Gram-Scale Synthesis of Flavoring Ketones in One Pot via Alkylation–Decarboxylation on Benzylic Carbon Using a Commercial Solid Acid Catalyst

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ABSTRACT: The gram-scale synthesis of important flavoring ketones via alkylation of acetoacetic ester on substituted benzylic carbon followed by decarboxylation using a heterogeneous, commercial, solid acid catalyst is reported. The flavoring ketones were synthesized by the alkylation of acetoacetic ester, which proceeds through an S_N1-type reaction to generate an alkylated (β-ketoester) intermediate at the benzylic carbon, which is decarboxylated under the acidic condition. Among the solid acid catalysts used, Amberlyst-15 was found to be the best catalyst under the solvent-free condition. This protocol was successfully employed for the synthesis of various flavoring ketones such as raspberry ketone and ginger ketone with almost complete conversion and 82% isolated yield. The para-donating groups on the benzylic alcohol showed a high rate of reaction. The catalyst was easily recovered and reused 6 times without losing its activity and selectivity. Moreover, this reaction was demonstrated at a 10 g scale, which implicated the potential applicability of the protocol in the industry.

1. INTRODUCTION

The rapid change in the lifestyle has created many noteworthy and antagonistic impacts on humans' health. This brings about an exponential increase in the demand for food additives and substitutes like monosodium glutamate, sodium benzoate, trans fat, sodium nitrite, guar gum, artificial sweeteners, and artificial flavoring agents. However, these food additives possess alarming health issues such as weight gain, hypertension, and vitamin deficiency. To overcome these rising issues, flavoring aryl ketones are known to be useful as they aid in burning subcutaneous fats, serve as dietary supplements, promote weight loss, are used in skin-lightening cosmetics, and have anti-inflammatory and anti-oxidative activities. Hence, aryl ketones are very demanding compounds in flavoring agents, fragrances, pharmaceuticals, and agrochemical industries.\(^1\) The aryl ketones mainly raspberry ketones (RKs), 4-methoxybenzyl acetone (MBA), and ginger ketone (GKs) are phenolic compounds that are mostly used in the aforementioned applications. The market value of these naturally extracted ketones (US$ 3000/kg) ranks second behind vanillin.\(^2\) Thus, a significant interest lies toward alternative synthetic methods for the synthesis of such ketones.

Several methodologies involving C–C bond formation have been developed for the synthesis of these flavoring ketones.\(^3\) The primary synthetic routes for the synthesis of aryl ketones involve Friedel–Craft alkylation of substituted phenol, methyl vinyl ketone, or 4-hydroxy-2-butanone using p-TSA and aluminum-exchanged clay as the catalyst.\(^4\) Another method involves the base-catalyzed aldol condensation followed by a palladium-catalyzed reduction for the synthesis of aryl 2-butanones (Scheme 1).\(^2a\) Similarly, the Wittig reaction, Heck coupling reaction,\(^5−7\) biological oxidation, and Clemmensen reduction\(^8\) have also been reported as an alternative synthetic
routes for these desired products. Also, Bunce et al. reported a two-step synthesis of RK, MBA, and GK using phenol derivatives, methyl vinyl ketones, and Amberlyst-15 (Ab-15) as a catalyst with 50−80% yield of the final product.4 Further, cation-exchanged resin and clay materials like Dowex-50W and Zr4+ ion-exchanged montmorillonite clay have also been used for this reaction. Moreover, HCl-modified montmorillonite acid catalyst and modified β-zeolite have been utilized for the alkylation of phenol.9−13 Wang et al. reported a method to use additives (teta-n-butylammonium fluoride (TBAF) and ZnCl2 as a catalyst) for the decarboxylative Csp3−Csp3 coupling to produce aryl ketones.14b However, the report emphasized the use of several additives and transition metals.

The alkylation of different derivatives of acetoacetic ester (AAE) represents one of the most common methodologies in organic transformations. The generation of cations on allylic/benzylic species using a commercial solid acidic catalyst provides enormous scope in organic synthesis.15−20 However, several challenges need to be addressed to carry out the reaction at milder conditions and low E values.21−24 Also, the traditional methods for the synthesis of ketones utilized a stoichiometric amount of an alkaline/alkaline metal as the base. Herein, we report a modified strategy for the synthesis of different types of aryl ketones via alkylation of substituted benzylic carbons (particularly para-electron-donating groups) with acetoacetic ester (AAE) using a solid Bronsted acid catalyst in one pot under mild reaction conditions.25−27 The avoidance of base as an additive prevents the formation of waste byproducts and thus makes the protocol ecofriendly for the formation of ketones.

