A FACILE PREPARATION OF PHTHALIMIDES AND A NEW APPROACH TO THE SYNTHESIS OF INDOPROFEN VIA CARBONYLATION +

Chalasani S.N.Prasad, Ravi Varala and Srinivas R. Adapa*
Inorganic Division, Indian Institute of Chemical Technology,
Hyderabad-500 007, India

Abstract: This report describes an improved synthesis of a heterocyclic propionic acid, 2-4(1-oxo-2-isoindolinyl) phenyl propionic acid, Indoprofen (I) via carbonylation, a potent anti-inflammatory agent[1] and an analgesic. The synthesis highlights the preparation of Indoprofen starting from readily available o-toluic acid and p-amino acetophenone by a sequence of reactions that included oxidative addition of carbonylation.

Introduction

Phthalimides are versatile intermediates for the synthesis of biologically active heterocyclic as well as pharmaceutical products. Phthalimide derivatives with phenyl acetic and phenyl propionic acid were found to possess anti-inflammatory and analgesic properties[1]. Being interested in exploiting the carbonylation method[2-3], we have taken up total synthesis of Indoprofen (1) [4-5] starting from o-toluic acid and culminating with carbonylation which is a key step in introducing carboxylic group in the molecule.

During the course of the synthesis of Indoprofen, we tried to prepare different phthalimide analogues, which were found to possess biological activity. Firstly, we wish to report a simple and efficient method for the one pot synthesis of pthalimides[6] in a novel way using stoichiometric quantities of phthalic anhydride and substituted aniline with out leaving unwanted by products (Table.1) Subsequent reduction and condensation with appropriate reagent, results in the synthesis of biologically active phthalimide analogues. The yields are fairly good, the reaction conditions are mild and work up is easier. The initial step i.e. the condensation between phthalic anhydride and substituted aniline gave ultra pure compound in good yield. Substituted anilines (0.11 mol) are added drop-wise to the phthalic anhydride (0.10 mol) suspension in methanol solution, and heated on water bath for 30 min. at 50-60° C. Left the reaction mixture at room temperature for overnight and resultant products are formed as crystals. This we are reporting for the first time as against the conventional method where the condensation takes place at fuming temperatures of phthalic anhydride and substituted aniline[6]. In the previous conventional methods reported, acidic catalysts having dehydrating nature[3] and high boiling solvents are used for the condensation to take place.

Table 1. Reaction of Phthalic anhydride with different substituted amines:

S.No	Amine	Product	Yield (%)
1.	Aniline	Phthalimide	80
2.	Methoxy aniline	Methoxy phthalimide	65
3.	Chloro aniline	Chloro phthalimide	65
4.	4 – Hydroxy aniline	4 – hydroxy phthalimide	60
5.	2 – Hydroxy aniline	2 – hydroxy phthalimide	65
6.	Anisidine	Methyl phthalimide	57

Results and Discussions

Indoprofen 2-[4-(1-oxo-2-isoindolinyl phenyl)] propionic acid, is a useful anti-inflammatory agent, which belongs to a class of 2-aryl propionic acid with heterocyclic moiety in the para-position. Very few synthetic strategies of Indoprofen are available in literature, most of them are covered by patents[4], and its chemistry is not known except a report by Kametani et.al[5]. To date, the most productive synthesis of indoprofen involves three synthetic methods.

