A Novel Access to Pyrido[4,3-*d*]pyrimidine Scaffold

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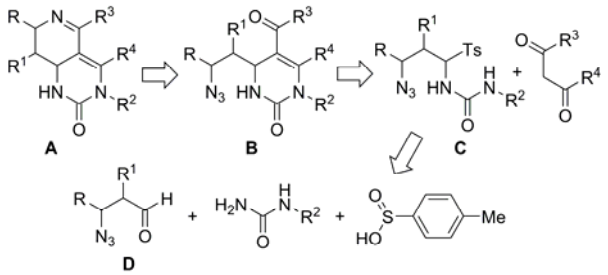
Abstract: A general four-step approach to 1,2,3,7,8,8a-hexahydropyrido[4,3-*d*]pyrimidin-2-ones via Staudinger/intramolecular aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones promoted by PPh_3 was developed. Synthesis of the starting pyrimidinones included preparation of 3-azidoaldehydes by the addition of hydrazoic acid to α,β-unsaturated aldehydes, transformation of 3-azidoaldehydes into *N*-[(3-azido-1-tosyl)alkyl]ureas followed by the reaction with 1,3-diketone enolates and dehydration of the resulting products under acidic conditions.

Keywords: Azidoaldehydes; Tetrahydropyrimidines; Pyrido[4,3-*d*]pyrimidines; Ureidoalkylation; Staudinger reaction; aza-Wittig reaction.

Introduction

Pyridopyrimidines are of current interest due to their multifaceted pharmacological profiles.[1] Among them, pyrido[4,3-*d*]pyrimidines remain relatively less explored in spite of their interesting applications. For example, they manifest remarkable inhibitory properties against epidermal growth factor receptor tyrosine kinase[2] and dihydrofolate reductase.[3] These compounds possess antioxidant,[4] antitumor,[5] antiulcer,[6] antibacterial,[7] and pesticidal activities.[8] The described syntheses of pyrido[4,3-*d*] pyrimidines mainly start with either pyridine or pyrimidine precursor which is modified to annulate the other ring.[1] However, to the best of our knowledge, Staudinger/intramolecular aza-Wittig reaction,[9] a powerful strategy for nitrogen heterocycles construction has never been applied to pyrido[4,3-*d*] pyrimidines synthesis.

Previously, we developed a completely general and flexible approach to the synthesis of various 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones, specifically, 5-acyl-substituted ones, based on ureidoalkylation of ketone enolates with α-tosyl-substituted *N*-alkylureas or *N*-alkylthioureas.[10] We have hypothesized that pyrido[4,3-*d*]pyrimidin-2-one scaffold **A** could be assembled from 5-acyl-4-(2-azidoalkyl)pyrimidines **B** using Staudinger/aza-Wittig sequence (Scheme 1). The synthesis of pyrimidines **B** could include ureidoalkylation of enolates of 1,3-diketones with *N*-(3-azido-1-tosylalkyl)ureas **C** followed by dehydration of the resulting products. Azides **C** could be obtained by three-component condensation of 3-azidoaldehydes **D**, *p*-toluenesulfinic acid, and ureas.



Scheme 1. Retrosynthesis of pyrido[4,3-*d*]pyrimidin-2-ones
via ureidoalkylation/Staudinger/aza-Wittig reactions.

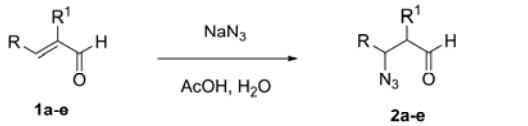
Here, we describe hexahydropyrido[4,3-*d*]pyrimidines synthesis via Staudinger/aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones promoted by PPh_3. A three-step preparation of the starting pyrimidines using transformation of 3-azidoaldehydes into *N*-[(3-azido-1-tosyl)alkyl]ureas followed by reaction with enolates of dibenzoylmethane, benzoylacetone, acetylacetone, or ethyl 2,4-dioxo-4-phenylbutanoate and dehydration of resulting products under acidic conditions is described. The procedure for preparative synthesis of 3-azidoaldehydes by the addition of hydrazoic acid to α,β-unsaturated aldehydes is also reported.

