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Catalytic Cycloaminomethylation of Ureas and Thioureas with *N*,*N*-Bis(methoxymethyl)alkanamines

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Abstract—An efficient procedure has been developed for the synthesis of 5-alkyl-1,3,5-triazinan-2-ones, 5-alkyl-1,3,5-triazinane-2-thiones, and 2,6-dialkylhexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8(1*H*,5*H*)-diones by reactions of urea, thiourea, and tetrahydroimidazo[4,5-*d*]imidazole-2,5-(1*H*,3*H*)-dione with *N*,*N*-bis(methoxymethyl)alkanamines in the presence of $SmCl_3 \cdot 6H_2O$ as catalyst.

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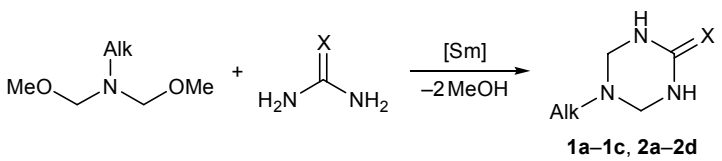
One of the most widely known method for the synthesis of substituted 1,3,5-triazinan-2-ones is based on the Mannich reaction of ureas with primary amines and formaldehyde or of primary amines with *N*,*N*-bis(hydroxymethyl)urea [1–5]. The use in this reaction of aqueous formaldehyde at elevated temperature reduces the selectivity for triazinan-2-ones [2–4].

We have recently synthesized 5-substituted 1,3,5-triazinan-2-ones and 1,3,5-triazinane-2-thiones by catalytic cycloaminomethylation of ureas and thioureas with *N*,*N*,*N*′,*N*′-tetramethylmetanediamine and primary amines [6], as well as with aromatic carboxylic acid hydrazides [7]. In continuation of our studies in this line, in the present work we examined reactions of urea and its derivatives (thiourea, glycoluril) with *N*,*N*-bis(methoxymethyl)alkanamines in the presence of catalysts based on *d* and *f* elements with the goal of developing catalytic methods for the selective synthesis of substituted 1,3,5-triazinanes. These compounds are promising as building blocks for the preparation of antitumor [8–10], antiviral, and antibacterial agents [11], pesticides [12], fuel bioprotectors, and lubricating oils [13]. The choice of *N*,*N*-bis(methoxymethyl)alkanamines as aminomethylating agents toward urea and thiourea was determined by high reactivity of the latter in the catalytic heterocyclizations of α,ω-diols [14] and dithiols [15] to N- and S-heterocycles.

The reaction of urea with an equimolar amount of *N*,*N*-bis(methoxymethyl)cyclohexan-1-amine was used as model process to evaluate the catalytic activity of various catalysts based on *d* and *f* elements (Fe, Co, Pd, Ti, Zr, Cu, Sm, Yb). It was found that 5 mol % of $SmCl_3 \cdot H_2O$ ($CHCl_3$–EtOH, 1 : 2 by volume; 60°C, 6 h) ensured the best yield of 5-cyclohexyl-1,3,5-triazinan-2-one (**1a**, 52%). The yield of **1a** in aliphatic (hexane, cyclohexane) and aromatic (benzene, toluene) solvents was lower than <10%, and it did not exceed 5% in the absence of a catalyst. Under the given conditions, the reactions of urea and thiourea with *N*,*N*-bis(methoxymethyl)alkanamines in the presence of 5 mol % of $SmCl_3 \cdot 6H_2O$ selectively

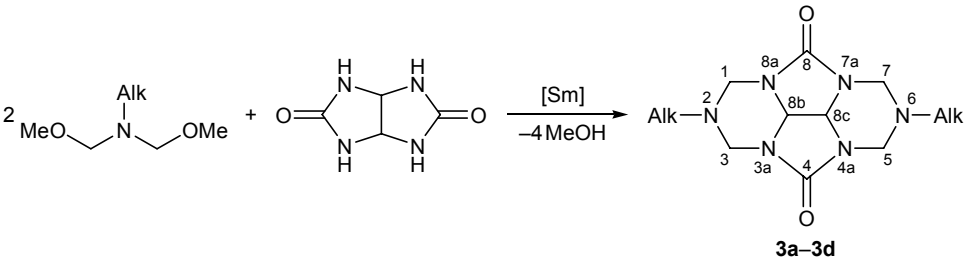
Scheme 1.



