CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900633

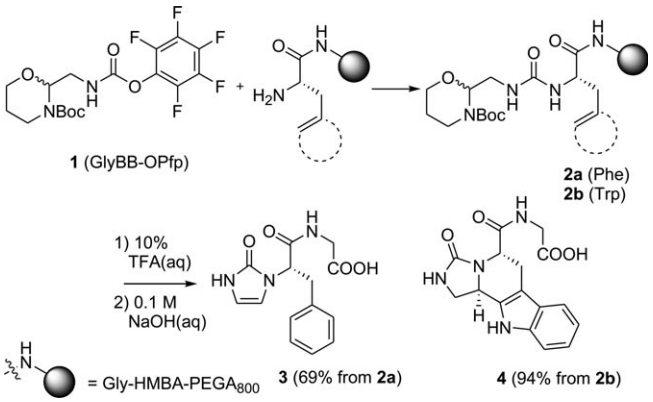
Imidazolones in Diastereoselective Cyclization Reactions and Cu^{II}-Catalysed Cross-Coupling Reactions

Frederik Diness and Morten Meldal*[a]

Imidazolones are pharmaceutically interesting compounds and constitute essential substructures of receptor antagonists with activities in the low nanomolar regime. The targets include the neurokinin-1 receptor,[1] the CGRP receptor,[2] the dopamine receptors[3] and the angiotensin II receptor.[4] Imidazolones are also found in potent PDE4 inhibitors,[5] in subtype selective β_3-adrenergic receptor agonists[6] and in $GABA_A$ receptor ligands.[7] Furthermore, the imidazolone substructure is present in the natural nikkomycin X antibiotic.[8] However, the chemistry of this heterocycle has received little attention, although imidazolones are intermediates in the synthesis of natural compounds, such as biotin,[9] slagenins,[10] axinohydantoins[11] and oroidin-derived alkaloids.[12] Only few systematic studies of the synthesis[2,3,13] and the reactivity[14] of imidazolones have been reported and therefore, the synthetic versatility of these compounds has not been explored.

In search of constrained small molecules derived from peptides, the chemistry of 3-Boc-(1,3)-oxazinane (Box) masked amino aldehydes[15] in electrophilic aromatic substitution-cyclization (EASCy) reactions has been explored.[16]

During this work the Box-masked α-amino aldehyde building block **1** was coupled with the N-terminus of a resin-bound Phe-Gly dipeptide to give compound **2a** (Scheme 1). Exposure of **2a** to 10% aqueous TFA afforded the 1,4-substituted imidazolone **3**[17] as the only product. This was in contrast to the result obtained for the same reaction with a resin-bound Trp-Gly dipeptide (**2b**), which gave the corresponding 1,2,3,4-tetrahydro-β-carboline derivative **4**[17] with a purity in excess of 95%. The different outcome of the reactions of **2a** and **2b** with acid was found to be independent of the acidity. Aqueous TFA (10–100%), HCl (1.0 M), and H_2SO_4 (1.0 M) worked equally well and provided the same results.



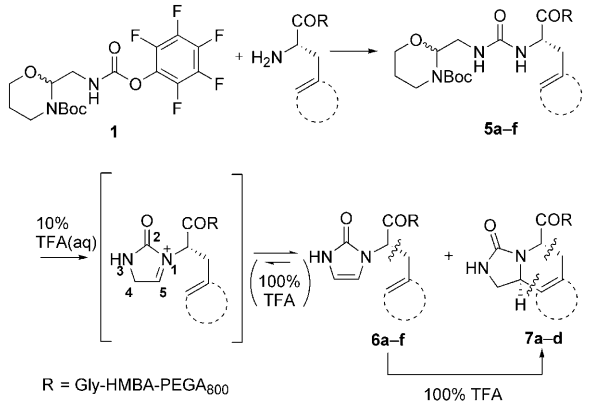
Scheme 1. Formation of imidazolone or EASCy product. Yields reported are those of the pure isolated products.

