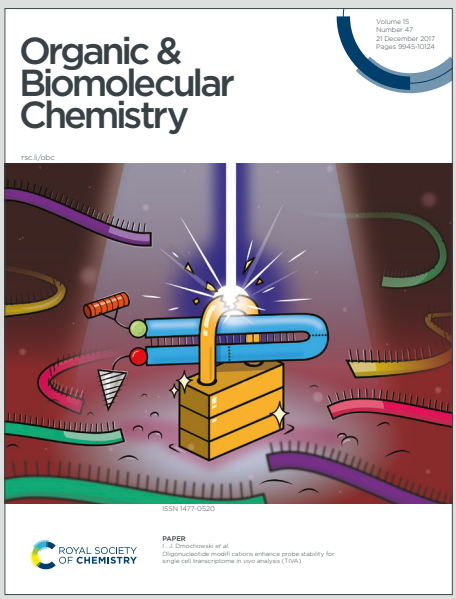
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: T. K. Nguyen, G. D. Titov, O. V. Khoroshilova, M. A. Kinzhalov and N. V. Rostovskii, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB00693A.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB00693A

ARTICLE

Light-induced one-pot synthesis of pyrimidine derivatives from vinyl azides

Tuan K. Nguyen, Gleb D. Titov, Olesya V. Khoroshilova, Mikhail A. Kinzhalov,* Nikolai V. Rostovskii*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A one-pot procedure for the synthesis of tetrasubstituted dihydropyrimidine and pyrimidine derivatives from α-azidocinnamates was developed. The synthesis is based on the finding that the outcome of LED photolysis of α-azidocinnamates depends on the light wavelength employed. Blue light (455 nm) leads to the formation of 2*H*-azirines only, but violet light (395 nm), UV-A light (365 nm), or sunlight result in the transformation of the *in situ* formed 2*H*-azirines to 1,3-diazabicyclo[3.1.0]hex-3-enes. Under basic catalysis (DBU), the latter were isomerized to 1,6-dihydropyrimidines which were oxidized to pyrimidines using DDQ. A successful use of Cs_2CO_3 as a base and air as an oxidant was also demonstrated.

Introduction

Pyrimidine derivatives are one of the most important biologically active heterocycles.[1] In particular, both pyrimidines and dihydropyrimidines are known to display antibacterial,[2] antiviral,[3] anticancer,[4] anti-HIV,[5] antimalarial activities,[6] and others (**Figure 1**).[7] In addition, pyrimidines have found applications in photophysics[8] and polymer chemistry.[8g, 9]

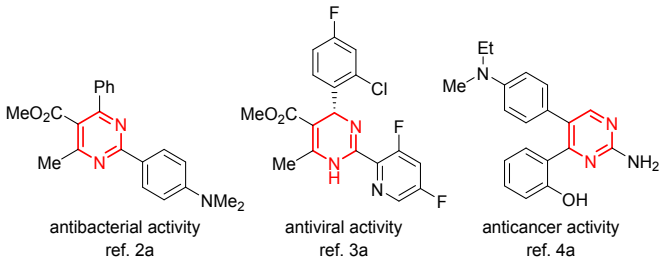
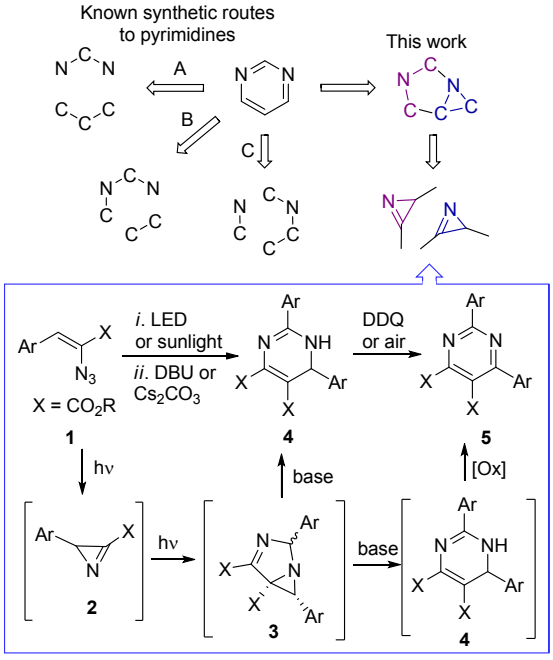


Figure 1. Examples of bioactive pyrimidine derivatives.

There are several basic approaches to the construction of a pyrimidine core (**Scheme 1**). They include the Pinner-like condensation of amidines with 1,3-dicarbonyl compounds (route A), cycloaddition reaction of 1,3-diazadienes (or 1,3,5-triazines) with alkynes or alkenes (route B), cycloaddition reaction of 2-azadienes (or 1,2,3-triazines) with nitriles (route C), and others.[10] Due to the demand for pyrimidine derivatives in various fields, new methods for their synthesis are actively being developed.[11,12] However, they often use specific substrates and/or reagents[11f, 11g, 13] or harsh conditions,[11g, 12e, 13d, 14] and only some of them are suitable for the preparation of functionalized multisubstituted pyrimidine derivatives.



Scheme 1. Synthetic routes to pyrimidines.

In the last decade, vinyl azides, in particular α-azidocinnamates (**Scheme 1**, compound **1**), have been widely utilized as a key three-atom synthon for the formation of nitrogen heterocycles[15] such as pyrroles, pyrazines, indoles, etc. Under thermolysis or photolysis, vinyl azides can produce highly strained three-membered heterocycles – 2*H*-azirines (**Scheme 1**, compound **2**),[16] which can act as dipolarophiles or source of highly reactive dipole species – nitrile ylides.[16-17] In 1998, Meth-Cohn and coworkers studied photolysis of α-azidocinnamates by 300 W Xenon-mercury lamp and mentioned that one of the

[a] Saint Petersburg State University, 7/9 Universitetskaya Nab., Saint Petersburg, 199034 Russian Federation; e-mail's: m.kinzhalov@spbu.ru, n.rostovskiy@spbu.ru

Electronic Supplementary Information (ESI) available: Full details of photochemical experiments, spectroscopic data for prepared compounds and details of the X-ray diffraction studies. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0OB00937A

products observed in the complex reaction mixture, namely 1,3-diazabicyclo[3.1.0]hex-3-ene derivative (**Scheme 1**, compound **3**), can be transformed to a 1,6-dihydropyrimidine derivative under storage or under treatment with triethylamine.[18] Only one example of the 1,6-dihydropyrimidine was described, but its yield was not reported.

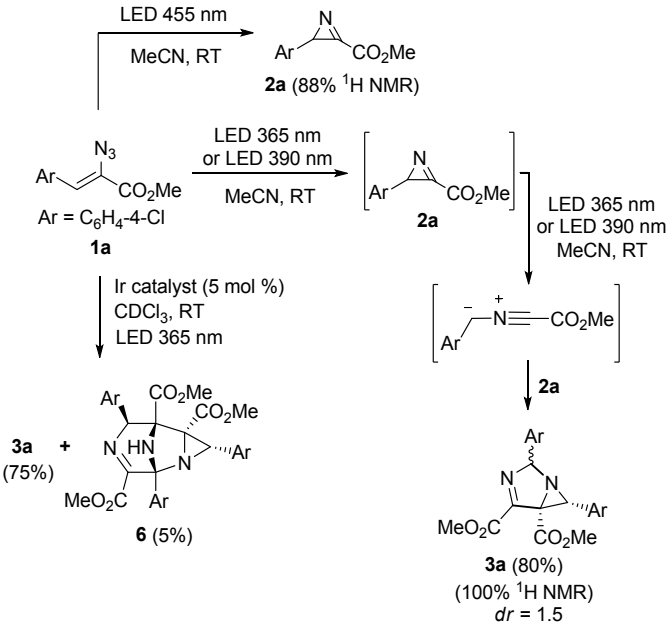
We assumed that the photolysis of α-azidocinnamates followed by the formation of 1,6-dihydropyrimidines and aromatization could be a good candidate for the construction of hard-to-synthesize tetrasubstituted pyrimidine derivatives bearing aryl substituents at the C2 and C4 positions and carbonyl substituents at the C5 and C6 positions. In previous works, a few examples of such pyrimidines were synthesized exclusively by the cycloaddition of dimethyl acetylenedicarboxylate with 1,2-dihydro-1,3,5-triazine,[19] 1,3-diazabuta-1,3-dienes,[20] or 1,2,4-selenodiazoles (**Scheme S1**).[21]

Departing from the previous literature, and in connection with our interests in utilizing 2*H*-azirines and parent vinyl azides for the synthesis of important heterocycles[22] and in the progress of new eco-friendly synthetic methods in organic chemistry,[23] we started the development of a new preparative procedure for the synthesis of tetrasubstituted 1,6-dihydropyrimidines **4** and pyrimidines **5** from α-azidocinnamates (**Scheme 1**).

