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A facile synthesis of unsymmetrical ureas

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ABSTRACT

A facile and versatile method for the synthesis of unsymmetrical ureas from readily available reagents is reported. In the first step trifluoroethylchloroformate is reacted with a stoichiometric amount of a primary amine to give an intermediate trifluoroethyl carbamate. The addition of a second amine (primary or secondary) to the trifluoroethyl carbamate furnishes corresponding unsymmetrical ureas in 75–85% yield. A simple workup procedure, the high yields obtained, and the purity of the isolated products are suitable for the parallel synthesis of combinatorial libraries of unsymmetrical ureas with high structural and functional diversity.

1. Introduction

The structural unit of substituted ureas is found in many natural compounds, biologically active molecules, dyes, corrosion inhibitors etc.[1,2] The conformational rigidity and unique hydrogen bonding properties of substituted ureas have been used in the design of highly sophisticated functional molecules, such as anion receptors,[3] self-assembling molecular capsules,[4] and catenanes.[5]

The urea structural unit has four points of diversity that can be used for generating large collections of organic compounds. Presently many synthetic methods are available for the preparation of di-, tri-, and tetrasubstituted unsymmetrical ureas.[2] The most general method for the synthesis of unsymmetric ureas involves the reaction of an isocyanate and an amine. The preparation of the isocyanate from the primary amine and bis(trichloromethyl)carbonate (BTC) and the reaction of the isocyanate with the second amine were successfully combined in a one-pot procedure.[6] However, the sensitivity of the reaction to traces of water and the functional group intolerance caused by the high reactivity of both BTC and the isocyanate put considerable limitations on the scope of the urea synthesis. Unsymmetrical ureas can also be prepared by the coupling of an alkyl[7] or aryl[8,9] carbamate with an amine. The method tolerates a variety of functional groups but suffers from laborious purification of the products from small amounts of symmetrical ureas that are often formed as byproducts. In addition, some alkyl carbamates are inert and can only react with metal amides. Another efficient approach to unsymmetrical ureas bearing three or four different substituents consists of dealkylation of benzyl-substituted tertiary amines by reaction with a stoichiometric amount of phosgene or BTC and the subsequent treatment of the intermediate carbamoyl chloride with primary or secondary amines.[10] This methodology affords unsymmetrical ureas in high yields and with no contamination by their symmetrical congeners. However, the use of phosgene or BTC in all above procedures has several drawbacks. These reagents are toxic and reactive and they were shown to react with some ureas to give various degradation products.[11]

Although there have been reports on the use of different phosgene surrogates[2] and alkyl carbonates[12] in the synthesis of unsymmetrical ureas, they have not received a widespread attention on account of their limited applicability to large-scale processes. Additionally, none of the reported methods could be reliably applied in parallel syntheses of sized combinatorial libraries for high throughput screening.[13] In this context the use of alternative reagents and the development of new synthetic routes to unsymmetrical ureas are necessary. In this contribution we report a facile and versatile method for the preparation of diverse di- and trisubstituted unsymmetrical ureas from trifluoroethyl carbamates.

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Thus far many of the syntheses of substituted ureas from alkyl carbamates reported suffer from limitations, such as insufficient reactivity of carbamates[14] used and laborious electrochemical approaches to generating trifluoroethyl carbamates.[15] Additionally, the latter carbamates underwent condensations with amines under harsh reaction conditions in the presence of sodium hydride limiting the scope of the reaction.

