International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://theaspd.com/index.php

Preparation Of Etoricoxib By Continuous Flow

Jayant Kulkarni[1], Rakshit Ameta[2*], Seema Kothari[3*]

[1]Pacific Academy Of Higher Education And Research University (PAHER) Department of Chemistry, Pratapnagar Extenssion, Airport road, Daberi, Udaipur - 313003 (Rajasthan) INDIA,E-mail jayant25@gmail.com,
[2*]Pacific Academy Of Higher Education And Research University (PAHER) Department of Chemistry, Pratapnagar Extenssion, Airport road, Daberi, Udaipur - 313003 (Rajasthan) INDIA, Email: rakshitameta9@gmail.com[2]
[3*]Pacific Academy Of Higher Education And Research University (PAHER) Department of Chemistry, Pratapnagar Extenssion, Airport road, Daberi, Udaipur - 313003 (Rajasthan) INDIA, E-mail : seemakothari250@gmail.com
*Corresponding Author: Rakshit Ameta[2], Seema Kothari[3],
*E-mail : rakshitameta9@gmail.com[2], seemakothari250@gmail.com[3],

ABSTRACT:
The present invention relates a single solvent, highly efficient flow synthesis of a pharmaceutically active ingredient Etoricoxib (5-chloro-3-(4-methanesulfonylphenyl)-6'-methyl-[2,3'] bipyridine.
In this synthesis approach, the reaction was carried out in the flow reactor with controlled reaction conditions which offered the desired product with 65-70% yield and remarkable quality.

KEYWORDS: *Flow chemistry, Etoricoxib, Flow synthesis, API, Continuous synthesis.*

INTRODUCTION :

Over the last hundred years, chemists have achieved outstanding progress in examining and explore chemistry. Organic synthesis achieved notable milestones in the synthesis of complicated natural products, active pharmaceutical ingredients (APIs) and agrochemicals. These multistep syntheses were conducted by using a generalised technique which includes a number of successive reaction steps which at last lead to the desired targeted compound. This linear approach was very flexible [1] which gives a wide range of potential synthetic group conversion and the continuous development of newer and more specific fields by producing shorter, more efficient and more sustainable routes of synthesis to desired compounds.

On the other hand, over the period of a century, equipment, tools and techniques to conduct reactions in the lab have not changed much in more. This lack of advancement in the technology restricts the capabilities of chemists, because many chemical conversions are either poor or impractical under the possible conditions in the lab scale as well as on the large scale. The synthetic society systematically addressed these challenges and concluded that we need to embrace and cultivate alternative technology which will understand the capabilities of organic synthesis. They insist conducting the reactions with machines instead of using traditional equipment, and here Flow chemistry comes into the limelight.

Nowadays the transition from traditional batch process in flasks to highly advanced flow chemistry process in flow reactor is a growing trend to enhance synthetic chemistry methods. Flow chemistry [2] implies a philosophical inversion of conventional batch synthesis processes by considering its advantages and disadvantages for chemical functional group conversion. A traditional batch reaction represents the chemical reaction in the presence of reagents or catalyst and solvents in the specific conditions in the flask. These entire contents get agitated, cooled or heated, exposed to UV light, sonicated, or pressurized to drive the reaction pathway in the forward direction. After completion of the reaction, these conditions were removed and after successive workups the desired compound was isolated. In contrast, a flow process maintains a flow reactor at consistent and précised conditions of temperature and pressure through which reaction mass moves. This small difference between the traditional batch process and flow process makes flow reactor conditioning and

chemical reacting conditions more defined so that it allows better reaction parameter control during the entire course of reactions. For an example like gas-liquid reactions, speedy reactions, hazardous reactions (toxic/explosive), those involving unstable, moisture sensitive or poisonous reaction intermediates and photochemical reactions, flow chemistry is a better option.

Apart from individual chemical transformations, flow chemistry offers multiple advantages in an integrated synthesis by linking numerous reaction modules for molecules synthesis.[3-5] In the conventional multistep syntheses, to ensure desired yield and quality, intermediates are isolated and properly analyzed with the help of available analytical methods before approaching to the next step. This entire process makes the overall manufacturing process lengthy and generates chemical waste. On the other hand flow chemistry has one of the beautifications, that multistep reactions can be arranged in sequential manner without isolating intermediates, which results in a continuous running process. In-line or on-line purification methodologies can be implemented with a telescoping method where reaction generated side products could further react or degrade the desired generated compound. The quality of generated material could be assessed at any point in the streamlined sequence using in-line or on-line process analytical techniques (PATs).

Flow chemistry provides opportunities to chemists to explore novel effective methodologies, as well as to extend the limits of conventional chemical transformations [6]. The capabilities to conduct reactions in a safe mode are difficult at under high pressure, with elevated temperatures and lesser concentrations, but flow chemistry gives us an opportunity to conduct these types of reactions in flow mode. That's why nowadays most industries are going to implement continuous flow chemistry across nearly all areas of chemical synthesis [7]. The adaptation of numerous API syntheses from batch to continuous flow has also been thoroughly reviewed and will not be discussed in this perspective [8-11]. Beyond being a facilitating technology for novel chemical entities, one of the most appealing features is that it allows for automation, the integration of reactions, inline purification, and even subsequent inline analysis of biological assays. Still, there are some challenges and flow chemists are working on the same to get rid of it.

