Microwave-Assisted Synthesis of N-Monosubstituted Urea Derivatives

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Abstract: An easy and rapid procedure for the preparation of N-monosubstituted ureas via reaction between potassium cyanate and a wide range of amines is described. The procedure was performed under microwave irradiation using water as solvent. This methodology is particularly attractive since it provides ureas in high yield and purity.

Key words: urea, potassium cyanate, microwave, *N*-carbamoyl derivatives

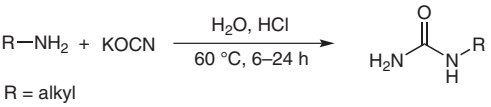
N-Monosubstituted ureas are an important class of organic compounds occurring both in natural products[1] and in synthetic compounds.[2] The synthesis of ureas remains of great interest owing to their wide applications in pharmaceutical and agrochemical industry due to their tranquillizing, anticonvulsant, antidiabetic and herbicidal properties.[3]

The classical approaches to N,N′-symmetrical or unsymmetrical disubstituted ureas are based on the reaction of primary amines with toxic phosgene or its derivatives (an hazardous material, difficult to handle and unsafe to store),[4] of primary or secondary amines with isocyanates (themselves toxic and usually prepared from phosgene),[5] or on the direct insertion of CO or CO_2 into amino compounds in the presence of different catalysts in organic solvents (at high pressure and temperature).[2b,6]

Recently a two-step synthesis of monosubstituted ureas was reported.[7] The method consists of the reaction between an amine with 4-nitrophenyl-*N*-benzylcarbamate[8] followed by hydrogenolysis. Artuso et al.[9] reported another two-step synthesis to prepare *N*-alkylureas employing *S*,*S*-dimethyl dithiocarbonate (DMDTC) as a phosgene substitute. The first step between the alkyl amine and DMDTC was carried out in water at room temperature, the intermediate obtained was reacted in the second step with ammonia in water–dioxane at temperatures varying between 50 °C and 70 °C.

The classical approach to N-monosubstituted ureas is the reaction between sodium or potassium cyanate and an amine in aqueous solution in the presence of one equivalent of HCl (Scheme 1).[10] The protocol is very simple but requires long reaction times (from 6 h to 24 h at 60 °C).

Using aliphatic amine the reaction occurs quickly, whereas with aromatic amines the procedure needs to be catalyzed by a second molecule of amine or ammonium ion as well as by added buffers.[11]



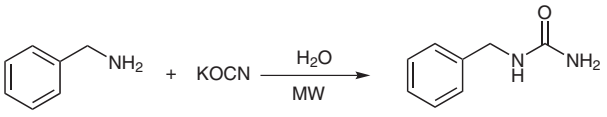
Scheme 1 Classical approach to N-monosubstituted ureas

In this context the synthesis of *N*-carbamoyl amino acids by the treatment of α-amino acids with sodium or potassium cyanate should be mentioned.[12] The methodology is easy but requires long reaction times (from 10 h to 70 h at 50–60 °C) and the efficiency is dependent on pH or temperature.

Following our interest in the use of techniques for decreasing the reaction time and improving yields, we investigated the effect of MW irradiation on the reaction among one equivalent of benzylamine, five equivalents of KOCN, and one equivalent of HCl in water as solvent. The reaction was carried out in a sealed tube (10-mL pressure-rated reaction vial) in a self-tuning single mode irradiating synthesizer, operating at 70 °C for four hours (Table 1, entry 1). After cooling, the precipitate formed was filtered, and washed with hexane and Et_2O. The crude urea was dissolved in MeOH, and the residue was filtered off. The desired *N*-benzylurea was isolated in a pure form and in high yield (90%) by evaporating the solvent under reduced pressure.

In order to reduce the reaction time we have performed the reaction under different MW conditions;[13] in particular operating at 80 °C for one hour (Table 1, entry 2), 100 °C for 28 minutes (Table 1, entry 3), 120 °C for seven minutes (Table 1, entry 4). The reaction was monitored by TLC until disappearance of starting amine.

