

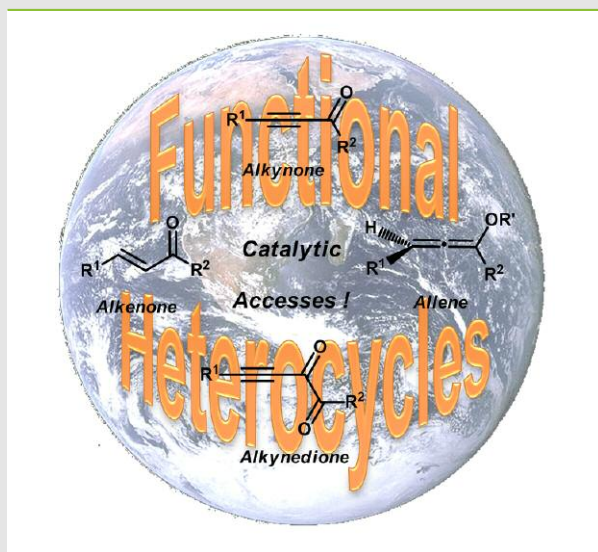
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/06

SYNSTORIES

■ **Three-Component Synthesis of Ynediones by a Glyoxylation/Stephens–Castro Coupling Sequence**



■ **Palladium-Mediated Intracellular Chemistry**

■ **Mild Decarboxylative Activation of Malonic Acid Derivatives by 1,1'-Carbonyldiimidazole**

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Dear readers,

In an ideal world, academia and pharmaceutical industry would always work together in a synergistic manner, pursuing the same goals (although from different perspectives and by different means) with joint efforts.

Unfortunately, in the real world this is not always easy or possible, but when it happens, the outcome of these joint efforts and collaborations are often outstanding and result in great benefits for both parties, for the society and for the economy as well. The problem is that industry and academia sometimes speak different languages and don't know each other sufficiently well. In my experience, it takes a great deal of effort and time to make a contact and overcome this communication barrier, but when this happens, the resulting collaborations are generally very rewarding and leading to great results. I am always very keen to host contributions to **SYNFORM** from the industry, because I think this helps to improve the mutual knowledge and understanding between industrial and academic researchers. I am therefore particularly happy that this issue of **SYNFORM** features a **SYNSTORY** article from Pfizer's Dr. D. Lafrance and his group (USA), who discovered a novel mild and efficient methodology for preparing α -substituted carboxylic acids from malonates. The second **SYNSTORY** comes from Scotland, where the group of Professor M. Bradley discovered an exciting way to exploit cells as "living reactors" to host and perform intracellular organic reactions mediated by catalysts like palladium, which is xenobiotic and even toxic for cells, for the production of bioactive compounds. Last but not least, there is a **SYNSTORY** on a reaction identified and developed by Professor T. J. J. Müller (Germany), for the synthesis of highly functionalized indoles using a novel three-component strategy.

