Tetrahedron 66 (2010) 2210–2221

Contents lists available at ScienceDirect

Tetrahedron

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

# Straightforward carbamoylation of nucleophilic compounds employing organic azides, phosphines, and aqueous trialkylammonium hydrogen carbonate

Andrey Yagodkin [a,b], Kerstin Löschcke [a,†], Janne Weisell [c], Alex Azhayev [a,b,*]

[a] School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Yliopistonranta 1C, FI-70211 Kuopio, Finland
[b] Metkinen Chemistry, Microkatu 1, Microtower, Osa R, FI-70211 Kuopio, Finland
[c] Department of Biosciences, Biocenter Kuopio, Faculty of Science and Forestry, University of Eastern Finland, FI-70211 Kuopio, Finland

ARTICLE INFO

*Article history:*
Received 1 September 2009
Received in revised form 23 November 2009
Accepted 4 January 2010
Available online 20 January 2010

ABSTRACT

In the presence of aqueous trialkylammonium hydrogen carbonate, the Staudinger reaction leads to the intermediate formation of the corresponding isocyanate, which, in turn, reacts further with a nucleophilic reagent also present in the mixture and results in carbamoylation with good yield. On the basis of this reaction a practical carbamoylation procedure was devised and a comparative study on suitability of different solvents and phosphorus (III) derivatives for carbamoylation reaction was conducted. The versatility of the method was demonstrated by examples with different classes of nucleophilic compounds that included the aminomethyl resin and natural compounds that display poor solubility in organic solvents.



## 1. Introduction

The carbamoylation of nucleophilic compounds gives rise to various useful derivatives. Ureas, for example, are useful in many biological activities; e.g., as pharmaceutical products and their precursors, agroprotective agents, and plant growth regulators.[1] In pharmaceuticals, the urea moiety can be found in anti-convulsants, tranquillizers,[1] antineoplastics,[2,3] anti-malaria agents,[4] anti-diabetic drugs,[5,6] and HIV-1 protease inhibitors.[7,8]

The conventional procedures to generate ureas are the reaction of various amines with the highly toxic phosgene or sophisticated phosgene derivatives.[9] Alternatively, another approach is to perform carbamoylation of nucleophilic compounds, e.g., to synthesize non-symmetrical substituted ureas,[10] generated by the addition of nucleophilic compounds to isocyanates. Hence, there is a clear need to obtain straightforward methods for isocyanate synthesis.

In 1968, Bennet and Hardy published a synthesis for phenylisocyanate that was based on the formation of nitrene from an azide compound, which reacted with carbon monoxide[11] at high temperatures (160–180 °C) and high pressures (200–300 atm). Near the same time, Collman et al. reported the syntheses of isocyanates from azides and carbon monoxide in the presence of iridium complexes.[12,13] Phenyl azide has also been shown to undergo a carbamoylation reaction in a catalytic process involving the action of rhodium complexes and carbon monoxide at high pressures (150–300 atm) and high temperatures (160–180 °C) in the formation of phenylisocyanate.[14,15] Based on these initial findings, Langstrom et al. successfully developed methods for the synthesis of various $^{11}C$-labeled compounds via isocyanates.[16,17]

Phosphinimines (iminophosphoranes) have been claimed to be useful in the preparation of alkyl- and arylisocyanates in early 1980s. Molina et al.[18] described an efficient method for the conversion of alkyl- and aryliminophosphoranes (generated from the corresponding amines and triphenylphosphine dibromide) into isocyanates, where a key step was the reaction of phosphinimine with carbon dioxide, which was passed through a solution in boiling benzene. This approach allowed for the preparation of eight isocyanates in high yield. A similar approach was used by Kovacs et al.[19,20] to prepare cyclic carbamates by simultaneous bubbling of carbon dioxide into the reaction mixture. The same approach was employed by Marsura et al. for the preparation of β-cyclodextrin 'dimers' with the use of urea linkers.[21] An extension of this method utilized a polymer assisted one-pot phosphinimine reaction with a polymer-bound triphenylphosphine to generate various cyclodextrin urea derivatives.[22] Another modification of this one-pot phosphinimine reaction used supercritical carbon dioxide ($sCO_2$) as a solvent and reagent.[23] Indeed, $sCO_2$ in the presence of triphenylphosphine or polymer-bound triphenylphosphine resulted in the desired urea cyclodextrin derivatives within reasonable times and in good yields.

The present report also depicts carbamoylation of nucleophilic compounds, employing organic azides as well as triphenylphosphine, polymer-bound triphenylphosphine, and some triaryl- or

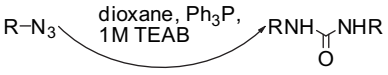
* Corresponding author. Tel.: +358 407364885.
*E-mail address:* Alex.Azhayev@uef.fi (A. Azhayev).
† Present address: Pharmaceutical Institute, University of Bonn, An der Immenburg 4, 53112 Bonn, Germany.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.017

alkyldiaryl phosphines. However, the new procedure, described here in detail, employs an aqueous trialkylammonium hydrogen carbonate buffer (triethylammonium hydrogen carbonate, TEAB or trimethylammonium hydrogen carbonate, TMAB), added to an organic solvent as a convenient source of carbon dioxide. We believe that the possibility to perform carbamoylation reactions via the formation of an isocyanate intermediates in solutions, containing aqueous buffer, considerably broadens the application of such an approach for the synthesis of derivatives of a number of compounds with extremely low solubility in organic solvents that tends to improve in the presence of water. It should be noted that this procedure appears to be extremely simple. It does not require any special equipment for generation of $sCO_2$, transition metal complexes or, more importantly, there is no need to use hazardous highly toxic gases such as phosgene or carbon monoxide. We believe that this procedure may be carried out in any chemical laboratory.

## 2. Results and discussion

Earlier, while studying various conditions required for the removal of a 4-azidobutiryl group, which served as a protection of the hydroxyl function,[24] we noticed that the use of a triphenylphosphine–dioxane–aqueous 1 M TEAB combination (instead of the conventional triphenylphosphine–dioxane–water mixture) resulted in the formation of an anomalous product at a high yield. This product proved to be a symmetrical urea, bearing the substituent R contained in the initial azido-compound (Scheme 1).

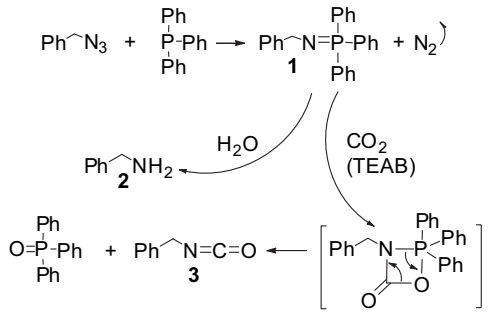



**Scheme 1.**

In order to explain this phenomenon, we suggested that the formation of the corresponding intermediate isocyanate followed Staudinger's generation of the phosphinimine from the azide.[25]

With the aim to support this assumption and to verify the limits of the approach we performed a detailed investigation of the reaction, employing a number of organic azides, nucleophilic compounds, and phosphines.

Initially, we decided to study the simple model reaction of benzylazide and triphenylphosphine in the presence of TEAB. Theoretically, in our case (Scheme 2) the phosphinimine **1**, generated from benzylazide may undergo a reaction with either water (from the buffer) to form the corresponding benzylamine **2** or with $CO_2$ (from the TEAB) to give rise to the corresponding reactive isocyanate **3**. Alternatively, compound **1** may undergo both transformations at the same time.




**Scheme 2.**

Thus, we have compared the courses of these two reactions—a textbook Staudinger reaction of benzylazide with triphenylphosphine in dioxane in the presence of water and the same Staudinger reaction in the presence of aqueous 2 M TEAB. Figure 1 demonstrates the changes in the $^1$H NMR spectrum of benzylazide–triphenylphosphine mixture in dioxane in the presence of water at room temperature and at different time points.

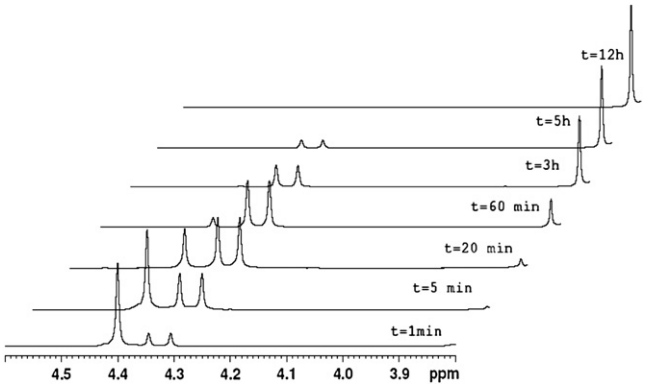



**Figure 1.** $^1$H NMR spectra of benzylazide–triphenylphosphine mixture at different time points in dioxane-$d_8$ in the presence of $D_2O$ at room temperature.

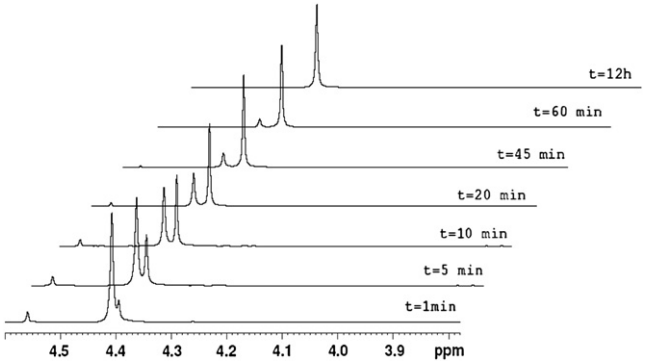
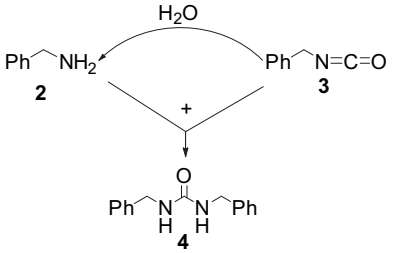
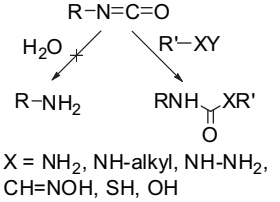



**Figure 2.** $^1$H NMR spectra of a benzylazide–triphenylphosphine mixture at different time points in dioxane-$d_8$ in the presence of 3 M TEAB, prepared in $D_2O$, at room temperature.




