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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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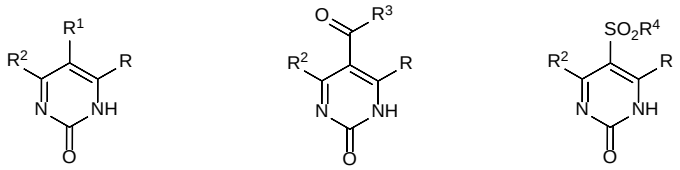
Abstract: A novel four-step methodology for the synthesis of 5-acyl- and 5-arylsulfonyl-1,2-dihydropyrimidin-2-ones has been developed. The reaction of readily available *N*-[(1-acetoxy-2,2,2-trichloro)ethyl]-ureas with Na-enolates of 1,3-diketones, β-oxoesters, or α-arylsulfonylketones followed by heterocyclization-dehydration 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, eliminate $CHCl_3$ 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** R^1 = H, alkyl, aryl) (Figure 1) are of considerable interest due to their wide range of biological activities [1]. These compounds have been extensively studied, and effective methods for their synthesis have been developed [2]. In contrast, 5-acyl-1,2-dihydropyrimidin-2-ones (**1b** R^3 = alkyl, aryl, alkoxy, etc.) have been studied less widely. A number of methods including condensations of (C-C-C-N-C-N)- [3], (C-C-C-N + C-N)- [4], and (C-C-C + N-C-N)-types [3b, 5], dehydrogenation [6] and oxidation [7] of corresponding 1,2,3,4-tetrahydropyrimidin-2-ones, catalytic acylation of 5-trialkylstannylpyrimidines [8], and hydrolysis of appropriate 2-functionalized pyrimidines [8, 9] has 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**.

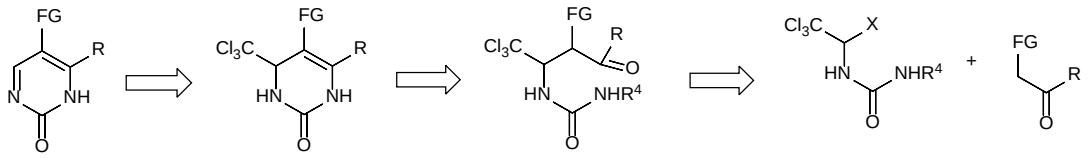


1a **1b** **1c**

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**.

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** R^4 = aryl) [10, 11]. Thus, the development of a general approach to the synthesis of 5-functionalized 1,2-dihydropyrimidin-2-ones is important.

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 [12], we hypothesized that 5-functionalized 1,2-dihydropyrimidin-2-ones (**1b,c** R^2 = 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 [13a-c].



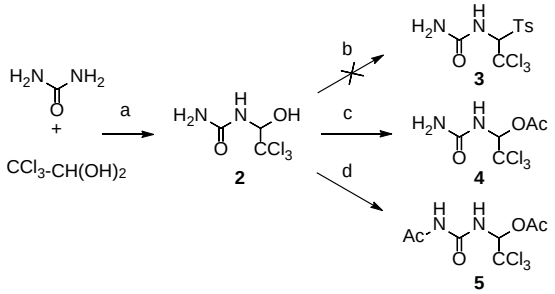
FG = functional group; X = good leaving group (Ts, OAc, etc.); R^4 = H, Ac.

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.

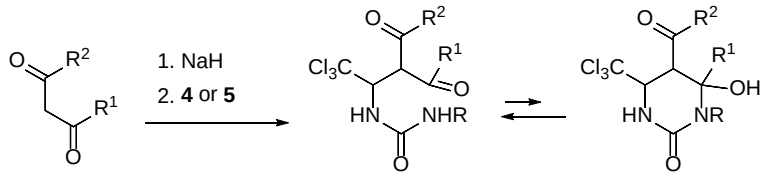
2. Results and discussion

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 [13a-c]. However, the synthesis of tosyl derivative **3** bearing a trichloromethyl group failed (Scheme 2) while acetoxy derivatives **4** and **5** [14] were conveniently prepared by treatment of the readily available **2** [15] with Ac_2O in pyridine and Ac_2O in the presence of H_2SO_4, respectively. Based on the ability of the acetoxy group to serve as a good leaving group in various reactions of ureidoalkylation [16, 17], 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 [13a-c].



