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α-HALOALKYL HALOFORMATES AND RELATED COMPOUNDS 3.[1] A FACILE SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL UREAS *via* CHLOROMETHYL CARBAMATES

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ABSTRACT - Chloromethyl carbamates were prepared by the reaction of chloromethyl chloroformates with amines and found to produce mono-, symmetrically or unsymmetrically di- and trisubstituted ureas including their N-hydroxy and N-alkoxy derivatives in moderate to good yield.

Ureas have importance as pesticides and pharmaceuticals. The unsymmetrically disubstituted urea unit is a frequent structural feature of many enzyme inhibitors and peptidomimetics.[3-5] A number of methods are known for the synthesis of ureas[6] but many procedures utilize phosgene or phosgene-based isocyanates or carbamoyl chlorides. To avoid the use of the highly toxic phosgene or of the isocyanates alternative synthetic methods have been published in the last decades. These procedures often employ symmetrically or unsymmetrically substituted activated derivatives of carbonic acid as bifunctional carbonylating agents such as

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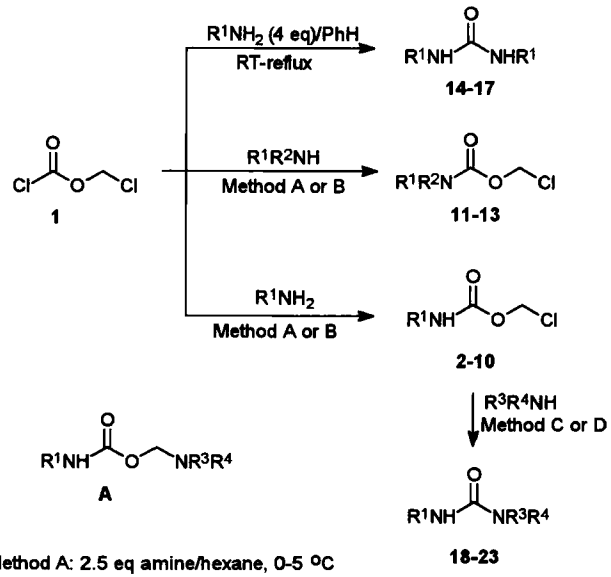
1,1'-carbonyldiimidazole and -1,2,4-triazole,[7] 3,3'-carbonylbis[5-phenyl-1,3,4-oxadiazole-2(3H)-thione],[8] di(2-pyridyl) carbonate,[9] bis(4-nitrophenyl) carbonate[10] 2(S),3-pyridinediyl thiolcarbonate,[11] 5-nitrobenzo-1,3-dioxol-2-one,[12] 4,6-diphenylthieno[3,4-*d*]-1,3-dioxol-2-one 5,5-dioxide,[13] bis(trichloromethyl) carbonate ("triphosgene"),[4,14] (phenoxycarbonyl)tetrazol[15] and a number of chloroformates, *e.g.* p-nitrophenyl,[16] 2,4,5-trichlorophenyl,[17] trichloromethyl ("diphosgene"),[18] 1-chloroethyl and 1,2,2,2-tetrachloroethyl[19] and norborn-5-en-2,3-dicarboximidyl[20] chloroformates. Related method based on the decomposition of N-substituted trichloroacetamides in the presence of bases was also reported.[21] However, many of these reagents go back to phosgene or are unsuitable for the synthesis of unsymmetrical ureas.

Recently we have reported that chloromethyl carbonates prepared from chloromethyl chloroformate (CMCF) (**1**) are smoothly transformed to carbamates upon treatment of amines.[22] CMCF (**1**) is easily available by photochlorination of methyl formate[23,24] or methyl chloroformate[25,26]. The high nucleofugacity of the chloromethoxide anion and its easy decomposition to formaldehyde and chloride ion makes the chloromethyl carbonates good acylating agents under mild conditions. Dichloromethyl carbonates obtained from dichloromethyl chloroformate were found to react similarly.[1] Here we report our studies on the reaction of chloroformate **1** with amines. The resulting chloromethyl N-mono- and N,N-disubstituted carbamates are transformed into mono-, symmetrically and unsymmetrically di-, and trisubstituted ureas, including N-hydroxylated and N-alkoxylated derivatives.

The chloromethyl N-alkyl carbamates **2-8** and N,N-dialkyl carbamates **11,13** were prepared from chloroformate **1** with 2.5 equivalent of the corresponding amine (Method A). Previously Sennyey *et al.*[19] reported the analogous synthesis of 1,2,2,2-tetrachloroethyl carbamates at reflux temperature without any excess of amine or added base, although an easy thermal hydrogen chloride elimination from the 1-chloroethyl and 1,2,2,2-tetrachloroethyl carbamates is reported elsewhere.[27] With excess of amine as acid scavenger, the reaction took place below -5 °C giving yields usually higher than 70%. As by-products only small amount of symmetrical



Method A: 2.5 eq amine/hexane, 0-5 °C
Method B: 1 eq amine/1 eq TEA/CH_2Cl_2, 0-5 °C
Method C: 2 eq amine/hexane or EtOH/RT-reflux
Method D: 1 eq amine/1 eq TEA/EtOH, RT

