

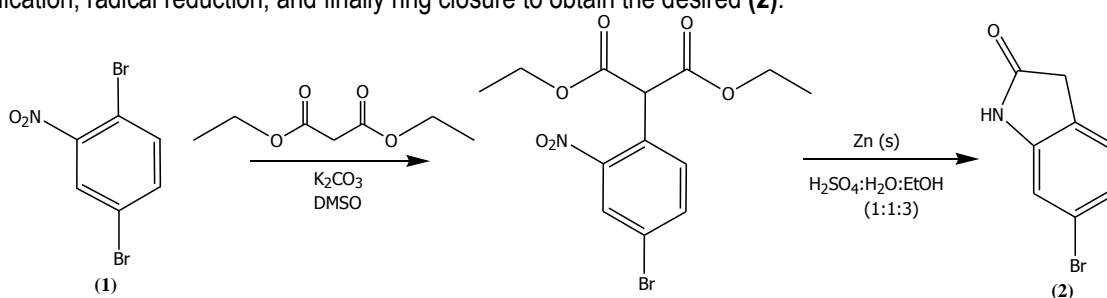
# Synthesis of 6-bromo-2-oxindole from 2,5-dibromonitrobenzene: A more detailed and modified pathway.

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**ABSTRACT:** This present work reports a modified and more detailed experimental and purification procedure to synthesize 6-bromo-2-oxindole (**2**). The cost to obtain (**2**) in commercial is relatively more expensive than to synthesize from its precursor, known as 2,5-dibromonitrobenzene (**1**). This synthesis procedure involved two consecutive steps. The first step involved the nucleophilic attacked of (**1**) by diethyl malonate and formed an intermediate, i.e. diethyl-2-(4-bromo-2-nitrophenyl) malonate. For the second step, this intermediate undergone acid hydrolysis, decarboxylation, reesterification, radical reduction, and finally ring closure to obtain the desired (**2**).



**KEYWORDS:** 6-Bromo-2-oxindole; Nucleophilic attack; Decarboxylation; Radical Reduction; Ring Closure

Received 3 Mac 2017 Revised 20 Jun 2017 Accepted 23 Jun 2017 Online 21 July 2017

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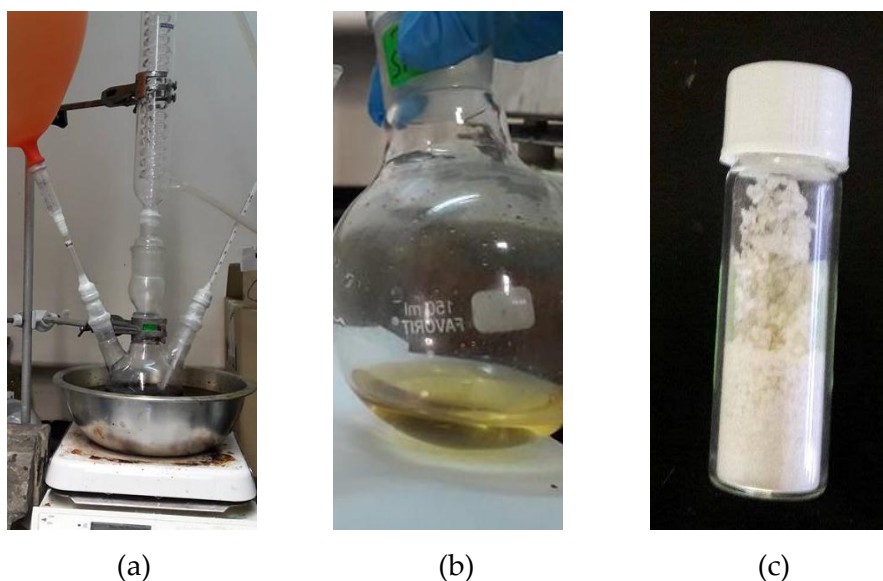
## INTRODUCTION

