Orthoamides and Iminium Salts, LXXV [1]. Contribution to the Formation of 2-Formyl-1,1,3,3-tetramethylguanidine and the Isomeric 1,1-Dimethyl-3-dimethylaminomethylene-urea

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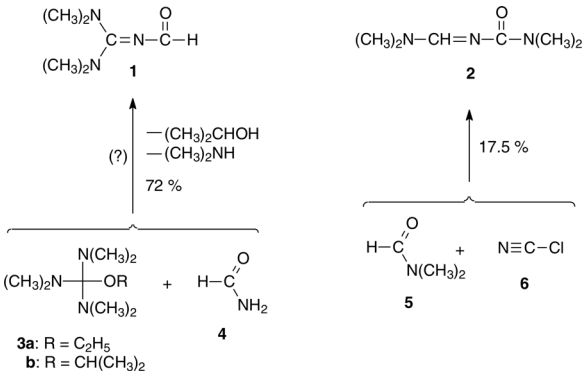
Dedicated to Professor Ernst Anders on the occasion of his 70th birthday

2-Formyl-1,1,3,3-tetramethylguanidine (**1**) could be prepared from tris(dimethylamino)ethoxymethane (**3a**) and formamide (**4**). Surprisingly, guanidine **1** does not result from the reaction of 1,1,3,3-tetramethylguanidine with formylating reagents such as dimethylamino-methoxy-acetonitrile (**8**) or the *N*,*N*-dimethylformamide-dimethylsulfate adduct (**9**), rather the isomeric 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**) is formed. The structure of **2** was confirmed by NMR spectroscopy and crystal structure analysis.

Key words: Guanidines, Formamide, DMF-DMS Adduct, 1,3-Hydride Shift

Introduction

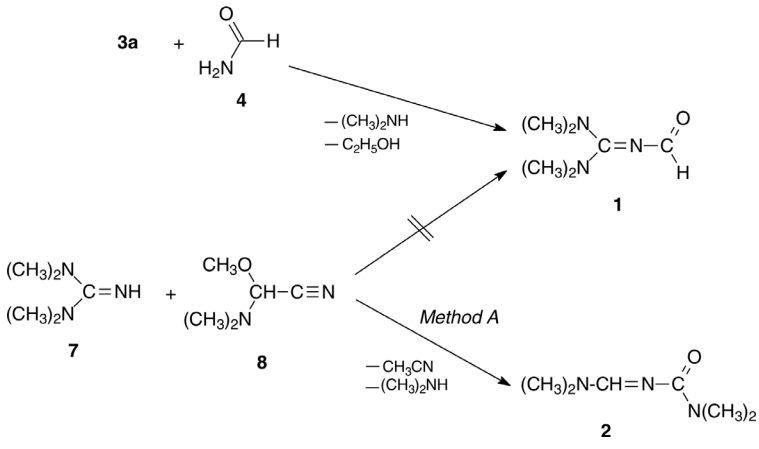
2-Formyl-1,1,3,3-tetramethylguanidine (**1**) and 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**) are constitutional isomers, and their preparation has already been reported earlier in the literature. Guanidine **1** was prepared from formamide (**4**) by treatment with tris(dimethylamino)isopropyloxymethane (**3b**) (Scheme 1) [2]. Compound **1** was reported to be obtained as an oil, which solidified on purification to give crystals with m. p. 54 – 56 °C; however, it was not fully characterized, and no spectral data have been reported.



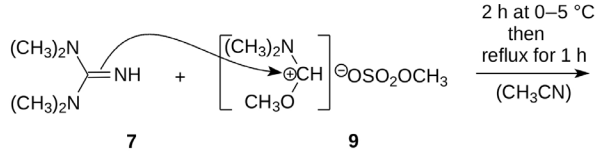
Scheme 1. Synthetic methods for the preparation of 2-formyl-1,1,3,3-tetramethylguanidine (**1**) and 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**).