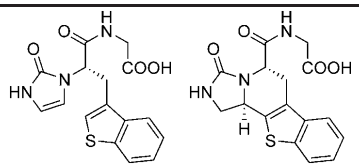
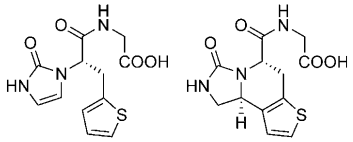
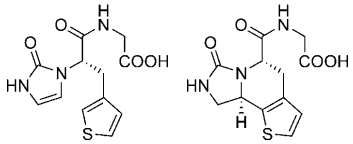
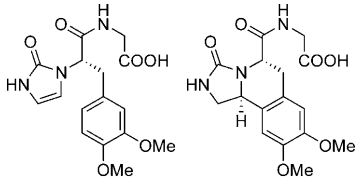
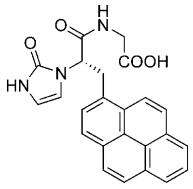
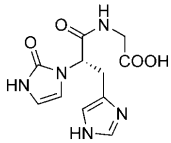
We therefore speculated how the nature of the C-nucleophile may influence the reactivity. Building block **1** was coupled to a range of dipeptides on solid support affording the unsymmetrical ureas **5a–f**. When exposed to 10% aqueous TFA all except two of the compounds gave the corresponding imidazolone as the only product (Table 1). The two exceptions were the more reactive thiophen-3-yl and 3,4-dimethoxyphenyl derivatives, which both in addition to the imidazolones (**6c** and **6d**) as the major components gave the corresponding 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine and 1,2,3,4-tetrahydroisoqinoline products (**7c** and **7d**) in 34 and 7%, respectively. As a point of interest, it was noted that subsequent exposure of the resin-bound imidazolones containing 3,4-dimethoxybenzene, thiophene or benzothiophene (entry **a** to **d**, Table 1) to 100% TFA for 12 h, quantitatively converted these into the cyclized products. The purities of the final EASCy products (**7a–d**) were excellent (>95%) and the diastereoselectivity was better than 19:1 for all compounds. The remaining imidazolones, **6e** and **6f**, were completely stable towards the treatment with 100% TFA. All

[a] Dr. F. Diness, Prof. Dr. M. Meldal
SPOCC Center
Carlsberg Laboratory
Gamle Carlsberg Vej 10
2500 Valby (Denmark)
Fax: (+45) 33 27 47 08
E-mail: mpm@crc.dk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900633.

Table 1. Formation of imidazolones and EASCy products with π-nucleophiles.



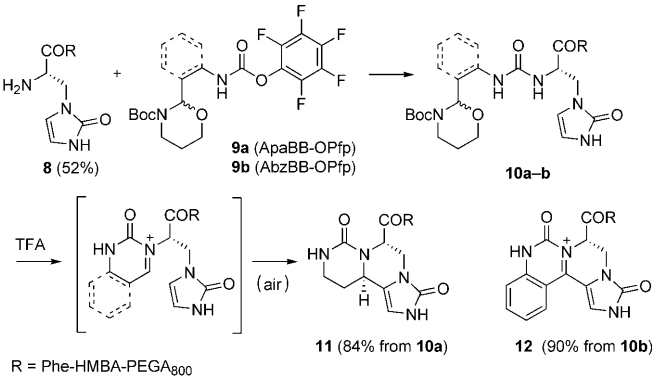
Entry	Product **6**/(**7**)	10% aq. TFA Ratio **6**/**7**[a] (purity [%])[b] Yield [%][c]	100% TFA Ratio **6**/**7**[a] (purity [%])[b] Yield [%][c]
a		100:0 (95) 58	0:100 (96) 19
b		100:0 (95) 68	0:100 (98) 68
c		66:34 (92) nd[d]	0:100 (97) 45
d		93:7 (98) 76	0:100 (97) 38
e		100:0 (99) nd	100:0 (99) 16
f		100:0 (99) nd	100:0 (99) 72

[a] Determined by HPLC and NMR. [b] Determined by HPLC of crude material cleaved off the resin. [c] Yield of isolation. The products were isolated on a 1–12 mg scale [d] Not determined.

analysed products were cleaved from the resin with 0.1 M aqueous NaOH before characterisation.

