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5-Triazolyluracils and Their N^1-Sulfonyl Derivatives: Intriguing Reactivity Differences in the Sulfonation of Triazole $N^{1'}$-Substituted and $N^{1'}$-Unsubstituted Uracil Molecules

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Keywords: Nucleobases / Sulfonylation / Substituent effects / Regioselectivity / Density functional calculations

We describe the synthesis of novel C5-triazolyl derived N^1-sulfonylpyrimidines through Cu^I-catalyzed alkyne–azide cycloaddition followed by sulfonylation of the formed C5-triazolyl derivatives with various sulfonyl chlorides under basic conditions. In the latter step, an intriguing difference in the reactivity of the pyrimidine N^1 was observed that depended on the nature of the substituent at a distant triazole $N^{1'}$ site. The $N^{1'}$-unsubstituted compounds gave very small amounts of sulfonylation products, whereas $N^{1'}$-substituted systems produced high yields of the respective N^1-sulfonyl-5-(1,2,3-triazol-4-yl)uracils. Computational analysis revealed a close correlation between the strength of the employed base catalysts and their abilities to increase the nucleophilicity of the uracil N^1 atom through subsequent deprotonation, leading to more products. Following this step, the phosphazene *t*Bu–P4 superbase was applied in the sulfonylation, resulting in exclusive formation of the triazole $N^{1'}$-unsubstituted N^1-sulfonylpyrimidines.

Introduction

In our earlier synthetic studies focused on novel candidates for antitumor agents,[1,2] we have shown that pyrimidine derivatives containing sulfonamide pharmacophores at the N^1 position of the pyrimidine ring exhibit promising anticancer activity both under in vitro[3,4] and in vivo[5] conditions. The N^1-sulfonylpyrimidines (Figure 1, A) showed potent growth inhibitory effects against human tumour cell lines, whereas the effects on normal human fibroblasts were much smaller.[3a] Pyrimidine nucleobase derivatives of this type were found to inhibit the activities of specific enzymes involved in DNA/RNA synthesis and they showed the ability to induce apoptosis in human tumour cells.[3a,6] In vivo experiments have shown that some N^1-sulfonylcytosine derivatives have strong antitumor activity against mouse mammary carcinoma.[5a]

In the quest to develop novel biologically active compounds for the treatment of cancer, the widely used Cu^I-catalyzed Huisgen alkyne–azide 1,3-dipolar cycloaddition (CuAAC) giving 1,4-disubstituted 1,2,3-triazole ring[7] emerges as the method of choice for further synthetic modification of N^1-sulfonylpyrimidines (Figure 1, B–C).

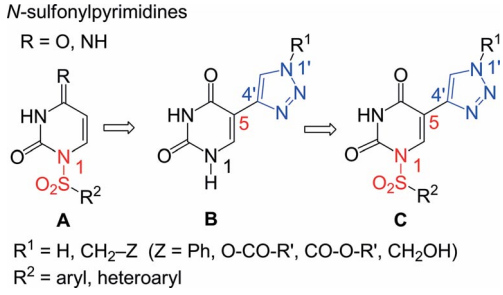

Figure 1. Structures of N^1-sulfonylpyrimidines (**A**), 5-(1,2,3-triazol-4-yl)uracil derivatives (**B**), and N^1-sulfonyl-5-(1,2,3-triazol-4-yl)-uracil derivatives (**C**).

Previous research efforts in drug design showed that introduction of the 1,2,3-triazole fragment in nucleic acid-based agents increased the bioavailability of the compound by increasing the lipophilicity, which, in turn, also enabled better diffusion through the cell membrane.[8] In addition, oligonucleotides containing a triazole moiety at the pyrimidine C5 position are capable of forming duplexes of higher stability because of enhanced π–π stacking interactions.[9] It was also reported that the DNA/RNA duplex formed by oligonucleotides containing a few consecutive triazole-modified nucleotides exhibited increased thermal stability because of the additional stabilisation by the stacking interactions among triazoles located in the major groove.[10]

In this work, we report the development of a synthetic strategy towards the C5–1,2,3-triazolyl derived N^1-sulfonyl-

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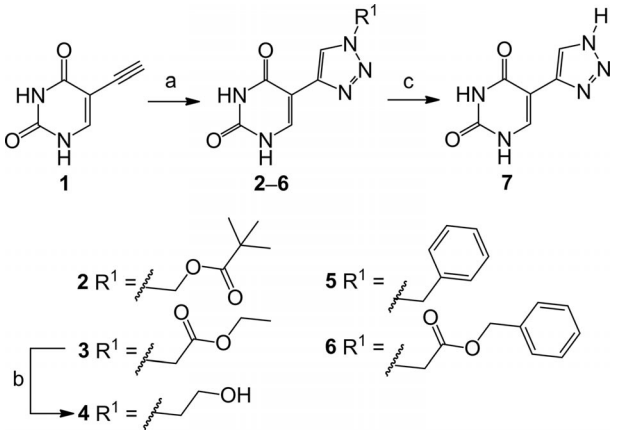
pyrimidine derivatives **C** (Figure 1) that contain three well-known pharmacophores: a nucleobase, a 1,2,3-triazole,[11] and a sulfonyl fragment, which might jointly promote their biological activity. The approach is based on the readily accessible 5-ethynyluracil, which undergoes the Cu^{I}-catalysed cycloaddition reaction with azides generated in situ to give a new class of C5–1,2,3-triazolyl nucleobase analogues (**B**) that are sulfonated at the N^1 position using the methodology previously developed for other pyrimidine derivatives.[1–3,12] However, the outcome of the latter condensation unexpectedly depends on the nature of the substituent at a very distant $N^{1'}$ position of the 1,2,3-triazole ring, resulting in either low yields or no products for R^1 = H (Figure 1), while enabling the preparation of the respective N^1-sulfonylpyrimidine derivatives **C** in high yields with $R^1 \neq$ H. This enables the construction of libraries of compounds of type **C** in a highly efficient way in amounts necessary for biological testing. The observed reactivity differences were interpreted by computations as principally being a consequence of different basicity strengths of the employed base catalysts, which produce different protonation forms of pyrimidines entering the condensation.

Results and Discussion

Synthesis

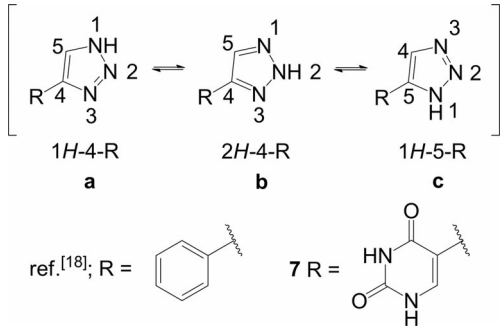
Starting from the commercially available uracil, 5-iodouracil was easily obtained by using iodine in 1,4-dioxane and nitric acid, as described earlier.[13,14] Sonogashira coupling of 5-iodouracil and trimethylsilylacetylene (TMSA),[15] followed by removal of the TMS group with 1 M NaOH, gave 5-ethynyluracil **1** in 94% yield (Scheme 1).[16]



Scheme 1. Copper-catalyzed 1,3-dipolar cycloaddition of 5-ethynyluracil **1** with azides prepared in situ. *Reagents and conditions*: (a) i. R^1-X, EtOH/H_2O, DMEDA, NaN_3, CuI, Na-ascorbate, 100 °C, 1 h; ii. alkyne **1**, DMEDA, CuI, Na-ascorbate, 100 °C, 0.5 h; (b) DME, $NaBH_4$, MeOH, reflux, 60%; (c) **2** in dioxane, NH_3 (aq.), room temp., 1.5 h, 100%.

