Novel application of Leuckart–Wallach reaction for synthesis of tetrahydro-1,4-benzodiazepin-5-ones library†

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A novel and efficient strategy has been developed to synthesize privileged tetrahydro-1,4-benzodiazepines with excellent yields and purities; this synthetic pathway was established by the revitalization of the Leuckart–Wallach (LW) reaction *via* solid-phase synthesis.

The series of compounds containing the tetrahydro-1,4-benzodiazepine scaffold are an important class of prototypical "privileged" structures associated with various biological activities and therapeutic uses. The benzodiazepine family is commonly classified as a central nervous system (CNS) suppressant due to its anxiolytic, anticonvulsant, sedative, and muscle relaxant activities. It is used in various marketed drugs such as Alprazolam, Bromazepam, Chlorazepate, and Valium.[1] 1,4-Benzodiazepines also demonstrate therapeutic activities and are used as antibiotics,[2] antiulcers,[3] and anti-HIV agents;[4] they are also used as Ras farnesyltransferase inhibitors.[5]

Interestingly, 1,4-benzodiazepin-5-ones have not been studied extensively as compared to the other 1,4-benzodiazepine series such as 1,4-benzodiazepin-2-one and 1,4-benzodiazepin-2,5-dione in terms of their synthesis or biological activities. There is a list of reports on the synthetic methodology of 1,4-benzodiazepin-5-ones which involves aromatic substitution and Schmidt rearrangement (Fig. 1).[6] However, these methods involve multiple steps with harsh reaction conditions, and usually, limited derivatization is possible through modification only after the formation of the core skeleton.[6] Yoshida *et al.* have reported an orthogonal method *via* aryne nucleophilic substitution with dimethyl urea.[7] This method is quite unique and straightforward, but it can only provide limited diversity and has low practicability in library construction. By an extension of our previous study, *N*-acyliminium cyclization[8] appears to be a practical method to synthesize the desired core skeleton—tetrahydro-1,4-benzodiazepin-5-one.

With expectations of interesting biological activities, we initiated the development of a practical synthetic pathway for library construction. Wang and coworkers reported a two-step method for synthesizing dihydro-1,4-benzodiazepin-5-one, which can be reduced to tetrahydro-1,4-benzodiazepin-5-one.[9] However, we aimed to identify a single-step transformation instead of a transformation with three individual steps. Therefore, we rationalized the key step in the synthetic transformation for tetrahydro-1,4-benzodiazepin-5-one as intramolecular reductive amination

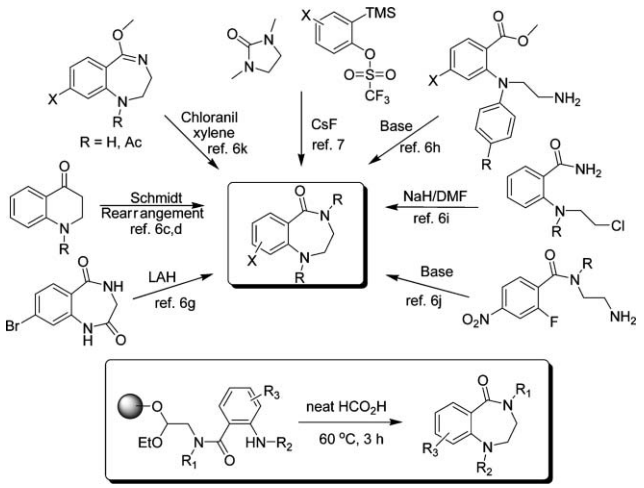
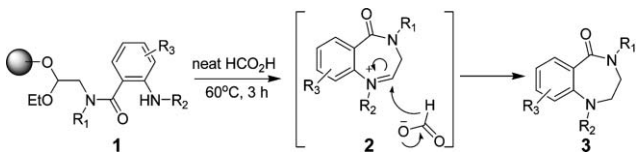


Fig. 1 Reported methods and our synthetic strategy for the construction of tetrahydro-1,4-benzodiazepin-5-one.

using neat formic acid as the reducing agent, which is known as the Leuckart–Wallach (LW) reaction (Scheme 1). The LW reaction is attractive in synthetic chemistry because ketones or aldehydes can be transformed directly to the corresponding secondary or primary alkyl amines using a single reaction vessel, without the isolation of the imine intermediates.[10] However, the scant literature on the applications of the LW reaction may be due to the following shortcomings: the requirement of high temperatures, undesired formation of *N*-formyl by-products, and difficulty in ensuring the selective synthesis of primary amines.[11]

Bearing these limitations in mind, we designed an intramolecular LW reaction to construct a privileged tetrahydro-1,4-benzodiazepin-5-one skeleton. In particular, we introduced bromoacetal resin as a solid support for the *in-situ* generation of iminium intermediates during the acidolytic cleavage step following the LW reaction: this modification extends the scope of the outdated LW reaction. From extensive screening of the reaction conditions, we recognized that iminium formation and hydrogen transfer did not proceed under any precedent reaction conditions; complex mixtures with varying quantities of unsaturated



Scheme 1 Key transformation toward tetrahydro-1,4-benzodiazepin-5-one *via* intramolecular Leuckart–Wallach reduction.

