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One-pot protocol for N-alkylation of purine, pyrimidine and azole derivatives via alcohols using Ph_3P/I_2: simple route for carboacyclic nucleoside synthesis

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ABSTRACT

A simple and efficient synthetic protocol for the one-pot N-alkylation of nucleobases and their related N-heterocycles via alcohols utilizing the combination of PPh_3 and I_2 is reported. In this protocol purine, pyrimidine and azole derivatives underwent the N-alkylation reaction with diverse primary alcohols using Ph_3P/I_2 in the presence of Et_3N-K_2CO_3 in anhydrous DMF to give the *N*-alkyl adducts (carboacyclic nucleosides) in good yields (up to 90%). The influence of some parameters in this reaction including type of solvent, base, reagents and temperature was discussed. In addition, this protocol has proved the favorable selectivity towards primary hydroxyl versus secondary hydroxyl group in diols.

1. Introduction

Since the discovery of acyclovir as a potent antiviral agent, extensive efforts have been made to develop other new acyclic nucleoside analogues.[1] Among acyclic nucleoside analogues, carboacyclic nucleosides are a prominent type of nucleosides exhibiting considerable antiviral and anticancer activities.[2] In this connection, the emergence of the well-established antiviral and anticancer drugs such as (S)-DHPA, EHNA, Penciclovir (PCV) and Famciclovir (FCV) has widely increased the scientists' insights into design and synthesis of new chemotherapeutic agents for overcoming cancer and viral-caused dispositions (Fig. 1).

The most common, rapid and straightforward route to access carboacyclic nucleosides involves C–N bond formation through the N-alkylation reaction of nucleobases or other related N-heterocycles with varied types of carbon-electrophiles such as RX (R=alkyl; X=halide,[3] OTs[4] and OMs[5]), epoxides,[6] Michael acceptors,[7] esters,[8] carbonates,[9] ethers[10] and acetals.[11]

Despite the usefulness of the above carbon-electrophiles in N-alkylation reactions, the high risk of toxicity has limited their applicability in large scale synthesis. Alkyl halides, epoxides and Michael acceptors are known today as harmful carbon-electrophiles with incontrovertible carcinogenic properties.[12–14] Therefore, employing a carbon electrophile with a lower toxicity and environmental cost is essential. To overcome this problem, the direct N-alkylation of nucleobases with alcohols would be a highly advantageous and attractive strategy, since alcohols are known as

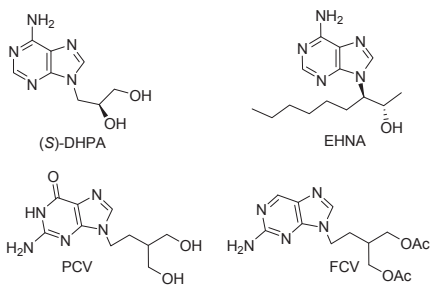

Fig. 1. The structure of some famous carboacyclic nucleoside analogues.

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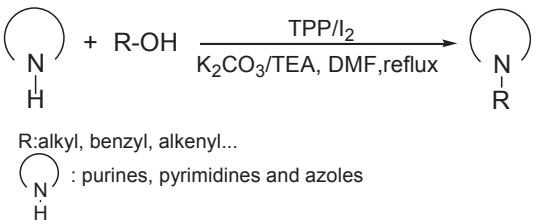
0040-4020/

versatile reagents having less toxicity, easily handled and widely available with respect to related alkyl halides. In general, Mitsunobu approaches[15] for N-alkylation of nucleobases with alcohols are the most established and developed procedures. Nevertheless, the N-alkylation of nucleobases with alcohols through the Mitsunobu conditions suffers from two main disadvantages comprising (i) the use of an expensive diethyl azodicarboxylate (DEAD), and (ii) an explosive nature of DEAD. These drawbacks considerably have restricted the applicability of Mitsunobu conditions in large scale synthesis of N-alkylated nucleobases.

The combination of triphenylphosphine (TPP) and iodine is an interesting reagent used in various organic transformations mainly in conversion of alcohols into the corresponding alkyl iodides.[16] In addition this combination is involved in the conversion of thiols,[17] and enols[18] into iodides, reduction of various sulfur derivatives to sulfides or thiols,[17] reduction of epoxides,[19] iodohydrins,[20] and vicinal diols[21] to alkenes, synthesis of iodohydrins from epoxides,[22] esterification of carboxylic acids,[23] acetalizations of carbonyl groups,[24] dehydrating agent[25] and also upgrading agent for Beckmann rearrangement.[26]

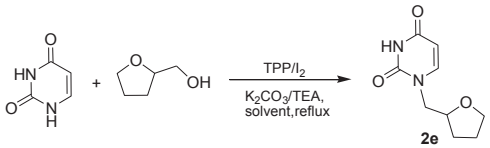
Apart from a few known combinations of TPP/I_2 with some assisting agents like imidazole[27] and other bases,[16] the combination of TPP/I_2 with nucleophiles was rarely studied and reported.[28] The TPP/I_2/Nucleophile combination is an attractive mixture providing a straightforward route to establish diverse C–Nu bonds through alcohols.

