# Development of a New Route to 3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid (DFPA) – A Key Building Block for Novel Fungicides

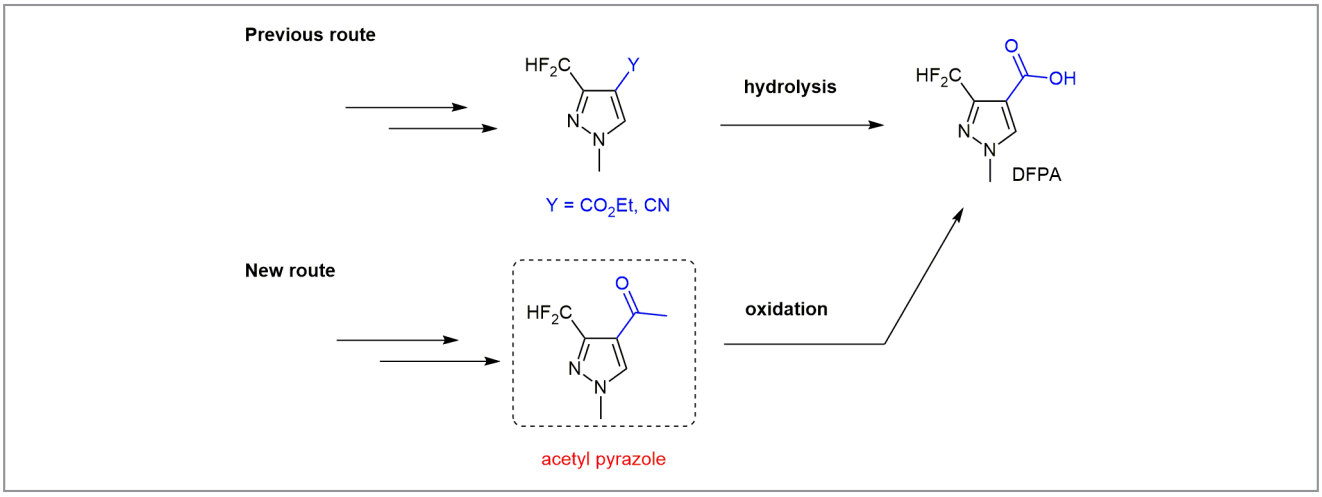
Poster #36 (Poster Award Winner), 22nd International Symposium on Fluorine Chemistry (ISFC-22), July 22–27, 2018, University of Oxford (UK)

3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (DFPA) is a key intermediate in the synthesis of succinate dehydrogenase inhibitors (SDHI), a new class of fungicides: six recently marketed compounds and four compounds currently in development have the same DFPA scaffold. Therefore, the global demand for this key intermediate is growing rapidly. For this reason, Yosuke Ochi and co-workers at the Asahi Glass Company (currently AGC Inc.) (Japan) started to develop an original route. Mr. Ochi said: "In most of the conventional routes (for a recent review, see *J. Fluorine Chem.* **2013**, *152*, 2–11), DFPA is synthesized by hydrolysis of a pyrazole ester (or nitrile), and there was no report on the preparation of DFPA from an acetyl pyrazole. Thus, we developed the new route using an acetyl pyrazole as a key intermediate of DFPA (Scheme 1)."

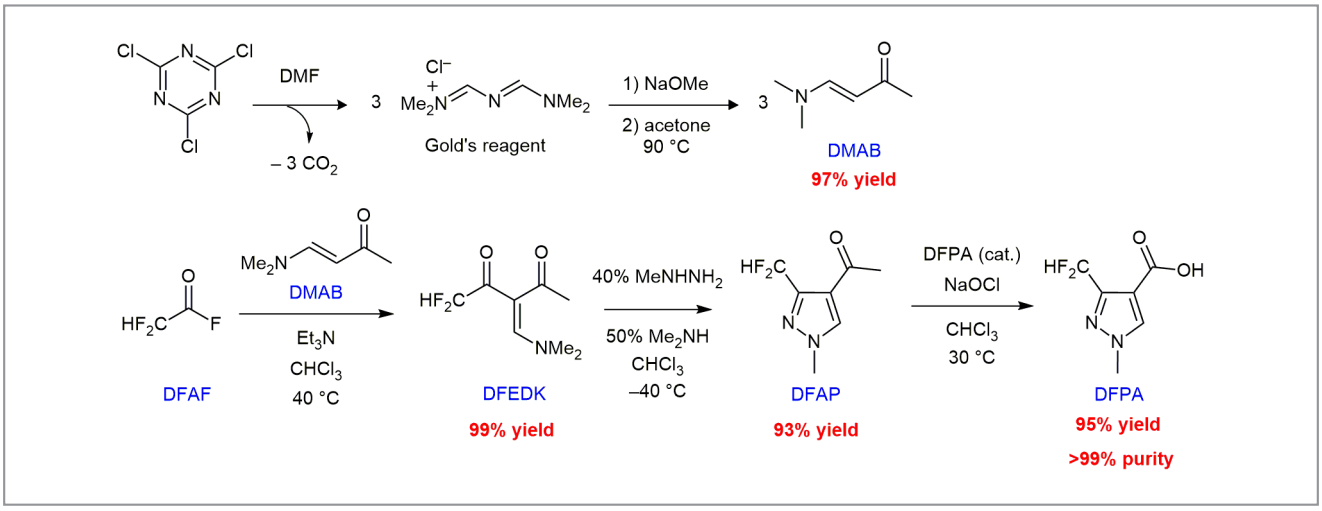
Mr. Ochi explained: "In our new route, each step of the reaction proceeds quantitatively and DFPA is obtained with very high purity. Moreover, we can utilize our in-house raw materials and technologies, such as difluoroacetyl fluoride (DFAF), chloroform, and NaOCl." The starting material, dimethylaminovinyl methyl ketone (DMAB), is prepared via a well-known method using acetone, ethyl formate, and dimethylamine. However, the group developed an alternative route to DMAB using Gold's reagent. "The new route is more cost-effective compared with the previous one (patent application WO2018074411)," remarked Mr. Ochi. He continued: "The difluoroacetylation of DMAB proceeds quantitatively using $Et_3N$ to trap HF. In the cyclization step, the addition of $Me_2NH$ controls the formation of several isomers and the trace amount of isomers generated can be removed efficiently by crystallization. The oxidation of an acetyl pyrazole with NaOCl is a very clean reaction, and DFPA is obtained in up to 99% purity. In this reaction, we use DFPA as a phase-transfer catalyst to make the reaction proceed smoothly (Scheme 2)."

