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Solid-Phase Synthesis of 4,7,8-Trisubstituted 1,2,3,4-Tetrahydro-benzo[*e*][1,4]diazepin-5-ones

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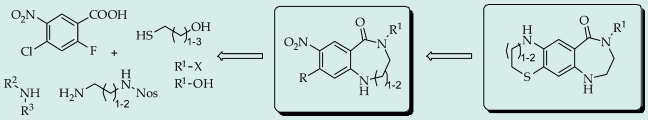
Supporting Information

ABSTRACT: Solid-phase synthesis of 1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones with use of polystyrene resin is described. The starting material was polymer supported 1,2-diaminoethane and as a key synthon, 4-chloro-2-fluoro-5-nitrobenzoic acid was used. The synthetic approach allows the preparation of derivatives with variable substitution at positions 4 and 8. Additionally, a skeletal diversity was increased when the nitro group was reduced and some benzene fused heterocycles were prepared. An expansion of a diazepinone to a benzodiazocinone scaffold was also successful although some limitations in a diversity of target derivatives were observed.



KEYWORDS: *benzodiazepinones, benzodiazocinones, thiazines, thiazepines, bisheterocycles, solid-phase synthesis*

INTRODUCTION

Use of polyfunctional building blocks (i.e., more than three different functional groups) in combination with solid-phase synthesis concepts enables quick access to a number of various organic substances, particularly when diversity oriented synthesis is applied. In our ongoing research, we have been focused on use of 4-chloro-2-fluoro-5-nitrobenzoic acid for the preparation of various heterocyclic scaffolds. Although the substance is commercially available and represents an excellent starting material for number of chemical transformations, its use in organic synthesis has been very rare so far. Our current effort aims to prepare benzene fused heterocycles (BFHs) that comprise two different heterocyclic scaffolds in various combinations located at opposite sides of a central benzene ring (Scheme 1).

Quite recently, we published two articles dedicated to the mentioned area. In our initial work, 4-chloro-2-fluoro-5-nitrobenzoic acid was used for the "right side" heterocycle formation and 3-hydroxypyridin-4(1*H*)-one scaffold was introduced.[1] The second contribution was focused on the "left side" heterocycle formation and methodology for the preparation of various nitrogen-containing scaffolds was developed (Figure 1).[2]

In this contribution, we focused on an expansion of the right side heterocycles group to increase the number of scaffolds available for future synthesis of BFHs library. We aimed at the 1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one derivatives **I** (Figure 1). The preparation of such diazepinones has been described several times with use of solution-phase synthesis. For instance, a regioselective reduction of 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-2,5-dione with use of $LiAlH_4$ was published.[3] Alternatively, a benzodiazepine scaffold was synthesized by a cyclization approach from anthranilamide derivatives,[4,5] 2-nitrobenzoylchloride,[6] or 2-chloro-3-nitrobenzoic acid[7] as the starting material. Also an interesting synthetic pathway starting from *o*-nitroanilin and acrylonitrile was described[8] taking advantage of the cyclization to a 6-membered scaffold with use of Eaton reagent[9] and subsequent ring expansion by Schmidt reaction.[10] Solid-phase synthesis of some 1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones has been published once with use of bromoacetal resin and Leuckart-Wallach reaction.[11]

Concerning biological activity of the discussed compounds, the amount of relevant information is limited. Some derivatives substituted with alkyl at N^4 position were tested as psychotropic agents but such activity was not detected.[12] On the other hand, interesting biological properties were observed at some bisheterocyclic derivatives (imidazobenzodiazepinones **II** and diazepinoindol-1-ones **III**) that act as inhibitors of poly(ADP ribosa)polymerase (PARP-1),[13,14] an enzyme responsible for apoptosis and DNA reparation. Research in this area is quite intensive and number of dedicated articles and patents appeared recently. Except this, an imidazobenzodiazepinone scaffold can be found in a structure of Flumazenil (Anexate) **IV**, a clinically used antidote for central nervous system (CNS) benzodiazepines intoxication.

This article describes a novel approach for the preparation of 1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones **I** with use of high throughput organic synthesis (HTOS) approach applicable for the future use of the developed methodology for combinatorial synthesis of BFHs depicted in a Scheme 1.

