

Proceedings

A New Approach to 5-Functionalized 1,2-Dihydropyrimidin-2-ones/imines via Base-Induced Chloroform Elimination from 4-Trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones/imines [†]

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[†] Presented at the 22nd International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2018; Available Online: <https://sciforum.net/conference/ecsoc-22>.

Published: 14 November 2018

Abstract: A novel four-step methodology for the synthesis of 5-acyl- and 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones has been developed. The reaction of readily available *N*-[(1-acetoxy-2,2,2-trichloro)ethyl]-ureas with Na-enolates of 1,3-diketones, β -oxoesters, or α -arylsulfonylketones followed by heterocyclization–dehydration of the oxoalkylureas formed gave 5-acyl- or 5-arylsulfonyl-4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones. The latter, in the presence of strong bases, eliminates CHCl_3 to give the target compounds. The above methodology was also used in the synthesis of 5-acyl-1,2-dihydropyrimidin-2-imines starting from *N*-[(1-acetoxy-2,2,2-trichloro)ethyl]-*N'*-guanidine.

Keywords: 1,2,3,4-Tetrahydropyrimidin-2-ones/imines; 1,2-Dihydropyrimidin-2-ones/imines; amidoalkylation; aromatization

1. Introduction

5-Non-functionalized 1,2-dihydropyrimidin-2-ones (**1a** $\text{R}^1 = \text{H}$, alkyl, aryl) (Figure 1) are of considerable interest due to their wide range of biological activities [1–5]. These compounds have been extensively studied, and effective methods for their synthesis have been developed [6–8]. In contrast, 5-acyl-1,2-dihydropyrimidin-2-ones (**1b** $\text{R}^3 = \text{alkyl}$, aryl, alkoxy, etc.) have been studied less widely. A number of methods, including condensations of (C-C-C-N-C-N)- [9–11], (C-C-C-N + C-N)- [12], and (C-C-C + N-C-N)-types [10,13,14], dehydrogenation [15] and oxidation [16–23] of the corresponding 1,2,3,4-tetrahydropyrimidin-2-ones, catalytic acylation of 5-trialkylstannylpyrimidines [24], and hydrolysis of appropriate 2-functionalized pyrimidines [24–30], have been reported for the synthesis of pyrimidines **1b**. However, the synthetic methods generally efficient in the preparation of **1a** tend to give poor yields in the specific case of **1b**.

Other 5-functionalized 1,2-dihydropyrimidin-2-ones remain hitherto practically inaccessible. For example, there are only a few reports on the synthesis of 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones (**1c** $\text{R}^4 = \text{aryl}$) [31,32]. Thus, the development of a general approach to the synthesis of 5-functionalized 1,2-dihydropyrimidin-2-ones is important.

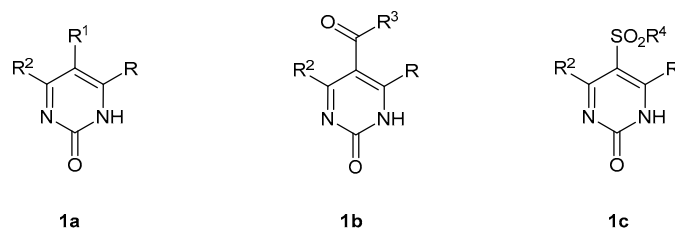
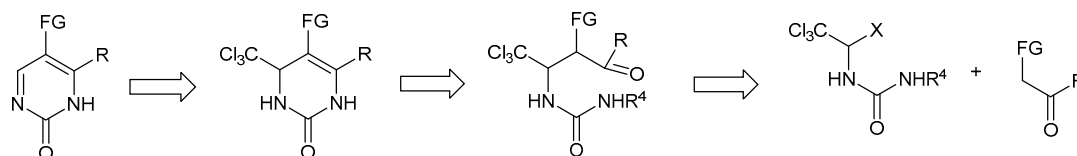


Figure 1. Structures of 1,2-dihydropyrimidin-2-ones **1a**, 5-acyl-1,2-dihydropyrimidin-2-ones **1b**, and 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones **1c**.