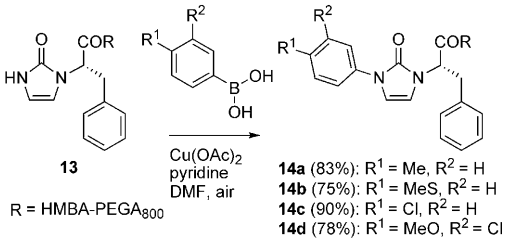
In all these reactions the acid initially deprotects the aldehyde, which instantaneously reacts with the urea nitrogen to afford a mixture of the *N,O*-hemiacetal (not shown) and the cyclic *N*-carbamyliminium ion (see Table 1). The *N*-carbamyliminium ion may then be attacked by the electrons of the neighbouring C–H bond of the ring, which with loss of a proton gives the imidazolone (**6a–f**). The *N*-carbamyliminium ion may alternatively be attacked by the π-electrons in the aromatic side chain of the subsequent amino acid to afford the corresponding cyclized product (**7a–d**). It may be assumed that the conversion of the cyclic *N*-carbamyliminium ion to the imidazolone is reversible under the strongly acidic conditions and equilibrium between the two forms is established. The fraction of *N*-carbamyliminium ion present in the equilibrium is then susceptible to irreversible attack by a reactive C-nucleophile to form the corresponding cyclized product. Neither the transformation of imidazolones to EASCy products nor other examples of nucleophilic attack on imidazolones have been described previously. EASCy products containing the saturated 4,4-disubstituted imidazoldin-2-one core structure have been reported,[18] however, in this case the 4,4-disubstitution prevented formation of an imidazolone. In one report a single product containing a mixture of the imidazolone and the cyclized 1,2,3,4-tetrahydroisoqinoline product has been described.[19]

Due to the success with using electron-rich heterocycles as nucleophiles in the EASCy reaction we have also explored imidazolones as nucleophile in this reaction. The imidazolone **8** was formed on resin from a 2,3-diamino propionic acid containing dipeptide by the method described above (Table 1). The EASCy reaction was tested using two other building blocks (**9a–b**),[15c] which after coupling and exposure to TFA gave the corresponding cyclized product (**11**) or the oxidized cyclized product (**12**) respectively (Scheme 2). The purities of **11** and **12** were 82 and 76%, respectively. The charged iminium product **12** is believed to arise through rapid oxidation upon exposure to air of the initially formed cyclic product. This finding is in accordance with other results of EASCy reaction using the Abz-derived building block (**9b**), which we previously reported.[16]



Scheme 2. Imidazolones as π-nucleophile in EASCy reactions. Yields reported are those of the pure isolated products.

We further explored the copper(II)-catalysed oxidative *N*-arylation[20] of the imidazolone products with aryl boronic acids. The imidazolones proved to be excellent substrates for this type of coupling and the application of imidazolone **13** gave the corresponding products (**14a–d**) with purities in excess of 95% (Scheme 3).



Scheme 3. Formation of *N*-aryl imidazolones. Yields reported are those of the pure isolated products.

The ability to act selectively as nucleophile or electrophile under the same reaction conditions and serve as substrate for copper catalysed cross couplings shows that imidazolones are very versatile compounds in the synthesis of complex heterocyclic scaffolds. The simple procedures and quantitative nature of these reactions opens up for facile access to new types of optically pure compounds with potential use as pharmaceutical substances.

Experimental Section

General aspects: All purchased chemicals were used without further purification. All solvents were HPLC-grade. $PEGA_{800}$ resin was obtained from VersaMatrix A/S. See ref. [17] and Supporting Information for the full characterisation of all products.

