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Der Pharma Chemica, 2012, 4 (3):1292-1295
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Studies on preparation of 2-Acetylbenzimidazole

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ABSTRACT

*o-Phenylenediamine **(1)** was condensed with lactic acid **(2)** under Philips conditions to obtain the previously known 2-(α-hydroxyethyl)benzimidazole **(3).** Oxidation of **3** with $K_2Cr_2O_7$ in dil. H_2SO_4 using the literature method gave the previously reported 2-acetylbenzimidazole **(4).** Several methods have been tried using various oxidising agents / dehydrogenating agents to optimise the preparation of **4** from **3**.*

INTRODUCTION

The study of the chemistry of benzimidazoles has been and continues to be one of the most active and fascinating areas of heterocyclic chemistry. The benzimidazole ring system has been found in many naturally occurring compounds of great chemical and biochemical interest[1, 2]. There are number of benzimidazoles known - ranging from simple to some of the most complex structures - in Organic Chemistry and there are several synthetic derivatives which find applications as drugs, pharmaceuticals, agrochemicals etc. In continuation of our earlier work on synthesis of 2-substitutedbenzimidazoles[3 – 5], we now wish to report our studies on oxidation of 2-(α-hydroxyethyl)benzimidazole.

MATERIALS AND METHODS

Experimental Section:

Preparation of 4 from 3:

1. With $K_2Cr_2O_7$: To a solution of **3** (8.1 gm, 50mM) in dil H_2SO_4 (5% 40 ml) was added at RT a solution of $K_2Cr_2O_7$ (9.8 gms, 50mM) in water (60 ml) and conc. H_2SO_4 (20 ml) in a dropwise fashion, over a period of 20 mins. The reaction mixture was stirred vigorously during addition. The separated solid was filtered and washed with water (3 x 10ml). The precipitate was resuspended in water (50 ml) and treated very carefully with aq. NH_3 to a pH of 6.0 – 6.5. The suspension was stirred for 0.5 hr and filtered. The residue was washed with water (3 x 10 ml) and dried to obtain **4**.

2. With MnO_2: To a solution of **3** (1.62gm, 10mM) in methylethylketone (30ml), was added solid MnO_2 (1.72gm, 20 mM) and the solution was heated under reflux for 4 hrs. During this period the progress of the reaction was monitored on TLC for the disappearance of the starting material **3**. No product formation was observed on TLC and starting material was recovered on processing the reaction mixture by filtration and evaporation of the filtrate.

3. With MnO_2 by physical grinding: A mixture of **3** (1.62gm, 10mM) and MnO_2 (1.72gm, 20mM) were ground together in a mortar and pestle for 1 hrs. During this period, the progress of the reaction was monitored on TLC for the disappearance of the starting material **3**. No product formation was observed on TLC and starting material was recovered on processing the reaction mixture by dissolution in acetone, filtration of mixture and evaporation of the acetone filtrate.

4. With H_2O_2 / gl. AcOH: To a solution of **3** (1.62gm, 10mM) in glacial AcOH (10ml) at 0°C was added a solution of H_2O_2 (30 %, 8ml) in glacial AcOH (5ml) dropwise with stirring under ice-cold conditions over a period of 15 mins. After completion of addition, the reaction mixture was allowed to warm up by removing the ice-chest and stirred at RT for 1 hr. At the end of this period, the reaction mixture was poured into ice-cold water (50ml). The aq. acidic solution was neutralised with satd. aq. $NaHCO_3$ (5 %) to pH of 7.0. The separated product was filtered, washed with water and dried to obtain **4.**

5. With $CaOCl_2$: To a solution of **3** (1.62gm, 10mM) in methylethylketone (30ml), was added solid $CaOCl_2$ (1.42gm, 10 mM) and the solution was heated under reflux for 3 - 4 hrs. During this period, the progress of the reaction was monitored on TLC for the disappearance of the starting material **3**. No product formation was observed on TLC and starting material was recovered on processing the reaction mixture by filtration and evaporation of the filtrate.

6. With m-CPBA: To a solution of **3** (1.62gm, 10mM) in glacial AcOH (10ml) at 0°C was added m-CPBA (1.72gm, 10mM) in glacial AcOH (5ml) with stirring under ice-cold conditions over a period of 15 mins. After completion of addition, the reaction mixture was allowed to warm up by removing the ice-chest and stirred at RT for 3 – 4 hr. At the end of this period, the reaction mixture was poured into ice-cold water (50ml). The aq. acidic solution was neutralised with satd. aq. $NaHCO_3$ (5 %) to pH of 7.0. A small quantity of white solid separated out, which was filtered carefully washed and dried. It was found to be starting material **3** only (TLC, M.P & M.M.P).