Results and Discussion

3-Azidoaldehydes served as starting compounds for the synthesis of pyrido[4,3-*d*]pyrimidines. The described methods of their preparation include oxidation of 3-azido alkohols,[11] reduction of 3-azido esters,[12] reaction of 3-tosyloxy aldehydes with sodium azide,[13] and addition of hydrazoic acid to α,β-unsaturated aldehydes.[14] However, 3-azidoaldehydes were prepared only on a small scale (<1 g) and usually used in further reactions without purification. Our initial task focused on preparation of pure 3-azidoaldehydes on a multigram scale. We used the method based on the reaction of sodium azide with α,β-unsaturated aldehydes **1a-e** in aqueous acetic acid which seems to be the most promising.

3-Azidopropanal (**2a**) was prepared by the addition of aqueous solution of NaN_3 (1.5 equiv) to a cooled (-12 °C) solution of acrolein in acetic acid (Scheme 2). The product was isolated from the reaction mixture as a yellowish oil in 62% yield after extraction with diethyl ether followed by neutralization of the ether extracts with aqueous Na_2CO_3, drying, and evaporation of the solvent under reduced pressure. We failed to remove diethyl ether completely and achieve constant mass of the residue due to high volatility of azide **2a**. According to ^1H NMR data, the crude **2a** always contained a small quantity of diethyl ether. We attempted to purify the crude **2a** by fast vacuum distillation at 48-59 °C/15-20 mmHg collecting the main fraction in an ice-cooled flask. As a result, azide **2a** was obtained as a colorless transparent liquid (53% yield from acrolein). However, the distilled **2a** was unstable and decomposed in the receiving flask already during distillation. After some time, we

observed slow gas evolution (probably HN_3) from the main fraction and a minor decrease in vacuum. Therefore, 3-azidopropanal (**2a**) was used immediately after distillation.



1, 2 a R = R^1 = H; **b** R = Me, R^1 = H; **c** R = Et, R^1 = H; **d** R = H, R^1 = Me; **e** R = H, R^1 = Et.

Scheme 2. Synthesis of 3-azidoaldehydes **2a-e**.

We extended this method to the preparation of other 3-azidoaldehydes **2b-e**. In contrast to acrolein, crotonaldehyde (**1b**) reacted with NaN_3 (1.5 equiv) in aqueous acetic acid more slowly affording only 72% conversion after 4.25 h at -12 °C according to ^{1}H NMR spectroscopic analysis of a sample of the reaction mixture dissolved in D_2O. Increase in the reaction temperature improved conversion which changed to 83% after additional 55 min at 0 °C, and then to 93% after 1.5 h at 25 °C. The work-up of the reaction mixture as described above for **2a** gave practically pure azide **2b** containing only 3% of the starting material. The obtained results prompted us to examine the addition of HN_3 to aldehydes **2b-e** more thoroughly using ^{1}H NMR spectroscopy. The selected data are given in Table 1.

Table 1. ^{1}H NMR study of the reaction of aldehydes **1b-e** with NaN_3 in aqueous AcOH at 25 °C.

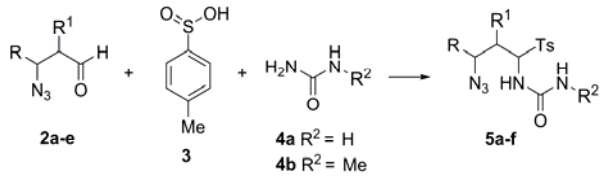
				Molar ratio of **2**:**1**[a] after:			
Entry	**1**	**1**:NaN_3[b]	**2**	1 h	2 h	3 h	work-up
1	**1b**	1:1.5	**2b**	92:8	92:8	92:8	97:3
2	**1b**	1:2.5	**2b**	96:4	96:4	96:4	98:2
3	**1c**	1:1.5	**2c**	-	90:10	92:8	94:6
4	**1d**	1:2.5	**2d**	74:26	87:13	-	98:2
5	**1e**	1:2.5	**2e**	69:31	84:16	-	95:5

[a] According to ^{1}H NMR spectroscopy for samples of reaction mixtures after 1, 2, 3 hours (entries 1, 2, 4, 5: extracts in $CDCl_3$; entry 3: solutions in D_2O), and for crude products after work-up (in $CDCl_3$).
[b] Molar ratio.

