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IMPROVED AND SKILLFUL SYNTHESIS OF (±) FENOPROFEN, AN IMPORTANT ANTI-INFLAMMATORY AGENT

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Abstract: Several of the alpha-aryl-propionic acids are used as critical pharmaceutical agents much similar to how ibuprofen, ketoprofen, and flurbiprofen are used as non-steroidal anti-inflammatory agents. Many synthetic routes for producing arylpropionic acids have been proposed over the few years. Several of the present studies are focused on preparing pharmaceutically useful alpha-aryl-propionic acids. . The healing efficacy of this class of medicine is properly attested through the introduction and massive use of more than a dozen of compounds exemplified by ibuprofen, ketoprofen, flurbiprofen, and fenoprofen. It has been proven that appropriate alpha halo ketone can be easily transformed to ester, which on further hydrolysis yields alpha-aryl-propionic acid. A new and convenient synthesis of ether linkage utilizing Ullmann reaction has been suggested as an important step in the synthesis of Fenoprofen. In this paper, we report the total synthesis of Fenoprofen.

Keywords: Fenoprofen, Ullmann reaction, alpha halo ketone, alpha-aryl-propionic acid.

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INTRODUCTION

Several 2-arylpropionic acids have been described as non-steroidal anti-inflammatory agents (NSAIs), which are useful in the treatment of osteoarthritis and rheumatoid arthritis.[1] Some NSAIs also are used to treat several long term health problems. There are three general classes of drugs commonly used in the treatment of rheumatic arthritis: (a) non-steroidal anti-inflammatory agents (NSAIs) [2] such as celecoxib, diclofenac sodium, ibuprofen, etc., (b) glucocorticoids[3] such as betamethasone, prednisone etc., and (c) disease modifying anti-rheumatic drugs[4] (DMARs) such as hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, etc. The key objective of these drugs is to reduce inflammation leading to a subsequent reduction in pain intensity and improved function. In addition to anti-inflammatory effects, these agents are also known to have mild to moderate analgesic properties. Examples of some non-steroidal anti-inflammatory drugs (NSAIDs) include ibuprofen, indomethacin, nabumetone, naproxen, and others. These drugs are helpful in the treatment of mild to moderate pain, fever, and inflammation. They are effective in reducing the levels of prostaglandins, chemicals that are responsible for causing these ailments. [6] Fenoprofen, a NSAID, functions by blocking the activity of cyclooxygenases, which in turn lowers the level of prostaglandins. As a result, inflammation, swelling, pain, and fever are reduced.

Aspirin is one of the NSAIs agents which has largely been replaced by the other NSAIDs as the initial drug of choice for the management of inflammation due to its higher dosage requirement and high rate of gastrointestinal toxicity[7]. There are a large number of NSAIs available which are equally efficacious at full dosages. Fenoprofen is commercially available non-steroidal anti-inflammatory and analgesic drug used for the treatment of pain and inflammation caused due to rheumatoid arthritis and osteoarthritis. There are several synthetic routes available for the manufacture of Fenoprofen . One of the processes involves the reaction of 3-phenoxy chlorobenzene with sodium cyanoacetate followed by methylation and latter hydrolysis of cyano group.[8] Some other processes include the electrochemical synthesis of 2-aryl propionic acids by carbonyl group insertion by reaction of alpha methyl benzyl chlorides and carbon dioxide by [Co(Salen)].[9] The key step in the construction of diaryl ether unit during the synthesis of fenoprofen is by means of Ullmann reaction. This has been proved to be useful in a variety of transformation in organic synthesis.

The preparation of 3-bromoacetophenone was done using bromine and aluminium chloride.[10] Previously, the preparation of 3-bromo propiophenone was reported by reaction using 3-bromobenzonitrile and ethyl magnesium bromide. We optimized the synthesis of 3-bromopropiophenone from propiophenone, bromine, and aluminum chloride. It must be noted that the reaction using meta bromination with the commercially available propiophenone (**2)** is an important step in the synthesis of fenoprofen. Again, temperature plays a crucial role in this reaction.

