A New, Easy Access to the 6-Aminoperhydro-1,4-diazepine Scaffold under Ultrasound and Microwave Irradiation

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Abstract: A novel, efficient, and rapid synthesis of the 6-aminoperhydro-1,4-diazepine scaffold is reported. It was promoted by microwave or sequential ultrasound/microwave irradiation under solvent-free conditions or in solution. Protected ethylenediamine derivatives and *N*-Boc-serinol dimesylate underwent rapid cyclization to give 6-aminoperhydro-1,4-diazepine derivatives in excellent yields and with high selectivity, whereas the same reaction failed or gave negligible yields under conventional heating. Cesium or potassium ions catalyzed the ring closure by coordinating the sulfonamide groups. All relevant work reported to date in the literature mostly concern about the syntheses of either 1*H*-tetrahydro-1,4-diazepine-2,5-dione or substituted 1,4-benzodiazepines, while the few published procedures for the preparation of 6-aminoperhydro-1,4-diazepines involved several steps, required long reaction times and afforded low yields. By the present method, access to 6-aminoperhydro-1,4-diazepines becomes much easier and faster.

Key words: heterocycles, synthesis, catalysis, cyclizations, ligands, ring closure

The synthesis of heterocycles can be regarded as an important factor in the supply of novel drugs, because a heterocyclic ring constitutes an essential feature of many biologically active compounds. Seven-membered heterocycles with two hetero atoms in 1,4 position provide interesting scaffolds for combinatorial chemistry because of their unique pharmacological activity on the central nervous system – widely popularized in the case of 1,4-benzodiazepines.[1] Several substituted analogues of 6-aminoperhydro-1,4-diazepine are well-known serotonin and dopamine receptor antagonists.[2] In recent years a variety of 1,4-diazepines have been reported as peptidomimetic scaffolds,[3] as anti-HIV agents,[4] as inhibitors of peptidoglycan synthesis[5] and platelet aggregation,[6] as inhibitors of protein kinase[7] and matrix metalloproteinase (MMPs),[8] as 5-HTH$_3$ (5-hydroxytryptamine) receptor antagonists,[9] and otherwise as biological tools.[10] The search for efficient peptidomimetics has led to the synthesis of numerous peptides containing a ring system that acts as a conformationally constrained core. The identification of novel ligands having high affinities for various receptors and enzymes still remains a major goal in biochemistry. In particular, the increasing need to provide finely tuned macrocycles for medicinal chemistry applications makes it desirable to develop novel and convenient synthetic procedures for their preparation.

It is well known that seven-membered heterocyclic compounds lacking a fused aromatic nucleus are difficult to synthesize.[11] Although the literature reports several synthesis of tetrahydro-1,4-diazepine-2,5-dione and substituted 1,4-benzodiazepines, we found only three references describing the synthesis of parent 6-aminoperhydro-1,4-diazepine, a compound that could be used as an interesting core for the synthesis of potential drugs. A synthetic procedure has been reported for (*R*)-6-amino-1-ethyl-4-methylperhydro-1,4-diazepine, which is the amine moiety of AS-8112, a novel and potent dopamine (D_2 and D_3) and 5-HT H_3 receptor antagonist, commonly used as an antiemetic agent.[12] It involved several steps, required a long reaction time, and afforded extremely low yields of the desired product. Another paper dealt with a solid-phase synthesis of the hitherto unreported 3,6-disubstituted 1*H*-tetrahydro-1,4-diazepine-2,5-dione by a microwave-assisted Miller cyclization.[13] More recently, the synthesis and coordination properties of 6-aminoperhydro-1,4-diazepine[14] were described. This route, however, is lengthy (six steps) and involves the handling of potentially explosive azides. After taking stock of published work, we decided to develop a general and versatile access to this class of heterocycles. Relying on our experience in synthetic procedures involving power ultrasound (US)[15] and microwaves (MW),[16] alone or combined,[17] we decided to apply them to the synthesis of 6-aminoperhydro-1,4-diazepine derivatives by cyclization of a protected ethylenediamine derivative with *N*-Boc-serinol dimesylate in the presence of alkali metal carbonate (K_2CO_3 or Cs_2CO_3). Thus, aiming to synthesize the 6-aminoperhydro-1,4-diazepine scaffold, we explored four different reaction conditions: 1) heating in an oil bath under vigorous magnetic stirring; 2) intense, short sonication (3 min, 120 W) using a probe equipped with a titanium horn, followed by MW irradiation in an open vessel fitted with a condenser (1 h, 350 W, the flask being cooled by circulation of refrigerated fluid) (this sequential US/MW irradiation was repeated 2–3 times); 3) intense, short sonication (3 min, 120 W), followed by MW irradiation in a pressure-resis-

