Tetrahedron 68 (2012) 214–225

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 1,2,3-triazolo-nucleosides via the post-triazole N-alkylation

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ARTICLE INFO

Article history:
Received 18 July 2011
Received in revised form 5 October 2011
Accepted 17 October 2011
Available online 24 October 2011

Keywords:
1,2,3-Triazoles
2*H*-1,2,3-Triazole
N-Unsubstituted-1,2,3-triazole
Nucleosides
Click chemistry

ABSTRACT

2-Substituted-2*H*-1,2,3-triazolo-nucleosides with 3-phosphonopropyl, 2-hydroxyethyl, 2-cyanoethyl, carbamoylmethyl, or 1-deoxy-2,5-anhydro-D-mannitol-1-yl on the triazole N-2 nitrogen atom were obtained via the DBU-promoted N-alkylation of 3-(pivaloyloxymethyl)-1-[(*NH*-1,2,3-triazol-4-yl)methyl] thymine with diethyl 3-bromopropylphoshonate, 2-bromoethanol, acrylonitrile, methyl bromoacetate, or 3,4,6-tris(*O*-benzoyl)-2,5-anhydro-D-mannitol 1-tosylate. The N-2/N-1 regioselectivity of the alkylation varied from 57/43 (methyl bromoacetate) to 97/3 (diethyl 3-bromopropylphoshonate). The 1-substituted-1*H*-1,2,3-triazoles, when formed in the appreciated amount in the alkylation reaction, were converted into the corresponding 1-substituted-1*H*-1,2,3-triazolo-nucleosides. The substitution pattern of 2-substituted-2*H*-1,2,3-triazolo-nucleosides was confirmed by $^{1}H-^{15}N$ HMBC NMR spectra; the triazole nitrogen atoms were identified through their correlations with the triazole *exo*-cyclic protons.

1. Introduction

The discovery of azidothymidine (Fig. 1, AZT) and ribavirine (Fig. 1) as antiviral drugs provided an inspiration for the synthesis and biological evaluation of their 1,2,3-triazolo-analogues. Generally, the 1,2,3-triazole framework offers the 1*H*-, 2*H*- or 4*H*-substitution pattern, depending on the position of the substituents in the ring.[1] However, the majority of the 1,2,3-triazolo-nucleosides described to date bear the 1*H*-1,2,3-triazole residue in their structure. Taking into account the 1*H*-1,2,3-triazole-substitution pattern, these analogues can be classified as 1,4-disubstited-,[2,3] 1,5-disubstited-,[4] or 1,4,5-trisubstituted-1*H*-1,2,3-triazoles.[5] The two former subclasses of analogues have attracted considerable interest since the copper-[6] or ruthenium-mediated[4d,7] azide–alkyne cycloaddition was developed for the regioselective synthesis of 1,4- or 1,5-disubstited-1*H*-1,2,3-triazoles, respectively. The role of the triazole residue in the structure of the aforementioned nucleoside analogues is schematically shown in Fig. 1: (i) a substituent in a sugar[2,4a–f] or a nucleobase[2a,c,4g] moiety of the parent nucleoside (structures **A** or **B**), (ii) a nucleobase surrogate (structures **C**[2a–c,4h–n,5]), or (iii) a spacer between the nucleobase and the sugar or a sugar mimic (structures **D**[2a,b,3]). Nucleoside analogues bearing an *N*-unsubstituted-1,2,3-triazole residue or a 2-substituted-2*H*-1,2,3-triazole framework are much less explored (Fig. 1, compounds **1**–**3**). To the best of our knowledge, compound **1**[8] represents the only example of the *N*-unsubstituted-1,2,3-triazolo-nucleoside. Among analogues bearing the 2-substituted-2*H*-1,2,3-triazole framework, the only derivatives **2**[9] with the triazole in the role of the nucleobase surrogate were described to date. Literature data on 2-substituted-2*H*-1,2,3-triazoles bearing a nucleobase residue are also limited. Only a few 2-(purin-8-yl)-2*H*-1,2,3-triazoles **3**[10] were reported. Among them, the butyl derivative **3a** (ST 1535) has received great attention because of its pronounced antiparkinsonian activity.[11] A small number of the *N*-unsubstituted- or 2-substituted-2*H*-1,2,3-triazolo-nucleoside analogues might be considered as one of the factors restricting systematic structure–activity relationship (SAR) studies of 1,2,3-triazolo-nucleosides. In the field of non-nucleoside 1,2,3-triazoles, the SAR studies taking into account 2-substituted-2*H*-1,2,3-triazoles led to the identification of several 2-substituted-2*H*-1,2,3-triazole-derived local anaesthetics,[12a–c] Kv 1.5 channel blockers,[12d] antitubercular agents,[12e] or anti-inflammatory agents.[12f] Recently, a novel 2-substituted-2*H*-1,2,3-triazole-based drug candidate (Merck & Co., MK-4305) has been approved for phase III clinical trials for the treatment of primary insomnia.[13] In the field of 1,2,3-triazolo-nucleosides, the reported SAR studies have been focused mostly on isomeric 1,4-/1,5-disubstituted-1*H*-1,2,3-triazolo-nucleosides.[4a,b,i,l,m] Since nucleoside analogues bearing the 2-substituted-2*H*-1,2,3-triazol-2-yl residue represent a relatively narrow class of compounds, an effect of the triazole N-2 substitution pattern on biological properties of 1,2,3-triazolo-nucleosides has not been fully explored. A SAR study, comparing compound **2a** (Fig. 1) and its triazole N-1 isomer (Fig. 1, compound **C**, n=1, R=4-C(O)NH_2, S=β-D-2-deoxyribofuranosyl) in terms of their base-pairing

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doi:10.1016/j.tet.2011.10.067

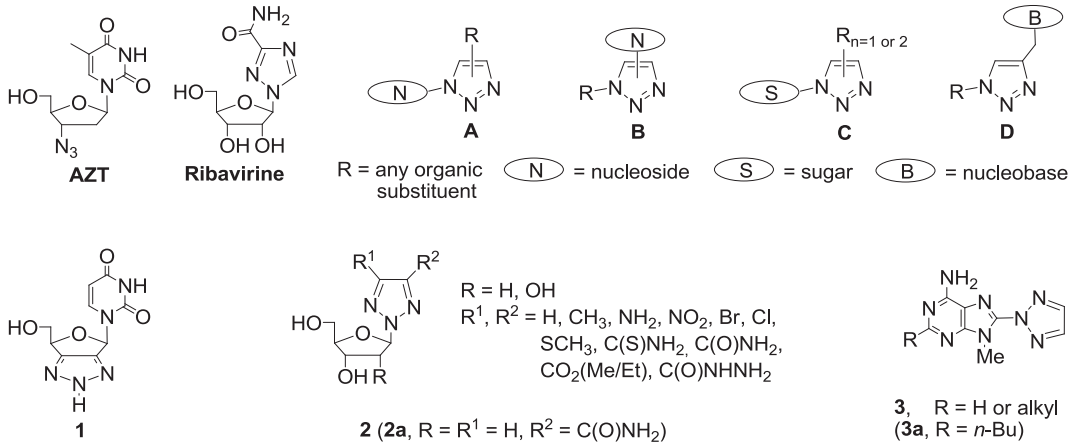


Fig. 1. Schematic representations of 1,4- or 1,5-disubstituted-1*H*-1,2,3-triazolo-nucleosides (structures **A**–**D**) as well as the reported 1,2,3-triazolo-nucleosides with the *N*-unsubstituted- or 2-substituted-2*H*-1,2,3-triazole framework.

properties during *Taq* polymerase-catalyzed biosynthesis of DNA, was reported.[9a] In this study, **2a** showed more favourable base-pairing properties than its triazole N-1 isomer. As suggested in the original paper, the advantageous base-pairing properties of **2a** might be determined by the specific electronic distribution within its triazole residue. In the light of the above-mentioned biological activities of 2-substituted-2*H*-1,2,3-triazoles, the synthesis of novel 2-substituted-2*H*-1,2,3-triazolo-nucleosides is of interest because of their potential bioactivity.[14]

Among the aforementioned 1,2,3-triazolo-nucleosides **A**–**D** (Fig. 1), analogues **D**3 have recently attracted considerable attention because of their pronounced physicochemical features[3d] or biological[2a,b] activity (such as antiviral,[3b] antitumour,[3a] antimicrobial[3g]) or enzyme-binding[3j] properties. However, their 2-substituted-2*H*-1,2,3-triazole congeners have not yet been described. Herein we report a series of 1,2,3-triazolo-analogues of AZT, compounds **4**, **5** and **6** (Fig. 2). Compounds **5** and **6** are isomeric derivatives of *NH*-1,2,3-triazole **4**, bearing a substituent on the triazole N-2 or N-1 nitrogen atom, respectively. The different substitution pattern of compounds **4**, **5** and **6** within the triazole ring would be expected to have an effect on their biochemical properties.

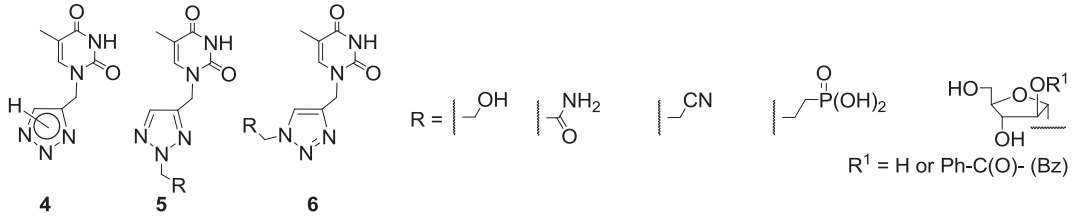


Fig. 2. The target analogues of AZT.

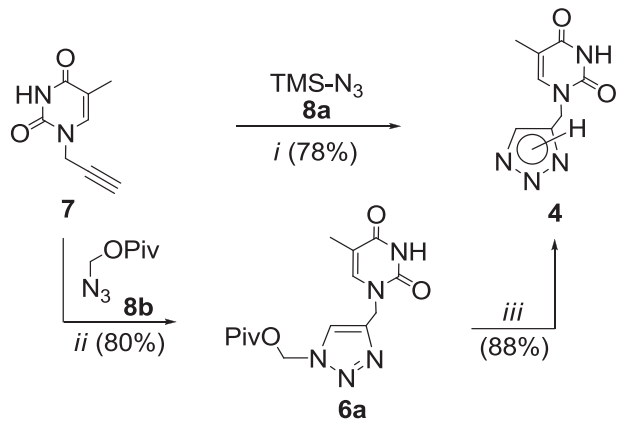
2. Results and discussion

A literature survey of synthetic routes to 2-substituted-2*H*-1,2,3-triazoles[1,12,15] led us to an assumption that a methodology involving a triazole N-alkylation of *NH*-1,2,3-triazole **4** (or its pyrimidine-protected form) would be a convenient approach to the target compounds **5**. Although the N-alkylation of *NH*-1,2,3-triazoles can be considered as one of the most commonly used methods for the synthesis of structurally diverse 2-substituted-2*H*-1,2,3-triazoles,[16] its application in the chemistry of nucleoside analogues has been limited to the synthesis of compounds **2** (Fig. 1).[9e–i] However, owing to the harsh reaction conditions used (a protonic acid and a prolonged heating at above 120 °C), the applicability of this method for the preparation of **5** might be limited. Therefore in the presented study, we focused on developing an efficient protocol for alkylation of **4** under milder reaction conditions than those used for the preparation of **2**. We chose to evaluate our methodology with biologically important[17] functionalities, such as sugar, hydroxyalkyl, phosphonoalkyl, or carbamoyl. Based on the literature on the alkylation reactions of non-nucleoside *NH*-1,2,3-triazoles,[1] we expected that some of the alkylations performed in this study would give the target triazole N-2-alkylated products accompanied by the corresponding triazole N-1 isomers. Therefore, the scope and limitations concerning the applicability of the triazole N-alkylation method for the efficient preparation of isomeric derivatives **5** and **6** were investigated.

