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SHORT COMMUNICATION

The Study of the Reaction of Morpholine with 4-Bromobenzaldehyde in the Presence and Absence of Copper(I) Iodide

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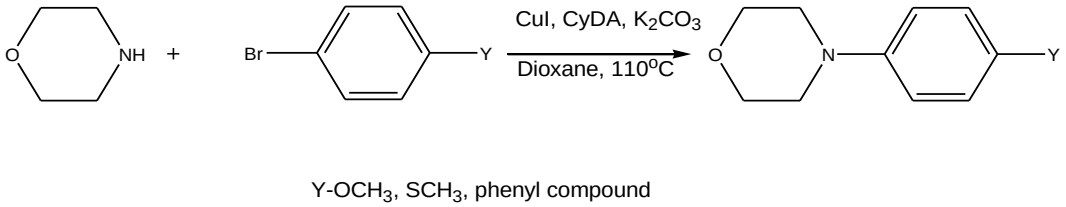
ABSTRACT

This short communication reports the comparison of the reaction between morpholine with 4-bromobenzaldehyde in the condition with and without copper (I) iodide (CuI) as the catalyst. The reactions were carried out at 110 ^{o}C under reflux condition for 24 hours, and the products were analysed using gas chromatography mass spectroscopy (GCMS). The GC results showed that the conversion of the product without CuI catalyst was higher than the reaction with catalyst under the same condition. Side product also was observed in the reaction without catalyst, which is because the morpholine was actually also attacked to the carbon in the carbonyl group of 4-bromobenzaldehyde to produce 4-bromobenzoic acid morpholide.

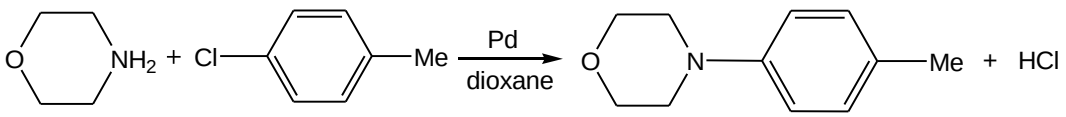
Keywords: Morpholine, 4-morpholine-4-yl-benzaldehyde, 4-bromobenzoic acid morpholide

The synthesis of phenyl morpholine in normal organic synthesis methods is not easy and it is carried out in the presence of catalyst in the reaction. For example, cross coupling reaction involved formation of C-N bonding using copper (I) iodide as the active catalyst has been studied by Beletskaya and Cheprakov (2004) (Scheme 1).



Scheme 1. Synthesis of morpholine derivatives using cross-coupling reaction.

Apart of using copper (I) iodide, the cross-coupling reaction mediated by palladium catalyst between morpholine and chlorotoluene to form 4-tolyl-morpholine was also reported (Hillier *et al*., 2002) (Scheme 2). Potassium butan-1-olate was used as a base in order to neutralize the formation of HCl from the reaction and the yield obtained was 84%.



Scheme 2. Synthesis of 4-tolyl-morpholine.

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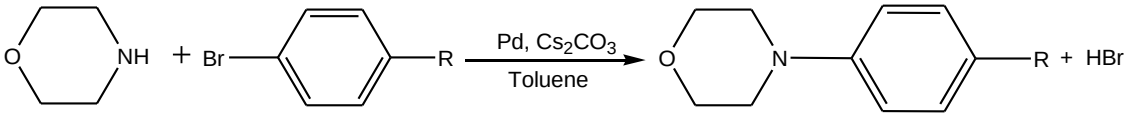
Another reaction was reported by Lundgren and co-workers (Lundgren *et al*., 2010), in which the cross coupling reaction was also mediated by palladium (Scheme 3).

Moreover, the reaction used more expensive base such as Cs_2CO_3 or $LiN(SiMe_3)_2$ and toluene as the solvent, which resulted the yield of 99%.