This new method is practical and cost-effective for large-scale production. The group has already conducted pilot-scale production with this method.

Mr. Ochi concluded: "We would like to thank the R&D division in Chiba and Yokohama for their help in the process optimization and scale-up, and the analytical science team for identifying impurities. Finally, we are grateful to the manufacturing group in the Wakasa plant for their support during pilot-scale production."




**Scheme 1** Approaches to the preparation of DFPA




**Scheme 2** Preparation of DFPA using Gold's reagent

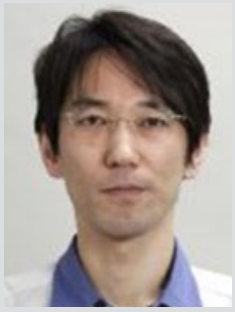
## About the authors

*Y. Ochi*

**Yosuke Ochi** was born in Hyogo, Japan in 1986. He received his Bachelor's (2009) and Master's (2011) degrees from Kyoto University (Japan) under the guidance of Professor Seijiro Matsubara. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of a manufacturing route for organic compounds in the field of specialty chemicals.

*Y. Ishibashi*

**Yuichiro Ishibashi** was born in Chiba, Japan in 1977. He received his Bachelor's (2000) and Master's (2002) degrees from the University of Tokyo (Japan) under the supervision of Professor Koichi Narasaka. Currently, he is working at AGC Inc. (Japan).



*Dr. M. Sawaguchi*

**Masanori Sawaguchi** was born in Hokkaido, Japan in 1974. He received his Bachelor's (1997) and Master's (1999) degrees, and his PhD, from Hokkaido University (Japan) under the guidance of Professor N. Yoneda in 2001. From 2000 to 2002, he worked at Hokkaido University as a JSPS Research Fellow. Currently, he is working at AGC Inc. (Japan).

*S. Kawaguchi*

**Satoshi Kawaguchi** was born in Gifu, Japan in 1981. He received his Bachelor's (2004) and Master's (2006) degrees from Nagoya University (Japan) under the supervision of Professors Tadao Kondo and Keigo Aoi. He is currently working on the development of fluorinated organic compounds at AGC Inc. (Japan).

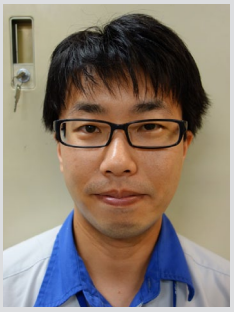
>>

*N. Miyake*

**Noriaki Miyake** was born in Tokyo, Japan in 1979. He received his Bachelor's (2002) and Master's (2004) degrees from Tokyo Institute of Technology (Japan) under the guidance of Professor Tomoya Kitazume. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of fluorinated organic compounds in the field of specialty chemicals.

*Y. Yamazaki*

**Yusuke Yamazaki** was born in Nagoya, Japan in 1986. He received his Bachelor's (2010) and Master's (2012) degrees from Nagoya University (Japan) under the guidance of Professor Susumu Saito. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of fluorinated organic compounds in the field of specialty chemicals.



*S. Shimizu*

**Shota Shimizu** was born in Saitama, Japan in 1988. He received his Bachelor's (2012) and Master's (2014) degrees from the University of Tokyo (Japan) under the guidance of Professor Shū Kobayashi. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of a manufacturing route for organic compounds in the field of specialty chemicals.

© Georg Thieme Verlag Stuttgart • New York – Synform **2018/12**, A197–A199 • Published online: November 19, 2018 • DOI: 10.1055/s-0037-1609809