

Within our Q3 newsletter we are delighted to announce our new alliance with Pareon Chemicals Ltd, the launch of our Premium Fragment Collection and new additions to our >65,000 BIONET compound collection. We continue to add new BIONET products on a monthly basis and updates are available for download on our recently launched new website, which has improved 'search & buy' functionality as well as details on our chemistry services, scale-up and consultancy offerings. See www.keyorganics.net for our new look!

We also present an interesting case study that describes the process development and scale-up of an agrochemical intermediate where we improved a five step synthesis to two steps and increased product yield from 12% to 75%. Our new route afforded 1.3 Kg of product in two weeks and exemplifies our capabilities in new route development and expedient scale-up. Our back page interview is with Dr Matthew Stent who is Head of Services at Key Organics and manages our team of over 15 highly experience chemists. Our forthcoming attendance at conferences and exhibitions are also profiled.

New & Versatile Chiral Templates



On 28th May, we announced our exclusive and global supply agreement with Pareon Chemicals Ltd. Pareon is a supplier of both established and exciting novel intermediates for drug design, biologically important molecules and natural products.

The company is the brainchild of the internationally renowned synthetic chemist Professor Phil Parsons FRSC, with co-directors Dr. Stephen Rushton, Dr. Lee Walsh and Dr. David Bennet.

Both Key Organics and Pareon are embarked on a strategy to increase their range of new and exciting products and technologies such that this partnership makes good strategic sense. Key Organics has access to a global customer base within the life sciences sector and excellent customer service and compound handling infrastructure that ensures that products are dispatched on the same day. The agreement between the parties provides for the exclusive, global supply of Pareon's products by Key Organics. In addition, both companies wish to collaborate in order to further grow their differentiated technology and service offerings within the life sciences sector. Figure 1 exemplifies the versatility of the Chiral Oxazolidinone Template which is one of many new compounds that are now available from Key Organics via our new shop and website.

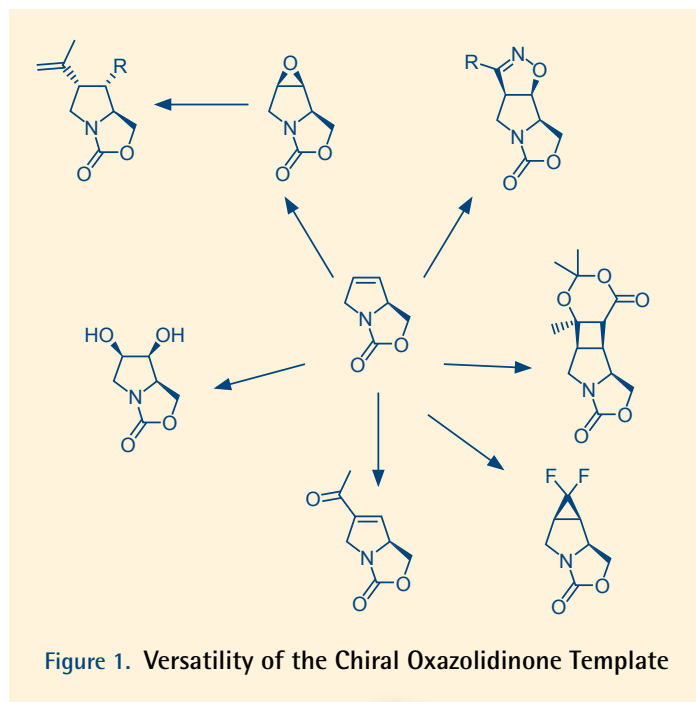


Figure 1. Versatility of the Chiral Oxazolidinone Template

Looking For Consultancy?