Etoricoxib, marketed under the brand name Arcoxia, is a selective inhibitor of COX-2 that was developed and brought to market by Merck. As of now it has received approval in 63 countries globally, with the exception of the United States, where the food and drug administration issued a non-approvable letter to Merck, requesting further data.[12] The drug was patented in 1996 and approved for medical use in 2002.[13]

NSAIDs (Non-steroidal anti-inflammatory drugs) works by blocking cyclo-oxygenase (COX) to treat inflammatory diseases. The homeostasis of gastrointestinal (GI) tract [14] is one of the primary COX isozymes, with additional roles. By following the identification of an inducible COX isozyme, multiple groups has been looking for selective COX-2 inhibitors[15]. According to the reasoning behind these studies, a particular COX-2 inhibitor will significantly decrease the side effect profile, which includes stomach ulcers, that is frequently linked to long-term use of conventional NSAIDs.

Recently, Merck has conducted an evaluation of a new series of pyridines derivatives to assess their capacity to reduce the COX. The substituent introduction at C5 position of the central pyridine resulted in optimal inhibition of COX-2. Among these pyridine derivatives, Etoricoxib emerged as a highly potent and selective COX-2 inhibitor with an improved gastrointestinal safety profile. The effective synthesis of trisubstituted pyridines through the annulations of ketone with vinamidinium salts has been previously reported in multiple publications [16-17], but here we propose very simple, safe and less time consuming Etoricoxib synthesis with the help of flow chemistry.

MATERIALS AND METHODS:

In this paper Etoricoxib API (Scheme -1) was synthesized with the help of flow chemistry (Figure -1). Over here the main interesting part was the synthesis of a pyridine ring by treating ketosulfone and phosphate salt in the

presence of KTB, liquor ammonia and ammonium acetate. This reaction specially shows pyridine ring construction with the help of flow chemistry.

The advantages of flow chemistry are fast and efficient method, easy to handle and easy to automate with delivering good yields. These features motivated us to improve flow methodology to synthesize Etoricoxib.

At first, the effect of other polar solvents like DMSO, DMAc, THF and non polar solvents like MTBE, cyclohexane etc had been studied on the reaction pathway and its direct reflection on the percentage yield. When experiments were conducted with MTBE and Cyclohexane, then solubility issue of starting material Ketosulfone and KTB were observed. To make both of soluble, very large amount of solvent were required and due to which rate of reaction was very slow. Hence, polar solvents were used to solve this problem. Rate of reaction was appreciable and impurity percentage was less in DMF as compared to other solvents. Hence DMF was selected as a reaction solvent.

Initially, reaction between Ketosulfone and phosphate salt was conducted with very dilute condition (0.05M each solution) to avoid chocking. After completion of the reaction, we reduced solvent contribution and finally landed up to 0.32M Ketosulfone and 0.6M phosphate salt.

Incorporation of KTB was also difficult due to its solid nature and less solubility affinity in the organic solvents. We had observed the best results were obtained when 5% KTB (WRT ketosulfone) was used during reaction.

It was observed that there was inter relation between reaction temperature and residence time. At lower temperature (40°C), reaction takes more time for completion (4 Minutes) and at higher temperature (120°C) reaction complies in 10 sec, but reaction mass turns to radish wine colour and next cyclization reaction didn't complies. Hence we concluded this reaction at 90°C with 40 sec residence time.

Next cyclization reaction was more challenging. Combination of liquor ammonia and ammonium acetate helps to stabilize the intermediate. Hence more equivalence of this buffer solution required to complies the reaction, which finally optimized with 1.93 Eq.

Initially we had dissolved ammonium acetate in water and mixed with liq.ammonia for reaction. But as water percentage increases, residence time also increases. Hence we diluted ammonium acetate in liq.ammonia itself and fixed it as 1.2M solution.

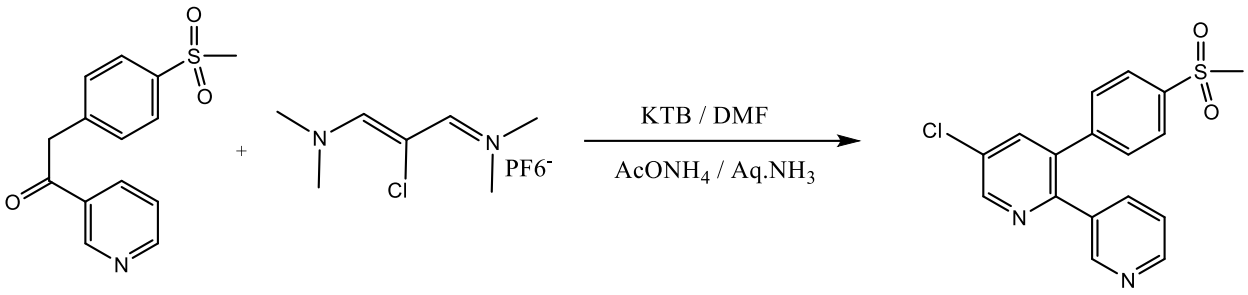
Now, for second reaction, temperature study was really an interesting part. There was direct prapotrtnality between reaction temperature and residence time. According to study, this reaction complies in 40sec at 130°C, but for the sake of flow set-up simplicity and easy to operate the same, we brought both of the reactions in a single temperature zone.

RESULTS AND DISCUSSION:

Chemicals of laboratory quality were procured from S.D. Fine Chemicals (Mumbai, India) for the synthesis. The melting point was determined using open capillary tubes in a Hicon, India apparatus, and the results were left uncorrected. Every reaction progress was regularly observed via thin-layer chromatography (TLC) with Merck silica gel 60 F254 coated aluminum plates and solvent system Methanol : Dichloromethane was used as mobile phases. By using a TMS internal reference standard (chemical shifts in δ), ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) were recorded on DMSO-d^{6} solution in a 5 mm tube on a Varian 400 MHz Unity Inova.