RESULTS AND DISCUSSION

Our initial strategy for the preparation of target compounds was based on immobilization of ethanolamine to a polystyrene resin equipped with an acid labile backbone amide linker (BAL). The polymer supported ethanolamine **1** was subsequently arylated with 4-chloro-2-fluoro-5-nitrobenzoic and intermediate **2** was obtained. In a next step, the terminal hydroxy group was reacted

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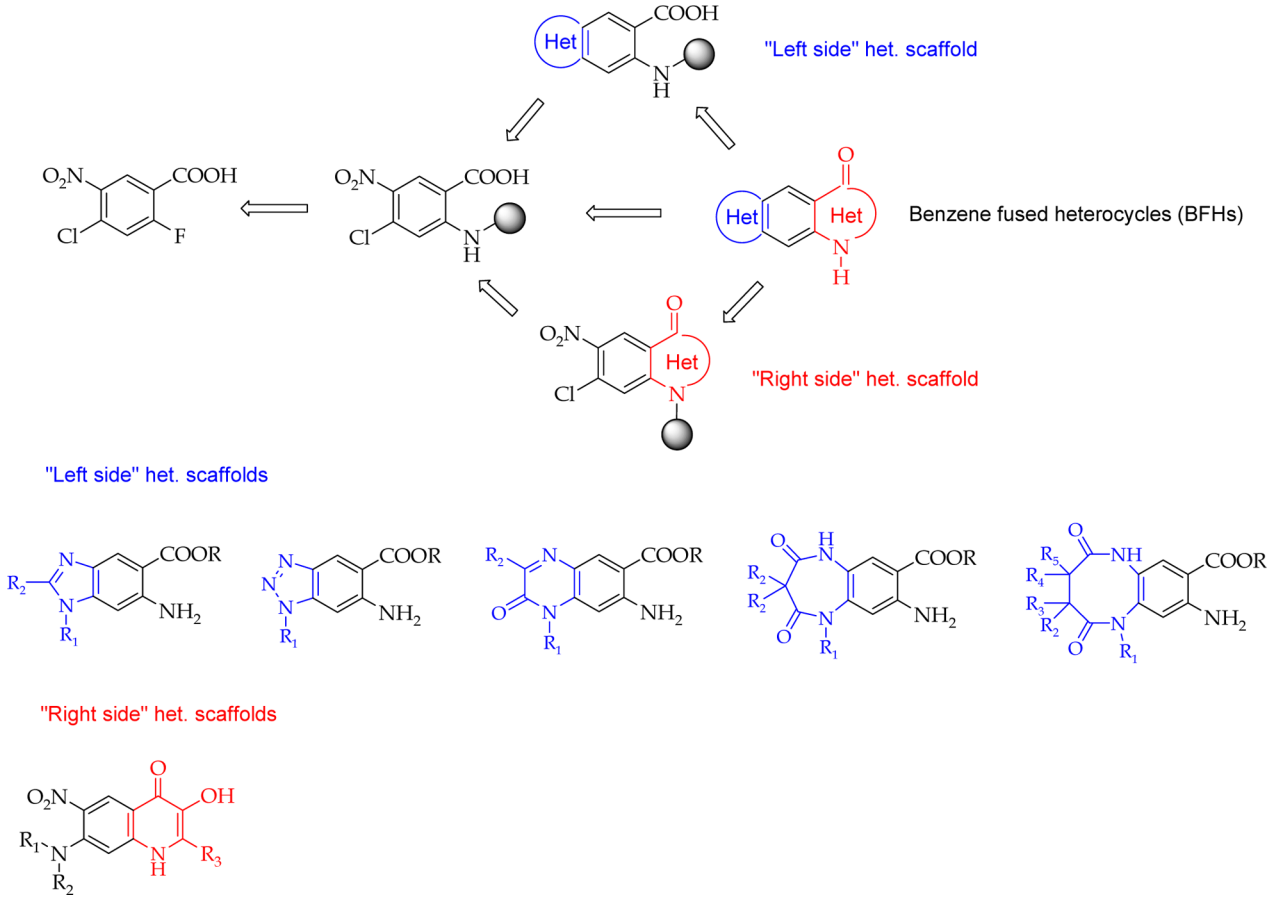
Scheme 1. Applicability of 4-Chloro-2-fluoro-5-nitrobenzoic Acid in BFHs Synthesis and Heterocyclic Scaffolds Reported Previously



