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A novel, microwave-assisted method for the synthesis of alicyclic-condensed 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-ones

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ABSTRACT

An efficient, high-yielding method has been developed for the synthesis of cycloalkane-fused and phenyl-substituted 1,4-diazepin-5-ones from β-amino acids. The process involves the oxidative cleavage of a terminal olefin bond and an acid-catalyzed, microwave-assisted intramolecular condensation step.

Although the preparation and pharmaceutical properties of 1,4-benzodiazepines have been well documented, less attention has been paid to their saturated analogues. To the best of our knowledge, there has been only one report on the synthesis of cycloalkane-condensed 1,4-diazepinones.[1] However, certain 1,4-diazepin-5-ones exhibit significant biological properties, for example, as lymphocyte function-associated antigen-1 inhibitors,[2] anticonvulsants,[3] HIV-1 reverse transcriptase inhibitors,[4] pharmacophores for structure–activity relationships,[5] and most recently, γ-turn-like mimics.[6]

We report here an efficient, microwave (MW)-assisted method for the preparation of *cis*- and *trans*-cyclohexane- and *cis*-cyclopentane-condensed 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-ones.

Starting from racemic *cis*- and *trans*-2-aminocyclohexane-carboxylic acids **1** and **12** and cispentacin[7] **2**, Cbz (benzyloxycarbonyl) protection of the amino group followed by amidation with allylmethylamine or allyl(*p*-methoxy)benzylamine and subsequent oxidative cleavage of the carbon–carbon double bond furnished the corresponding formylmethyl carboxamides **6**–**8** and **14** (Scheme 1). An initial attempt, to perform the oxidative cleavage in a one-pot fashion, according to a literature procedure,[8] resulted in a low yield of the desired carbonyl compound **6**. However, the stepwise procedure reported for carbohydrate derivatives by Sharma and Nielsen[9] resulted in compounds **6**–**8** and **14** in overall yields of 71–79%.[10]

The reaction of *cis*-cyclohexane derivative **6** (R^1 = Me) in the presence of 10 mol % *p*-TsOH in dry CH_2Cl_2 in a MW reactor at 100 °C for only 5 min resulted in complete conversion to 1,4-diazepin-5-one **9** in 90% yield.[11] For cyclopentane derivative **7** (R^1 = Me), application of the same method gave compound **10** in 81% yield. The method also proved adaptable for *trans*-cyclohexane derivative **14**, providing 1,4-diazepin-5-one **15** in an excellent (88%) yield. Broadening the scope of the transformation led to the synthesis of the PMB-protected derivative **8** (n = 2, R^1 = PMB), which furnished diazepinone **11** in 83% yield.

We next investigated the scope and limitations of the ring closure. 7-Phenyl-5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-one **18** was formed in 83% yield from compound **17**, itself synthesized from (±)-β-phenylalanine[12] **16** (Scheme 2) via the process established for **1**, **2** and **12** in Scheme 1.

Our efforts to apply this method to anthranilic acid derivatives failed to yield the desired 1,4-benzodiazepin-5-ones. One possible explanation is that decreasing the nucleophilicity of the aniline nitrogen with a Cbz group inhibits nucleophilic attack on the aldehyde moiety. However, for *N*-methyl- and *N*-benzylanthranilamides, a similar method involving the application of acetal derivatives has been reported for the construction of 1,4-benzodiazepin-5-ones.[13]

In conclusion, β-amino acid-derived allylamides have been transformed efficiently into the corresponding aldehydes by applying a dihydroxylation/reduction/oxidative cleavage sequence. The formylmethyl derivatives obtained were cyclized to 1,4,6,7-tetrahydro-1,4-diazepin-5-ones in high yields in an acid-promoted

