Two Pathways for the Reaction of Ethyl 4-Chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with Thiophenolates: Ring Expansion versus Nucleophilic Substitution

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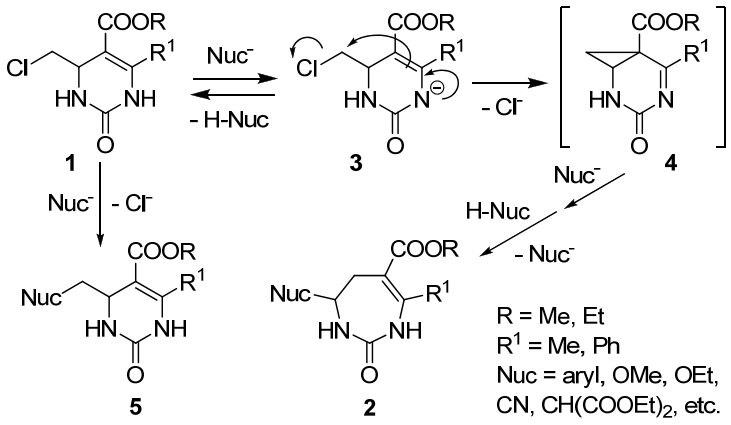
Abstract

Ethyl 4-methyl-2-oxo-7-phenylthio-2,3,6,7-tetrahydro-1*H*-1,3-diazepine-5-carboxylate and/or ethyl 6-methyl-2-oxo-4-(phenylthiomethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate were obtained in the reaction of ethyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with PhSNa or PhSK with or without PhSH, depending on the reagent ratio, reaction time or temperature, as a result of ring expansion and/or nucleophilic substitution. The reaction pathway was affected strongly by the basicity-nucleophilicity of the reaction media. The results obtained were confirmed by reactions of 4-mesyloxymethyl-6-methyl-5-tosyl-1,2,3,4-tetrahydropyrimidin-2-one with PhSNa/PhSH and ethyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with NaCN/HCN or $NaCH(COOEt)_2/CH_2(COOEt)_2$.

Keywords: 1,2,3,4-Tetrahydropyrimidin-2-ones; 2,3,4,5-Tetrahydro-1*H*-1,3-diazepin-2-ones; Ring expansion; Nucleophilic substitution.

Introduction

Ring expansion reactions are widely used in organic chemistry,[1] particularly in the synthesis of nitrogen-containing heterocycles.[1,2] An important example of one-carbon ring expansion is the transformation of tetrahydropyrimidines **1** into tetrahydro-1,3-diazepin-2-ones **2** by treatment with nucleophilic reagents (Scheme 1).[3]



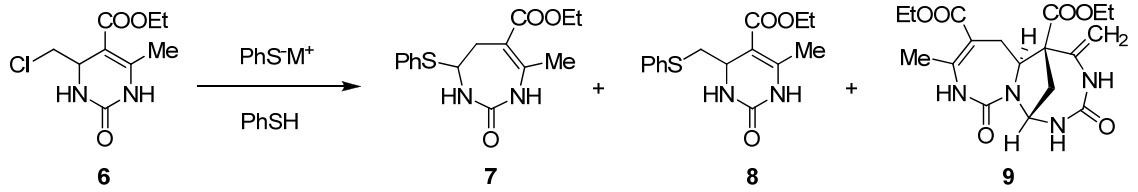
Scheme 1. Two possible pathways for the reaction of pyrimidines **1** with nucleophilic reagents: ring expansion or nucleophilic substitution.

It was postulated[3] that diazepinones **2** form via the cyclopropane-containing bicyclic intermediates **4** (Scheme 1) which result from proton abstraction from the N(1)H group under the action of nucleophiles followed by intramolecular nucleophilic substitution of chlorine in anions **3**. Clearly, this reaction depends not only on nucleophilicity, but also on the basicity of the nucleophile. For example, direct nucleophilic substitution of chlorine resulting in pyrimidines **5** cannot be excluded a priori under certain reaction conditions. However, the influence of reaction conditions on the reaction of compounds **1** with nucleophiles remained unexplored.[3] Therefore, study of the effect of the nucleophilicity and basicity of the nucleophile, the reagent ratio, the solvent, time and temperature on the reaction of compounds **1** with nucleophiles is interesting. In this research we used readily available pyrimidinone **6** as the starting material and PhSNa or PhSK as nucleophiles which demonstrate strong nucleophilicity and relatively low basicity.[4] The nucleophiles were generated by treatment of PhSH with NaH or KOH in an appropriate solvent.