	2,14	3,15	4,18	5,19	6,16	7,17,20	8,21	9,22	10,23	11,24	12,25	13
R1	iPr	Bu	iBu	tBu	cHx	Bn	PhCHMe	Ph	4-ClC$_6$H$_4$	Et	Ph	
R2	H	H	H	H	H	H	H	H	H	Et	Me	

	a	b	c	d	e	f	g	h	i	j	k	l
R3	H	iPr	sBu	tBu	cHx	Bn	Me	Et	iPr		H	Me
R4	H	H	H	H	H	H	Me	Et	iPr		OH	OMe

ureas were formed. The preparation of chloromethyl carbamates **9, 10, 12** from aromatic amines required the use of triethyl amine as a co-base (Method B). Carbamates **2-13** can be stored at room temperature for months without considerable decomposition; secondary carbamates **2-8** and particularly the N-aryl derivatives **9, 10** are more labile than tertiary carbamates **11, 13**. However, a vigorous decomposition of products **2-13** was observed at elevated temperature (120-150 °C).

When the benzene solution of CMCF (**1**) was treated with 4 equivalents of a primary amine at reflux temperature the N,N'-dialkyl ureas **14-17** were obtained in moderate yields. Noteworthy the reaction of CMCF (**1**) with secondary amines

failed to give ureas, only carbamates **11, 12** could be detected and isolated. The formation of ureas **14-17** demonstrates the leaving group property of the chloromethoxy functionality in chloromethyl N-alkyl carbamates.

To check the scope and limits of their reactivity, carbamates **2-13** were treated with various amines. Secondary carbamates **2-10** afforded the expected ureas **18-23** under mild conditions (Table) and no formation of carbamate **A**, the product of a nucleophilic displacement in the chloromethoxy group, was observed. The reaction is fairly sensitive to steric factors. Thus, α-branching in the carbamoyl functionality lowered the yield of the urea (Entries 2-4 or 6,16, Table). An additional evidence was supplied by the formation of N-benzyl N'-*tert*-butyl urea (**19f=20d**). This compound could be prepared in two ways: either from carbamate **5** with benzylamine (Entry 2, Table) or from carbamate **7** with *tert*-butylamine (Entry 9, Table). The latter route resulted in double yield which fact reveals the role of α-branchings in the carbamoyl unit. These two experiments support an acylation mechanism with considerable S_N character instead of a two-step, addition-elimination type mechanism with tetrahedral intermediate. The steric bulk of the amine reagent exerted a similar although weaker influence on the outcome of the reaction. (Entries 3,4 or 7,9, Table).

Another conclusion is that the reactions performed in the more polar ethanol resulted in higher yields than in the nonpolar hexane (*cf.* Entries 7,8 or 12,13 or 14,15, Table). However, the use of hexane medium promoted the precipitation of the urea and allowed an easy work-up, thus, this procedure may also have synthetic value. Advantage of hexane was demonstrated by the treatment of carbamate **7** with aqueous ammonia (Entry 5, Table) and of carbamate **9** with aqueous dimethyl amine solution (Entry 18, Table). A modest yield of urea was achieved in both cases in spite of the strongly basic conditions.

In contrast to the secondary carbamates **2-10**, the tertiary substrates **11-13** failed to afford any tri- or tetrasubstituted ureas. When N,N-diethyl carbamate **11** was treated with benzylamine in hexane for 54 h under the conditions of Method B, 53% of starting material was recovered but no formation of N-benzyl N',N'-diethyl

Table. Synthesis and Physical Constants of Unsymmetrical Ureas **19-24**

Entry	Reagents	Method	Conditions			Product	Yield
			Solvent	Temp.	Time (h)		(%)
1	**4** + $sBuNH_2$	C	hexane	reflux	3.5	**18c**	32
2	**5** + $BnNH_2$	C	hexane	RT	1.5	**19f**	18
3	**5** + iPr_2NH	C	hexane	RT	3.0	**19i**	0[a]
4	**5** + piperidine	C	hexane	reflux	3.5	**19j**	23[b]
5	**7** + NH_3	[c]	hexane-H_2O	RT	2.1	**20a**	22
6	**7** + $iPrNH_2$	C	hexane	RT	4.0	**20b**	69
7	**7** + $sBuNH_2$	C	hexane	reflux	4.0	**20c**	48
8	**7** + $sBuNH_2$	C	EtOH	RT	24	**20c**	59
9	**7** + $tBuNH_2$	C	hexane	RT	3.25	**20d=19f**	35
10	**7** + $cHxNH_2$	C	CH_2Cl_2	RT	5.0	**20e**	31
11	**7** + $cHxNH_2$	C	hexane	RT	1.4	**20e**	66
12	**7** + Et_2NH	C	hexane	40 °C	3.75	**20h**	37[d]
13	**7** + Et_2NH	C	EtOH	RT	24	**20h**	56[d]
14	**7** + iPr_2NH	C	hexane	40 °C	7.0	**20i**	36[d]
15	**7** + iPr_2NH	C	EtOH	RT	22	**20i**	78
16	**8** + $iPrNH_2$	C	hexane	RT		**21b**	45
17	**9** + $sBuNH_2$	C	PhH	[e]	6	**22c**	75
18	**9** + Me_2NH	[c]	hexane-H_2O	RT	21	**22g**	47
19	**9** + Me_2NH	C	EtOH	RT	4	**22g**	81
20	**9** + piperidine	C	hexane	[e]	6	**22j**	59
21	**9** + NH_2OH	D	EtOH	RT	3.5	**22k**	39
22	**10** + $cHxNH_2$	C	EtOH	RT	3.5	**23e**	71
23	**10** + Me_2NH	C	EtOH	RT	23	**23g**	89
24	**10** + NH_2OH	D	EtOH	RT	7.25	**23k**	75
25	**10** + MeNHOMe	D	EtOH	RT	3.5	**23l**	94