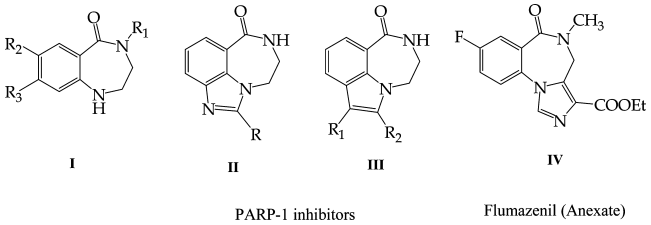


Figure 1. Target general structure **I** and already reported biologically active analogous derivatives **II**–**IV**.

with methansulfonylchloride to obtain the reactive ester **3** that should enable replacement of the hydroxy group with primary amines resulting in N^4 substitution of the target scaffold (Scheme 2). Unfortunately, a presence of a base (pyridine) caused an activation of a carboxylic group and azlactone **4** was detected as a side product (about 40%, LC-MS traces). We tried to protect the carboxylate with help of methylester formation, but the intermediate **2** exhibited an unexpected resistance toward various methods (Mitsunobu reaction with methanol, esterification with methyl iodide, or diazomethane) and only up to 10% of a desired methylester was detected in each case. Alternatively, we also tried to use the methylester of 4-chloro-2-fluoro-5-nitrobenzoic acid for immobilization on resin **1** (Scheme 2, step ii), but we did not obtain the sufficiently pure product due to a side reaction caused by the amide formation (30–40%, HPLC-UV traces).

An alternative strategy consisted in a preparation of *N*-(2-aminoethyl)-2-nitrobenzenesulfonamide with use of solution-phase synthesis and its subsequent immobilization to a polystyrene resin-BAL system (Scheme 3). The 2-nitrobenzenesulfonyl (2-Nos) protected, polymer supported diamine **5a** was then arylated with 4-chloro-2-fluoro-5-nitrobenzoic acid to obtain intermediate **6a**. Advantageously, the 2-Nos group enabled an alkylation of the nitrogen atom to incorporate various ligands R^1 (see Figure 2) to a position 4 of the target diazepinones. Two alternative methods were tested: (i) alkylation with alkylhalides and (ii) alkylation with alcohols under Mitsunobu protocol. Reaction with ethyl iodide in a presence of a tertiary base such as triethylamine (TEA) or diisopropylethylamine (EDIPA) led to alkylation of N–H group but also partial esterification of a carboxylic group was observed. When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead, the esterification was quantitative and only double-alkylated intermediate **7a**{*1*} was detected. The same reaction conditions (i.e., 0.5 M solution of alkylhalide in DMF, 16 h) were successfully tested for benzylbromide. The Mitsunobu reaction was tested for various alcohols (see Figure 2) and in each case the double alkylated intermediates **7a**{3–7} in an excellent purity were obtained. From a combinatorial point of view, the modification based on Mitsunobu alkylation represents much more favorable alternative with respect to number of commercially available alcohols.

In the next step the Nos protective group had to be removed. Such a cleavage is typically performed with 0.6 M solution of mercaptoethanol and 0.2 M DBU in DMF for 5 min.[15] In our case, the Nos group was not cleaved under such conditions and additionally a partial substitution of the chlorine atom with

