Tetrahedron 67 (2011) 866–871

Contents lists available at ScienceDirect

Tetrahedron

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

The optimized microwave-assisted decomposition of formamides and its synthetic utility in the amination reactions of purines

Lucie Čechová, Petr Jansa, Michal Šála, Martin Dračínský, Antonín Holý, Zlatko Janeba *

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, CZ-166 10 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 28 July 2010
Received in revised form 23 November 2010
Accepted 13 December 2010
Available online 17 December 2010

Keywords:
Microwave-assisted synthesis
DMF
Formamides
Dehalogenative amination
Purines

ABSTRACT

The microwave-assisted decomposition of DMF was thoroughly studied and the reaction conditions (temperature, solvent effect, and effect of additives, such as acids, bases, and salts) were optimized for its use in amination reactions. The applicability of this expedient methodology in purine chemistry and with various formamides is demonstrated.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

N,*N*-Dimethylformamide (DMF) is one of the most common protic polar solvents in organic synthetic chemistry and is the solvent of choice for a wide range of organic reactions. Nonetheless, DMF is much more than a solvent since it is quite a reactive molecule. DMF can react either as a nucleophilic or an electrophilic agent and also has interesting coordination properties. Depending on the reaction conditions, DMF can be the source of various key intermediates in organic synthesis, such as carbon monoxide, dimethylamine, the formyl group, and formate.[1]

Many biologically active compounds possess either a *N*-methylamino or *N*,*N*-dimethylamino motif within their molecules, which is also true in the chemistry of nucleic acids components.[2–4] The synthesis of adenosine nucleosides substituted at the N-6 position has usually been carried out by a condensation of protected sugars (e.g., ribosides) with mercuric chloride salts of N^6-substituted adenines.[5] These procedures often suffer from low yields and the formation of undesired regioisomers. A more expedient method is the nucleophilic displacement of the halogen atom at the C-6 position of a purine by amines.[6–10] The nucleophilic displacement of a 6-(1,2,4-triazol-4-yl) moiety with dimethylamine also gives the corresponding N^6,N^6-dimethylaminopurine derivatives of nucleosides and 2′-deoxynucleosides quantitatively.[11] Another novel synthetic route to N^6-substituted adenines involves regioselective alkylation of the adenine exocyclic nitrogen by the Mitsunobu reaction.[12]

As early as in 1954 Coppinger[13] reported an efficient method (yields >90%) for the preparation of *N*,*N*-dimethylamides by simple heating of the corresponding acid chloride or anhydride with *N*,*N*-dimethylformamide (DMF). Since then, reactions of activated aromatic or heteroaromatic halides with DMF at elevated temperature for the preparation of *N*,*N*-dimethylamino substituted compounds have occasionally been reported.[14–21]

Microwave-assisted (MW-assisted) organic synthesis has become a very rapidly developing area of chemistry and provides a number of advantages over the standard heating techniques, such as clean reactions, improved reaction yields, shorter reaction times, easy work-ups, and solvent-free reaction conditions. Diverse organic reactions have recently been reported to proceed under microwave irradiation.[22]

Also several examples of reactions using a MW-assisted decomposition of formamides have recently been described. The MW-assisted decomposition of formamide to generate ammonia in situ has been used as a tool for the synthesis of nitrogen containing heterocyclic compounds.[23] Sharma et al.[24] have described a novel MW-assisted procedure for the desulfitative dimethylamination of 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones using a DMF/H_2O mixture in the presence of sodium carbonate. The *N*,*N*-dimethylaminated products were obtained in high yields (63–96%) in relatively short reaction times (20–60 min) when compared to the reactions under the conventional heating (usually in hours). To the

* Corresponding author. Tel.: +420 220183143; fax: +420 220183560; e-mail address: janeba@uochb.cas.cz (Z. Janeba).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.040

best of our knowledge, this is the first report on a MW-assisted dimethylamination reaction using DMF as a reagent.[24]

The aim of this study was to develop and optimize dehalogenative amination (nucleophilic aromatic substitution, S_NAr) using the MW-assisted decomposition of formamides and apply the methodology for the modification of purine derivatives, i.e., compounds of pharmaceutical interest. Such a procedure would offer an alternative method for the amination of heterocyclic compounds.

2. Results and discussion

2.1. Optimization of the microwave-assisted decomposition of DMF

The microwave-assisted decomposition of DMF was studied in a sealed vessel and monitored automatically by the increase of pressure. Such a sealed vessel system was also used for the subsequent amination reactions under microwave irradiation.

Initially, a solution of 9-benzyl-6-chloropurine (**1**, 0.5 mmol) in DMF (5 mL) was being irradiated at various temperatures (Fig. 1). DMF starts to decompose at 170 °C (Fig. 1). At 190 °C marked decomposition of DMF was observed and this temperature was chosen for further optimizations.

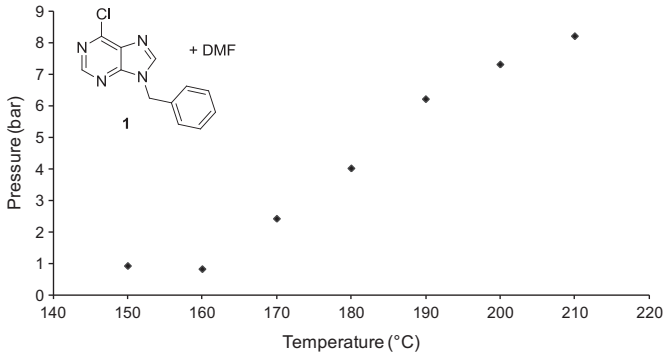


Fig. 1. Effect of temperature on the microwave-assisted decomposition of DMF in a mixture of DMF and compound **1** (1 min reaction time) as indicated by change in pressure.

For the use of alternative or more expensive formamides, the reaction may need to be conducted in a suitable solvent. Thus, the solvent effect on the decomposition of DMF was studied. Irradiation (190 °C, 1 min) of DMF (1 mL) in a wide range of solvents (5 mL) indicated the accelerated decomposition of DMF in toluene, THF, and acetic acid (entries 4, 7, and 9, respectively, Table 1). On the other hand, solvents like EtOH, MeOH, and water did not facilitate the decomposition of DMF (entries 2, 3, and 6, respectively, Table 1).