The 1,2,3-triazole ring was synthesised directly from unprotected **1** by using sodium azide, alkyl halides, and an in situ azidation/cycloaddition protocol (Scheme 1).[10] This reaction allows the $N^{1'}$ substituent of the 1,2,3-triazole ring to be easily varied through the use of a range of alkyl halides. Compounds **2**, **3**, **5** and **6** were obtained in 81–100% yields. NMR spectroscopic analysis of the isolated products clearly indicate that no 1,5-disubstituted regioisomers were present, as was the case with some purines reported previously.[17] Derivative **4** was obtained in 60% yield by the reduction of **3** with sodium borohydride in 1,2-dimethoxyethane (DME). Compound **2** was treated with ammonia to give **7**, lacking an $N^{1'}$ substituent, in quantitative yield.[10]

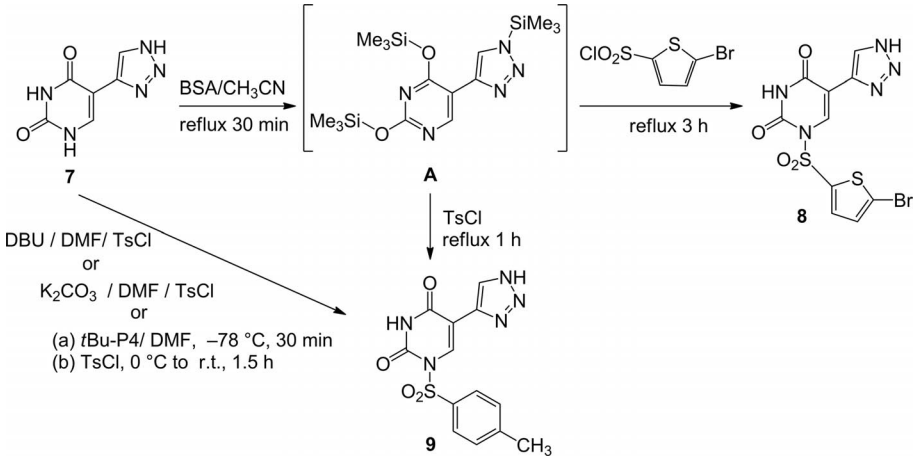
First we examined the condensation of **7**, having the unsubstituted triazole ring, with selected sulfonyl chlorides as the most direct access to N^1-sulfonyluracil derivatives. It is known that monosubstituted triazoles can exist as a mixture of three different tautomers, with the 2*H*-4-Ph tautomer **b** being the most stable in both the crystal and gas phase,[18] whereas 1*H*-4-Ph (**a**) and 1*H*-5-Ph (**c**) possess 3.9 and 4.8 kcal mol^{-1} higher total Gibbs free-energy, respectively, than **b** in the gas phase (Scheme 2, R = phenyl). On the other hand, in aqueous solution, 1*H* (**a**) and 2*H* (**b**) tautomers have practically identical energies and both are present.[18] Hence, under basic conditions and depending on the strength of the base, in the reaction involving **7** with sulfonyl chlorides, sulfonylation at both the N^1 pyrimidine and the triazole $N^{1'}$ position may be expected.



Scheme 2. Possible tautomeric forms of monosubstituted 1,2,3-triazoles.

Base/solvent systems that have been frequently used in similar condensation reactions were examined, including: (1) pyridine, (2) bis(trimethylsilyl)acetamide (BSA) in acetonitrile, (3) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide (DMF), and (4) K_2CO_3 in DMF.[1] Method (1) failed to give any N^1-sulfonylated uracil derivative, whereas methods (3) and (4) using tosyl chloride gave only 9 and 11% of **9**, respectively. With method (2) using BSA/acetonitrile, the sufonylated products **8** and **9** were obtained in poor yields (6 and 8%, respectively) using commercially available 5-bromothiophene-2-sulfonyl chloride or tosyl chloride (Scheme 3). The results of these synthetic studies show that, although formed in low yields, only N^1-sulfonyl pyrimidine products could be identified, indicating that sulfonylation occurred at the pyrimidine N^1 atom preferentially.

In an attempt to improve the yields, the use of much stronger NaH base was examined. In three parallel experiments, derivative **7** (1 equiv.) was dissolved in anhydrous DMF, and NaH (1, 2, or 3 equiv.) was added followed by



Scheme 3. Synthesis of monosubstituted 1,2,3-triazolo N^1-sulfonyluracil derivatives **8** and **9**.

the addition of tosyl chloride. The products were isolated by preparative TLC. In the reaction involving equimolar quantities of **7**, NaH, and tosyl chloride, the formation of **9** could not be observed by TLC, and the starting material **7** was completely recovered. In the reactions with 2 and 3 equiv. NaH, the formation of N^1-sulfonylated **9** as a sole product was observed; **9** was isolated in 5.5 and 11% yield, respectively. In both reactions, 80% of the starting material was recovered.

It was found that the yield was not improved either upon extremely prolonged reaction time (2 weeks) with 20% excess of tosyl chloride or by increasing the reaction temperature (microwave assisted synthesis at 150 °C). However, these results clearly indicated that an increase in the amount of employed base promoted the reaction, suggesting that subsequent deprotonation of the initial formed **7** enhanced its reactivity. Unfortunately, the increase in the reaction yield was not significant, which could be attributed to known difficulties and side-reactions occurring with the application of strongly nucleophilic NaH as a base catalyst in DMF.[19]

In the same vein, and according to the computational results presented herein (see below), it was reasonable to assume that the application of the phosphazene *t*Bu–P4 base, as one of the strongest nonionic superbases with low nucleophilicity ($pK_{BH}+ \approx 42.7$ in MeCN),[20] would produce higher yields of the condensation reactions of derivative **7** with tosyl chloride. To test this hypothesis, we performed additional experiments, the results of which are presented in Scheme 3 and Table 1.

Derivative **7** (1 equiv.) was dissolved in anhydrous DMF, cooled to –78 °C and *t*Bu–P4 was added. The reaction mixtures were stirred for 30 min at –78 °C, removed to an ice bath and tosyl chloride was added. The progress of the reaction was monitored by TLC. Initial experiments resulted in the recovery of **7** (Table 1, entries 1–4), whereas performing the reactions under the conditions shown in entry 5 resulted in complete conversion of derivative **7** into the desired product **9** within 1 h. The latter result strongly supports our hypothesis that triple-deprotonation of **7** facilitates condensation. Notably, isolation of product **9** (21, 47, and 58% yields were obtained, depending on the method of isolation) was difficult because of both the large excess of *t*Bu–P4 base and the instability of the formed N^1–S bond during isolation. Considerable degradation of **9** occured after each additional chromatographic purification.

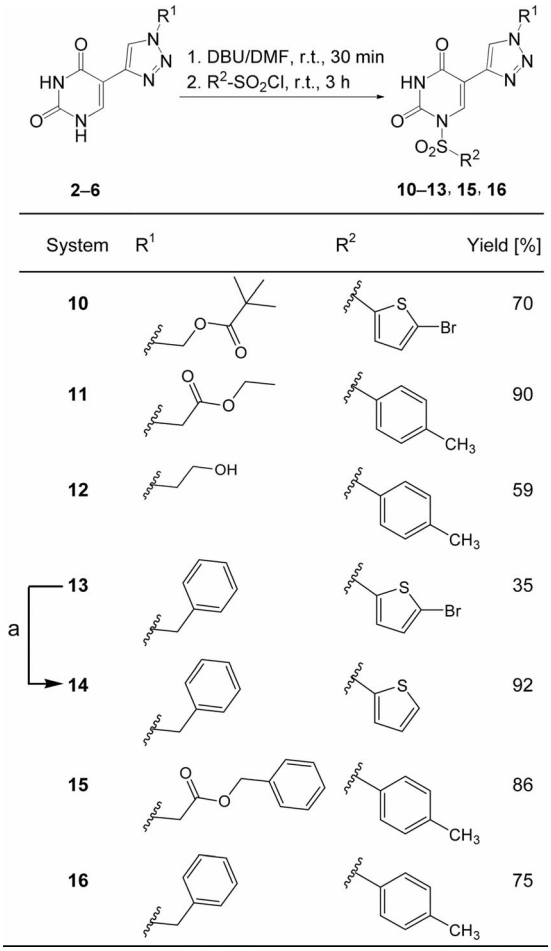
Table 1. Condensation reactions of **7** with tosyl chloride and *t*Bu–P4 superbase.

