Synthesis of fused uracils: pyrano[2,3-d]pyrimidines and 1,4-bis(pyrano[2,3-d]pyrimidinyl)benzenes by domino Knoevenagel/Diels-Alder reactions

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Abstract Knoevenagel condensation of barbituric acids with aromatic aldehydes containing one or two formyl groups was carried out. 5-Arylidenebarbituric acids underwent smooth hetero-Diels-Alder (HDA) reactions with enol ethers to afford cis and trans diastereoisomers of pyrano[2,3-d]pyrimidine-2,4-diones and 5,5′-(1,4-phenylene)-bis[2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione] derivatives in excellent yields (75–88 %). Syntheses were realized by Knoevenagel condensation and HDA reaction in four different reaction conditions: Knoevenagel condensation in water and Diels-Alder reaction in methylene chloride solution, Knoevenagel condensation in water and Diels-Alder reaction without solvent, three-component one-pot reaction in methylene chloride solution, or three-component one-pot reaction in water. All reactions were carried out without catalyst at room temperature. The reactions of malononitrile with Knoevenagel condensation products of barbituric acids and heteroaromatic aldehydes or terephthalaldehyde were examined and did not provide corresponding pyranopyrimidines.

Keywords Cycloadditions · Drug research · Michael addition · One-pot synthesis

Introduction

Pyran derivatives are common structural subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids [1, 2]. Uracil is one of the five nucleobases and therefore an important component of nucleic acids. Uracil and its fused derivatives, such as pyrano[2,3-d]pyrimidines, pyrido[2,3-d]pyrimidines, pyrazo[3,4-d]pyrimidines, or pyrimido[4,5-d]pyrimidines, are reported to have a wide range of biological activities such as antiallergic [3], antihypertensive [4], cardioactive [5], bronchodilator [6], antibronchitic [7], or antitumor [8] activity. The preparation of the compounds containing a pyran and an uracil ring poses significant synthetic challenges. 3,4-Dihydro-2H-pyran can be efficiently synthesized by inverse-electron-demand hetero-Diels-Alder (HDA) reactions of α,β-unsaturated carbonyl compounds representing an 1-oxa-1,3-butadiene system with enol ethers [9–11]. It has been stated that introducing an electron-withdrawing group in the 1-oxa-1,3-diene systems can enhance their reactivity [12–15]. In our recent work, we showed that intermolecular and intramolecular HDA reactions are a powerful tool in the synthesis of 2H-pyran and polycyclic 2H-pyran derivatives [16–24]. Also recently, as a continuation of the investigations of organic reactions performed in aqueous medium, a green approach to the synthesis of fused uracils 2-thioxopyrano[2,3-d]pyrimidin-4-ones and pyrano[2,3-d]pyrimidin-2,4-diones was made. Three-component one-pot syntheses of annulated uracils were performed in aqueous suspensions by domino Knoevenagel/Diels-Alder reactions without a catalyst and at room temperature [25]. In our last work we also investigated inverse-electron demand Diels-Alder cycloadditions of sterically hindered cycloalkylidene derivatives of benzoyl acetonitrile and N,N′-dimethylbarbituric acid with enol ethers, cyclic enol ethers, and also sterically hindered cycloalkylidenecycloalkanes [26]. Fused spirouracils and fused dispirouracils can be obtained by this method.

The same α,β-unsaturated carbonyl compounds, obtained by Knoevenagel condensation of the appropriate CH acids...
and aromatic aldehydes, can be used as substrates in pyran synthesis by conjugate addition-cyclization with malononitrile or cyanoacetate [27–29]. Pyrano[2,3-d]pyrimidine derivatives can be prepared by conjugate addition-cyclization of malononitrile to 5-arylidenebarbituric acids, or general procedures include the reaction of arylidenemalononitriles with barbituric acids under traditional hot reaction conditions [30, 31] or under microwave irradiation [32]. Recently, the synthesis of pyrano[2,3-d]pyrimidines by simply ball-milling a stoichiometric mixture of an aldehyde, malononitrile, and barbituric acids without any catalyst or solvent was described [33]. Also microwave-assisted three-component cyclocondensation of aldehydes, malononitrile, and barbituric acids proceeds in the absence or presence of triethylamine to afford pyrano[2,3-d]pyrimidines [34]. Direct condensation of aldehydes, malononitrile, and barbituric acids in aqueous media has been reported under heating [35] or under ultrasound irradiation [36].

Therefore, 5-arylidene derivatives of barbituric acids seem to be excellent intermediates in pyran synthesis both by HDA reaction and by conjugate addition-cyclization.

**Results and discussion**

The main aim of the studies was the synthesis of new (1,4-phenylene)bis[2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione] derivatives containing two fused uracil moieties joined by a benzene ring. Syntheses were realized by Knoevenagel condensation and HDA reaction in four different reaction conditions: A—Knoevenagel condensation in water and HDA reaction in methylene chloride as solvent, B—Knoevenagel condensation in water and HDA reaction without solvent, C—three-component one-pot reaction in methylene chloride as solvent, and D—three-component one-pot reaction in water. All the reactions were carried out at room temperature in the absence of catalyst.