Table 1
Effect of solvents on the microwave-assisted decomposition of DMF (190 °C, 1 min reaction time, solvent/DMF ratio 5:1) as indicated by change in pressure

Entry	1	2	3	4	5	6	7	8	9
Solvent	DMF	EtOH	MeOH	Toluene	Dioxane	Water	THF	MeCN	AcOH
Pressure (bar)	0.2	0	0	0.6	0.3	0	0.6	0	2.3

Surprisingly, irradiation of neat DMF resulted in a much lower pressure (0.2 bar, entry 1, Table 1) and thus a much slower decomposition rate, as compared to the pressure (6.2 bar, Fig. 1) of the irradiated mixture of DMF with compound **1** under otherwise identical conditions (190 °C, 1 min). This interesting finding led us to investigate further the effect of some other chemicals (Lewis acids, inorganic salts, and HCl) on the decomposition rate of DMF (Table 2).

The data clearly showed that in general, additives facilitate the MW-assisted decomposition of DMF and especially the presence of

Table 2
Effect of various additives (0.5 mmol in 5 mL DMF) on the microwave-assisted decomposition of DMF (180 °C, 1 min reaction time) as indicated by change in pressure

Entry	1	2	3	4	5	6	7
Additives	$BF_3{\cdot}Et_2O$	$FeCl_3$	**1**+$FeCl_3$	$CuSO_4$	$Zn(OAc)_2$	HCl	**1**+HCl
Pressure (bar)	0.8	1.8	2.3	0.3	1.2	5.4	10

HCl in the reaction mixture dramatically accelerates the process (entries 6 and 7, Table 2). This finding offers an explanation for the dramatic difference of the decomposition rate of neat DMF when compared to the mixture of compound **1** in DMF. In the latter case, dimethylamine formed during the decomposition of DMF reacts immediately with the chloro derivative **1**. In the course of the nucleophilic aromatic substitution, HCl is generated, which subsequently catalyzes the further decomposition of DMF. This reaction under the described conditions is autocatalytic.

Increasing the quantity of concentrated aqueous HCl evidently accelerates the reaction (Fig. 2, blue dots). Since water does not facilitate the decomposition of DMF (entry 6, Table 1), we switched to the anhydrous 5.7 M solution of HCl in DMF. The results show that the successive addition of anhydrous HCl markedly increases the decomposition rate of DMF (Fig. 2, violet dots).

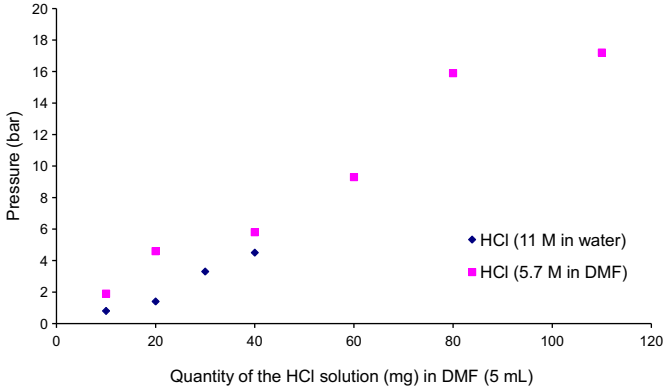


Fig. 2. Effect of the amount of HCl on the microwave-assisted decomposition (180 °C, 1 min reaction time) of DMF (5 mL) as indicated by change in pressure.

This compelling data encouraged us to reoptimize the reaction temperature further. We have speculated that the amination reactions with addition of HCl could proceed at lower temperatures and thus under milder reaction conditions, providing that the starting compounds are stable in acids.

A mixture of DMF (5 mL) and anhydrous HCl (60 mg of 5.7 M DMF solution) was irradiated at various temperatures for 1 min (Fig. 3). The rate of the decomposition of DMF in the presence of HCl at 180 °C is considerably increased (9.3 bar, Fig. 3) as compared to the

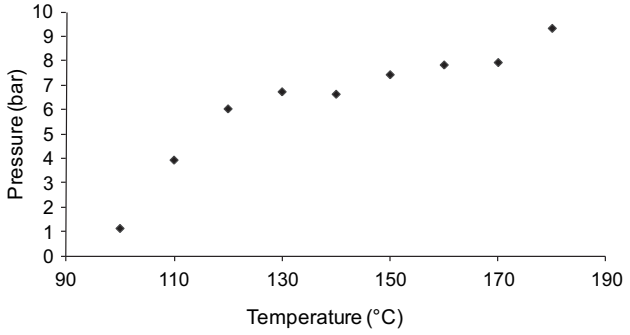


Fig. 3. Effect of temperature on the microwave-assisted decomposition of DMF (5 mL) in the presence of anhydrous HCl (60 mg of 5.7 M DMF solution) as indicated by change in pressure (1 min reaction time).

decomposition of neat DMF at 190 °C (0.2 bar, entry 1, Table 1). Moreover, the significant decomposition rate of DMF (3.9 bar, Fig. 3) in the presence of HCl can be reached at a temperature as low as 110 °C.

The MW-assisted amination with DMF was reported in the presence of various bases.[24,25] We have irradiated (180 °C, 1 min) mixtures of DMF (5 mL) with several commonly used bases (0.5 mmol, Table 3). The highest decomposition rate of DMF was observed with *t*-BuOK (entry 1, Table 3), but the reaction mixture turned dark brown.