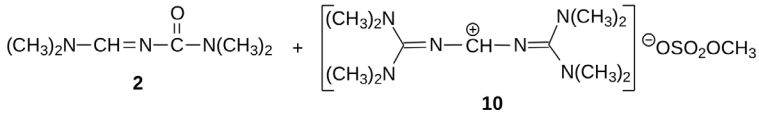
The second title compound, 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**), was described as colorless prisms with m. p. 50 °C [3a]. It was prepared by reaction of *N*,*N*-dimethylformamide (**5**) with cyanogen chloride Cl-C≡N (**6**) (Scheme 1). This product has been characterized by means of IR and ^{1}H NMR (60 MHz) spectroscopy, and its picrate (m. p. 148 – 151 °C). In the reaction of *N*,*N*-dimethylformamide-diethylacetal with urea a complex product mixture has been obtained, in which compound **2** could be detected by means of mass spectrometry [3b].

While studying some new formylating agents for aromatic compounds [4], our attention was attracted by the *N*-formylguanidine **1**, whose preparation from formamide and tris(dimethylamino)isopropyloxymethane (**3b**) [2] seemed to be rather simple. In order to produce **1** and to examine its formylating potential, we reproduced the known procedure [2] which uses the reaction of tris(dimethyamino)ethoxymethane (**3a**) with formamide (**4**) (Scheme 2).



Scheme 2. Preparation of 2-formyl-1,1,-3,3-tetramethylguanidine (**1**) and 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**).





Scheme 3. Reaction products **2** and **10** from 1,1,3,3-tetramethylguanidine (**7**) and *N*,*N*-dimethylformamide-dimethylsulfate adduct (**9**) (Method B).

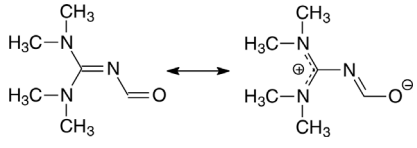


Fig. 1. Resonance structure of *N*-formylguanidine **1**.

An oily product with no tendency to crystallization was isolated, and its structure (**1**) could unambiguously be verified by its spectral data. In the ^{1}H NMR spectrum all four *N*-methyl groups are magnetically equivalent and display a sharp singlet for 12 H at δ = 2.97 ppm. This is an indication of the existence of free rotation around the C–N bonds in the partially zwitterionic structure of **1** (Fig. 1) at ambient temperature. The second ^{1}H singlet at δ = 8.54 ppm is ascribed to the formyl proton of compound **1**.

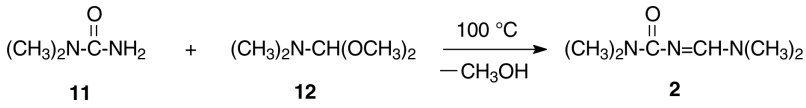
Results and Discussion

We were looking for an alternative synthetic approach to formylguanidine **1**, namely, by formylation of 1,1,3,3-tetramethylguanidine (TMG) (**7**) with dimethylaminomethoxyacetonitrile (**8**) [5]. Surprisingly, however, the low-melting solid thus obtained was not identical with the oily one prepared from formamide as mentioned above. Its structure was proved to be 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**) (Scheme 2, Method A) on the basis of its ^{1}H NMR and ^{13}C NMR spectra and an X-ray crystallographic analysis.

According to Method B (Scheme 3) the result of the aforementioned reaction was fully confirmed by the reaction of TMG (**7**) with the *N*,*N*-dimethylformamide-dimethylsulfate adduct (**9**) where the first step in Scheme 3 was expected to be the same as in the reaction of TMG (**7**) with dimethylaminomethoxyacetonitrile (**8**) described in Scheme 2.

In this case, compound **2** was only isolated as a by-product (yield 18 %) since the main product was found to be a viscous liquid, probably *N*,*N*′-bis(diaminomethylene)formamidinium methylsulfate (**10**) (Scheme 3) which features a strongly resonance-stabilized cation. However, the latter compound could not be completely purified to be fully characterized.

