Synthesis of Alicyclic *N*-Substituted 1,3-Amino Alcohols via 1,3-Oxazines

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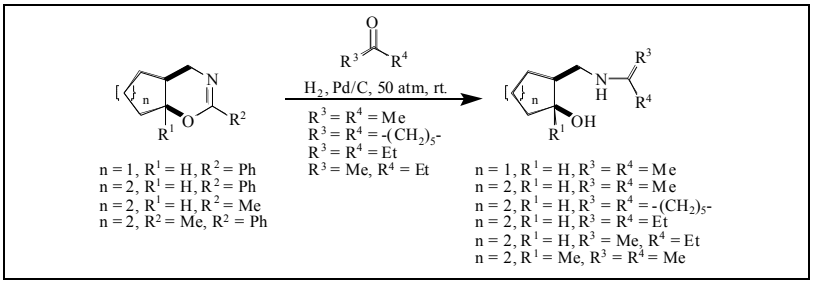

Alicyclic *N*-substituted 1,3-amino alcohols **13-18** were prepared in a facile way in a one-pot procedure from 1,3-oxazines **5-8** in the presence of a ketone **9-12**. The complex reaction involves palladium-catalyzed reduction, debenzylation and/or transimination and further reduction.

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INTRODUCTION

Amino alcohols are of great interest because of their biological and structural importance. Since 1,3-amino alcohols are convenient starting materials for the synthesis of various 1,3-heterocycles [1-4], the simple and economic preparation of these compounds is a key factor. Additionally, enantiopure 1,3-amino alcohols may serve as excellent chiral auxiliaries in enantioselective transformations [5-7]. Although, 1,2-amino alcohols have been thoroughly investigated [8], methods for the preparation and transformation of 1,3-amino alcohols are still undergoing development [9-13]. Alicyclic 1,3-amino alcohols can be obtained by several methods, *e.g*. through reduction of the appropriate β-amino acid, amino esters [1] or 2-hydroxycycloalkanecarbonitrile [14-16], or *via* the catalytic reduction of cycloalkane-fused 1,3-oxazines [17-19]. In most cases, the further alkyl substitution of the nitrogen atom requires reductive alkylation, for example.

Our present aim was to develop a simple one-pot procedure for the synthesis of alicyclic *N*-alkyl substituted 1,3-amino alcohols, starting from cycloalkane-fused 1,3-oxazines **5-8**.

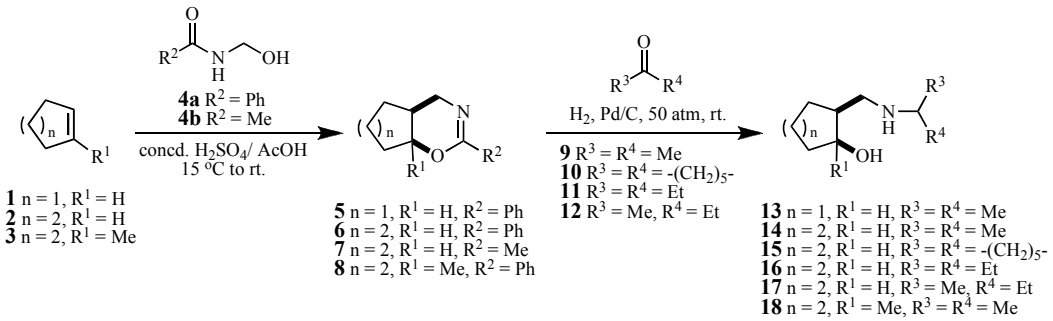
RESULTS AND DISCUSSION

The synthetic route for the preparation and transformation of cycloalkane-fused 5,6-dihydro-4*H*-1,3-oxazines **5-8** is shown in Scheme 1.

Starting from cycloalkenes **1-3**, the 1,4-cycloaddition of *N*-hydroxymethylacylamides (**4a** and **b**) furnished 1,3-oxazines **5-8** stereospecifically, according to literature data [17,18]; and, in the case of 1-methyl-1-cyclohexene **3**, the reaction was regiospecific also, in accordance with Markovnikov's rule [19].