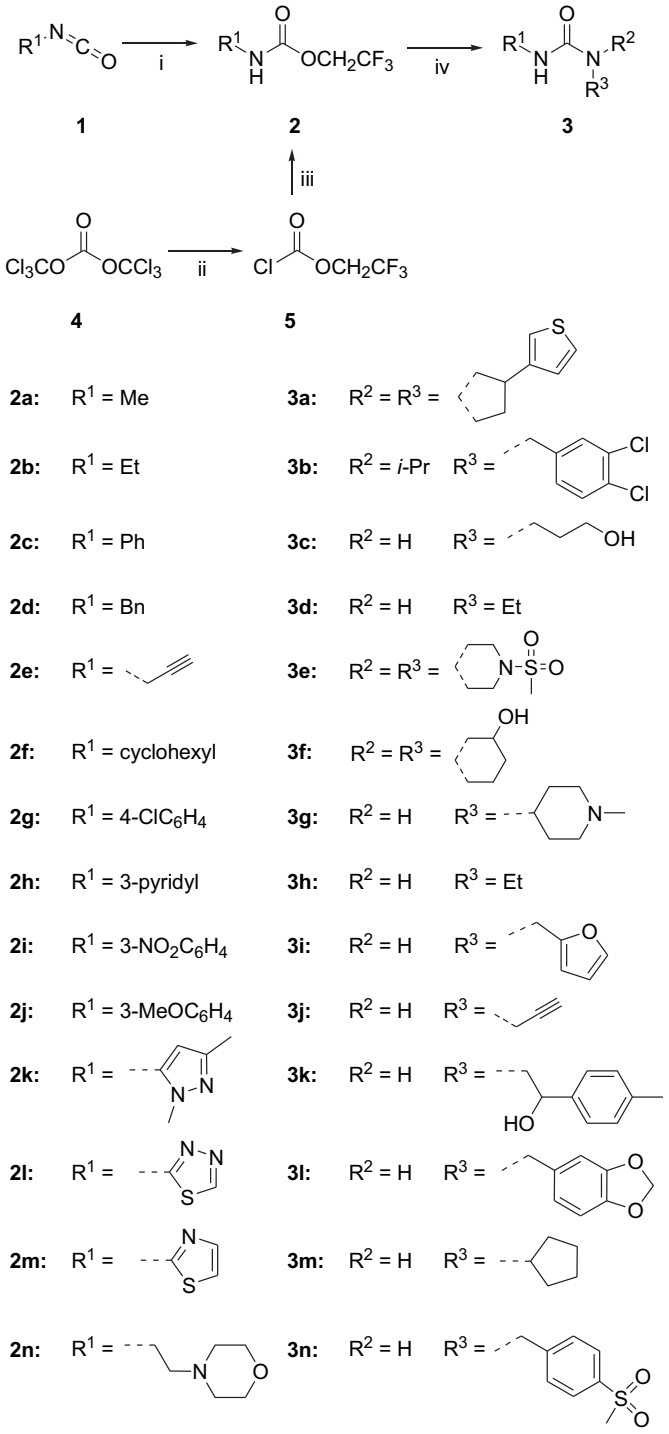
2. Results and discussion

On account of their moderate electrophilicity trifluoroethyl carbamates were considered as the most suitable reagents for the synthesis of unsymmetrical ureas. The reaction of isocyanates **1** with trifluoroethanol in toluene/hexane mixture in the presence of Et_3N as a base resulted in trifluoroethyl carbamates **2** (Scheme 1), which upon precipitation from the reaction mixture were purified by washing with hexane and drying under vacuum. The reaction of trifluoroethyl carbamates **2** with amines afforded unsymmetrical urea derivatives **3** in 75–85% isolated yields. In order to expand the scope of the synthesis of unsymmetrical urea derivatives a more versatile synthetic procedure was developed. The reaction of bis(trichloromethyl)carbonate (BTC) **4** with 3 equiv of trifluoroethanol in *o*-dichlorobenzene/Et_3N at 0–20 °C afforded trifluoromethylchlorocarbonate **5** in an 80% yield (Scheme 1). To our knowledge, this method for the preparation of **5** has not been published. Alternative routes to **5** involve insertion of carbon monoxide into trifluoroethyl hypochlorite[16] and cleavage of *O*-trifluoroethyl-*S*-ethyl carbonochloridothioate with sulfuryl chloride.[17] Applying our method compound **5** was synthesized in multigram quantities and purified by distillation. Simple purification, high yield, and the stability of compound **5** make it an optimal unsymmetrical phosgene surrogate for the synthesis of trifluoroethyl carbamates and hence unsymmetrical urea derivatives. Trifluoroethylchloroformate **5** readily reacted with both aliphatic and aromatic primary amines at ambient temperature in DMF/Et_3N to give trifluoroethyl carbamates **2** in nearly quantitative yields. The synthesized trifluoroethyl carbamates **2** were purified by simple recrystallization from 2-propanol. Notably, the reaction of trifluoroethylchloroformate with primary amines under mild conditions described above gave no symmetrical ureas apparently due to decreased reactivity of carbonyl groups of intermediates **2** compared to those of starting material **5**. The structure and purity of trifluoroethyl carbamates **2** obtained by both methods shown in Scheme 1 were confirmed by means of ^1H and ^{13}C NMR spectroscopy and LC/MS. The ^1H NMR spectra of compounds **2** recorded in DMSO-d_6 contain one singlet for the NH groups, one characteristic multiplet for the methylene protons of the trifluoroethyl groups, and one set of signals for the R^1 group.

The reaction of trifluoroethyl carbamates **2** with primary and secondary amines occurs in MeCN at elevated temperature (Scheme 1) to afford unsymmetrical urea derivatives **3** in 75–85% yields. Ureas **3** were purified through precipitation with water, filtering, washing with water/2-propanol mixture, and drying in vacuum at room temperature.

On the basis of the above results we developed a one-pot procedure for the synthesis of the unsymmetrically substituted ureas. The reaction of trifluoroethylchloroformate with 1 equiv of a primary amine R^1NH_2 in CH_3CN at room temperature gave trifluoroethyl carbamates **2**. A second amine was added in situ to the reaction mixture and the solution was heated at 100 °C in a pressure tube giving rise to the corresponding unsymmetrical urea.

The structure and purity of compounds **3** were confirmed by ^1H and ^{13}C NMR spectroscopy and LC/MS analysis. The ^1H NMR spectra of ureas **3** with R^2=H recorded in DMSO-d_6 contain two signals for the nonequivalent NH protons and characteristic signals for groups R^1 and R^3. The ^1H NMR spectra of trisubstituted ureas **3** show one signal for the NH protons and sets of signals for residues R^1, R^2, and R^3.



