Pure Appl. Chem., Vol. 77, No. 1, pp. 155–161, 2005.
DOI: 10.1351/pac200577010155

Creating chemical diversity space by scaffold decoration of dihydropyrimidines*

Doris Dallinger and C. Oliver Kappe‡

Institute of Chemistry, Karl-Franzens-University Graz, Austria

Abstract: The demand for diverse compound libraries for screening in drug discovery and materials science is the driving force behind the development of new technologies for rapid parallel and combinatorial synthesis. The focus of this article will be on the scaffold decoration of biologically active dihydropyrimidines (DHPMs) of the Biginelli type, exploring the diversity on all six positions around the scaffold. This opens up the generation of a very large number of analogs given the commercial availability of the building blocks that are used in the functionalization process.

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. In an ideal case, the individual building blocks are commercially available or are easily synthesized, and cover a broad range of structural variations. MCRs are providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of "drug-like" molecules for biological screening, since the combination of three or more small-molecular-weight building blocks in a single operation leads to high combinatorial efficacy in creating diversity. Over the last decade, industrial and academic researchers have made such powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial and parallel synthesis [1].

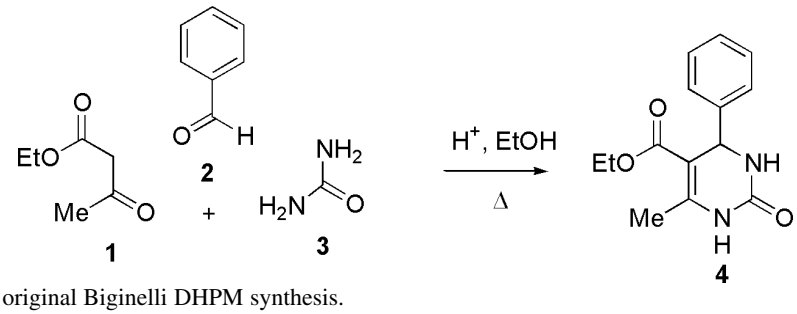
One prominent MCR that produces an interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidine (DHPMs) synthesis. In 1893, P. Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and urea (**3**) [2]. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified as 3,4-dihydropyrimidin-2(1*H*)-one **4** (Scheme 1), and this reaction is nowadays referred to as "Biginelli reaction", "Biginelli condensation", or as "Biginelli DHPM synthesis" [3–6].

While the early examples of this cyclocondensation process typically involved a β-ketoester, aromatic aldehyde, and urea, the scope of this heterocycle synthesis has now been extended considerably

*Paper based on a presentation at the 24th International Symposium on the Chemistry of Natural Products and the 4th International Congress on Biodiversity, held jointly in Delhi, India, 26–31 January 2004. Other presentations are published in this issue, pp. 1–344.

‡Corresponding author E-mail: oliver.kappe@uni-graz.at

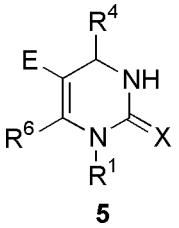
by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives [6]. For this particular heterocyclic scaffold, the acronym DHPM has been adopted in the literature and is also used throughout this review. Owing to the importance of MCRs in combinatorial chemistry, there has been a renewed interest in the Biginelli reaction, and the number of publications and patents describing the synthesis of novel DHPM analogs is constantly growing. In the present review article, we focus on synthetic methods published up to the year 2000 that are suitable for the decoration of DHPM libraries in a high-throughput or combinatorial format.



Scheme 1 The original Biginelli DHPM synthesis.

SCAFFOLD SYNTHESIS

Many methods are nowadays available for synthesizing libraries of DHPMs of the Biginelli type. Those include standard solution-phase methods, the use of polymer-supported catalysts, and the use of polymer supports where one of the three building blocks is anchored to a solid-phase resin, a fluorous-phase tag, or a soluble polymer, i.e., a dendrimer [6]. Given the diversity in building block selection that is tolerated in the Biginelli reaction, it is evident that a large number of DHPM derivatives of the general formula **5** can be synthesized by combination of a relatively small number of (commercially available or proprietary) individual building blocks. Employing 20 aldehydes (point of diversity R^4), 10 CH-acidic carbonyl derivatives (points of diversity E and R^6), and 5 (thio)urea analogs (points of diversity X and R^1) in a Biginelli-type condensation would lead to a library of 1000 DHPM compounds, with a total of five diversity points around the DHPM core. It is, therefore, not surprising that a literature search for the general DHPM structure **5** (chart) in the Chemical Abstracts Registry database led to well over 10 000 hits. It is interesting to note, however, that only a small fraction of these compounds has been published in the chemical literature (<1000) [7]. On the other hand, more than half the 10 000 structures of type **5** are commercially available, typically from companies specializing in chemical library generation. Since the preparation of combinatorial libraries has been reviewed recently [6], no further details will be provided herein.