1a–1c, **2a–2d**

[Sm] = $SmCl_3 \cdot 6H_2O$; **1**, X = O; **2**, X = S; Alk = *cyclo*-C_6H_{11} (**a**), *t*-Bu (**b**), $HO(CH_2)_2$ (**c**), *i*-Pr (**d**).

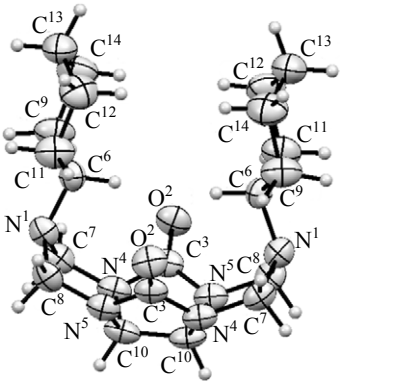
Scheme 2.



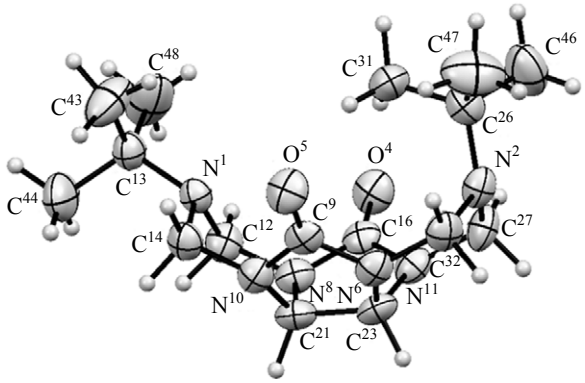
Alk = *cyclo*-C_6H_{11} (**a**), *t*-Bu (**b**), $HO(CH_2)_2$ (**c**), *i*-Pr (**d**); [Sm] = $SmCl_3 \cdot 6H_2O$.

afforded 5-alkyl-1,3,5-triazinan-2-ones **1a**–**1c** and 5-alkyl-1,3,5-triazinane-2-thiones **2a**–**2d** in 30–58% yield (Scheme 1).

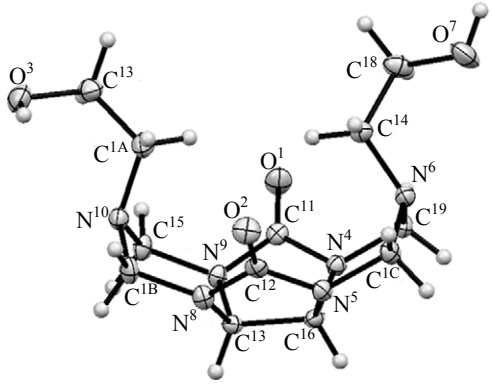
The structure of compounds **1a**–**1c** and **2a**–**2d** was determined by ^1H and ^{13}C NMR spectroscopy and MALDI–TOF mass spectrometry, as well as by comparing their physicochemical characteristics with those of authentic samples. In order to extend the scope of catalytic cycloaminomethylation and obtain new fused aza heterocycles containing 1,3,5-triazinane fragments, the heterocyclization was carried out with glycoluril {tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione}. Under analogous conditions (5 mol % $SmCl_3 \cdot 6H_2O$, 60°C, $CHCl_3$–EtOH, 6 h), glycoluril reacted with *N*,*N*-bis(methoxymethyl)cyclohexanamine at a molar ratio of 1:2 to produce ~81% of 2,6-dicyclohexylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dione (**3a**). The yield of **3a** in the absence of a catalyst did not exceed 15%. Glycoluril was also brought into reaction with



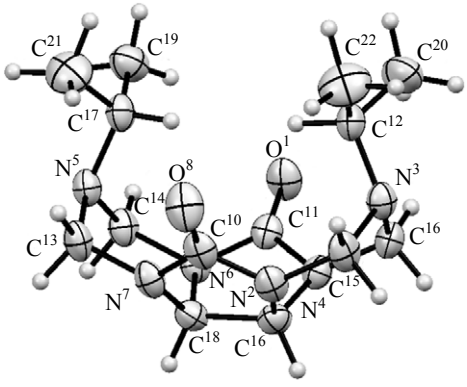
3a



3b



3c



3d

Structures of molecules **3a**–**3d** according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