7. With 10 % HNO_3: A solution of **3** (1.62gm, 10mM) and 10% HNO_3, (10 ml) was stirred at RT for 3 - 4 hrs. During this period the progress of the reaction was monitored on TLC for the disappearance of the starting material **3**. At the end of this period, the reaction mixture was poured into ice-cold water (50ml). The aq. acidic solution was neutralised with satd. aq. $NaHCO_3$ (5 %) to pH of 7.0. The separated solid was filtered, washed with water and dried. It was found to be starting material **3.** (TLC, M.P. and M.M.P).

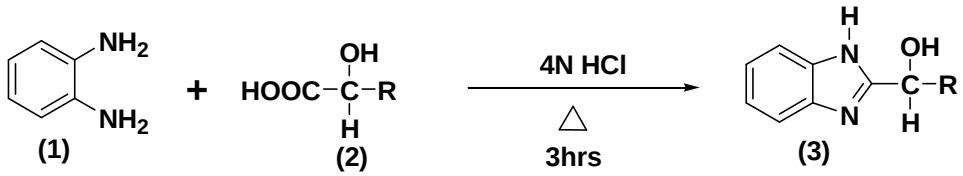
8. With 50 % HNO_3: A solution of **3** (1.62gm, 10mM) and 50% HNO_3 (10 ml), was stirred at RT for 3 - 4 hrs. During this period the progress of the reaction was monitored on TLC for the disappearance of the starting material **3** and the reaction mixture is further heated under reflux for 3 - 4 hrs. At the end of this period, the reaction mixture was poured into ice-cold water (50ml). The aq. acidic solution was neutralised with satd. aq. $NaHCO_3$ (5 %) to pH of 7.0. The separated solid was filtered, washed with water and dried. It was found to be starting material **3.** (TLC, M.P and M.M.P)

9. With CAN: To a solution of **3** (1.62gm, 10mM) in methylethylketone (30 ml), was added solid CAN (1.35gm, 2.5 mM) and the reaction mixture was stirred at RT 3 - 4 hrs. At the end of this period, the reaction mixture was poured into ice-cold water (50ml). The separated solid was filtered and washed with water (3x10ml) and dried to obtain **4**.

RESULTS AND DISCUSSION

o-Phenylendiamine **(1)** was condensed with lactic acid **(2)** under Philips conditions[6] to obtain the previously known 2-(α-hydroxyethyl)benzimidazole[7, 8] **(3)** as a crude, fairly water soluble product.

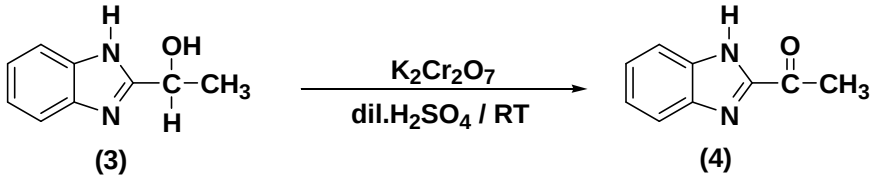
Scheme-1



3, which is a racemic mixture of two optically active enantiomeric compounds, could be readily purified by dissolving in hot acetone, treating with charcoal in hot condition, filtration, concentration and cooling to yield a crystalline precipitate of **3**, which was found to be pure on TLC.

Oxidation[9-10] of **3** with $K_2Cr_2O_7$ in dil. H_2SO_4 gave the previously reported 2-acetylbenzimidazole[11] **(4).** The reported procedures for the preparation of **4** involve oxidation of **3** with $K_2Cr_2O_7$ in dil.H_2SO_4 followed by careful neutralisation of the reaction mixture with aq.NH_3 to a pH of 5.5-6.0, resulting in the formation of **4,** which is filtered, washed with water and dried. Yield is reported to be around 60% with the product being sufficiently homogeneous and pure on TLC. Similar were the results obtained in our work.

