December 2020

Key Organics

Chemistry | Innovation | Quality

Newsletter

What a strange year 2020 has been! Here at Key Organics we have managed to stay operational throughout the year, obviously with changes to working practices as everyone working in our industry will be familiar with. We'd like to thank our customers, suppliers and collaborators both old and new for continuing to work with us during the pandemic and we hope that everyone has a relaxing Christmas break and a healthy and happy 2021.

Our last shipping days are 21st December for UK and the rest of Europe and 18th December for the Rest of the World, we are closed from the 25th December until the 4th January 2021.

Process Development & Scale-up Service

Expertise in the scale-up of synthetic routes to prepare multigram to kilogram quantities of compounds for further studies.

Key Organics has supported many drug discovery programs, from hit validation to preclinical studies. We have particular expertise in the scale-up of synthetic routes to prepare multigram quantities of a lead compound for further studies. As many of our customers work to tight deadlines, we seek to optimise the efficiency of a scale-up route by reducing the number of steps and finding alternatives to chromatographic purification. Our chemists work closely with our in-house analytical team to ensure that final compounds meet or exceed the purity specification required by the customer, we can also provide SDS, BSE/TSE, GMO statements as needed by the client.

We have in house experience of synthesizing various salts of the desired compound to aid salt screening and polymorphism studies.

Our capabilities include:

- Process Chemistry R&D to deliver robust routes
- Scale-up of intermediates and final compounds (Kg scale)
- Synthesis of development quantities of intermediates and of final compounds
- Full reaction profiling
- Production of the necessary documentation to assist the transition into GMP manufacture
- Procurement

Our current suite of equipment features:

- Up to 20 litre vessels with temperature range of -20°C to +150°C
- Dedicated 10lt vacuum jacketed vessel capable of -78°C via Huber 905 Unistat including precision and reproducible reaction dosing system.
- Biotage 150 large scale flash chromatography unit capable of handling up to kg quantities of materials. Access to wide range of separation media resulting in very low impurity contamination.
- State of the art Buchi 220 pro rotary evaporator with up to 20lt capacity offering excellent and efficient solvent removal with minimal fugitive losses maximising environmental protection.
- 2" wiped-film still specifically for the distillation of heat sensitive material with a flow rate of 0.1-3litres/hr.
- 500ml to 2lt vacuum jacketed vessels capable of full calorimetry and reaction profiling at -78°C to +150°C reaction temperatures.
- Hastelloy and stainless steel autoclaves up to 4 litres capable of undertaking high pressure (200 bar) and high temperature (+200°C) hydrogenation, ring reductions and carbonylations.

Compound Storage and Stability Testing

Using our storage space and facilities, we are ready to store your powder and liquid samples, format them on demand as required and distribute them to your site locations around the world. This service eliminates the need to have an organized compound repository on site while keeping your libraries easily accessible. Our storage conditions range from storage at ambient temperature to a cooled and refrigerated environment. We can also perform regular QC checks to monitor compound integrity during storage and provide valuable stability data.

DRUG DISCOVERY PROCESS MAP

Target Discovery | Lead Finding | Lead Optimization | **Candidate Selection** | **Pre-Clinical** | Phase I | Phase II | Phase III | Product Approval

- Screening compounds
- Fragment libraries
- Procurement / supply
- Competitor compounds

- Custom synthesis
- Contract research (FTE)
- Intermediates / building blocks
- Scale up (10-100's g)

- Scale up (kg)
- Route development
- Labelled compounds
- Impurity / metabolite synthesis
- Intermediates / building blocks
- Procurement / supply

PolyActiva

"Over four years and two different programs Key Organics have delivered for us right from the start. From initial engagement through to shipping and delivery it has been seamless. The expert chemists at Key Organics have delivered high quality material and data, rigorous process development and creative solutions to the inevitable problems that arise. Last-minute requests and the all too frequent changes in scope have been accommodated without fuss. While the chemistry has been exemplary the innovative solutions extend beyond the lab. A recent project would not have got internal approval without creativity, flexibility and input from their BD.

In one project I am particularly pleased about, the process development and scale up work, carried out by Key Organics, on a critical component from our crude discovery route enabled them to provide material we simply didn't have the internal capacity to deliver; this fed directly into the supply chain for our phase 1 program.

The first-class communication, discussions and the thorough and detailed reporting, which is essential when you're on the other side of the world, has made my life that much easier. My confidence in Key Organics is the same as if they were in my own lab down the hall and I will be using Key Organics again and would do so more if I were able."

Dr Andrew Donohue Head of Chemistry, PolyActiva Pty.Ltd.