Results and Discussion

The reaction of **6** with PhSNa (1.08 equiv) in dry MeCN at rt for 7 hours yielded diazepinone **7** as the product of ring expansion (Scheme 2). According to the ^{1}H NMR spectrum, the crude material contained 3 mol% of tetrahydropyrimidinone **8**, a product of nucleophilic substitution of chlorine in **6** (Table 1, entry 1). Diazepinone **7** formed with complete selectivity under similar conditions in the reaction of **6** with PhSNa (1.10 equiv) in dry THF (rt, 7 h) (entry 2), however, 9 mol% of starting material **6** was recovered. When EtOH was used as the solvent, the rate of the reaction of **6** with PhSK (1.10 equiv) decreased

dramatically (conversion of **6** was only 8% after 7 h at rt), and the selectivity also decreased (**7**:**8** = 7:1) (entry 3).



6 **7** **8** **9**

Scheme 2. Reaction of pyrimidine **6** with PhSNa or PhSK.

Table 1
Reactions of pyrimidine **6** with PhSNa or PhSK

Entry	Solvent	Base	Molar ratio of **6**:PhSH:Base	Molar ratio of **6**:PhSNa:PhSH or **6**:PhSK:PhSH	Conditions	Molar ratio[a] of products **7**:**8**:**6**
1	MeCN	NaH	1.00:1.08:1.09	1.00:1.08:0	rt, 7 h	97:3:0
2	THF	NaH	1.00:1.10:1.10	1.00:1.10:0	rt, 7 h	91:0:9
3	EtOH	KOH	1.00:1.13:1.10	1.00:1.10:0.03	rt, 7.5 h	7:1:92
4	MeCN	NaH	1.00:2.02:1.10	1.00:1.10:0.92	rt, 7 h	48:43:9
5	MeCN	NaH	1.00:2.21:1.05	1.00:1.05:1.16	rt, 7.2 h	9:61:30
6	MeCN	NaH	1.00:3.00:1.10	1.00:1.10:1.90	rt, 7 h	0:35:65
7	MeCN	NaH	1.00:3.00:1.10	1.00:1.10:1.90	reflux, 7 h	15:85:0
8	MeCN	NaH	1.00:3.29:1.10	1.00:1.10:2.19	rt, 47.9 h	1:93:6
9	MeCN	NaH	1.00:3.32:1.10	1.00:1.10:2.22	rt, 72.7 h	0:97:3
10	MeCN	NaH	1.00:2.24:1.05	1.00:1.05:1.19	rt, 48.2 h	6:89:5
11	MeCN	NaH	1.00:2.20:1.10	1.00:1.10:1.10	reflux, 8 h	33:67:0
12	MeCN	NaH	1.00:3.26:1.08	1.00:1.08:2.18	reflux, 8.1 h	16:84:0
13	MeCN	NaH	1.00:4.43:1.10	1.00:1.10:3.33	reflux, 8.1 h	11:89:0
14	EtOH	KOH	1.00:2.23:1.10	1.00:1.10:1.13	rt, 7 h	16:6:78
15	MeCN	NaH	1.00:2.01:2.00	1.00:2.00:0.01	rt, 7 h	93:7:0[b]
16	MeCN	NaH	1.00:3.31:1.10	1.00:1.10:2.21	reflux, 29 h	11:89:0

[a] According to ^{1}H NMR data of the crude products.
[b] 83 mol% of **7**+**8** and 17 mol% of bis-diazepinone **9**.

Thiophenol (PhSH) strongly affected the ratio of **7**:**8** and the rate of the reaction. The amount of pyrimidine **8** increased with a rise in the amount of PhSH in the reaction of **6** with PhSNa (1.05-1.10 equiv) in MeCN at rt for 7 hours (entries 1, 4-6). Pyrimidine **8** formed with complete selectivity when 1.90 equivalents of PhSH were used (entry 6). However, the reaction rate decreased significantly with an increase in the amount of PhSH (entries 1, 4-6).