This synthesis step was modified from the article published by Grenier and co-workers in 2012 (Grenier *et al.*, 2012; Wang *et al.*, 2014). However, the previous paper did not report clear details about how to remove the added zinc in the second batch of solution mixture. Hence, this paper reports a more detailed experimental procedure to synthesize the 6-bromo-2-oxindole (**2**). The (**2**) can also be purchased commercially but for one gram, it costs more than one thousand ringgit. This cost can be effectively reduced and larger amount could be obtained by synthesize (**2**) from (**1**) based on this procedure reported in this paper. This (**2**) could be used as the precursor to synthesize an organic compound known as 6,6'-dibromoisindigo, which is widely used as an acceptor unit of conjugated polymer in the application of polymeric solar cell (Papageorgiou & Borer, 1988; Mei *et al.*, 2010; Bogdanov *et al.*, 2011; Bogdanov & Mironov, 2011; Zhang *et al.*, 2011; Bogdanov *et al.*, 2012; Stalder *et al.*, 2013; Kim *et al.*, 2014; Lei, Wang, & Pei, 2014; Wang *et al.*, 2014; Jiang *et al.*, 2016). Furthermore, there are some other pathways to synthesize various derivatives of (**2**), which can be applied in many other fields (Marti & Carreira, 2003; Trost & Brennan, 2009; Jia & Kündig, 2009; Peddibhotla, 2009; Ashraf *et al.*, 2012; Deng *et al.*, 2016).

## METHODOLOGY

2,5-dibromonitrobenzene (**1**) (10.00 g, 35.60 mmol, 1.00 equiv.) and potassium carbonate anhydrous (49.20 g, 356 mmol, 10 equiv. to **1**) were added in 53.4 mL of dry dimethyl sulfoxide (DMSO) under nitrogen atmosphere. The reaction mixture was then warmed up to 50°C. Another set

of solution mixture was prepared by placing diethylmalonate (27.15 mL, 28.51 g; 178 mmol, 5.00 equiv. to **1**) into 26.7 mL of DMSO, after which this solution mixture was dropwisely added into the warmed reaction mixture for more than an hour. The reaction was then allowed to react for 18 hours at 50°C. After that, 200 mL of distilled water was added into the resulting mixture. The reaction mixture was then transferred into a separating funnel and extracted three times with 150 mL of diethyl ether. The combined organic layer was washed with distilled water and the resulting light yellow organic layer was rotatory evaporated to remove the diethyl ether. The obtained yellowish oily solution, which theoretically contained both diethyl-2-(4-bromo-2-nitrophenyl) malonate intermediate and unreacted diethyl malonate, was dissolved into another set of prepared solution mixture. This solvent mixture contains water (65.5 mL), sulfuric acid (65.5 mL), and ethanol (196.5 mL) in ratio 1:1:3. The resulting mixture was refluxed under nitrogen atmosphere. When the reflux began, zinc powder (39.24 g, 600 mmol) was added slowly into the mixture. After that, the reaction mixture was continued to reflux for an hour, before another batch of zinc powder with same amount was added slowly. The mixture was refluxed for another 2 hours. The obtained mixture was dropped into 890 mL of distilled water and was left overnight. The resulting suspension was filtered and the white residue was washed over with distilled water for several time before dissolved into dichloromethane. The organic layer was washed again with two portions of distilled water, then dried over Na<sub>2</sub>SO<sub>4</sub>. The used Na<sub>2</sub>SO<sub>4</sub> was filtered off and the dichloromethane was evaporated off via rotatory evaporator to separate out the final white cotton-liked solid product which yielded 5.93 g (**2**) (27.97 mmol,  $\gamma$ =78.57 %). Finally, the white product was stored for the usage of the following step under temperature 2-8°C.