**Scheme 3.**




X = $NH_2$, NH-alkyl, $NH-NH_2$, CH=NOH, SH, OH

**Scheme 4.**

**Table 1**
Carbamoylation of basic nucleophilic compounds (free bases, entries 1–13), employing procedure **A**[a]

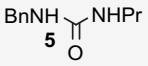
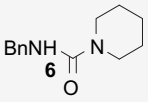
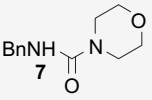
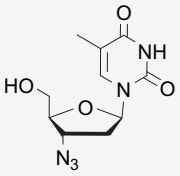
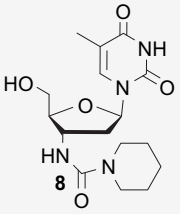
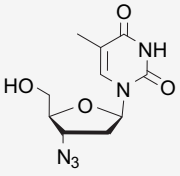
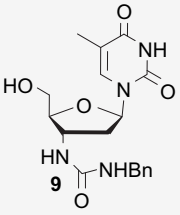
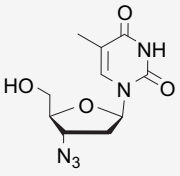
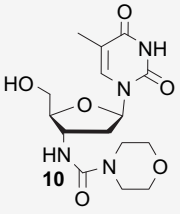
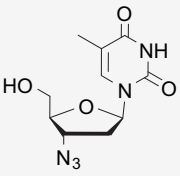
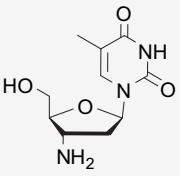
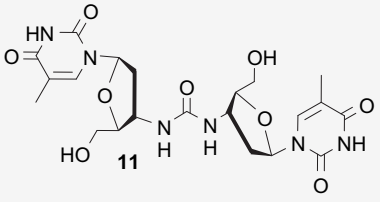
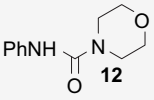
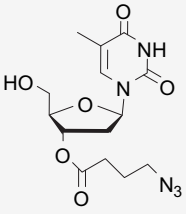
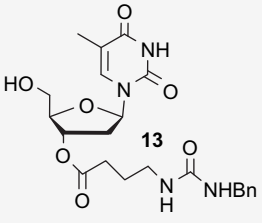
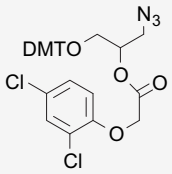
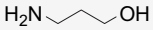
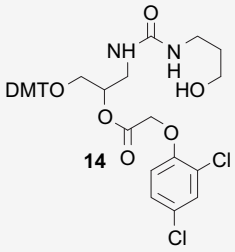
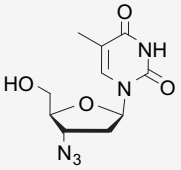
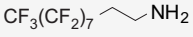
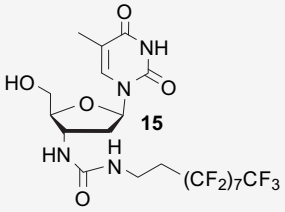
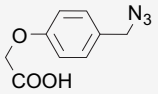
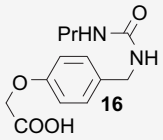
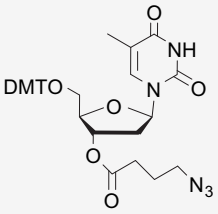
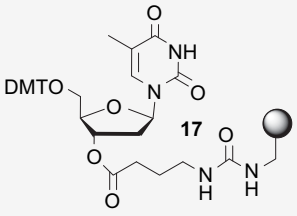
| Entry | Organic Azide (R-$N_3$) | Nucleophilic compound | Yield | | Product |
|---|---|---|---|---|---|
| | | | %[b] | %[c] | |
| 1 | $BnN_3$ | $PrNH_2$ | >99 | 71 |  **5** |
| 2 | $BnN_3$ |  | 90 | 64 |  **6** |
| 3 | $BnN_3$ |  | 94 | 68 |  **7** |
| 4 |  |  | 96 | 73 |  **8** |
| 5 |  | $BnNH_2$ | 93 | 76 |  **9** |
| 6 |  |  | 94 | 85 |  **10** |
| 7 |  |  | 97 | 65 |  **11** |
| 8 | $PhN_3$ |  | 96 | 63 |  **12** |
| 9 |  | $BnNH_2$ | 81 | 56 |  **13** |

**Table 1** (*continued*)

| Entry | Organic Azide (R-$N_3$) | Nucleophilic compound | Yield % [b] | Yield % [c] | Product |
|---|---|---|---|---|---|
| 10 |  |  | 91 | 55 |  **14** |
| 11 |  |  | 76 | 59 |  **15** |
| 12 |  | $PrNH_2$ | 80 | 78 |  **16** |
| 13 |  | AMPS[d] | — | 87[e] |  **17** |

[a] See Experimental and Supplementary data for details.
[b] Yields were determined by integration of all RP HPLC peaks at 260 nm, with the exception of peaks of the initial compounds and the corresponding triphenylphosphine oxide.
[c] Isolated yield.
[d] AMPS=macroporous aminomethylpolystyrene.
[e] Isolated yield was calculated as % ratio of the amount of AMPS bound DMT groups versus DMT groups of the 5′-*O*-DMT-3′-*O*-(4-azidobutiryl)thymidine.

One can observe the gradual decrease of the singlet intensity at about 4.4 ppm (corresponding to the $-CH_2-$ group of the initial benzylazide) within the first 60 min in parallel with the gradual growth of the doublet intensity (4.33 ppm, $J_{P-H}$=16 Hz) corresponding to the $-CH_2-$ group of phosphinimine **1** along with the appearance of a low intensity singlet at 3.79 ppm corresponding to the $-CH_2-$ group of benzylamine **2**. Further monitoring of the reaction demonstrated that the singlet corresponding to benzylazide was completely absent after 4 h, while the doublet, corresponding to phosphinimine appears to be present even 5 h after the start of the reaction. Eventually, after 12 h, only one singlet can be found, which corresponds to benzylamine in this region of $^1$H NMR spectrum. Evidently, both processes, the Staudinger reaction of phosphinimine formation as well as generation of benzylamine from the phosphinimine by hydrolysis appear to be relatively slow reactions, which take several hours to complete.

Interestingly, the Staudinger reaction gives completely different products in the presence of aqueous triethylammonium hydrogen carbonate buffer (Fig. 2).

As in the previous case (Fig. 1), one can observe the gradual decrease of the singlet intensity at 4.41 ppm (corresponding to the $-CH_2-$ group of the initial benzylazide) within more than 60 min. However, in contrast to the previous experiment, there is no evidence, i.e., no doublet, corresponding to the $-CH_2-$ group of phosphinimine **1** observed. In this case, one can detect the appearance of two new signals—one singlet at 4.56 ppm and another singlet at 4.40 ppm within less than 1 min of reaction time. As supported by $^1$H NMR measurements with authentic samples, whereas the singlet at 4.56 ppm corresponds to the $CH_2$-group of isocyanate **3** (Schemes 2 and 3), the singlet at 4.40 ppm corresponds to the $CH_2$-groups of *N*,*N*′-dibenzylurea **4** (Scheme 3).

Figure 2 allows assuming that during the course of reaction the concentration of isocyanate **3** remains nearly proportional to that of the initial benzylazide. The concentrations of both compounds gradually decline, with signal corresponding to **3** (4.56 ppm) becoming practically non-detectible after 45 min and signal of benzylazide (4.41 ppm) becoming very small after 60 min. In parallel, the concentration of urea **4** gradually increases. The singlet at 4.40 ppm, corresponding to the *N*,*N*′-dibenzylurea **4**, reaches its maximum within 12 h. This singlet appears to be the only $CH_2$-group related signal in the reaction mixture, indicating that the reaction is complete.

The results of the experiments outlined in Figure 2 makes it possible to draw the following conclusion. The rate limiting step of the reaction appears to be the formation of the phosphinimine **1**. In the presence of aqueous 3 M TEAB, rather than being hydrolyzed to

**Table 2**
Carbamoylation of weakly basic nucleophilic compounds (entry 14), salts of basic nucleophilic compounds (entries 17, 21, 26), non-basic nucleophilic compounds (entries 15, 16, 18–20,22,23,27) or in situ generated basic nucleophilic compounds (entries 24,25), employing procedure **B**[a]

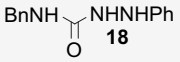
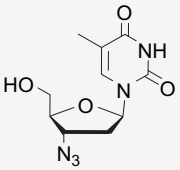
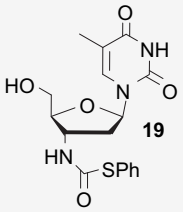
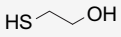
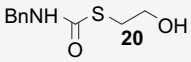
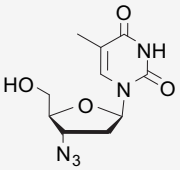
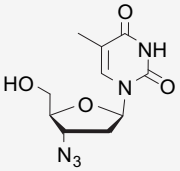
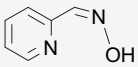
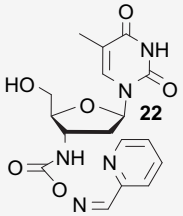
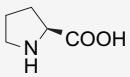
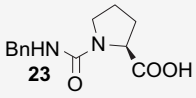
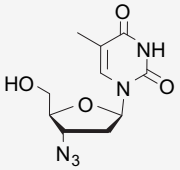
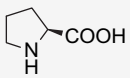
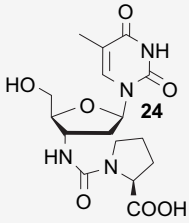
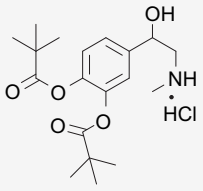
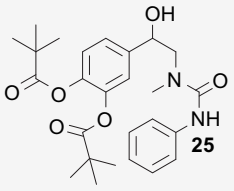
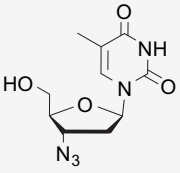
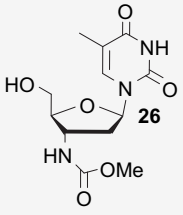
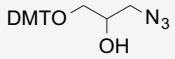
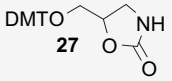
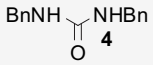
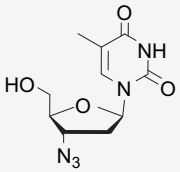
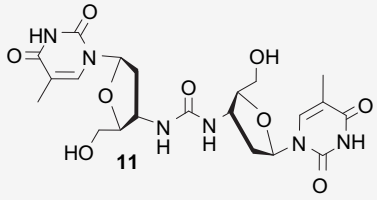
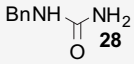
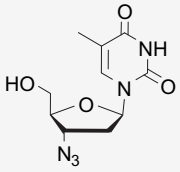
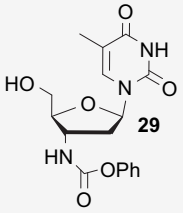
| Entry | Organic Azide (R-$N_3$) | Nucleophilic compound | Yield | | Product |
|---|---|---|---|---|---|
| | | | %[b] | %[c] | |
| 14 | $BnN_3$ | $PhNHNH_2$ | 87 | 69 |  **18** |
| 15 |  | PhSH | 95 | 58 |  **19** |
| 16 | $BnNH_3$ |  | 83 | 48 |  **20** |
| 17 |  | $CH_3ONHCH_3 \cdot HCl$ | 84 | 76 |  **21** |
| 18 |  |  | 64 | 43 |  **22** |
| 19 | $BnN_3$ |  | 94 | 53 |  **23** |
| 20 |  |  | 97 | 57 |  **24** |
| 21 | $PhN_3$ |  | 92 | 69 |  **25** |
| 22[d] |  | Methanol | 77 | 57 |  **26** |