In Method C, 1,1-dimethylurea (**11**) is reacted with *N*,*N*-dimethylformamide-dimethylacetal (DMF-



Scheme 4. 1,1-Dimethyl-3-dimethylaminomethylene-urea (**2**) from 1,1-dimethylurea (**11**) and DMF-DMA (**12**) (Method C).

Table 1. Crystal structure data for **2**.

Formula	$C_6H_{13}N_3O$
M_r	143.19
Crystal size, mm^3	$0.32 \times 0.25 \times 0.18$
Temperature, K	100(2)
Crystal system	triclinic
Space group	$P\bar{1}$ (no. 2)
a, Å	7.0182(3)
b, Å	10.5055(4)
c, Å	11.9481(5)
α, deg	66.943(2)
β, deg	76.914(2)
γ, deg	82.617(3)
V, Å^3	788.73(6)
Z	4
D_{calcd}, g cm^{-3}	1.21
$\mu(\mathrm{Mo}K_\alpha)$, mm^{-1}	0.1
$F(000)$, e	312
θ range, deg	3.21 – 27.85
hkl range	$\pm 9, \pm 13, \pm 15$
Refl. measured	24360
unique	3709
R_{int}	0.0255
R_σ	0.0875
Parameters refined	285
R_1 / wR_2 (all reflections)	0.0837 / 0.1847
R_1 / wR_2 for 2924 refl. with $I \geq 2\sigma(I)$	0.0650 / 0.1674
GoF (F^2)	1.121
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	0.348 / −0.297

Table 2. Selected bond lengths (Å) and angles (deg) for **2** with estimated standard deviations in parentheses.

O1–C3	1.240(2)	N3–C5	1.456(2)	O2–C9–N4	120.2(2)
O2–C9	1.241(2)	N4–C9	1.362(2)	O2–C9–N5	125.9(2)
N1–C3	1.362(2)	N4–C7	1.451(3)	O1–C3–N1	120.7(2)
N1–C1	1.450(2)	N4–C8	1.456(3)	O1–C3–N2	125.6(2)
N1–C2	1.455(2)	N5–C10	1.309(2)	N1–C3–N2	113.7(2)
N2–C4	1.308(2)	N5–C9	1.397(2)	N2–C4–N3	122.2(2)
N2–C3	1.397(2)	N6–C10	1.327(2)	N4–C9–N5	113.9(2)
N3–C4	1.333(2)	N6–C12	1.453(2)	N5–C10–N6	122.2(2)
N3–C6	1.452(3)	N6–C11	1.457(2)		
Hydrogen bonds[a]					
D–H···A		d(D–H)	d(H···A)	d(D···A)	◁(D–H···A)
C4–H4···O2		0.98(2)	2.420	3.357(2)	159.3(2)
C10–H10···O1		0.94(2)	2.455	3.308(2)	150.9(2)
C12–H12A···O1		0.99(2)	2.464	3.399(2)	156.7(2)
C5–H5A···O2		0.97(2)	2.514	3.441(2)	159.7(2)

[a] D = hydrogen bond donor, A = hydrogen bond acceptor.

DMA) (**12**) to afford the product **2** as well (Scheme 4). This is a further example of the well-known *N*-formylation of primary carboxamides by means of DMF-DMA (**12**) [6]. This reaction can be considered as a chemical evidence for the structure of **2**.