Table 3
Effect of various bases (0.5 mmol in 5 mL DMF) on the microwave-assisted decomposition of DMF (180 °C, 1 min) as indicated by change in pressure

Entry	1	2	3	4
Base	*t*-BuOK	K_2CO_3	DMAP	Et_3N
Pressure (bar)	3.0	0.2	2.4	0

When a mixture of 9-benzyl-6-chloropurine (0.5 mmol) and *t*-BuOK (0.5 mmol) in DMF (5 mL) was irradiated at 180 °C, a colorful and complex reaction mixture with a moderate yield (50%) of the N^6,N^6-dimethyladenine analog **10** was obtained (entry 2, Table 4). A cleaner reaction mixture and better yield (62%) of derivative **10** was obtained from the reaction using DMAP (4-dimethylaminopyridine, entry 3, Table 4). Nevertheless, an analogous reaction of the compound **1** in DMF with the addition of anhydrous HCl proved to be superior since it provided a clean reaction mixture and a high yield of the derivative **10** (96%, entry 4, Table 4) but even analogous reaction in neat DMF at 210 °C gave 92% yield of **10** (entry 1, Table 4).

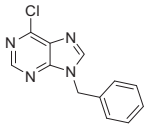
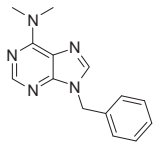
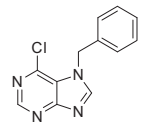
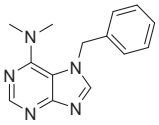
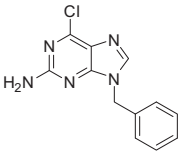
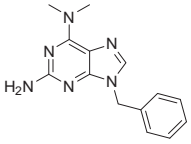
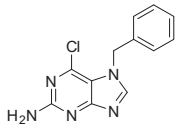
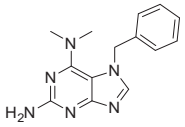
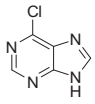
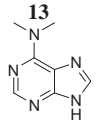
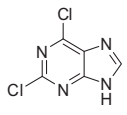
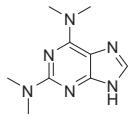
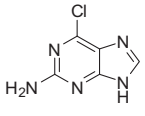
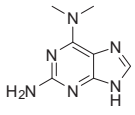
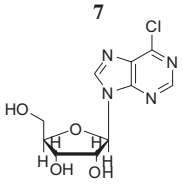
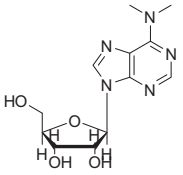
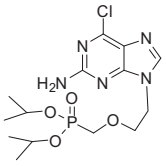
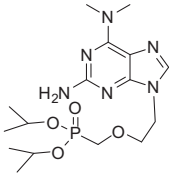
2.2. Application of the microwave-assisted decomposition of formamides in purine chemistry

The encouraging results of the optimized conditions for the MW-assisted decomposition of DMF prompted us to apply this method to amination reactions, namely for the derivatization of various 6-chloropurine derivatives, including N^9- and N^7-benzylated purines **1**–**4**, free purine bases **5**–**7**, riboside **8**, and acyclic nucleoside phosphonate **9** (Table 4).

The DMF solutions of the 6-chloropurines **1**–**9** were irradiated (180–210 °C) for the given period of time (Table 4). Their reactivity and the yields of the obtained products correspond to their electronic and steric properties. The yields of the N^6,N^6-dimethylamino products **10**–**18** are generally high (48–96%) and only the reaction of 2,6-dichloropurine **6** gave the bis substituted purine base **15** in 35% yield (entry 9, Table 4). Owing to the lability of the nucleosidic bond of the riboside **8**, the desired amination product **17** was isolated in very low yield (15%) while the free base **14** was obtained as the main product (63%, entry 11, Table 4).

The yields of the described MW-assisted amination of 6-chloropurines with DMF are comparable to the yields of the classical nucleophilic aromatic substitution of 6-chloropurines with dimethylamine, but reaction times are markedly shorter. Thus, the reported yields of 9-benzyl purine derivatives **10** and **12** are 87% (15 h at ambient temperature)[26] and 92% (20 h at 60 °C),[27] respectively, whereas we have obtained compound **10** in 92% yield (1 min at 210 °C, entry 1, Table 4) and compound **12** in 81% yield (3 min at 180 °C, entry 6, Table 4). The reported yields of 6-(dimethylamino)purine **14** are 81% (12 h at 150 °C),[28] 84.5% (14 h at 110 °C),[29] and 95% (24 h at ambient temperature),[30] compared to our 82% yield of product **14** (10 min at 180 °C, entry 8, Table 4). Finally, we have prepared compound **16** in 83% yield in 50 min (180 °C, entry 10, Table 4), whereas the yield of the derivative **16** prepared by nucleophilic aromatic substitution was reported as 97% in 16 h at 110 °C.[29] Moreover, no need to use solvents is another advantage of our new methodology.

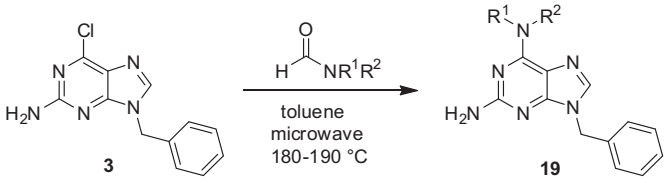
Table 4
MW-assisted dimethylamination of 6-chloropurines **1**–**9** with DMF

Entry	Substrate	Time (min)	Product	Yield[a] (%)
1	 **1**	1	 **10**	92
2		25		50[b]
3		7		62[c]
4		2		96[d]
5	 **2**	3	 **11**	70
6	 **3**	3	 **12**	81
7	 **4**	9	 **13**	57
8	 **5**	10	 **14**	82
9	 **6**	21	 **15**	35
10	 **7**	50	 **16**	83
11	 **8**	4	 **17** +**14**	15 63
12	 **9**	3	 **18**	48

Reaction conditions: MW irradiation in DMF at 180–210 °C.
[a] Isolated yields.
[b] *t*-BuOK added.
[c] DMAP added.
[d] HCl added.