Entry	**7** [equiv.]	TsCl [equiv.]	*t*Bu-P4 [equiv.]	Yield of **9** [%]	Recovery of **7** [%]
1	1	1	1	not observed[a]	80
2	1	1	2	trace[a]	60
3	1	1	3	trace[a]	31
4	1	2	1	not observed[a]	100
5	1	2	3	100[a] / 21–58[b]	–

[a] Monitored by TLC. [b] Isolated yield.

We then turned our attention to the condensation of $N^{1'}$-substituted triazoles **2**–**6** and various sulfonyl chlorides (Table 2). The reaction of **2** with BSA/acetonitrile gave **10** in only 15% yield. However, by using DBU in DMF, **10** was obtained in 70% yield. Employing the latter reaction conditions with **3**–**6** and sulfonyl chlorides, the respective N^1-sufonylated products were obtained in good to excellent yields (Table 2). Product **13**, having a 5-bromothiophene-2-sulfonyl group at the N^1 position, was efficiently transformed into **14** (92% yield) by removing the bromine under catalytic hydrogenolysis. In addition, the preparation of **8**, containing the $N^{1'}$-unsubstituted triazole ring, was examined by using ammonium hydroxide/dioxane mixture and $N^{1'}$-pivaloyloxymethyl derivative **10**.[10] However, a product mixture consisting of **2**, **7**, and 5-bromothiophene-2-sulfonic acid was obtained as a result of cleavage of the N^1-sulfonylbromothiofene and $N^{1'}$-pivaloyloxy-methyl groups. Similarly, the catalytic hydrogenolysis of the *N*-benzyl group from **14** with ammonium formate in MeOH gave undesired product 5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)uracil (**5**) instead of the $N^{1'}$-unsubstituted triazole derivative, demonstrating the instability of the N^1–S bond under these conditions.

Table 2. Condensation reaction of 1,4-disubstituted triazoles **2**–**6** with tosyl chloride or 5-bromothiophene-2-sulfonyl chloride.[a]



[a] Reaction conditions for the conversion of **13** into **14**: H_2 (42 psi), Pd/C (10%), CH_2Cl_2/MeOH (1:1), r.t., 48 h.

Computational Mechanistic Studies

To rationalize the observed reactivity trends, we examined the conformations of **7** and **5**, and their deprotonated forms, in DMF solution (Figure 2). 1*H*-4-Derivative **7a** is the most stable form of **7** (Scheme 2), but this was only 0.1 kcal mol^{-1} lower in energy than **7b**, thus mimicking the situation reported for the system in aqueous solution.[18] In the gas phase, the situation is reversed, meaning that **7b** is the global minimum, being 1.6 kcal mol^{-1} more stable than **7a**, which is in line with previous reports.[18] First deprotonation of both **7** and **5** corresponds to removing the uracil N^1 proton with pK_a values of 12.0 and 14.0, respectively. In **7**, deprotonation at $N^{1'}$ and N3 sites gives 0.9 and 4.8 kcal mol^{-1} less stable conjugate bases, whereas in **5**, N3 deprotonation is 5.2 kcal mol^{-1} less favourable. This suggests that monoanionic **7**$^-$ is the predominant form of this molecule in DMF, whereas **5** is roughly in **5**$\rightarrow$**5**$^-$ equilibrium, because the autoprotolysis constant for DMF is around 27–29.[21] Molecule **7** could undergo a second deprotonation by removing the triazole $N^{1'}$ proton (pK_a = 17.5), whereas N3 deprotonation is 13.1 kcal mol^{-1} less feasible. The N3–H group on uracil is more acidic in **5** (pK_a = 29.9) than in **7** (pK_a = 32.7), which could be attributed to a positive influence of the attached benzyl moiety in stabilising the **5**$^{2-}$ dianion. To put these data into perspective, we also calculated the pK_a values in DMF of the basic catalysts we employed in condensation reactions and obtained pK_a (DBUH$^+\rightarrow$DBU) = 15.0; pK_a ($HCO_3^-\rightarrow CO_3^{2-}$) = 20.5, and p$K_a$ ($H_2CO_3\rightarrow HCO_3^-$) = 11.3.

Pyridine is a very weak base, with a pK_a of 3.57 measured in DMF.[22] This mismatch with the uracil acidity is also evidenced in, for example, water, in which the pK_a values of pyridine and uracil assume 5.3 and 9.5, respectively.[23] Therefore, in pyridine, both **7** and **5** will remain unionised. All attempts to model either the transition state structure or the product of the nucleophilic attack of the unionised uracil N^1 atom in **7** and **5** with tosyl chloride (Me-Ph-SO_2Cl), selected here as a model reactant, failed because the complex decomposed to reactants, suggesting that unionised N^1 is not sufficiently nucleophilic for the reaction. Even with a very electrophilic MePh-SO_2^+ cation, **7** forms a very weak nonbonding complex, with a N^1–S distance of 2.168 Å and interaction free energy of only ΔG_{INT} = –1.5 kcal mol^{-1}. This we rationalise with the atomic charge on the N^1 atom of –0.64 |e| in **7**, which was the least negative for this reaction centre amongst all protonation

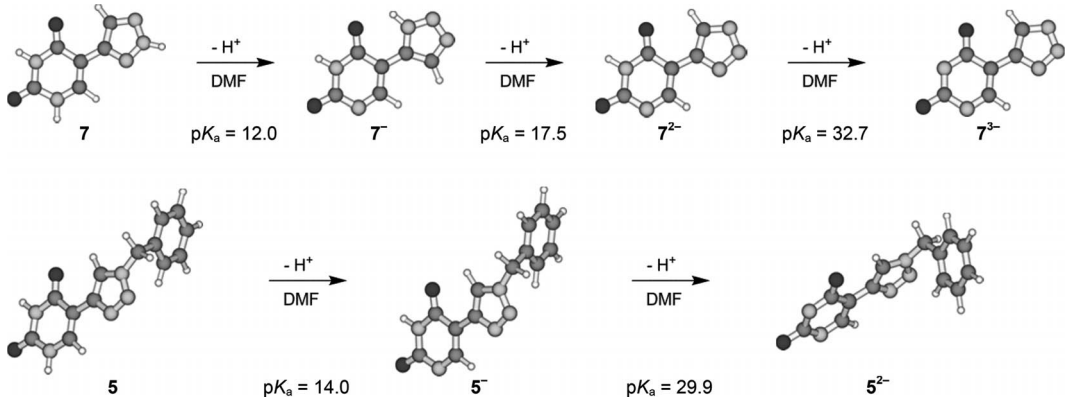
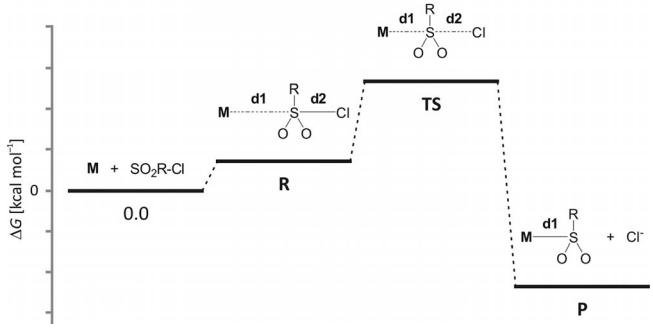


Figure 2. Acid-base equlibria of systems **7** and **5** together with the calculated pK_a values in DMF corresponding to the most favourable deprotonation reactions.

forms of the system **7**. Together, these results explain why the investigated condensation of **7** and **5** was unsuccessful when performed in pyridine solution.