2.1. Synthesis

NH-1,2,3-Triazoles are commonly synthesized by the cycloaddition of alkynes and hydrazoic acid[18] (or its equivalents, such as sodium azide,[19] trimethylsilyl azide[20] or the selected organic azides[21]). In our study, **4** was obtained from 1-propargylthymine[22] (**7**) with two methods (Scheme 1). In the first of them, the cycloaddition of **7** with trimethylsilyl azide (TMS–N_3, **8a**) at 120 °C, followed by the treatment of a crude reaction mixture with methanol at 20–22 °C, gave **4** in 78% yield. In the second method, the CuI/diisopropylethyl amine (DIPEA)-catalyzed coupling of **7** with pivaloyloxymethyl azide[21c] (**8b**) in tetrahydrofuran (THF) at 70 °C gave the pivaloyloxymethyl derivative **6a** in 80% yield. Then, the treatment of **6a** with a methanolic NH_4OH at 20–22 °C afforded **4** in 88% yield. The combined yield of **4** from this two-step synthesis (70%) was lower than that obtained with the use of **8a**. However, this disadvantage was compensated by a lower cost of the reagents used, including reagents needed for the preparation of pivaloyloxymethyl azide (**8b**), and the possibility of carrying out the coupling reaction under milder, non-anhydrous conditions. The effective de-pivaloyloxymethylation of **6a** with NH_4OH instead of

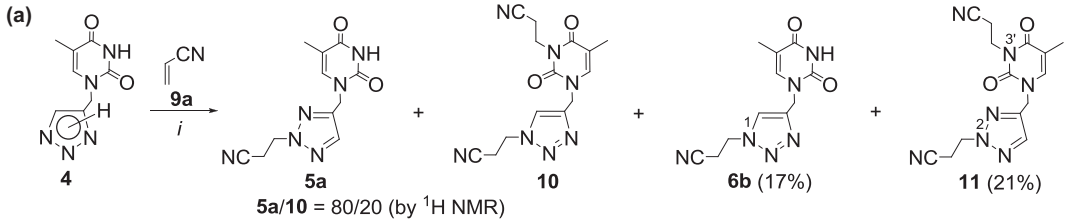
aqueous sodium hydroxide, as recommended in the original work[21c] on 1-(pivaloyloxymethyl)-1*H*-1,2,3-triazoles, let us to avoid the subsequent acidification of the reaction mixture. In a consequence, the isolation of the reaction product was simplified.



Scheme 1. Reagents and conditions: (i) 1. toluene, 120 °C, 1 day; 2. MeOH, 20–22 °C, 30 min; (ii) CuI, DIPEA, THF, 70 °C, overnight.

The preliminary alkylation of **4** with acrylonitrile (**9a**) is shown in Scheme 2a. The alkylation of *NH*-1,2,3-triazoles has been commonly reported under basic conditions, mainly in the presence of K_2CO_3 or Na_2CO_3.[12,16] However under these conditions, we expected of a simultaneous alkylation of **4** on the pyrimidine N-3 nitrogen atom. This expectation was based on our experience on the preparation of **7** from thymine and propargyl bromide in the presence of K_2CO_3,[3i] where 1,3-dipropargylthymine was formed in ca. 40% yield. Therefore, in the preliminary reaction of **4** with **9a** we employed triethylamine (NEt_3) as a base. Literature data on the preparation of 1-(2-cyanoethyl)thymine[23] revealed that thymine did not undergo alkylation on the N-3 nitrogen atom with acrylonitrile in the presence of NEt_3. Additionally, tertiary amines[16f] (including NEt_3) have been reported to promote the N-2 alkylation of *NH*-1,2,3-triazoles in good regioselectivity. As seen in Scheme 2a, the reaction of **4** with **9a** gave four products. Column chromatography of the reaction mixture afforded a **5a**/**10** mixture in a molar ratio of 80/20 (by ^{1}H NMR spectroscopic analysis), 1-(2-cyanoethyl)-derivative **6b** (17% yield) and 2,3′-bis(2-cyanoethyl)-derivative **11** (21% yield). In order to prevent the concomitant alkylation of **4** on the pyrimidine N-3 nitrogen atom, the pyrimidine-protected derivative **13** was prepared and then its reactions with **9a** in the presence of various bases were examined (Scheme 2b). Thus, the reaction of **7** with chloromethyl pivalate (PivO-CH_2Cl) in the presence of K_2CO_3 gave **12** in 93% yield. Then, the treatment of **12** with TMS–N_3 (**8a**), under the same conditions as those used for **4**, afforded **13** in 79% yield. Next, treatment of **13** with **9a** in the presence of NEt_3, under the same conditions as that used for **4**, afforded the 2-(2-cyanoethyl) derivative **14a** in 51% yield and the 1-(2-cyanoethyl) derivative **15a** in 38% yield. The same reaction carried out in the presence of DIPEA yielded a **14a**/**15a** mixture in a ratio of 55/45. Analogously, the reaction carried out in the presence of pyridine (Py) gave the **14a**/**15a** mixture in a ratio of 58/42. Additionally, compared to the reactions conducted in the presence of NEt_3 or DIPEA, the conversion of the starting **13** was very low (49% by ^{1}H NMR spectroscopic analysis). The highest **14a**/**15a** ratio was achieved with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the additive; **14a** was obtained in 81% yield. The minor product **15a** (16% yield) was readily separated by column chromatography.

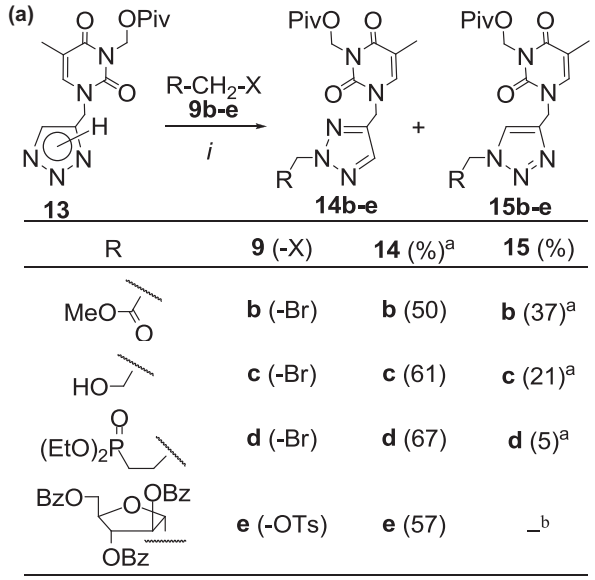
Next, derivative **13** was reacted with bromides **9b**–**d** or tosylate **9e** in the presence of DBU (Scheme 3a). While a commercially available methyl bromoacetate (**9b**), 2-bromoethanol (**9c**) or diethyl 3-bromopropylphosphonate (**9d**) were used as purchased, the sugar-derived tosylate **9e** was obtained from 1-*O*-benzoyl-2,5-anhydro-D-mannitol[24] (**16**) via the monobenzoyl tosylate **17** (Scheme 3b). The **14**/**15** combined yields obtained from the alkylations of **13** with **9b**–**d** varied from 87% for **9b** to 69% for **9e**. The N-2-substituted products **14b**–**d** were readily separated from the corresponding N-1 isomers **15b**–**d** by column chromatography. The sugar derivative **15e** was the only exception; column chromatography of the reaction mixture afforded **14e** in 57% yield and a **14e**/**15e** mixture in a ratio of 70/30 ratio (by ^{1}H NMR spectroscopic analysis) in 12% combined yield. Taking into account the isolated yields of the products obtained from the reactions performed with bromides **9b**–**d**, the preference to alkylation of **13** at the triazole N-2 nitrogen atom increased in the series of **9b**<**9c**<**9d**. An explanation of this finding is rather difficult at the present stage of our study. Steric effects or a specific nature of the R-substituent on the electrophilic carbon site of **9b**–**d** might be considered as a factor influencing the course of the alkylation reaction.[25]



Base	NEt_3	DIPEA	Py	DBU
Conversion of **13** [%][a]	100	100	49	100
14a/**15a**	51/38[b]	55/45[c]	58/42[c]	81/19[c]; 81/16[b]

[a]Based on the consumption of **13** by ^{1}H NMR spectroscopic analysis. [b]From the isolated yields [%]. [c]From ^{1}H NMR spectroscopic analysis, based on intensities of signals due to the triazole H-5 proton.

Scheme 2. Reagents and conditions: (i) NEt_3, DMF, 20–22 °C, 1 d; (ii) PivO-CH_2Cl, K_2CO_3, DMF, 20–22 °C, 2 days; (iii) 1. toluene, 120 °C, overnight; 2. MeOH, 20–22 °C, 1 h; (iv) Base (NEt_3, DIPEA, Py or DBU), DMF, 20–22 °C, 1 day.



R	9 (-X)	14 (%)[a]	15 (%)
MeO–C(=O)–	b (-Br)	b (50)	b (37)[a]
HO–	c (-Br)	c (61)	c (21)[a]
(EtO)2P(=O)–	d (-Br)	d (67)	d (5)[a]
BzO, OBz, OBz	e (-OTs)	e (57)	–[b]

[a]Isolated yield. [b]Not isolated from a **14e**/**15e** mixture of 70/30, respectvely, by ^{1}H NMR spectroscopic analysis. The **14e**/**15e** combined yield was 69%.

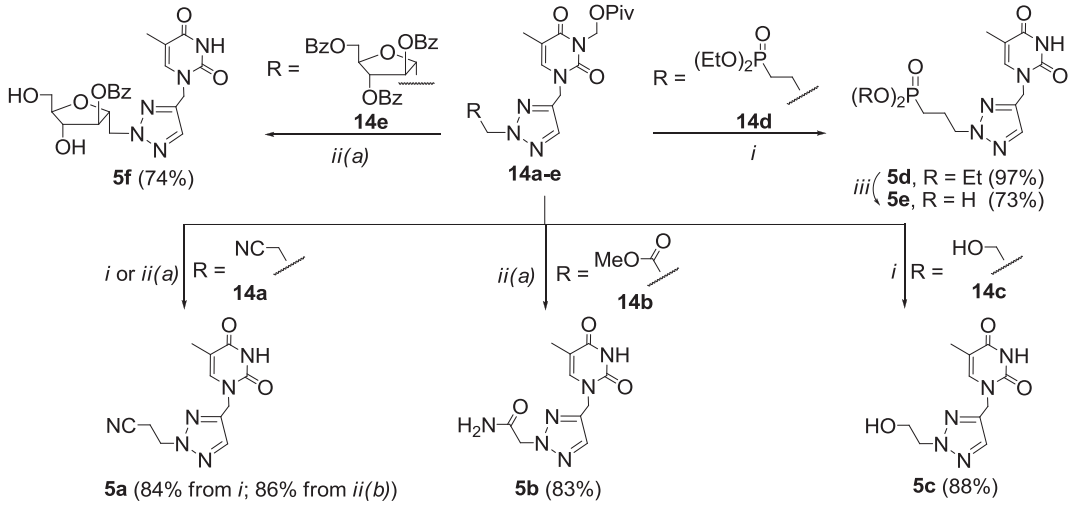
Scheme 3. Reagents and conditions: (i) DBU, DMF, 20–22 °C, 1 day; (ii) BzCl, Py, 20–22 °C, 1 day; (iii) TsCl, Py, 20–22 °C, 1 day.

