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 PPh₃ 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 kinase² 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-alkythioureas.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.
Here, we describe hexahydropyrido[4,3-\textit{d}]pyrimidines synthesis via Staudinger/aza-Wittig reaction of 5-acyl-4-(\textit{\beta}-azidoalkyl)-1,2,3,4-tetrahydroprymidin-2-ones promoted by PPh\textsubscript{3}. A three-step preparation of the starting pyrimidines using transformation of 3-azidoaldehydes into N-[1-(3-azido-1-tosyl)alkyl]ureas followed by reaction with enolates of dibenzoylmethane, benzoyleacetone, acetylaceetone, 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 \textit{\alpha},\textit{\beta}-unsaturated aldehydes is also reported.

Results and Discussion
3-Azidoaldehydes served as starting compounds for the synthesis of pyrido[4,3-\textit{d}]pyrimidines. The described methods of their preparation include oxidation of 3-azido alkohols\textsuperscript{11}, reduction of 3-azido esters\textsuperscript{12}, reaction of 3-tosyloxy aldehydes with sodium azide\textsuperscript{13}, and addition of hydrazoic acid to \textit{\alpha},\textit{\beta}-unsaturated aldehydes\textsuperscript{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 \textit{\alpha},\textit{\beta}-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\textsubscript{3} (1.5 equiv) to a cooled (-12 \textdegree\text{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\textsubscript{2}CO\textsubscript{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 \textsuperscript{1}H 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 \textdegree\text{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.

![Scheme 2](image)

**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$_2$O. 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>
<thead>
<tr>
<th>Entry</th>
<th>1:NaN$_3$</th>
<th>Molar ratio of 2:1$^a$ after:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1:1.5</td>
<td>2b</td>
</tr>
<tr>
<td>1</td>
<td>1b</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>74:26</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>69:31</td>
</tr>
</tbody>
</table>

$^a$ 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$_2$O), and for crude products after work-up (in CDCl$_3$).

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, $\alpha$-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-toluenesulfonic 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.](image)

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-toluenesulfonic acid (3) and ureas 4a,b.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Isomer ratio</th>
<th>Yield (%)</th>
<th>Reaction conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, 4a, H$_2$O, 24 h</td>
<td>5a, 84</td>
<td>-</td>
<td>2a, 4a, H$_2$O, 24 h</td>
</tr>
<tr>
<td>2</td>
<td>2a, 4b, H$_2$O, 24 h</td>
<td>5b, 90</td>
<td>-</td>
<td>2a, 4b, H$_2$O, 24 h</td>
</tr>
<tr>
<td>3</td>
<td>2b, 4a, 25% aq HCOOH, 8 h</td>
<td>5c, 92</td>
<td>55:45</td>
<td>2b, 4a, 25% aq HCOOH, 8 h</td>
</tr>
<tr>
<td>4</td>
<td>2c, 4a, 30% aq EtOH, 16 h</td>
<td>5d, 92</td>
<td>58:42</td>
<td>2c, 4a, 30% aq EtOH, 16 h</td>
</tr>
<tr>
<td>5</td>
<td>2d, 4a, 30% aq EtOH, 19 h</td>
<td>5e, 79</td>
<td>82:18</td>
<td>2d, 4a, 30% aq EtOH, 19 h</td>
</tr>
<tr>
<td>6</td>
<td>2e, 4a, 30% aq EtOH, 18 h</td>
<td>5f, 83</td>
<td>63:37</td>
<td>2e, 4a, 30% aq EtOH, 18 h</td>
</tr>
</tbody>
</table>

*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 1H 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.](image)

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 1H NMR data, this diastereomer had (4R*,5R*,6R*)-configuration with equatorial orientation of the substituents at C-5 and C-6 (J5-H,6-H = 11.7, JN(1)H,6-H ≈ 0 Hz) and axial orientation of the hydroxyl group (J5-H,OH = 0.7 Hz) in DMSO-d6.
Table 3. Reaction of azidoalkyl ureas 5a-c with 1,3-diketones 6a-c in the presence of NaH at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5</th>
<th>6</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>NaH:6 molar ratio</th>
<th>Solvent</th>
<th>Reaction time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Isomer ratio c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>1.10:1.11</td>
<td>MeCN</td>
<td>7.75</td>
<td>8a</td>
<td>75</td>
<td>d</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>6b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>1.00:1.02</td>
<td>MeCN</td>
<td>8.33</td>
<td>7b</td>
<td>79</td>
<td>52:48</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>6c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>1.05:1.01</td>
<td>THF</td>
<td>8</td>
<td>7c</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>1.00:1.02</td>
<td>MeCN</td>
<td>8</td>
<td>7d</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5b</td>
<td>6b</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>1.02:1.05</td>
<td>MeCN</td>
<td>8.25</td>
<td>7e</td>
<td>82</td>
<td>59:41</td>
</tr>
<tr>
<td>6</td>
<td>5b</td>
<td>6c</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>1.05:1.00</td>
<td>THF</td>
<td>8.08</td>
<td>7f</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>5c</td>
<td>6b</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>1.01:1.02</td>
<td>MeCN</td>
<td>8</td>
<td>7g</td>
<td>75</td>
<td>27:28:19:26</td>
</tr>
</tbody>
</table>

a The amount of the corresponding sulfone 5 is 1.00 equivalent.
b Isolated yields.
c According to 1H NMR spectra of the crude products.
d A single diastereomer with (4R*,5R*,6R*)-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 NaHCO₃ work-up and filtration with >95% purity (1H 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 CHCl₃ 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; R³ = Ph, R⁴ = COOEt) in THF (rt, 8 h). However, after removal of solvent and addition of saturated aqueous NaHCO₃ 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.

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 presence 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 NaHCO₃ 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 latter 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 PPh₃ (Scheme 6).

\[ R_1O \quad R_2 \quad R_3 \quad R_4 \]
\[ N_3 \quad HN \quad NH \]
\[ 9a,b,d-g,L,m \]
\[ PhP \quad R_1O \quad R_3 \quad R_4 \]
\[ N \quad HN \quad NH \]
\[ 11a-h \]
\[ R_1N \quad R_2 \quad R_3 \quad R_4 \]
\[ PhP \quad P \quad N \quad HN \]
\[ 10a-h \]
\[ R_1N \quad R_2 \quad R_3 \quad R_4 \]
\[ PhP \quad P \quad N \quad HN \]
\[ 12a-h \]

**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 PPh₃ (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-d₆ 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-($\beta$-azidoalkyl)pyrimidines 9a,b,d-g,l,m promoted by PPh$_3$. |
|---|---|---|---|---|---|---|---|
| Entry | Starting material | Isomer ratio | R | R$^1$ | R$^2$ | 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*,8aS*)-10/(7'R*,8aR*)-10. According to $^1$H NMR spectra of the crude products.
e A single diastereomer with (7'R*,8aS*)-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 PPh₃ 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 dibenzoymethane, benzoylacetonate, acetylacetonate, 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 amidalkylation 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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References