The extent of conversion of compound **6** in the reaction with PhSNa in the presence of PhSH (1.90-2.22 equiv) increased with reaction time or temperature. Indeed, the reaction of **6** with PhSNa (1.10 equiv) in refluxing MeCN in the presence of PhSH (1.90 equiv) was

complete in 7 hours, while the selectivity of the reaction decreased significantly (entry 7). However, the selectivity remained high at rt and over long reaction times (entries 8 and 9).

A relationship between the ratio of **7**:**8** and the amount of PhSH was also observed at rt and over long reaction times (entry 8 vs entry 10), refluxing the reaction mixture (entry 11 vs entry 12 vs entry 13), and when EtOH was used as the solvent (entry 3 vs entry 14).

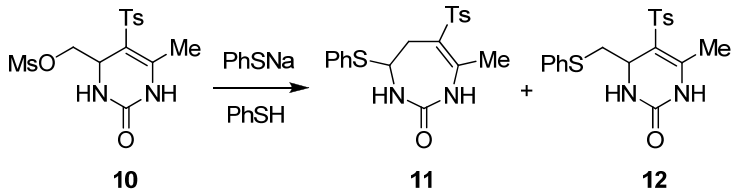
On using a greater excess of the nucleophile PhSNa (2.00 equiv), bis-diazepinone **9**[5] (17 mol%) formed along with **7** and **8** in the ratio 93:7 (entry 15).

Under the optimal conditions diazepinone **7** was obtained in the reaction of **6** with PhSNa (1.08 equiv) in MeCN at rt for 7 hours (entry 1), and pyrimidinone **8** was prepared by reaction of **6** with PhSNa (1.10 equiv) in the presence of 2.22 equivalents of PhSH in MeCN at rt for 73 hours (entry 9).

Transformation of **6** into **7** and/or **8** is kinetically controlled. In fact, heating a mixture of **6**, PhSNa and PhSH in MeCN for 8 or 29 hours at reflux resulted in mixtures of **7** and **8** in similar ratios (Table 1, entry 12 vs entry 16). Moreover, reflux of **7**, PhSH and PhSNa (1.0:1.9:0.1, respectively) in MeCN followed by evaporation of the solvent and aqueous work-up gave only **7** in 88% yield.

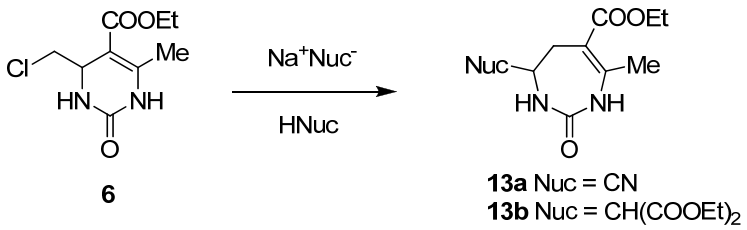
From the results obtained we suggest that the reaction of **6** with PhSNa and PhSK proceeds via two possible mechanisms. In aprotic solvents (MeCN or THF) and a highly basic reaction media without PhSH, the thiophenolate-anion acts as a base and abstracts a proton from N(1)H to give anion **3** (R = Et, R^1 = Me) (see Scheme 1), which further affords diazepinone **7**. Addition of PhSH inhibits anion **3** formation and therefore causes a decrease in the amount of diazepinone **7**. Probably, in this case, compound **6** reacts with PhSNa via an S_N2 mechanism, resulting in pyrimidine **8**. Since chlorine is a rather poor leaving group, the rate of reaction is low, and heating at reflux or a long reaction time is necessary for completion of the reaction. The low rate of reaction of **6** with PhSK in EtOH can be explained by the decreased basicity and nucleophilicity of PhSK in a polar protic solvent.