Taking into consideration the reported formation of imines from α -trichloromethyl-substituted secondary amines and amides by elimination of chloroform in the presence of bases [33–36], we hypothesized that 5-functionalized 1,2-dihydropyrimidin-2-ones (**1b,c** R² = H) could be obtained starting from the corresponding 4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones. Synthesis of the latter is presented in our retrosynthetic plan (Scheme 1) and includes ureidoalkylation of enolates of α -functionalized ketones [37–41].



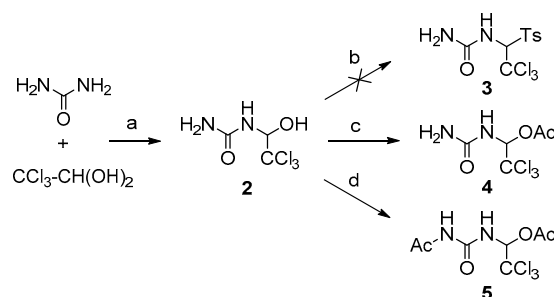
FG = functional group; X = good leaving group (Ts, OAc, etc.); R⁴ = H, Ac.

Scheme 1. Retrosynthesis of 5-functionalized 1,2-dihydropyrimidin-2-ones.

Here, we describe a novel convenient approach to 5-acyl-1,2-dihydropyrimidin-2-ones **1b** and 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones **1c** via 4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones as key intermediates. The application of this approach to the synthesis of 5-acyl-1,2-dihydropyrimidin-2-imines are also reported.

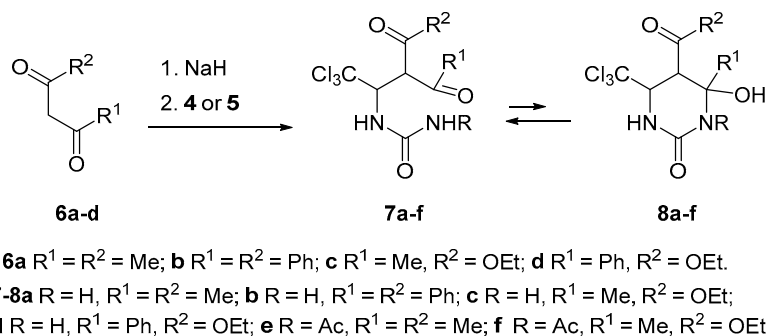
2. Results and Discussion

In our previous experience, α -tosyl-substituted *N*-alkylureas proved very useful starting materials for the preparation of various 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones by ureidoalkylation of α -functionalized ketones [37–41]. However, the synthesis of tosyl derivative **3** bearing a trichloromethyl group failed (Scheme 2), while acetoxy derivatives **4** and **5** [42] were conveniently prepared by treatment of the readily available **2** [43] with Ac₂O in pyridine and Ac₂O in the presence of H₂SO₄, respectively. Based on the ability of the acetoxy group to serve as a good leaving group in various reactions of ureidoalkylation [44–49], we hypothesized that compounds **4** and **5** might also be used in the synthesis of compounds **7** under the conditions similar to those applicable for ureidoalkylation of α -substituted ketones with α -tosyl-substituted *N*-alkylureas [37–41].



Scheme 2. Synthesis of ureidoalkylating agents **4** and **5**. Reagents and conditions: (a) H₂O, rt; (b) 4-MeC₆H₄S(O)OH, H₂O, rt or heating; (c) Ac₂O, py, rt, 75%; and (d) Ac₂O, H₂SO₄, rt, 79%.

Sodium enolates of 1,3-dicarbonyl compounds **6a,b** and β -oxoesters **6c,d** generated in situ by treating the corresponding CH-acids with an equivalent amount of NaH reacted with urea **4** for 2.7–4.3 h at room temperature to give the products of acetoxy group substitution, *N*-oxoalkylureas **7a–d**, in 70–95% yield (Scheme 3, Table 1).



Scheme 3. Synthesis of ureas **7a–f** by reaction of sodium enolates of 1,3-diketones **6a,b** and β -oxoesters **6c,d** with **4** and **5**.

Table 1. Reaction of ureas **4** and **5** with sodium enolates of **6a–d** ^a.