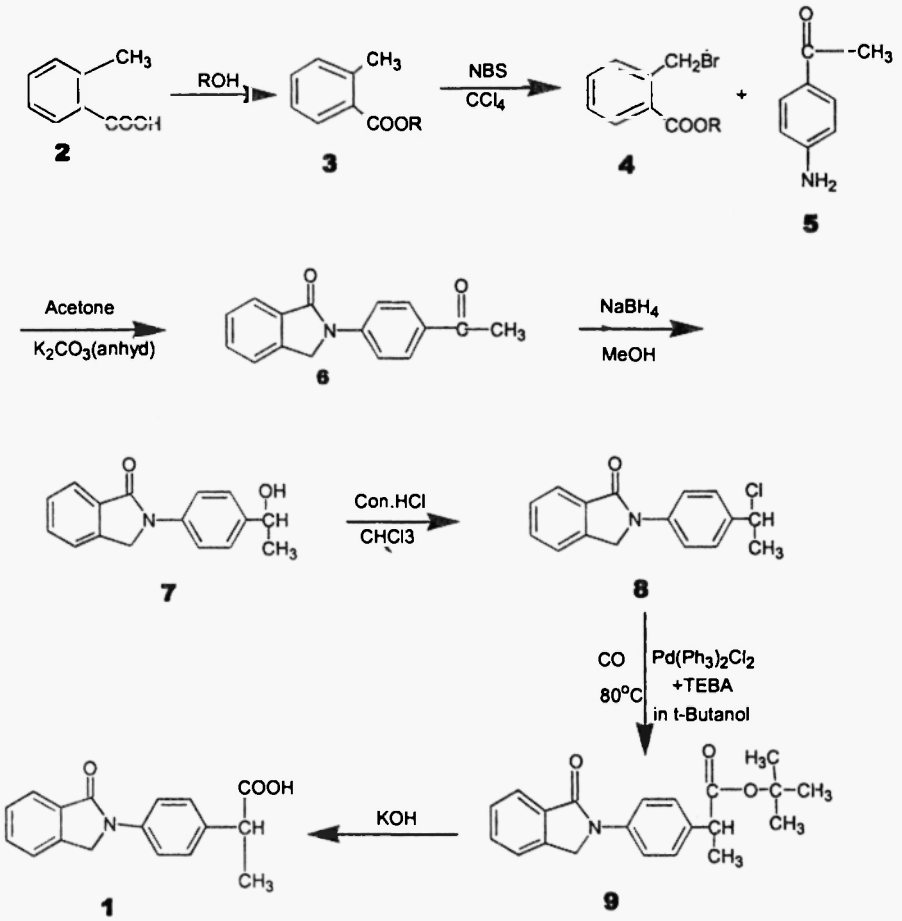
The chemistry in the above reported methods involves cumbersome procedures to some extent and formation of isomeric mixtures and their separation. This prompted us to adopt simple and less cumbersome classical organic procedures like reduction of ketone, halogenation etc., and finally carbonylation of halogenated product and followed the scheme**1** to synthesise indoprofen.

In recent years, increasing importance has been placed on the utilization of carbon monoxide for organic synthesis. . In our earlier studies we have described the use of CO and Pd $(PPh_3)_2Cl_2$ homogenised with a phase transfer catalyst (TEBA) and successfully achieved the resultant products[2,3]. In continuation of our efforts, we would like to describe considerably more convenient synthesis of compound (I) based on palladium catalyzed carbonylation, homogenising with a quaternary ammonium salt. The advantages of palladium catalyzed carbonylation[8] reactions, are that they even occur at low concentrations (0.05%) and temperature 50^0C. We investigated carbonylation reactions using palladium metal complexes such as Pd $(PPh_3)_2$ Cl_2, which is a non-volatile, non-toxic, air stable and can be easily synthesised from its precursor-$PdCl_2$. This catalyst operates under mild conditions (<100%, 1atm) with catalytical amount (0.5-1.5mole%) and convenient to handle in any laboratory with minimum facilities. The carbonylation chemistry developed by Reppe et.al[9a-b], catalyzed by transition metal complexes with CO, the latter not only stabilizes the lower oxidation state of these metals and also adds a molecule to the organic substrate, represents routes for the synthesis of different functional groups from a wide variety of feed stocks.

The readily available 4-amino acetophenone (**5**) was condensed at N-position with alkyl ortho bromo methyl benzoate (**4**) at ambient conditions i.e, in the presence of acetone and anhydrous potassium carbonate, with this achievement.i.e, the synthesis of 4(1-oxo-2-isoindolinyl) acetophenone (**6**), the scheme (**1**) was successfully implemented.