In order to establish the universal applicability of the described MW-assisted methodology in synthetic organic chemistry, a series of N^6-substituted 9-benzyl-2,6-diaminopurine derivatives **19** was prepared using various formamides (Table 5). All reactions were carried out in toluene since this solvent had previously been shown to be the solvent of choice for the described procedure (entry 4, Table 1). Treatment of compound **3** with *N*-methylformamide, *N*-ethylformamide, and *N*,*N*-diethylformamide under the MW-assisted conditions (180–190 °C) afforded the corresponding N^6-methyladenine **19a** (66%), N^6-ethyladenine **19b** (59%), and N^6,N^6-diethyladenine **19c** (60%) derivatives, respectively (entries 1–3, Table 5). A similar amination of the compound **3** with *N*-*tert*-butylformamide (190 °C, 330 min) proceeded very slowly and only 30% of the expected product **19d** was obtained after a prolong period of time (entry 4, Table 5). The obtained data indicate that the yields of these amination reactions depend both on the nucleophilicity and bulkiness of the corresponding amine released during the MW-assisted decomposition of formamides. The lowest yield gave the reaction with *N*-*tert*-butylformamide (entry 4, Table 5), which under the microwave conditions releases relatively bulky *tert*-butylamine. Moreover, there is clear evidence that aminations carried out in solvent require prolonged irradiation (over 30 min, Table 5) compared to the analogous procedure in neat formamide (DMF, 3 min, entry 6, Table 4).

Table 5
MW-assisted amination reactions of 2-amino-6-chloropurine derivative **3**



Entry	*t* (min)	Formamide	Product	Yield[a] (%)
1	30	*N*-Methylformamide	**19a** R^1=H, R^2=Me	66
2	62	*N*-Ethylformamide	**19b** R^1=H, R^2=Et	59
3	56	*N*,*N*-Diethylformamide	**19c** R^1=R^2=Et	60
4	330	*N*-*tert*-Butylformamide	**19d** R^1=H, R^2=*t*-Bu	30

[a] Isolated yield.

Although the recently described MW-assisted nucleophilic displacement reactions of 6-chloropurines with amines give the corresponding products in high yields (86–95%) and short reaction times (>6 min),[9] our new amination method affords an alternative and convenient route of efficient synthesis of N^6-substituted adenine derivatives.

3. Conclusions

A convenient microwave-assisted procedure for the dimethylaminations (and generally alkyl- and dialkyl-aminations) of various compounds was elaborated. The present study proved that MW-assisted decomposition of formamides is an extremely useful tool in modern synthetic organic chemistry, which can be used as a convenient alternative to the classical nucleophilic aromatic substitutions using amines. The main advantages of the described MW-assisted amination procedure as compared to the reactions using conventional heating are short reaction times, high yields, and simple workups. Furthermore, an important safety issue may lie in the elimination of the handling of dangerous and volatile amines. The optimum temperature for the described MW-assisted amination procedure with DMF was found to be 180–190 °C but under the acid catalysis it can be as low as 110 °C. The aminations can be carried out either in neat formamide or in suitable solvents, e.g., toluene. The reaction conditions of the MW-assisted formamide decompositions were thoroughly optimized and were used in nucleophilic substitution reactions and with various formamides. In total, 13 compounds were prepared with this expedient methodology, six of which (**13**, **18**, **19a**–**d**) for the first time. The procedure proved to be the method of choice for the introduction of substituted amino functions into organic molecules and for the facile and convenient modification of compounds of biological interest.

4. Experimental section

4.1. General methods

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa, and compounds were dried at 2 kPa over P_2O_5. Melting points were determined on a Stuart SMP3 melting point apparatus. TLC was performed on TLC aluminum sheets—silica gel 60 F_{254} (MERCK KGaA, Germany) in chloroform–methanol. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 27 °C with a Bruker Avance II 600 and/or Bruker Avance II 500 spectrometers operating at 600.0 or 500.0 MHz in ^{1}H and 150.9 or 125.7 MHz in ^{13}C. Hydrogen and carbon spectra were referenced to TMS or to residual solvent signals (δ 2.50 and 39.7 for DMSO and 77.0 for $CDCl_3$). The ESI mass spectra were measured with an LCQ Fleet spectrometer (Thermo Fisher Scientific). The standard 70 eV mass spectra were recorded in the mass range of 25–800 using a 4 min solvent delay. The temperatures of the transfer line, ion source, and quadrupole were 280, 230, and 150 °C, respectively. Elemental microanalysis was performed using a PE 2400 Series II CHNS/O Analyzer (Perkin–Elmer, USA). IR spectra were recorded on an FTIR spectrometer Bruker IFS 55 (Equinox) in $CHCl_3$.

4.2. General microwave-assisted procedure

All reactions were carried out in CEM Discover (Explorer) microwave apparatus, 24-position system for 10-mL vessels sealed with Teflon septum. It was operated at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The solutions were steadily stirred during the reaction. The temperature was measured with an IR sensor on the outer of the process vessel. The vials were cooled to ambient temperature with gas jet cooling system. The pressure was measured with an inboard CEM Explorer pressure control system (0–21 bar).

Compounds and/or additives were dissolved in appropriate formamide or formamide/solvent mixture and added into a 10-mL reaction vessel containing a stirring bar. The vessel was sealed with a Teflon septum and heated under MW irradiation for the set time and temperature using maximum power (300 W).

4.3. Synthesis of compound 10 in the presence of additives

Mixtures of **1** (122 mg, 0.5 mmol) and *t*-BuOK (56 mg, 0.5 mmol), DMAP (62 mg, 0.5 mmol), or HCl (53 mg of 5.7 M HCl/DMF) in DMF (6 mL) were heated under microwave irradiation at 180 °C for 25 min, 7 min, and 2 min, respectively. Each reaction mixture was evaporated in vacuo and the residue applied onto a silica gel column and flash chromatographed (chloroform/MeOH, 19:1) to afford **10** as white solid in 50% (63 mg), 62% (7 mg), and 96% (122 mg) yield, respectively. The ^{1}H and ^{13}C NMR spectra were identical with compound **10** prepared by General procedure 4.3.

