공학석사학위논문

Cu-catalyzed synthetic process for acetaminophen from dihalobenzenes

다이할로벤젠으로부터 아세트아미노펜을 합성하는 구리촉매화 공정 연구

2013 年 2 月

서울대학교 대학원

화학생물공학부

김중원

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Cu-catalyzed synthetic process for acetaminophen from dihalobenzenes

by

Kim Jung Won

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Thesis Adviser: Young Gyu Kim

Abstract

Kim Jung Won

Chemical and biological engineering

The Graducate School of

Seoul National University

Up to now, various kind of non-opioid analgesic drugs have been developed and their developments have been progressed to the improvement or the complement of weak point of the former analgesics at each time. In these days, one of them, acetaminophen (1) is known for the most widely used analgesics in the world on the account of the many advantages in terms of the medicinal application and few adverse effects in comparison with other analgesics.

However, the former synthetic process of acetaminophen (1) have many problems such as, generation of undesired isomer and use of strong, toxic acid and so on. These problems accompany additional purification steps and recycle of waste acids, finally, bring about the additional cost that affect the production cost of acetaminophen (1).

In this paper, we are going to discuss our efforts to develop both an efficient and an economic process for acetaminophen (**1**) using Cu-catalyzed reaction from dihallobenzenes. We could not only improve the drawbacks of the former synthetic process, but also could make the synthetic process more eco-friendly under mild reaction conditions and the synthetic steps shorter without the additional purification.

Key words: dihalobenzenes, acetamidation, hydroxylation,

Student number: 2011-21026

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Ac	acetyl
d	doublet
δ	chemical shift, ppm
DMEDA	*N,N*-dimehtylethylenediamine
DMF	dimethylforamide
DMSO	dimethylsulfoxide
eq	equivalent
EDA	ethylenediamine
EtOAc	ethylacetate
GC	gas chromatography
hr	hours

HRMS	high resolution mass spectrum
J	coupling constant(s)
L	ligand
min	minute(s)
M	mol per liter
NMR	nuclear magnetic resonance
ppm	part per million
s	singlet
TLC	thin-layer chromatography
TMEDA	tetramethyleethylenediamine
THF	tetrahydrofuran
UV	ultraviolet spectrum

Introduction

Non-opioid analgesic drugs work as an inhibitors of the cyclooxygenase(COX) enzymes that participate in prostaglandin synthesis from arachidonic acid, and show a pain relieving and alleviating a fever. [1]

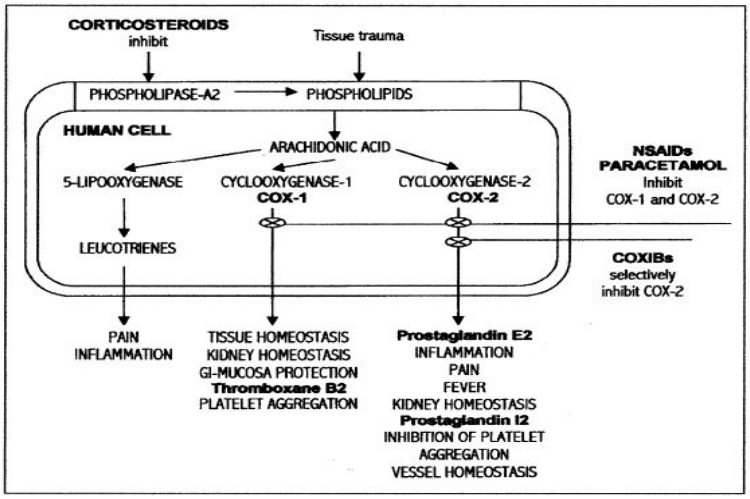


Figure 1. Drug interaction with the arachidonic acid cascade and pain-related biosynthesis.

Unlike the opioid analgesics that induce a central pain-reliving and a physical dependence, non-opioid analgesic drugs have no drug abuse. However, comparatively, non-opioid analgesic drugs have so low maximum efficacy in comparison with opioids that they are usually used at the dull pain. Despite of a weak pain-

relieving effect, some of them are used not only as a medicine for rheumatic disease on the account of their strong anti-inflammatory effect, but also are used for a medicine of hyperuricemia due to their strong uricosuric effect.

Because of the extensive medicinal application of non-opioid analgesic drugs, today, there are lots of efforts to develop both an efficient and an economic process for them through the different methodology. These endeavors are not limited to the modern society but started from the past. So, first of all, we need to know about the brief history with regards to the development of non-opioid analgesic drugs before we introduce our research plan.

1. History of non-opioid analgesic drugs.

1.1 Salicylic acid

The beginning of the 19th century may be characterized by a dramatic change in medicinal practice. Well known therapeutic extracts, such as opium, could be dissected into different molecules including morphine, which was isolated and crystrallized by the German pharmacist Sertürner as early as 1805. Shortly after, Piria (Italy) and Löwenich (Switzerland) extracted the glycoside of salicylic acid from willow bark and other plant. [2]

On the other hand, it proved difficult to obtain sufficient quantities of pure materials from plant source in the early days of the 19th century. Only after the oil of wintergreen had been discovered as a 'Gautheria procumbens' in 1843 was it possible to safety the physicians' need for large quantities of salicylic acid for the treatment of rheumatic disease. Thus, the drug supply became a problem particularly during the many wars of the 19th century. [2]

Consequently, the chemist at the universities of continental Europe began to concentrate on the synthetic production of

drugs. In 1874, Kolbe synthesized the salicylic acid through a method known as Kolbe-Schmitt reaction. [2]

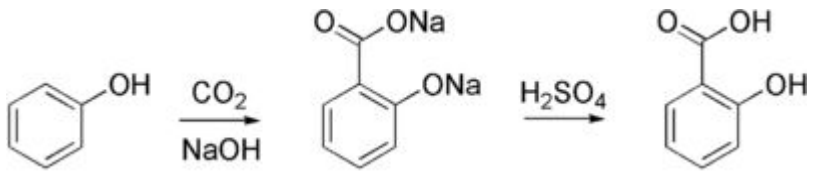


Figure 2. Kolbe-schmitt reaction.

Sodium salicylate is commercially prepared by treating sodium phenolate with carbon dioxide at high pressure (100 atm) and high temperature (390 K). Acidification of the product with sulfuric acid gives salicylic acid. [2]

Salicylic acid is known for its ability to ease aches and pains and reduce fevers. Due to these medicinal properties, it is used as an anti-inflammatory drug. Some researchers believe that salicylate is an essential micronutrient in the human diet, potentially qualifying as a vitamin, namely Vitamin S.[2]

1.2 Antipyrine, Pyramidon and dipyrone

In 1875, Otto Fisher produced a kairine, a semisynthetic antipyretic compound. His pupil and at Erlangen, Ludiwig Knorr used phenylhydrazine and together with acetate-esters produced a new fully synthetic drug, antipyrine, the 'mother' of all modern antipyretic analgesics.[2]

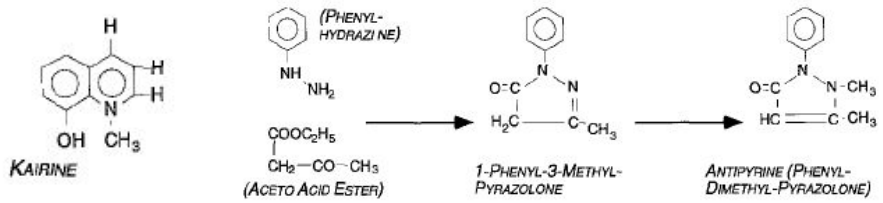


Figure 3. Kairine, pyrazolon and antipyrine.

After that time, the chemists, in particular Friedrich Stolz, were actively searching for further improvements of antipyrine by methylation, suggested further substitution of antipyrine with methyl groups. 4-methyl antipyrine was more active, but also slightly more toxic. The similar held true for 3-methyl-antipyrine. Filehne then suggested adding N-methyl-group, since morphine contains a methylated N-atom, which is necessary for its activity. Consequently, 4-aminoantipyrine was synthesized and methylated. This led to the 4-amino-dimehtyl-antipyrine, better known as Pyramidon. This compound was at

least three times as active as antipyrine. This correlates nicely with a later investigation, showing that within the phenazone (antipyrine) series positioning of methylated N-atoms in the 4 position increases the activity in terms of cyclooxigenase inhibition.[2]

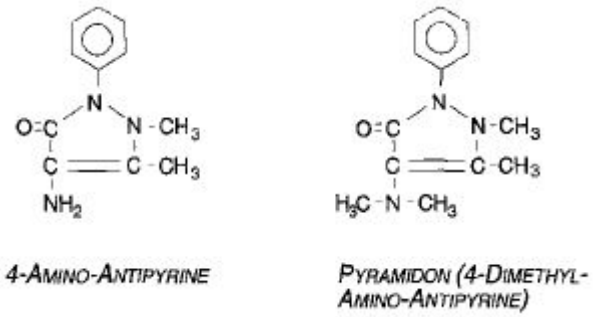


Figure 4. 4-Amino-antipyrine and Pyramidon.

Other Suggestions came from the clinicians. They wanted to use pyrazolone (Figure 2) compounds in seriously ill patients and suggested a soluble, ie injectable, form. Antipyrine and many antipyrine derivatives are not sufficiently water-soluble at high concentration. The chemists produced a pro-drug by combining 4-amidoantipyrine with formaldehydsulphate. This compound carried with it the hopes of the management, indicated by the fact that the brand name 'Melburin' contains the original name of the company (Meister Luise & Brüning) in an abbreviated form.

Still, it was not very successful in the market place and shortly thereafter was replaced by the analogue pro-drug of Pyramidon. This proved to be very effective and was well accepted by the public. This compound (dipyrone) came with the new name 'Novalgin' the enthusiastic reports by the clinicians compared Novalgin even with morphine. [2]

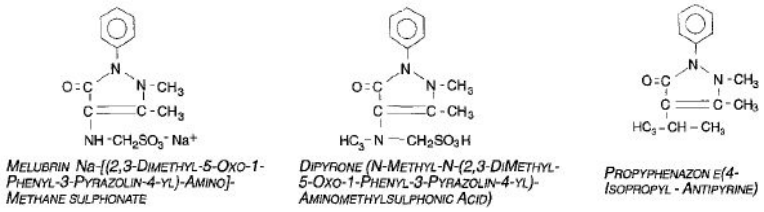


Figure 5. Melubrin, dipyrone and propyphenazone.