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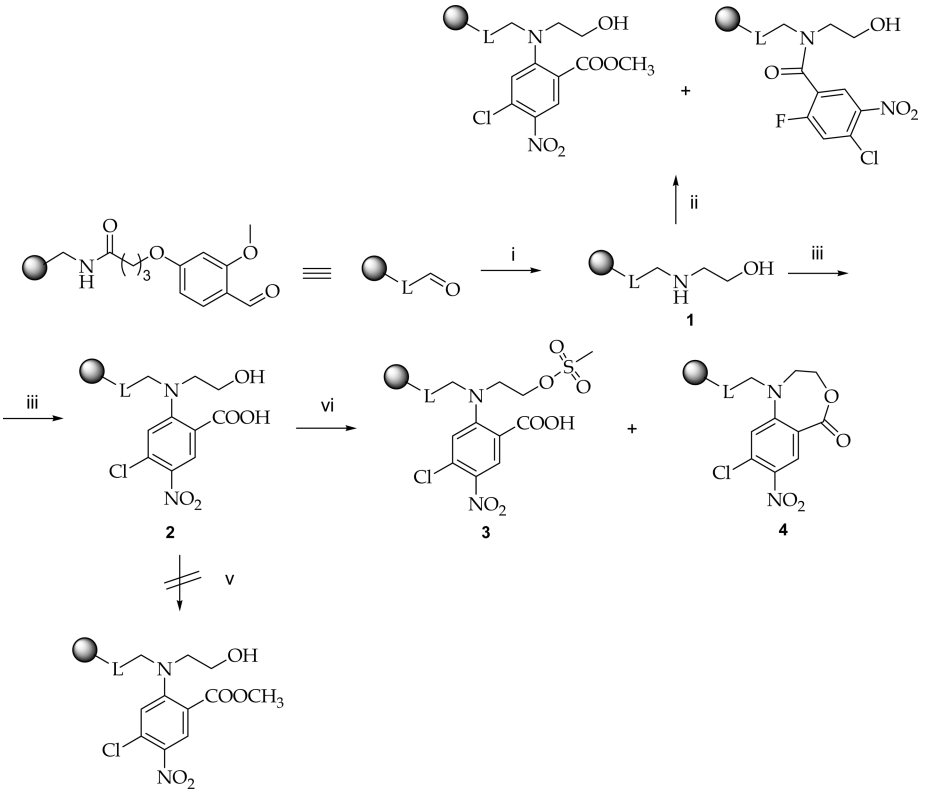
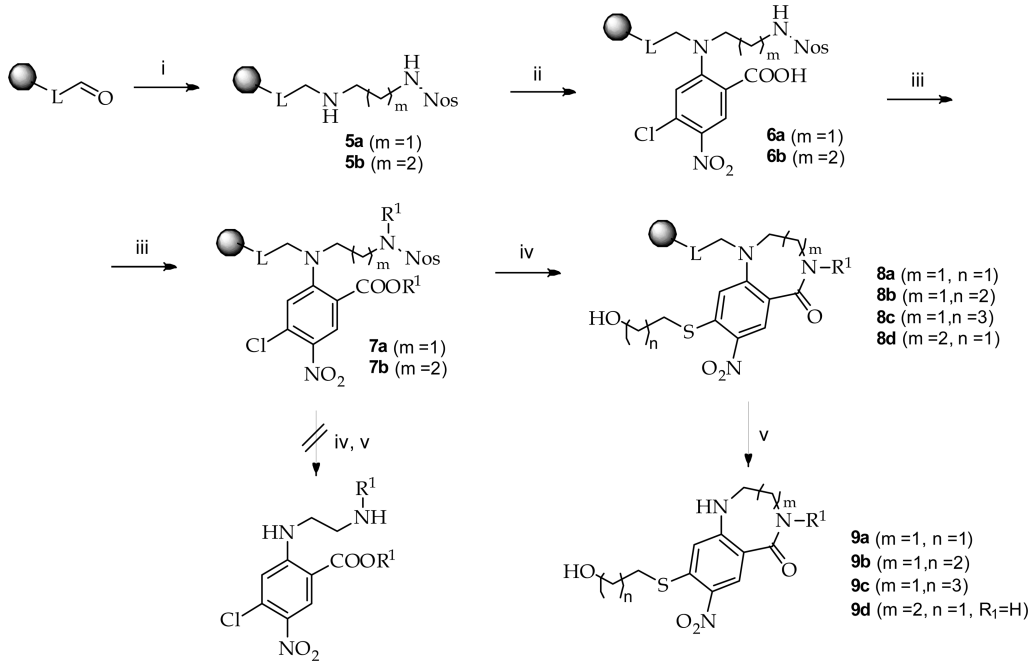
Scheme 2. Unsuccessful Strategy for the Preparation of Target Compounds[a]



[a]Reagents and conditions: (i) ethanolamine, 10% AcOH in *N,N*-dimethylformamide (DMF), overnight then $NaBH(OAc)_3$, 5% AcOH in DMF, 4 h; (ii) 4-chloro-2-fluoro-5-nitrobenzoic acid methylester, diisopropylethylamine (EDIPA), dimethylsulfoxide (DMSO), 50 °C, overnight; (iii) 4-chloro-2-fluoro-5-nitrobenzoic acid, diisopropylethylamine (EDIPA), dimethylsulfoxide (DMSO), 50 °C, overnight (iv) methyl iodide, DBU, DMF, overnight or diazomethane, ether, overnight or methanol, PPh_3, diisopropylazodicarboxylate (DIAD), anhydrous THF, rt, overnight; (v) methansulfonylchloride, pyridine, 1 h.

