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Application of IBX Method for the Synthesis of Ketones from Carboxylic Acids

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Methoxy phenyl propionic acid and some derivatives are converted to ketones using a new method. All classical methods to obtain ketones from carboxylic acids via acid halide consistently gave very low yields and regularly generated intermolecular cyclisation products or polymeric materials. However, high ketones yields are obtained by using the new IBX method.

Key Words: IBX (o-iodoxy benzoic acid), methoxy phenyl propionic acid, ketone, Oxidation.

Introduction

One of the most common reactions in chemistry is the synthesis of ketones from acids[1−4]. First, the acid is changed into its chloride. Then the acid chloride reacts with an organometallic reagent or gives a Friedel-Crafts type reaction in the presence of Lewis acids. These methods are very useful for most aliphatic acid halides and good yields can be obtained in this way. However, if this method is used for propionic acid, which contains the methoxy phenyl group, very low yields of ketones (5-12%) are obtained.

Attempts at increasing the yields of ketones also failed using the Corey-House method[5,6]. These attempts led either to the formation of polymeric material and intractable tar as reaction products or to intermolecular cyclisation reactions, which were isolated after the reaction.

In this study, the critical point in the classical method is the halogenation of the acids. After the acid halide is obtained, other molecules either react with this acid halide or can cause intermolecular cyclisation reactions due to the high reactivity of the methoxy phenyl group on the molecule. For this reason, obtaining and controlling the acid chloride formation is very difficult. Furthermore, further reactions with the obtained small amount of acid chloride, using Grignard reagent, are very difficult under normal conditions. Additionally, the alkylation reaction of this type of acid chloride with Grignard reagent always provides dialkylation products instead of mono alkylation ones because reducing the reaction temperature

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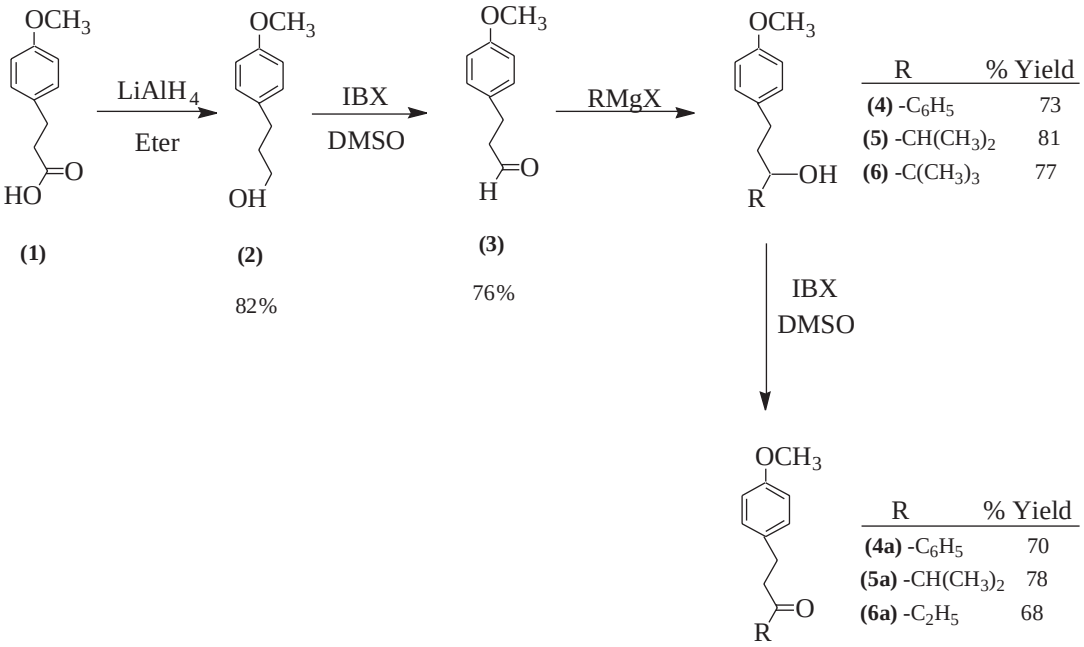
in order to obtain mono alkylation products leads to another problem of solubility. This is why there are no significant studies about this kind of ketone synthesis in the scientific literature.



Experimental

Preparation of IBX: A sample of 22.5 g (90.7 mmol) 2-iodobenzoic acid was added to a solution of potassium peroxymonosulphate ($2KHSO_5.KHSO_4.K_2SO_4$: oxone) (54.3 g, 88.3 mmol) and 300 mL of water were stirred in a water bath at a temperature range of 70-75 °C for 3 h with a mechanical stirrer. The mixture was slowly cooled to 5 °C and again stirred for 1.5 h at the same temperature. As a result, there occurred the formation of white crystals, which were filtered. The solid product was washed with a water acetone mixture and dried in a vacuum oven to give 21.2 g (75.7 mmol) of o-iodoxy benzoic acid (IBX) as white crystals 83% yield.

General procedure oxidation of alcohols with IBX: A sample of 11 mmol of recrystallised IBX and 10 mmol of general alcohols were added to (27.5 mL) DMSO to form 0.4 M of solution and this mixture was stirred at room temperature for 4 h. Water (20 mL) was then added to the reaction mixture to precipitate 2-iodobenzoic acid crystals, and these crystals were decanted. The mother liquid was extracted with ether (3 x 25 mL), washed with $NaHCO_3$ solution, and dried over $MgSO_4$ to obtain aldehydes or ketones.