Scheme 1. The preparation of unsymmetrical ureas. Reagents and conditions: (i) trifluoroethanol, triethylamine, reflux, (ii) trifluoroethanol, triethylamine, rt, (iii) primary amine, stirring at rt, (iv) amine, 100 °C. The letter indices of compounds **2** and **3** are consistent, i.e., **3a** is prepared from **2a**.

3. Conclusions

The reaction of trifluoroethyl carbamates with primary and secondary amines provides a powerful method for the synthesis of various urea derivatives, which are useful as both synthetic intermediates and lead-like compounds for high throughput screening of biological activity. The balanced interplay of steric and electronic effects of both the carbamate unit and the trifluoroethoxy group seems to be responsible for the relatively high

stability of trifluoroethyl carbamates and their selective reactivity in the reactions with amines.

4. Experimental details

4.1. General

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer with TMS as an internal standard. Melting points were measured with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer Spectrum BX II (FT-IR). HPLC/MS analyses were performed on an Agilent 1100 LCMSD SL instrument (APCI mode). BTC, isocyanates, and amines were purchased from commercial sources and were used without further purification. Since characterization data for ureas **3c**,[18] **3d**,[19] and **3h**[20] are available from the literature only ^{1}H NMR spectra of these compounds were recorded to confirm their identity.

4.2. General procedure for the preparation of trifluoroethyl carbamates from isocyanate and trifluoroethanol

A solution of 0.3 mol of isocyanate, 0.32 mol trifluoroethanol, and 3 mL of triethylamine in 200 mL of a hexane/toluene mixture was heated to reflux for 4 h. Upon cooling to room temperature the precipitated product was filtered, washed with hexane, and dried under ambient conditions.

*4.2.1. Preparation of trifluoroethylchloroformate (**5**).* To a stirred suspension of 100 g (0.34 mol) of (tris)phosgene in 600 mL of *o*-dichlorobenzene, 100 g (1 mol) of trifluoroethanol, 2 mL of DMF, and 101 g (1 mol) of triethylamine were added at 0 °C. After 1 h of stirring the reaction mixture was allowed to warm to room temperature and the stirring continued for another 3 h. The reaction mixture was then distilled under atmospheric pressure and the fraction boiling below 130 °C was collected. This fraction was redistilled under atmospheric pressure affording 87 g of trifluoroethylchloroformate (bp 73 °C) and 23 g of bis(trifluoroethyl) carbonate (bp 118 °C).

4.3. General procedure for the preparation of trifluoroethyl carbamates (2) from amines and trifluoroethylchloroformate

To a stirred solution of 0.3 mol of an amine and 33.4 g (0.33 mol) of triethylamine in 150–200 mL of acetonitrile 50 g (0.3 mol) of trifluoroethylchloroformate was added dropwise. During the addition the temperature of the reaction mixture should be kept below 30 °C. Then the reaction mixture was stirred at room temperature for 1 h, diluted with water, and cooled to 0 °C. The precipitated product was filtered and recrystallized from 2-propanol. All compounds except **2a**, **b**, **d**, and **e** remained crystalline solids under ambient condition while the latter turned to oils upon reaching room temperature.

*4.3.1. Methylcarbamic acid 2,2,2-trifluoroethyl ester **2a**.* Colorless viscous oil (37 g, 76%), [Found: C, 30.34; H, 3.69; N, 8.90. $C_4H_6F_3NO_2$ requires C, 30.58; H, 3.85; N, 8.92%]; ν_{max} (KBr) 3333 (NH), 2982 (CH), 1707 (C=O), 1169, 1142 (CF), 1036 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.76 (d, 3H, $^3J_{H,H}$=6.5 Hz, CH_3), 4.49 (q, 2H, $^3J_{H,F}$=8.4 Hz, CH_2), 5.0 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 27.5, 60.8 (q, $^2J_{C,F}$=35 Hz), 123.1 (q, $^1J_{C,F}$=278 Hz), 15.3.

*4.3.2. Ethylcarbamic acid 2,2,2-trifluoroethyl ester **2b**.* Colorless viscous oil (46 g, 88%), [Found: C, 34.88; H, 4.83; N, 8.00. $C_5H_8F_3NO_2$ requires C, 35.09; H, 4.71; N, 8.19%]; ν_{max} (KBr) 3332 (NH), 2985, 2946, 2886 (CH), 1708 (C=O), 1164 (CF), 1049 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.00 (t, 3H, $^3J_{H,H}$=6.4 Hz), 2.91–3.19 (m, 2H, NCH_2), 4.53 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.65 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 14.9, 36.2, 60.7 (q, $^2J_{C,F}$=35 Hz), 123.2 (q, $^1J_{C,F}$=278 Hz), 154.4.