Results and discussion

Synthesis of intermediates 3 (1,3-diazabicyclo[3.1.0]hex-3-enes). We suggested that the use of the LED lamps, which emit high intensity light in a specific region of the spectrum, would lead to increasing selectivity of α-azidocinnamates photolysis. As a test of this hypothesis, we investigated the photolysis of representative azidocinnamate **1a** by different LEDs (**Figure 2** and **Table S1**). Indeed, the irradiation of the representative azidocinnamate **1a** by blue light (455 nm) in MeCN during 2.5 h at RT afforded only azirine **2a** (88% yield, hereinafter the ^{1}H NMR yields are given unless otherwise stated) (**Scheme 2**). No any other reaction was observed even upon prolonged irradiation of the reaction mixture. An addition of a photoredox catalyst, viz. $[Ru(bpy)_3](BF_4)_2$[24] or $[Ir(ppy)_2(CNC_6H_4\text{-}4\text{-}Cl)_2](OTf)$,[25] to **1a** solution and irradiation also gave azirine **2a** as a single product (**Table S2**). Analogously, the photolysis of azidocinnamates **1b–g** by blue light resulted in the formation of azirines **2b–g** in 65–88% yield (**Table S3**). Unfortunately, α-azidochalcone (**Scheme 1,** X = Bz, Ar = Tol) and azidocinnamate bearing *p*-NO_2 group on the phenyl ring (X = CO_2Me, Ar = 4-$NO_2C_6H_4$) failed to afford the corresponding azirines **2**. The prolonged irradiation of azidocinnamate **1a** by 465 nm light did not lead to any reaction. These data are consistent with Farney and Yoon results of the absence of a photochemical reaction upon irradiation of dienyl azides by 465–470 nm light.[26]

When we carried out irradiation of **1a** by a shorter wavelength LED (425 and 410 nm), the reaction mixture showed the presence of an equimolar mixture of azirine **2a** along with new products – two diastereomeric "dimers" of azirine – 1,3-diazabicyclo[3.1.0]hex-3-enes **3a** (**Figure 2**, **Scheme 2**). A further decrease of the irradiation wavelength up to 395 nm led to a total conversion of **1a** to dimers **3a** after 2.5 h. The irradiation of **1a** by UV-A light (LED 365 nm) also led to a quantitative yield of dimers **3a** (80% isolated yield). Analogously, the photolysis of azidocinnamate **1b** gave dimers **3b** in 70% isolated yield (for details see SI, section S2.3). In order to find out whether azirine **2a** is involved in the formation of "dimers" **3a**, a control experiment was performed. Pure azirine **2a** was irradiated by the UV-A light (LED 365 nm) for 2.5 h, which led to complete conversion of **2a** to dimers **3a**. Hence, "dimers" **3** are the products of photochemical dimerization of azirines **2**. The dimerization probably proceeds through 1,3-dipolar cycloaddition of a nitrile ylide to the C=N bond of the azirine.[18]



Scheme 2. Irradiation of α-azidocinnamate **1a** with 365–455 nm LED.

Thus, we demonstrated for the first time that the outcome of the α-azidocinnamates photolysis depends on the light wavelength employed.[27] While the irradiation by blue light (455 nm) leads to the formation of 2*H*-azirines only, the irradiation by violet (395 nm) or UV-A light (365 nm) results in the transformation of the *in situ* formed 2*H*-azirines to 1,3-diazabicyclo[3.1.0]hexenes.

DOI: 10.1039/D0OB00685A

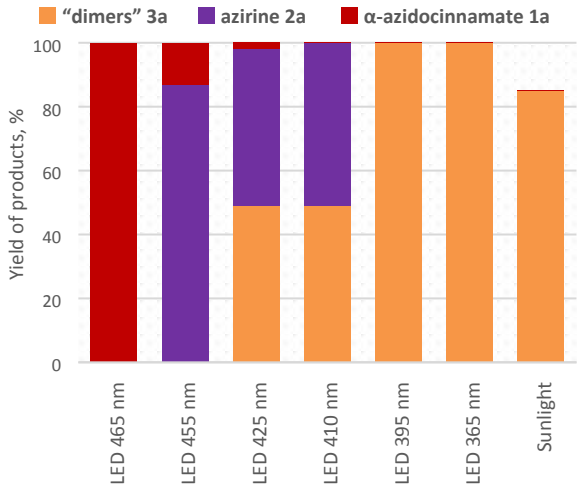


Figure 2. Results of photolysis of α-azidocinnamate **1a** by different light sources for 2.5 h (for details, see **Table S1** in SI).

An addition of a photoredox catalyst, viz. $[Ir(ppy)_2(CNC_6H_4\text{-}4\text{-}Cl)_2](OTf)$[25] (1 mol %), to the solution of α-azidocinnamate **1a** in MeCN and irradiation by UV-A light did not affect the direction of the reaction and the reaction rate as well and led to the generation of **3a** in a quantitative yield after 2.5 h (**Table S6**). At the same time, a change of the solvent from MeCN to $CDCl_3$ and an increase in the catalyst loading (3 mol %) led to reduced selectivity of the photolysis. In this case, one more product, namely tricyclic compound **6** (**Scheme 2**, **Figure 3**), was formed along with dimers **3a** (for details see SI, section S2.4).

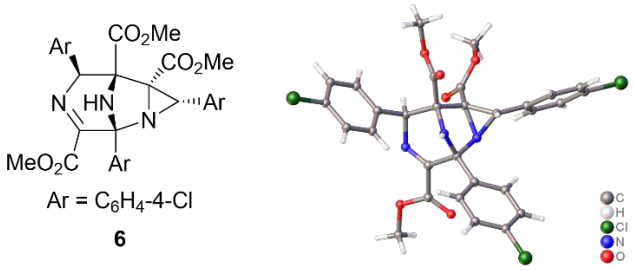


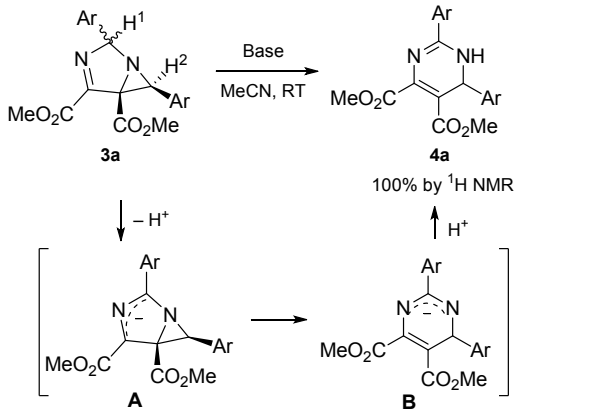
Figure 3. Molecular structure of **6** from single crystal X-ray analysis.

Finally, we showed that the synthesis of "dimers" **3** from α-azidocinnamates **1** can be performed using natural sunlight as a source of light. Irradiation of the solution of representative α-azidocinnamate **1a** in MeCN under natural sunlight for 2.5 h led to the desired dimers **3a** in 85% overall yield (**Figure 2**).

In further experiments, we used the UV-A light LED (365 nm) since the wavelength 365 nm is incorporated in the commercially available photoreactors,[28] which allows to standardize the method for laboratory and industrial use.

Isomerization of 1,3-diazabicyclo[3.1.0]hex-3-enes to 1,6-dihydropyrimidines. As highlighted in the introduction, the "dimers" of azirine can isomerize to 1,6-dihydropyrimidines under Et_3N catalysis,[18] but, to the best of our knowledge, this reaction has not been investigated in detail.

In this study, we observed that isomerization of two diastereomers of **3a** into 1,6-dihydropyrimidine **4a** in MeCN proceeded slowly in the presence of medium-strength organic bases, viz. Et_3N or DABCO, and almost quantitative yield of 1,6-dihydropyrimidine **4a** was achieved after 2.5 h at RT (**Scheme 3**, **Table S7**). The use of a strong organic base (1,8-diazabicyclo [5.4.0]undec-7-ene (DBU)) or medium (*N*-methylmorpholine) for the isomerization of **3a** afforded **4a** quantitatively after 15 min; isolated yields were 93%. At the same time, in the presence of a weak base (pyridine) the isomerization did not occur. The DBU-catalyzed isomerizations of separated diastereomers of **3a** afforded **4a** in nearly quantitative yield in each case. We also tested inorganic bases (K_2CO_3 and Cs_2CO_3) for the isomerization. The reaction proceeded only with Cs_2CO_3 (1 h) to give **4a** in nearly quantitative yield. From the mechanistic point of view, the isomerization probably starts from the removal of more acidic hydrogen atom (H^1) of **3a** to form carbanion intermediate **A**. Further ring opening of aziridine ring followed by protonation leads to dihydropyrimidine **4a**.

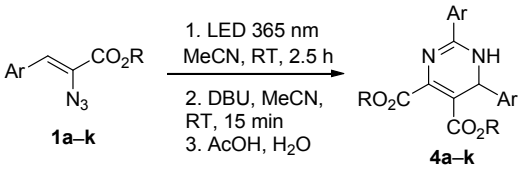


Scheme 3. Isomerization of **3a** into 1,6-dihydropyrimidine **4a**.

