 H), 1.92 (dt, J = 12.5, 5.1 Hz, 1 H), 2.92 (ddd, J = 8.5, 5.9, 4.7 Hz, 1 H), 7.22–7.45 (m, 5 H);



Scheme 3 Plausible mechanism for carbene stabilization and cyclopropanation by [Bmim]OH/$CuCr_2O_4$

^{13}CNMR (100 MHz, $CDCl_3$) δ(ppm): 19.3, 27.1, 32.5, 125.2, 127.8, 129.3, 142.3; IR (KBr) $\bar{\nu}$ (cm^{-1}): 695, 745, 917, 964, 1020, 1107, 1465, 1495, 1555, 2876, 3049, 3400; Rf = 0.60 (methanol:ammonia: 9:1).

The best results were obtained using (*E*)-3-(4-methoxyphenyl)acrylic acid as starting material (Table 2, entry 3) which indicates that the electron-donating groups such as a methoxy group (–OMe) stabilized the transition state (Scheme 3).

Mechanistic aspects

The hydrogen bond has an important role in both the structure of [Bmim]OH and the carbene structure. The imidazolium cation in IL acts as a powerful hydrogen-bond donor, and the anion can acts as an acceptor [30]. The carbene produced by the impact hydroxide ions to iodoform generally possess high basicities, which makes it very strong hydrogen-bond acceptor (Scheme 3).

According to the donor–acceptor properties, a hydrogen bond between 1-butyl-3-methylimidazolium cation and the carbene was observed. A polar interaction between the iodide anions and carbene also helps to stabilize the complex formed.

Due to the relatively strong hydrogen bond and the polar interaction, the complexes (Scheme 3, **ILSC**) which have been formed in this way are low-energy intermediates. So, the formation of the ionic liquid stabilized thr carbene **ILSC**, and subsequently the product is preferred. As a result, using this catalyst, the reaction efficiency and product yield are increased (Table 2, entries 6–13). The best results were achieved when a polar aprotic solvent such as THF was used (Table 2, entry 12). It seems that the polar aprotic solvent helps the substrate dissolution and the intermediate **ILSC** stabilization through the polar–polar intermolecular interactions. Indeed, the reaction products can be recovered from the organic phase, while the catalyst remains immobilized in the ionic liquid phase. Therefore, this strategy has a good potential for catalyst immobilization and to prevent transition metal leakage into the products.

As mentioned in the "Introduction", the cyclopropanation step is the predominant challenge in tranylcypromine total synthesis. This could be due to a number of reasons: first, due to angle strain in small-size cycloalkanes, the cyclopropanation reaction is performed under harsh conditions. Second, because of the chirality of the resulting composition, this cyclopropanation reaction is diastereoselective. Considering that there are two stereogenic centers in 2-phenylcyclopropanecarboxylic acid **A**, the key intermediate, there is the possibility of the formation of four stereoisomers. The application of styrene and ethyl diazoacetate as raw materials leads to the formation of a mixture of (±)-cis and (±)-trans stereoisomers. The most important step during the synthesis of tranylcypromine sulfate is the cyclopropanation of styrene, so that trans isomers can only be generated in a diastereoselective manner. On the other hand, the complete separation of stereoisomers involves the addition of several purification steps, thereby reducing the overall yield of the final product. However, the single trans isomer lacks some side effects that the racemate exhibits, and (±)-trans isomers have been already approved as racemates in pharmaceutical formulations [31]. So, there is no need to further separate the racemic mixture of the (±)-trans isomers.

Reusability of catalyst

The reusability performance of a catalytic system was investigated in the cyclopropanation reaction. After completion of the reaction and work-up of the products, the aqueous phase incorporating the basic ionic liquid and copper chromite spinel nanoparticles was concentrated under vacuum and recycled for subsequent reactions without further purification. The catalytic system was reused for 5 reactions along with a gradual decrease in activity (Fig. 3). Although there is a possibility of catalyst leakage into the organic phase, due to the relatively strong interactions between the polar ionic liquid and the copper chromite spinel nanoparticles, the leakage is minimal. As a consequence, the catalytic performance remains almost constant without any remarkable reduction in activity for the subsequent reactions (93, 90, 88, 85 and 84 % for the 1st, 2nd, 3rd, 4th and 5th runs, respectively).

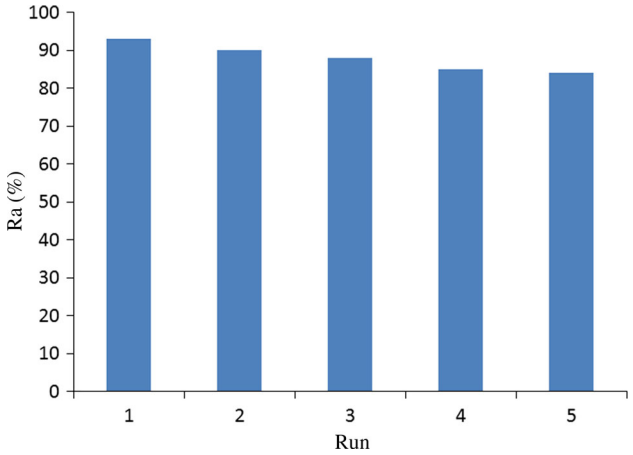


Fig. 3 Recyclability of the catalytic system for the cyclopropanation reaction of trans-cinnamic acid with iodoform

Conclusion

In conclusion, this method for the synthesis of (±)-trans-2-phenylcyclopropanecarboxylic acid **A** as a key intermediate for tranylcypromine sulfate synthesis is, as reported in this paper, an efficient procedure with clean work-up. This method is a useful alternative to other methods described in the literature: the number of overall steps was reduced; commercially available chemicals were used; the heterogeneous catalytic system was easy separable; and environmental hazards were decreased with no need for the separation of the stereoisomers. These advantages of this approach, along with the increased overall yield, make it a suitable choice to produce tranylcypromine sulfate on an increased scale.

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