

The Synthesis of N-Substituted Ureas I: The N-Alkylation of Ureas

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Summary. Urea and N-alkylureas are N'-alkylated in low yields using aprotic dipolar solvents, like dimethylsulfoxide, solid potassium hydroxide, and alkyl halides. Phase transfer catalysis with tetrabutylammonium chloride in refluxing toluene results in high yield regioselective N'-alkylation of N-alkylureas by means of alkyl halides, tosylates, mesylates, and sulfates as alkylating agents and alkali hydroxide as the base – however, N-arylureas are not alkylated under these conditions. Kinetic studies point to a S_N2 type reaction which obeys the Kornblum rule.

Keywords. N-substituted Ureas; N-Alkylation; Kornblum rule; Regioselectivity; Phase transfer.

Zur Synthese N-substituierter Harnstoffe I: Die N-Alkylierung von Harnstoffen

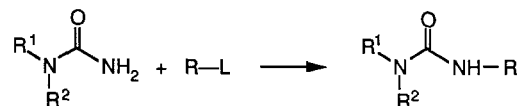
Zusammenfassung. Harnstoffe und N-alkylierte Harnstoffe werden in aprotisch dipolaren Lösungsmitteln, wie Dimethylsulfoxid, durch Alkylhalogenide in Gegenwart von Kaliumhydroxid in geringen Ausbeuten N'-alkyliert. Phasentransferkatalyse mit Tetrabutylammoniumchlorid in kochendem Toluol ergibt aus N-Alkylharnstoffen bei Verwendung von Alkyl-Halogeniden, Tosylaten, Mesylaten und Sulfaten als Alkylierungsmittel und Alkalihydroxid als Base hohe Ausbeuten der regioselektiv N'-alkylierten Derivate – allerdings werden N-Arylharnstoffe unter diesen Bedingungen nicht umgesetzt. Untersuchung der Kinetik ergab Hinweise auf eine S_N2-Typ Reaktion, die der Regel von Kornblum gehorcht.

Introduction

Urea is celebrated as the ancestor of synthetic organic chemistry in most textbooks of organic chemistry [1]. Its chemistry has been exploited in a variety of directions [2], and urea and several of its derivatives are of main industrial importance [3]. Nevertheless, a few white patches remained in the vast map of urea chemistry. For example, in the light of an increasing sensibilization of the public towards ecology, there might be a need to synthesize N-substituted ureas avoiding the rather well established roads [2] of isocyanate or phosgene chemistry.

This goal could be achieved in principle by N-alkylation of available ureas according to the formula scheme (R^1, R^2, \dots H, alkyl, aryl; $L \dots$ leaving group; $R \dots$ alkyl). However, literature states that alkylations of ureas yield more or less exclusively O-alkylureas, and there are only a few exceptions to this long standing

dogma [2]. One example is the acid catalyzed alkylation of urea with *tert*-butanol [4] which proceeds regioselectively to yield the N-alkylated product (contrary to what would be anticipated from the application of the Kornblum rule [5] or the allopolarization concept [6]). The other one with this kind of regioselectivity is the reaction of certain benzylic alcohols with substituted ureas under acidic conditions [7] – one should be aware however, that the reaction conditions used in all the other cases producing O-alkylation are of S_N1 type, i. e., they obey the Kornblum rule.



Nevertheless there is a rare observation that N-alkylation under rather drastic S_N2 conditions might be feasible: urea is N-alkylated by means of benzyl chloride using metallic sodium (i. e., sodium amide) in liquid ammonia [8]; however, as pointed out in this report, other primary alkyl halides failed to do so. Thus, this paper investigates the possibilities of using advanced S_N2 alkylation techniques in order to selectively alkylate ureas at the nitrogen atom.

Results and Discussion

There are mainly two ways one could envisage to improve on nucleophilic substitution reactions of amides at the nitrogen atom. One is to use a strong base in aprotic dipolar solvents [9, 10], the other one is to apply phase transfer catalysis [11, 12].

