

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/261325493>

Bis(2,2,2-trifluoroethyl) Carbonate as a Condensing Agent in One-Pot Parallel Synthesis of Unsymmetrical Aliphatic Ureas

ARTICLE · APRIL 2014

DOI: 10.1021/co500025f · Source: PubMed

CITATIONS

3

READS

69

8 AUTHORS, INCLUDING:



[Pavel Mykhailiuk](#)

National Taras Shevchenko University of Kyiv

100 PUBLICATIONS 639 CITATIONS

SEE PROFILE

Bis(2,2,2-trifluoroethyl) Carbonate as a Condensing Agent in One-Pot Parallel Synthesis of Unsymmetrical Aliphatic Ureas

Andrey V. Bogolubsky,[†] Yurii S. Moroz,^{*,†,‡} Pavel K. Mykhailiuk,^{*,†,§} Dmitry S. Granat,^{†,§} Sergey E. Pipko,[‡] Anzhelika I. Konovets,^{†,||} Roman Doroschuk,[§] and Andrey Tolmachev^{†,‡}

[†]Enamine Ltd., 23 Matrosova Street, Kyiv, 01103, Ukraine

[‡]ChemBioCenter, Kyiv National Taras Shevchenko University, 61 Chervonotkatska Street, Kyiv, 02094, Ukraine

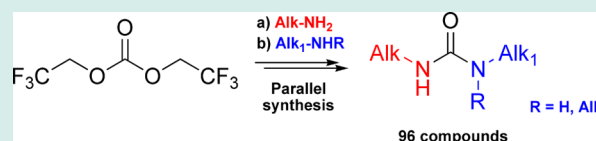
[§]Department of Chemistry, Kyiv National Taras Shevchenko University, 64 Volodymyrska Street, Kyiv, 01601, Ukraine

^{||}The Institute of High Technologies, Kyiv National Taras Shevchenko University, 4 Glushkov Street, Building 5, Kyiv, 03187, Ukraine

S Supporting Information

ABSTRACT: One-pot parallel synthesis of unsymmetrical aliphatic ureas was achieved with bis(2,2,2-trifluoroethyl) carbonate. The procedure worked well for both the monosubstituted and functionalized alkyl amines and required no special conditions (temperature control, order, or rate of addition). A library of 96 diverse ureas was easily synthesized.

KEYWORDS: bis(2,2,2-trifluoroethyl)carbonate, functionalized amines, unsymmetrical aliphatic ureas, one-pot approach, parallel synthesis



INTRODUCTION

Compounds with a motif of urea have found wide application in organic, combinatorial, and medicinal chemistry, organo-catalysis, and material science.^{1,2} Many drugs (e.g., cariprazine, hetrazan, sorafenib) and agrochemicals (e.g., cumyluron, cycluron, tebuthiuron) contain the fragment of urea (Figure 1). Our ongoing research on the urea-based bioactive molecules focuses on the aliphatic compounds, $\text{Alk}-\text{N}(\text{R})-\text{C}(\text{O})-\text{N}(\text{R}_1)-\text{Alk}_1$ ($\text{R}, \text{R}_1 = \text{H}, \text{Alk}$); the saturated carbon atoms provide more flexibility to the molecule allowing to effectively explore a chemical space in three dimensions and reduce the negative effects of the flat “aromatic” fragments (e.g., increasing solubility, decreasing toxicity).^{3–9}