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://theaspd.com/index.php

General procedure:



Ketosulfone (1) Phosphate salt (2) Etoricoxib API

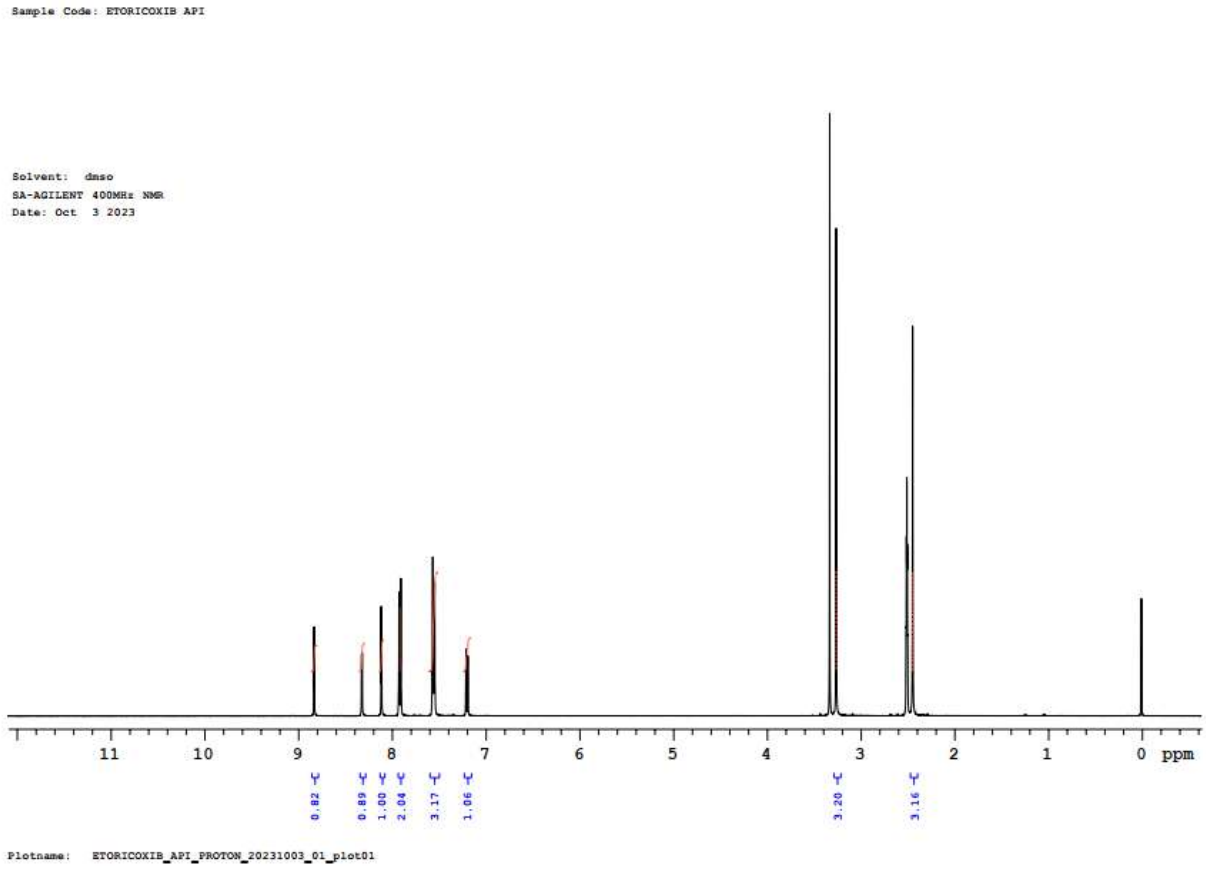
[SCHEME – 1]