When compound **6** was hydrogenated in the presence of additional acetone and 10% palladium on charcoal as catalyst under 50 atm at room temperature, *N*-isopropyl 1,3-amino alcohol **14** was obtained in 91% yield. During the optimization of the reaction, the amount of acetone could be successfully reduced to 1.2 equivalents without a noteworthy decrease in yield. Next, we extended the method to cyclopentene- and methylcyclohexene-fused

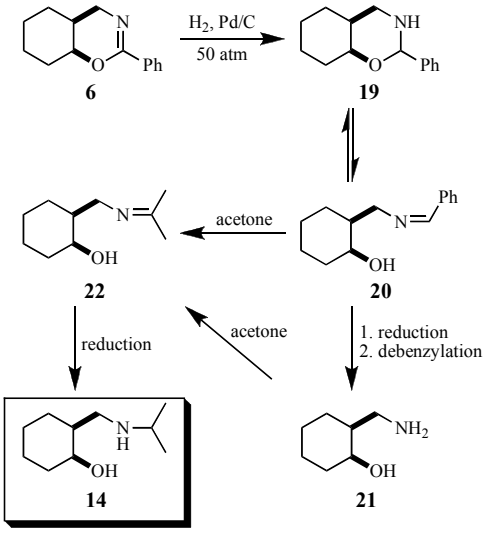
Scheme 1



oxazines **5** and **8**. The yields of the corresponding *N*-isopropyl-substituted amino alcohols **13** and **18** were 37 and 43%, respectively. In the following step, the reaction based on oxazine **6** was extended to aliphatic and alicyclic ketones **10-12**, and under the similar conditions described above, derivatives **15-17** were obtained in 50-71% yields, respectively.

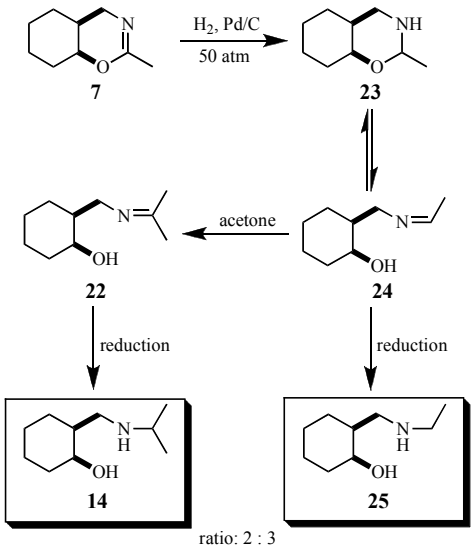
The pathway proposed for the preparation of *N*-isopropyl derivative **14** as a representative is indicated in Scheme 2. The initial step is the reduction of the C=N double bond of **6** to form saturated oxazine **19**, which is in ring-chain tautomeric equilibrium [20] with imine **20**. From this intermediate **20**, imine **22** would be formed through the two pathways; (a) amino alcohol **21**, which is formed by the reduction of the C=N double bond on compound **20** and followed by debenzylation [21] give compound **22** by the reductive alkylation with acetone; (b) imine **22** is produced by the transimination of **20** with acetone directly [22]. Compound **14** would be formed by the reduction of **22**.

Scheme 2



To acquire evidence concerning the above mechanisms, a method was applied in which primary amino alcohol intermediate **21** could not be formed (Scheme 3). 2-Methyl-5,6-dihydro-4*H*-oxazine **7**, prepared from cyclohexene and *N*-hydroxymethylacetamide [17], was submitted to reduction in the presence of acetone. As expected, the ^{1}H nmr spectrum of the product indicated the presence of *N*-isopropyl derivative **14** as the minor, and *N*-ethyl derivative **25** as the major components, in a ratio of 2:3. Compound **14** can be formed only *via* trans-iminated product **22**. The above experiment clearly proves the competitive reaction pathways given in Scheme 2. Major component **25** was identified by comparison with the nmr, ir and ms spectra of pure *cis*-2-ethylamino-methyl-1-cyclohexanol hydrochloride, prepared according to a literature procedure [21].

Scheme 3



Thus, we have developed a simple method for the synthesis of *cis*-*N*-alkyl-substituted cycloalkane-based 1,3-amino alcohols from the readily available dihydro-1,3-oxazines. Although the reaction involves a number of possible intermediates, the *N*-substituted amino alcohols were produced in acceptable to excellent yields as single products. This one-pot method might well prove competitive to the widely applied two-step reductive alkylation technique.

EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded on a Bruker Avance DRX400 spectrometer at 400.13 MHz (^{1}H δ=0 (TMS)) and 100.61 MHz (^{13}C), in an appropriate solvent. Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference. Coupling Constants (J) are given in Hz. Melting points were determined on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Ft-ir spectra were recorded on a Perkin-Elmer model 1000 spectrophotometer. Low-resolution CR = 1000-1500 mass spectra were run on a Finnigan MAT95S double focusing mass spectrometer. Samples were introduced directly into the ion source. The electron impact ion source conditions were: temperature 170 °C; electron energy 20 eV; ion current 150 mA.

N-Hydroxymethylbenzamide [23] **(4a),** *N*-hydroxymethyl-acetamide [24] (**4b**), the 5,6-dihydro-4*H*-1,3-oxazine derivatives [17] (**5-7**) and 6-methyl-2-phenyl-5,6-dihydro-4*H*-cyclohexa[e]-[1,3]oxazine [19] (**8**) were prepared according to literature processes.

***cis*-2-Phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*e*][1,3]ox-azine (5).** This compound was obtained from 20.0 g (0.132 mol) of *N*-hydroxymethylbenzamide and 10.81 g (0.159 mol) of

cyclopentene as a pale-yellow oil, in a yield of 16.56 g (62%); ir: 697, 1120, 1654, 2937 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50-2.30 (m, 7H), 3.52 (dd, 1H, J = 2.52, 16.62 Hz), 3,73 (dd, 1H, J = 5.54, 16.62 Hz), 4.56-4.60 (m, 1H), 7.33-7.43 (m, 3H), 7.90-7.95 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 22.4, 27.7, 33.7, 36.7, 44.9, 79.2, 127.5, 128.5, 129.0, 130.7, 131.8, 134.8, 156.0; ms: m/z 201 (M^+), 134, 105, 77, 67. Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.45; H, 7.62; N, 7.10.

***cis*-2-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (6).** This compound was obtained from 29.32 g (0.194 mol) of *N*-hydroxymethylbenzamide and 20.0 g (0.243 mol) of cyclohexene as a colorless oil, in a yield of 13.88 g (30%); ir: 695, 1121, 1652, 2929, 3059 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30-2.10 (m, 9H), 3.40 (dd, 1H, J = 2.0, 16.62 Hz), 3.66 (dd, 1H, J = 5.54, 16.62 Hz), 4.38-4.43 (m, 1H), 7.32-7.43 (m, 3H), 7.91-7.97 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 20.9, 25.0, 25.9, 31.0, 32.6, 37.1, 49.5, 73.2, 127.4, 128.5, 130.7, 134.7, 155.5; ms: m/z 215 (M^+), 134, 105, 94, 77, 67. Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.22; H, 7.92; N, 6.43.

***cis*-2-Methyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (7).** This compound was obtained from 6.5 g (73.03 mmol) of *N*-hydroxymethylacetamide and 7.5 g (91.29 mmol) of cyclohexene as a pale-yellow oil, in a yield of 2.15 g (42%); ir: 1001, 1219, 1677, 2929, 3275 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20-2.10 (m, 12H), 3.13 (dd, 1H, J = 1.51, 16.12 Hz), 3.40 (ddd, 1H, J = 1.51, 5.54, 16.12 Hz), 4.18-4.23 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 20.7, 21.8, 24.7, 25.7, 30.7, 32.0, 48.6, 72.8, 157.7; ms: m/z 153 (M^+), 94, 82, 72, 67. Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.47; H, 9.85; N, 8.99.

***cis*-8a-Methyl-2-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (8).** This compound was obtained from 30.0 g (0.198 mol) of *N*-hydroxymethylbenzamide and 22.90 g (0.238 mol) of 1-methylcyclohexene as a white solid, in a yield of 25.35 g (56%); ir: 699, 1118, 1646, 2929, 3053 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20-1.80 (m, 11H), 1.99 (d, 1H, J = 13.56 Hz), 3.33 (d, 1H, J = 17.12 Hz), 3.81 (dd, 1H, J = 5.54, 17.12 Hz), 7.32-7.42 (m, 3H), 7.90-7.98 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 22.5, 25.6, 26.3, 27.5, 27.8, 36.8, 38.4, 41.1, 48.0, 75.8, 127.5, 128.5, 129.2, 130.7, 135.2, 155.1; ms: m/z 229 (M^+), 134, 122, 108, 105, 96, 81, 77, 68. Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.48; H, 8.39; N, 6.20.