Many other derivatives of antipyrine (phenazone) may be found in the pre-WW2 literature. None of these compounds, with possibly exception of propylphenazon, in which the 4-amino-group is substituted by a propyl group, really proved to be a market success. Propyphenazone was synthesized by Stenz and patented by Hoffman-LaRoche. Propyphenazone was as effective as Pyramidon (Figure 3) [2]. However, like many old and approved substances after almost 100 or more years of use, antipyrine (phenazone), propyphenazone and particularly the leading compound dipyrone have been associated with some serious side effects, namely agranulocytosis and shock reactions.

Liver and kidney damage as well as CNS side effects were also observed. Moreover, the first selective COX-2 inhibitors have so far failed to demonstrate their sufficient efficiency as analgesics. The time to peak is always in the range of 3-4 hours - too long for fast pain relief. [2]

1.3 Aspirin.

Though the middle decades of the 19th centuries the use of salicylate medicines including salicin, salicylic acid and sodium salicylate grew considerably, and physicians increasingly knew what to expect from these medicines; reduction of pain, fever and inflammation. However, the unpleasant side effects, particularly, gastric irritation, limited their usefulness. By the 1880s, the German chemical industry, jump-started by the lucrative development of dyes from coal tar, was branching out to investigate the potential of new tar-derived medicines. In 1897, Hoffman, scientist at the drug and dye firm Bayer, began investigating acetylsalicylic acid at a less-irritating replacement for standard common salicylate medicines. Other chemists had attempt to this before as well, by acetylating salicylic acid using acetylcholoride with a sodium salt of salicylic acid to make acetylsalicylic acid (ASA). However this method did not produce

pure ASA. So Hoffman found a better method for making ASA, from salicylic acid refluxed with acetic anhydride. [2]

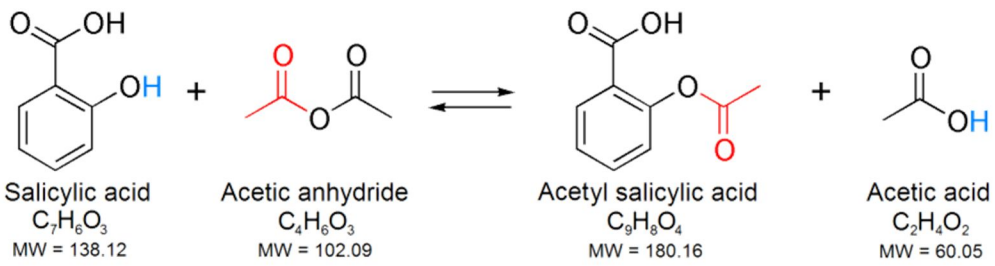


Figure 6. Synthesis of aspirin.

By 1899, Bayer had dubbed this dug Aspirin and was selling it around the world. The word 'Aspirin' was Bayer's brand name, rather than the generic name of the drug.[2]

Aspirin's popularity declined after the development of acetaminophen (paracetamol) in 1956. In the 1960s and 1970s, John Vane and others discovered the basic mechanism of aspirin's effects, while clinical trials and other studies from the 1960s to the 1980s established asprin's efficiency as an anti-clotting agent that reduces the risk of clotting diseases. Aspirin sales revived considerably in the last decades of the 20th century, and remain strong in the twenty-first with wide spread use as a preventive treatment for heart attacks and strokes. [2]

1.4 Paracetamol (Acetaminophen).

Paracetamol (acetaminophen) is virtually the sole survivor of the so-called "aniline derivatives" or "aniline analgesics": acetanilide, phenacetin and paracetamol (acetaminophen). Phenacetin and paracetamol are both derivatives of acetanilide. [3]

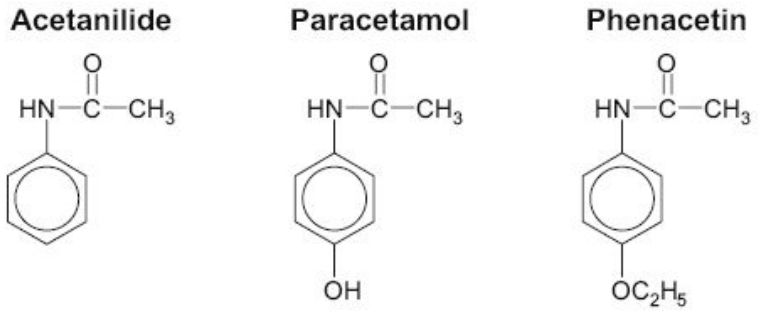


Figure 7. Chemical structures of "aniline derivatives"

Acetanilide was serendipitiously found to possess antipyritic activity and quickly introduced into medical practice under the name of antiferin Chan and Hepp, and was shown to possess analgesic as well as antipyritic activities. But its inacceptable toxic effects, the most alarming being cyanosis due to methemoglomeia, prompted the search for less toxic aniline derivatives. A number of compounds were tested. The most satisfactory came out to be phenacetin (acetophenetidin) and *N*-acetyl-*p*-aminophenol (acetaminophen, paracetamol). Paracetamol had been synthesized by Morse in 1878 [3]

Phenacetin and paracetamol were introduced into clinical use in 1887 by von Mering, who soon discarded paracetamol in favor of phenacetin, because he assumed that the latter was less toxic [3]

Albeit in part overshadowed by aspirin, introduced into medicine by Dresser in 1899, phenacetin has known for many decades an extraordinary popularity and indiscriminately used, especially as an ingredient of proprietary analgesic mixtures (particularly over-the-counter "headache mixtures", usually containing pheacetin, an aminopyrine derivative or asprin, caffeine, and sometimes a barbiturate) and widely advertised to the public. [3]

The chronic overuse/abuse of such mixtures by the laity, sometimes in prodigious amounts over periods of years, caused many serious chronic intoxications characterized by anemia, methemoglobinemia, and severe renal damage, with a high incidence of papillary necrosis (analgesic nephropathy) [3]

In 1948, Brodie and Axelod demonstrated that the major metabolite responsible for the analgesic action of acetanilide and phenacetin is paracetamol, while methemoglobinemia is produced by another metabolite phenylhydroxylamine. [3]

So, Paracetamol was "rediscoverd" and marketed since the mid 1950s. It rapidly gained in popularity, and in many countries,

including the United Kingdom, paracetamol sales exceeded those of aspirin since about 1980. This was accompanied by the virtual commercial demise of phenacetin, blamed as the cause of "analgesic nephropathy", hematological toxicity, and psychotropic effects which may contribute to its liability for abuse.[3]

In comparison with other analgesics, Acetaminophen has many advantages. First, It is a widely used over-the-counter drugs with no specific side effects. Second, it has lots of available forms at each common brand names; Tylenol, Panadol (tablet, capsule), OFIRMEV (intravenous). [3]

Figure 8. Common brand names of acetaminophen

Last, it has not only one of the largest share in the world pharmaceutical market and but also it is the most prescribed medicine in the world. [3]

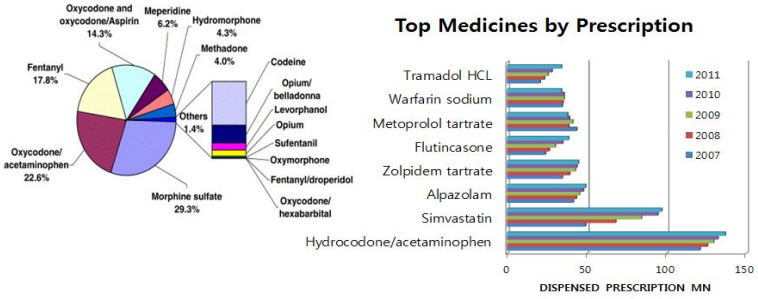


Figure 9. Market share and top medicines by prescription.

2. Research plan.

We expected that if we developed the new efficient synthetic process for acetaminophen, it could be a good contribution for the mass production of acetaminophen more economically. First of all, we need to know about the former synthetic process to compare each other.

2.1. Former synthetic process.

The former synthetic process is started from the phenol.

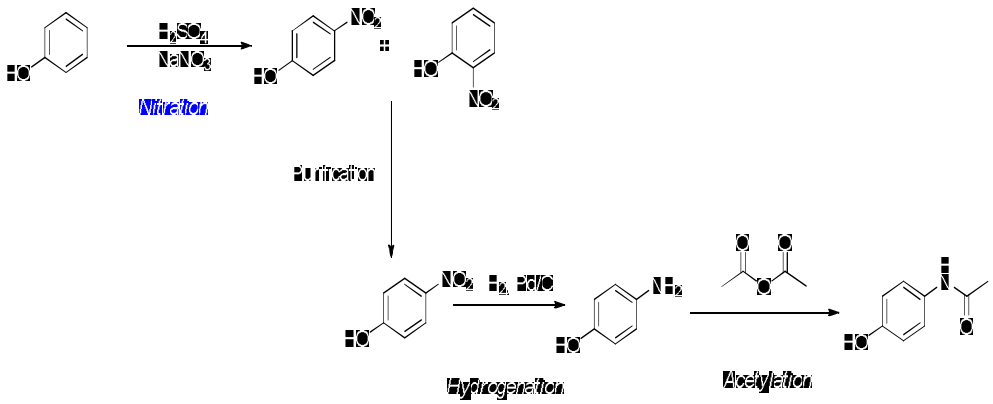


Figure 10. The former synthetic process.

At first, nitration is happened using sodium nitrate and sulfuric acid. As a result, two kind of isomers are made; *p*-nitrophenol and *o*-nitrophenol. The *p*-nitrophenol is separated by the

purification step. Next, through the hydrogenation, 4-aminophenol is made, and finally, acetylation is happened. Therefore, we could obtain the final target product, Acetaminophen. [3]

However this former synthetic process has significant disadvantages. these disadvantages come from the first step, nitration. First, because of the use of strong acid (ie. Sulfuric acid), the reaction condition is very harsh and recover the waste acid is required. Second, two isomers, *p*-nitrophenol and *o*-nitrophenol, are made. it means that the additional purification step is necessary. Radically, these drawbacks bring about the additional cost and could affect the production cost of the acetaminophen. So we proposed new synthetic process to solve these problems. [3]

2.2. New synthetic process.

If the reaction had not via the nitrobenzene and two functional groups, hydroxyl group and acetamide group, had been introduced, we would have thought that we would be able to solve the problems. So we used '*para*-' substituted dihalobenzenes to prevent the production of isomer problem. These two halogen functional groups make the introduction of

other functional groups easier to the benzene. Next, we introduced catalytic process to make the reaction condition milder. Therefore, we could propose the new synthetic process containing two step, acetamidation and hydroxylation. [4], [5]

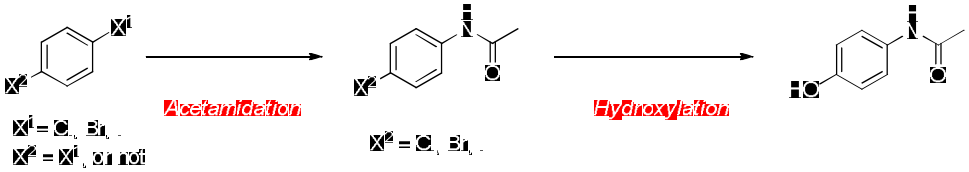


Figure 11. New synthetic process for acetaminophen

And this is the mechanism that we propose.