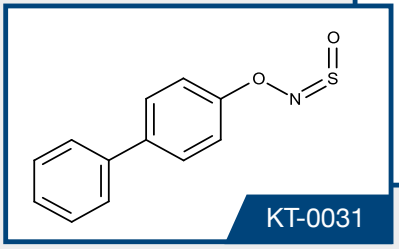
TopiVert

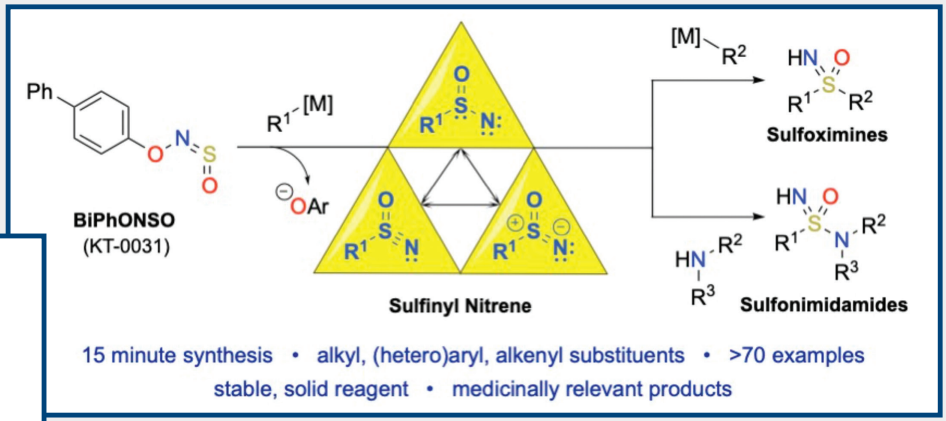
"I have been extremely impressed by Key Organics' professionalism and candour during separate multi-gram re-synthesis and route development projects carried out recently. In particular, Key communicated clearly and rapidly with me when any obstacles to project delivery were encountered. Their swift and frank communication gave us time to jointly devise solutions which ensured that objectives were achieved while working to tight deadlines. Key's ability to formulate innovative routes to important organic compounds is also first rate. In this regard, they dramatically improved the availability of one of our crucial intermediates by developing some neat chemistry that relied upon unconventional thinking."

Dr Matthew Fyfe,
Head of Chemistry, TopiVert

BiPhONSO, a versatile reagent for the synthesis of Sulfoximines and Sulfonimidamides.

Following the recent publication by Willis *et al*, Key Organics are pleased to offer BiPhONSO as a versatile reagent for the synthesis of Sulfoximines and Sulfonimidamides.





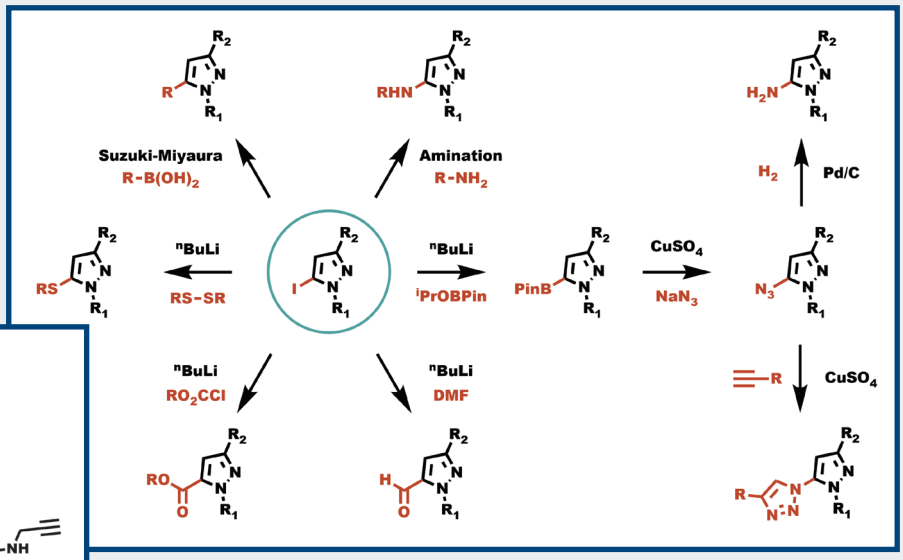
Reference: Harnessing Sulfinyl Nitrenes: A Unified One-Pot Synthesis of Sulfoximines and Sulfonimidamides: Thomas Q. Davies, Michael J. Tilby, Jack Ren, Nicholas A. Parker, David Skolc, Adrian Hall, Fernanda Duarte, and Michael C. Willis, : *J. Am. Chem. Soc. 2020, 142, 15445−15453*

Highly versatile 5-iodopyrazole building blocks

A range of highly versatile 5-iodopyrazole building blocks are now available through our collaboration with Redbrick Molecular, please enquire for analogues and larger amounts.