To generate a library of the $\text{Alk}-\text{N}(\text{R})-\text{C}(\text{O})-\text{N}(\text{R}_1)-\text{Alk}_1$ ureas, we chose a parallel synthesis, which allows for preparing large sets of organic compounds. We then examined existing synthetic approaches looking for an optimal, cost- and time-effective method, that would account for the following requirements to parallel synthesis: (a) one-pot procedure with an easy purification protocol; (b) moisture stable starting reagents, which would allow creating highly diverse sets of compounds; and (c) addition of all components concurrently and without temperature control. These criteria made most reported approaches inapplicable for the parallel synthesis: phosgene,^{11,12} triphosgene^{13,14} are toxic reagents; gases CO_2 ,¹⁵ H_2 ,¹⁶ are inconvenient in handling; many isocyanates^{17,18} and carbamates^{19,20} are commercially unavailable; highly active 1,1'-carbonyldiimidazole^{21,22} and chloroformates^{23–26} need special care to prevent formation of the side products (symmetrical ureas in case of highly nucleophilic alkyl amines or chlorinated compounds in case of functionalized amines, e.g., amino

alcohols). We therefore focused on the methods utilizing carbonates, for example, diethyl carbonate, bis(phenyl) carbonate and bis(*p*-nitrophenyl) carbonate.^{27–30} The typical two-step procedure includes the interaction of a carbonate with the first amine forming a carbamate, which further reacts with the second amine to form the urea (Scheme 1). This method allows for the synthesis of the trisubstituted $\text{Alk}-\text{N}(\text{H})-\text{C}(\text{O})-\text{N}(\text{R})-\text{Alk}_1$ ureas because an *N,N*-disubstituted carbamate is not capable of forming the required intermediate.^{23,30}

Initial experiments showed that nonactivated diethyl carbonate had low reactivity. On the other hand, highly reactive bis(phenyl) carbonate and bis(*p*-nitrophenyl) carbonate required dropwise addition and temperature control to prevent formation of symmetrical ureas. These drawbacks violated the requirements specified above, thus limiting the application of these carbonates in the parallel synthesis.

De Aguirre and Collot¹⁸ previously reported that the rate of urea formation from the carbamate depends on the pK_a value of the corresponding alcohol, for example, *p*-nitrophenol ($\text{pK}_a \approx 7$) > phenol ($\text{pK}_a \approx 10$) > ethanol ($\text{pK}_a \approx 16$). Relying on this correlation, we proposed an alternative reagent, bis(2,2,2-trifluoroethyl) carbonate (**1**). The pK_a value of 2,2,2-trifluoroethanol is ~ 12 , which is between phenol and ethanol and provides moderate activity to reagent **1**. This feature makes bis(2,2,2-trifluoroethyl) carbonate a promising substitute to other carbonates helping to overcome the associated drawbacks. Herein, we demonstrate a successful application of

Received: February 19, 2014

Revised: March 27, 2014

Published: April 2, 2014



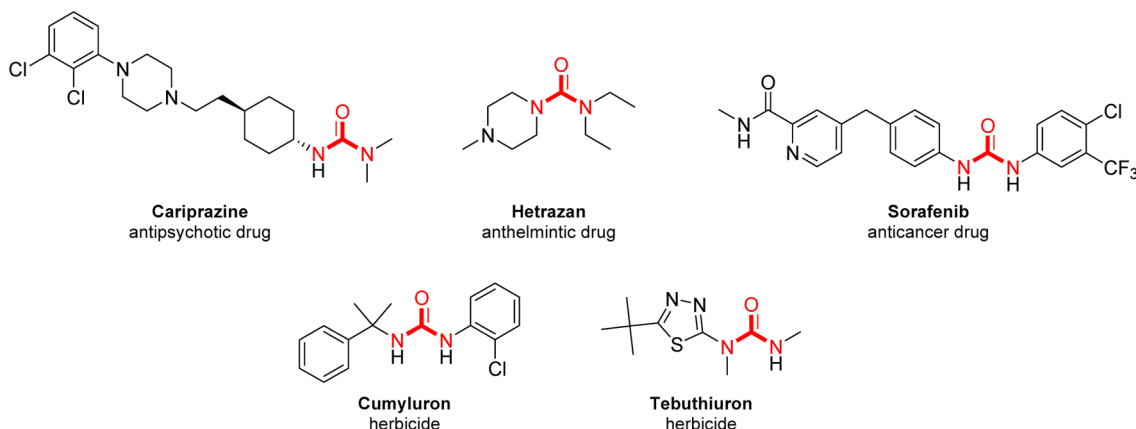
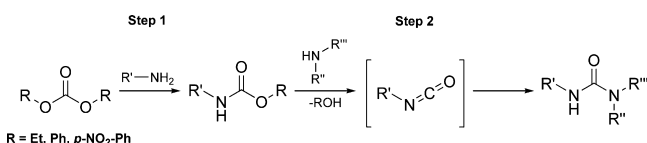