First, procedures A–D were examined for the Knoevenagel condensation of barbituric acids with aromatic aldehydes containing only one formyl group and HDA reactions with enol ether. 5-Arylidenebarbituric acids 3a–3c, as potential heterodienes in Diels-Alder reactions, were synthesized by condensations of N,N'-dimethylbarbituric acid (1a) or barbituric acid (1b) with aromatic aldehydes 2a–2c in water without catalyst and at room temperature according the procedure described in the literature [37] (Scheme 1). The condensations occurred smoothly and were completed in just an hour, giving excellent yields (95–98%) of Knoevenagel products 3a–3c. The cycloaddition reactions of 3a–3c with a tenfold excess of ethyl vinyl ether 4 were performed with methylene chloride as the solvent (conditions A) or in the absence of solvent (conditions B) at room temperature for the time given in Table 1. New 2H-pyrano[2,3-d]pyrimidine-2,4(3H)-diones 5a–5c were obtained in 77–88% yields (Scheme 1; Table 1). Next, three-component one-pot synthesis of uracils 5a–5c by domino Knoevenagel/Diels-Alder reactions was investigated in methylene chloride (conditions C) or in aqueous medium (conditions D). The experimental procedure was simple: equimolar amounts of barbituric acid 1a or 1b and aromatic aldehyde 2a–2c were mixed with a tenfold excess of enol ether 4 in methylene chloride (conditions C) or in aqueous medium (conditions D) (Scheme 1; Table 1). The progress of the reactions was monitored by TLC. The ratios of the cis/trans...
diastereoisomers of the pyrano[2,3-\(d\)]pyrimidine-2,4-diones 5a–5c were determined on the basis of \(^1\)H NMR spectra of the crude products, analyzing the signals of protons 5-H and 7-H. The unexpected 5-methyl-substituted derivatives of pyrano[2,3-\(d\)]pyrimidines 6a–6b were obtained in aqueous medium (conditions D). This was determined on the basis of \(^1\)H NMR spectra of the crude products. Formation of these compounds can be explained as the result of the three-component reaction of barbituric acid 1a or 1b, the in situ generated acetaldehyde and ethyl-vinyl ether 4. The addition of water to ether 4 catalyzed by barbituric acid provides a hemiacetal, which undergoes ethanol elimination to produce the enol tautomer or finally keto tautomer of acetaldehyde. Only compounds cis-6a and trans-6a were separated in small amounts by column chromatography.

All diastereoisomers of compounds 5a–5c were very easily separated by column chromatography using \(t\)-butyl methyl ether as an eluent because the difference between \(R_t\) (cis) and \(R_t\) (trans) was approximately 0.2. Cycloadducts cis-5a–5c were the major products in all reactions. Three-component one-pot syntheses of pyrano[2,3-\(d\)]pyrimidines performed in aqueous medium (conditions D) were faster than those executed in dichloromethane or under solvent-free conditions, and cis/trans selectivity was significantly improved.

In the second step of the studies, it was decided to test the synthetic approach to the Knoevenagel condensation of barbituric acid with an aromatic aldehyde containing two formyl groups, terephthalaldehyde. HDA reactions with enol ether were performed in conditions A–D. Condensation of \(N,N'\)-dimethylbarbituric acid with terephthalaldehyde (2d) was carried out in water without catalyst and at room temperature, giving Knoevenagel product 3d with 97% yield after 1 h (Scheme 2). It is worth noting that there is only one synthetic method for this compound described in the literature [38], but it required drastic conditions, with acetic acid and sulfuric acid as the reactive media. The cycloaddition reactions of 3d with a tenfold excess of enol ethers 4a–4c were performed with methylene chloride as the solvent (conditions A) or in the absence of solvent (conditions B) at room temperature for the time given in Table 2. Also three-component one-pot syntheses of compounds 7a–7c by domino Knoevenagel/Diels-Alder reactions were investigated in conditions C and D. Equimolar amounts of \(N,N'\)-dimethylbarbituric acid and 1,4-benzenedicarbaldehyde were mixed with a tenfold excess of enol ethers 4a–4c in methylene chloride (conditions C) or in aqueous medium (conditions D) (Scheme 2; Table 2). 5,5'-\(1,4\)-Phenylene)bis[2H-pyrano[2,3-\(d\)]pyrimidine-2,4-(3H)-dione] derivatives 7a–7c were obtained in 75–82% yields. The progress of the reactions was monitored by TLC. The ratios of the cis/trans diastereoisomers of cycloadducts 7a–7c were determined on the basis of \(^1\)H NMR spectra of crude products, analyzing the signals of protons 5-H and 7-H. Cycloadducts cis-7a–7c were the major products. The unexpected pyrano[2,3-\(d\)]pyrimidines 6a–6c (conditions D) and 8a–8c (conditions C, D) were also obtained in small amounts. It was determined on the basis of \(^1\)H NMR spectra of the crude products. Formation of compounds 6a–6c was explained above. Cycloadducts 8a–8c were obtained as the result of Knoevenagel reaction of barbituric acid 1a and only one formyl group of dicarbaldelyde 2d. Only compounds cis-6a, trans-6a, cis-8a, and trans-8a were isolated by column chromatography.

The three-component one-pot syntheses of pyrano[2,3-\(d\)]pyrimidines 7a–7c performed in aqueous medium (condition D) were faster than those executed in dichloromethane or under solvent-free conditions, and cis/trans selectivity was the highest for these reactions.

Compounds 5a–5c, 6a, 7a–7c, and 8a were characterized by \(^1\)H, \(^{13}\)C NMR, IR, and elemental analysis. \(^1\)H and

