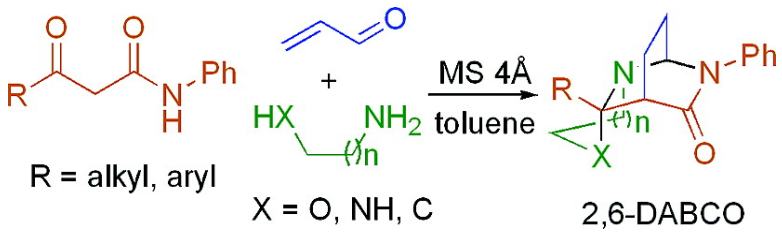
Communication

Multicomponent Domino Reaction from β-Ketoamides: Highly Efficient Access to Original Polyfunctionalized 2,6-Diazabicyclo[2.2.2]octane Cores

Frdric Liby-Muller, Thierry Constantieux, and Jean Rodriguez

J. Am. Chem. Soc., **2005**, 127 (49), 17176-17177• DOI: 10.1021/ja055885z • Publication Date (Web): 17 November 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/17/2005

Multicomponent Domino Reaction from β-Ketoamides: Highly Efficient Access to Original Polyfunctionalized 2,6-Diazabicyclo[2.2.2]octane Cores

Frédéric Liéby-Muller, Thierry Constantieux,* and Jean Rodriguez*

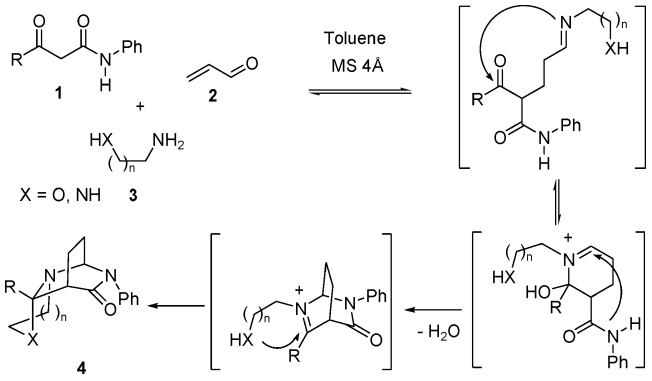
Université Paul Cézanne (Aix-Marseille III), CNRS UMR 6178, SYMBIO, Faculté des Sciences et Techniques Case D12-13397 Marseille Cedex 20, France

Received August 26, 2005; E-mail: jean.rodriguez@univ.u-3mrs.fr

Creation of molecular complexity and diversity[1] from simple substrates, while combining economic aspects[2,3] with environmental ones,[4] constitutes a great challenge in modern organic chemistry, both from academic and industrial points of view.[5] Multicomponent reactions[6] (MCRs) involving domino processes[7] have emerged as powerful tools to reach this near ideal goal.[8] Looking for novel lead structures of pharmaceutical, catalytic, or even academic interests, we are involved in the development of new MCRs from 1,3-dicarbonyl compounds.[9] In this context, we recently reported a molecular sieves promoted one-pot synthesis of polycyclic *N*,*O*-, *N*,*S*-, and *N*,*N*-aminals from 1,3-dicarbonyls, α,β-unsaturated aldehydes, and nucleophilic heterofunctionalized amines.[10] This Michael addition initiated sequence evolves through an intramolecular trapping of an in situ formed ene−iminium intermediate.

Although a large variety of 1,3-dicarbonyl compounds, such as 1,3-diketones or β-ketoesters, have been involved in MCRs, quite surprisingly, utilization of β-ketoamides bearing both electrophilic and nucleophilic centers has not stimulated much interest so far.[11] In this communication, we report a conceptually novel multicomponent domino reaction from simple β-ketoamides, which are involved not only as substrates but also as nucleophilic partners, leading to original scaffolds having a highly functionalized 2,6-diazabicyclo[2.2.2]octane skeleton (2,6-DABCO)[12] (Scheme 1). The key steps of the present one-pot process are the successive formation of two iminium intermediates, trapped in situ by two different nucleophiles, one being substrate **1** itself and the other one resulting from the heterofunctionalization of amine **3**.

Scheme 1. Three-Component Synthesis of 2,6-DABCO Skeletons **4**



The scope of this novel MCR was examined using various easily available starting materials under standard conditions (Figure 1). A range of valuable new elaborated polycyclic structures were synthesized in good to excellent yields by simply heating a toluene solution of β-ketoamides **1**, acrolein **2**, and functionalized amines **3**.[13] The reaction was conducted in the presence of 4 Å molecular

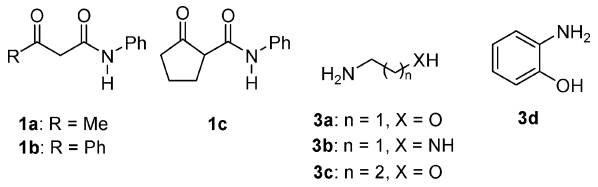


Figure 1. Starting materials for the three-component reaction.