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

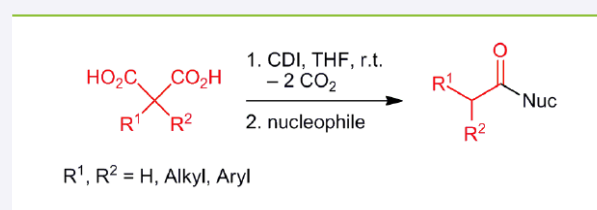
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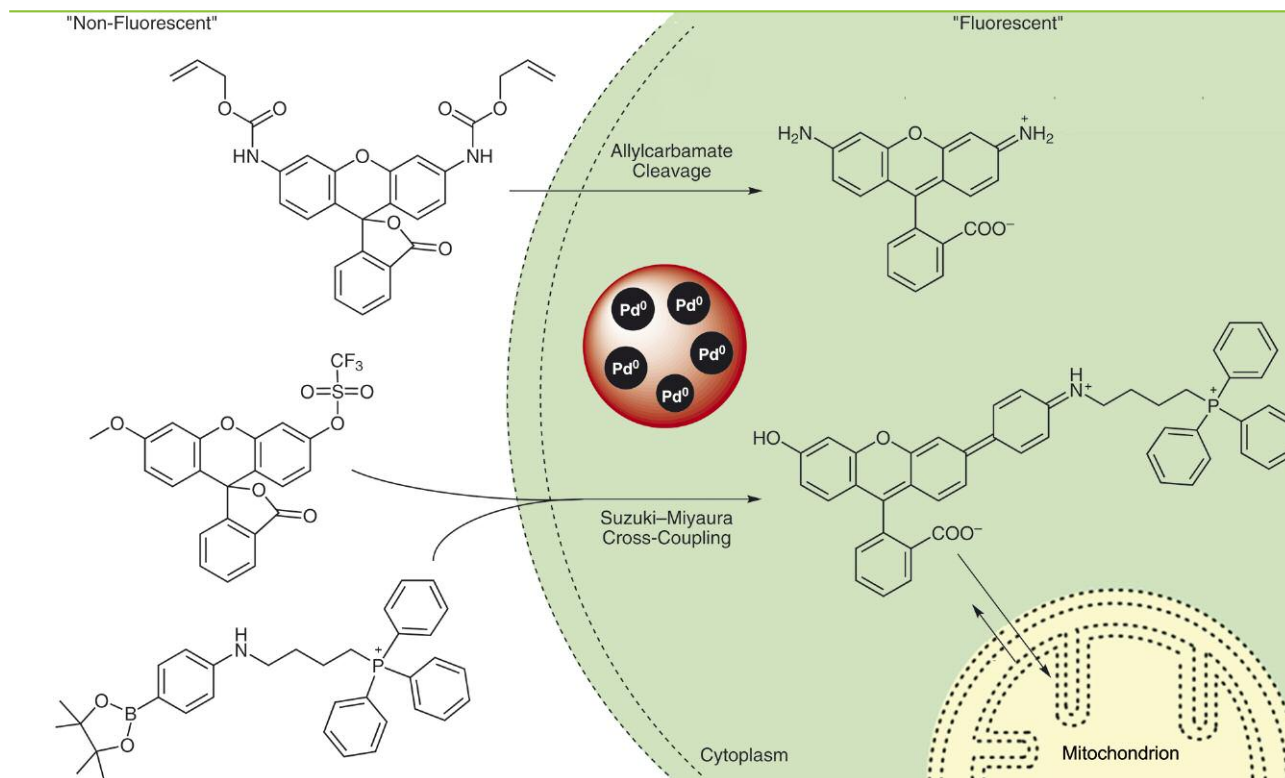
If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