General Procedure for the Preparation of Alicyclic 1,3-Amino Alcohols 13-18. The appropriate oxazine and ketone (10 equivalents, except for compounds **13** and **14**, 1.2 equivalents) were stirred with 0.11 g of 10% palladium-on-charcoal in 25 mL of methanol under 50 atmospheres of hydrogen at room temperature for 24 hours. After the mixture had been filtered, the solvent was evaporated off and the oily residue was purified as the hydrochloride salt from ethanol/diethyl ether.

***cis*-2-(*N*-Isopropylaminomethyl)-1-cyclopentanol hydrochloride (13).** This compound was obtained from 0.5 g (2.49 mmol) of **5** and 0.18 g (2.99 mmol) of acetone as white crystals, in a yield of 0.18 g (37%); mp: 121-123 °C; ir: 1009, 1590, 2963, 3386 cm^{-1}; ^1H nmr (deuteriowater): δ 1.35-1.55 (m, 7H), 1.60-1.78 (m, 2H), 1.82-2.05 (m, 3H), 2.15-2.27 (m, 1H), 3.11 (dd, 1H, J = 7.55, 12.59 Hz), 3.29 (dd, 1H, J = 7.55, 12.59 Hz), 3.46-3.55 (m, 1H), 4.33-4.38 (m, 1H); ^{13}C nmr (deuteriowater): δ 18.5, 18.7, 21.7, 27.3, 34.3, 41.9, 45.5, 51.6, 73.8; ms: m/z 157 (M^+), 142, 124, 81, 72, 58, 44, 36. Anal. Calcd. for $C_9H_{20}ClNO$: C, 55.80; H, 10.41; N, 7.23. Found: C, 55.92; H, 10.37; N, 7.10.

***cis*-2-(*N*-Isopropylaminomethyl)-1-cyclohexanol hydrochloride (14).** This compound was obtained from 0.5 g (2.33 mmol) of **6** and 0.17 g (2.8 mmol) of acetone as white crystals, in a yield of 0.44 g (91%); mp: 199-201 ºC; ir: 976, 1449, 1585, 2931, 3403 cm^{-1}; ^1H nmr (deuteriowater): δ 1.29-1.80 (m, 13H), 1.95 (br s, 1H), 2.99 (dd, 1H, J = 7.55, 12.59 Hz), 3.15 (dd, 1H, J = 6.55, 12.59 Hz), 3.39-3.50 (m, 1H), 4.00 (br s, 1H); ^{13}C nmr (deuteriowater): δ 18.5, 18.6, 20.5, 23.7, 24.8, 31.8, 38.4, 47.2, 51.7, 68.5; ms: m/z 171 (M^+), 156, 95, 72, 67, 56, 44. Anal. Calcd. for $C_{10}H_{22}ClNO$: C, 57.82; H, 10.67; N, 6.74. Found: C, 57.70; H, 10.55; N, 6.65.

***cis*-2-(*N*-Cyclohexylaminomethyl)-1-cyclohexanol hydrochloride (15).** This compound was obtained from 0.5 g (2.33 mmol) of **6** and 0.23 g (23.4 mmol) of cyclohexanone as white crystals, in a yield of 0.41 g (71%); mp: 234-237 ºC; ir: 981, 1458, 1589, 2934, 3373 cm^{-1}; ^1H nmr (deuteriowater): δ 1.10-2.13 (m, 20H), 3.01 (dd, 1H, J = 7.05, 13.09 Hz), 3.07-3.22 (m, 2H), 3.99 (br s, 1H); ^{13}C nmr (deuteriowater): δ 20.5, 23.6, 24.4, 24.9, 25.0, 29.2, 29.3, 31.8, 38.4, 47.0, 58.3, 68.6, 115.4; ms: m/z 211 (M^+), 180, 168, 131, 119, 112, 69, 56. Anal. Calcd. for $C_{13}H_{26}ClNO$: C, 63.01; H, 10.58; N, 5.65. Found: C, 62.97; H, 10.47; N, 5.58.