[a] 74 % unreacted starting material was recovered.
[b] 22 % unreacted starting material was recovered.
[c] See Experimental Part
[d] Isolated by column chromatography (toluene-abs. metanol (10:1, v/v))
[e] 5 hrs stirring at room temperature followed by 1 hr reflux.

urea (**20h**), available from secondary carbamate **7** and diethylamine in 37% yield (*cf.* Entry 12, Table), was observed. The only reaction of the tertiary carbamates **11-13** was their slow decomposition to the parent secondary amine. Thus, N-methylaniline was isolated (75%) from the reaction mixture of carbamate **12** and cyclohexylamine in ethanol solution at room temperature after a 7-h period. The

sharp difference in the reactivity of secondary and tertiary carbamates is not unprecedented, a same behavior was reported for some other activated carbonic acid derivatives.[9-11,13] To explain the difference, steric hindrance in the tertiary carbamate has been suggested[13] but the lack of hydrogen bond-type interaction between the N-H and the carbonyl oxygen may also destabilize the transition state.

Hydroxylamine and N,O-dimethyl hydroxylamine reacted successfully as amine components with N-aryl carbamates **9, 10** (Entries 21, 24 and 25, Table). Ambident nucleophile hydroxylamine was found to react exclusively as N nucleophile. The same selectivity was reported for trichloromethyl carbamates[4] and (acyloxyalkyl) α-ethers[28] and could be rationalized in terms of the favored interaction between the carbonyl center with high kinetic electrophilicity and the more basic nitrogen atom. Since other 1-chloroalkyl carbamates failed to yield any urea products and even 1,2,2,2-tetrachloroethyl carbamates afforded ureas only in modest yield[19], the structure of the chloroalkyloxy nucleofug seem to play a decisive role.

In summary, we have demonstrated that chloromethyl N-alkyl and N-aryl carbamates can be used for the synthesis of mono-, symmetrically or unsymmetrically di- and trisubstituted ureas including their N-hydroxy and N-alkoxy derivatives.

Experimental

Triethylamine was distilled from LAH. CMCF (**1**) was prepared by photochlorination[24]. Mp's were measured on a Boetius hot-stage apparatus. IR spectra were measured on a Perkin-Elmer 283 or Perkin-Elmer 16 PC FT-IR spectrometer in KBr discs unless otherwise stated. ^{1}H NMR (200 MHz) spectra were acquired on a Bruker WP 200 SY instrument in $CDCl_3$ solution with the internal standard TMS (δ = 0 ppm). Microanalyses were measured on a Carlo Erba EA 1106 analyser. MS (EI, 70 eV) was taken on a VG-7035 GC-MS-DS system. GC was measured on a Chrom 5 gas chromatograph equipped with capillar column (2.4 m, 3% OV-101); carrier gas: N_2, starting temperature: 70 °C for 2 min, temperature gradient: 10 °C/min up to 210-250 °C). TLC's were performed on Kieselgel 60 F_{254} (Merck) sheets and were detected under UV light or in iodine chamber. Kieselgel 60 (0.063-0.2 mm) was used for column chromatography. Anhydrous $MgSO_4$ served as drying agent. Yields are not optimized.

Synthesis of Chloromethyl Carbamates 2-13; General Procedures.

Method A. A solution of the amine (0.15 mol) in hexane (50 mL) was added dropwise to a cooled (-5 to -10 °C) and stirred solution of CMCF (**1**) (5.28 mL, 60.0 mmol) in hexane (100 mL) in 1 h. Stirring was continued for 1-4 h, then the precipitate was filtered off and washed with water. Solid carbamates were purified by crystallization from hexane or toluene-hexane mixture. In the case of liquid carbamates, the filtrate was washed successively with 10 % aq HCl, 5 % aq $NaHCO_3$ and water. Drying, evaporation under reduced pressure and short column chromatography (hexane-EtOAc = 4:1, v/v or toluene-EtOAc = 4:1, v/v) afforded the pure product.

Method B. A solution of aniline (0.10 mol) and triethylamine (15.0 mL, 0.107 mol) in abs. CH_2Cl_2 (35 mL) was dropped into the cooled (0-5 °C) and stirred solution of CMCF (**1**) (9.25 mL, 0.105 mol) in abs. CH_2Cl_2 (100 mL) in 45 min. When the reaction was complete (TLC monitoring), the mixture was poured on crushed ice (150 mL). Extraction with CH_2Cl_2 (2x100 mL), drying, evaporation and crystallization from hexane-toluene mixture furnished the pure product.