With a pK_a of 15.0, DBU can efficiently deprotonate both systems to their monoanionic forms $\mathbf{7}^-$ and $\mathbf{5}^-$. The latter reacts with Me-Ph-SO_2Cl by forming a reactive complex that is 3.6 kcal mol^{-1} higher in energy than that of the separated reactants (Table 3). From there, it takes 9.7 kcal mol^{-1} to arrive at the transition state for the formation of the N^1–S chemical bond (ν_{IMAG} = 182*i* cm^{-1}), thus leading to a total activation free energy $\Delta G^{\ddagger}$ of 13.3 kcal mol^{-1}. Following that, the desired product is formed with a chloride anion, Cl^-, departing as the leaving group. In the product, the N^1–S bond length is 1.748 Å, being reduced from 3.524 and 2.366 Å in the respective reactants and transition state. The overall reaction is favourable and fairly exergonic with $\Delta_r G$ = –11.8 kcal mol^{-1}, making this process thermodynamically spontaneous. The kinetic and thermodynamic parameters of this reaction, together with the obtained yield of 75% (Table 2, compound **16**), will serve as a reference point for other reaction pathways. In contrast to $\mathbf{5}^-$, bringing $\mathbf{7}^-$ close to Me-Ph-SO_2Cl is favourable and the energy is lowered by –0.4 kcal mol^{-1}. Nevertheless, the reaction barrier raises to 15.6 kcal mol^{-1} (ν_{IMAG} = 189*i* cm^{-1}), with an increase of 2.3 kcal mol^{-1} relative to $\mathbf{5}^-$, suggesting that this reaction proceeds around 50 times slower for $\mathbf{7}^-$. This fact, together with the reduced exergonicty ($\Delta_r G$ = –7.2 kcal mol^{-1}), and the longer N^1–S bond of 1.756 Å in the product **7**–SO_2R, provides an explanation for why the condensation of **7** with DBU/DMF resulted either in poor yields or even with no expected products at all (Table 2).

Table 3. Free-energy profiles for different protonation states of systems **5** and **7** with Me-Ph-SO_2Cl in DMF solution obtained by the (SMD)/MP2/6-311++G(2df,2pd)//(SMD)/M06–2X/631+G(d) model. Bond lengths d1 and d2 correspond to the separation between N^1(uracil)···S and S···Cl$^-$, respectively.



	Relative energy [kcal mol^{-1}]			Geometry [Å]	
System	Reactants	Transition state	Products		
(M)	(R)	(TS)	(P)	d1	d2
5^-	3.6	13.3	–11.8	3.524 (R) 2.366 (TS) 1.748 (P)	2.113 (R) 2.310 (TS)
7^-	–0.4	15.2	–7.2	3.953 (R) 2.329 (TS) 1.756 (P)	2.101 (R) 2.327 (TS)
7^{2-}	3.0	13.5	–16.9	3.997 (R) 2.426 (TS) 1.742 (P)	2.104 (R) 2.284 (TS)
7^{3-}	6.4	9.0	–37.4	3.296 (R) 2.544 (TS) 1.708 (P)	2.138 (R) 2.311 (TS)

Potassium carbonate (K_2CO_3) is a stronger base than DBU in DMF by more than five orders of magnitude. With its pK_a value of 20.5, it is capable of deprotonating **7** to its dianion $\mathbf{7}^{2-}$, by removing both the uracil N^1 and triazole $N^{1'}$ protons (Figure 2). The reaction of $\mathbf{7}^{2-}$ with Me-Ph-SO_2Cl is very favourable ($\Delta_r G$ = –16.9 kcal mol^{-1}), with further reduction in the product N^1–S bond to 1.742 Å, whereas the calculated barrier ($\Delta G^{\#}$ = 13.5 kcal mol^{-1}) is lower than that for $\mathbf{7}^-$ by 1.7 kcal mol^{-1}. This explains why **7**, when used with K_2CO_3, gives more product than with DBU. Nevertheless, the increase in the reaction yield is not spectacular because the calculated reaction barrier is 0.2 kcal mol^{-1} higher than for $\mathbf{5}^-$. It turns out that this subtle difference in the reaction kinetics is enough that, under these conditions, the reaction yield for $\mathbf{7}^{2-}$ is reduced almost seven times relative to $\mathbf{5}^-$, being only 11%. Nevertheless, utilising K_2CO_3 as a base represents a clear advancement in comparison with DBU/DMF, for which the reaction involving **7** was unsuccessful, because, in the latter case, it starts with monoanionic $\mathbf{7}^-$, which also appears to be insufficiently nucleophilic for successful condensation. Interestingly, deprotonation of the triazole amino group increases the negative charge on the reacting uracil N^1 atom from –0.68 |e| ($\mathbf{7}^-$) to –0.71 |e| ($\mathbf{7}^{2-}$) through the resonance effect, providing one of the factors for the enhanced reactivity of the dianion.

Along this line, it is interesting to investigate the reactivity of the trianion $\mathbf{7}^{3-}$, for which the NBO charge analysis predicts further negative charge build-up on the N^1 atom to as much as –0.80 |e|. This is, indeed, reflected in the reaction profile, because the activation free energy drops significantly to $\Delta G^{\ddagger}$ = 9.0 kcal mol^{-1}, and the overall transformation becomes largely exergonic, with $\Delta_r G$ = –37.4 kcal mol^{-1} (Table 3), which is closely followed by the shortest N^1–S distance of 1.708 Å in all of the investigated products. These results suggest that a base with the appropriate basicity (pK_a value above 30 in DMF) would make the complete reaction more feasible, which would proceed around 1500 times faster than for $\mathbf{5}^-$, with the latter exhibiting the second lowest activation free energy studied here. This was exactly the case in a reaction involving **7** with three equivalents of *t*Bu–P4 superbase, which exhibited measured pK_a values of 42.7 and 30.3 in acetonitrile and dimethyl sulfoxide (DMSO),[20] respectively, which is clearly a base that is strong enough to both generate a trianion $\mathbf{7}^{3-}$ and enable its complete transformation (Table 1). This fact underlines the decisive impact of the increased nucleophilicity of the reacting uracil N^1 atom on the feasibility of forming condensation products, which is a result of the subsequent deprotonation of the reactants.

Conclusions

In this work we showed that novel C5–1,2,3-triazolyl-derived pyrimidines **2**–**6** can be prepared by the Cu^{I}-catalysed Huisgen alkyne–azide 1,3-dipolar cycloaddition (CuAAC) reactions from easily accessible 5-ethynyluracil **1**, sodium azide, and alkyl halides by using an in situ azidation/cycloaddition protocol. This approach allows the $N^{1'}$ substituent of the 1,2,3-triazole ring to be easily varied through the use of a range of alkyl halides. Compounds **2**, **3**, **5** and **6** were obtained in 81–100% yields. Derivative **4** was obtained by the reduction of **3** with sodium borohydride/DME in 60% yield. Compound **2** was treated with ammonia to give **7**, lacking an $N^{1'}$ triazole substituent, in quantitative yield.

We also showed that C5–1,2,3-triazolyl-derived N^1-sulfonylpyrimidine derivatives **10**–**13**, **15** and **16**, bearing various substituents at the $N^{1'}$ triazole nitrogen, could be prepared in 35–90% yields by the condensation reaction of pyrimidine derivatives **2**–**6** and various sulfonyl chlorides under basic conditions (DBU) in DMF. In contrast, under the same reaction conditions or by using other bases such as pyridine, K_2CO_3 in DMF, and BSA in acetonitrile, derivative **7**, lacking the $N^{1'}$ triazole substituent, gave either trace amounts or no respective N^1-sufonylated products at all. The observed reactivity differences between the $N^{1'}$-unsubstituted triazole **7**, and **2**–**6**, bearing various $N^{1'}$ substituents, appears intriguing considering the remote position of substituents to the preferred pyrimidine N^1 sulfonylation site.

The results of the computational analysis aided in the interpretation of the observed reactivities and revealed a tight connection between the strength of the employed base catalyst and its ability to increase the nucleophilicity of the reacting uracil N^1 atom through subsequent deprotonation, which is evident in the negative charge buildup on this site from –0.64 and –0.68 to –0.71 and –0.80 |e| in **7**, $\mathbf{7}^-$, $\mathbf{7}^{2-}$ and $\mathbf{7}^{3-}$, respectively. In addition, the calculated free-energy profiles are found to be fully consistent with the observed reaction yields. Following computational results, the application of the nonionic superbase catalyst with low nucleophilicity, *t*Bu–P4, in the condensation of **7** with tosyl chloride gave complete conversion into the desired product **9** (TLC monitoring), which was, however, isolated in 21–58% yields due to cleavage of the unstable N^1–S bond.

Therefore, we can conclude that the experimental findings and computational results presented herein are consistent in suggesting that the present synthetic strategy offers a promising route towards new families of biologically active N^1-sulfonyl-5-(1,2,3-triazol-4-yl)uracil derivatives.