2. RESULTS AND DISCUSSION

The alkylation of acetoacetic ester to benzylic and substituted benzylic alcohols catalyzed by the solid acid catalyst produce corresponding ketones. The first step of the reaction occurred via an SN1-type reaction followed by decarboxylation, which results in flavoring ketones. The fact that the para-donating groups increase the electrophilic nature (E factor) of the benzylic carbon facilitates the nucleophilic substitution on sub-benzylic alcohol.28,29 Considering these facts, we carried the C−C bond formation on various benzylic carbons and sub-benzylic alcohols using various industrial solid Bronsted acid catalysts. Among different electron-donating groups, −OH and −OMe groups present on the para position of the benzylic alcohol were chosen for the synthesis of industrially essential ketones like RK and GK. We selected 4-hydroxybenzyl alcohol (4BA) as the model substrate for this protocol and further optimized the reaction conditions (Scheme 2).

For the alkylation reaction, MAA and the catalyst were charged and stirred at 120 °C followed by the slow addition of 4BA in a borosilicate glass tube sealed by a silicone septum. The reaction was monitored by TLC and GC−MS. After the complete consumption of the substrate, the reaction was cooled to room temperature. The decarboxylation was carried out by adding dilute HCl using a syringe (2 equiv HCl in 10 mL of water) and stirred at 150 °C for 4 h in the borosilicate glass tube. The results of the different solid acid catalysts for this reaction are presented in Table 1. When the reaction was carried out in the absence of the catalyst, only 10% conversion of the 4BA was observed (Table 1, entry 1). Indion-130 gave 90% conversion of 4BA with 60% yield of the ketone, while Indion-190 gave almost complete conversion of 4BA with 65% yield of the ketone, respectively (Table 1, entries 2 and 3). The use of Amberlyte-IR-120H and Amberlyst-15 as catalysts produced the corresponding ketones with isolated yields of 74 and 82%, respectively (Table 1, entries 4 and 5). Thus,
Amberlyst-15 was used as the catalyst for further reaction optimization. After the alkylation reaction, the catalyst was separated and reused 6 times, consequently without any loss in the development of the yield and conversion of the substrate (see the SI, Table S3). The major product was isolated by column chromatography and characterized by GC−MS (see the SI, Figures S1−S10) and 13C and 1H NMR (see the SI, Figures S11−S22).

The effect of variation in the catalytic amount is tabulated in Table S1. It was observed that an increase in the catalyst amount initially gave only 60−65% conversion of the substrate (Table S1, entries 1 and 2). On further increasing the catalyst amount, the substrate was completely converted with 90% selectivity toward the desired product (Table S1, entry 3). This may be as a result of an increase in the rate of alkylation of active methylene with an increase in the catalytic site. A further increase in the catalytic amount led to a decrease in the selectivity of the product (Table S1, entries 5 and 6). It was also observed that the byproduct obtained by the self-cyclization of methyl acetocacetate gave 3-methylcyclohex-2-en-1-one and led to double alkylation of benzyl alcohol on methyl acetocacetate. In the nucleophilic substitution reactions, the temperature and solvent play an important role, for example, polar solvents favor the SN1-type reaction and nonpolar solvents favor the SN2-type reaction. Considering this in mind, we further studied the effect of temperature and solvents on RK synthesis.

The effect of the solvent on the conversion of the 4BA and selectivity toward the corresponding ketone was studied at reflux temperature. When the reaction was performed in nonpolar solvents, it gave almost no conversion of the substrates (see the SI, Table S2, entries 1 and 2). Generally, the SN1 type of reaction is favored by the polar protic solvents. Therefore, we used methanol as a solvent. Only 5% of BA was converted with 30% selectivity towards the desired product (Table S2, entry 2), and the major condensed product was observed, which could be formed by condensation with the hydroxyl group on the substrates (see the SI, Figure S10). However, when we carried out the reaction under solvent-free conditions and at 120 °C temperature, the conversion of BA and selectivity towards the corresponding ketone significantly increased (Table S2, entries 5−7). It was observed at the lower reaction temperature (<120 °C), there was only a slight conversion of 4BA to the desired product. Thus, the catalyst served to produce the kinetically controlled product, etherified 4BA at the lower temperatures. The GC−MS analysis confirmed the formation of the self-condensed product of 4BA (see the SI, p. S7, m/z 200, Figure S10), cyclization of MAA (see the SI, Figure S9), and the formation of aldol byproducts. The higher temperature favored the conversion of 4BA toward the RK with high selectivity. Among the different benzylic substrates used, it was found that different para-electron-donating groups like −OH and −OMe stabilized the formed benzylic carbocation. The positive influence of the para-electron-donating group on the benzylic ring of the alcohol for the ketone formation was further confirmed by employing different substituted benzylic carbons as substrate.