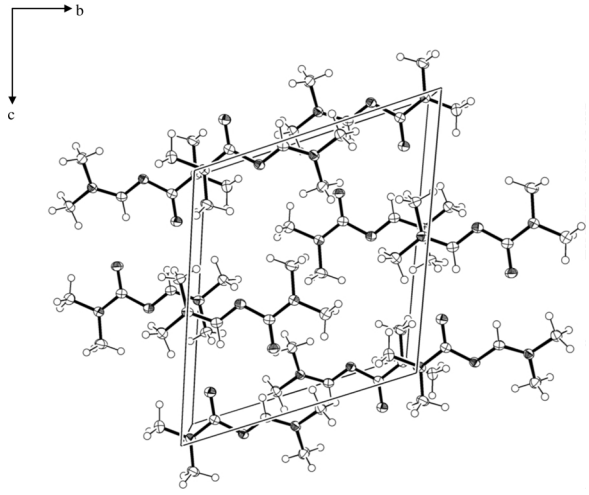
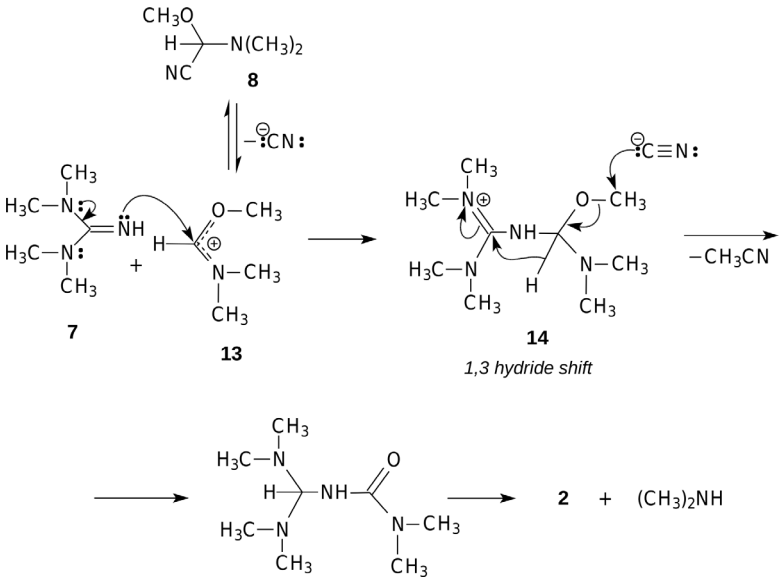


Fig. 2. Projection of the unit cell of 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**) along the crystallographic *a* axis.

At r. t. all four *N*-methyl groups of **2**, both in $CDCl_3$ and in [D$_6$]DMSO, show four different chemical shifts in the range δ = 2.92 – 3.07 ppm ($CDCl_3$) and 3.00 – 3.14 ppm ([D$_6$]DMSO) in its highly resolved ^{1}H NMR spectrum (s. Experimental Section). Hence, rotation around the C–N bonds is hindered in both solvents due to conjugation with the corresponding polarized double bonds. The signal of the aldehyde-like methine proton is observed as a singlet at δ = 8.29 ($CDCl_3$) and 8.38 ppm ([D$_6$]DMSO). These values agree with those reported in lit. [2a]: two singlets at δ = 2.98 (6H) and 3.02 (6H) for the *N*-methyl groups, and δ = 8.3 (s, 1H) for the methine proton (60 MHz spectra).

The structure and configuration of compound **2** was finally confirmed by means of X-ray crystallographic analysis. It crystallizes in the triclinic space group $P\bar{1}$ (Table 1) with Z = 4. It thus contains two crystallographically non-equivalent molecules in the unit cell. Fig. 2 shows a view of the unit cell along the *a* axis. Hydrogen bonds between the carbonyl-oxygen atoms of the urea moiety and the methine hydrogen atoms H4 and H10 as well as the hydrogen atoms H5A and H12A of the methyl groups have been observed [d(O–H) = 2.420 – 2.514 Å; Table 2 and Fig. 3]. Taking this hydro-



Scheme 5. Explanation of the formation of compound **2**.