Then, 1,6-dihydropyrimidines **4a–k** were synthesized from α-azidocinnamates **1a–k** without isolation of intermediate 1,3-diazabicyclo[3.1.0]hex-3-enes **3** (**Scheme 4**). The exposition of the solutions of α-azidocinnamates **1a–k** in MeCN to UV-A light (LED 365 nm) for 2.5 h and succeeding addition of 0.3 equiv. of DBU in the reaction mixtures led to 1,6-dihydropyrimidines **4a–k**, which were isolated by column chromatography in 70–97% yields (**Table 1**). Dihydropyrimidines **4a–k** are previously unknown compounds, and they were characterized by high-resolution ESI^+-MS, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. It is known that in general there is an equilibrium of 1,4- and 1,6-dihydropyrimidine tautomers in solutions.[10d] The existence of compounds **4** in solutions at room temperature in form of a 1,6-dihydropyrimidine tautomer was confirmed by the ^1H-^1H NOESY NMR spectra of **4d** and **4f** in DMSO-d_6 (**Figures S32 and S37**). In addition, the structures of **4d** and **4f** were confirmed by a single-crystal X-ray diffraction (**Figure 4**). In the structures **4d** and **4f**, the position of hydrogen atom at the nitrogen atom was determined from the difference electron density map. Bond length and bond angle data for **4d** and **4f** are in the expected range (**Tables S12–**

S17). The solid state structures are stabilized by N–H···O intramolecular (**4d**) or intermolecular (**4f**) hydrogen bonds (**Table S14** and **S17**).

Thereby, both in solution and solid state the 1,6-dihydropyrimidine tautomeric form was observed for compounds **4**. We also calculated energies of 1,6- and 1,4-dihydropyrimidine tautomers by DFT method. Indeed, the 1,6-isomer turned out to be 4.4 kcal/mol more stable than the 1,4-isomer (see SI, Section S6).



Scheme 4. One-pot synthesis of 1,6-dihydropyrimidines **4a–k** from α-azidocinnamates **1a–k**.

Table 1. Isolated yields of 1,6-dihydropyrimidines **4a–k** and pyrimidines **5a–k**.

Entry	Ar	R	Yield of **4**,[a] %	Yield of **5**,[b] %
1	4-ClC_6H_4	Me	97 (**4a**)	95 (**5a**)
2	4-BrC_6H_4	Me	93 (**4b**)	95 (**5b**)
3	4-IC_6H_4	Me	70 (**4c**)	81 (**5c**)
4	2-$MeOC_6H_4$	Me	91 (**4d**)	90 (**5d**)
5	4-$MeOC_6H_4$	Me	91 (**4e**)	85 (**5e**)
6	2,4-$Cl_2C_6H_3$	Me	91 (**4f**)	85 (**5f**)
7	4-MeC_6H_4	Me	93 (**4g**)	90 (**5g**)
8	4-FC_6H_4	Me	94 (**4h**)	90 (**5h**)
9	4-$CF_3C_6H_4$	Me	95 (**4i**)	95 (**5i**)
10	naphthalen-2-yl	Me	73 (**4j**)	94 (**5j**)
11	4-$MeOC_6H_4$	*n*-Bu	42 (**4k**)	89 (**5k**)

[a] One-pot procedure from α-azidocinnamate **1**. [b] From dihydropyrimidines **4** using DDQ.

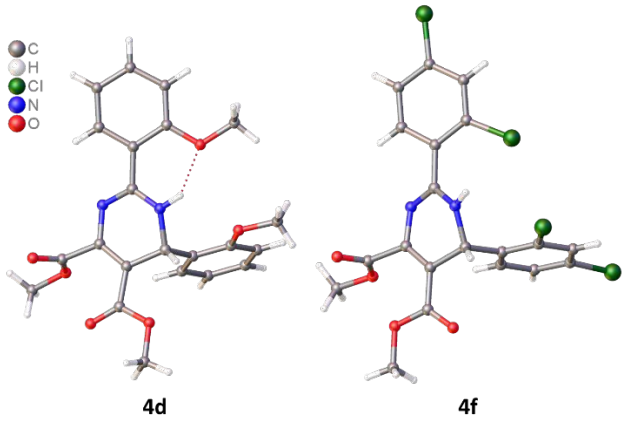
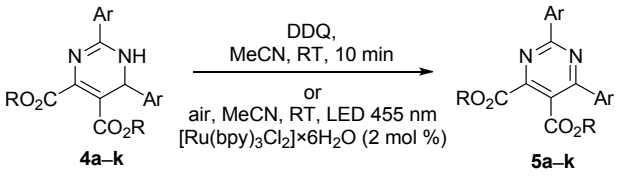


Figure 4. Molecular structures of **4d** and **4f** from single crystal X-ray analysis.

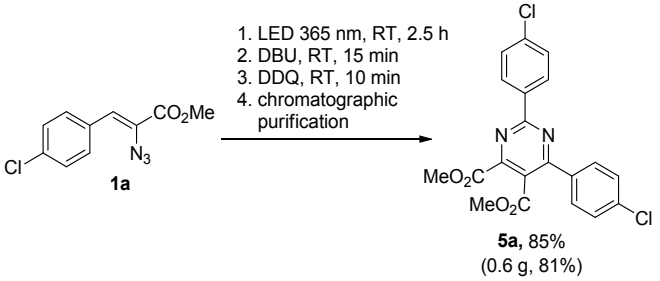
Oxidation of 1,6-dihydropyrimidines to pyrimidines. The aromatization of 1,6-dihydropyrimidines **4a–k** using 1 equiv. of organic oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), proceeded completely in less than ten minutes and led to pyrimidines **5a–k**, which were isolated by column chromatography in 81–95% yields (**Scheme 5**, **Table 1**). Pyrimidines **5a–k** were characterized by high-resolution ESI^+-MS, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy.

In an effort to make the aromatization reaction of 1,6-dihydropyrimidines more suitable for the chemical industry and more environmentally-friendly, several conditions for the oxidation of 1,6-dihydropyrimidine **4a** to pyrimidine **5a** were tested (**Table S8**). Molecular oxygen and air are the most abundant and cheapest oxidants available, and accordingly they are used extensively in organic synthesis.[29] The reaction of dihydropyrimidine **5b** with $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (2 mol %) under air or with bubbling air in MeCN under irradiation with blue LED gave the desired pyrimidine **6b** in 85 % yield after 10 h. The use of bubbling air enriched by oxygen (up to 30% O_2) allowed to reduce reaction time to 4 h with the same yield of the product. In the control experiment, no desired product was observed without the photoredox catalyst or light, indicating that the photoredox catalysis is necessary for the oxidation process (**Table S8**). In addition, when the reaction was performed under an argon atmosphere, no product was observed that proved the participation of molecular oxygen in the reaction (**Table S8**).



Scheme 5. Aromatization of 1,6-dihydropyrimidines **5a–k** to pyrimidines **6a–k**.

One-pot synthesis of pyrimidines from α-azidocinnamates. One-pot reactions are highly valuable in organic synthesis.[30] In this work, a one-pot protocol for the synthesis of pyrimidines **5** from α-azidocinnamates was also developed (**Scheme 6**). In particular, it was found that oxidation of dihydropyrimidines **4** to pyrimidines **5** by DDQ can be accomplished without preliminary removal of DBU. The final one-pot procedure consisted of photolysis of **1a** in acetonitrile, successive treatment with DBU and DDQ in the same solvent and in the same vessel, followed by chromatographic purification. The reaction was carried out on 20 and 850 mg scale and gave pyrimidine **5a** in 81–85% yield.



Scheme 6. One-pot synthesis of pyrimidine **5a** from α-azidocinnamate **1a**.

Conclusion

The irradiation of α-azidocinnamates by blue light (455 nm) leads to the formation of 2*H*-azirines only, while the irradiation by violet (395 nm) or UV-A light (365 nm) results in the transformation of the *in situ* formed 2*H*-azirines to 1,3-

DOI: 10.1039/D0OB00693A

diazabicyclo[3.1.0]hexenes. Based on these results a one-pot procedure for the synthesis of tetrasubstituted dihydropyrimidine and pyrimidine derivatives from α-azidocinnamates was developed. The synthesis consists of the following stages: (*i*) LED light induced formation of 1,3-diazabicyclo[3.1.0]hex-3-enes, (*ii*) DBU-catalyzed isomerization of 1,3-diazabicyclo[3.1.0]hex-3-enes to 1,6-dihydropyrimidines, (*iii*) aromatization of 1,6-dihydropyrimidines using DDQ. A successful use of sunlight at the first stage, Cs_2CO_3 at the second stage, and air at the third stage was also demonstrated.

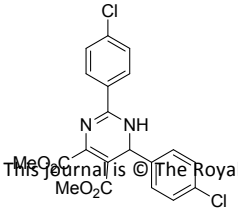
Experimental

Melting points were determined on a melting point apparatus SMP30. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 spectrometer in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI) mass spectra were measured on a Bruker MaXis mass spectrometer. Single crystal X-ray data were collected by means of Agilent Technologies SuperNova (Single source at offset/far, HyPix3000), Agilent Technologies SuperNova (Dual, Cu at zero, Atlas) and Agilent Technologies Xcalibur (Mo, Eos) diffractometers. Crystallographic data for the structures **4d** (CCDC 1994004), **4f** (CCDC 1994005) and **6** (CCDC 1994003) have been deposited with the Cambridge Crystallographic Data Centre. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on Macherey-Nagel silica gel 60 M (0.04–0.063 mm). Acetonitrile was distilled from P_2O_5 and stored over anhydrous K_2CO_3. Commercially available DBU and DDQ were used. **1a**,**b**,**d**–**j** were prepared by the reported procedure.[15c] Their spectral data matched that reported in the literature.[15c, 15d, 15g] Spectral data for α-azidocinnamates **1c**,**k**, azirines **2a**–**g**, 1,3-diazabicyclo[3.1.0]hex-3-enes **3a**,**b** and compound **6** are included in the SI (sections S2 and S7).