SCHEME – 1: SYNTHESIS OF ETORICOXIB

Solution preparation

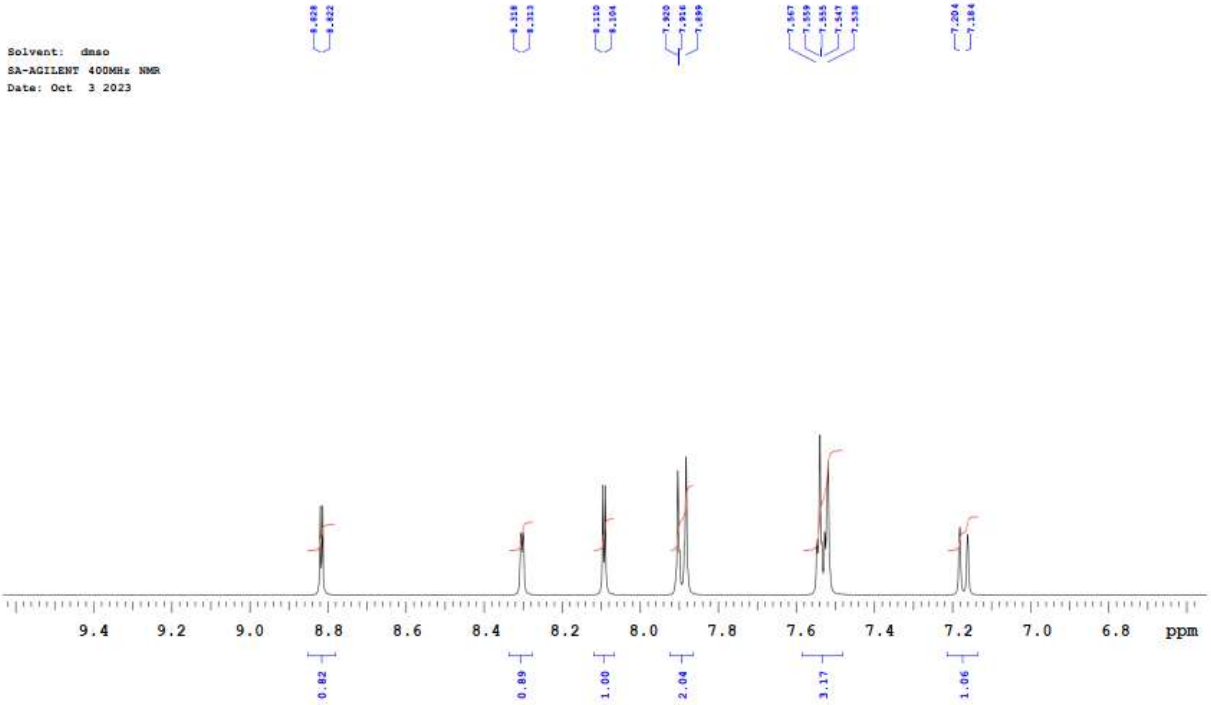
- Starting material ketosulfone (1) was dissolved and diluted in DMF to get 0.32M clear solution
- Phosphate salt (2) + KTB was dissolved and diluted in DMF to get 1.3M clear solution
- Liq. ammonia + ammonium acetate was diluted in water get 1.2M clear solution.

Data 1

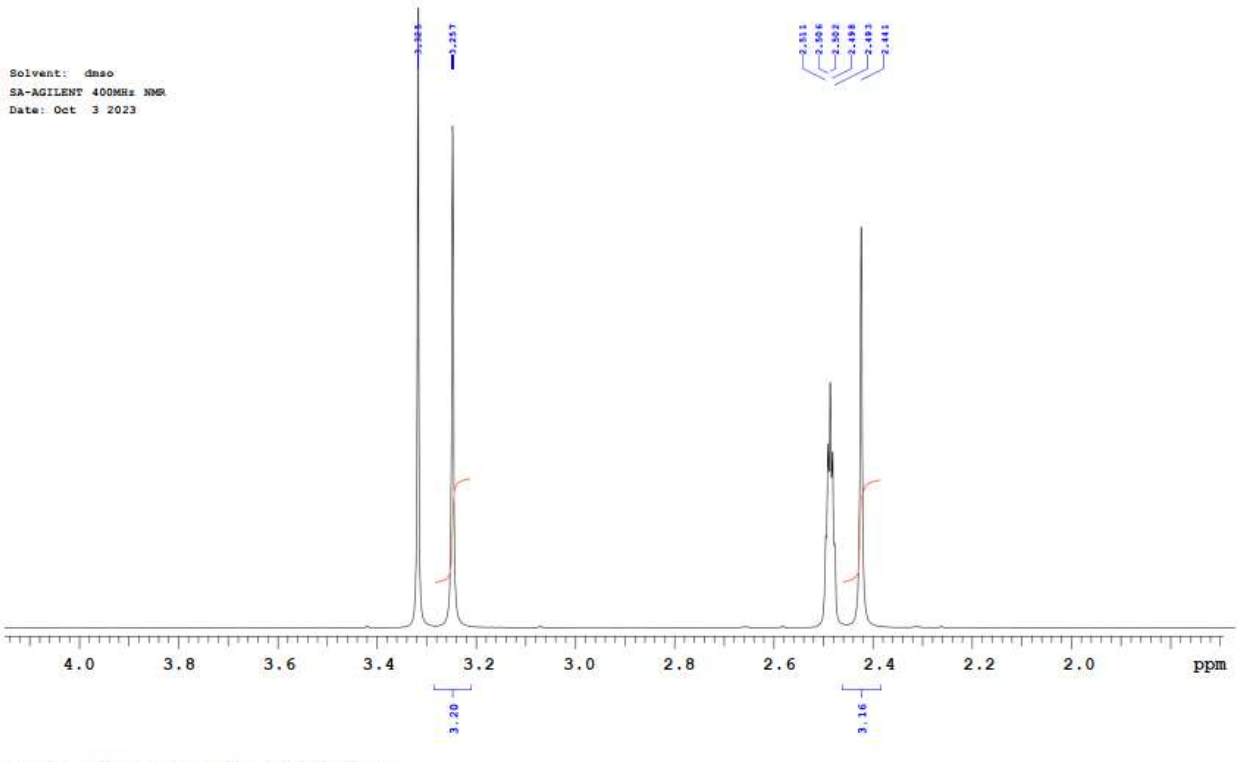


International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://theaspd.com/index.php