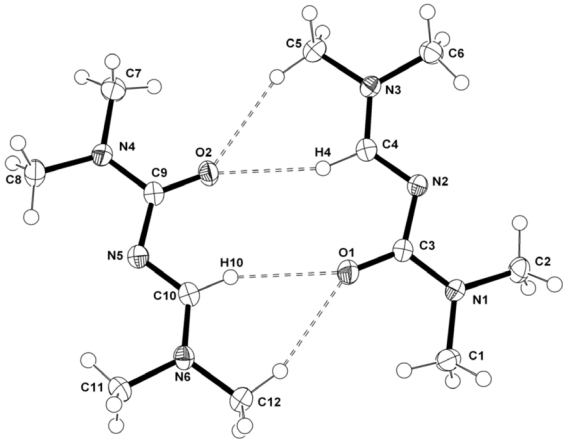
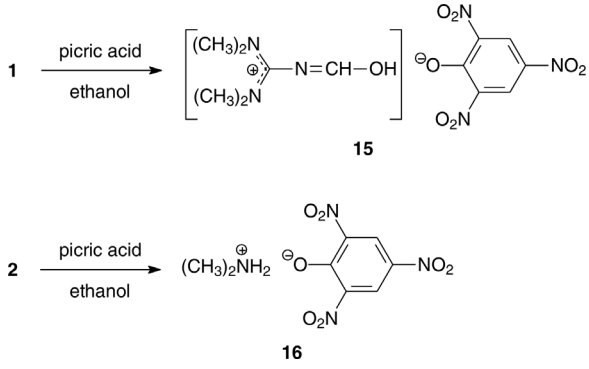


Fig. 3. View of two 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**) molecules connected *via* C–H···O hydrogen bonds (dashed lines) into a dimer.



Scheme 6. Picrates **15** and **16** obtained from *N*-formylguanidine **1** and dimethylaminomethylene-urea **2**.

gen bonding situation into account, dimeric molecules connected *via* (weak) C–H···O hydrogen bonds are formed (Fig. 3), which are the main structural motif in the crystal structure of **2**. The experimental N–C bond lengths are in the range as expected for N–C single or double bonds (d(N–C)$_{double}$ = 1.308(2) – 1.309(2) Å; d(N–C)$_{single}$ = 1.450(2) – 1.457(2) Å; Table 2). Furthermore the C–O and N–C distances of the urea moiety are well comparable with the crystal structure data of solid N,N,N',N'-tetramethylurea at 200 K (d(C–O) = 1.226 Å; d(N–C) = 1.370; 1.451 – 1.460 Å [8]).

The formation of the substituted urea **2** under the conditions given for Methods A and B could be reasonably explained by initial addition of the guanidine to a delocalized iminium ion of type **13**, followed by 1,3 hydride shift in the adduct **14** thus formed (Scheme 5). Simultaneous attack of the cyanide ion on the methyl group should promote this step. After subsequent elimination of dimethylamine, the final stable product **2** is produced.

By treatment of *N*-formylguanidine **1** with picric acid in ethanol the guanidinium picrate **15** (m. p. 173 – 176 °C) could be prepared (Scheme 6). In contrast, from the analogous reaction with dimethylaminomethylene-urea **2**, dimethylammonium picrate (**16**) was obtained. Obviously the amidine function of **2** is cleaved with release of dimethylamine under the conditions applied. The dimethylamine thus formed reacts with picric acid to give **16** (Scheme 6).

Conclusion

2-Formyl-1,1,3,3-tetramethylguanidine (**1**) could only be synthesized from tris(dimethylamino)ethoxymethane and formamide. We found that the very stable urea derivative **2** can be prepared from N,N,N',N'-tetramethylguanidine and formylating agents as **8** and **9**, most likely by an intermediate hydride shift.

Experimental Section

General information.

Melting points were determined on a Büchi 450 aparatus. TLC: Macherey & Nagel pre-coated plastic sheets SIL_{254} with silica gel, layer 0.2 mm; eluted with methylene chloride-acetone-ethanol 6 : 3 : 1 (v/v).