In an attempt for converting certain alcohols into the corresponding alkyl iodides using the combination of TPP/I_2/imidazole in anhydrous DMF at elevated temperature (>100 °C), we witnessed that beside the generation of expected alkyl iodides, a few portions of *N*-alkyl imidazoles were also obtained. In continuation of this study, we found the addition of an appropriate base to reaction mixture extensively improved production of the perquisite *N*-alkyl imidazole adducts. Inspired by this experiment, other examined N-heterocyclic compounds like purine and pyrimidine nucleobases also were led to their corresponding *N*-alkyl adducts. Given our long-standing interest in synthesis of carboacyclic nucleosides through one-pot N-alkylation of nucleobases via alcohols,[29] we now report the one-pot N-alkylation of nucleobases via alcohols using the combination of TPP/I_2 in refluxing DMF (anhyd) in the presence of triethylamine (TEA) and K_2CO_3 as a basic mixture (Scheme 1).



Scheme 1. One-pot N-alkylation of nucleobases via alcohols using TPP/I_2 in the presence of K_2CO_3/TEA in DMF.

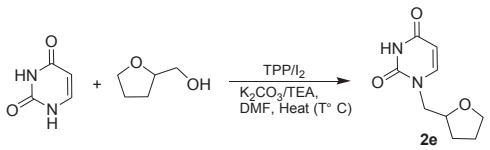
Table 1
The influence of solvent type on sample reaction[a]



Entry	Solvent	Time (h)	Yield[d] (%)
1	DMF	10	49
2	DMF[b]	6	70
3	DMSO	15	27
4	MeCN	20	14
5	HMPA	26	27
6	NMP	9	54
7	THF	12	36
8	Toluene	48	12
9	Acetone	36	21
10	bmim[Br][c]	30	58
11	PEG 200[c]	72	NR[e]
12	H_2O	72	NR

[a] Reaction conditions: uracil (1 mmol), alcohol (1 mmol),TPP (1 mmol), I_2 (1 mmol), K_2CO_3 (1 mmol), TEA (1 mmol) and solvent (5 mL).
[b] Anhydrous DMF.
[c] The reaction was conducted at 100 °C.
[d] Isolated yield.
[e] No reaction.

Table 2
The influence of temperature on sample reaction[a]



Entry	T °C	Time (h)	Yield[b] (%)
1	25	6	NR[c]
2	25	12	NR
3	25	18	NR
4	50	6	10
5	50	12	12
6	50	18	22
7	75	6	15
8	75	12	21
9	75	18	32
10	100	6	30
11	100	12	48
12	100	18	55
13	125	6	57
14	125	12	61
15	125	18	67
16	Reflux	6	70
17	Reflux	12	70
18	Reflux	18	70

[a] Reaction conditions: uracil (1 mmol), alcohol (1 mmol),TPP (1 mmol), I_2 (1 mmol), K_2CO_3 (1 mmol), TEA (1 mmol) and DMF (5 mL).
[b] Isolated yield.
[c] No reaction.

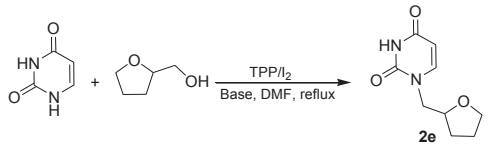
2. Results and discussion

To optimize the reaction conditions, we examined the reaction of uracil with (tetrahydro-furan-2-yl)-methanol as a sample reaction. First, we focused our attention on the choice of an appropriate solvent. For this purpose, we investigated the effect of various traditional solvents. The results are shown in Table 1.

As indicated in Table 1, among the examined solvents, the use of anhydrous DMF gained the best result and thus anhydrous DMF was employed for all next studied reactions (Table 1, entry 2). Also, the use of normal DMF, NMP and bmim[Br] as a room temperature ionic liquid led to reasonable yields of **2e** (Table 1, entries 1, 6, 10) whereas, the other tested solvents displayed the negligible yield of the desire product. In addition, protic solvents like water or polyethylene glycol (PEG) failed to expedite the reaction even if the reactions were prolonged over 72 h.

