Template-Induced Enantioselectivity in the Reductive Radical Cyclization of 3-(3-Iodopropoxy)propenoic Acid Derivatives Depending on the Binding Motif

Peter Kapitán, Thorsten Bach*
Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax +49(89)28913315; E-mail: thorsten.bach@ch.tum.de
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Abstract: Different binding motifs HXC=O have been screened in the enantioselective radical cyclization of various linear derivatives of 3-(3-iodopropoxy)propenoic acid. The reactions were performed in the presence of an enantiomerically pure, chiral 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one derivative, which acts as a hydrogen-bonding template. The cyclized products were obtained in good to excellent yields (66–88%). Enantioselectivities up to 59% ee were achieved.

Key words: cyclizations, enantioselectivity, lactams, radical reactions, supramolecular chemistry

Enantioselective radical reactions have received considerable attention in recent years. Among these reactions, conjugate addition reactions are particularly useful as they often allow for the formation of a carbon–carbon bond and a new stereogenic center. Enantioselective radical–cyclization reactions of acrylates are rare. In the single example (up to 48% ee) reported to date, a chiral Lewis acid was employed to control the conformation of the acrylate and to provide an efficient enantioface differentiation. A 5-exo-trig cyclization of chiral β-alkoxyvinyl sulfoxides has been reported for the construction of tetrahydrofurans with good diastereoselectivity.

In this study, we conducted 5-exo-trig radical cyclization reactions with various derivatives of the title compound, 3-(3-iodopropoxy)propenoic acid. These compounds react in the presence of tributyltin hydride and an appropriate initiator to give the corresponding tetrahydrofurans (Scheme 1). The former β-carbon atom of the acrylic acid derivative is converted into a stereogenic center at C-2 of the tetrahydrofuran, with the radical addition step (intermediate 3) being stereoselectivity determining. In earlier work, we have shown that a radical cyclization reaction in the presence of a chiral template can proceed enantioselectively if binding of the substrate to the template is feasible by hydrogen bonding. Quinolones have been shown to exhibit a very effective binding motif for this coordination, often allowing high enantioselectivities. Other binding motifs have not yet been extensively studied. Since a modification of ‘HX’ of the acrylic acid at the terminal carboxy group was considered to be facile, we speculated that we could use this specific cyclization to identify viable binding motifs for association. In an ideal scenario, the fragment HXC=O (depicted as O in Figure 1) binds by two hydrogen bonds to the template.

The starting materials 1 for the radical cyclization were prepared from methyl propiolate (4) and 3-chloropropenoic acid via intermediate ester 5 (Scheme 2). Saponification led to 3-(3-chloropropoxy)propenoic acid (6), which was used as starting material for amide 1a and benzimidazolone 1d (Table 1). They were generated via the respective chloro derivative by a Finkelstein reaction (Method A). While amide formation (product 1a) was facile with gaseous ammonia, benzimidazolone was deprotonated (NaH, DMF) prior to acylation (product 1d). The Finkelstein reaction could also be used to convert 3-(3-chloropropoxy)propenoic acid (6) into the title compound 1b, from which the derivatives 1c, 1e–g were synthesized via the corresponding 3-(3-iodopropoxy)propenoyl chloride (Method B). Detailed reactions conditions are provided in the experimental section.

Racemic products 2 were smoothly obtained in all cases by treating the corresponding precursors 1 with tributyltin hydride and an initiator, yields ranging between 74 and 94% (Table 1). Except for the reaction of 1e to 2c, which required AIBN as the initiator in refluxing benzene, all reactions were conducted in toluene at ambient temperature using triethylborane as the initiator. Separation of enantiomers by chiral HPLC (Daicel Chiralpak AD-H) was possible in all cases. This fact facilitated the assessment of the enantiomeric excess (ee) for reactions which were conducted in the presence of template 7 (Figure 1). In the latter set of reactions, the radical cyclization was performed at –78 °C in toluene employing 2.5 equivalents of the complexing reagent 7.