Aprotic Dipolar Solvents

The best results for N-alkylations of ureas were obtained using freshly powdered potassium hydroxide in dimethyl sulfoxide solutions as described for the N-alkylation of amides [10]. Four examples of this kind of reaction are shown in Table 1. Using sodium amide in dimethyl sulfoxide mainly results in decomposition of educt and product ureas. The optimized but rather moderate yields shown in Table 1 could not be improved by changing temperature or reaction time. Primary alkyl chlorides and secondary alkyl halides proved to be unsuited for this type of alkylation procedure.

Table 1. Alkylation of ureas with alkyl halides using potassium hydroxide in dimethyl sulfoxide, room temperature, 1 hour reaction time

Urea	Alkyl halide	Product	Yield (%)
Urea	1-Iodohexane	N-Hexylurea	21
Urea	1-Bromodecane	N-Decylurea	12
N-Butylurea	1-Bromobutane	N,N'-Dibutylurea	17
N-Butylurea	1-Chlorobutane	N,N'-Dibutylurea	≤ 1

Table 2. Alkylation of N-alkyl-ureas using solid sodium hydroxide as base and tetrabutylammonium chloride as phase transfer catalyst in refluxing toluene

Substrate	Reagent	Product	Time (h)	Yield (%)
N-Ethylurea	1-Bromobutane	N-Butyl-N'-ethylurea	2	71
N-Butylurea	1-Bromobutane	N,N'-Dibutylurea	2	82
N-Butylurea	1-Chlorobutane	N,N'-Dibutylurea	2	21
N-Butylurea	1-Chlorobutane	N,N'-Dibutylurea	16	67
N-Butylurea	2-Bromopropane	N-Butyl-N'-isopropylurea	2	25
N-Butylurea	2-Bromopropane	N-Butyl-N'-isopropylurea	16	18
N-Butylurea	Bromoethane	N-Butyl-N'-ethylurea	2	76
N-Butylurea	Diethylsulfate	N-Butyl-N'-ethylurea	2	80
N-Butylurea	Ethyltosylate	N-Butyl-N'-ethylurea	2	74
N-Butylurea	Ethylmesylate	N-Butyl-N'-ethylurea	2	71
N-Isopropylurea	1-Bromobutane	N-butyl-N'-isopropylurea	2	58
N- <i>tert</i> -Butylurea	1-Bromobutane	N-Butyl-N'- <i>tert</i> -butylurea	2	47
Morpholine-N-Carboxamide	1-Bromobutane	N'-Butyl-morpholine-N-Carboxamide	2	85
Morpholine-N-Carboxamide	2-Bromopropane	N'-Isopropyl-morpholine-N-Carboxamide	2	16
Pyrrolidine-N-Carboxamide	1-Bromobutane	N'-Butyl-pyrrolidine-N-Carboxamide	2	41
Pyrrolidine-N-Carboxamide	1-Bromobutane	N'-Butyl-pyrrolidine-N-Carboxamide	16	70

Phase Transfer Catalysis

Amides are N-alkylated in refluxing benzene by alkyl halides in high yields using tetrabutyl- or benzyltriethylammonium hydrogensulfate as the phase transfer catalysts and solid potassium hydroxide or its aqueous solution as the base [12].

As shown by means of the examples given in Table 2, N-alkylureas and N,N-dialkylureas are regioselectively alkylated at the N'-position by primary alkyl halides as well as by the corresponding tosylates, mesylates, and sulfates. The catalyst used was tetrabutylammonium chloride in about five mole percent concentration. As the reaction medium refluxing toluene was chosen (avoiding toxic benzene on the one hand and providing the temperature necessary to effect reaction; refluxing xylene did not result in significant improvements). With secondary halides the yields are somewhat reduced, nevertheless, this kind of synthesis is still applicable. Table 2 also demonstrates a moderate dependence of the reaction yields on the steric requirements of the substituents at the urea nitrogen atom as indicated by the N'-butylation in the series of *n*-butyl-, isopropyl-, and *tert*-butyl-urea. However, in some cases (e. g.: N,N'-dibutylurea by alkylation with 1-chlorobutane) unsatisfactory yields may be improved by lengthening the reaction time, although the thermal instability of certain alkylated ureas may interfere (e. g.: N-butyl-N'-isopropylurea).

