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Articles

A Convenient Method of Synthesis of Unsymmetrical Urea Derivatives

Grażyna Groszek*

Faculty of Chemistry, Rzeszów University of Technology, W Pola 2, 35-959 Rzeszów, Poland

Abstract:

A method for the preparation of unsymmetrical urea derivatives that may contain functional groups such as hydroxyl, amine, amide, and carboxyl is described. The method consists of a one-pot modified Curtius rearrangement starting with appropriate aromatic acid chloride and carried out in a nonaqueous system

Introduction

Unsymmetrical ureas are known to be active herbicides and pharmaceuticals. Another application of this kind of chemical derivative is in supramolecular chemistry as receptors for anions[1] and for studying intramolecular hydrogen bonding in investigations aimed at developing molecular receptors and peptide conformational templates.[2]

Typical methods for the preparation of ureas consist of the addition of an appropriate amine to an isocyanate or the reaction of an amine with carbamoyl halides. In both cases, phosgene is used as a supporting substrate. An alternative, phosgene-free process for the synthesis of unsymmetrical ureas is the reductive carbonylation of nitro derivatives catalyzed by metal compounds of groups VII−X metals,[3] where the yield can be as high as 73%. Some nontransition elements such as selenium, sulfur, or tellurium have also been found to catalyze this reaction.[4] Unfortunately, in the latter case, small, but detectable, amounts of the toxic catalysts have been found to be present in the final product.[3]

Combinatorial solid-phase organic synthesis (SPOS) is a powerful tool for preparing libraries of drug-like organic molecules. Unsymmetrical ureas are examples of chemicals obtained by using this method.[5] However, although the compounds were synthesized in high purity and good yield, SPOS runs only on a small scale.

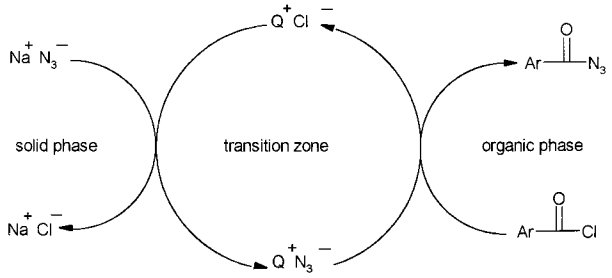
We have developed an operationally simple, high-yield modification of the Curtius rearrangement for the synthesis of unsymmetrical ureas. In its original embodiment, a serious problem of this process is the hydrolysis of isocyanates. A trace of water favored formation of urethanes, byproducts that are very hard to remove. Furthermore, during incomplete conversion of acid chloride to azide, undesired amide can be formed in the last step.

An advantage of the method reported herein is the wide range of its applications to the synthesis of a variety of urea derivatives containing different functional moieties, for example, hydroxyl, carboxyl, amine, or amide groups.

Results and Discussion

The method involves the reaction of aromatic acid chloride **1** with sodium azide in toluene with TEBA-Cl as a phase-transfer catalyst (PTC). In the next step, the solid was filtered off and then heated to complete rearrangement to isocyanate **2**. Finally, a suitable amine derivative was added (Scheme 1).

Product **3** was obtained in high-yield owing to nonaqueous conditions and to the presence of PTC catalyst. The substitution of chlorine by azide anion occurred according to the mechanism proposed by Mąkosza[6] at the phase boundary between solid and liquid phases. Sodium azide was insoluble in organic phase; therefore, a transition zone was formed between solid and organic phases, where the substitution reaction takes place. The diagram below illustrates the proposed mechanism of the reaction.



Q^+ — benzyltriethylammonium cation

The Curtius rearrangement was monitored with the use of IR by observing the disappearance of the azide group bands (at 2138 cm^{-1}) and the appearance of the characteristic isocyanate band at 2255 cm^{-1}. Table 1 below summarizes the results for various aliphatic amines.

In the case of urea derivatives with an amino group in the side chain, we have found it necessary to protect one

* To whom correspondence should be addressed. E-mail: ggroszek@prz.rzeszow.pl.

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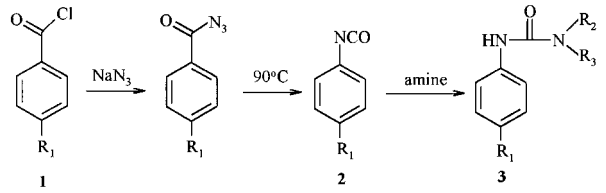
Scheme 1



amino group using a BOC group, followed by deprotection in the last step (Scheme 2).