*2-Formyl-1,1,3,3-tetramethyl-urea (**1**)*

From tris-(dimethyamino)ethoxymethane (**3a**) and formamide (**4**). A mixture of 18.9 g (0.1 mol) of tris(dimethylamino)ethoxymethane (**3a**) and 4.5 g (0.1 mol) of formamide (**4**) in 100 mL cyclohexane was heated in a flask provided with a 15 cm Vigreux column (KOH-drying tube). The compounds boiling in the range 73 – 80 °C were distilled off. The residue was then distilled in an oil pump vacuum (about 0.1 Torr) to give a first fraction of 5.5 g with b. p. 27 – 28 °C, n_D^{20} = 1.4554 (tetramethylurea), a second fraction of 1.4 g with b. p. 52 – 53 °C, n_D^{20} = 1.4552 (tetramethylurea), and a third fraction of 2.3 g (yield 16 %) of pure **1** with b. p. 91 – 94 °C, n_D^{20} = 1.5056, with no tendency to crystallization even after staying for 4 d at −20 °C. This product is not identical (TLC, m. p., IR) with the crystalline compound **2** obtained by Methods A–C (see below). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97 (s, 12H, 4× N-Me), 8.54 (s, 1H, C*H*O). – ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 40.36 (4× N-Me), 163.61 [N-C(=N)-N], 170.36 (CHO). – IR (ATR): ν = 3321, 3172, 1688 (C=O), 1610, 1387 cm^{-1}. – GC-MS: m/z (%) = 143 (7) $[M]^+$, 142 (9) $[M–1]^+$, 126, 99, 85, 71, 44 (100), 42. – $C_6H_{13}N_3O$ (143.19): for elemental analysis see picrate **15**.

*Picrate **15**:* Prepared from picric acid (453 mg; 2 mmol) in 5 mL of ethanol and a solution of guanidine **1** (289 mg; 2 mmol) in 2 mL of ethanol. On standing for 2 d at 6 – 9 °C (refrigerator) the fine yellow precipitate was filtered and washed with ethanol and ether. Yield of air-dried picrate **15** 376 mg (50 %), m. p. 173 – 176 °C (dec.) (ethanol). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.07 (s, 12H, 4× N-CH_3), 8.46 (s, 1H, N=CH-O), 8.61 (s, 2H$_{arom.}$, 3′-H, 5′-H), 11.16 (br. s, 1H, OH). – ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 40.8 (4 C, 4× N-Me), 124.2 (C-4), 125.2 (C-3, C-5), 141.8 (C-2, C-6), 155.7 (br., 1C), 160.8 (C-1), 163.2 (br., 1C, N=C-O). – $C_{12}H_{16}N_6O_8$ (372.29): calcd. C 38.71, H 4.33, N 22.57; found C 38.80, H 4.47, N 22.45. The picrate **15** is stable at r. t.

*1,1-Dimethyl-3-dimethylaminomethylene-urea (**2**)*

Method A: From dimethylaminomethoxyacetonitrile (**8**)

To a solution of 30.0 g (0.26 mol) of **8** in 100 mL of cyclohexane 29.4 g (0.25 mol) of tetramethylguanidine (**7**) was added dropwise, and the reaction mixture was distilled with stirring over a 15 cm Vigreux column (KOH drying tube). An azeotropic mixture of cyclohexane-methanol (b. p. *ca.* 56 °C) was collected, and evolution of dimethylamine was observed. The heating temperature was increased to 110 °C until the distillation ceased. All volatile components were removed at 40 °C *in vacuo*, and the residue was fractionally distilled in an oil pump vacuum. A pale-yellow liquid with b. p. 89 – 97 °C crystallized in the condenser to give 13.2 g (36 %) 1,1-dimethyl-3-dimethylaminomethylene-urea (**2**), TLC homogeneous. Repetitions: yields 31 – 52 %. An analytically pure sample was recrystallized twice from pentane, colorless prisms with m. p. 54 – 55 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07 (br. s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 2.96 (s, 3H, NCH_3), 2.92 (br. s, 3H, NCH_3), 8.29 (s, 1H, N=CH-); (500 MHz, [D$_6$]DMSO): 3.00 (br. s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 3.14 (br. s, 3H, NCH_3), 8.38 (s, 1H, N=CH-). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 34.64, 35.65, 36.79, 40.77 (4× NCH_3), 159.86 (*C*H=N), 164.37 (C=O). – $C_6H_{13}N_3O$ (143.19): calcd. C 50.34, H 9.15, N 29.34; found C 50.25, H 9.06, N 29.30.