Sample Code: ETORICOXIB API



Plotname: ETORICOXIB_API_PROTON_20231003_01_plot02



Plotname: RETORICOXIB_API_PROTON_20231003_01_plot03

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://theaspd.com/index.php

exp1H CARBON

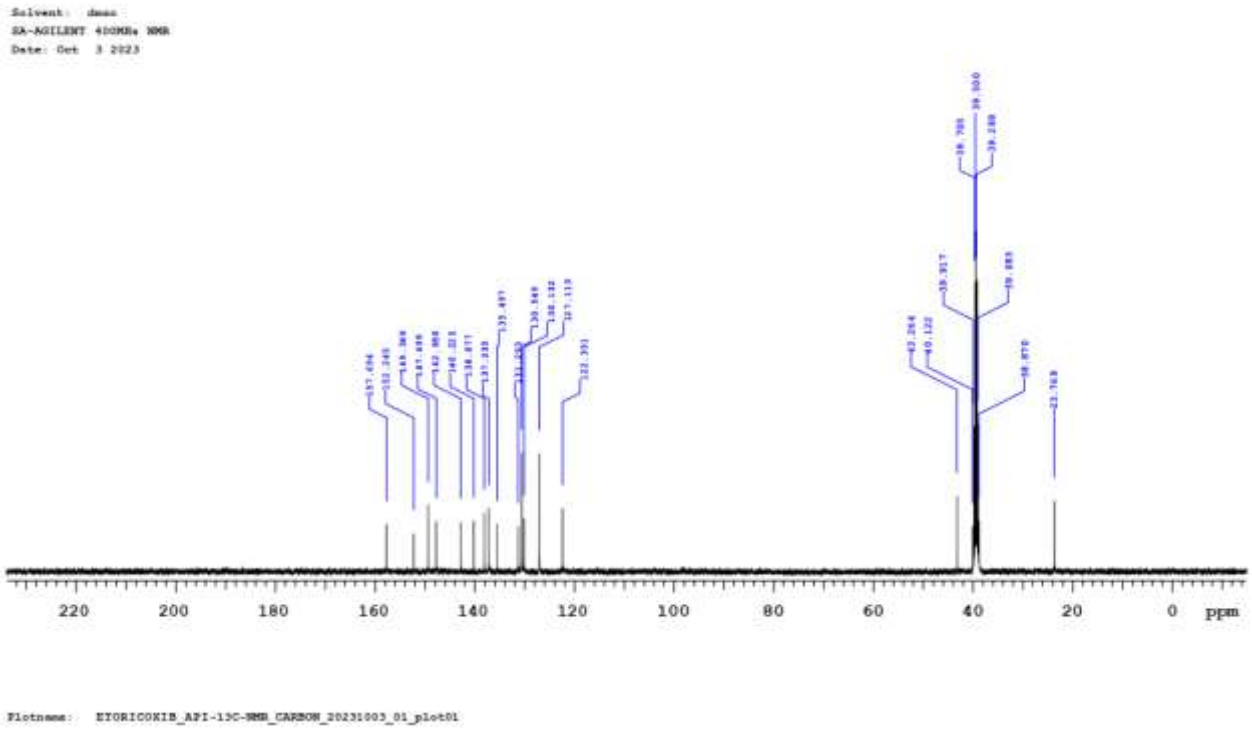
SAMPLE		PREACQUISITION			
date	Oct 3 2023	satmode		n	
solvent	dmso	wet		n	
file	/home/agilent-	SPECIAL			
/data/2	023/Oct/RBP-	temp	no	used	
-I-A864	-04-13C-NMR-	gain		38	
20231003 01/RBP-I-		spin		20	
-A864-04-13C-NMR C-		hst	8.000		
ARBON 20231003 01.-		pw90	14.100		
	fid	alfa	10.000		

ACQUISITION		FLAGS	
sw	25000.0	il	n
at	1.311	in	n
np	65536	dp	Y
fb	17000	hs	nn
bs	4	PROCESSING	
ss	8	lb	2.00
d1	3.000	fn	not used
at	1800	DISPLAY	
ct	128	sp	-1486.1
TRANSMITTER		wp	24999.2
tn	C13	rfl	5450.1
sfrq	100.547	rfp	3971.2
tof	1530.8	rp	148.1
tpwr	56	lp	8
pw	7.050	PLOT	
DECOUPLER		wc	268
dn	H1	sc	8
dof	0	vs	73
dm	YYY	th	3
decsave	w	nn cdc	ph
dpwr	41		
dmf	9524		

Plotname: ETORICOXIB_API-13C-NMR_CARBON_20231003_01_plot04

INDEX	FREQUENCY	PPM	HEIGHT
1	15854.0	157.694	10.2
2	15306.2	152.245	8.2
3	15017.0	149.369	16.4
4	14849.2	147.699	10.6
5	14761.7	146.828	10.7
6	14697.7	146.225	11.8
7	13861.8	138.077	12.6
8	13797.1	137.235	11.8
9	13622.4	135.497	10.3
10	13199.7	131.293	9.8
11	13126.9	130.569	25.7
12	13083.8	130.132	11.4
13	12760.1	127.119	25.5
14	12304.8	122.391	13.7
15	4349.6	43.264	16.3
16	4033.8	40.122	9.7
17	4013.2	39.917	11.4
18	3991.8	39.705	62.1
19	3946.4	39.248	62.8
20	3949.8	39.288	62.8
21	3929.2	39.083	11.8
22	3907.9	38.870	11.1
23	2389.6	23.769	15.3

