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A simple synthesis of ketone from carboxylic acid using tosyl chloride as an activator

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ABSTRACT

An effective process for the conversion of carboxylic acid to ketone has been discovered. In this process, carboxylic acid has been activated using *p*-toluene sulphonyl group. Under the optimized condition, aromatic, aliphatic heteroaromatic carboxylic acids have been proved to be good substrates for this methodology. The byproduct of this reaction can be removed very easily during work up process. Also, one equivalent of organometallic reagent is sufficient to complete this transformation.

Being a ubiquitous moiety, carbonyl group particularly ketone has been considered as one of the most important functionalities in organic chemistry [1]. Therefore, accessibility of ketone based on a simple chemical reaction is still demanding. Till now, efforts have been made to access ketone from different starting materials such as alcohol, aldehyde, amide etc [2]. One notable method which has been studied extensively, involves the conversion of carboxylic acid to ketone [3]. Easy accessibility and stable nature of the carboxylic acid have attracted the curiosity of organic chemists for this purpose. Generally, acids are transformed to the desired ketones by using a suitable organometallic reagent *via* Wenreib amide intermediate [4]. Other metal catalyzed processes are also well known for this conversion [5].

To overcome the drawbacks associated with some metal catalyzed reactions, recently we have reported a convenient way for the conversion of carboxylic acid to ketone in a one pot fashion using DCC as a carboxylic acid activator [6]. In that methodology, a problem related to byproduct separation made the process less viable in organic synthesis (Scheme 1). Therefore, attention was paid on searching for an activating agent which after reaction, can be separated easily from the product. Consequently, our efforts for this transformation have been discussed herein.

So far, Wenreib amide concept has been widely accepted among synthetic community for the conversion of carboxylic acid to ketone. In this aspect, intermediate **A** (Fig. 1) plays a crucial role to produce ketone at low temperature. Keeping the image of the intermediate **A** (Fig. 1) in mind, we anticipated to generate a similar type intermediate such as **B** (Fig. 1) which might fulfill our purpose. The intermediate **B** could be obtained during the reaction between organometallic compound (R′-M, Scheme 1) and mixed anhydride **4** (Scheme 1) at low temperature.

With this intention, *p*-toluenesulfonyl chloride (tosyl chloride, TsCl) has been selected for this task. Sulphonyl chlorides are frequently used for various transformations in synthetic chemistry as for example, protection of alcohol and amine, synthesis of amide, ester from carboxylic acid etc. [7]. To explore the versatility of this reagent in organic synthesis, we thought to utilize in the conversion of carboxylic acid to ketone, which was unexplored till date [8]. We envisioned that as tosyl protected alcohol **8** can be easily converted to the product **10**, if treated with a carbon or heteroatom based nucleophile [9], therefore tosyl protected acid **9** could be converted to the ketone **11** in a more facile manner based on a similar type of reaction (Scheme 2).

This difference in reactivity, between **8** and **9** can be rationalized based on the electrophilic character of the carbon which is attached with the O-protected tosyl group (Scheme 2). To ensure these assumptions, we started the investigation using benzoic acid as initial substrate.

Thus, a reaction was carried out using commercially available benzoic acid (**1a**, Table 1, 0.5 mmol) and TsCl (0.5 mmol) in presence of 4-(dimethylamino)pyridine (DMAP, 0.5 mmol) in THF (2.5 mL) at room temperature under N_2 atmosphere. After 1 h, a new compound formation has been observed (monitored by TLC) along with the formation of pyridinium salt. Into it, *n*-BuLi (1 mmol, 1.6 M in hexanes) was added dropwise at low

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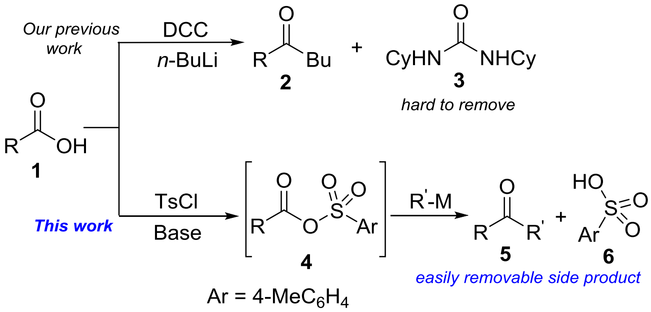


Scheme 1. Ketone synthesis: A comparative study.