Entry	Starting Material	Solvent	Reaction Time, h	Molar Ratio (4/6 or 5/6)	Product	Diastereomeric Ratio ^b	Yield, % ^c	
1	6a	4	MeCN	3.3	1:1	7a	-	70
2	6b	4	THF	4.3	1:1	7b	-	89
3	6c	4	MeCN	4	1.1:1	7c	57:43	86
4	6d	4	MeCN	2.7	1.1:1	7d	72:28	95
5	6d	4	MeCN	5.75	1:1	7d	83:17	91
6	6d	4	MeCN	9.3	1:1	7d	84:16	90
7	6a	5	MeCN	4.4	1:1	7e	-	82
8	6c	5	MeCN	4.2	1.1:1	7f	75:25	69

^a At room temperature. ^b Established by ¹H NMR data of crude product. ^c All yields refer to isolated material homogeneous spectroscopically and by thin-layer chromatography (TLC).

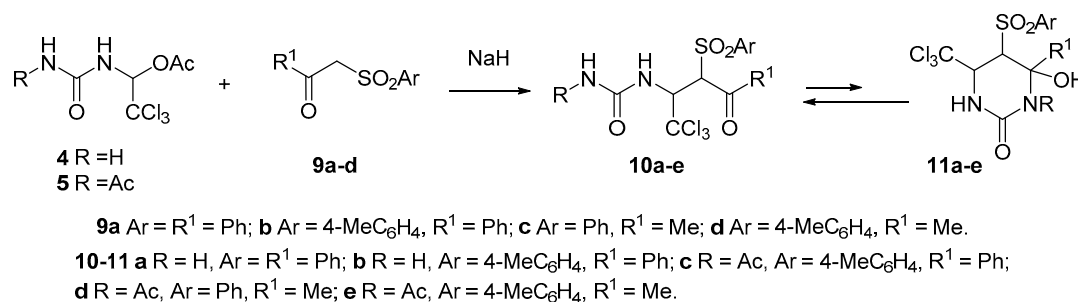
Anhydrous MeCN was used as a solvent for preparation of compounds **7a,c–d**; however, for compound **7b** anhydrous THF was used because the solubility of the enolate of **6b** in MeCN was very low and the resulting extremely dense suspension hampered the completion of reaction of NaH with **6b**.

Following the same procedure, urea **5** reacted with the sodium enolate of **6a** and **6c** in MeCN (rt, 4.2–4.4 h) to give oxoalkylureas **7e** and **7f** in 82 and 69% yield, respectively (Scheme 3, Table 1).

IR-, ¹H-, and ¹³C-NMR spectra indicated that compounds **7a–f** only existed in acyclic form both in solid state and in DMSO-*d*₆ solution. Their cyclic isomers **8a–f** (Scheme 3) were not detected by any spectroscopic methods.

Compounds **7c,d,f** were formed as mixtures of two diastereomers (Table 1). The diastereoselectivity of the product formation depended on the structures of both reagents and was higher with **5** than with **4** (entry 3 vs. entry 8) and with **6d** than with **6c** (entry 3 vs. entry 4). The reaction time did not affect the ratio of diastereomers (entry 5 vs. entry 6). The use of a greater excess of a nucleophile slightly reduced the stereoselectivity (entry 5 vs. entry 4), which indicated that these reactions were controlled by both kinetic and thermodynamic factors.

Sodium enolates of ketones bearing the arylsulfonyl group at the α -position generated in situ by treating the corresponding CH-acids **9a–d** with an equivalent amount of NaH reacted with ureas **4** and **5** (MeCN or THF, rt, 4–9 h) to give products of nucleophilic substitution of the acetoxy group, sulfones **10a–e**, in a 76–90% yield (Scheme 4, Table 2).



Scheme 4. Synthesis of oxoalkylureas 10a–e.

Table 2. Reaction of ureas 4 and 5 with sodium enolates of 9a–d at rt.