Table 1 shows that the addition of HN_3 to crotonaldehyde (**1b**) proceeded rapidly (<1 h) at room temperature to give a 92:8 equilibrium mixture of **2b** and **1b**, respectively (entry 1). A greater excess of NaN_3 only slightly shifted this equilibrium to **2b** (entry 2). Compared with **1b**, the rate of the addition decreased insignificantly when pent-2-enal (**1c**) was used (entry 1 vs entry 3). In contrast to aldehydes **1a-c**, α-alkyl substituted aldehydes **1d,e** reacted much more slowly even if 2.5 equivalents of NaN_3 were used (entries 4, 5).

Based on ^{1}H NMR experiments, we developed a simple medium-scale procedure for preparation of azidoaldehydes **2b-e**. According to this procedure, an aqueous solution of NaN_3 (1.5-2.5 equiv) was added to a solution of aldehyde **1b-e** in AcOH followed by stirring of the resulting reaction mixture for 3-4 h at room temperature. Azidoaldehydes **2b-e** were obtained in 51-71% yields after extractive work-up, neutralization, drying, and distillation of crude products. Compared with **2a**, compounds **2b-e** were stable upon distillation but gradually decomposed during storage at room temperature (slowly in $CDCl_3$ solutions, faster in liquid phase) (NMR spectroscopy data). Stability of azides **2b-e**, especially in $CDCl_3$ solutions, significantly increased upon storage at -18 °C.

We used freshly distilled 3-azidoaldehydes **2a-e** as starting materials for the synthesis of the required ureidoalkylation reagents. The synthesis involved three-component condensation of **2a-e**, *p*-toluenesulfinic acid (**3**), and urea (**4a**) or *N*-methylurea (**4b**) to give the corresponding *N*-[(3-azido-1-tosyl)alk-1-yl)ureas **5a-f** (Scheme 3).



Scheme 3. Synthesis of ureidoalkylation reagents, *N*-[(3-azido-1-tosyl)alk-1-yl]ureas **5a-f**.

Optimized reaction conditions for preparation of ureas **5a-f** and their yields are summarized in Table 2.

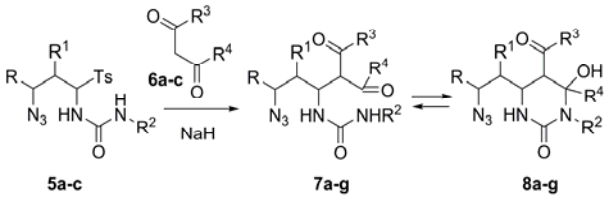
Table 2. Reaction of 3-azidoaldehydes **2a-e** with *p*-toluenesulfinic acid (**3**) and ureas **4a**,**b**.

Entry	**2**	**4**	Reaction conditions[a]	**5**	Yield (%)[b]	Isomer ratio[c]
1	**2a**	**4a**	H_2O, 24 h	**5a**	84	-
2	**2a**	**4b**	H_2O, 24 h	**5b**	90	-
3	**2b**	**4a**	25% aq HCOOH, 8 h	**5c**	92	55:45
4	**2c**	**4a**	30% aq EtOH, 16 h	**5d**	92	58:42
5	**2d**	**4a**	30% aq EtOH, 19 h	**5e**	79	82:18
6	**2e**	**4a**	30% aq EtOH, 18 h	**5f**	83	63:37

[a] Room temperature; 1:1:5 molar ratio of **2**:**3**:**4** for the synthesis of **5a,c-f** and 1:1:1.5 molar ratio of **2**:**3**:**4** for the synthesis of **5b**.
[b] Isolated yields.
[c] According to ^{1}H NMR spectra of the crude products.