4.4. General procedure for the preparation of compounds 10–16

A solution of **1** (1.10 g, 4.5 mmol), **2** (244 mg, 1 mmol), **3** (649 mg, 2.5 mmol), **4** (518 mg, 2 mmol), **5** (310 mg, 2 mmol), **6** (190 mg, 1 mmol) or **7** (340 mg, 2 mmol) in DMF (6 mL for 0.5 mmol of starting compound) was divided into several vials. Each vial

contained starting compound (0.5 mmol) and DMF (6 mL). The solutions were heated under microwave irradiation. Reaction mixtures were collected and evaporated in vacuo. For **10**, **11**, **12**, **13**, and **16** the residue was applied on silica gel column and flash chromatographed. For **14** and **15** the residue was partitioned between water (60 mL) and EtOAc (50 mL). The water layer was extracted with EtOAc (3×40 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated.

*4.4.1. 9-Benzyl-6-(dimethylamino)purine (**10**)*[26,31]. The reaction mixture was heated at 210 °C for 1 min. Yield 1.045 g (92%) of white solid, mp 129 °C (lit.[26] mp 126–128 °C, lit.[31] mp 131–132 °C); R_f (5% MeOH/$CHCl_3$) 0.83; ^{1}H NMR ($CDCl_3$): 8.39 (1H, s, H-8), 7.69 (1H, s, H-2), 7.33–7.26 (5H, m, H-3′, H-4′, H-2′), 5.35 (2H, s, CH_2), 3.53 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$): 155.0 (C-4), 152.6 (C-2), 150.7 (C-6), 138.0 (C-8), 135.9 (C-1′), 128.9 (C-3′), 128.1 (C-4′), 127.6 (C-2′), 120.0 (C-5), 46.9 (CH_2), 38.5 (CH_3). GC–MS: 253.2. For $C_{14}H_{15}N_5$ (253.3) calculated: 66.38% C, 5.97% H, 27.65% N; found 66.27% C, 5.89% H, 27.42% N.

*4.4.2. 7-Benzyl-6-(dimethylamino)purine (**11**)*[31]. The reaction mixture was heated at 190 °C for 3 min. Column chromatography chloroform/MeOH (19:1) afforded 177 mg (70%) of white solid, mp 135–136 °C (lit.[31] mp 134–135 °C); R_f (5% MeOH/$CHCl_3$) 0.51; ^{1}H NMR ($CDCl_3$): 8.65 (1H, s, H-8), 7.99 (1H, s, H-2), 7.34–7.32 (3H, m, H-3′, H-2′), 7.12 (2H, m, H-2′), 5.53 (2H, s, CH_2), 3.04 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$): 161.5 (C-4), 156.1 (C-6), 152.2 (C-2), 146.7 (C-8), 135.5 (C-1′), 129.1 (C-3′), 128.5 (C-4′), 126.9 (C-2′), 115.3 (C-5), 50.8 (CH_2), 41.6 (CH_3). GC–MS: 253.2. For $C_{14}H_{15}N_5$ (253.3) calculated: 66.38% C, 5.97% H, 27.65% N; found 65.57% C, 6.05% H, 27.04% N.

*4.4.3. 2-Amino-9-benzyl-6-(dimethylamino)purine (**12**)*[27]. The reaction mixture was irradiated at 180 °C for 3 min. Column chromatography in EtOAc/acetone/EtOH/water (40:3:4:3) gave 434 mg (67%) of white solid, mp 184 °C; R_f (5% MeOH/$CHCl_3$) 0.47; ^{1}H NMR (DMSO-d_6): 7.80 (1H, s, H-8), 7.34–7.19 (5H, m, H-3′, H-4′, H-2′), 5.85 (2H, s, NH_2), 5.20 (2H, s, CH_2), 3.34 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6): 159.5 (C-2), 154.7 (C-4), 152.7 (C-6), 137.5 (C-8), 136.3 (C-1′), 128.4 (C-3′), 127.3 (C-4′), 126.9 (C-2′), 113.5 (C-5), 45.3 (CH_2), 37.5 (CH_3). ESIMS, *m*/*z* (%): 269.2 (MH^+) (100). For $C_{14}H_{16}N_6$ (268.14) calculated: 62.67% C, 6.01% H, 31.32% N; found: 62.63% C, 6.13% H, 30.93% N.

*4.4.4. 2-Amino-7-benzyl-6-(dimethylamino)purine (**13**).* The reaction mixture was irradiated at 180 °C for 9 min. Column chromatography in EtOAc/acetone/EtOH/water (15:3:4:3) afforded 305 mg (57%) of white solid, mp 180–182 °C; R_f (5% MeOH/$CHCl_3$) 0.31; ν_{max} (liquid film) 3525 and 3419 (NH_2), 2801 and 1414 (CH_3), 1600, 1581, 1571, and 1486 (purine), 1497, 1455, 1030, and 697 cm^{-1} (phenyl); ^{1}H NMR (DMSO-d_6): 8.22 (1H, s, H-8), 7.30–7.25 (3H, m, H-3′, H-4′), 7.09–7.07 (2H, m, H-2′), 5.85 (2H, s, NH_2), 5.41 (2H, s, CH_2), 2.87 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6): 163.9 (C-4), 159.2 (C-2), 156.1 (C-8), 146.9 (C-6), 137.4 (C-1′), 128.5 (C-3′), 127.5 (C-4′), 126.7 (C-2′), 108.1 (C-5), 50.0 (CH_2), 40.8 (CH_3). ESIMS, *m*/*z* (%): 269.3 (MH^+) (100). For $C_{14}H_{16}N_6$ (268.32) calculated: 62.67% C, 6.01% H, 31.32% N; found: 58.77% C, 5.88% H, 29.33% N.