We would also like to emphasise that the calculated pK_a values for all three acidic N-H sites in **7** [pK_a(N^1) = 12.0; pK_a($N^{1'}$) = 17.5; pK_a(N3) = 32.7] could be of interest in designing further organic synthesis and for the construction of various novel conjugates of C5–1,2,3-trazolyl uracils.

Experimental Section

General Information: Solvents were distilled from appropriate drying agents shortly before use. TLC was carried out on DC-plastikfolien Kieselgel 60 F254 and preparative thick-layer (2 mm) chromatography was done on Merck 60 F254. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. UV spectra were recorded with a Philips PU8700 UV/Vis spectrophotometer. IR spectra were obtained as KBr pellets with a Perkin–Elmer 297 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in [D$_6$]DMSO with a Varian Gemini 300 (300/75 MHz) spectrometer using [D$_6$]DMSO as the internal standard. High-resolution mass spectra (HRMS) were obtained with a Micromass Q-Tof2 hybrid quadrupole time-of-flight mass spectrometer.

General One-Pot Procedure for 1,3-Dipolar Cycloadditions (CuAAC): Sodium azide (2 mmol), CuI (0.2 mmol), sodium ascorbate (0.1 mmol) and *N*,*N*′-dimethylethylenediamine (DMEDA) (0.3 mmol) were added to a solution of the alkyl halide (2 mmol) in EtOH/H_2O (7:3, 5 mL). The mixture was heated at 100 °C for 1 h, then 5-ethynyluracil **1** (0.8 mmol), sodium ascorbate (0.1 mmol), CuI (0.2 mmol) and DMEDA (0.3 mmol) were added. The mixture was heated at 100 °C for 30 min and concentrated under reduced pressure.

5-(1-Pivaloyloxymethyl-1*H*-1,2,3-triazol-4-yl)uracil (2): According to the general CuAAC procedure, chloromethyl pivalate (297 μL, 2 mmol, 97%) was used to give the product **2**. The crude material was recrystallised immediately from methanol, yield 190 mg (81%); white solid, m.p. 245–248 °C; R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 228 (4.3), 290 (4.2) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3165, 3076, 1755, 1710, 1672, 1553, 1445, 1433, 1238, 1117, 1030 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.25–11.45 (br. s, 2 H, NH-1, NH-3), 8.45 (s, 1 H, H-6), 8.08 (s, 1 H, H-5′), 6.34 (s, 2 H, CH_2), 1.12 (s, 9 H, 3×CH_3) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 176.5 (s, C=O), 162.0 (s, C-4), 150.5 (s, C-2), 139.4 (s, C-4′), 138.0 (d, C-6), 122.8 (d, C-5′), 103.2 (s, C-5), 70.0 (t, CH_2), 38.2 [s, $(CH_3)_3C$-], 26.4 (q, CH_3) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{12}H_{16}N_5O_4$ [M + H]$^+$ 294.1202; found 294.1185.

Ethyl 2-[4-(Uracil-5-yl)-1*H*-1,2,3-triazol-1-yl]acetate (3): According to the general CuAAC procedure, ethyl bromoacetate (223 μL, 2 mmol) was used to give the product **3**. The crude material was recrystallised immediately from methanol, yield 212 mg (quant.); white solid; m.p. 255–258 °C; R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 232 (4.1), 290 (3.9) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3157, 3142, 3074, 1754, 1713, 1682, 1639, 1452, 1398, 1229, 1207 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.39 (s, 1 H, NH-3), 11.18 (br. s, 1 H, NH-1), 8.38 (s, 1 H, H-6), 8.06 (s, 1 H, H-5′), 5.41 (s, 2 H, CH_2), 4.18 (dd, J = 7.1, 14.2 Hz, 2 H, CH_2), 1.22 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 167.2 (s, C=O), 162.1 (s, C-4), 150.5 (s, C-2), 139.00 (s, C-4′), 137.6 (d, C-6), 123.4 (d, C-5′), 103.7 (s, C-5), 61.4 (t, CH_2), 50.3 (t, CH_2), 13.9 (q, CH_3) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{10}H_{12}N_5O_4$ [M + H]$^+$ 266.0889; found 266.0885.

Deprotection of 3: 5-[1-(2-Hydroxyethyl)-1*H*-1,2,3-triazol-4-yl]uracil (4): To a suspension of 5-triazolyl derivative **3** (100 mg, 0.377 mmol) in DME (4 mL), sodium borohydride (74.3 mg, 1.885 mmol) was added. The white suspension was heated to reflux for 20 min and then a mixture of DME (2 mL) and methanol (337 μL, 8.29 mmol) was added dropwise. The resulting cloudy mixture was heated to reflux overnight and the solvent was evaporated under reduced pressure. The residue was purified by preparative chromatography (CH_2Cl_2/MeOH, 3:1) to give the product **4**, yield 50 mg (60%); white solid; m.p. 267–269 °C; R_f = 0.2 (CH_2Cl_2/MeOH, 6:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 232 (4.12), 291 (3.97) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3240, 3173, 3107, 3066, 1716, 1670, 1553, 1443, 1370, 1217 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]-

DMSO): δ = 11.40 (s, 1 H, NH-3), 11.19 (br. s, 1 H, NH-1), 8.29 (s, 1 H, H-6), 8.02 (s, 1 H, H-5′), 5.02 (t, J = 5.2 Hz, 1 H, OH), 4.42 (t, J = 5.3 Hz, 2 H, CH_2OH), 3.77 (dd, J = 5.1, 10.4 Hz, 2 H, CH_2CH$_2$OH) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 162.2 (s, C-4), 150.6 (s, C-2), 138.8 (s, C-4′), 137.3 (d, C-6), 122.4 (d, C-5′), 104.0 (s, C-5), 59.9 (t, CH$_2$), 52.1 (t, CH$_2$) ppm. HRMS (ESI-TOF): m/z calcd. for $C_8H_{10}N_5O_3$ [M + H]$^+$ 224.0784; found 224.0773.

5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)uracil (5): According to the general CuAAC procedure, benzyl bromide (243 μL, 2 mmol) was used to give the product **5**. The crude material was recrystallised immediately from the methanol/dichloromethane, yield 190 mg (81%); white solid; m.p. 270–272 °C; R_f = 0.5 (CH$_2$Cl$_2$/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 231 (4.1), 291 (4.0) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3221, 3151, 3065, 3032, 1728, 1682, 1551, 1456, 1425, 1227, 1045 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.40 (s, 1 H, NH-3), 11.19 (br. s, 1 H, NH-1), 8.37 (s, 1 H, H-6), 8.02 (s, 1 H, H-5′), 7.30–7.40 (m, 5 H, Ph), 5.63 (s, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 162.2 (s, C-4), 150.6 (s, C-2), 139.3 (s, Ph), 137.6 (d, C-6), 136.2 (s, C-4′), 128.8 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 122.0 (d, C-5′), 103.8 (s, C-5), 52.7 (t, CH$_2$) ppm. HRMS (ESI-TOF): m/z calcd. for $C_{13}H_{12}N_5O_2$ [M + H]$^+$ 270.0991; found 270.0971.

Benzyl 2-[4-(Uracil-5-yl)-1*H*-1,2,3-triazol-1-yl]acetate (6): According to the general CuAAC procedure, benzyl 2-bromoacetate (330 μL, 2 mmol, 96%) was used to give the product **6**. The crude material was recrystallised immediately from methanol, yield 260 mg (quant.); white solid; m.p. 292–295 °C; R_f = 0.4 (CH$_2$Cl$_2$/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 231 (4.1), 291 (4.0) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3215, 3160, 3065, 3034, 1744, 1724, 1682, 1553, 1493, 1223, 1203 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 11.43 (s, 1 H, NH-3), 11.22 (br. s, 1 H, NH-1), 8.42 (s, 1 H, H-6), 8.06 (s, 1 H, H-5′), 7.38 (m, 5 H, Ph), 5.51 (s, 2 H, OCH$_2$Ph), 5.21 (s, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]-DMSO): δ = 167.3 (s, C=O), 162.2 (s, C-4), 150.6 (s, C-2), 139.0 (s, Ph), 137.6 (d, C-6), 135.4 (s, C-4′), 128.5 (d, Ph), 128.3 (d, Ph), 128.1 (d, Ph), 123.5 (d, C-5′), 103.7 (s, C-5), 66.7 (t, O*C*H$_2$Ph), 50.3 (t, N*C*H$_2$CO) ppm. HRMS (ESI-TOF): m/z calcd. for $C_{15}H_{14}N_5O_4$ [M + H]$^+$ 328.1046; found 328.1025.