Figure 1. Drugs and agrochemicals bearing the motif of urea.¹⁰

Scheme 1. Preparation of Unsymmetrical Ureas Utilizing Carbonates

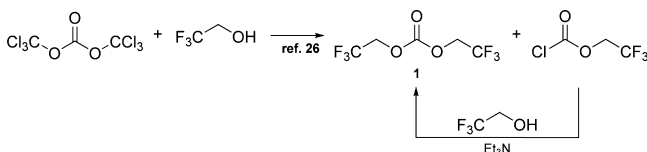


reagent **1** in the parallel synthesis of the unsymmetrical $\text{Alk-N(H)-C(O)-N(R)-Alk}_1$ ureas derived from mono and functionalized alkyl amines.

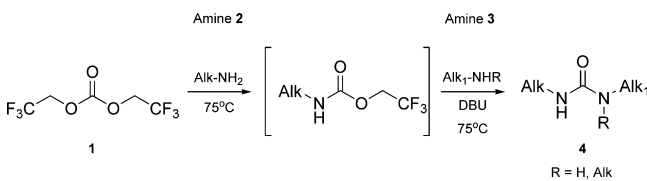
RESULTS AND DISCUSSION

Bis(2,2,2-trifluoroethyl) carbonate (**1**) is formed along with trifluoroethylchloroformate in approximately 1/3 ratio in the

Scheme 2. Synthesis of Bis(2,2,2-trifluoroethyl) Carbonate



Scheme 3. One-Pot Synthesis of Unsymmetrical Aliphatic Ureas



reaction between triphosgene and trifluoroethanol (Scheme 2).²⁶ The reagents can be easily separated by fractional distillation under atmospheric pressure. Trifluoroethylchloroformate can be converted to reagent **1** by the reaction with trifluoroethanol in the presence of triethylamine as a base.

To determine and optimize the conditions of parallel synthesis, we created a diverse library of ureas from primary and secondary alkyl amines out of our database. We arbitrary selected amines with variable structural motifs increasing diversity of the library (Tables S1 and S2, in the Supporting Information). While selecting amino substrates for the first step of the procedure (Scheme 3), we omitted the secondary

amines. Then, we conducted 96 parallel reactions [synthesis of a full combinatorial set (>2700) was beyond the scope of this work] in a one-pot two-step fashion.

Set-up of several experiments at the same time leads to errors associated with measuring quantities of starting reagents, reducing purity of the final product. To decrease effects of these errors, reagent **1** was added in an excess (1.5 equiv) to the amine. After completion of the reaction, the unreacted bis(2,2,2-trifluoroethyl) carbonate was distilled off under reduced pressure along with the solvent, while crude trifluoroethyl carbamate remained in the tube. We, however, found that volatile trifluoroethyl carbamates, derived from lower amines (methyl-, propyl-, allyl-, etc.), were partially removed along with the carbonate during the distillation, which led to decreasing the overall yield. To overcome this problem, the lower amines were introduced in the second step of the procedure.