Crystallographic data and structure refinement parameters for compounds **3a**–**3d**

Parameter	**3a**	**3b**	**3c**	**3d**
Formula	$C_{20}H_{32}N_6O_2$	$C_{16}H_{28}N_6O_2$	$C_{12}H_{20}N_6O_4$	$C_{14}H_{24}N_6O_2$
Molecular weight	388.507	336.433	312.325	308.380
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	*C*2/*c*	$P2_1/c$	$P22_12_1$	$P2_1/n$
a, Å	15.3964(13)	12.8000(7)	6.38723(15)	13.2014(11)
b, Å	16.434(2)	12.2472(7)	12.4481(3)	7.7892(5)
c, Å	7.8035(6)	22.6270(17)	16.8336(3)	14.9799(10)
α, deg	90.00	90.00	90.00	90.00
β, deg	97.341(7)	92.962(6)	90.00	95.016(7)
γ, deg	90.00	90.00	90.00	90.00
V, Å^3	1958.2(4)	3542.3(4)	1338.42(5)	1534.47(19)
Z	4	6	4	5
d_{calc}, mg/mm^3	1.182	1.312	1.638	1.257
F(000)	736.0	1464.0	660.0	605.0
$2\Theta_{max}$, deg	62.26	62.44	62.16	61.9
Total number of reflections	3508	12706	3871	8253
Number of independent reflections (R_{int})	2105 (0.0181)	7299 (0.0273)	3077 (0.0094)	4408 (0.0162)
Goodness of fit *S*	1.138	0.976	0.820	1.006
R/w*R* [$I \geq 2\sigma(I)$]	0.0624/0.1604	0.0650/0.1616	0.0327/0.0948	0.0477/0.1310
R/*w*R	0.0835/0.1840	0.1335/0.2159	0.0350/0.0987	0.0637/0.1465
Residual electron density peaks, min/max, *e* Å^{-3}	0.24/–0.32	0.14/–0.15	0.22/–0.24	0.24/–0.25

some other *N*,*N*-bis(methoxymethyl)alkanamines. We thus obtained 2,6-dialkylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-diones **3b**–**3d** in 60–80% yield (Scheme 2).

The structure of **3a**–**3d** was proved by ^{1}H and ^{13}C NMR data (including two-dimensional techniques), IR and mass spectra, and X-ray analysis. In the ^{13}C NMR spectra of **3a**–**3d**, carbonyl carbon atoms of the tetracyclic skeleton characteristically resonated at δ_C 158.98–159.67 ppm, and signals from the CH_2 and CH group were observed at δ_C 57–61 and 64–66 ppm, respectively. The geminal coupling constant ^2J between the axial and equatorial protons of the methylene groups was equal to 12–13 Hz.

According to the X-ray diffraction data, the hexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]-fluorene-4,8-dione fragment in molecules **3a**–**3d** has a bowl-like structure, where two vicinal triazinane rings are fixed by paired urea bonds closing five-membered imidazole rings (see figure). The five-membered ring planes in **3a**–**3d** form dihedral angles of 71.62, 71.46, 108.52, and 71.11°, respectively, and have an *envelope* conformation with the C=O carbon atom deviating by 0.205–0.229 Å from the plane formed by the other atoms. The triazinane rings adopt a *chair* conformation. The alkyl substituents in **3a**, **3c**, and **3d** occupy axial positions and are oriented *syn*. One *tert*-butyl group in **3b** is axial, while the other occupies an intermediate position between axial and equatorial. Obviously, the large size of *tert*-butyl groups prevents them from being oriented strictly axially.

Thus, catalytic cycloaminomethylation of urea and its derivatives with *N*,*N*-bis(methoxymethyl)alkanamines provides an efficient method for the selective synthesis of 5-alkyl-1,3,5-triazinan-2-ones, 5-alkyl-1,3,5-triazinane-2-thiones, and 2,6-dialkylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-diones.