**Table 2** (*continued*)

| Entry | Organic Azide (R-$N_3$) | Nucleophilic compound | Yield %[b] | Yield %[c] | Product |
|---|---|---|---|---|---|
| 23 |  | — | 76 | 66 |  **27** |
| 24 | $BnN_3$ | — | 98 | 64 |  **4** |
| 25 |  | — | 93 | 69 |  **11** |
| 26 | $BnN_3$ | Ammonium acetate | 87 | 67 |  **28** |
| 27 |  | PhOH | 51 | 31 |  **29** |

[a] See Supplementary data for experimental details.
[b] Yields were calculated by integration of all RP HPLC peaks at 260 nm, with the exception of peaks of the initial compounds and the corresponding triphenylphosphine oxide.
[c] Isolated yield.
[d] Synthesis of carbamate **26** was performed in methanol as the solvent (see also Table 4), using procedure **B**.

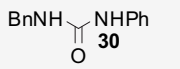
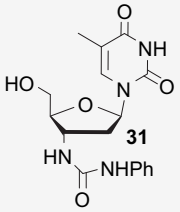
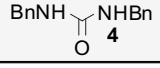
the benzylamine **2**, the iminophosphorane **1** undergoes a rapid (at least on the time scale of NMR experiment) addition with $CO_2$ to give rise to the benzylisocyanate **3** (Scheme 1).

Subsequently, benzylisocyanate **3**, which is subjected to partial hydrolysis, forms benzylamine **2**, which in turn instantly reacts with the remaining isocyanate **3** to give the urea **4** as a final product (Scheme 3). As shown in a separate experiment with an authentic sample of benzylisocyanate, the complete conversion of **3** into **4** under the same reaction conditions requires less than the time needed to undertake one $^1$H NMR spectrum measurement. On the basis of this proposed mechanism, we postulated that if a compound with a nucleophilicity higher than that of water is present in the mixture from the very start, then the reaction will lead to the formation of the corresponding carbamoyl derivative. Thus, this method could provide simple access to a number of non-symmetrical ureas, thiocarbamates, and carbamates (Scheme 4).

Our present work demonstrates examples of carbamoylation for different types of nucleophilic compounds while employing the trialkylammonium hydrogen carbonate buffer as a convenient source of carbon dioxide. Both buffers tested; i.e., TEAB and TMAB, perform equally well in the new method, and gave similar yields of the target compounds. The synthetic procedures **A**–**C**, employed to generate compounds in Tables 1–3 are described in detail in the Experimental. Entries 1–12, in Table 1, show carbamoylation of basic nucleophilic compounds (synthetic procedure **A**), including the carbamoylation of a polymer-bound basic nucleophilic compound—aminomethylpolystyrene (entry 13, Table 1).

Table 2 corresponds to synthetic procedure **B**. Several entries—14, 17, 21, and 26, in Table 2 show the reaction with weakly basic nucleophiles or salts of basic nucleophiles, and entries 15, 16, 18–20, 22–25 and 27, in Table 2 show reaction with non-basic nucleophilic compounds or strong nucleophiles generated in situ by hydrolysis of the intermediate isocyanate, resulting in the corresponding symmetrical ureas. Examples of carbamoylation of weakly basic nucleophilic compounds (entries 28 and 29,

**Table 3**
Carbamoylation of weakly basic nucleophilic compounds (entries 28, 29) and an in situ generated basic nucleophilic compound (entry 30), employing polymer-bound triphenylphosphine and procedure **C**[a]

| Entry | Azide (R-$N_3$) | Nucleophilic compound | Yield %[b] | Yield %[c] | Product |
|---|---|---|---|---|---|
| 28 | $BnN_3$ | $PhNH_2$ | 75 | 57 |  **30** |
| 29 | AZT[d] | $PhNH_2$ | 86 | 52 |  **31** |
| 30 | $BnN_3$ | — | 89 | 59 |  **4** |

[a] See Supplementary data for experimental details.
[b] Yields were calculated by integration of all RP HPLC peaks at 260 nm, with the exception of peak, corresponding to aniline.
[c] Isolated yield.
[d] 3′-Azido-3′-deoxythymidine.

Table 3) or in situ generated basic nucleophilic compound (entry 30, Table 3) employing a polymer-bound triphenylphosphine are also depicted as synthetic procedure **C**.

It is worth noting that procedure **B**—carbamoylation, employing a weakly basic, non-basic or an in situ generated strong basic nucleophilic compound, may be described here as general. This procedure consists of mixing the components—e.g., organic azide, weakly basic, non-basic or no nucleophilic compound, triphenylphosphine and TEAB or TMAB buffer and allowing the reaction to run to completion at rt in a tightly closed vessel. Procedure **A** utilizes amines as basic nucleophilic compounds. Obviously, addition of strongly basic amines to a mixture containing aqueous trialkylammonium hydrogen carbonate results in the conversion of hydrogen carbonate into carbonate, which will diminish the concentration of free carbon dioxide in solution and, consequently reduce the yield. Therefore, it is essential that aliphatic amines, when employed as nucleophilic compounds, must be initially neutralized. If a salt of the required amine appears to be readily available, it may be introduced into the carbamoylation reaction as such. As most of the amines in Table 1 are usually available in the form of free bases, procedure **A** incorporates the preliminary conversion of these bases into the corresponding hydrogen carbonates by saturation of the amine solution in TEAB or TMAB with gaseous carbon dioxide. Procedure **C**, being similar to procedure **B**, utilizes the polymer-bound triphenylphosphine (Table 3), which requires the reaction to be run at elevated temperatures due to the reduced reactivity of the latter compound.

In order to investigate the range of utility for the present approach, we conducted a comparative study of the reaction between benzylazide with triphenylphosphine in the presence of 2 M TEAB in various solvents to produce *N*,*N*′-dibenzylurea **4** (Table 4).

From the values presented in Table 4, dioxane appears to be the optimum solvent for the carbamoylation reaction. However, the use of acetonitrile, 2-propanol, bis-(2-methoxyethyl)-ether, and acetone also provides satisfactory yields of **4**. When ethanol and methanol are employed as solvents, the formation of the target urea (70% and 23% correspondingly) was accompanied by the formation of the corresponding ethylcarbamate (16%) and methyl carbamate (59%) (Table 4). Therefore, this approach may serve as a convenient method for the synthesis of methyl carbamates, when the appropriate method of separation of products is elaborated.

**Table 4**
Yields of *N*,*N*′-dibenzylurea **4**, synthesized by the carbamoylation reaction, employing benzylazide, triphenylphosphine, 2 M TEAB, and various solvents[a]

| Solvent | Yield of urea **4**[b]% |
|---|---|
| 1,4-Dioxane | 98 |
| 2-Propanol | 94 |
| Acetonitrile | 81 |
| bis-(2-Methoxyethyl)-ether | 81 |
| Acetone | 79 |
| *N*-Methylpyrrolidinone | 67 |
| Ethanol | 70 (+16% of ethyl benzylcarbamate) |
| Dimethylsulfoxide | 49 |
| Methanol | 23 (+59% of methyl benzylcarbamate) |
| DMF | 0 |

[a] See Supplementary data for experimental details.
[b] Yields were calculated by integration of all RP HPLC peaks at 260 nm, with the exception of peaks of the initial triphenylphosphine and the corresponding triphenylphosphine oxide. Yields given in Table 4 are approximations, as yield calculations were based on the assumption that the extinction coefficients of all compounds in the reaction mixture (excluding peaks of the initial triphenylphosphine and the corresponding triphenylphosphine oxide) are equal.

Carbamoylation of nitrogen and sulfur nucleophilic compounds resulted in good to excellent yields of products (Tables 1–3). Moreover, even weakly nucleophilic hydroxyl groups of alcohols may participate in the reaction under certain circumstances; e.g., methyl carbamate **26** (Table 2) with an excess of methanol, or the formation of a cyclic product, carbamate **27** (Table 2). The reaction with phenol and AZT gave the corresponding phenyl carbamate **29** in a satisfactory yield (Table 2). Conversely, no corresponding carbamates were found in the reaction mixture with *p*-nitrophenol or pentafluorophenol and 3′-azido-3′-deoxythymidine (AZT). In the case with *p*-nitrophenol this approach gave symmetrical urea in high yields, being virtually the single product, excluding the initial triphenylphosphine and the corresponding phosphine oxide. In the case with pentafluorophenol a mixture of two compounds—symmetrical urea (24%) along with the corresponding 3′-amino-3′-deoxythymidine (76%) were found as two products of the reaction.

We also compared the potency of the various phosphines in the reaction with benzylazide in the presence of 2 M TEAB in dioxane (Table 5).