Deprotection of 2: 5-(1*H*-1,2,3-Triazol-4-yl)uracil (7): A solution of 5-triazolyl derivative **2** (100 mg, 0.341 mmol) in a mixture of dioxane and concentrated aqueous ammonia (1:3 v/v,74 mL) was stirred at room temperature for 1.5 h. The clear colourless solution was concentrated under reduced pressure, and the residue was crystallised from water to obtain product **7**, yield 61 mg (quant.); white solid; m.p. > 300 °C; R_f = 0.6 (CH$_2$Cl$_2$/MeOH, 3:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 231 (4.23), 290 (4.12) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3140, 3084, 3032, 1761, 1720, 1683, 1549, 1429, 1389, 1234 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 14.87 (br. s, 1 H, NH-1′), 11.39 (br. s, 2 H, NH-1, NH-3), 8.12 (s, 1 H, H-5′), 7.97 (s, 1 H, H-6) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 162.2 (s, C-4), 150.6 (s, C-2), 138.4 (d, C-6), 128.7 (s, C-4′), 119.8 (d, C-5′), 103.4 (s, C-5) ppm. HRMS (ESI-TOF): m/z calcd. for $C_6H_6N_5O_2$ [M + H]$^+$ 180.0521; found 180.0513.

1-(5-Bromothiophene-2-sulfonyl)-5-(1*H*-1,2,3-triazol-4-yl)uracil (8)

BSA/CH$_3$CN Procedure: To a suspension of 5-triazolyl derivative **7** (121.3 mg, 0.677 mmol) in anhydrous acetonitrile (2 mL), BSA (523 μL, 2.03 mmol, 95%) was added dropwise and the reaction mixture was heated to reflux for 30 min. The colourless solution was then cooled to 0 °C and the 5-bromothiophene-2-sulfonyl chloride (157.4 mg, 0.677 mmol, 97%) was added. The reaction mixture was stirred for an additional 3 h under reflux and quenched with a small amount of methanol. The resulting solid (unreacted **7**) was filtered off. The filtrate was evaporated and the residue was purified by preparative chromatography (CH$_2$Cl$_2$/MeOH, 9:1) to give the product **8**, yield 15 mg (6%); white solid; m.p. 173–175 °C; R_f = 0.4 (CH$_2$Cl$_2$/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, dm^3 mol^{-1} cm^{-1}) = 234 (4.11), 289 (4.21) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3456, 3096, 1720, 1701, 1686, 1541, 1437, 1393, 1256, 1178, 1022 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 15.30 (br. s, 1 H, NH-1′), 12.18 (br. s, 1 H, NH-3), 8.62 (s, 1 H, H-5′), 8.45 (s, 1 H, H-6), 7.96 (d, J = 4.2 Hz, 1 H, H-3′′ or H-4′′), 7.50 (dd, J = 4.2 Hz, 1 H, H-3′′ or H-4′′) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 159.8 (s, C-4), 149.8 (s, C-2), 146.7 (s, C-4′), 138.6 (d, C-5′), 138.5 (d, C-6), 138.4 (s, C-2′′), 135.1 (d, C-3′′), 131.6 (d, C-4′′), 124.8 (s, C-5′′), 100.9 (s, C-5) ppm. HRMS (ESI-TOF): m/z calcd. for $C_{10}H_7BrN_5O_4S_2$ [M + H]$^+$ 403.9123; found 403.9112.

1-(*p*-Tolylsulfonyl)-5-(1*H*-1,2,3-triazol-4-yl)uracil (9)

BSA/CH$_3$CN Procedure: To a suspension of 5-triazolyl derivative **7** (100 mg, 0.56 mmol) in anhydrous acetonitrile (2 mL), BSA (431 μL, 1.67 mmol, 95%) was added dropwise and the reaction mixture was heated to reflux for 30 min. The colourless solution was then cooled to 0 °C and *p*-toluenesulfonyl chloride (tosyl chloride, TsCl) (106.4 mg, 0.56 mmol) was added. The reaction mixture was stirred for an additional 1 h under reflux and quenched with a small amount of methanol. The resulting solid (unreacted **7**) was filtered off. The filtrate was evaporated and the residue was purified by preparative TLC (CH$_2$Cl$_2$/MeOH, 9:1) to give product **9** (15 mg, 8%) as a white powder.

DBU/DMF Procedure: To a solution of 5-triazolyl derivative **7** (100 mg, 0.56 mmol) in anhydrous DMF (3 mL) under an argon atmosphere, DBU (86 μL, 0.56 mmol, 97%) was added dropwise. The colourless solution was stirred at room temperature for 30 min, then cooled to 0 °C and tosyl chloride (106.4 mg, 0.56 mmol) was added. The resulting clear yellow mixture was stirred at room temperature for an additional 3 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (CH$_2$Cl$_2$/MeOH, 9:1) to give product **9** (17 mg, 9%) as a white powder.

K$_2$CO$_3$/DMF Procedure: To a suspension of 5-triazolyl derivative **7** (100 mg, 0.56 mmol) and K$_2$CO$_3$ (77.2 mg, 0.56 mmol) in anhydrous DMF (3 mL) cooled to 0 °C under an argon atmosphere, tosyl chloride (106.4 mg, 0.56 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (CH$_2$Cl$_2$/MeOH, 9:1) to give the product **9** (20.5 mg, 11%) as a white powder.

General *t*Bu-P4/DMF Procedure: Derivative **7** (1 mmol) was dissolved in anhydrous DMF (4.2 mL), cooled to –78 °C in a dry ice/acetone cooling bath under an argon atmosphere, and *t*Bu–P4 (3 mmol, 0.8 M in hexane) was added. The solution was stirred for 30 min at –78 °C, then placed into an ice bath and warmed to 0 °C. After addition of tosyl chloride (2 mmol) at 0 °C, the reaction solution was warmed slowly to room temperature and vigorous stirring was continued for 1.5 h.

Method A: According to the general *t*Bu–P4/DMF procedure, derivative **7** (42.5 mg, 0.237 mmol), *t*Bu–P4 (890 μL, 0.712 mmol, 0.8 M in hexane), and tosyl chloride (90.46 mg, 0.474 mmol) were used. The reaction was quenched with 1 M HCl (712 μL, 0.712 mmol), the solvent was removed under reduced pressure, and the oil residue was purified by preparative chromatography to obtain the product **9**. The plates were developed two times in a mixture of CH$_2$Cl$_2$/EtOAc (3:1) and additionally in a mixture CH$_2$Cl$_2$/

MeOH (9:1) to give the product **9** (16.6 mg, 21%) as a white solid.

Method B: According to the general *t*Bu–P4/DMF procedure, derivative **7** (15 mg, 0.084 mmol), *t*Bu–P4 (314 μL, 0.251 mmol, 0.8 M in hexane) and tosyl chloride (31.93 mg, 0.167 mmol) were used. The solvent was removed under reduced pressure and the oil residue was purified by preparative chromatography to obtain the product **9**. The plates were developed two times in a mixture of CH_2Cl_2/EtOAc (3:1) and additionally in a mixture of CH_2Cl_2/MeOH (9:1) to give the product **9** (13 mg, 47%) as a white solid.