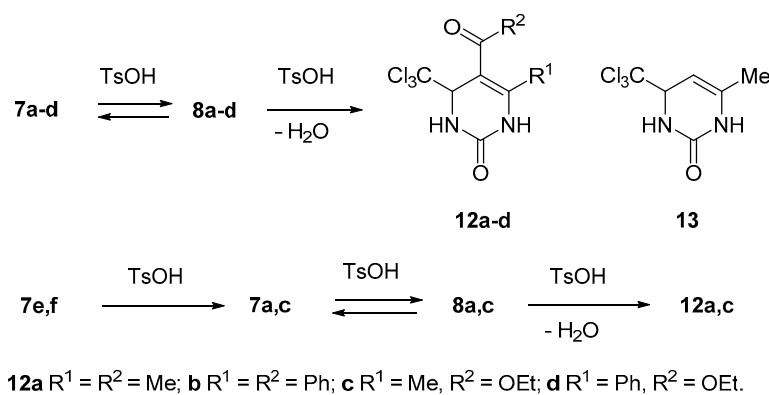
Entry	Starting Material	Solvent	Reaction Time, h	Product	Diastereomeric Ratio ^a (R*,S*)-10/(R*,R*)-10	Yield, ^b %	
1	4	9a	MeCN	4	10a	95:5	88
2	4	9a	THF	4.5	10a	88:12	76
3	4	9b	MeCN	5	10b	91:9	85
4	5	9b	MeCN	8	10c	97:3	88
5	5	9c	MeCN	4	10d	85:15	85
6	5	9d	MeCN	9	10e	85:15	86
7	5	9d	THF	6.5	10e	86:14	90

^a According to ¹H NMR data of crude products. ^b For isolated compounds.

Reactions of 9a–d with 4 and 5 proceeded with high diastereoselectivity to give sulfones 10a–e in 70–94% diastereomeric excesses (Table 2). The polarity of the solvent had a slight effect on diastereoselectivity (Entry 1 vs. Entry 2; Entry 6 vs. Entry 7). *N*-Acyl-substituted urea 5 reacted with enolate of 9b with higher diastereoselectivity compared with urea 4 (Entry 3 vs. Entry 4).

Based on the values of vicinal couplings of protons in the NH-CH-CH moiety, we have concluded that the minor diastereomers of 10a–e in DMSO-*d*₆ solution exist in a conformation with an anti–anti orientation of the named protons (³J_{NH,CH} = 10.1–10.8 Hz, ³J_{CH,CH} = 8.8–9.0 Hz), while the orientation of the protons for major diastereomers is anti for NH-CH and gauche for CH-CH moieties (³J_{NH,CH} = 9.5–9.6 Hz, ³J_{CH,CH} = 1.5–1.8 Hz).

Next, refluxing solutions of ureas 7a–f in the presence of TsOH (Scheme 5) led to 4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones 12a–d. The dependence of the yields of 12a–d on the reaction conditions is outlined in Table 3.



Scheme 5. Synthesis of 5-acyl-4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones 12a–d.

Table 3. Synthesis of pyrimidinones **12a–d** from ureas **7a–f** ^a.

Entry	Starting Material	Solvent	Molar Ratio of 7:TsOH	Reaction Time, h	Product(s)	Molar Ratio of 12a:13 ^b	Yield of 12, %
1	7a	MeCN	1:0.3	0.6	12a	-	95
2	7a	PhMe	1:1.13	1.0	12a + 13	73:27	-
3	7a	EtOH	1:1.13	1.0	12a + 13	94:6	-
4	7a	EtOH	1:0.5	1.25	12a + 13	94:6	-
5	7a	EtOH	1:0.3	0.63	12a + 13	90:10	-
6	7a	MeOH	1:0.5	1.75	12a + 13	62:38	-
7	7b	MeCN	1:1	2.2	12b	-	91
8	7c	MeCN	1:0.3	1.0	12c	-	93
9	7c	PhMe	1:1.1	1.0	12c	-	84
10	7d	MeCN	1:0.5	33	12d	-	81
11	7d	MeCN	1:3.0	14.2	12d	-	75
12	7e	EtOH	1:1.5	2.0	12a + 13	79:21	-
13	7f	EtOH	1:2.0	3.0	12c	-	77

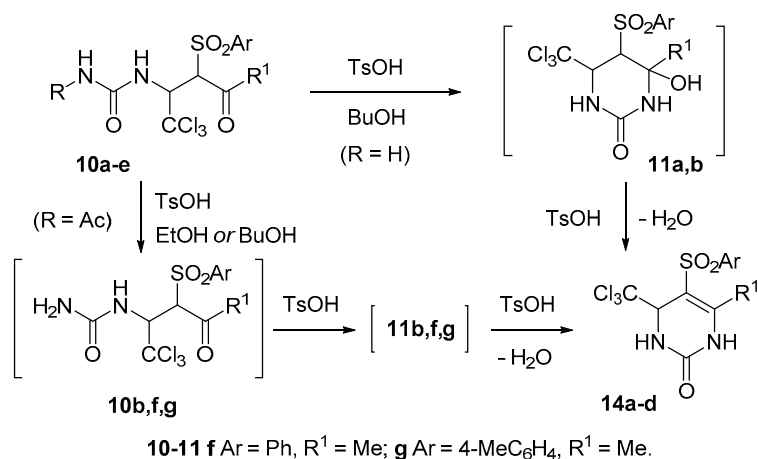
^a Boiling in the presence of TsOH. ^b Based on ¹H NMR spectrum of crude product.