In continuation of this research we used 4-mesyloxymethyl-5-tosyltetrahydropyrimidine (**10**) as the starting material in a reaction with PhSNa in the presence of PhSH. We found that **10** readily reacted with PhSNa in MeCN to give 4-phenylthio-6-tosyltetrahydro-1,3-diazepinone (**11**) (Scheme 3).[6] As expected, when compound **10** was reacted with PhSNa/PhSH (1:1.08:2.47) in MeCN (rt, 23.7 h), pyrimidinone **12** formed along with diazepinone **11** (**12**:**11** = 56:44). The amount of **12** increased up to 92% in this reaction, when a 1:1.24:3.82 ratio of the reagents was used (MeCN, rt, 42.4 h).



Scheme 3. Reaction of pyrimidine **10** with PhSNa/PhSH.

We also attempted to obtain products of direct nucleophilic substitution of the chlorine in the reaction of **6** with other nucleophiles. However, reaction of **6** with NaCN and HCN (1.00:1.28:2.75) in DMSO (rt, 32 h) resulted in a mixture of diazepine **13a** and starting material **6** in a ratio of 41:59 (Scheme 4). Analogously, diazepinone **13b** formed as a single product in the reaction of **6** with $NaCH(COOEt)_2/CH_2(COOEt)_2$ (1:1.09:2.23) in MeCN (rt, 33.4 h).



Scheme 4. Reaction of pyrimidine **6** with NaCN/HCN or $NaCH(COOEt)_2/CH_2(COOEt)_2$.

Exclusive formation of the products of pyrimidine ring expansion in the reactions of **6** with NaCN/HCN or $NaCH(COOEt)_2/CH_2(COOEt)_2$ versus PhSNa(PhSK)/PhSH could be explained by the higher basicity of NaCN or $NaCH(COOEt)_2$ compared with PhSNa or PhSK.[7]

The structures of **7**, **8** and **12** were established unambiguously from their ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **7** in DMSO-d_6 demonstrated long-range couplings between N(1)H and one of the 6-H protons ($^4J_{N(1)H,6\text{-}He}$ = 0.9 Hz) and between 4-CH_3 and the other 6-H proton ($^5J_{4\text{-}CH3,6\text{-}Ha}$ = 1.3 Hz). Higher values for the vicinal $^3J_{N(1)H,7\text{-}H}$ and geminal $^2J_{6\text{-}He,6\text{-}Ha}$ coupling constants (6.1 and 15.1 Hz, respectively) for diazepine **7** compared with the corresponding constants for pyrimidines **8** and **12** ($^3J_{N(3)H,4\text{-}H}$ = 3.4-4.1 Hz, $^2J_{CH(A),CH(B)}$ = 13.7-13.8 Hz) were observed. In the ^{13}C NMR spectrum of diazepine **7** we observed the chemical shift of the N-CH fragment at 61.32 ppm, while for pyrimidines **8** and **12** these occured at 49.75 and 49.85 ppm, respectively. The 2-D NMR spectral data (^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC) also confirmed unambiguously the structures of diazepinones **7** and **8**.

Conclusion

In summary, the reaction of 5-functionalized 4-(X-CH_2)-1,2,3,4-tetrahydropyrimidin-2-ones (X = good leaving group) with nucleophilic reagents resulted in the products of ring expansion (2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones) and/or products of direct substitution of the leaving group (1,2,3,4-tetrahydropyrimidin-2-ones) depending on the reaction conditions. The outcome of the reaction was determined by the nucleophilicity-basicity of the reaction media. Diazepinones **7** and **11** formed in the reaction of **6** and **10** with strong nucleophiles PhSNa or PhSK possessing relatively low basicity (pK_a = 10.3 in DMSO). However, the reaction of **6** and **10** with PhSNa or PhSK in the presence of their conjugate acid (PhSH) gave diazepinones **7** and **11** along with the respective pyrimidines **8** and **12**. An increase in the amount of PhSH led to a significant increase in pyrimidine formation, while the rate of the conversion of starting materials into products decreased. In aprotic solvents, almost pure pyrimidines **8** and **12** were obtained when more than 2 equivalents of PhSH were used. However, the reaction of **6** with more basic nucleophiles, NaCN or $NaCH(COOEt)_2$ (pK_a = 12.9 and 15.9, respectively, in DMSO) with or without their conjugate acids yielded only the diazepinones **13a**,**b**.

We envisage that our findings may be of value for other similar one-carbon ring expansion reactions.[1,2]

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