Next, we explored the influence of different temperatures (Table 2). At rt, the reaction was not progressed even if extended for some

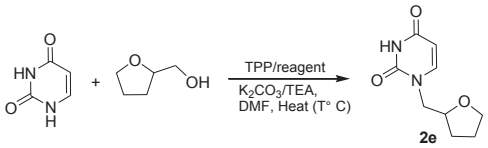
Table 3
The influence of various bases on sample reaction[a]



Entry	Base	Time (h)	Yield (%)[e]
1	—	72	NR[f]
2	DBU	8	65
3	DBN	10	60
4	DABCO	18	51
5	DMAP	11	55
6	NMM[b]	9	62
7	TEA	12	62
8	K_2CO_3	15	58
9	MgO	48	25
10	K_2CO_3/TEA[c]	6	70
11	KOH	12	56
12	Al_2O_3[d]	48	32

[a] Reaction conditions: uracil (1 mmol), alcohol (1 mmol),TPP (1 mmol), I_2 (1 mmol), base (1 mmol) and DMF (5 mL).
[b] *N*-methyl morpholine.
[c] 1:1 ratio was used.
[d] Basic alumina.
[e] Isolated yield.
[f] No reaction.

Table 4
The comparison of TPP/I_2 performance with other similar reagents[a]



Entry	Reagent	Time (h)	Yield (%)[e]
1	I_2	6	70
2	Br_2	12	51
3	NCS[b]	14	38
4	NBS[c]	10	41
5	NIS[d]	8	40
6	DBDMH[e]	9	53
7	ICC[f]	18	56
8	NCTSA-Na[g]	16	22

[a] Reaction conditions: uracil (1 mmol), alcohol (1 mmol), TPP (1 mmol), reagent (1 mmol), K_2CO_3 (1 mmol), TEA (1 mmol) and DMF (5 mL).
[b] N-Chlorosuccinimide.
[c] N-Bromosuccinimide.
[d] N-Iodosuccinimide.
[e] 1,3-Dibromo-5,5-dimethyl hydantoin.
[f] Isocyanuric chloride.
[g] *N*-Chloro-*p*-toluenesulfonamide sodium.

period of times. However, as expected, by the gradual increment in temperature, the yields were improved and in this regard, the best result was obtained at reflux (Table 2, entry 16).

Since the weak nucleophilic nature of nucleobases and related analogues, the use of an efficient base for enhancing the nucleophilicity power of these compounds is crucial. In this context, we evaluated the effect of some inorganic and organic bases (Table 3). As Table 3 indicates, in the absence of the base, the reaction did not occur (Table 3, entry 1). The best result was observed when an equimolar ratio of K_2CO_3/TEA was used. The combination of K_2CO_3/TEA (Table 3, entry 10) was previously experienced by our research group to be an appropriate basic mixture for N-alkylation of nucleobases in DMF.[29a,c] It is worth mentioning that the used of each of these bases in a single form yielded **2e** in a lower quantity and longer reaction time. Other bases yielded the desired product in low to moderate yields.

To find out the performance of TPP/I_2 against the other combinations of TPP with halogens or positive-halogen containing reagents, we studied the effect of TPP in combination with Br_2, NBS, NCS, NIS, 1,3-Dibromo-5,5-dimethyl hydantoin (DBDMH), isocyanuric chloride (ICC) and *N*-chloro-*p*-toluenesulfonamide sodium (NCTSA-Na) salt (Table 4, entries 2–8) on a model reaction. As shown in Table 4, the employment of TPP/Br_2 combination in a sealed tube yielded in a moderate amount (Table 4, entry 2). In addition, the combination of TPP with some electrophilic-halogen containing imides like NCS, NBS, NIS, DBDMH, ICC and NCTSA-Na salt (Table 4, entries 3–8) have progressed the sample reaction in variable yields and times (Table 4, entries 3–8).

With the optimal reaction conditions in hand, we screened the versatility and the scope of this protocol. In this regard, three important types of N-heterocyclic cores comprising purines, pyrimidines and azole derivatives were examined since they generally exhibit the strong tendency to interact with biomolecules in the cells. Thereupon, these N-heterocycles were effectively N-alkylated using the new protocol with a set of structurally diverse alcohols bearing various functionalities (Table 5).

Purines like adenine, N6-benzyladenine, theophylline and theobromine were efficiently N-alkylated with alcohols using the above protocol. It is noteworthy that the N-alkylations were performed in a regioselective manner. For purine bases as ambident nucleophiles, the N-alkylation from N7 and N1 sites were achieved for theophylline and theobromine, respectively; whereas, for adenine or N6-benzyladenine the alkylation was conducted through N9 sites, dominantly. In addition, the marginal quantities of N7-alkyl adducts for N6-benzyladenine and adenine were also produced which are <10% for N6-benzyladenine and <10–20% for adenine, accordingly.[30] These ratios of isomers were allocated by GC analysis. The alkylation from other nucleophilic sites of used purines was not detected.