The formation of C-O bond using 3,4,7,8-tetramethyl-1,10-phenanthroline (Me4Phen) or 1,10-phenanthroline as a ligand improves the Cu-catalyzed cross-coupling reactions of aryl halides with primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols under mild reaction conditions.[11] Ullmann ether synthesis is an efficient method for the synthesis of diaryl ethers and is performed at 90°C using either aryl iodides or aryl bromides as the substrates under the assistance of amino acids.[12] Another general method involves developing a mild, palladium-free synthetic protocol for the cross-coupling reaction of aryl iodides and thiols using Cu catalyzed reaction and neocuproine ligand at high temperatures.[13]

Another efficient method for the synthesis of diaryl ethers under inexpensive ligand and mild conditions is the Ullmann-type coupling of aryl bromides or iodides with phenols. A number of diaryl ethers are obtained with excellent yields in acetonitrile in the presence of Cs_2CO_3 and catalytic copper(I) oxide.[14]The arylation of ethyl acetoacetate, ethyl benzoyl acetate, and dialkyl malonate under the catalysis of CuI and L-proline in DMSO proceed smoothly at lower temperatures in good yields. Both aryl iodides and aryl bromides are compatible with these reaction conditions.[15] The efficacy of copper-mediated cross-coupling reactions can be fairly increased with the initiation of mild reaction conditions and ability to employ catalytic amounts of copper. Again, the utilization of diamine-based ligands are of high importance in the synthesis of pharmaceuticals and designed materials.[16] By employing (2-pyridyl) acetone as a new supporting ligand, the copper-catalyzed coupling reactions of aryl halides with various phenolic moieties gives good yields under mild conditions. This reaction displays great functional groups compatibility and excellent reactive selectivity.[17] In this study, we have developed an effective new strategy for the synthesis of fenoprofen in good yield from propiophenone.

2. EXPERIMENTAL

2.1. General method

All manipulations were performed using standard Schlenk techniques under a dry nitrogen atmosphere. All the experiments were performed in flame-dried Schott Duran® bottles. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck; 0.25 mm thickness) and visualized under UV light followed by spraying with 5% solution of phosphomolybdic acid (PMA) in ethanol, subsequently followed by charring with a heat gun. Column chromatography was performed on 60 silica gel (Merck; 230-400 mesh). All other reagents of analytic grade were used without any further purification. ^{1}H-NMR (hydrogen-1 NMR) and ^{13}C (carbon-13 NMR) were recorded using Varian NMR 500 instrument (NMR Laboratory, Urbana, IL) at 500 MHz. The chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal and external standards for ^{1}H-NMR. Mass spectra were recorded on a Shimadzu 2010s mass spectrometer (Shimadzu Biotech, Manchester, UK). The IR spectra were recorded on a Spectrum 100 spectrometer (Waltham, MA, USA).

2.2. Procedure for the synthesis of (±) fenoprofen (1)

3-Bromopropiophenone (3):

Aluminium chloride ($AlCl_3$) (67.0 g, 502 mmol) was taken in 500 mL RBF. Propiophenone, **2** (27.0 g, 201 mmol) was added drop wise (highly exothermic) over the period of 10-15 min (temperature reaches ~ 80°C), a molten mass formed. Stir it at same temperature for 10 min. Bromine (12.46 mL, 241 mmol) was added drop wise over a period of 20 min. Continue the stirring at room temperature for 1.5 hrs. Reaction mass was poured over Concentrated HCl and ice mixture under vigorous stirring. Slowly the solid was precipitated out. Washed the solid with ice water for 3 times. Filter the solid and air dried to afford **2** (27.0 g, 63%). (mp 39°C); IR: 1691, 1567, 1458, 1417, 1211 Cm^{-1}. ^{1}H NMR (DMSO d_6): 8.08 (s, 1H); 7.97-7.94(m, 1H); 7.85-7.83(m, 1H); 7.51-7.48(m, 1H); 3.08(q, *J* = 7.2 Hz, 2H); 1.05(t, *J* = 7.2 Hz, 3H). MS$[M+H]^+$ Calculated for $C_9H_{10}BrO$:m/z 214.08, found 214.70.