EXPERIMENTAL

The progress of reactions was monitored by TLC using Sorbfil plates. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400.13 and 100.62 MHz, respectively, using DMSO-d_6 as solvent and reference (δ 2.50, δ_C 39.50 ppm). The IR spectra were recorded on a Bruker Vertex 70v spectrometer from samples dispersed in mineral oil. The mass spectra were obtained on a Bruker Autoflex III MALDI–TOF spectrometer with α-cyano-4-hydroxycinnamic or 2,5-dihydroxybenzoic acid as matrix; samples were prepared by the dried drop technique (chloroform, 1:10). The melting points were determined on a PHMK 80/2617 melting point apparatus. Pure compounds were isolated by column chromatography on KSK silica gel (50–160 μm). The spectral parameters of compounds **1** and **2** coincided with those reported in [6].

Cycloaminomethylation of urea and thiourea with *N*,*N*-bis(methoxymethyl)alkanamines (*general procedure***).** A mixture of 10 mmol of *N*,*N*-bis(methoxymethyl)alkanamine in 1 mL of chloroform, 0.5 mmol of $SmCl_3 \cdot 6H_2O$, and 10 mmol of urea or thiourea in 2 mL of ethanol was stirred for 6 h at 60°C. 5-Alkyl-1,3,5-triazinan-2-ones **1a**–**1c** and 5-alkyl-1,3,5-triazinane-2-thiones **2a**–**2d** were isolated by silica gel column chromatography.

5-Cyclohexyl-1,3,5-triazinan-2-one (1a). Yield 52%, colorless crystals, mp 203–205°C; published data [6]: mp 204–205°C.

5-*tert*-Butyl-1,3,5-triazinan-2-one (1b). Yield 48%, colorless crystals, mp 183–184°C; published data [6]: mp 182–184°C.

5-(2-Hydroxyethyl)-1,3,5-triazinan-2-one (1c). Yield 35%, colorless crystals, mp 174–176°C; published data [6]: mp 173–176°C.

5-Cyclohexyl-1,3,5-triazinane-2-thione (2a). Yield 58%, colorless crystals, mp 172–173°C; published data [6]: mp 172–174°C.

5-*tert*-Butyl-1,3,5-triazinane-2-thione (2b). Yield 50%, colorless crystals, mp 170–172°C; published data [6]: mp 169–172°C.

5-(2-Hydroxyethyl)-1,3,5-triazinane-2-thione (2c). Yield 44%, colorless crystals, mp 161–162°C; published data [6]: mp 160–162°C.

5-Isopropyl-1,3,5-triazinane-2-thione (2d). Yield 30%, colorless crystals, mp 152–155°C; published data [6]: mp 153–155°C.

Cycloaminomethylation of tetrahydroimidazo-[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (glycoluril) with *N*,*N*-bis(methoxymethyl)alkanamines (*general procedure***).** A mixture of 20 mmol of *N*,*N*-bis(methoxymethyl)alkanamine in 2 mL of chloroform, 0.5 mmol of $SmCl_3 \cdot 6H_2O$, and 10 mmol of glycoluril in 4 mL of ethanol was stirred for 6 h at 60°C. 2,6-Dialkylhexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]-fluorene-4,8(1*H*,5*H*)-diones **3a**–**3d** were isolated from the reaction mixtures by silica gel column chromatography.

2,6-Dicyclohexylhexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8(1*H*,5*H*)-dione (3a). Yield 81%, colorless crystals, mp 214–216°C, R_f 0.60 (acetone). IR spectrum, ν, cm^{-1}: 2923–2854, 1708, 1463, 1443–1377, 1235, 1161, 1046, 954, 869, 745. ^{1}H NMR spectrum, δ, ppm: 1.15–1.17 m (10H, CH_2), 1.50 br.s (2H, CH_2), 1.68 br.s (4H, CH_2), 2.06 br.s (4H, CH_2), 2.46 br.s (2H, CH), 3.99 d and 4.98 d (8H, 1-H, 3-H, 5-H, 7-H, ^2J = 13.2 Hz), 5.29 s (2H, 8b-H, 8c-H). ^{13}C NMR spectrum, δ_C, ppm: 24.38 (CH_2), 25.88 (CH_2), 30.16 (CH_2), 54.35 (2-CH, 6-CH), 57.26 (C^1, C^3, C^5, C^7), 65.39 (C^{8b}, C^{8c}), 158.98 (C^4, C^8). Mass spectrum: *m*/*z* 427.237 [*M* + K]$^+$. Calculated: *M* 388.507.