Three-component condensation of 3-azidopropanal (**2a**), sulfinic acid **3**, and urea (5 equiv) or *N*-methylurea (1.5 equiv) smoothly proceeded in water at room temperature for 24 h to give substituted ureas **5a**,**b** as white solids in 84 and 90% yields, respectively (entries 1 and 2). In contrast, the reactions of other azidoaldehydes **2b-e** with acid **3** and urea in water at room temperature afforded only gummy materials containing the expected azidoalkyl ureas **5c-f** along with considerable amount of various byproducts (NMR spectroscopy data). Compound **5c** was successfully prepared in a yield of 92% by sequential addition of acid **3** and a fivefold excess of urea to a solution of 3-azidobutanal (**2b**) in 25% aqueous HCOOH (entry 3). However, only complex mixtures formed in the reactions of aldehydes **2c-e** with **3** and **4a** when aqueous HCOOH was used in various concentrations. Condensation of these aldehydes with **3** and **4a** cleanly proceeded in 30% aqueous EtOH to give the expected products **5d-f** in 79-92% yields (entries 4-6). Under optimal conditions (Table 2), sulfones **5a-f** precipitated from the reaction mixtures formed after the addition of all reagents as white solids. They were isolated by filtration with >95% purity according to ^{1}H NMR spectra of the crude products and used in the ureidoalkylation step without additional purification. Compounds **5c-f** were obtained as mixtures of two diastereomers (Table 2).

According to the retrosynthetic plan (Scheme 1), the next step of the pyrido[4,3-*d*]pyrimidin-2-one scaffold synthesis involved two-step transformation of sulfones **5** into the corresponding 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones using our previously developed methodology for pyrimidine ring construction.[10] First, we studied ureidoalkylation of sodium enolates of acetylacetone, benzoylacetone, and dibenzoylmethane with sulfones **5a-c** in dry MeCN or THF (Scheme 4, Table 3). The enolates were generated by treatment of the corresponding CH-acids **6a-c** with NaH.



Scheme 4. Ureidoalkylation of Na-enolates of 1,3-diketones **6a-c** with sulfones **5a-c**.

The reaction of sulfone **5a** with the Na-enolate of **6a** readily proceeded at room temperature in 7 h 45 min to give a product of nucleophilic substitution of the tosyl group, the corresponding ureido ketone **7a** which spontaneously and completely cyclized into hydroxypyrimidinone **8a** under the reaction conditions. Pyrimidine **8a** was isolated in 75% yield as a single diastereomer (Table 3, entry 1). According to ^{1}H NMR data, this diastereomer had (4*R**,5*R**,6*R**)-configuration with equatorial orientation of the substituents at C-5 and C-6 ($^3J_{5\text{-H},6\text{-H}}$ = 11.7, $^3J_{\text{N(1)H},6\text{-H}} \approx 0$ Hz) and axial orientation of the hydroxyl group ($^4J_{5\text{-H,OH}}$ = 0.7 Hz) in DMSO-d_6.

Table 3. Reaction of azidoalkyl ureas **5a-c** with 1,3-diketones **6a-c** in the presense of NaH at room temperature.

Entry	**5**	**6**	R	R^1	R^2	R^3	R^4	NaH:**6** molar ratio[a]	Solvent	Reaction time (h)	Product	Yield (%)[b]	Isomer ratio[c]
1	**5a**	**6a**	H	H	H	Me	Me	1.10:1.11	MeCN	7.75	**8a**	75	d
2	**5a**	**6b**	H	H	H	Ph	Me	1.00:1.02	MeCN	8.33	**7b**	79	52:48
3	**5a**	**6c**	H	H	H	Ph	Ph	1.05:1.01	THF	8	**7c**	90	-
4	**5b**	**6a**	H	H	Me	Me	Me	1.00:1.02	MeCN	8	**7d**	54	-
5	**5b**	**6b**	H	H	Me	Ph	Me	1.02:1.05	MeCN	8.25	**7e**	82	59:41
6	**5b**	**6c**	H	H	Me	Ph	Ph	1.05:1.00	THF	8.08	**7f**	91	-
7	**5c**	**6b**	Me	H	H	Ph	Me	1.01:1.02	MeCN	8	**7g**	75	27:28:19:26