General procedure for the Ullmann coupling of 3-bromopropiophenone with phenol:

A pressure tube equipped with Teflon cap was charged with magnetic stir bar, [Cu] catalyst (5-10 mol%), Base (2 eq.), 3-bromopropiophenone (1 eq.), and phenol (1.2 eq.) in a suitable solvent (mentioned in Table 2). The

tube was evacuated and purged with argon for 20 min. Under a counter flow of argon ligand (Lig 1- Lig 8) was added. The tube was refilled with argon and sealed. The reaction mixture was heated to the indicated temperature (80-120°C) for the required time. After cooling to the room temperature, reaction mixture was diluted with ethyl acetate (25 mL), and then passed through a bed of celite to remove inorganic salts and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum.

1-(3-phenoxyphenyl) propan-1-one (4):

To a solution of Cs_2CO_3 (29.97 g, 92 mmol), 3-bromopropiophenone, **2** (10.0 g, 46 mmol), Phenol (6.62 g, 70 mmol), in dry DMF (100 mL) was added 1-(pyridin-2-yl) propan-2-one (1.24 g, 9.2 mmol). Contents were degassed for 30 min under vacuum, and then added Cu(I)Br (0.659 g, 4.6 mmol), again degassed for 10 min. under vacuum. Contents were heated at 120°C for 16 hrs. Reaction was monitored by TLC, water was added and extracted with ethyl acetate, and brine washing was given to organic layer, dried and evaporated. Crude compound was purified by column chromatography to afford **4** (7.34 g, 69.18%). IR: 1687, 1581, 1489, 1435, 1247 Cm^{-1}. ^{1}H-NMR: DMSO-d6: 7.75-7.05(m, 9H), 2.98(q, *J* = 7.2 Hz, 2H), 1.06(t, *J* = 7.2 Hz, 3H). MS[M+H]$^+$ Calculated for $C_{15}H_{15}O_2$:m/z 227.11, found 227.15.

α- Chloro-3-phenoxypropiophenone (5):

To a solution of 1-(3-phenoxyphenyl) propan-1-one, **4** (5.0 g, 22.22 mmol) in DMF (25 mL) was added Copper chloride. $2H_2O$ (7.50 g, 44.44mmol), followed by LiCl (0.932 g, 22.22mmol) and heated at 80-90°C for 15 h with constant stirring. The reaction mixture was cooled and poured over 0.5 N HCl (50 mL) and extracted with diethyl ether (30 mL X 3). The combined extract was successively washed by 0.5N HCl, aq. NaHCO3 solution, water and brine. The organic layer was dried over anhydrous sodium sulfate, filters and evaporated. The residue was purified by column chromatography on SiO_2 (100-200 mesh) using hexane as eluent to afford **5**(3.75 g, 65.10%). IR: 1691, 1580, 1488, 1436, 1258 Cm^{-1}. ^{1}H-NMR (DMSO d_6): 7.82-7.05(m, 9H), 5.73(q, *J* = 6.8 Hz, 1H), 1.58(t, *J* = 6.8 Hz, 3H). MS[M+Na]$^+$ Calculated for $C_{15}H_{13}ClO_2$m/z 260.06, found 283.85

α -Hydroxy-3-phenoxy propiophenone dimethyl acetal (6):

To a freshly prepared sodium methoxide, compound α- Chloro-3-phenoxy propiophenone, **5** (2.0 g, 7.67 mmol) in methanol (10 mL) was added drop wise under nitrogen atmosphere over 30 min. Reaction was monitored by TLC. Water was added and extracted with diethyl ether (20 mL X 3). Water washing was given to ether layer. Organic layer was dried over anhydrous sodium sulfate, filters and evaporated to afford **6** (1.6 g, 72.72%). ^{1}H-NMR: DMSO-d6: 7.45-7.35(m, 3H), 7.20-7.08(m, 2H), 7.04-6.95(m, 4H), 4.68(d, *J* = 4.4 Hz, 1H), 3.93(m, 1H), 3.18(s, 3H), 3.10(s, 3H), 0.78(d, *J* = 6.5 Hz, 3H).