*4.4.5. 6-(Dimethylamino)purine (**14**)*[28–30]. The reaction mixture was heated at 180 °C for 10 min. Yield 271 mg (82%) of white solid, mp 262 °C (lit.[30] mp 265–266 °C, lit.[31] mp 257 °C, lit.[32] mp 259–260 °C); R_f (5% MeOH/$CHCl_3$) 0.31; ^{1}H NMR (DMSO-d_6): 12.96 (1H, br s, NH), 8.18 and 8.08 (2×1H, s, H-2 and H-8), 3.43 (6H, br s, CH_3). ^{13}C NMR (DMSO-d_6): 154.3 (C-4), 151.9 (C-2), 151.3 (C-6), 137.9 (C-8), 119.0 (C-5), 38.0 (CH_3). HRMS (ESI) *m*/*z* $C_7H_{10}N_5$ $[M+H]^+$ calcd: 164.0931. Found: 164.0930.

*4.4.6. 2,6-Bis(dimethylamino)purine (**15**).* The reaction mixture was heated at 180 °C for 25 min. Yield 72 mg (35%), mp 250–251 °C; R_f (5% MeOH/$CHCl_3$) 0.42; ν_{max} (liquid film) 2815 and 1424 (CH_3), 3455, 3113, and 3073 (NH), 1607, 1582, 1539, 1512, 1388, and 1339 cm^{-1} (purine); ^{1}H NMR (DMSO-d_6): 12.27 (1H, br s, NH), 7.67 (1H, s, H-8), 3.38 (6H, br s, CH_3), 3.05 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6): 159.0, 154.2, 153.7, 134.7, 113.0, 37.7, and 37.2. HRMS (ESI) *m*/*z* $C_9H_{15}N_6$ $[M+H]^+$ calcd: 207.1353. Found: 207.1352.

*4.4.7. 2-Amino-6-(dimethylamino)purine (**16**)*[29]. The reaction mixture was heated at 180 °C for 50 min. Column chromatography EtOAc/acetone/EtOH/water (15:3:4:3) afforded 300 mg (83%) of yellowish product, mp 252 °C (lit.[29] mp 263 °C); R_f (5% MeOH/$CHCl_3$) 0.28; ^{1}H NMR (DMSO-d_6): 12.16 (1H, br s, NH), 7.66 (1H, s, H-8), 5.68 (2H, s, NH_2), 3.36 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6): 159.6, 154.8, 153.6, 134.6, 113.6, 37.8. HRMS (ESI) *m*/*z* $C_7H_{11}N_6$ $[M+H]^+$ calcd: 179.1040. Found: 179.1039.

4.5. 6-(Dimethylamino)-9-(β-D-ribofuranosyl)purine (17)[5,11]

A solution of **8** (0.574 g, 2 mmol) in DMF (24 mL) was heated under microwave irradiation at 190 °C for 4 min and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography in hexane/chloroform/methanol (6:4:1) to give 205 mg (63%) of **14** (^{1}H and ^{13}C NMR data identical with compound **14** in 4.4.5) and 91 mg (15%) of **17** as white solid. Mp 184 °C (lit.[5] mp 183–184 °C, lit.[11] mp 182–183 °C); R_f (5% MeOH/$CHCl_3$) 0.25; ^{1}H NMR (DMSO-d_6): 8.37 (1H, s, H-8), 8.21 (1H, s, H-2), 5.91 (1H, d, $J_{1'-2'}$=6.0, H-1′), 5.45 (1H, d, $J_{OH\text{-}2'}$=6.2, OH-2′), 5.38 (1H, dd, $J_{OH\text{-}5'}$=4.6 and 6.9, OH-5′), 5.19 (1H, d, $J_{OH\text{-}3'}$=4.7, OH-3′), 4.58 (1H, dd, $J_{2'-1'}$=11.2, $J_{2'-3'}$=5.9, H-2′), 4.15 (1H, dd, $J_{3'-2'}$=4.7, $J_{3'-4'}$=8.1, H-3′), 3.96 (1H, dd, $J_{4'-5'}$=3.4 and 3.6, H-4′), 3.68 (1H, m, H-5′$_a$), 3.55 (1H, m, H-5′$_b$), 3.45 (6H, vbr s, CH_3). ^{13}C NMR (DMSO-d_6): 154.5 (C-6), 151.8 (C-2), 150.1 (C-4), 138.7 (C-8), 120.0 (C-5), 88.0 (C-1′), 85.9 (C-4′), 73.7 (C-2′), 70.7 (C-3′), 61.7 (C-5′), 38.1. ESIMS, *m*/*z* (%): 296.2 (MH^+) (100). For $C_{12}H_{17}N_5O_3$ (279.3) calculated: 48.81% C, 5.80% H, 23.72 N; found 49.05% C, 5.87% H, 22.95% N.

4.6. 2-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy] ethyl}-6-(dimethylamino)-purine (18)

A solution of **9** (0.392 g, 1 mmol) in DMF (12 mL) was heated under microwave irradiation at 190 °C for 3 min and the solvent was evaporated in vacuo. The residue was partitioned between water (50 mL) and EtOAc (40 mL), extracted with EtOAc (2×30 mL), dried over $MgSO_4$, filtered, and evaporated to give 192 mg (48%) of **18** as colorless oil; R_f (5% MeOH/$CHCl_3$) 0.38; ^{1}H NMR (DMSO-d_6): 7.66 (1H, s, H-8), 5.79 (2H, s, NH_2), 4.52 (2H, m, CH–^{i}Pr), 4.14 (2H, t, $J_{1'-2'}$=5.2, H-1′), 3.81 (2H, t, $J_{2'-1'}$=5.2, H-2′), 3.76 (2H, d, J_{H-P}=8.4, CH_2–P), 3.35 (6H, br s, CH_3), 1.19 (3H, d, J_{vic}=6.2, CH_3), 1.16 (3H, d, J_{vic}=6.2, CH_3). ^{13}C NMR (DMSO-d_6): 159.6 (C-2), 154.8 (C-4), 152.8 (C-6), 136.83 (C-8), 113.7 (C-5), 70.4 (d, $J_{C,P}$=11.6, C-2′), 70.3 (d, $J_{C,P}$=6.5, POC), 64.8 (d, $J_{C,P}$=164.0, CH_2–P), 42.1 (C-1′), 37.7 (CH_3), 23.9 (d, $J_{C,P}$=3.8, CH_3), 23.8 (d, $J_{C,P}$=4.5, CH_3). ESIMS, *m*/*z* (%): 401.2 (MH^+) (100). For $C_{16}H_{29}N_6O_4P$ (400.41) calculated: 47.99% C, 7.3% H, 20.99% N; found 45.88% C, 7.69% H, 19.44% N.