The yields remained very good in most cases, entry 7 being the exception, and the products 2 were obtained in...

enantiomerically enriched form. Remarkably, the simple binding motifs carboxylic amide (H₂NCO) and carboxylic acid (HOCO) accounted for significant ee values, indicating that a binding of substrates 1a and 1b (entries 1, 2) to template 7 occurs and that the binding persists in the radical cyclization process via intermediates 3.

In addition, the enantioselective reaction course also indicates that there is a conformational preference with regard to rotation around the CO–Cα bond (Figure 1). Linear amides are constrained by the geometrical properties of the amide bond, in particular by the almost perfect planarity around the C–N bond, which shows partial double bond character. One would consequently expect an s-trans conformation to be preferred for the CO–Cα bond due to 1,3-allylic strain. The expectation is substantiated by recent calculations conducted on acrylamide.12 As a consequence of the preferred s-trans conformation, the

Figure 1 Complexation of template 7 with substrates 1a–g

Table 1 Reaction Conditions, Yields and Enantioselectivities in the Radical Cyclization Reaction of Substrates 1a–g

<table>
<thead>
<tr>
<th>Entry</th>
<th>HX</th>
<th>Method</th>
<th>Substrate</th>
<th>Initiator (equiv)</th>
<th>Template 7 (equiv)</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>A</td>
<td>1a</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2a</td>
<td>83</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>87</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>–</td>
<td>1b</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2b</td>
<td>94</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>70</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>B</td>
<td>1c</td>
<td>AIBN (0.20)</td>
<td>–</td>
<td>80</td>
<td>2c</td>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>83</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>A</td>
<td>1d</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2d</td>
<td>85</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>86</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>B</td>
<td>1e</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2e</td>
<td>74</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>73</td>
<td>59</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>UV (300 nm)</td>
<td>2.5</td>
<td>–75</td>
<td></td>
<td>80</td>
<td>55</td>
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<tr>
<td>6</td>
<td>N</td>
<td>B</td>
<td>1f</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2f</td>
<td>84</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Et₃B (0.25)</td>
<td>2.5</td>
<td>–78</td>
<td></td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>B</td>
<td>1g</td>
<td>Et₃B (0.25)</td>
<td>–</td>
<td>25</td>
<td>2g</td>
<td>74</td>
<td>–</td>
</tr>
</tbody>
</table>

a Preparation according to Method A or B, as specified in Scheme 2.
b Yield of isolated product 1a, c–g.
c Radical reactions were conducted at a substrate concentration of 15 mM in toluene as the solvent (see experimental section).
d Yield of isolated product 2a–g.
major enantiomer of the radical cyclization should be formed by Si-face attack at carbon atom C_b (Figure 1). We considered hydrazides as carboxylic acid derivatives which could possibly exhibit an increased preference for the s-trans conformation, but the results recorded with the hydrazine derivates, e.g. with 1f and 1g, were disappointing (Table 1, entries 6, 7). The linear urea 1e (entry 3) was equally unsuited for achieving high enantiomeric excesses. It was also the only substrate in which the cyclization could not be induced by triethylborane in the absence of template 7; AIBN was required for initiation at elevated temperature. Interestingly, the triethylborane-initiated cyclization did work in the presence of template 7 at –78 °C but, as already mentioned, the enantiomeric excess of product 2e was very low. In contrast, the cyclic ureas 1d and 1e (entries 4 and 5) delivered relatively high enantioselectivities given the distance between the binding motif and the reaction center at C_b. Indeed, binding to the template presumably occurs via two hydrogen bonds at the lactam part of the urea, which is four bonds away from the prostereogenic carbon atom C_b. Due to this distance, the tetrahydronaphthalene backbone is apparently no longer capable of completely shielding one of the two enantiotopic faces around C_b. The possibility that the polar initiator triethylborane is responsible for a decreased enantioselectivity was ruled out by initiating the cyclization of 1e to 2e with UV light. The enantiomeric excess recorded with this protocol (55% ee) was, in fact, slightly lower than the ee obtained in the triethylborane case (59% ee, entry 5).

