Base-Promoted Cascade Transformation of Tetrahydropyrimidinones into Novel Tricyclic bis-Diazepinones

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Abstract

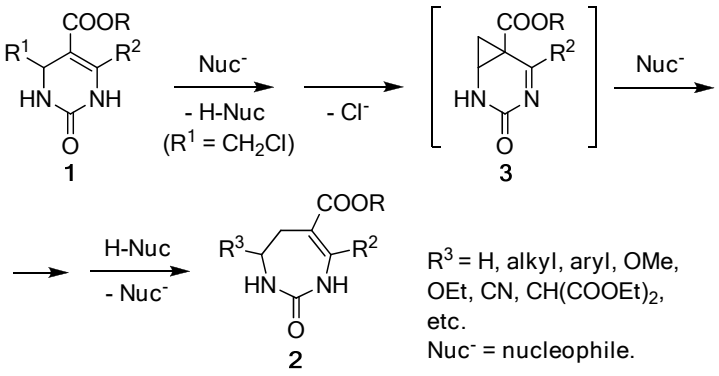
In the presence of strong bases (NaH, DBU, KOH), ethyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and 4-mesyloxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one are transformed into novel tricyclic compounds, diethyl 9-methyl-5-methylene-3,11-dioxo-2,3,4,5,6a,7,10,11-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]-triazocine-6,8(1*H*)-dicarboxylate and 9-methyl-5-methylene-6,8-ditosyl-1,2,4,5,6,6a,7,10-octahydro-1,6-methano[1,3]diazepino[1,7-e][1,3,5]triazocine-3,11-dione, respectively.

Keywords: 1,2,3,4-Tetrahydropyrimidin-2-ones; 2,3,6,7-Tetrahydro-1*H*-1,3-diazepin-2-ones; Ring expansion; [1,3]Diazepino[1,7-*e*][1,3,5]triazocines.

Introduction

Biginelli compounds, **1**, are readily available heterocycles[1] with a wide range of biological activity (Scheme 1).[2] In contrast, their seven-membered analogues **2** are poorly accessible. Although several of these compounds have demonstrated promising antihypertensive action,[3] further studies of biological activity of compounds **2** are hindered by the lack of efficient methods for their preparation.

The only reported approach to diazepinones **2** consists of the treatment of **1** (R = Me, Et; R^1 = CH_2Cl; R^2 = Me, Ph) with nucleophilic agents such as $NaBH_4$, NaCN, sodium malonate, Grignard reagents, sodium succinimide, MeONa and EtONa (Scheme 1).[3-7] The formation of diazepinones **2** was postulated to proceed *via* proton abstraction from N(1)H followed by intramolecular nucleophilic substitution at CH_2Cl to give a bicyclic intermediate **3** containing a cyclopropane ring.[5,6] Subsequent ring expansion in **3** led to diazepinones **2.** Summarizing their observations, the authors[5,6] concluded that the basic properties of the nucleophilic agent were important for the success of the reaction.

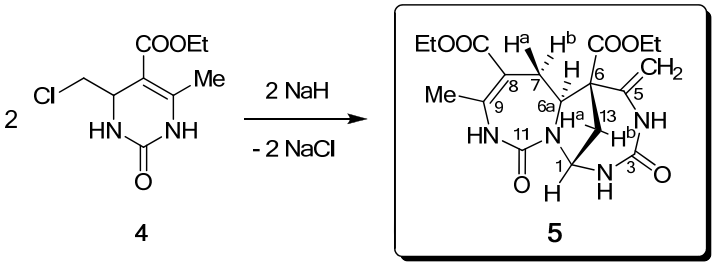


Scheme 1. Synthesis of 2,3,6,7-tetrahydro-1*H*-1,3-diazepin-2-ones **2** by reaction of 4-chloromethyl substituted Biginelli compounds **1** with nucleophiles.

In our attempt to reveal the mechanistic details of this transformation, we studied the reaction of **1** with strong, non-nucleophilic bases without addition of nucleophilic agents using readily available pyrimidinone **4**[5,6] as a model compound.

Results and Discussion

When treated with NaH (1.1 equiv) in anhydrous MeCN at room temperature, compound **4** rapidly reacted to form, as evidenced by TLC, a single product **5** which was isolated after evaporation and aqueous work-up in 78% yield (Scheme 2).



Scheme 2. NaH-promoted diastereoselective transformation of **4** to [1,3]diazepino[1,7-*e*][1,3,5]triazocine **5**.