Scheme 2. Synthesis of ureidoalkylating agents **4** and **5**. Reagents and conditions: (a) H_2O, rt; (b) 4-$MeC_6H_4S(O)OH$, H_2O, rt or heating; (c) Ac_2O, py, rt, 75%; (d) Ac_2O, H_2SO_4, 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).



6a $R^1 = R^2$ = Me; **b** $R^1 = R^2$ = Ph; **c** R^1 = Me, R^2 = OEt; **d** R^1 = Ph, R^2 = OEt.
7-8a R = H, $R^1 = R^2$ = Me; **b** R = H, $R^1 = R^2$ = Ph; **c** R = H, R^1 = Me, R^2 = OEt;
d R = H, R^1 = Ph, R^2 = OEt; **e** R = Ac, $R^1 = R^2$ = Me; **f** R = Ac, R^1 = Me, R^2 = OEt.

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 ^{1}H NMR data of crude product.
[c] All yields refer to isolated material homogeneous spectroscopically and by TLC.

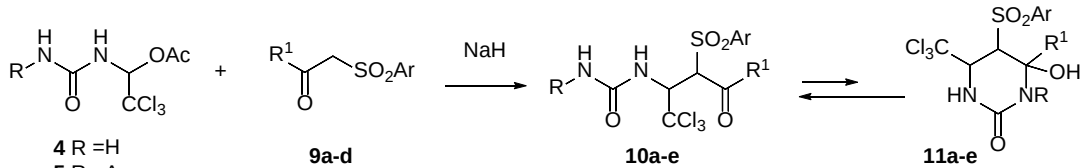
Anhydrous MeCN was used as a solvent for preparation of compounds **7a**,**c**-**d**; however, for compound **7b** anhydrous THF was used because the solubility of the enolate of **6b** in MeCN was very low and the resulting extremely dense suspension hampered the completion of reaction of NaH with **6b**.

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-, ^{1}H- and ^{13}C-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 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 76-90% yield (Scheme 4, Table 2).



9a Ar = R^1 = Ph; **b** Ar = 4-MeC_6H_4, R^1 = Ph; **c** Ar = Ph, R^1 = Me; **d** Ar = 4-MeC_6H_4, R^1 = Me.
10-11 **a** R = H, Ar = R^1 = Ph; **b** R = H, Ar = 4-MeC_6H_4, R^1 = Ph; **c** R = Ac, Ar = 4-MeC_6H_4, R^1 = Ph;
d R = Ac, Ar = Ph, R^1 = Me; **e** R = Ac, Ar = 4-MeC_6H_4, R^1 = Me.

Scheme 4. Synthesis of oxoalkylureas **10a-e**.

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

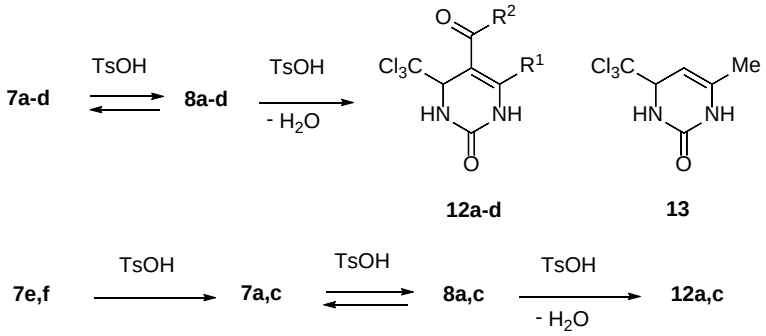
Entry	Starting material		Solvent	Reaction time, h	Product	Diastereomeric ratio[a] (*R**,*S**)-**10**/(*R**,*R**)-**10**	Yield,[b] %
1	**4**	**9a**	MeCN	4	**10a**	95:5	88
2	**4**	**9a**	THF	4.5	**10a**	88:12	76
3	**4**	**9b**	MeCN	5	**10b**	91:9	85
4	**5**	**9b**	MeCN	8	**10c**	97:3	88
5	**5**	**9c**	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 ^{1}H 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.