Scheme-2

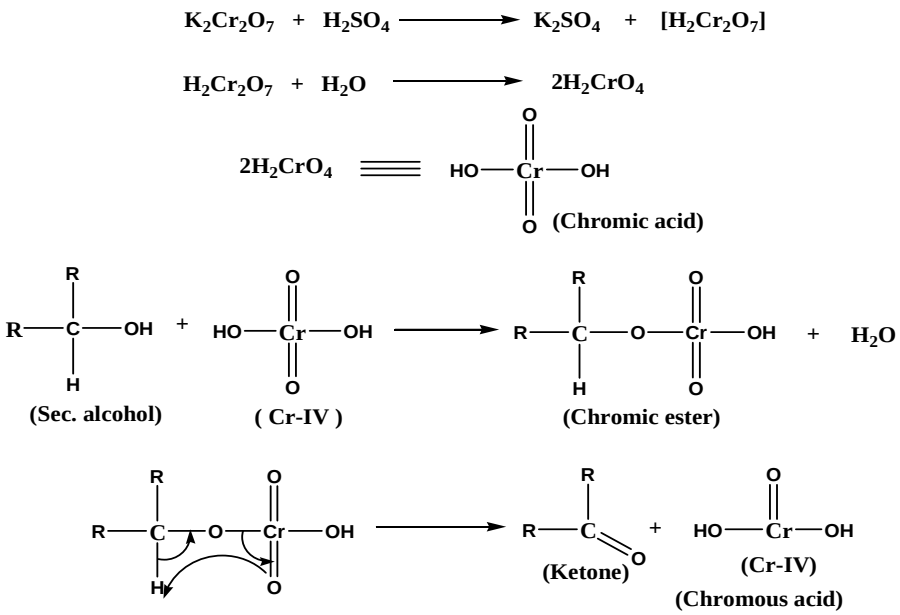


(3) **(4)**

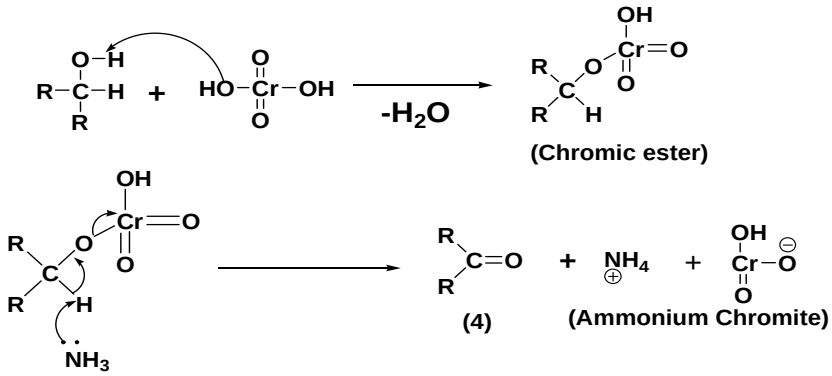
It has been observed that in the above reaction, the pH of the solution during neutralisation with aq.NH_3 should be close to neutral, preferably between 5.5-6.0 and should not exceed 7.0. If the pH of the solution exceeds 7.0, i.e., if it goes to basic side, then the yield of the product **4** goes down considerably, as **4** is reasonably soluble in dil.aq. alkaline solutions and the product purity also suffers due to improper precipitations of chromium salts in reduced oxidation states formed as a result of reduction of the dichromate.

There are two probable mechanisms for the oxidation of **3** to **4** by $K_2Cr_2O_7$ which are shown below:-

First-Mechanism:



Second-Mechanism:



Oxidation Studies:

In the above reaction, involving oxidation of 2-hydroxyethylbenzimidazole **(3)** with $K_2Cr_2O_7$, it was observed in a series of runs that the yields tapered off to around 60%. Since 2-acetylbenzimidazole **(4)** was needed in the present work in reasonably large amounts, it was considered worthwhile to explore alternative methods for the preparation of **4**.

The oxidation reaction of **3** to **4** was studied with different oxidising agents with a view to see if **4** can be obtained in higher yields, greater purity and using a reagent cheaper than the Analar dichromate.

Table: 1 Preparation of 4 from 3 by oxidising using different reagents:

S.No.	Substrate	Oidising agent	Reaction Conditions	Product	Reaction Status	Yield (%)
1	**3**	$K_2Cr_2O_7$	Stirring at RT	**4**	Completed	72 %
2	**3**	MnO_2	Refluxing/ 3-4hrs	**4**	Not moving	Nil
3	**3**	MnO_2	Physical grinding	**4**	Not moving	Nil
4	**3**	H_2O_2 / AcOH	Stirring RT/ 3hrs	**4**	Completed	55 %
5	**3**	$CaOCl_2$	Refluxing/ 3hrs	**4**	Not moving	Nil
6	**3**	m-CPBA	Stirring RT/ 3-4hrs	**4**	Not moving	Nil
7	**3**	10% HNO_3	Stirring RT / 3-4hrs	**4**	Not moving	Nil
8	**3**	50% HNO_3	Stirring RT / 3-4hrs	**4**	Not moving	Nil
9	**3**	50% HNO_3	Δ/100^{o}C / 3-4hrs	**4**	Not moving	Nil
10	**3**	CAN	MEK/ RT/ 3-4hrs	**4**	Completed	50 %

The oxidising agents used were MnO_2, H_2O_2 in glacial acetic acid, bleaching powder, m-CPBA, ceric ammonium nitrate (CAN), cupric acetate (in acetic acid) and nitric acid. The results are shown in Table-1.

It is obvious from these results that only a few oxidising agents like CAN and H_2O_2 (in glacial acetic acid) gave comparable yields to $K_2Cr_2O_7$. The others did not fare well.

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