General procedure for the synthesis of dihydropyrimidines 4a–k

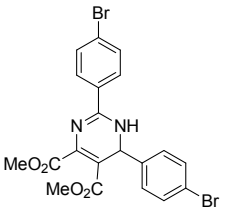
Azidocinnamate **1** (25 mg, 0.076–0.114 mmol) was dissolved in MeCN (0.7 mL) in an NMR tube or a Pyrex screw cap tube. The solution was purged by argon for 5–10 min and then irradiated with 365 nm LED (3W, the LED was placed opposite to the solution at a distance of 2 cm from the tube) at RT under stirring for 2.5–14 h (control by TLC). After that, DBU (2.5 μL, 0.3 equiv) was added, and the reaction mixture was stirred at RT for 15 min. The reaction mixture was poured into water (3 mL) acidified with AcOH (3 μL). Product **4** was extracted with EtOAc (2×2 mL) and dried with Na_2SO_4. The solvent was removed on a rotary evaporator, and the product was purified by column chromatography on silica gel (PE – EtOAc, 3 : 1).

Dimethyl 2,6-bis(4-chlorophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4a)



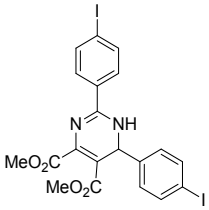
Yellow oil (21 mg, yield 97%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.61 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 5.56 (s, 1H, CH), 7.04 (br s, 1H, NH), 7.27–7.33 (m, 6H, H_{Ar}), 7.64 (d, *J* = 8.5 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 51.9, 52.7, 52.9, 105.2, 128.3, 128.7, 128.9 (2C), 129.2, 131.2, 134.5, 138.4, 142.0, 149.0, 157.0, 165.0, 168.1. HR ESI$^+$-MS, *m/z*: [M+H]$^+$ calcd for $C_{20}H_{17}N_2{}^{35}Cl_2O_4^+$, 419.0560; found, 419.0581.

Dimethyl 2,6-bis(4-bromophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4b)



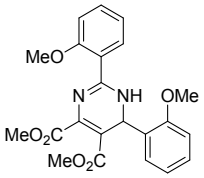
Yellow oil (21 mg, yield 93%).^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.63 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.72 (br s, 1H, NH), 7.26 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.47 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.51 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.59 (d, *J* = 8.4 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 52.0, 52.7, 53.1, 105.5, 122.9, 127.1, 128.6, 128.8, 131.6, 132.0, 132.3, 142.5, 148.9, 157.1, 164.9, 168.0. HR ESI$^+$-MS, *m/z*: [M+H]$^+$ calcd for $C_{20}H_{17}N_2{}^{79}Br^{81}BrO_4^+$, 508.9530; found, 508.9522.

Dimethyl 2,6-bis(4-iodophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4c)



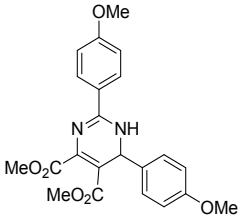
Yellow solid (16 mg, yield 70%), mp 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.63 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.55 (s, 1H, CH), 6.71 (br s, 1H, NH), 7.12 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.44 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.67 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.72 (d, *J* = 8.4 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 52.0, 52.7, 53.4, 94.5, 99.3, 105.5, 128.7, 128.8, 132.2, 137.9, 138.2, 143.1, 148.9, 157.2, 165.0, 168.0. HR ESI$^+$-MS, *m/z*: [M+H]$^+$ calcd for $C_{20}H_{17}I_2N_2O_4^+$, 602.9273; found, 602.9272.

Dimethyl 2,6-bis(2-methoxyphenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4d)



Yellow solid (20 mg, yield 91%), mp 190–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.65 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.98 (s, 6H, CH_3), 6.01 (s, 1H, CH), 6.88–7.02 (m, 4H, H_{Ar}), 7.24–7.41 (m, 3H, H_{Ar}), 8.32–8.36 (m, 1H, H_{Ar}), 8.74 (br s, 1H, NH). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 48.8, 51.6, 52.5, 55.4, 56.0, 99.8, 110.4, 111.6, 120.2, 121.1, 121.4, 127.8, 129.1, 130.0, 132.2, 133.0, 152.2, 156.1, 157.8, 158.0, 165.6, 168.6. HR ESI$^+$-MS, *m/z*: [M+H]$^+$ calcd for $C_{22}H_{23}N_2O_6^+$, 411.1551; found, 411.1551.

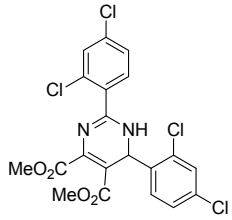
Dimethyl 2,6-bis(4-methoxyphenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4e)



Yellow oil (20 mg, yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.64 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 5.56 (s, 1H, CH), 6.35 (br s, 1H, NH), 6.86 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.89 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.34 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.72 (d, *J* = 8.9 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 51.6, 52.4, 52.9, 55.2,

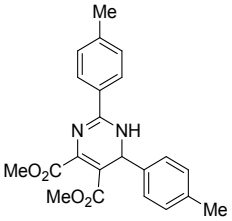
55.3, 104.9, 113.9, 114.2, 125.3, 128.1, 129.1, 136.5, 149, 157.4, 159.6, 162.6, 165.4, 168.3. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{22}H_{23}N_2O_6^+$, 411.1551; found, 411.1571.

Dimethyl 2,6-bis(2,4-dichlorophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4f)



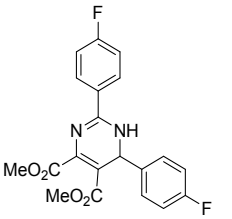
Yellow solid (21 mg, yield 94%), mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.66 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 6.08 (s, 1H, CH), 6.90 (br s, 1H, NH), 7.26–7.34 (m, 3H, H_{Ar}), 7.41–7.45 (m, 2H, H_{Ar}), 7.66 (d, *J* = 8.6 Hz, 1H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 49.4, 52.2, 52.8, 103.4, 127.7, 128.3, 129.7, 130.26, 130.34, 130.5, 132.5, 132.7, 132.9, 135.3, 136.5, 138.1, 150.4, 156.8, 164.5, 167.3. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{20}H_{15}N_2{}^{35}Cl_3{}^{37}ClO_4^+$, 488.9751; found, 488.9750.

Dimethyl 2,6-bis(4-methylphenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4g)



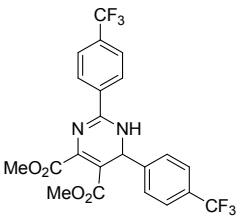
Yellow solid (20 mg, yield 93%), mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.55 (br s, 1H, NH), 7.13 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.17 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.30 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.63 (d, *J* = 8.1 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 21.1, 21.5, 51.7, 52.5, 53.4, 105.5, 126.9, 127.2, 129.4, 129.6, 130.3, 138.3, 141.1, 142.6, 149.3, 157.9, 165.4, 168.3. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{22}H_{23}N_2O_4^+$, 379.1652; found, 379.1677.

Dimethyl 2,6-bis(4-fluorophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4h)



Yellow oil (20 mg, yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.64 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.61 (s, 1H, CH), 6.62 (br s, 1H, NH), 7.00–7.09 (m, 4H, H_{Ar}), 7.36–7.39 (m, 2H, H_{Ar}), 7.73–7.76 (m, 2H, H_{Ar}). ^{13}C{^{1}H,^{19}F} NMR (100 MHz, $CDCl_3$, δ): 51.8, 52.6, 52.8, 105.3, 115.8, 115.9, 128.6, 129.0, 129.6, 139.6, 149.0, 157.0, 162.7, 165.1 (2C), 168.2. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{20}H_{17}N_2F_2O_4^+$, 387.1151; found, 387.1163.

Dimethyl 2,6-bis(4-(trifluoromethyl)phenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4i)

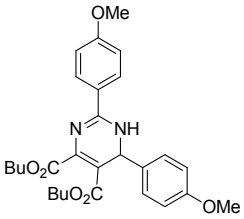


Yellow low-melting solid (21 mg, yield 95%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.67 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 5.75 (s, 1H, CH), 6.78 (br s, 1H, NH), 7.55 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.61–7.69 (m, 4H, H_{Ar}), 7.89 (d, *J* = 8.3 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 52.1, 52.8, 53.2, 105.7, 123.5 (q, *J* = 273 Hz), 125.7, 126.2, 127.3, 127.7, 133.7, 134.0, 135.9, 146.9, 148.8, 156.8, 164.7, 167.9 (one signal of CF_3 group is not observed). ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$, δ): –63.10, –62.73. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{22}H_{17}N_2F_6O_4^+$, 487.1087; found, 487.1090.

Dimethyl 2,6-bis(naphthalen-2-yl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4j)

Yellow low-melting solid (16 mg, yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.61 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 5.81 (s, 1H, CH), 6.95 (br s, 1H, NH), 7.45–7.56 (m, 4H, H_{Ar}), 7.61 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.75–7.86 (m, 8H, H_{Ar}), 8.21 (s, 1H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 51.8, 52.6, 54.0, 105.4, 123.7, 124.8, 125.9, 126.3 (2C), 126.7, 127.6, 127.7, 127.9 (2C), 128.3, 128.5, 128.9, 129.2, 130.2, 132.5, 133.26, 133.30, 134.9, 141.1, 149.3, 158.1, 165.3, 168.3. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{28}H_{23}N_2O_4^+$, 451.1652; found, 451.1647.