Our experienced scientists, project managers and business professionals regularly provide consultancy services to our customers and we are delighted to now expand this offering such that we can now undertake projects in the following areas:

- ✓ Enabling technologies in chemistry drug delivery and manufacturing
- ✓ Intellectual property licensing and transaction support
- ✓ Market competition and sector analysis
- ✓ Project management of technology transfer and effect scale up and commercial manufacturing
- ✓ All areas of synthetic organic chemistry methodology and process R&D
- ✓ Analytical chemistry, identification and quantification of impurities, residue analysis and degradation products



New BIONET Premium Fragment Library Launched

Our 'Premium Fragment Library' consists of 931 fragments with experimentally assured aqueous solubility data, high purity (>95%), excellent diversity (Diversity Coefficient = 0.78) which were selected on the basis of 'Rule of Three' criteria, chemical tractability and potential for fragment evolution (*Table 1*). Please contact us or visit our website for a complete SD or PDF file download.

All BIONET fragment libraries are available custom-weighted in milligram or microgram quantities. Customers are able to purchase the entire library or selected compounds. We also offer a bespoke fragment library design service and deliver this in a variety of formats to meet your needs. Please contact us for more information.

Characteristic	BIONET Premium Fragment
cLogP	≤ 3
Rotatable bonds	≤ 3
H Bond donors	≤ 3
H Bond acceptors	≤ 3
MW	≤ 300
TPSA	≤ 60Å ²
Purity	≥ 95%
Aqueous solubility	> 1mM
DMSO solubility	200mM
Diversity coefficient	0.78

Table 1. Premium Fragment Data

BIONET



New Key Organics Website and BIONET Shop Launch

Our BIONET brand recently celebrated its 25th anniversary which coincided with the launch of our new website and shop that now contains over 65,000 stock items of intermediates, fragments, biochemicals and screening compounds. Many new products are added on a monthly basis and available for download as an SD or PDF file, alternatively we can send updates directly to you via e-mail following registering your details with us.

Why Buy Direct?

Given we manufacture over 90% of our products, buying direct from Key Organics can save you up to 150% on agent and re-seller prices; we provide a no-quibble guarantee, same day dispatch and excellent front, and back-end customer support. All products are available in a variety of pack sizes and we can offer many products at development quantities through our refurbished scale-up facility. cGMP material can be supplied through our partnership network where we have access to facilities in the UK, mainland Europe, North America, Asia and Australasia.

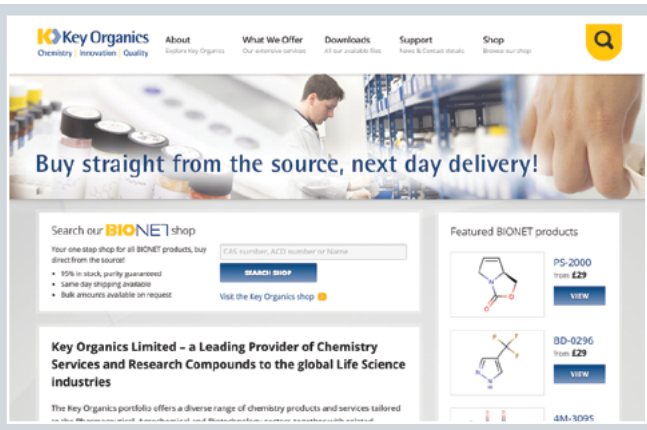


BIONET Guarantees:

As a research and development based company, we recognise the importance of quality, reliability and value for money. We offer a no-quibble guarantee and are one of the most responsive companies in the industry with next day delivery in Europe and same-day shipment for global customers.

New Design & Ease of Use:

Our new site was designed with ease of product search in mind and to enable our customers to find information quickly and the new navigation toolbar facilitates this.