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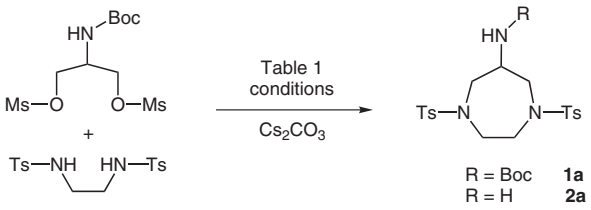
tant closed vessel (200 W, 2 h, 150 °C); and 4) solid reagents and base, after being finely mixed in a mortar, were directly irradiated with MW (4 times for 5 min, 600 W, with interposed pauses of 1 min). A summary of the results is shown in Scheme 1 and Table 1.



Scheme 1 Synthesis of 6-amino-1,4-ditosylperhydro-1,4-diazepine

An essential precondition for MW to exhibit its promoting effect was a very high degree of dispersion of solid alkali carbonate, as was effected by US. We also carried out the reaction by omitting prior sonication of the reaction mixture. In this case, lower conversions and consequently lower yields of desired product were obtained. No conversion was observed when only ultrasound was used.

It is a well-established fact that MW speeds up nucleophilic substitutions by rapidly and efficiently heating the reaction mixture and/or stabilizing their more polar transition states.[16] Out of a variety of solvents studied for our cyclization, DMF and acetonitrile performed best; the latter was chosen because it can be easily removed during the workup. We found that all MW-assisted reactions, whether neat or in solution, gave the Boc-free heterocycle (except entry 2 in Table 1) as main product in very short reaction times and excellent isolated yields. Best results were achieved with acetonitrile in a pressure-resistant closed vessel (Table 1, entry 3) and under solvent-free conditions (Table 1, entry 10).

Aiming to optimize the procedure, we compared the effects of different alkali metal carbonates and two organic bases; conditions were according to protocol P3 of Table 1. Cesium carbonate (Table 2, entry 3) gave the best result, with an overall yield of 93%, immediately followed by potassium carbonate (75%). Lithium carbonate (Table 2, entry 1) only yielded by-products, probably because of concurrent polymerization processes; with triethylamine and DBU no reaction occurred (Table 2, entries 6 and 7). The addition of a phase-transfer catalyst (tetrabutylammonium bromide, TBAB Table 2, entry 4) to Cs_2CO_3 did not increase the yield nor did it change the protected/unprotected primary amine ratio. A similar result was obtained when Cs_2CO_3 and triethylamine were used together (Table 2, entry 5). These findings indicate that the nature of the alkali metal ion significantly affects the cyclization, the most active one being Cs; Li is probably too small to promote the reaction.

We surmise that sulfonate groups (ethylenediamine sulfonamide and *N*-Boc-serinol dimesylate) are coordinated by an alkali metal ion, which holds the two moieties close to each other and brings them in a favorable position for cyclization to occur. After ring closure and consequent mesylate removal, the alkali ion, coordinated by the sulfonate and Boc carbonyl groups, behaves as a Lewis acid in promoting the cleavage of the Boc group (Figure 1). This hypothesis is supported by crude mechanic and dynamic calculations which highlight the role of Cs ions in pulling together the ethylenediamine and serinol moieties, also indicating that after cyclization, the Cs ion binds to the carbamate oxygen.