Due to its rather limited solubility in toluene, urea itself could not be alkylated satisfactorily under the reaction conditions given above. Only a few percent of N-

and N,N'-alkylated ureas could be isolated. Even the use of ultrasound dispersion did not result in an improvement. Experiments to N-alkylate N-arylureas in dimethylsulfoxide or under phase transfer conditions also failed (in this case ammonia is released and hydroxyl is substituted instead to yield a carbamic acid which then decomposes into an aromatic amine and carbon dioxide).

With respect to mechanistic details the reaction of N-butylurea with 1-bromobutane was investigated. When substrate and reagent were applied in 1 : 1 and 1 : 2 molar ratios, quenching of the reaction mixture after ten minutes afforded a yield of N,N'-dibutylurea which was twice as high in the latter case. This result corroborates a reaction mechanism in which the reaction velocity is dependent as well on the concentration of the substrate as on that of the reagent. Accordingly, N-alkylations of ureas follow a S_N2 mechanism and should therefore obey the Kornblum rule – this point is well documented by the examples given above.

Experimental Part

Melting points were taken by means of differential scanning calorimetry using the Perkin Elmer DSC2 and DSC7 instruments. The scanning rate was 20°C/min and the peak onset was recorded as the melting point. ¹H-, ¹³C-, IR-, and M-spectra were recorded using the Bruker-AC-200-, Biorad-FTS-45-, Digilab FTS-20E-, and Varian-MAT-311-A-instruments. NMR signal assignments were achieved using DEPT and 2D-hetero-COSY techniques.

Urea and N-isopropylurea were obtained from the Chemie Linz Ges.m.b.H., N-ethylurea, N-butylurea, N-*tert*-butylurea and the alkylating agents came from Fluka, N-morpholinecarboxamide and N-pyrrolidinecarboxamide were prepared according to Ref. [13, 14].

Procedure (A) for Alkylations in Dimethylsulfoxide

2.25 g (40 mmol) of powdered potassium hydroxide are suspended in 20 ml of dimethylsulfoxide, which was dried over 4 Å molecular sieve, under argon atmosphere. After 10 min 10 mmol of urea or N-alkylurea and 10 mmol of alkylating agent are added to this vigorously stirred suspension. After stirring for additional 50 min the reaction mixture is poured into 150 ml of distilled water and extracted twice with 100 ml chloroform and twice with 100 ml dichloromethane. The organic layers are collected, washed with distilled water three times, dried over sodium sulfate and the solvent is removed under reduced pressure. The product is purified by crystallization.

Procedures (B 2, B 16) for Phase Transfer Catalyzed Alkylations

20 mmol N-substituted urea, 3.20 g (80 mmol) sodium hydroxide, or alternatively 4.50 g (80 mmol) potassium hydroxide (both may be in pellet form and need not to be powdered, and both give the same results), 0.55 g (4 mmol) dry potassium carbonate and 280 mg (1 mmol) tetrabutylammonium chloride (Fluka; purified by crystallization from acetone and dried over silica gel at 90–100°C under argon atmosphere) are suspended in 40 ml of toluene, which is dried by distillation over metallic sodium and benzophenone, and 20 mmol of alkylating agent (haloalkane, methanesulfonic ester, 4-toluenesulfonic ester or 10 mmol of dialkyl sulfate) are added. The vigorously stirred reaction mixture is heated to reflux and kept at this temperature for a reaction time between 2 (B 2) and 16 h (B 16). After cooling below 100°C the reaction mixture is poured into 150 ml of cold distilled water and extracted with 50 ml chloroform and 50 ml dichloromethane. The collected organic layers are washed with 100 ml distilled water, the aqueous layer reextracted with 50 ml chloroform and 50 ml dichloromethane, the organic layers collected again, dried over sodium sulfate and the solvent removed in vacuo at 55°C. The product is purified by crystallization from the solvent given.

