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Synthesis and regioselective N- and O-alkylation of 1H- or 3H-[1,2,3]triazolo[4,5-d]pyrimidine-5,7(4H,6H)-diones (8-azaxanthines) and transformation of their 3-alkyl derivatives into 1-alkyl isomers

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Synthesis and Regioselective *N*- and *O*-Alkylation of 1*H*- or 3*H*-[1,2,3]-Triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-Azaxanthines) and Transformation of their 3-Alkyl Derivatives into 1-Alkyl Isomers

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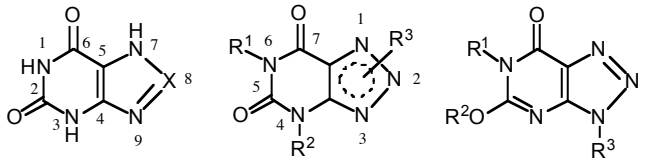
This paper is dedicated to Emeritus Prof. Fumio Yoneda (Kyoto University, Kyoto, Japan) on the occasion of his 77th birthday.

Abstract: Several alkylating agents, *e.g.* alkyl halides and dimethyl sulfate, were employed in aprotic solvents under a variety of conditions for alkylation of mono and disubstituted 1*H*- or 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones, which were prepared by cyclization of the appropriate 5,6-diaminouracils with nitrous acid. The alkylation on the triazole ring in the presence of anhydrous potassium carbonate took place simultaneously at the 1- and 2-positions with the priority at the 2-position. The similar alkylation on the pyrimidine ring with an equivalent alkylating reagent took place only at the 4-position. The alkylation of the 3,6-disubstituted derivatives at room temperature led to the 5-*O*-alkylation accompanied with the 4-*N*-alkylation, but at high temperature only the 4-*N*-alkylation took place. The 3,4,6-trisubstituted derivatives underwent transformation with excess alkylating agents at high temperature leading to the formation of 1,4,6-trisubstituted derivatives with elimination of the 3-substituent.

Key words: 8-azaxanthines, triazolopyrimidines, regioselectivity, alkylations, transformation

Fused pyrimidines, *e.g*. naturally occurring purines, xanthines (I) and their analogues, possess wide biological activities such as antiviral[1] and antitumor activities[1c,d, 2] as well as xanthine oxidase inhibitory activities.[3] In the past few decades, tremendous efforts have been directed to the search of potential anticancer and antiviral drugs without adverse effects, but very effective

and less toxic one has not been found yet. Analogues of naturally occurring purine bases are valuable tools in defining chemical interactions involved in a specific biological response. Structural alternations of xanthine have resulted in several potent antagonists in biological systems,[4] *e.g*. caffeine and theophylline exhibit a variety of pharmacological actions[4f] including antiasthmatic, diuretic, respiratory stimulant, central stimulant, cardiac stimulant, and analgesic adjuvant activities. Adenosine has different roles in modulating the function of the cardiovascular, endocrine, and nervous systems.[5] A variety of analogues of xanthine with different substituents at the different positions have been assessed for potency and selectivity as antagonists at adenosine receptors.[4] Hence, the alkylation of xanthine has been studied intensively,[4b, 6] but the chemistry of 8-azaxanthine (II) has remained largely unexplored area in spite of their biological significance.[7] The limited but encouraging success of clinical treatment[8] of neoplastic diseases in man or other animals by certain purine derivatives and related compounds has prompted us to synthesize and study the biological activity of purine derivatives and their analogues. Therefore, a program on synthesis of fused pyrimidine derivatives for biological evaluation has been in progress in our laboratory. The synthesis of 7*H*- and 9*H*-[1,2,4]-triazolo[3,4-*i*]purines,[9a, b] 7*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones[9c, d] with potential xanthine oxidase inhibitory activities, 7-azapteridine antibiotics with potent anti-viral[9e] and anti-tumor activities[9f] as well as deazaflavin[9g, h] with redox system has been reported. In connection with this program, we communicated in a recent preliminary communication[9i] the reliable synthesis of substituted 1*H*-, 2*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (III) and the transformation of the 3-alkyl derivatives into 1-alkyl isomers, and the first study of their regioselective *O*- (IV) and *N*-alkylation (III). Herein we report full details of the synthesis of substituted 1*H*-, 2*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (III) as well as comprehensive study of their regioselective alkylation and transformation in comparison with xanthine in view of evaluating the positional basis biological activity.

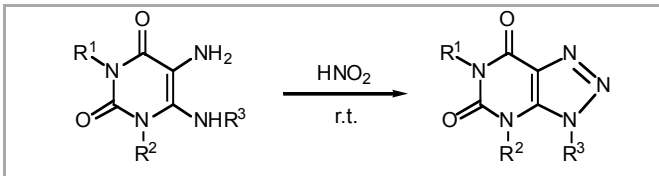


X = CH: **Xanthine (I)**
X = N: **8-Azaxanthine (II)**

(**III**) (**IV**)

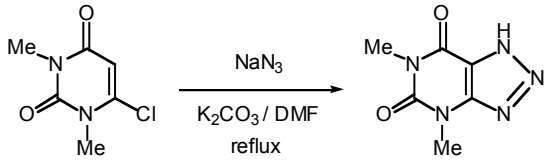
The desired 1*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimi-dine-5,7(4*H*,6*H*)-diones (8-azaxanthines) **2a-z** were synthesized according to the previously outlined procedure.[10, 11] Namely,

6-chlorouracils[12] were converted to the requisite 6-aminouracils by heating with appropriate amines, which on subsequent treatment with nitrous acid gave the corresponding 6-amino-5-nitrosouracils. The reduction for nitroso group into amino group was carried out with sodium dithionite in dilute alkali solution,[13] but the reduction of some hydrophobic nitroso compounds, *e.g*. 6-*n*-heptyl and 6-*n*-octylamino derivatives in aqueous medium, did not proceed smoothly enough. In completing the reduction within the shorter time, an addition of methanol was necessary. The final cyclization of the appropriate 5,6-diaminouracils **1a-z** leading to the formation of substituted 1*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine-5,7(4*H*,6*H*)-diones **2a-z** was accomplished by treating with nitrous acid at room temperature in good yield (Scheme 1). The compound **2z** was also prepared by one path reaction from 6-chloro-1,3-dimethyluracil **3**,[12c] *i.e*. heating compound **3** with sodium azide in the presence of potassium carbonate in *N*,*N*-dimethylform-amide afforded the compound **2z** in 67% yield *via* the formation of 6-azido-1,3-dimethyluracil.[12c]



1a-z **2a-z**

a: R^1= R^2= H, R^3= Me
b: R^1= R^2= H, R^3= Pr
c: R^1= R^2= H, R^3= *i*-Pr
d: R^1= R^2= H, R^3= Bu
e: R^1= R^2= H, R^3= *i*-Bu
f: R^1= R^2= H, R^3= Cyclopentyl
g: R^1= R^2= H, R^3= Heptyl
h: R^1= R^2= H, R^3= Octyl
i: R^1= R^2= H, R^3= $PhCH_2CH_2$
j: R^1= R^2= H, R^3= 2-MeC_6H_4
k: R^1= R^2= H, R^3= 3-MeC_6H_4
l: R^1= R^3= Me, R^2= H
m: R^1= Me, R^2= H, R^3= *i*-Pr
n: R^1= Me, R^2= H, R^3= *i*-Bu
o: R^1= Me, R^2= H, R^3= Cyclopentyl
p: R^1= Me, R^2= H, R^3= Cyclohexyl
q: R^1= Me, R^2= H, R^3= Octyl
r: R^1= Me, R^2= H, R^3= Ph
s: R^1= Me, R^2= H, R^3= Bn
t: R^1= Me, R^2= H, R^3= $PhCH_2CH_2$
u: R^1= Me, R^2= H, R^3= 2-MeC_6H_4
v: R^1= Me, R^2= H, R^3= 3-MeC_6H_4
w: R^1= Me, R^2= H, R^3= 4-MeC_6H_4
x: R^1= Me, R^2= R^3= H
y: R^1= R^3= H, R^2= Me
z: R^1= R^2= Me, R^3= H



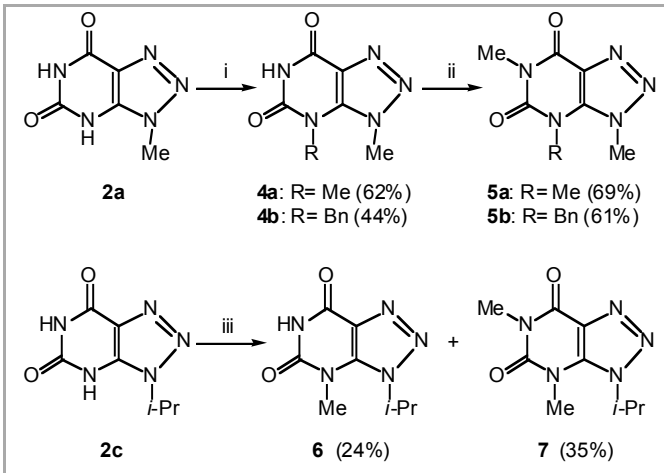
3 **2z** (67%)

Scheme 1

When 3-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **2a** was treated with an equivalent methyl iodide in the presence of anhydrous potassium carbonate in dry *N*,*N*-dimethylformamide at boiling temperature afforded only the 3,4-dimethyl derivative **4a** in 62% yield (Scheme 2). Similarly, benzylation of **2a** with an equivalent benzyl bromide under

same conditions gave the 4-benzyl-3-methyl derivative **4b** in 44% yield. Thus, the alkylation on the pyrimidine ring for the [1,2,3]triazolo[4,5-*d*]pyrimidine system took place not at the 6-position but at the 4-position in spite of steric repulsion of the substituents at the 3-position and the 4-position. In the ^{1}H NMR (DMSO-d_6) spectrum, the singlet signal at δ 3.60 of **4a**, assigned to methyl protons at the 4-position, was closer to other 4-*N*-methylated derivatives (δ 3.33–3.45) than 6-*N*-methylated derivatives (δ 3.18–3.38), and the mp 254–255 °C was also identical with reported mp 256 °C.[10] It is noteworthy that the value (δ 3.60) shifts from the usual value (δ 3.45 for methyl at the 4-position of **10**) to 1.5 ppm low magnetic field due to the peri-interaction of the substituents between 3- and 4-position.