Conversion of **14a**–**e** into the target 2,4-disubstituted-2*H*-1,2,3-triazoles **5a**–**f** is shown in Scheme 4. Derivatives **14a**, **14b**, **14c** and **14e** were converted into **5a**, **5b**, **5c** or **5f**, respectively, under the treatment with a methanolic NH_4OH, or a methanolic NH_3, at 20–22 °C; the yields of products varied from 74% to 86%. Phosphonate **14d** was transformed into the final **5e** in two steps: (1) depivaloyloxymethylation of **14d** with a methanolic NH_4OH at 20–22 °C, and (2) de-alkylation of the resulting **5d** with trimethylsilyl bromide (TMSBr) at 20–22 °C, followed by treatment of the crude reaction mixture with methanol at 20–22 °C. The total yield of **5e** from **14d** was 71%.

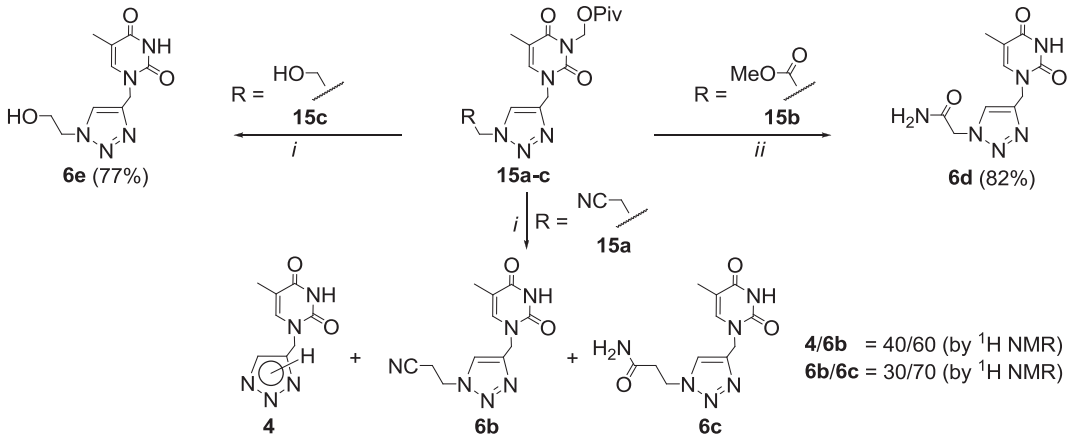
Preparation of 1-substituted-1*H*-1,2,3-triazoles **6b**–**i** is depicted in Schemes 5 and 6. Formation of **15a**–**c** in relatively high yields (Schemes 2 and 3) inspired us to transform them into their pyrimidine-deprotected forms (Scheme 5). Interestingly, **15a** (or **6b** as its pyrimidine-deprotected form) proved to be much more sensitive to NH_3 than **5a**. While **5a** was stable in a methanolic NH_3 for 2 months, the treatment of **15a** with a methanolic NH_4OH at 20–22 °C resulted in the formation of a complex mixture. The expected **6b** was accompanied by **4**, a product of a retro-Michael de-cyanoethylation, and amide **6c**. The column chromatography of the mixture afforded a **4**/**6b** mixture in a ratio of 40/60 (by ^{1}H NMR spectroscopic analysis) and a **6b**/**6c** mixture in a ratio of 30/70 (by ^{1}H NMR spectroscopic analysis). On the other hand, treatment of **15b** or **15c** with a methanolic NH_3, or a methanolic NH_4OH at 20–22 °C afforded **6d** (82% yield) or **6e** (77% yield), respectively. Compound **6e** was also obtained in 78% yield by the CuI/DIPEA-catalyzed 'click' coupling of **7** with 2-azidoethanol[26] (**8c**) in tetrahydrofuran (THF) at 70 °C (Scheme 6a). Finally, the azide–alkyne 'click' coupling method was applied to complete a series of the target of 1,2,3-triazolo-nucleosides (Scheme 6a). Under the previously used conditions, the coupling of **7** with diethyl 3-azidopropylphosphonate[27] (**8d**) or the sugar-derived azide **8e** (the synthesis of which is shown in Scheme 6b) gave **6f** (76% yield) or **6g** (70% yield), respectively. In the next step, derivatives **6f** and **6g** were converted into the final compounds **6h** and **6i**, respectively. The de-alkylation of **6f** with TMSBr, under the same conditions as those described for de-alkylation of derivative **5d**, gave 1-(3-phosphonopropyl)-1*H*-1,2,3-triazole derivative **6h** in 85% yield. The de-benzoylation of **6g** with a methanolic NH_3, under the same conditions as those described for deprotection of derivative **14e**, gave **6i** in 86% yield.

2.2. Structure elucidation

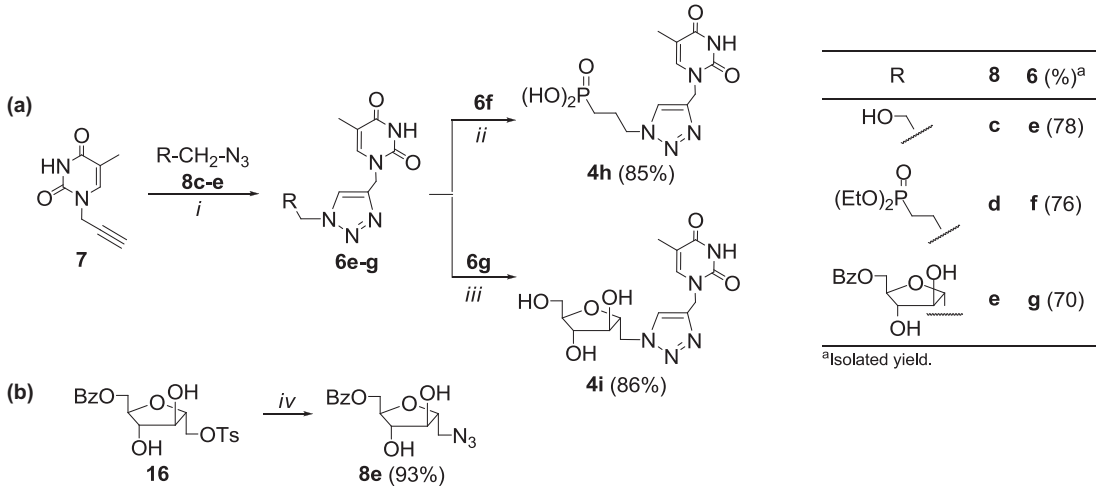
The ^{1}H and ^{13}C chemical shifts for the triazole N-2 substituted compounds **5** (**a**, **c**, **f**), **11** and **14a** as well as for the triazole N-1 substituted compounds **6** (**a**, **b**, **e**, **i**) were fully assigned by ^{1}H–^{13}C HMBC NMR experiments (Tables 1 and 2). In the ^{1}H–^{13}C HMBC NMR spectra of compounds **6** (**a**, **b**, **e**, **i**), the ^{1}H–^{13}C HMBC correlation of H-1a↔C-5 was observed. In the ^{1}H NMR spectra, the signal due to the triazole H-5 proton of the N-2 substituted triazoles **5** (**a**, **c**, **f**) occurred at higher field (7.67–7.78 ppm) compared to the signal of the corresponding N-1 substituted isomers **6** (**b**, **e**, **i**) (8.00–8.14 ppm). In the ^{13}C NMR spectra, the signal due to the triazole C-5 carbon atom of compounds **5** (**a**, **c**, **f**), occurred at lower



Scheme 4. Reagents and conditions: (i) NH_4OH, MeOH, 20–22 °C, overnight; (ii) NH_3/MeOH, 20–22 °C: (a) 3 days, or (b) overnight; (iii) 1. TMSBr, acetonitrile, 20–22 °C, overnight; 2. MeOH, 20–22 °C, 1 h.



Scheme 5. Reagents and conditions: (i) NH_4OH, MeOH, 20–22 °C, overnight; (ii) NH_3/MeOH, 20–22 °C, 3 days.

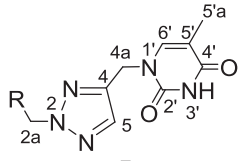


R	8	6 (%)[a]
HO	c	e (78)
$(EtO)_2P(O)$	d	f (76)
BzO, OH, OH	e	g (70)

[a]Isolated yield.

Scheme 6. Reagents and conditions: (i) CuI, DIPEA, THF, 70 °C, overnight; (ii) 1. TMSBr, acetonitrile, 20–22 °C, overnight; 2. MeOH, 20–22 °C, 1 h; (iii) NH_3/MeOH, 20–22 °C, 3 days; (iv) NaN_3, Bu_4NHSO_4, DMF, 50 °C, 3 days.

Table 1
Numbering and ^1H chemical shift assignments in selected 2-substituted-2*H*-1,2,3-triazoles and 1-substituted-1*H*-1,2,3-triazoles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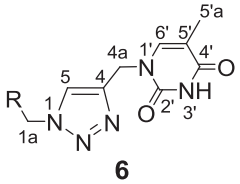
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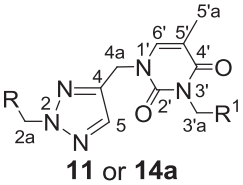
11 or **14a**

	5a	5c	5f	6a	6b	6e	6i	11	14a
R	NC–(2b)	HO–(2b)	HO, Ph, O, 5", 4", 3", 2", 1", OH	t-Bu, O, O	NC–(1b)	HO–(1b)	Ph, O, 5", OH, 4", 3", 2", 1"	NC–(2b)	NC–(2b)
R^1								NC–(3'b)	t-Bu, O, O

	1a	1b	2a	2b	5	Other signals
5a[a]			4.69	3.13	7.78	4a (4.93), 3′ (11.38), 5′a (1.75), 6′ (7.59)
5c[a]			4.39	3.79–3.86	7.68	(4a, OH) (4.89), 3′ (11.32), 5′a (1.75), 6′ (7.59)
5f[b]			4.59, 4.63		7.67	4a (4.97), 5′a (1.86), 6′ (7.50), 1″ (4.27–4.30), 2″ (3.98), 3″ (4.02), 4″ (3.79–3.82), 5″ (3.58, 3.65), Ph (7.41–7.88)
6a[a]	6.27				8.19	4a (4.90), 3′ (11.29), 5′a (1.73), 6′ (7.60), *t*-Bu (1.09)
6b[a]	4.64	3.17			8.14	4a (4.91), 3′ (11.31), 5′a (1.75), 6′ (7.61)
6e[a]	4.37	3.76			8.01	4a (4.89), 3′ (11.28), 5′a (1.75), 6′ (7.61), OH (5.01)
6i[b]	4.62, 4.65				8.00	4a (4.97), 5′a (1.84), 6′ (7.48), 1″ (4.16–4.19), 2″ (3.85), 3″ (4.11), 4″ (4.02–4.05), 5″ (4.40, 4.47), Ph (7.47–8.04)
11[a]			4.66	3.13	7.79	4a (5.01), 3′a (4.07), 3′b (2.83), 5′a (1.82), 6′ (7.71)
14a[a]			4.67	3.13	7.80	4a (5.01), 3′a (5.78), 5′a (1.82), 6′ (7.75), *t*-Bu (1.09)

[a] In DMSO-d_6.
[b] In CD_3OD.