Picrate: In an attempt to characterize this product as a picrate we isolated yellow crystals with m. p. 159 – 161 °C (ethanol) which correspond to dimethylammonium picrate (lit. [7]: m. p. 161 °C). – $C_8H_{10}N_4O_7$ (274.19): calcd. C 35.04, H 3.68, N 20.43; found C 35.01, H 3.82, N 20.41. Its constitution was confirmed also by means of ^{1}H NMR and ^{13}C NMR spectroscopy (in [D$_6$]DMSO). It can be inferred that under these conditions compound **2** decomposes by elimination of dimethylamine. For the alleged picrate of **2** described in the literature [3a] a melting point of 148 – 151 °C was reported, and we suppose that the authors have also obtained the dimethylammonium picrate.

Method B: From N,N-dimethylformamide-dimethylsulfate adduct (**9**) and 1,1,3,3-tetramethylguanidine (**7**) (Scheme 3).

To a solution of 23.0 g (0.2 mol) of 1,1,3,3-tetramethylguanidine (**7**) in 50 mL of anhydrous acetonitrile 20.0 g (0.1 mol) of DMF-DMS adduct **9** was added dropwise under stirring and ice-cooling at 0 – 5 °C for 2 h. Thereafter the reaction mixture was heated under reflux for 1 h. The solvent and some dimethylamine were removed *in vacuo*. The yellow viscous residue was extracted with anhydrous ether (5 × 50 mL). The solvent was removed from this extract by distillation, and the oily residue was dried *in vacuo*. It solidified on

cooling to give pure **2** which is identical (TLC, IR, m. p.) to the products obtained by Method A or C. Yield 2.57 g (18 %), almost colorless solid. The ether-insoluble layer was also dried *in vacuo* to afford a pale-yellow viscous fluid (25.7 g), probably corresponding to a rather impure compound with the structure **10** (Scheme 3). The crude compound **10** possesses properties of an ionic liquid.

Method C: From 1,1-dimethylurea (**11**) and *N*,*N*-dimethylformamide-dimethylacetal (**12**)

A suspension of 1.8 g (0.02 mol) of 1,1-dimethylurea (**11**) (m. p. 160 – 170 °C; prepared from *N*,*N*-dimethylcarbamoyl chloride and ammonia) and 4.5 g (0.038 mol) of **12** (DMF-DMA) was heated with stirring and continuous distillation of methanol over a 20 cm Vigreux column at 100 °C (KOH drying tube). The urea dissolved slowly, and about 2 mL of a methanol/DMF-DMA mixture distilled off within 2 h. Heating was continued at 110 °C for further 4 h. The reaction mixture was evaporated *in vacuo*. The yellowish oily residue was then extracted with boiling pentane. After cooling, from the pentane extract the almost colorless product **2** crystallized, which was identical with the product obtained by application of Methods A and B (IR, TLC and m. p.).

*Crystal structure determination of **2***

X-Ray single-crystal diffraction data were collected on a Bruker-Nonius Kappa CCD diffractometer, using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). A single crystal, coated with perfluorinated oil, was mounted on the tip of a glass fiber. Because the crystal liquefies immediately in the air, the data collection was performed under a stream of nitrogen at 100 K. Unit cell parameters were obtained by indexing of the peaks in the first 10 frames and refined by employing the whole data set. All frames were integrated and corrected for Lorentz and polarization effects. The structure was solved by Direct Method using SHELXS-97 [9]. All non-hydrogen atoms were located and refined anisotropically by full-matrix least-squares using SHELXL-97 [10]. All hydrogen atoms were found in the final difference Fourier maps and allowed to refine freely with isotropic displacement parameters. The results of the crystal structure analysis are presented in the Tables 1 and 2. For the preparation of the structural images the program ORTEP-III was used [11].

CCDC 767479 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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