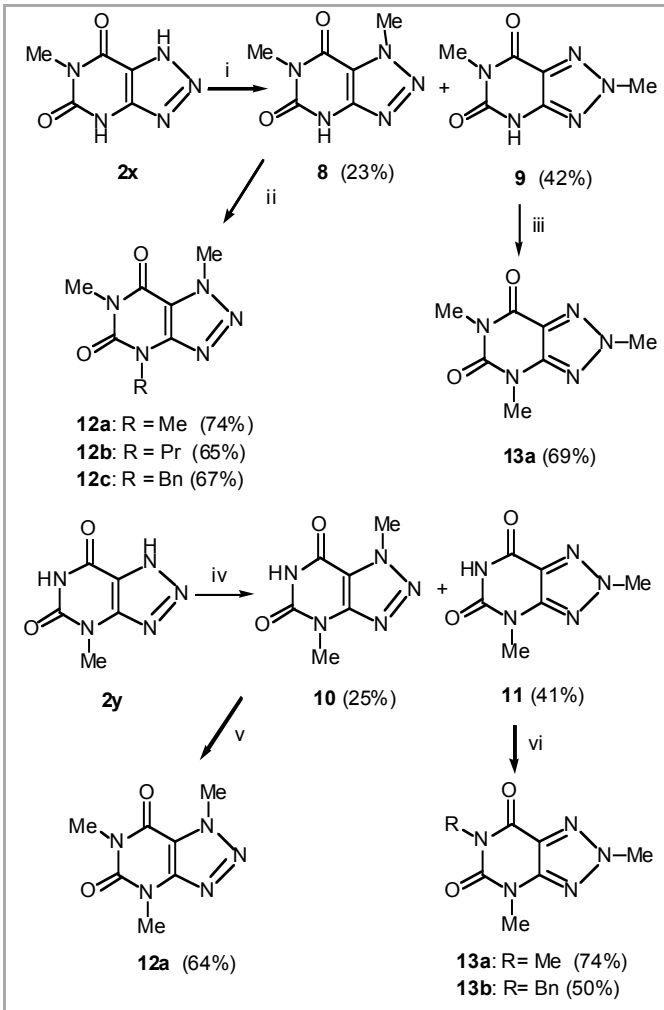
The chemical shift at δ 5.40 due to the 4-*N*-CH_2Ph protons of **4b** was also consistent with the value at δ 5.33 for 4-*N*-CH_2Ph protons of another derivative **12c**. The similar reaction of **2c** with 4 equivalent methyl iodide at 60 °C for overnight gave a mixture of 3-isopropyl-4-methyl **6** and 3-isopropyl-4,6-dimethyl derivative **7** in 24% and 35% yield, respectively. Even in the presence of excess methylating agent in the reaction, the monomethylated derivative **6** was isolated together with **7**. Therefore, it is obvious that the electrophilic substitution reaction on the pyrimidine ring happens more preferentially at the 4-position than at the 6-position.



Scheme 2

The methylation of the 6-methyl derivative **2x** with an equimolecular methyl iodide in *N*,*N*-dimethylformamide at boiling temperature resulted in the formation of two regioisomers of 1,6-dimethyl **8** and 2,6-dimethyl derivative **9** in 23% and 42% yield, respectively (Scheme 3). The same methylation of 4-methyl derivative **2y** also led to two regioisomers of 1,4-dimethyl **10** and 2,4-dimethyl derivative **11** in 25% and 41% yield, respectively. Therefore, it is clear that the methylation on the [1,2,3]-triazolo[4,5-*d*]pyrimidine system with an equivalent alkylating

reagent takes place not on the pyrimidine ring but only on the triazole ring. ^{1}H NMR spectra of the methylated products provided sufficient evidence for methylation at the triazole ring. That is, the chemical shifts for all *N*-CH_3 protons attached to the triazole ring usually appear at δ 4.0–4.4, whereas for *N*-CH_3 protons attached to the pyrimidine ring these appear at δ 3.2–3.8. We observed the chemical shift in the former region (δ 4.0–4.3) for the newly appeared *N*-CH_3 protons attributable to a methyl group on the triazole ring. Some di-*N*-alkyl derivatives (*e.g.* **4a**,**b**, **8–11**) were converted smoothly into tri-*N*-alkyl derivatives (**5a**,**b**, **12a–c**, **13a**,**b**) with appropriate alkyl halides in *N*,*N*-dimethyl-formamide at room temperature or at reflux temperature in good yields.

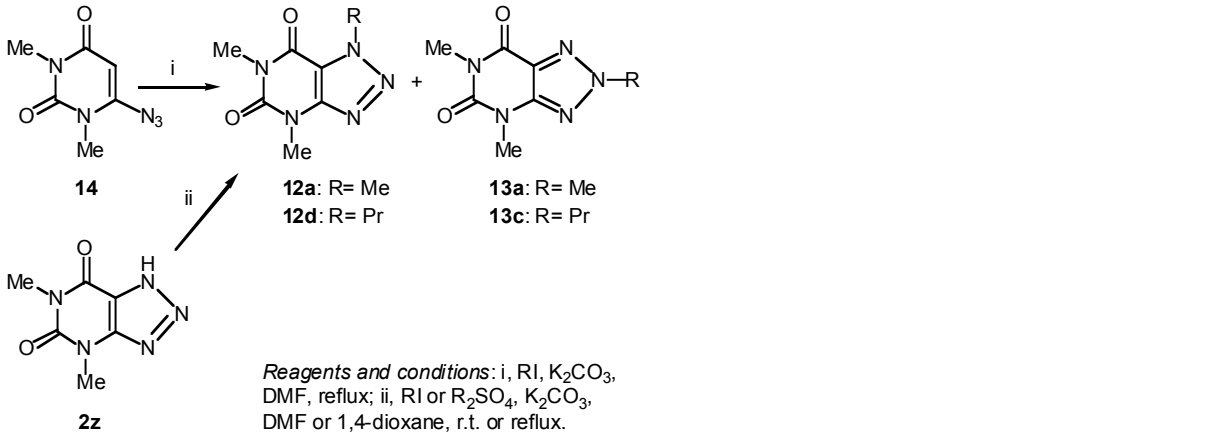


Reagents and conditions: i, MeI (equiv), K_2CO_3, DMF, reflux; ii, RX, K_2CO_3, DMF, r.t. or reflux; iii, MeI, K_2CO_3, DMF, r.t.; iv, MeI (equiv), K_2CO_3, DMF, reflux; v, MeI, K_2CO_3, DMF, reflux; vi, RX, K_2CO_3, DMF, reflux.

Scheme 3

Senga *et al.* reported[14] that heating 4-azido-1,3-dimethyl-uracil **14** with alkyl halide in the presence of potassium carbonate in *N*,*N*-dimethylformamide under reflux gave only

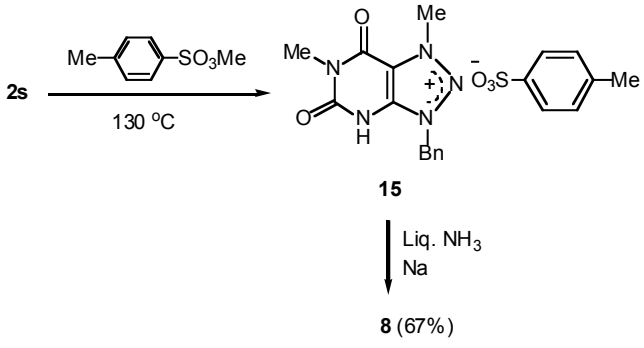
1-alkyl-4,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine-5,7(4*H*,6*H*)-diones **12a**,**d**. In the same reactions, we isolated the 2-alkyl derivatives **13a**,**c** as the major product along with the 1-alkyl isomers **12a**,**d** as shown in Scheme 4. We also carried out the direct alkylation of **2z** with appropriate alkylating agents in dry *N*,*N*-dimethylformamide as well as in 1,4-dioxane at room temperature or boiling temperature to afford always a mixture of two regioisomers of 1- and 2-alkyl derivatives. In all cases, the alkylation on the triazole ring got priority at the 2-position over at the 1-position.



Scheme 4

As described in the above alkylation of **2x**, **2y** and **2z**, it was clarified that the alkylation on the triazole ring always took place simultaneously at the 1- and 2-positions without at the 3-position. Thereupon, we prepared many 3-alkylated triazolopyrimidine derivatives **2a–z** by the definitive method as can be seen in Scheme 1, whose physical and spectral data were quite different from the 1- and 2-alkylated products. The UV spectra for the alkylated compounds also contributed good evidence to assign the alkylated position, since the UV spectrum of the 1- or 2-alkylated each compound in ethanol showed only one maximum absorption band, while the 3-positional analog showed two maximum absorption bands. It is noteworthy that the most preferential alkylation was observed at the 2-position rather than at the 1-position, which might be due to the least electronic and inductive environment around the 2-position. For the differentiation of the 1- and 2-positional isomers, we prepared the 1,6-dimethylated derivative **8** according to the Scheme 5, which on subsequent methylation yielded the 1,4,6-trimethylated derivative **12a** as described in Scheme 3. That is, heating compound **2s** with *p*-toluenesulfonic acid methyl ester at 130 °C gave the 3-benzyl-1,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidinium tosylate **15**.[10] Commonly, removal of benzyl group from any compound is carried out by catalytic

reduction, which is somehow complex method. We developed a simple and convenient method for removal of the benzyl group from the benzyl-triazolopyrimidinium tosylate system. Namely, we used sodium in liquid ammonia for the removal of benzyl group of **15** to produce the compound **8** in highly pure state and good yield. The ^{1}H NMR spectra also provided evidence for discrimination of the 1- and 2-positional isomers exhibiting chemical shift for 1-methyl or 1-methylene protons in the little more down field than that of 2-methyl or 2-methylene protons. For example, the chemical shift assigned to the 1-methyl protons of compound **12a** appeared at δ 4.37, whereas for the 2-methyl protons of **13a** it appeared at δ 4.28. The UV spectra also demonstrated the difference between the 1- and 2-positional isomers. That is, a maximum absorption band for the 1-positional isomers **8**, **10**, **12a–d** appeared at longer wavelength (276–280 nm) than that for the 2-positinal isomers **9**, **11**, **13a–c** (273–277 nm). Considering the above spectral analysis, we can allege that Senga *et al.*[14] mistook to assign the proper position for alkylation. We found the melting points 220–222 °C (lit.,[10] 223–224 °C) for 1,4,6-trimethyl **12a**, 38–39 °C for 4,6-dimethyl-1-propyl **12d**, 195–197 °C (lit.,[10] 197 °C) for 2,4,6-trimethyl **13a** and 79–80 °C for 4,6-dimethyl-2-propyl **13c** derivatives, whereas they reported mps 202–203 °C and 78–79 °C for compounds **12a** and **12d**, respectively. Therefore, considering the melting points of the 1- and 2-positional isomers, it can be said that in fact they did not isolate the 1-positional isomers but isolated the 2-positional isomers.