Methyl α - (3-phenoxy phenyl propionate) (7):

To a solution of dimethylacetal, **6** (1.2 g, 3.9 mmol) and triethyl amine (1.05 mL, 7.5 mmol) was taken in dry DCM (12 mL) was cooled to -5^{0}C and sulfuryl chloride (0.835 g, 6.2 mmol) in dry DCM (12 mL) was added drop-wise by maintaining the reaction temperature -5°C under dry conditions under constant stirring. After complete addition of sulfuryl chloride, the reaction mixture was allowed to attain room temperature and stirred at same temperature for overnight, sat. aq. $NaHCO_3$ was added to it. The aqueous layer was extracted with DCM. The combined organic

layer was washed with water and brine, dried the organic layer, evaporated. The crude compound was purified by column chromatography over silica (100-200 mesh) using 10% Ethyl acetate in hexane to afford **7 (**0.65 g, 64.35%). IR: 1736, 1583, 1486, 1443, 1241 $cm^{-1.}$ ^{1}H-NMR (DMSO-d_6): 7.45-6.85(m, 9H), 3.78(q, *J* = 7.2 Hz, 1H), 3.58(s, 3H), 1.37(d, *J* = 7.2 Hz, 3H). MS[M]$^+$ Calculated for $C_{16}H_{16}O_3$**:**m/z 256.11, found 256.5.

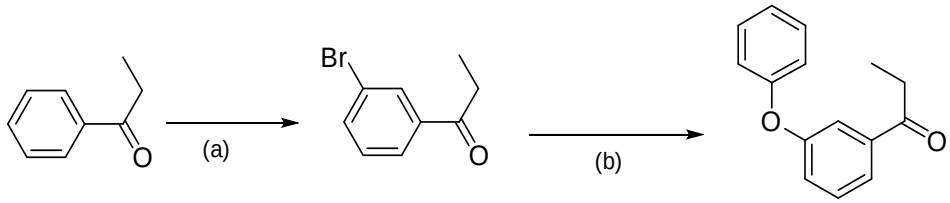
α -(3-phenoxy phenyl) propionic acid (1):

To a solution of ester, **7** (0.5 g, 0.0019 moles) in methanol (5 mL) was added 10 % aq. NaOH for alkaline hydrolysis. Contents were stirred at room temperature for 2h at room temperature. After completion of reaction acidified with 1 N HCl and extracted with ethyl acetate, dried and evaporated to afford, α-(3-phenoxy phenyl) propionic acid, **1 (**0.41 g, 86.86%). bp 169°C. **IR:** 1709, 1583, 1487, 1244 cm^{-1}**.** ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.35(s, 1H) 7.45-6.85(m, 9H), 3.67(q, *J* = 7.2 Hz, 1H), 1.30(d, *J* = 7.2 Hz, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 175.10, 156.75, 156.50, 143.48, 130.04, 129.97, 123.51, 122.49, 118.70, 117.66, 116.75, 44.54, 18.47. MS[M-H]$^-$: Calculated for $C_{15}H_{13}O_3$ m/z 241.09, found 240.90.

3. RESULT AND DISCUSSION

At first, we synthesized 3-bromopropiophenone (**3**) from propiophenone using bromine and aluminum chloride. The diaryl ether was (**4**) synthesized by Ullmann reaction using 3-bromopropiophenone and phenol. For the optimization of the Ullmann reaction, screening of various ligands (Lig 1- Lig 8) was done using different copper-catalyzed coupling reactions as shown in scheme 1**.**

I. Scheme 1:



2 **3** **4**

Reagents and conditions: (a) $AlCl_3$, Br_2, r.t., 1.5 h, 63%; (b) Phenol, **3**, 5-10 mol% [Cu], 10 mol% Lig 1-Lig 8, Base, Solvent, Ar, 80-110°C, 12-24h; 69%