Synthesis of imidazolone and EASCy products (3, 4, 6a–f, 7a–d, 11, 12 and 13): Dry $PEGA_{800}$ resin (50–150 mg, 0.30–0.38 mmol g^{-1}, 15–57 μmol) derivatized with the HMBA linker and amino acid was swelled in DMF (for the preparation of the funtionalised resin see reference [15b]). The building block (3.0 equiv) (**1**, **9a** or **9b**) was dissolved in DMF (10 mL g^{-1} resin) and the solution was added to the resin. After 12 h the resin was washed with DMF (6×2 min), CH_2Cl_2 (6×2 min) and lyophilized. The dry $PEGA_{800}$ resin with HMBA linker, peptide and building block attached (**2a–b**, **5a–f**, **10a** or **10b**) was swelled in aqueous 10% TFA (1 h). The resin was washed with 10% aqeous TFA (2×2 min). Further reaction with TFA was applied when necessary to complete conversion (see Supporting Information). The resin was washed with H_2O until the eluate had pH 5–7. The resin was washed with DMF (6×2 min), CH_2Cl_2 (6×2 min) and lyophilized. The compound was cleaved from the resin by swelling the dry $PEGA_{800}$ resin with the attached HMBA linker and compound in 0.1 M aqueous NaOH (10 mL g^{-1} resin). After 2 h aqueous 0.1 M HCl was used for neutralization. Resin was extracted with H_2O (2× 2 min) and acetonitrile/H_2O 70:30 (2×2 min). The solvent from the extract was removed in vacuo giving the product (**3**, **4**, **6a–f**, **7a–d**, **11**, **12** and **13**), as a solid with a white to pale yellow colour.

Copper(II)-promoted *N*-arylation of imidazolone product of GlyBB-Phe-Gly-HMBA-$PEGA_{800}$ (14a–d): The imidazolone product **13** (60 mg, ~0.35 mmol g^{-1}, 21 μmol) was swelled in DMF. Aryl boronic acid (210 μmol), $Cu(AcO)_2$ (7.5 mg, 42 μmol) and DIPEA (134 mg, 1.05 mmol) were added to the resin. Crusted molecular sieves 3 Å (~100 mg) was added and mixture stirred with dry air bubbling through (12 h). The resin was washed with DMF (6×2 min), 1% aqueous TFA (3×2 min), H_2O (6×2 min), DMF (6×2 min), CH_2Cl_2 (6×2 min) and lyophilized. The compound (**14a–d**) was cleaved off the resin as described above.

Acknowledgements

The financial support to the SPOCC Center from the Danish National Research Foundation is gratefully acknowledged.

Keywords: autooxidation · cross-coupling · solid-phase synthesis · stereoselective synthesis · urea

[1] a) L. C. Meurer, P. E. Finke, K. A. Owens, N. N. Tsou, R. G. Ball, S. G. Mills, M. MacCoss, S. Sadowski, M. A. Cascieri, K.-L. Tsao, G. G. Chicchi, L. A. Egger, S. Luell, J. M. Metzger, D. E. MacIntyre, N. M. J. Rupniak, A. R. Williams, R. Hargreaves, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4504; b) P. E. Finke, L. C. Meurer, D. L. Levorse, M. MacCoss, S. Sadowski, M. A. Cascieri, K.-L. Tsao, G. G. Chicchi, J. M. Metzger, D. E. MacIntyre, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4497.

[2] C. S. Burgey, C. A. Stump, D. N. Nguyen, J. Z. Deng, A. G. Quigley, B. R. Norton, I. M. Bell, S. D. Mosser, C. A. Salvatore, R. Z. Rutledge, S. A. Kane, K. S. Koblan, J. P. Vacca, S. L. Graham, T. M. Williams, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5052.

[3] R. W. Carling, K. W. Moore, C. R. Moyes, E. A. Jones, K. Bonner, F. Emms, R. Marwood, S. Patel, A. E. Fletcher, M. Beer, B. Sohal, A. Pike, P. D. Leeson, *J. Med. Chem.* **1999**, *42*, 2706.

[4] D. B. Reitz, D. J. Garland, M. B. Norton, J. T. Collins, E. J. Reinhard, R. E. Manning, G. M. Olins, S. T. Chen, M. A. Palomo, E. G. McMahon, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1055.

[5] J. I. Andrés, J. M. Alonso, A. Diaz, J. Fernandez, L. Iturrino, P. Martinez, E. Matesanz, E. J. Freyne, F. Deroose, G. Boeckx, D. Petit, G. Diels, A. Megens, M. Somers, J. V. Wauwe, P. Stoppie, M. Cools, F. D. Clerck, D. Peeters, D. D. Chaffoy, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 653.