Method C: According to the general *t*Bu–P4/DMF procedure, derivative **7** (30 mg, 0.167 mmol), *t*Bu–P4 (628 μL, 0.502 mmol, 0.8 M in hexane) and tosyl chloride (63.86 mg, 0.335 mmol) were used. The solution was diluted with hexane, the hexane phase was removed, and the DMF layer was evaporated under reduced pressure. The oil residue was purified by preparative chromatography (CH_2Cl_2/EtOAc, 3:1) to give the product **9**, yield 55.82 mg (58%); white solid; m.p. 238–240 °C; R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 229 (4.26), 264 (4.06), 296 (4.17) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3447, 3069, 1713, 1678, 1637, 1593, 1445, 1394, 1198, 1161 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 15.05 (br. s, 1 H, NH-1′), 11.49 (br. s, 1 H, NH-3), 8.44 (s, 1 H, H-5′), 8.04 (s, 1 H, H-6), 7.90 (d, *J* = 8.4 Hz, 2 H, Ph), 7.49 (d, *J* = 8.0 Hz, 2 H, Ph), 2.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 162.0 (s, C-4), 150.5 (s, C-2), 147.1 (s, C-4′), 145.8 (s, Ph), 141.8 (d, C-5′), 138.1 (d, C-6), 132.0 (s, Ph), 130.6 (d, Ph), 128.1 (d, Ph), 101.0 (s, C-5), 21.4 (q, *C*H$_3$) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{13}H_{12}N_5O_4S$ $[M + H]^+$ 334.0605; found 334.0592.

General Procedure for Condensation of 1,4-Disubstituted Triazoles 2–6 with Sulfonyl Chlorides

DBU/DMF Procedure: To a solution of appropriate 5-triazolyl derivative (0.341 mmol) in anhydrous DMF (2 mL), DBU (0.341 mmol, 97%) was added dropwise. The clear, colourless solution was stirred at room temperature for 30 min. The solution was then cooled to 0 °C and the appropriate sulfonyl chloride (0.341 mmol) was added. The resulting clear yellow mixture was stirred at room temperature for an additional 3 h. The solvent was evaporated under reduced pressure and the residue was purified by crystallisation from methanol to afford the product.

1-(5-Bromothiophene-2-sulfonyl)-5-(1-pivaloyloxymethyl-1*H*-1,2,3-triazol-4-yl)uracil (10): According to DBU/DMF general procedure, 5-triazolyl derivative **2** (100 mg, 0.341 mmol) and 5-bromothiophene-2-sulfonyl chloride (79.3 mg, 0.341 mmol, 97%) were used to give the product **10**, yield 124 mg (70%); white solid; m.p. 233–235 °C; R_f = 0.7 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 237 (4.2), 290 (4.3) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3217, 3150, 3096, 1730, 1720, 1693, 1537, 1448, 1429, 1389, 1257, 1188, 1140, 1022 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.25 (br. s, 1 H, NH-3), 8.64 (s, 1 H, H-6), 8.56 (s, 1 H, H-5′), 7.97 (d, *J* = 4.3 Hz, 1 H, H-3″ or H-4″), 7.50 (d, *J* = 4.2 Hz, 1 H, H-3″ or H-4″), 6.38 (s, 2 H, CH_2), 1.12 (s, 9 H, 3×CH_3) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 176.5 (s, C=O), 161.0 (s, C-4), 153.7 (s, C-2), 146.8 (s, C-4′), 138.7 (d, C-6), 138.0 (s, C-2″), 135.1 (d C-3″), 132.4 (d, C-4″ or C-5′), 131.7 (d, C-4″ or C-5′), 124.9 (s, C-5″), 106.9 (s, C-5), 70.1 (t, CH_2), 38.2 [s, $(CH_3)_3C$-], 26.5 (q, CH_3) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{16}H_{17}BrN_5O_6S_2$ $[M + H]^+$ 517.9804; found 517.9796.

Ethyl 2-{4-[(1-*p*-Tolylsulfonyl)uracil-5-yl]-1*H*-1,2,3-triazol-1-yl}-acetate (11): According to DBU/DMF general procedure, 5-triazolyl derivative **3** (148 mg, 0.558 mmol) and tosyl chloride (106.4 mg, 0.558 mmol) were used to give the product **11**., yield 210 mg (90%); white solid; m.p. 240–242 °C; R_f = 0.6 (CH_2Cl_2/MeOH, 20:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 230 (4.35), 287 (4.08) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3169, 3104, 3055, 1738, 1680, 1594, 1466, 1436, 1383, 1261, 1231, 1192, 1176, 1084, 1045, 1013 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.07 (br. s, 1 H, NH-3), 8.76 (s, 1 H, H-6), 8.50 (s, 1 H, H-5′), 8.01 (d, *J* = 8.5 Hz, 2 H, Ph), 7.50 (d, *J* = 8.2 Hz, 2 H, Ph), 5.46 (s, 2 H, C*H*$_2$), 4.19 (dd, *J* = 7.1, 14.2 Hz, 2 H, C*H*$_2$), 2.43 [s, 3 H, CH_3(Ph)], 1.23 (t, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 167.2 (s, C=O), 161.1 (s, C-4), 146.6 (s, C-2), 146.5 (s, Ph), 137.7 (s, C-4′), 132.9 (s, Ph), 132.4 (d, C-6), 129.9 (d, Ph), 129.3 (d, Ph), 124.8 (d, C-5′), 106.9 (s, C-5), 61.5 (t, CH_2), 50.4 (t, CH_2), 21.2 [q, CH_3(Ph)], 14.0 (q, CH_3) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{17}H_{18}N_5O_6S$ $[M + H]^+$ 420.0978; found 420.0974.

1-(*p*-Tolylsulfonyl)-5-[1-(2-hydroxyethyl)-1*H*-1,2,3-triazol-4-yl]uracil (12): According to DBU/DMF general procedure, 5-triazolyl derivative **4** (30 mg, 0.134 mmol) and tosyl chloride (25.6 mg, 0.134 mmol) were used to give product **12**, yield 30 mg (59%); white solid; m.p. 236–238 °C; R_f = 0.5 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 231 (4.20), 286 (3.39) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3418, 3160, 3107, 1710, 1686, 1649, 1630, 1594, 1448, 1431, 1259, 1188, 1176, 1159, 1084, 1070, 1040, 1022 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.06 (s, 1 H, NH-3), 8.73 (s, 1 H, H-6), 8.40 (s, 1 H, H-5′), 8.00 (d, *J* = 8.5 Hz, 2 H, Ph), 7.50 (d, *J* = 8.1 Hz, 2 H, Ph), 4.47 (t, *J* = 5.4 Hz, 2 H, C*H*$_2$OH), 3.9–4.3 (br. s, 1 H, CH$_2$O*H*), 3.79 (t, *J* = 5.3 Hz, 2 H, C*H*$_2$CH$_2$OH), 2.43 [s, 3 H, CH_3(Ph)] ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]-DMSO): δ = 161.1 (s, C-4), 146.6 (s, C-2), 146.5 (s, Ph), 137.5 (s, C-4′), 132.9 (s, Ph), 132.1 (d, C-6), 129.9 (d, Ph), 129.2 (d, Ph), 123.8 (d, C-5′), 107.1 (s, C-5), 59.9 (t, CH_2), 52.3 (t, CH_2), 21.2 [q, CH_3(Ph)] ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{15}H_{16}N_5O_5S$ $[M + H]^+$ 378.0872; found 378.0852.

1-(5-Bromothiophene-2-sulfonyl)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)uracil (13): According to the DBU/DMF general procedure, 5-triazolyl derivative **5** (250 mg, 0.928 mmol) and 5-bromothiophene-2-sulfonyl chloride (209.4 mg, 0.928 mmol, 97%) were used to give the product **13**, yield 150 mg (35%); white solid; m.p. 204–207 °C; R_f = 0.8 (CH_2Cl_2/MeOH, 9:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 235 (4.3), 290 (4.3) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3062, 1751, 1742, 1698, 1678, 1541, 1460, 139, 1259, 1182 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.21 (br. s, 1 H, NH-3), 8.60 (s, 1 H, H-6), 8.50 (s, 1 H, H-5′), 7.97 (d, *J* = 4.2 Hz, 1 H, H-3″ or H-4″), 7.50 (d, *J* = 4.2 Hz, 1 H, H-3″ or H-4″), 7.32–7.38 (m, 5 H, Ph), 5.67 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 161.2 (s, C-4), 146.9 (s, C-2), 138.6 (d, C-6), 138.0 (s, Ph), 136.0 (s, C-4′), 135.2 (s, C-2″), 131.8 (d, C-3″ or C-4″), 131.6 (d, C-3″ or C-4″), 128.8 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 124.8 (s, C-5″), 123.5 (d, C-5′), 107.4 (s, C-5), 52.8 (t, CH_2) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{17}H_{13}BrN_5O_4S_2$ $[M + H]^+$ 493.9592; found 493.9591.