Primary alcohols with a simple aliphatic side chain, aliphatic side chain bearing various functionalities comprising allylic, benzylic, aryl, ether and also other alcohols with heterocyclic-conjugate residues were applied for N-alkylation of purine nucleobases. Nevertheless, the secondary alcohols seldom react with nucleobases using the current procedure. As an instance, the reaction of theophylline with 1-phenyl-ethanol led to a low yield of **1m** (≈8%) which was determined by GC analysis. In addition, tertiary alcohols like *t*-butyl alcohol and/or 2-phenyl-propan-2-ol were not altered.

In the same way as purines, pyrimidines as well as azoles were N-alkylated with different primary alcohols (Table 5). Uracil, 5-nitrouracil, thymine and 6-azauracil showed the considerable regioselectivity for alkylation from N1-site; nevertheless, a few N1,N3-dialkyl adducts were also produced in trace amount (10–15%) which was assigned by GC analysis.[31]

We also established a competitive reaction between a mixture consist of primary verses secondary alcohols under optimized condition to realize the selectivity of this protocol. To this end, a mixture of two isomeric alcohols comprising 1-phenylethanol (1 equiv) and 2-phenylethanol (1 equiv) was used to react with theophylline (1 equiv) in the presence of TPP (1 equiv) and I_2 (1 equiv). Due to Scheme 2, in the presence of primary alcohol, the secondary alcohol has no chance to react with theophylline. Thus, compound **1l** was the single product which was assigned by GC-analysis.

We also achieved the reaction of thymine with 3-phenoxy-propane-1,2-diol using current protocol to understand the reactivity trend between two different types of hydroxyl moieties in a molecule (Scheme 3).

Table 5
One-pot N-alkylation of nucleobases via alcohol using TPP/I_2[a]

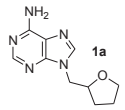
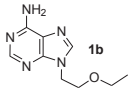
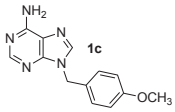
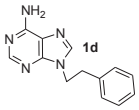
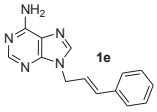
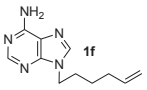
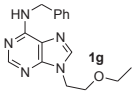
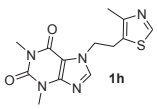
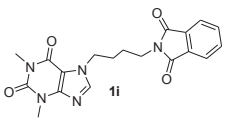
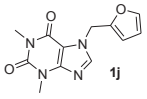
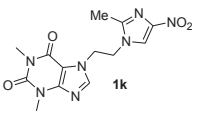
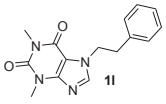
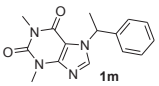
Entry	Product	Time (h)	Yield (%)[b]
1	 1a	15	68
2	 1b	12	75
3	 1c	11	72
4	 1d	11	76
5	 1e	10	69
6	 1f	15	78
7	 1g	9	71
8	 1h	12	80
9[c]	 1i	14	84
10	 1j	8	86
11[d]	 1k	12	90
12	 1l	6	89
13	 1m	48	8

Table 5 (*continued*)

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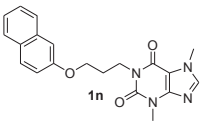
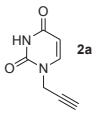
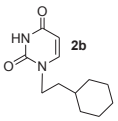
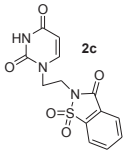
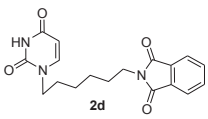
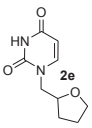
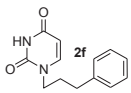
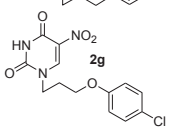
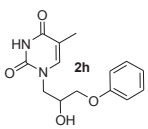
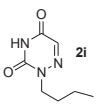
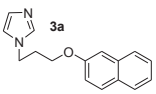
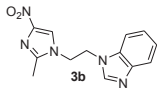
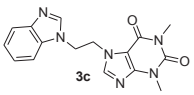
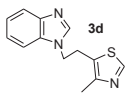
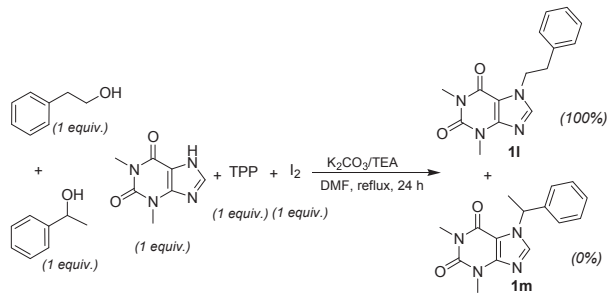
14	 1n	18	63
15	 2a	20	66
16	 2b	8	75
17[e]	 2c	8	72
18[f]	 2d	10	76
19	 2e	6	70
20	 2f	13	74
21	 2g	10	82
22	 2h	18	80
23	 2i	9	67
24	 3a	14	78