2.1. Substrate Scope. The broader applicability of the developed protocol was extended to different substituted benzyl alcohols and benzyl carbons and is summarized in Table 2. The reaction of BA and vanillyl alcohol with AAE gave almost complete conversion with 82 and 76% yields, for the desired products respectively (Table 2, entries 1 and 2). It was observed that the interaction of the catalyst with the donating group substituted at the para position of the benzylic alcohols gave the maximum yields (22−82%) of desired products with no double alkylation side product (Table 2, entries 1−15). However, in the absence of an electron-donating group, the yield of the desired product decreased (Table 2, entry 4). The decrease in the yield of products (1h−1m) may be attributed to the steric hindrance of the methyl group coming from ethyl 2-methyl acetocetate (1h, i, l, and 1m) and the chlorine from methyl 2-chloroacetocetate (1j). It was observed that the enol formation of diketone by the catalyst was trace (Table 2, entries 8, 9, 12, and 13).

The maximum selectivity of aryl ketones was observed in 1i and 1l owing to the presence of a single acidic proton of active methylene compounds (Table 2, entries 9 and 12). The low conversion of the substrate may be attributed to the steric hindrance in the molecule. The methyl-substituted benzylic alcohol gave 35% yield of the desired product 1o (Table 2, entry 15). The presence of the electron-withdrawing group decreases the stability of the carboxylate and is not suitable for this protocol. For example, 4-(hydroxymethyl)benzonitrile gave only 3% yield of the desired product.

After the successful demonstration of benzylic alcohol substrates for the synthesis of aryl ketones, the same reaction protocol was applied to benzylamine and benzyl chloride substrates to obtain the corresponding ketones. Thus, under the optimized conditions, benzylamine was used as a substrate with the catalyst and stirred for half an hour followed by the slow addition of AAE, which gave a good yield of β-enameino ester (Table 2, entry 16). Similarly, the reaction of benzyl chloride with MAA gave 31% yield of the corresponding ketone (Table 2, entry 17). Among the aryl ketones, raspberry ketone and ginger ketones have huge market potential in food industries. Considering the industrial point of view, we scaled-up reaction at 10 g scale for both RK and GK under the optimized conditions. No change in the yield as well as the selectivity of RK and GK at the 10 g scale was observed. This demonstrates the potential applicability of this protocol at an industrial level.

2.2. Plausible Mechanism. The plausible mechanism for the formation of raspberry ketone via alkylation−decarboxylation is shown in Scheme 3.

The catalyst initially protonates the ketonic carbonyl group from methyl acetocetate to form the respective enol, as shown in Scheme 3. This formed enol attacks the stable carbocaticonic sp² carbon species formed by the protonation of benzyl alcohol owing to the activation−stabilization of the alcohol and attains aromaticity. The addition of dilute hydrochloric acid in the second step hydrolyzes the ester to acid. The desired ketone product was formed by decarboxylation via a zwiterion-type intermediate.
3. CONCLUSIONS

In conclusion, the present synthetic protocol utilizes a greener and an efficient route for the synthesis of flavoring ketones using AAE and substituted benzylic carbons catalyzed by a commercial heterogeneous solid Brønsted acid catalyst. The reaction takes place in one pot via alkylation followed by decarboxylation to produce aryl ketones selectively. Several strong solid acid catalysts were screened for the alkylation of AAE, wherein Amberlyst-15 was found to be an efficient catalyst for this reaction. The reaction successfully proceeded under the solvent-free condition and was suitable for all of the substrates to produce the aryl ketones with excellent yield. Notably, the electron-donating groups present on the para position of the benzylic carbon easily interacted with the catalyst for the alkylation of AAE, while in the case of electron-withdrawing substituents, the reaction was hindered. In particular, synthetic products like ginger and raspberry ketones can be further utilized for the formation of an important potent antibiofilm agent like (S)-6-gingerol via aldol condensation. Thus, the present protocol can serve better in the production of aryl ketones at the industrial level.

4. EXPERIMENTAL SECTION

4.1. Materials and Methods. Indion-190, Amerlyst-15 (SD-fine, India), methyl acetoacetate (SRL, India), 4-hydroxybenzyl alcohol (Spectrochem), vanillyl alcohol, and 4-methoxybenzyl alcohol (TCI Chemicals, India) were used as received without further purification.