Kinetics

0.58 g (5 mmol) N-butylurea, 0.80 g (20 mmol) sodium hydroxide, 0.14 g (1 mmol) potassium carbonate and 70 mg (0.05 mmol) tetrabutylammonium chloride (I), and 1.16 g (10 mmol) N-butylurea, 1.60 g (40 mmol) sodium hydroxide, 0.28 g (2 mmol) potassium carbonate and 140 mg (0.1 mmol) tetrabutylammonium chloride (II) were suspended in 20 ml toluene. In both cases 0.68 g (5 mmol) 1-bromobutane were added and the well stirred solution was heated to reflux. After 10 min the reaction was quenched by addition of 20 ml distilled water. The reaction mixture was worked up as described above and the yields of N,N'-dibutylurea were determined: I: 30 mg (0.1741 mmol; turnover $X_{t1} = 0.03482$), II: 62 mg (0.3588 mmol; turnover $X_{t2} = 0.07176$).

N,N'-Dibutylurea

This compound [15, 16] was prepared using procedure (A) from 1.16 g (10 mmol) N-butylurea and 1.36 g (10 mmol) 1-bromobutane; Yield: 0.59 g = 17%. It was also prepared using methods (B 2) and (B 16) from 2.32 g (20 mmol) N-butylurea and 2.74 g (20 mmol) 1-bromobutane or 1.84 g (20 mmol) 1-chlorobutane; Yield(B 2); 2.83 g = 82% (1-bromobutane); 0.72 g = 21% (1-chlorobutane); yield(B 16): 2.58 g = 75% (1-bromobutane); 2.31 g = 67% (1-chlorobutane). Purification by crystallization from *n*-hexane. M. p. 60.1°C; M. p. [15] 65°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 5.91 (t, 2, NH, $J_{\text{CH}_2\text{NH}} = 5.9$ Hz), 3.13 (dt, 4 H, butyl-1, $J_{\text{CH}_2\text{NH}} = 5.9$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.7$ Hz), 1.50–1.32 (m (tq), 8 H, butyl-2 und 3, $J_{\text{CH}_2\text{CH}_3} = 7.0$ Hz), 0.91 (t, 6 H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 7.0$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 159.64 (C=O), 39.87 (CH₂, butyl-1), 32.56 (CH₂, butyl-2), 20.08 (CH₂, butyl-3), 13.76 (CH₃, butyl-4) ppm. IR (KBr): 3 343, 1 622 (C=O), 1 580, 1 462, 1 234 cm⁻¹.

N-Hexylurea

This compound [17] was prepared using procedure (A) from 0.60 g (10 mmol) urea and 2.12 g (10 mmol) 1-iodohexane. Yield: 303 mg = 21%. Purification by crystallization from chloroform. M. p. 102.6°C; M. p. [17] 108.5–109°C. ¹H-NMR (DMSO, δ, 200 MHz): 5.90 (t, 1 H, NH, $J_{\text{CH}_2\text{NH}} = 5.3$ Hz), 5.36 (s, 2 H, NH₂), 2.91 (dt, 2 H, hexyl-1, $J_{\text{CH}_2\text{NH}} = 5.3$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.4$ Hz), 1.31–1.23 (m, 8 H, hexyl-2-5, $J_{\text{CH}_2\text{CH}_3} = 6.5$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.4$ Hz), 0.85 (t, 3 H, hexyl-6, $J_{\text{CH}_2\text{CH}_3} = 6.5$) ppm. ¹³C-NMR (DMSO, δ, 50 MHz): 158.81 (C=O), 39.21 (CH₂, hexyl-1), 31.13, 30.02, 26.14, 22.16 (CH₂, hexyl-2 to 5), 13.94 (CH₃, hexyl-6) ppm. IR (KBr): 3 399, 1 659 (C=O), 1 603, 1 533, 1 481, 1 468 cm⁻¹.