Scheme 3. Synthesis of various morpholine derivatives.

From preliminary study, we found that the cross coupling reaction of morpholine with 4-bromobenzaldehyde can be carried out in the condition without catalyst. Herein, we report the study of the reaction between morpholine with 4-bromobenzaldehyde by comparing the reaction product composition, time and products in the condition of with and without CuI as the catalyst. The mechanisms of the product and side-product formation are also discussed in this short communication as well.

The morpholine derivatives from the reaction were identified by using gas chromatography-mass spectroscopy (GC-MS). The molecular weight of the resulted compound was recorded using Perkin Elmer GC-MS with fitted of 30 m fused silica BPX-5 capillary column with operating condition of injector temperature at 250ºC, detector temperature 300ºC, the oven temperature at the 20 ºC/min from 50-280ºC. Helium gas was used as the carrier gas.

To an oven-dried 100 mL round bottom flask with magnetic stirring bar was added with CuI (0.003 g, 0.015 mmol), potassium carbonate (0.166 g, 1.2 mmol), morpholine (0.1 g, 1.2 mmol) and 4-bromobenzaldehyde (0.185 g, 1.0 mmol) and DMF (1 mL). The mixture was stirred at room temperature for 2 hours and transferred to preheated oil bath at 110ºC for 24 hours. The reaction was then cooled to room temperature and left for overnight. The solvent was removed *in vacuo* to yield yellow oil and analysed using GCMS. Similar procedures were performed again in the condition without CuI.

The reaction of morpholine with 4-bromobenzaldehyde in the presence of CuI was successfully produce 4-morpholine-4-yl-benzaldehyde and the mechanism was shown in Figure 1 (Sperotto *et al*., 2010a). The reaction was initiated when the copper(I) metal centre forms a bond with morpholine to give a copper(I)-morpholine species **II**. At the same time, the copper centre formed a three coordination Cu(III) species **IV** *via* oxidative addition by forming a bond with 4-bromobenzaldehyde and iodide. Then, the copper(III) species forms bond between morpholine and benzaldehyde to give 4-morpholine-4-yl-benzaldehyde via reductive elimination, and the oxidation state of Cu(III) has returned to Cu(I).

The reaction sample was analysed using GCMS and the GC result showed two signals at the retention time of 5.97 and 10.22 min (Figure 2).

The mass spectrum shows the original molecular mass of the peak at retention time 10.22 min was *m/z* 191, which is same with the mass of 4-morpholin-4-yl-benzaldehyde. This indicates that the reaction between 4-bromobenzaldehyde and morpholine using CuI catalyst was successful, but the composition was only 20% based on the GC result. In fact, 4-bromobezaldehyde was not fully reacted with morpholine as there are still 80% of 4-bromobenzaldehyde as in the GC spectrum which is represented by the retention time of 5.97 min.