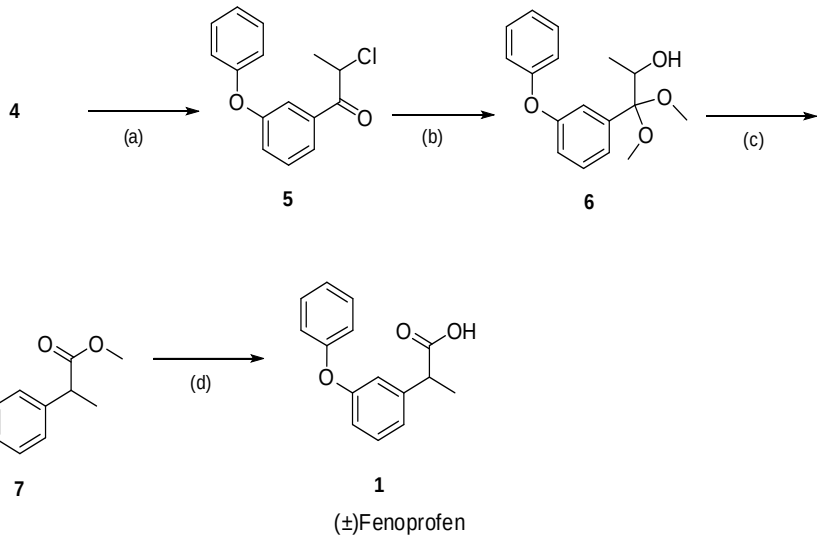
A variety of ligands such as 1,10-phenanthroline (Lig 1), 3,4,7,8-tetramethyl-1,10- phenanthroline (Lig 2), N, N-dimethylglycine.HCl (Lig 3), neocuproine (Lig 4), salicylaldoxime (Lig 5), L-proline (Lig 6), N-N-dimethylcyclohexane-1,2-diamine (Lig 7), and 1-pyridin-2-yl-propan-2-one (Lig 8) were screened in the reaction of phenol with 3-bromopropiophenone using the following catalyst system: 5-10 mol % CuI, 10 mol % ligand including the base in suitable solvent from 80°C-120°C from 12-24h (Table 1). Employing 1-(pyridin-2-yl) propan-2-one as a new supporting ligand, the copper-catalyzed coupling reactions of aryl bromide (3-bromopropiophenone) with phenol successfully proceeded in good yields. In this study, a new facile approach towards the synthesis of 1-(3-phenoxyphenyl) propan-1-one via Ullmann coupling, catalyzed by Cu(I)Br for the construction of diaryl ether fragment is described (**Entry 8 - Table 1**). Structures of ligands **Lig 1- Lig 8** were shown in **Figure 1**.

After optimizing the ligand (1-pyridin-2-ylpropan-2-one) via the Ullmann coupling condition, we were required to improve the yield of the reaction. For that purpose, screening of variety of catalysts and bases were carried out. We found that using copper bromide (CuBr), Lig 8, Cs_2CO_3 as a base in dimethyl sulfoxide solvent gives better yield (**Entry 3 - Table 2**).

After optimized Ullmann coupling condition, we used compound **4**, for the synthesis of fenoprofen. Earlier, fenoprofen could be readily prepared via cyanation reaction (NaCN, KCN, K_3FeCN_6). However, to avoid the usage of these hazardous cyanating reagents, we have proposed a better method for the synthesis of (±) fenoprofen. Our proposed method can prove to be more effective facilitating easy accessibility of raw materials as well as the use of special techniques for bulk synthesis. This is the safest route to synthesize fenoprofen. To summarize, we propose a simple and convenient method for the synthesis of Fenoprofen (**Figure 2**).