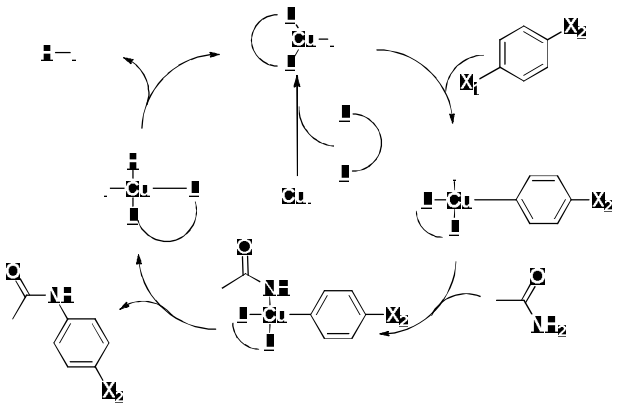


Figure 12. Proposed mechanism of acetamidation.

The catalyst makes the complex with the ligand. The oxidative addition of the dihalobenzenes is followed by the insertion of the acetamide. Next further two steps, elimination and reductive elimination, are progressed and finally we are able to obtain the intermediate which is para-substituted haloacetanilide. [4], [5]

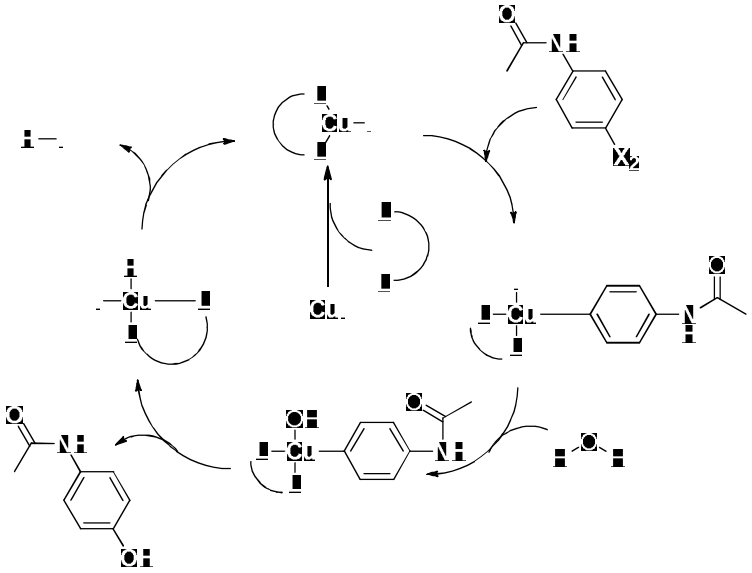


Figure 13. Proposed mechanism of hydroxylation.

The mechanism of the hydroxylation is very similar with that of the acetamidation. The catalyst makes the complex with the ligand. The oxidative addition of the *para*-substituted haloacetanilide. is followed by the insertion of the water. Next further two steps, elimination and reductive elimination, are

progressed and finally we are capable of obtaining the acetaminophen as a final target compound. [4], [5]

In light of these mechanisms, we did the screening of the reaction parameters (acetamide, Cu catalyst, base, ligand, solvent, reaction time, temperature) and concentrated on optimization to find the best reaction conditions.[10], [11], [12]

Results and discussion.

Among the many starting materials, dihalobenzenes, we started our experiment using *p*-diiodobenzne (PDIB) because the reactivity of the iodine functional groups is better than that of the other halogen functional groups (bromine and chlorine). Entirely, we planned to make the optimized reaction conditions at each two steps, acetamidation and hydroxylation, using PDIB and to apply this optimized reaction conditions to other substrates in sequence.

1. Acetamidation.

1.1 Screening of the amount of acetamide

We optimized the amount of acetamide through the screening of the amount of acetamide under this reaction conditions. (Table 1)

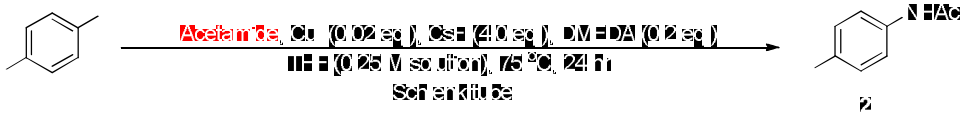


Table 1. Screening of the amount of acetamide

Entry	Amount of acetamide (eq)	Isolation yield (%)	SM recovered (%)
1	1.0	28	49
2	2.0	42	27
3	3.0	39	42
4	4.0	61	31
5	5.0	55	32
6	6.0	47	27
7	7.0	42	41
8	8.0	38	50

Table 1 showed that 4.0 equivalent of acetamide make the best reaction result in terms of the isolation yield and make the SM recovered section minimized. Too large amount (8.0 eq) and too small amount (1.0 eq) of acetamide showed the reverse results

between the isolation yield and SM recovered section. Therefore, we optimized the amount of acetamide as 4.0 equivalents.

1.2 Screening of Cu catalysts.

We optimized the kind and the amount of the Cu catalyst under this reaction condition.

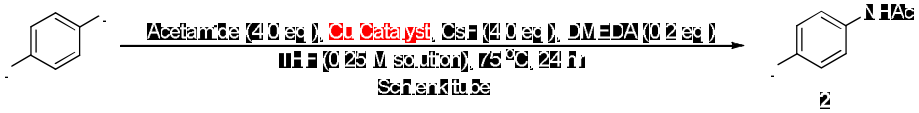


Table 2. Screening of the kind of Cu catalyst.

Entry	Cu catalyst (0.02 eq)	Isolation yield (%)	SM recovered (%)
1	CuI	61	31
2	CuBr	50	42
3	CuCl	40	50
4	$Cu(OAc)_2$	38	61
5	$Cu(OTf)_2$	27	69

First, we tried to optimize the kind of Cu catalyst. At entry 1, using CuI, showed the best reaction result in terms of the isolation yield and showed minimum figure at the aspect of the SM recovered section. Entirely, Cu catalysts which contain Cu(I); CuI, CuBr and CuCl showed the better results than Cu

catalysts containing Cu(Ⅱ); $Cu(OAc)_2$ and $Cu(OTf)_2$. Therefore, we selected the CuI as an optimized Cu Catalyst. (Table 2)

Next, we optimized the amount of CuI

Table 3. Screening of the amount of CuI.

Entry	Amount of CuI (eq.)	Isolation yield (%)	SM recovered (%)
1	0.02	61	31
2	0.03	52	22
3	0.04	51	37
4	0.05	48	42
5	0.06	31	55
6	0.08	28	57
7	0.10	27	60

It seemed that increasing the amount of CuI, decreased the reaction yield beyond 0.02 equivalents and sharply decreased at entry 5, Therefore, we selected 0.02 equivalent as the optimized amount of CuI. (Table 3)

1.3 Screening of Bases.

We optimized the kind and the amount of the base under this reaction condition.

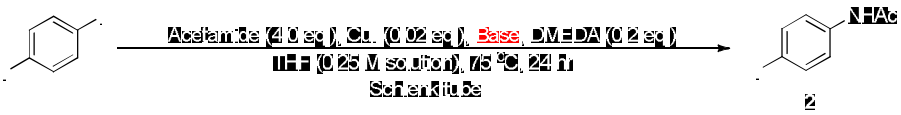


Table 4. Screening of the kind of Bases.

Entry	Base (4.0 eq)	Isolation yield (%)	SM recovered (%)
1	CsF	61	31
2	K_3PO_4	50	32
3	Pyridine	42	51
4	K_2CO_3	41	50
5	Cs_2CO_3	31	62
6	Na_2CO_3	22	60
7	TBAH	11	55

At entry 1, CsF showed the best results in terms of the isolation yield. Except CsF and K_3PO_4, amine bases (Pyridine and TBAH) and bases that contain carbonate functional group did not show good reaction yields. They could not exceed 50 percent of the isolation yield. Instead, the more amounts of the starting materials were recovered. Therefore, we selected CsF as the optimized base. (Table 4)

Next, we optimized the amount of CsF

Table 5. Screening of the amount of CsF

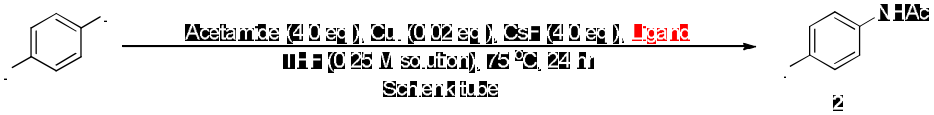
Entry	Amount of CsF (eq.)	Isolation yield (%)	SM recovered (%)
1	1.0	34	55
2	2.0	39	38
3	3.0	41	39
4	4.0	61	31
5	5.0	42	51
6	8.0	31	48
7	9.0	28	50
8	10.0	27	48

From entry 1 to entry 5, we used the amount of CsF at regular interval, 1.0 equivalent. Up to entry 3, the isolation yield increased slightly. By the way, the isolation yield sharply increased about 20 percent at entry 4 and the isolation yields sharply decreased at entry 5. With regards to this tendency, we expected that the isolation yield would show the reverse tendency when we increased the amount of the CsF more than 4.0 equivalent. We used large amounts of CsF from entry 6. The results were matched with our expectation. Through this results and tendency, we could know about the relationship between the

amount of CsF and isolation yield and could optimize the amount of CsF, 4.0 equivalent. (Table 5)

1.4 Screening of ligands

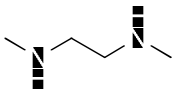
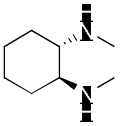
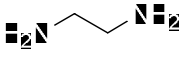
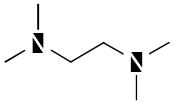
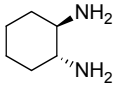
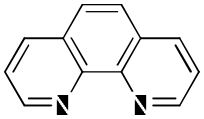
We optimized the kind and the amount of the ligand under this reaction condition.