Chloromethyl N-isopropyl carbamate (2). Yield: 42% (Method A, 1.25h). Oil, GC RT = 7.0 min. IR (neat) 3325 (NH), 2976, 1735 (C=O), 1520 (Amide-II), 1460, 1368, 1235, 1085, 740, 690 cm^{-1}. ^1H NMR 1.19 (d, 6H, $CHMe_2$), 3.87 (m, 1H, $CHMe_2$), 4.85 (br s, 1H, NH), 5.75 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_5H_{10}ClNO_2$ (151.59): C, 39.62; H, 6.65; N, 6.65. Found: C, 39.43; H, 6.79; N, 8.99.

Chloromethyl N-butyl carbamate (3). Yield: 80% (Method A, 1.25 h). Oil, GC RT = 9.9 min. IR (neat) 3330 (NH), 2955, 2922, 2867, 1725 (C=O), 1520 (Amide-II), 1456, 1439, 1240, 1115, 1060, 1040, 695 cm^{-1}. ^1H NMR 0.93 (t, 3H, Me), 1.23-1.59 (m, 4H, $Me(CH_2)_2CH_2$), 3.24 (q, 2H, $Me(CH_2)_2CH_2$), 4.90 (br s, 1H, NH), 5.75 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_6H_{12}ClNO_2$ (165.62): C, 43.51; H, 7.30; N, 8.46. Found: C, 43.44; H, 7.03; N, 8.57.

Chloromethyl N-isobutyl carbamate (4). Yield: 71% (Method A, 1.25 h). Oil, GC RT = 9.0 min. IR (neat) 3325 (NH), 2958, 2923, 1730 (C=O), 1530 (Amide-II), 1236, 1116, 1087, 1029, 693 cm^{-1}. ^1H NMR 0.93 (d, 6H, Me_2), 1.80 (m, 1H, Me_2CHCH_2), 3.06 (dd, 2H, Me_2CHCH_2), 4.99 (br s, 1H, NH), 5.76 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_6H_{12}ClNO_2$ (165.62): C, 43.51; H, 7.30; N, 8.46. Found: C, 43.59; H, 7.12; N, 8.33.

Chloromethyl N-*tert*-butyl carbamate (5). Yield: 52% (Method A, 1.33 h). Mp 58.5-60 °C. GC RT = 6.9 min. IR 3336 (NH), 2978, 2965, 1753, 1718 (C=O), 1532 (Amide-II), 1270, 1218, 1110, 1088, 684 cm^{-1}. ^1H NMR 1.35 (s, 3H, tBu), 4.85 (br s, 1H, NH), 5.72 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_6H_{12}ClNO_2$ (165.62) C, 43.51; H, 7.30; N, 8.46. Found: C, 43.36; H, 7.25; N, 8.35.

Chloromethyl N-cyclohexyl carbamate (6). Yield: 79% (Method A, 2.75 h). Mp 38-41 °C. GC RT = 12.5 min. IR 3335 (NH), 2940, 2868, 1725 (C=O), 1539 (Amide-II), 1457, 1321, 1282, 1260, 1238, 1142, 1067, 703 cm^{-1}. ^1H NMR 1.03-1.43, 1.75, 1.95 (m, 10 H, $(CH_2)_5$), 3.53 (m, 1H, CHN), 4.88 (br s, 1H, NH), 5.75 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_8H_{14}ClNO_2$ (191.66): C, 50.14; H, 7.36; N, 7.31. Found: C, 49.98; H, 7.30; N, 7.07.

2.6 % N,N'-dicyclohexyl urea (**17**) was also isolated as by-product.

Chloromethyl N-benzyl carbamate (7). Yield: 91% (Method A, 1.25 h). Mp 49-51 °C. GC RT = 14.5 min. IR 3300 (NH), 1720 (C=O), 1554 (Amide-II), 1440, 1278, 1258, 1190, 1051, 702 cm^{-1}. ^1H NMR 4.42 (d, J = 6, 2H, PhC**H**$_2$), 5.24 (br s, 1H, NH), 5.78 (s, 2H, OCH_2Cl), 7.31 (m, 5H, Ph). Anal. Calcd. for $C_9H_{10}ClNO_2$ (199.64): C, 54.15; H, 5.05; N, 7.02. Found: C, 54.27; H, 5.02; N, 6.79.

Chloromethyl N-(1-phenylethyl) carbamate (8). Yield: 68% (Method A, 1.33 h). Mp 51.5-52.5 °C. IR 3318 (NH), 1740, 1708 (C=O), 1532 (Amide-II), 1236, 1074, 1058, 700 cm^{-1}. ^1H NMR 1.53 (d, 3H, Me), 4.89 (m, 1H, PhC**H**Me), 5.18 (br s, 1H, NH), 5.69, 5.78 (AB q, 2H, OCH_2Cl), 7.32 (m, 5H, Ph). Anal. Calcd. for $C_{10}H_{12}ClNO_2$ (213.66): C, 56.21; H, 5.66; N, 6.56. Found: C, 55.98; H, 5.60; N, 6.35.