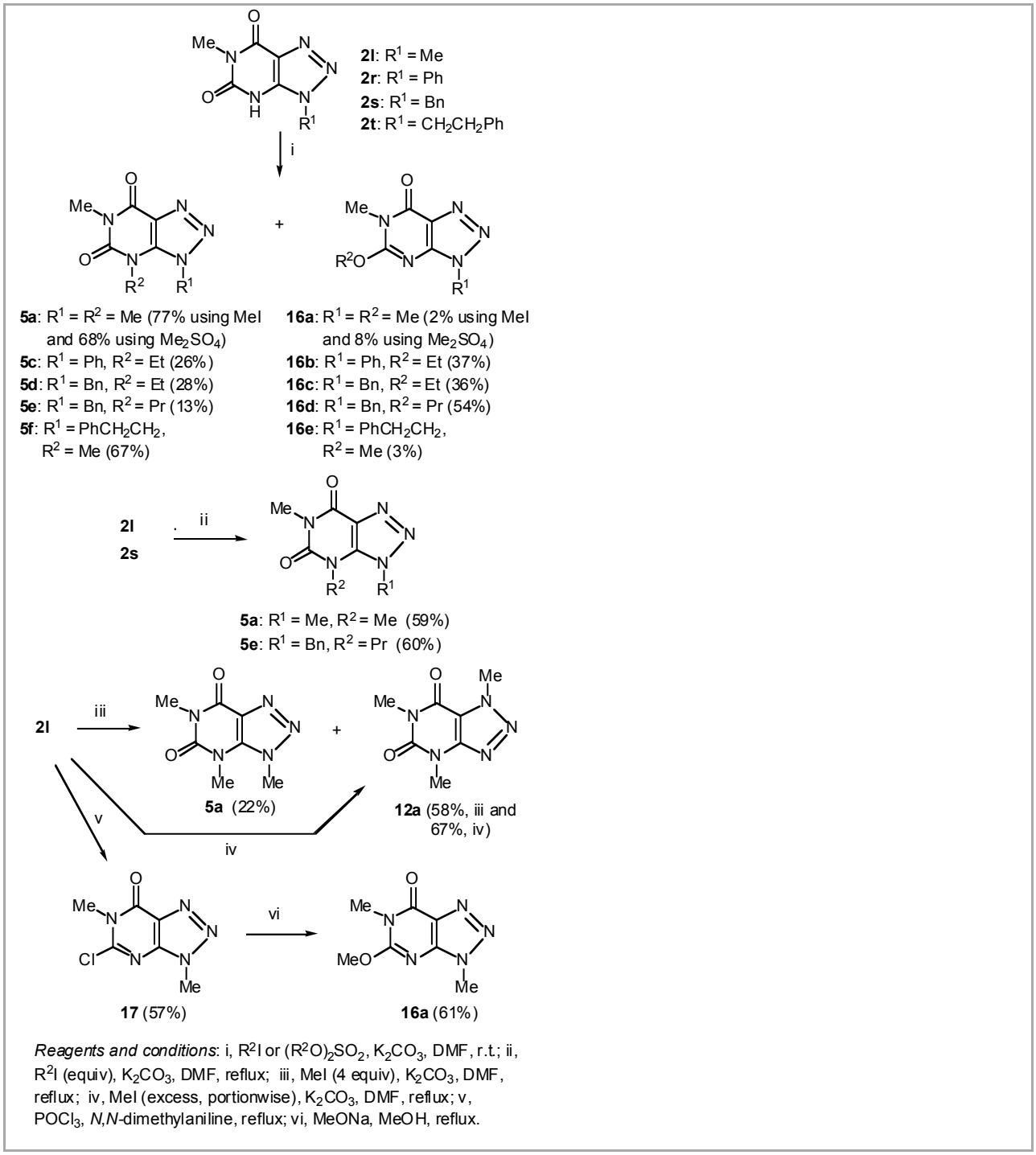


Scheme 5

A superior and novel regioselective alkylation on 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones was accomplished in a simple way, which led to the 5-*O*-alkylation along with 4-*N*-alkylation (Scheme 6). The 5-*O*-alkylation on xanthine and 8-azaxanthine has not been claimed by anyone so far. Thus treatment of 3,6-disubstituted derivatives **2l**, **r**–**t** with excess an appropriate alkyl halide or dimethyl sulfate in the presence of potassium carbonate in *N*,*N*-dimethylformamide at room temperature gave the corresponding mixture of the 4-*N*-alkylated **5a**, **c–f** and 5-*O*-alkylated isomers **16a–e** (i). The

ratio of yields between these two regioisomers was highly affected by size of both the alkylating agents and the 3-substituents. The 5-*O*-alkylation took place in preference to the 4-*N*-alkylation due to the steric repulsion between the bulkyer alkylating agents and 3-substituents, and the opposite result was achieved in the less steric repulsion. For example, when 3,6-dimethyl derivative **2l** was treated with methyl iodide at room temperature, the *O*-methylation (**16a**) of 2% took place with 77% *N*-methylation (**5a**), and the same methylation with dimethyl sulfate yielded the *O*-methylation and *N*-methylation in 8% (**16a**) and 68% (**5a**), respectively. The ethylation of 6-methyl-3-phenyl derivative **2r** with ethyl iodide also contributed the clarification of more steric effect giving the *O*-ethyl isomer **16b** and *N*-ethyl isomer **5c** in 37% and 26% yield, respectively. The effect of great steric repulsion in the propylation of 3-benzyl-6-methyl derivatives (**2s**), which afford a mixture of the *O*-propyl derivative (**16d**, 54% yield) along with *N*-propyl isomer (**13c**, 13% yield), was observed. In contrast to the room temperature, at heating temperature with an equivalent alkyl halide only the 4-*N*-alkylation happened, *e.g*. compounds **2l** and **2s** gave the corresponding **5a** and **5e** in 59% and 60% yield, respectively (ii). However, in the case of the reaction with excess alkyl halide at heating under reflux, the transformation of alkyl group at the 3-position into the 1-position took place principally in single step. For example, heating compound **2l** with four equivalent methyl iodide in *N*,*N*-dimethylformamide at boiling temperature afforded a mixture of compounds **5a** and **12a** in 22% and 58% yield, respectively (iii). The same reaction with more excess methyl iodide (*ca*. 10 eq, added dropwise) at boiling temperature gave only the compound **12a** in 67% yield (iv). The formation of only the 4-*N*-alkylated products (**5a**, **c-f**) with an equivalent alkylating agent at high temperature can be explained by the following fact. That is to say, the adequate energy is supplied to overcome the steric repulsion to afford only the comparatively more stable *N*-alkylated products. In order to confirm the 5-*O*-alkylation, we prepared compound **16a** by the modified procedure[15] outlined previously, *i.e*. heating 5-chloro derivative **17** with sodium methoxide in methanol afforded 5-*O*-methyl derivative **16a** (61%), whose physical and spectral data were quite identical in all respect with the first fraction isolated by column chromatography from a mixture of products obtained by the methylation of **2l** at room temperature. The IR, ^{1}H NMR, ^{13}C NMR and UV spectra for the *O*-alkyl and *N*-alkyl isomers provided clear evidence for discrimination and identification of these products. Usually the IR spectra for 8-azaxanthines show two maximum absorption bands in the regions of 1660–1700 and 1715–1750 cm^{-1} due to the 5-CO and 7-CO groups, respectively. In the case of the *O*-alkylated derivatives, the absorption bands based on the 5-CO in the region of 1660–1700 cm^{-1} disappeared. This clearly indicated the disappearance of the 5-oxo group due to the formation of 5-*O*-alkyl derivatives. Moreover, the ^{1}H NMR spectra displayed significant evidence showing the chemical shift for 5-*O*-C*H* protons (δ 4.04–4.61 for

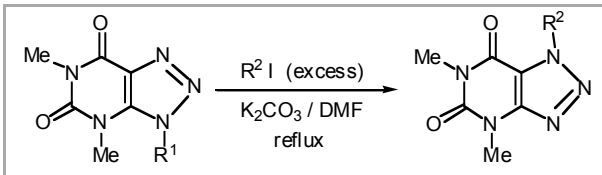
compounds **16a-e**) in the more down field than that of 4-*N*-C*H* protons (δ 3.41–3.98 for compounds **5a**, **c–f**) due to the inductive effect. It is also noteworthy that the chemical shift for the methyl/methylene group attached to the 3-position of 4-*N*-alkylated products appeared in the more down field as compared with the compound having no substituent at the 4-position, *e.g.* δ 4.35 (3-CH_3 for compound **5a**) and δ 4.82–5.81 (3-CH_2 for compound **5d–f**), due to the steric repulsion with the 4-substituent. On the contrary, these values at the 3-position for the 5-*O*-alkylated products appeared in the upper field of δ 4.14 (3-CH_3 for compound **16a**) and δ 4.67–5.59 (3-CH_2 for compound **16c–e**), because the 5-*O*-alkyl group and 3-substitent are too far away to cause interaction. The UV spectra of the 3,4,6-trisubstituted derivatives **5a–f** showed two maximum absorption bands at 240–243 and 256–257 nm, whereas the *O*-alkylated derivatives **16a–e** exhibited only one band at 250–263 nm. The ^{13}C NMR spectra of compounds **5a**, **12a**, **13a** and **16a** were also measured. The chemical shift assigned to carbon of the methyl group attached to the oxygen appears much more down field (δ 56.63 for compound **16a**) than that of any other methyl group (δ 28.21–42.98 for compounds **5a**, **12a**, **13a**) attached to nitrogen due to the inductive effect. Thus, by comparison of several spectral data we distinguished and established the 5-*O*-alkylation along with the 4-*N*-alkylation for 8-azaxanthines.