Table 1 MW Reaction Conditions



Entry	Temp	Time	Yield
1	70 °C	4 h	90%
2	80 °C	1 h	90%
3	100 °C	28 min	55%
4	120 °C	7 min	25%

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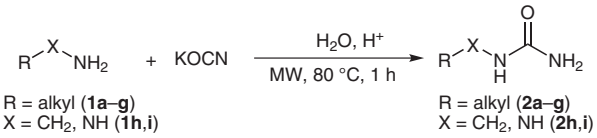
The increasing of temperature concurrent with decreasing of reaction time showed a significant variation of chemical yield, so a temperature of 80 °C and a reaction time of one hour (Table 1, entry 2) were found to be the best MW conditions. In fact, an increase in temperature resulted in an enhanced amount of by-products.[14]

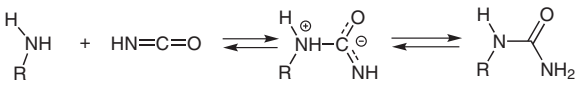
After the reaction had been optimized on a small scale, we turned our attention to the large-scale synthesis. The reaction was carried out in a sealed 80-mL vessel provided with fiber optic temperature controller operating at 80 °C for one hour (Scheme 2).



Scheme 2 Synthesis of N-monosubstituted ureas by MW irradiation

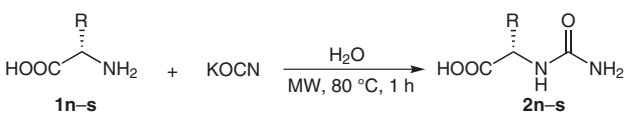
Next, we decided to investigate the versatility of this methodology using a series of alkyl amine under these optimized conditions.[15] A collection of N-monoalkylureas was easily prepared in good to high yields as showed in Table 2. We observed that the methodology is applicable as it is to N-substituted hydrazines too (Table 2, entries 8 and 9). While using aromatic amines (Table 2, entries 10–12), we observed that the best results were obtained using acetic acid instead of HCl because the reaction of weakly basic nucleophiles with cyanic acid is dependent on pH.[11]

As reported by Williams et al.[11a] the mechanism of reaction may be consistent with the attack of nitrogen atom on cyanic acid (Scheme 3) with formation of a dipolar intermediate. A proton-transfer step makes possible the conversion of the initially formed zwitterionic intermediate into the uncharged urea product (Scheme 3). Strongly basic amines, for which attack is rate determining exhibit no general acid or basic catalysis, while in the reaction of anilines, the rate-limiting step is the proton transfer of the zwitterionic intermediate which does not occur at low value of pH.



Scheme 3 Mechanism of reaction of amine with cyanic acid

The reaction is not limited to use with aliphatic, N-substituted hydrazines and anilines and but works well with amino acids too. In this case the reaction did not require the presence of any acid owing to the good solubility of amino acid in water (Scheme 4).



Scheme 4 Synthesis of N-monosubstituted ureas from α-amino acids by MW irradiation

The workup of the reaction is simple. The aqueous reaction mixture was brought to pH 2 by the addition of a 6 N HCl solution, and then the desired urea precipitated. The products were recovered in pure form and high yield.

Significant racemization of the chiral center of the α-amino acids did not take place under the condition employed, as revealed by the optical rotation value of the product **2q** compared with that reported in the literature.[18]