The synthesis of alpha halo ketone **(5)** from 3-phenoxy propiophenone **(4)** using copper chloride and lithium chloride in *N*,*N*-dimethyl formamide (DMF) was optimized.[18] Earlier the conversion of alpha halo ketone to aryl propionic acid was reported by photochemical transformation using propylene oxide and aqueous acetone.[19] This alpha haloketone was converted to alpha hydroxyl acetal intermediate (**6**) using sodium methoxide.[18, 20] The intermediate (**6**) converts into its chlorosulfonyl ester in situ and it rearranges to its methyl ester **(7)** in high yields.[21] The final fenoprofen (**1**) was isolated in excellent (87%) yields by basic hydrolysis of methyl ester with high purity. The sequence of reaction employed is depicted in below scheme **2**. The structure was confirmed by IR, mass, ^{1}H-NMR and ^{13}C-NMR.

Scheme 2:



Reagents and conditions: (a) $CuCl_2$, LiCl, DMF, 90°C, 15 h; 65% (b) NaOMe, MeOH; 72% (c) Et_3N, SO_2Cl_2, r.t., 16 h; 64% (d) aq. NaOH, MeOH, r.t., 2h, 87%.

4. CONCLUSION

Here, an efficient copper-catalyzed synthesis of diaryl ethers from phenol and 3-bromopropiophenone was developed after screening of different ligands (Lig 1- Lig 8). Out of legends screened, 1-(pyridin-2-yl) propan-2-one

was found to give a better yield. The CuBr-Lig 8 catalytic system showed an excellent yield at higher temperature. Our report provides an attractive addition to the existing strategies implemented for the synthesis of diaryl ethers via Ullmann coupling. We developed a concise and convenient new strategy for the synthesis of (±) fenoprofen in good yield from propiophenone with several prominent advantages of easy operation, convergence, and broad scope of applicability.

ACKNOWLEDGMENT

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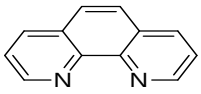
5. REFERENCES

Table 1 Standardization of Ullmann reaction using different ligands.

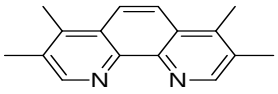
Entry	Ligand	Base	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	Lig 1	Cs_2CO_3	Toluene	80	12	26
2	Lig 2	Cs_2CO_3	Toluene	110	24	12
3	Lig 3	Cs_2CO_3	1,4-dioxne	90	24	38
4	Lig 4	^tBuONa	Toluene	110	16	--
5	Lig 5	Cs_2CO_3	DMF	110	24	13
6	Lig 6	Cs_2CO_3	DMSO	90	22	18
7	Lig 7	K_3PO_4	DMSO	80	24	16
8	Lig 8	Cs_2CO_3	DMSO	120	24	45

Table 2 Improvement of the yield of Ullmann reaction using different catalyst and bases.

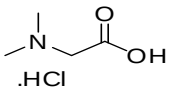
Entry	Catalyst	Base	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	CuCl	Cs_2CO_3	NMP	130	12	12
2	CuBr	K_3PO_4	Toluene	100	24	28
3	CuBr	Cs_2CO_3	DMSO	120	16	69
4	CuI	Cs_2CO_3	Dioxane	90	24	41
5	CuI	K_2CO_3	DMA	120	7	18
6	CuI	K_3PO_4	Toluene	110	18	36
7	CuI	Cs_2CO_3	Toluene	110	24	16
8	CuI	Cs_2CO_3	Dioxane	100	24	12



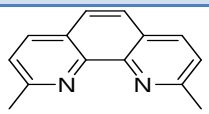
Lig 1



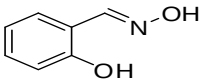
Lig 2



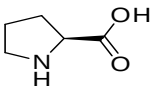
Lig 3



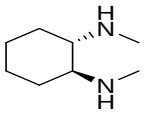
Lig 4



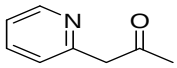
Lig 5



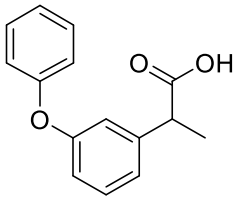
Lig 6



Lig 7



Lig 8



(±) Fenoprofen (**1**)

Figure 1 Structures of ligands **Lig 1- Lig 8**.

Figure 2 Chemical structure of (±) Fenoprofen.

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