Scheme 6

We mentioned in the above paragraph that the methylation of 3,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimi-dine-5,7(4*H*,6*H*)-dione **2l** with excess methyl iodide at heating temperature involved some transformation of the 3-methyl derivative (**5a**) into the 1-methyl isomer (**12a**) (iii and iv). Therefore, it should be noted that the alkylation demeanour of xanthine and 8-azaxanthine has some similarities. Usually the alkylation[6] on the imidazole ring of xanthine takes place at the 7-postion, but not at the 9-position. Beside, in 1976 we reported the first transformation[6a] of 9-substituted xanthines into the 7-substituted xanthines

with excess of alkylating agents in aprotic solvent under heating *via* the formation of quaternary xanthinium derivatives alkylated at the 7-position and 9-position followed by elimination of the 9-substituent. Herein we also successfully performed the similar transformation of 3-alkyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimi-dine-5,7(4*H*,6*H*)-diones (8-azaxanthines) into their 1-alkyl derivatives as shown in Scheme 7. For example, heating 3,4,6-trimethyl derivative **5a** with excess methyl iodide and propyl iodide in presence of potassium carbonate in *N*.*N*-dimethylformamide at boiling temperature resulted in the formation of the 1,4,6-trimethyl **12a** and 4,6-dimethyl-1-propyl derivative **12d** in 53% and 61% yield, respectively, *via* the elimination of the 3-methyl group. Similarly, compounds **5f** and **7** with excess methyl iodide afforded **12a** in 49% and 47% yield with the removal of phenethyl and isopropyl group from the 3-position, respectively. On heating of the 3,4,6-trialkyl derivative (**5a**) itself without alkyl halide in *N*,*N*-dimethylformamide, no corresponding transformation was observed. Therefore, a simple thermal transformation was excluded. This necessity of extra alkylating agent suggests that the transformation is accompanied with alkylation at the 1-position of the 3-alkylated triazole moiety, formation of the quaternary salt, and elimination of alkyl group at the 3-position like xanthine to afford the corresponding 1-alkylated derivatives. The physical and spectral data of these transformed compounds were quite identical in all respects with the authentic samples prepared by another methods as shown in Scheme 4.



5a: R^1 = Me
5f: R^1 = CH_2CH_2Ph
7: R^1 = *i*- Pr

12a: R^2 = Me (53% from **5a**, 49% from **5f** and 47% from **7**)
12d: R^2 = Pr (61% from **5a**)

Scheme 7

Thus, this can be concluded that the direction of the electrophilic substitution toward 1*H*- and 3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-aza-xanthines) suggests an important information on the electronic and inductive effects and steric repulsion of the alkyl groups at various positions. The triazole ring contains a single 'tautomeric' hydrogen atom and the alkylation in aprotic solvents suggests that the proton locates not as the 3-*N*H but as the 1-*N*H and 2-*N*H tautomers. Beside, the 4-*N*H proton of imide on the pyrimidone ring also remains as the lactam and lactim tautomers. Hence, the alkylation of the 3,6-disubstituted derivatives at room temperature led to the 5-*O*-alkylation accompanied with the 4-*N*-alkylation, but at high temperature only the 4-*N*-alkylation took place. The transformation of the 3-alkylated derivatives

into the 1-alkylted isomers is facile like xanthine with excess alkyl halide under heating conditions. An order can be made for alkylation at different positions on the trizolopyrimi-dinediones according to the priority as follows: *N*2 > *N*1 > *N*4 > *N*6. Since xanthine and 8-azaxanthine have a great deal of coincidence in structure as well as affinity toward electrophile, so this can be expected that the positional alternation of 8-azaxanthine will result in potent biological activity. Therefore, the convenient synthesis for 8-azaxanthines is noteworthy to explore the biological activities in this area, and further analogues syntheses and biological activities are in progress.

Mps were determined using a Yanagimoto micro-melting point hot stage apparatus and were uncorrected. IR spectra were obtained on a JASCO FT/IR-200 spectrophotometer in Nujol mulls. ^{1}H NMR spectra were recorded using a VXR 300 MHz spectrometer and chemical shift values were expressed in δ values (ppm) relative to TMS as an internal standard. Coupling constants are given in Hz. ^{13}C NMR (75 MHz) spectra were also obtained using the same spectrometer. UV spectra were recorded in EtOH with a Beckman DU-68 spectrophotometer, and absorption values in italic refers to wave length at which shoulders or inflexions occur in the absorption. Microanalyses were measured using a Yanako CHN Corder MT-5-apparatus. Reaction progress was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F_{254} Plate-Merck) using the solvent systems of A (AcOEt–EtOH, 4:1) and B (*n*-hexane–EtOAc, 1:5) and products were visualized by UV light. Column chromatography was accomplished on Daisogel IR-60 (63/210 μm, Daiso Co.). All compounds were obtained as colorless crystals with a few pale yellow crystals.

Preparation of 2a–z; General Procedure

A mixture of the desired 5,6-diaminouracils (7.0 mmol) and 10% HCl (15 mL) was cooled to *ca.* 5 °C in ice-water and a solution of sodium nitrite (12 mmol) in water (3 mL) was added to the mixture dropwise with stirring over 10 min. Then, the mixture was stirred at r.t. for 2–5 h. The solid deposited was collected by filtration, washed with water and dried to afford the corresponding **2a–z**, which were recrystallised from appropriate solvents.

3-Methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2a)

Yield: 0.90 g (77%); mp 311–313 °C (H_2O) (lit.[10] 312 °C); R_f = 0.21 (A).

^{1}H NMR (DMSO-d_6): δ = 3.98 (s, 3 H, CH_3), 11.11 (s, 1 H, 6-NH), 12.33 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 247 (3.98), 276 nm (3.83).

3-Propyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2b)

Yield: 0.98 g (72%); mp 281–283 °C (EtOH); R_f = 0.31 (A).

IR (Nujol): 3210, 3090 (NH), 1735, 1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.84 (sext, *J* = 7.2 Hz, 2 H, N-$CH_2C\mathit{H}_2$), 4.31 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 11.10 (s, 1 H, 6-NH), 12.31 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 249 (4.13), *281* nm (3.85).

Anal. Calcd for $C_7H_9N_5O_2$: C, 43.08; H, 4.65; N, 35.88. Found: C, 42.94; H, 4.57; N, 36.03.

3-Isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2c)

Yield: 1.01 g (74%); mp 306–308 °C (EtOH) (lit.[16] 303–306 °C); R_f = 0.35 (A).

^{1}H NMR (DMSO-d_6): δ = 1.51 (d, *J* = 6.6 Hz, 6 H, 2 x CH_3), 4.80 (sept, *J* = 6.6 Hz, 1 H, CH), 11.16 (s, 1H, 6-NH), 12.25 (s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 249 (4.23), *281* nm (3.84).

3-Butyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2d)

Yield: 1.01 g (69%); mp 272–273 °C (EtOH); R_f = 0.38 (A).

IR (Nujol): 3210, 3050 (NH), 1720, 1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.24–1.32 (m, 2 H, N-$CH_2CH_2C\mathit{H}_2$), 1.73–1.78 (m, 2 H, N-$CH_2C\mathit{H}_2$), 4.34 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 11.19 (s, 1 H, 6-NH), 12.35 (s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 250 (4.03), *281* nm (3.78).

Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.65; H, 5.19; N, 33.34.

3-Isobutyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2e)

Yield: 0.88 g (60%); mp 285–287 °C (EtOH); R_f = 0.37 (A).

IR (Nujol): 3170, 3050 (NH), 1730, 1680 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 0.88 (d, *J* = 6.6 Hz, 6 H, 2 x CH_3), 2.04–2.18 (m, 1 H, CH), 4.17 (d, *J* = 7.2 Hz, 2 H, CH_2), 11.20 (s, 1 H, 6-NH), 12.38 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 250 (4.18), *282* nm (3.81).

Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.69; H, 5.24; N, 33.20.

3-Cyclopentyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2f)

Yield: 1.02 g (66%); mp 299–301 °C (EtOH); R_f = 0.37 (A).

IR (Nujol): 3160, 3080 (NH); 1730, 1680 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 1.63–1.70 (m, 2 H, cyclopentyl-H), 1.80–1.86 (m, 2 H, cyclopentyl-H),

2.02–2.13 (m, 4 H, cyclopentyl-H), 4.88–4.98 (m, 1 H, N-CH), 11.18 (s, 1 H, 6-NH), 12.30 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 249 (4.1), 280 nm (3.95).

Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.96; H, 4.91; N, 31.74.

3-Heptyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2g)

Yield: 1.39 g (79%); mp 276–278 °C (EtOH); R_f = 0.44 (A).

IR (Nujol): 3170, 3060 (NH); 1730, 1690 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.26–1.32 (m, 8 H, $CH_2[CH_2]_4CH_3$), 1.82–1.99 (m, 2 H, N-CH_2CH_2), 4.37 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 10.22 (s, 1 H, 6-NH), 12.43 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 249 (4.06), 279 nm (3.95).

Anal. Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 52.47; H, 6.65; N, 27.57.

3-Octyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2h)

Yield: 1.50 g (81%); mp 273–275 °C (EtOH); R_f = 0.47 (A).

IR (Nujol): 3210, *3050* (NH); 1725, 1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 0.85 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.15–1.38 (br s, 10 H, $CH_2[CH_2]_5CH_3$), 1.72–1.82 (m, 2 H, N-CH_2CH_2), 4.33 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 11.17 (s, 1 H, 6-NH), 12.31 (s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 249 (4.12), 277 nm (3.86).

Anal. Calcd for $C_{12}H_{19}N_5O_2$: C, 54.32; H, 7.22; N, 26.40. Found: C, 54.34; H, 7.21; N, 26.19.

3-Phenethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2i)

Yield: 1.66 g (92%); mp 300–302 °C (MeOH); R_f = 0.37 (A).

IR (Nujol): 3170, 3070 (NH); 1735,1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 3.10 (t, *J* = 7.5 Hz, 2 H, Ph-CH_2), 4.58 (t, *J* = 7.5 Hz, 2 H, N-CH_2), 7.17–7.30 (m, 5 H, Ph-H), 11.18 (s, 1 H, 6-NH), 12.31 (s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 250 (4.18), 280 (4.03).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.95; H, 4.36; N, 27.06.

3-*o*-Tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2j)

Yield: 1.48 g (87%); mp 281–283 °C (EtOH); R_f = 0.40 (A).