Heterocyclization–dehydration of **7a–d** proceeded smoothly in MeCN as a solvent to give **12a–d** in high yields (75–95%, Table 3, entries 1, 7–11). Reaction of **7a,c** was complete after 0.5–1 h in the presence of TsOH (0.3 equiv, entries 1, 8). By comparison with compounds **7a,c**, their counterparts **7b,d**, which possess a less electrophilic carbonyl group, were converted into **12b,d** (entries 7, 10–11) using a greater amount of catalyst or/and longer reaction time. Pyrimidine **12c** was also readily synthesized from **7c** using toluene as a solvent (entry 9).

In contrast to the smooth conversion of **7a** into **12a** in MeCN, refluxing **7a** in EtOH, MeOH, or toluene in the presence of TsOH led to the formation of **12a** plus the product of its deacetylation, pyrimidine **13** (entries 2–6). Presumably, **13** was obtained as a result of the acid-promoted deacetylation of **7a** followed by heterocyclization and dehydration of the intermediate formed. The data listed in Table 3 indicates that the formation of **13** was favored in more polar solvents (entry 4 vs. entry 6), at higher reaction temperature (entry 2 vs. entry 3), and in protic solvents (entry 1 vs. entry 5). The amount of catalyst had no appreciable effect on the ratio of **12a** to **13** (entry 3 vs. entry 4 vs. entry 5).

5-Arylsulfonyl-substituted tetrahydropyrimidines **14a–d** were obtained by the reflux of sulfones **10a–e** in alcohols (EtOH, *n*-BuOH) in the presence of TsOH (1–4 equiv) (Scheme 6, Table 4).

Formation of compounds **14a,b** from **10a,b** proceeds via heterocyclization of intermediate hydroxypyrimidines **11a,b** followed by dehydration. In case of *N*-acetylureas **10c–e**, the first step is *N*-deacylation into corresponding ureas **10b,f,g** followed by cyclization into hydroxypyrimidines **11b,f,g** and fast dehydration into tetrahydropyrimidines **14b–d**. The data presented in Table 4 shows that the result of the reaction depends on the structure of the starting compounds and reaction conditions. The rate of pyrimidine **14** formation increases with increasing reaction temperature (Entry 7 vs. Entry 8) and quantity of TsOH (Entry 3 vs. Entry 4; Entry 6 vs. Entry 7). *N*-deacylation of **10c–e** proceeds much faster than subsequent transformation of obtained **10b,f,g** into **14b–d** (Entry 2 vs. Entry 4; Entries 3, 6, and 7). Benzoyl-containing ureas **10a–c** react significantly slower comparing with acetyl-containing ureas **10d,e** (Entries 1, 2, and 4 vs. Entries 5 and 8). Apparently, cyclization of *N*-deacylated ureas **10a,b,f,g** into the corresponding hydroxypyrimidines (**11**), which is affected by electrophilicity of carbonyl group and steric bulk of R¹, is the rate-determining step of compounds **14a–d** formation.



10-11 f Ar = Ph, R¹ = Me; **g** Ar = 4-MeC₆H₄, R¹ = Me.

14a Ar = R¹ = Ph; **b** Ar = 4-MeC₆H₄, R¹ = Ph; **c** Ar = Ph, R¹ = Me; **d** Ar = 4-MeC₆H₄, R¹ = Me.

Scheme 6. Synthesis of 5-arylsulfonyl-4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones **14a–d**.

Table 4. Transformation of **10a–e** into **14a–d** ^a.