In summary, the results indicate that the association to template 7 increases for acrylic acid derivatives in the order hydrazide < amide < acid < cyclic urea. The as yet incomplete enantioselectivity in the case of ureas 1d and 1e is most likely due to the insufficient face differentiation exerted by the tetrahydronaphthalene shield of template 7. To prove this assumption and to employ the urea binding motif in a general fashion, further experiments will be directed at the synthesis of templates with even more extended shields. Studies along these lines are underway in our laboratories and will be reported in due course.

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Anhydrous Et_3N and CH_2Cl_2 were distilled from CaH_2 prior to use. Common solvents (Et_2O, pentane, EtOAc, CH_2Cl_2, MeOH) were distilled prior to use. All other solvents and reagents were used as received. TLC was performed on glass plates (0.25 mm silica gel 60, F_254); detection was by coloration with ceric ammonium molybdate or phosphomolybdic acid. Column chromatography was performed on silica gel (230–400 mesh; ca. 50 g for 1 g of material to be separated) with the eluent mixture indicated. 1H and 13C NMR signals were determined by DEPT experiments and standard two-dimensional NMR experiments. IR spectra were recorded with a Perkin-Elmer 1600 instrument and mass spectra were recorded with an Agilent 5973 or a Finnigan MAT 8200 mass spectrometer. The unstable iodo compounds 1, for some of which MS (EI) and/or HRMS data could not be obtained, were not stored but used immediately after preparation.

3-Chloropropyl 3-(3-Chloropropoxy)propenoate (5)
Et_3N (3 mL) was added to a stirred soln of methyl propionate (4: 5.0 g, 59.5 mmol) and 3-chloropropyl (15 mL) in CH_2Cl_2 (60 mL) at 0 °C. After an exothermic reaction, the solution was stirred at rt for 2 h, then washed with 1 N HCl (20 mL) and H_2O (20 mL), and dried (Na_2SO_4). Kugelrohr distillation (155 °C/0.2 mbar) gave 5.

Yield: 6.1 g (45%); R_S = 0.25 (Et_2O–pentane, 1:3).

IR (neat): 2962 (w), 2880 (w), 1707 (s), 1620 (s), 1440 (s), 1329 (m), 1285 (m), 1207 (m), 1116 (vs), 1038 (m) cm⁻¹.

1H NMR (360 MHz, CDCl_3): δ = 2.13 (vrt. quin, J = 6.5 Hz, 2 H, 2'-H), 2.18 (vrt. quin, J = 6.5 Hz, 2 H, 2'-H), 3.62–3.69 (2 × t, J = 6.5 Hz, 4 H, 3'-H, 3''-H), 4.03 (t, J = 5.8 Hz, 2 H, 1''-H), 4.28 (t, J = 5.8 Hz, 2 H, 1'-H), 5.24 (d, J = 12.6 Hz, 1 H, 2-H), 7.61 (d, J = 12.6 Hz, 1 H, 3-H).

13C NMR (90 MHz, CDCl_3): δ = 32.1 (t), 32.2 (t), 41.2 (t), 41.7 (t), 61.0 (t), 67.6 (t), 97.0 (d), 162.7 (d), 167.9 (s).

MS (EI, 70 eV): m/z (%) = 240/242 (31/1) [M⁺], 205/207 (14/5), 177/179 (15/7), 147/149 (100/33), 101 (21), 71 (89).


3-Chloropropoxy propenoic Acid (6)
A mixture of ester 5 (6.0 g, 25.0 mmol) in 0.5 N aq NaOH (115 mL) was stirred at 40 °C for 24 h. The aqueous layer was washed with Et_2O (2 × 25 mL), then acidified with 6 N HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and the solvent was removed to afford 6 as white crystals.