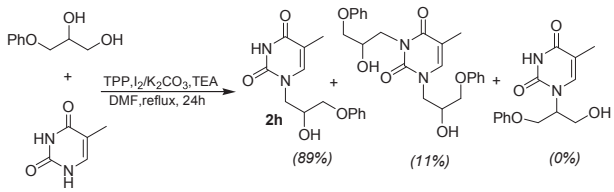
Table 5 (*continued*)

Entry	Product	Time (h)	Yield (%)[b]
25[g]	 3b	12	83
26[h]	 3c	16	86
27	 3d	14	73

[a] Reaction conditions: uracil (1 mmol), alcohol (1 mmol), TPP (1 mmol), I_2 (1 mmol), K_2CO_3 (1 mmol), TEA (1 mmol) and DMF (5 mL).
[b] Isolated yields for shown structures.
[c] From reaction of 2-(4-hydroxy-butyl)-isoindole-1,3-dione with theophylline.
[d] From reaction of 2-(2-methyl-4-nitro-imidazol-1-yl)-ethanol with theophylline.
[e] From reaction of 2-(2-hydroxy-ethyl)-1,1-dioxo-1,2-dihydro-1l6-benzo[d] isothiazol-3-one with uracil.
[f] From reaction of 2-(6-hydroxy-hexyl)-isoindole-1,3-dione with uracil.
[g] From reaction of 2-(1*H*-benzo[d]imidazol-1-yl)ethanol with 2-methyl-4-nitro-imidazole.
[h] From reaction of 7-(2-hydroxy-ethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione with benzimidazole.



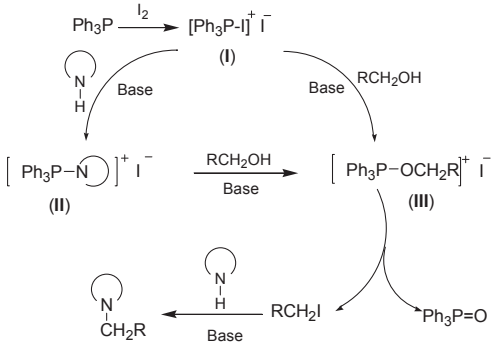
Scheme 2. The competitive reaction between primary vs. secondary alcohols using TPP/I_2/K_2CO_3/TEA in DMF. The conversion yields were assigned by GC-analysis.



Scheme 3. The difference in reactivity between primary vs. secondary hydroxyl groups in N-alkylation of thymine via 3-phenoxy-propane-1,2-diol.

As shown in Scheme 3, thymine is majorly N1-alkylated through replacing with primary hydroxyl moiety to afford adduct **2h**; whereas, the generation of the other one possible isomer (in which could be obtained by the secondary hydroxyl moiety replacement) was not observed. In addition to adduct **2h**, the N1, N3-dialkyl adduct of thymine was also obtained in a trace amount.

In terms of reaction mechanism, we believe that the reaction is conducted by the primary nucleophilic attack of TPP to iodine giving iodotriphenylphosphonium iodide (I) as a reactive intermediate (Scheme 4). In the synthesis of alkyl iodide from alcohol using the combination of TPP/I_2/imidazole, Garegg and co-workers[32] have proved by ^{31}P NMR studies that the role of



Scheme 4. A plausible mechanism for one-pot N-alkylation reaction of nucleobases via alcohols using TPP/I_2 combination.

imidazole is mainly to facilitate the conversion, through the generation of imidazolium triphenylphosphonium iodide intermediate. Similarly with imidazole, we believe that purines, pyrimidines and azoles achieve the P–N bond to gain the intermediate (II). In continuation, (II) reacts further with alcohols to produce the intermediate (III). The intermediate (III) also can be obtained directly from iodotriphenylphosphonium iodide (I) which eventually converts to alkyl iodide. The in situ produced alkyl iodide reacts with the base activated nucleobase to yield the corresponding *N*-alkyl nucleobase adduct. To verify the possibility of such a mechanism, both GC and TLC analysis have confirmed the production of the corresponding alkyl iodide especially in the early reaction times.

3. Conclusion

In conclusion, we have developed a facile, simple and highly convenient protocol for one-pot N-alkylation of nucleobases via alcohols using the combination of TPP/I_2 in the presence of a basic mixture of K_2CO_3/TEA. The influence of various parameters effective in this current protocol including solvent, base, temperature and reagent has been discussed. Using this protocol, the nucleobases like purines, pyrimidines and azoles were regioselectively N-alkylated in good to excellent yields. This synthetic methodology found to be a suitable route for N-alkylation reaction via primary alcohols, whereas the secondary and tertiary alcohols were failed to react with nucleobases.