2

In this case, We experimented with the optimization of the kind of ligand using two forms of it, acyclic amine ligands (DMEDA, TMEDA, EDA) and cyclic amine ligands (1,10-phenanthroline, *trans*-*N,N*-dimethylcyclohexane-1,2-diamine, *trans*-1,2-diaminocyclohexane). DMEDA and trans-*N,N*-dimetylcyclohexane-1,2-diamine showed the good reaction results in terms of the isolation yield at each forms. By the way, both of them showed similar reaction yields about in the 10 percentage. However, if we consider the cost effect of the entire synthetic process, the cost of DMEDA was cheaper than that of trans-*N,N*-dimethylcyclohexane-1,2-diamine. Therefore, we selected DMEDA as an optimized ligand. (Table 6)

Table 6. Screening of the kind of ligands.

Entry	Bases (4.0 eq)	Isolation yield (%)	SM recovered (%)
1	 DMEDA	61	31
2	 *trans*-N,N'-Dimethylcyclohexane-1,2-diamine	55	37
3	 EDA	48	21
4	 TMEDA	35	48
5	 *trans*-1,2-diaminocyclohexane	31	44
6	 1,10-Phenanthroline	33	50

Next, we optimized the amount of the DMEDA

Table 7 Screening of the amount of DMEDA

Entry	Amount of DMEDA (eq.)	Isolation yield (%)	SM recovered (%)
1	0.1	58	14
2	0.2	61	31
3	0.3	56	16
4	0.4	45	47
5	0.5	32	48
6	0.8	22	61
7	0.9	20	62
8	1.0	18	66

At entry 2, 0.2 equivalent of the DMEDA showed the good reaction results in terms of the isolation yield. Entry 1, 3 also showed the good results but the total figure of the isolation yield and SM recovered of each of them, 72 percent, was smaller than that of the entry 2, 92 percent. Other entries using beyond 0.4 equivalent of DMEDA showed the sharply decreased isolation yields but showed larger figure of SM recovered in comparison with entry 1, 2, 3. It seemed that the use of too much amount of DEMDA was not good for the reaction results. Therefore, we could optimize the amount of DMEDA, 0.2 equivalents. (Table 7)

1.5 Screening of solvents.

We optimized the kind and the amount of the solvent under this reaction condition.

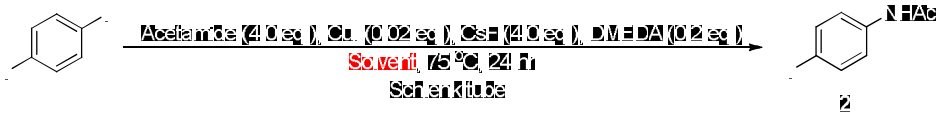


Table 8. Screening of the kind of solvents.

Entry	Solvent (0.25 M solution)	Isolation yield (%)	SM recovered (%)
1	THF	61	31
2	Dioxane	48	30
3	DMF	42	40
4	Toluene	23	62
5	EtOAc	21	67
6	Trifluoroehanol	0	88

At entry 1, the use of THF showed the best reaction yield and Entry 2, 3 showed reaction yields beyond 50 percent. But Entry 4, 5 did not show good reaction yields. Entry 6, the reagents did no dissolve in the trifluoroethanol as a result, the reaction could not occur. Therefore, we selected THF as an optimized solvent. (Table 8)

Next, we optimized the amount of THF

Table 9. Screening of the amount of THF.

Entry	Amount of THF (M solution)	Isolation yield (%)	SM recovered (%)
1	1.000	32	58
2	0.800	38	55
3	0.500	42	38
4	0.250	61	31
5	0.125	52	30
6	0.100	51	28

Entry 4, 0.250 M solution of the THF showed the good reaction results in terms of the isolation yields. Relatively, at low concentration (Entry 3, 4, 5 and 6) showed better results than at high concentration (Entry 1, 2) in terms of the isolation yields. Actually, we could observe the inefficient stirring phenomenons at extremely high concentration (Entry 1) and at extremely low concentration (Entry 6). Accordingly, It has come to our attention that the concentration factor seems to have larger effect on the reaction yield at the large scale of reactor in the commercial plant than at the small scale of reactor in the laboratory because it is also related with the efficiency of the stirring. (Table 9)

1.6 Screening of reaction times.

We optimized the reaction time under this reaction conditions.

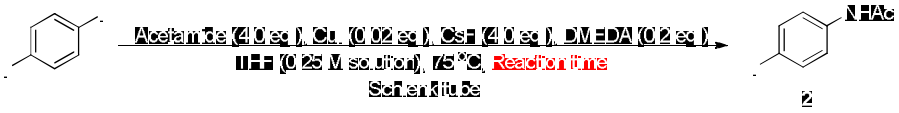


Table 10. Screening of the reaction time

Entry	Reaction time (hr)	Isolation yield (%)	SM recovered (%)
1	3	42	28
2	6	45	30
3	9	41	17
4	12	43	29
5	15	53	38
6	18	55	30
7	24	61	31
8	48	47	48
9	72	50	37

We could not find the accurate tendency between the reaction time and isolation yield. From entry 1 to entry 4, They showed the similar reaction result at the aspect of the isolation yield, and each of them were in the range of the aberration. The reaction yields of entry 5 and 6 are also in the range of the aberration but the absolute figure increased comparing former entries. Entry 7 showed the best reaction yield and the latter entries showed the lower reaction yields in comparison with entry 7. It seems that too long and short reaction times are not proper at the reaction. (Table 10)

1.7 Screening of temperatures.

We optimized the temperature under this reaction condition.

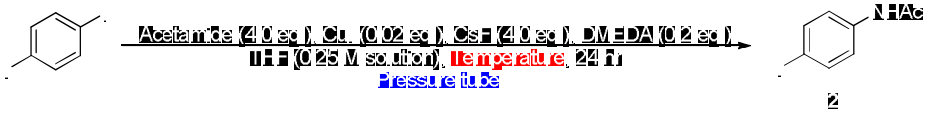


Table 11. Screening of the temperatures

Entry	Temperature(℃)	Isolation yield (%)	SM recovered (%)
1	40	38	28
2	50	42	33
3	60	44	27
4	75	61	18
5	100	48	25
6	130	38	50
7	180	12	48

We could not observe the boiling phenomenon from entry 1 to 3. and the reaction yields were not good. We increased the temperature to 75 ℃ At entry 3, and could observe the boiling phenomenons. The reaction yield was higher than former entries. The latter entries showed the decreased reaction yields in sequence. Therefore, we could optimized the proper temperature, 75 ℃ through these results. (Table 11)

1.8. Pressure, another factor for results

As we know, the temperature has close relationship with the pressure. The boiling point also shows different and various value in commensurate with pressure. We thoght it could be another variable factor that could affect the reaction results. So, we tried to figure out the effect of the pressure at acetamidation. In this case, we applied the optimized reaction parameters; CuI (0.02 eq.) CsF (4.0 eq.), DMEDA (0.2 eq.), THF (0.25 M solution), 24 hr, as a reaction condition. And, we used pressure tube to apply the pressure instead of using schlenk tube. We did the screening of temperatures again because we mentioned that the pressure affects the temperature and the boiling point of THF. We anticipated the temperature (75 ℃) that we optimized would be changed.

We did the screening of temperature under this condition using pressure tube to verify the new optimized temperature and to figure out the effect of the pressure..

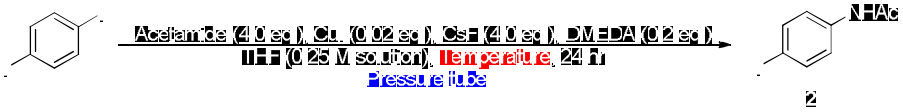


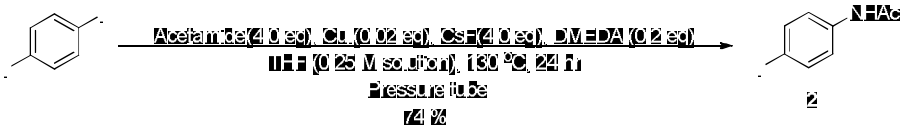
Table 12. Screening of the temperatures

- Pressure tube -

Entry	Temperature (℃)	Isolation yield (%)	SM recovered (%)
1	70	22	70
2	75	28	67
3	100	58	22
4	130	74	18
5	140	60	31
6	160	57	22
7	180	55	28

We experimented with acetamidation at the temperatures which was a little higher than that of the boiling point of THF (67 ℃) at entry 1 and 2. As we anticipated, we could not observe any boiling phenomenon and the reaction yields were too low. After that, We experimented at higher temperature than entry 1 and 2. We could observe a little boiling phenomenon in the pressure

tube at entry 3 and could obtain higher reaction yield than entry 1 and entry 2. Further increase in temperature showed the best reaction yield, 74 percent, at entry 4. Entry 5, 6, 7 showed similar reaction yield each other, but not higher than entry 3.(Table 11) In comparison with the Table 11, we could know that the entire reaction yield increased. Through these results, we could verify that the pressure factor is important in acetamidation and could optimize the new temperature, 130 ℃, Therefore we could determine the final optimized reaction conditions in acetamidation above this.



Scheme 1. Final optimized reaction condition of acetamidation

1.9. Application to other substrates

We applied the final optimized reaction conditions of acetamidation from *p*-diiodobenzene to other substrates

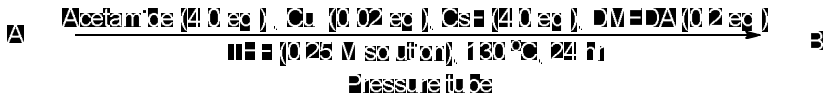
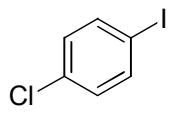
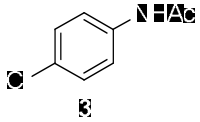
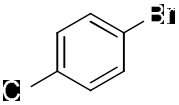
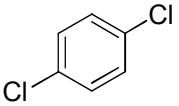
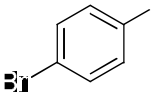
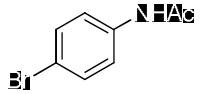
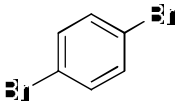
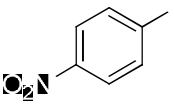
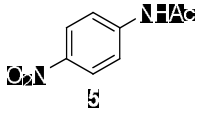
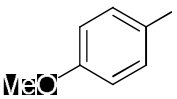
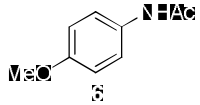


Table 13. Applicatioin to other substrates

Entry	A	B	Isolation Yield (%)	SM recovered (%)
1		 3	97	0
2			84	10
3			66	31
4		 4	94	0
5			68	22
6		 5	94	0
7		 6	96	0

Entry 1, 4 showed better reaction yields than when we used PDIB, and all the starting materials were disappeared. Entry 3 and entry 5 did not show good reaction results in comparison with entry 1, 2 and 4, and also their figures were similar PDIB. Entirely, The isolation yields of the dihalobenzenes which contain different halogen groups at the *para* position were higher than that of the dihalobenzenes containing the same halogen groups at *para* position. Some selectivity problems might affect these results. Also, Entry 6 and 7, we would like to know whether this optimized reaction condition would be applied to other substrates not containing dihalogen groups but containing monohalogen group and other functional groups at *para* position. The reaction yield was very high at each compound.