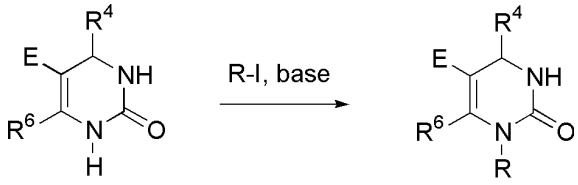
R^1 = H, alkyl
R^4 = H, alkyl, (het)aryl, carbohydrate
R^6 = H, alkyl, aryl
E = ester, acyl, amide, nitro, nitrile, phosphono
X = O, S, NR

SCAFFOLD DECORATION

Notwithstanding the larger number of DHPM derivatives that can be prepared in a one-pot Biginelli MCR, it is clear that a much larger number of very interesting heterocycles having the DHPM scaffold can be obtained by chemical functionalization of the six diversity points around the DHPM core. In the following sections, each individual position around the heterocyclic ring is addressed.

The N1 position

DHPMs **5** possess a rather acidic N1-H due to the presence of an enamide moiety (O=C–C=C–NH). Therefore, the N1 proton is removed first on treatment with base. Thus, DHPMs **5** are alkylated regiospecifically at N1 when treated with alkyl halides in the presence of a suitable base (Scheme 2) [8]. Similarly, trimethyl phosphate has been employed to methylate Biginelli compounds at N1 where the N3 position is protected by an acetyl group [9]. Under more drastic conditions (e.g., dimethyl sulfate/NaH) N1-alkylated derivatives **5** can be further alkylated at N3 to yield dialkyl derivatives **6** [10].

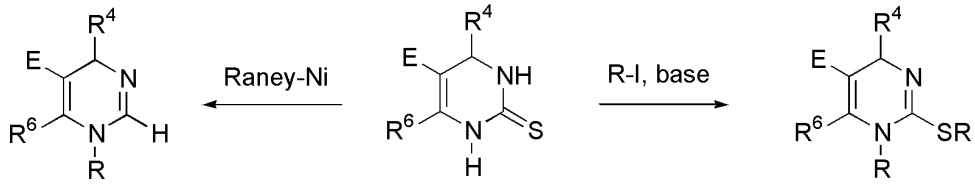


5 **6**

Scheme 2 Alkylation of DHPMs at N1.

The C2 position

Little or no chemistry has been published on functionalizing the C2 position at the Biginelli DHPMs for the cyclic urea case (DHPM **5**, X = O). However, for cyclic thioureas of type **7** easy derivatization is possible by, e.g., S-alkylation with alkyl halides in the presence of base. Many examples of this alkylation procedure, providing 2-alkylthio-1,4-dihydropyrimidines of type **8** in very high yields have been reported (Scheme 3) [9,11]. On the other hand, 2-unsubstituted 1,4-dihydropyrimidines of type **9** are usually obtained by reductive desulfurization of DHPMs **7** with Raney-Ni [11].



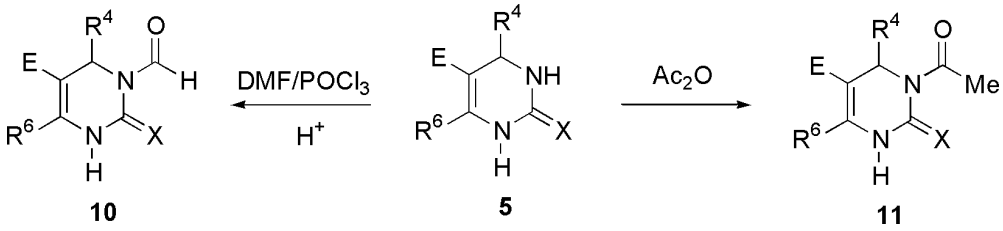
9 **7** **8**

Scheme 3 S-Alkylation and desulfurization of dihydropyrimidine-2-thiones.