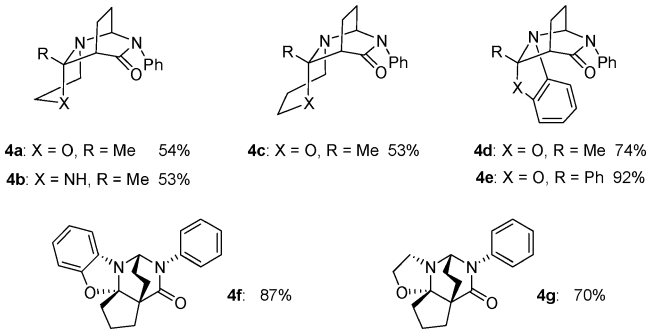


Figure 2. 2,6-DABCO scaffolds from the MCR.

sieves, acting both as dehydrating agent and as heterogeneous catalyst of the initial Michael addition, as shown before.[10,14]

These neutral heterogeneous conditions proved to be of general applicability, and products **4** were obtained by simple filtration through a short pad of Celite, with generally very high chemical purity (Figure 2).

All of the products have a highly functionalized and original 2,6-DABCO core, bearing two chemically differentiable nitrogen atoms which may confer interesting synthetic potentialities. For example, the use of acyclic β-ketoamide **1a** in combination with amines **3a**−**c** led to the formation of tricyclic lactams **4a**−**c**, while aromatic amine **3d** gave the expected tetracyclic compounds **4d** and **4e** from β-ketoamides **1a** and **1b**, respectively. Alternatively, cyclic β-ketoamide **1c** also afforded a one-pot access to spiro-type polycyclic lactams **4f** and **4g** in good yields. In all cases, the formation of a single product illustrates the remarkable chemo-, regio-, and diastereoselectivity of the sequence resulting in a wide increase in complexity starting from very simple and easily accessible achiral substrates. The structural elucidation and the attribution of the relative stereochemistry rest upon NMR analysis and was unequivocally confirmed by X-ray diffraction of single crystals obtained by slow evaporation of the solvent in the case of 2,6-DABCO **4d** (Figure 3).[15]

To further demonstrate the generality of this methodology, we projected to create a new C−C bond in the last step of the sequence via a Pictet−Spengler-type intramolecular cyclization[17] involving 1-(2-aminoethyl)pyrrole **3e**[18] (Scheme 2). Under the same experimental conditions, the expected tetracyclic 2,6-DABCO derivative **4h**, having a biologically relevant fused pyrrolopiperazine nucleus,[19,20]

10.1021/ja055885z CCC: $30.25

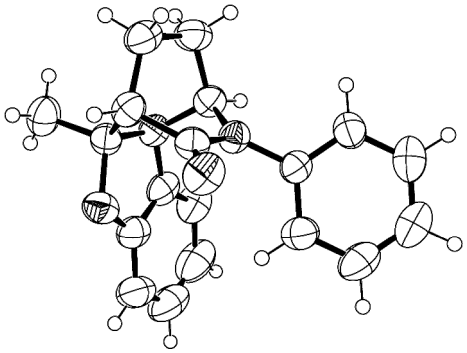
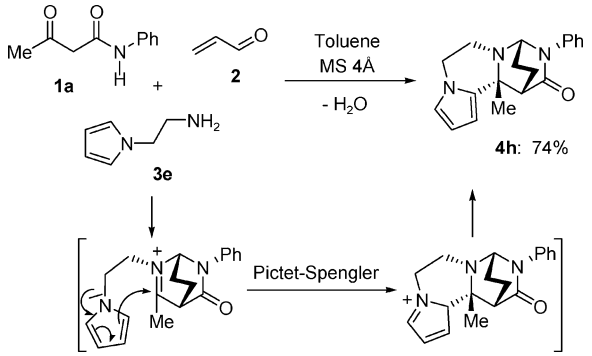


Figure 3. ORTEP diagram of lactam **4d**.[16]

Scheme 2. Carbon−Nucleophilic Functionalized Amine in the MCR



was isolated as one single diastereomer, in good yield and with high chemical purity.

In all cases, the totally diastereoselective obtention of a single product is observed with concomitant formation of up to three new cycles, five different bonds including two C−C ones, and up to five stereogenic centers, two of them being chemically differentiable nitrogen atoms. Moreover, the one-pot sequence is step- and atom-economic and also ecologically benign since water is the only byproduct, easily trapped by molecular sieves.