The protection of one amino group in 1,3-diaminopropane was carried out using the method described by Krapcho and Kuel.[9] To characterize compound **6**, we employed the deprotection procedure described by Nudelman et al.[10] The reason for this was that free amine **6** was unstable under standard conditions; hence, it had to be characterized in the form of hydrochloride. Unfortunately, the original Nudelman procedure failed in our case. Compound **6** could not be isolated as a monohydrochloride. We found it necessary to obtain amine **6** as a solid by using an excess of acetyl chloride and methanol (see Experimental Section). Possibly this modification resulted in the formation of a multihydrochloride of amine **6**, involving more than one N−H group.

The synthesis of urea derivatives with carboxylic or amide groups or both was performed according to the procedure described by Paal and Zitelmann[11] (shown in Scheme 3).

During the synthesis of compounds **7a**−**b**, it was necessary to change the order of addition of reagents (isocyanate derivative was added to the solution of amino acid sodium salt).

Formation of compound **7a** was always accompanied by formation of a byproduct (1,3-bis(4-methoxyphenyl)urea). The problem did not occur during synthesis of compound **7b**.

Experimental Section

Melting points were determined on a Boëtuis apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Tesla BS 587 A (80 MHz) or Varian Gemini (200 MHz) instruments. Chemical shifts are expressed in ppm (δ) referred to TMS, coupling constants (J) are in Hz. IR and UV spectra were recorded on Perkin-Elmer Paragon 1000 and Hewlett-Packard 8453 instruments, respectively. Mass spectra were obtained on an AMD-604 spectrometer. Microanalyses were performed on Fisons EA-1108 apparatus. TLC plates were silica gel 60 F_{254} Merck, and silica gel Merck 70−230 mesh were used for column chromatography.

Solvents were distilled and dried if required; other materials were commercial.

The General Procedure for Synthesis of Unsymmetrical Ureas (3). A solution of the appropriate acid chloride (0.022 mol) in anhydrous toluene (40 cm^3), containing benzyltriethylammonium chloride (3×10^{-3} mol) and sodium azide (0.088 mol) was stirred vigorously at room temperature for 24 h. Then, the reaction mixture was filtered, and from the filtrate one-fourth of the volume of solvent was distilled off. The residue was kept at 90 °C for ca. 22 h until the reaction was complete as determined by IR. After the mixture cooled to room temperature, the amine (0.033 mol) was added. The agitation was continued for 30 min, before the excess of amine and solvent was removed using a rotary evaporator. The crude urea derivative was crystallized or recrystallized.

1-*tert*-Butyl-3-(4-methoxyphenyl)urea (3c): ^{1}H NMR ($CDCl_3$) 1.3 (s, 9H, 3 × C**H**$_3$); 3.7 (s, 3H, OC**H**$_3$); 5.1 (s, 1H, N**H**); 6.8, 7.2 (2m, 5H arom and N-**H**). ^{13}C NMR ($CDCl_3$) 29.3 (C-9); 50.4 (C-8); 55.5 (C-10); 114.4, 123.3 (C-2, C-6 and C-3, C-5); 131.9 (C-1); 156.0, 156.1 (C-7 and C-4). IR (KBr), ν (cm^{-1}) 1511 (N−C═O); 1558 (C−H arom); 1600 (N−H amide); 1648 (C═O); 2965 (C−H); 3338 (N−H). UV (ethanol), (nm) $\lambda_{max} = 245$ ($\epsilon = 19654$) for $c = 0.1036$ mg/10 cm^3. HR-EIMS (70 eV), m/z: calcd for $C_{12}H_{18}N_2O_2$ 222.13683, found 222.13746. Anal. Calcd for $C_{12}H_{18}N_2O_2$ [%] C 64.84, H 8.1, N 12.60; found 64.84, 8.18, and 12.40, respectively.

1-(2-Hydroxyethyl)-3-(4-methoxyphenyl)urea (3d): ^{1}H NMR (DMSO-d_6) 3.1 (q, $J = 5.6$, 2H, N−C**H**$_2$); 3.4 (m, 2H, C**H**$_2$−O); 3.7 (s, 3H, O−C**H**$_3$); 4.7 (br s, 1H, O**H**); 6.1 (t, $J = 5.2$, 2H, N**H**); 7.8, 7.3 (2m, 4H arom); 8.3 (s, 1H, N**H**). ^{13}C NMR 41.8 (C-8); 55.1 (C-10); 60.1 (C-9); 113.8, 119.2 (C-2, C-6 and C-3, C-5); 133.7 (C-1); 153.8, 155.5 (C-7 and C-4). IR (KBr), ν (cm^{-1}) 1529 (N−C═O); 1583 (C−H arom); 1611 (N−H amide); 1631 (C═O); 2937 (C−H); 3309 (N−H); 3517 (OH). UV (ethanol), (nm) $\lambda_{max} = 243$ ($\epsilon = 34223$), $c = 0.192$ mg/10 cm^3. HR-LSIMS(+) calcd 211.10827 [for $C_{10}H_{15}N_2O_3$) (M + H)$^+$], found 211.10676. Anal. Calcd for $C_{10}H_{14}N_2O_3$ [%] C 57.13, H 6.71, N 13.32; found 57.10, 6.71, and 13.34, respectively.