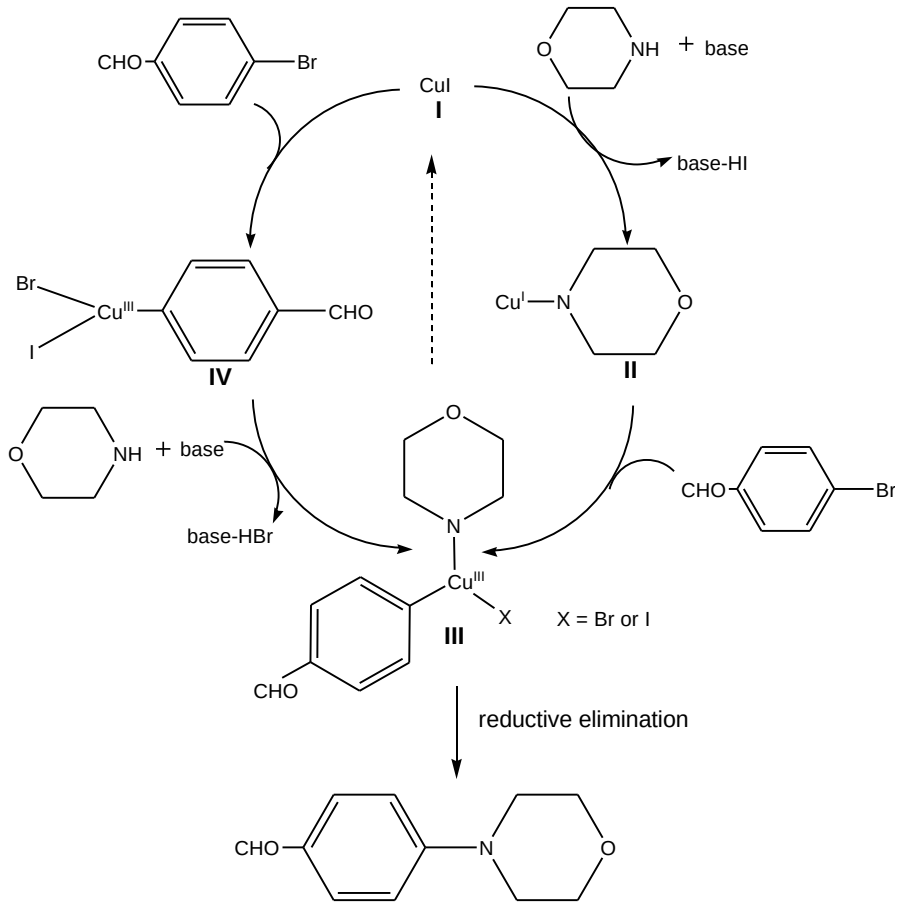


Figure 1. Catalytic cycle of the copper(I) iodide (Sperotto *et al*., 2010b).

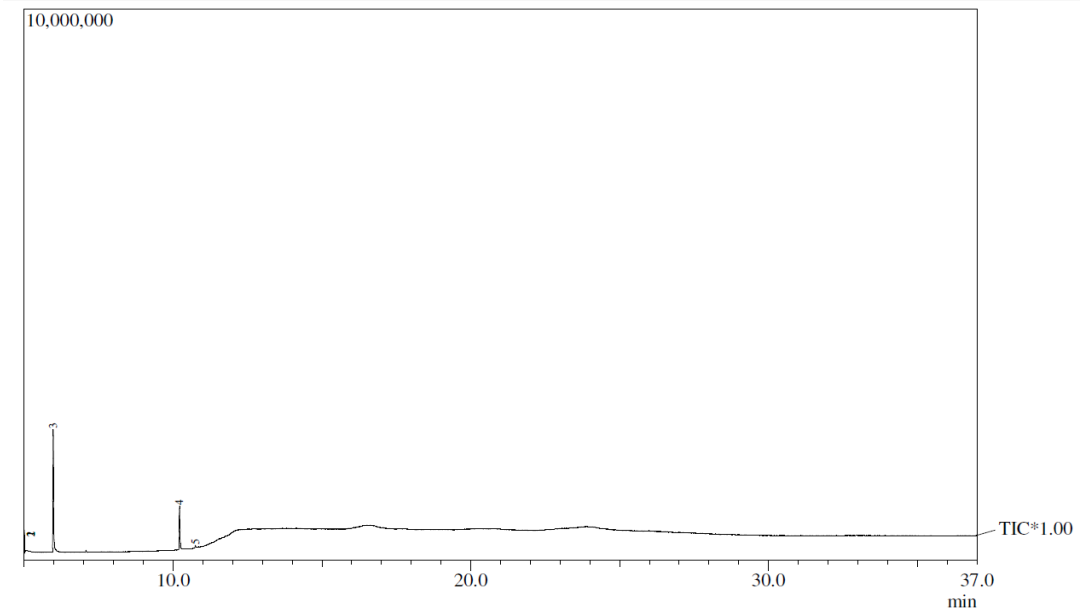


Figure 2. Gas chromatogram of 4-morpholin-4-yl-benzaldehyde at 10.22 min of retention time in the presence of CuI.