Palladium-Mediated Intracellular Chemistry

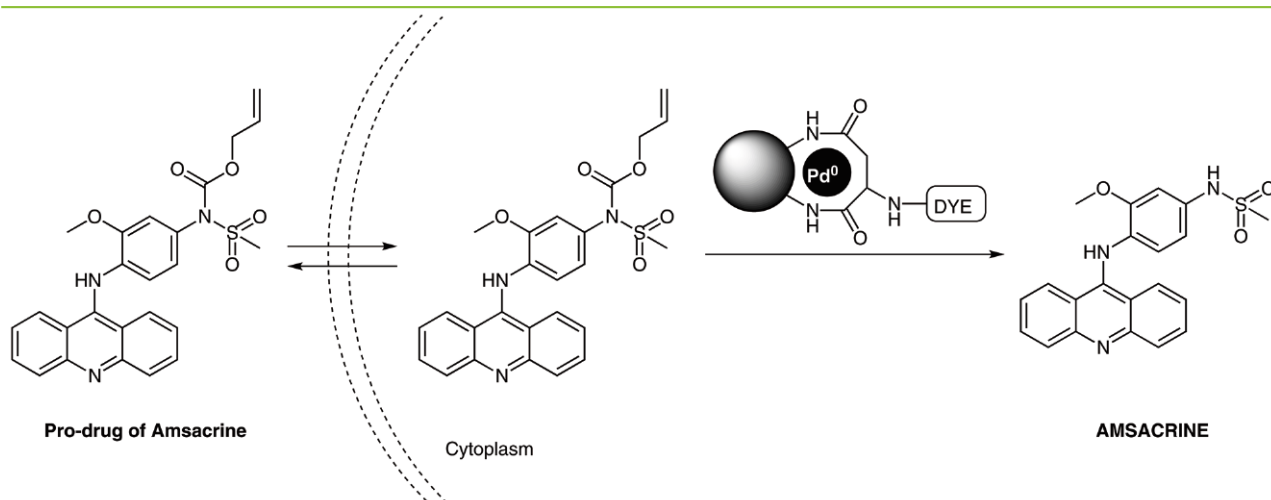
Nat. Chem. **2011**, *3*, 239–243

Exploiting cells as ‘living reactors’ to host and perform tailored intracellular organic reactions mediated by exogenous or even xenobiotic catalysts for the production of bioactive compounds, such as enzyme inhibitors and modulators of intracellular biochemical events, at first glance could seem fiction rather than science. Nonetheless, this striking technology, which could be dubbed ‘Intracellular Organic Synthesis’, is becoming reality thanks to the work of groups like that of Professor Mark Bradley from the University of Edinburgh (UK) which developed a technology allowing for the use of palladium catalysis to perform reactions which do not normally take place inside cells.

“Palladium is a metal that does not naturally occur in biological systems - in fact it is extremely toxic. By immobilization on our polymeric support we have succeeded in introducing this metal into cells without toxicity,” said Dr. Emma Johansson, a Swiss National Science Foundation Fellow in the Bradley group. Dr. Rosario Sanchez-Martin, another co-author of this paper who is now a lecturer at the University of Granada (Spain), explained that since the Bradley group developed the microsphere-mediated delivery technology, the inspiring idea of using this as the solid support for devising an intracellular heterogeneous catalyst has been the group’s biggest challenge so far.



Bradley's group has shown for the first time the catalytic use of Pd(0) inside cells to break and make bonds. Palladium nanoparticles trapped within polystyrene microspheres can enter cells and mediate a variety of Pd(0)-catalyzed reactions such as allylcarbamate cleavage and Suzuki-Miyaura cross-coupling.



Scope of the technology: Pd(0)-mediated in cellulo synthesis has potential for many applications such as the synthesis of inhibitors of cell function. Alloc protection of amsacrine led to a measurable reduction of the cytotoxic properties relative to free amsacrine. This fact was used to investigate whether amsacrine could be released in situ by the catalytic activity of cell-containing Pd(0) microspheres. Cells incubated with Alloc-protected amsacrine showed up to 7-fold reduction of cell viability in cultures pre-loaded with Pd(0) microspheres.

“We have shown that coupling reactions which are normally confined to a synthetic laboratory – where organic solvents and high temperatures are often used – can be performed in water at 37 °C using our immobilized catalyst. That these reactions can occur under physiological conditions is the reason we can now do this type of chemistry in cells and living organisms,” said Professor Bradley.

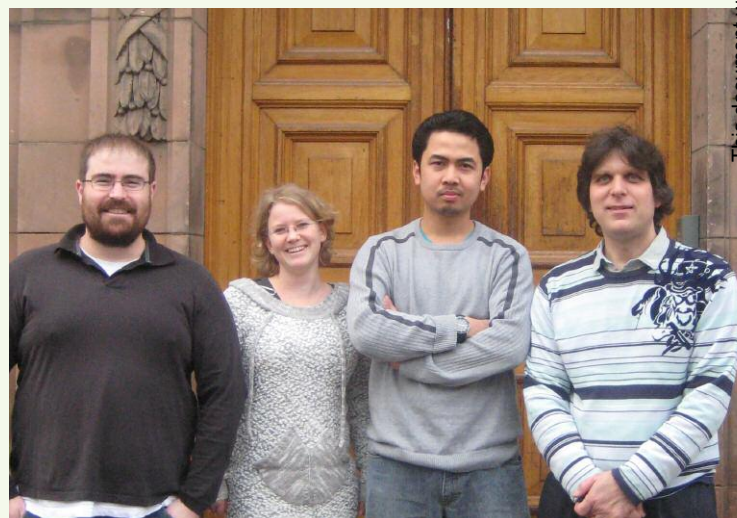
“By the introduction of Pd(0) microspheres directly at the site of a tumor it may be possible to synthesize a therapeutic (or chemotherapeutic) agent directly and exclusively at the site of a tumor, which could significantly reduce the toxic effects to the rest of the body,” said Professor Bradley.

The scope of this striking technology could well be extended to other metal catalysts and other types of reactions. “By judicious choice of the metal ion and the reactive groups used we can direct and control the synthesis or release of novel molecules directly and specifically inside cells. We are now investigating the use of metals other than palladium,” confirmed Dr. Johansson.