4. Experimental

4.1. General

All materials were purchased from either *Fluka* or *Merck*. Solvents were purified by standard procedures, and stored over 3 Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes. IR spectra were obtained using a Shimadzu FTIR-8300 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brüker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^1H NMR signals are s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, etc. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m*/*z*; rel%). Elemental analyses were performed on a Perkin–Elmer 240-B microanalyzer.

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4.2. General procedure for one-pot N-alkylation of nucleobases via alcohols using TPP/I_2

In a double-necked round bottom flask (100 mL) equipped with a condenser was added a mixture, consisting of alcohol (1 mmol), TPP (1 mmol), I_2 (1 mmol) Et_3N (1 mmol), K_2CO_3 (1 mmol), and the desire nucleobase (1 mmol) in anhydrous DMF (5 mL).[33] The mixture was heated at reflux. Heating was continued until TLC indicated no further improvement in the conversion (Table 5). The solvent was evaporated under vacuum and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2×100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by short column chromatography on silica gel eluting with proper solvents.

4.3. Data for new compounds

*4.3.1. 1,3-Dimethyl-7-(2-(4-methylthiazol-5-yl)ethyl)-1H-purine-2,6(3H,7H)-dione (**1h**).* Column chromatography purification on silica gel with *n*-hexane/EtOAc (1:1) afforded creamy solid (2.44 g, 80%); mp=185–186 °C; R_f (EtOAc) 0.31; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 2.28 (s, 3H, C=CCH$_3$), 3.29 (s, 3H, N(3)–CH$_3$), 3.33 (t, 2H, *J*=7.0 Hz, C=CCH$_2$), 3.46 (s, 3H, N(1)–CH$_3$), 4.42 (t, 2H, *J*=7.0 Hz, NCH$_2$), 7.96 (s, 1H, C(8)–H, theophylline), 8.87 (s, 1H, C(2)–H, thiazole); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 16.5, 27.4, 30.8, 33.6, 52.7, 108.4, 130.5, 145.1, 149.7, 151.1, 152.0, 152.9, 155.7; IR (KBr) ν cm^{-1}: 3070, 2965, 1715, 1703, 1571, 1450; MS [*m/z* (%)]: 305 (14.2); Anal. Calcd for $C_{13}H_{15}N_5O_2S$: C, 51.13; H, 4.95; N, 22.94; S, 10.50. Found: C, 51.21; H, 5.07; N, 22.85; S, 10.56.

*4.3.2. 7-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**1i**).* Column chromatography purification on silica gel with *n*-hexane/EtOAc (1:1) afforded white solid (3.20 g, 84%); mp=234–235 °C; R_f (EtOAc) 0.43; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 1.47–1.53 (m, 2H, CH$_2$), 1.77–1.82 (m, 2H, CH$_2$), 3.18 (s, 3H, N(3)–CH$_3$), 3.36 (s, 3H, N(1)–CH$_3$), 3.51 (t, 2H, *J*=6.6 Hz, NCH$_2$), 4.19 (t, 2H, *J*=6.6 Hz, NCH$_2$), 7.65–7.72 (m, 4H, aryl), 8.03 (s, 1H, C(8)–H, theophylline); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 27.1, 29.4, 30.4, 32.2, 41.1, 49.5, 107.3, 127.1, 132.0, 132.7, 145.6, 150.5, 151.4, 154.9, 170.1; IR (KBr) ν cm^{-1}: 3100, 2947, 1718, 1706, 1590, 1532, 1448; MS [*m/z* (%)]: 381 (18.7); Anal. Calcd for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.93; H, 5.16; N, 18.25.

*4.3.3. 2-(6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)hexyl)isoindoline-1,3-dione (**2d**).* Column chromatography purification on silica gel with *n*-hexane/EtOAc (1:2) afforded white solid (2.59 g, 76%); mp=150–151 °C; R_f (EtOAc) 0.59; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 1.23–1.36 (m, 4H, 2CH$_2$), 1.63–1.66 (m, 4H, 2CH$_2$), 3.60–3.74 (m, 4H, 2NCH$_2$), 5.59 (d, 1H, *J*=7.8 Hz, C(5)–H, uracil), 7.70 (d, 1H, *J*=7.8 Hz, C(6)–H, uracil), 7.88–7.96 (m, 4H, aryl), 11.29 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 25.9, 26.3, 27.3, 28.0, 41.2, 47.9, 101.9, 127.2, 132.1, 133.0, 141.6, 151.4, 163.4, 169.5; IR (KBR) ν cm^{-1}: 3240, 3035, 2968, 1730, 1710, 1590, 1472; MS [*m/z* (%)]: 341 (18.9); Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.40; H, 5.73; N, 12.19.