**Table 5**
Yields of *N*,*N*′-dibenzylurea **4**, synthesized by the carbamoylation reaction, employing benzylazide, various phosphines, 2 M TEAB, and dioxane[a]

| Phosphine | Yield[b]% |
|---|---|
| Triphenylphosphine | 98% |
| Methyldiphenylphosphine | 95% |
| 3-(Diphenylphosphino)benzenesulphonic acid sodium salt | 89% |
| Diphenyl-2-pyridylphosphine | 78% |
| Dimethylphenylphosphine | 71% (0.7)[c] |
| Tributylphosphine | 37% (0.65)[c] |
| Methoxydiphenylphosphine | 29% (0.7)[c] |
| Dimethoxyphenylphosphine | 5% (0.15)[c] |
| Tri-2-furylphosphine | 1% |

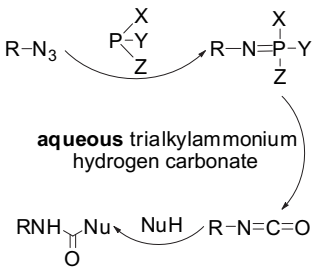
[a] See Supplementary data for experimental details.
[b] Yields were accessed by integration of RP HPLC peaks at 260 nm, with the exception of peaks of the initial phosphines and the corresponding phosphine oxides. Yields given in Table 5 are approximate since yield calculation was based on the assumption that the extinction coefficients of all compounds in the reaction mixture (excluding peaks of the initial phosphines and the corresponding phosphine oxides) are equal.
[c] The ratios of peak areas for target compound **4** in reactions using various phosphines in dioxane to the peak area of **4** in a control reaction, employing triphenylphoshpine in dioxane, are given in brackets.

From the values presented in Table 5, triphenylphosphine appears to be a superb reagent in the carbamoylation process, while methyldiphenylphosphine, 3-(diphenylphosphino)-benzenesulphonic acid sodium salt, and diphenyl-2-pyridylphosphine also proved to be effective reagents in this carbamoylation procedure. The possibility of performing the carbamoylation of nucleophilic compounds, using solvents that are more polar than dioxane and employing phosphines that demonstrate a better solubility in aqueous organic solvents, e.g., 3-(diphenylphosphino)-benzenesulphonic acid sodium salt and diphenyl-2-pyridylphosphine, seems to be especially important if this method is to be applied with the different natural compounds (amino acids, modified nucleosides, and even oligonucleotides), that display a limited solubility in organic solvents.

## 3. Conclusion

In summary, novel approach proved to be a convenient and efficient method to carbamoylate various nucleophilic functions (Scheme 5).

Due to the simplicity of substitution with the azide ion, the preparation of organic azides can be readily accomplished in many cases. The novel straightforward procedure, which does not require special equipment for the in situ transformation of azides into intermediate isocyanates in polar aqueous organic media, is expected




**Scheme 5.**

to expand the synthetic availability for various classes of carbamoyl derivatives.[26] This statement may be especially relevant for natural compounds displaying poor solubility in moderately polar organic solvents (e.g., amino acids, nucleosides, etc.).

It is worth noting that this approach works well with modified solid surfaces and polymers that have nucleophilic functional groups.

We believe that such a simple method could be of broad interest for synthetic and medicinal chemists.

## 4. Experimental procedures

### 4.1. General

Gradient column chromatography was run using two C-601 pump modules, a C-615 pump controller, and borosilicate glass columns (Büchi). Lichroprep RP-18 (40–63 μm) or Silicagel 60 (40–63 μm) (Merck) was employed for flash column chromatography using gradient of acetonitrile in water or methanol in dichloromethane for the purification of compounds reported herein. Analytical RP HPLC was performed employing a gradient Waters 'Breeze' chromatograph on a xBridge® $RP_{18}$ (5 μm, 4.6×150 mm, Waters) column using a gradient elution with acetonitrile (from 0 to 80% over 30 min) in 0.1 M triethylammonium acetate, pH 8.5, followed by isocratic elution with 80% acetonitrile in 0.1 M triethylammonium acetate, pH 8.5; flow rate 1 ml/min.

NMR spectra were collected with an Avance 500 spectrometer (Bruker) in DMSO-$d_6$, $CDCl_3$, $CD_3CN$ or dioxane-$d_8$. High resolution mass spectra (HRMS) were obtained with Applied Biosystems QSTAR XL instrument using ESI. Exact masses of compounds were calculated using the built in calculator of Analyst QS software.

Whereas characterization data for novel compounds is given herein, the corresponding data for all compounds synthesized by the present method, along with $^1H$ and $^{13}C$ NMR spectra may be found in Supplementary data.

### 4.2. Synthetic procedure A

Carbamoylation, employing basic nucleophilic compounds. A mixture of basic nucleophilic compound (1 mmol) or aminomethylpolystyrene (AMPS, 0.25 mmol/g of amino group loading, 4 g) and freshly prepared 2 M trialkylammonium hydrogen carbonate buffer (TEAB or TMAB), pH 7.5–8.0 (1 ml) was saturated with carbon dioxide at 0 °C. Dioxane (12 ml) and organic azide (0.75 mmol), followed by triphenylphosphine (1.33 mmol) were quickly added to the reaction mixture. The reaction flask was tightly closed, vigorously shaken until complete dissolution of components, and then left for 24 h at rt. In case of heterogeneous reaction mixtures (entries 10, 11, and 13, Table 1) the vigorous shaking was continued for 24 h. The reaction mixture was evaporated to dryness. The resulting products were isolated, using silica gel flash chromatography (compounds **9**, **13**–**15**), reverse phase flash chromatography (compounds **6**–**8**, **10**) or crystallization from appropriate solvents (compounds **5**, **11**, **16**). In case of nucleoside bound polymer **17** (entry 13, Table 1), the resin was filtered, thoroughly washed with dioxane, and finally dried in vacuo.

### 4.3. Synthetic procedure B

Carbamoylation, employing a weakly basic, non-basic or in situ generated strong basic nucleophilic compounds. The organic azide (0.75 mmol) was added to a mixture of the freshly saturated 2 M trialkylammonium hydrogen carbonate buffer (1 ml) and 12 ml of dioxane (synthesis of compounds **4**, **11**, **18**–**21**, **25**–**29**) or 12 ml of 2-propanol (synthesis of compounds **22**–**24**), in the presence or absence of a nucleophilic component (1 mmol). Triphenylphosphine (1.33 mmol) was added to the reaction mixture, the reaction flask was tightly closed, vigorously shaken until complete dissolution of components, and then left for 24 h at rt. In the case of heterogeneous reaction mixtures (entries 17–19, Table 2), vigorous shaking was continued for 24 h. The reaction mixture was evaporated to dryness. The resulting products were isolated, using silica gel flash chromatography (compound **17**) or reverse phase flash chromatography (compounds **19**, **26**) or crystallization from appropriate solvents (compounds **4**, **11**, **17**, **18**, **24**, **25**, **29**). In the case of L-proline derivatives **22** and **23**, the reaction mixtures were evaporated to dryness, the residue was dissolved in dichloromethane, extracted with 5% aqueous ammonium hydroxide, aqueous extracts were acidified with hydrochloric acid to produce pure viscous pale yellow oily products.

### 4.4. Synthetic procedure C

Carbamoylation, employing polymer-bound triphenylphosphine (Table 3). The organic azide (0.5 mmol) was added to a mixture of the freshly saturated 2 M TEAB (0.8 ml) and dioxane (10 ml), in the presence or absence of a nucleophilic component (2.5 mmol). Polymer-bound triphenylphosphine (2.0 g, 0.8 mmol/g triphenylphosphine residues loading) was added to the reaction mixture. The reaction flask was tightly closed and vigorously shaken for 48 h at 40 °C. The resin was filtered, washed with 3 ml of dioxane. The combined filtrate and washings were evaporated to dryness and the products were isolated using reverse phase flash chromatography (compounds **30**, **31**) or crystallization from the appropriate solvent (compound **4**).

### 4.5. Testing various solvents

Generation of *N*,*N*′-dibenzylurea **4**, employing benzylazide, triphenylphosphine, 2 M TEAB, and various solvents was performed as described above for Synthetic procedure **B**. The results of these experiments are given in Table 4.

### 4.6. Testing various phosphines

Generation of *N*,*N*′-dibenzylurea **4**, employing benzylazide, dioxane, 2 M TEAB, and various phosphines was performed as described above for Synthetic procedure **B**. The results of these experiments are given in Table 5.

### 4.7. *N*-((2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)piperidine-1-carboxamide (8)

Purified by crystallization from acetonitrile to give white crystals. Mp 205–206 °C. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.26 (1H, s, NH-3 of pyrimidine), 7.77 (1H, s, H-5 of pyrimidine), 6.65 (1H, d, $J$=7.0 Hz, terahydrofuran–N*H*CON), 6.19 (1H, t, $J$=6.5 Hz, H-1 of tetrahydrofuran), 5.01 (1H, t, $J$=5.3 Hz, OH), 4.22 (1H, m, H-3 of tetrahydrofuran), 3.78 (1H, m, H-4 of tetrahydrofuran), 3.63 (1H, m,

H-5a of tetrahydrofuran), 3.55 (1H, m, H-5b of tetrahydrofuran), 3.27 (4H, m, H-2a,b and H-6a,b of piperidine), 2.15 (2H, m, H-2a,b of tetrahydrofuran), 1.78 (3H, s, $CH_3$), 1.52 (2H, H-4a,b of piperidine), 1.41 (4H, m, H-3a,b and H-5a,b of piperidine). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 157.5 (s, NHCON), 150.9 (s, C-2 of pyrimidine), 136.7 (s, C-6 of pyrimidine), 109.8 (s, C-5 of pyrimidine), 85.9 (s, C-1 of tetrahydrofuran), 83.9 (s, C-4 of tetrahydrofuran), 61.9 (s, C-5 of tetrahydrofuran), 50.3 (s, C-3 of tetrahydrofuran), 44.7 (s, C-2 and C-6 of piperidine), 37.9 (s, C-2 of tetrahydrofuran), 25.8 (s, C-3 and C-5 of piperidine), 24.6 (s, C-4 of piperidine), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{16}H_{25}N_4O_5$, 353.1825; found, 353.1840.