### Table 1: Synthesis of the cycloadducts 5a–5c by Knoevenagel condensation and HDA reaction in the reaction conditions A–D

| Entry | Method | \(R^1\) | \(R^2\) | \(5\) | \(5\) | \(6\) | Reaction time/h | Yield/% of \(5\) | Ratio of cis-5/ trans-5 |
|-------|--------|--------|--------|------|------|------|----------------|----------------|------------------|
| 1     | A      | 1a     | 2a     | 3a   | 5a   | –    | 15             | 87             | 1.8:1            |
| 2     | B      | 1a     | 2a     | 3a   | 5a   | –    | 12             | 86             | 1.6:1            |
| 3     | C      | 1a     | 2a     | –    | 5a   | –    | 15             | 84             | 2.5:1            |
| 4     | D      | 1a     | 2a     | –    | 5a   | 6a   | 7              | 82             | 7.2:1            |
| 5     | A      | 1a     | 2b     | 3b   | 5b   | –    | 13             | 81             | 2.3:1            |
| 6     | B      | 1a     | 2b     | 3b   | 5b   | –    | 12             | 82             | 1.8:1            |
| 7     | C      | 1a     | 2b     | –    | 5b   | –    | 13             | 87             | 2.5:1            |
| 8     | D      | 1a     | 2b     | –    | 5b   | 6a   | 6              | 86             | 6.9:1            |
| 9     | A      | 1b     | 2c     | 3c   | 5c   | –    | 24             | 86             | 2.0:1            |
| 10    | B      | 1b     | 2c     | 3c   | 5c   | –    | 20             | 77             | 1.5:1            |
| 11    | C      | 1b     | 2c     | –    | 5c   | –    | 22             | 82             | 2.2:1            |
| 12    | D      | 1b     | 2c     | –    | 5c   | 6b   | 12             | 88             | 5.6:1            |

\(^{a}\) Isolated yields after column chromatography

\(^{b}\) Ratio based on \(^1\)H NMR (300 MHz) spectra of crude products

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\(R^1\) and \(R^2\) represent the substituents on the aromatic ring of the aldehyde.

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**Table 2** Synthesis of the cycloadducts 7a–7c by Knoevenagel condensation and HDA reaction in the reaction conditions A–D

| Entry | Method | 1 | 2 | 3 | 4 | R¹ | R² | 6 | 7 | 8 | Reaction time/h | Yield/% of 7⁺ | Ratio of cis-7/ trans-7⁻ |
|-------|--------|---|---|---|---|-----|-----|---|---|---|-----------------|----------------|--------------------------|
| 1     | A      | 1a | 2d | 3d | 4a | C₂H₅ | H   | –  | 7a | 8a | 18              | 82             | >100:1                   |
| 2     | B      | 1a | 2d | 3d | 4a | C₂H₅ | H   | –  | 7a | 8a | 16              | 81             | >100:1                   |
| 3     | C      | 1a | 2d | 3d | 4a | C₂H₅ | H   | –  | 7a | 8a | 15              | 80             | >100:1                   |
| 4     | D      | 1a | 2d | 3d | 4a | C₂H₅ | H   | 6a | 7a | 8a | 8               | 82             | >100:1                   |
| 5     | A      | 1a | 2d | 3d | 4b | i-Bu | H   | –  | 7b | 8b | 18              | 81             | 6.3:1                    |
| 6     | B      | 1a | 2d | 3d | 4b | i-Bu | H   | 7b | 8b | 17             | 78             | 5.9:1                    |
| 7     | C      | 1a | 2d | –  | 4b | i-Bu | H   | 7b | 8b | 15             | 77             | 6.5:1                    |
| 8     | D      | 1a | 2d | –  | 4b | i-Bu | H   | 6b | 7b | 8b | 8               | 76             | 8.1:1                    |
| 9     | A      | 1a | 2d | 3d | 4c | CH₃  | CH₃ | –  | 7c | 8c | 24              | 78             | 5.3:1                    |
| 10    | B      | 1a | 2d | 3d | 4c | CH₃  | CH₃ | –  | 7c | 8c | 20              | 75             | 5.5:1                    |
| 11    | C      | 1a | 2d | –  | 4c | CH₃  | CH₃ | 7c | 8c | 18             | 82             | 5.2:1                    |
| 12    | D      | 1a | 2d | –  | 4c | CH₃  | CH₃ | 6c | 7c | 8c | 10              | 80             | 7.5:1                    |

a Isolated yields after column chromatography
b Ratio based on ¹H NMR (300 MHz) spectra of crude products

¹³C signal assignments were confirmed by two-dimensional COSY and HETCOR NMR spectra. The relative cis and trans configuration of the C-5, C-7 substituents were assigned on the basis of ¹H NMR spectra. They were deduced from the chemical shift values and coupling constants of the protons attached to C-5 and C-7 of the dihydropyran ring that exists in a half-chair conformation (Table 3).

In the ¹H NMR spectra of the major diastereoisomers cis-5a–5c, cis-6a, cis-7a–7c, and cis-8a, the signal of 5-H (5-H and 5'-H for cis-7a–7c) appeared as a doublet of doublets at δ = 3.76–4.13 ppm (for cis-6a, ddq...
Table 3. Signals of proton 5-H and 7-H in $^1$H NMR spectra of products 5a–5c, 6a, 7a–7c, and 8a.

| Compound | $\delta$ 5-H | $\delta$ 7-H | $J_{\text{ax}}/\text{ax}$ | $J_{\text{eq}}/\text{eq}$ |
|----------|--------------|--------------|----------------|----------------|
| cis-5a   | 4.00         | 5.38         | 4.11           | 5.17           |
|          | 7.5/5.1      | 4.8/2.7      | 5.7/5.4        | 7.5/2.4        |
| cis-5b   | 4.02         | 5.38         | 4.12           | 5.17           |
|          | 7.5/5.1      | 4.5/2.7      | 5.7/5.1        | 7.8/2.7        |
| cis-5c   | 3.76         | 5.41         | 3.81           | 5.08           |
|          | 7.2/4.8      | 4.5/2.4      | 5.4/4.8        | 8.1/2.4        |
| cis-6a   | 2.88 ddq     | 5.40         | 2.98 ddq       | 5.30           |
|          | 6.9/6.9/3.3  | 3.3/3.0      | 6.9/6.9        | 8.1/2.7        |
| cis-7a   | 4.00         | 5.31         | –              | –              |
|          | 7.2/6.3      | 5.7/2.7      | –              | –              |
| cis-7b   | 3.99         | 5.07         | 4.12           | 5.28           |
|          | 7.5/6.0      | 6.0/2.4      | 9.3/4.8        | 5.7/2.4        |
|          | 4.03         | 5.11         | 4.19           | 5.32           |
|          | 6.9/5.4      | 8.4/3.0      | 5.4/3.9        | 4.2/3.0        |
| cis-7c   | 3.97         | –            | trans-7c       | 3.93           |
|          | 7.2/5.1      | 11.7/6.6     | –              | 6.6/1.1        |
| cis-8a   | 4.13         | 5.42         | trans-8a       | 4.20           |
|          | 7.5/5.1      | 4.5/2.7      | 6.3/6.0        | 6.9/2.4        |