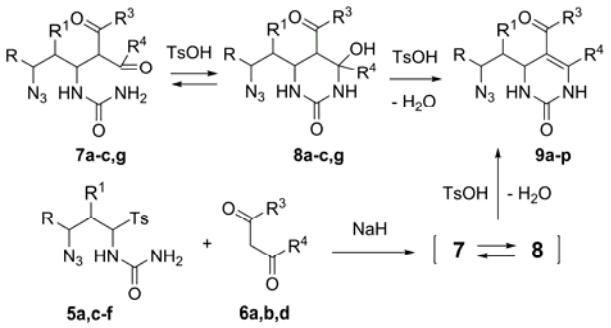
[a] The amount of the corresponding sulfone **5** is 1.00 equivalent.
[b] Isolated yields.
[c] According to ^{1}H NMR spectra of the crude products.
[d] A single diastereomer with (4*R**,5*R**,6*R**)-configuration.

In contrast to the reaction of **5a** with the Na-enolate of **6a**, all other reactions of **5a-c** with Na-enolates of **6a-c** (MeCN or THF, rt, 8-8.33 h) gave only the corresponding acyclic ureido ketones **7b-g** in 54-91% yields (Scheme 4; Table 3, entries 2-7).

The products **8a**, **7b-g** were readily isolated after removal of solvent followed by aqueous $NaHCO_3$ work-up and filtration with >95% purity (^{1}H NMR spectroscopy data) and were used in further syntheses without additional purification. Their yields were good, except compound **7d** (54%). The moderate yield of **7d** can be explained by partial loss of the product during aqueous work-up because of enhanced solubility of **7d** in water. Our attempt to improve yield of **7d** using extractive work-up of a mother liquor with $CHCl_3$ failed. Compounds **7b,e,g** were obtained as diastereomeric mixtures (Table 3).

We also attempted to react sulfone **5e** with the Na-enolate of **6b** in MeCN (rt, 8 h) and sulfone **5a** with the Na-enolate of **6d** (Scheme 4; R^3 = Ph, R^4 = COOEt) in THF (rt, 8 h). However, after removal of solvent and addition of saturated aqueous $NaHCO_3$ to the resulting residues, only gummy materials were obtained that did not solidify even upon prolonged manipulations. Therefore, it became evident that in these and similar cases the synthesis of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones should be performed using an one-pot procedure directly from sulfones **5** without isolation of the ureidoalkylation products **7**, **8** from the reaction mixtures. Previously, we demonstrated that this one-pot procedure is often very effective for the pyrimidine synthesis.[10f,g,i]

Thus, we developed two different synthetic methods for preparation of tetrahydropyrimidines **9a-p** (Scheme 5). First, we examined the transformation of hydroxypyrimidine **8a** and ureido ketones **7b,c,g** into the corresponding tetrahydropyrimidines **9a,f,g,k**. It was found that dehydration of **8a** cleanly proceeded in refluxing EtOH for 1 h in the presence of TsOH (0.19 equiv) to give pyrimidine **9a** in 77% yield (Table 4, entry 1). The yield of **9a** decreased to 63% when this reaction was carried out under similar conditions but in refluxing MeCN.



Scheme 5. Synthesis of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones **9a-p**.

Table 4. Synthesis of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones **9a-p**.