In conclusion, this novel multicomponent domino reaction, based on the reactivity of two different iminium intermediates, constitutes a good illustration of the potentialities of β-ketoamides in MCRs. The sequence generates molecules with a high level of complexity from simple achiral and readily accessible substrates. The operational simplicity and good chemical yields, combined with step- and atom-economic aspects, make this new heterocycle synthetic strategy highly attractive and promising for the development of original DABCO compounds of potential synthetic and biologic interests.

Acknowledgment. This paper is dedicated to Dr. Jean-Pierre Dulcère on the occasion of his 60th birthday. This research was supported by a grant from the CNRS and the Conseil Régional PACA. Thanks are expressed to Dr. Hugues Bienaymé (Pierre Fabre Urologie) for his support and fruitful discussions. Pr. Jean-Marc Pons (careful proof reading), Dr. Michel Giorgi (X-ray analysis), and Dr. Robert Faure (NMR spectra interpretations) are also gratefully acknowledged.

Supporting Information Available: Complete experimental procedures and characterizations. This material is available free of charge via the Internet: http://pubs.acs.org.

References

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(2) Step-economy: (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem*. **2002**, *74*, 25. (b) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. *Pure Appl. Chem*. **2003**, *75*, 143. (c) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Craske, M. L.; Horan, J. C.; Meyer, T. *Curr. Drug Discovery Technol*. **2004**, *1*, 1. (d) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc*. **2005**, *127*, 2836.
(3) Atom-economy: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed*. **1995**, *34*, 258. (c) Trost, B. M. *Acc. Chem. Res*. **2002**, *35*, 695.
(4) For a special issue in environmental chemistry, see: *Chem. Rev*. **1995**, *95*, 3.
(5) Weber, L.; Illgen, M.; Almstetter, M. *Synlett* **1999**, 366.
(6) (a) For a recent monograph, see: *Multicomponent Reactions*, Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. For some recent reviews of MCRs, see: (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J*. **2000**, *6*, 3321. (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed*. **2000**, *39*, 3168. (d) Zhu, J. *Eur. J. Org. Chem*. **2003**, 1133. (e) Orru, R. V.; de Greef, M. *Synthesis* **2003**, 1471. (f) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed*. **2005**, *44*, 1602.
(7) For representative reviews, see: (a) Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115. (b) Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol*. **1998**, *2*, 363. (c) Rodriguez, J. *Synlett* **1999**, 505.
(8) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind*. **1997**, 765.
(9) (a) For a recent review on the utilization of 1,3-dicarbonyl derivatives in MCRs, see: Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem*. **2004**, 4957. See also: (b) Habib-Zahmani, H.; Hacini, S.; Charonnet, E.; Rodriguez, J. *Synlett* **2002**, 1827. (c) Simon, C.; Liéby-Muller, F.; Peyronel, J. F.; Constantieux, T.; Rodriguez, J. *Synlett* **2003**, 2301.
(10) Simon, C.; Peyronel, J. F.; Rodriguez, J. *Org. Lett*. **2001**, *3*, 2145.
(11) For a recent contribution from our group in this field, see ref 9b.
(12) (a) Zhalubovskis, R. A.; Kalme, Z. A.; Duburs, G. Y. *Chem. Heterocycl. Compd*. **1998**, *34*, 503. (b) For utilization of 1,4-diazabicyclo[2.2.2]octane in the Baylis−Hillman reaction, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev*. **2003**, *103*, 811.
(13) At the moment, only *N*-aryl amides and β-unsubstituted acroleins give reproducible results.
(14) Simon, C.; Peyronel, J.-F.; Clerc, F.; Rodriguez, J. *Eur. J. Org. Chem*. **2002**, 3359.
(15) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 279010. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223−336−033; e-mail: deposit@ccdc.cam.ac.uk).
(16) Two rotamers, which differ by the position of the phenyl group on the nitrogen of the amide part, were present in the same crystalline unit. To clarify the figure, only one rotamer is drawn.
(17) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges*. **1911**, *44*, 2030. (b) For a review, see: Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797.
(18) Jirkovsky, I.; Baudy, R. *Synthesis* **1981**, 481.
(19) Compounds with a related structure are found in some families of natural occurring marine alkaloids. For a recent review, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. See also: (b) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc*. **2003**, *125*, 6344. (c) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett*. **2004**, *6*, 3881. (d) Davis, F. A.; Deng, J. *Org. Lett*. **2005**, *7*, 621.
(20) Synthetic pyrazine nuclei are known to present a large spectrum of biological activities, such as antiamnesic, antihypoxic, psychotropic, antihypersensitive, or aldose reductase inhibitor properties.

JA055885Z