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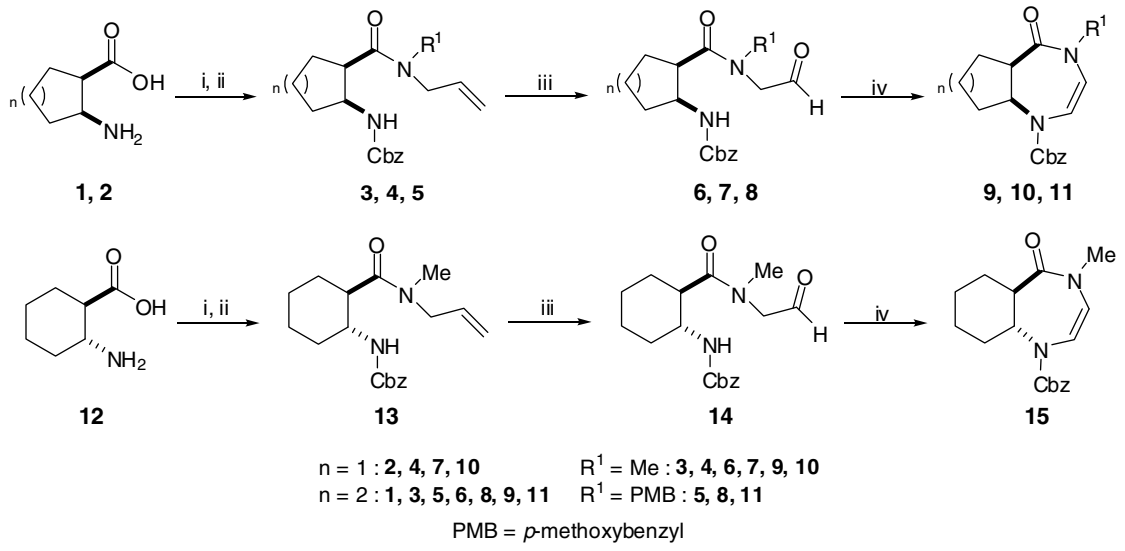
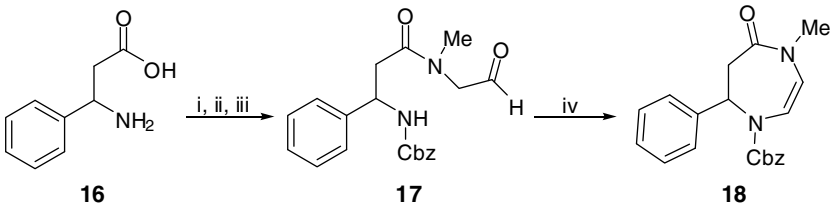


Scheme 1. Reagents and conditions: (i) CbzCl, NaOH, CH_2Cl_2, rt (81–90%); (ii) $(COCl)_2$, CH_2Cl_2, rt, 4 h, then Et_3N, R^1-allylamine, CH_2Cl_2, rt, overnight (83–88%); (iii) (a) $RuCl_3{\cdot}nH_2O$, $NaIO_4$, $CH_3CN/EtOAc/H_2O$, 0 °C, 5 min, (b) $NaBH_4$, THF/H_2O, rt, 20 min, (c) $NaIO_4$, THF/H_2O, 0–5 °C, 30 min (71–79% for the three steps); (iv) *p*-TsOH, CH_2Cl_2, MW, 100 °C, 5 min (81–90%).



Scheme 2. Reagents and conditions: as in Scheme 1. Yields: (i) 83%, (ii) 79%, (iii) 63%, (iv) 83%.

MW-assisted condensation reaction. The method proved not to be restricted to cycloalkane-derived β-amino acids, and the nitrogens can be orthogonally protected (R^1 = PMB), which opens up the possibility for further transformations.