### 4.8. 1-Benzyl-3-((2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)urea (9)

Purified by crystallization from acetonitrile to give white crystals. Mp 173–176 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.26 (1H, br s, H-5 of pyrimidine), 7.76 (1H, s, H-5 of pyrimidine), 7.35–7.15 (4.4H, m, phenyl), 6.46 (1H, d, $J$=7.3 Hz, terahydrofuran–N*H*CONH), 6.35 (1H, t, $J$=5.7 Hz, NHCON*H*–benzyl), 6.15 (1H, t, $J$=6.3 Hz, H-1 of tetrahydrofuran), 5.06 (1H, t, $J$=5.2 Hz, OH), 4.20 (3H, m, $CH_2$ of benzyl and H-3 of tetrahydrofuran), 3.73 (1H, m, H-4 of tetrahydrofuran), 3.65 (1H, m, H-5a of tetrahydrofuran), 3.56 (1H, m, H-5b of tetrahydrofuran), 2.21 (1H, m, H-2a of tetrahydrofuran), 3.27 (4H, m, H-2a,b and H-6a,b of piperidine), 2.21 (1H, m, H-2a of tetrahydrofuran), 2.10 (1H, m, H-2b of tetrahydrofuran), 1.78 (3H, s, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 158.2 (s, NHCONH), 150.9 (s, C-2 of pyrimidine), 141.2 (s, C-1 of phenyl), 136.6 (s, C-6 of pyrimidine), 128.7 (s, C-3 and C-5 of phenyl), 127.4 (s, C-2 and C-6 of phenyl), 127.02 (s, C-4 of phenyl), 109.8 (s, C-5 of pyrimidine), 86.0 (s, C-1 of tetrahydrofuran), 83.8 (s, C-4 of tetrahydrofuran), 61.7 (s, C-5 of tetrahydrofuran), 50.3 (s, C-3 of tetrahydrofuran), 43.4 (s, $CH_2$ of benzyl), 38.2(s, C-2 of tetrahydrofuran), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{18}H_{23}N_4O_5$, 365.1668; found, 365.1661.

### 4.9. 5,9 *N*-((2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)morpholine-4-carboxamide (10)

Purified by crystallization from acetonitrile to give white crystals. Mp 156–159 °C. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 9.60(1H, s, NH-3 of pyrimidine), 7.70 (1H, s, H-5 of pyrimidine), 6.17 (1H, dd, $J$=5.3 Hz and $J$=6.6 Hz, H-1 of tetrahydrofuran), 5.62 (1H, d, $J$=6.9 Hz, terahydrofuran–N*H*CON), 4.33 (1H, m, H-3 of tetrahydrofuran), 3.93 (1H, t, $J$=5.8 Hz, OH), 3.77 (2H, m, H-4 and H-5a of tetrahydrofuran), 3.69 (1H, m, H-5b of tetrahydrofuran), 3.60 (4H, t, $J$=4.7 Hz, H-2a,b and H-6a,b of morpholine), 3.31 (4H, t, $J$=4.7 Hz, H-3a,b and H-5a,b of morpholine), 2.35 (2H, m, H-2a,b of tetrahydrofuran), 1.85 (3H, s, $CH_3$). $^{13}$C NMR (125 MHz, $CD_3CN$): $\delta$ 164.1 (s, C-4 of pyrimidine), 157.9 (s, NHCON), 150.7 (s, C-2 of pyrimidine), 136.3 (s, C-6 of pyrimidine), 109.9 (s, C-5 of pyrimidine), 85.7 (s, C-1 of tetrahydrofuran), 83.9 (s, C-4 of tetrahydrofuran), 66.1 (s, C-2 and C-6 of morpholine), 61.3 (s, C-5 of tetrahydrofuran), 50.1 (s, C-3 of tetrahydrofuran), 43.9 (s, C-3 and C-5 of morpholine), 37.3 (s, C-2 of tetrahydrofuran), 11.7 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{15}H_{23}N_4O_6$, 355.1618; found, 355.1611.

### 4.10. 1,3-Bis((2*S*,3*R*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)urea (11)

Purified by crystallization from acetone to give white crystals. Mp 204–208 °C. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 11.28 (2H, s, 2×NH-3 of pyrimidine), 7.75 (2H, s, 2×H-5 of pyrimidine), 6.37 (2H, d, $J$=7.2 Hz, N*H*CON*H*), 6.14 (2H, t, $J$=6.2 Hz, 2×H-1 of tetrahydrofuran), 5.06 (2H, t, $J$=4.8 Hz, 2×OH), 4.17 (2H, m, 2×H-3 of tetrahydrofuran), 3.72 (2H, m, 2×H-4 of tetrahydrofuran), 3.65 (2H, m, 2×H-5a of tetrahydrofuran), 3.54 (2H, m, 2×H-5b of tetrahydrofuran), 2.19 (2H, m, 2×H-2a of tetrahydrofuran), 2.01 (2H, m, 2×H-2b of tetrahydrofuran), 1.78 (6H, s, 2×$CH_3$). $^{13}$C NMR (125 MHz, $CD_3CN$): $\delta$ 164.2 (s, 2×C-4 of pyrimidine), 157.7 (s, NHCON), 150.9 (s, 2×C-2 of pyrimidine), 136.6 (s, 2×C-6 of pyrimidine), 109.8 (s, 2×C-5 of pyrimidine), 85.8 (s, 2×C-1 of tetrahydrofuran), 83.8 (s, 2×C-4 of tetrahydrofuran), 61.7 (s, 2×C-5 of tetrahydrofuran), 50.2 (s, 2×C-4 of tetrahydrofuran), 38.1(s, 2×C-2 of tetrahydrofuran), 12.7 (s, 2×$CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{21}H_{29}N_6O_9$, 509.1996; found, 509.1991.

### 4.11. (2*R*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl-4-(3-benzylureido)butanoate (13)

Purified by crystallization from acetone to give white crystals. Mp 162–165 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.25 (0.9H, NH-3 of pyrimidine), 7.74 (1H, s, H-5 of pyrimidine), 7.34–7.18 (4.4H, m, phenyl), 6.30 (1H, t, $J$=5.9 Hz, NHCON*H*–Bn), 6.19 (1H, dd, $J$=6.0 Hz, $J$=8.5 Hz, H-1 of tetrahydrofuran), 6.00 (1H, t, $J$=5.6 Hz, CO(CH$_2$)$_3$N*H*CONH), 5.27–5.17 (2H, m, H-3 of tetrahydrofuran and OH), 4.20 (2H, d, $J$=5.9 Hz, C*H*$_2$–phenyl), 3.97 (1H, m, H-4 of tetrahydrofuran), 3.63 (2H, br s, H-5a and H-5b of tetrahydrofuran), 3.04 (2H, dt, $J$=6.5 Hz, $J$=12.7, CH$_2$CH$_2$C*H*$_2$NH), 2.34 (2H, t, $J$=7.4, COC*H*$_2$CH$_2$CH$_2$), 2.31–2.19 (2H, m, H-2a and H-2b of tetrahydrofuran), 1.78 (3H, s, $CH_3$), 1.65 (2H, m, $J$=7.0 Hz, $J$=14.2, CH$_2$C*H*$_2$CH$_2$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 172.8 (s, O*C*OCH$_2$), 164.1 (s, C-4 of pyrimidine), 158.5 (s, NHCONH), 150.9 (s, C-2 of pyrimidine), 141.4 (s, C-1 of phenyl), 136.3 (s, C-6 of pyrimidine), 128.6 (s, C-3 and C-5 of phenyl), 127.5 (s, C-2 and C-6 of phenyl), 127.0 (s, C-4 of 2,4-dichlorophenyl), 110.2 (s, C-5 of pyrimidine), 85.1 (s, C-1 of tetrahydrofuran), 84.2 (s, C-4 of tetrahydrofuran), 75.1 (s, C-3 of tetrahydrofuran), 61.8 (s, C-5 of tetrahydrofuran), 43.4 (s, *C*H$_2$-phenyl), 39.0 (s, OCOCH$_2$CH$_2$*C*H$_2$NH), 37.0 (s, C-2 of tetrahydrofuran), 31.4 (s, OCO*C*H$_2$CH$_2$CH$_2$NH), 25.9 (s, OCOCH$_2$*C*H$_2$CH$_2$NH), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{22}H_{29}N_4O_7$, 461.2036; found, 41.2046.

### 4.12. 1-(Bis(4-methoxyphenyl)(phenyl)methoxy)-3-(3-(3-hydroxypropyl)ureido)propan-2-yl-2-(2,4-dichlorophenoxy)acetate (14)

Purified by flash reverse phase column chromatography to give pale yellow oil. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 7.5–6.82 (16H, m, phenyl, 2×4-methoxy*phenyl*, 2,4-dichlorophenyl), 5.13 (1H, m, 2,4-dichlorophenoxyacetyl-OC*H*), 5.07 (2H, m, 2×NH), 4.79 (1H, s, 2,4-dichlorophenyl-OC*H*$_a$, 4.78 (1H, s, 2,4-dichlorophenyl-OC*H*$_b$, 3.76 (6H, s, 2×OCH$_3$), 3.45–3.12 (9H, m, bis(4-methoxyphenyl)(phenyl)methyl-OC*H*$_2$, NHC*H*$_2$CH$_2$C*H*$_2$OH, OH, 2,4-dichlorophenoxyacetyl-OCHC*H*$_2$NH), 1.51 (2H, m, NHCH$_2$C*H*$_2$CH$_2$OH). $^{13}$C NMR (125 MHz, $CD_3CN$): $\delta$ 167.9 (s, COO), 158.9 (s, NHCONH), 158.7(s, 2×C-4 of 4-methoxyphenyl), 152.6 (s, C-1 of 2,4-dichlorophenyl), 145.0 (s, C-1 of phenyl), 135.8 (s, 2×C-1 of 4-methoxyphenyl), 130.0 (s, C-3 and C-5 of phenyl), 129.8 (s, C-3 of 2,4-dichlorophenyl), 128.0 (s, C-2 and C-6 of phenyl), 127.9 (s, C-2 and C-6 of 4-methoxy*phenyl*), 127.8 (s, C-5 of 2,4-dichlorophenyl), 126.9 (s, C-4 of 2,4-dichlorophenyl), 126.0 (s, C-4 of phenyl), 123.2 (s, C-2 of 2,4-dichlorophenyl), 114.9 (s, C-6 of 2,4-dichlorophenyl), 113,1 (s, C-3 and C-5 of 4-methoxy*phenyl*), 86.0 [s, (4-methoxyphenyl)$_2$phenyl)-*C*, 73.8 (s, 2,4-dichlorophenoxyacetyl-O*C*H), 66.0 (s, (4-methoxyphenyl)$_2$phenyl)methyl-OCH$_2$), 62.7 (s, 2,4-dichlorophenyl-OCH$_2$CO), 58.5 (s, NHCH$_2$CH$_2$*C*H$_2$O), 54.9 (s, 2×–OCH$_3$), 40.13 (s, 2,4-dichlorophenoxyacetyl-OCH*C*H$_2$NH), 36.3 (s, NHCH$_2$*C*H$_2$CH$_2$O), 33.1 (s, NH*C*H$_2$CH$_2$CH$_2$O). HRMS ESI ($m/z$):

[(M+Na)$^+$] calcd for $C_{36}H_{38}N_2O_8Cl_2Na$, 719.1903; found, 719.1901; [(M+K)$^+$] calcd for $C_{36}H_{38}N_2O_8Cl_2K$, 735.1642; found, 735.1640.