Fig. 1. Preferred cis/trans configurations and conformations of cycloaducts 5a–5c, 6a, 7a–7c, and 8a based on $^1$H NMR analysis.

$\delta = 2.88$ ppm with coupling constants $^3J = 6.9–7.5$ and 4.8–6.3 Hz) because of coupling with two protons at C-6 (Table 3). Thus, 5-H (5-H and 5'-H for cis-7a–7c) occupies the pseudo-equatorial position, and the aromatic group adopts the pseudo–axial orientation (Fig. 1). The $^1$H NMR spectra of cis-5a–5c, cis-6a, cis-7a–7c, and cis-8a reveal the signals of proton 7-H (7-H and 7'-H for cis-7a–7c) as a doublet of doublets at $\delta = 5.07–5.42$ ppm with two small coupling constants $^3J = 3.3–6.0$ Hz ($^4J = 8.4$ Hz only for cis-7b) and 2.4–3.0 Hz. Thus, 7-H (7-H and 7'-H for cis-7a–7c) is in the equatorial position, and the alkoxy group occupies the axial position (Fig. 1).

For the minor diastereoisomers trans-5a–5c, trans-6a, trans-7a–7c, and trans-8a; the protons attached to C-5 (C-5' for trans-7a–7c) give rise to a doublet of doublets with coupling constants $^3J = 5.4–11.7$ and 3.9–6.6 Hz at $\delta = 3.81–4.20$ ppm (for trans-6a, ddq $\delta = 2.98$ ppm). Thus, 5-H (5-H and 5'-H for trans-7a–7c) is pseudo-axial, and the $^2R^2$ moiety occupies the pseudo-equatorial position (Fig. 1). The proton 7-H (7-H and 7'-H for trans-7a–7c) of trans-5a–5c, trans-6a, trans-7a–7c, and trans-8a resonates at $\delta = 5.08–5.32$ ppm as a doublet of doublets with two coupling constants ($^3J = 4.2–8.1$ and 2.4–3.0 Hz). This suggests that for trans-5a–5c, trans-6a, trans-7a–7c, and trans-8a, the conformation with an axial alkoxy group is preferred because of stabilization by the anomeric effect (Fig. 1).

According to the literature, the Knoevenagel condensation products obtained by condensation of barbituric acids and aromatic aldehydes are excellent reagents in pyran synthesis by conjugate addition-cyclization [27–36]. There is no information for the same reactions using heteroaromatic aldehydes or terephthalaldehyde. Therefore, in the next step, the Michael addition-cyclization of malononitrile with $\alpha,\beta$-unsaturated carbonyl compounds obtained by Knoevenagel condensation of barbituric acids and heteroaromatic aldehydes or terephthalaldehyde was examined. The reactions of acids 1a, 1b with heteroaromatic aldehydes 2e, 2f in water at room temperature gave the condensation products 3e and 3f with stoichiometric yields after 1 h. Heating of 3e or 3f with malononitrile 9 under reflux in water for 1 h (method E, Scheme 3; Table 4, entries 1, 7, 13) or under reflux in acetonitrile in the presence of piperidine for 3 h (method F, Scheme 3; Table 4, entries 2, 8, 14) did not result in compounds 12.

Therefore, in the next step of the studies, the three-component one-pot reactions of acids 1a, 1b, aldehydes 2e, 2f, and malononitrile 9 without solvent at 100 °C (method G, Scheme 3; Table 4, entries 3, 9, 15) or in water (method H, Scheme 3; Table 4, entries 4, 10, 16) were examined. There was no trace of the desired products 12 after 1 h of heating, and compounds 3e–3g were obtained in excellent 85–93 % yields as the only products. Therefore, the next attempts to synthesize the compounds 12 were undertaken. Aldehydes 2e, 2f were first stirred with malononitrile 9 in water at room temperature, and after 1 h the condensation products 10a and 10b were isolated with stoichiometric yields. Further, the mixture of compounds 10a, 10b was.
Table 4 Reactions of barbituric acids 1a, 1b, heteroaromatic aldehydes 2e, 2f, and malononitrile 9 in the reaction conditions E–H