IR (Nujol): 3170, 3050 (NH); 1730,1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 2.08 (s, 3 H, CH_3), 7.41–7.54 (m, 4 H, Ar-H), 11.28 (s, 1 H, 6-NH),

12.34 (s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 255 (4.23), *281* nm (3.97).

Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.50; H, 3.93; N, 28.49.

3-*m*-Tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2k)

Yield: 1.41 g (83%); mp 295–297 °C (EtOH); R_f = 0.27 (A).

IR (Nujol): 3170, 3040 (NH); 1730,1700 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 7.39–7.45 (m, 4 H, Ar-H), 11.32 (s, 1 H, 6-NH), 12.38 (br s, 1 H, 4-NH).

UV (EtOH): λ_{max} (log ε) = 276 (4.18), 289 nm (4.18).

Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.30; H, 3.89; N, 28.54.

3,6-Dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2l)

Yield: 0.96 g (76%); mp 298 °C (decomp., H_2O) (lit.[10] 296 °C); R_f = 0.35 (A).

^{1}H NMR (DMSO-d_6): δ = 3.20 (s, 3 H, 6-N-CH_3), 3.99 (s, 3 H, 3-N-CH_3), 12.69 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.05), *278* nm (3.88).

3-Isopropyl-6-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2m)

Yield: 0.91 g (62%); mp 269–271 °C (EtOH); R_f = 0.61 (A).

IR (Nujol): 3170 (NH); 1730, 1665 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 1.52 (d, *J* = 6.6 Hz, 6 H, C*H*$_3$CHC*H*$_3$), 3.19 (s, 3 H, N-CH_3), 4.81 (sept, *J* = 6.6 Hz, 1 H, CH), 12.57 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.10), *281* nm (3.90).

Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.62; H, 5.20; N, 33.47.

3-Isobutyl-6-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2n)

Yield: 1.11 g (71%); mp 241–243 °C (EtOH); R_f = 0.64 (A).

IR (Nujol): 3150 (NH); 1720, 1680 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 0.88 (d, *J* = 6.6 Hz, 6 H, C*H*$_3$CHC*H*$_3$), 2.07–2.16 (m, 1 H, CH), 3.19 (s, 3 H, N-CH_3), 4.20 (d, *J* = 7.2 Hz, 2 H, N-CH_2), 12.63 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.25), *282* nm (3.91).

Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.19; H, 5.77; N, 31.10.

3-Cyclopentyl-6-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2o)

Yield: 1.30 g (79%); mp 272–275 °C (EtOH); R_f = 0.62 (A).

IR (Nujol): 3170 (NH); 1750, 1670 cm^{-1} (CO).

^1H NMR (DMSO-d_6): δ = 1.63–1.72 (m, 2 H, cyclopentyl-H), 1.78–1.88 (m, 2 H, cyclopentyl-H), 1.97–2.15 (m, 4 H, cyclopentyl-H), 3.19 (s, 3 H, N-CH_3), 4.86–4.98 (m, 1 H, N-CH), 12.61 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.14), *281* nm (3.95).

Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 50.94; H, 5.57; N, 29.82.

3-Cyclohexyl-6-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2p)

Yield: 1.24 g (71%); mp 294–296 °C (EtOH); R_f = 0.67 (A).

IR (Nujol): 3140 (NH); 1740, 1665 cm^{-1} (CO).

^1H NMR (DMSO-d_6): δ = 1.25–1.49 (m, 3 H, Cy-H), 1.69–1.91 (m, 5 H, Cy-H), 2.0–2.04 (m, 2 H, Cy-H), 3.22 (s, 3 H, N-CH_3), 4.40–4.49 (m, 1 H, N-CH), 12.59 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.06), 281 nm (3.78).

Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 53.00; H, 6.05; N, 28.00.

6-Methyl-3-octyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2q)

Yield: 1.78 g (91%); mp 182–184 °C (EtOAc); R_f = 0.68 (A).

IR (Nujol): 3170 (NH); 1735, 1660 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.6 Hz, 3 H, CH_2CH_3), 1.25–1.38 (m, 10 H, $CH_2[CH_2]_5CH_3$), 1.92–2.01 (m, 2 H, N-CH_2CH_2), 3.45 (s, 3 H, N-CH_3), 4.46 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 12.29 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 250 (4.08), 282 nm (3.92).

Anal. Calcd for $C_{13}H_{21}N_5O_2$: C, 55.90; H, 7.58; N, 25.07. Found: C, 55.68; H, 7.36; N, 24.86.

6-Methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2r)

Yield: 1.58 g (93%); mp 295–297 °C (EtOH); R_f = 0.51 (A).

IR (Nujol): 3220 (NH); 1735, 1685 cm^{-1} (CO).

^1H NMR (DMSO-d_6): δ = 3.23 (s, 3 H, CH_3), 7.61–7.65 (m, 5 H, Ph-H), 12.75 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = *279* (4.23), 289 nm (4.26).

Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.09; H, 3.83; N, 29.11.

3-Benzyl-6-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2s)

Yield: 1.44 g (80%); mp 238–240 °C (EtOH) (lit.[10] 240–241 °C); R_f = 0.60 (A).

^1H NMR (DMSO-d_6): δ = 3.19 (s, 3 H, CH_3), 5.63 (s, 2 H, CH_2), 7.29–7.40 (m, 5 H, Ph-H), 12.84 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.05), 281 nm (3.99).

6-Methyl-3-phenethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2t)

Yield: 1.60 g (84%); mp 304–306 °C (EtOH); R_f = 0.65 (A).

IR (Nujol): 3140 (NH); 1730, 1660 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 3.11 (t, *J* = 7.5 Hz, 2 H, Ph-CH_2), 3.18 (s, 3 H, CH_3), 4.61 (t, *J* = 7.5 Hz, 2 H, N-CH_2), 7.18–7.27 (m, 5 H, Ph-H), 12.63 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.08), 277 nm (3.99).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.28; H, 4.88; N, 25.63.

6-Methyl-3-*o*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2u)

Yield: 1.37 g (76%); mp 254–256 °C (EtOH); R_f = 0.66 (A).

IR (Nujol): 3160 (NH); 1735, 1680 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H, Ar-CH_3), 3.40 (s, 3 H, N-CH_3), 7.32–7.52 (m, 4 H, Ar-H), 12.28 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 252 (4.07), 282 nm (3.66).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.86; H, 4.38; N, 27.00.

6-Methyl-3-*m*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2v)

Yield: 1.40 g (78%); mp 245–247 °C (EtOH); R_f = 0.61 (A).

IR (Nujol): 3200 (NH); 1720, 1660 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$): δ = 2.47 (s, 3 H, Ar-CH_3), 3.42 (s, 3 H, N-CH_3), 7.34–7.49 (m, 4 H, Ar-H), 12.28 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = *277* (4.15), 290 nm (4.19).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.10; H, 4.42; N, 27.29.

6-Methyl-3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2w)

Yield: 1.50 g (83%); mp 282–284 °C (EtOH); R_f = 0.60 (A).

IR (Nujol): 3140 (NH); 1740, 1665 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 2.46 (s, 3 H, Ar-CH_3), 3.25 (s, 3 H, N-CH_3), 7.40 (d, *J* = 8.1 Hz, 2 H, Ar-*m*H), 7.49 (d, *J* = 8.1 Hz, 2 H, Ar-*o*H), 12.69 (br s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = *277* (4.18), 290 nm (4.21).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.05; H, 4.47; N, 27.10.

6-Methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2x)

Yield: 0.92 g (79%); mp 259–261 °C (H_2O) (lit.[17] 261 °C); R_f = 0.46 (A).

^{1}H NMR (DMSO-d_6): δ = 3.24 (s, 3 H, CH_3), 12.11 (br s, 1 H, 4-NH), 15.75 (br s, 1 H, 3-NH).

UV (EtOH): λ_{max} (log ε) = 264 nm (4.03).

4-Methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2y)

Yield: 1.09 g (93%); mp 314–315 °C (H_2O) (lit.[17] 316 °C); R_f = 0.40 (A).

^{1}H NMR (DMSO-d_6): δ = 3.40 (s, 3 H, CH_3), 11.37 (s, 1 H, 6-NH), 15.65 (br s, 1 H, 3-NH).

UV (EtOH): λ_{max} (log ε) = 265 nm (4.03).

4,6-Dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2z)

Yield: 1.19 g (94%); mp 251–252 °C (EtOH) (lit.[11] 252–253 °C); R_f = 0.49 (A).

^{1}H NMR (DMSO-d_6): δ = 3.25 (s, 3 H, 6-N-CH_3), 3.44 (s, 3 H, 4-N-CH_3), 15.90 (br s, 1 H, 3-NH).

UV (EtOH): λ_{max} (log ε) = 268 nm (4.0).

Preparation of 4,6-Dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2z) by Another Method

A mixture of 6-chloro-1,3-dimethyluracil (**3**, 1.0 g, 5.73 mmol), sodium azide (0.40 g, 6.15 mmol) and anhyd K_2CO_3 (0.80 g, 5.79 mmol) in DMF (50 mL) was heated under reflux for 1.5 h. Then, the solvent was evaporated to dryness *in vacuo* and the residue was dissolved in water (15 mL). The solution was acidified with dilute HCl and was kept in refrigerator for overnight. The solid deposited was collected by filtration followed by washing with water to give the compound **2z** (0.70 g, 67%), which was identical in all respects with the authentic sample prepared by the above general procedure.

Methylation of 3-Methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2a)

To a mixture of **2a** (0.4 g, 2.39 mol) and anhyd K_2CO_3 (0.50 g, 3.62 mmol) in dry DMF (20 mL), MeI (0.34 g, 2.39 mmol) was added at r.t., and the mixture was heated under reflux for 2 h. After the solvent was evaporated to dryness *in vacuo*, the residue was dissolved in water (6 mL) and the resulting solution was acidified with dilute HCl. After keeping the solution in refrigerator for several hours, the solid deposited was collected by filtration, washed with a small quantity of cold water and dried to give the 3,4-dimethyl derivative (**4a**, 0.27 g, 62%); mp 254–255 °C (EtOAc) (lit.[10] 256 °C); R_f = 0.12 (B).

^{1}H NMR (DMSO-d_6): δ = 3.60 (s, 3 H, 4-N-CH_3), 4.27 (s, 3 H, 3-N-CH_3), 11.51 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 238 (4.06), 255 nm (4.04).