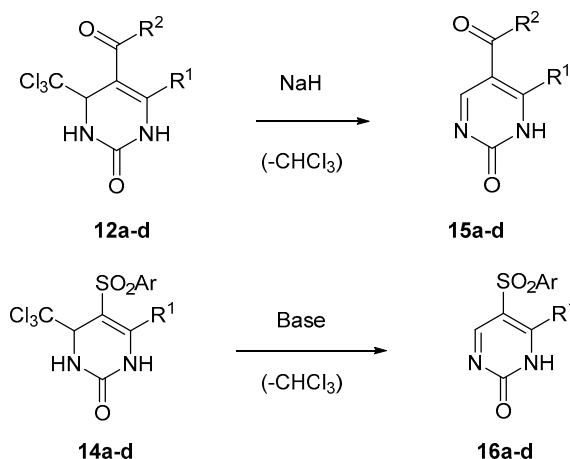
Entry	Starting Material	Solvent	Molar Ratio of 10:TsOH	Reaction Time, h	Product(s)	Molar ratio of Products, 14:10 ^b	Isolated Yield of 14, %
1	10a	<i>n</i> -BuOH	1:4.0	31	14a	-	63
2	10b	<i>n</i> -BuOH	1:4.0	25	14b	-	75
3	10c	<i>n</i> -BuOH	1:3.1	5	14b + 10b ^c	28:72	-
4	10c	<i>n</i> -BuOH	1:4.0	18	14b	-	72
5	10d	<i>n</i> -BuOH	1:2.0	2	14c	-	93
6	10e	EtOH	1:1.1	26	14d + 10g ^d	68:32	-
7	10e	EtOH	1:2.1	16.5	14d + 10g ^d	80:20	-
8	10e	<i>n</i> -BuOH	1:2.0	2	14d	-	92

^a Reflux in alcohols in the presence of TsOH. ^b According to ¹H NMR data. ^c Diastereomer mixture, 85:15. ^d Diastereomer mixture, 84:16.

Thus, under optimal conditions, reflux of **10a–e** in BuOH in the presence of 2–4 equiv of TsOH led to the smooth formation of pyrimidines **14a–d** in 63–93% yields.

Finally, aromatization of tetrahydropyrimidines **12a–d** by NaH (1.2–1.25 equiv) in an aprotic solvent at room temperature led to formation of the corresponding 5-acyl-1,2-dihydropyrimidin-2-ones **15a–d** in good yields (Scheme 7). The reaction proceeded best in THF (for **15a,c,d**) and, for **15b**, in DME while the more polar MeCN failed to give satisfactory yields even with a prolonged reaction time (24 h) and a greater excess of NaH (up to 1.5 equiv).

Analogously, treatment of tetrahydropyrimidines **14a–d** with strong bases in aprotic solvents resulted in the formation of the corresponding 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones **16a–d** (Scheme 7). Target pyrimidines (**16a–d**) were obtained by the reaction of **14a–d** (rt, MeCN, 1.2–3.3 h) with NaH (1.1 equiv) in 80–98% yields. The rate of elimination decreased with a decrease in the base strength. When compound **14d** was treated with DBU (2.1 equiv) in MeCN, aromatization was completed in five days and led to the formation of **16d** in 96% yield. Reaction of **14c** with sodium malonate in MeCN did not proceed at rt and was complete only after reflux for 1 h, resulting in **16c** in 85% yield. Compound **14d** being treated with NaH (1.1 equiv) in THF (rt, 2 h) gave compound **16d** in 90% yield.

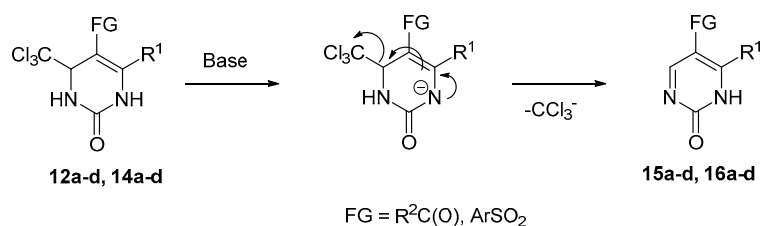


15a R¹ = R² = Me; **b** R¹ = R² = Ph; **c** R¹ = Me, R² = OEt; **d** R¹ = Ph, R² = OEt.

16a Ar = R¹ = Ph; **b** Ar = 4-MeC₆H₄, R¹ = Ph; **c** Ar = Ph, R¹ = Me; **d** Ar = 4-MeC₆H₄, R¹ = Me.