Table 2 Synthesis of *N*-Monoalkylureas

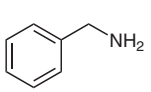
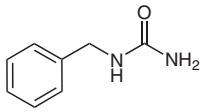
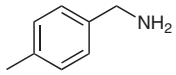
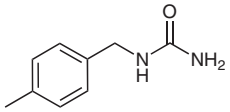
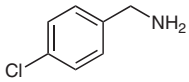
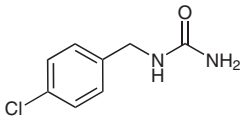
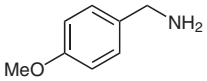
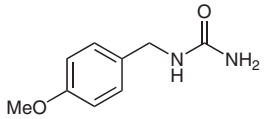
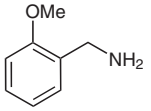
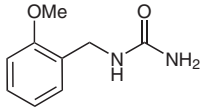
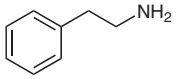
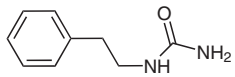
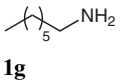
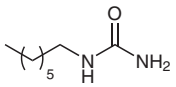
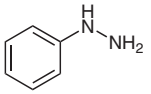
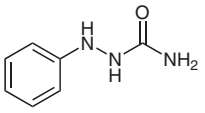
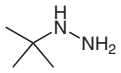
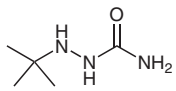
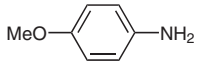
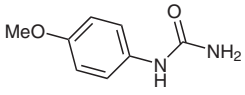
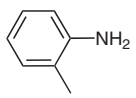
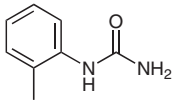
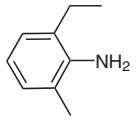
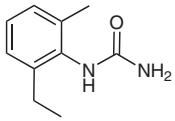
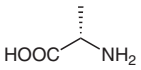
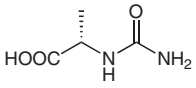
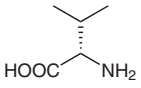
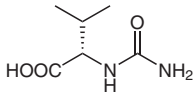
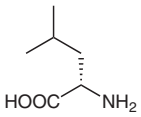
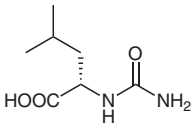
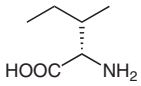
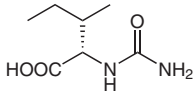
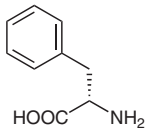
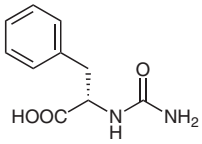
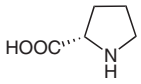
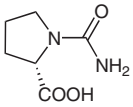
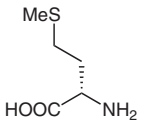
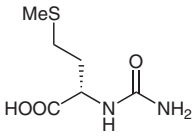
Entry	Amine	Urea[a]	Yield[b]
1	 **1a**	 **2a**	88%
2	 **1b**	 **2b**	86%
3	 **1c**	 **2c**	75%
4	 **1d**	 **2d**	86%
5	 **1e**	 **2e**	87%
6	 **1f**	 **2f**	73%
7	 **1g**	 **2g**	85%
8	 **1h**	 **2h**	74%
9	 **1i**	 **2i**	85%
10	 **1j**	 **2j**	87%

Table 2 Synthesis of *N*-Monoalkylureas (continued)

Entry	Amine	Urea[a]	Yield[b]
11	 **1k**	 **2k**	88%
12	 **1l**	 **2l**	75%
13	 **1m**	 **2m**	86%
14	 **1n**	 **2n**	83%
15	 **1o**	 **2o**	78%
16	 **1p**	 **2p**	90%
17	 **1q**	 **2q**	89%
18	 **1r**	 **2r**	68%
19	 **1s**	 **2s**	85%

[a] All the ureas were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS or elemental analysis.
[b] Overall isolated yield.

In conclusion we have developed an easy microwave-assisted procedure for converting a set of various amines into N-substituted ureas even in large scale. The methodology uses mild reaction conditions and cheap and commercially available reagents, is high-yielding and allows the recovery of the desired product by an easy and convenient workup.

