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Synthesis of 1,4-diazepin-5-ones under microwave irradiation and their reduction products

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Abstract—A new efficient access to 1,4-diazepane derivatives is described via a microwave assisted synthesis of 7-substituted-1,4-diazepin-5-ones, which proceeds rapidly in good yields. Catalytic reduction gave 1,4-diazepan-5-ones and 1,4-diazepanes whereas a ring opening was observed by hydride reduction when a phenyl group occupies the *N*-benzylic position.

Small peptides often exhibit in vitro pharmacological activity but their lack of oral bioavailability prevents them from being used as drugs. Special attention has been given to replace peptidic moieties by rigid residues, such as heterocyclic rings or constrained peptidomimetics, with the aim to mimic their bioactive conformation and therefore to confer an in vivo activity. Seven-membered rings like benzodiazepine are very attractive compounds and a large number of strategies have used this heterocycle to develop original compounds. For example, benzodiazepines were introduced in the design of (i) anticonvulsant or anxiolytic hypnotic agents; (ii) farnesyltransferase inhibitors or (iii) CCK2 ligands.[1]

We focussed our attention on particularly attractive templates to develop new anticancer agents, that is, the 7-substituted-2,3,4,5-tetrahydro-1,4-diazepin-5-ones **A**, 7-substituted-1,4-diazepan-5-ones **B** and full-reduced 7-substituted-1,4-diazepanes **C** (Fig. 1). These heterocycles can be considered as dipeptidomimetics by rigidification of an intramolecular hydrogen bond in a γ-turn.[2] Moreover, they represent an alternative to the classical benzodiazepine scaffold.

To the best of our knowledge, no efficient synthesis describes the way to obtain the saturated 1,4-diazepane ring. Here we report the synthesis of the substituted 1,4-diazepanes **C** and of their precursors, 1,4-diazepin-5-ones **A** and 1,4-diazepan-5-ones **B**.

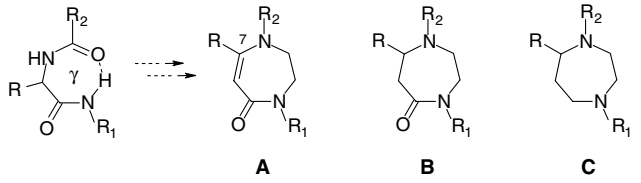

Figure 1. Analogy between a hydrogen bond in a γ-turn and the seven-member rings such as 1,4-diazepane derivatives **A**–**C**.

In the course of our investigations in the diazepane series, we wished to consider a versatile and efficient approach leading easily to diazepanes bearing an aryl or an alkyl substituent on C-7. According to these considerations, we defined the synthetic route outlined in Scheme 1. The first step of the synthesis was the cyclization of various β-ketoesters **1a**–**h** (β-ketoesters **1e**–**h** were prepared according to a previously reported method,[3] whereas β-ketoesters **1a**–**d** were commercially available) with ethylenediamine **2** to give 2,3,4,5-tetrahydro-1,4-diazepin-5-ones **3a**–**h**, using a modification of a described procedure:[4] the two reactants were heated at reflux in xylene for 8 h to achieve azeotropic removal of water and ethanol. Yields and LC/MS analysis provided evidence for the formation of various by-products, which resulted from several side reactions depending on the reaction conditions (Scheme 2). For example, condensation of