Acylations at N3

The regioselective N3-acylation of DHPMs is of the utmost importance for the synthesis of aza-analogs of nifedipine-related dihydropyridines and therefore has attracted much attention in recent years [3]. The formylation of DHPMs **5** by DMF/$POCl_3$ furnishes the corresponding N3-formylated derivatives **10** with complete regioselectivity (Scheme 4) [9]. Similarly, only N3-acylated products (**11**) are formed in the reaction of DHPM **5** with acid anhydrides or acid chlorides [9]. In cases where the N1 position

is protected, e.g., by an alkyl group, acetylation naturally occurs at N3. In contrast to the acetylation reactions described above, the alkoxycarbonylation of Biginelli compounds with, e.g., ethyl chloroformate and base, is more troublesome leading to mixtures of N1 and N3 derivatized products depending on the substitution pattern around the DHPM ring [12].



Scheme 4 N3-Formylation and N3-acetylation of DHPMs **5**.

Modification of the C4 position

Out of the three building blocks in the Biginelli reaction, it is the aldehyde component, which can be varied to the largest extent (Fig. 1). In general, the reaction works best with aromatic aldehydes. These can be substituted in the *o*-, *m*-, or *p*-position with either electron-withdrawing or -donating groups. Good yields are usually obtained with *m*- or *p*-substituted aromatic aldehydes carrying electron-withdrawing substituents [7]. For *o*-substituted benzaldehydes having bulky substituents, yields can be significantly lower. Heterocyclic aldehydes derived from furan, thiophene, and pyridine rings also generally furnish acceptable yields of the corresponding DHPM products [7]. Aliphatic aldehydes typically provide only moderate yields in the Biginelli reaction unless special reaction conditions are employed, such as Lewis acid catalysts/solvent-free methods, or using the aldehydes in protected form. The C4 unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons. Of particular interest are reactions where the aldehyde component is derived from a carbohydrate [13]. In such transformations, DHPMs having a sugar-like moiety in position 4 (*C*-nucleoside analogs) are obtained. Also of interest is the use of masked amino acids as building blocks [13]. In a few cases, bisaldehydes have been used as synthons in Biginelli reactions [7].