Dibutyl 2,6-bis(4-methoxyphenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (4k)

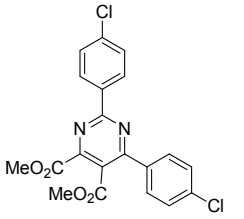


Yellow oil (9 mg, yield 42%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.88 (t, *J* = 7.4 Hz, 3H, Bu), 0.98 (t, *J* = 7.4 Hz, 3H, Bu), 1.23–1.32 (m, 4H, Bu), 1.42–1.57 (m, 4H, Bu), 1.73–1.80 (m, 2H, Bu), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.98–4.11 (m, 2H, OCH_2), 4.26–4.38 (m, 2H, OCH_2), 5.57 (s, 1H, CH), 6.36 (br s, 1H, NH), 6.85–6.92 (m, 4H, H_{Ar}), 7.36 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.72 (d, *J* = 8.7 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 13.6, 13.7, 19.0, 19.1, 30.4, 30.5, 53.1, 55.2, 55.4, 64.4, 65.5, 105.1, 113.9, 114.2, 125.6, 128.3, 129.1, 136.7, 149.3, 157.0, 159.6, 162.6, 165.1, 168.1. HR ESI$^+$-MS, *m/z*: $[M+H]^+$ calcd for $C_{28}H_{35}N_2O_6^+$, 495.2490; found, 495.2484.

General procedure for the synthesis of pyrimidines 5a–k

To a solution of **4** (0.018–0.053 mmol) in EtOAc (1 mL) DDQ (1 equiv.) was added. The reaction mixture was stirred at RT for 10 min, EtOAc was evaporated, and the product was purified by column chromatography on silica gel (PE – EtOAc, 10 : 1).

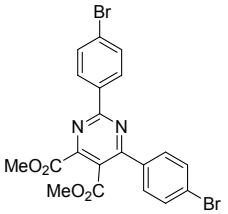
Dimethyl 2,6-bis(4-chlorophenyl)pyrimidine-4,5-dicarboxylate (5a)



Colorless solid (20 mg, yield 95%), mp 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.85 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 7.47–7.52 (m, 4H, H_{Ar}), 7.75 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 8.52 (d, *J* = 8.7 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.2, 53.6, 123.0, 129.01, 129.04, 130.0, 130.3, 134.5, 135.3, 137.3, 138.3, 155.2, 156.4, 163.8, 164.4, 167.0. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{14}N_2{}^{35}Cl_2NaO_4^+$, 439.0223; found, 439.0245.

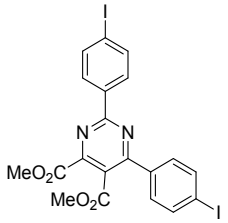
Dimethyl 2,6-bis(4-bromophenyl)pyrimidine-4,5-dicarboxylate (5b)

DOI: 10.1039/D0OB00934A



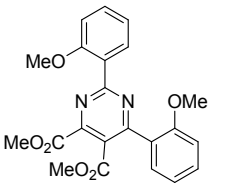
Colorless solid (20 mg, yield 95%), mp 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.85 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 7.64–7.69 (m, 6H, H_{Ar}), 8.44 (d, J = 8.6 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.2, 53.6, 123.1, 125.7, 127.0, 130.2, 130.4, 131.98, 132.00, 134.9, 135.7, 155.3, 163.9, 164.5, 164.7, 167.0. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{14}N_2{}^{79}Br^{81}BrNaO_4^+$, 528.9193; found, 528.9191.

Dimethyl 2,6-bis(4-iodophenyl)-1,6-dihydropyrimidine-4,5-dicarboxylate (5c)



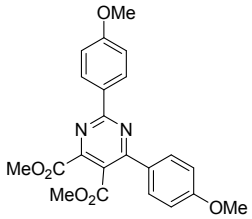
Yellow solid (13 mg, yield 81%), mp 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.85 (s, 3H, CH_3), 4.05 (s, 3H, CH_3), 7.52 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.84–7.89 (m, 4H, H_{Ar}), 8.28 (d, J = 8.4 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.2, 53.6, 97.9, 99.5, 123.1, 130.2, 130.4, 135.5, 136.3, 137.95, 137.99, 155.3, 164.1, 164.60, 164.63, 167.0. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{14}N_2I_2NaO_4^+$, 622.8935; found, 622.8964.

Dimethyl 2,6-bis(2-methoxyphenyl)pyrimidine-4,5-dicarboxylate (5d)



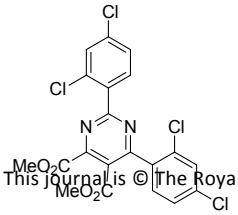
Yellow solid (18 mg, yield 90%), mp 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.74 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 4.01 (s, 3H, CH_3), 6.93 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.01–7.14 (m, 3H, H_{Ar}), 7.41–7.47 (m, 2H, H_{Ar}), 7.67–7.69 (m, 1H, H_{Ar}), 7.81–7.83 (m, 1H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 52.4, 53.3, 55.1, 56.1, 110.4, 112.3, 120.7, 121.2, 122.3, 126.5, 127.4, 131.2, 131.7, 131.8, 131.9, 156.47, 156.53, 158.1, 164.1, 165.8, 166.1, 166.3. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{20}N_2NaO_6^+$, 431.1214; found, 431.1213.

Dimethyl 2,6-bis(4-methoxyphenyl)pyrimidine-4,5-dicarboxylate (5e)



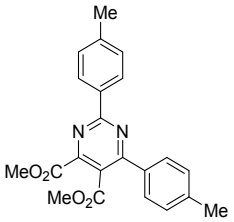
Colorless solid (17 mg, yield 85%), mp 162–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.85 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.04 (s, 3H, CH_3), 7.00–7.03 (m, 4H, H_{Ar}), 7.81 (d, J = 8.9 Hz, 2H, H_{Ar}), 8.54 (d, J = 8.9 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 52.9, 53.4, 55.4 (2C), 114.0, 114.1, 121.5, 129.0, 129.5, 130.4, 130.7, 155.0, 161.8, 162.7, 164.2, 164.6, 165.2, 167.9. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{20}N_2NaO_6^+$, 431.1214; found, 431.1224.

Dimethyl 2,6-bis(2,4-dichlorophenyl)pyrimidine-4,5-dicarboxylate (5f)



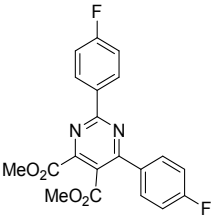
Yellow low-melting solid (18 mg, yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.77 (s, 3H, CH_3), 4.05 (s, 3H), 7.38–7.44 (m, 3H, H_{Ar}), 7.52–7.55 (m, 2H, H_{Ar}), 7.88 (d, J = 8.4 Hz, 1H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.2, 53.7, 123.5, 127.4, 128.8, 129.7, 130.8, 130.9, 131.2, 133.15, 133.24, 134.2, 134.29, 134.32, 136.6, 137.1, 156.4, 164.4, 164.6, 164.9. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ $C_{20}H_{12}N_2{}^{35}Cl_4NaO_4^+$, 508.9414; found, 508.9401.

Dimethyl 2,6-bis(4-methylphenyl)pyrimidine-4,5-dicarboxylate (5g)



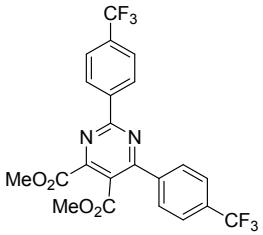
Yellow solid (18 mg, yield 90%), mp 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.45 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.05 (s, 3H, CH_3), 7.32 (d, J = 8.1 Hz, 4H, H_{Ar}), 7.72 (d, J = 8.1 Hz, 2H, H_{Ar}), 8.48 (d, J = 8.1 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 21.5, 21.6, 52.9, 53.4, 122.4, 128.6, 128.9, 129.4 (2C), 133.6, 134.3, 141.0, 142.2, 154.9, 164.6, 165.1, 165.3, 167.6. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{20}N_2NaO_4^+$, 399.1315; found, 399.1331.

Dimethyl 2,6-bis(4-fluorophenyl)pyrimidine-4,5-dicarboxylate (5h)



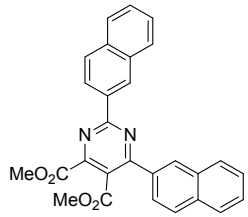
Colorless solid (18 mg, yield 90%), mp 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.85 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 7.17–7.24 (m, 4H, H_{Ar}), 7.80–7.83 (m, 2H, H_{Ar}), 8.58–8.61 (m, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.1, 53.5, 115.8, 115.9, 122.7, 130.9, 131.2, 132.2, 133.0, 155.1, 163.7, 164.37, 164.41, 164.8, 165.4, 167.2. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{14}N_2F_2NaO_4^+$, 407.0814; found, 407.0816.