Chloromethyl N-phenyl carbamate (9). Yield: 73% (Method B, 3.75 h). Mp 80-82 °C. IR 3318 (NH), 1718 (C=O), 1600, 1540 (Amide-II), 1443, 1612, 1241, 1210, 1070, 748, 683 cm^{-1}. ^1H NMR 5.83 (s, 2H, OCH_2Cl), 6.92 (br s, 1H, NH), 7.11 (m, 1H, one H of Ph), 7.29-7.44 (m, 4H, rest H's of Ph). Anal. Calcd. for $C_8H_8ClNO_2$ (185.61): C, 51.77; H, 4.34; N, 7.55. Found: C, 51.93; H, 4.12; N, 7.51.

Chloromethyl N-(4-chlorophenyl) carbamate (10). Yield: 80% (Method B, 4 h). Mp 81.5-82 °C. IR 3294 (NH), 1745, 1723 (C=O), 1599, 1541 (Amide-II), 1490, 1308, 1220, 1081, 827, 667 cm^{-1}. ^1H NMR 5.83 (s, 2H, OCH_2Cl), 6.78 (br s, 1H, NH), 7.38, 7.30 (A_2B_2 q, 4H, 2,3,5,6-H). Anal. Calcd. for $C_8H_7Cl_2NO_2$ (220.06): C, 43.67; H, 3.21; N, 6.37. Found: 43.35; H, 3.16; N, 6.57.

Chloromethyl N,N-diethyl carbamate (11). Yield: 92% (Method A, 1.25 h). Oil, Lit.[26] bp 54-55 °C/1.1 mmHg. GC RT = 7.6 min. IR (neat) 2982, 2940, 1728 (C=O), 1480, 1446, 1423, 1384, 1268, 1226, 1142, 1076, 1021, 763, 708 cm^{-1}. ^1H NMR 1.15 (t, 6H, CH_2CH_3), 3.33 (2xq, 4H, CH_2CH_3), 5.82 (s, 2H, OCH_2Cl).

Caution! A vigorous decomposition which resulted in low isolated yield (24%) was observed during the attempted distillation at normal pressure, bp ca. 188-190 °C.

Chloromethyl N-methyl-N-phenyl carbamate (12). Yield: 73% (Method B, 4 h). Oil. IR (neat) 1727 (C=O), 1597, 1493, 1446, 1376, 1330, 1294, 1146, 1113, 1076, 1064, 1034, 1021, 764 cm^{-1}. ^1H NMR 3.35 (s, 3H, NMe), 5.75 (s, 2H, OCH_2Cl), 7.25, 7.39 (m, 5H, Ph). Anal. Calcd. for $C_9H_{10}ClNO_2$ (199.64): C, 54.15; H, 5.05; N, 7.02. Found: C, 53.88; H, 5.34; N, 6.77.

1-(Chloromethoxycarbonyl)piperidine (13). Yield: 85% (Method A, 1.66 h). Oil, GC RT = 10.7 min. IR (neat) 2930, 2854, 1725 (C=O), 1444, 1420, 1382, 1333, 1283, 1256, 1227, 1140, 1080, 1027, 947, 852, 758, 692 cm^{-1}. ^1H NMR 1.59 (m, 6H, 3,4,5-CH_2), 3.48 (m, 4H, 2,6-CH_2), 5.80 (s, 2H, OCH_2Cl). Anal. Calcd. for $C_7H_{12}ClNO_2$ (177.63): C, 47.33; H, 6.81; N, 7.89. Found: C, 47.12; H, 7.05; N, 7.67.

Synthesis of Symmetrical Ureas 14-17; General Procedure.

A solution of the primary amine (0.121 mol) in abs. benzene (15 mL) was added in 10 min to a stirred solution of CMCF (1) (2.6 mL, 29.73 mmol) in abs. benzene (15 mL). The mixture was refluxed for 1 h, cooled to room temperature and allowed to stand at 0 °C for 2 h. Filtration, washing with benzene and water gave the pure urea.

N,N'-diisopropylurea (14). Yield: 61 %. Mp 188-191 °C. Lit.[29] mp 192 °C. IR 3337 (NH), 2963, 1620 (C=O), 1570 (Amide-II), 1520, 1463, 1248, 1169, 1129 cm^{-1}. ^1H NMR 1.15 (d, 12H, Me), 3.85 (m, 2H, CH), 4.20 (br s, 2H, NH).

N,N'-dibutylurea (15). Yield: 42 %. Mp 65-68 °C. Lit.[30] mp 71 °C. IR 3338 (NH), 2962, 2938, 2876, 1630 (C=O), 1582 (Amide-II), 1467, 1282, 1247 cm^{-1}. ^1H NMR 0.92 (t, 3H, Me), 1.39 (m, 4H, $NHCH_2(CH_2)_2Me$), 3.11 (t, 2H, $NHCH_2(CH_2)_2Me$), 4.82 (br s, 2H, NH).

N,N'-dicyclohexylurea (16). Yield: 54 %. Mp 232 °C. Lit.[31] mp 229-230 °C.

N,N'-dibenzylurea (17). Yield: 32 %. Mp 169-171 °C. Lit.[32] mp 170-173 °C. IR 3328 (NH), 3038, 1633 (C=O), 1577 (Amide-II), 1496, 1457, 1260, 753, 732, 698 cm^{-1}. ^1H NMR (DMSO-d_6) 4.24 (d, 4H, CH_2), 6.45 (t, 2H, NH), 7.27 (m, 10H, Ph).