*4.3.4. 1-((Tetrahydrofuran-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione (**2e**).* Column chromatography purification on silica gel with *n*-hexane/EtOAc (1:1) afforded yellow oil (1.37 g, 70%); R_f (EtOAc) 0.48; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 1.85–1.93 (m, 4H, CH$_2$CH$_2$), 3.65–3.82 (m, 5H, NCH$_2$CH, OCH$_2$), 5.70 (d, 1H, *J*=7.9 Hz, C(5)–H, uracil), 7.63 (d, 1H, *J*=7.9 Hz, C(6)–H, uracil), 12.10 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 26.3, 34.6, 52.7, 71.1, 77.9, 103.6, 142.7, 152.5, 164.3; IR (liquid film) ν cm^{-1}: 3281, 3050, 2937, 1728, 1712, 1570, 1452; MS [*m/z* (%)]: 196 (9.8); Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.17; H, 6.28; N, 14.19.

*4.3.5. 1-(3-Phenylpropyl)pyrimidine-2,4(1H,3H)-dione (**2f**).* Column chromatography purification on silica gel with *n*-hexane/EtOAc (2:1) afforded white solid (1.70 g, 74%); mp=107–108 °C; R_f (EtOAc) 0.42; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 1.88–1.91 (m, 2H, PhCH$_2$CH$_2$), 2.55 (t, 2H, *J*=7.0 Hz, PhCH$_2$), 3.67 (t, 2H, *J*=7.0 Hz, NCH$_2$), 5.52 (d, 1H, *J*=7.3 Hz, C(5)–H, uracil), 7.25 (d, 1H, *J*=7.3 Hz, C(6)–H, uracil), 7.59–7.65 (m, 5H, aryl), 11.23 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 27.3, 33.7, 47.3, 103.1, 126.9, 128.2, 128.9, 137.9, 142.3, 151.8, 164.0; IR (KBR) ν cm^{-1}: 3300, 3080, 2961, 1425, 1710, 1542, 1449; MS [*m/z* (%)]: 230 (12.5); Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.94; H, 6.02; N, 12.25.

*4.3.6. 1-(2-(2-Methyl-4-nitro-1H-imidazol-1-yl) ethyl)-1H-benzo [d] imidazole (**3b**).* Column chromatography purification on silica gel with EtOAc afforded pale yellow solid (2.25 g, 83%); mp 223–224 °C; R_f (MeOH/EtOAc, 1:10) 0.30; ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm}: 1.82 (s, 3H, CH$_3$), 4.43 (t, 2H, *J*=6.2 Hz, NCH$_2$), 4.68 (t, 2H, *J*=6.2 Hz, NCH$_2$), 7.17–7.20 (m, 2H, aryl), 7.49 (d, 1H, *J*=7.5 Hz, aryl), 7.65 (d, 1H, *J*=7.5 Hz, aryl), 8.01 (s, 1H, C(5)–H, imidazole), 8.16 (s, 1H, C(2)–H, benzimidazole); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm}: 12.0, 44.0, 46.1, 109.8, 119.4, 121.9, 122.1, 122.5, 133.5, 143.1, 143.8, 145.0, 145.4; IR (KBr) ν cm^{-1}: 3210, 3100, 2980, 2895, 1532, 1472, 1357; MS [*m/z* (%)]: 271 (33.2); Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.51; H, 4.89; N, 25.83.

*4.3.7. 7-(2-(1H-Benzo[d]imidazole-1-yl)ethyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3c**).* Column chromatography purification on silica gel with MeOH/EtOAc (1:14) afforded pale yellow solid (2.78 g, 86%); mp=244–245 °C; R_f (MeOH/EtOAc, 1:5) 0.24; ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm}: 3.44 (s, 3H, N(3)–CH$_3$), 3.54 (s, 3H, N(1)–CH$_3$), 4.67–4.71 (m, 4H, NCH$_2$CH$_2$N), 6.98 (s, 1H, C(2)–H, benzimidazole), 7.28–7.42 (m, 4H, aryl), 7.59 (s, 1H, C(8)–H, theophylline); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm}: 29.4, 31.4, 50.3, 56.2, 105.9, 115.1, 117.1, 124.3, 126.2, 133.0, 136.1, 142.6, 146.1, 149.6, 152.0, 155.7; IR (KBr) ν cm^{-1}: 3094, 2952, 1718, 1702, 1479; MS [*m/z* (%)]: 324 (20.4); Anal. Calcd for $C_{16}H_{16}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. Found: C, 59.37; H, 5.06; N, 25.98.