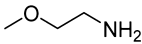
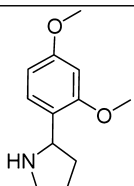
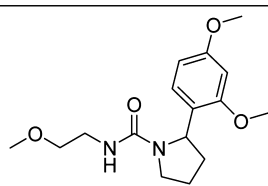
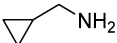
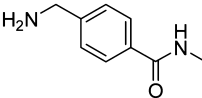
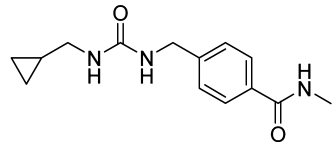
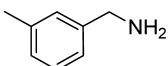

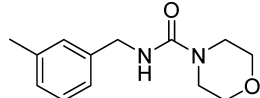
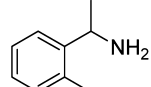
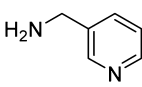
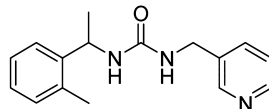
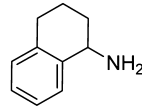
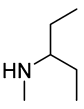
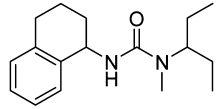
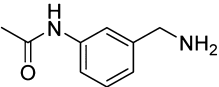
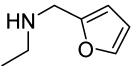
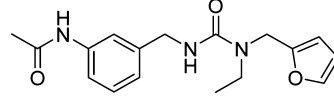
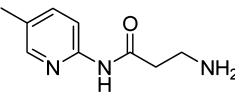

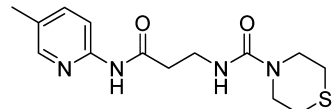
The reaction between the formed alkyl carbamate and the second amino component required a catalytic base (0.3 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) to proceed: the weaker acidity of the NH proton of the alkyl trifluoroethyl carbamates compared with the aryl derivatives prevents forming the isocyanate intermediates with the second amine by itself.²⁶

Second step involves extraction with CHCl_3 and solvent evaporation to afford the $\text{Alk-N(H)-C(O)-N(R)-Alk}_1$ ureas in moderate to high yields and high purity. Volatility of 2,2,2-trifluoroethanol results in removal along with the solvent, which is another advantage over the phenols. Additional purification by flash chromatography was performed only in 35% of the experiments. The impurities (in most cases unreacted amine **3**) were well separated from the product simplifying the purification (Figures S1–S30, in the Supporting Information). LC-MS analysis of the crude mixtures also confirmed the absence of the symmetrical ureas, which supported our suggestion on higher stability of trifluoroethyl carbamates compared with phenyl and *p*-nitrophenyl analogues.

The identities and purities of the synthesized $\text{Alk-N(H)-C(O)-N(R)-Alk}_1$ ureas were confirmed by ^1H and ^{13}C NMR spectroscopy and LC-MS analysis. The representative examples are shown in Tables 1 and 2, and the full list is given in Tables S1 and S2, in the Supporting Information.

The proposed approach allows synthesizing ureas from mono and functionalized amines bearing amino group (entries 1–4, in Table 2), hydroxyl (alkyl and aryl) (entries 5–14, in Table 2) groups, and pyrazole moieties (entries 15–20, in Table 2), which are commonly utilized in drug design due to

Table 1. Representative Examples of Ureas Derived from Monofunctional Amines 2

Entry	Amine 2	Amine 3	Urea 4	Yield ^a (%)
1				46
2				33
3				32
4				62
5				46
6				88
7				76

^aIsolated yield.

their ability to interact with a target protein through formation of H-bonds or other electrostatic contacts. The average yields were lower for the ureas synthesized from amino alcohols (entries 15–38, in Table S2, in the Supporting Information) and alkyl amino phenols (entries 39–55, in Table S2, in the Supporting Information) than those for other types of amines. The proposed method failed in the reactions where 2- or 3-amino alcohols were introduced as the first amino component, because of the formation of cyclic carbamates. Condensation of these alcohols with the trifluoroethyl carbamates in the second step resolved the issue, as well as showed a potency of preparing ureas derived from two functionalized amines (e.g., entries 6, 11, and 15, in Table 2). The average yields for the trisubstituted ureas were comparable to those for the disubstituted; therefore, the catalytic base was the main driving force in the second step of the reaction.