No ureas formed from CMCF (**1**) and diethyl amine or piperidine under the same conditions. From the reaction mixture of diethyl amine and **1** only carbamate **11** (20%) was isolated.

Synthesis of Unsymmetrical Ureas 18-23; General Procedures.

Method C. A solution of the amine (30.00 mmol) in the solvent (10 mL) specified in the Table was added dropwise to the stirred suspension or solution of chloromethyl carbamate **2-10** (15.00 mmol) in the same solvent (20 mL). After completion of the reaction the precipitate was filtered off and when hexane was used as solvent, the solid was washed with water and the residue was crystallized from hexane or hexane-EtOAc.

When ethanol, dichloromethane or benzene were used as solvent, the reaction mixture was poured into water, extracted with diethyl ether (3x50 mL). The organic extracts were washed successively with 5 % aq HCl, 5 % aq $NaHCO_3$ and water and dried. After removal of the solvent the residue was purified by crystallization.

Method D. A solution of triethylamine (11.2 mL, 80.00 mmol) in ethanol (30 mL) was added dropwise to the stirred solution of the carbamate **9** or **10** (20.00 mmol) and hydroxylammonium chloride or N,O-dimethylhydroxylammonium chloride (40.00 mmol) in ethanol (30 mL) at room temperature in 1 h. Stirring was continued for a period given in Table 2, then the mixture was neutralized with 2M aq HCl and concentrated *in vacuo*. The residue was triturated with water (20 mL), filtered off and recrystallized from ethanol-water.

For conditions and yields see the Table.

N-Isobutyl-N'-*sec*-butylurea (18c). Mp 85-88 °C. IR 3340 (NH), 2961, 2925, 1628 (C=O), 1568 (Amide-II), 1273, 1245 (Amide-III) cm^{-1}. Anal. Calcd. for $C_9H_{20}N_2O$ (172.27): C, 62.75; H, 11.70; N, 16.26. Found: C, 62.54; H, 11.85; N, 15.99.

N-Benzyl-N'-*tert*-butylurea (19f=20d). Mp 110-112 °C. IR 3362, 3322 (NH), 2975, 1635 (C=O), 1570 (Amide-II), 1530, 1452, 1359, 1290, 1221 (Amide-III) cm^{-1}. ^1H NMR 1.32 (s, 9H, tBu), 4.30 (d, J = 5.6, $PhCH_2$), 4.36, 4.62 (2x br s, 2x1H, 2xNH), 7.29 (m, 5H, Ph). Anal. Calcd. for $C_{12}H_{18}N_2O$ (206.29): C, 69.87; H, 8.79; N, 13.58. Found: C, 69.98; H, 8.55; N, 13.64.

1-[(*tert*-Butylamino)carbonyl]piperidine (19j). Mp 142-144 °C. IR 3370 (NH), 2938, 2850, 1624 (C=O), 1530 (Amide-II), 1476, 1456, 1392, 1360, 1284, 1272,

1256, 1214 (Amide-III), 1134, 990 cm^{-1}. ^1H NMR 1.35 (s, 9H, tBu), 1.56 (m, 6H, 3,4,5-CH_2), 3.26 (m, 4H, 2,6-CH_2), 4.30 (br s, 1H, NH). MS 184 (M^+, 23), 169 (13), 128 (13), 127 (13), 112 (59), 99 (3.5), 74 (100), 69 (30), 57 (30.5). Anal. Calcd. for $C_{10}H_{20}N_2O$ (184.28): C, 65.18; H, 10.94; N, 15.20. Found: C, 64.98; H, 11.00; N, 15.14.

N-Benzyl-N'-isopropylurea (20b). Mp 117-120 °C. IR 3321 (NH), 2961, 1618 (C=O), 1567 (Amide-II), 1464, 1450, 1243 (Amide-II), 691 cm^{-1}. ^1H NMR (DMSO-d_6) 1.06 (d, 6H, CH**Me**$_2$), 3.77 (m, 1H C**H**Me$_2$), 4.26 (d, J = 5.8, 1H, PhC**H**$_2$), 4.76 (d, 1H, NHPr^i), 5.21 (t, 1H, NHBn), 7.27 (m, 5H, Ph). Anal. Calcd. for $C_{11}H_{16}N_2O$ (192.26): C, 68.72; H, 8.39; N, 14.57. Found: C, 68.51; H, 8.52; N, 14.73.

N-Benzyl-N'-*sec*-butylurea (20c). Mp 90-93 °C. IR 3322 (NH), 2960, 1621 (C=O), 1574 (Amide-II), 1450, 1267, 1240 (Amide-III), 692 cm^{-1}. ^1H NMR 0.86 (t, 3H, CHMeCH$_2$**Me**),1.07 (d, 3H, CH**Me**CH$_2$Me), 1.39 (dt, 2H, CHMeC**H**$_2$Me), 3.65 (m, 1H, C**H**MeCH$_2$Me), 4.31 (d, J = 5.6, 1H, PhC**H**$_2$), 4.38, 4.88 (2x br s, 2x1H, 2xNH), 7.31 (m, 5H, Ph). Anal. Calcd. for $C_{12}H_{18}N_2O$ (206.29): C, 69.87; H, 8.79; N, 13.58. Found: C, 69.68; H, 8.71; N, 13.44.