Acknowledgements

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Supplementary data

Supplementary data including characterization data and copies of NMR spectra (^{1}H and ^{13}C NMR) for all compounds associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.06.069. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Chu, C. K.; Cutler, S. J. J. *Heterocycl. Chem.* **1986**, *23*, 289–319.
2. De Clercq, E. In *Advances in Antiviral Drug Design*; Johnsson, N. G., Ed.; JAI: Greenwich, 1993; Vol. 1, pp 88–164.
3. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Moosavi-Movahedi, A. A.; Kosari, M. *Helv. Chim. Acta* **2007**, *90*, 730–737.
4. Holý, A.; Dvořáková, H.; Milena, J.; Buděšínský, M. M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 4073–4088.
5. Choi, J. R.; Cho, D.-G.; Roh, K. Y.; Hwang, J.-T.; Ahn, S.; Jang, H. S.; Cho, W.-Y.; Kim, K. W.; Cho, Y.-G.; Kim, J.; Kim, Y.-Z. *J. Med. Chem.* **2004**, *47*, 2864–2869.

6. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2004**, 583–589.
7. Khalafi-Nezhad, A.; Zare, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419–424.
8. Amblard, F.; Nolan, S. P.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 537–544.
9. Xu, Z.-Q.; Joshi, R. V.; Zemlicka, J. *Tetrahedron* **1995**, *51*, 67–76.
10. Obika, S.; Takashima, Y.; Matsumoto, Y.; Kuromaru, K.; Imanishi, T. *Tetrahedron Lett.* **1995**, *36*, 8617–8620.
11. Han, Y.-K.; Paquette, L. A. *J. Org. Chem.* **1979**, *44*, 3733–3734.
12. Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*, 3rd ed.; John Wiley & Sons, 2007.
13. Ehrenberg, L.; Hussain, S. *Mutat. Res./Rev. Genet. Toxicol.* **1981**, *86*, 1–113, http://dx.doi.org/10.1016/0165-1110(81)90034-8
14. Stack, V. T. *Ind. Eng. Chem.* **1957**, *49*, 913–917.
15. (a) Fletcher, S. *Org. Chem. Front.* **2015**, *2*, 739–752; (b) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
16. Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 1836.
17. Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802–3812.
18. Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210–223.
19. Sonnet, P. E. *Synthesis* **1980**, 828–830.
20. Garlaschelli, L.; Vidari, G. *Gazz. Chim. Ital.* **1987**, *117*, 251–253.
21. Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469–470.
22. Caputo, R.; Ferreri, C.; Noviello, S.; Palumbo, G. *Synthesis* **1986**, 499–501.
23. Caputo, R.; Corrado, E.; Ferreri, C.; Palumbo, G. *Synth. Commun.* **1986**, *16*, 1081–1087.
24. Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis* **1987**, 386–389.
25. Walters, M. A.; Hoem, A. B.; Arcand, H. R.; Hegeman, A. D.; McDonough, C. S. *Tetrahedron Lett.* **1993**, *34*, 1453–1456.
26. Sakai, I.; Kawabe, N.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3381–3383.
27. Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126–6130.
28. Castedo, L.; Marcos, C. F.; Monteagudo, M.; Tojo, G. *Synth. Commun.* **1992**, *22*, 677–681.
29. (a) Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A.; Zare, A.; Parhami, A. *Tetrahedron* **2008**, *64*, 1778–1785; (b) Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Asrari, Z.; Behrouz, M.; Amini, Z. *Synthesis* **2009**, 3067–3076; (c) Soltani Rad, M. N.; Behrouz, S.; Zarenezhad, E.; Kaviani, N. *J. Iran. Chem. Soc.* **2015**, *12*, 1603–1612; (d) Soltani Rad, M. N.; Behrouz, S.; Najafi, H. *Synthesis* **2014**, *46*, 1380–1388.
30. (a) Lu, W.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Org. Chem.* **2007**, *72*, 5012–5015; (b) Kjellberg, J.; Johansson, N. G. *Tetrahedron* **1986**, *42*, 6541–6544; (c) Zhong, M.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 8901–8906; (d) Singh, D.; Wani, M. J.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 4665–4668.
31. Boncel, S.; Gondela, A.; Walczak, K. *Synthesis* **2010**, 1573–1589.
32. Garegg, P. J.; Regberg, T.; Stawinski, J.; Strornberg, R. *J. Chem. Soc. Perkin Trans. (II)* **1987**, 271–274.
33. DMF (bp 153 °C) can be evaporated in vacuo using rotary evaporator if the efficient unit's vacuum system is capable of sufficiently low pressure. For instance, DMF can be boiled below 80 °C if the vacuum is reduced to 5 Torr or less. However, if the efficient vacuum pump is not available, then the surrogate procedure can be employed in which the reaction mixture is diluted in water (100 mL). Then, $CHCl_3$ (100 mL) is added and the organic phase is separated. The separated $CHCl_3$ is washed subsequently with water (3×100 mL) and then evaporated to obtain the crude product.

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