***cis*-2-{*N*-(1-Ethylpropyl)aminomethyl}-1-cyclohexanol hydrochloride (16).** This compound was obtained from 0.5 g (2.33 mmol) of **6** and 2.01 g (23.3 mmol) of diethyl ketone as white crystals, in a yield of 0.28 g (51%); mp: 142-145 ºC; ir: 979, 1458, 1591, 3373 cm^{-1}; ^1H nmr (deuteriowater): δ 0.97 (t, 6H, J = 7.55 Hz), 1.27-1.77 (m, 13H), 1.99 (br s, 1H), 3.02 (dd, 1H, J = 6.04, 12.59 Hz), 3.10-3.25 (m, 2H), 4.07 (br d, 1H, J = 3.02 Hz); ^{13}C nmr (deuteriowater): δ 8.9, 9.0, 20.8, 22.4, 23.4, 25.2, 31.6, 37.9, 47.3, 61.8, 69.1; ms: m/z 198 (M^+), 182, 170, 152, 100, 95, 70, 58, 41. Anal. Calcd. for $C_{12}H_{26}ClNO$: C, 61.12; H, 11.11; N, 5.94. Found: C, 60.96; H, 10.97; N, 6.03.

***cis*-2-(*N*-*sec*-Butylaminomethyl)-1-cyclohexanol hydrochloride (17).** This compound was obtained from 0.5 g (2.33 mmol) of **6** and 1.68 g (23.3 mmol) of 2-butanone as white crystals of the diastereomeric mixture, in a yield of 0.26 g (50%); mp: 156-161 ºC; ir: 979, 1458, 1592, 3365 cm^{-1}; ^1H nmr (deuteriowater): δ 0.97 (t, 3H, J = 7.55 Hz), 1.27-1.85 (m, 15H), 1.97 (br s, 1H), 2.95-3.07 (m, 1H), 3.13-3.30 (m, 2H), 4.01 (br s, 1H); ^{13}C nmr (deuteriowater): δ 9.4, 15.3, 20.5, 20.7, 23.5, 23.7, 24.9, 25.0, 25.9, 31.7, 31.8, 38.2, 47.1, 47.2, 56.8, 68.8; ms: m/z 185 (M^+), 170, 156, 138, 95, 86, 44. Anal. Calcd. for $C_{11}H_{24}ClNO$: C, 59.57; H, 10.91; N, 6.32. Found: C, 59.42; H, 10.98; N, 6.25.

***cis*-2-(*N*-Isopropylaminomethyl)-1-methyl-1-cyclohexanol hydrochloride (18).** This compound was obtained from 0.5 g (2.18 mmol) of **8** and 1.26 g (21.8 mmol) of acetone as white crystals, in a yield of 0.21 g (43%); mp: 121-123 °C; ir: 1597, 2429, 2940, 3457 cm^{-1}; ^1H nmr (deuteriowater): δ 1.24-1.78 (m, 18H), 3.00 (dd, 1H, J = 8.56, 13.09 Hz), 3.30 (dd, 1H, J = 4.03, 13.09 Hz), 3.40-3.50 (m, 1H); ^{13}C nmr (deuteriowater): δ 18.4, 18.9, 21.6, 24.1, 25.9, 27.8, 38.8, 42.7, 46.5, 51.8, 72.0; ms: m/z 185 (M^+), 170, 152, 109, 96, 81, 72, 44. Anal. Calcd. for $C_{11}H_{24}ClNO$: C, 59.57; H, 10.91; N, 6.32. Found: C, 59.63; H, 10.88; N, 6.26.

***cis*-2-(*N*-Ethylaminomethyl)-1-cyclohexanol hydrochloride (25).** Compound **7** (0.5 g, 3.27 mmol) was stirred with 0.15 g of 10% palladium-on-charcoal in 30 mL of methanol, under 50 atmospheres of hydrogen at room temperature for 24 hours.

