SYNFORM: People, Trends and Views in Synthetic Organic Chemistry

2010/04

SYNSTORIES

- Catalytic Alkylation of Methyl N-Heteroaromatics with Alcohols
- Novel Highly Efficient Cu(I)-Catalyzed Synthesis of N-Heterocycles

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like:
marketing@thieme-chemistry.com
Dear readers,

This issue of SYNFORM is thinner than usual because its journalistic nature and monthly frequency is not always in line with the busy agenda of the protagonists, namely the scientists who contribute with their time and material to the production of SYNFORM. However, quality and quantity are very different measures and this quantitatively light issue, very much focused on nitrogen heterocycles, can count on two high-quality pieces of organic chemistry. The first one reports on a novel catalytic homologation of a methyl substituent of azines (pyridine, pyrimidine, etc.) developed by Professor R. Kempe (Germany). The second SYNSTORY is all about a copper(I)-catalyzed synthesis of five-, six- and seven-membered N-heterocycles starting from alkynes. Quality is already here, for more quantity let’s wait for the next issue...

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
Alcohols are not among the most versatile compounds in organic synthesis. Indeed, they have a rather limited reactivity, but it is possible to temporarily convert alcohols into the corresponding carbonyl compounds, which are more amenable to different synthetic transformations, through a metal-catalyzed removal of hydrogen. This technique is known as “borrowing hydrogen” methodology (as proposed by J. M. J. Williams: Adv. Synth. Catal. 2007, 349, 1555) or “hydrogen autotransfer” reaction (as named by M. Yus: Angew. Chem. Int. Ed. 2007, 46, 2358). Recently, the group of Professor Rhett Kempe from the University of Bayreuth (Germany) has reported a novel reaction based on this technique. This methodology allows for the homologation of a methyl substituent of different azines (pyridine, pyrimidine, etc.) exploiting primary alcohols (mainly substituted benzylic alcohols), which are probably converted into transient reactive aldehydes by means of an iridium catalyst, as alkylation agents. The reaction produces a rather wide range of homologated alkyl azines in generally good yields with a turnover number (TON) of up to ca. 50 with 2-amino-4-methylpyrimidines, whereas lower TONs were observed with other substrates. Concerning the efficiency aspect, Professor Kempe said “We need more active catalysts to be able to efficiently homologate methyl groups of whatever N-heterocycles are out there.” Professor Kempe acknowledged the great contributions given by the paper’s co-author, Dr. Benoit Blank: “Dr. Blank is a highly talented student who graduated recently and decided to work with BASF. He performed all of the experimental work.” According to Professor Kempe, the “borrowing hydrogen” or “hydrogen autotransfer” methodology is of great potential not just in...
C–N but also in catalytic C–C coupling chemistry. “Let's just imagine the large variety of bond formations that aldehydes can undergo,” concluded Professor Kempe. This reaction certainly expands the arsenal of useful methods available to organic chemists.
Quick and efficient access to diversified classes of biologically active lead compounds is an essential part of drug discovery. In the search for bioactivity, heterocycles of different ring sizes, with different substitution patterns, constitute extremely important structure classes (e.g., alkaloids). Recently, the group led by Professors Gerald B. Hammond and Bo Xu from the University of Louisville (Kentucky, USA) reported a novel methodology which represents a useful addition to the arsenal of synthetic tools available to organic and medicinal chemists. The method makes use of a starting amino-alkyne which undergoes a tandem Cu(I)-catalyzed intramolecular hydroamination/intermolecular alkynylation reaction with a terminal alkyne, affording an array of five-, six- and seven-membered 2-alkynyl N-heterocycles in excellent yields.

“The need to map new chemical spaces through cascade reactions in an atom-economical fashion inspired us to develop an efficient and environmentally friendly method to access biologically important N-heterocycles containing five-, six-, or seven-membered rings with various substitution patterns,” said Professor Hammond.

According to Professor Xu, addition of a nucleophile to an alkyne using late transition metal catalysts like gold or palladium is a well-known process. “But a tandem addition of two different nucleophiles to an alkyne is not a common strategy,” he said. “In our approach, we envisioned an intramolecular secondary amine attack on an electrophilically activated alkyne, with the resulting activated cyclic enamine intermediate then becoming a new electrophilic precursor capable of reacting with a second nucleophile – such as a terminal alkyne – to give a new addition product.” Professor Hammond and his associate, Professor Xu, explained that this essentially corresponds to a double addition to a triple bond. “The virtue of this transformation is that it sets up the stage for further transformations (e.g., cycloisomerization) that will furnish even more diverse N-heterocyclic products.” They call this strategy a ‘cyclization-triggered addition’. “Our method has some clear advantages over the literature methods: i) it is highly efficient (close to quantitative yields); ii) it uses cheap and environmentally friendly copper(I) bromide catalyst; iii) N-heterocycles containing either five-, six-, or seven-membered rings can be accessed in a one-pot procedure, using one single method for all cases; iv) it has a broader scope (unactivated alkynes – both terminal and non-terminal alkynes – can be used); and v) there is no need to protect the amine,” concluded Professor Hammond.

Matteo Zanda

J. Han  Prof. B. Xu  Prof. G. B. Hammond
COMING SOON

SYNFORM 2010/05
is available from April 20, 2010

In the next issues:

SYNSTORIES

- Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes (Focus on an article from the current literature)
- Direct Conversion of Arylamines to Pinacol Boronates (Focus on an article from the current literature)
- Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Transition-Metal-Catalyzed Oxidative Heck Reactions (by B. Karimi)

SYNLETT
Account on: Deracemisation of Secondary Alcohols via Biocatalytic Stereoinversion (by W. Krouitl)

SYNFACTS
Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Synthesis of (E)- and (Z)-Tamoxifen

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 71 393 786
Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
Assistant Scientific Editor: Steffanie Baumann, steffanie.baumann@thieme.de, phone: +49 711 8931 776
Assistant Scientific Editor: Christiane Kemper, christiane.kemper@thieme.de, phone: +49 711 8931 778
Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
Production Editor: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
Production Assistant: Theodora Scholz, theodora.scholz@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sahine Heller, sahine.heller@thieme.de, phone: +49 711 8931 744
Marketing: Thomas Krämer, thomas.kraemer@thieme.de, phone: +49 711 8931 772
Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2010 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACS.

Publication Policy
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. In those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNFACS
The Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA. To order: customerservices@thieme.com or use the Web site facilities at www.thieme.com. Phone: +1 212 760 0888
Order toll-free within the USA: +1 800 782 3488
Fax: +1 212 947 1112
Airfreight and mailing in the USA by Publications Expediters Inc., 200 Meacham Ave., Elm nt NY 11003. Periodicals postage paid at Jamaica NY 11431.
Europe, Africa, Asia, and Australia: Thieme Publishers, Rüdigerstraße 14, 70469 Stuttgart, Germany. To order: customerservices@thieme.de or use the Web site facilities at www.thieme.com.
For further inquiries please contact Mrs. Birgild Härter:
Phone: +49 711 8931 421; Fax: +49 711 8931 410
Current list prices are available through www.thieme-chemistry.com.

Online Access via Thieme-connect
The online versions of SYNFORM as well SYNTHESIS, SYNFACS and SYNFACS are available through Thieme-connect (www.thieme-connect.com/ejournals) where you may also register for free trial accounts.
For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices.
The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: products@thieme.de, phone: +49 711 8931 407

Manuscript Submission to SYNTHESIS and SYNLETT
Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com. Use of the Word template helps to speed up the refereeing and production process.

Copyright
This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher’s consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart - New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.

products@thieme.de, phone: +49 711 8931 407