### 4.13. 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)-3-((2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)urea (15)

Purified by flash silica gel column chromatography to give pale yellow foam. $^1$H NMR (500 MHz, $CD_3CN$–DMSO-$d_6$, 5:1): $\delta$ 10.62 (0.7H, br s, NH-3 of pyrimidine), 7.69 (1H, d, $J$=1 Hz, H-5 of pyrimidine), 6.29 (1H, d, $J$=7.3 Hz, NHCON*H*–tetrahydrofuran), 6.16 (1H, t, $J$=6.1 Hz, H-1 of tetrahydrofuran), 5.80 (1H, t, $J$=5.8 Hz, OH), 4.54 (0.9H, br s, heptadecafluorodecyl–N*H*CONH), 4.24 (1H, m, H-3 of tetrahydrofuran), 3.75–3.68 (3H, m, H-4 and H-5a of tetrahydrofuran), 3.64 (1H, m, H-5b of tetrahydrofuran), 3.41 (2H, q, $J$=6.7 Hz, NHC*H*$_2$CH$_2$(CF$_2$)$_7$CF$_3$, 2.37) (2H, m, NHCH$_2$C*H*$_2$(CF$_2$)$_7$CF$_3$), 2.27–2.12 (2H, m, H-2a and H-2b of tetrahydrofuran), 1.82 (3H, d, $J$=1 Hz, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 158.1 (s, NHCONH), 150.9 (s, C-2 of pyrimidine), 136.0 (s, C-6 of pyrimidine), 122.0–107.0 (m, (*C*F$_2$)$_7$*C*F$_3$), 109.9 (s, C-5 of pyrimidine), 85.9 (s, C-1 of tetrahydrofuran), 83.8 (s, C-4 of tetrahydrofuran), 61.4 (s, C-5 of tetrahydrofuran), 49.7 (s, C-3 of tetrahydrofuran), 37.8 (s, C-2 of tetrahydrofuran), 32.0 (m, *C*H$_2$CH$_2$(CF$_2$)$_7$CF$_3$, 31.2 (t, $J$=20.7 Hz, CH$_2$*C*H$_2$(CF$_2$)$_7$CF$_3$, 11.8 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{21}H_{20}F_{17}N_4O_5$, 731.1162; found, 731.1163.

### 4.14. 2-(4-((3-Propylureido)methyl)phenoxy)acetic acid (16)

Purified by crystallization from dichloromethane to give white crystals. Mp 162–165 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.97 (0.9H, br s, COO*H*), 7.15 (2H, d, $J$=7.2 Hz, H-3, H-5 of 1,4-substituted phenyl), 6.84 (2H, d, $J$=7.1 Hz, H-2, H-5 of 1,4-substituted phenyl), 6.19 (1H, br s, NH), 5.88 (1H, br s, NH), 4.63 (2H, s, C*H*$_2$O–C$_6$H$_4$–CH$_2$NH), 4.12 (2H, m, CH$_2$O–C$_6$H$_4$–CH$_2$N*H*), 2.96 (2H, m, C*H*$_2$CH$_2$CH$_3$), 1.37 (2H, m, CH$_2$C*H*$_2$CH$_3$), 0.84 (3H, t, $J$=6.9 Hz, CH$_2$CH$_2$C*H*$_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 170.7 (s, COOH), 158.5 (s, NHCONH), 157.0 (s, (s, C-1 of 1,4-substituted phenyl),), 133.91 (s, C-4 of 1,4-substituted phenyl), 128.7 (s, C-3 and C-5 of 1,4-substituted phenyl), 114.6 (s, C-2 and C-6 of 1,4-substituted phenyl), 65.0 (s, *C*H$_2$O–C$_6$H$_4$–CH$_2$NH), 42.8 (s, CH$_2$O–C$_6$H$_4$–*C*H$_2$NH), 41.6 (s, *C*H$_2$CH$_2$CH$_3$), 23.7 (s, CH$_2$*C*H$_2$CH$_3$), 11.8 (s, CH$_2$CH$_2$*C*H$_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{13}H_{19}N_2O_4$, 267.1345; found, 267.1339.

### 4.15. Thymidine bound solid support for oligonucleotide synthesis (17)

Solid support **17** contained 32 μmol of DMT groups per gram of resin[27] and performed well in oligonucleotide synthesis.[28]

### 4.16. *N*-Benzyl-2-phenylhydrazinecarboxamide (18)

Purified by crystallization from 1,2-dichloroethane to give white crystals. Mp 133–135 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.86 (1H, s, NHN*H*–phenyl), 7.61 (1H, s, N*H*NH–phenyl), 7.30–7.10 (6H, m, *phenyl*–CH$_2$ and H-3, H-5 of NHNH–*phenyl*), 7.03 (1H, br m, N*H*CH$_2$-phenyl), 6.73 (3H, m, H-2, H-6 and H-4 of NHNH–*phenyl*), 4.23 (2H, d, $J$=6.3 Hz, phenyl–C*H*$_2$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 159.8 (s, NHCONHNH), 150.0 (s, C-1 of NHNH–*phenyl*), 141.4 (s, C-1 of CH$_2$–*phenyl*), 129.2 (s, C-3,C-5 of NHNH–*phenyl*), 128.5 (s, C-3 and C-5 of CH$_2$–*phenyl*), 127.4 (s, C-2 and C-6 of CH$_2$–*phenyl*), 126.9, (s, C-4 of CH$_2$-*phenyl*), 119.2 (s, C-4 of NHNHCH$_2$-*phenyl*), 112.8 (s, C-2 and C-6 of NHNHCH$_2$-*phenyl*), 42.9 (s, *C*H$_2$-phenyl). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{14}H_{16}N_3O$, 242.1293; found, 242.1292.

### 4.17. *S*-Phenyl (2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-ylcarbamothioate (19)

Purified by crystallization from acetone to give white crystals. Mp 120–124 °C. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 9.38 (1H, s, NH-3 of pyrimidine), 7.63 (1H, s, H-5 of pyrimidine), 7.55–7.40 (4.2H, m, *S-phenyl*), 6.93 (1H, d, $J$=6.5 Hz, SCON*H*–tetrahydrofuran), 6.20 (1H, t, $J$=6.3 Hz, H-1 of tetrahydrofuran), 4.45 (1H, m, H-3 of tetrahydrofuran), 3.88 (1H, m, H-4 of tetrahydrofuran), 3.79 (1H, d, $J$=11.6 Hz, H-5a of tetrahydrofuran), 3.68 (1H, d, $J$=11.9 Hz, H-5b of tetrahydrofuran), 3.29 (0.9H, m, OH), 2.32 (2H, m, H-2a,b of tetrahydrofuran), 1.82 (3H, s, $CH_3$). $^{13}$C NMR (125 MHz, $CH_3CN$): $\delta$ 165.6 (s, NHCOS), 164.0 (s, C-4 of pyrimidine), 150.6 (s, C-2 of pyrimidine), 136.3 (s, C-6 of pyrimidine), 135.3 (s, C-1 of *S-phenyl*), 129.3 (s, C-2 and C-6 of *S-phenyl*), 129.1 (s, C-3 and C-5 of *S-phenyl*), 128.3 (s, C-4 of *S-phenyl*), 110.2 (s, C-5 of pyrimidine), 84.8 (s, C-1 of tetrahydrofuran), 84.3 (s, C-4 of tetrahydrofuran), 61.3 (s, C-5 of tetrahydrofuran), 51.1 (s, C-3 of tetrahydrofuran), 37.1 (s, C-2 of tetrahydrofuran), 11.6 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{17}H_{20}N_3O_5S$, 378.1124; found, 378.1124.

### 4.18. 3-((2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl) tetrahydrofuran-3-yl)-1-methoxy-1-methylurea (21)

Purified by crystallization from acetonitrile to give white crystals. Mp 170–173 °C. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 9.36 (1H, s, NH of pyrimidine), 7.67 (1H, d, $J$=1.1 Hz, H-6 of pyrimidine), 6.55 (1H, d, $J$=7.4 Hz, N*H*CON(CH$_3$)OCH$_3$), 6.19 (1H, dd, $J$=5.1 Hz, $J$=6.9 Hz, H-1 of tetrahydrofuran), 4.35 (1H, m, H-3 of tetrahydrofuran), 3.84–3.77 (2H, m, H-4, H-5a of tetrahydrofuran), 3.70–3.66 (1H, m, H-5b of tetrahydrofuran), 3.65 (3H, s, NHCON(CH$_3$)OC*H*$_3$), 3.55 (1H, t, $J$=5.9 Hz, OH), 3.03 (3H, s, NHCON(C*H*$_3$)OCH$_3$), 2.42–2.36 (1H, m, H-2a of tetrahydrofuran), 2.34–2.28 (1H, m, H-2b of tetrahydrofuran), 1.85 (1H, d, $J$=1.1 Hz, $CH_3$). $^{13}$C NMR (125 MHz, $CH_3CN$): $\delta$ 163.9 (s, C-4 of pyrimidine), 160.2 (s, NHCON(CH$_3$)OCH$_3$), 150.6 (s, C-2 of pyrimidine), 136.3 (s, C-6 of pyrimidine), 110.0 (s, C-5 of pyrimidine), 85.2 (C-1 of tetrahydrofuran), 84.1 (C-4 of tetrahydrofuran), 61.2 (s, NHCON(CH$_3$)OCH$_3$), 61.1 (C-5 of tetrahydrofuran), 49.2 (C-3 of tetrahydrofuran), 37.3 (C-2 of tetrahydrofuran), 34.7 (s, NHCON(*C*H$_3$)OCH$_3$), 11.6 (s, $CH_3$). HRMS ESI ($m/z$): [(M+H)$^+$] calcd for $C_{13}H_{21}N_4O_6$, 329.1461; found, 329.1470; [(M+Na)$^+$] calcd for $C_{13}H_{20}N_4O_6Na$, 351.1281; found, 351.1271.

