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# General approach to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones via nucleophile-mediated ring expansion of tetrahydropyrimidines

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ABSTRACT

A general six-step approach to 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones has been developed. The key step involves a ring expansion reaction of 4-mesyloxymethyl- or 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one mediated by nucleophilic reagents.



## 1. Introduction

Monocyclic 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones (e.g., **1**, Fig. 1) are poorly accessible heterocyclic compounds. As for functionalized diazepinones **1**, some of which are useful in the treatment of cardiovascular disorders,[1] hitherto they remain practically

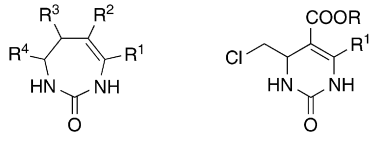
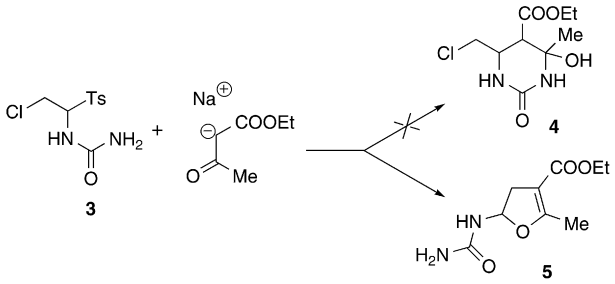



**Figure 1.** Structures of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1** and 4-chloromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **2**.

unknown with only rare examples being described in the literature.[1–3] A promising method of their preparation is based on the ring expansion of chloromethyl-substituted tetrahydropyrimidinones **2** (Fig. 1) under the action of external nucleophilic agents to provide esters of 2-oxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylic acids.[1,3] The major disadvantage of this approach is the low availability of the starting compounds **2**.[4] This confines application of this approach to synthesis of various diazepines.

Previously, we have developed a general synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones(thiones) based on the reaction of readily available α-tosyl-substituted *N*-alkylureas or *N*-alkylthioureas with enolates of carbonyl compounds followed by dehydration of obtained 4-hydroxyhexahydropyrimidin-2-ones (thiones).[5] We attempted to synthesize pyrimidines **2** using this approach. However, reaction of urea **3** with the sodium enolate of ethyl acetoacetate led to unexpected formation of 5-ureido-4,5-dihydrofuran **5** (Scheme 1)[6] instead of hydroxypyrimidine **4**. Obviously, formation of compound **5** can be explained by the presence of an additional electrophilic center at β-position to nitrogen in **3**.[7]




**Scheme 1.** Synthesis of 5-ureido-4,5-dihydrofuran **5** by reaction of urea **3** with the sodium enolate of ethyl acetoacetate.

We hypothesized that α-tosyl-substituted *N*-alkylureas bearing a functional group at β-position (e.g., acyloxy group), which can be transformed into a good leaving group (e.g., Cl, Br, OMs, OTs, etc.) at

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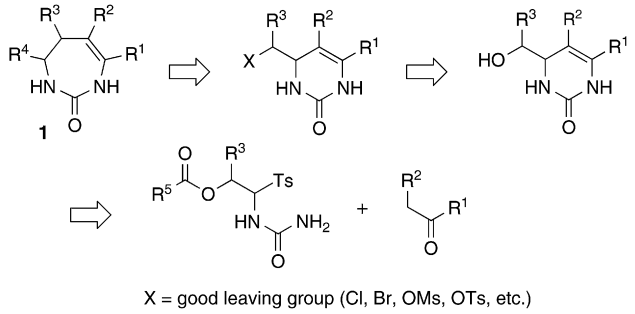
the final stages of synthesis, can serve as starting compounds for the synthesis of diazepines **1**. Our retrosynthetic plan is shown in Scheme 2 and includes preparation of 4-hydroxymethyl-1,2,3,4-tetrahydropyrimidin-2-ones as key compounds.



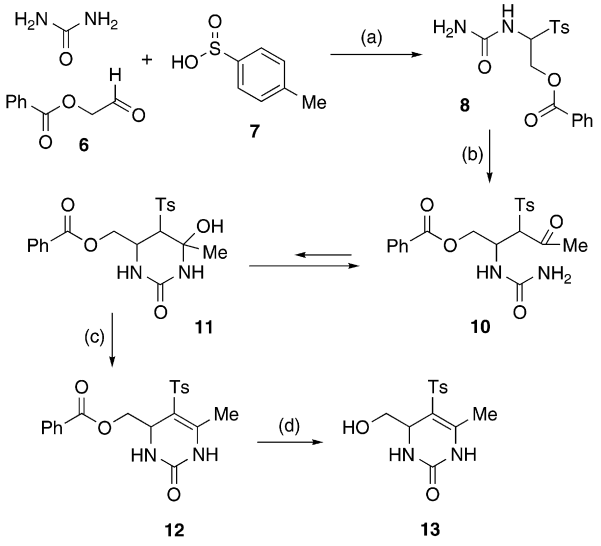

**Scheme 2.** Retrosynthesis of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **1**.

In this communication we describe the application of this strategy to the synthesis of previously unknown 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones.