[6] E. M. Naylor, E. R. Parmee, V. J. Colandrea, L. Perkins, L. Brockunier, M. R. Candelore, M. A. Cascieri, L. F. Colwell, L. Deng, W. P. Feeney, M. J. Forrest, G. J. Hom, D. E. MacIntyre, C. D. Starader, L. Tota, P.-R. Wang, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 755.

[7] R. W. DeSimone, C. A. Blum, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2723.

[8] H.-P. Fiedler, R. Kurth, J. Langhärig, J. Delzer, H. Zähner, *J. Chem. Technol. Biotechnol.* **1982**, *32*, 271.

[9] For a review, see: J. P. De Clercq, *Chem. Rev.* **1997**, *97*, 1755.

[10] A. C. Barrios Sosa, K. Yakushijin, D. A. Horne, *Org. Lett.* **2000**, *2*, 3443.

[11] A. C. B. Sosa, K. Yakushijin, D. A. Horne, *J. Org. Chem.* **2002**, *67*, 4498.

[12] P. J. Dransfield, A. S. Dilley, S. Wang, D. Romo, *Tetrahedron* **2006**, *62*, 5223.

[13] For generation of imidazolones in solution see: a) R. Duschinsky, L. A. Dolan, *J. Am. Chem. Soc.* **1946**, *68*, 2350; b) P. J. Stoffel, A. J. Speziale, *J. Org. Chem.* **1962**, *27*, 3079; c) T. Taguchi, Y. Sato, K. Watanabe, T. Mukaiyama, *Chem. Lett.* **1974**, *401*; d) Y. S. Lee, C. S. Kim, H. Park, *Heterocycles* **1994**, *38*, 2605; e) J. A. Markwalder, R. S. Pottorf, S. P. Seitz, *Synlett* **1997**, 521; f) S. Wendeborn, T. Winkler, I. Foisy, *Tetrahedron Lett.* **2000**, *41*, 6387; g) G. Mloston, M. Celeda, *Helv. Chim. Acta* **2000**, *83*, 728; h) S.-H. Lee, B. Clapham, G. Koch, J. Zimmermann, K. D. Janda, *Org. Lett.* **2003**, *5*, 511; i) C. C. Llopart, C. Ferrer, J. A. Joule, *Can. J. Chem.* **2004**, *82*, 1649; j) S.-H. Lee, K. Yoshida, H. Matsushita, B. Clapham, G. Koch, J. Zimmermann, K. D. Janda, *J. Org. Chem.* **2004**, *69*, 8829; k) H. Cerecetto, A. Gerpe. M. Gonzalez, O. E. Piro, E. E. Castellano, *Lett. Org. Chem.* **2005**, *2*, 501; l) J. T. Lee, H. Mah, K. D. Nam, D. Shin,

D.-C. Ha, H.-G. Hahn, *J. Cmb. Chem.* **2008**, *10*, 803. For generation of imidazolones on solid-phase see: m) J.-F. Cheng, C. Kaiho, M. Chen, T. Arrhenius, A. Nadzan, *Tetrahedron Lett.* **2002**, *43*, 4571; n) G. Rossé, J. Strickler, M. Patek, *Synlett* **2004**, 2167; o) M. Patek, A. S. Weichsel, B. Drake, M. Smrcina, *Synlett* **2005**, 1322; p) M. Yamashita, S.-H. Lee, G. Koch, J. Zimmermann, B. Clapham, K. D. Janda, *Tetrahedron Lett.* **2005**, *46*, 5495.