Dimethyl 2,6-bis(4-(trifluoromethyl)phenyl)pyrimidine-4,5-dicarboxylate (5i)



Colorless solid (20 mg, yield 95%), mp 119–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.87 (s, 3H, CH_3), 4.10 (s, 3H, CH_3), 7.78–7.84 (m, 4H, H_{Ar}), 7.93 (d, J = 8.4 Hz, 2H, H_{Ar}), 8.71 (d, J = 8.2 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 53.3, 53.7, 123.7 (q, J = 273 Hz), 123.9 (q, J = 273 Hz), 123.93, 125.7 (2C), 129.1, 129.3, 132.7 (q, J = 32.9 Hz), 133.5 (q, J = 32.5 Hz), 139.0, 140.1, 155.4, 163.5, 164.44, 164.46, 166.6. ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$, δ): –62.94, –62.93. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{14}N_2F_6NaO_4^+$, 507.0750; found, 507.0753.

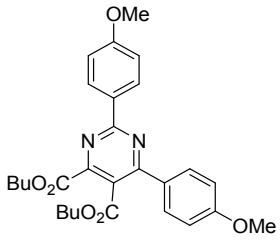
Dimethyl 2,6-bis(napthalen-2-yl)pyrimidine-4,5-dicarboxylate (5j)



Colorless solid (15 mg, yield 94%), mp 111–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.86 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 7.54–7.66 (m, 4H, H_{Ar}), 7.92–8.08 (m, 7H, H_{Ar}), 8.39 (s, 1H, H_{Ar}), 8.72 (dd, J = 4.3 Hz, 1.7 Hz, 1H, H_{Ar}), 9.20 (s, 1H, H_{Ar}). ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$, δ): 53.0, 53.5, 123.1, 125.3, 125.4, 126.4, 126.8, 127.6, 127.7, 127.8, 128.4, 128.5, 128.9, 129.2, 129.5, 129.8, 133.0, 133.2, 133.6, 134.2, 134.4, 135.2, 155.2, 164.7, 165.1, 165.5, 167.5. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{20}N_2NaO_4^+$, 471.1315; found, 471.1302.

Di-*n*-butyl 2,6-bis(4-methoxyphenyl)pyrimidine-4,5-dicarboxylate (5k)



Colorless solid (8 mg, yield 89%), mp 49–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.87 (t, *J* = 7.4 Hz, 3H, Bu), 1.02 (t, *J* = 7.4 Hz, 3H, Bu), 1.18–1.26 (m, 2H, Bu), 1.48–1.61 (m, 4H, Bu), 1.79–1.86 (m, 2H, Bu), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.24 (t, *J* = 6.6 Hz, 2H, OCH_2), 4.45 (t, *J* = 6.7 Hz, 2H, OCH_2), 7.02 (d, *J* = 8.8 Hz, 4H, H_{Ar}), 7.80 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.56 (d, *J* = 8.8 Hz, 2H, H_{Ar}). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 13.6, 13.7, 18.9, 19.1, 30.2, 30.5, 55.4 (2C), 66.0, 66.5, 113.9, 114.0, 121.6, 129.1, 129.8, 130.4, 130.7, 155.7, 161.6, 162.6, 164.0, 164.7, 165.0, 167.4. HR ESI$^+$-MS, *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{32}N_2NaO_6^+$, 515.2153; found, 515.2148.

One-pot procedure for the synthesis of pyrimidine 5a

Azidocinnamate **1a** (20 mg, 0.084 mmol) was dissolved in MeCN (0.5 mL) in an NMR tube. The solution was purged with argon for 10 min and then irradiated with 365 nm LED (3W, the LED was placed opposite to the solution at a distance of 2 cm from the tube) at RT under stirring for 2.5 h (control by TLC). Then, DBU (13 mg of 10% solution in MeCN (8.5 μmol)) was added, and the reaction mixture was stirred at RT for 15 min. After the reaction completion (control by TLC), DDQ (9.5 mg, 0.042 mmol) was added. After 10 min stirring at RT, the reaction mixture was poured into water (3 mL) acidified with AcOH (3 μL). The product was extracted with EtOAc (3×2 mL), organic layers were washed with 5% $NaHCO_3$ (3×1 mL) and dried with Na_2SO_4. The drying agent was filtered off, the solvent was removed on a rotary evaporator, and the product was purified by column chromatography on silica gel (PE – EtOAc, 3 : 1) to give **5a** (15 mg, yield 85%). According to this protocol (LED 395 nm, 30 W, 2.5 h, in a Pyrex tube), using proportional amounts of reagents and solvents, the reaction of 850 mg of **1a** was carried out to give 605 mg (yield 81%) of pyrimidine **5a.**

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support of the Russian Science Foundation (№ 19-73-10090). This research used resources of the Magnetic Resonance Research Centre, Chemical Analysis and Materials Research Centre, Centre for X-ray Diffraction Studies, and Chemistry Educational Centre of the Research Park of St. Petersburg State University.

Notes and references

View Article Online
DOI: 10.1039/D0OB00693A

1. (a) I. M. Lagoja, *Chem. Biodivers.*, 2005, **2**, 1–50. DOI: 10.1002/cbdv.200490173; (b) S. Kumar and B. Narasimhan, *Chem. Cent. J.*, 2018, **12**, 38. DOI: 10.1186/s13065-018-0406-5; (c) V. Sharma, N. Chitranshi and A. K. Agarwal, *Int. J. Med. Chem.*, 2014, **2014**, 31. DOI: 10.1155/2014/202784.
2. (a) A. R. Gholap, K. S. Toti, F. Shirazi, M. V. Deshpande and K. V. Srinivasan, *Tetrahedron*, 2008, **64**, 10214–10223. DOI: 10.1016/j.tet.2008.08.033; (b) M. B. Deshmukh, S. M. Salunkhe, D. R. Patil and P. V. Anbhule, *Eur. J. Med. Chem.*, 2009, **44**, 2651–2654. DOI: 10.1016/j.ejmech.2008.10.018; (c) B. Parrino, D. Schillaci, I. Carnevale, E. Giovannetti, P. Diana, G. Cirrincione and S. Cascioferro, *Eur. J. Med. Chem.*, 2019, **161**, 154–178. DOI: 10.1016/j.ejmech.2018.10.036; (d) S. Chitra, D. Devanathan and K. Pandiarajan, *Eur. J. Med. Chem.*, 2010, **45**, 367–371. DOI: 10.1016/j.ejmech.2009.09.018; (e) C. Mallikarjunaswamy, L. Mallesha, D. G. Bhadregowda and O. Pinto, *Arab. J. Chem.*, 2017, **10**, S484–S490. DOI: 10.1016/j.arabjc.2012.10.008.
3. (a) K. Deres, C. H. Schröder, A. Paessens, S. Goldmann, H. J. Hacker, O. Weber, T. Krämer, U. Niewöhner, U. Pleiss, J. Stoltefuss, E. Graef, D. Koletzki, R. N. A. Masantschek, A. Reimann, R. Jaeger, R. Groß, B. Beckermann, K.-H. Schlemmer, D. Haebich and H. Rübsamen-Waigmann, *Science*, 2003, **299**, 893. DOI: 10.1126/science.1077215; (b) S. Bai, S. Liu, Y. Zhu and Q. Wu, *Tetrahedron Lett.*, 2018, **59**, 3179–3183. DOI: 10.1016/j.tetlet.2018.07.020.
4. (a) F. Xie, H. Zhao, L. Zhao, L. Lou and Y. Hu, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 275–278. DOI: 10.1016/j.bmcl.2008.09.067; (b) A. Ghith, K. M. Youssef, N. S. M. Ismail and K. A. M. Abouzid, *Bioorg. Chem.*, 2019, **83**, 111–128. DOI: 10.1016/j.bioorg.2018.10.008; (c) M. K. Abd elhameid, N. Ryad, A.-S. My, M. R. mohammed, M. M. Ismail and S. El Meligie, *Chem. Pharm. Bull.*, 2018, **66**, 939–952. DOI: 10.1248/cpb.c18-00269; (d) C. Sun, C. Chen, S. Xu, J. Wang, Y. Zhu, D. Kong, H. Tao, M. Jin, P. Zheng and W. Zhu, *Bioorg. Med. Chem.*, 2016, **24**, 3862–3869. DOI: 10.1016/j.bmc.2016.06.032; (e) N. Kaur, K. Kaur, T. Raj, G. Kaur, A. Singh, T. Aree, S.-J. Park, T.-J. Kim, N. Singh and D. O. Jang, *Tetrahedron*, 2015, **71**, 332–337. DOI: 10.1016/j.tet.2014.11.039; (f) J. Jadhav, A. Juvekar, R. Kurane, S. Khanapure, R. Salunkhe and G. Rashinkar, *Eur. J. Med. Chem.*, 2013, **65**, 232–239. DOI: 10.1016/j.ejmech.2013.04.021.
5. (a) H.-H. Lu, P. Xue, Y.-Y. Zhu, X.-L. Ju, X.-J. Zheng, X. Zhang, T. Xiao, C. Pannecouque, T.-T. Li and S.-X. Gu, *Bioorg. Med. Chem.*, 2017, **25**, 2491–2497. DOI: 10.1016/j.bmc.2017.03.009; (b) K. Jin, Y. Sang, E. De Clercq, C. Pannecouque and G. Meng, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3491–3495. DOI: 10.1016/j.bmcl.2018.10.010.
6. D. Kumar, S. I. Khan, B. L. Tekwani, P. Ponnan and D. S. Rawat, *Eur. J. Med. Chem.*, 2015, **89**, 490–502. DOI: 10.1016/j.ejmech.2014.10.061.
7. (a) P. Liu, Y. Yang, Y. Tang, T. Yang, Z. Sang, Z. Liu, T. Zhang and Y. Luo, *Eur. J. Med. Chem.*, 2019, **163**, 169–182. DOI: 10.1016/j.ejmech.2018.11.054; (b) W. D. Shipe, S. S. Sharik, J.