This revolutionary concept promises great developments in the area of science at the interface between organic chemistry and biology. “This technology has opened great opportunities in the area of intracellular catalysis. Although it is still in the early stages of development, we strongly believe that it will have a massive impact in addressing fundamental problems in cell biology such as biomolecular labeling. Furthermore, it can be applied in future drug development strategies and for other biomedical purposes,” said Rahimi Yusop, currently a final-year PhD student in the Bradley group.

“We consider this work as a proof of concept: from now on, palladium can be used to synthesize unnatural chemicals in living organisms,” concluded Dr. Asier Unciti-Broceta, another co-author of this work and currently an academic fellow in the Edinburgh Cancer Research Centre. “What’s next is up to researcher’s creativity, although we have a couple of things in mind, such as the use of palladium catalysts captured within implants for local activation of prodrugs.”

About the authors



From left: Dr. A. Unciti-Broceta, Dr. E. Johansson, R. Yusop, Prof. M. Bradley

Rahimi Yusop earned his BSc in Oleochemistry and MSc in Chemistry from the Universiti Kebangsaan Malaysia (UKM). His MSc at the Advanced Oleochemical Technology Division was sponsored by the Malaysian Palm Oil Board (MPOB). He is currently finishing his PhD under the supervision of Professor Mark Bradley at the School of Chemistry and is funded by the Malaysian government and the University of Edinburgh. His work focuses on palladium chemistry and its application in chemical biology, as well as designing and synthesizing small molecules for chemical probes and biological imaging.

Asier Unciti-Broceta received an MPharm in Pharmacy and an MSc in Organic and Medicinal Chemistry from the University of Granada (Spain) in 1999 and 2001, respectively, and performed his PhD in Medicinal Chemistry (same university), sponsored by the *Ramón Areces Foundation*, under the supervision of Professor Espinosa. In 2005 Asier moved to Edinburgh to work in Professor Mark Bradley's group at the School of Chemistry of the University of Edinburgh. Since then, he has developed his research activity at the interface of chemistry and biomedicine, with particular focus on cell delivery systems. In 2008 he was awarded a *Proof of Concept Award* (Scottish Enterprise) to lead the translation of a novel DNA delivery carrier into a commercial product, resulting in the creation of the spin-out company *Deliverics Ltd.* Since October 2010, Asier holds an academic fellowship in the Edinburgh Cancer Research Centre and now shares his time between academia and industry. Asier was recently awarded the *Nexus Young Life Scientist of 2010*.

Emma Johansson obtained her MSc in Chemistry at Gothenburg University (Sweden) in 2003 and her PhD at the University of Bern (Switzerland) in 2008. She joined Professor Mark Bradley's group in 2009, receiving a Swiss National Science Foundation Research Fellowship followed by a Novartis Foundation Research Fellowship. Her research within the group is focused on the efficient delivery of therapeutic molecules, materials and biomolecules into cells for the analysis of cellular function and for the development of novel therapeutic applications.

Mark Bradley's first academic position was as a Royal Society Research Fellow at the University of Southampton (UK, 1991–1999) where he was promoted to a Chair in Combinatorial Chemistry in 1997. In February 2005 he moved to the Uni-

versity of Edinburgh as Professor of High-Throughput Chemical Biology. Professor Bradley's research interests are focused on the application of the tools and techniques of chemistry to address biological problems and needs, typically with a high-throughput twist. This has led to the commercialization of a number of technologies through licensing and spin-outs. Three themes dominate at this time: the development of non-DNA-based microarray platforms for cell- and enzymatic-based assays, the development of chemistry that enables efficient cellular delivery of proteins, nucleic acids, sensors and small molecules, and direct translational research with clinicians in a number of areas. Professor Bradley's group has published widely in the combinatorial and chemical biology arena with over 220 articles, in the form of peer-reviewed papers, reviews and book chapters.