In conclusion, current study demonstrates the simple and effective one-pot parallel synthesis of unsymmetrical ureas with the Alk–N(H)–C(O)–N(R)–Alk₁ functionality (R = H, Alk). The procedure employs bis(2,2,2-trifluoroethyl) carbonate (1)

that smoothly reacts with alkyl amines, requires no special conditions (temperature control, order or rate of addition), and demonstrates high regioselectivity to form the trifluoroethyl carbamates, but not symmetrical ureas. The obtained carbamates can be further converted to ureas only in the presence of the catalytic base. The proposed approach easily gave the diverse library of unsymmetrical ureas derived from mono- and functionalized amines. Potential limitation of the approach: interaction of reagent 1 with lower amines or 2-, 3-amino alcohols, can be resolved by introducing these substrates in the second step. Understanding the potency of the urea-based compounds in combinatorial and medicinal chemistry, we believe that the reported herein procedure allows expanding variety of saturated compounds with the Alk–N(H)–C(O)–N(R)–Alk₁ functionality.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures, full list of the synthesized ureas, ¹H, ¹³C NMR, and LC-MS spectra for the selected

Table 2. Representative Examples of Ureas Derived from Amines 2 Bearing Additional Functionality

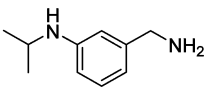
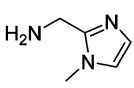
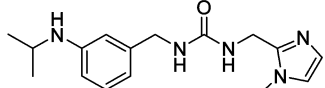
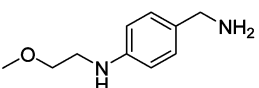
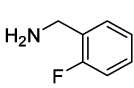
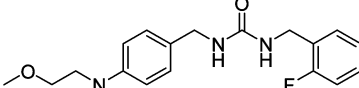
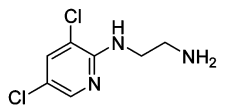

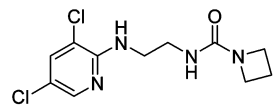
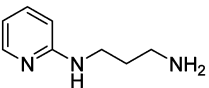
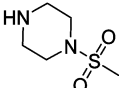
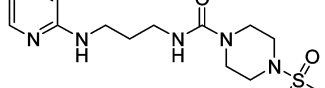
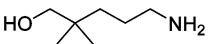
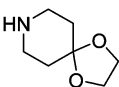
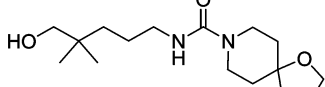
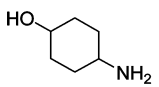
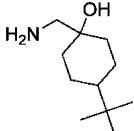
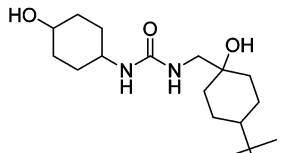
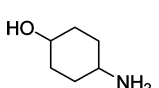
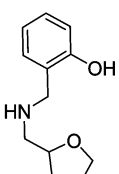
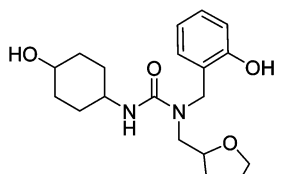
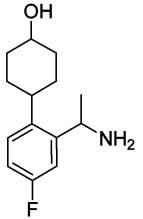
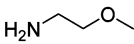
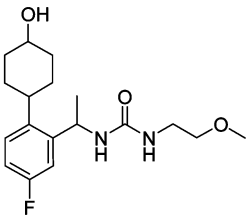
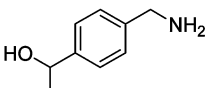
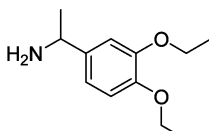
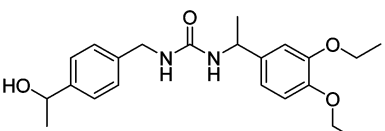
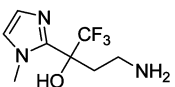