### 4.19. (*Z*)-Picolinaldehyde *O*-(2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-ylcarbamoyl oxime (22)

Purified by crystallization from acetonitrile to give white crystals. Mp 218–219 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.32 (1H, s, NH of pyrimidine), 8.68 (0.8H, d, $J$=3.6 Hz, H-6 of picoline), 8.48 (0.7H, s, N*H*COO N=CH–picoline), 8.12–8.02 (1.9H, m, H-6 of pyrimidine and H-3 of picoline), 7.95 (1H, m, H-4 of picoline), 7.78 (1H, s, NHCOO N=C*H*–picoline), 7.53 (0.9H, m, H-5 of picoline), 6.23 (1H, t, $J$=5.9 Hz, H-1 of tetrahydrofuran), 5.12 (1H, m, OH), 4.30 (1H, m, H-3 of tetrahydrofuran), 3.91 (1H, m, H-4 of tetrahydrofuran), 3.67 (1H, m, H-5a of tetrahydrofuran), 3.59 (1H, m, H-5b of tetrahydrofuran), 2.28 (2H, m, H-2a and H-2b of tetrahydrofuran), 1.79 (3H, s, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 154.7 (s, NHCOON=CH–picoline), 154.3 (s, NHCOON=*C*H–picoline), 150.9 (C-2 of picoline), 150.4 (s, C-2 of pyrimidine), 150.1 (C-6 of picoline), 137.6 (s, C-6 of pyrimidine), 136.8 (C-4 of picoline), 126.2 (C-5 of picoline), 122.4 (C-3 of picoline), 109.9 (s, C-5 of pyrimidine), 84.8 (C-1 of tetrahydrofuran), 83.9 (C-4 of tetrahydrofuran), 61.6 (C-5 of tetrahydrofuran), 51.3 (C-3 of tetrahydrofuran), 37.5 (C-2 of

tetrahydrofuran), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{17}H_{20}N_5O_6$, 390.1414; found, 390.1409.

### 4.20. (*S*)-1-(Benzylcarbamoyl)pyrrolidine-2-carboxylic acid (23)

Upon the completion of reaction, the mixture was evaporated to dryness, the residue was dissolved in dichloromethane, extracted with 5% aqueous ammonium hydroxide, aqueous extracts were acidified with hydrochloric acid to give pure product as pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.25 (1H, br s, COOH), 7.35–7.25 (4.1H, m, phenyl), 5.11 (0.8H, br s, NH), 4.48 (1H, m, H-2 of pyrrolidine), 4.45 (2H, s, $CH_2C_6H_5$), 3.37 (1H, m, H-5a of pyrrolidine), 3.21 (1H, m, H-5b of pyrrolidine), 2.49 (1H, m, H-3a of pyrrolidine), 2.05 (3H, m, H-3a of pyrrolidine and H-4a,b of pyrrolidine). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 173.2 (s, *C*OOH), 158.8 (s, NH*CO*–pyrrolidine), 138.5 (s, C-1 of phenyl), 128.7 (s, C-3 and C-5 of phenyl), 127.7 (s, C-3 and C-5 of phenyl), 127.6 (s, C-4 of phenyl), 60.1 (s, C-2 of pyrrolidine), 46.2 (s, C-5 of pyrrolidine), 44.9 (s, *C*$H_2$-phenyl), 27.5 (s, C-3 of pyrrolidine), 24.7 (s, C-4 of pyrrolidine). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{13}H_{17}N_2O_3$, 249.1239; found, 249.1241; [$(M+Na)^+$] calcd for $C_{13}H_{16}N_2O_3Na$, 271.1058; found, 271.1056.

### 4.21. (*S*)-1-((2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-ylcarbamoyl)pyrrolidine-2-carboxylic acid (24)

Upon the completion of reaction, the mixture was evaporated to dryness, the residue was dissolved in dichloromethane, extracted with 5% aqueous ammonium hydroxide, aqueous extracts were acidified with hydrochloric acid to give pure product as pale yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.29 (1H, s, NH of pyrimidine), 7.77 (1H, d, $J$=0.9 Hz, H-6 of pyrimidine), 6.58 (1H, d, $J$=7.1 Hz, N*H*CO–pyrrolidine), 6.20 (1H, t, $J$=6.5 Hz, H-1 of tetrahydrofuran), 5.03 (1H, br s, OH), 4.30–4.10 (2H, m, H-3 of tetrahydrofuran and H-2 of pyrrolidine), 3.75 (1H, m, H-4 of tetrahydrofuran), 3.62 (1H, m, H-5a of tetrahydrofuran), 3.53 (1H, m, H-5b of tetrahydrofuran), 3.28 (2H, H-5a and H-5b of pyrrolidine), 2.25–2.05 (3H, m, H-5a and H-5b of tetrahydrofuran and H-3a of pyrrolidine), 1.91–1.80 (3H, m, H-3b and H-4a and H-4b of pyrrolidine), 1.77 (3H, br s, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 174.9 (s, *C*OOH), 164.2 (s, C-4 of pyrimidine), 156.4 (s, NH*CO*–pyrrolidine), 150.9 (s, C-2 of pyrimidine), 136.8 (s, C-6 of pyrimidine), 109.8 (s, C-5 of pyrimidine), 86.0 (C-1 of tetrahydrofuran), 83.9 (C-4 of tetrahydrofuran), 61.8 (C-5 of tetrahydrofuran), 59.0 (s, C-2 of pyrrolidine), 50.7 (C-3 of tetrahydrofuran), 46.1 (s, C-5 of pyrrolidine), 37.8 (C-2 of tetrahydrofuran), 29.7 (s, C-3 of pyrrolidine), 24.5 (s, C-4 of pyrrolidine), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{16}H_{23}N_4O_7$, 383.1567; found, 383.1571.

### 4.22. 4-(1-Hydroxy-2-(1-methyl-3-phenylureido)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) (25)

Purified by crystallization from acetonitrile to give white crystals. Mp 206–208 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.40 (1H, s, OH), 7.44 (2.0H, d, $J$=7.9 Hz, H-2 and H-6 of phenyl), 7.33–7.19 (5.0H, m, H-3, H-4, H-5 of phenyl and H-3, H-6 of 1,2-phenylene), 6.93 (1H, t, $J$=7.2 Hz, H-5 of 1,2-phenylene), 5.93 (1H, s, NH), 4.88 (1H, m, phenylene–C*H*(OH)–$CH_2$), 3.46 (2H, d, $J$=5.7 Hz, $CH_2$), 2.92 (3H, s, NHCONC$H_3$), 1.29 (9H, s, ($CH_3$)$_3$C), 1.28 (9H, s, ($CH_3$)$_3$C). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 175.8 (s, COO), 175.7 (s, COO), 156.3 (s, NHCON), 142.9 (s, C-1 of 1,2-phenylene), 142.4 (s, C-2 of 1,2-phenylene), 141.6 (s, C-1 of phenyl), 141.0 (s, C-4 of 1,2-phenylene), 128.7 (s, C-3 and C-5 of phenyl), 124.5 (s, C-4 of phenyl), 123.6 (s, C-5 of 1,2-phenylene), 122.1 (s, C-6 of 1,2-phenylene), 121.4 (s, C-3 of 1,2-phenylene), 120.1 (s, C-2 and C-6 of phenyl), 71.1 (s, CHOH), 57.1 (s, $CH_2N$), 39.5 (s, ($CH_3$)$_3$*C*), 39.0 (s, ($CH_3$)$_3$*C*), 36.4 (s, $CH_3N$), 27.3 (s, 2×(*C*$H_3$)$_3$C). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{26}H_{35}N_2O_6$, 471.2495; found, 471.2485; [$(M+Na)^+$] calcd for $C_{26}H_{34}N_2O_6Na$, 493.2315; found, 493.2291.

### 4.23. Methyl (2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-ylcarbamate (26)

Purified by crystallization from acetonitrile to give white crystals. Mp 102–105 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.26 (1H, s, NH-3 of pyrimidine), 7.75 (1H, s, H-6 of pyrimidine), 7.57 (1H, d, $J$=6.9 Hz, NH–CO–N*H*–tetrahydrofuran), 6.14 (1H, t, $J$=6.4 Hz, H-1 of tetrahydrofuran), 5.05 (1H, t, $J$=5.1 Hz, of tetrahydrofuran), 4.12 (1H, m, H-3 of tetrahydrofuran), 3.77 (1H, m, H-4 of tetrahydrofuran), 3.64 (1H, m, H-5a of tetrahydrofuran), 3.54 (3H, s, $CH_3O$), 3.52 (1H, m, H-5b of tetrahydrofuran), 2.20 (1H, m, H-2a of tetrahydrofuran), 2.11 (1H, m, H-2b of tetrahydrofuran), 2.07 (3H, s, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 156.7 (s, NHCOO), 150.8 (s, C-2 of pyrimidine), 136.7 (s, C-6 of pyrimidine), 109.8 (s, C-5 of pyrimidine), 85.2 (s, C-1 of tetrahydrofuran), 83.9 (s, C-4 of tetrahydrofuran), 61.6 (s, C-5 of tetrahydrofuran), 51.9 (s, $CH_3O$), 51.0 (s, C-3 of tetrahydrofuran), 37.7 (s, C-2 of tetrahydrofuran), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{12}H_{18}N_3O_6$, 300.1195; found, 300.1206; [$(M+Na)^+$] calcd for $C_{12}H_{17}N_3O_6Na$, 322.1015; found, 322.1017.