2. Hydroxylation.

2.1. Screening of Cu catalysts.

We optimized the kind and the amount of the Cu catalyst under this reaction condition.

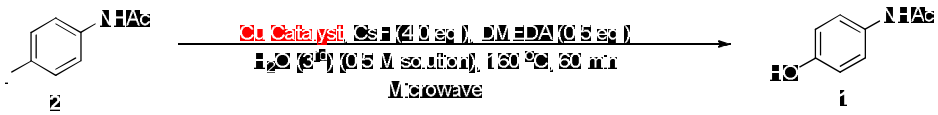


Table 14. Screening of the kind of Cu catalyst.

Entry	Cu catalyst (0.02 eq)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	CuI	65	12	20
2	CuBr	58	6	32
3	CuCl	54	17	24
4	$Cu(OAc)_2$	48	21	28
5	$Cu(OTf)_2$	38	14	39

Entry 1, using CuI showed the best reaction result. At entry 2, the reaction yield was in the range of aberration when comparing with entry 1. However considering SM recovered section, CuI was better than CuBr. This table showed the similar tendency at the acetamidation. The Cu catalysts that contain Cu(I); CuI, CuBr, CuCl showed better reaction results at the aspect of the

isolation yield than the Cu catalysts that contain Cu(Ⅱ); $Cu(OAc)_2$, $Cu(OTf)_2$. (Table 13)

Next, we optimized the amount of CuI

Table 15. Screening of the amount of CuI.

Entry	Amount of CuI (eq.)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	0.02	28	22	30
2	0.04	32	18	21
3	0.06	54	19	29
4	0.08	58	17	24
5	0.10	65	12	20
6	0.15	52	18	28
7	0.20	31	12	30

We applied the amount of CuI, 0.02 equivalents, that was optimized from acetamidation. But the reaction results were not as good as the result coming from acetamidation. We increased the amount of the CuI after entry 1. The reaction yield sharply increased at entry 3 and shows maximum figure at entry 5. The latter entries showed the decreased tendency. It seems that too low amount of CuI (entry 1) and the opposite amount of CuI (entry 7) is not good. (Table 15)

2.2. Screening of bases.

We optimized the kind and the amount of the base under this reaction condition.

2 1

Table 16. Screening of the kind of Bases.

Entry	Base (4.0 eq)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	CsF	65	12	20
2	K_3PO_4	51	18	22
4	K_2CO_3	35	17	30
5	Cs_2CO_3	31	22	39
6	Na_2CO_3	28	15	30

Like acetamidation, CsF showed the best reaction yield. The tendency and the sequence were also similar with the acetamidation. The bases containing carbonate functional group (entry 4, 5, 6) showed the similar isolation yield in the range of aberration, and their absolute figures were not high. (Table 16)

Next, we optimized the amount of CsF.

Table 17. Screening of the amount of CsF

Entry	Amount of CsF (eq.)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	1.0	38	9	28
2	2.0	58	17	11
3	4.0	65	12	20
4	6.0	56	20	18
5	8.0	31	14	26

First of all, we applied the optimized amount of CsF coming from acetamidation, 4.0 equivalent at entry 3. Next we increased and decreased the amount of the CsF. Extremely small and large amount of CsF showed very low reaction yields (entry 1, entry 5). Entry 2 and entry 4 showed reaction yield beyond 50 percent. This figure was not higher than entry 3, but some advantages seem to exist in other aspects. Unlike Entry 3, these entries showed opposite figures between the SM recovered and acetanilide section. It means that the reactions do not bring about more side effects. Instead, they give us some possibilities and clues that the reaction could be progressed to the acetaminophen, the final product if we controlled the amount of CsF more accuratelly or other reaction parameters. (Table 17)

2.3. Screening of ligands.

We optimized the kind and the amount of the ligand under this reaction condition.

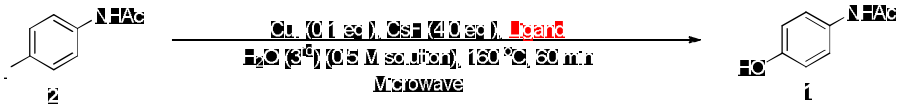
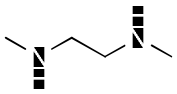
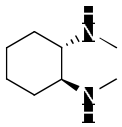
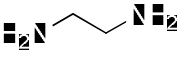
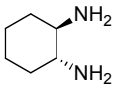


Table 18. Screening of the kind of ligands.

Entry	Bases (4.0 eq)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	 DMEDA	65	12	20
2	 *trans*-*N*,*N*-Dimethylcyclohexane-1,2-diamine	60	18	27
3	 EDA	44	12	28
4	 *trans*-1,2-diaminocyclohexane	31	17	30

Like acetamidation, we used two types of amine ligands; cyclic amine ligands (*trans*-*N,N*-dimethylcyclohexane-1,2-diamine, *trans*-1,2-diaminocyclohexane) and acyclic amine ligands (DMEDA, EDA). Entry 1 and entry 2 showed the good reaction

yields at each type of amine ligands. Entry 2 showed the similar isolation yield and this figure was in the range of an error about 5 percent. But condsidering the cost effect, the cost of DMEDA is much cheaper that of *trans*-*N,N*-dimethylcyclohexane-1,2-diamine. Therefore, DMEDA seems to be more proper ligand. (Table 18)

Next, we optimized the amount of DMEDA

Table 19. Screening of the amount of DMEDA

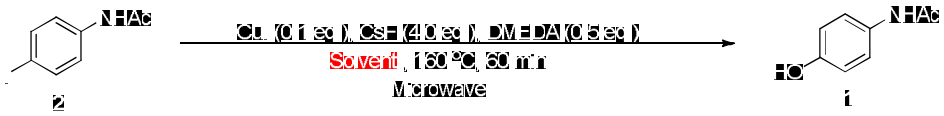
Entry	Amount of DMEDA (eq.)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	0.1	50	18	30
2	0.2	44	11	29
4	0.5	65	12	20
5	0.8	38	22	28
6	1.0	31	21	32

We applied the amount of DMEDA, 0.2 equivalents, to the hydroxylation because this amount was optimized from acetamidation, but the reaction yield was above 50 percent. After that we increased and decreased the amount of the DMEDA. Entry 4 showed the best reaction yield. The latter entries showed that the isolation yields decreased but the amount of acetanilide increased in commensurate with the

increase in the amount of DMEDA. Therefore, we could optimize the amount of DMEDA, 4.0 equivalents. (Table 19)

2.4. Screening of solvents.

We optimized the kind and the amounts of the base under this condition.



Hydroxylation is required for the source of hydroxy functional groups. In this case, we concentrated on the water quality and focused on the use of aqueous solution containing hydroxy groups.

Table 20. Screening of the solvents.

Entry	Solvent (0.5 M solution)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	H_2O (3^{rd})	65	12	20
2	H_2O (1^{st})	62	15	23
3	KOH (aq)	26	38	19
4	NaOH (aq)	25	46	12

We could know that the effect of water quality was not the key factor that could affect the reaction results. They showed very similar reaction results (entry1, 2) However, at entry 3 and 4, when we used aqueous solution of KOH and NaOH, we could observe that the reaction yields sharply decreased. Therefore we selected H_2O (3^{rd}) as an optimized solvent. (Table 20)

Next, we optimized the amount of H_2O (3^{rd})

Table 21. Screening of the amount of H_2O (3^{rd})

Entry	Amount of H_2O (3^{rd}) (M solution)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	1.000	38	33	18
2	0.500	65	12	20
3	0.250	56	22	13
4	0.125	53	18	26

Entry 2, 0.500 M solution showed the best isolation yield. Entry 1 showed low yield, but other entries showed reaction yield beyond the 50 percent. We concluded that the dilute concentration was better than the high concentration, relatively. (Table 21)

2.5. Screening of reaction time.

We optimized reaction time under this reaction condition.

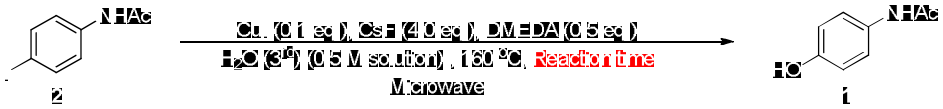


Table 22. Screening of reaction times.

Entry	Reaction time (min)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	15	38	32	12
2	30	55	20	13
3	45	58	18	19
4	60	65	12	20
5	120	57	11	28

Entry 4 showed the best reaction results in terms of the isolation. However, the reaction time seemed not to be the critical factor to affect the reaction yields. Except entry 1, they showed the similar reaction yield and not far different each other. Remarkably, we needed to focus on the amount or the acetanilide. As the reaction time increased, the amount of acetanilide increased, and SM recovered section showed opposite tendency in comparison with acetanilide. This tendency gave us a clue to

try to use other apparatus, pressure tube instead of microwave reactor. (Table 21)

2.6. Screening of temperatures.

We optimized reaction time under this reaction condition.

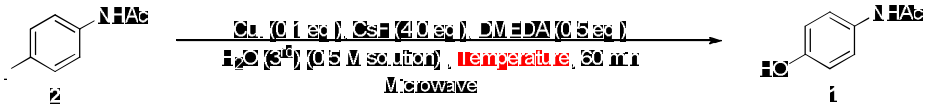


Table 23. Screening of temperatures.