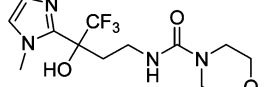
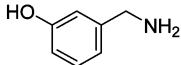
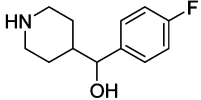
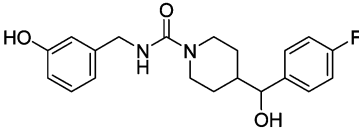
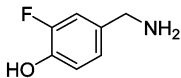
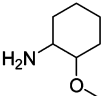
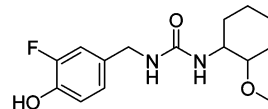
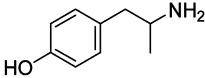
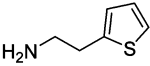
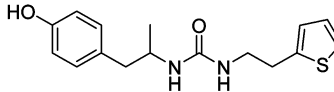
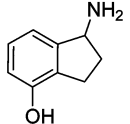
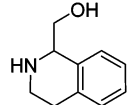
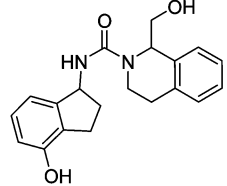
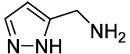
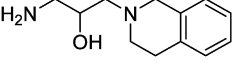
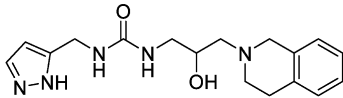
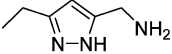
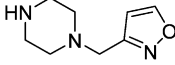
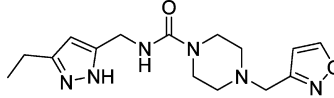
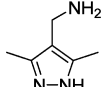
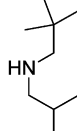
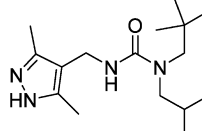
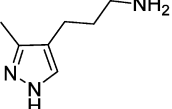
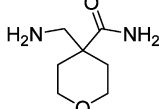
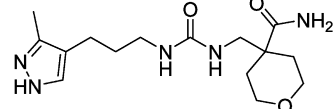
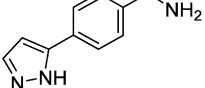
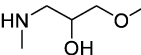
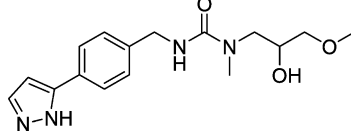
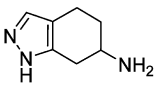
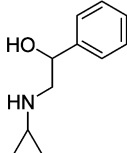
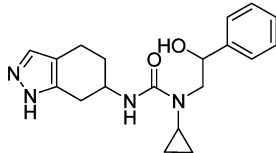
Entry	Amine 2	Amine 3	Urea 4	Yield ^a (%)
1				45
2				86
3				73
4				49
5				74
6				52
7				45
8				88
9				43
10				30

Table 2. continued

Entry	Amine 2	Amine 3	Urea 4	Yield ^a (%)
11				57
12				34
13				85
14				49
15				48
16				73
17				40
18				38
19				33
20				80

^aIsolated yield.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: ysmoroz@mail.enamine.net.

synthesized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

*E-mail: Pavel.Mykhailiuk@mail.enamine.net; Pavel.Mykhailiuk@gmail.com.