Table 2
^{13}C chemical shift assignments in selected 2-substituted-2*H*-1,2,3-triazoles and 1-substituted-1*H*-1,2,3-triazoles

	1a	1b	2a	2b	5	Other signals
5a[a]			49.75	17.91	133.87	4 (144.24), 4a (42.02), 2′ (150.81), 4′ (164.34), 5′ (109.11), 5′a (12.00), 6′ (141.06), CN (118.19)
5c[a]			57.05	59.56	133.09	4 (143.39), 4a (42.08), 2′ (150.81), 4′ (164.34), 5′ (109.05), 5′a (12.00), 6′ (141.14)
5f[b]			57.74		134.63	4 (144.95), 4a (43.58), 2′ (152.76), 4′ (166.79), 5′ (111.59), 5′a (12.24), 6′ (142.62), 1″ (83.43), 2″ (79.95), 3″ (78.52), 4″ (85.83), 5″ (63.03), Ph (128.62, 129.51, 132.92, 134.94), Ph–*C*(O)– (172.37)
6a[a]	70.08				124.78	4 (143.00), 4a (42.07), 2′ (150.73), 4′ (164.27), 5′ (108.92), 5′a (11.94), 6′ (141.15), *t*-Bu (26.47, 38.23), *t*-Bu-*C*(O)– (176.45)
6b[a]	45.00	18.38			123.78	4 (142.79), 4a (42.20), 2′ (150.70), 4′ (164.25), 5′ (108.87), 5′a (11.93), 6′ (141.12), CN (118.10)
6e[a]	52.28	59.81			124.01	4 (142.27), 4a (42.21), 2′ (150.77), 4′ (164.34), 5′ (108.89), 5′a (12.00), 6′ (141.22)
6i[b]	52.93				126.27	4 (143.90), 4a (43.65), 2′ (152.66), 4′ (166.73), 5′ (111.55), 5′a (12.22), 6′ (142.55), 1″ (82.91), 2″ (79.25), 3″ (78.64), 4″ (82.75), 5″ (65.48), Ph (129.65, 130.63, 131.22, 134.38), Ph–*C*(O)– (167.81)
11[a]			49.67	17.82	133.84	4 (143.92), 4a (43.27), 2′ (150.58), 3′a (36.21), 3′b (15.47) 4′ (162.77), 5′ (108.25), 5′a (12.49), 6′ (140.16), CN (118.14, 118.41)
14a[a]			49.70	17.83	133.90	4 (143.76), 4a (43.23), 2′ (150.29), 3′a (64.94), 4′ (162.39), 5′ (108.26), 5′a (12.39), 6′ (140.94), CN (118.08), *t*-Bu (26.62, 38.24), *t*-Bu-*C*(O)– (176.60)

[a] In DMSO-d_6.
[b] In CD_3OD.

field (133.09–134.63 ppm) compared to the signal of the corresponding N-1 substituted isomers **6** (**b**, **e**, **i**) (123.78–126.27 ppm). The triazole N-2-substitution pattern of compounds **5** was confirmed by the ^{1}H–^{15}N HMBC NMR spectra of **14a** and **5c**. As shown in the spectrum of **14a** (Fig. 3), the interactions between the H-2a protons and the triazole nitrogen atoms (i.e., H-2a↔N-2 and N-1↔H-2a↔N-3) were observed in these spectra. The N-2 resonance (−129.2 ppm for **14a**, or −127.4 ppm for **5c**) was distinguished of from those corresponding to the N-1 or N-3 nitrogen atom by the correlation of H-2b↔N-2. The N-1 resonance (−49.6 ppm for **14a**, or −49.2 ppm for **5c**) and the N-3 resonance (−54.8 ppm for **14a**, or −54.6 ppm for **5c**) were differentiated by the correlations of H-5↔N-1↔H-2a as well as H-4a↔N-3↔H-2a. Moreover, the spectra featured the interaction of both the H-4a protons and the H-6′ protons with the pyrimidine N-1′ nitrogen atom (−250.4 ppm for **14a**, or −249.1 ppm for **5c**).

of potential alkylating reagents (e.g., Michael acceptors or alkyl halides) or their precursors (e.g., alcohols), our approach to compounds **5** offers an opportunity to synthesize (2-substituted-2*H*-1,2,3-triazol-4-ylmethyl)nucleosides with a variety of biologically important functionalities. As shown on the example of compound **14b**, derivatives with an alkoxycarbonyl function might be further modified, for instance by an amidation reaction. The 1-substituted-1*H*-1,2,3-triazoles, when formed in the appreciated amount in the alkylation reaction, were converted into the corresponding 1-substituted-1*H*-1,2,3-triazolo-nucleosides **6**. The ^{1}H–^{15}N HMBC NMR spectra of compounds **14a** and **5c** were particularly informative and useful for verification of the N-2 substitution pattern of the target compounds **5**, since all signals due to the triazole nitrogen atoms were observed and assigned through their correlations with the triazole *exo*-cyclic protons. A study on the improvement and

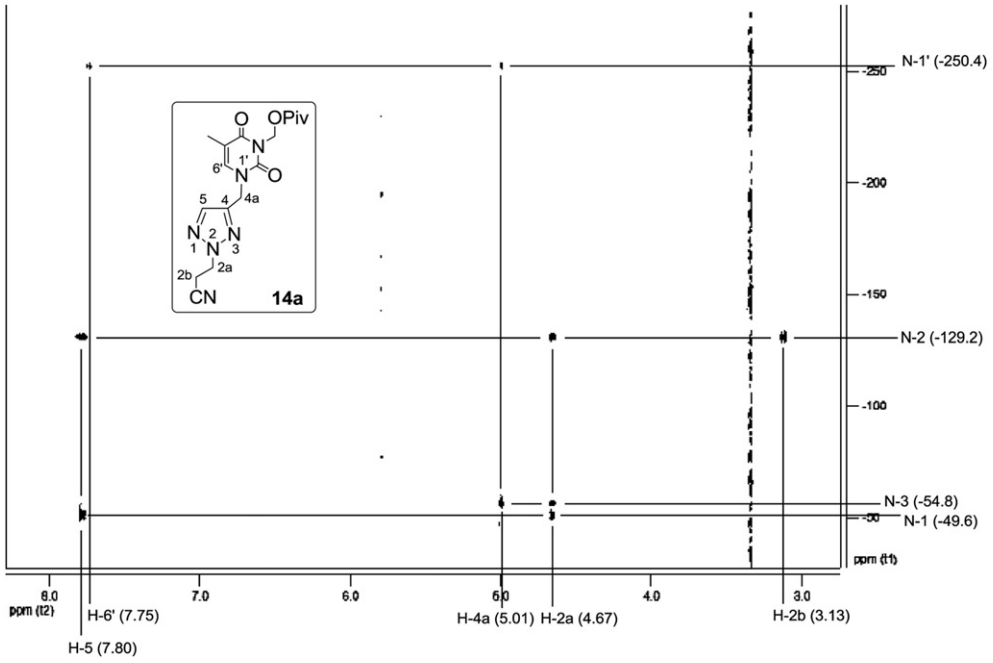

Fig. 3. ^{1}H–^{15}N HMBC NMR spectrum of **14a** (DMSO-d_6).

3. Conclusion

The post-triazole N-alkylation process was successfully applied to the synthesis of 2-substituted-2*H*-1,2,3-triazolo-nucleosides **5**. Taking into account the broad commercial availability extension of the presented methodology for the synthesis of highly functionalized 2-substituted-2*H*-1,2,3-triazolo-nucleosides is now in progress. This study, including a SAR analysis of the obtained compounds, will be a subject of a forthcoming publication.

4. Experimental

4.1. Materials and methods

Pre-coated Merck silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC, 0.2 mm); spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (200–400 mesh, Merck). Optical rotations were measured with a PolAAr32 polarimeter. High Resolution Mass Spectra (Electrospray Ionisation, ESI) were performed on a Mariner® spectrometer unless otherwise indicated. The NMR spectra were measured on a Varian Gemini-200BB spectrometer (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz) or a Varian VNMRS spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz). ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent signals: $CDCl_3$, δ_H (residual $CHCl_3$) 7.26 ppm, δ_C 77.16 ppm; DMSO-d_6, δ_H (residual DMSO-d_5) 2.50 ppm, δ_C 39.52 ppm; or CD_3OD (residual CH_3OH) 3.31 ppm, δ_C 49.00 ppm; signals are quoted as 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), 'br s' (broad singlet), and 'dd' (doublet of doublets). Coupling constants *J* are reported in Hertz. The ^{1}H–^{13}C or ^{1}H–^{15}N HMBC (Heteronuclear Multiple Bond Correlation) spectra were measured on a Varian VNMRS spectrometer. ^{15}N chemical shifts in **5c** or **14a** are reported in parts per million (ppm) relative to the signal of CH_3NO_2 as an external standard. Anhydrous $MgSO_4$ was employed as a drying agent. Volatiles were distilled off under reduced pressure on a rotating evaporator. The concentration of ammonium hydroxide used was 25 wt %. The concentration of a methanolic solution of NH_3 used was 7 N (Sigma–Aldrich).

4.2. 5-Methyl-1-[*NH*-1,2,3-triazol-4-ylmethyl]pyrimidine-2,4(1*H*,3*H*)-dione (4) from 7 and 8a

Trimethylsilyl azide (**8a**, 576 mg, 5.0 mmol, 0.6 mL) was added to a solution of 1-propargylthymine (**7**) (200 mg, 1.0 mmol) in anhydrous toluene (2 mL). The mixture was heated in an oil bath (120 °C) for 1 day under argon and volatiles were distilled off. The residue was dissolved in methanol (10 mL). The solution was kept at 20–22 °C for 1 h and then volatiles were distilled off. The residue was treated with cold methanol and **4** was filtered off as a white solid and dried on air (162 mg, 78%, mp >230 °C dec). δ_H (200 MHz, DMSO-d_6) 1.75 (d, 3H, $^4J_{H,H}$ 1.2), 4.92 (s, 2H), 7.60 (q, 1H, $^4J_{H,H}$ 1.2), 7.81 (s, 1H), 11.31 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6, CF_3CO_2H) 12.03, 42.03, 109.06, 128.84 (br), 141.27, 142.06, 150.89, 164.42. HRMS *m*/*z* calcd for $C_8H_9N_5O_2Na$ $[M+Na]^+$ 230.0654; found 230.0659.

4.3. 5-Methyl-1-[NH-1,2,3-triazol-4-ylmethyl]pyrimidine-2,4(1H,3H)-dione (4) from 7 and 8b

*4.3.1. 5-Methyl-1-[(1-(pivaloyloxymethyl)-1H-1,2,3-triazol-4-yl) methyl]pyrimidine-2,4(1H,3H)-dione (**6a**).* Diisopropylethylamine (190 mg, 1.4 mmol, 250 μL) was added to a mixture of 1-propargylthymine (**7**) (267 mg, 1.6 mmol), pivaloyloxymethyl azide (**8b**) (240 mg, 1.5 mmol), copper(I) iodide (30 mg, 0.16 mmol) and THF (15 mL). The mixture was heated at 70 °C (an oil bath) overnight and filtered through a Celite® pad. The pad was washed with THF (10 mL). The filtrates were collected and evaporated to dryness under reduced pressure. Column chromatography of the residue ($CHCl_3$/MeOH, 99/1, v/v) gave **6a** (423 mg, 80%) as a white solid (mp 166–168 °C). δ_H (500 MHz, DMSO-d_6) 1.09 (s, 9H), 1.73 (d, 3H, $^4J_{H,H}$ 1.0), 4.90 (s, 2H), 6.27 (s, 2H), 7.60 (q, 1H, $^4J_{H,H}$ 1.0), 8.19 (s, 1H), 11.29 (br s, 1H). δ_C (125 MHz, DMSO-d_6) 11.94, 26.47, 38.23, 42.07, 70.08, 108.92, 124.78, 141.15, 143.00, 150.73, 164.27, 176.45. HRMS *m*/*z* calcd for $C_{14}H_{19}N_5O_4Na$ $[M+Na]^+$ 344.1329; found 344.1325.

*4.3.2. 5-Methyl-1-[NH-1,2,3-triazol-4-ylmethyl]pyrimidine-2,4(1H,3H)-dione (**4**).* A mixture of **6a** (228 mg, 0.7 mmol), ammonium hydroxide (10 mL) and methanol (5 mL) was stirred at 20–22 °C overnight. Volatiles were distilled off. The residue was triturated with a cooled methanol and **4** as a white solid was filtered off and dried on air (129 mg, 88%). The NMR spectra were consistent with those described in Section 4.2.