4.7. Preparation of compounds 19a–d

A solution of **3** (260 mg, 1 mmol) in a mixture of the corresponding formamide (1 mL) and toluene (5 mL) was irradiated and solvents were evaporated in vacuo. The residue was partitioned between water (50 mL) and EtOAc (40 mL). The water layer was extracted with EtOAc (2×30 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. Product was isolated by column chromatography on silica gel in a EtOAc/acetone/EtOH/water (40:3:4:3) mixture.

*4.7.1. 2-Amino-9-benzyl-6-(methylamino)purine (**19a**).* A mixture of **3** (260 mg, 1 mmol) and *N*-methylformamide (1 mL) in toluene (5 mL) was irradiated at 190 °C for 30 min to afford 168 mg (66%) of white solid, mp 186 °C; R_f (10%, MeOH/$CHCl_3$) 0.67; ν_{max} (liquid film) 3529 and 3422 (NH_2), 3451, 2969, and 1408 (NHMe), 1599, 1536, 1496, 1439, 1396, and 1349 (purine), 3092, 3068, and 3035 (CH_2—phenyl), 1496, 1454, 1167, 1077, and 1030 cm^{-1} (phenyl); ^1H NMR (DMSO-d_6): 7.76 (1H, s, H-8), 7.32 (2H, m, H3′), 7.26 (1H, m, H-4′), 7.2–7.23 (3H, m, H2′, NH), 5.90 (2H, br s, NH_2), 5.20 (2H, s, CH_2), 2.89 (3H, br s, CH_3). ^{13}C NMR (DMSO-d_6): 160.55 (C-2), 155.61 (C-6), 151.0 (C-4), 137.88 (C-1′), 137.27 (C-8), 128.77 (C-3′), 127.62 (C-4′), 127.24 (C-2′), 113.59 (C-5), 45.62 (CH_2), 27.23 (CH_3). HRMS (ESI) *m*/*z* $C_{13}H_{15}N_6$, $[M+H]^+$ calcd: 255.1353 Found: 255.1353.

*4.7.2. 2-Amino-9-benzyl-6-(ethylamino)purine (**19b**).* A mixture of **3** (260 mg, 1 mmol) and *N*-ethylformamide (1 mL) in toluene (5 mL) was irradiated at 180 °C for 62 min to afford 158 mg (59%) of white solid, mp 180–183 °C; R_f (10%, MeOH/$CHCl_3$) 0.73; ν_{max} (liquid film) 3528 and 3424 (NH_2), 2976, 2878, 1479, and 1383 (NHEt), 1600, 1530, 1493, 1438, 1400, and 1344 (purine), 3092, 3068, and 3035 (CH_2—phenyl), 1493, 1455, 1318, 1166, 1077, and 1030 cm^{-1} (phenyl); ^1H NMR (DMSO-d_6): 7.77 (1H, s, H-8), 7.32 (2H, m, H3′), 7.26 (1H, m, H4′), 7.20–7.23 (3H, m, H-2′, NH), 5.85 (2H, br s, NH_2), 5.19 (2H, s, 1′-CH_2), 3.44 (2H, br s, CH_2), 1.14 (3H, t, $J_{CH3-CH2}$=7.1, CH_3). ^{13}C NMR (DMSO-d_6): 160.54 (C-2), 154.97 (C-6), 151.0 (C-4), 137.88 (C-1′), 137.26 (C-8), 128.77 (C-3′), 127.62 (C-4′), 127.25 (C-2′), 113.4 (C-5), 45.59 (1′-CH_2), 34.1 (CH_2), 15.36 (CH_3). HRMS (ESI) *m*/*z* $C_{14}H_{17}N_6$, $[M+H]^+$ calcd: 269.1509. Found: 269.1509.

*4.7.3. 2-Amino-9-benzyl-6-(diethylamino)purine (**19c**).* A mixture of **3** (260 mg, 1 mmol) and *N*,*N*-diethylformamide (1 mL) in toluene (5 mL) was irradiated at 180 °C for 56 min to afford 178 mg (60%) of white solid, mp 97–99 °C; R_f (10%, MeOH/$CHCl_3$) 0.81; ν_{max} (liquid film) 3527 and 3419 (NH_2), 2979, 2935, 2873, 1465, 1379, and 1368 (NEt_2), 1591, 1572, 1528, 1493, 1443, 1404, and 1321 (purine), 3092, 3068, and 3025 (CH_2—phenyl), 1493, 1455, 1080, and 1030 cm^{-1} (phenyl); ^1H NMR (DMSO-d_6): 7.79 (1H, s, H-8), 7.32 (2H, m, H-3′), 7.26 (1H, m, H-4′), 7.23 (2H, m, H-2′), 5.78 (2H, br s, NH_2), 5.20 (2H, s, 1′-CH_2), 3.86 (4H, br s, CH_2), 1.15 (6H, t, $J_{CH3-CH2}$=7, CH_3). ^{13}C NMR (DMSO-d_6): 159.97 (C-2), 153.68 (C-6), 152.9 (C-4), 137.85 (C-1′), 136.82 (C-8), 128.76 (C-3′), 127.61 (C-4′), 127.28 (C-2′), 113.21 (C-5), 45.55 (1′-CH_2), 41.9 (CH_2), 13.6 (CH_3). HRMS (ESI) *m*/*z* $C_{16}H_{21}N_6$, $[M+H]^+$ calcd: 297.1822. Found: 297.1823.