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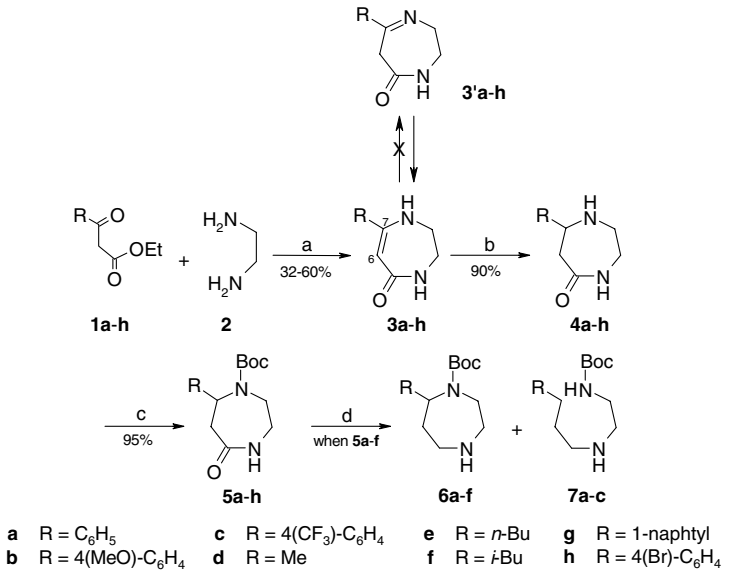
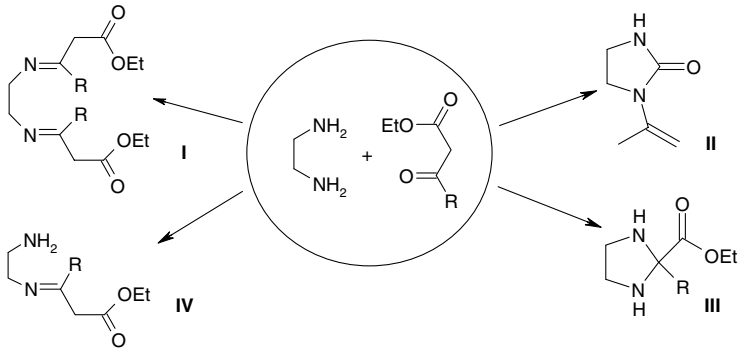


Scheme 1. Reagents and conditions: (a) (1) xylene, reflux, 8 h or (2) xylene, microwave irradiation, 10 min; (b) H_2, 50 bars, 10% Pd/C, MeOH, 60 °C, 24 h; (c) $(Boc)_2O$, DIEA, dioxane/water (4:1), rt, 48 h; (d) $LiAlH_4$, THF, rt, 24 h.



Scheme 2. By-products observed after reaction of a β-ketoester with ethylenediamine.

ethylenediamine with ethyl benzoylacetate **1a** gave mainly 2,3,4,5-tetrahydro-1,4-diazepin-5-one **3a** at 40% yield whereas ethyl acetoacetate **1d** gave 2,3,4,5-tetrahydro-1,4-diazepin-5-one **3d** and bis(iminoester) **I** (R = Me) at 32% and 30% yields, respectively. These results illustrate the difficulty to establish the adequate experimental conditions to selectively obtain the target products.

Other works[5] on similar compounds stated that the rate of formation of by-products depend on parameters such as pH, reaction time and solvent.

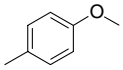
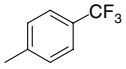
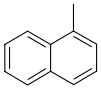
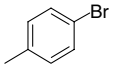
We found xylene as the best solvent for limiting formation of imidazolidinone **II**, imidazolidine **III** and imine **IV**. Basic conditions (pyridine, alcoholic potassium hydroxide) have also been explored[6] but did not allowed here to upgrade the yield of **3a** from **1a**, whereas an acidic medium increased the yield of imidazolidine **III**. The better conditions to obtain 2,3,4,5-tetrahydro-1,4-diazepin-5-ones **3a**–**h** were azeotropic distillation in neutral medium (Table 1, method A). In addition, analysis of the ^1H NMR spectra assigned to **3a**–**h** the structure of conjugated enaminolactams rather than the one of the corresponding non-conjugated system of iminolactams (**3′a**–**h**).

The application of microwave dielectric heating for conducting organic reactions is an emerging technique which constitutes a good technique for any reaction where water and/or alcohol are formed[7] and often leads to better yields and cleaner products. In an attempt to increase the rate of cyclization into diazepinones **3a**–**h**, the reaction was carried out in a flask equipped with a Dean–Stark apparatus under microwave irradiation.[8] Replacement of thermal heating by microwave irradiation (Table 1, method B) significantly shortened reaction time and improved the yields (47–60%) in each run of experiments.

1,4-Diazepan-5-ones **5a**–**h** were next obtained according to a two-step procedure by catalytic reduction of the ethylenic bond of diazepinones **3a**–**h**, followed by protection of the amine group as carbamate (Scheme 1).