Table 1 A Comparative Study of Conventional versus US/MW and MW-Assisted Cyclization

Entry	Method[a]	Solvent	Time (h)	Temp (°C)	Ratio **1/2** [b]	Overall yield (%)
1	P1	MeCN	120	reflux	5:0	5
2	P2	MeCN	3	reflux	60:0	60
3	P3	MeCN	2	150	9:84	93
4	P1	DMF	5	110	19:0	19
5	P2	DMF	3	110	14:62	76
6	P3	DMF	2	150	3:87	90
7	P2	1,4-dioxane	v3	70	0:5	5
8	P3	1,4-dioxane	2	150	30:5	35
9	P4	solvent-free	0.3	77	13:74	87
10	P4	solvent-free, Al_2O_3	0.3	71	7:82	89

[a] Reaction conditions: P1: heating in an oil bath under magnetic stirring; P2: sonication (120 W, 3 min) followed by MW irradiation (350 W, 1 h) in a cooled reactor. This cycle was repeated 2–3 times; P3: sonication (120 W, 3 min) followed by MW irradiation in a pressure-resistant closed vessel (150 °C, 2 h, 200 W); P4: all reagents were intimately mixed in a mortar, then irradiated with MW (600 W) for 5 min. The irradiation was repeated 4 times, with interposed pauses of 1 min.
[b] **1**: 6-Boc-amino-1,4-diazepine; **2**: 6-amino-1,4-diazepine.

Table 2 Effects of Various Bases on MW/US-Assisted Cyclization of Ditosylethylenediamine with *N*-Boc-serinol Dimesylate[a]

Entry	Base	Ratio **1**/**2**[b]	Conversion (%)	Yield (%)
1	Li_2CO_3	0:0	90	0
3	K_2CO_3	6:69	75	75
3	Cs_2CO_3	9:84	93	93
4	Cs_2CO_3, TBAB	6:87	93	93
5	Cs_2CO_3, Et_3N	5:86	91	91
6	Et_3N	0:0	0	0
7	DBU	0:0	0	0

[a] In MeCN (closed vessel, 150 °C for 2 h).
[b] **1**: 6-Boc-amino-1,4-diazepine; **2**: 6-amino-1,4-diazepine.

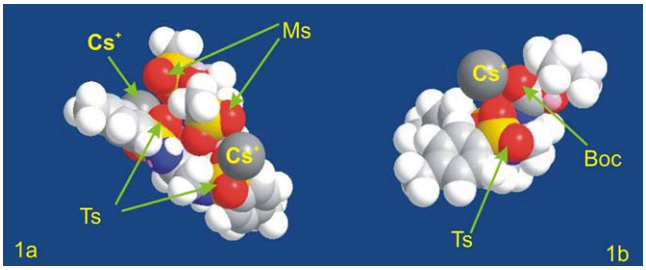
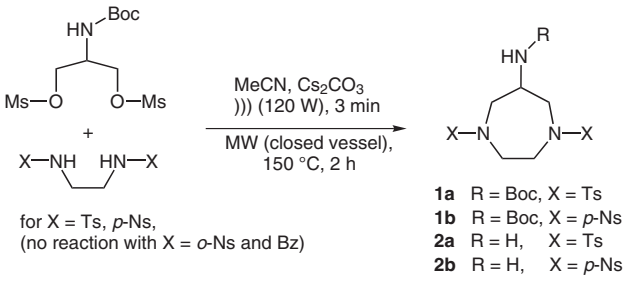


Figure 1 Coordination of cesium ions to sulfonate (1a) and Boc carbonyl groups (1b)