*4.3.3. Phenylcarbamic acid 2,2,2-trifluoroethyl ester **2c**.* Colorless solid (60 g, 90%), mp 71–73 °C; [Found: C, 49.17; H, 3.82; N, 6.26. $C_9H_8F_3NO_2$ requires C, 49.32; H, 3.68; N, 6.39%]; ν_{max} (KBr) 3326 (NH), 3068, 2972 (CH), 1716 (C=O), 1604 (C_{ar}H), 1162 (CF), 1099 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.55 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.05 (t, 1H, $^3J_{H,H}$=7.8 Hz, ArH), 7.28 (t, 2H, $^3J_{H,H}$=7.8 Hz, ArH), 7.43 (d, 2H, $^3J_{H,H}$=7.8 Hz, ArH), 10.08 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 60.4 (q, $^2J_{C,F}$=35 Hz), 119.0, 123.6, 124.2 (q, $^1J_{C,F}$=278 Hz), 129.3, 138.8, 152.2.

*4.3.4. Benzylcarbamic acid 2,2,2-trifluoroethyl ester **2d**.* Colorless viscous oil (58 g, 80%), [Found: C, 51.35; H, 4.54; N, 5.78. $C_{10}H_{10}F_3NO_2$ requires C, 51.51; H, 4.32; N, 6.01%]; ν_{max} (KBr) 3316 (NH), 2922, 2851 (CH), 1708 (C=O), 1161, 1148 (CF), 1054 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.24 (d, 2H, $^3J_{H,H}$=6.4 Hz, NCH_2), 4.51 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.20–7.35 (m, 5H, ArH), 8.07 (t, 1H, $^3J_{H,H}$=6.4 Hz, NH); δ_C (125 MHz, DMSO-d_6) 44.5, 60.3 (q, $^2J_{C,F}$=35 Hz), 124.3 (q, $^1J_{C,F}$=278 Hz), 127.4, 127.5, 128.8, 139.6, 155.2.

*4.3.5. Prop-2-ynylcarbamic acid 2,2,2-trifluoro-ethyl ester **2e**.* Colorless viscous oil (47 g, 84%), [Found: C, 39.72; H, 3.52; N, 7.49. $C_6H_6F_3NO_2$ requires C, 39.79; H, 3.34; N, 7.73%]; ν_{max} (KBr) 3314 (NH), 2977, 2938 (CH), 1708 (C=O), 1170 (CF), 1048 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.10 (s, 1H, CH), 3.76 (d, 2H, $^3J_{H,H}$=6.5 Hz, NCH_2), 4.55 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 8.1 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 31.0, 61.6 (q, $^2J_{C,F}$=35 Hz), 72.0, 78.9, 122.9 (q, $^1J_{C,F}$=278 Hz), 154.2.

*4.3.6. Cyclohexylcarbamic acid 2,2,2-trifluoroethyl ester **2f**.* Colorless solid (63 g, 92%), mp 80–81 °C; [Found: C, 47.96; H, 6.50; N, 6.14. $C_9H_{14}F_3NO_2$ requires C, 48.00; H, 6.27; N, 6.22%]; ν_{max} (KBr) 3321 (NH), 2938, 2922, 2856 (CH), 1699 (C=O), 1169 (CF), 1068 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.00–1.24 (m, 5H, CH_2 CY), 1.49–1.76 (m, 5H, CH_2 CY), 3.30 (m, 1H, NCH), 4.55 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.53 (d, 1H, $^3J_{H,H}$=6.4 Hz, NH); δ_C (125 MHz, DMSO-d_6) 25.0, 25.6, 32.9, 50.4, 59.9 (q, $^2J_{C,F}$=35 Hz), 124.3 (q, $^1J_{C,F}$=278 Hz), 153.9.

*4.3.7. 4-Chlorophenylcarbamic acid 2,2,2-trifluoroethyl ester **2g**.* Colorless solid (72 g, 93%), mp 72–74 °C; [Found: C, 42.43; H, 2.86; N, 5.31. $C_9H_7ClF_3NO_2$ requires C, 42.62; H, 2.78; N, 5.52%]; ν_{max} (KBr) 3304 (NH), 2923, 2851 (CH), 1702 (C=O), 1590, 1532 (C_{ar}H), 1161 (CF), 1091 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.77 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.20 (d, 2H, $^3J_{H,H}$=7.8 Hz, ArH), 7.52 (d, 2H, $^3J_{H,H}$=7.8 Hz, ArH), 10.3 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 60.5 (q, $^2J_{C,F}$=35 Hz), 124.1 (q, $^1J_{C,F}$=278 Hz), 120.5, 127.4, 129.2, 137.9, 152.1.

*4.3.8. Pyridin-3-ylcarbamic acid 2,2,2-trifluoro-ethyl ester **2h**.* Colorless solid (61 g, 89%), mp 75–77 °C; [Found: C, 43.50; H, 3.42; N, 12.77. $C_8H_7F_3N_2O_2$ requires C, 43.65; H, 3.20; N, 12.72]; ν_{max} (KBr) 3357 (NH), 1733 (C=O), 1618, 1593, 1564 (C_{ar}H), 1174, 1154 (CF), 1103 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.8 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.30–7.40 (m, 1H, ArH), 7.85–7.94 (m, 1H, ArH), 8.20–8.27 (m, 1H, ArH), 8.70 (s, 1H, ArH), 10.45 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 60.7 (q, $^2J_{C,F}$=35 Hz), 124.1 (q, $^1J_{C,F}$=278 Hz), 124.2, 125.9, 135.6, 140.84, 144.6, 152.3.