Entry	Starting material	R	R^1	R^3	R^4	Reaction conditions	Product	Yield (%)[a]	Isomer ratio[b]
1	**8a**	H	H	Me	Me	TsOH (0.19 equiv), EtOH, reflux, 1 h	**9a**	77	-
2	**5a+6a**	H	H	Me	Me	(i) **6a** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.32 equiv), THF, reflux, 1.67 h	**9a**	61	-
3	**5c+6a**	Me	H	Me	Me	(i) **6a** (1.04 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.32 equiv), THF, reflux, 1.92 h	**9b**	47	86:14
4	**5d+6a**	Et	H	Me	Me	(i) **6a** (1.06 equiv), NaH (1.02 equiv), THF, rt, 8 h (ii) TsOH (1.30 equiv), THF, reflux, 1.92 h	**9c**	74	65:35
5	**5e+6a**	H	Me	Me	Me	(i) **6a** (1.06 equiv), NaH (1.02 equiv), THF, rt, 8 h (ii) TsOH (1.30 equiv), THF, reflux, 1.92 h	**9d**	63	56:44
6	**5f+6a**	H	Et	Me	Me	(i) **6a** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.31 equiv), THF, reflux, 1.83 h	**9e**	76	69:31
7	**7b**	H	H	Ph	Me	TsOH (0.20 equiv), EtOH, reflux, 1 h	**9f**	89	-
8	**7g**	Me	H	Ph	Me	TsOH (0.21 equiv), EtOH, reflux, 45 min	**9g**	88	55:45
9	**5d+6b**	Et	H	Ph	Me	(i) **6b** (1.02 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.31 equiv), THF, reflux, 1.5 h	**9h**	82	55:45
10	**5e+6b**	H	Me	Ph	Me	(i) **6b** (1.06 equiv), NaH (1.03 equiv), THF, rt, 8 h (ii) TsOH (1.30 equiv), THF, reflux, 1.58 h	**9i**	79	50:50
11	**5f+6b**	H	Et	Ph	Me	(i) **6b** (1.02 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.30 equiv), THF, reflux, 1.83 h	**9j**	73	67:33
12	**7c**	H	H	Ph	Ph	TsOH (1.01 equiv), EtOH, reflux, 2.25 h	**9k**	21	-
13	**5a+6d**	H	H	Ph	COOEt	(i) **6d** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8.17 h (ii) TsOH (1.32 equiv), THF, reflux, 3.17 min	**9l**	60	-
14	**5c+6d**	Me	H	Ph	COOEt	(i) **6d** (1.03 equiv), NaH (1.02 equiv), THF, rt, 8 h (ii) TsOH (1.30 equiv), THF, reflux, 2.5 h	**9m**	62	63:37
15	**5d+6d**	Et	H	Ph	COOEt	(i) **6d** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.40 equiv), THF, reflux, 2.33 h	**9n**	73	62:38
16	**5e+6d**	H	Me	Ph	COOEt	(i) **6d** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.43 equiv), THF, reflux, 2.33 h	**9o**	19	60:40
17	**5f+6d**	H	Et	Ph	COOEt	(i) **6d** (1.03 equiv), NaH (1.01 equiv), THF, rt, 8 h (ii) TsOH (1.40 equiv), THF, reflux, 2.33 h	**9p**	14	50:50

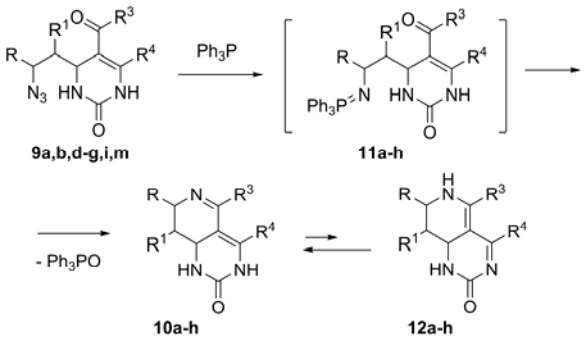
[a] Isolated yields.
[b] According to ^{1}H NMR spectra of the crude products.