N-Benzyl-N'-cyclohexylurea (20e). Mp 162-164 °C. IR 3320 (NH), 2925, 2849, 1634 (C=O), 1576 (Amide-II), 1449, 1311, 1270, 1250, 1233 (Amide-III), 691 cm^{-1}. ^1H NMR (DMSO-d_6) 1.00-1.35, 1.50-1.78 (2xm, 10H, 2,3,4,5,6-CH_2), 3.35 (m, 1H, 1-C**H**), 4.18 (d, J = 6.0, 2H, PhC**H**$_2$), 5.83 (d, J = 8.0, 1H, N**H**cHx), 6.17 (d, J = 6.0, 1H, N**H**Bn). Anal. Calcd. for $C_{14}H_{20}N_2O$ (232.33): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.11; H, 8.87; N, 11.89.

N-Benzyl-N',N'-diethylurea (20h). Mp 44-46 °C. IR 3360 (NH), 2976, 2930, 1624 (C=O), 1534 (Amide-II), 1496, 1452, 1406, 1378, 1360, 1284, 1212 (Amide-III), 726, 698 cm^{-1}. ^1H NMR 1.14 (t, 6H, Me), 3.27 (q, 4H, C**H**$_2$Me), 4.42 (d, 2H, PhC**H**$_2$), 4.85 (brs, 1H, NH), 7.30 (m, 5H, Ph).Anal. Calcd. for $C_{12}H_{18}N_2O$ (206.29): C, 69.87; H, 8.79; N, 13.58. Found: C, 69.58; H, 8.73; N, 13.74.

N-Benzyl-N',N'-diisopropylurea (20i). Mp 73-75 °C. IR 3330 (NH), 2920, 2848, 1626 (C=O), 1532 (Amide-II), 1452, 1428, 1358, 1331, 1207, 1162, 720, 700, 691 cm^{-1}. ^1H NMR 1.25 (d, 6H, CH**Me**$_2$), 3.90 (m, 2H, C**H**Me$_2$), 4.46 (br s, 3H, NH + PhC**H**$_2$), 7.32 (m, 5H, Ph). Anal. Calcd. for $C_{14}H_{22}N_2O$ (234.34): C, 71.76; H, 9.46; N, 11.95. Found: C, 71.87; H, 9.69; N, 11.83.

N-Isopropyl-N'-(1-phenylethyl)urea (21b). Mp 116-119 °C. IR 3334 (NH), 2966, 1626 (C=O), 1570, 1494, 1248, 750, 700 cm^{-1}. ^1H NMR 1.01, 1.05 (2xs, 2x3H, CH**Me**$_2$), 1.42 (d, 3H, CH**Me**), 3.81 (m, 1H, C**H**Me$_2$), 4.44 (d, 1H, N**H**iPr), 4.78 (m, 1H, PhC**H**), 4.96 (d, 1H, N**H**CHMePh), 7.30 (m, 5H, Ph). Anal. Calcd. for $C_{12}H_{18}N_2O$ (206.29): C, 69.87; H, 8.79; N, 13.58. Found: C, 69.66; H, 8.64; N, 13.68.

N-*sec*-Butyl-N'-phenylurea (22c). Mp 153-154 °C. IR 3348 (NH), 2963, 2923, 1639 (C=O), 1593, 1527 (Amide-II), 1497, 1441, 1310, 1235 (Amide-III), 1161, 747, 693 cm^{-1}. ^1H NMR 0.90 (t, 3H, CHMeCH$_2$**Me**), 1.11 (d, 3H, CH**Me**CH$_2$Me), 1.44 (dt, 2H, CHMeC**H**$_2$Me), 3.80 (m, 1H, C**H**MeCH$_2$Me), 4.98 (br s, 1H, N**H**sBu), 6.90 (br s, 1H, PhN**H**), 7.04 (m, 1H, one H of Ph), 7.27 (m, 4H, rest H's of Ph). Anal. Calcd. for $C_{11}H_{16}N_2O$ (192.26): C, 68.72; H, 8.39; N, 14.57. Found: C, 69.02; H, 8.42; N, 14.40.

N,N-Dimethyl-N'-phenylurea (22g). Mp 129-130 °C, lit.[34] mp 133-134 °C. IR 3338 (NH), 1641 (C=O), 1593, 1527 (Amide-II), 1484, 1437, 1370, 1305, 1241 (Amide-III), 1182, 748, 689 cm^{-1}. ^1H NMR 3.02 (s, 6H, NMe_2), 6.35 (br s, 1H, PhN**H**), 7.02 (m, 1H, one H of Ph), 7.24-7.41 (m, 4H, rest H's of Ph).