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10. *Representative analytical data for aldehyde* **8**: Colourless oil; yield 79%, ^{1}H NMR (400.13 MHz, $CDCl_3$, δ): 9.41 (s, 1H), 7.30–7.39 (m, 5H), 7.02–7.10 (m, 2H), 6.81–6.90 (m, 2H), 5.46 (d, *J* 7.6 Hz, 1H), 5.11 (s, 2H), 4.51 (q, *J* 15.7 Hz, 2H), 3.91 (d, *J* 4.9 Hz, 2H), 3.76–3.85 (m, 4H), 3.29 (d, *J* 4.1 Hz, 1H), 2.17–2.28 (m, 1H), 1.92–2.02 (m, 1H), 1.37–1.77 (m, 6H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 197.2, 174.5, 159.5, 155.9, 136.6, 129.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 114.5, 114.3, 66.5, 55.8, 55.4, 55.2, 49.5, 40.5, 29.3, 26.4, 22.7, 22.2. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39; O, 18.24. Found: C, 68.29; H, 6.73; N, 6.50; O, 18.39.
11. *General procedure for the preparation of 5H-1,4,6,7-tetrahydro-1,4-diazepin-5-ones* **9–11**, **15** *and* **18**: A CEM Discover 10 ml MW vial was charged with 0.3 mmol of compounds **6–8**, **14** or **17**, 5.7 mg (10 mol %) of *p*-toluenesulfonic acid and 2 ml of anhydrous dichloromethane, and was sealed with a Teflon cap. The vial was irradiated at 100 °C (200 W) for 5 min, with a 1.5 min ramp time. Next, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on Merck silica gel (0.063–0.200 mm); elution with 1:1 *n*-hexane/ethyl acetate gave the pure compounds. *Compound* **9**: white solid; yield 90%, mp 76–77 °C, ^{1}H NMR (400.13 MHz, $CDCl_3$, δ): 7.31–7.47 (m, 5H), 6.40 (br s, 1H), 5.05–5.28 (m, 3H), 4.37 (d, *J* 10.0 Hz, 1H), 3.08 (s, 3H), 2.94 (s, 1H), 2.34 (d, *J* 12.5, 1H), 1.85–2.06 (m, 2H), 1.68–1.83 (m, 2H), 1.27–1.60 (m, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 171.9, 153.8, 136.2, 129.8, 129.2, 129.0, 128.8, 127.9, 114.3, 111.9, 68.6, 62.5, 43.9, 37.0, 36.6, 29.7, 25.8, 21.3. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91; O, 15.27. Found: C, 69.04; H, 6.92; N, 8.75; O, 15.44. *Compound* **10**: colourless oil; yield 81%, ^{1}H NMR (400.13 MHz, $CDCl_3$, δ): 7.31–7.39 (m, 5H), 6.31 (d, *J* 6.5 Hz, 1H), 5.41 (d, *J* 6.5 Hz, 1H), 5.13–5.25 (m, 2H), 4.65–4.72 (m, 1H), 2.99–3.10 (m, 4H), 2.19–2.29 (m, 2H), 1.57–1.95 (m, 4H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 173.3, 151.2, 136.6, 129.2, 129.1, 129.0, 128.8, 128.7, 119.8, 119.4, 69.4, 68.7, 48.6, 35.9, 29.8, 26.7, 22.4. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33; O, 15.98. Found: C, 68.07; H, 6.82; N, 9.45; O, 15.74. *Compound* **11**: colourless oil; yield 83%, ^{1}H NMR (400.13 MHz, $CDCl_3$, δ): 7.29–7.39 (m, 5H), 7.19 (d, *J* 8.1 Hz, 2H), 6.84 (d, *J* 9.1 Hz, 2H), 6.39 (br s, 1H), 5.07–5.24 (m, 3H), 4.74 (d, *J* 14.1 Hz, 1H), 4.56 (d, *J* 14.1 Hz, 1H), 4.37 (d, *J* 10.1 Hz, 1H), 3.78 (s, 3H), 2.96 (s, 1H), 2.38 (d, *J* 12.1 Hz, 1H), 1.89–2.05 (m, 2H), 1.77 (d, *J* 14.1 Hz, 1H), 1.29–1.56 (m, 4H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 171.9, 159.7, 136.5, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.3, 129.2, 129.1, 129.0, 128.7, 114.7, 110.5, 68.8, 62.8, 55.9, 51.5, 44.3, 31.1, 30.0, 26.1, 21.7. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66; O, 15.22. Found: C, 71.27; H, 6.90; N, 6.81; O, 15.37. *Compound* **15**: white solid; yield 88%, mp 79–80 °C, ^{1}H NMR (400.13 MHz, $CDCl_3$, δ): 7.31–7.42 (5H, m), 6.39 (1H, br s), 5.15–5.25 (m, 2H), 5.10 (d, *J* 4.0 Hz, 1H), 4.36 (d, *J* 10.1 Hz, 1H), 3.08 (s,3H), 2.94 (br s, 1H), 2.34 (d, *J* 12.9 Hz, 1H), 1.86–2.02 (m, 2H), 1.71–1.83 (m, 1H), 1.22–1.61 (m, 4H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 171.4, 153.3, 135.9, 128.7, 128.6, 128.5, 128.3, 128.1, 113.8, 111.4, 68.2, 62.1, 43.5, 36.2, 30.3, 29.2, 25.4, 21.0. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91; O, 15.27. Found: C, 68.93; H, 7.11; N, 9.02; O, 15.13. *Compound* **18**: colourless oil; yield 83%, ^{1}H NMR (DMSO-d_6, 400.13 MHz, 319.3 K) 7.12–7.34 (m, 10H), 6.64 (d, *J* 8.5 Hz, 1H), 5.74–5.78 (m,

1H), 5.39–5.46 (m, 1H), 5.12 (brs, 2H), 2.98–3.10 (m, 2H), 2.77 (s, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 169.9, 152.6, 136.4, 129.5, 129.4, 129.3, 129.2, 129.1, 128.2, 128.1, 125.9, 125.8, 125.7, 115.8, 113.8, 68.9, 60.8, 59.8, 43.1, 35.6. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; O, 14.27. Found: C, 71.23; H, 6.12; N, 8.26; O, 14.20.

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