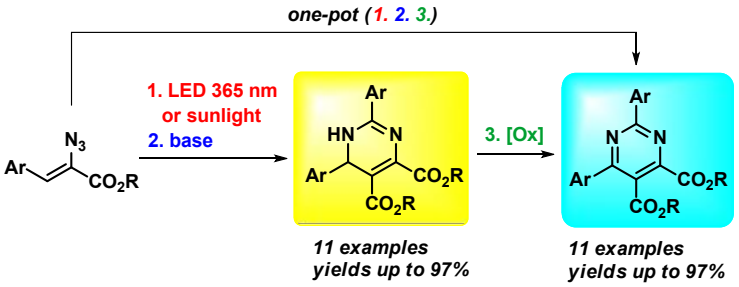
C. Barrow, G. B. McGaughey, C. R. Theberge, J. M. Uslaner, Y. Yan, J. J. Renger, S. M. Smith, P. J. Coleman and C. D. Cox, *J. Med. Chem.*, 2015, **58**, 7888–7894. DOI: 10.1021/acs.jmedchem.5b00983; (c) S. N. Mokale, S. S. Shinde, R. D. Elgire, J. N. Sangshetti and D. B. Shinde, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4424–4426. DOI: 10.1016/j.bmcl.2010.06.058; (d) M. Teleb, F.-X. Zhang, J. Huang, V. M. Gadotti, A. M. Farghaly, O. M. AboulWafa, G. W. Zamponi and H. Fahmy, *Bioorg. Med. Chem.*, 2017, **25**, 1926–1938. DOI: 10.1016/j.bmc.2017.02.015; (e) H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi and K. Aisaka, *J. Med. Chem.*, 1989, **32**, 2399–2406. DOI: 10.1021/jm00130a029.

8. (a) K. Itami, D. Yamazaki and J.-i. Yoshida, *J. Am. Chem. Soc.*, 2004, **126**, 15396–15397. DOI: 10.1021/ja044923w; (b) S. Achelle, J. Rodríguez-López, N. Cabon and F. R.-l. Guen, *RSC Adv.*, 2015, **5**, 107396–107399. DOI: 10.1039/C5RA21514E; (c) Y. Kubota, Y. Ozaki, K. Funabiki and M. Matsui, *J. Org. Chem.*, 2013, **78**, 7058–7067. DOI: 10.1021/jo400879g; (d) Y. Kubota, K. Kasatani, T. Niwa, H. Sato, K. Funabiki and M. Matsui, *Chem. Eur. J.*, 2016, **22**, 1816–1824. DOI: 10.1002/chem.201503625; (e) X. Wang, Q. Liu, F. Qi, L. Li, H.-D. Yu, Z. Liu and W. Huang, *Dalton Trans.*, 2016, **45**, 17274–17280. DOI: 10.1039/C6DT03469A; (f) Y. Kubota, K. Kasatani, H. Takai, K. Funabiki and M. Matsui, *Dalton Trans.*, 2015, **44**, 3326–3341. DOI: 10.1039/C4DT03318C; (g) H. Nitadori, T. Takahashi, A. Inagaki and M. Akita, *Inorg. Chem.*, 2012, **51**, 51–62. DOI: 10.1021/ic200291t; (h) P. A. Scattergood, A. M. Ranieri, L. Charalambou, A. Comia, D. A. W. Ross, C. R. Rice, S. J. O. Hardman, J.-L. Heully, I. M. Dixon, M. Massi, F. Alary and P. I. P. Elliott, *Inorg. Chem.*, 2020, **59**, 1785–1803. DOI: 10.1021/acs.inorgchem.9b03003; (i) S. Ellairaja, N. Krithiga, S. Ponmariappan and V. S. Vasantha, *J. Agric. Food Chem.*, 2017, **65**, 1802–1812. DOI: 10.1021/acs.jafc.6b04790.
9. Y. Maimaiti, N. Dongmulati, S. Baikeri, C. Yang, X. Wei and X. Maimaitiyiming, *Mater. Chem. Phys.*, 2019, **223**, 569–575. DOI: 10.1016/j.matchemphys.2018.11.016.
10. (a) M. D. Hill and M. Movassaghi, *Chem. Eur. J.*, 2008, **14**, 6836–6844. DOI: 10.1002/chem.200800014; (b) M. Radi, S. Schenone and M. Botta, *Org. Biomol. Chem.*, 2009, **7**, 2841–2847. DOI: 10.1039/B906445A; (c) M. Mahfoudh, R. Abderrahim, E. Leclerc and J.-M. Campagne, *Eur. J. Org. Chem.*, 2017, **2017**, 2856–2865. DOI: 10.1002/ejoc.201700008; (d) H. Cho, *HETEROCYCLES*, 2013, **87**, 1441. DOI: 10.3987/REV-13-771.
11. (a) J. Chen, H. Meng, F. Zhang, F. Xiao and G.-J. Deng, *Green Chem.*, 2019, **21**, 5201–5206. DOI: 10.1039/C9GC02077B; (b) E. Schmitt, B. Rugeri, A. Panossian, J.-P. Vors, S. Pazenok and F. R. Leroux, *Org. Lett.*, 2015, **17**, 4510–4513. DOI: 10.1021/acs.orglett.5b02184; (c) S. Lee, J. Sim, H. Jo, M. Viji, L. Srinu, K. Lee, H. Lee, V. Manjunatha and J.-K. Jung, *Org. Biomol. Chem.*, 2019, **17**, 8067–8070. DOI: 10.1039/C9OB01629E; (d) T. Xie, Y.-W. Zhang, L.-L. Liu, Z.-L. Shen, T.-P. Loh and X.-Q. Chu, *Chem. Commun.*, 2018, **54**, 12722–12725. DOI: 10.1039/C8CC07409G; (e) L. Su, K. Sun, N. Pan, L. Liu, M. Sun, J. Dong, Y. Zhou and S.-F. Yin, *Org. Lett.*, 2018, **20**, 3399–3402. DOI: 10.1021/acs.orglett.8b01324; (f) C. H. Low, J. N. Rosenberg, M. A. Lopez and T. Agapie, *J. Am. Chem. Soc.*, 2018, **140**, 11906–11910. DOI: 10.1021/jacs.8b07418; (g) S. Wang, N. Luo, Y. Li and C. Wang, *Org. Lett.*, 2019, **21**, 4544–4548. DOI: 10.1021/acs.orglett.9b01436; (h) R. Mondal, S. Sinha, S. Das, G. Chakraborty and N. D. Paul, *Adv. Synth. Catal.*, 2020, **362**, 594–600. DOI: 10.1002/adsc.201901172; (i) T. Shi, F. Qin, Q. Li and W. Zhang, *Org. Biomol. Chem.*, 2018, **16**, 9487–9491. DOI: 10.1039/C8OB02694G; (j) E. Szennyes, É. Bokor, P. Langer, G. Gyémánt, T. Docsa, Á. Sipos and L. Somsák, *New J. Chem.*, 2018, **42**, 17439–17446. DOI: 10.1039/C8NJ04035D; (k) K. P. Cheremnykh, V. A. Savelyev, M. A. Pokrovskii, D. S. Baev, T. G. Tolstikova, A. G. Pokrovskii and E. E. Shults, *Med. Chem. Res.*, 2019, **28**, 545–558. DOI: 10.1007/s00044-019-02314-8.
12. (a) N. Deibl, K. Ament and R. Kempe, *J. Am. Chem. Soc.*, 2015, **137**, 12804–12807. DOI: 10.1021/jacs.5b09510; (b) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier and K. Kirchner, *J. Am. Chem. Soc.*, 2016, **138**, 15543–15546. DOI: 10.1021/jacs.6b10433; (c) W. Guo, J. Liao, D. Liu, J. Li, F. Ji, W. Wu and H. Jiang, *Angew. Chem. Int. Ed.*, 2017, **56**, 1289–1293. DOI: 10.1002/anie.201608433; (d) X.-Q. Chu, W.-B. Cao, X.-P. Xu and S.-J. Ji, *J. Org. Chem.*, 2017, **82**, 1145–1154. DOI: 10.1021/acs.joc.6b02767; (e) C. Xu, S.-F. Jiang, X.-H. Wen, Q. Zhang, Z.-W. Zhou, Y.-D. Wu, F.-C. Jia and A.-X. Wu, *Adv. Synth. Catal.*, 2018, **360**, 2267–2271. DOI: 10.1002/adsc.201800180.
13. (a) E. Gayon, M. Szymczyk, H. Gérard, E. Vrancken and J.-M. Campagne, *J. Org. Chem.*, 2012, **77**, 9205–9220. DOI: 10.1021/jo301675g; (b) E. Schmitt, B. Commare, A. Panossian, J.-P. Vors, S. Pazenok and F. R. Leroux, *Chem. Eur. J.*, 2018, **24**, 1311–1316. DOI: 10.1002/chem.201703982; (c) R. P. Frutos, X. Wei, N. D. Patel, T. G. Tampone, J. A. Mulder, C. A. Busacca and C. H. Senanayake, *J. Org. Chem.*, 2013, **78**, 5800–5803. DOI: 10.1021/jo400720p; (d) J.-L. Zhan, M.-W. Wu, F. Chen and B. Han, *J. Org. Chem.*, 2016, **81**, 11994–12000. DOI: 10.1021/acs.joc.6b02181; (e) E. D. Anderson and D. L. Boger, *J. Am. Chem. Soc.*, 2011, **133**, 12285–12292. DOI: 10.1021/ja204856a; (f) E. D. Anderson, A. S. Duerfeldt, K. Zhu, C. M. Glinkerman and D. L. Boger, *Org. Lett.*, 2014, **16**, 5084–5087. DOI: 10.1021/ol502436n; (g) N. Sharma, T. S. Chundawat, S. C. Mohapatra and S. Bhagat, *Synthesis*, 2016, **48**, 4495–4508. DOI: 10.1055/s-0036-1588588.
14. (a) Y. Jiao, S. L. Ho and C. S. Cho, *Synlett*, 2015, **26**, 1081–1084. DOI: 10.1055/s-0034-1380410; (b) M. Lin, Q.-z. Chen, Y. Zhu, X.-l. Chen, J.-j. Cai, Y.-m. Pan and Z.-p. Zhan, *Synlett*, 2011, **2011**, 1179–1183. DOI: 10.1055/s-0030-1259954; (c) W. Guo, C. Li, J. Liao, F. Ji, D. Liu, W. Wu and H. Jiang, *J. Org. Chem.*, 2016, **81**, 5538–5546. DOI: 10.1021/acs.joc.6b00867.
15. (a) J. Fu, G. Zanoni, E. A. Anderson and X. Bi, *Chem. Soc. Rev.*, 2017, **46**, 7208–7228. DOI: 10.1039/C7CS00017K; (b) B. Hu and S. G. DiMagno, *Org. Biomol. Chem.*, 2015, **13**, 3844–3855. DOI: 10.1039/C5OB00099H; (c) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500–7501. DOI: 10.1021/ja072219k; (d) J. Bonnamour and C. Bolm, *Org. Lett.*, 2011, **13**, 2012–2014. DOI: 10.1021/ol2004066; (e) A. Hossain, S. K. Pagire and O. Reiser, *Synlett*, 2017, **28**, 1707–1714. DOI: 10.1055/s-0036-1590888; (f) C. Gao, B. Li, X. Geng, Q. Zhou, X. Zhang and X. Fan, *Green*