Scheme 2 Synthesis of different *N*,*N*′-disubstituted 6-aminoperhydro-1,4-diazepines

In order to evaluate this hypothesis, we replaced the tosyl groups on the ethylenediamine precursor with either *o*- or *p*-nosyl or benzyl groups, and reacted each of the three derivatives with Boc-serinol dimesylate (Scheme 2). We found that with *p*-nosylate, the heterocycle was obtained in good overall yield (60%, ratio **1**/**2** = 10:50), whereas the *o*-nosyl and benzyl derivatives did not react at all. These results are fully consistent with our hypothesis. In the *o*-nosyl derivative, a nitro group stands in the position *ortho* to the sulfonate; thus the alkali metal ion, being coordinated by both the nitro and sulfonate oxygen atoms, would be kept away from the mesyl group, and so its template effect would be nil. Further, the presence of bulky substituent at the *ortho* position (*o*-nosyl groups) does not favor the coordination of Cs metal ions to sulfonate groups. As a result, there is no reaction and both starting materials can be recovered quantitatively. The same result was observed with *N*,*N*′-dibenzylethylenediamine, in which no oxygen is available for metal coordination.

To conclude, we have developed two novel, easy, and highly efficient protocols for the synthesis of the 6-aminoperhydro-1,4-diazepine scaffold using Cs_2CO_3 (or alternatively K_2CO_3) as a base. One is a solvent-free, MW-assisted protocol; the other employs US/MW irradiation in acetonitrile. Both procedures afforded the desired heterocycle in high yield, without any by-product, whereas the same reaction failed when carried out under conventional conditions. Advantages of the method are atom economy, a clean reaction in one step with no side products, and good selectivity for the desired heterocycle.

All chemicals were purchased either from Sigma–Aldrich Co. or Lancaster Synthesis GmbH and were used without purification unless otherwise stated. NMR spectra were recorded on a Bruker Avance 300 spectrometer (operating at 7 Tesla). ESI mass spectra were recorded on a Waters Micromass ZQ apparatus. MW-promoted reactions were carried out in a MicroSYNTH Milestone oven. The sonochemical apparatus used in the present work was developed in the authors' laboratory[18] in collaboration with Danacamerini (Torino, Italy).

Cyclization of *N*,*N*′-Ditosylethylenediamine with *N*-Boc-serinol Dismesylate

Under Conventional Conditions: *N*,*N*′-Ditosylethylenediamine (367 mg, 1 mmol) and *N*-Boc-serinol dimesylate (315 mg, 1 mmol) were dissolved in the appropriate solvent (50 mL, see Table 1), then solid Cs_2CO_3 (3.26 g, 10 mmol) was added. The mixture was stirred at the temperatures indicated in Table 1, under N_2; reaction times are also listed in Table 1. Finally the solvent was removed under reduced pressure and the crude product purified by silica-gel column chromatography (eluent: hexane–EtOAc, 1:1). The pure product **1** was obtained as a white solid (yields are reported in Table 1).

Sequential US/MW-Promoted Cyclization (Open Vessel): *N*,*N*′-Ditosylethylenediamine (400 mg, 1.09 mmol), *N*-Boc-serinol dimesylate (343 mg, 1.09 mmol), the base Cs_2CO_3 or K_2CO_3 (10 mmol) and DMF (50 mL) were mixed in a 250 mL round-bottomed flask. The mixture was sonicated for 3 min at 120 W, then placed in MW oven and irradiated for 1 h at 350 W, the flask being cooled by circulation of refrigerated fluid. The reacted mixture was filtered and the filtrate was evaporated under reduced pressure to give a crude oil. The pure crystalline product was obtained as previously described.