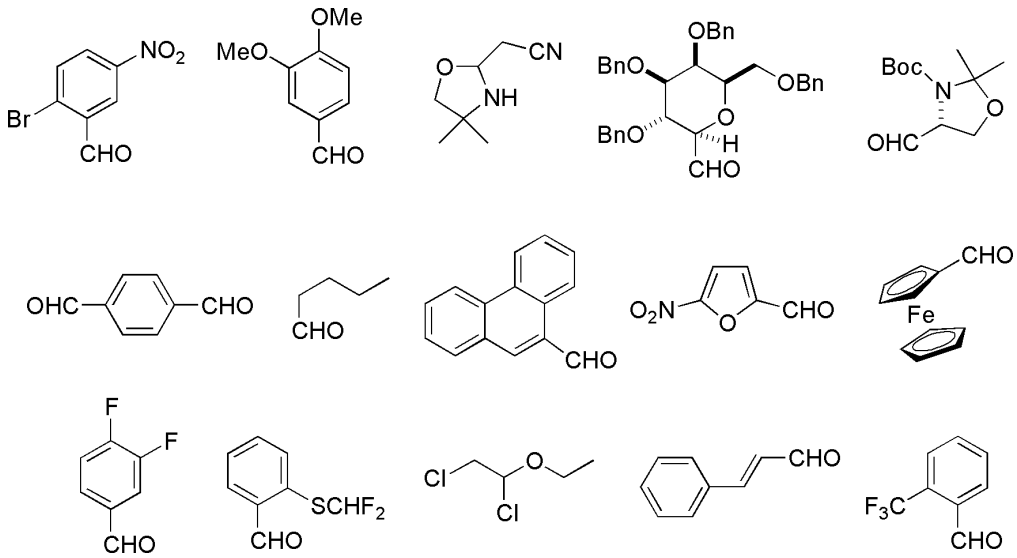


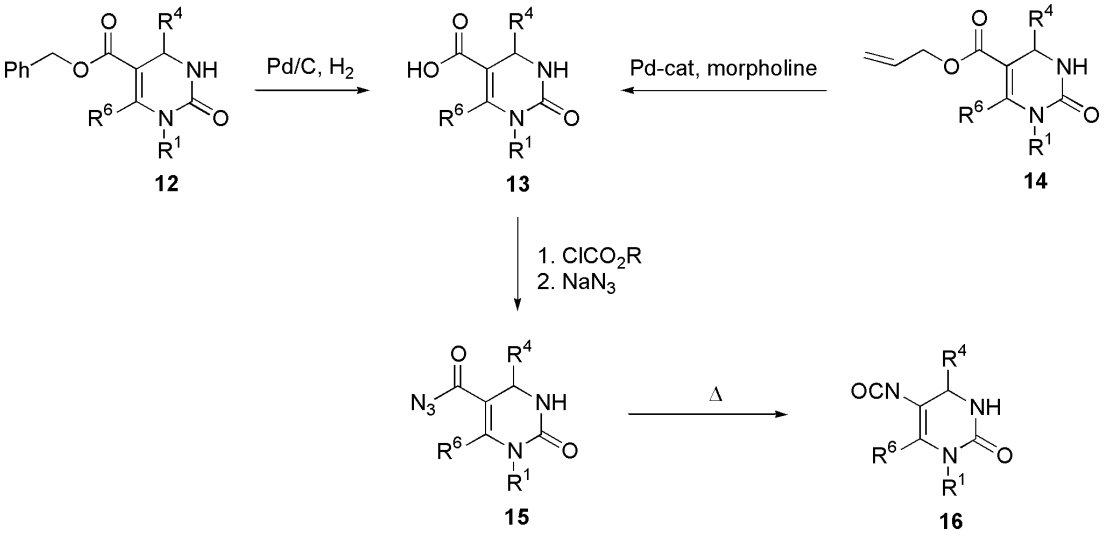
Fig. 1 Aldehyde building blocks used for diversity exploitation at C4 of DHPMs.

Since there is apparently so much diversity in the building blocks that can be employed, little work has been published on the post-condensation derivatization of an, e.g., aromatic substituent at the C4 position of the DHPM ring.

Derivatization of the C5 position

The ester group at position 5 of the DHPMs **5** (E = ester) is rather unreactive toward hydrolysis or nucleophiles. However, the hydrogenolysis of benzyl esters **12** or deprotection of allyl esters **14** constitute elegant methods for the synthesis of the free carboxylic acids of type **13**, which serve as valuable starting materials for further decoration of the DHPM scaffold at the C5 position (Scheme 5) [14].

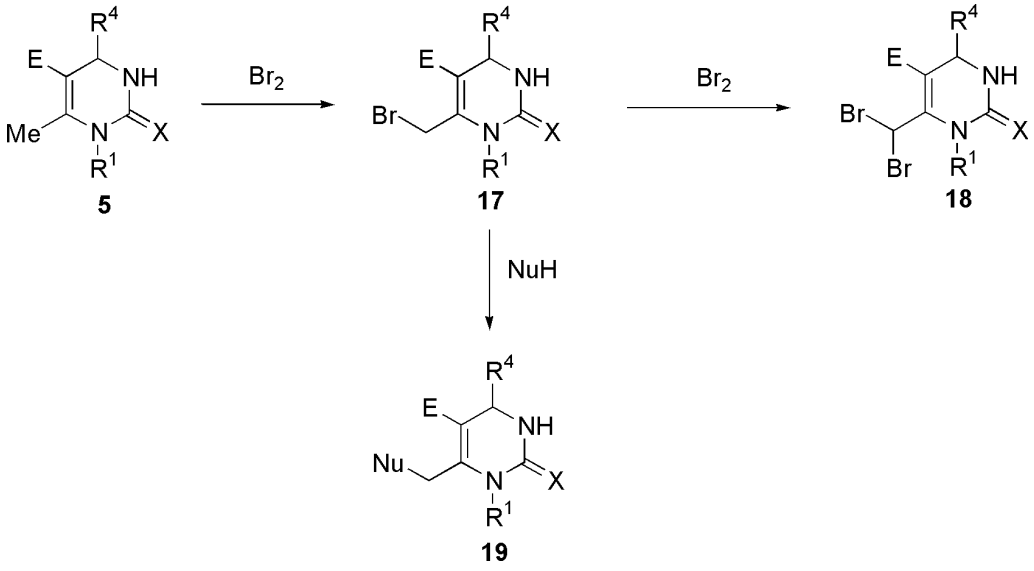
It has also been demonstrated that DHPM-5-carboxylic acids can be transformed into carboxylic azides **15**, which in turn undergo Curtius rearrangement to give isocyanates **16** [10]. The reaction sequence provides an easy access to the scarcely reported class of 5-aminodihydropyrimidines, as **16** can be reacted with a number of nucleophiles, e.g., ethanol, to yield urethanes [10].