Scheme 3. Successful Strategy for the Preparation of Target Compounds (see Figure 2 for R^1)[a]



[a]Reagents and conditions: (i) *N*-(2-aminoethyl)-2-nitrobenzenesulfonamide or *N*-(3-amino-propyl)-2-nitrobenzenesulfonamide, 10% AcOH in DMF, overnight, then $NaBH(OAc)_3$, 5% AcOH in DMF, 4 h; (ii) 4-chloro-2-fluoro-5-nitrobenzoic acid, EDIPA, DMSO, 50 °C, overnight; (iii) ethyl iodide or benzylbromide, DBU, DMF, rt, overnight or alcohol, DIAD, PPh_3, anhydrous THF, rt, overnight; (iv) mercaptoalcohol, DBU, DMF, rt, overnight, then (only for **8d**) EDIPA, DMSO, 80 °C, overnight; (v) 50% TFA in DCM, rt, 1 h.

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mercaptoethanol was observed. When the reaction time was prolonged to 16 h and the concentration of DBU was increased to 0.6 M, only diazepinone derivatives **9a**{*1*−*7*} were detected indicating the cyclization to a seven membered ring took place spontaneously after the cleavage of a protective group. To prove the cyclization step took place on-resin (also the cyclization in solution during a cleavage step was possible) we made the test with Fmoc-OSu: when the resin **8a** was treated with Fmoc-OSu solution the appearance of Fmoc-derived compounds have not been detected. The same course of

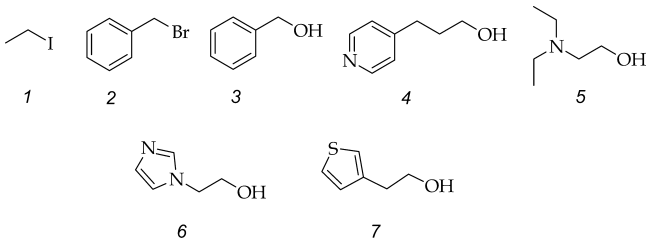


Figure 2. Building blocks successfully used for the preparation intermediates **7a**{R^1}.

Table 1. List of Prepared Diazepinones 9

Compound	R^1	n	Crude purity[a]	Yield[b]
9a{*1*}		1	83%	80%
9a{*2*}		1	81%	69%
9a{*4*}		1	73%	69%
9a{*5*}		1	82%	78%
9a{*6*}		1	82%	57%
9a{*7*}		1	70%	68%
9c{*1*}		3	73%	63%
9c{*2*}		3	67%	62%

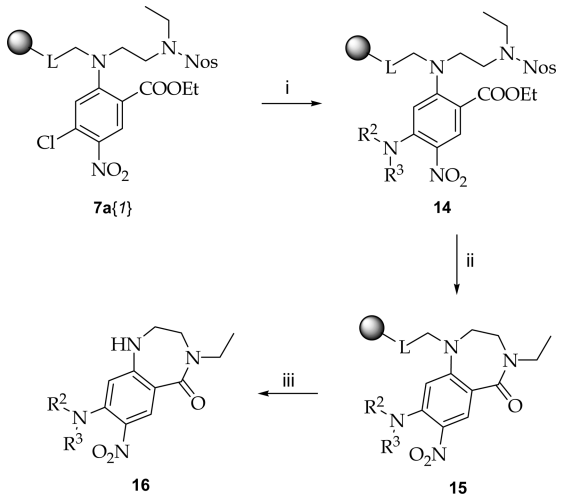
[a]Purity of crude product after entire reaction sequence; integrated HPLC-UV traces. [b]Overall yields after preparative HPLC purification.