[14] For Fiedel–Craft reaction see: a) R. A. Schnettler, R. C. Dage, J. M. Grisar, *J. Med. Chem.* **1982**, *25*, 1477. For reaction with Br_2 see: b) R. Seo, T. Ishizuka, A. A.-M. Abdel-Aziz, T. Kunieda, *Tetrahedron Lett.* **2001**, *42*, 6353. For reduction with H_2 see: c) C.-D. Li, M. H. Lee, A. C. Sartorelli, *J. Med. Chem.* **1979**, *22*, 1030; d) J. Akester, J. Cui, G. Fraenkel, *J. Org. Chem.* **1997**, *62*, 431; e) T. Ichikawa, M. Yamada, M. Yamaguchi, T. Kitazaki, Y. Matsushita, K. Higashikawa, K. Itoh, *Chem. Pharm. Bull.* **2001**, *49*, 1110; f) N. Yasuda, Y. Hsiao, M. S. Jensen, N. R. Rivera, C. Yang, K. M. Wells, J. Yau, M. Palucki, L. Tan, P. G. Dormer, R. P. Volante, D. L. Hughes, P. J. Reider, *J. Org. Chem.* **2004**, *69*, 1959. For *N*-alkylation and *N*-acylation see: g) N. A. Meanwell, S. Y. Sit, J. Gao, H. S. Wong, Q. Gao, D. R. S. Laurent, N. Balasubramanian, *J. Org. Chem.* **1995**, *60*, 1565.

[15] a) T. Groth, M. Meldal, *J. Comb. Chem.* **2001**, *3*, 34; b) T. Groth, M. Meldal, *J. Comb. Chem.* **2001**, *3*, 45; c) F. Diness, J. Beyer, M. Meldal, *QSAR Comb. Sci.* **2004**, *23*, 130.

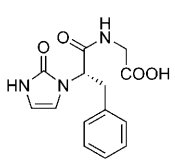
[16] F. Diness, J. Beyer, M. Meldal, *Chem. Eur. J.* **2006**, *12*, 8056.

[17] Data for imidazolone product **3** and EASCy product **4**. Imidazolone product from GlyBB-Phe-Gly-HMBA-PEG$_{800}$ (**3**): ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 13.28–11.68 (brs, 1H), 9.78 (s, 1H), 8.56 (t, J = 5.8 Hz, 1H), 7.31–7.10 (m, 5H), 6.62 (dd, J = 2.1, 2.9 Hz, 1H), 6.24 (t, J = 2.7 Hz, 1H), 4.95 (dd, J = 4.8, 10.7 Hz, 1H), 3.77 (d, J = 5.8 Hz, 1H), 3.19 (dd, J = 4.9, 14.4 Hz, 1H), 3.06 ppm (d, J = 10.8, 14.1 Hz, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 170.9, 170.2, 137.3, 128.9, 128.1, 126.4, 116.7, 110.2, 107.1, 55.4, 40.7, 37.1, 30.7 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{14}H_{16}N_3O_4$ $[M+H]^+$: 290.1135, found: 290.1123. Yield: 10.2 mg (69%). EASCy product from GlyBB-Trp-Gly-HMBA-PEG$_{800}$ (**4**): ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 13.14–11.75 (brs, 1H), 8.44 (t, J = 6.0 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.07 (dt, J = 2.4, 15.4 Hz, 1H), 7.02–6.84 (m, 2H), 5.17 (d, J = 6.5 Hz, 1H), 4.75 (d, J = 7.0 Hz, 1H), 3.83–3.63 (m, 3H), 3.47 (dd, J = 2.8, 8.9 Hz, 1H), 3.31 (d, J = 15.7 Hz, 1H), 3.47 ppm (dd, J = 1.8, 7.8 15.9 Hz, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.2, 170.6, 161.6, 136.0, 132.5, 126.5, 121.2, 118.5, 117.7, 111.1, 105.7, 51.0, 49.6, 43.3, 40.9, 20.1 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{16}H_{17}N_4O_4$ $[M+H]^+$: 329.1244, found: 329.1253. Yield: 12.2 mg (94%).

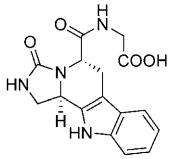
[18] a) S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *Heterocycles* **1983**, *20*, 2411; b) I. Osante, M. I. Collado, E. Lete, N. Sotomayor, *Eur. J. Org. Chem.* **2001**, 1267.

[19] S. Kano, Y. Yuasa, S. Shibuya, *Synth. Commun.* **1985**, *15*, 883.

[20] For reviews see: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; b) D. M. T. Chan, P. Y. S. Lam in *Boronic Acids*, 1st ed. (Ed.: D. Hall), Wiley-VCH, Weinheim, **2005**, pp. 205.



3



4

Received: March 10, 2009
Published online: June 19, 2009