4.4. Reaction of 4 with acrylonitrile (9a)

Triethylamine (122 mg, 1.2 mmol, 170 μL) was added to a solution of **4** (225 mg, 1.1 mmol) in anhydrous DMF (5 mL). The mixture was stirred at 20–22 °C for 30 min and then acrylonitrile (**9a**) (62 mg, 1.5 mmol, 80 μL) was added in one portion. The mixture was stirred at 20–22 °C for 1 day and then ethyl acetate (25 mL) was added. The solution was washed with water (5 mL) and brine (5 mL) and dried. Volatiles were distilled off. Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) of the residue gave a **5a**/**10** mixture of 80/20 molar ratio (80 mg), **6b** (45 mg, 17%, a white solid, mp >224 °C dec) and **11** (65 mg, 21%, colourless oil). The **5a**/**10** molar ratio was based on relative intensities of the triazole H-5 proton signals: **5a**, 7.78 ppm; **10**, 8.16 ppm. 1-[(2-(2-*Cyanoethyl*)-2*H*-1,2,3-*triazol*-4-*yl*)*methyl*]-5-*methylpyrimidine*-2,4(1*H*,3*H*)-*dione* (**5a**) *and* 3-(2-*cyanoethyl*)-1-[(1-(2-*cyanoethyl*)-1*H*-1,2,3-*triazol*-4-*yl*) *methyl*]-5-*methylpyrimidine*-2,4(1*H*,3*H*)-*dione* (**10**). δ_H (200 MHz, DMSO-d_6) 1.74 (s, 2.4H), 1.82 (s, 0.6H), 2.82 (t, 0.4H, $^3J_{H,H}$ 6.5), 3.13 (t, 2H, $^3J_{H,H}$ 6.5), 4.06 (t, 0.4H, $^3J_{H,H}$ 6.5), 4.67 (t, 2H, $^3J_{H,H}$ 6.5), 4.92 (s, 1.6H), 5.00 (s, 0.4H), 7.58 (s, 0.8H), 7.74 (s, 0.2H), 7.78 (s, 0.8H), 8.16 (s, 0.2H), 11.32 (br s, 1H). LRMS *m*/*z* calcd for: (a) $C_{11}H_{12}N_6O_2Na$ $[M+Na]^+$ 283.09; found 283.1 (**5a**), and (b) $C_{14}H_{15}N_7O_2Na$ $[M+Na]^+$ 336.1; found 336.1 (**10**). HRMS *m*/*z* calcd for $C_{14}H_{15}N_7O_2Na$ $[M+Na]^+$ 336.1185; found 336.1169 (**10**). For spectral data of **5a**, see: Section 4.9.5.1. 1-[(1-(2-*Cyanoethyl*)-1*H*-1,2,3-*triazol*-4-*yl*)*methyl*]-5-*methylpyrimidine*-2,4(1*H*,3*H*)-*dione* (**6b**). δ_H (500 MHz, DMSO-d_6) 1.75 (d, 3H, $^4J_{H,H}$ 1.0), 3.17 (t, 2H, $^3J_{H,H}$ 6.5), 4.64 (t, 2H, $^3J_{H,H}$ 6.5), 4.91 (s, 2H), 7.61 (q, 1H, $^4J_{H,H}$ 1.0), 8.14 (s, 1H), 11.31 (s, 1H). δ_C (125 MHz, DMSO-d_6) 11.93, 18.38, 42.20, 45.00, 108.87, 118.10, 123.78, 141.12, 142.88, 150.70, 164.25. HRMS *m*/*z* calcd for $C_{11}H_{12}N_6O_2Na$ $[M+Na]^+$ 283.0919; found 283.0914. 3-(2-*Cyanoethyl*)-1-[(2-(2-*cyanoethyl*)-2*H*-1,2,3-*triazol*-4-*yl*)*methyl*]-5-*methylpyrimidine*-2,4(1*H*,3*H*)-*dione* (**11**). δ_H (500 MHz, DMSO-d_6) 1.82 (d, 3H, $^4J_{H,H}$ 1.0), 2.83 (t, 2H, $^3J_{H,H}$ 6.5), 3.13 (t, 2H, $^3J_{H,H}$ 6.5), 4.07 (t, 2H, $^3J_{H,H}$ 6.5), 4.66 (t, 2H, $^3J_{H,H}$ 6.5), 5.01 (s, 2H), 7.71 (q, 1H, $^4J_{H,H}$ 1.0), 7.79 (s, 1H). δ_C (125 MHz, DMSO-d_6) 12.49, 15.47, 17.82, 36.21, 43.27, 49.67, 108.25, 118.14, 118.41, 133.84, 140.16, 143.92, 150.58, 162.77. HRMS *m*/*z* calcd for $C_{14}H_{15}N_7O_2Na$ $[M+Na]^+$ 336.1185; found 336.1183.

4.5. 3-(Pivaloyloxymethyl)-1-propargylthymine (12)

Anhydrous K_2CO_3 (5.53 g, 40.0 mmol) was added to a solution of **7** (1.32 g, 8.0 mmol) in anhydrous DMF (25 mL). The mixture was stirred at 20–22 °C for 30 min and then chloromethyl pivalate (2.41 g, 16.0 mmol, 2.3 mL) was added in one portion. The mixture was stirred at 20–22 °C for 2 days and filtered through a Celite® pad. The pad was washed with DMF (10 mL). Filtrates were collected and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$) gave **12** (2.07 g, 93%) as a white solid (mp 93–96 °C). δ_H (500 MHz, $CDCl_3$) 1.17 (s, 9H), 1.96 (s, 3H), 2.48 (t, 1H, $^4J_{H,H}$ 2.5), 4.56 (d, 2H, $^3J_{H,H}$ 2.5), 5.95 (s, 2H), 7.28 (s, 1H). δ_C (125 MHz, $CDCl_3$) 13.12, 27.12, 37.65, 38.92, 65.33, 75.48, 76.34, 110.84, 137.46, 150.56, 162.70, 177.60. HRMS (EI, 70 eV) *m*/*z* calcd for $C_{14}H_{18}N_2O_4$ M^+ 278.1267; found 278.1277.

4.6. 5-Methyl-3-(pivaloyloxymethyl)-1-[(*NH*-1,2,3-triazol-4-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (13)

Treatment of **12** (1.32 g, 4.7 mmol) with trimethylsilyl azide (**8a**) (2.77 g, 24 mmol, 3.2 mL) under the conditions described in Section

4.2 gave **13** (1.20 g, 79%) as colourless oil, after column chromatography ($CHCl_3$/MeOH, 95/5, v/v). δ_H (500 MHz, $CDCl_3$) 1.15 (s, 9H), 1.92 (s, 3H), 5.04 (s, 2H), 5.98 (s, 2H), 7.31 (s, 1H), 7.80 (s, 1H), 13.25 (br s, 1H, NH). δ_C (50 MHz, $CDCl_3$) 13.09, 27.10, 38.98, 43.61, 65.19, 110.81, 130.26 (br), 139.23, 141.74 (br), 151.06, 163.01, 177.90. HRMS *m*/*z* calcd for $C_{14}H_{19}N_5O_4Na$ $[M+Na]^+$ 344.1329; found 344.1318.

4.7. Reaction of 13 with acrylonitrile (9a) in the presence of NEt_3

According to the procedure described in Section 4.4, the reaction was performed from 280 mg (0.9 mmol) of **13**. Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) of the residue gave **14a** (172 mg, 51%, colourless oil) and **15a** (128 mg, 38%, colourless oil). 1-[(2-(2-*Cyanoethyl*)-2*H*-1,2,3-*triazol*-4-*yl*)*methyl*]-5-*methyl*-3-(*pivaloyloxymethyl*)*pyrimidine*-2,4(1*H*,3*H*)-*dione* (**14a**). δ_H (500 MHz, $CDCl_3$) 1.16 (s, 9H), 1.92 (d, 3H, $^4J_{H,H}$ 1.0), 3.03 (t, 2H, $^3J_{H,H}$ 7.0), 4.67 (t, 2H, $^3J_{H,H}$ 7.0), 4.95 (s, 2H), 5.95 (s, 2H), 7.16 (q, 1H, $^4J_{H,H}$ 1.0), 7.66 (s, 1H). δ_H (500 MHz, DMSO-d_6) 1.09 (s, 9H), 1.82 (d, 3H, $^4J_{H,H}$ 1.0), 3.13 (t, 2H, $^3J_{H,H}$ 6.0), 4.67 (t, 2H, $^3J_{H,H}$ 6.0), 5.01 (s, 2H), 5.78 (s, 2H), 7.75 (q, 1H, $^4J_{H,H}$ 1.0), 7.80 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.93, 18.38, 26.96, 38.88, 43.24, 49.91, 65.06, 110.70, 116.15, 134.85, 138.59, 143.49, 150.78, 162.64, 177.46. δ_C (125 MHz, DMSO-d_6) 12.39, 17.83, 26.62, 38.24, 43.23, 49.70, 64.94, 108.26, 118.08, 133.90, 140.94, 143.76, 150.29, 162.39, 176.60. HRMS *m*/*z* calcd for $C_{17}H_{22}N_6O_4Na$ $[M+Na]^+$ 397.1595; found 397.1588. 1-[(1-(2-*Cyanoethyl*)-1*H*-1,2,3-*triazol*-4-*yl*)*methyl*]-5-*methyl*-3-(*pivaloyloxymethyl*)*pyrimidine*-2,4(1*H*,3*H*)-*dione* (**15a**). δ_H (200 MHz, $CDCl_3$) 1.18 (s, 9H), 1.94 (d, 3H, $^4J_{H,H}$ 1.2), 3.04 (t, 2H, $^3J_{H,H}$ 6.6), 4.64 (t, 2H, $^3J_{H,H}$ 6.6), 4.98 (s, 2H), 5.94 (s, 2H), 7.35 (q, 1H, $^4J_{H,H}$ 1.2), 7.84 (s, 1H). δ_C (50 MHz, $CDCl_3$) 13.08, 19.44, 27.15, 38.96, 43.98, 45.87, 65.17, 110.73, 116.14, 124.43, 139.22, 142.73, 150.98, 162.84, 177.67. HRMS *m*/*z* calcd for $C_{17}H_{22}N_6O_4Na$ $[M+Na]^+$ 397.1595; found 397.1588.

4.8. Reactions of 13 with acrylonitrile (9a) in the presence of DIPEA, Py or DBU

The reactions were conducted in accordance with the procedure described in Section 4.4, using **13** (100 mg, 0.3 mmol) and DIPEA, Py or DBU (0.36 mmol) instead of NEt_3. After the usual work-up, a ^1H NMR spectrum of the crude reaction mixture was recorded (200 MHz, $CDCl_3$). Conversion of **13** was calculated as a ratio between the intensity of the signal corresponding to the triazole H-5 proton of **13** (7.80 ppm) and combined intensities of the signals corresponding to the triazole H-5 proton of **14a** (7.66 ppm) and **15a** (7.84 ppm). The **14a**/**15a** ratio was determined from the intensities of signals corresponding to the triazole H-5 proton of **14a** and **15a**. The reaction carried out in the presence of DBU, when repeated from 480 mg (1.5 mmol) of **13**, gave **14a** (454 mg, 81%) and **15a** (90 mg, 16%), after column chromatography ($CHCl_3$/MeOH, 99/1, v/v).