*4.3.9. 4-Nitrophenylcarbamic acid 2,2,2-trifluoroethyl ester **2i**.* Yellowish solid (77 g, 95%), mp 99–100 °C; [Found: C, 40.79; H, 2.82; N, 10.55. $C_9H_7F_3N_2O_4$ requires C, 40.92; H, 2.67; N, 10.60%]; ν_{max} (KBr) 3387 (NH), 3103 (C_{ar}H), 1737 (C=O), 1539 (NO_2), 1180, 1157 (CF), 1100

(C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.70 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.55 (t, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 7.75 (d, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 7.90 (d, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 8.49 (s, 1H, Ar*H*), 10.10 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 61.1 (q, $^2J_{C,F}$=35 Hz), 113.0, 118.1, 124.0 (q, $^1J_{C,F}$=278 Hz), 125.0, 130.8, 140.2, 148.6, 152.2.

4.3.10. 3-Methoxyphenylcarbamic acid 2,2,2-trifluoroethyl ester ***2j***. Colorless solid (69 g, 90%), mp 59–61 °C; [Found: C, 47.97; H, 4.15; N, 5.52. $C_{10}H_{10}F_3NO_3$ requires C, 48.20; H, 4.04; N, 5.62%]; ν_{max} (KBr) 3303 (NH), 2926 (CH), 1750 (C=O), 1612, 1555 (C_{ar}H), 1163, 1151 (CF), 1099, 1051 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.65 (s, 3H, OCH_3), 4.75 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 6.6 (d, 1H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 7.00 (d, 1H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.22 (t, 1H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 10.05 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 55.5, 60.4 (q, $^2J_{C,F}$=35 Hz), 105.0, 108.9, 111.3, 124.1 (q, $^1J_{C,F}$=278 Hz), 130.2, 140.0, 152.1, 160.2.

4.3.11. (2,5-Dimethyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trifluoroe thyl ester ***2k***. Colorless solid, mp 100–102 °C; [Found: C, 40.28; H, 4.33; N, 17.50. $C_8H_{10}F_3N_3O_2$ requires C, 40.51; H, 4.25; N, 17.72%]; ν_{max} (KBr) 3179 (NH), 2957, 2846 (CH), 1741 (C=O), 1568 (C_{ar}H), 1178, 1163 (CF), 1087 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.1 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 4.75 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 8.70 (s, 1H, Ar*H*), 10.05 (br s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 14.1, 35.4, 61.0 (q, $^2J_{C,F}$=35 Hz), 98.8, 124.0 (q, $^1J_{C,F}$=278 Hz), 136.5, 146.0, 152.6.

4.3.12. [1,3,4]Thiadiazol-2-yl-carbamic acid 2,2,2-trifluoroethyl ester ***2l***. Colorless solid (58 g, 84%), mp 217–218 °C; [Found: C, 26.22; H, 1.84; N, 18.28. $C_5H_4F_3N_3O_2S$ requires C, 26.44; H, 1.77; N, 18.50%]; ν_{max} (KBr) 3170 (NH), 2929 (CH), 1744 (C=O), 1172, 1153 (CF), 1107 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.99 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 9.20 (s, 1H, Ar*H*), 12.8 (br s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 61.8 (q, $^2J_{C,F}$=35 Hz), 123.5 (q, $^1J_{C,F}$=278 Hz), 149.5, 153.5, 161.5.

4.3.13. Thiazol-2-yl-carbamic acid 2,2,2-trifluoro-ethyl ester ***2m***. Colorless solid (60 g, 87%), mp 172–173 °C; [Found: C, 31.60; H, 2.37; N, 12.26. $C_5H_5F_3N_2O_2S$ requires C, 31.86; H, 2.23; N, 12.39%]; ν_{max} (KBr) 3225 (NH), 2925 (CH), 1727 (C=O), 1164, 1148 (CF), 1098 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.90 (q, 2H, $^3J_{H,F}$=8.4 Hz, OCH_2), 7.25 (d, 1H, $^3J_{H,H}$=2.3 Hz, Ar*H*), 7.41 (d, 1H, $^3J_{H,H}$=2.3 Hz, Ar*H*), 12.10 (br s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 61.3 (q, $^2J_{C,F}$=35 Hz), 114.2, 124.1 (q, $^1J_{C,F}$=278 Hz), 138.1, 153.2, 160.2.