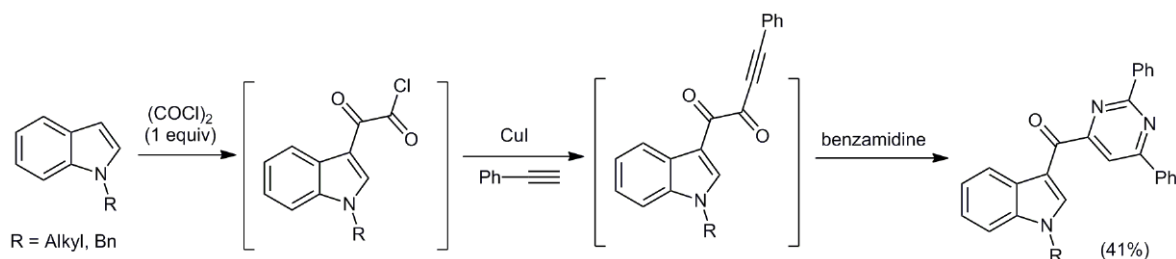
Dr. R. M. Sanchez-Martin

Rosario M. Sanchez-Martin's background is in medicinal chemistry and for the past nine years she has been working in the area of delivery systems. She graduated in Pharmacy in 1997 from the University of Granada (Spain). Afterwards she obtained a Master Degree in Pharmacy with Honors and started her PhD in Professor Espinosa's group in the Department of Medicinal Chemistry at the University of Granada where

she worked on the design, synthesis and evaluation of novel inhibitors of the Ras/choline kinase pathway, as potential anti-cancer drugs. In 2002, after completing her PhD at the University of Granada with Distinction Cum Laude, she took on a position as a post-doctoral researcher in Professor Bradley's group where she was involved in the synthesis and evaluation of microspheres and other devices (peptoids, dendrimers and cationic lipids) as carrier systems. Following from this, Dr. Sanchez-Martin was awarded a Royal Society Dorothy Hodgkin Fellowship (2006) to build up her independent research at the School of Chemistry in the University of Edinburgh. Recently she has moved back to the University of Granada where she has taken a Lecturer position in Medicinal Chemistry.

Three-Component Synthesis of Ynediones by a Glyoxylation/Stephens–Castro Coupling Sequence

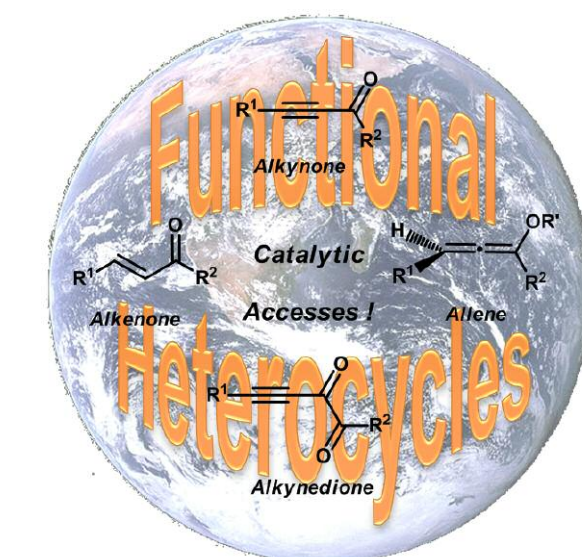
Angew. Chem. Int. Ed. **2011**, *50*, 2966–2969



An example of the novel synthetic methodology applied to the synthesis of an indolyl pyrimidine

Highly functionalized heterocycles occupy a central position in modern organic chemistry, owing to their versatility and use for a number of applications, spanning from drug discovery to materials science to biomedicine and imaging. Their synthesis is not always straightforward and the search for novel synthetic methodologies to prepare them in an efficient and selective manner continue to be a priority for synthetic organic chemists. Recently, the group of Professor Thomas J. J. Müller from the Heinrich-Heine-Universität Düsseldorf (Germany) have identified and developed a new synthesis of highly functionalized indoles based on a novel three-component strategy.

“Our primary topic of interest is the advancement of heterocycle syntheses based upon multi-component reactions initiated by transition-metal catalysis,” said Professor Müller. “Over the years, we have developed a reactivity-based concept where key intermediates of heterocyclic and synthetic chemistry become accessible under mild conditions, eventually in a catalytic fashion.” According to Professor Müller, three-carbon building blocks, such as alkynones, alkenones or allenyl ethers are indeed accessible by virtue of Sonogashira coupling (for the most recent review, see: T. J. J. Müller *Top. Heterocycl. Chem.* **2010**, *25*, 25–94). “In turn, the reaction conditions are so mild that many subsequent organic elementary steps can be literally concatenated to consecutive one-pot syntheses and domino reactions,” he continued. “It is not necessary to emphasize the relevance of heterocycle synthesis in modern medicinal chemistry or materials science; nevertheless, we always use our newly developed methodological tools to sharpen them in illustrative syntheses of hetero- and carbo-



cyclic frameworks with peculiar biological or photonic functionality.”