Entry	Temperature (℃)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	100	28	42	14
2	130	50	32	19
3	160	65	12	20
4	180	45	22	30

Entry 3 showed the best reaction yield. We could not observe the boiling phenomenon in the microwave reaction because we could not see the inside of it where the reaction occurred, but we guessed that the boiling phenomenon did not occur considering the case that we had already experienced at acetamidation. The low yield of entry 1 seemed to prove our guess. Like the screening of reaction time, they showed the similar tendency about the amount of acetanilide. So we focused

on this tendency and tried to reduce the amount of the acetnilide. (Table 23)

2.7. Endeavor to decrease the amount of acetanilide.

Unlike acetamidation, the problem of hydroxylation was the generation of undesired product, acetanilide. As we mentioned at the former paragraph, we focused on the relationship between the reaction time, temperature and the amount of acetanilide. As the reaction time and the temperature increased, the amount of acetanilide was commensurate with them. We thought that this results seemed to come from the use of the microwave reactor because the reaction condition is known for harsh condition due to the microwave, pressure and temperature. In these factors, we guessed that the microwave might strongly affect the generation of acetanilide. So, we planned to use the pressure tube like the same manner at acetamidation and tried to optimize the reaction temperature through the screening of it.

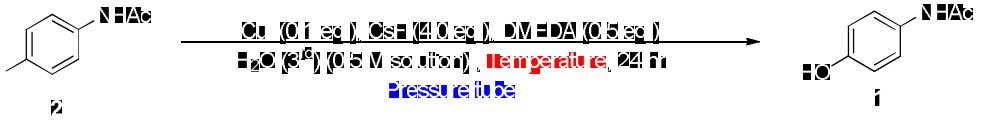


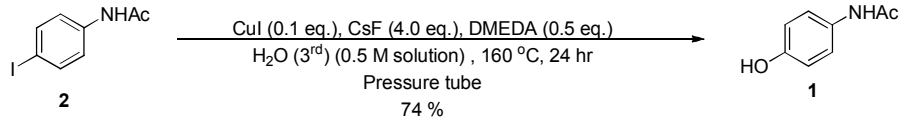
Table 24. Screening of reaction times.

- pressure tube -

Entry	Temperature (℃)	Isolation yield (%)	SM recovered (%)	Acetanilide (%)
1	120	55	18	11
2	130	67	20	10
3	140	57	25	9
4	150	64	19	7
5	160	74	17	8
6	170	63	20	9
7	180	51	21	6

Unfortunately, we could not find some relationship between the temperature and reaction yield. Entry 5, 160℃, also showed the best reaction yield either the microwave reactor did and entire entries showed the improved reaction yields. Moreover, the amount of acetanilide decreased in comparison with the use of microwave. It seemed to be reasonable that the decreased amount of acetanilide compensate for the increased the production of 1. Therefore, we could conclude that the use of pressure tube seemed to decrease the side effect, the amount of

acetanilide and increase the generation of 1 simultaneously. (Table. 23) Therefore, the final optimized reaction conditions of hydroxylation are above this.



Scheme 2. Final optimized reaction condition of hydroxylation.

2.8. Application to other substrates

We applied the optimized reaction conditions.

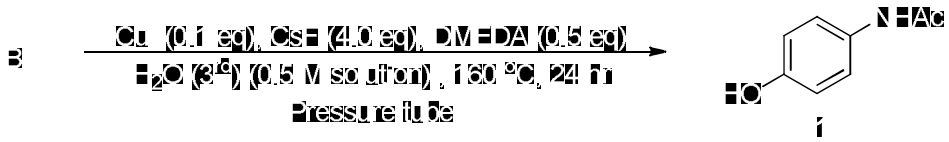
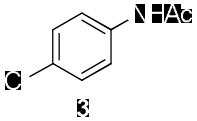
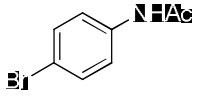


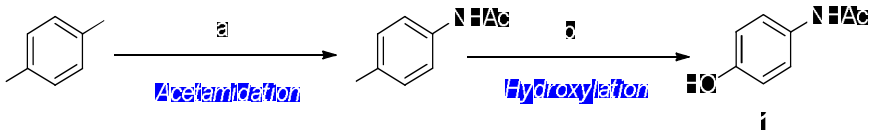
Table 25. Application to other substrates

Entry	B	Isolation Yield (%)	SM recovered (%)	Acetanilide (%)
1	 3	68	16	12
2	 4	75	12	7

B, 3 and 4, came from the Table 12. The use of 3, 4 showed similar reaction results when we using 2. We did not use 5 and 6 at the hydroxylation because they did not have halogen groups after the acetamidation.

Conclusion

We could optimize the best reaction conditions at each step, acetamidation and hydroxylation, through the screening of the reaction parameters; acetamide, Cu-cataylst, base, ligand, solvent, reaction time and temperature, using *p*-diiodobenzene (PDIB).



Reagents and conditions

(a) Acetamide (4.0 eq.), Cu (0.02 eq.), Cs2CO3 (4.0 eq.), DMEDA (0.2 eq.), H2O (0.25 M solution)
i 80 °C, 24 hr, Pressure tube, 74 %
(b) Cu (0.1 eq.), Cs2CO3 (4.0 eq.), DMEDA (0.5 eq.)
i 80 °C, 24 hr, Pressure tube, 74 %

Scheme 3. Final optimized reaction conditions of new synthetic process.

When we applied these optimized reaction conditions to other substrates, at acetamidation, we found, entirely, they showed moderate reaction yields. Especially, 1-chloro-4-iodobenzne and 1-bromo-4-iodo-benzene showed very high reaction yield (97 % and 94 % in sequence). These figures were beyond the reaction yield of PDIB (74 %). Considering only acetamidation,

1-chloro-4-iodobenzene seemed to be more proper than 1-bromo-4-iodo-benzene. However, at hydroxylation, the reaction yield of **4** (75 %) was better than that of **3** (68 %). The **4** came from the 1-bromo-4-iodo-benzene and the **3** came from 1-chloro-4-iodobenzene. Therefore, we concluded that considering the entire reaction yield of two steps, 1-bromo-4-iodo-benzene was the best starting materials.

Consequently, we could not only prove the feasibility of the new synthetic process that we proposed as we applied it to PDIB and other substrate, but also could find the best starting material for the process. These results are expected to contribute the eco-friendly and economical mass production of **1.**

Experimental Details

General Procedures

1. Acetamidation

Materials are purchased from commercial suppliers and used without further purification. Starting material, acetamide, Cu-catalyst, base, ligand and solvent are added to the schlenk tube (pressure tube). Degassing is performed by Ar(g) for 1 minute. The schlenk tube (pressure tube) is installed to the oil bath. The reaction is checked with SiO_2 TLC plate (Hexane : EtOAc = 2 : 1), and then monitored under UV light (254 nm) if the schlenk tube is used. (The reaction cannot be checked with SiO_2 TLC plate if we use the pressure tube). Extraction is performed by ethyl acetate and 1st distilled water. Sodium sulfate (Na_2SO_4) is added to remove the residue water in the organic layer. The organic layer is filtered by a vacuum aspirator. Purification is performed by column chromatography on silica gel 60 (70-230 mesh). ^1H and ^{13}C NMR spectra are measured at 400 MHz respectively in DMSO-d_6 or $CDCl_3$-d and data are reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, couploing constant in Hz.). Gas

chromatography analyses are done with a capillary column (30 m x 0.25 mm).

1. Hydroxylation

2, **3**, **4**, Cu-catalyst, base, ligand and solvent are added to the microwave tube (pressure tube). Degassing is performed by Ar(g) for 1 minute. The microwave tube is installed to the microwave reactor (The pressure tube is intalled to the oil bath). Extraction is performed by ethyl acetate and 1st distilled water. Sodium sulfate (Na_2SO_4) is added to remove the residue water in the organic layer. The organic layer is filtered by a vacuum aspirator. Purification is performed by column chromatography on silica gel 60 (70-230 mesh). ^{1}H and ^{13}C NMR spectra are measured at 400 MHz respectively in DMSO-d_6 or $CDCl_3$-d and data are reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz.). Gas chromatography analyses are done with a capillary column (30 m x 0.25 mm).

1: ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 6.68 (d, 2H, *J*=8.0, 2.05), 7.34 (d, 2H, *J*=8.0, 2.00), 9.15 (s, 1H), 9.66 (s, 1H); ^{13}C NMR δ 24.18, 115.64, 121.32, 131.49, 153.60, 168.00; HRMS (CI) calcd for $C_8H_{10}NO_2$ 152.0172 [(M+ H]$^+$)], found 152.0174

2: ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 7.43 (d, 2H, *J*=8.0, 2.09), 7.62 (d, 2H, *J*=8.0, 2.03), 10.05 (s, 1H); ^{13}C NMR δ 24.53, 86.73, 121.66, 137.75, 139.60, 168.94; HRMS (CI) calcd for C_8H_8INO 261.9279 [(M+ H]$^+$)], found 261.9728

3: ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H), 7.35 (d, 2H, *J*=12.0, 2.00), 7.63 (d, 2H, *J*=12.0, 2.05), 10.09 (s, 1H); ^{13}C NMR δ 24.41, 120.95, 126.98, 128.99, 138.72, 168.89; HRMS (CI) calcd for C_8H_8ClNO170.0373 [(M+ H]$^+$), found 170.0372

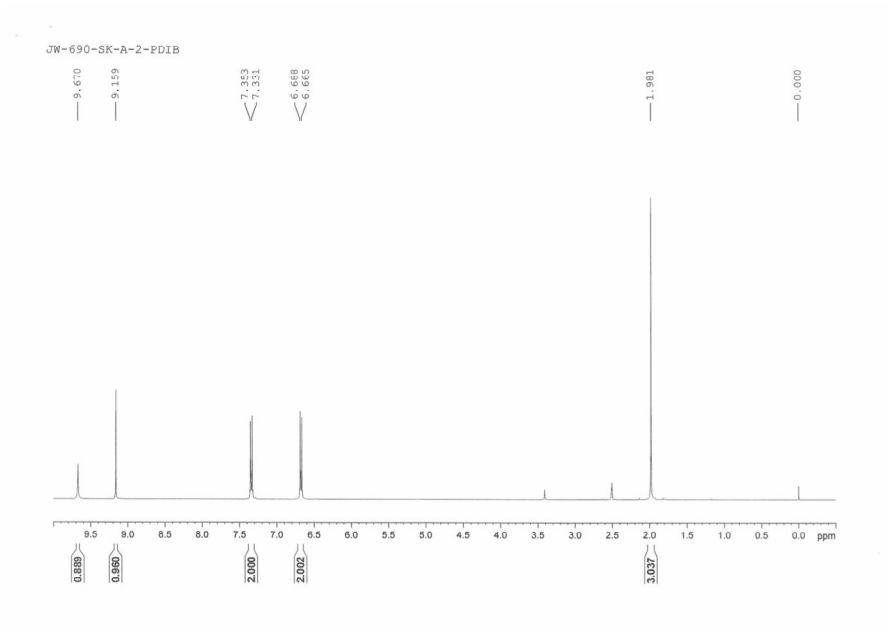
4: ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 7.48 (d, 2H, *J*=12.0, 2.00), 7.57 (d, 2H, *J*=12.0, 1.89), 10.08 (s, 1H); ^{13}C NMR δ 24.47, 114.95, 121.34, 131.91, 139.14, 168.91; HRMS (CI) calcd for C_8H_8BrNO 213.9868 [(M+ H]$^+$), found 213.9866