Yield: 3.1 g (76%); mp 93 °C; R_S = 0.62 (CH_3Cl–MeOH, 10:1).

IR (KBr): 3421 (br), 3100 (m), 3087 (m), 2962 (m), 2927 (m), 2897 (m), 1700 (vs), 1610 (vs), 1466 (m), 1306 (s), 1208 (vs), 731 (s) cm⁻¹.

1H NMR (360 MHz, CDCl_3): δ = 2.17 (vrt. quin, J = 6.1 Hz, 2 H, 2'-H), 3.66 (t, J = 6.1 Hz, 2 H, 3'-H), 4.04 (t, J = 5.8 Hz, 2 H, 1'-H), 5.22 (d, J = 12.6 Hz, 1 H, 2-H), 7.67 (d, J = 12.6 Hz, 1 H, 3-H), 11.05 (br s, 1 H, OH).

13C NMR (90 MHz, CDCl_3): δ = 31.6 (t), 40.7 (t), 67.5 (t), 96.3 (d), 164.0 (d), 173.4 (s).

MS (EI, 70 eV): m/z (%) = 164/166 (207) [M⁺], 146/148 (3/1), 101 (25), 88 (50), 76 (30), 70 (56), 55 (6), 49 (13), 41 (100).

HRMS (EI): m/z calc’d for C_17H_17ClO_3: 164.0240; found: 164.0240.

3-(3-Iodopropoxy)propenoic Acid Derivatives (1a)
Oxalyl chloride (170 μL, 3.2 equiv) was added to a soln of acid 6 (100 mg, 0.61 mmol) in CH_3Cl_2 (2 mL), and the mixture was heated for 1 h under reflux. The mixture was concentrated under reduced pressure to afford crude 3-(3-chloropropoxy)propenoic chloride. Ammonia was introduced over 5 min to a soln of this acid chloride in CH_3Cl_2 (5 mL) at –15 °C. The solvent was removed and the crude product was purified by column chromatography (CH_3Cl_2–MeOH, 200:1 → 50:1). The resulting amide (72 mg, 0.44 mmol) and Nal (166 mg, 2.5 equiv) were heated in acetone (15 mL) under reflux for 48 h. The acetone was removed, the residue was suspended in H_2O (10 mL) and the product was extracted with CH_3Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give 1a as white crystals.

Yield: 111 mg (71%); mp 138–140 °C; R_S = 0.56 (CH_3Cl–MeOH, 10:1).

IR (KBr): 3345 (br), 3080 (w), 2947 (m), 2924 (m), 2874 (m), 1676 (s), 1593 (vs), 1419 (m), 1330 (m), 1203 (s), 1128 (s), 1025 (m), 825 (m) cm⁻¹.

1H NMR (360 MHz, DMSO-d₆): δ = 2.09 (virts. quin, J = 6.6 Hz, 2 H, 2'-H), 3.20 (t, J = 6.7 Hz, 2 H, 3'-H), 3.82 (t, J = 5.9 Hz, 2 H, 1'-H), 5.28 (d, J = 12.4 Hz, 1 H, 2-H), 5.74 (br s, 1 H, NH), 6.50 (br s, 1 H, NH), 7.39 (d, J = 12.4 Hz, 1 H, 3-H).

13C NMR (90 MHz, DMSO-d₆): δ = 34.7 (t), 32.0 (t), 69.8 (t), 99.7 (s), 158.3 (d), 167.7 (s).

MS (EI, 70 eV): m/z (%) = 255 (1) [M⁺], 239 (2), 184 (12), 169 (18), 128 (15), 98 (28), 41 (100).

HRMS (EI): m/z calcd for C₇H₉N₂O₃: 192.0446; found: 192.0449.

Yield: 750 mg (97%); mp 118–119 °C; Rf = 0.62 (CH₂Cl₂–MeOH, 1:2) as yellowish crystals.

To a soln of (1H-1,2,4-triazol-1-yl)-1,3-dihydro-2H-benzimidazol-2-one (1d) (104 mg, 0.37 mmol) and Na2SO4 was added to give 1d as white crystals.