12a R^1 = R^2 = Me; **b** R^1 = R^2 = Ph; **c** R^1 = Me, R^2 = OEt; **d** R^1 = Ph, R^2 = OEt.

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 ^{1}H NMR spectrum of crude product.

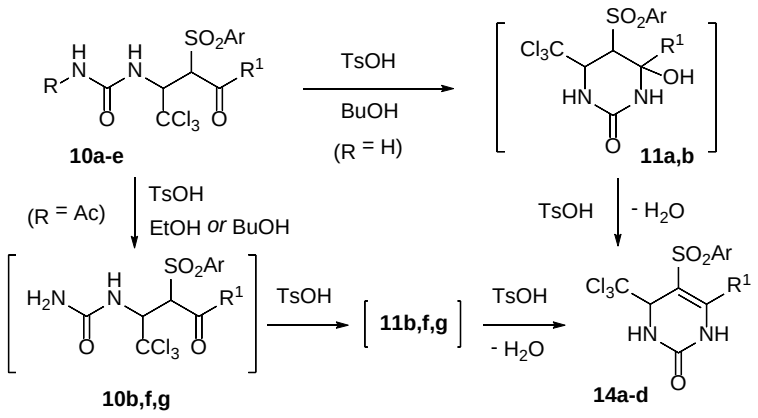
Heterocyclization-dehydration of **7a**-**d** proceeded smoothly in MeCN as a solvent to give **12a**-**d** in high yields (75-95%, Table 3, entries 1, 7-11). Reaction of **7a**,**c** was complete after 0.5-1 h in the presence of TsOH (0.3 equiv, entries 1, 8). By comparison with compounds **7a**,**c**, their counterparts **7b**,**d**, that 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 deacylation of **7a** followed by heterocyclization and dehydration of the intermediate formed. The data listed in Table 3 indicates that the formation of **13** was favoured 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 в **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, 4 vs. Entries 5, 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 R^1, is the rate-determining step of compounds **14a-d** formation.



10-11 f Ar = Ph, R^1 = Me; **g** Ar = 4-MeC_6H_4, R^1 = Me.

14a Ar = R^1 = Ph; **b** Ar = 4-MeC_6H_4, R^1 = Ph; **c** Ar = Ph, R^1 = Me; **d** Ar = 4-MeC_6H_4, R^1 = 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**	*n*-BuOH	1:4.0	31	**14a**	-	63
2	**10b**	*n*-BuOH	1:4.0	25	**14b**	-	75
3	**10c**	*n*-BuOH	1:3.1	5	**14b** + **10b**[c]	28:72	-
4	**10c**	*n*-BuOH	1:4.0	18	**14b**	-	72
5	**10d**	*n*-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**	*n*-BuOH	1:2.0	2	**14d**	-	92

[a] Reflux in alcohols in the presence of TsOH.

[b] According to ^{1}H NMR data.