Benzylation of 3-Methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2a)

A mixture of **2a** (0.3 g, 1.80 mmol), anhyd K_2CO_3 (0.37 g, 2.68 mmol) and benzyl bromide (0.31 g, 1.81 mmol) in dry DMF (15 mL) was heated under reflux for 4 h. After the solvent was evaporated to dryness *in vacuo*, the residue was dissolved in water (6 mL) and the resulting solution was acidified with dilute HCl. The solid deposited was collected by filtration to give the 4-benzyl-3-methyl derivative (**4b**, 0.2 g, 44%); mp 257–259 °C (EtOH); R_f = 0.27 (B).

IR (Nujol): 3180 (NH); 1735, 1695 cm^{-1} (CO).

^{1}H NMR (DMSO-d_6): δ = 3.95 (s, 3 H, N-CH_3), 5.40 (s, 2 H, N-CH_2), 7.21–7.36 (m, 5 H, Ph-H), 11.65 (s, 1 H, NH).

UV (EtOH): λ_{max} (log ε) = 237 (4.19), 254 nm (4.27).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.18; H, 4.50; N, 27.24.

Methylation of 3-Isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2c)

A mixture of **2c** (0.5 g, 2.56 mmol), anhyd K_2CO_3 (1.0 g, 7.26 mmol) and MeI (1.45 g, 10.22 mmol) in dry DMF (25 mL) was heated at 60 °C for overnight. After the solvent was evaporated to dryness *in vacuo*, the residue was dissolved in water (10 mL) and the resulting solution was acidified with dilute HCl. The products cropped were extracted with CH_2Cl_2 from the solution and the extract was dried over anhyd $MgSO_4$. After evaporating the eluent *in vacuo*, two products were separated by column chromatography using *n*-hexane-EtOAc (5:3) as eluent to give the 4-methyl-3-isopropyl-3*H*- (**6**) and 4,6-dimethyl-3-isopropyl-3*H*- derivative (**7**).

6: Yield: 0.13 g (24%); mp 234–236 °C (*n*-hexane-EtOAc); R_f = 0.21 (B).

IR (Nujol): 3200 (NH); 1730, 1690 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$): δ = 1.75 (d, *J* = 6.6 Hz, 6 H, CH_3CHCH_3), 3.73 (s, 3 H, 4-N-CH_3), 5.05 (sept, *J* = 6.6 Hz, 1 H, CH), 9.97 (br s, 1 H, 6-NH).

UV (EtOH): λ_{max} (log ε) = 236 (4.23), 256 nm (4.20).

Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.80; H, 5.19; N, 33.27.

7: Yield: 0.2 g (35%); mp 147–149 °C (*n*-hexane-EtOAc); R_f = 0.36 (B).

IR (Nujol): 1720, 1680 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$): δ = 1.76 (d, *J* = 6.6 Hz, 6 H, CH_3CHCH_3), 3.45 (s, 3 H, 6-N-CH_3), 3.79 (s, 3 H, 4-N-CH_3), 5.04 (sept, *J* = 6.6 Hz, 1 H, CH).

UV (EtOH): λ_{max} (log ε) = 240 (4.12), 256 nm (4.15).

Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.08; H, 5.78; N, 31.27.

Methylation of 6-Methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2x)

To a mixture of **2x** (0.6 g, 3.59 mol) and anhyd K_2CO_3 (0.75 g, 5.43 mmol) in dry DMF (35 mL), MeI (0.51 g, 3.59 mmol) was added at r.t. and the mixture was heated under reflux for 2 h. The solvent was evaporated to dryness *in vacuo*, and the residue was dissolved in water (8 mL). The resulting solution was acidified with dilute HCl and was kept in refrigerator for several hours. The precipitate deposited was collected by filtration. The two products cropped were separated by column chromatography using *n*-hexane-EtOAc (3:1) as eluent to give the 1,6-dimethyl-1*H*- (**8**) and 2,6-dimethyl-2*H*- derivative (**9**).

8: Yield: 0.15 g (23%); mp 274–276 °C (EtOAc) (lit.[10] 276–278 °C); $R_f = 0.42$ (B).
^{1}H NMR (DMSO-d_6): δ = 3.20 (s, 3 H, 6-N-CH_3), 4.25 (s, 3 H, 1-N-CH_3), 12.33 (s, 1 H, NH).
UV (EtOH): λ_{max} (log ε) = 276 nm (3.85).

9: Yield: 0.27 g (42%); mp 314–315 °C (EtOAc) (lit.[10] 317–318 °C); $R_f = 0.40$ (B).
^{1}H NMR (DMSO-d_6): δ = 3.20 (s, 3 H, 6-N-CH_3), 4.23 (s, 3 H, 2-N-CH_3), 12.17 (s, 1 H, NH).
UV (EtOH): λ_{max} (log ε) = 273 nm (4.00).

Methylation of 4-Methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2y)

The methylation of **2y** was accomplished with an equiv MeI exactly following the above method to give the two regioisomers of 1,4-dimethyl-1*H*- (**10**) and 2,4-dimethyl-2*H*-derivatives (**11**). The solvent system used for separation of these isomers by column chromatography was *n*-hexane-EtOAc (5: 2).

10: Yield: 25%; mp 295–297 °C (EtOAc) (lit.[10] 296–297 °C); $R_f = 0.41$ (B).
^{1}H NMR (DMSO-d_6): δ = 3.45 (s, 3 H, 4-N-CH_3), 4.26 (s, 3 H, 1-N-CH_3), 11.59 (s, 1 H, NH).
UV (EtOH): λ_{max} (log ε) = 279 nm (3.86).

11: Yield: 41%; mp 268–270 °C (EtOAc) (lit.[10] 274 °C); $R_f = 0.40$ (B).
^{1}H NMR (DMSO-d_6): δ = 3.33 (s, 3 H, 4-N-CH_3), 4.25 (s, 3 H, 2-N-CH_3), 11.47 (s, 1 H, NH).
UV (EtOH): λ_{max} (log ε) = 276 nm (4.00).

Methylation of Compounds 4a,b and 8–11; General Procedure

A mixture of the dialkylated derivatives (**4a,b**, **8–11**, 1.1 mmol), anhyd K_2CO_3 (0.23 g, 1.66 mmol) and MeI (0.47 g, 3.31 mmol) in dry DMF (15 mL) was stirred at r.t. or heating under reflux for 2–30 h. After the solvent was evaporated *in vacuo*, water was added (8 mL) to the

residue and the resulting solution was acidified with dilute HCl. The product was extracted with CH_2Cl_2 from the solution and the extract was dried over anhyd $MgSO_4$. The eluent was evaporated *in vacuo* and the resulting crude products were recrystallized from appropriate organic solvents to afford the corresponding trialkylated derivatives **5a**, **5b**, **12a**, **13a**, **12a** and **13a** in 69%, 61%, 74%, 69%, 64% and 74% yield, respectively.

3,4,6-Trimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (5a)

Mp 219–221 °C (EtOAc) (lit.[18] 222 °C); R_f = 0.17 (B).

^{1}H NMR ($CDCl_3$): δ = 3.44 (s, 3 H, 6-N-CH_3), 3.79 (s, 3 H, 4-N-CH_3), 4.35 (s, 3 H, 3-N-CH_3).

^{13}C NMR ($CDCl_3$): δ = 28.32 (6-N-CH_3), 30.95 (4-N-CH_3), 36.54 (3-N-CH_3), 124.83 (7a-C), 140.31(3a-C), 150.38 (7-C), 156.96 (5-C).

UV (EtOH): λ_{max} (log ε) = 240 (4.06), 257 nm (4.08).

4-Benzyl-3,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (5b)

Mp 179–181 °C (EtOAc) (lit.[15] 180–182 °C); R_f = 0.36 (B).

^{1}H NMR (DMSO-d_6): δ = 3.38 (s, 3 H, 6-N-CH_3), 4.05 (s, 3 H, 3-N-CH_3), 5.50 (s, 2 H, N-CH_2), 7.34–7.46 (m, 5 H, Ph-H).

UV (EtOH): λ_{max} (log ε) = 243 (4.21), 257 nm (4.24).

1,4,6-Trimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (12a)

Mp 220–222 °C (*n*-hexane-EtOAc) (lit.[10] 223–224 °C); R_f = 0.49 (B).

^{1}H NMR ($CDCl_3$): δ = 3.42 (s, 3 H, 6-N-CH_3), 3.67 (s, 3 H, 4-N-CH_3), 4.37 (s, 3 H, 1-N-CH_3).

^{13}C NMR ($CDCl_3$): δ = 28.34 (6-N-CH_3), 30.28 (4-N-CH_3), 37.17 (1-N-CH_3), 113.14 (7a-C), 150.29 (3a-C), 150.91 (7-C), 153.64 (5-C).

UV (EtOH): λ_{max} (log ε) = 280 nm (3.88).

2,4,6-Trimethyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (13a)

Mp 195–197 °C (*n*-hexane-EtOAc) (lit.[10] 197 °C); R_f = 0.47 (B).

^{1}H NMR ($CDCl_3$): δ = 3.44 (s, 3 H, 6-N-CH_3), 3.56 (s, 3 H, 4-N-CH_3), 4.28 (s, 3 H, 2-N-CH_3).

^{13}C NMR ($CDCl_3$): δ = 28.45 (6-N-CH_3), 30.90 (4-N-CH_3), 42.98 (2-N-CH_3), 125.10 (7a-C), 149.61(3a-C), 151.20 (7-C), 156.14 (5-C).

UV (EtOH): λ_{max} (log ε) = 276 nm (4.00).

Propylation of 1,6-Dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (8)

A mixture of **8** (0.2 g, 1.1 mmol), anhyd K_2CO_3 (0.23 g, 1.66 mmol) and propyl iodide (0.37 g,

2.18 mmol) in dry DMF (15 mL) was heated under reflux for 4 h. After the solvent was evaporated *in vacuo*, water was added (8 mL) to the residue and the resulting solution was acidified with dilute HCl. Then, the product was extracted with CH_2Cl_2 from the solution and the extract was dried over anhyd $MgSO_4$. Removal of the eluting solution *in vacuo* and purification by recrystallisation from *n*-hexane-EtOAc afforded the 1,6-dimethyl-4-propyl-1*H*- derivative (**12b**); yield: 0.16 g (65%); mp 73–74 °C (*n*-hexane-EtOAc); R_f = 0.68 (B).