N-Decylurea

This compound [18] was prepared by procedure (A) from 0.60 g (10 mmol) urea and 2.21 g (10 mmol) 1-bromodecane. Yield: 240 mg = 12%. Purification by crystallization from chloroform. M. p. 110.5°C; M. p. [18] 113°C. ¹H-NMR (DMSO, δ, 200 MHz): 5.87 (t, 1 H, NH, $J_{\text{CH}_2\text{NH}} = 6.0$ Hz), 5.34 (s, 2 H, NH₂), 2.91 (dt, 2 H, decyl-1, $J_{\text{CH}_2\text{NH}} = 6.0$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.2$ Hz), 1.24 (m, 16 H, decyl-2 to 9, $J_{\text{CH}_2\text{CH}_3} = 6.6$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.2$ Hz), 0.86 (t, 3 H, decyl-10, $J_{\text{CH}_2\text{CH}_3} = 6.6$ Hz) ppm. ¹³C-NMR (DMSO, δ, 50 MHz): 158.67 (C=O), 39.11 (CH₂, decyl-1), 31.29, 30.00, 29.07, 28.98, 28.84, 28.71, 26.42, 22.09 (CH₂, decyl-2 to 9), 13.93 (CH₃, decyl-10) ppm. IR (KBr): 3 393, 1 659 (C=O), 1 603, 1 535, 1 468, 1 350 cm⁻¹.

N-Butyl-N'-ethylurea

This compound [19] was prepared using method (B 2) from 2.32 g (20 mmol) N-butylurea and 2.16 g (20 mmol) 1-bromoethane, 2.48 g (20 mmol) ethylmesylate or 4.00 g (20 mmol) ethyltosylate or 1.54 g (10 mmol) diethyl sulfate. Yield: 2.19 g = 76% (1-bromoethane); 2.05 g = 71% (ethylmesylate); 2.13 g = 74% (ethyltosylate); 2.31 g = 80% (diethyl sulfate); Yield starting from 1.76 g (20 mmol) N-ethylurea and 2.74 g (20 mmol) 1-bromobutane according to method (B 2): 2.05 g = 71%. Purification

by crystallization from *n*-hexane. M. p. 57.6°C; M. p. [19] 57–58°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 5.74 (2t, 2H; 2NH), 3.22–3.12 (m, 4H, butyl-1 and ethyl-1), 1.46–1.32 (m, 4H, butyl-2 and 3), 1.11 (t, 3H, ethyl-2-, $J_{\text{CH}_2\text{CH}_3} = 6.5$ Hz), 0.91 (t, 3H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 6.5$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 159.44 (C=O), 39.87 (CH₂, butyl-1), 34.86 (CH₂, ethyl-1), 32.51 (CH₂, butyl-2), 20.07 (CH₂, butyl-3), 15.57 (CH₃, ethyl-2), 13.78 (CH₃, butyl-4) ppm. IR (KBr): 3318, 1626(C=O), 1585, 1242cm⁻¹.

N-Butyl-*N'*-isopropylurea [C₈H₁₈N₂O]

was prepared using the methods (B 2) and (B 16) from 2.32 g (20 mmol) *N*-butylurea and 2.46 g (20 mmol) 2-bromopropane. Yield (B 2): 0.79 g = 25%; yield (B 12): 0.57 g = 18%. Yield (B 2) starting from 2.04 g (20 mmol) *N*-isopropylurea and 2.74 g (20 mmol) 1-bromobutane: 1.84 g = 58%. Purification by crystallization from *n*-hexane. M. p. 75.7°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 5.71 (t, 1H, butyl-NH, $J_{\text{CH}_2\text{NH}} = 5.5$ Hz), 5.49 (d, 1H, isopropyl-NH, $J_{\text{CHNH}} = 7.9$ Hz), 3.86 (dse, 1H, isopropyl-CH, $J_{\text{CHNH}} = 7.9$ Hz, $J_{\text{CHCH}_3} = 6.5$ Hz), 3.14 (dt, 2H butyl-1; $J_{\text{CH}_2\text{NH}} = 5.5$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.7$ Hz), 1.49–1.27 (m, 4H, butyl-2 and 3, $J_{\text{CH}_2\text{CH}_3} = 7.0$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.7$ Hz), 1.12 (d, 6H, isopropyl-CH₃, $J_{\text{CHCH}_3} = 6.5$ Hz), 0.91 (t, 3H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 7.0$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 158.72(C=O), 41.62 (CH, isopropyl-CH), 39.89 (CH₂, butyl-1), 32.56 (CH₂, butyl-2), 23.45 (CH₃, isopropyl-CH₃), 20.09 (CH₂, butyl-3), 13.80 (CH₃, butyl-4) ppm. IR (KBr): 3340, 1622(C=O), 1575, 1242 cm⁻¹. MS (70 eV; 40°C): *m/e* (%) = 158 (12, *M*⁺), 143 (3), 87 (4), 58 (17), 44 (100), 43 (15), 41 (15), 31 (83), 30 (89).