4.3.14. (2-Morpholin-4-yl-ethyl)-carbamic acid 2,2,2-trifluoroethyl ester ***2n***. Colorless solid (64 g, 81%), mp 42–44 °C; [Found: C, 41.99; H, 6.03; N, 10.70. $C_9H_{15}F_3N_2O_3$: C, 42.19; H, 5.90; N, 10.93%]; ν_{max} (KBr) 3200 (NH), 2972, 2951 (CH), 1730 (C=O), 1162, 1143 (CF), 1116 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.26–2.44 (m, 6H, N(CH_2)$_3$), 3.15 (q, 2H, $^3J_{H,H}$=6.4 Hz, HNCH_2), 3.50–3.61 (m, 4H, O(CH_2)$_2$), 4.55 (q, 2H, $^3J_{H,F}$=8.4 Hz, CF$_3$CH_2), 7.55 (br s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 38.2, 53.7, 57.8, 60.1 (q, $^2J_{C,F}$=35 Hz), 66.6, 124.2 (q, $^1J_{C,F}$=278 Hz), 154.8.

4.3.15. General procedure for the preparation of unsymmetrical ureas. To a solution of 2 mmol of a trifluoroethyl carbamate and 2 mmol of an amine in 2 mL of acetonitrile, 0.2 mmol of DBU (in case of aliphatic trifluoroethyl carbamates) was added. The reaction mixture was heated in a pressure tube at 100 °C for 4 h. Then 0.5–2 mL of water was added to the hot reaction mixture. The product precipitated from the solution upon cooling to room temperature. The precipitate was filtered, washed with a 1:1 water/2-propanol solution (1–2 mL), and dried under ambient conditions.

4.3.16. 3-Thiophen-3-yl-pyrrolidine-1-carboxylic acid methylamide ***3a***. Colorless solid (357 mg, 85%), mp 142–143 °C; [Found: C, 56.92; H, 6.84; N, 13.16. $C_{10}H_{14}N_2OS$ requires C, 57.11; H, 6.71; N, 13.32]; ν_{max} (KBr) 3358 (NH), 3108, 2971, 2937, 2875 (CH), 1618 (C=O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.78–1.85 (m, 2H, CH_2(Pyr)), 1.85–1.89 (m, 1H, C*H*(Pyr)), 2.00–2.10 (m, 1H, C*H*(Pyr)), 2.55 (d, 3H, $^3J_{H,H}$=4.0 Hz, NCH_3), 3.08–3.13 (m, 2H, NCH_2(Pyr)), 3.45–3.48 (m, 1H, NC*H*(Pyr)), 5.90 (br s, 1H, N*H*), 6.97 (d, 1H, $^3J_{H,H}$=4.8 Hz, Ar*H*), 7.13–7.16 (m, 1H, Ar*H*), 7.43–7.46 (m, 1H, Ar*H*); δ_C (125 MHz, DMSO-d_6) 23.8, 27.4, 33.8, 46.3, 56.5, 120.3, 126.3, 127.0, 146.7, 157.4.

4.3.17. 1-(3,4-Dichlorobenzyl)-3-ethyl-1-isopropyl-urea ***3b***. Colorless solid (462 mg, 80%), mp 92–94 °C; [Found: C, 53.74; H, 6.45; N, 9.53. $C_{13}H_{18}Cl_2N_2O$ requires C, 53.99; H, 6.27; N, 9.69%]; ν_{max} (KBr) 3356 (NH), 2970, 2932, 2871 (CH), 1624 (C=O), 766 (CCl) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.99–1.01 (m, 9H, 3CH_3), 3.06 (q, 2H, $^3J_{H,H}$=6.6 Hz, CH$_3$CH_2), 4.25–4.28 (m, 1H, (CH$_3$)$_2$C*H*), 4.35 (s, 2H, ArCH_2), 6.35 (br s, 1H, N*H*), 7.20 (d, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 7.44 (s, 1H, Ar*H*), 7.57 (d, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 16.1, 21.2, 35.5, 43.3, 46.3, 127.4, 129.1, 130.7, 131.1, 143.3, 157.9, 208.9.

4.3.18. 1-(3-Hydroxy-propyl)-3-phenyl-urea ***3c***. Colorless solid (322 mg, 83%), mp 111–113 °C; published mp 110–111 °C.[18]

4.3.19. 1-Benzyl-3-ethyl-urea ***3d***. Colorless solid (306 mg, 86%), mp 96–98 °C; published mp 97–98 °C.[19]

4.3.20. 4-Methanesulfonylpiperazine-1-carboxylic acid prop-2-ynylamide ***3e***. Colorless solid (378 mg, 77%), mp 89–90 °C; [Found: C, 43.88; H, 6.37; N, 17.02. $C_9H_{15}N_3O_3S$ requires C, 44.07; H, 6.16; N, 17.13%]; ν_{max} (KBr) 3321 (NH), 2959, 2926, 2854 (CH), 1639 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.60 (s, 1H, CC*H*), 2.77 (s, 3H, SCH_3), 3.08–3.12 (m, 4H, Sn(CH_2)$_2$), 3.49 (m, 4H, N(CH_2)$_2$), 3.80 (s, 2H, HNCH_2), 7.00 (br s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 30.1, 34.5, 43.5, 45.7, 72.9, 83.0, 157.0.