IR (Nujol): 1715, 1680 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 1.0 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.85 (sext, *J* = 7.5 Hz, 2 H, N-CH_2CH_2), 3.43 (s, 3 H, 6-N-CH_3), 4.15 (t, *J* = 7.5 Hz, 2 H, 4-N-CH_2), 4.38 (s, 3 H, 1-N-CH_3).

UV (EtOH): λ_{max} (log ε) = 280 nm (4.02).

Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.27; H, 5.76; N, 31.34.

Benzylation of Compounds 8 and 11; General Procedure

Benzylation of **8** and **11** with two equiv benzyl bromide was carried out according to the above procedure to give **12c** and **13b** in 67 and 50%, respectively.

4-Benzyl-1,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (12c)

Yield: 67%; mp 134–136 °C (*n*-hexane-EtOAc); R_f = 0.58 (B).

IR (Nujol): 1720, 1670 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 3.41 (s, 3 H, 6-N-CH_3), 4.36 (s, 3 H, 1-N-CH_3), 5.33 (s, 2 H, N-CH_2), 7.28–7.36 (m, 3 H, Ph-*m*,*p*H), 7.57 (dd, $J_{o,p}$ = 1.8 Hz, $J_{o,m}$ = 7.8 Hz, 2 H, Ph-oH).

UV (EtOH): λ_{max} (log ε) = 280 nm (4.03).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.42; H, 4.89; N, 25.65.

6-Benzyl-2,4-dimethyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (13b)

Yield: 50%; mp 118–120 °C (*n*-hexane-EtOAc); R_f = 0.63 (B).

IR (Nujol): 1730, 1680 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 3.53 (s, 3 H, 4-N-CH_3), 4.28 (s, 3 H, 2-N-CH_3), 5.22 (s, 2 H, N-CH_2), 7.25–7.30 (m, 3 H, Ph-*m*,*p*H), 7.51 (dd, $J_{o,p}$ = 1.8 Hz, $J_{o,m}$ = 7.8 Hz, 2 H, Ph-*o*H).

UV (EtOH): λ_{max} (log ε) = 277 nm (4.20).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.94; H, 4.90; N, 25.85.

Cyclization with Methylation of 6-Azido-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (14)

A mixture of **14** (0.5 g, 2.76 mmol), anhyd K_2CO_3 (0.57 g, 4.12 mmol) and MeI (1.18 g, 8.31

mmol) in dry DMF (30 mL) was heated under reflux for 1.5 h. After the same work-up as mentioned in the method (i) gave **12a** and **13a** in 28% and 41% yield, respectively, which were quite identical in all respect with the methylated products of compound **2z**.

Cyclization with Propylation of 6-Azido-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (14)

A mixture of **14** (0.3 g, 1.66 mmol), anhyd K_2CO_3 (0.34 g, 2.46 mmol) and propyl iodide (0.84 g, 4.94 mmol) in dry DMF (20 mL) was heated under reflux for 1.5 h. After the similar work-up and chromatography as mentioned in the method (iii), the compounds **12d** and **13c** were obtained in 19% and 49% yield, respectively, which were quite identical in all respect with the propylated products of compound **2z**.

12d: Yield: 0.07 g (19%); mp 38–39 °C (*n*-octane-EtOAc); R_f = 0.65 (B).

IR (Nujol): 1715, 1670 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.02 (sext, *J* = 7.2 Hz, 2 H, N-CH_2CH_2), 3.43 (s, 3 H, 6-N-CH_3), 3.69 (s, 3 H, 4-N-CH_3), 4.67 (t, *J* = 7.2 Hz, 2 H, N-CH_2).

UV (EtOH): λ_{max} (log ε) = 279 nm (4.03).

Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.31; H, 5.77; N, 31.53.

13c: Yield: 0.18 g (49%); mp 79–80 °C (*n*-octane-EtOAc); R_f = 0.60 (B).

IR (Nujol): 1725, 1670 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.06 (sext, *J* = 7.2 Hz, 2 H, N-CH_2CH_2), 3.44 (s, 3 H, 6-N-CH_3), 3.56 (s, 3 H, 4-N-CH_3), 4.45(t, *J* = 6.9 Hz, 2 H, N-CH_2).

UV (EtOH): λ_{max} (log ε) = 277 nm (4.17).

Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.10; H, 5.65; N, 31.32.

Alkylation of 4,6-Dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (2z); General Procedure

Methylation:

(i) A mixture of **2z** (0.5 g, 2.76 mmol), anhyd K_2CO_3 (0.57 g, 4.12 mmol) and MeI (1.18 g, 8.31 mmol) in dry DMF (30 mL) was heated under reflux for 1.5 h. After the solvent was evaporated to dryness *in vacuo*, water (10 mL) was added to the residue and the resulting solution was kept in refrigerator for overnight. The solid deposited was collected by filtration followed by washing with water. The two isomers cropped were separated by column chromatography using *n*-hexane-EtOAc (7:2) as eluent to give the first and second fraction as 1,4,6-trimethyl-1*H*- (**12a**)

and 2,4,6-trimethyl-2*H*- derivative (**13a**) in 17% and 55% yield, respectively.

(ii) The above methylation of **2z** with MeI at r.t. for 8 h gave **12a** and **13a** in 28% and 42% yield, respectively.

(iii) A mixture of **2z** (0.35 g, 1.93 mmol), K_2CO_3 (0.54 g, 3.91 mmol) and dimethyl sulfate (0.49 g, 3.88 mmol) in dry DMF (20 mL) was heated under reflux 4 h. After the similar work-up and chromatography as mentioned in the method (i), the products **12a** and **13a** were obtained in 21% and 35% yield, respectively.

(iv) The above methylation of **2z** with dimethyl sulfate at r.t. 8 h gave **12a** and **13a** in 30% and 44% yield, respectively.

(v) A mixture of **2z** (0.35 g, 1.93 mmol), anhyd K_2CO_3 (0.54 g, 3.91 mmol) and dimethyl sulfate (0.49 g, 3.88 mmol) in dry 1,4-dioxane (30 mL) was heated under reflux for 6 h. After the similar work-up and chromatography as mentioned in the method (i), the compounds **12a** and **13a** were obtained in 22% and 36% yield, respectively.

Propylation:

A mixture of **2z** (0.5 g, 2.76 mmol), anhyd K_2CO_3 (0.57 g, 4.12 mmol) and propyl iodide (1.41 g, 8.31 mmol) in dry DMF (25 mL) was heated under reflux for 2 h. After the solvent was evaporated *in vacuo*, water (10 mL) was added to the residue and the resulting solution was acidified with dilute HCl. The products were extracted with CH_2Cl_2 from the solution and the extract was dried over anhyd $MgSO_4$. Evaporation of the eluent *in vacuo* and separation of the products by column chromatography on silica gel using *n*-hexane-EtOAc (9:2) afforded the 4,6-dimethyl-1-propyl-1*H*- (**12d**) and 4,6-dimethyl-2-propyl-2*H*-derivatives (**13c**) in 16% and 62% yield, respectively.

Debenzylation of 3-Benzyl-1,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidinium tosylate (15)

To a mixture of **15**[10] (1.2 g, 2.71 mmol) and liquid ammonia (20 mL) under cooling in dry ice with acetone, a few small pieces of sodium were added slowly with stirring until the permanent blue color solution existed. Then, a little ammonium chloride was added into the solution to remove the blue color. After excess ammonia of the solution was evaporated, water (8 mL) was added to the residue. The resulting solution was acidified with 10% HCl and was kept in refrigerator for several hours. The deposited solid was collected by filtration, washed with water and *n*-hexane to afford the product **8** (0.33 g, 67%).

Regioselective Alkylation of 3,6-Disubstituted 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (2l, r–t) at Room Temperature; General Procedure

A mixture of 3,6-disubstituted derivatives (**2l, r–t**, 2.9 mmol), anhyd K_2CO_3 (5.8 mmol) and an appropriate alkylating agent (8.7 mmol) in dry DMF (25 mL) was stirred at r.t. for 1–2 d. After the solvent was evaporated *in vacuo*, water (12 mL) was added to the residue and the resulting solution was acidified with dilute HCl. The products were extracted from the solution with CH_2Cl_2 and the extract was dried over anhyd $MgSO_4$. Evaporation of the eluent *in vacuo* and separation of the residual products by column chromatography using *n*-hexane-EtOAc as eluting solvent always gave the corresponding a mixture of 4-*N*-alkylated and 5-*O*-alkylated isomers.
(i) Methylation of **2l** with MeI gave the 4-*N*-methyl (**5a**) and 5-*O*-methyl (**16a**) isomers in 77% and 2% yield, respectiely, whereas with dimethyl sulfate, the same isomers of **5a** (68%) and **16a** (8%) were obtained. (ii) Ethylation of **2r** with ethyl iodide gave the 4-*N*-ethyl (**5c**) and the 5-*O*-ethyl (**16b**) isomers in 26% and 37% yield, respectively. (iii) Ethylation of **2s** with ethyl iodide gave the 4-*N*-ethyl (**5d**) and 5-*O*-ethyl (**16c**) isomers in 28% and 36% yield, respectively. (iv) Propylation of **2s** with propyl iodide gave the 4-*N*-propyl (**5e**) and 5-*O*-propyl (**16d**) isomers in 13% and 54% yield, respectively. (v) Methylation of **2t** with methyl iodide gave the 4-*N*-methyl (**5f**) and 5-*O*-methyl (**16e**) isomers in 67% and 3% yield, respectively.

5c: Mp 170–172 °C (*n*-octane-EtOAc); R_f = 0.63 (B).
IR (Nujol): 1725, 1680 cm^{-1} (CO).
^{1}H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.47 (s, 3 H, N-CH_3), 3.74 (q, *J* = 6.9 Hz, 2 H, 4-N-CH_2), 7.51–7.55 (m, 2 H, Ph-*m*H), 7.61–7.69 (m, 3 H, Ph-*o*,*p*H).
UV (EtOH): λ_{max} (log ε) = 243 (4.18), 256 nm (4.21).
Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.41; H, 4.85; N, 25.76.