5: ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H), 7.81 (d, 2H, *J*=16.0, 2.00), 8.20 (d, 2H, *J*=12.0, 2.04), 10.55 (s, 1H); ^{13}C NMR δ 24.14, 118.46, 124.86, 141.92, 145.36, 169.26; HRMS (CI) calcd for $C_8H_8N_2O_3$ 181.0613 [(M+H]$^+$), found 181.0614

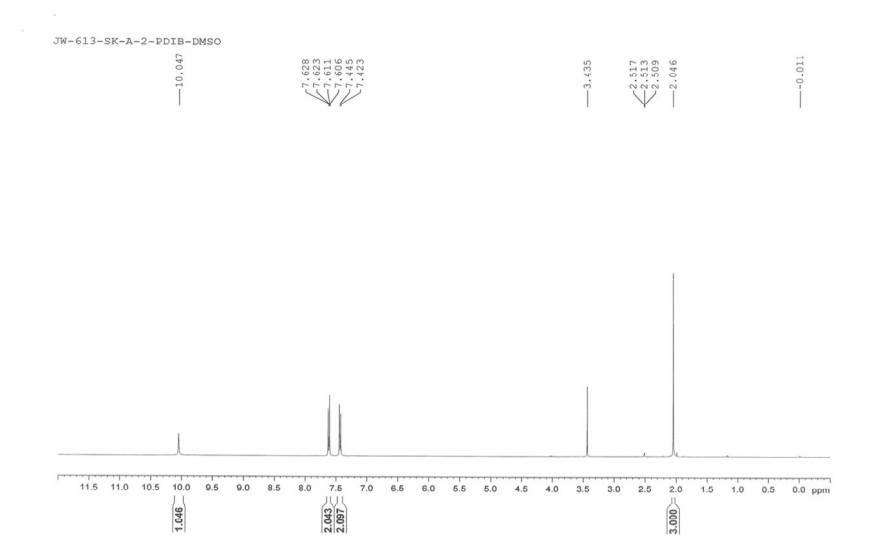
6: ^{1}H NMR ($CDCl_3$-*d*) δ 2.11 (s, 3H), 3.77 (s, 3H) 6.82 (d, 2H, *J*=16.0, 2.05), 7.39 (d, 2H, *J*=16.0, 2.00), 8.10 (s, 1H); ^{13}C NMR δ 24.06, 55.42, 114.01, 122.11, 131.19, 156.35, 168.90; HRMS (CI) calcd for $C_9H_{11}NO_2$ 166.0868 [(M+H]$^+$), found 166.0871

APPENDICES

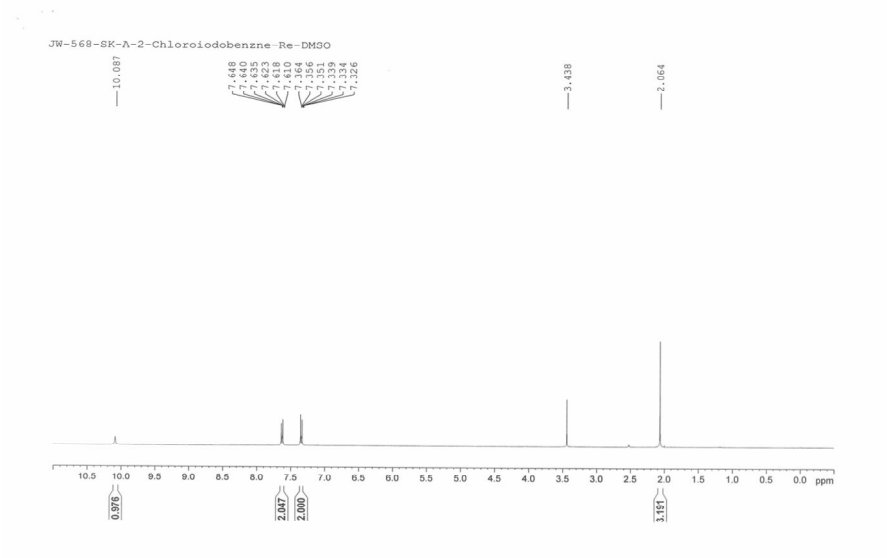
List of ^{1}H NMR Spectra of selected compound.



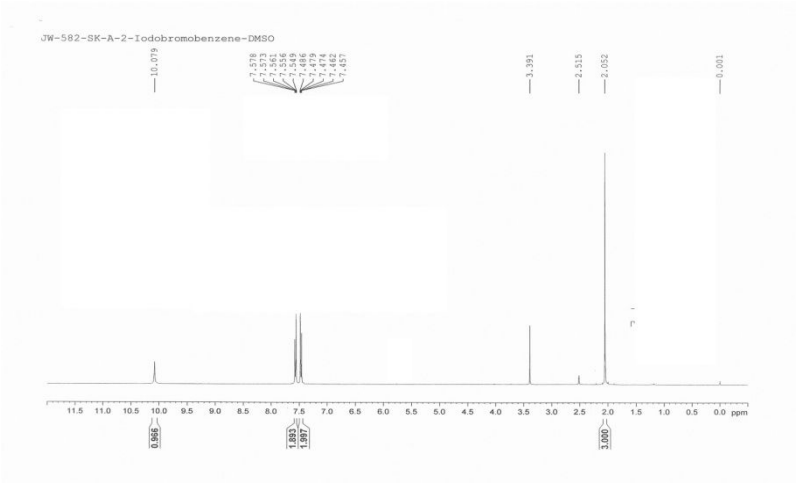
400 MHz ^{1}H NMR spectra (DMSO-*d6*) of compound **1**



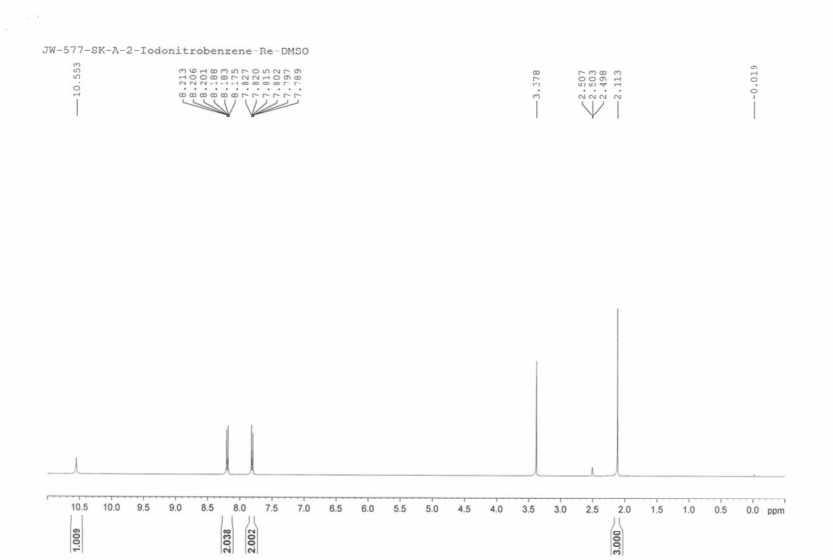
400 MHz ^{1}H NMR spectra (DMSO-*d6*) of compound **2**



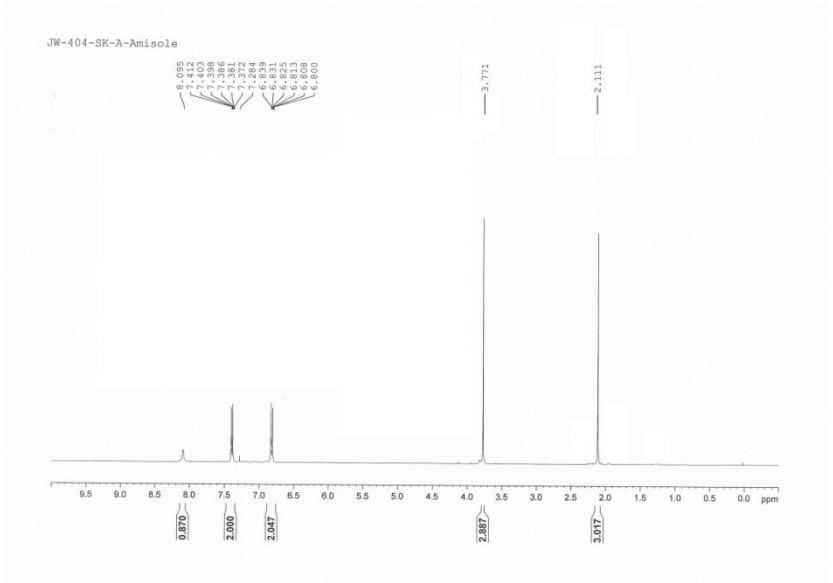
400 MHz ^{1}H NMR spectra (DMSO-*d6*) of compound **3**