4.3.21. 3-Hydroxypiperidine-1-carboxylic acid cyclohexylamide ***3f***. Colorless solid (340 mg, 75%), mp 74–76 °C; [Found: C, 63.57; H, 9.94; N, 12.32. $C_{12}H_{22}N_2O_2$ requires C, 63.68; H, 9.80; N, 12.38%]; ν_{max} (KBr) 3342 (OH), 3276 (NH), 2936, 2851 (CH), 1613 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.02–1.38 (m, 7H, C_{alk}*H*), 1.52–1.75 (m, 7H, C_{alk}*H*), 2.48–2.51 (m, 1H, C_{alk}*H*), 2.30–2.33 (m, 1H, C_{alk}*H*), 3.43–3.46 (m, 2H, NCH_2), 3.58–3.61 (m, 1H, C_{alk}*H*), 3.68–3.73 (m, 1H, C_{alk}*H*), 4.51 (d, 1H, $^3J_{H,H}$=4.6 Hz, O*H*), 5.75 (d, 1H, $^3J_{H,H}$=5.1 Hz, N*H*); δ_C (125 MHz, DMSO-d_6) 23.6, 25.6, 25.9, 33.6, 33.9, 44.0, 49.6, 51.4, 65.8, 157.2.

4.3.22. 1-(4-Chlorophenyl)-3-(1-methylpiperidin-4-yl)-urea ***3g***. Colorless solid (460 mg, 86%), mp 154–155 °C; [Found: C, 58.23; H, 6.90; N, 15.64. $C_{13}H_{18}ClN_3O$ requires C, 58.31; H, 6.78; N, 15.69]; ν_{max} (KBr) 3298 (NH), 2937 (CH), 1627 (C=O), 1587, 1571 (C_{ar}H) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.43–1.47 (m, 2H, C_{alk}*H*), 2.77–2.82 (m, 2H, C_{alk}*H*), 1.99–2.02 (m, 2H, C_{alk}*H*), 2.18 (s, 3H, NCH_3), 2.64–2.68 (m, 2H, C_{alk}*H*), 4.46–4.49 (m, 1H, HNC*H*), 6.00 (d, 1H, $^3J_{H,H}$=4.9 Hz), 7.15 (d, 2H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 7.45 (d, 2H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 8.26 (s, 1H, ArN*H*); δ_C (125 MHz, DMSO-d_6) 32.6, 46.5, 54.4, 119.5, 124.9, 128.9, 140.0, 154.8.

4.3.23. 1-Ethyl-3-pyridin-3-yl-urea ***3h***. Colorless solid (250 mg, 76%), mp 123–125 °C; published mp 123–124 °C.[20]

4.3.24. 1-Furan-2-ylmethyl-3-(3-nitrophenyl)-urea ***3i***. Colorless solid (423 mg, 81%), mp 131–133 °C; [Found: C, 54.96; H, 4.41; N, 16.01. $C_{12}H_{11}N_3O_4$ requires C, 55.17; H, 4.24; N, 16.09%]; ν_{max} (KBr) 3317 (NH), 2922 (CH), 1638 (C=O), 1593, 1569 (C_{ar}H), 1540 (NO_2), 1242 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.32 (d, 2H, $^3J_{H,H}$=5.0 Hz, HNCH_2), 6.26–6.28 (m, 1H, Ar*H*), 6.40–6.42 (m, 1H, Ar*H*), 6.75 (br s, 1H, CH$_2$N*H*), 7.52 (t, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 7.60 (s, 1H, Ar*H*), 7.67 (d, 1H, $^3J_{H,H}$=8.1 Hz, Ar*H*), 7.77 (d, 1H, $^3J_{H,H}$=8.1 Hz,

Ar*H*), 8.52 (s, 1H, Ar*H*), 9.10 (s, 1H, ArN*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6,) 36.7, 107.1, 110.9, 112.2, 116.1, 124.2, 130.4, 142.2, 142.5, 148.6, 153.3, 155.2.

4.3.25. 1-(3-Methoxyphenyl)-3-prop-2-ynyl-urea ***3j***. Colorless solid (322 mg, 79%), mp 107–109 °C; [Found: C, 64.53; H, 5.83; N, 13.61. $C_{11}H_{12}N_2O_2$ requires C, 64.69; H, 5.92; N, 13.72%]; ν_{max} (KBr) 3364 (NH), 3262 (CH), 1643 (C=O), 1610, 1598 (C_{ar}H), 1555 (NO_2), 1106 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.13 (s, 1H, C*CH*), 3.74 (s, 3H, OCH_3), 3.86–3.91 (m, 2H, HNCH_2), 6.85 (t, 1H, $^3J_{H,H}$=7.4 Hz, Ar*H*), 6.91 (t, 1H, $^3J_{H,H}$=7.4 Hz, Ar*H*), 6.90 (d, 1H, $^3J_{H,H}$=7.4 Hz, Ar*H*), 7.17 (t, 1H, $^3J_{H,H}$=9.1 Hz,CH_2N*H*), 8.00 (s, 1H, ArN*H*), 8.08 (d, 1H, $^3J_{H,H}$=7.4 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 29.1, 56.2, 73.4, 82.4, 111.2, 118.7, 121.0, 121.8, 129.6, 148.0, 155.2.