Yield: 140 mg (41%); mp 158–160 °C; Rf = 0.78 (EtOAc–pentane, 1:1).

IR (neat): 3088 (w), 3069 (w), 2971 (m), 2938 (m), 2875 (m), 1678 (s), 1610 (s), 1421 (m), 1334 (m), 1300 (m), 1212 (s), 1164 (s), 941 (m), 824 (m) cm⁻¹.

1H NMR (360 MHz, CDCl₃): δ = 2.28 (virts. quin, J = 6.0 Hz, 2 H, 2'-H), 3.25 (t, J = 6.5 Hz, 2 H, 3'-H), 4.12 (t, J = 6.1 Hz, 2 H, 1'-H), 5.74–7.12 (m, 4 H, 2-H, 3-H, 4-H), 7.66 (d, J = 12.7 Hz, 1 H, 3-H), 11.0 (br s, 1 H, OH).

13C NMR (90 MHz, CDCl₃): δ = 3.1 (t), 32.3 (t), 70.5 (t), 96.3 (d), 164.0 (d), 173.3 (s).

MS (EI, 70 eV): m/z (%) = 372 (37) [M⁺], 239 (100), 169 (81), 134 (30), 106 (12), 71 (25), 41 (68).


1-[3-(3-Iodopropoxy)propenoyl]-1,3-dihydro-2H-benzimidazol-2-one (1f)

Oxalyl chloride (0.11 mL, 3.3 equiv) was added to a soln of acid 1b (100 mg, 0.39 mmol) in CH₂Cl₂ (4 mL) and the mixture was heated under reflux for 1 h. Then, the mixture was concentrated under reduced pressure. The resulting acid chloride was dissolved in MeCN (2 mL) and added dropwise to a suspension of crushed quartz (55 mg, 1.2 equiv) in MeCN (8 mL) under reflux. After 30 min under reflux, the solvent was removed, the residue was suspended in H₂O (10 mL) and the product was extracted with CH₂Cl₂ (3 × 15 mL). The combined extracts were dried (Na₂SO₄) and the solvent was removed to give 1f as white crystals.

Yield: 47 mg (36%); Rf = 0.70 (CH₂Cl₂–MeOH, 10:1).

IR (neat): 3263 (m), 2925 (w), 2875 (w), 1687 (s), 1644 (s), 1586 (m), 1479 (m), 1343 (s), 1300 (s), 1187 (m), 1145 (s), 1038 (m) cm⁻¹.

1H NMR (360 MHz, CDCl₃): δ = 1.95–2.00 (m, 2 H, 5-H, 5'-H), 2.21 (virts. quin, J = 6.1 Hz, 2 H, 2'-H), 3.28 (t, J = 6.9 Hz, 2 H, 3'-H), 3.36 (dt, J = 2.6, 6.1 Hz, 2 H, 2'-H), 3.94 (t, J = 6.1 Hz, 2 H, 1'-H), 5.55 (d, J = 12.6 Hz, 1 H, 2-H), 7.12 (br s, 1 H, NH), 7.59 (d, J = 12.6 Hz, 1 H, 3'-H), 7.86 (br s, 1 H, NH), 9.88 (br s, 1 H, NH).

13C NMR (90 MHz, CDCl₃): δ = 31.1 (t), 32.0 (t), 71.0 (t), 98.8 (d), 154.2 (s), 161.6 (d), 167.2 (s).

MS (EI, 70 eV): m/z (%) = 284 (15), 256 (20), 211 (9) [M⁻], 172 (61), 155 (27), 127 (43), 100 (100), 84 (60), 56 (91).