After the mixture had been filtered, the solvent was evaporated off and the oily residue was purified as the hydrochloride salt from ethanol/diethyl ether, in a yield of 0.19 g (30%); mp: 163-168 ºC; ir: 975, 1449, 2927, 3402 cm^{-1}; ^1H nmr (deuteriowater): δ 1.26-1.78 (m, 12H), 1.97 (m, 1H), 2.99 (dd, 1H, J = 7.05, 12.59 Hz), 3.07-3.17 (m, 3H), 3.99 (br s, 1H); ^{13}C nmr (deuteriowater): δ 10.8, 20.4, 23.6, 24.7, 31.8, 38.3, 43.9, 49.7, 68.5; ms: m/z. Anal. Calcd. for $C_9H_{20}ClNO$: C, 55,80; H, 10.41; N, 7,23. Found: C, 55.85; H, 10.43; N, 7.21.

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REFERENCES AND NOTES

[1] Szakonyi, Z.; Martinek, T.; Hetényi, A.; Fülöp, F. *Tetrahedron: Asymmetry*, **2000,** *11*, 4571.

[2] Gyónfalvi, S.; Szakonyi, Z.; Fülöp, F. *Tetrahedron: Asymmetry*, **2003**, *14*, 3965.

[3] Palkó, M.; Hetényi, A.; Fülöp, F. *J. Heterocyclic Chem*., **2004**, *41*, 69.

[4] Stájer, G.; Miklós, F.; Kanizsai, I.; Csende, F.; Sillanpää, R.; Sohár, P. *Eur. J. Org. Chem.*, **2004**, *17*, 3701.

[5] Vilaplana, M. J.; Molina, P.; Arques, A.; Andres, C.; Pedrosa, R. *Tetrahedron: Asymmetry*, **2002**, *13*, 5.

[6] de Oliveira, L. F.; Costa, V. E. U. *Tetrahedron: Asymmetry*, **2004**, *15*, 2583.

[7] Szakonyi, Z.; Balázs, Á.; Martinek, T. A.; Fülöp, F. *Tetrahedron: Asymmetry*, **2006**, *17*, 199.

[8] Ager, D. J.; Prakash, J.; Schaad, D. R. *Chem. Rev*., **1996**, *96*, 835.

[9] Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry*, **1999**, *10*, 3409.

[10] Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc*., **2003**, *125*, 11276.

[11] Raghavan, S.; Rajender, A.; Joseph, S. C.; Rasheed, M. A.; Kumar, K. R. *Tetrahedron: Asymmetry*, **2004**, *15*, 365.

[12] Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem*., **2005**, *70*, 8148.

[13] Kaliappan, K. P.; Das, P.; Kumar, N. *Tetrahedron Lett*., **2005**, *46*, 3037.

[14] Fülöp, F.; Huber, I.; Bernáth, G.; Honig, H.; Seufer-Wasserthal, P. *Synthesis*, **1991**, 43.

[15] Fülöp, F.; Huber, I.; Bernáth, G. *Sci. Pharm*., **1996**, *64*, 367.

[16] Dehli, J. R.; Gotor, V. *J. Org. Chem*., **2002**, *67*, 6816.

[17] Simon, L.; Talpas, G. S.; Fülöp, F.; Bernáth, G. *Acta Chim. Hung*., **1985**, *118*, 139.

[18] Katritzky, A. R.; Shcherbakova, I. V.; Tack, R. D.; Dai, X. Q. *Tetrahedron*, **1993**, *49*, 3907.

[19] Szakonyi, Z.; Fülöp, F.; Bernáth, G.; Evanics, F.; Riddell, F. G. *Tetrahedron*, **1998**, *54*, 1013.

[20] Lázár, L.; Fülöp, F. *Eur. J. Org. Chem*., **2003**, *16*, 3025.

[21] Fülöp, F.; Simon, L.; Simon-Talpas, G.; Bernáth, G. *Synth. Comm*., **1998**, *28*, 2303.

[22] Jun, C.-H.; Hong, J.-B. *Org. Lett*., **1999**, *1*, 887.

[23] Branchaud, B. P.; Tsai, P. *J. Org. Chem*., **1987**, *52*, 5475.

[24] Albericio, F.; Grandas, A.; Porta, A.; Pedroso, E.; Giralt, E. *Synthesis*, **1987**, 271.