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. Substituted Ureas. Methods of Synthesis and Applications. *Russ. Chem. Rev.* **1985**, *54*, 249–261.
- (2) Gallou, I. Unsymmetrical Ureas. Synthetic Methodologies and Application in Drug Design. *Org. Prep. Proced. Int.* **2007**, *39*, 355–383.
- (3) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 46–58.
- (4) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756.
- (5) Ritchie, T. J.; Macdonald, S. J. F. The Impact of Aromatic Ring Count on Compound Developability—Are Too Many Aromatic Rings a Liability in Drug Design? *Drug Discovery Today* **2009**, *14*, 1011–1020.
- (6) Yang, Y.; Engkvist, O.; Llinàs, A.; Chen, H. Beyond Size, Ionization State, and Lipophilicity: Influence of Molecular Topology on Absorption, Distribution, Metabolism, Excretion, and Toxicity for Druglike Compounds. *J. Med. Chem.* **2012**, *55*, 3667–3677.
- (7) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. The Impact of Aromatic Ring Count on Compound Developability: Further Insights by Examining Carbo- and Hetero-Aromatic and -Aliphatic Ring Types. *Drug Discovery Today* **2011**, *16*, 164–171.
- (8) Morley, A. D.; Pugliese, A.; Birchall, K.; Bower, J.; Brennan, P.; Brown, N.; Chapman, T.; Drysdale, M.; Gilbert, I. H.; Hoelder, S.; et al. Fragment-Based Hit Identification: Thinking in 3D. *Drug Discovery Today* **2013**, *18*, 1221–1227.
- (9) Ishikawa, M.; Hashimoto, Y. Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry. *J. Med. Chem.* **2011**, *54*, 1539–1554.
- (10) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; et al. ChEMBL: A Large-Scale Bioactivity Database for Drug Discovery. *Nucleic Acids Res.* **2012**, *40*, D1100–D1107.
- (11) Gibson, F. S.; Park, M. S.; Rapoport, H. Bis[[4-(2,2-Dimethyl-1,3-Dioxolyl)methyl]-Carbodiimide (BDDC) and Its Application to Residue-Free Esterifications, Peptide Couplings, and Dehydrations. *J. Org. Chem.* **1994**, *59*, 7503–7507.
- (12) Mitchell, M. A.; Kelly, R. C.; Wicniewski, N. A.; Hatzenbuehler, N. T.; Williams, M. G.; Petzold, G. L.; Slightom, J. L.; Siemieniuk, D. R. Synthesis and DNA Crosslinking by a Rigid CPI Dimer. *J. Am. Chem. Soc.* **1991**, *113*, 8994–8995.
- (13) Maya, I.; López, Ó.; Maza, S.; Fernández-Bolaños, J. G.; Fuentes, J. A Facile Access to Ureido Sugars. Synthesis of Urea-Bridged B-Cyclodextrins. *Tetrahedron Lett.* **2003**, *44*, 8539–8543.
- (14) Sanna, V.; Pintus, G.; Roggio, A. M.; Punzoni, S.; Posadino, A. M.; Arca, A.; Marceddu, S.; Bandiera, P.; Uzzau, S.; Sechi, M. Targeted Biocompatible Nanoparticles for the Delivery of (–)-Epigallocatechin 3-Gallate to Prostate Cancer Cells. *J. Med. Chem.* **2011**, *54*, 1321–1332.
- (15) Peterson, S. L.; Stucka, S. M.; Dinsmore, C. J. Parallel Synthesis of Ureas and Carbamates From Amines and CO₂ under Mild Conditions. *Org. Lett.* **2010**, *12*, 1340–1343.
- (16) Mohy El Dine, T.; Chapron, S.; Duclos, M.-C.; Duguet, N.; Popowycz, F.; Lemaire, M. One-Pot, Solvent-Free Access to Unsymmetrical Ureas by Palladium-Catalysed Reductive Alkylation Using Molecular Hydrogen. *Eur. J. Org. Chem.* **2013**, *2013*, 5445–5454.