Conjugation of the ethylenic group with the lactam function and/or without a 7-phenyl substituent de-

Table 1. Comparative yields for synthesis of the 2,3,4,5-tetrahydro-1,4-diazepin-5-ones **3a**–**h** under thermal and microwave conditions

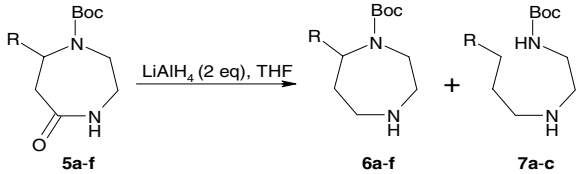
Compound	R	Method A[a] Yield (%)	Method B[b] Yield (%)
3a		40	60
3b		39	58
3c		36	55
3d		32	47
3e		35	48
3f		38	54
3g		41	57
3h		40	55

[a] Method A: xylene, thermal heating, azeotropic distillation, 8 h.
[b] Method B: xylene, microwave irradiation (300 W), azeotropic distillation, 10 min.

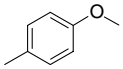
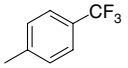
creased its reactivity towards reduction and required harsher conditions than the ones usually adopted (hydrogen pressure: 50 bars, 60 °C, 24 h, 10% Pd/C). The N-protection reaction was carried out in almost quantitative yields (>95%) by using di-*tert*-butyl dicarbonate and *N*,*N*-diisopropylethylamine. Reduction of 1,4-diazepan-5-ones **5a**–**f** into 1,4-diazepanes, that represent potential building units in peptidic drug design, was thoroughly examined. Treatment with metal hydrides such as boron derivatives (BH_3–THF, $BH_3{\cdot}Me_2S$) or with a mixture of monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$), prepared in situ from $LiAlH_4$ and $AlCl_3$,[9] resulted only in a decarbamoylation of the starting materials.

Surprisingly, the reduction of compound **5a** carried out with $LiAlH_4$ (2 equiv) was not chemoselective (Table 2) and performed an unexpected ring opening[10] that was not observed on 1-*tert*-butoxycarbonyl-2-phenylpiperidin-3-one[11] or on a 3-amino-1-*tert*-butoxycarbonyl-2-phenylpiperidine (in CP-99,994, $NaBH_4$ as hydride).[12] Chromatographic and LC/MS analysis indicated that reduction (into diazepane **6a**) and hydrogenolysis (into ethanediamine **7a**) occurred simultaneously whereas a complete conversion of lactams **5a**–**c** into amines **7a**–**c** was effective when the stoichiometry of $LiAlH_4$ rose to 4 equiv. Furthermore, a comparative study of this reaction done with 7-aryl and 7-alkyl 1,4-diazepan-5-ones (**5b**,**c** and **5d**–**f**, respectively) showed the exclusive occurrence of a ring opening when a phenyl ring was present (**5a**), whatever the electronic influence of its substituent (4-methoxy for **5b**, 4-trifluoromethyl for **5c**); this reactivity is reminiscent of the lithium reductive opening of nitrogen-containing heterocycles, such as 2-phenylpyrrolidine,[13] or may be compared with the classical catalytic hydrogenolysis of *N*-benzylamines.

Table 2. Reduction of 1,4-diazepan-5-ones **5a**–**f** with $LiAlH_4$



5a-f **6a-f** **7a-c**

Entry	R	**6** Yield (%)	**7** Yield (%)
a		20	13
b		18	10
c		22	7
d		55	0
e		51	0
f		57	0

In conclusion, a straightforward method for the synthesis of 2,3,4,5-tetrahydro-1,4-diazepin-5-ones was optimized using microwave irradiation, which offers several advantages including good yields, short reaction time and limited formation of by-products. The corresponding 1,4-diazepan-5-ones were easily obtained by catalytic hydrogenation and their reduction with $LiAlH_4$ gave 1,4-diazepanes. This reduction led to an unexpected ring opening when an aryl substituent is present on the vicinal carbon of the carbamate-protected amine, thus limiting the yields of diazepanes.

