Synthesis of the β-keto acids from benzimidazolium iodides and ethyl malonate

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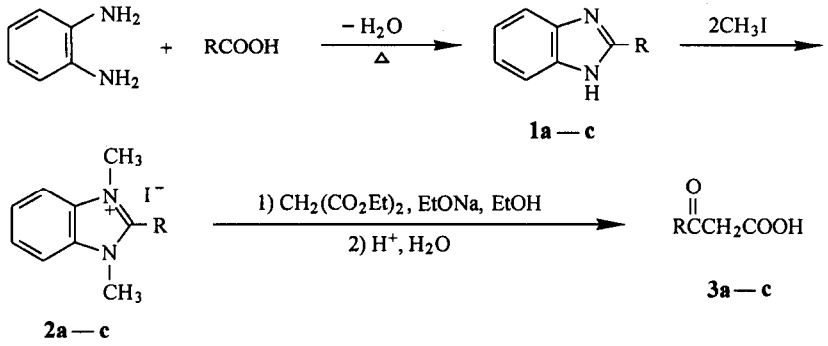
The reaction of benzimidazole methiodide with ethyl malonate in the existence of base was studied, and a new convenient synthetic method of the β-keto acid was provided.

Keywords β-Keto acid, benzimidazolium iodide, ethyl malonate, synthesis

It has been reported that β-keto acid and some of its derivatives showed significant activities in the metabolism of carboxylic acid. β-Keto acid has been synthesized in several ways. Matsumura *et al*. prepared the β-keto acid from the reaction of carbon dioxide carrier 2-morpholinoimidazolinomagnesium complex with active methylene compound.[1] Milton *et al*. claimed the preparation of β-keto acid from the hydrolysis of the corresponding ester by glacial acetic acid and concentrated hydrochloric acid.[2] Barnick *et al*. developed a new method for the synthesis of the β-keto acid, the carboxylic acids were converted into acid chlorides and subjected to treatment with the mono-anion of bis (trimethylsilyl) malonate at 0℃, followed by the short treatment with water at room temperature leading to hydrolysis and decarboxylation of the intermediate triacyl compound to yield the β-keto acid.[3]

We reported the addition-hydrolysis reaction of benzimidazole methiodide salts with nucleophile such as Grignard reagents, and a new method for the preparation of aldehydes and ketones was provided.[4] In this paper, the reaction of benzimidazolium salts with nucleophile ethyl malonate anion was studied, and a new convenient and useful synthetic method of the β-keto acid was provided (Scheme 1)

Scheme 1



Benzimidazole **1a—c** was prepared from 1,2-benzenediamine and carboxylic acid,[5] and the benzimidazolium iodide **2a—c** was obtained via quaterisation.[6]

The procedure for the preparation of the β-keto acid **3a—c**: 15 mL of anhydrous ethanol and 0.46 g (0.02 mol) of sodium cut in small pieces were placed in a 250

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mL three necked round-bottomed flask fitted with a condenser and a mechanical stirrer, 3.2 g (0.02 mol) of ethyl malonate was added until all the sodium was dissolved. The stirring was started and the solution was heated to gentle boiling. To the boiling solution 0.02 mol of benzimidazolium iodide was added over a period of about 30 min. The reflux and stirring were continued for 16—18 h, then a 10% solution of hydrochloride was added slowly, and the resulting mixture was heated at 60—65℃ for 30 min with stirring. The solvent was removed, and after the residue was dissolved in glacial acetic acid, concentrated hydrochloride was added dropwise until the solution became slightly turbid. The mixture was allowed to stand at room temperature for 45—48 h, and the resulting white crystals were collected, and recrystallized from acetone to give pure β-keto acids. The experimental data are listed in Table 1.

Table 1 Experimental data of compounds **1a—3c**

Compd.	R	mp (℃)	Yield (%)
1a	C_7H_{15}	143—144(Lit[5]: 144.5—145.0)	86.5
1b	$C_{15}H_{31}$	98—100(Lit[5]: 96.5—97.0)	85.4
1c	CH_3	178—179(Lit[5]: 177—177.5)	78.5
2a	C_7H_{15}	210—211[a]	82.4
2b	$C_{15}H_{31}$	187—188[b]	86.7
2c	CH_3	256—258(Lit[7]: 256)	76.4
3a	C_7H_{15}	82—84(Lit[8]: 83—84)	65.4
3b	$C_{15}H_{31}$	101—102(Lit[2]: 103—104)	54.5
3c	CH_3	102—104(Lit[9]: 104—105)[c]	61.5

[a] Calcd: C, 51.35; H, 6.68; N, 7.48. Found: C, 51.64; H, 6.92; N, 7.21. [b] Calcd: C, 59.25; H, 8.44; N, 5.76. Found: C, 58.97; H, 8.35; N, 5.50. [c] mp of oxime.

The mechanism of the reaction for benzimidazolium iodide with nucleophile reagent has been proposed in our previous paper.[4] The reaction details described in this paper are reasonably explained by a similar addition reaction of ethyl malonate anion with quaternary C = N bond of benzimidazolium iodide, and the obtained benaimidazolidine can be converted into the corresponding β-keto acid via hydrolysis.

In view of poor result obtained from the reaction of benzimidazole with nucleophile, it may be concluded that the formation of quaternary ammonium salt probably assists the addition reaction by increasing the polarity of C = N bond being attacked by ethyl malonate anion. Further studies of this reaction are being continued in our laboratory.

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