Table 2. List of Prepared [1,4]Thiazines 13a and [1,4]Thiazepines 13b

Compound	R^1	n	Crude purity[a]	Yield[b]
13a{*1*}		1	78%	47%
13b{*1*}		2	73%	51%
13a{*2*}		1	93%	27%
13b{*2*}		2	82%	63%

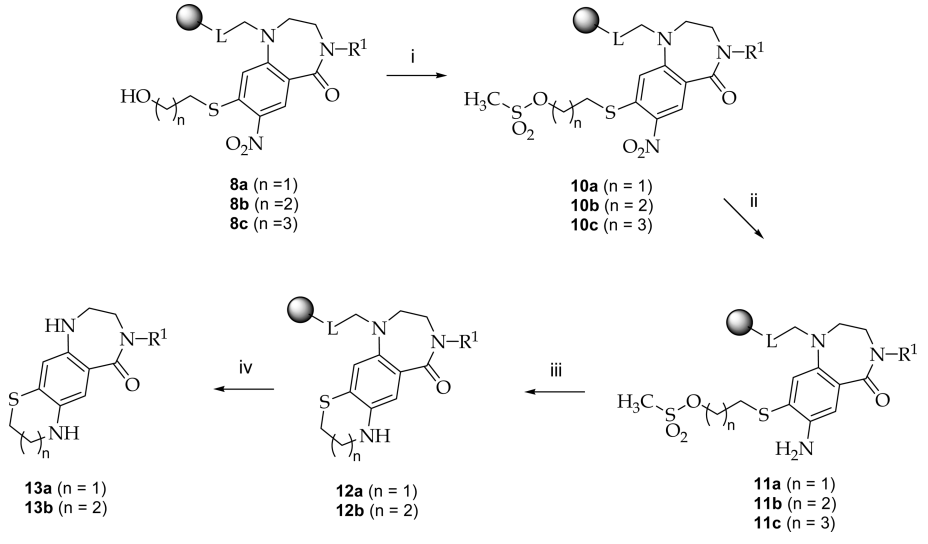
[a]Purity of crude product after entire reaction sequence; integrated HPLC-UV traces. [b]Overall yields after preparative HPLC purification.

Scheme 5. Synthesis of 8-*N*-Substituted 1,2,3,4-Tetrahydrobenzo[*e*][1,4]diazepin-5-ones (for $R^{2,3}$, See Figure 3)[a]



[a]Reagents and conditions: (i) Amine, DMSO, 150 °C, 200 W, 5 min.; (ii) mercaptoethanol, DBU, DMF, rt, overnight; (iii) 50% TFA in DCM, rt, 1 h.

Scheme 4. Preparation of [1,4]Thiazine and [1,4]Thiazepine Containing Bisheterocycles (for R^1 see Table 2)[a]



[a]Reagents and conditions: (i) MsCl, pyridine, rt, 30 min.; (ii) $SnCl_2 \cdot 2H_2O$, EDIPA, DMF, overnight; (iii) EDIPA, DMSO, 80 °C, 16 h; (iv) 50% TFA in DCM, rt, 1 h.

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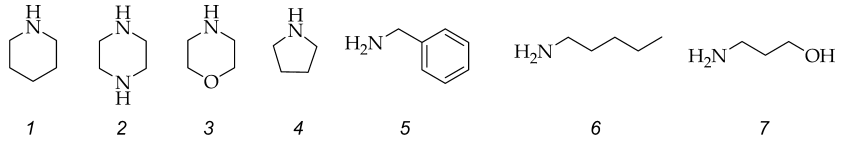

Figure 3. List of successfully tested amines.

reaction was observed when mercaptoethanol was replaced with mercaptopropanol and mercaptobutanol, respectively. The appropriate diazepinones were obtained in very good, crude purity (see Table 1).

The smooth nucleophilic substitution of intermediates **7** with mercaptoalcohols is quite surprising as we know from our previous results that harsh conditions are needed for similar reaction with primary and secondary amines including strong nucleophiles (piperidine, pyrrolidine).[1,2] On the other hand, the formation of diazepinones **8** can be advantegously employed for the preparation of thiazine and thiazepine scaffold containing bisheterocycles which demonstrates a very first application of 4-chloro-2-fluoro-5-nitrobenzoic acid in a synthesis of BFHs depicted in a Scheme 1. For this purpose, resins **8a**{*1*}, **8a**{*2*}, **8b**{*1*}, **8b**{*2*}, **8c**{*1*}, and **8c**{*2*} were reacted with methansulfonyl chloride in pyridine followed by the reduction of the nitro group with tin(II) chloride dihydrate. After reduction we observed only about 10% of a tricyclic target products **12a**{*1*}, **12a**{*2*}, **12b**{*1*}, and **12b**{*2*}, for a quantitative cyclization the appropriate resins **11a** and **11b** had to be treated with 0.2 M EDIPA in DMSO at 80 °C for 16 h. Thiazine and thiazepine rings were successfully formed giving the target compounds in an excellent crude purity (78−93%, LC-MS traces). In contrast, the preparation of eight membered ring, [1,4]thiazocane, was unsuccessful. Although the mesylation gave an appropriate intermediates **11c**{*1*} and **11c**{*2*} and also their reduction proceeded well, the final ring closure did not take place even under harsh conditions (including a microwave heating).