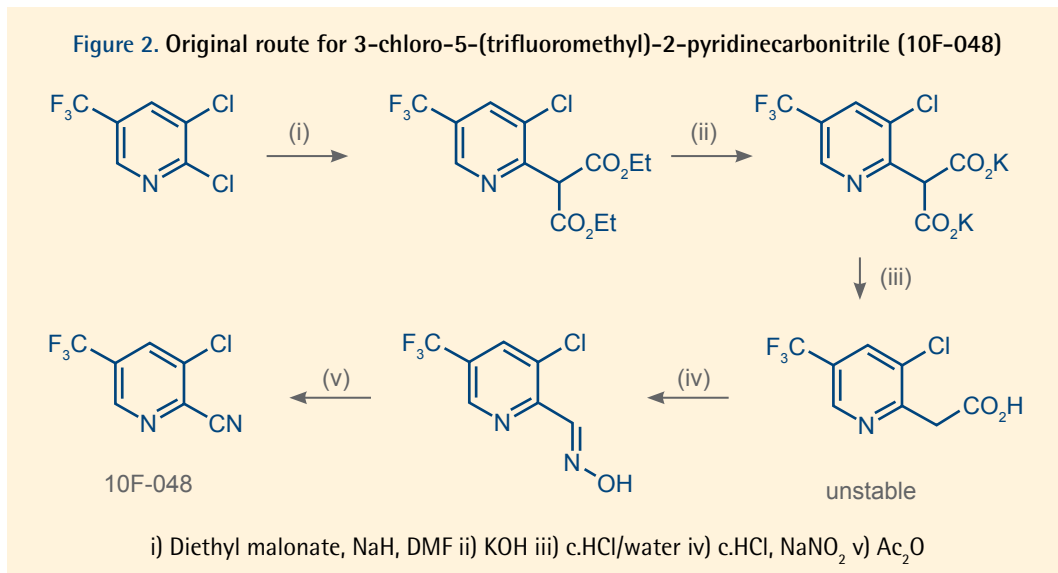
Product searches can be undertaken through CAS or IUPAC name plus compound class, drawn structures can also be searched. For compounds that are not listed we are able to undertake custom R&D within our experienced services team. We routinely scale up to kilogram quantities and provide process-related impurity identification and quantification services. Our experienced analytics team is equipped with analytical and preparative LC-MS, chiral HPLC and NMR plus additional techniques on-site.

Visit the Key Organics Online Shop for BIONET products: <http://shop.keyorganics.net/>

Process Development & Scale-up: Case Study

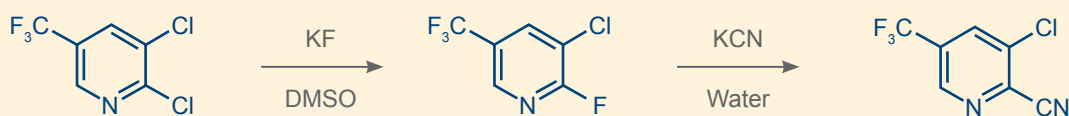
3-Chloro-5-(trifluoromethyl)-2-pyridinecarbonitrile (KOL 10F-048, CAS: 80194-70-3) is a starting material used as agrochemical precursor. Our objective was to develop a cost effective and development-scale process that was reproducible and able to deliver >1 Kg of product within 6 weeks. Evaluation of the original synthesis from the readily available 2,3-dichloro-5-(trifluoromethyl)pyridine precursor was undertaken with the view to optimising key, low-yielding steps (*Figure 2*). However this approach involved the use of sodium hydride in DMF to form the di-ester from which the corresponding carboxylic acid proved to be thermally unstable and, at relatively low temperatures, readily decomposed to form the picoline (2-methyl pyridine).

The dehydration of the hydroxylamine was also thermally sensitive and restricted within a very narrow temperature window. Reaction initiates at ~60°C but decomposition is rapid if the temperature rises above 65°C., reproducibility and yields are also highly variable and the overall yield is typically ca. 12% such that this pathway was deemed unsuitable for scale-up.



Alternative approaches such as direct reaction with of the "dichloropyridine" with Na/K cyanide afforded low yields and/or no product could be isolated. Halogen exchange to afford the 2-bromo derivative with subsequent displacement using Na/K cyanide also afforded complex mixtures or low product yields. Optimisation using Cu(II)cyanide also proved problematic and this approach was abandoned.