The reaction of 4-bromobenzaldehyde with morpholine without CuI catalyst was also carried out under the same condition with the one using catalyst and analysed by GCMS. The GC result showed two signals at the retention time of 10.21 and 10.73 min, respectively (Figure 3).

The product of 4-morpholin-4-yl-benzaldehyde was represented to the signal at 10.21 min retention time with the mass of *m/z* 191, which has been discussed at the previous section. The product composition was about 74% which was unexpectedly higher than the reaction yield in the presence of CuI.

The success of product composition, 4-morpholin-4-yl-benzaldehyde, even under the condition without catalyst could be due to the fact that the aldehyde group in 4-bromobenzaldehyde is an electron withdrawing group. It caused a bond breaking between bromine and phenyl ring, and at the same time, the morpholine acts a nucleophile which could promote the formation of a new Csp^2-N bond (Basu *et al*., 2007) (Scheme 4).

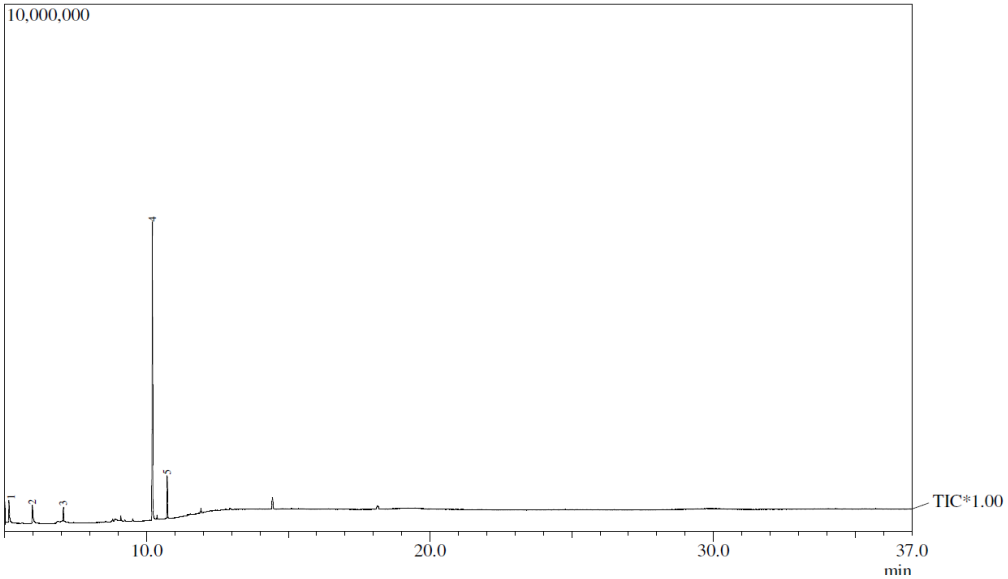
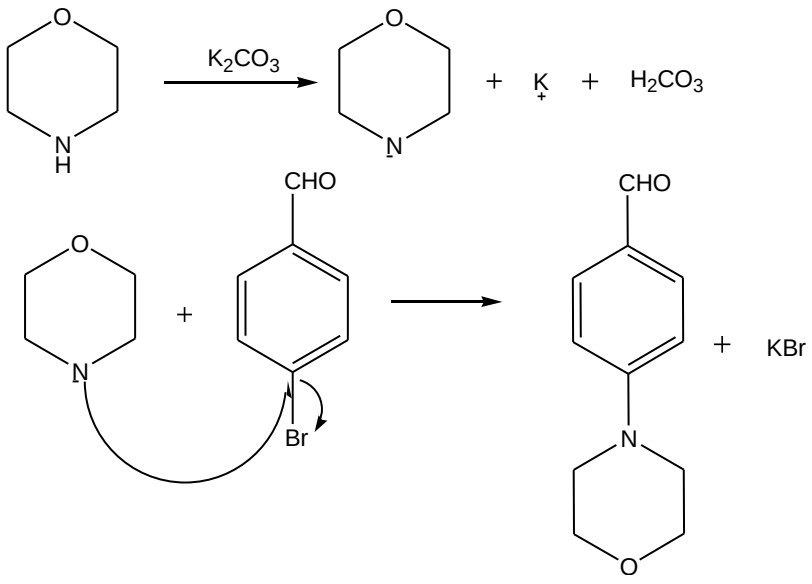