Sequential US/MW-Promoted Cyclization (Closed Vessel): *N*,*N*′-Ditosylethylenediamine (400 mg, 1.09 mmol), *N*-Boc-serinol dimesylate (343 mg, 1.09 mmol), the base Cs_2CO_3 or K_2CO_3 (10 mmol), and the appropriate solvent (50 mL) were placed in a pressure-resistant closed vessel (Milestone). The mixture was sonicated for 3 min at 120 W, and then irradiated with MW (200 W, 150 °C) for 2 h. Finally it was cooled and filtered; the filtrate was evaporated under vacuum and purified by silica gel column chromatography. The same procedure was applied to *N*,*N*′-di-*o*-nosyl-, *N*,*N*′-di-*p*-nosyl- and *N*,*N*′-dibenzylethylenediamine.

Solvent-Free MW-Promoted Cyclization: *N*,*N*′-Ditosylethylenediamine (400 mg, 1.09 mmol), *N*-Boc-serinol dimesylate (343 mg, 1.09 mmol), and Cs_2CO_3 (10 mmol) were mixed together by grinding in an agate mortar (with or without the addition of 3 g of neutral alumina) and the resulting mixture was irradiated at 600 W for 5 min. During this time, the temperature of the solid reached 75–80 °C. The irradiation was repeated 4 times, with interposed pauses

of 1 min. The mixture was cooled down to r.t., MeOH was added and resulting mixture was filtered to separate the excess of base. The filtrate was evaporated under vacuum to yield a crude oil, which was purified as previously described. Both the *N*-Boc-protected and the deprotected heterocycle were obtained as white crystalline solids.

6-*tert*-Butyloxycarbonylamino-1,4-ditosylperhydro-1,4-diazepine (1)

White crystalline solid: mp 148–149 °C (dec.).

HPLC analysis: Column X-Terra (Waters) RP-C18 4.6 × 150 mm, 5 μm; sample: 1% in H_2O–MeCN (1:1), injection volume 10 μL. Flow: 1 mL/min, detector wavelength: 215, 230, 254 nm; solvent: H_2O–MeCN gradient; time/MeCN (%) = 0/20, 7.5/20, 15/23, 26/60, 33.5/100, 44/100.

IR (KBr): 3406, 2976, 2930, 2870, 1757, 1709, 1597, 1510, 1454, 1331, 1286, 1159, 1089, 1012, 995, 914, 814, 721, 653 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.06 Hz, 4 H), 7.30 (d, *J* = 8.06 Hz, 4 H), 3.60 (dd, *J* = 20.86, 5.86 Hz, 2 H), 3.40 (m, 5 H), 3.21 (dd, *J* = 19.71, 5.13 Hz, 2 H), 2.42 (s, 6 H), 1.44 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 144.0, 135.8, 129.9, 126.9, 79.6, 53.2, 52.8, 50.4, 28.4, 21.6.

ESI-HRMS: *m*/*z* calcd for [MH^+]: 524.1889; found: 524.1877.

Anal. Calcd for $C_{24}H_{33}N_3O_6S_2$: C, 55.05; H, 6.35; N, 8.02. Found: C, 54.95; H, 6.28; N, 8.15.

6-Amino-1,4-ditosylperhydro-1,4-diazepine (2)

White crystalline solid; mp 198–199 °C (dec.).

IR (KBr): 3391, 2976, 2872, 1750, 1599, 1495, 1338, 1196, 1161, 1089, 1078, 1012, 933, 816, 790, 767, 657 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 6 H), 3.18 (m, 2 H), 3.38 (m, 2 H), 3.6 (m, 4 H), 4.12 (m, 1 H), 7.35 (d, *J* = 13.6 Hz, 4 H), 7.71 (d, *J* = 10.8 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 130.3, 127.9, 127.3, 55.4, 52.8, 51.6, 21.9.

ESI-HRMS: *m*/*z* calcd for [MH^+]: 424.1365; found: 424.1350.

Anal. Calcd for $C_{19}H_{25}N_3O_4S_2$: C, 53.88; H, 5.95; N, 9.92. Found: C, 53.95; H, 5.75; N, 10.04.

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