| Entry | Reagent R | Method | Reagent R | Product | Yield/% of 3 |
|-------|-----------|--------|-----------|---------|-------------|
| 1     | 1a        | CH₃    | 2e        | 9       | 3e          |
| 2     | 1a        | CH₃    | 2e        | F       | 9           |
| 3     | 1a        | CH₃    | 2e        | G       | 9           |
| 4     | 1a        | CH₃    | 2e        | H       | 9           |
| 5     | 2e        | 2-Thienyl | 9       | E       | 1a, CH₃    | 10a | 3e | 91 |
| 6     | 2e        | 2-Thienyl | 9       | F       | 1a, CH₃    | 10a | 3e | 85 |
| 7     | 1b        | H       | 2e        | E       | 9           |
| 8     | 1b        | H       | 2e        | F       | 9           |
| 9     | 1b        | H       | 2e        | G       | 9           |
| 10    | 1b        | H       | 2e        | H       | 9           |
| 11    | 2e        | 2-Thienyl | 9       | E       | 1b, H      | 10a | 3f | 90 |
| 12    | 2e        | 2-Thienyl | 9       | F       | 1b, H      | 10a | 3f | 81 |
| 13    | 1a        | CH₃    | 2f        | E       | 9           |
| 14    | 1a        | CH₃    | 2f        | F       | 9           |
| 15    | 1a        | CH₃    | 2f        | G       | 9           |
| 16    | 1a        | CH₃    | 2f        | H       | 9           |
| 17    | 2f        | 2-Furyl | 9       | E       | 1a, CH₃    | 10b | 3g | 88 |
| 18    | 2f        | 2-Furyl | 9       | F       | 1a, CH₃    | 10b | 3g | 79 |
heated to reflux with barbituric acids 1a or 1b in water for 1 h (method E, Scheme 3; Table 4, entries 5, 11, 17) or heated to reflux in acetonitrile in the presence of piperidine for 3 h (method F, Scheme 3; Table 4, entries 6, 12, 18). In these cases also, the only compounds, isolated in good yields of 79–91 % after the reactions, were condensation products 3e–3g. This result suggests that in the first step of the reactions (Table 4, entries 5, 6, 11, 12, 17, 18), the Michael adducts 11 are furnished (Scheme 3). Intermediates 11 did not undergo cyclization with formation of pyrano[2,3-d]pyrimidine derivatives 12, but the elimination of malononitrile led to undesired 3e–3g.

At the end of the study, the reaction procedures E–H presented above were examined for acid 1a, terephthalaldehyde 2d, and malononitrile 9. The reaction of 1a with aldehyde 2d in water at room temperature gave condensation product 3d with almost stoichiometric yield after 1 h. When compound 3d was heated with malononitrile 9 in water for 1 h (method E, Scheme 4) or in acetonitrile in the presence of piperidine for 3 h (method F, Scheme 4), the expected compound 13 was not obtained.

However, when the three-component one-pot reactions of acid 1a, aldehyde 2d, and malononitrile 9 were heated at 100 °C (method G, Scheme 4) without solvent for 1 h or in water under reflux (method H, Scheme 4), compound 3d was obtained in excellent yield (87–91 %).

In conclusion, new fused uracils of possible pharmacophore, the pyrano[2,3-d]pyrimidines and (1,4-phenylene)bis-[2H-pyrano[2,3-d]pyrimidine-2,4(3H)-diones], were obtained by domino Knoevenagel/Diels-Alder reactions in different reaction conditions. All reactions were carried out without catalyst and at room temperature. Three-component one-pot syntheses of fused uracils performed in aqueous medium were faster than those executed in dichloromethane or under solventless conditions, and cis/trans selectivity was the highest for these reactions. The reactions of malononitrile with Knoevenagel condensation products of barbituric acids and heteroaromatic aldehydes or terephthalaldehyde were examined, and they do not provide corresponding pyranopyrimidines. The presented methods avoid the use of catalysts and the heating of reaction mixtures for long times at high temperatures, and the advantages of the presented
syntheses are also the excellent yields and short reactions times.

**Experimental**

All chemicals were purchased and used without any further purification. The melting points were determined on a Boetius hot stage apparatus. The IR spectra were recorded on a Nicolet IR 200 FT-IR, Thermo Scientific spectrophotometer. NMR spectra were recorded on Bruker Avance II 300 (1H: 300.18 MHz, 13C: 75.48 MHz) in CDCl3 or DMSO-d6 with TMS as an internal standard. Microanalyses were performed with a Euro EA 3000 Elemental Analyzer; their results agreed satisfactorily with the calculated values. 5-Arylidenebarbituric acids were also separated and recrystallized in small amounts.

**Procedures for the synthesis of pyrano[2,3-d]-pyrimidine-2,4-diones 5a–5c, 6a, 8a, and 5,5′-(1,4-phenylene)bis[2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione] derivatives 7a–7c**

**Procedure A**

A solution of 4.0 mmol 3a–3d (1.29 g 3a, 1.11 g 3b, 0.99 g 3c, 1.64 g 3d) in dry CH2Cl2 (50 cm3 for 3a, 3b, and 100 cm3 for 3c, 3d) and 40 mmol (10 equivalents) of enol ethers 4a–4c (3.8 cm3 4a, 5.2 cm3 4b, 3.8 cm3 4c) was kept at room temperature for the time given in Tables 1 or 2. The progress of the reactions was monitored by TLC. The solvent and excess of ethers were evaporated, and the mixture was separated and purified by the method described in procedure A. The solvent mixture was separated and purified by the method described in procedure A. Products 5a–5c, 7a–7c were obtained with yields listed in Tables 1 or 2. The diastereoisomers of product 8a were also separated and recrystallized in small amounts.

**Procedures for the synthesis of pyrano[2,3-d]-pyrimidine-2,4-diones 5a–5c, 6a, 8a, and 5,5′-(1,4-phenylene)bis[2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione] derivatives 7a–7c**

**Procedure A**

A solution of 4.0 mmol 3a–3d (1.29 g 3a, 1.11 g 3b, 0.99 g 3c, 1.64 g 3d) in dry CH2Cl2 (50 cm3 for 3a, 3b, and 100 cm3 for 3c, 3d) and 40 mmol (10 equivalents) of enol ethers 4a–4c (3.8 cm3 4a, 5.2 cm3 4b, 3.8 cm3 4c) was stirred with a tenfold excess (40 mmol) of enol ethers 4a–4c with yields listed in Tables 1 or 2. The diastereoisomers of product 8a were also separated and recrystallized in small amounts.