Figure 3. Gas chromatogram of 4-morpholin-4-yl-benzaldehyde at 10.21 min of retention time without CuI.



Scheme 4. The mechanism of 4-morpholin-4-yl-benzaldehyde.

The signal at 10.73 min retention time is attributed to 4-bromobenzoic acid morpholide. The original mass of *m/z* 270 with two mass signals in the ration of 50:50 indicates the presence of bromine atom in the structure (Figure 4). The formation of this compound showed that the morpholine which acts as nucleophile also attack to the carbonyl group of aldehyde which resulted 4-bromobenzoic acid morpholide (Scheme 5).

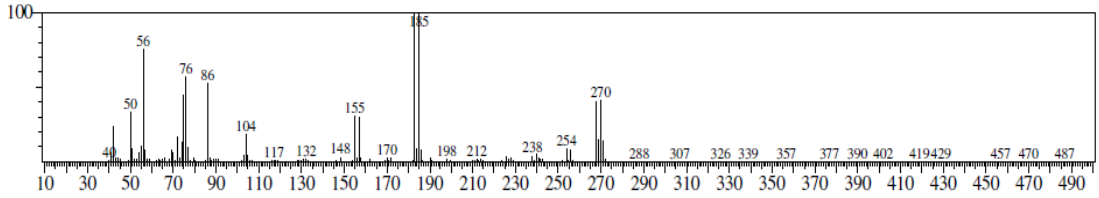
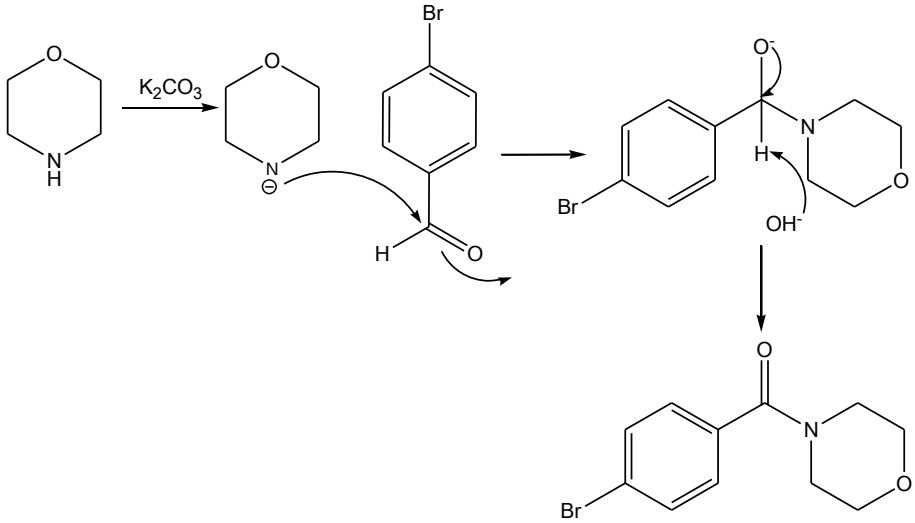


Figure 4. The mass spectrum for the signal at 10.73 min in its gas chromatogram.



Scheme 5. The mechanism of nucheophilic attack of morpholine to carbonyl group.

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