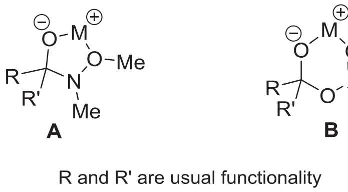
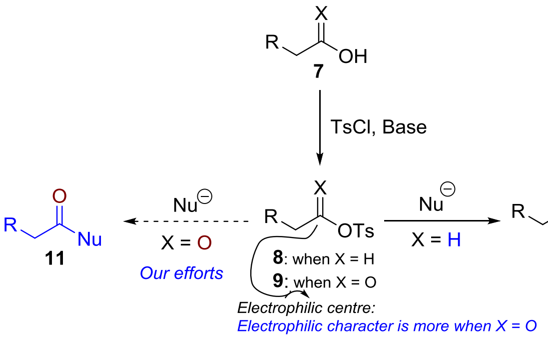
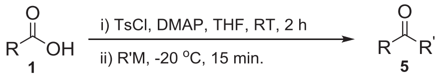


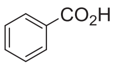
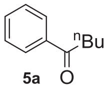
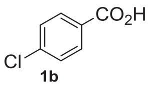
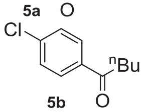
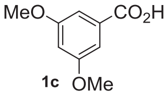
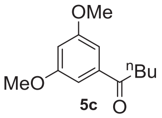
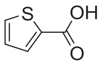
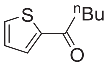
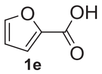
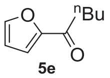
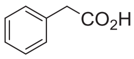
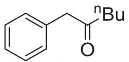
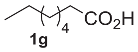
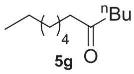
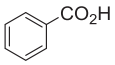
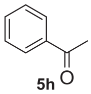
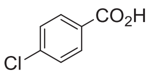
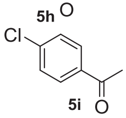
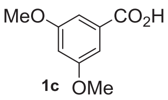
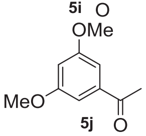
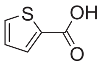
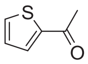
Fig. 1. Intermediate formed during the interaction of Wenreib amide and organometallic reagent.



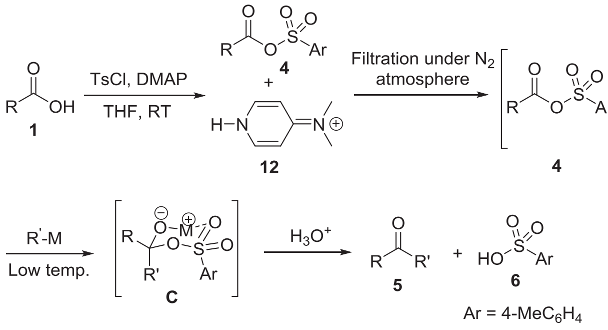
Scheme 2. Activation of carboxylic acid using tosyl chloride.

Table 1
Substrate scope of ketone synthesis using TsCl: Reactions were carried out in 0.5–1 mmol scale under N_2 atmosphere; Yields refer to the isolated yield; ^{a}For this n-BuLi was used, ^{b}For this MeMgBr was used.