**Procedure B**

A mixture of 4.0 mmol of one of the 5-arylidenebarbituric acids 3a–3d (1.29 g 3a, 1.11 g 3b, 0.99 g 3c, 1.64 g 3d) with a tenfold excess (40 mmol) of one of the enol ethers 4a–4c (3.8 cm3 4a, 5.2 cm3 4b, 3.8 cm3 4c) was stirred without solvent at room temperature for the time given in Tables 1 or 2. The progress of the reactions was monitored by TLC. The solvent mixture was separated and purified by the method described in procedure A. Products 5a–5c, 7a–7c were obtained with yields listed in Tables 1 or 2.

**Procedure C**

Equimolar amounts (4.0 mmol) of barbituric acid 1a (0.625 g) or 1b (0.51 g) and aldehydes 2a–2d (0.74 g 2a, 0.56 g 2b, 0.5 cm3 2c, 0.27 g (2.0 mmol) 2d) were mixed with a tenfold excess (40 mmol) of enol ethers 4a–4c (3.8 cm3 4a, 5.2 cm3 4b, 3.8 cm3 4c) in 100 cm3 dry CH2Cl2 at room temperature for the time given in Tables 1 or 2. The progress of the reactions was monitored by TLC. The solvent and excess of ethers were evaporated, and the mixture was separated and purified by the method described in procedure A. Products 5a–5c, 7a–7c were obtained with yields listed in Tables 1 or 2. The diastereoisomers of product 8a were also separated and recrystallized in small amounts.
(H, ddd, J = 13.8, 4.8, 2.4 Hz, 6-H), 2.20 (1H, ddd, J = 13.8, 7.5, 6.3 Hz, 6-H), 3.29 (3H, s, N-Me), 3.43 (3H, s, N-Me), 3.65 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.95 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 4.11 (1H, dd, J = 5.7, 5.4 Hz, 5-H), 5.17 (1H, dd, J = 7.5, 2.4 Hz, 7-H), 7.06 (2H, dd, J = 8.4 Hz, Ar), 7.42 (2H, d, J = 8.4 Hz, Ar) ppm; 13C NMR (75.5 MHz, CDCl3); δ = 15.1, 28.0, 28.7, 33.6, 35.9, 66.0, 88.2, 101.2, 120.5, 128.8, 131.8, 142.8, 142.9, 151.3, 154.5, 162.0 ppm.

(5RS,7SR)-5-(4-Chlorophenyl)-7-ethoxy-1,5,6,7-
tetrahydro-1,3-dimethyl-2H-pyrano[2,3-d]pyrimidine-
2,4(3H)-dione (cis-5b, C17H18ClN2O3)

Colorless crystals; mp: 141–142 °C; Rf = 0.41 (t-BuOMe); IR (powder): ν = 2,992, 2,959, 2,887, 1,725, 1,654, 1,503, 1,280, 1,188, 1,046, 1,016 cm⁻¹; 1H NMR (300 MHz, CDCl3); δ = 1.13 (3H, t, J = 7.2 Hz, OCH2CH3), 2.14 (1H, ddd, J = 14.4, 5.1, 4.8 Hz, 6-H), 2.33 (1H, ddd, J = 14.1, 7.5, 2.7 Hz, 6-H), 3.28 (3H, s, N-Me), 3.43 (3H, s, N-Me), 3.58 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.86 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 4.02 (1H, ddd, J = 7.5, 5.1 Hz, 5-H), 5.38 (1H, dd, J = 4.5, 2.7 Hz, 7-H), 7.12 (2H, d, J = 8.4 Hz, Ar), 7.21 (2H, d, J = 8.4 Hz, Ar) ppm; 13C NMR (75.5 MHz, CDCl3); δ = 14.9, 28.0, 28.7, 33.4, 35.4, 65.5, 89.1, 102.0, 128.2, 128.7, 131.8, 142.2, 151.2, 155.1, 162.1 ppm.

(5RS,7RS)-5-(4-Chlorophenyl)-7-ethoxy-1,5,6,7-
tetrahydro-1,3-dimethyl-2H-pyran[2,3-d]pyrimidine-
2,4(3H)-dione (trans-5b, C17H18ClN2O3)

Colorless crystals; mp: 153–155 °C; Rf = 0.59 (t-BuOMe); IR (powder): ν = 3,004, 2,960, 2,912, 2,887, 1,720, 1,651, 1,505, 1,178, 1,118, 1,035 cm⁻¹; 1H NMR (300 MHz, CDCl3); δ = 1.27 (3H, t, J = 6.9 Hz, OCH2CH3), 2.07 (1H, ddd, J = 14.1, 5.1, 2.7 Hz, 6-H), 2.20 (1H, ddd, J = 13.8, 7.5, 6.3 Hz, 6-H), 3.29 (3H, s, N-Me), 3.43 (3H, s, N-Me), 3.65 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.98 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 4.12 (1H, dd, J = 5.7, 5.1 Hz, 5-H), 5.17 (1H, dd, J = 7.8, 2.7 Hz, 7-H), 7.11 (2H, d, J = 8.4 Hz, Ar), 7.27 (2H, d, J = 8.4 Hz, Ar) ppm; 13C NMR (75.5 MHz, CDCl3); δ = 15.1, 28.0, 28.7, 33.5, 36.0, 66.0, 88.3, 101.4, 128.6, 128.8, 132.4, 142.2, 151.3, 154.5, 162.1 ppm.