Scheme 5 Preparation and functionalization of dihydropyrimidine-5-carboxylic acids.

Reactions at the C6 substituent

In general, acetoacetates are employed in the Biginelli reaction, and, therefore, in most cases, a methyl group is placed at the C6 position of the pyrimidine ring [7]. Functionalization of this methyl group is easily achieved by stepwise bromination. Stepwise substitution of the methyl group upon bromination yields 6-bromomethyl **17** and 6-dibromomethyl derivatives **18**, respectively [15]. The bromomethyl compounds **17** are susceptible to a number of nucleophilic substitution reactions. Thus, DHPMs of type **17** can be reacted with number of O, S, and N nucleophiles to form the corresponding 6-substituted Biginelli compounds **19** (Scheme 6) [15,16].



Scheme 6 Bromination of the C6 methyl group in DHPMs.

Apart from the traditional methods of derivatization of the six diversity points around the DHPM core some of the more complex strategies leading to polycyclic analogs are outlined in Fig. 2.

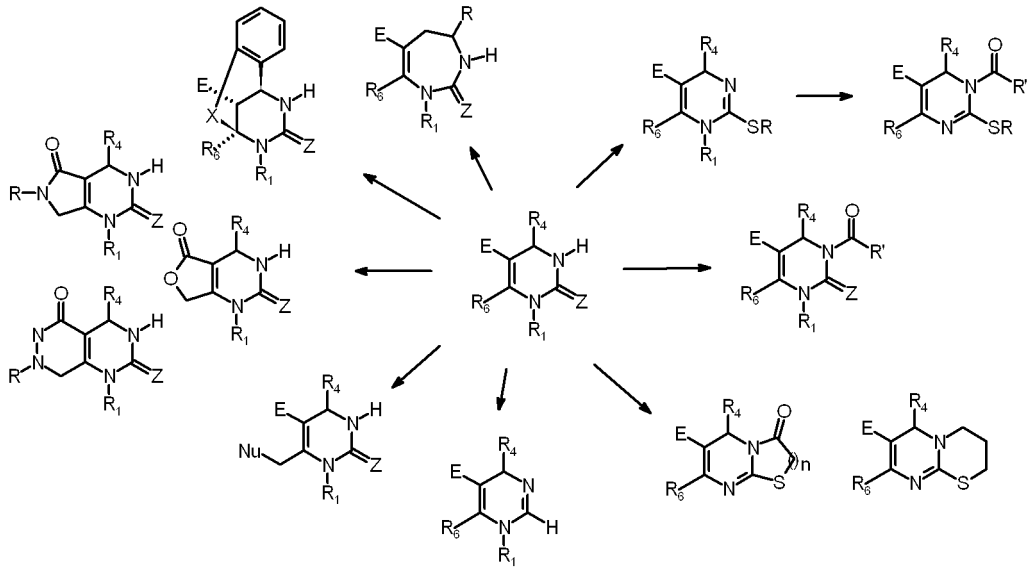


Fig. 2 Scaffold decoration of DHPMs.

CONCLUSION

While in the past a lot of work has been reported on the synthesis of DHPMs of the Biginelli type, the focus is now shifting toward methods of scaffold decoration. Since the DHPM scaffold offers six diversity points around its core, a large number of analogs of this privileged heterocyclic core can be synthesized and screened. The present review has summarized the standard methods of derivatization known in the literature. Work from our laboratory nowadays focuses on rapid analoging methods com-

bining microwave-assisted synthesis with high-throughput purification methods such as the use of polymer-supported scavengers, fluorous reagents, and solid-phase extraction (SPE) techniques [17].