1-[3-(3-Iodopropoxy)propenoyl]pyrazolidine (1f)

Et₃N (166 µL, 3 equiv) was added to a mixture of pyrazolidine dihydrochloride (84 mg, 1.5 equiv) in CH₂Cl₂ (5 mL). To this solution, 3-(3-iodopropoxy)propenoyl chloride (0.39 mmol), prepared as described above (see 1e), dissolved in CH₂Cl₂ (2 mL) was added.
and the mixture was stirred for 30 min at r.t. The mixture was concentrated and the product was purified by column chromatography (CH$_2$Cl$_2$–MeOH, 200:1 → 100:1) to give 1f as an unstable yellowish oil.

Yield: 94 mg (78%); $R_f$ = 0.70 (CH$_2$Cl$_2$–MeOH, 10:1).

IR (neat): 3382 (br), 3198 (br), 2970 (m), 2873 (m), 1666 (s), 1414 (s), 1362 (w), 1206 (w), 1183 (w), 1063 (m) cm$^{-1}$.

HRMS (EI): $m/z$ (%) = 246 (7) [M+] $\rightarrow$ 134 (100), 106 (10), 71 (15).

HRMS (EI): $m/z$ calcd for C$_7$H$_{12}$N$_2$O$_3$: 172.0848; found: 172.0848.

1-(Tetrahydrofuran-2-ylacetyl)-1,3-diiodo-2H-benzimidazol-2-one (2d)

Yield: 86%; mp 118–120 °C; $[\alpha]_{D}^{25}$ = 7.4 (c 0.31, MeOH); 37% ee; $R_f$ = 0.65 (EtOAc–pentane, 1:1).

IR (KBr): 3205 (w), 3064 (w), 2957 (m), 2928 (m), 2856 (m), 1730 (s), 1531 (s), 1452 (s), 1312 (m), 1191 (m), 1115 (m), 969 (m), 756 (s) cm$^{-1}$.

HRMS (EI): $m/z$ (%) = 246 (7) [M+] $\rightarrow$ 134 (100), 106 (10), 71 (15).

HRMS (EI): $m/z$ calcd for C$_{13}$H$_{14}$N$_2$O$_3$: 246.1005; found: 246.1004.
MS (El+, 70 eV): m/z (%) = 212 (6) [M+], 195 (2), 184 (58), 169 (45), 153 (15), 143 (39), 127 (5), 111 (12), 101 (100), 85 (35), 71 (61), 56 (25), 43 (41).

HRMS (El): m/z calcd for C12H16N2O2: 220.1211; found: 220.1210.

1-(Tetrahydrofuran-2-ylacetyl)pyrazolidine (2f)

Yield: 88%; Rf = 0.60 (CH2Cl2–MeOH, 10:1).

IR (neat): 3462 (w), 2957 (w), 2875 (w), 1639 (s), 1596 (m), 1450 (m), 1382 (m), 1320 (w), 1259 (m), 1058 (m), 974 (m), 752 (s) cm–1.

HRMS (EI): m/z calcd for C12H16N2O2: 220.1211; found: 220.1210.

1H NMR (360 MHz, CDCl3): δ = 1.52–1.62 (m, 1 H, 4-H), 1.85–2.98 (m, 2 H, 3-H, 4-H), 2.04–2.13 (m, 1 H, 3-H), 2.49 (dd, J = 15.1, 8.2 Hz, 1 H, 2-Ha), 2.55 (dd, J = 15.1, 3.8 Hz, 1 H, 2-Ha), 3.78–3.84 (m, 1 H, 5-H), 3.92–3.98 (m, 1 H, 5-H), 4.15–4.22 (m, 1 H, 2-Hb), 5.28 (brs, 1 H, NH), 6.82–6.90 (m, 3 H, HAr), 7.19–7.23 (m, 2 H, HAr), 8.31 (brs, 1 H, NH).

13C NMR (90 MHz, CDCl3): δ = 20.2 (CH2), 29.0 (CH), 37.1 (CH), 40.1 (CH), 46.7 (CH), 48.3 (CH2), 55.3 (CH), 123.7 (C), 125.4 (C), 126.1 (C), 129.0 (CH), 145.3 (C), 167.0 (C).

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