Entry	Substrate	Product	Yield (%)
1	 1a	 5a	75^a
2	 1b	 5b	71^a
3	 1c	 5c	63^a
4	 1d	 5d	60^a
5	 1e	 5e	56^a
6	 1f	 5f	55^a
7	 1g	 5g	58^a
8	 1a	 5h	80^b
9	 1b	 5i	75^b
10	 1c	 5j	70^b
11	 1d	 5k	78^b

temperature (-20 °C) and satisfyingly the desired ketone **5a** was obtained which was confirmed by using ^{1}H NMR spectroscopy. Based on this preliminary result, we concentrated to optimize the reaction conditions on benzoic acid in presence of n-BuLi. A few reactions were performed to get the best yield of the desired ketone **5a** in THF solvent. After varying the reaction conditions, best yield of **5a** was obtained when one equivalent of TsCl was added to the equimolar amount of carboxylic acid in THF at room temperature for 2 h, followed by slow addition of n-BuLi (2 equivalents) at −20 °C. Further, we determined to reduce the amount of organometallic reagent during the reaction. After careful thinking about the reaction mechanism, a process has been developed, where the pyridinium salt (**12**, Scheme 3) has been filtered from the medium before adding the nucleophile. Thus we optimized the reaction conditions [10] with one equivalent of organometallic reagent and various aliphatic, aromatic and heteroaromatic carboxylic acids were converted to the corresponding ketones in good yields under this condition. Aromatic carboxylic acids containing electron poor as well as electron rich ring systems found as excellent substrates. Pleasingly, chloro functionality (Entry 2, Table 1), ether group (Entry 3 Table 1) are stable enough under optimum conditions. Moreover, heteroaromatic acids (Entry 4 and 5, Table 1) yielded the desired ketones in reasonable amounts. Experiment with aliphatic acids (Entry 6 and 7, Table 1) was satisfactory to produce the desired ketone. Next, to explore the potentiality of this methodology, we decided to perform the reaction using organomagnesium reagent. Few reactions have been performed using methyl magnesium bromide as a nucleophile (Entry 8, 9, 10 and 11, Table 1). Gratifyingly, acteophenone and 4-chloroacetophenone



Scheme 3. A proposed mechanistic pathway.

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were isolated in excellent amount from the reaction mixture under standard reactions conditions.

Also, aromatic acid having electron rich ring (Entry 10, Table 1) showed good result under the conditions. Thiophene 2- carboxylic acid was reacted with the organometallics in excellent manner to yield the desired ketone. All the results of our experiment are summarized in Table 1.

A probable mechanism of the reaction has been shown in Scheme 3. Carboxylic acid **1** in presence of a base reacts with tosyl chloride at room temperature, to form a mixed anhydride **4**, [8,11] which can be separated through simple filtration technique under inert condition. Then slow addition of nucleophile at −20 °C into **4** leads to the formation of an intermediate **C** (Scheme 3). This intermediate seems to be stable at low temperature through the chelation in presence of a metal ion. Finally, quenching of the intermediate **C** at cold condition produces the desired ketone **5** along with *p*-toluene sulphonic acid **6**. During the work up process, ketone **5** could be accessed easily, as the by-product **6** can be removed by washing with bicarbonate solution and water.

In conclusion, a simple and effective method for the synthesis of ketone from carboxylic acid has been developed. In this process, aromatic, aliphatic and heteroaromatic carboxylic acids were reacted with tosyl chloride in the presence of DMAP, which upon addition of an organometallic compound provided the desired ketones in exclusive manner. The key advantage of this process is: the ketone has been accessed from acid using one equivalent of organometallic reagent. Also the byproduct of this reaction can be removed easily during the work-up process. Detail studies on this transformation using soft nucleophiles and using aliphatic acids are under investigation in our laboratory and will be disclosed in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151084.

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[10] Experimental procedure: To a stirred solution of carboxylic acid **1** (1 mmol) and TsCl (1 mmol) in THF (5 mL), DMAP (1 mmol) was added at room temperature under N_2 atmosphere. After 2h (to ensure the complete conversion, checked by TLC), the mixture was filtered under N_2 atmosphere and the filtrate was cooled to −20 °C. Then, R-M (1 mmol) was added dropwise to the reaction mixture at that temperature. After 15 min. the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) at −20 °C. The mixture was warmed to room temperature and extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with 10% $NaHCO_3$ solution (20 mL × 3), water (20 mL × 3), brine (20 mL) and finally dried over $MgSO_4$. The volatiles were evaporated under reduced pressure to get a crude mass which was then purified by column chromatography on silica gel to obtain pure ketone **5**.

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