4.9. Reaction of 13 with alkylating agents 9b–e in the presence of DBU

*4.9.1. 1-[(2-(Methoxycarbonylmethyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**14b**) and 1-[(1-(methoxycarbonylmethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**15b**).* According to the procedure described in Section 4.4, compounds **14b** and **15b** were synthesized from **13** (321 mg, 1.0 mmol) and methyl bromoacetate (**9b**). Column chromatography of the residue ($CHCl_3$/MeOH, 99/1, v/v) gave **14b** (197 mg, 50%) and **15b** (143 mg, 37%) as colourless oils. Compound **14b**, δ_H (200 MHz, $CDCl_3$) 1.09 (s, 9H), 1.84 (d, 3H, $^4J_{H,H}$ 0.8), 3.70 (s, 3H), 4.91 (s, 2H), 5.14 (s, 2H), 5.88 (s, 2H), 7.15 (q, 1H, $^4J_{H,H}$ 0.8), 7.62 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.83, 26.88, 38.69, 43.26, 52.81, 55.23, 64.99, 110.34, 134.88, 138.83, 143.57, 150.72, 162.63, 166.93, 177.37. HRMS *m*/*z* calcd for $C_{17}H_{23}N_5O_6Na$ $[M+Na]^+$ 416.1541; found 416.1550. Compound **15b**, δ_H (200 MHz, $CDCl_3$) 1.09 (s, 9H), 1.84 (d, 3H, $^4J_{H,H}$ 0.8), 3.62 (s, 3H), 4.93 (s, 2H), 5.12 (s, 2H), 5.85 (s, 2H), 7.33 (q, 1H, $^4J_{H,H}$ 0.8), 7.80 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.83, 26.91, 38.73, 43.68, 53.04, 54.62, 64.96, 110.26, 125.16, 139.30, 142.27, 150.77, 162.72, 166.56, 177.47. HRMS *m*/*z* calcd for $C_{17}H_{23}N_5O_6Na$ $[M+Na]^+$ 416,1541; found 416.1553.

*4.9.2. 1-[(2-(2-Hydroxyethyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**14c**) and 1-[(1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**15c**).* According to the procedure described in Section 4.4, compounds **14b** and **15b** were synthesized from **13** (320 mg, 1.0 mmol) and 2-bromoethanol (**9c**). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **14c** (223 mg, 61%) and **15c** (78 mg, 21%) as colourless oils. Compound **14c**, δ_H (200 MHz, $CDCl_3$) 1.09 (s, 9H), 1.84 (d, 3H, $^4J_{H,H}$ 0.8), 3.22 (br s, 1H, OH), 3.99–4.02 (m, 2H), 4.43–4.48 (t, 2H, $^3J_{H,H}$ 5.0), 4.89 (s, 2H), 5.88 (s, 2H), 7.17 (q, 1H, $^4J_{H,H}$ 0.8), 7.56 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.87, 26.93, 38.75, 43.46, 56.98, 60.64, 65.04, 110.40, 133.87, 139.04, 142.60, 150.77, 162.75, 177.54. HRMS *m*/*z* calcd for $C_{16}H_{23}N_5O_5Na$ $[M+Na]^+$ 388.1597; found 388.1584. Compound **15c**, δ_H (200 MHz, $CDCl_3$) 1.13 (s, 9H), 1.86 (d, 3H, $^4J_{H,H}$ 1.2), 3.33 (br s, 1H, OH), 3.96–4.01 (t-like m, 2H), 4.42–4.47 (t-like m, 2H), 4.91 (s, 2H), 5.87 (s, 2H), 7.34 (q, 1H, $^4J_{H,H}$ 1.2), 7.81 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.90, 26.99, 38.84, 43.85, 52.81, 60.86, 65.02, 110.40, 124.74, 139.46, 141.83, 150.87, 162.85, 177.71. HRMS *m*/*z* calcd for $C_{16}H_{23}N_5O_5Na$ $[M+Na]^+$ 388.1597; found 388.1603.

*4.9.3. 1-[(2-(3-(Diethoxyphosphoryl)propyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**14d**) and 1-[(1-(3-(diethoxyphosphoryl)propyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methyl-3-(pivaloyloxymethyl)pyrimidine-2,4(1H,3H)-dione (**15d**).* According to the procedure described in Section 4.4, compounds **14d** and **15d** were synthesized from **13** (321 mg, 1.0 mmol) and diethyl 3-bromopropylphosphonate (**9d**). Column chromatography of the residue ($CHCl_3$/MeOH, 99/1, v/v) gave **14d** (334 mg, 67%) and **15d** (27 mg, 5%) as colourless oils. Compound **14d**, δ_H (200 MHz, $CDCl_3$) 1.18 (s, 9H), 1.31 (t, 6H, $^3J_{H,H}$ 7.0), 1.68–1.82 (m, 2H), 1.94 (d, 3H, $^4J_{H,H}$ 1.2), 2.14–2.36 (m, 2H), 4.01–4.18 (quintet-like m, 4H), 4.50–4.58 (t-like m, 2H), 4.94 (s, 2H), 5.97 (s, 2H), 7.16 (q, 1H, $^4J_{H,H}$ 1.2), 7.61 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.75, 16.26 (d, $J_{C,P}$ 5.7), 22.62 (d, $J_{C,P}$ 142.6), 22.82 (d, $J_{C,P}$ 4.6), 26.79, 38.58, 43.23, 54.68 (d, $J_{C,P}$ 17.1), 61.51 (d, $J_{C,P}$ 6.9), 64.88, 110.18, 133.68, 138.83, 142.42, 150.60, 162.53, 177.23. HRMS *m*/*z* calcd for $C_{21}H_{34}N_5O_7NaP$ $[M+Na]^+$ 522.2094; found 522.2101. Compound **15d**, δ_H (200 MHz, $CDCl_3$) 1.12 (s, 9H), 1.27 (t, 6H, $^3J_{H,H}$ 7.0), 1.59–1.77 (m, 2H), 1.88 (d, 3H, $^4J_{H,H}$ 1.2), 2.06–2.28 (m, 2H), 3.97–4.12 (quintet-like m, 4H), 4.54 (t, 2H, $^3J_{H,H}$ 6.8), 4.92 (s, 2H), 5.89 (s, 2H), 7.32 (q, 1H, $^4J_{H,H}$ 1.2), 7.67 (s, 1H). δ_C (125 MHz, $CDCl_3$) 12.88, 16.44 (d, $J_{C,P}$ 5.9), 22.63 (d, $J_{C,P}$ 143.0), 23.62 (d, $J_{C,P}$ 3.9), 26.98, 38.78, 43.79, 50.16 (d, $J_{C,P}$ 15.5), 61.83 (d, $J_{C,P}$ 5.9), 65.05, 110.37, 123.81, 139.24, 142.08, 150.83, 162.73, 177.45. HRMS *m*/*z* calcd for $C_{21}H_{34}N_5O_7NaP$ $[M+Na]^+$ 522.2094; found 522.2103.

*4.9.4. 1-((2-(((2R,3R,4R,5R)-3,4-Dibenzoyloxy-5-(benzoyloxymethyl)tetrahydrofuran-2-yl)methyl)-2H-1,2,3-triazol-4-yl)methyl)-3-(pivaloyloxymethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**14e**) and 1-((1-(((2R,3R,4R,5R)-3,4-dibenzoyloxy-5-(benzoyloxymethyl)tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(pivaloyloxymethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**15e**). 4.9.4.1. ((2R,3S,4S,5R)-3,4-Dihydroxy-5-(tosyloxymethyl)tetrahydrofuran-2-yl)methyl benzoate (**17**).* A mixture of 1-*O*-benzoyl-2,5-anydromannitol (**16**) (1.2 g, 4.4 mmol) and Py (8 mL) was cooled on an ice bath and tosyl chloride (930 mg, 4.9 mmol) was added in

four portions within 30 min. The mixture was stirred at 20–22 °C for 1 day and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/acetone, 85/15, v/v) gave **17** (970 mg, 53%) as colourless oil. $[\alpha]_D^{27}$ +19.2 (*c* 0.130, MeOH). δ_H (200 MHz, $CDCl_3$) 2.38 (s, 3H), 4.06–4.25 (m, 8H), 4.10–4.35 (m, 2H), 7.25–7.29 (m, 2H), 7.36–7.43 (m, 2H), 7.50–7.54 (m, 1H), 7.73–7.77 (m, 2H), 7.98–8.02 (m, 2H). δ_C (50 MHz, $CDCl_3$) 21.71, 64.56, 69.41, 77.69, 77.73, 80.01, 80.76, 128.06, 128.53, 129.62, 129.84, 130.02, 132.26, 133.39, 145.31, 166.99. HRMS *m*/*z* calcd for $C_{20}H_{22}O_8N_8SNa$ $[M+Na]^+$ 445.0933; found 445.0945.

*4.9.4.2. (2R,3R,4R,5R)-2-(Benzoyloxymethyl)-5-(tosyloxymethyl) tetrahydrofuran-3,4-diyl dibenzoate (**9e**).* A mixture of **17** (166 mg, 0.4 mmol) and Py (3 mL) was cooled on an ice bath and benzoyl chloride (274 mg, 2.0 mmol, 230 μL) was added in one portion. The mixture was stirred at 20–22 °C overnight and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (20 mL), washed with water, hydrochloric acid (5%, 3 mL), water (3 mL) and dried. The solvent was distilled off. Column chromatography of the residue (CH_2Cl_2) gave **9e** (196 mg, 80%) as colourless oil. $[\alpha]_D^{27}$ −11.7 (*c* 0.426, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 2.37 (s, 3H), 4.41 and 4.43 (AB part of the ABX system, 2H, $^3J_{AX}$ 3.0, $^3J_{BX}$ 3.5, $^2J_{AB}$ 10.7), 4.47–4.49 (m, 1H), 4.50–4.53 (m, 4H), 4.59 and 4.65 (AB part of the ABX system, 2H, $^3J_{AX}$ 4.0, $^3J_{BX}$ 6.0, $^2J_{AB}$ 11.8), 5.56–5.58 (m, 1H), 5.69–5.71 (m, 1H), 7.34–7.55 (m, 7H), 7.57–7.90 (m, 3H), 7.80–7.82 (m, 2H), 7.98–7.80 (m, 2H), 8.04–8.08 (m, 2H), 8.15–8.18 (m, 4H). δ_C (50 MHz, $CDCl_3$) 21.66, 64.51, 69.38, 79.48, 79.53, 81.64, 81.76, 128.21, 128.52, 128.63, 128.75, 128.92, 129.41, 129.67, 129.88, 129.92, 129.96, 130.14, 133.44, 133.34, 133.89, 133.94, 145.31, 165.57, 165.59, 166.27. HRMS *m*/*z* calcd for $C_{34}H_{30}O_{10}S$ Na $[M+Na]^+$ 653.1449; found 653.1465.

*4.9.4.3. 1-((2-(((2R,3R,4R,5R)-3,4-Dibenzoyloxy-5-(benzoyloxymethyl)tetrahydrofuran-2-yl)methyl)-2H-1,2,3-triazol-4-yl) methyl)-3-(pivaloyloxymethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**14e**) and 1-((1-(((2R,3R,4R,5R)-3,4-dibenzoyloxy-5-(benzoyloxymethyl)tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl) methyl)-3-(pivaloyloxymethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**15e**).* Treatment of **13** (114 mg, 0.4 mmol) with tosylate **9e** according to the procedure described in Section 4.4, followed by column chromatography of the residue ($CHCl_3$), gave **14e** (155 mg, 57%) and a **14e**/**15e** mixture (32 mg). The **14e**/**15e** ratio of 80/20 was determined from the relative intensities of the triazole H-5 proton signals (500 MHz, $CDCl_3$; **14e**, δ_H 5.94 ppm; **15e**, δ_H 5.91 ppm). Compound **14e**, $[\alpha]_D^{27}$ +5.2 (*c* 0.192, MeOH). δ_H (500 MHz, C_6D_6) 1.11 (s, 9H), 1.59 (d, 3H, $^4J_{H,H}$ 1.0), 4.34 (s, 2H), 4.41–4.44 (m, 1H), 4.52–4.66 (m, 4H), 4.79–4.83 (m, 1H), 5.66–5.67 (t-like m, 1H), 5.73–5.74 (t-like m, 1H), 6.10 (s, 2H), 6.27 (q, 1H, $^4J_{H,H}$ 1.0), 6.99–7.03 (m, 5H), 7.07 (m, 4H), 7.34 (s, 1H), 8.93–8.94 (m, 2H), 8.06–8.07 (m, 2H), 8.14–8.16 (m, 2H). δ_C (50 MHz, C_6D_6) 12.89, 27.13, 38.91, 43.19, 55.77, 63.84, 65.85, 79.77, 79.82, 82.53, 82.63, 110.03, 128.59, 128.75, 128.80, 129.39, 129.61, 130.10, 130.13, 130.17, 130.42, 133.94, 133.58, 133.69, 134.77, 138.46, 143.91, 150.92, 162.48, 165.40, 165.46, 166.09, 177.19. HRMS *m*/*z* calcd for $C_{41}H_{41}N_5O_{11}Na$ $[M+Na]^+$ 802.2700; found 802.2684. The **14e**/**15e** mixture, δ_H (500 MHz, $CDCl_3$) 1.15 (s, 1.8H), 1.16 (s, 7.2H), 4.60–4.92 (m, 8H), 5.53–5.56 (m, 0.4H), 5.67–5.70 (m, 1.6H), 5.91(s, 0.4H), 5.94 (s, 1.6H), 7.12 (s, 0.8H), 7.29 (s, 0.2H), 7.34–7.62 (m, 9H), 7.63 (s, 0.8H), 7.87 (s, 0.2H), 7.96–8.07 (m, 6H).