The acetophenone (**6**) was subjected to selective reduction of carbonyl group in the side chain with sodium borohydride and methanol without affecting the carbonyl group in the heterocyclic ring. The secondary alcohol (**7**) was chlorinated with conc. HCl in the presence of chloroform at ambient temperature as against the conventional method of bromination with hydrobromic acid (HBr) at elevated temperatures. Finally the secondary chloro compound (**8**) was t-butoxy carbonylated, as it is a good protecting group and has advantages over the corresponding methyl or ethyl esters, owing to its stability under basic conditions and the earlier methods for introducing the group, however, have drawbacks such as the need to use reagents (such as

phosgene, isobutene, and BuLi) coupled with multistep procedures, etc[10-11]. The t-butoxy carbonylation is done under CO atmosphere, catalysed by bis(triphenyl phosphine) palladium(II) chloride) and homogenised by triethyl benzyl ammonium chloride(TEBA)(to increase yield) in t-butanol at 80°C to yield t-butyl-4(1-oxo-2-isoindolinyl)phenyl]propionate. This propionate upon hydrolysis with aqueous alkali gave the required indoprofen (1).



Scheme 1

Experimental:

Melting points were uncorrected and measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. The Infra red spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The ^{1}H NMR spectra were recorded on Gemini Varian (200MHz) NMR spectrometer, using Deuterochloroform solutions using TMS (tetra methyl silane) as internal standard. Mass spectroscopic analysis was performed at an Ionization potential of 70 eV [scanned on VG 70-70H(micromass)]

spectrometer in EI mode. Elemental analyses were carried out with a Cario Erba Model 1106 Elemental Analyzer.

Preparation of Ethyl-O-methyl benzoate 3:

In a single neck 100 ml round bottom flask fitted with refluxing condenser taken o-toluic acid (**2**)(7 grms.,0.05 mole) and absolute alcohol(50 ml),the mixture was refluxed using isomantle for 6hrs.The excess alcohol was removed by rotary evaporator, diluted, extracted with ethyl acetate.The organic extract was washed with saturated solution of Sodium bicarbonate in order to remove unreacted acid finally with distilled water and dried over anhydrous sodium sulfate,the solvent was removed by rotavapor, thus obtained Ethyl-o-methyl benzoate (**3**)4.5 gms.,(64%)in yield. Its NMR was taken and compared with standard spectrum and proceeded to the next step.

Ethyl-O-Bromo methyl benzoate 4:

In a single neck 100 ml round bottom flask with refluxing condenser, taken ethyl-o-methyl benzoate (**3**) (3.5 gms, 0.02 mole), N-bromosuccinimide (3 grms, 0.05 mole) and carbon tetra chloride (60 ml.), and refluxed for 6 hrs. After cooling the mixture, it was poured into a 250ml. beaker containing ice pieces and water. Extracted the organic product with additional carbon tetra chloride (250 ml) washed with cold distilled water, dried over anhydrous magnesium chloride. The solvent CCl_4 was removed under vacuum, the crude product was passed through a column containing neutral alumina ,a lachrymatic compound was obtained with a yield of 3.25 gms.(90%).IR(KBr) 1680 cm^{-1}(C=O)cm^{-1}.^{1}HNMR ($CDCl_3$): 0.9 (3H, t, -CH_2-CH_3); 1.3 (2H, q, -CH2-CH_3); 2.6 (3H, S, -CH_2-Br); 7.2 - 7.6 (4H, m, Ar-H); .Mass (m/e) 244 (M^+); Found: C 49.18; H 4.51; O 13.11. Calcd for $C_{10}H_{11}O_2Br$: C 49.18; H 4.50; O 13.11%.

4-(1-oxo-2-isoindolinyl) acetophenone 6:

In a two neck 100 ml. Round flask fitted with an air condenser, taken o-bromo methyl benzoate (5.0 gm., 0.2 mole) and 4-amino acetophenone (**5**) (3.0 gm, 0.2 mole). Added acetone(50 ml) and stirred well at room temperature on magnetic stirrer and added slowly anhydrous potassium carbonate(4 gms.) in 20 minutes, the stirring was continued over night. The undissolved salt was filtered off, the solvent was removed in a rotavapor. Thus obtained a solid substance, recrystallised in benzene and chloroform solvent system. Pale yellow needle 4-(1-oxo-2-isoindolinyl) acetophenone (**6**) was obtained 4.5 grms.(90%) yield with m.p 245^{0}C.IR(KBr)1700(C=O) and 1600 (-C=O) cm^{-1}.H^{1}NMR($CDCl_3$): 2.6 (3H, S, -CH_3); 1.3 (2H, q, -CH_2-N); 4.93 (2H, S, CH_2); 7.5-8.2 (4H, m, Ar-H); Mass (m/e) 251(M^+). Found: C 76.25; H 5.24; N 5.61. Calcd for $C_{16}H_{13}NO_2$: C 76.47, H 5.22, N 5.57%.