Ureido ketones **7b** and **7g** smoothly underwent cyclization-dehydration in refluxing EtOH in the presence of TsOH to give the corresponding pyrimidines **9f** and **9g** in high yields (entries 7 and 8). In contrast, the reduced electrophilicity of the benzoyl carbonyl groups in dibenzoylmethane derivative **7c**

extremely hampered the cyclization-dehydration of this compound to afford pyrimidine **9k**. In this case greater amounts of TsOH (>0.5 equiv) and longer reaction times were required for completion of conversion of the starting material in refluxing EtOH or MeCN. These conditions led to formation of a significant amount of various byproducts that complicated isolation of **9k** and sharply decreased its yield. Compound **9k** was obtained in pure form only in 21% yield by refluxing **7c** in EtOH in the presense of 1.01 equiv of TsOH for 2 h 15 min followed by isolation of **9k** using silica gel column chromatography (entry 12). In this experiment dibenzoylmethane (**6c**) was isolated in a 30% yield as one of the byproducts.

Next, we developed a convenient one-pot synthesis of tetrahydropyrimidines **9a-e,h-j,l-p** based on the reaction of sulfones **5a,c-f** with Na-enolates of **6a,b,d** in THF (rt, 8-8.17 h) followed by the addition of 1.30-1.43 equiv of TsOH and heating at reflux for 1.5-3.17 h (Table 4, entries 2-6, 9-11, 13-17). The completion of the second step was monitored by TLC. Tetrahydropyrimidines **9** were isolated from the reaction mixtures after removal of the solvent, aqueous $NaHCO_3$ work-up of the resulting residues, and filtration of the obtained solids. Generally, the yields of pyrimidines **9** varied from moderate to high (47-82%) with the exception of compounds **9o,p**. The latters were isolated by silica gel column chromatography in only 19 and 14% yield, respectively (entries 16, 17). Notably, the yield of pyrimidine **9a** obtained from **5a** and **6a** in the one-pot procedure was slightly higher (61%) than the overall yield in two steps (58%) (entry 2 vs entry 1).

The final step of the synthesis of pyrido[4,3-*d*]pyrimidin-2-ones **10** was intramolecular Staudinger/aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)pyrimidines **9** promoted by PPh_3 (Scheme 6).



Scheme 6. Synthesis of pyrido[4,3-*d*]pyrimidin-2-ones **10a-h** from 5-acyl-4-(β-azidoalkyl)pyrimidines **9a**,**b**,**d-g**,**i**,**m** via intramolecular Staudinger/aza-Wittig reaction.

Initially, we studied the reaction of **9a** with PPh_3 (1.1 equiv) in various solvents (THF, MeCN, and 1,4-dioxane) at reflux for 1.5 h. The obtained reaction mixtures were evaporated in vacuo to dryness, and the composition of 5-acetyl substituted pyrimidine residues dissolved in DMSO-d_6 was determined

using ^{1}H NMR spectroscopy. The starting material disappeared in all cases, and the expected pyridopyrimidine **10a** formed as the main heterocyclic product. However, the reaction in THF, besides 45% of **10a**, gave two other compounds in a ratio of 30:25 that seem to be intermediates of incomplete conversion of **9a** into **10a**. According to ^{1}H NMR spectrum, one of them (30%) was iminophosphorane **11a**. These intermediates were absent in refluxing 1,4-dioxane, but significant amount of side products formed along with **10a**. Refluxing MeCN gave the better result furnishing pyridopyrimidine **10a** plus the above intermediates in a ratio of 83:13:4, respectively. An increase in the reaction time to 6 h was necessary to achieve complete conversion of **9a** into **10a** in MeCN at reflux (^{1}H NMR spectroscopy data).

The reaction of 5-benzoyl substituted pyrimidine **9f** with PPh_3 (1.1 equiv) in refluxing THF for 6 h was studied. Although the starting material was consumed, no traces of the bicyclic product **10e** were detected in the ^{1}H NMR spectrum of the crude reaction mixture.