Inspired by the catalytic access to alkynones via catalytic carbonylative alkylation (*Angew. Chem. Int. Ed.* **2005**, *44*, 6951), Professor Müller and his co-workers considered that oxalyl chloride is an interesting electrophilic surrogate for the introduction of carbonyl groups onto π -nucleophiles. “Indeed,” confirmed Professor Müller, “the glyoxylation of indoles, pyrroles, furans and many electron-rich π -systems paved the way to the glyoxylchloride derivatives, which were

subsequently transformed in the palladium-catalyzed coupling by concomitant loss of one carbonyl group: the glyoxylation–decarbonylative coupling was born and Eugen Merkul was the first to foster this unique chemistry and to rock the cradle of this reactivity-based one-pot concept (*Chem. Eur. J.* **2009**, *15*, 5006). Soon thereafter,” continued Professor Müller, “we reasoned that the bi-catalytic Sonogashira catalyst system could potentially spring a surprise upon stepping back by omitting the palladium catalyst. One step back leaves two carbonyl groups in. The topic of this communication was unraveled and rewarded us with a straightforward access to an unexplored, very densely functionalized multi-electrophile, i.e. the ynedione scaffold (*Angew. Chem. Int. Ed.* **2011**, *50*, 2966).”

Professor Müller explained that the project was launched by Eugen Merkul during his doctoral thesis. He discovered that omitting the palladium catalyst led to maintenance of both carbonyl groups by virtue of the catalytic Castro alkynylation. During his bachelor thesis, Janis Dohe, together with Eugen, elaborated the methodology to ynediones with several heterocyclic substrates for the glyoxylation step. Finally, Charlotte Gers and Eugen expanded the methodological scope of the sequence within Charlotte’s master’s thesis and illustrated the synthetic utility by several one-pot four-component syntheses of heterocycles. Finally, Frank Rominger was in charge of X-ray crystal structure analyses, which were solved at the University of Heidelberg (Germany).

This new synthetic strategy holds promise of finding important applications in the field of applied organic chemistry. ■

Matteo Zanda

About the authors



From left: E. Merkul, J. Dohe, C. Gers, Prof. Thomas J. J. Müller (Dr. F. Rominger was not present for this photograph)

Mild Decarboxylative Activation of Malonic Acid Derivatives by 1,1'-Carbonyldiimidazole

Org. Lett. **2011**, *13*, 2322–2325

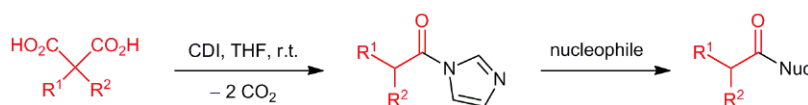
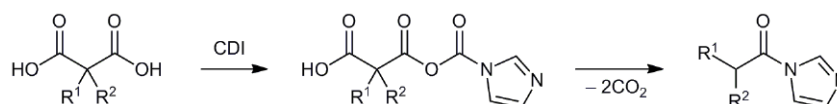
Malonic acid derivatives are extraordinarily versatile building blocks in organic synthesis. Among their most attractive features is the possibility to readily homologate the α -carbon by removal of the acidic proton and subsequently react with an electrophile. When this is combined with a decarboxylation reaction, the methodology becomes a powerful strategy to synthesize α -substituted carboxylic acids. Unfortunately, the decarboxylation reaction can be problematic and often requires high temperatures and harsh conditions, thus precluding its use with sophisticated or labile substrates. Recently, the research group led by Dr. Danny Lafrance from the Development Science and Technology of Pfizer Inc. (Groton, Connecticut, USA) has identified a new methodology allowing for the use of much milder conditions for the decarboxylation of malonic acid derivatives.

The mechanism of this decarboxylation reaction relies on the activation of the malonate by an acyl imidazole fragment originated by treatment with *N,N*-carbonyldiimidazole (CDI).