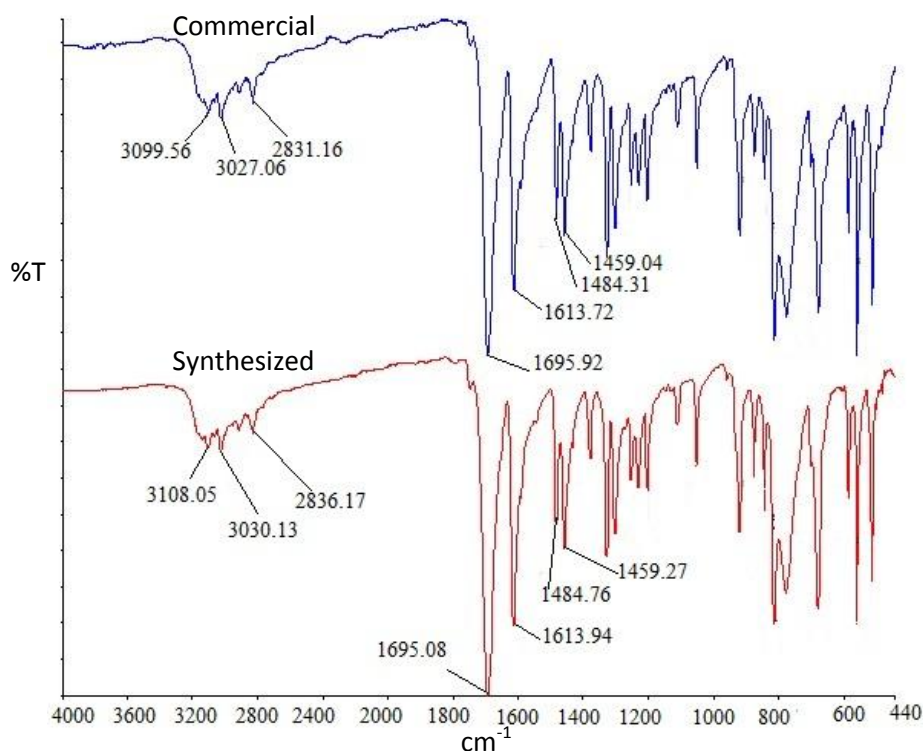


**Figure 1:** (a) The reaction setup, (b) the yellowish oily intermediate, and (c) the white product (**2**).

## RESULT AND DISCUSSION

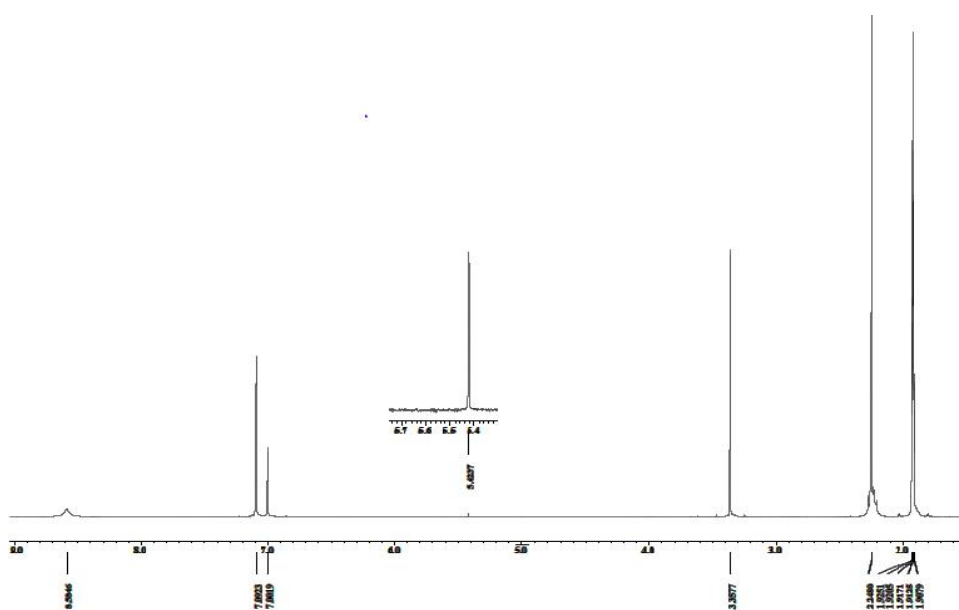
In the reference journal, there was no detail about how to remove the zinc powder after the product was crystallized overnight. When the experiment was conducted, it was noticed that some zinc powder still present on the residue after filtration. Hence, the white residue was dissolved again in the dichloromethane and the remained zinc powder was washed out with distilled water through extraction technique. The purity of the synthesized (**2**) was primarily tested by TLC run on silica-coated aluminum plate with 1:1 of n-hexane/ethyl acetate eluent. The  $R_f$  = 0.56. The synthesized (**2**) was characterized by FTIR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR. The melting point of (**2**) is lied in between 218-222°C range. The FTIR spectrum obtained from the synthesized (**2**) was compared with the