4.3.26. 1-(2,5-Dimethyl-2H-pyrazol-3-yl)-3-(2-hydroxy-2-p-tolylethyl)-urea ***3k***. Colorless solid (472 mg, 75%), mp 82–84 °C; [Found: C, 62.24; H, 7.17; N, 19.18. $C_{15}H_{20}N_4O_2$ requires C, 62.48; H, 6.99; N, 19.43%]; ν_{max} (KBr) 3559 (OH), 3337, 3259 (NH), 2936, 2901, 2870 (CH), 1639 (C=O), 1097 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.05 (s, 3H, $C_6H_4CH_3$), 2.29 (s, 3H, PyrCCH_3), 3.13–3.15 (m, 1H, HNC*H*), 3.26–3.28 (m, 1H, HNC*H*), 3.50 (s, 3H, PyrNCH_3), 4.56–4.59 (m, 1H, C_6H_4CH), 5.51 (d, 1H, $^3J_{H,H}$=4.0 Hz, O*H*), 5.86 (s, 1H, Pyr*H*), 6.34 (t, 1H, $^3J_{H,H}$=5.1 HzCH_2N*H*), 7.15 (d, 2H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 7.25 (d, 2H, $^3J_{H,H}$=7.9 Hz, Ar*H*), 8.41 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 14.2, 21.2, 35.1, 47.7, 72.0, 107.4, 126.5, 129.1, 136.6, 138.7, 141.1, 145.6, 154.8.

4.3.27. 1-Benzo[1,3]dioxol-5-ylmethyl-3-[1,3,4]thiadiazol-2-yl-urea ***3l***. Colorless solid (445 mg, 80%), mp 159–160 °C; [Found: C, 47.29; H, 3.75; N, 19.93. $C_{11}H_{10}N_4O_3S$ requires C, 47.48; H, 3.62; N, 20.13%]; ν_{max} (KBr) 3412, 3392 (NH), 2886 (CH), 1709 (C=O), 1590 (C_{ar}H), 1040 (C–O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.25 (d, 2H, $^3J_{H,H}$=4.8 Hz, HNCH_2), 5.98 (s, 2H, OCH_2O), 6.79 (d, 1H, $^3J_{H,H}$=7.8 Hz, Ar*H*), 6.85–6.90 (m, 2H, Ar*H*), 7.05 (br s, 1H, CH_2N*H*), 9.00 (s, 1H, Ar*H*), 11.0 (s, 1H, ArN*H*); δ_C (125 MHz, DMSO-d_6) 43.4, 101.4, 108.4, 108.6, 121.0, 133.7, 146.7, 147.8, 148.0, 154.1, 161.0.

4.3.28. 1-Cyclopentyl-3-thiazol-2-yl-urea ***3m***. Colorless solid (359 mg, 85%), mp 196–198 °C; [Found: C, 51.11; H, 6.26; N, 19.84. $C_9H_{13}N_3OS$ requires C, 51.16; H, 6.20; N, 19.89%]; ν_{max} (KBr) 3292 (NH), 2925, 2894, 2852 (CH), 1666 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.43–1.47 (m, 2H, C_{alk}*H*), 1.53–1.56 (m, 2H, C_{alk}*H*), 1.56–1.59 (m, 2H, C_{alk}*H*), 1.94–1.97 (m, 2H, C_{alk}*H*), 4.00 (m, 1H, HNC*H*), 6.35 (br s, 1H, AlkN*H*), 6.80 (d, 1H, $^3J_{H,H}$=3.5 Hz, Ar*H*), 7.15 (d, 1H, $^3J_{H,H}$=3.5 Hz, Ar*H*), 10.00 (s, 1H, ArN*H*); δ_C (125 MHz, DMSO-d_6) 23.6, 33.2, 51.6, 112.2, 137.7, 153.8, 160.5.

4.3.29. 1-(4-Methanesulfonylbenzyl)-3-(2-morpholin-4-yl-ethyl)-urea ***3n***. Colorless solid (565 mg, 83%), mp 77–78 °C; [Found: C, 52.67; H, 6.92; N, 12.22. $C_{15}H_{23}N_3O_4S$ requires C, 52.77; H, 6.79; N, 12.31%]; ν_{max} (KBr) 3257 (NH), 2981, 2956, 2879 (CH), 1730 (C=O) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.45 (m, 6H, N(CH_2)$_3$), 3.03 (s, 3H, SCH_3), 3.08–3.12 (m, 2H, HNCH_2), 3.52–3.57 (m, 4H, O(CH_2)$_2$), 4.38 (d, 2H, $^3J_{H,H}$=6.4 Hz, ArCH_2), 5.85 (br s, 1H, N*H*), 6.55 (br s, 1H, N*H*), 7.50 (d, 2H, $^3J_{H,H}$=7.8 Hz, Ar*H*), 7.95 (d, 2H, $^3J_{H,H}$=7.8 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 36.9, 43.1, 44.2, 53.8, 58.7, 66.7, 127.4, 128.1, 139.5, 147.9, 158.5.

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