*4.9.5. Preparation of **5a**–**f** from **14a**–**e**. 4.9.5.1. 1-[(2-(2-Cyanoethyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**5a**).* According to the procedure described in Section 4.3.2, **5a** was obtained from **14a** (247 mg, 0.6 mmol). Crystallisation of the residue (methanol) gave **5a** (138 mg, 84%) as a white solid (mp >155 °C dec). δ_H (200 MHz, DMSO-d_6) 1.75 (br s, 3H), 3.13 (t, 2H, $^3J_{H,H}$ 6.2), 4.69 (t, 2H, $^3J_{H,H}$ 6.2), 4.93 (s, 2H), 7.59 (br s, 1H), 7.78 (s, 1H), 11.38 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.00, 17.91, 42.02, 49.75, 109.11, 118.19, 133.87, 141.06, 144.24, 150.81, 164.34. HRMS *m*/*z* calcd for $C_{11}H_{12}N_6O_2Na$ $[M+Na]^+$ 283.0914; found 283.0921. The treatment of **14a** (158 mg, 0.4 mmol) with a methanolic solution of NH_3 (20 mL) at 20–22 °C overnight gave **5a** (90 mg, 86%).

*4.9.5.2. 1-[(2-(Carbamoylmethyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**5b**).* A mixture of **14b** (158 mg, 0.4 mmol) and a methanolic solution of NH_3 (25 mL) was stirred at 20–22 °C for 3 days. Volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v and then MeOH) gave **5b** (89 mg, 83%) as a white solid (mp 168 °C dec). δ_H (200 MHz, DMSO-d_6) 1.75 (s, 3H), 4.90 (s, 2H), 5.05 (s, 2H), 7.34 (br s, 1H, NH_2), 7.60 (br s, 1H), 7.68 (br s, 1H, NH_2), 7.71 (s, 1H). δ_C (50 MHz, $CDCl_3$) 12.04, 42.06, 56.47, 109.05, 133.68, 141.19, 143.91, 150.89, 164.47, 167.37. HRMS *m*/*z* calcd for $C_{10}H_{12}N_6O_3Na$ $[M+Na]^+$ 287.0867; found 287.0870.

*4.9.5.3. 1-[(2-(2-Hydroxyethyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**5c**).* According to the procedure described in Section 4.3.2, **5c** was synthesized from **14c** (170 mg, 0.5 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **5c** (103 mg, 88%) as a white solid (mp 151–153 °C). δ_H (200 MHz, DMSO-d_6) 1.75 (d, 3H, $^4J_{H,H}$ 1.0), 3.79–3.86 (m, 2H), 4.39 (t, 2H, $^3J_{H,H}$ 5.4), 4.89 (s, 2H), 7.59 (q, 1H, $^4J_{H,H}$ 1.0), 7.68 (s, 1H), 11.32 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.00, 42.08, 57.05, 59.56, 109.05, 133.09, 141.14, 143.39, 150.81, 164.34. HRMS *m*/*z* calcd for $C_{10}H_{13}N_5O_3Na$ $[M+Na]^+$ 274.0916; found 274.0910.

*4.9.5.4. 1-[(2-(3-(Diethoxyphosphoryl)propyl)-2H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**5d**).* According to the procedure described in Section 4.3.2, **5d** was synthesized from **12d** (287 mg, 0.6 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **5d** (213 mg, 97%) as colourless oil. δ_H (200 MHz, $CDCl_3$) 1.15 (t, 6H, $^3J_{H,H}$ 7.0), 1.52–1.69 (m, 2H), 1.73 (d, 3H, $^4J_{H,H}$ 1.2), 1.95–2.19 (m, 2H), 3.87–4.02 (quintet-like m, 4H), 4.35 (t, 2H, $^3J_{H,H}$ 6.8), 4.81 (s, 2H), 7.10 (q, 1H, $^4J_{H,H}$ 1.2), 7.51 (s, 1H), 10.47 (br s, 1H, NH). δ_C (50 MHz, $CDCl_3$) 12.10, 16.19 (d, $J_{C,P}$ 6.1), 22.46 (d, $J_{C,P}$ 142.3), 22.76 (d, $J_{C,P}$ 4.6), 42.12, 54.59 (d, $J_{C,P}$ 17.5), 61.62 (d, $J_{C,P}$ 6.1), 110.96, 133.75, 139.79, 142.66, 151.06, 164.61. HRMS *m*/*z* calcd for $C_{15}H_{24}N_5O_5NaP$ $[M+Na]^+$ 408.1413; found 408.1419.

*4.9.5.5. 5-Methyl-1-[(2-(3-phosphonopropyl)-2H-1,2,3-triazol-4-yl)methyl]pyrimidine-2,4(1H,3H)-dione (**5e**).* A mixture of **5d** (180 mg, 0.5 mmol) and anhydrous acetonitrile (10 mL) was cooled on an ice bath and trimethylsilyl bromide (770 mg, 5.0 mmol, 660 μL) was added dropwise. The mixture was left at 20–22 °C overnight and volatiles were distilled off. The residue was dissolved in methanol (10 mL). The mixture was stirred at 20–22 °C for 1 h and concentrated to dryness under reduced pressure. The residue was dissolved in water (50 mL) and extracted with dichloromethane (3×20 mL). The aqueous phase was evaporated to dryness under reduced pressure. Lyophilization of the residue gave **5e** (110 mg, 73%) as a yellowish oil. δ_H (200 MHz, DMSO-d_6) 1.42–1.59 (m, 2H), 1.73 (s, 3H), 1.94–2.10 (m, 2H), 4.10–4.44 (m, 4H), 4.88 (s, 2H), 7.56 (s, 1H), 7.68 (s, 1H), 10.30 (br s, 1H, NH). δ_C (50 MHz, $CDCl_3$) 12.23, 24.69 (d, $J_{C,P}$ 137.7), 23.71 (d, $J_{C,P}$ 3.7), 42.43, 54.80 (d, $J_{C,P}$ 18.1), 109.47, 133.41, 141.47, 143.81, 151.09, 164.75. HRMS *m*/*z* calcd for $C_{11}H_{15}N_5O_5P$ $[M]^-$ 328.0811; found 328.0805.

*4.9.5.6. 1-((2-(((2R,3S,4R,5R)-3-Benzoyloxy-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)-2H-1,2,3-triazol-4-yl) methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**5f**).* According to

the procedure described in Section 4.9.5.2, **5f** synthesized from **14e** (110 mg, 0.14 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **5f** (47 mg, 74%) as colourless oil. $[\alpha]_D^{27}$ +30.6 (*c* 0.638, MeOH). δ_H (500 MHz, CD_3OD) 1.86 (d, 3H, $^4J_{H,H}$ 1.0), 3.58 and 3.65 (AB part of an ABX system, 2H, $^2J_{AB}$ 11.5, $^3J_{AX}$ 4.0, $^3J_{BX}$ 5.0), 3.79–3.82 (m, 1H), 3.98 (dd, 1H, $^3J_{H,H}$ 5.0, $^3J_{H,H}$ 5.0), 4.02 (dd, 1H, $^3J_{H,H}$ 5.0, $^3J_{H,H}$ 5.5), 4.27–4.30 (m, 1H), 4.59 and 4.63 (AB part of an ABX system, 2H, $^2J_{AB}$ 14.0, $^3J_{AX}$ 4.5, $^3J_{BX}$ 3.0), 4.97 (s, 2H), 7.41–7.47 (m, 2H), 7.50 (q, 1H, $^4J_{H,H}$ 1.0), 7.52–7.55 (m, 1H), 7.67 (s, 1H), 7.86–7.88 (m, 2H). δ_H (125 MHz, CD_3OD) 12.24, 43.58, 57.74, 63.03, 78.52, 79.95, 83.43, 85.83, 111.59, 128.62, 129.51, 132.92, 134.63, 134.94, 142.62, 144.95, 152.76, 166.79, 172.37. HRMS *m*/*z* calcd for $C_{21}H_{23}N_5O_7Na$ $[M+Na]^+$ 480.1495; found 480.1492.

4.10. Preparation of 6b–i

*4.10.1. 1-[(1-(2-Cyanoethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**6b**), 1-[(1-(2-carbamoylethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**6c**) and 5-methyl-1-[NH-1,2,3-triazol-4-ylmethyl]pyrimidine-2,4(1H,3H)-dione (**4**).* According to the procedure described in Section 4.3.2, the treatment of **15a** (89 mg, 0.2 mmol) with a methanolic solution of NH_4OH gave 27 mg of a **4**/**6b** mixture (40/60 ratio) and 29 mg of a **6b**/**6c** mixture (30/70 ratio). The component ratio in the mixtures was established from ^1H NMR spectroscopic analysis (200 MHz, DMSO-d_6), based on the relative intensity of the triazole H-5 proton: **2**, 7.81 ppm; **6b**, 8.15 ppm; or **6c**, 7.99 ppm. The **4**/**6b** mixture, δ_H (200 MHz, DMSO-d_6) 1.75 (s, 3H from **4**+3H from **6b**), 3.17 (t, $^3J_{H,H}$ 7.0, 2H from **6b**), 4.64 (t, $^3J_{H,H}$ 7.0, 2H from **6b**), 4.92 (s, 2H from **4**+2H from **6b**), 7.60 (s, 1H from **4**), 7.62 (s, 1H from **6b**), 7.81 (s, 1H from **4**), 8.15 (s, 1H from **6b**). The **6b**/**6c** mixture, δ_H (200 MHz, DMSO-d_6) 1.74 (s, 3H from **6b**+3H from **6c**), 2.68 (t, $^3J_{H,H}$ 6.6, 2H from **6c**), 3.17 (t, $^3J_{H,H}$ 7.0, 2H from **6b**), 4.51 (t, $^3J_{H,H}$ 6.6, 2H from **6c**), 4.63 (t, $^3J_{H,H}$ 7.0, 2H from **6b**), 4.87 (s, 2H from **6c**), 4.91 (s, 2H from **6b**), 6.94 (1H from **6c**, NH_2), 7.45 (1H from **6c**, NH_2), 7.59 (s, 1H from **6c**), 7.63 (s, 1H from **6b**), 7.99 (s, 1H from **6c**), 8.15 (s, 1H from **6b**). HRMS *m*/*z* calcd for $C_{11}H_{14}N_6O_3Na$ $[M+Na]^+$ 301.1025; found 301.1029. For spectral data of **4** or **6b**, see procedure in Sections 4.2 or 4.4, respectively.