N-Butyl-*N'*-*tert*-butylurea [C₉H₂₀N₂O]

was prepared using method (B 2) from 2.32 g (20 mmol) *N*-*tert*-butylurea and 2.74 g (20 mmol) 1-bromobutane: Yield: 1.62 g = 47%. Purification by crystallization from *n*-hexane. M. p. 71.0°C. ¹H-NMR (CDCl₃, δ, 200 MHz), 5.42 (t, 1H, butyl-NH, $J_{\text{CH}_2\text{NH}} = 5.9$ Hz), 5.24 (s, 1H, *tert*-butyl-NH), 3.09 (q, 2H, butyl-1, $J_{\text{CH}_2\text{NH}} = 5.9$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.0$ Hz), 1.44–1.37 (m; 4H, butyl-2 and 3, $J_{\text{CH}_2\text{CH}_3} = 6.9$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.0$ Hz), 1.31 (s, 9H, *tert*-butyl-CH₃), 0.90 (t, 3H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 6.9$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 158.53 (C=O), 49.86 (C, *tert*-butyl-C), 39.71 (CH₂, butyl-1), 32.53 (CH₂, butyl-2), 29.60 (CH₃, *tert*-butyl-CH₃), 20.11 (CH₂, butyl-3), 13.81 (CH₃, butyl-4) ppm. IR (KBr): 3362, 1636 (C=O), 1562, 1450, 1362, 1279 cm⁻¹. MS (70 eV; 40°C): *m/e* (%) = 172 (8, *M*⁺), 157 (8), 58 (100), 57 (15), 44 (7), 41 (13).

N'-Butyl-morpholine-*N*-carboxamide [C₉H₁₈N₂O₂]

was prepared using method (B 2) from 2.60 g (20 mmol) *N*-morpholinecarboxamide and 2.74 g (20 mmol) 1-bromobutane: Yield: 3.17 g = 85%. Purification by crystallization from toluene. M. p. 72.9°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 5.41 (t, 1H, NH, $J_{\text{CH}_2\text{NH}} = 6.0$ Hz), 3.66 (t, 4H, morpholine-CH₂O, $J_{\text{CH}_2\text{CH}_2} = 5.0$ Hz), 3.36 (t, 4H, morpholine-CH₂-N, $J_{\text{CH}_2\text{CH}_2} = 5.0$ Hz), 3.19 (dt, 2H, butyl-1, $J_{\text{CH}_2\text{NH}} = 6.0$ Hz, $J_{\text{CH}_2\text{CH}_2} = 6.7$ Hz), 1.52–1.27 (m, 4H, butyl-2 und 3, $J_{\text{CH}_2\text{CH}_2} = J_{\text{CH}_2\text{CH}_3} = 6.7$ Hz), 0.92 (t, 3H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 6.7$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 158.09 (C=O), 66.44 (CH₂, morpholine-CH₂O), 43.92 (CH₂, morpholine-CH₂N), 40.52 (CH₂, butyl-1), 32.23 (CH₂, butyl-2), 19.98 (CH₂, butyl-3), 13.73 (CH₃, butyl-4) ppm. IR (KBr): 3352, 1622 (C=O), 1543, 1271, 1111 cm⁻¹. MS (70 eV, 70°C): *m/e* (%) = 186 (12, *M*⁺), 155 (7), 129 (8), 114 (35), 100 (5), 88 (8), 87 (51), 86 (32), 72 (6), 70 (27), 58 (6), 57 (100), 56 (23), 55 (5), 44 (18), 42 (20), 41 (11).