### 4.24. 5-((Bis(4-methoxyphenyl)(phenyl)methoxy) methyl) oxazolidin-2-one (27)

Purified by flash reverse phase column chromatography to give pale yellow oil. $^1$H NMR (500 MHz, $CD_3CN$): $\delta$ 7.50–7.20 (9H, m, H-2, H-3, H-4, H-5, H-6 of phenyl and 2×H-2, 2×H-6 of 4-methoxyphenyl), 6.85 (4H, m, 2×H-3, 2×H-5 of 4-methoxyphenyl), 5.66 (1H, br s, NH), 4.70 (1H, m, H-5 of oxazolidin-2-one), 3.79 (6H, s, 2×$CH_3O$), 3.53 (1H, t, $J$=8.8 Hz, OC*H*a*H*b-oxazolidin-2-one), 3.29 (2H, m, OCHa*Hb*-oxazolidin-2-one and H-4a of oxazolidin-2-one), 3.14 (1H, dd, $J$=4.9 Hz and $J$=10.5 Hz, H-4b of oxazolidin-2-one). $^{13}$C NMR (125 MHz, $CH_3CN$): $\delta$ 159.1 (s, NHCOO), 158.7 (s, 2×C-4 of 4-methoxyphenyl), 145.0 (s, C-1 of phenyl), 135.8 (s, 2×C-1 of 4-methoxyphenyl), 130.0 (s, 2×C-2 and 2×C-6 of 4-methoxyphenyl), 128.0 (s, C-3 and C-5 of phenyl), 127.9 (s, C-2 and C-6 of phenyl), 126.9 (s, C-4 of 4-methoxyphenyl), 113.12 (s, 2×C-3 and 2×C-5 of 4-methoxyphenyl), 85.9 (s, ($CH_3OC_6H_4$)$_2$$C_6H_5$*C*), 75.1 (s, C-5 of oxazolidin-2-one), 64.4 (s, O*C*$H_2$-oxazolidin-2-one), 54.9 (s, 2×$CH_3O$), 41.9 (s, C-3 of oxazolidin-2-one). HRMS ESI ($m/z$): [$(M+Na)^+$] calcd for $C_{25}H_{25}NO_5Na$, 442.1630; found, 442.1617; [$(M+K)^+$] calcd for $C_{25}H_{25}NO_5K$, 458.1370; found, 458.1355.

### 4.25. Phenyl (2*S*,3*S*,5*R*)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-ylcarbamate (29)

Purified crystallization from dichloromethane–acetonitrile, 9:1 to give white crystals. Mp 194–197 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.30 (1H, s, NH-3 of pyrimidine), 8.23 (1H, d, $J$=7.5 Hz, OCON*H*–tetrahydrofuran), 7.78 (1H, s, H-5 of pyrimidine), 7.42–7.10 (4.2H, m, *O-phenyl*), 6.21 (1H, t, $J$=6.6 Hz, H-1 of tetrahydrofuran), 5.12 (1H, t, $J$=5.1 Hz H-3 of tetrahydrofuran), 4.20 (0.9H, m, OH), 3.88 (1H, m, H-4 of tetrahydrofuran), 3.68 (1H, m, H-5a of tetrahydrofuran), 3.60 (1H, d, H-5b of tetrahydrofuran), 2.28 (2H, m, H-2a,b of tetrahydrofuran), 1.78 (3H, s, $CH_3$). $^{13}$C NMR

(125 MHz, DMSO-$d_6$): $\delta$ 164.2 (s, C-4 of pyrimidine), 154.4 (s, NHCOO), 151.4 (s, C-1 of *O-phenyl*), 150.9 (s, C-2 of pyrimidine), 136.7 (s, C-6 of pyrimidine), 129.7 (s, C-3 and C-5 of *O-phenyl*), 125.5 (s, C-4 of *O-phenyl*), 122.2 (s, C-2 and C-6 of *O-phenyl*), 109.9 (s, C-5 of pyrimidine), 85.1 (s, C-1 of tetrahydrofuran), 83.9 (s, C-4 of tetrahydrofuran), 61.7 (s, C-5 of tetrahydrofuran), 51.4 (s, C-3 of tetrahydrofuran), 37.6 (s, C-2 of tetrahydrofuran), 12.7 (s, $CH_3$). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{17}H_{20}N_3O_6$, 362.1352; found, 362.1335.

### 4.26. 1-((2*S*,3*S*,5*R*)-2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-3-phenylurea (31)

Purified by crystallization from acetonitrile to give white crystals. Mp 218–221 °C. $^1$H NMR (500 MHz, $CD_3CN$–DMSO-$d_6$, 4:1): $\delta$ 10.74 (1H, s, NH-3 of pyrimidine), 8.15 (1H, s, NHCON*H*–phenyl), 7.72 (1H, d, $J$=0.9 Hz, H-5 of pyrimidine), 7.40 (2H, m, H-2, H-6 of phenyl), 7.24 (2H, m, H-3, H-5 of phenyl), 6.94 (1H, m, H-4 of phenyl), 6.44 (1H, d, $J$=7.2 Hz, NHCON*H*$CH_2$–phenyl), 6.21 (1H, t, $J$=6.2 Hz, H-1 of tetrahydrofuran), 4.59 (1H, m, 5-OH of tetrahydrofuran), 4.34 (1H, m, H-3 of tetrahydrofuran), 3.82 (1H, m, H-4 of tetrahydrofuran), 3.76 (1H, m, H-5a of tetrahydrofuran), 3.68 (1H, m, H-5b of tetrahydrofuran), 2.30 (1H, m, H-2a of tetrahydrofuran), 2.22 (1H, m, H-2b of tetrahydrofuran), 1.83 (3H, d, $J$=0.9 Hz, $CH_3$). $^{13}$C NMR (125 MHz, $CD_3CN$–DMSO-$d_6$, 4:1): $\delta$ 164.2 (s, C-4 of pyrimidine), 155.5 (s, NH*C*ONH$C_6H_5$), 150.9 (s, C-2 of pyrimidine), 140.3 (s, C-1 of phenyl), 136.1 (s, C-6 of pyrimidine), 128.8 (s, C-3 and C-5 of phenyl), 121.7 (s, C-4 of phenyl), 118.3 (s, C-2 and C-6 of phenyl), 110.0 (s, C-5 of pyrimidine), 85.8 (s, C-1 of tetrahydrofuran), 83.9 (s, C-4 of tetrahydrofuran), 61.4 (s, C-5 of tetrahydrofuran), 49.7 (s, C-3 of tetrahydrofuran), 37.9 (s, C-2 of tetrahydrofuran), 11.9 (s, $CH_3$). HRMS ESI ($m/z$): [$(M+H)^+$] calcd for $C_{17}H_{21}N_4O_5$, 361.1512; found, 361.1505.

## Acknowledgements

Financial support by the Finnish Funding Agency for Technology and Innovation (TEKES), Metkinen Chemistry (www.metkinen-chemistry.com) and University of Eastern Finland is gratefully acknowledged. We thank Prof. Jouko Vepsäläinen for fruitful discussions and Dr. Ewen Macdonald and Dr. James Callaway for reading the manuscript.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.017.

## References and notes

1. Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 249–261.
2. Gurulingappa, H.; Amador, M. L.; Zhao, M.; Rudek, M. A.; Hidalgo, M.; Khan, S. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2213–2216.
3. Monneret, C.; Risse, R.; Ardouin, P.; Gouyette, A. *Eur. J. Med. Chem.* **2000**, *35*, 137–146.
4. Dominguez, J. N.; Caritza, L.; Rodrigues, J.; Gamboa de Dominguez, N.; Gut, J.; Rosenthal, P. J. L. *Med. Chem.* **2005**, *48*, 3654–3658.
5. Oikonomakos, N. G.; Kosmopoulou, M.; Zographos, S. E.; Leonidas, D. D.; Chrysina, E. D. .; Somsak, L.; Nagy, V.; Praly, J.-P.; Docsa, T.; Toth, B.; Gergely, P. *Eur. J. Biochem.* **2002**, *269*, 1684–1696.
6. Somsak, L.; Nagy, V.; Hadaly, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189.
7. Matsuda, K. *Med. Res. Rev.* **1994**, *14*, 271–305.
8. Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shich, H. S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288–291.
9. Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140–148.
10. Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. I. *Org. Chem.* **1992**, *57*, 7364–7366.
11. Bennet, R. P.; Hardy, W. B. *J. Am. Chem. Soc.* **1968**, *90*, 3295–3296.
12. Collman, J. P.; Kubota, M.; Hoskins, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 4809–4811.
13. Collman, J. P.; Kubota, M.; Vastine, F. D.; Sun, J. Y.; Kang, J. W. *J. Am. Chem. Soc.* **1968**, *90*, 5430–5434.
14. La Monica, G.; Genini, S. *J. Organomet. Chem.* **1981**, *216*, C35–C37.
15. La Monica, G.; Ardizzoia, G.; Maddinelli, G.; Tollari, S. *J. Mol. Catal.* **1986**, *38*, 327–330.
16. Doi, H.; Barletta, J.; Suzuki, M.; Noyori, R.; Watanabe, Y.; Långström, B. *Org. Biomol. Chem.* **2004**, *2*, 3063–3066.
17. Langstrom, B.; Barletta, J.; Doi, H.; Suzuki, M.; Noyori, R.; Watanabe, Y.; Karimi, F. Int. Patent. Appl. WO 2005/061445, 2005.
18. Molina, P.; Alajarin, M.; Arques, A. *Synthesis* **1982**, 596–597.
19. Kovacs, J.; Pinter, I.; Messmer, A.; Toth, G. *Carbohydr. Res.* **1985**, *141*, 57–65.
20. Kovacs, J.; Pinter, I.; Toth, G.; Györgydeak, Z.; Köll, P. *Carbohydr. Res.* **1993**, *239*, 95–106.
21. Sallas, F.; Marsura, A.; Petot, V.; Pinter, I.; Kovacs, J.; Jicsinszky, L. *Helv. Chim. Acta* **1998**, *81*, 632–645.
22. Porwanski, S.; Kryczka, B.; Marsura, A. *Tetrahedron Lett.* **2002**, *43*, 8441–8443.
23. Menuel, S.; Wagner, M.; Barth, D.; Marsura, A. *Tetrahedron Lett.* **2005**, *46*, 3307–3309.
24. Yagodkin, A.; Azhayev, A.; Roivainen, J.; Antopolsky, M.; Kayushin, A.; Korosteleva, M.; Miroshnikov, A.; Randolph, J.; Mackie, H. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 473–497.
25. Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861–886.
26. Yagodkin, A.; Azhayev, A. U.S. Patent Appl. 60/854,721, 2007; Int. Patent. Appl. WO 2008/049972, 2008.
27. Atkinson, T.; Smith, M. In *Oligonucleotide Synthesis. A Practical Approach*; Gait, M. J., Ed.; IRL: Oxford, 1984; pp 35–38.
28. Azhayev, A.; Antopolsky, M.; Tennilä, T.; Mackie, H.; Randolph, J. *Genet. Eng. News* **2005**, *25*, 54–57.