5d: Mp 162–164 °C (*n*-octane-EtOAc); R_f = 0.61 (B).
IR (Nujol): 1720, 1670 cm^{-1} (CO).
^{1}H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.42 (s, 3 H, N-CH_3), 3.98 (q, *J* = 7.2 Hz, 2 H, 4-N-CH_2), 5.81 (s, 2 H, 3-N-CH_2), 7.07-7.10 (m, 2 H, Ph-*m*H), 7.36-7.40 (m, 3 H, Ph-*o*,*p*H).
UV (EtOH): λ_{max} (log ε) = 242 (4.20), 256 nm (4.22).
Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.91; H, 5.34; N, 24.16.

5e: Mp 163–164 °C (*n*-octane-EtOAc); R_f = 0.66 (B).

IR (Nujol): 1720, 1680 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 0.93 (t, *J* = 7.8 Hz, 3 H, CH_2CH_3), 1.59 (sext, *J* = 7.8 Hz, 2 H, N-CH_2CH_2), 3.42 (s, 3 H, N-CH_3), 3.84 (t, *J* = 8.1 Hz, 2 H, 4-N-CH_2), 5.79 (s, 2 H, 3-N-CH_2), 7.05–7.08 (m, 2 H, Ph-*m*H), 7.37–7.42 (m, 3 H, Ph-*o*,*p*H).

UV (EtOH): λ_{max} (log ε) = 242 (4.21), 256 nm (4.23).

Anal. Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.25; H, 5.73; N, 23.54.

5f: Mp 185–187 °C (*n*-octane-EtOAc); R_f = 0.46 (B).

IR (Nujol): 1725, 1670 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 3.30 (t, *J* = 6.6 Hz, 2 H, Ph-CH_2), 3.36 (s, 3 H, 6-N-CH_3), 3.41 (s, 3 H, 4-N-CH_3), 4.82 (t, *J* = 6.9 Hz, 2 H, N-CH_2), 7.0–7.03 (m, 2 H, Ph-*m*H), 7.26-7.30 (m, 3 H, Ph-*o*,*p*H).

UV (EtOH): λ_{max} (log ε) = 242 (4.12), 257 nm (4.17).

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.71; H, 5.40; N, 24.21.

16a: Mp 175–177 °C (*n*-hexane-EtOAc) (lit.[15] 178–179 °C); R_f = 0.32 (B).

^1H NMR ($CDCl_3$): δ = 3.50 (s, 3 H, 6-N-CH_3), 4.09 (s, 3 H, 5-O-CH_3), 4.14 (s, 3 H, 3-N-CH_3).

^{13}C NMR ($CDCl_3$): δ = 28.21 (6-N-CH_3), 32.53 (3-N-CH_3), 56.63 (5-O-CH_3), 126.02 (7a-C), 147.41(3a-C), 155.64 (7-C), 157.28 (5-C).

UV (EtOH): λ_{max} (log ε) = 250 nm (4.18).

16b: Mp 164–166 °C (*n*-hexane-EtOAc); R_f = 0.69 (B).

IR (Nujol): 1720 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 1.51 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.55 (s, 3 H, N-CH_3), 4.61 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 7.43–7.48 (m, 1 H, Ph-*p*H), 7.53–7.59 (m, 2 H, Ph-*m*H), 8.09–8.12 (m, 2 H, Ph-*o*H).

UV (EtOH): λ_{max} (log ε) = 263 nm (4.36).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.38; H, 4.90; N, 25.61.

16c: Mp 110–111 °C (*n*-hexane-EtOAc); R_f = 0.65 (B).

IR (Nujol): 1720 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 1.47 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 3.48 (s, 3 H, N-CH_3), 4.56 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 5.59 (s, 2 H, N-CH_2), 7.32-7.39 (m, 5 H, Ph-H).

UV (EtOH): λ_{max} (log ε) = 252 nm (4.26).

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 59.21; H, 5.43; N, 24.16.

16d: oily amorphous; R_f = 0.71 (B).

IR (Nujol): 1720 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.86 (sext, *J* = 6.6 Hz, 2 H, O-CH_2CH_2), 3.49 (s, 3 H, N-CH_3), 4.45 (t, *J* = 6.6 Hz, 2 H, O-CH_2), 5.59 (s, 2 H, N-CH_2), 7.32-7.39 (m, 5 H, Ph-H).

UV (EtOH): λ_{max} (log ε) = 252 nm (4.27).

Anal. Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 59.91; H, 5.48; N, 23.15.

16e: Mp 119–121 °C (*n*-hexane-EtOAc); R_f = 0.56 (B).

IR (Nujol): 1710 cm^{-1} (CO).

^1H NMR ($CDCl_3$): δ = 3.29 (t, *J* = 7.2 Hz, 2 H, Ph-CH_2), 3.47 (s, 3 H, N-CH_3), 4.04 (s, 3 H, O-CH_3), 4.67 (t, *J* = 7.2 Hz, 2 H, N-CH_2), 7.12–7.15 (m, 2 H, Ph-*m*H), 7.23–7.28 (m, 3 H, Ph-*o,p*H).

UV (EtOH): λ_{max} (log ε) = 252 nm (4.35).

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.57; H, 5.23; N, 24.39.

Methylation of 2l under Heating

With an equiv MeI: A mixture of **2l** (0.3 g, 1.66 mmol), anhyd K_2CO_3 (0.34 g, 2.46 mmol) and MeI (0.24 g, 1.69 mmol) in dry DMF (15 mL) was heated under reflux for 2 h. After the similar work-up as noted above in general procedure and recrystallisation of the crude product from EtOAc afforded only the 4-*N*-methyl product **5a** (0.19 g, 59%).

With 4 equiv MeI: A mixture of **2l** (0.5 g, 2.76 mmol), anhyd K_2CO_3 (0.57 g, 4.12 mmol) and MeI (1.57 g, 11.06 mmol) in dry DMF (25 mL) was heated under reflux for 2 h. After the similar work-up as noted above in general procedure and separation by column chromatography of the mixture of products using *n*-hexane-EtOAc (5:2 → 1:1) gave the pruducts **5a** and **12a** in 22% and 58% yield, respectively.

With 10 equiv MeI: A mixture of **2l** (0.4 g, 2.21 mmol), anhyd K_2CO_3 (0.60 g, 4.34 mmol) and MeI (0.95 g, 6.69 mmol) in dry DMF (25 mL) was heated under reflux for 5 h. In this reaction, another portion of MeI (0.57 g, 4.02 mmol) was added to the reaction mixture after every one hour. After the solvent was evaporated to dryness *in vacuo*, water (10 mL) was added to the residue and the resulting solution was acidified with dilute HCl. The product was extracted with CH_2Cl_2 from the solution. Then, the usual work-up and purification by column chromatography using *n*-hexane-EtOAc (2:1) as eluent gave only the product **12a** (0.29 g, 67%).

Propylation of 2s under Heating

A mixture of **2s** (0.43 g, 1.67 mmol), anhyd K_2CO_3 (0.34 g, 2.46 mmol) and propyl iodide (0.29 g, 1.71 mmol) in dry DMF (15 mL) was heated under reflux for 2 h. After the similar work-up as mentioned in the methylation of **2l**, only the 4-*N*-propyl product (**5e**) was obtained in 60% yield.

Preparation of 3,6-Dimethyl-5-methoxy-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16a) *via* 17

To a solution of sodium (0.03 g, 1.3 mmol) dissolved in absolute MeOH (25 mL), compound **17**[15] (0.2 g, 1.0 mmol) was added and the mixture was heated under reflux for 30 min. After the solvent was evaporated to dryness *in vacuo*, and water (8 mL) was added to the residue and the resulting solution was acidified with dilute HCl. The product was extracted with CH_2Cl_2 from the solution and the extract was dried over anhyd $MgSO_4$. Evaporation of the eluent *in vacuo* and purification of the residual product by crystallization from *n*-hexane-EtOAc gave **16a** (0.12 g, 61%).

Transformation of 3,4,6-Trisubstituted Derivatives (5a,f, 7) into 1,4,6-Trisubstituted Derivatives (12a,d)

(i) ***3,4,6-Trimethyl derivative (5a) into 1,4,6-trimethyl derivative (12a)***: A mixture of **5a** (0.2 g, 1.03 mmol), anhyd K_2CO_3 (0.22 g, 1.59 mmol) and MeI (0.44 g, 3.1 mmol) in dry DMF (15 mL) was heated under reflux for 1 h. Then, another portion of MeI (0.29 g, 2.04 mmol) was added to the reaction mixture five times for after every one hour. Then, the solvent was evaporated to dryness *in vacuo* and water was added to the residue. After the resulting solution was acidified with dilute HCl, the product was extracted with CH_2Cl_2 from the solution, and the eluting solution was dried over anhyd $MgSO_4$. After the usual work-up and purification by column chromatography using *n*-hexane-EtOAc (2:1) as eluent, the compound **12a** was obtained in 53% yield.

(ii) ***4,6-Dimethyl-3-phenethyl derivative (5f) into 1,4,6-trimethyl derivative (12a)***: A mixture of **5f** (0.3 g, 1.05 mmol), anhyd K_2CO_3 (0.21 g, 1.52 mmol) and MeI (0.45 g, 3.17 mmol) in dry DMF (20 mL) was heated under reflux for 1 h. Then, another portion of MeI (0.3 g, 2.11 mmol) was added to the reaction mixture five times for very one hour. After evaporation of the solvent to dryness *in vacuo*, water was added to the residue and the resulting solution was acidified with dilute HCl. The product was extracted with CH_2Cl_2 from the solution. Then, the usual work-up and column chromatography for the product as noted above procedure gave **12a** in 49% yield.

(iii) ***3-Isopropyl-4,6-dimethyl derivative (7) into 1,4,6-trimethyl derivative (12a)***: This

transformation was carried out in the same manner as noted above procedure to give **12a** (47%).

(**iv**) ***3,4,6-Trimethyl derivative (5a) into 4,6-dimethyl-1-propyl derivative (12d)***: A mixture of **5a** (0.2 g, 1.03 mmol), anhyd K_2CO_3 (0.22 g, 1.59 mmol) and propyl iodide (0.35 g, 2.06 mmol) in dry DMF (15 mL) was heated under reflux for 4 h. Then, another portion of propyl iodide (0.25 g, 1.47 mmol) was added to the reaction mixture three times for every four hours. After the solvent was evaporated to dryness *in vacuo*, water was added to the residue and the resulting solution was acidified with dilute HCl. The product was extracted with CH_2Cl_2 from the solution. Then, the usual work-up and column chromatography using *n*-hexane-EtOAc (5:2) as eluent afforded the compound **12d** in 61% yield.

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