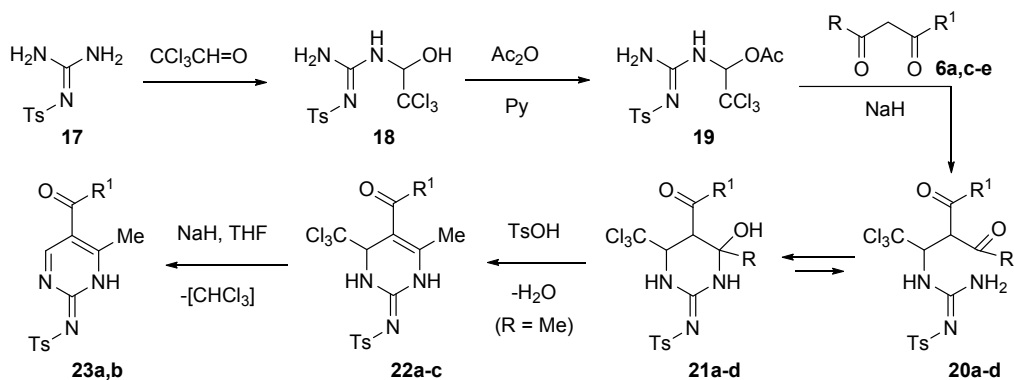
Scheme 7. Synthesis of 5-acyl-1,2-dihydropyrimidin-2-ones **15a-d** and 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones **16a-d**.

Transformation of **12a-d** into **15a-d** and **14a-d** into **16a-d** proceeds via elimination of chloroform. Proton abstraction from the more acidic N₍₁₎-H group in **12a-d**, **14a-d** followed by CCl₃-anion elimination leads to formation of **15a-d**, **16a-d** (Scheme 8).



Scheme 8. Base-induced transformation of **12a-d** and **14a-d** into **15a-d** and **16a-d**, respectively.

The above methodology was also used in the synthesis of 5-acyl-1,2-dihydropyrimidin-2-imines starting from *N*-[(1-acetoxy-2,2,2-trichloro)ethyl]-*N'*-guanidine **19** (Scheme 9). The latter was prepared by heating *N*-tosylguanidine with excess chloral without solvent, followed by treatment of the obtained methylol derivative **18** with Ac₂O in pyridine.



6a R = R¹ = Me; **c** R = Me, R¹ = OEt; **d** R = Ph, R¹ = OEt; **e** R = Me, R¹ = OMe.

20-21a R = R¹ = Me; **b** R = Me, R¹ = OEt; **b** R = Ph, R¹ = OEt; **d** R = Me, R¹ = OMe.

22a R = R¹ = Me; **b** R = Me, R¹ = OEt; **c** R = Me, R¹ = OMe.

23a R = Me, R¹ = OEt; **b** R = Me, R¹ = OMe.

Scheme 9. Synthesis of 5-acyl-1,2-dihydropyrimidin-2-imines **23**.

Acetate **19** reacted with the Na-enolates of CH-acids **6a,c-d** to give the corresponding products of the acetyl group substitution, compounds **20a-d**, which, under reaction conditions, completely (for R = Me) or partly (for R = Ph) cyclized into 4-hydroxypyrimidin-2-imines **21a-d**. Dehydration of the compounds obtained was readily carried out by boiling in EtOH in the presence of TsOH to afford the corresponding tetrahydropyrimidin-2-imines **22** in high yields. The treatment of carboxylates **22b,c** with NaH in THF proceeded with the elimination of chloroform to give the target alkyl 2-tosylimino-1,2-dihydropyrimidine-5-carboxylates **23a,b**.

3. Conclusions

We have developed a novel general approach to 5-acyl- and 5-arylsulfonyl-substituted 1,2-dihydropyrimidin-2-ones/imines that involved base-induced elimination of CHCl₃ from the corresponding 4-trichloromethyl-1,2,3,4-tetrahydropyrimidin-2-ones/imines. The latter were prepared using the reaction of readily available *N*-[(1-acetoxy-2,2,2-trichloro)ethyl]ureas and guanidines with Na-enolates of 1,3-diketones, β-oxoesters, or α-arylsulfonylketones, followed by acid-catalyzed heterocyclization–dehydration of the products formed.

Acknowledgments: This work was supported by the Russian Foundation for Basic Research (grant No. 18-33-00374).

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