Preliminary elucidation of the structure using ^{1}H and ^{13}C NMR showed that compound **5** contained two ethoxycarbonyl groups, three NH groups of two urea fragments, a methyl group attached to a double bond, and an exocyclic methylene group and did not contain any chloromethyl groups. The number of carbon and hydrogen atoms equaled 18 and 24, respectively. The combustion analysis agreed with the molecular formula $C_{18}H_{24}N_4O_6$. This suggested the

formation of a dimeric compound. Further detailed analysis of the ^{1}H and ^{13}C NMR spectra in DMSO-d_6, DMSO-d_6+D_2O, and pyridine-d_5, and of ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC and ^{1}H,^{13}C-HMBC data allowed us to determine the structure of **5** as diethyl 9-methyl-5-methylene-3,11-dioxo-2,3,4,5,6a,7,10,11-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]triazocine-6,8(1*H*)-dicarboxylate (Scheme 2). To the best of our knowledge, a tri-heterocyclic system of this type has never been described before.

The specific features of the ^{1}H NMR spectra of **5** are the presence of a long range coupling constant $^{5}J_{7\text{-H(a)},9\text{-CH3}}$ = 1.7 Hz, which is typical for diazepinones **2**,[5,6] and the zero value of the vicinal constant $J_{1\text{-H},13\text{-H(b)}}$. The significant difference in the chemical shifts of the geminal protons 7-Hb and 7-Ha (0.83 ppm in DMSO-d_6 and 1.26 ppm in pyridine-d_5) was also noticeable and may be explained by the presence of the two neighboring anisotropic ethoxycarbonyl groups.

The ^{1}H and ^{13}C NMR data showed that compound **5** existed as a single diastereomer. Its relative configuration was determined by ^{1}H,^{1}H-NOESY experiments (Figure 1).

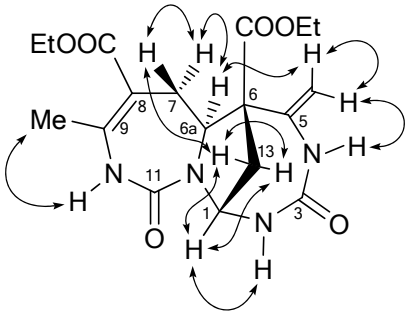


Figure 1. Diagnostic NOE relationships in **5**.

For example, NOEs were observed between 7-Ha and 13-Ha atoms and between one of the hydrogen atoms of the exocyclic methylene group and 6a-H. Calculations using semi-empirical methods AM1[8] showed that the distance between 6a-H and the nearest H in the methylene group in (1*R**,6*S**,6a*S**) and (1*R**,6*S**,6a*R**), the two possible diastereomers of **5**, equals 2.62 and 4.41 Å, respectively, and the distance between 7-Ha and 13-Ha equals 2.80 and 4.90 Å, respectively. Based on these data, the observed NOEs are only consistent with (1*R**,6*S**,6a*S**)-bis-diazepinone **5** (Scheme 2 and Figure 2).

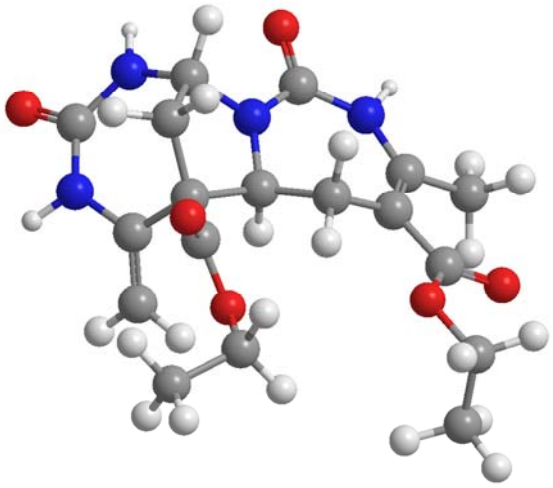
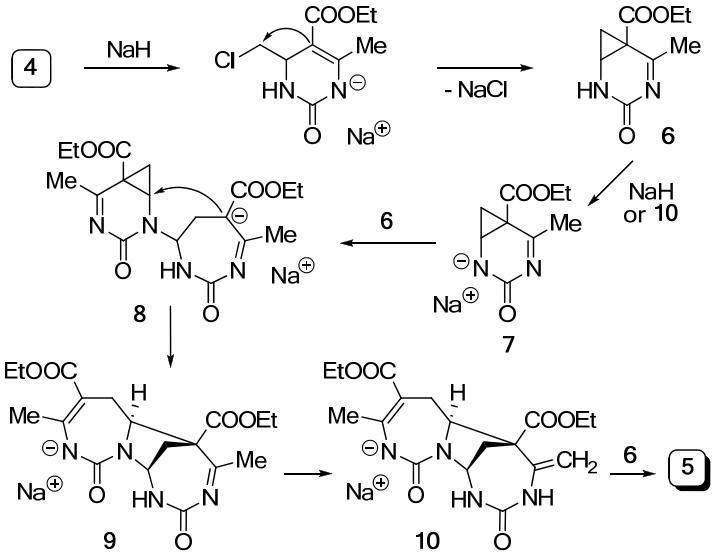