commercially purchased (**2**), as shown in **Figure 2**. Based on the comparison, both spectra exhibited similar peaks, which can be preliminary identified that all the desired functional groups are present in the synthesized (**2**).



**Figure 2** The comparison of FTIR spectra for the commercially obtained (**2**) (blue) and the synthesized (**2**) (red).

Moreover, the  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  results obtained by the synthesized (**2**) are reported as shown below. For this research, the sample was dissolved in acetonitrile- $d_3$  while the reference journal used DMSO- $d_6$ .  $^1\text{H-NMR}$  (600 MHz, Acetonitrile- $d_3$ , ppm)  $\delta$  8.58 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 5.42 (s, 1H), 3.36 (s, 2H).  $^{13}\text{C-NMR}$  (125 MHz, Acetonitrile- $d_3$ , ppm)  $\delta$  176.29, 144.96, 126.13, 125.29, 124.30, 120.36, 112.33, 35.24.



**Figure 2** The  $^1\text{H-NMR}$  spectrum of 6-bromo-2-oxindole (**2**).

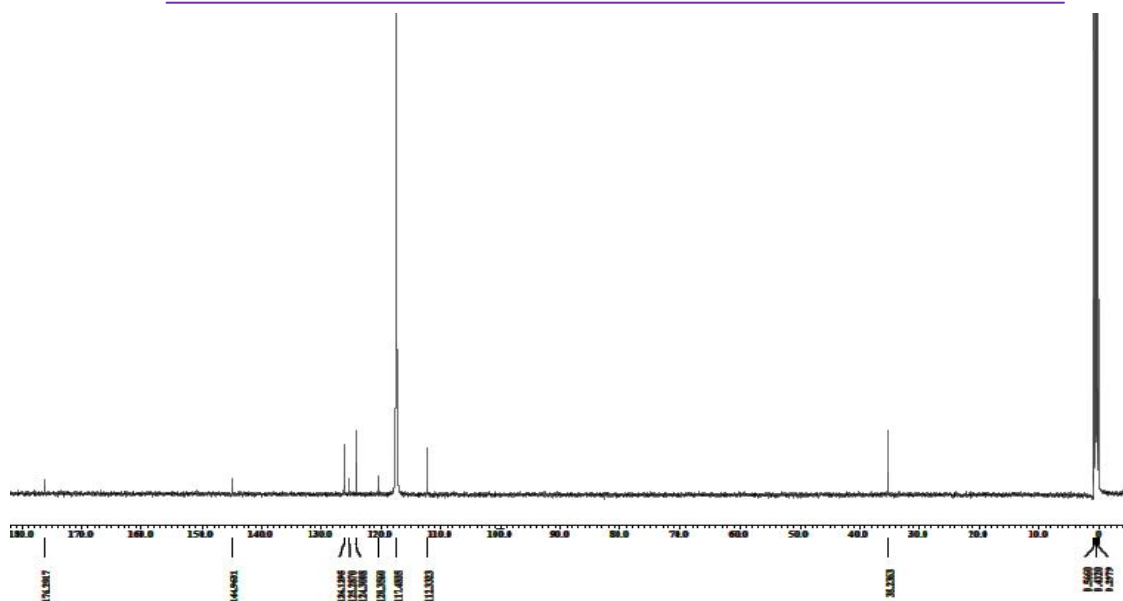
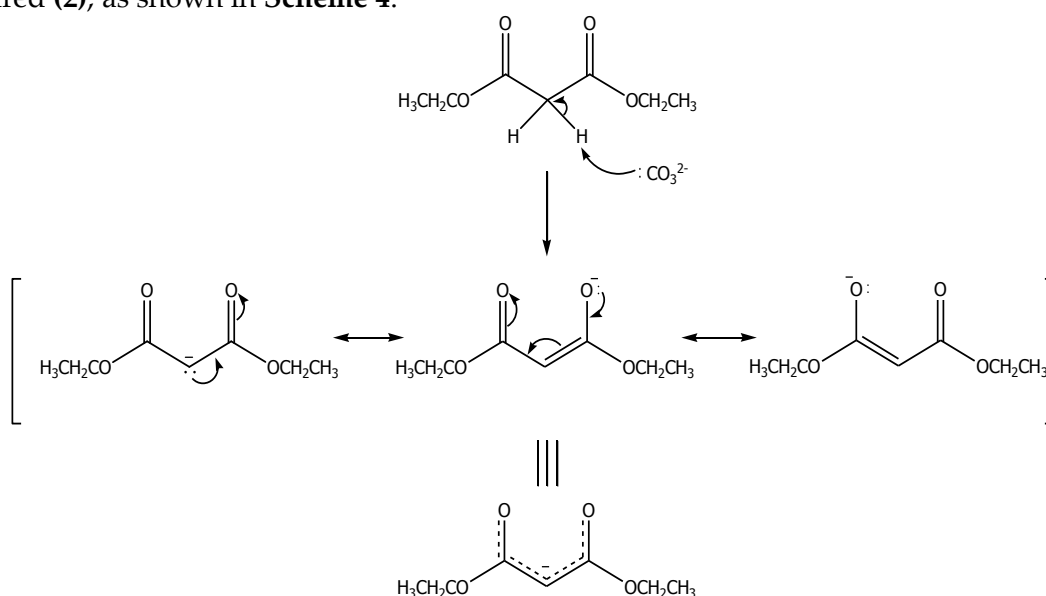
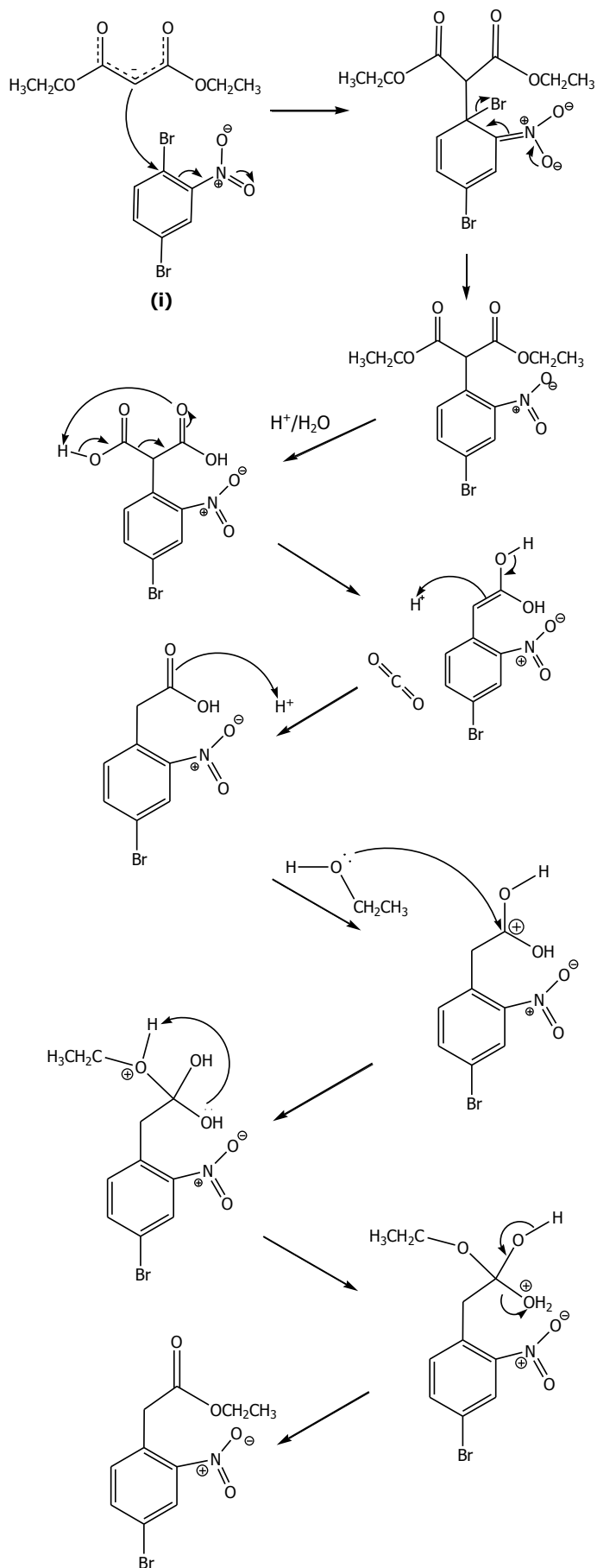