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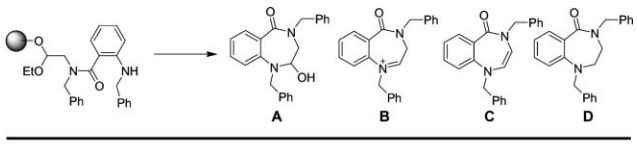


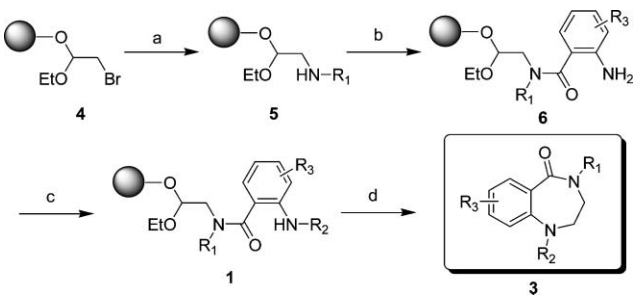
Reagents & condition	Results
30% aqueous TFA, r.t., overnight	trace A, decomposed
5% TFA in DCE, 60 °C, 5 h	B and decomposed side product
cat. pTSA in DCE, 60 °C, 3 h	B and decomposed side product
neat formic acid, r.t., overnight	B
neat formic acid, 60 °C, 3 h	D

Fig. 2 Reaction condition screening for an optimized procedure.

dihydro-1,4-benzodiazepin-5-one were identified. However, under the modified LW reaction condition using neat formic acid at 60 °C, we obtained the desired products with excellent yields and purities (see Fig. 2). Subsequently, we pursued the substrate generality under the optimized conditions. In fact, iminium ion **2** might exist in an equilibrated form between iminium ion **2** and enamine (when R_2 is an alkyl group) in acidic solvents, which can be converted into the desired product **3** through the reduction of intermediate **2** *via* the LW reaction. When R_2 is an electron-withdrawing group such as an acetyl, carbamate, or urea group, a messy reaction pattern was observed under the same reaction conditions, with uncyclized compounds as the major by-products; this pattern is probably caused by the inefficient cyclic imine formation of acyl aniline moieties along with *in-situ* generated aldehydes.

We recently reported a simple and expedient method for the synthesis of Δ^5-2-oxopiperazines; this method demonstrated the complete transformation of the *in-situ N*-acyliminium ions into unsaturated 6-membered enamides in neat formic acid, without the observation of reduced amine products through the LW reaction in a 6-membered ring system, even after a systematic screening of the reaction conditions.[12] In fact, there is a precedent for the elimination of the α-proton of the iminium ion as the dominant pathway in the 6-membered oxopiperazine system.[13] However, we observed exactly the opposite outcome in the 7-membered benzodiazepine system **3**.

The synthesis scheme for tetrahydro-1,4-benzodiazepin-5-ones is outlined in Scheme 2. To examine the scope of this reaction pathway, a series of representative compounds were synthesized using solid-phase parallel synthesis. The synthesis was initiated by the incorporation of the R_1 diversity element through the simple amination of the bromoacetal resin **4** with primary amines in



Scheme 2 General procedure of the pilot test for the synthesis of 1,4-benzodiazepin-5-ones. Reagents and conditions are as follows: (a) R_1NH_2, DMSO, 60 °C; (b) anthranilic acid, HATU, DIPEA, DMF, r.t.; (c) aldehyde or ketone, cat. AcOH, $NaBH_3CN$, DMF, r.t. or 50 °C; (d) neat HCO_2H, 60 °C, 3 h.

dimethyl sulfoxide (DMSO) at 60 °C. The bromoacetal resins utilized in this study were prepared in our laboratory from Wang resin to achieve high loading levels (loading level: 1.6 mmol/g). The resulting secondary amine **5** was coupled with anthranilic acid or chloro-anthranilic acid. The amidation was achieved by the activation of carboxylic acid with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium PF_6 (HATU) and the completion of the amidation step was monitored by using a negative chloranil test. The R_2 diversity element was explored by the reductive amination by the aniline of an aldehyde or ketone in dimethylformamide (DMF) to yield compound **1**. The final key transformation was carried out by the incubation of the resins using neat formic acid at 60 °C to synchronize the compound cleavage from the solid support and the *in-situ* generation of cyclic iminium ions; this was followed by the LW reduction with high efficiency. The final cleavage/cyclization step successfully provided the desired reduced product in high yields and purities without any nonvolatile by-products, thereby ensuring highly efficient library construction. Based on our sample test, all aliphatic and aromatic primary amines were found to be suitable for the R_1 diversification, without any effect on the yields and purities. Reductive amination of aliphatic and aromatic aldehydes or ketones for the R_2 diversification yielded the desired products without any significant by-products. However, in the case of 2-amino-4-chlorobenzoic acid (R_3 = *p*-Cl), a slightly lower purity was obtained. The results of the sample tests are listed in Table 1. (See Supporting Information for details) Further validation of our novel synthetic pathway using the LW reaction was accomplished with the construction of a pilot library with the tetrahydro-1,4-benzodiazepin-5-one core skeleton on a solid support using a parallel 96-deep-well filtration block platform. The molecular diversity of the core skeleton was expanded by the introduction of various R_1 elements using commercially available primary amines (as shown in Fig. 3B). The diversity scope of the R_2 position was extended by reductive amination of various aldehydes. The LC/MS purities of the crude final products after cleavage from the solid support using neat formic acid are represented with a 3D chart, which demonstrates the excellent purities and practicality (overall purity: >94% in Fig. 3A).