- (17) Gillies, E. R.; Fréchet, J. M. J. Synthesis and Self-Assembly of Supramolecular Dendritic “Bow-Ties”: Effect of Peripheral Functionality on Association Constants. *J. Org. Chem.* **2004**, *69*, 46–53.
- (18) De Aguirre, I.; Collot, J. Isocyanates Bloques: Etude Cinétique Et Thermodynamique. *Bull. Soc. Chim. Belges* **1989**, *98*, 19–30.
- (19) Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. Practical Synthesis of Unsymmetrical Ureas from Isopropenyl Carbamates. *J. Org. Chem.* **2005**, *70*, 6960–6963.
- (20) Ichikawa, Y.; Nishiyama, T.; Isobe, M. Stereospecific Synthesis of Urea-Tethered Neoglycoconjugates Starting from Glucopyranosyl Carbamates. *Tetrahedron* **2004**, *60*, 2621–2627.
- (21) Li, Z.; Nakagawa, O.; Koga, Y.; Taniguchi, Y.; Sasaki, S. Synthesis of New Derivatives of 8-oxoG-Clamp for Better Understanding the Recognition Mode and Improvement of Selective Affinity. *Bioorg. Med. Chem.* **2010**, *18*, 3992–3998.
- (22) Kaur, K.; Jain, M.; Khan, S. I.; Jacob, M. R.; Tekwani, B. L.; Singh, S.; Singh, P. P.; Jain, R. Synthesis, Antiprotazoal, Antimicrobial, B-Hematin Inhibition, Cytotoxicity and Methemoglobin (MetHb) Formation Activities of bis(8-Aminoquinolines). *Bioorg. Med. Chem.* **2011**, *19*, 197–210.
- (23) Azad, S.; Kumamoto, K.; Uegaki, K.; Ichikawa, Y.; Kotsuki, H. A New Practical Method for the Synthesis of Unsymmetrical Ureas via High-Pressure-Promoted Condensation of 2,2,2-Trichloroethyl Carbamates (Troc-Carbamates) with Amines. *Tetrahedron Lett.* **2006**, *47*, 587–590.
- (24) Agarkov, A.; Gilbertson, S. R. Preparation of a Library of Unsymmetrical Ureas Based on 8-Azabicyclo[3.2.1]octane Scaffold. *J. Comb. Chem.* **2008**, *10*, 655–657.
- (25) Kitteringham, J.; Shipton, M. R.; Voyle, M. A Simple Method for the Synthesis of Unsymmetrical Ureas. *Synth. Commun.* **2000**, *30*, 1937–1943.
- (26) Bogolubsky, A. V.; Ryabukhin, S. V.; Pipko, S. E.; Lukin, O.; Shivanyuk, A.; Mykytenko, D.; Tolmachev, A. A Facile Synthesis of Unsymmetrical Ureas. *Tetrahedron* **2011**, *67*, 3619–3623.
- (27) Souers, A. J.; Gao, J.; Wodka, D.; Judd, A. S.; Mulhern, M. M.; Napier, J. J.; Brune, M. E.; Bush, E. N.; Brodjan, S. J.; Dayton, B. D.; et al. Synthesis and Evaluation of Urea-Based Indazoles as Melanin-Concentrating Hormone Receptor 1 Antagonists for the Treatment of Obesity. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2752–2757.
- (28) Yoon, J.; Choi, H.; Lee, H. J.; Ryu, C. H.; Park, H.; Suh, Y.; Oh, U.; Jeong, Y. S.; Choi, J. K.; Park, Y.-H.; et al. Chain-Branched Acyclic Phenethylthiocarbamates as Vanilloid Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1549–1552.
- (29) Ballini, R.; Fiorini, D.; Maggi, R.; Righi, P.; Sartori, G.; Sartorio, R. TBD-Catalysed Solventless Synthesis of Symmetrically N,N'-Substituted Ureas from Primary Amines and Diethyl Carbonate. *Green Chem.* **2003**, *5*, 396–398.
- (30) Saliu, F.; Rindone, B. Organocatalyzed Synthesis of Ureas from Amines and Ethylene Carbonate. *Tetrahedron Lett.* **2010**, *51*, 6301–6304.