1-[(Phenylamino)carbonyl]piperidine (22j). Mp 166-169 °C (acetone-H_2O). IR 3280 (NH), 2920, 2848, 1626 (C=O), 1590, 1532 (Amide-II), 1497, 1477, 1445 (CH_2), 1410, 1301, 1240 (Amide-III), 1023, 748, 690 cm^{-1}. ^1H NMR 1.63 (m, 6H, 3,4,5-CH_2), 3.44 (m, 4H, 2,6-CH_2), 6.40 (br s, 1H, NH), 7.01 (m, 1H, one H of Ph), 7.22-7.39 (m, 4H, rest H's of Ph). Anal. Calcd. for $C_{12}H_{16}N_2O$ (204.27): C, 70.56; H, 7.89; N, 13.71. Found: C, 70.87; H, 8.06; N, 13.71.

N-Hydroxy-N'-phenylurea (22k). Mp 146-148 °C. IR 3384 (OH), 3240 (NH), 1630 (C=O), 1596, 1546 (Amide-II), 1500, 1448, 754, 728, 686 cm^{-1}. ^1H NMR (DMSO-d_6) 6.96 (m, 1H, 4-H), 7.25 (m, 2H, 3,5-H), 7.62 (d, J = 7.6, 2H, 2,6-H), 8.76, 8.82, 8.96 (3xs, 3x1H, 2xNH + OH). Anal. Calcd. for $C_7H_8N_2O_2$ (152.16): C, 55.26; H, 5.30; N, 18.41. Found: C, 55.12; H, 5.65; N, 18.55.

N-(4-Chlorophenyl)-N'-cyclohexylurea (23e). Mp 231-232 °C. IR 3335, 3280 (NH), 2936, 2853, 1630 (C=O), 1589, 1567 (Amide-II), 1492, 1314, 1250, 1230 (Amide-III), 1090 (Ar-Cl), 827 cm^{-1}. ^1H NMR (DMSO-d_6) 1.06-1.39, 1.52-1.82 (2xm, 10H, 2,3,4,5,6-CH_2), 3.43 (m, 1H, 1-C**H**), 6.11 (d, J = 7.8, 1H, N**H**cHx), 7.25 (d, J = 8.9, 2H, 2,6-H), 7.39 (d, J = 8.9, 2H, 3,5-H), 8.44 (s, 1H, ArN**H**). Anal. Calcd. for $C_{13}H_{17}ClN_2O$ (252.74): C, 61.78; H, 6.78; N, 11.08. Found: C, 61.68; H, 6.55; N, 10.97.

N-(4-Chlorophenyl)-N', N'-dimethylurea (23g). Mp 174-176 °C, lit.[35] mp: 174-175 °C. IR 3292 (NH), 1640 (C=O), 1589, 1526 (Amide-II), 1506, 1491, 1400, 1373, 1303, 1286, 1245 (Amide-III), 1187, 1086 (Ar-Cl), 826 cm^{-1}. ^1H NMR (DMSO-d_6) 2.92 (s, 6H, NMe_2), 7.26 (d, J = 8.9, 2H, 2,6-H), 7.51 (d, J = 8.9, 2H, 3,5-H), 8.40 (s, 1H, NH).

N-(4-Chlorophenyl)-N'-hydroxyurea (23k). Mp 265-266 °C (dec.). IR 3356 (OH), 3240 (NH), 1651 (C=O), 1598, 1550 (Amide-II), 1496, 1410, 1326, 1232 (Amide-III), 1092, 1083 (Ar-Cl), 834, 742 cm^{-1}. ^1H NMR (DMSO-d_6) 7.29 (d, J = 8.9, 2H, 2,6-H), 7.68 (d, J = 8.9, 2H, 3,5-H),8.94, 8.98, 9.00 (3xs, 3x1H, 2xNH + OH). Anal. Calcd. for $C_7H_7ClN_2O_2$ (186.60): C, 45.06; H, 3.78; N, 15.01. Found: C, 44.89; H, 3.86; N, 14.99.

N-(4-Chlorophenyl)-N'-methoxy-N'-methylurea (23l). Mp 74-76 °C, lit.[33] mp 80-83 °C. IR 3315 (NH), 1660 (C=O), 1588, 1527 (Amide-II), 1509, 1492, 1410, 1397, 1330, 1236 (Amide-III), 1086 (Ar-Cl), 824 cm^{-1}. ^1H NMR 3.19 (s, 3H, NMe), 3.77 (s, 3H, OMe), 7.27 (d, J = 8.9, 2H, 2,6-H), 7.42 (d, J = 8.9, 2H, 3,5-H), 7.57 (br s, 1H, NH).

N-Benzylurea (20a). Aqueous NH_3 solution (ca. 25%, 4.0 mL) was added dropwise to the intensively stirred mixture carbamate **7** (3.99 g, 20.00 mmol), hexane (30 mL) and water (15 mL) at room temperature in 6 min. After stirring for 2 h the precipitate was filtered off, washed with water and small amount of cold diethyl ether, and crystallized from hexane-abs. EtOH. Mp 145-148 °C, lit.[33] mp: 147-148 °C.

N,N-Dimethyl-N'-phenylurea (22g). Aqueous Me_2NH solution (33 %, 9.0 mL) was dropped to the intensively stirred mixture of carbamate **9** (4.00 g, 21.55

mmol), hexane (30 mL) and water (20 mL) at room temperature in 40 min. After stirring for 21 h the precipitate was filtered off, washed with water, and crystallized from hexane-EtOAc. Mp 129-130 °C, lit.[34] mp: 133-134 °C.

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