N'-Isopropyl-morpholine-*N*-carboxamide [C₈H₁₆N₂O₂]

was prepared using method (B 2) from 2.60 g (20 mmol) *N*-morpholinecarboxamide and 2.46 g (20 mmol) 2-bromopropane. Yield: 0.55 g = 16%. Purification by crystallization from toluene. M. p. 142.4°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 4.56 (d, 1H, NH, $J_{\text{CHNH}} = 6.7$ Hz), 3.97 (dse, 1H, isopropyl-

CH, $J_{\text{CHNH}} = 6.7$ Hz, $J_{\text{CHCH}_3} = 6.6$ Hz), 3.68 (t, 4 H, morpholine-CH₂O, $J_{\text{CH}_2\text{CH}_2} = 4.9$ Hz), 3.33 (t; 4 H, morpholine-CH₂N, $J_{\text{CH}_2\text{CH}_2} = 4.9$ Hz), 1.15 (d, 6 H, isopropyl-CH₃, $J_{\text{CHCH}_3} = 6.6$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 157.24 (C=O), 66.46 (CH₂, morpholine-CH₂O), 43.93 (CH₂, morpholine-CH₂N), 42.50 (CH, isopropyl-CH), 23.31 (CH₃, isopropyl-CH₃) ppm. IR (KBr): 3 342, 1 618 (C=O), 1 541, 1 261, 1 114 cm⁻¹. MS (70 eV; 40°C): m/e (%) = 172 (11, M^+), 141 (8), 114 (20), 87 (35), 86 (23), 70 (26), 58 (21), 57 (100), 56 (25), 44 (14), 43 (27), 42 (27), 41 (12), 32 (5).

N'-Butyl-pyrrolidine-*N*-carboxamide [C₉H₁₈N₂O]

was prepared using methods (B 2) and (B 16) from 2.28 g (20 mmol) N-pyrrolidinecarboxamide and 2.74 g (20 mmol) 1-bromobutane. Yield (B 2): 1.40 g = 41%; Yield (B 16): 2.38 g = 70%. Purification by crystallization from *n*-hexane. M. p. 66.2°C. ¹H-NMR (CDCl₃, δ, 200 MHz): 4.39 (t, 1 H, NH, $J_{\text{CH}_2\text{NH}} = 5.8$ Hz), 3.34 (t, 4 H, pyrrolidine-2 and 5, $J_{23} = 6.7$ Hz), 3.22 (dt, 2 H, butyl-1, $J_{\text{CH}_2\text{NH}} = 5.8$ Hz, $J_{\text{CH}_2\text{CH}_2} = 7.0$ Hz), 1.89 (tt, 4 H, pyrrolidine-3 und 4, $J_{23} = 6.7$ Hz, $J_{34} = 3.5$ Hz), 1.54–1.29 (m, 4 H, butyl-2 und 3, $J_{\text{CH}_2\text{CH}_2} = 7.0$ Hz, $J_{\text{CH}_2\text{CH}_3} = 7.1$ Hz), 0.92 (t, 3 H, butyl-4, $J_{\text{CH}_2\text{CH}_3} = 7.1$ Hz) ppm. ¹³C-NMR (CDCl₃, δ, 50 MHz): 156.96 (C=O), 45.41 (CH₂, pyrrolidine-2 and 5), 40.28 (CH₂, butyl-1), 32.61 (CH₂, butyl-2), 25.52 (CH₂, pyrrolidine-3 and 4), 20.03 (CH; butyl-3), 13.78 (CH₃, butyl-4) ppm. IR (KBr): 3 339, 1 622 (C=O), 1 543, 1 400, 1 366 cm⁻¹. MS (70 eV; 40°C): m/e (%) = 170 (23, M^+), 141 (13), 128 (6), 127 (8), 114 (13), 112 (11), 100 (11), 99 (7), 98 (93), 86 (21), 72 (17), 71 (31), 70 (100), 56 (24), 55 (40), 43 (49), 41 (10), 40 (25), 32 (9).

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