Synthesis of 1-(3-Aminopropyl)-3-(4-methoxyphenyl)-urea (6). Monoprotected 1,3-diaminopropane by BOC group was obtained as described by Krapcho et al.[9] in the form of oil (56% yield based on dicarbonate). ^{1}H NMR confirmed the structure of compound **4**.

The monoprotected diamine **4** (1.5 equiv) was added to isocyanate **2**, and the precipitate was filtrated off and dried in air, affording compounds **5** (86% yield) which was then submitted to further transformation.

To the stirred solution of compound **5** (0.3 g, 0.93 mmol) in acetone (10 cm^3) were added methanol (1.2 cm^3, 25 mmol) and acetyl chloride (1.1 cm^3, 15.5 mmol) at 0 °C (ice + water bath). After 30 min the reaction mixture was warmed to room temperature; the precipitate was filtered off and dried in air, affording compound **6** (0.19 g, 85% yield), mp 156−158 °C.

^{1}H NMR (DMSO-d_6) 1.7 (m, 2H, N−C**H**$_2$); 2.8 (m, 2H, N−C**H**$_2$); 3.2 (m, 2H, C**H**$_2$); 3.7 (s, 3H, O−C**H**$_3$); 6.8 and 7.3 (2m, 4H arom). ^{13}C NMR 28.0 (C-9); 35.9, 36.6 (C-8 and C-10); 55.1 (C-11); 113.7, 119.3 (C-2, C-6 and C-3, C-5); 133.6 (C-1); 153.8, 155.9 (C-7 and C-4). IR (KBr), ν (cm^{-1}) 1572 (N−C═O); 1511 (C−H arom); 1632 (C═O);

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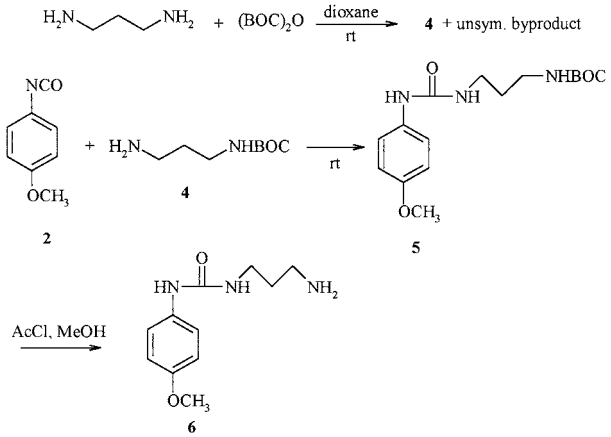
Table 1. **Characterization of urea derivatives 3**

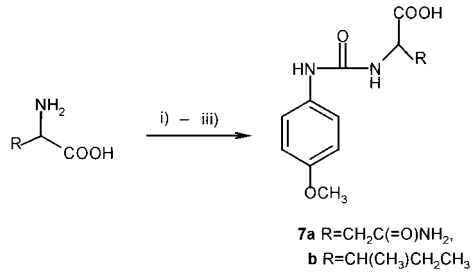
product	R_1	R_2	R_3	yield [%]	mp [°C]	literature mp [°C]
3a	OCH_3	C_2H_5	C_2H_5	93	61−63 (crude)	61.5−62[a]
3b	H	C_2H_5	C_2H_5	85	88−89 (acetone−hexane)	85[b]
3c	OCH_3	H	$C(CH_3)_3$	84	128−130 (acetone−hexane)	−
3d	OCH_3	H	CH_2CH_2OH	96	134−135 (acetone)	−

[a] Reference 7. [b] Reference 8.

Scheme 2



Scheme 3[a]



[a] i) NaOH aq; ii) *p*-$CH_3OPhNCO$; iii) H_2SO_4 aq

3002 (N−H); 3303, 3342 (2 × N−H). UV (ethanol), (nm) $\lambda_{max} = 234.0$ ($\epsilon = 20007$) for $c = 0.0896$ mg/10 cm^3. HR-LSIMS(+) calcd 224.13990 [(for $C_{11}H_{18}N_3O_2$)]; found 224.13863.