A versatile and highly attractive approach was subsequently developed at scale (*Figure 3*). The approach also utilises the same and commercially available 2,3-dichloro-5-(trifluoromethyl)-2-pyridine precursor which was directly converted to the 2-fluoro intermediate that was then directly converted to the title compound using aqueous KCN (*Figure 3*).



Key Process Features:

- The new pathway consists of only 2 steps, a substantial reduction in toxic waste, milder reaction conditions and was easily scalable with an overall yield of 75%
- This new methodology was successfully applied to similar compounds at scale
- In excess of 1.3kg of 3-Chloro-5-(trifluoromethyl)-2-pyridinecarbonitrile was produced in 2 weeks with a purity >99%

Of note, the initial fluorination step proceeded with ease and was readily amenable to rapid scale-up given that the reaction was carried out in mild conditions using potassium fluoride. The subsequent reaction with potassium cyanide has to be performed with great care, but is facile and carried out in mild conditions with minimal workup required. The final product is purified by low vacuum distillation and without the need for chromatography.

Upcoming Events:

9 July

Translating UK scientific excellence into global therapeutic strategies
Wellcome Trust Genome Campus, Hinxton, near Cambridge
www.onhelix.com

8 – 11 September

Medicinal Chemistry Symposium 2013 –
17th RSC-SCI MedChem Symposium
Churchill College, University of Cambridge, UK
www.rsc.org/ConferencesAndEvents/conference/alldetails.cfm?evid=112039

17 – 19 September

Chemoutsourcing
Ocean Place Resort & Spa, Long Beach, NJ, USA.
www.chemoutsourcing.com

25 – 27 September 2013

The 29th International Conference and Exhibition;
Chemical Process R&D
The Hotel Altis, Lisbon, Portugal
www.scientificupdate.co.uk

9 – 11 October

BioJapan 2013
Yokohama, Japan
www.ics-expo.jp/biojapan

22 – 24 October

CPHI Pharma Ingredients Event
Frankfurt, Germany
www.cphi.com/home

29 – 30 October

Crop World, Amsterdam
www.cropworld-global.com

Staff Interview

In this edition we interview
Dr. Matthew Stent
Head of Chemistry Services



Q: Please tell us a bit about yourself?

A: I grew up in Norfolk, and did my first degree at the University of Bristol, which included an industrial placement year with SmithKline Beecham at Harlow. After a DPhil with David Hodgson at Oxford University (novel asymmetric epoxide ring-opening methodology), I did a 2 year post-doc with Phil Magnus at the University of Texas, Austin (natural product synthesis). I have worked at Key Organics since 2005 and live locally in Camelford with my partner and two young daughters. Being based in Cornwall is a real bonus for someone who enjoys the outdoors, whether that's walking, cycling or going to the beach.

Q: What is your role within Key Organics?

A: I have been on the senior management team since mid-2008, and have had particular responsibility for managing all aspects of our Chemistry Services offering (non-catalogue) since 2011. Having recently qualified as an APMG accredited PRINCE2® Project Management Practitioner, I am the contact point for existing FFS/FFC clients, and have responsibility for quoting on new work, managing communication, operations and support for ongoing projects.

Q: What do you enjoy about working at Key Organics?

A: My role is very diverse and unpredictable, I get exposed to new chemistry and new challenges on a daily basis. Overall I really appreciate actually being able to still do what I have trained to do as a synthetic organic chemist. Managing our CRO work in a highly competitive environment is both very challenging and highly rewarding, and I am proud of the efficient, high quality service we provide.

Q: What do you think is Key Organics' greatest strength?

A: Simply, our people; their experience, skill and enthusiasm.

New Satellite Offices, Let's Meet-up!

We are now able to meet with customers at our new satellite offices at BioCity Nottingham and BioCity Scotland. Of course everyone is still welcome to visit HQ in Cornwall!

 **Key Organics**
Chemistry | Innovation | Quality

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