2,6-Di-*tert*-butylhexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8(1*H*,5*H*)-dione (3b). Yield 78%, colorless crystals, mp 158–160°C, R_f 0.70 (acetone). IR spectrum, ν, cm^{-1}: 2924–2854, 1706, 1464, 1350, 1264, 1207, 1164, 1016–926, 867, 813–738. ^{1}H NMR spectrum, δ, ppm: 1.06 m (18H, *t*-Bu), 3.84 d and 4.73 d (8H, 1-H, 3-H, 5-H, 7-H, ^2J = 12.4 Hz), 5.41 s (2H, 8b-H, 8c-H). ^{13}C NMR spectrum, δ_C, ppm: 27.00 (CH_3), 52.72 [**C**$(CH_3)_3$], 56.11 (C^1, C^3, C^5, C^7), 64.26 (C^{8b}, C^{8c}), 159.16 (C^4, C^8). Mass spectrum: *m*/*z* 375.398 [*M* + K]$^+$. Calculated: *M* 336.433.

2,6-Bis(2-hydroxyethyl)hexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8(1*H*,5*H*)-dione (3c). Yield 70%, colorless crystals, mp 217–220°C, R_f 0.60 (acetone). IR spectrum, ν, cm^{-1}: 3443, 2922–2843, 1713, 1619, 1172, 1125, 1047, 721. ^{1}H NMR spectrum, δ, ppm: 2.64 t (4H, 2-CH_2, 6-CH_2), 3.39–3.44 m (4H, C**H**$_2$OH), 4.25 d and 4.58 d (8H, 1-H, 3-H, 5-H, 7-H, ^2J = 13.5 Hz), 5.57 s (2H, 8b-H, 8c-H). ^{13}C NMR spectrum, δ_C, ppm: 53.32 (2-CH_2, 6-CH_2), 59.48 (CH_2OH), 60.42 (C^1, C^3, C^5, C^7), 64.71 (C^{8b}, C^{8c}), 159.67 (C^4, C^8). Mass spectrum, *m*/*z*: 335.292 [*M* + Na]$^+$, 351.258 [*M* + K]$^+$. Calculated: *M* 312.325.

2,6-Diisopropylhexahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8(1*H*,5*H*)-dione (3d). Yield 75%, colorless crystals, mp 157–162°C, R_f 0.60 (acetone). IR spectrum, ν, cm^{-1}: 2923–2855, 1713, 1457, 1365–1352, 1255, 1125, 1009, 960, 808, 762, 720. ^1H NMR spectrum, δ, ppm: 1.06 s (12H, CH_3), 2.82 m [2H, C**H**$(CH_3)_2$], 4.13 d and 4.73 d (8H, 1-H, 3-H, 5-H, 7-H, ^2J = 13.2 Hz), 5.51 s (2H, 8b-H, 8c-H). ^{13}C NMR spectrum, δ, ppm: 21.03 (CH_3), 47.09 [**C**H$(CH_3)_2$], 57.36 (C^1, C^3, C^5, C^7), 64.94 (C^{8b}, C^{8c}), 159.37 (C^4, C^8). Mass spectrum: *m*/*z*: 307.364 $[M - H]^+$. Calculated: *M* 308.380.

X-Ray analysis of compounds 3a–3d. Single crystals of **3a**–**3d** suitable for X-ray analysis were obtained by crystallization from hexane–ethyl acetate (1 : 1). The X-ray diffraction data were acquired on an XCalibur Eos automated four-circle diffractometer (graphite monochromator, MoK_α radiation, λ = 0.71073 Å; ω-scanning, $2\theta_{max}$ = 62°) using CrysAlis^{Pro} (Oxford Diffraction Ltd., version 1.171.36.20). The structures were solved by the direct method and were refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized from electron density maps, and their positions were refined in isotropic approximation. All calculations were performed using SHELX97 [16]. The principal crystallographic data and refinement parameters are given in table, and the corresponding crystallographic information files were deposited to the Cambridge Crystallographic Data Centre [CCDC entry nos. 972665 (**3a**), 972663 (**3b**), 986434 (**3c**), 972662 (**3d**)] and are available at *http://www.ccdc.cam.ac.uk/data_request/cif*.

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