*4.7.4. 2-Amino-9-benzyl-6-(tert-butylamino)purine (**19d**).* A mixture of **3** (260 mg, 1 mmol) and *N*-*tert*-butylformamide (1 mL) in toluene (5 mL) was irradiated at 190 °C for 330 min to afford 89 mg (30%) of oil; R_f (10%, MeOH/$CHCl_3$) 0.88; ν_{max} (liquid film) 3529 and 3425 (NH_2), 2977, 2875, 1479, and 1396 (NH-*t*-Bu), 1610, 1523, 1504, 1491, 1447, 1439, and 1348 (purine), 3091 and 3068 (CH_2—phenyl), 1504, 1491, 1455, 1316, 1167, 1076, and 1030 cm^{-1} (phenyl); ^1H NMR (DMSO-d_6): 7.76 (1H, s, H-8), 7.32 (2H, m, H-3′), 7.26 (1H, m, H-4′), 7.21 (2H, m, H-2′), 6.10 (1H, br s, NH), 5.86 (2H, br s, NH_2), 5.19 (2H, s, CH_2), 1.47 (9H, s, CH_3). ^{13}C NMR (DMSO-d_6): 160.11 (C-2), 154.89 (C-6), 150.95 (C-4), 137.87 (C-1′), 137.07 (C-8), 128.76 (C-3′), 127.61 (C-4′), 127.22 (C-2′), 113.84 (C-5), 51.28 (*C*-(CH_3)$_3$), 45.59 (CH_2), 29.28 (CH_3). HRMS (ESI) *m*/*z* $C_{16}H_{21}N_6$, $[M+H]^+$ calcd: 297.1822. Found: 297.1823.

Acknowledgements

This study was performed as a part of research project OZ40550506 of the Institute of Organic Chemistry and Biochemistry. It was supported by Centre for new antivirals and antineoplastics 1M0508 by the Ministry of Education, Youth and Sports of the Czech Republic, by Grant Agency of the Academy of Sciences of the Czech Republic through Project KJB400550903, and by Gilead Sciences and IOCB Research Centre.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.040.

References and notes

1. Muzart, J. *Tetrahedron* **2009**, *65*, 8313.
2. Waller, C. W.; Fryth, P. W.; Hutchings, B. L.; Williams, J. H. *J. Am. Chem. Soc.* **1953**, *75*, 2025.
3. Schnebli, H. P.; Hill, D. L.; Bennett, L. L. *J. Biol. Chem.* **1967**, *242*, 1997.
4. Kelley, J. L.; McLean, E. W.; Linn, J. A.; Krochmal, M. P.; Ferris, R. M.; Howard, J. L. *J. Med. Chem.* **1990**, *33*, 196.
5. Kissman, H. M.; Pidacks, C.; Baker, B. R. *J. Am. Chem. Soc.* **1955**, *77*, 18.
6. Robins, R. K.; Lin, H. H. *J. Am. Chem. Soc.* **1957**, *79*, 490.
7. Weiss, M. J.; Joseph, J. P.; Kissman, H. M.; Small, A. M.; Schaub, R. E.; McEvoy, F. J. *J. Am. Chem. Soc.* **1959**, *81*, 4050.
8. Wu, T. Y. H.; Schultz, P. G.; Ding, S. *Org. Lett.* **2003**, *5*, 3587.
9. Huang, L.-K.; Cherng, Y.-C.; Cheng, Y.-R.; Jang, J.-P.; Chao, Y.-L.; Cherng, Y.-J. *Tetrahedron* **2007**, *63*, 5323.
10. Neres, J.; Labello, N. P.; Somu, R. V.; Boshoff, H. I.; Wilson, D. J.; Vannada, J.; Chen, L.; Barry, C. E., III; Bennett, E. M.; Aldrich, C. C. *J. Med. Chem.* **2008**, *51*, 5349.
11. Miles, R. W.; Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 5951.
12. Fletcher, S. *Tetrahedron Lett.* **2010**, *51*, 2948.
13. Coppinger, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1372.
14. D'Amico, J. J.; Webster, S. T.; Campbell, R. H.; Twine, C. E. *J. Org. Chem.* **1965**, *30*, 3618.
15. Joseph, L.; Albert, A. H. *J. Heterocycl. Chem.* **1966**, *3*, 107.
16. Heindel, N. D.; Kennewell, P. D. *J. Chem. Soc., Chem. Commun.* **1969**, 38.
17. Watanabe, T.; Tanaka, Y.; Sekiya, K.; Akita, Y.; Ohta, A. *Synthesis* **1980**, 39.
18. Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2685.
19. Cho, Y. H.; Park, J. C. *Tetrahedron Lett.* **1997**, *38*, 8331.
20. Meszárosová, K.; Holý, A.; Masojídková, M. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1109.
21. Agarwal, A.; Chauhan, P. M. S. *Synth. Commun.* **2004**, *34*, 2925.
22. For a recent review see: (a) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2005; (b) *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, 2006; (c) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563.
23. Nouira, I.; Kostakis, I. K.; Dubouilh, C.; Chosson, E.; Iannelli, M.; Besson, T. *Tetrahedron Lett.* **2008**, *49*, 7033.
24. Sharma, A.; Mehta, V. P.; Van der Eycken, E. *Tetrahedron* **2008**, *64*, 2605.
25. Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232.
26. Kelley, J. L.; Krochmal, M. P.; Linn, J. A.; McLean, E. W.; Soroko, F. E. *J. Med. Chem.* **1988**, *31*, 606.
27. Butler, R. S.; Myers, A. K.; Bellarmine, P.; Abboud, K. A.; Castellano, R. K. *J. Mater. Chem.* **2007**, *17*, 1863.
28. LaMontagne, M. P.; Smith, D. C.; Wu, G.-S. *J. Heterocycl. Chem.* **1983**, *20*, 295.
29. Holý, A.; Votruba, I.; Tloušťová, E.; Masojídková, M. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1545.
30. Itaya, T.; Matsumoto, H.; Ogawa, K. *Chem. Pharm. Bull.* **1980**, *28*, 1920.
31. Albert, A.; Brown, D. J. *J. Chem. Soc.* **1954**, 2060.
32. Alves, M. J.; Carvalho, M. A.; Carvalho, S.; Dias, A. M.; Fernandes, F. H.; Proenca, M. F. *Eur. J. Org. Chem.* **2007**, 4881.