Figure 2. Geometry of **5** according to AM1 semi-empirical calculations.

One possible explanation of the diastereoselective transformation of **4** to **5** is presented in Scheme 3. Similar to the mechanism in Scheme 1, a bicyclic compound **6** is believed to serve as a key intermediate. In the absence of other nucleophiles, **6** undergoes nucleophilic substitution with its own conjugated base **7** followed by ring expansion to give **8**. An intramolecular nucleophilic substitution/ring expansion in **8** forms the second diazepine cycle to give **9**. Finally, acylimine-enamide tautomerization and protonation leads to the tricyclic compound **5**.



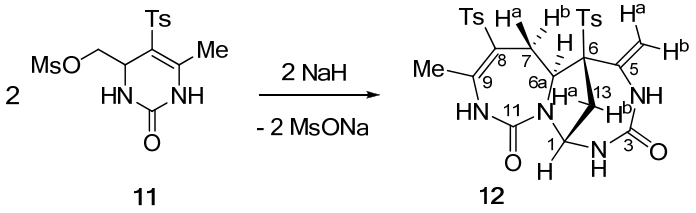
Scheme 3. A plausible pathway for the transformation of **4** to **5**.

We studied the influence of solvent, base, and molar ratio of the base with respect to **4** on the formation of **5**. In DMF, treatment of **4** with NaH (1.1 equiv) for 6 h at 20 ^{o}C resulted in

smooth formation of **5** (79%). In less polar THF or 1,4-dioxane containing NaH (1.1 equiv), compound **5** was formed along with a considerable amount of side products. When the amount of NaH was reduced from 1.1 to 0.95 equiv (MeCN, 20 °C), extensive formation of side products was observed. With DBU (1.35 equiv) in MeCN (20 °C, 24 h), the product **5** was obtained in 59% yield. In the presence of KOH (1.1 equiv) in MeCN, dimerization of **4** to **5** proceeded with the formation of side products due to the strong nucleophilic nature of KOH. When **4** was treated with weaker bases (DABCO or *i*-Pr_2NEt) in MeCN, only the starting material was recovered from the reaction mixture. The observations described above are in good agreement with the mechanism proposed in Scheme 3.

To confirm the proposed mechanism, detection of the intermediates **6**-**10** was attempted using ^{1}H NMR. A solution of **4** in DMSO-d_6 was treated with NaH in an NMR tube and the progress of the reaction was monitored by ^{1}H NMR. However, the NMR spectra only showed the gradual transformation of **4** into **5**, which was completed in 30 min. No intermediates were detected in the reaction mixture at any point, presumably because of their short lifetimes.

We have found that the base-promoted cascade transformation of tetrahydropyrimidines of type **4** described above is quite general. Being treated with NaH in MeCN (rt, 3 h) compound **11**[9] afforded tricyclic bis-diazepinone **12** in 92% yield (Scheme 4).



Scheme 4. Transformation of 4-mesyloxymethyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one **11** into tricyclic bis-diazepinone **12**.

Bis-diazepinone **12** formed as a single diastereomer with (1*R**,6*S**,6a*S**)-configuration according to ^{1}H-^{1}H ROESY data. NOEs were observed between 7-H^a and 13-H^a and between 6a-H and =CH^a.

Conclusion

In conclusion, we have found that, under anhydrous basic conditions, the fate of Biginelli compound **4** strongly depends on the nucleophilicity and the polarity of the reaction medium. While in the presence of strong external nucleophiles compounds **2** are formed,[3-7] exposure of

4 to strong non-nucleophilic bases results in a cascade transformation leading to the diastereoselective formation of the novel bis-diazepinone **5**.

References and Notes

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