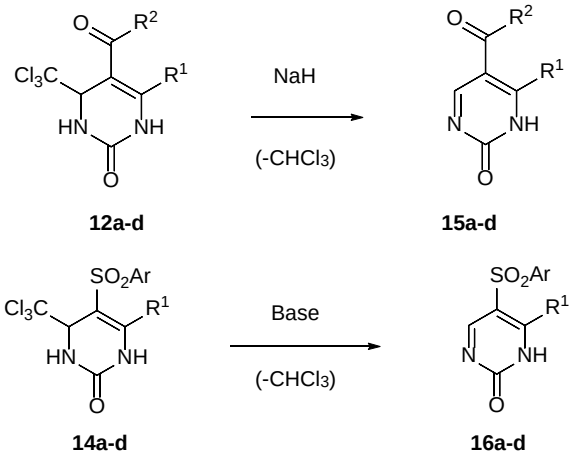
[c] Diastereomer mixture, 85:15.

[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 completed in 5 days and led to 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.



12a-d **15a-d**

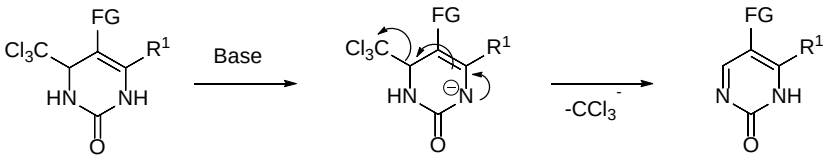
14a-d **16a-d**

15a $R^1 = R^2$ = Me; **b** $R^1 = R^2$ = Ph; **c** R^1 = Me, R^2 = OEt; **d** R^1 = Ph, R^2 = OEt.

16a Ar = R^1 = Ph; **b** Ar = 4-MeC_6H_4, R^1 = Ph; **c** Ar = Ph, R^1 = Me; **d** Ar = 4-MeC_6H_4, R^1 = 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 CCl_3-anion elimination leads to formation of **15a-d**, **16a-d** (Scheme 8).

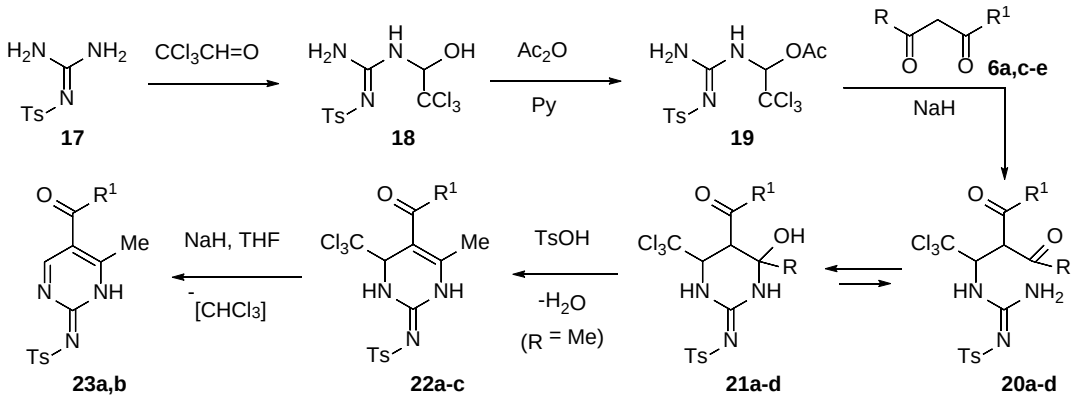


12a-d, 14a-d **15a-d, 16a-d**

FG = $R^2C(O)$, $ArSO_2$

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

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 Ac_2O in pyridine.



6a R = R^1 = Me; **c** R = Me, R^1 = OEt; **d** R = Ph, R^1 = OEt; **e** R = Me, R^1 = OMe.

20-21a R = R^1 = Me; **b** R = Me, R^1 = OEt; **b** R = Ph, R^1 = OEt; **d** R = Me, R^1 = OMe.

22a R = R^1 = Me; **b** R = Me, R^1 = OEt; **c** R = Me, R^1 = OMe.

23a R = Me, R^1 = OEt; **b** R = Me, R^1 = 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 involved base-induced elimination of $CHCl_3$ 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.

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