Synthesis of 2-[3-(4-Methoxyphenyl)ureido]succinamic Acid (7a). To the stirred aqueous solution of sodium hydroxide (8%, 10.12 cm^3, 0.022 mol) was added L-asparagine (2.97 g, 0.022 mol) at room temperature; then while the mixture was externally cooled (ice + water), 4-methoxyphenylisocyanate (0.022 mol) in acetone (10 cm^3) was added. The precipitate was filtered off and discarded. The filtrate was treated with sulfuric acid (5% aq) to pH ∼4 (litmus), and then the precipitate was filtered off, washed with water, and dried in air, affording product **7a** (3.81 g, 61% yield). For analysis, the product was crystallized from DMSO−water, mp 186−190 °C.

^{1}H NMR (DMSO-d_6) 2.5 (dd, $J = 15.9$, $J = 5.6$, 1H, C**H**$_2$); 2.67 (dd, $J = 15.9$, $J = 5.6$, 1H, C**H**$_2$); 3.68 (s, 3H, O−C**H**$_3$); 4.4 (dt, $J = 8.5$, $J = 5.2$, 1H, C**H**); 6.4 (d, $J = 8.5$, 1H, N**H**); 6.8 and 7.3 (2m, 4H arom); 6.9, 7.4 (2s, 2H, N**H**$_2$); 8.7 (s, 1H, N**H**); 12.5 (s, 1H, COO**H**). ^{13}C NMR 37.2 (C-9); 48. 9 (C-8); 55.1 (C-12); 113.9, 119.1 (C-2, C-6 and C-3, C-5); 133.5 (C-1); 153.9, 154.9 (C-7 and C-4); 171.8, 173.5 (C-10 and C-11). IR (KBr), ν (cm^{-1}) 1514 (N−C═O); 1570, 1591 (C−H arom and amide); 1672, 1720, and 1739 (3 × C═O); 3169 and 3282 (N−H amide); 3391 (N−H). UV (ethanol), (nm) $\lambda_{max} = 245$ ($\epsilon = 32946$), for $c = 0.052$ mg/10 cm^3. HR-LSIMS(+) calcd 282.10900 [for $C_{12}H_{16}N_3O_5$) $(M + H)^+$], found 282.10821. Anal. Calcd for $C_{12}H_{15}N_3O_5$ [%] C 51.24, H 5.38, N 14.94; found 51.40, 5.25, and 14.84, respectively.

Synthesis of 2-[3-(4-Methoxyphenyl)ureido]-3-methylpentanoic Acid (7b). Compound **7b** was obtained according to the procedure described above. The product was isolated as an oil via extraction with methylene chloride (3 × 100 cm^3) and then, after evaporation of solvent, crystallized from benzene−petroleum ether (40/60) affording acid **7b** (83% yield).

For analysis the products were recrystallized from ethanol−water, mp 107−110 °C.

^{1}H NMR (DMSO-d_6) 0. 9 (m, 6H, 2 × C**H**$_3$); 1.5 (m, 1H, C**H**); 1.4, 1.8 (2m, 2H, C**H**$_2$); 3.7 (s, 3H, O−C**H**$_3$); 4.2 (dd, $J = 8.7$, $J = 3.8$, 1H, N−C**H**); 6.3 (d, $J = 8.7$, 1H, N**H**); 6.8 and 7.3 (m, 4H, arom); 8.4 (s, 1H, N**H**), 12.5 (s,1H, COO**H**). ^{13}C NMR 11.4, 15.7 (C-12 and C-11); 24.6 (C-10); 37.1 (C-9); 55.1, 56.4 (C-11 and C-8); 113.9, 119.0 (C-2, C-6 and C-3, C-5); 133.3 (C-1); 153.9, 155.0 (C-7 and C-4); 173.7 (C-13). IR (KBr), ν (cm^{-1}) 1513, 1539 (N−C═O and C−H arom); 1614, 1646, and 1696 (2 × C═O and N−H amide); 2963 (OH); 3284, 3408 (N−H and COOH). HR-LSIMS(+) calcd 281.15272 [(for $C_{14}H_{21}N_2O_4$) $(M + H)^+$], found 281.15013. Anal. Calcd for $C_{14}H_{20}N_2O_4$ [%] C 59.99, H 7.19, N 9.99; found 59.95, 7.21, and 10.00, respectively.

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