## 2. Results and discussion

### 2.1. Synthesis of 4-mesyloxymethyl- and 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones

The key precursor for the synthesis of diazepinones, compound **13**, was prepared as shown in Scheme 3. First, readily available **6** was reacted with *p*-toluenesulfinic acid **7** and urea (5 equiv) in water (rt, 7.7 h) to give **8** in 85% yield. A fivefold excess of urea was used to prevent the formation of *N*,*N*′-disubstituted side product (see Ref. 5c). As evidenced by $^1$H NMR data, the crude **8** was 94% pure and was used in further transformations without additional purification.

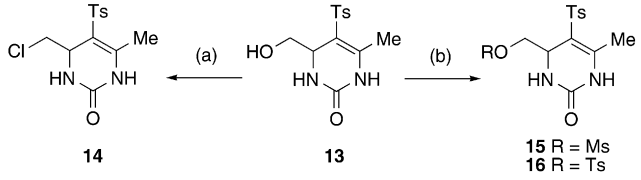


**Scheme 3.** Synthesis of 4-hydroxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one (**13**). Reagents and conditions: (a) $H_2O$, rt, 7.7 h, 85%; (b) $TsCH_2C(O)Me$ (**9**), NaH, MeCN, rt, 7.7 h, 84%; (c) 32 mol % TsOH, EtOH, reflux, 3.6 h, 75% or 51 mol % TsOH, MeCN, reflux, 2 h, 93%; (d) KOH, $H_2O$/EtOH, rt, 1.5 h, 91%.

Tosylacetone **9** was treated with NaH in MeCN to generate the respective Na-enolate, which was reacted with sulfone **8** (MeCN, rt, 7.7 h) to result in the substitution of the tosyl group in **8** and give a product in 84% yield. According to IR in solid phase and NMR in DMSO-$d_6$, the product structure was assigned to an open-chain oxoalkylurea **10** formed as a mixture of diastereomers (62:38), while the formation of an isomeric cyclic compound **11** did not occur in this instance.

Reflux of compound **10** in EtOH in the presence of TsOH (32 mol %) for 3.6 h led to cyclization of **10** into hydroxypyrimidine **11** followed by its dehydration to give tetrahydropyrimidine **12** in 75% yield. The yield of **12** was further improved (up to 93%) by using a greater amount of TsOH (0.5 equiv) in MeCN as a solvent under the reflux conditions (2 h). The benzoyl protection in **12** was readily removed by treatment with KOH (3 equiv) in EtOH/$H_2O$ to give compound **13** in 91% yield (Scheme 3). Thus, overall yield of **13** from **6** equals 60%.

In order to convert the hydroxyl group in **13** into a good leaving group we first attempted the synthesis of **14** by treatment of **13** with $SOCl_2$ under reflux conditions or with $SOCl_2$ in pyridine at 100 °C (Scheme 4). In both cases we obtained complex reaction mixtures where **14** was contaminated with a variety of by-products.



**Scheme 4.** Synthesis of 4-chloromethyl- (**14**), 4-mesyloxymethyl- (**15**), and 4-tosyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-ones (**16**). Reagents and conditions: (a) $SOCl_2$, reflux or $SOCl_2$, Py, 100 °C; (b) MsCl or TsCl, DMAP, $CHCl_3$, rt, 96% (for **15**) and 84% (for **16**).

In contrast, treatment of **13** with MsCl or TsCl (DMAP/$CHCl_3$) led to a smooth formation of respective *O*-mesyl- and *O*-tosyl-derivatives **15** and **16** (Scheme 4). Under optimized conditions (**13**/MsCl/DMAP or **13**/TsCl/DMAP in a ratio of 1:2:3) excellent yields of **15** and **16** (96 and 84%, respectively) were obtained, while pyridine and $NEt_3$ appeared to be ineffective in this instance. For example, the yield of **16** in reaction of **13** with TsCl in pyridine (rt, 5 days) was only 21%.

### 2.2. Ring expansion of 15 and 16 under nucleophilic conditions to form 1,3-diazepin-2-ones

Ring expansion of 4-chloromethyltetrahydropyrimidin-2-ones **2** under the action of strong nucleophilic agents to form 1,3-diazepin-2-ones has been described in the literature.[3] Similarly, 4-chloromethyl-1,4-dihydropyridines and related compounds have been reported to transform into dihydro- and tetrahydroazepines.[8]

It was reasonable to expect that compounds **15** and **16** would undergo a similar conversion to provide a relatively simple access to novel 4-substituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones. Indeed, when treated with NaCN in DMF for 5 h at room temperature, **15** gave 4-cyanodiazepinone **17** in 95% yield (Scheme 5). The latter was also obtained by the reaction of **15** and **16** with NaCN in MeCN plus a catalytic amount of 18-crown-6 (17–30 mol %) for 5.6 and 22.5 h, respectively, at room temperature in excellent yields (Scheme 5). In the absence of 18-crown-6, the progress of the reaction of **15** with NaCN in MeCN as a solvent was dramatically retarded. Under these conditions, after 3 days the reaction mixture consisted of pyrimidine **15** and diazepine **17** (23:77) as evidenced by $^1$H NMR. The reaction of tosyloxymethylpyrimidine **16** with NaCN in DMSO-$d_6$ as a solvent was studied by $^1$H and $^{13}$C NMR to reveal no long-lived intermediates. This experiment has shown that the only product of the reaction was diazepinone **17**.

In a similar fashion, compound **15** was reacted with sodium thiophenolate and the sodium salt of diethyl malonate (rt, MeCN) to give diazepinones **18** and **19** in 97% and 95% yields, respectively (Scheme 5).