2-[4-(1-oxo-2-isoindolinyl) Phenyl] Ethanol 7:

In a two necked 100 ml. Round bottom flask fitted with an air-condenser, placed 4-(1-oxo-2-isoindolinyl) acetophenone (6)(4.3 gms.,0.03 mole),anhydrous methanol (40 ml.),stirred well to make it homogenous

mixture, added slowly in installments sodium borohydride (1.2gms.,0.3 mole)while stirring continuously for an additional one hour. The solvent methanol was removed on a rotavapor, to the solid added water (40ml) at 0^0C,then 10% HCl (25ml) was added while stirring well. The organic substance extracted with chloroform washed it thoroughly with distilled water till it was free from acid. Dried over anhydrous Magnesium sulfate, removed the solvent over rotavapor. Thus obtained white fluffy solid was subjected to crystallization in benzene-chloroform system. A white fibrous needle like solid was obtained with yield 3.8 gms (88%) with melting point (164^0c). IR (KBr) 3400 (-OH) and 1640 (N-C=O) cm^{-1}. H^1NMR ($CDCl_3$): 1.5 (3H, d, $-CH_3$); 1.85 (1H, sec-OH); 4.85 (2H, S, CH_2-N); 4.85 (1H, q, -C-H); 7.5 - 8.2 (4H, m, Ar-H);. Mass (m/e): 253(M^+). Found: C 75.89; H 5.93; N 5.63; O 6.3. Calcd for $C_{16}H_{15}NO_2$: C 75.89; H 5.94; N 5.62; O 6.32%.

2-Chloro [4-(1-oxo-2-isoindolinyl) phenyl] Ethane 8:

In a two necked 100ml round bottom flask fitted with air condenser. Placed the compound (7) (3.00gm.,0.1mole) and added chloroform(20ml), stirred well before adding conc.HCl(10ml),noticed a change in the mixture opaque to clear homogeneity this mixture was stirred further for overnight.The water layer and organic layer were separated out by a separating funnel. The organic layer was washed free of acid, dried over anhydrous magnesium sulfate, the solvent chloroform was removed by rotavapor, crystallised in benzene-chloroform (1:1) solvent system. A white flaky substance of 2.00 gms.(66%) obtained with m.p137°C . IR (KBr) 1640cm^{-1}; H^1NMR ($CDCl_3$) : δ 1.85 (3H, d,-CH3); 4.8 (2H, S, CH_2-N); 5.1 (1H, q, C-H); 7.5 - 7.8 (9H, m, Ar-H); Mass (m/e) 271 (M^+). Found: C 70.72; H 5.16; N 5.16; O 5.9. Calcd for $C_{16}H_{14}NOCl$: C 70.72; H 5.15; N 5.15; O 5.87%.

2-t-butyl [4-(1-oxo-2-isoindolinyl) phenyl] Propionate 9:

In a 250ml. three necked flask fitted with a condenser, a gas bubbler and a dropping funnel, taken triphenyl phosphine (260mg.,0.001 mole), sodium acetate (150mg.) bis(triphenyl phosphine) palladium dichloride-Pd(PPh_3)$_2Cl_2$ (70mg.) as catalyst, triethyl benzyl ammonium chloride(TEBA) (150mg.) as co-catalyst and finally t-butanol(100ml.) Carbon monoxide gas was bubbled through the flask for 15minutes, then the flask was heated on a oil bath at 90^0c with constant stirring, after making the mixture in the flask homogenous, the compound (1.55 gm., 0.05 mole) in t-butanol (20 ml.) was added slowly under carbon monoxide atmosphere. The entire contents were stirred for 20 hours while passing carbon monoxide gas. Cooled the mixture filtered off to remove the catalyst and slowly added into beaker containing 10% HCl (20 ml). Extracted the organic matter by ethylacetate solvent (50-ml x3), washed thoroughly free from acid and dried over anhydrous magnesium sulfate. The solvent was removed on rotavapor, the crude dissolved in benzene was passed through a column containing silica gel (200 mesh) using benzene as elutant and obtained the product *t*-butyl ester with m.p 60^0c and yield of 800 mg(51.6%). IR(neat): 1700 (C=O); 1640(N-C=O) cm^{-1}; H^1NMR($CDCl_3$): 1.25 (9H, s,3CH_3); 1.5 (3H, d,-CH_3); 3.65 (1H, q, -C-H); 4.8 (2H, s, -CH_2-N-), 7.5 - 7.8 (9H, m, Ar- H); Mass: (m/e) 337(M^+). Found: C 74.77; H 6.82; N 4.15. Calcd for $C_{21}H_{23}NO_3$: C 74.77; H 6.814; N 4.16%.