400 MHz ^{1}H NMR spectra (DMSO-*d6*) of compound **4**

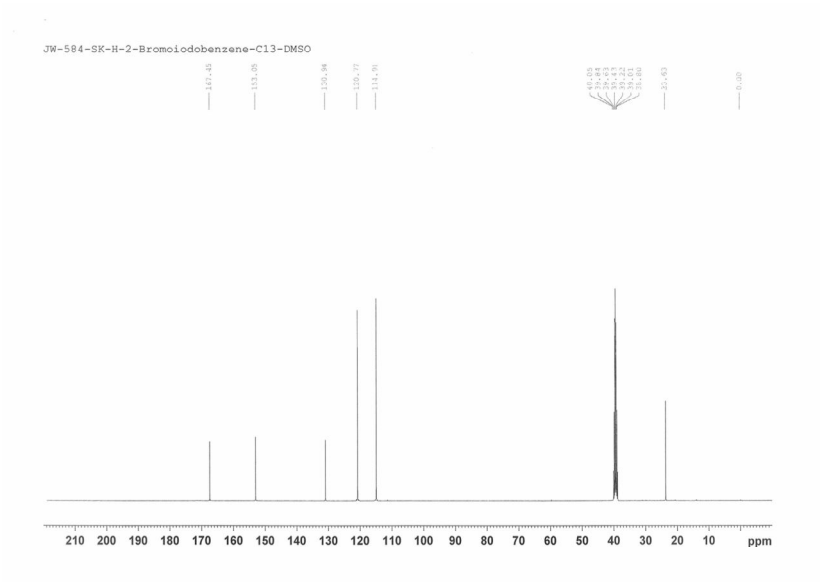


400 MHz ^{1}H NMR spectra (DMSO-*d6*) of compound **5**

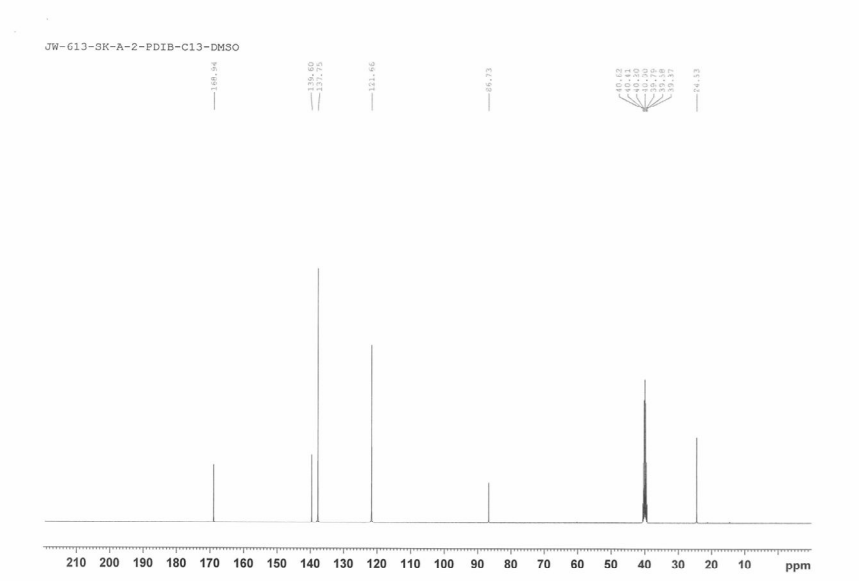


400 MHz ^{1}H NMR spectra ($CDCl_3$-*d*) of compound **6**

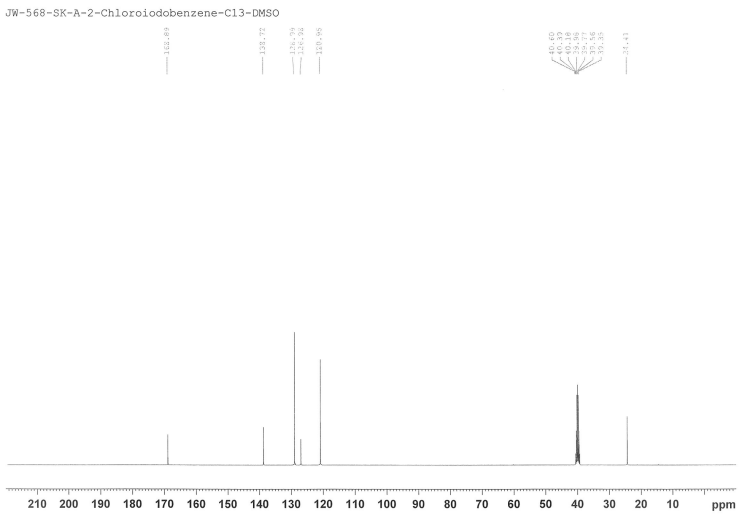
List of ^{13}C NMR Spectra of selected compound.



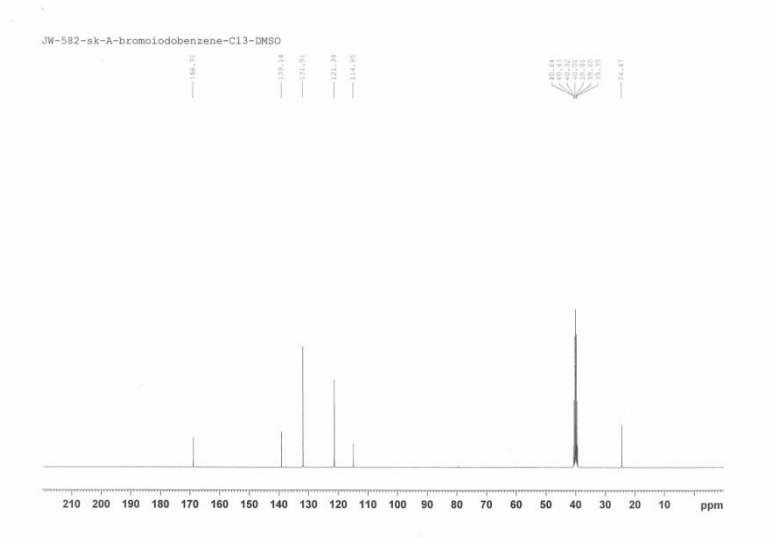
400 MHz ^{13}C NMR spectra (DMSO-*d6*) of compound **1**



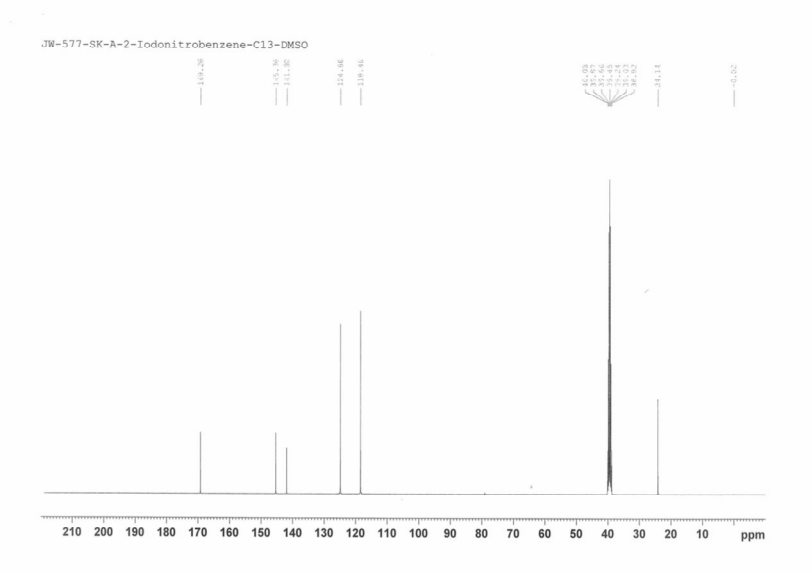
400 MHz ^{13}C NMR spectra (DMSO-*d6*) of compound



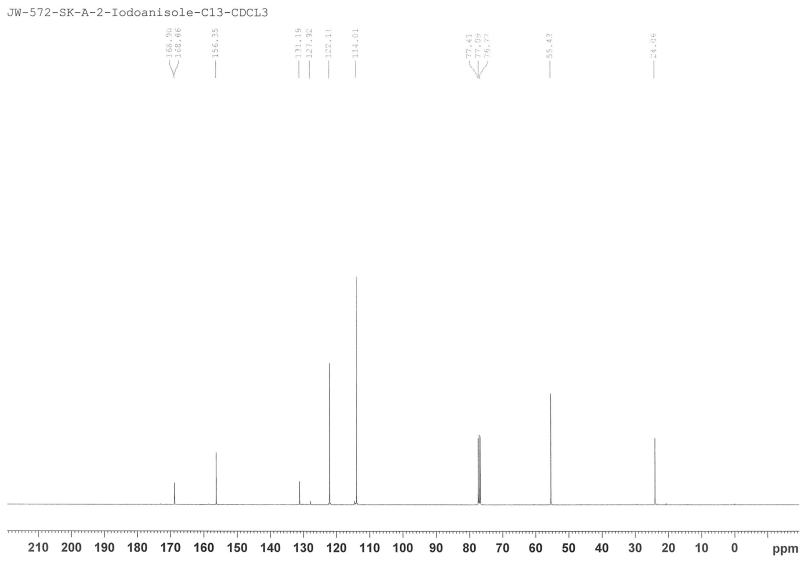
400 MHz ^{13}C NMR spectra (DMSO-*d6*) of compound **3**



400 MHz ^{13}C NMR spectra (DMSO-*d6*) of compound **4**



400 MHz ^{13}C NMR spectra (DMSO-*d6*) of compound **5**



400 MHz ^{13}C NMR spectra ($CDCl_3$-*d*) of compound **6**

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ABSTRACT IN KOREAN

김중원

화학생물공학부

서울대학교

지금까지 매우 다양한 비마약성 진통제들이 개발되어 왔고, 그 개발은 그 이전의 것들을 개선 혹은 보완하는 방향으로 진행되어왔다. 그 중에서도 아세트아미노펜은 다양한 의학적 응용이 가능하고, 부작용이 매우 적다는 장점으로 인해서 오늘날 세계에서 가장 널리 사용되는 진통제로 알려져 있다.

하지만 기존의 아세트아미노펜을 합성하는 공정은 원하지 않는 이성질체의 생성과 강하고 독성이 있는 산의 사용 등과 같은 문제점을 지니고 있다. 이러한 문제점들은 결국 추가적인 정제과정과 사용된 산의 회수 등의 문제점들을 수반하고 결국 추가적인 비용을 발생시켜 아세트아미노펜의 생산단가에 영향을 주게 된다.

이 논문을 통해서 우리는 구리촉매를 이용해서 다이할로벤젠으로부터 아세트아미노펜을 경제적이면서 효율적으로 만드는 새로운 합성 공정을 소개하고자 한다. 우리는 이 공정을 통해서 기존의 공정이 가진 단점들을 보완하였을 뿐만 아니라, 합성 공정을 좀 더 온화한 조건에서 진행시킬 수 있는 환경친화적이면서,

추가적인 정제과정을 필요로 하지 않도록 짧게 만들어 낼 수 있었다.

핵심어: 다이할로벤젠, 아세트아미데이션, 하이드록실레이션

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새해가 밝아오고 있습니다. 예전에 고 노무현 전 대통령이 당선되었을 때 고 김수환 추기경에게 기자들이 축하의 말씀 한마디 부탁한다는 말을 하자 추기경께서 하신 말씀이 “축하 인사는 노 대통령이 퇴임할 때 해주겠습니다”라는 말이었습니다. 시작도 중요하지만 항상 우리의 삶은 시작임과 동시에 끝이라는 말로도 귀결되듯이 올 한해 잘 마무리 하시고 모두에게 좋은 일 행복한 일 가득하시길 빌면서 이것으로 감사의 글을 마치도록 하겠습니다.