In conclusion, we successfully investigated the practical synthesis of privileged structures of tetrahydro-1,4-benzodiazepin-5-ones. The utility and generality of this synthetic pathway were established by the revitalization of the Leuckart–Wallach (LW) reaction through solid-phase synthesis. The key synthetic strategy involved sequential cyclic iminium formation and hydride transfer under an acidolytic cleavage condition, which yielded a saturated 7-membered privileged benzodiazepine structure. The optimized synthetic protocol was tolerant to various building blocks, and the robustness and practicality of our novel synthetic pathway were validated by the successful construction of a 96-member pilot library with excellent overall yields and purities. A large number of libraries can be realized with full diversification at the R_1, R_2, and R_3 positions; biological evaluations of this sample library are currently in progress. The evaluation results and complete realization of the tetrahydro-1,4-benzodiazepin-5-one library will be reported in due course.

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Table 1 Purities and yields of representative compounds (**3a–3p**)

Entry	R_1	R_2	R_3	[a]Yield (%)	[b]Purity (%)	MS (calcd)	[M + H] (found)
3a	Phenethyl	Benzyl	H	88	96.3	356.19	357.16
3b	4-CH_3O-benzyl	Benzyl	H	91	96.1	372.18	373.18
3c	Benzyl	Benzyl	H	80	98.9	342.17	343.17
3d	Isobutyl	Benzyl	H	94	99.7	308.19	309.19
3e	Phenethyl	3-Br-benzyl	H	92	98.5	434.10	435.08
3f	4-CH_3O-benzyl	3-Br-benzyl	H	90	97.8	450.09	451.10
3g	Benzyl	3-Br-benzyl	H	89	98.1	420.08	421.11
3h	Isobutyl	3-Br-benzyl	H	97	98.6	386.10	387.17
3i	Phenethyl	Cyclohexyl	H	93	98.8	348.22	349.29
3j	4-CH_3O-benzyl	Cyclohexyl	H	97	99.0	364.22	365.30
3k	Benzyl	Cyclohexyl	H	98	99.1	334.20	335.23
3l	Isobutyl	Cyclohexyl	H	88	98.3	300.22	301.25
3m	Phenethyl	Benzyl	*p*-Cl	78	98.8	390.15	391.21
3n	4-CH_3O-benzyl	Benzyl	*p*-Cl	84	86.8	406.14	407.22
3o	Benzyl	Benzyl	*p*-Cl	86	81.2	376.13	377.21
3p	Isobutyl	Benzyl	*p*-Cl	82	93.4	342.15	343.23

[a] Yields were calculated based on the loading amount of the bromoacetal resin, which is used as the solid support. [b] Purities were obtained by RP-HPLC/MS of the crude final products after cleavage from the solid support.

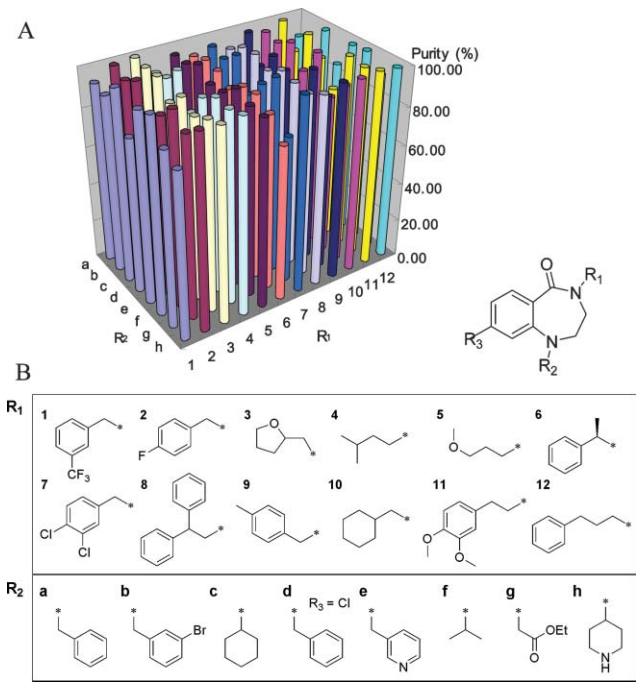

Fig. 3 A: Purities of a pilot library obtained by RP-HPLC/MS of the crude final products after cleavage using neat formic acid. B: Structures of the building blocks utilized for the pilot library construction (R_3 = H or Cl).

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