(5RS,7SR)-7-Ethoxy-1,5,6,7-tetrahydro-1,3,5-
trimethyl-2H-pyran[2,3-d]pyrimidine-2,4(3H)-dione
(cis-6a, C12H18N2O4)

Colorless crystals; mp: 79–80 °C; Rf = 0.37 (t-BuOMe); IR (powder): ν = 2,968, 2,934, 2,901, 2,879, 1,701, 1,625, 1,483, 1,183, 1,144, 1,102, 1,022 cm⁻¹; 1H NMR (300 MHz, CDCl3); δ = 1.26 (3H, t, J = 7.2 Hz, OCH2CH3), 1.35 (3H, d, J = 6.9 Hz, 5-CH3), 1.90 (1H, ddd, J = 13.4, 3.6, 3.3 Hz, 6-H), 2.05 (1H, ddd, J = 14.1, 6.9, 3.0 Hz, 6-H), 2.88 (1H, ddq, J = 6.9, 6.9, 3.6 Hz, 5-H), 3.34 (3H, s, N-Me), 3.36 (3H, s, N-Me), 3.65 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.89 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 5.40 (1H, dd, J = 3.3, 3.0 Hz, 7-H) ppm; 13C NMR (75.5 MHz, CDCl3); δ = 15.1, 20.1, 22.6, 27.9, 28.6, 33.4, 65.6, 92.0, 101.8, 151.2, 153.4, 162.7 ppm.

(5RS,7SR)-7-Ethoxy-1,5,6,7-tetrahydro-1,3,5-
trimethyl-2H-pyran[2,3-d]pyrimidine-2,4(3H)-dione
(trans-6a, C12H18N2O4)

Colorless crystals; mp: 88–90 °C; Rf = 0.43 (t-BuOMe); IR (powder): ν = 2,972, 2,931, 2,908, 2,883, 1,701, 1,630, 1,491, 1,182, 1,140, 1,098, 1,020 cm⁻¹; 1H NMR (300 MHz, CDCl3); δ = 1.26 (3H, d, J = 6.9 Hz, 5-CH3), 1.31 (3H, t, J = 7.2 Hz, OCH2CH3), 1.85 (1H, ddd, J = 13.8, 3.9, 2.7 Hz, 6-H), 1.94 (1H, ddd, J = 13.8, 8.1, 6.0 Hz, 6-H), 2.98 (1H, ddq, J = 6.9, 6.9, 3.9 Hz, 5-H), 3.33 (3H, s, N-Me), 3.35 (3H, s, N-Me), 3.73 (1H, dq, J = 9.6, 7.2 Hz, OCH2CH3), 3.76 (1H, dd, J = 7.2, 4.8 Hz, 5-H), 5.41 (1H, ddd, J = 4.5, 2.4 Hz, 7-H), 6.75 (2H, d, J = 9.0 Hz, Ar), 7.03 (2H, d, J = 8.4 Hz, Ar), 10.69 (1H, s, NH), 11.35 (1H, s, NH) ppm; 13C NMR (75.5 MHz, CDCl3); δ = 14.8, 31.4, 35.4, 54.8, 64.1, 87.8, 100.6, 112.8, 128.2, 136.3, 150.0, 156.3, 157.1, 163.4 ppm.

Synthesis of fused uracils
J = 9.6, 7.2 Hz, OCH2CH3), 4.01 (1H, dq, J = 9.6, 7.2 Hz, OCH2CH3), 5.30 (1H, dd, J = 8.1, 2.7 Hz, 7-H) ppm; 13C NMR (75.5 MHz, CDCl3): δ = 15.1, 20.8, 23.2, 27.9, 28.6, 34.6, 66.0, 91.6, 101.2, 151.2, 153.9, 162.6 ppm.

(5RS,7SR,5'SR,7'SR)-5',5'-[(1,4-Phenylene)bis[7-ethoxy-1,5,6,7-tetrahydro-1,3-dimethyl-2H-pyranol[2,3-d]pyrimidine-2,4(3H)-dione] (cis-7a, C9H34N4O9)

Colorless crystals; mp: >360 °C; Rf = 0.14 (t-BuOMe); IR (powder): ν = 2973, 2926, 2884, 1703, 1635, 1480, 1417, 1312, 1055, 1001 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ = 1.15 (3H, t, J = 7.2 Hz, OCH2CH3), 2.17 (2H, dd, J = 14.7, 6.3, 5.7 Hz, 6-H, 6'-H), 2.32 (2H, dd, J = 14.1, 7.2, 7.7 Hz, 6-H, 6'-H), 3.27 (6H, s, N-Me), 3.42 (6H, s, N-Me), 3.58 (2H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.86 (2H, dq, J = 9.3, 7.2 Hz, OCH2CH3), 4.00 (2H, dd, J = 7.2, 6.3 Hz, 5-H, 5'-H), 5.31 (2H, dd, J = 5.7, 2.7 Hz, 7-H, 7'-H), 7.05 (4H, br, Ar) ppm; 13C NMR (75.5 MHz, CDCl3): δ = 14.9, 27.9, 28.7, 34.0, 36.1, 65.5, 90.0, 102.5, 126.9, 141.1, 151.3, 153.5, 150.1, 162.1 ppm.