*4.10.2. 1-[(1-(Carbamoylmethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**6d**).* According to the procedure described in Section 4.9.5.2, **6d** was synthesized from **15b** (70 mg, 0.2 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v and then MeOH) gave **6d** (39 mg, 82%) as a white solid (mp >180 °C dec). δ_H (200 MHz, DMSO-d_6) 1.75 (s, 3H), 4.90 (s, 2H), 5.04 (s, 2H), 7.38 (br s, 1H, NH_2), 7.63 (br s, 1H), 7.73 (br s, 1H, NH_2), 8.01 (s, 1H). δ_C (50 MHz, $CDCl_3$) 11.98, 42.17, 51.42, 108.85, 125.15, 141.20, 142.18, 150.76, 164.31, 167.26. HRMS *m*/*z* calcd for $C_{10}H_{12}N_6O_3Na$ $[M+Na]^+$ 287.0867; found 287.0872.

*4.10.3. 1-[(1-(2-Hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**6e**). 4.10.3.1. Method A.* According to the procedure described in Section 4.3.2, **6e** was synthesized from **15c** (132 mg, 0.4 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **6e** (80 mg, 77%) as a white solid (mp 186–187 °C). δ_H (500 MHz, DMSO-d_6) 1.75 (s, 3H), 3.76 (m, 2H), 4.37 (t, 2H, $^3J_{H,H}$ 5.5), 4.89 (s, 2H), 5.01 (br s, 1H, OH), 7.61 (s, 1H), 8.01 (s, 1H), 11.28 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.00, 42.21, 52.28, 59.81, 108.89, 124.01, 141.22, 142.27, 150.77, 164.34. HRMS *m*/*z* calcd for $C_{10}H_{13}N_5O_3Na$ $[M+Na]^+$ 274.0916; found 274.0907.

4.10.3.2. Method B. According to the procedure described in Section 4.3.1, **6e** was obtained from **7** and 2-azidoethanol (**8c**) (48 mg, 0.55 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **6e** (105 mg, 78%).

*4.10.4. 1-[(1-(3-(Diethoxyphosphoryl)-1H-1,2,3-triazol-4-yl)) methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**6f**).* According to the procedure described in Section 4.3.1, **6f** was obtained from **7** and diethyl 3-azidopropylphosphonate (**8d**) (184 mg, 0.8 mmol). Column chromatography of the residue ($CHCl_3$/acetone, 95/5, v/v) gave **6f** (242 mg, 76%) as a white solid (mp 77–79 °C). δ_H (200 MHz, $CDCl_3$) 1.31 (t, 6H, $^3J_{H,H}$ 7.0), 1.64–1.73 (m, 1H), 1.77–1.81 (m, 1H), 1.90 (d, 3H, $^4J_{H,H}$ 1.2), 2.10–2.22 (m, 2H), 4.01–4.17 (quintet-like m, 4H), 4.41–4.48 (t, 2H, $^3J_{H,H}$ 7.0), 4.95 (s, 2H), 7.33 (q, 1H, $^4J_{H,H}$ 1.2), 7.75 (s, 1H), 9.05 (br s, 1H, NH). δ_C (50 MHz, $CDCl_3$) 12.44, 16.59 (d, $J_{C,P}$ 6.1), 22.78 (d, $J_{C,P}$ 142.7), 23.75 (d, $J_{C,P}$ 5.0), 43.07, 50.33 (d, $J_{C,P}$ 15.6), 62.00 (d, $J_{C,P}$ 6.5), 111.41, 124.04, 140.28, 142.28, 151.08, 164.24. HRMS *m*/*z* calcd for $C_{15}H_{24}N_5O_5NaP$ $[M+Na]^+$ 408.1413; found 408.1402.

*4.10.5. 1-((1-(((2R,3S,4S,5R)-3,4-Dihydroxy-5-(benzoyloxymethyl) tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**6g**). 4.10.5.1. ((2R,3S,4S,5R)-3,4-Dihydroxy-5-(azidomethyl)tetrahydrofuran-2-yl)methyl benzoate (**8e**).* Sodium azide (200 mg, 3.1 mmol) was added to a mixture of **16** (260 mg, 0.6 mmol), anhydrous DMF (12 mL) and tetrabutylammonium hydrogen sulfate (25 mg, 0.9 mmol). The mixture was stirred at 50 °C for 3 days and filtered through a Celite® pad. The pad was washed with DMF (10 mL). The filtrates were collected and evaporated to dryness under reduced pressure. Column chromatography of the residue ($CHCl_3$/MeOH, 95/5, v/v) gave **8e** (167 mg, 93%) as colourless oil. $[\alpha]_D^{27}$ +53.7 (*c* 0.354, MeOH). δ_H (500 MHz, $CDCl_3$) 3.36 and 3.54 (AB part of an ABX system, 2H, $^3J_{AX}$ 4.0, $^3J_{BX}$ 4.0, $^2J_{AB}$ 13.0), 4.01–4.03 (m, 1H), 4.14–4.17 (m, 4H), 4.19–4.24 (m, 1H), 4.46–4.49 (m, 2H), 7.38–7.41 (m, 2H), 7.52–7.54 (m, 1H), 8.00–8.03 (m, 2H). δ_C (125 MHz, $CDCl_3$) 52.01, 64.71, 77.85, 77.90, 80.52, 81.20, 128.58, 129.39, 129.82, 133.59, 167.40. HRMS *m*/*z* calcd for $C_{13}H_{15}N_3O_5Na$ $[M+Na]^+$ 316.0909; found 316.0911.

*4.10.5.2. 1-((1-(((2R,3S,4S,5R)-3,4-Dihydroxy-5-(benzoyloxymethyl)tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl) methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**6g**).* According to the procedure described in Section 4.3.1, **6g** was synthesized from **7** and **8e** (180 mg, 0.6 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v) gave **6g** (196 mg, 70%) as a white solid (mp 89–90 °C). $[\alpha]_D^{27}$ +25.2 (*c* 0.218, MeOH). δ_H (500 MHz, CD_3OD) 1.84 (s, d, 3H, $^4J_{H,H}$ 1.0), 3.85 (dd, 1H, $^3J_{H,H}$ 6.5, $^3J_{H,H}$ 5.5), 4.02–4.05 (m, 1H), 4.11 (dd, 1H, $^3J_{H,H}$ 6.0, $^3J_{H,H}$ 5.5), 4.16–4.19 (m, 1H), 4.40 and 4.47 (AB part of the ABX system, 2H, $^3J_{AX}$ 3.5, $^3J_{BX}$ 5.0, $^2J_{AB}$ 12.0), 4.62 and 4.65 (AB part of the ABX system, 2H, $^3J_{AX}$ 3.5, $^3J_{BX}$ 6.0, $^2J_{AB}$ 14.0), 4.97 (s, 1H), 7.47–7.52 (m, 2H), 7.48 (s, 1H), 7.60–7.63 (m, 1H), 8.00 (s, 1H), 8.02–8.04 (m, 2H). δ_C (125 MHz, CD_3OD) 12.22, 43.65, 52.93, 65.48, 78.64, 79.25, 82.75, 82.91, 111.55, 126.27, 129.65, 130.63, 131.22, 134.38, 142.55, 143.90, 152.66, 166.73, 167.81. HRMS *m*/*z* calcd for $C_{21}H_{23}N_5O_7Na$ $[M+Na]^+$ 480.1495; found 480.1490.

*4.10.6. 5-Methyl-1-[(1-(3-phosphonopropyl)-1H-1,2,3-triazol-4-yl) methyl]pyrimidine-2,4(1H,3H)-dione (**6h**).* According to the procedure described in Section 4.9.5.5, **6h** was obtained from **6f** (85 mg, 0.2 mmol). Lyophilization of the residue gave **6h** (62 mg, 85%) as a yellowish oil. δ_H (200 MHz, DMSO-d_6) 1.15–1.47 (m, 2H), 1.74 (br s, 3H), 1.85–2.16 (m, 2H), 4.30–4.42 (t-like m, 2H), 4.88 (s, 2H), 7.63 (br s, 1H), 8.09 (s, 1H). δ_C (125 MHz, DMSO-d_6) 11.93, 25.13, 25.83 (d, $J_{C,P}$ 136.1), 42.17, 50.14 (d, $J_{C,P}$ 14.6), 108.84, 123.55, 141.18, 142.28, 150.73, 164.28. HRMS *m*/*z* calcd for $C_{11}H_{15}N_5O_5P$ $[M]^-$ 328.0811; found 328.0805.

4.10.7. 1-((1-(((2R,3S,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-5-

methylpyrimidine-2,4(1H,3H)-dione (***6i***). According to the procedure described in Section 4.9.5.2, **6i** was synthesized from **6g** (160 mg, 0.4 mmol). Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v) gave **6i** (109 mg, 86%) as a white solid (mp 63–64 °C). $[\alpha]_D^{27}$ +42.9 (*c* 0.466, MeOH). δ_H (200 MHz, CD_3OD) 1.86 (s, 3H), 3–54-3.66 (m, 2H), 3.72–3.83 (m, 2H), 3.97–4.03 (m, 1H), 4.08–4.16 (m, 1H), 4.52–4.70 (m, 2H), 4.90 (s, 2H), 7.55 (s, 1H), 8.03 (s, 1H). δ_C (50 MHz, CD_3OD) 12.24, 43.64, 53.13, 62.98, 78.02, 79.37, 82.76, 85.39, 111.55, 126.31, 142.63, 143.85, 152.70, 166.81. HRMS *m*/*z* calcd for $C_{14}H_{19}N_5O_6Na$ $[M+Na]^+$ 376.1233; found 376.1219.

Acknowledgements

This work was financed by Warsaw University of Technology and by the European Union within the European Regional Development Fund; Project No. POIG.01.01.02-14-102/09. The authors thank Professor Adam Gryff-Keller and M.Sc. Sergey Molchanov, Warsaw University of Technology, for their invaluable help with the designing of 2D NMR experiments.

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25. It is worth noting that relatively few data are available on systematic examination of a relation between a structure of a tetragonal alkylating agent and an alkylation regioselectivity of *NH*-1,2,3-triazoles (the term of 'systematic investigation' means here a series of reactions between a specific *NH*-1,2,3-triazole derivative and different alkylating agents with the same leaving group, conducted under identical conditions). For instance, in the reported alkylations of *NH*-1,2,3-triazole an increase in N-2 selectivity was observed in the series: methyl iodide<ethyl bromide<methyl bromoacetate (Wang, X.-j.; Zhang, L.; Krishnamurthy, D.; Senanayake, C. H.; Wipf, P. *Org. Lett.* **2010**, *12*, p 4632). The favourable N-2 alkylation over N1/N3 one was suggested to result from the relative magnitude of the HOMO coefficients at the nitrogen atoms of the neutral 2*H*- and 1*H*-1,2,3-triazole. The HOMO control was postulated to have a more pronounced effect on directing bulky ethyl bromide or methyl bromoacetate than the sterically unhindered methyl iodide. On the other hand, the reported study on alkylation of 4-nitro-*NH*-1,2,3-triazole with phenyl bromoacetate or ethyl bromoacetate demonstrated that a specific character of the substituent on the electrophilic carbon site of the alkylating agent could play a role in the alkylation selectivity (Vereshchagin, L. I.; Kuznetsova, N. I.; Kirillova, L. P.; Shcherbakov, V. V.; Sukhanov, G. T.; Gareev, G. A. *Chem. Heterocycl. Compd.* **1986**, *22*, p 745). On the other hand, on varying from phenyl bromoacetate to ethyl bromoacetate the inversion of N-2/N-1 selectivity of the alkylation (i.e., from 67/33 to 33/67, respectively) was reported. However, plausible reasons for these observations (including an effect of the nitro group on the course of the reaction) were not discussed in the original paper.
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