To increase a diversity of diazepinones **9a−c**{R^1} we also tested a substitution of the chlorine atom at intermediate **7a**{*1*} with set of primary and secondary amines (Scheme 5). For similar reaction we have previously developed a procedure consisting in heating with amine solution in DMSO to 120 °C.[2] In our case, the reaction had to be very carefully optimized due to relatively low reactivity of the starting material toward nucleophilic substitution at position 4 and simultaneous sensitivity of ester toward nucleophilic adition resulting in amide formation. We tested different reaction temperatures and solvents (such as DMSO, *N*-methylpyrrolidone NMP, diethylene glycole diethyl ether), but the products were contaminated by the corresponding amides in each case in spite of the substitution being carried out at lower temperature 80 °C (conventional heating). In contrast, use of 10% of amine in DMSO under microwave heating (200 W, 150 °C, 5 min) surprisingly provided the target derivates **14**{*1*−*7*} without presence of the amide side products. This method was found to be suitable for both primary and secondary amines. Last step was the cyclization to derivatives **15**{*1*−*7*} according to previously discussed procedure. The final compounds **15**{*5*}, **15**{*6*}, and **15**{*7*} prepared from primary amines demonstrate applicability of the reaction sequence for the preparation of BFHs that contain the "left side" heterocyclic scaffolds of a type depicted in Scheme 1. Synthesis of such heterocycles was described in our previous paper[2] and it is based on the reduction to *o*-phenylenediamines and subsequent cyclocondenzation reactions with appropriate reagents.

Table 3. List of Prepared 8-*N*-(Di)substituted Diazepinones 16

compound	crude purity[a]	yield[b]
16{*1*}	76%	61%
16{*2*}	60%	52%
16{*3*}	78%	60%
16{*4*}	65%	61%
16{*5*}	84%	68%
16{*6*}	85%	80%
16{*7*}	80%	75%

[a]Purity of crude product after entire reaction sequence; integrated HPLC-UV traces. [b]Overall yields after preparative HPLC purification.

As the synthesis of benzodiazepinones **9a−c** from the polymer supported 1,2-diaminoethane proved to be simple and quite versatile, we were also interested in use of a similar approach for the preparation of analogous benzodiazocines **9d** (Scheme 3, m = 2). For this purpose, we prepared *N*-(3-amino-propyl)-2-nitro-benzenesulfonamide and immobilized such protected diamine to a polystyrene resin-BAL system to obtain appropriate intermediate **5b**.[16] Following the previously developed procedures the cyclization of *N*-unsubstituted derivative **8d** (R^1 = H) was successfully performed. In contrast to a preparation of derivatives **8a−c** the reaction did not take place simultaneously after the cleavage of a Nos group but high temperature was necessary for completion. When the preparation of *N*-substituted intermediates **8d** was tested (R^1 = ethyl or benzyl), the cyclization did not take place even under harsh conditions (including microwave heating to 150 °C) which indicates the synthesis of a benzodiazocine derivatives **8d** is limited only to N^4-unsubstituted derivatives in this case.

In conclusion we have developed an efficient method for solid-phase synthesis of diverse 1,2,3,4-tetrahydro-benzo [*e*][1,4]diazepin-5-ones from commercially available synthons (alcohols, amines). Twenty model compounds were prepared and fully characterized, the target substances were isolated in very good, crude purity and yields. Except applicability of the developed method for simple preparation of diverse 4,7,8-substituted benzodiazepinones the approach can be applied for combinatorial synthesis of libraries of BFHs (Scheme 1) with use of 4-chloro-2-fluoro-5-nitrobenzoic acid and previously described procedures.[2]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supporting Information contains details of experimental synthetic and analytical procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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