This fragment can be further exploited as an activated carboxy group which readily undergoes one-pot coupling reactions with amines and other nucleophiles producing a range of derivatives, including amides, hydroxylamines and esters, generally in high yields.

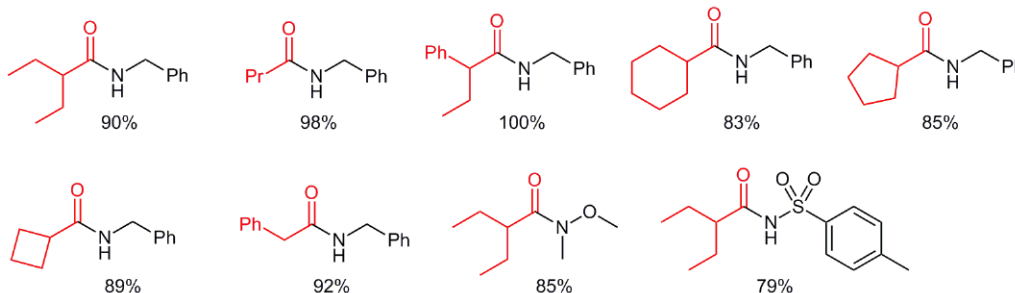
“The major point of interest regarding this process lies in the unprecedented mild conditions required to induce decarboxylation of a malonic acid derivative,” said Dr. Lafrance. “It certainly came as a surprise to us when we first realized that the only product formed upon adding simple CDI to a malonic acid solution was the clean acyl imidazole in quantitative yield and within five minutes at room temperature. It is exciting to realize that there are still very simple and useful chemical transformations to be discovered and developed,” he continued.

According to Dr. Lafrance, one can envision several applications for this reaction, beyond the obvious replacement of the traditional thermal decarboxylation when applicable. “The



$R^1, R^2 = \text{H, Alkyl, Aryl}$

Some representative products:



very mild and neutral conditions, high yield and selective character of this transformation may be appealing for academics working in the field of total synthesis,” he confirmed. “We are currently looking into the possibility of extrapolating this technology to enantioselective decarboxylative protonations, given the mild conditions under which an enolate is generated and trapped by an acidic proton. As a process chemist, it is also worth mentioning the green chemistry aspect of this finding, considering that it could potentially be employed at scale to induce decarboxylation without the need to heat a large reaction vessel for an extended period of time,” he concluded. ■

Matteo Zanda

About the author



D. Lafrance

Danny Lafrance was born in 1974 in Trois-Rivieres (Canada). He received a B.Sc. degree in chemistry in 1996 from Laval University (Canada) and then completed an M.Sc. degree at McGill University (Canada) under the supervision of Professor Bruce A. Arndtsen, working on the insertion of imines and carbon monoxide into manganese–alkyl bonds. He then left to join the process chemistry group of Schering-Plough (New Jersey, USA), where he learned the basics of scale-up chemistry. Since then he has occupied various positions in the field of process chemistry and scale-up development and, since 2006, he is working in the chemical development group of Pfizer in Groton, CT (USA).

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2011/07 is available from June 17, 2011

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Catalytic Asymmetric Chloroamination Reaction of α,β -Unsaturated γ -Keto Esters

(Focus on an article from the current literature)

■ Cleavage of Carbon–Carbon Bonds through the Mild Release of Trifluoroacetate

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Special Issue on “Organocatalysis” in issue 12/2011

SYNLETT

Account on: Synthesis of Highly Substituted Indoles via Diels–Alder/Plieninger Indolization Sequence: Applications in Total Synthesis

(by M. A. Kerr)

SYNFACTS

Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”:
[Synthesis of the Biaryl Core of Anacetrapib](#)

CONTACT + + + +

Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,
Via Mancinelli, 7, 20131 Milano, Italy,
e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Synform@chem.polimi.it
Fax: +39 02 23993080

Editorial Office

- Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
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stefanie.baumann@thieme.de, phone: +49 711 8931 776
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- Production Assistant: Thorsten Schön,
thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller,
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- Marketing: Julia Stötzner,
julia.stoetznern@thieme.de, phone: +49 711 8931 771
- Postal Address: SYNTHESIS/SYNLETT/SYNEFACTS, Editorial Office,
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