REFERENCES

1. For reviews on multicomponent reactions, see the following: (a) I. Ugi, A. Dömling, W. Hörl. *Endeavour* **18**, 115–122 (1984); (b) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. Keating. *Acc. Chem. Res.* **29**, 123–131 (1996); (c) L. F. Tietze and M. E. Lieb. *Curr. Opin. Chem. Biol.* **2**, 363–371 (1998); (d) A. Dömling. *Comb. Chem. High Throughput Screening* **1**, 1–22 (1998); (e) S. L. Dax, J. J. McNally, M. A. Youngman. *Curr. Med. Chem.* **6**, 255–270 (1999); (f) L. F. Tietze and A. Modi. *Med. Res. Rev.* **20**, 304–322 (2000); (g) H. Bienayme, C. Hulme, G. Oddon, P. Schmitt. *Chem. Eur. J.* **6**, 3321–3329 (2000); (h) I. Ugi and S. Heck. *Comb. Chem. High Throughput Screening* **4**, 1–34 (2001); (i) Weber. *Drug Disc. Today* **7**, 143–147 (2002); (j) A. Dömling. *Curr. Opin. Chem. Biol.* **6**, 306–313 (2002).
2. P. Biginelli. *Gazz. Chim. Ital.* **23**, 360–413 (1893).
3. For an extensive review of the first 100 years of the Biginelli reaction, see: C. O. Kappe. *Tetrahedron* **49**, 6937–6963 (1993).
4. For a more recent update on the Biginelli reaction, see: C. O. Kappe. *Acc. Chem. Res.* **33**, 879–888 (2000).
5. For a detailed mechanistic study on the Biginelli reaction, see: C. O. Kappe. *J. Org. Chem.* **62**, 7201–7204 (1997).
6. C. O. Kappe. *QSAR Comb. Sci.* **22**, 630–634 (2003).
7. For a tabular literature survey of all published DHPMs of type **4** prepared via three-component Biginelli condensation, see: C. O. Kappe and A. Stadler. *Org. React.* **63**, 1–116 (2004).
8. (a) T. George, R. Tahilramani, D. V. Metha. *Synthesis* 405–407 (1975); (b) H. Cho, Y. Takeuchi, M. Ueda, A. Mizuno. *Tetrahedron* **29**, 5405–5408 (1988).
9. C. O. Kappe and P. Roschger. *J. Heterocycl. Chem.* **26**, 55–64 (1989).
10. C. O. Kappe, G. Uray, P. Roschger, W. Lindner, C. Kratky, W. Keller. *Tetrahedron* **48**, 5473–5480 (1992).
11. E. L. Khanina, D. Mucenice, V. P. Kadysh, G. Duburs. *Khim. Geterotsikl. Soedin.* 1076–1082 (1986).
12. K. S. Atwal, G. C. Rovnyak, B. C. O'Reilly, J. Schwartz. *J. Org. Chem.* **54**, 5898–5907 (1989).
13. A. Dondoni and A. Massi. *Mol. Diversity* **6**, 261–270 (2003).
14. (a) G. Zigeuner, C. Knopp, H. Blaschke. *Monatsh. Chem.* **107**, 587–603 (1976); (b) B. Schnell, W. Krenn, K. Faber, C. O. Kappe. *J. Chem. Soc., Perkin Trans. 1*, 4382–4389 (2000).
15. G. Zigeuner, H. Hamberger, H. Blaschke, H. Sterk. *Monatsh. Chem.* **97**, 1408–1421 (1966).
16. C. O. Kappe. *Liebigs Ann. Chem.* 505–507 (1990).
17. (a) D. Dallinger and C. O. Kappe. *Synlett* 1901–1903 (2002); (b) D. Dallinger, N. Yu. Gorobets, C. O. Kappe. *Org. Lett.* **5**, 1205–1208 (2003); (c) D. Dallinger, N. Yu. Gorobets, C. O. Kappe. *Mol. Diversity* **7**, 229–245 (2003); (d) A. Lengar and C. O. Kappe. *Org. Lett.* **6**, 771–774 (2004); (e) B. Khanetskyy, D. Dallinger, C. O. Kappe. *J. Comb. Chem.* **6**, 889–892 (2004).