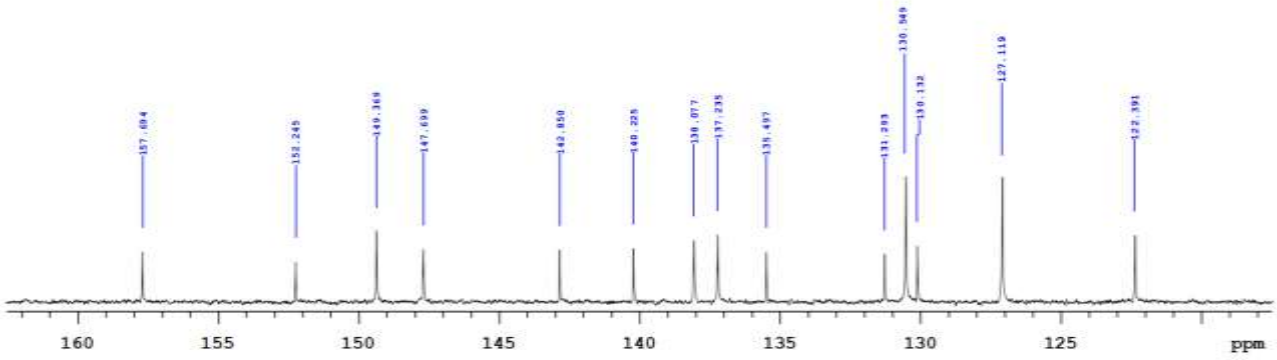
Data 2



Plotname: ETORICOXIB_API-13C-NMR_CARBON_20231003_01_plot01

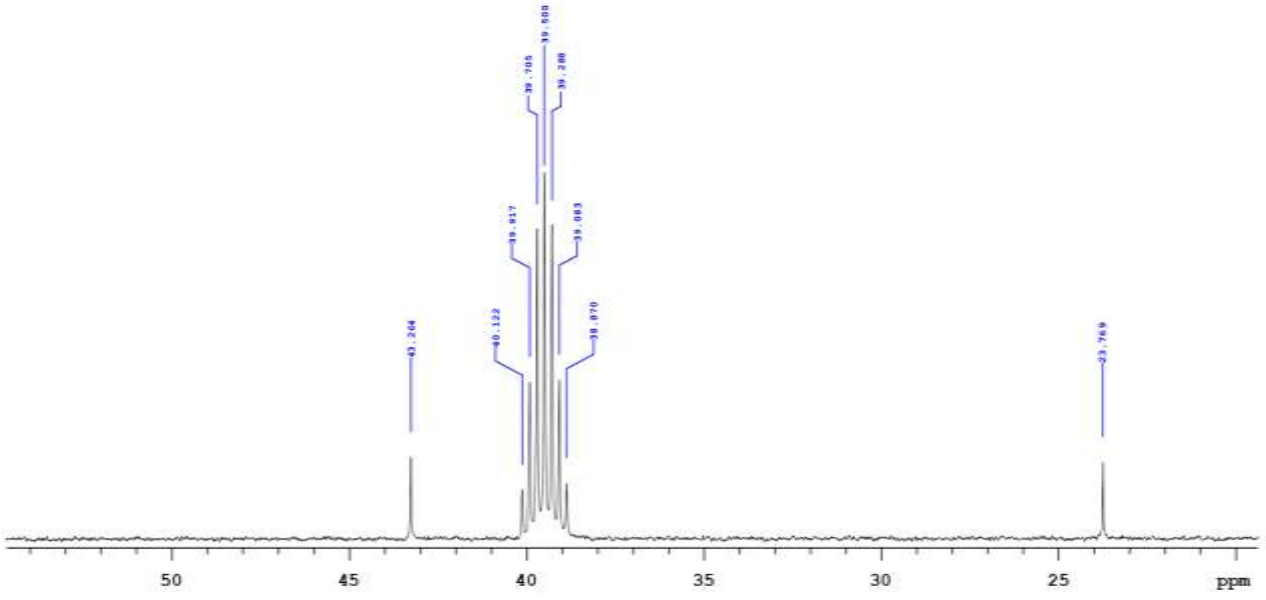
International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://theaspd.com/index.php

Solvent: dmso
SA-AGILENT 400MHz NMR
Date: Oct 3 2023

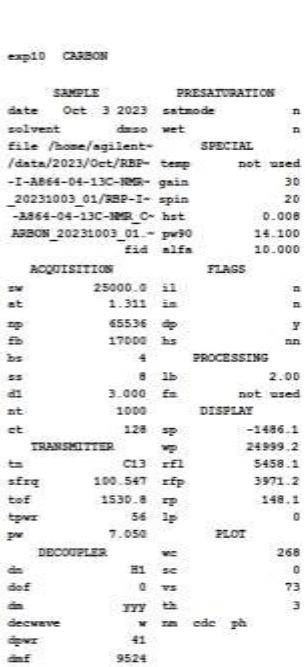


Plotname: ETORICOXIB_API-13C-NMR_CARBON_20231003_01_plot02

Solvent: dmso
SA-AGILENT 400MHz NMR
Date: Oct 3 2023



Plotname: ETORICOXIB_API-13C-NMR_CARBON_20231003_01_plot03



```
exp10  CARBON

      SAMPLE           PRESATURATION
date    Oct  3 2023  satmode          n
solvent       dmso  wet              n
file /home/agilent~       SPECIAL
/data/2023/Oct/RBP~  temp       not used
-I-A864-04-13C-NMR~  gain            30
_20231003_01/RBP-I~  spin            20
 -A864-04-13C-NMR_C~ hst          0.008
 ARBON_20231003_01.~ pw90        14.100
                fid  alfa        10.000
   ACQUISITION             FLAGS
sw          25000.0  il               n
at              1.311  in             n
np             65536  dp               y
fb             17000  hs              nn
bs                 4       PROCESSING
ss                 8  lb            2.00
d1             3.000  fn        not used
nt              1000       DISPLAY
ct               128  sp         -1486.1
   TRANSMITTER      wp         24999.2
tn               C13  rfl         5458.1
sfrq        100.547  rfp         3971.2
tof          1530.8  rp           148.1
tpwr             56  lp               0
pw             7.050       PLOT
    DECOUPLER        wc             268
dn                H1  sc               0
dof                0  vs              73
dm               yyy  th               3
decwave            w  nm  cdc  ph
dpwr              41
dmf             9524
```