Acknowledgements

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8. *General microwave irradiation procedure for the preparation of 1,4-diazepin-5-ones* **3a**–**h** *(Table 1, Method B)*: 7-Phenyl-2,3,4,5-tetrahydro-1,4-diazepin-5-one (**3a**): The reaction was carried out at atmospheric pressure in an open microwave oven (CEM Discover®) along with a built-in magnetic stirrer. A long-neck quartz vessel was used equipped with an external azeotropic Dean–Stark apparatus. Ethylenediamine (4.7 g, 78 mmol) was added to ethyl benzoylacetate (15 g, 78 mmol) in dry xylene (50 mL). The mixture was heated at 135 °C while stirring under microwave irradiation (300 W) for 10 min. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The product was washed with diethyl ether and filtered (8.8 g, 60% yield). $R_f = 0.25$ (CH_2Cl_2–MeOH 9/1). Mp 206 °C [lit.[4] mp 207–209 °C]. IR (neat): 1626 (CO), 1550 (CN). ^{1}H NMR (300 MHz, $CDCl_3$): 3.49–3.53 (m, 2H, C*H*$_2$NH), 3.64–3.68 (m, 2H, C*H*$_2$NHCO), 4.91 (m, 1H, N*H*), 5.00 (s, 1H, C*H*), 6.10 (m, 1H, N*H*CO), 7.38–7.41 (m, 3H, ar), 7.51–7.53 (m, 2H, ar).
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10. *Example of reduction of the 1,4-diazepan-5-ones* **5a**–**h** *with LiAlH$_4$ (Table 2, entry a)*: 1,4-Diazepan-5-one **5a** (5 g, 17 mmol) was diluted in anhydrous THF (200 mL) before $LiAlH_4$ (2.6 g, 34 mmol) was added slowly at 0 °C. After stirring for 24 h at room temperature, the reaction was quenched by adding water dropwise (15 mL) at 0 °C, then 10% aqueous sodium hydroxide (100 mL). The precipitate was filtered off and the filtrate was concentrated. The residue was submitted to column chromatography (methylene dichloride–methanol 95:5) to give two major products:
1-tert-Butoxycarbonyl-7-phenyl-1,4-diazepane (**6a**): $R_f =$ 0.62 (CH_2Cl_2–MeOH 9/1). m = 0.95 g (20% yield). IR (neat): 1697 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 1.50 (s, 9H, C*H*$_3$), 1.85–1.89 (m, 1H, CHC*H*$_2$CH$_2$NH), 2.03–2.12 (m, 1H, CHC*H*$_2$CH$_2$NH), 2.13 (m, 1H, N*H*), 2.82–2.95 (m, 1H, CHCH$_2$C*H*$_2$NH), 3.13–3.19 (m, 1H, CHCH$_2$C*H*$_2$NH), 3.36–3.75 (m, 5H, C*H*$_2$C*H*$_2$N(Boc)C*H*), 7.21–7.45 (m, 5H, ar). ^{13}C NMR (75 MHz, $CDCl_3$): 29.4 (*C*H$_3$), 38.4 (CH*C*H$_2$CH$_2$NH), 44.8 (*C*H$_2$NBoc), 49.6 (*C*H$_2$NHCH$_2$), 65.1 (*C*H), 125.8 (ar). MS (APCI$^+$) $m/z = 277$ (MH$^+$).
1-tert-Butoxycarbonyl-2-(3-phenylpropyl)ethane-1,2-diamine (**7a**): $R_f = 0.40$ (CH_2Cl_2–MeOH 9/1). $m = 0.60$ g (13% yield). IR (neat): 1697 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H, C*H*$_3$), 1.79–1.84 (m, 3H, CH$_2$C*H*$_2$CH$_2$N*H*), 2.62–2.72 (m, 6H, C*H*$_2$CH$_2$C*H*$_2$NHC*H*$_2$), 3.21–3.23 (m, 2H, C*H*$_2$NHBoc), 5.07 (m, 1H, N*H*Boc), 7.18–7.27 (m, 5H, ar). ^{13}C NMR (75 MHz, $CDCl_3$): 28.4 (*C*H$_3$), 31.6 (CH$_2$*C*H$_2$CH$_2$), 33.6 (*C*H$_2$ar), 40.2 (*C*H$_2$NHBoc), 49.0 (*C*H$_2$NH*C*H$_2$), 125.8 (ar), 128.4 (ar). MS (APCI$^+$) $m/z = 279$ (MH$^+$).
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