Figure 3 The  $^{13}\text{C}$ -NMR spectrum of 6-bromo-2-oxindole (**2**).

The chemical reaction happens in the entire process can be explained through the following mechanism schemes. First of all, diethyl malonate reacts with the  $\text{K}_2\text{CO}_3$ , an anhydrous strong base. The carbonate ions removed a proton,  $\text{H}^+$  ion on the alpha carbon of diethyl malonate. The resulting electron pair on the alpha carbon was delocalized amongst both adjacent carbonyl groups of the diethyl malonate. The reaction mechanism is shown in **Scheme 1**. This strong nucleophilic diethyl malonate ion was then undergo nucleophilic attack on the ortho-position of the nitro group of (**1**), and kick out the attached bromine. The resulting intermediate, known as diethyl-2-(4-bromo-2-nitrophenyl) malonate, was first extracted from the former reaction mixture and then dropped into another set of solution mixture contains sulphuric acid, water and ethanol. In this second sub-step, the diesters group of the intermediate was converted into diacid group. This acid hydrolysis was followed by decarboxylation, After that, reesterification was happened with the present of ethanol in the solution mixture to obtain a monoester. The mechanism for this reaction was illustrated in **Scheme 2**. According to the methodology in previous chapter, zinc powder was added after reflux began. The addition of zinc powder radically reduced the nitro group into amine group (Kumar & Lokanatha Rai, 2012; Raju, Ragul, & Sivasankar, 2009), as depicted in **Scheme 3**. Finally, the amine group nucleophile attacks intramolecularly to the ester carbonyl, which resulted in ring closure to form the desired (**2**), as shown in **Scheme 4**.



Scheme 1: Formation of strong nucleophilic diethyl malonate ion.



**Scheme 2:** The nucleophilic attack, acid hydrolysis, decarboxylation and reesterification of (1).





## CONCLUSION

The 6-bromo-2-oxindole (**2**) was successfully synthesized from 2,5-dibromonitrobenzene (**1**) in large quantity, i.e. > 5.90 g, through a series of nucleophilic attack, acid hydrolysis, decarboxylation, reesterification and intramolecular ring closure reaction. Hence, (**2**) is able to obtain in bulk quantity through this procedure with a cheaper cost as compared to the commercial price.

## ACKNOWLEDGEMENTS

Thanks for the University Malaysia Sabah for the facilities. This work was financial supported by Fundamental Research Grant Scheme under FRG0413-SG-1/2015 grant and MyBrain15.

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