INDEX	FREQUENCY	PPM	HEIGHT
1	15854.0	157.694	10.2
2	15306.2	152.245	8.2
3	15017.0	149.369	14.4
4	14849.2	147.699	10.8
5	14361.7	142.850	10.7
6	14097.7	140.225	11.0
7	13881.8	138.077	12.6
8	13797.1	137.235	13.8
9	13622.4	135.497	10.3
10	13199.7	131.293	9.8
11	13124.9	130.549	25.7
12	13083.0	130.132	11.4
13	12780.1	127.119	25.5
14	12304.8	122.391	13.7
15	4349.6	43.264	16.3
16	4033.8	40.122	9.7
17	4013.2	39.917	31.4
18	3991.8	39.705	62.1
19	3971.2	39.500	73.3
20	3949.8	39.288	62.8
21	3929.2	39.083	31.8
22	3907.9	38.870	11.1
23	2389.6	23.769	15.3

Plotname: ETORICOXIB_API-13C-NMR_CARBON_20231003_01_plot04

Flow rates and equivalence calculations:

Sr No		Ketosulfone (1)	Phosphate salt (2) + KTB	Liq.Ammonia + Amonium aetate
1	Molarity	0.32 M	1.3M WRT salt	1.2M WRT NH_3
2	Mol. Wt	275.32	161.65	17.03
3	Flow rate	9.45 ml/min	5.54 ml/min	5 ml/min
4	Active (g/min)	0.83 g/min	0.53 g/min (Phosphate salt)	0.1 g/min (Liq. NH_3)
5	Moles	0.0030	0.0032	0.0058
6	M/R	1.0	1.06	1.93

TABLE 1: FLOW RATES AND EQUIVALENCE CALCULATIONS

Ketosulfone (1) diluted in DMF and phosphate salt (2) mixed with KTB diluted in DMF were combined in 10ml reactor (1st reactor) at 90°C with residence time 40 Sec to give highly unstable open ring compound which on addition of liq. ammonia and ammonium acetate mixture gives cycalized desired product in 20ml static mixture (2nd reactor) at 90°C with residence time 1Min. This reaction moves through a back pressure regulator set to 3 – 3.5 bar (Zaiput, BPR-10). Reaction progress was analyzed by TLC. After entire collection, reaction mass quenched by water and extracted with toluene at 10-15°C. Combined organic layer washed with NaCl solution to get rid of moisture. Separated organic layer distilled under vacuum to get oil which on IPA crystallization gives pure Etoricoxib API with overall yield 65 - 70% (WRT 1)

Flow reaction set-up:

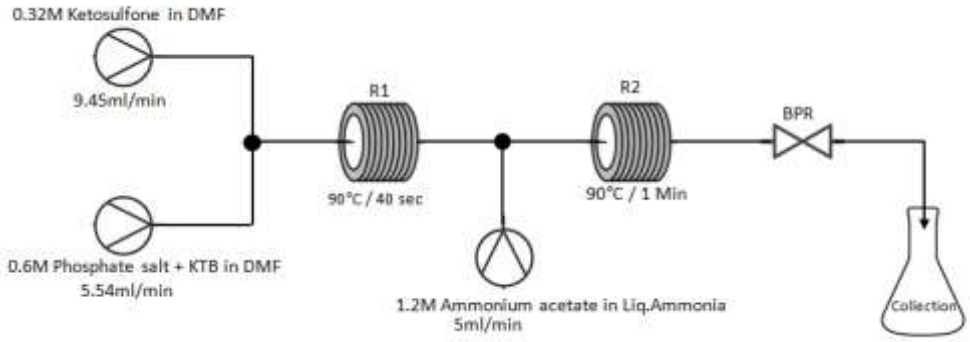


FIGURE 1: FLOW REACTION SET-UP

1H NMR:
Yellow solid Etoricoxib (5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine) mp : 134-135°C
δ2.44 (3H,s),
δ 3.25 (3H,s),
δ7.18 4– 7.204 (1H,d) J= 8Hz,
δ7.538 - 7.567 (3H,m) J = 3.34Hz,
δ 7.890 – 7.920 (2H,d), J = 8.4Hz,
δ 8.104 – 8.110 (1H,d), J = 2.4Hz,
δ 8.313 – 8.318 (1H,d), J = 2Hz,
δ 8.288 – 8.822 (1H,d), J = 2.4Hz

13C NMR:
Yellow solid Etoricoxib (5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine) mp : 134-135°C
δ 23.769 (1C,s),
δ 43.264 (1C,s),
δ 112.391 (1C,s),
δ 127.119 (1C,s),
δ 130.132 (1C,s),
δ 130.549 (1C,s),
δ 131.293 (1C,s),
δ 135.497 (2C,s),
δ 137.235 (2C,s),
δ 138.077 (1C,s),
δ 140.225 (1C,s),
δ 142.850 (1C,s),
δ 147.699 (1C,s),
δ 149.369 (1C,s),
δ 152.245 (1C,s),
δ 157.694 (1C,s)

CONCLUSION:
In summary, we achieved a flow protocol for the synthesis of Etoricoxib API. We found that this was safe and easy to handle process for manufacturing. According to the best our knowledge, it would be the first attempt to synthesize pyridine ring centered bulk drug with the help of flow chemistry.

CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGMENTS:
The authors are thankful to Pacific Academy of Higher Education and Research University (PAHER), Department of Chemistry for utilizing their facilities to complete the work.

SUPPORTING INFORMATION:
Attached ^{1}H NMR, ^{13}C NMR with this

ABBREVIATIONS AND CONVENTIONS:

API	Active Pharmaceutical Ingredient
NMR	Nuclear Magnetic Resonance
COX	Cyclooxygenase
NSAID	Non-steroidal anti-inflammatory drugs
DMSO	Dimethyl sulfoxide
DMF	N,N-Dimethyl Form amide
DMAc	Dimethyl Acetamide
THF	Tetrahydrofurtan
MTBE	Methyl tertiary butyl ether
KTB	Potassium tert- butoxide
WRT	With Respect To
TLC	Thin Layer Chromatography
Ml	Milliliter
°C	Degree Celsius
Min	Minute
BPR	Back pressure regulator
M	Molar
Sec	Seconds
NaCl	Sodium Chloride
IPA	Iso propyl alcohol
Mol wt	Molecular Weight
TMS	Tetra methyl silane
MHz	Mega Hertz
G	Gram
g/min	Gram per minute
ml/min	Milliliter per minute
DM Water	De mineralized water
Hrs	Hours
Mp	Melting Point

REFERENCES:
1. Nicolaou KC, Hale CRH and Nilewski C, Constructing molecular complexity and diversity: total synthesis of natural products of biological and medicinal importance, Chemical society reviews, 2012, 41, 5185 – 5238, doi : https://doi.org/10.1039/C2CS35116A
2. Baumann M, Baxendale I R, The synthesis of active pharmaceutical ingredient by using flow chemistry, Beilstein journal of organic chemistry, 2015, 11, 1194–1219, doi : https://doi.org/10.3762/bjoc.11.134
3. Kobayashi S, Flow fine synthesis, high yielding and selective organic synthesis by flow methods, Chemistry an asian journal, 2016,11(4), 425 – 436, doi: https://doi.org/10.1002/asia.201500916
4. Pastre J C, Browne D L and Ley SV, Flow chemistry synthesis of natural products, Chemical society reviews, 2013, 42, 8849 – 8869, doi : https://doi.org/10.1039/C3CS60246J

5. Britton J, Raston C L, Multistep continous flow synthesis, Chemical society review, 2017, 46, 1250–1271, doi : : https://doi.org/10.1039/C6CS00830E
6. Plutschack MB, Pieber B and Gilmore K, The hitchhiker's guide to flow chemistry, Chemical reviews, 2017, 117 (18), 11796 – 11893, doi : 10.1021/acs.chemrev.7b00183
7. Kockmann N, Roberge D, Harsh reaction conditions in flow micro-reactors for pharmaceutical production, Chemical engineering technology, 2009, 32 (11), 1682 – 1694, doi : https://doi.org/10.1002/ ceat.200900355
8. Movsisyan M, Battilocchio C and Ley S, Taming hazardous chemistry by continuous flow chemistry, Chemical society review, 2016, 45, 4892 – 4928, doi : https://doi.org/10.1039/C5CS00902B
9. Kockmann N, Thenee P and Fleischer – Trebes C, Safety assessment in development and operation of modular continuous flow process, Reaction chemistry and engineering, 2017, 2, 258 – 280, doi : https://doi.org/10.1039/C7RE00021A
10. Gutmann B, Cantillo D and Kappe C O, Continuous flow technology - a tool for the safe manufacturing of active pharmaceutical ingredients, Angewandte chemie, 2015, 54 (23), 6688 – 6728, doi : https://doi.org/10.1002/anie.201409318
11. Porta R, Benaglia M and Puglisi A, Organic process research and development, 2016, vol 20, issue 1, pp 2 – 25, doi : https://doi.org/10.1021/acs.oprd.5b00325
12. Merck & company INC (Jobs) receives no approvable letter from FDA for Arcoxia (Etoricoxib) , Biospace, 2007
13. Fischer J and Ganellin CR, Analogue based drug discovery, 2006, John wiley & sons, Hoboken p 504
14. Griswold D E, Adams J L, Constitutive cyclo-oxygenase (COX-1) and inducible cyclo-oxygenase (COX-2): rationale for selective inhibition and progress to date, Medicine research revision,1996,16, 181 - 206, doi : 10.1002/(SICI)1098-1128(199603)16:2<181::AID-MED3>3.0.CO;2-X
15. Friesen R W, Brideau C and Chan C, 2-Pyridinyl-3-(4-methylsulfonyl)phenyl pyridines : selective and orally active cyclo-oxygenase-2 inhibitors, Biological and medicinal chemistry letters, 1998, 8 (19), 2777 – 2782, doi : 10.1016/s0960-894x(98)00499-5
16. Marcoux J F, Corley E G and Rossen K, Annulation of ketones with vinamidinium hexafluorophosphate salts : An efficient preparation of trisubstuted pyridines, Organic letters, 2000, 15 (2), 2339 – 2341, doi : 10.1021/ol006097b
17. Bartholomaus P and Kerry G, Integrating flow processing – challenges in continuous multistep synthesis, Journal of flow chemistry, 2017, 7,129 -136, doi : 10.1556/1846.2017.00016