Therefore, the results obtained show that the transformation of pyrimidines **9** into bicycles **10** is controlled predominantly by the intramolecular aza-Wittig reaction. Specifically, the rate of this step depends on electrophilicity of carbonyl group and steric factors in iminophosphoranes **11**. Based on these data, further we carried out all the pyrido[4,3-*d*]pyrimidines syntheses in refluxing MeCN for 5.5-8 h (Table 5).

Table 5. Synthesis of pyrido[4,3-*d*]pyrimidin-2-ones **10a-h** via intramolecular Staudinger/aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)pyrimidines **9a**,**b**,**d-g**,**i**,**m** promoted by PPh_3.[a]

Entry	Starting material[b]	Isomer ratio	R	R^1	R^3	R^4	Time (h)	Product	Yield (%)[c]	Isomer ratio[d]
1	**9a**	-	H	H	Me	Me	5.5	**10a**	94	-
2	**9b**	86:14	Me	H	Me	Me	7	**10b**	84	90:10
3	**9d**	56:44	H	Me	Me	Me	6	**10c**	87	57:43
4	**9e**	69:31	Et	H	Me	Me	6	**10d**	55	65:35
5	**9f**	-	H	H	Ph	Me	7	**10e**	95	-
6	**9g**	55:45	Me	H	Ph	Me	8	**10f**	96	54:46
7	**9i**	50:50	H	Me	Ph	Me	6	**10g**	90	49:51
8	**9m**	67:37	Me	H	Ph	COOEt	6	**10h**	26	e

[a] Reactions were carried out in refluxing MeCN in the presence of 1.13-1.18 equiv of PPh_3.
[b] Crude starting materials were used.
[c] Isolated yields.
[d] (7*R**,8a*S**)-**10**/(7*R**,8a*R**)-**10**. According to ^{1}H NMR spectra of the crude products.
[e] A single diastereomer with (7*R**,8a*S**)-configuration was isolated by column chromatography.

Since compounds **10a-c** were slightly soluble in MeCN, they precipitated from the reaction mixtures and were isolated in pure form in 84-94% yields by filtration. Compounds **10d-h** were isolated in up to 96% yield using silica gel column chromatography of the residues obtained after evaporation of the reaction mixtures. Low yield of ethyl carboxylate **10h** (26%) is caused by formation of a huge amount of various byproducts (^{1}H NMR spectroscopy data).

According to NMR data, pyrido[4,3-*d*]pyrimidines **10b-d,f,g** formed as mixtures of two diastereomers in ratios that are close to isomer ratios in the starting pyrimidines **9b,d,e,g,i** (Table 5). Only compound **10h** was obtained as a single diastereomer indicating that the second isomer of **10h** did not form in the intramolecular aza-Wittig reaction of intermediate **11h**.

Conclusion

A general four-step approach to 1,2,3,7,8,8a-hexahydropyrido[4,3-*d*]pyrimidin-2-ones via Staudinger/intamolecular aza-Wittig reaction of 5-acyl-4-(β-azidoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones promoted by PPh_3 was developed. Synthesis of the starting pyrimidinones included transformation of 3-azidoaldehydes into *N*-[(3-azido-1-tosyl)alkyl]ureas followed by reaction with enolates of dibenzoylmethane, benzoylacetone, acetylacetone, or ethyl 2,4-dioxo-4-phenylbutanoate and dehydration of the resulting products under acidic conditions. We believe that this approach to pyrido[4,3-*d*]pyrimidine scaffold is very promising since both components of the amidoalkylation reaction can be widely varied. Furthermore, the prepared hexahydropyrido[4,3-*d*]pyrimidin-2-ones can be aromatized or reduced by routine procedures expanding the synthetic utility of the method.

Medium-scale synthesis of 3-azidoaldehydes based on the reaction of α,β-unsaturated aldehydes with hydrazoic acid generated from sodium azide and aqueous acetic acid was also developed. High availability of 3-azidoaldehydes provides an opportunity for wider application of these compounds in organic synthesis.

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