Acknowledgment

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References and Notes

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(15) **Representative Procedure for the Synthesis of *N*-Alkylureas; 1-Phenethylurea (2f)**
A stirred solution of 2-phenethylamine (2.3 mL, 18 mmol) in 1 N HCl (18 mL) and H_2O (9 mL) was treated with KOCN (7.3 g, 90 mmol) and then the mixture was irradiated to 80 °C for 1 h in a sealed tube (CEM designed 10-mL pressure-rated reaction vial) in a self-tuning single mode CEM Discover Focused synthesizer. The mixture was chilled rapidly to r.t., by passing compressed air through the microwave cavity for 3 min. After the cooling to r.t., the precipitate formed was filtered, and washed with hexane and Et_2O. The crude urea was dissolved in MeOH, the residue was filtered off. The desired 1-phenethylurea (**2f**) was isolated, by evaporating the solvent under reduced pressure, in a pure form and in high yield (2.3 g, 73%) as a crystalline white solid; mp 114–115 °C [lit.[16] 115 °C]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64 (q, *J* = 6.6 Hz, 2 H), 3.17 (q, *J* = 6.4 Hz, 2 H), 5.43 (br s, 2 H), 5.94 (br s, 1 H), 7.23 (m, 5 H). ^{13}C NMR (75 MHz, DMSO): δ = 36.2, 40.8, 125.9, 128.3, 128.6, 139.8, 158.1. MS: *m*/*z* = 164 [M$^+$]. Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.78; H, 7.32; N, 16.98.
Representative Procedure for the Synthesis of *N*-Arylureas; 1-*o*-Tolylurea (2k): A stirred solution of *o*-toluidine (1.9 mL, 18 mmol) and AcOH (1.7 mL, 30 mmol) in H_2O (27 mL) was treated with KOCN (7.3 g, 90 mmol) and then was irradiated to 80 °C for 1 h in a sealed tube (CEM designed 10-mL pressure-rated reaction vial) in a self-tuning single mode CEM Discover Focused synthesizer. The mixture was chilled rapidly to r.t., by passing compressed air through the microwave cavity for 3 min. After the cooling to r.t., the precipitate formed was filtered, and washed with hexane and Et_2O. The crude urea was dissolved in MeOH, and the residue was filtered off. The desired 1-*o*-tolylurea (**2k**) was isolated by evaporating the solvent under reduced pressure in a pure form and in high yield (2.4 g, 88%) as a white solid; mp 186–188 °C (lit.[17] 191 °C). ^{1}H NMR (300 MHz, DMSO): δ = 2.18 (s, 3 H), 6.03 (br s, 2 H), 6.86 (m, 1 H), 7.09 (m, 2 H), 7.72 (br s, 1 H), 7.77 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, DMSO): δ = 17.4, 120.4, 121.5, 125.5, 126.6, 129.5, 137.7, 155.7. MS: *m*/*z* = 150 [M$^+$]. Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.76; H, 6.65; N, 18.66.
Representative Procedure for the Synthesis of *N*-Carbamoyl L-Amino Acids; *N*-Carbamoyl-L-phenylalanine (2q): A stirred solution of L-phenylalanine (3.0 g, 18 mmol) in H_2O (27 mL) was treated with KOCN (7.3 g, 90 mmol) and then was irradiated to 80 °C for 1 h in a sealed tube (CEM designed 10-mL pressure-rated reaction vial) in a self-tuning single mode CEM Discover Focused synthesizer. The mixture was chilled rapidly to r.t., by passing compressed air through the microwave cavity for 3 min. After the cooling to r.t., the mixture was acidified to pH 2 with 6 N HCl. The obtained solid was filtered and washed with cold H_2O (3 × 5 mL) and dried under vacuum to yield the *N*-carbamoyl-L-phenyl alanine (**2q**) in a pure form and in high yield (3.4 g, 90%) as a white solid; mp 192–194 °C (lit.[18] 191–192 °C); $[\alpha]^{20}_D$ +38.7 (*c* = 1, MeOH).[18] ^{1}H NMR (300 MHz, DMSO): δ = 2.90 (m, 2 H), 4.32 (m, 1 H), 5.62 (br s, 2 H), 6.16 (br d, *J* = 8.4 Hz, 1 H), 7.22 (m, 5 H).[18] ^{13}C NMR (75 MHz, DMSO): δ = 37.6, 53.7, 126.3, 128.2, 129.2, 137.5, 158.1, 173.9.[18] MS: *m*/*z* = 208 [M$^+$].[18] Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.71; H, 5.79; N, 13.44.

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