2[4-(1-oxo-2-isoindonoyl) phenyl] Propionic acid 1:

In a 50ml single flask fitted with a refluxing condenser, taken *t*-butyl-2[1-oxo-2-isoindonyl)Phenyl] Propionate(9) (200mg) added 50% KOH solution(5 ml.) and refluxed for one hour on an oil bath at 100^0c.The sodium salt of the compound poured into a beaker containing 50 ml. of water. Extracted with chloroform, washed the organic extract with 10% HCl (5 ml). Then the chloroform extract was dried over anhydrous magnesium sulfate. Concentrated the extract on a rotavapor. The resulting precipitate was collected and recrystallised from ethanol to obtain the compound (**I**)(100 mg.,40%) as colorless scales with m.p 214^0c(lit.m.p.213-214^{0}C). Characterized the compound by spectral analysis. IR (KBr) 1640 (N-C=O) 1680 (-C=O); 3500 (-OH) cm^{-1} H^1 NMR (DMSO-d_6): 1.37(3H,J=7 Hz.,-CH-CH_3); 3.68 (1H, q, -CH-CH_3); 4.9 (2H, S, CH_2-N); 7.2-8.0 (8H, m, Ar-H); Mass(m/e) 281 (M+). Found: C 72.13; H 5.39; N 4.94. Calcd for $C_{17}H_{15}NO_3$: C 72.58;H 5.37; N 4.98%.

Acknowledgements:

The authors are thankful to the Director, and Dr B.M.Choudary, the Head of the Division for their encouragement.

References:

1. R.A. Sherrer and M.W. Whitehouse, *" Anti inflammatory Agents, Chemistry and Pharmacology''*, **Vol.1,** Academic Press, New York, San Francisco and London, 1974.
2. R. Srinivas . Adapa and Chalasani.S.N. Prasad, *J. Chem. Soc. Perkin.Trans-1*,,pp. 1707 (1989).
3. Chalasani. S.N. Prasad and Srinivas R Adapa, *Indian. J.Chem.* **30B**,pp. 1067-1068 (1991).
4. J.H. Schauble and E. Hertz, *J.Org.Chem.* **35**, pp.2529 (1970).
5. T.Kametani , K. Kigasawa , M. Hiiragi , H. Ishimaru, S. Haga, and K. Shirayama.,*J.Heterocycl.Chem.***15**,369,(1978).
6. " *The Chemistry of Amides''*, A.L.J.Beckwith,pp.73,(1973).
7. *Comprehensive Org. Synthesis* **Vol.16**,pp.409
8. L Cassar.., G.P. Chiusoli and F. Guerrieri, *Synthesis* pp.509 (1973).
9. (a) Reppe.W., German Patent No.,,855,110 (1939)
   (b) Reppe, " Chemistry in Britain'', 38,(1993)
10. (a) B.Abramovitch, J.C.Shivers,B.E.Hudson, *J.Am.Chem.Soc.***65**, 986 (1943).
    (b) Y.Hayase, W.Schilling, W.K.Chan,and G.S.Bates,ibid.**99**,6756 (1977).
11. (a) T.Mukaiyama, M.Usui, E.Shimada and K.Saigo, *Chem. Lett.* 1045 (1975); (b) W.Szeja,*Synthesis* 402,(1980); (c) B.Ravindranath and P.Srinivas, *Tetrahedron* **40**, 1623 (1984)