Hydrogenolysis of 13: 1-(Thiophene-2-sulfonyl)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)uracil (14): 5-Triazolyl derivative **13** (100 mg, 0.202 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2/MeOH (120 mL) and 10% Pd/C (20 mg) was added. The reaction mixture was treated with hydrogen gas (42 psi) in a Parr hydrogenation apparatus for 48 h. The mixture was filtered through a Celite pad and washed with boiling methanol (20 mL). The combined methanol filtrates were concentrated under reduced pressure and the crude material was purified using crystallisation with a CH_2Cl_2/MeOH mixture to obtain the product **14**, yield 77 mg (92%); white solid; m.p. 240–243 °C; R_f = 0.6 (CH_2Cl_2/MeOH, 20:1). UV (MeOH):

λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 231 (4.3), 287 (4.1) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3215, 1734, 1697, 1541, 1448, 1257, 1182 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 12.12 (br. s, 1 H, NH-3), 8.66 (s, 1 H, H-6), 8.48 (s, 1 H, H-5′), 8.28 (dd, *J* = 5.0, 1.4 Hz, 1 H, H-3′′ or H-4′′ or H-5′′), 8.11 (dd, *J* = 4.0, 1.5 Hz, 1 H, H-3′′ or H-4′′ or H-5′′), 7.30–7.39 (m, 6 H, Ph, H-3′′ or H-4′′ or H-5′′), 5.67 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 160.9 (s, C-4), 146.5 (s, C-2), 138.5 (d, C-6), 137.9 (d, C-3′′ or C-4′′ or C-5′′), 137.9 (s, Ph or C-2′′), 135.9 (s, C-4′), 134.6 (s, Ph or C-2′′), 131.9 (d, C-3′′ or C-4′′ or C-5′′), 128.7 (d, Ph), 128.1 (d, C-3′′ or C-4′′ or C-5′′), 128.0 (d, Ph), 127.9 (d, Ph), 123.4 (d, C-5′), 107.2 (s, C-5), 52.8 (t, CH_2) ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{17}H_{14}N_5O_4S_2$ [M + H]$^+$ 416.0487; found 416.0468.

Benzyl 2-{4-[(1-*p*-Tolylsulfonyl)uracil-5-yl]-1*H*-1,2,3-triazol-1-yl}-acetate (15): According to the DBU/DMF general procedure, 5-triazolyl derivative **6** (100 mg, 0.306 mmol) and tosyl chloride (58.3 mg, 0.306 mmol) were used to give the product **15**, yield 126 mg (86%); white solid; m.p. 215–217 °C; R_f = 0.7 (CH_2Cl_2/MeOH, 20:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 231 (4.37), 285 (4.11) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3313, 3139, 1736, 1682, 1543, 1448, 1385, 1254, 1191, 1175, 1020 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 12.07 (br. s, 1 H, NH-3), 8.76 (s, 1 H, H-6), 8.53 (s, 1 H, H-5′), 8.01 (d, *J* = 8.4 Hz, 2 H, Ph), 7.50 (d, *J* = 8.2 Hz, 2 H, Ph), 7.37–7.41 (m, 5 H, Ph), 5.56 (s, 2 H, OCH_2Ph), 5.22 (s, 2 H, CH_2), 2.43 [s, 3 H, CH_3(Ph)] ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 167.2 (s, C=O), 161.1 (s, C-4), 146.6 (s, C-2), 146.5 (s, Ph), 137.8 (s, Ph), 135.4 (s, C-4′), 132.9 (s, Ph), 132.4 (d, C-6), 129.9 (d, Ph), 129.3 (d, Ph), 128.5 (d, Ph), 128.3 (d, Ph), 128.1 (d, Ph), 124.9 (d, C-5′), 106.8 (s, C-5), 66.8 (t, O*C*H_2Ph), 50.4 (t, N*C*H_2CO), 21.2 [q, *C*H_3(Ph)] ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{22}H_{20}N_5O_6S$ [M + H]$^+$ 482.1134; found 482.1120.

1-(*p*-Tolylsulfonyl)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)uracil (16): According to the DBU/DMF general procedure, 5-triazolyl derivative **5** (50 mg, 0.186 mmol) and tosyl chloride (35.4 mg, 0.186 mmol) were used to give the product **16**, yield 59 mg (75%); white solid; m.p. 204–206 °C; R_f = 0.7 (CH_2Cl_2/MeOH, 20:1). UV (MeOH): λ_{max} (log ε, $dm^3 mol^{-1} cm^{-1}$) = 230 (4.33), 286 (4.01) nm. IR (KBr): $\tilde{\nu}_{max}$ = 3057, 1747, 1594, 1560, 1492, 1458, 1330, 1085 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 12.04 (br. s, 1 H, NH-3), 8.73 (s, 1 H, H-6), 8.49 (s, 1 H, H-5′), 7.99 (d, *J* = 8.4 Hz, 2 H, Ph), 7.49 (d, *J* = 8.3 Hz, 2 H, Ph), 7.33–7.38 (m, 5 H, Ph), 5.67 (s, 2 H, CH_2Ph), 2.42 [s, 3 H, CH_3(Ph)] ppm. ^{13}C NMR (75 MHz, APT, [D$_6$]DMSO): δ = 161.2 (s, C-4), 146.6 (s, C-2), 146.4 (s, Ph), 138.0 (s, Ph), 136.0 (s, C-4′), 132.9 (s, Ph), 132.3 (d, C-6), 129.8 (d, Ph), 129.2 (d, Ph), 128.7 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 123.4 (d, C-5′), 106.9 (s, C-5), 52.8 (t, *C*H_2Ph), 21.2 [q, *C*H_3(Ph)] ppm. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{20}H_{18}N_5O_4S$ [M + H]$^+$ 424.1079; found 424.1090.

Computational Details: As a good compromise between accuracy and computational feasibility, all molecular geometries were optimised by the efficient M06-2X/6-31+G(d) model. Thermal corrections were extracted from the corresponding frequency calculations without the application of scaling factors. The final single-point energies were attained with a highly flexible 6-311++G(2df,2pd) basis set using the MP2 approach for reaction free-energies and M06-2X DFT functional for pK_a values. To account for the solvation effects, we included, during both the geometry optimization and single-point energy evaluation, the SMD polarisable continuum model[24] utilising dielectric constants of 37.219 for DMF and 35.688 for MeCN, giving rise to (SMD)/MP2/6-311++G(2df,2pd)//(SMD)/M06-2X/6-31+G(d) and (SMD)/M06-2X/6-311++G-(2df,2pd)//(SMD)/M06-2X/6-31+G(d) models employed here, which turned out to be very accurate in estimating both pK_a and reaction thermodynamic values in solution.[25] All of the transition state structures were verified to have the appropriate imaginary frequency, from which the corresponding reactants and products were determined using the Intrinsic Reaction Coordinate (IRC) procedure.[26] pK_a values were calculated in a relative fashion using $AH + B_{REF}^- \rightarrow A^- + B_{REF}H$ equation, and employing the following reference bases ($B_{REF}H$): Ph_2NH (pK_a = 25.50)[27] for the N–H deprotonation in **5** and **7**, *N*,*N*,*N*′,*N*′-tetramethylguanidine (pK_a = 13.65)[27] for DBUH$^+$ and pyridineH$^+$, H_3PO_4 (pK_a = 8.48)[28] and $H_2PO_4^-$ (pK_a = 10.58)[28] for the first and second deprotonation of H_2CO_3, respectively. Atomic charges were obtained through the Natural Bond Orbital (NBO)[29] analysis at the (SMD)/M06-2X/6-31+G(d) level. All of the calculations were performed using the Gaussian 09 software.[30]

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