REDBRICK MOLECULAR

https://www.redbrickmolecular.com



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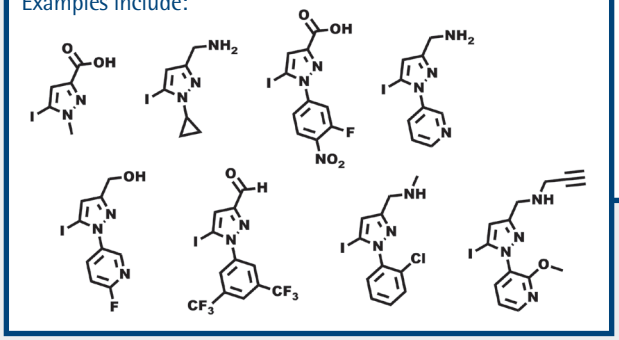


Reference:
Alkyne [3 + 2] Cycloadditions of Iodosydnones Toward Functionalized 1,3,5-Trisubstituted Pyrazoles, Duncan L. Browne, John B. Taylor, Andrew Plant, and Joseph P. A. Harrity, J. *Org. Chem. 2010, 75, 984–987*

Key Organics Premium and Fluorine Fragment Libraries exclude fragments likely to form aggregates.

The spin–spin relaxation Carr–Purcell– Meiboom–Gill NMR experiment has been employed to detect and remove aggregate species from Key Organics Premium and Fluorine Fragment libraries [1]

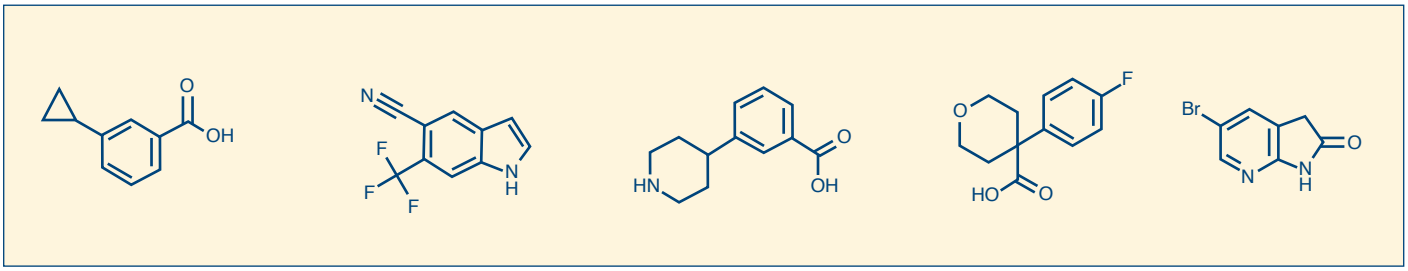
Small molecules can self-assemble in aqueous solution into a wide range of nanoentity types and sizes (dimers, n-mers, micelles, colloids, etc.), each having their own unique properties. This has important consequences in the context of drug discovery including issues related to nonspecific binding, off-target effects, and false positives and negatives. The spin–spin relaxation Carr–Purcell– Meiboom–Gill NMR experiment is sensitive to molecular tumbling rates and can expose larger aggregate species that have slower rotational correlations. The strategy easily distinguishes lone-tumbling molecules versus nanoentities of various sizes. The technique is highly sensitive to chemical exchange between single molecule and aggregate states and can therefore be used as a reporter when direct measurement of aggregates is not possible by NMR.

All fragments in Key Organics Premium and Fluorine Fragment Libraries have been analysed by 1H NMR and 1H CPMG* for:

- **Structure verification**
- **Purity**
- **Aqueous Solubility**
- ***Aggregation**

All customers are supplied with the following data package for each aqueous soluble fragment purchased:

- **19F NMR pdf and Raw data files**
- **1H NMR pdf and Raw data files**
- **NMR chemical shifts supplied in excel and sd file format**



[1] Exposing Small-Molecule Nanoentities by a Nuclear Magnetic Resonance Relaxation Assay. *J. Med. Chem. 2019, 62, 7885–7896.*

We will be exhibiting and/or attending the following exhibitions and conferences in the coming months:

14th to 15th April 2021	37th Process Development Symposium	Online Webinar

Key Organics will be attending a mixture of virtual and physical events as appropriate in 2021.
Watch this space!

For more information, please visit: https://www.keyorganics.net/about/exhibition-conference-attendance

Staff Interview Daniel Griffiths, Analytical Chemist

Q: Please tell us a bit about yourself?

A: I have a BSc Chemistry with Industrial Experience from Cardiff University. I did my year experience in Computational Chemistry working at GlaxoSmithKline. Here I compared different algorithms to compile a Fragment Database for use in drug discovery and wrote a computer program based on the results I obtained. With regards to hobbies I have a vast array of circus skills and am a good chess player.

Q: What is your role within Key Organics?

A: I am an Analytical Chemist. I prepare compounds for analysis and use different analytical techniques to calculate purities of compounds. I use NMR, LCMS and GC to generate data and reports which I then interpret as well as carry out general maintenance on the instruments.

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

A: I enjoy the independence and responsibility for repairing and maintaining the equipment and the analysis of data. There is a large satisfaction in repairing equipment especially if you know you have identified the problem and fixed the issue quickly.

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

A: The people. Whilst unfortunately during lockdown we have not been able to see so much of each other. If anyone needs a hand with anything, someone else is always willing to help. This coupled with the high level of skill required to develop some of the compounds sought after; the effective online communication; efficiency of the compound handling unit; maintenance; office staff and management fit together to make a great team.

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