(5RS,7SR,5'SR,7'SR)-5',5'-[(1,4-Phenylene)bis[1,5,6,7-tetrahydro-7-isotutoxy-1,3-dimethyl-2H-pyranol[2,3-d]pyrimidine-2,4(3H)-dione] (cis-7b, C23H36N6O12)

Colorless crystals; mp: >360 °C; Rf = 0.24 (t-BuOMe); IR (powder): ν = 2959, 2927, 2864, 2853, 1702, 1636, 1458, 1162, 1154, 1047, 1006 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ = 0.90 (12H, d, J = 6.6 Hz, OCH2CH2CH3), 1.67 (2H, m, OCH2CH2CH3), 2.02 (2H, ddd, J = 13.8, 4.8, 2.4 Hz, 6-H, 6'-H), 2.20 (2H, ddd, J = 13.8, 8.4, 6.0 Hz, 6-H), 3.30 (6H, s, N-Me), 3.41 (6H, s, N-Me), 3.54 (1H, dd, J = 9.0, 6.3 Hz, OCH2CH2CH3), 3.67 (1H, dd, J = 9.0, 6.6 Hz, OCH2CH2CH3), 3.99 (1H, dd, J = 7.5, 6.0 Hz, 5-H), 4.03 (1H, dd, J = 6.9, 5.4 Hz, 5'-H), 5.07 (1H, dd, J = 6.0, 2.4 Hz, 7-H), 5.11 (1H, dd, J = 8.4, 3.0 Hz, 7'-H), 7.00 (2H, br, Ar), 7.05 (2H, br, Ar) ppm; 13C NMR (75.5 MHz, CDCl3): δ = 19.0, 19.5, 27.8, 28.3, 28.5, 33.5, 33.7, 36.0, 36.1, 71.2, 78.8, 80.8, 88.3, 101.8, 102.0, 127.3, 127.5, 141.6, 141.7, 151.3, 155.5, 162.3 ppm.

(5RS,7SR,5'SR,7'SR)-5',5'-[(1,4-Phenylene)bis[1,5,6,7-tetrahydro-7-methoxy-1,3,7-trimethyl-2H-pyranol[2,3-d]pyrimidine-2,4(3H)-dione] (trans-7c, C9H34N4O9)

Colorless crystals; mp: >360 °C; Rf = 0.39 (t-BuOMe); IR (powder): ν = 2981, 2952, 2885, 1697, 1631, 1486, 1449, 1172, 1069, 1047, 1018 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ = 1.53 (3H, s, 7-CH3), 1.56 (3H, s, 7'-CH3), 2.11 (2H, dd, J = 14.1, 7.2 Hz, 6-H, 6'-H), 2.31 (2H, dd, J = 14.1, 6.0 Hz, 6-H, 6'-H), 3.19 (6H, s, OCH3), 3.29 (6H, s, N-Me), 3.42 (6H, s, N-Me), 3.97 (2H, dd, J = 7.2, 5.1 Hz, 5-H, 5'-H), 7.03 (4H, br, Ar) ppm; 13C NMR (75.5 MHz, CDCl3): δ = 22.3, 27.9, 28.6, 34.3, 39.8, 49.6, 88.9, 105.6, 126.7, 126.9, 140.9, 151.4, 155.2, 162.2 ppm.

(5RS,7SR,5'SR,7'SR)-5',5'-[(1,4-Phenylene)bis[1,5,6,7-tetrahydro-7-methoxy-1,3,7-trimethyl-2H-pyranol[2,3-d]pyrimidine-2,4(3H)-dione] (trans-7d, C9H34N4O9)

Colorless crystals; mp: 335–337 °C; Rf = 0.19 (t-BuOMe); IR (powder): ν = 2975, 2937, 2898, 1703, 1634, 1571, 1486, 1379, 1170, 1092, 1004 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ = 1.26 (3H, t, J = 7.2 Hz, OCH2CH3), 2.22 (1H, ddd, J = 14.1, 4.8, 4.5 Hz, 6-H), 2.38 (1H, ddd, J = 14.4, 7.5, 2.7 Hz, 6-H), 3.28 (3H, s, N-Me), 3.45 (3H, s, N-Me), 3.57 (1H, dq, J = 9.3, 6.9 Hz, OCH2CH3), 3.84 (1H, dq, J = 9.3, 7.2 Hz, OCH2CH3), 4.13 (1H, dd, J = 7.5, 5.1 Hz, 5-H), 5.42 (1H, dd, J = 4.5, 2.7 Hz, 7-H), 7.36 (2H, d, J = 8.4 Hz, Ar), 7.78 (2H, d, J = 8.4 Hz, Ar), 9.95 (1H, s, CHO) ppm; 13C NMR (75.5 MHz, CDCl3): δ = 14.8, 28.0, 28.8, 33.9, 35.0, 66.5, 88.4, 101.7, 128.1, 129.7, 134.8, 151.1, 151.2, 155.2, 162.7, 192.0 ppm.

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(5RS,7RS)-7-Ethoxy-5-(4-formylphenyl)-1,5,6,7-tetrahydro-1,3-dimethyl-2H-pyran-2,3-dione (trans-8a, C₁₈H₂₀N₂O₅)

Colorless crystals; mp: 168–170 °C; R₁ = 0.29 (t-Bu-OMe); IR (powder): ν = 2,951, 2,898, 2,823, 2,732, 1,698, 1,634, 1,574, 1,488, 1,169, 1,118, 1,043, 1,005 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.26 (3H, t, J = 7.2 Hz, OCH₂C₆H₃), 2.09 (1H, ddd, J = 13.8, 6.0, 2.4 Hz, 6-H), 2.27 (1H, ddd, J = 13.8, 7.2, 6.6 Hz, 6-H), 3.28 (3H, s, N-Me), 3.44 (3H, s, N-Me), 3.67 (1H, dq, J = 9.3, 6.9 Hz, OCH₂CH₃), 3.95 (1H, dq, J = 9.6, 7.2 Hz, OCH₂CH₃), 4.20 (1H, dd, J = 6.3, 6.0 Hz, 5-H), 5.24 (1H, dd, J = 6.9, 2.4 Hz, 7-H), 7.37 (2H, d, J = 8.1 Hz, Ar), 7.83 (2H, d, J = 8.4 Hz, Ar), 9.97 (1H, s, CHO) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 15.0, 28.0, 28.7, 34.2, 35.9, 66.0, 88.3, 100.9, 127.9, 130.2, 135.2, 151.1, 151.2, 155.4, 162.0, 191.7 ppm.

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