General procedure for Grignard reactions: In a 3-necked flask, 1.1 mol of magnesium turnings and 1 mol of alkyhalides (bromobenzene, isopropyl chlorides and ethyl bromides) in dry ether were slowly added and stirred under a nitrogen atmosphere. Heat was used when necessary.

3-(4-Methoxyphenyl)-1-phenyl-propanol (4): A sample of 32 mmol prepared Grignard reagent in dry ether was mixed with an aldehyde **(3)** 4.78 g (29.15 mmol) solution in ether and the reaction mixtures were allowed to stay overnight at room temperature. Hydrolysed with conc. HCl and extracted with ether, the obtained product **(4)** was recrystalised under hexane, and colourless crystals were obtained in good

yields, 4.93 g (73%), mp: 61.3-62.1^{o}C (lit., [7], mp: 62-63 °C), ^{1}H-NMR (DMSO–d_6); 1.92 (2H, m, -CH_2-), 2.50 (2H, m, -CH_2-), 2.6 (1H, b, -OH), 3.75 (3H, s, -OCH_3), 4.5 (1H, m, -CHOH), 6.85-7.45 (9H, m, arom.); IR (KBr/cm^{-1}), 3360 (OH).

3-(4-Methoxyphenyl)-1-phenyl-propanone (4a): As in the above general procedure, oxidation of alcohols with IBX, 2.78 (11.5 mmol) of dissolved alcohols **(4)** in DMSO (17 mL) was slowly added to a mixture of 3.6 g (12.0 mmol) IBX in DMSO (14 mL), and the mixture was stirred at room temperature for 4 h. Water (30 mL) was then added to the reaction mixture to precipate **(4a).** The product recrystalized under an ethanol-water mixture to produce colourless crystals in good yields (70%) mp: 67.2-67.8 °C (lit., [7], mp: 68 °C), ^{1}H-NMR(DMSO–d_6); 2.85 (2H, t,-CH_2-), 3.20 (2H, t, -CH_2-), 3.7 (3H, s, -OCH_3), 6.85-8.0 (9H, m, arom); IR (KBr/cm^{-1}), 1680 (C=O).

1-(4-Methoxyphenyl)-4-methyl-3-pentanol (5): The same reaction for **(4)** was continued for the preparation of **(5)** and the crude product was purified by column chromotography with ethylacetate: hexane (3:2) to give 6.24 g (30 mmol) (81%) of 1-(4-methoxyphenyl)-4-methyl-3-pentanol **(5)** as colourless crystals. ^{1}H-NMR (DMSO); 0.9 (6H, dd, 2 -(CH_3)), 1.8 (2H, m, -CH_2-), 1.8 (1H,m,-CH-), 2.5 (2H, m,-CH_2-), 3.3 (1H, m, -CH-), 3.6 (1H, b, -OH), 3.9 (3H, S, -OCH_3), 6.8-7.1 (4H, dd, arom); IR (KBr/cm^{-1}), 3408 (OH).

1-(4-Methoxyphenyl)-4-methyl-3-pentanone (5a): The same general procedure was applied in order to obtain this product, and **(5a)** was obtained in good yields (78%) as a liquid. bp: 206-208 °C, ^{1}H-NMR(DMSO–d_6); 0.9-1.0 (6H, dd, 2-CH_3), 1.6 (2H, t, -CH_2-), 2.7 (1H, m,-CH-), 2.85 (2H, t, -CH_2-), 3.7 (3H, s, -OCH_3), 6.9-7.2 (4H, dd, arom). IR; 1721 cm^{-1}(C=O).

1-(4-Methoxyphenyl)-3-pentanol (6): The same reaction procedure for **(4)** was applied in order to obtain this compound, and 3.95 g (20.3 mmol) (77%) of **(6)** was obtained in good yields. ^{1}H-NMR(DMSO–d_6); 0.95 (3H,m-CH_3), 1.5 (2H, m, -CH_2-), 1.8 (2H, m, -CH_2-), 3.25 (1H,m,-CH-), 3.75 (1H, b, -OH-), 3.85 (3H, s, -OCH_3), 6.9-7.1 (4H, dd, arom); IR, 3360 (OH).

1-(4-Methoxyphenyl)-3-pentanone (6a): The same procedure was applied in order to obtain this reaction, and 3 g (15.6 mmol) of **(6a)** was obtained in good yields (68%) as a liquid bp: 148.5-149,5 °C/10 mmHg (lit.,[8], bp: 148,5-149/9.5 torr). ^{1}H-NMR (DMSO–d_6); 1.05(3H, t, -CH_3), 2.30 (2H, t, -CH_2), 2.7 (2H, t, -CH_2-), 2.90 (2H, m,-CH_2), 3.85 (3H, s, -OCH_3), 6.9-7.2 (4H, dd, arom.). IR; 1685 cm^{-1} (C=O).

Results and Discussion

We tried to obtain ketones using a method different from the classical method. In short, this new method depends on the reduction and oxidation of the carbonyl groups. In these reactions, oxidation is carried out with the new oxidation reagent, IBX (*o*-iodoxybenzoic acid), which has recently been found to be a good oxidation agent[9–13]. Cheap and non-toxic, IBX, a selective oxidation reagent, is therefore very suitable for oxidising alcohols to aldehyde or ketones. We reduced the acids to alcohols with $LiAlH_4$, and then we oxidised them with IBX to form aldehyde. After the mono alkylation of aldehydes with the Grignard reagent (RMgX), the obtained alcohols were re-oxidised with IBX to the ketones. High ketone yields are the result. All of the alcohols and ketones thus prepared are known compounds and are pure products. All were compared (^{1}H NMR, mp, IR) with genuine samples prepared independently.

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