Chem., 2019, **21**, 5113–5117. DOI: 10.1039/C9GC02001B; (g) Y. Liu, J. Wei and C.-M. Che, *Chem. Commun.*, 2010, **46**, 6926–6928. DOI: 10.1039/C0CC01825B.

16. A. F. Khlebnikov, M. S. Novikov and N. V. Rostovskii, *Tetrahedron*, 2019, **75**, 2555–2624. DOI: 10.1016/j.tet.2019.03.040.
17. J. Xuan, X.-K. He and W.-J. Xiao, *Chem. Soc. Rev.*, 2020. DOI: 10.1039/C9CS00523D.
18. O. Meth-Cohn, N. J. R. Williams, A. MacKinnon and J. A. K. Howard, *Tetrahedron*, 1998, **54**, 9837–9848. DOI: 10.1016/S0040-4020(98)00537-7.
19. V. M. Cherkasov, N. A. Kapran and V. N. Zavatskii, *Chem. Heterocycl. Comp.*, 1969, **5**, 266–268. DOI: 10.1007/BF00943937.
20. A. Guzman, M. Romero, F. X. Talamas, R. Villena, R. Greenhouse and J. M. Muchowski, *J. Org. Chem.*, 1996, **61**, 2470–2483. DOI: 10.1021/jo952106w.
21. Y. Takikawa, S. Hikage, Y. Matsuda, K. Higashiyama, Y. Takeishi and K. Shimada, *Chem. Lett.*, 1991, **20**, 2043–2046. DOI: 10.1246/cl.1991.2043.
22. (a) N. V. Rostovskii, J. O. Ruvinskaya, M. S. Novikov, A. F. Khlebnikov, I. A. Smetanin and A. V. Agafonova, *J. Org. Chem.*, 2017, **82**, 256–268. DOI: 10.1021/acs.joc.6b02389; (b) A. V. Agafonova, I. A. Smetanin, N. V. Rostovskii, A. F. Khlebnikov and M. S. Novikov, *Org. Chem. Front.*, 2018, **5**, 3396–3401. DOI: 10.1039/C8QO00982A; (c) A. R. Khaidarov, N. V. Rostovskii, A. A. Zolotarev, A. F. Khlebnikov and M. S. Novikov, *J. Org. Chem.*, 2019, **84**, 3743–3753. DOI: 10.1021/acs.joc.8b03205; (d) P. A. Sakharov, N. V. Rostovskii, A. F. Khlebnikov, T. L. Panikorovskii and M. S. Novikov, *Org. Lett.*, 2019, **21**, 3615–3619. DOI: 10.1021/acs.orglett.9b01043; (e) I. A. Smetanin, M. S. Novikov, A. V. Agafonova, N. V. Rostovskii, A. F. Khlebnikov, I. V. Kudryavtsev, M. A. Terpilowski, M. K. Serebriakova, A. S. Trulioff and N. V. Goncharov, *Org. Biomol. Chem.*, 2016, **14**, 4479–4487. DOI: 10.1039/C6OB00588H; (f) N. V. Rostovskii, P. A. Sakharov, M. S. Novikov, A. F. Khlebnikov and G. L. Starova, *Org. Lett.*, 2015, **17**, 4148–4151. DOI: 10.1021/acs.orglett.5b01883.
23. (a) M. A. Kinzhalov, K. V. Luzyanin, V. P. Boyarskiy, M. Haukka and V. Y. Kukushkin, *Organometallics*, 2013, **32**, 5212–5223. DOI: 10.1021/om4007592; (b) S. A. Timofeeva, M. A. Kinzhalov, E. A. Valishina, K. V. Luzyanin, V. P. Boyarskiy, T. M. Buslaeva, M. Haukka and V. Y. Kukushkin, *J. Catal.*, 2015, **329**, 449–456. DOI: 10.1016/j.jcat.2015.06.001; (c) N. V. Rostovskii, A. V. Agafonova, I. A. Smetanin, M. S. Novikov, A. F. Khlebnikov, J. O. Ruvinskaya and G. L. Starova, *Synthesis*, 2017, **49**, 4478–4488. DOI: 10.1055/s-0036-1590822; (d) A. V. Agafonova, I. A. Smetanin, N. V. Rostovskii, A. F. Khlebnikov and M. S. Novikov, *Synthesis*, 2019, **51**, 4582–4589. DOI: 10.1055/s-0039-1690200; (e) P. A. Sakharov, A. N. Koronatov, A. F. Khlebnikov, M. S. Novikov, A. G. Glukharev, E. V. Rogacheva, L. A. Kraeva, V. V. Sharoyko, T. B. Tennikova and N. V. Rostovskii, *RSC Adv.*, 2019, **9**, 37901–37905. DOI: 10.1039/C9RA09345A.
24. J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113. DOI: 10.1039/B913880N.
25. (a) M. A. Kinzhalov, A. A. Eremina, A. S. Smirnov, V. V. Suslonov, V. Y. Kukushkin and K. V. Luzyanin, *Dalton Trans.*, 2019, **48**, 7571–7582. DOI: 10.1039/C9DT01138B; (b) A. A. Eremina, M. A. Kinzhalov, E. A. Katlenok, A. S. Smirnov, E. V. Andrusenko, E. A. Pidko, V. V. Suslonov and K. V. Luzyanin, *Inorg. Chem.*, 2020, **59**, 2209–2222. DOI: 10.1021/acs.inorgchem.9b02833.
26. E. P. Farney and T. P. Yoon, *Angew. Chem. Int. Ed.*, 2014, **53**, 793–797. DOI: 10.1002/anie.201308820.
27. S. Protti, D. Ravelli and M. Fagnoni, *Photochem. Photobiol. Sci.*, 2019, **18**, 2094-2101. DOI: 10.1039/C8PP00512E.
28. C. C. Le, M. K. Wismer, Z.-C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies and D. W. C. MacMillan, *ACS Cent. Sci.*, 2017, **3**, 647–653. DOI: 10.1021/acscentsci.7b00159.
29. (a) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329–2364. DOI: 10.1021/cr050523v; (b) C. Bian, A. K. Singh, L. Niu, H. Yi and A. Lei, *Asian J. Org. Chem.*, 2017, **6**, 386–396. DOI: 10.1002/ajoc.201600563; (c) A. A. Ghogare and A. Greer, *Chem. Rev.*, 2016, **116**, 9994–10034. DOI: 10.1021/acs.chemrev.5b00726.
30. (a) Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880. DOI: 10.1039/c5sc02913a; (b) W. Yi, X. Zeng and S. Gao, in *Green Techniques for Organic Synthesis and Medicinal Chemistry*, 2018, pp. 407–439. DOI: 10.1002/9781119288152.ch16.

View Article Online
DOI: 10.1039/D0OB00693A



A one-pot synthesis of tetrasubstituted dihydropyrimidine and pyrimidine derivatives was developed on the basis of UV-LED photolysis of α-azidocinnamates as a key stage.