4.2. Procedure for the Alkylation−Decarboxylation Reaction Using Industrial-Grade Solid Acidic Amberlyst-15. In a typical reaction protocol, 16.11 mmol acetoacetic ester and 40 mg of Amberlyst-15 were stirred for 20 min followed by the slow addition of 16.11 mmol benzylic substrate in a borosilicate glass tube, which is then sealed by a silicone septum. Then, the reaction mixture was stirred at 120 °C for 2 h and the progress of the reaction was monitored by TLC. After the completion of alkylation, the reaction mixture was allowed to cool till room temperature and then 1.00 mL (2 equiv) of HCl in 10 mL of water was added using a syringe and stirred at 150 °C for 4 h in the borosilicate glass tube. The reaction mixture was cooled and washed 3 times with a saturated solution of NaHCO₃. The crude obtained was filtered, washed with water, and extracted using ethyl acetate (3 times extraction and concentrated). The pure product was obtained by column chromatography using silica gel (100−200 mesh) as a stationary phase and hexane/ethyl acetate (90:10) as an eluent. Yields were calculated based on the isolated yield.

| Entry | Reactant | Product | Yield (%) |
|-------|----------|---------|-----------|
| 1.    |          |         | 82        |
| 2.    |          |         | 76        |
| 3.    |          |         | 75        |
| 4.    |          |         | 34        |
| 5.    |          |         | 65        |
| 6.    |          |         | 74        |
| 7.    |          |         | 55        |
| 8.    |          |         | 47        |
| 9.    |          |         | 39        |
| 10.   |          |         | 22        |
| 11.   |          |         | 65        |
| 12.   |          |         | 35        |
| 13.   |          |         | 45        |
| 14.   |          |         | 3         |
| 15.   |          |         | 35        |
| 16.   |          |         | 99        |
| 17.   |          |         | 31        |

*Reaction conditions: benzyl derivative (16.11 mmol), AAE (16.11 mmol), 40 mg of Ab-15, 2 h. For decarboxylation, 2 equiv HCl in 10 mL of water, 150 °C, 4 h. *Isolated yield.

Scheme 3. Plausible Mechanism for the Formation of Raspberry Ketone from 4BA and MAA

Table 2. Scope of the Alkylation−Decarboxylation of Various Benzyl Carbon Substrates Catalyzed by Amberlyst-15

| Entry | Reactant | Product | Yield (%) |
|-------|----------|---------|-----------|
| 1.    |          |         | 82        |
| 2.    |          |         | 76        |
| 3.    |          |         | 75        |
| 4.    |          |         | 34        |
| 5.    |          |         | 65        |
| 6.    |          |         | 74        |
| 7.    |          |         | 55        |
| 8.    |          |         | 47        |
| 9.    |          |         | 39        |
| 10.   |          |         | 22        |
| 11.   |          |         | 65        |
| 12.   |          |         | 35        |
| 13.   |          |         | 45        |
| 14.   |          |         | 3         |
| 15.   |          |         | 35        |
| 16.   |          |         | 99        |
| 17.   |          |         | 31        |
products. The analysis of the product mixture was carried out by GC (Agilent 7890B, HP-5 column, 30 m length, 0.25 mm internal diameter) with an FID detector and GC–MS (Shimadzu, QP-2010/TQ 8040, Japan). A 5% diphenyl- and 95% dimethylsioxane universal capillary column was used for the analysis purpose. The quantification of the FID response was done by a standard calibration curve. Products were characterized by GC–MS, 1H NMR, and 13C NMR (see Figures S1–S22). Chemical shifts were recorded in CDCl₃ or DMSO-d₆ solutions referenced to tetramethylsilane (TMS) (0.00 ppm) or CDCl₃ (7.26 ppm) and DMSO-d₆ (2.50 ppm) for 1H NMR and CDCl₃ (77 ppm) and DMSO-d₆ (39.5 ppm) for 13C NMR. For the 10 g scale reaction, a similar procedure was followed using 80.64 mmol benzylic substrate, 80.64 mmol methyl acetocetate, and 200 mg of Ab-15 in the reaction.

**ASSOCIATED CONTENT**

1 Spectroscopic, experimental, and analytical data as well as the original copy of GC–MS and 1H and 13C NMR spectra of all new compounds (PDF)

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**Author Contributions**

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**Notes**

The authors declare no competing financial interest.

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