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N-Alkylation Reaction in the Synthesis of Tetra-Substituted Glycoluryls

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Abstract. A new method is suggested herein for the synthesis of tetrasubstituted glycolurils by treatment of disubstituted glycolurils (di-tert-butylglycolurils, di-isopropylglycoluril) with alkylating agents such as methyl iodide, ethyl bromide and benzyl chloride in acetonitrile in the presence of KOH. Optimum conditions for the preparation of the target product in high yield were studied by the example of the synthesis of dibenzyl-di-tert-butylglycoluril: time 3 h and reaction temperature 75ºC at a 1:4 M/M molar ratio of disubstituted glycoluril to benzyl chloride. Thus, the target product yield was 83%. It was also found that benzyl chloride should be used as the alkylating agent because the product yield under the same equal conditions was higher with benzyl chloride than with benzyl bromide which in turn is more toxic and less available.

Keywords: ureas, glycoluryls, disubstituted glycoluryls, N-alkylation, heterocycles.

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Реакция N-алкилирования в синтезе тетразамещенных гликольурилов

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Аннотация. Предложен новый способ получения тетразамещенных гликольурилов, заключающийся в обработке дизамещенных гликольурилов (дитрет-бутилгликольурила, диизопропилгликольурила) алкилирующими агентами: йодистый метил, бромистый этил и хлористый бензил в среде ацетонитрила в присутствии основания КОН. На примере получения дибензил-дитрет-бутилгликольурила изучены оптимальные условия для получения продукта с высоким выходом: продолжительность 3 ч и температура реакции 75 ºС при мольном соотношении дизамещенного гликольурила к бензил хлориду 1:4 моль/моль. Таким образом, выход целевого продукта составил 83 %. Также установлено, что в качестве алкилирующего агента следует использовать хлористый бензил в связи с тем, что выход продукта в одних и тех же условиях выше, чем при использовании бромистого бензила, который, в свою очередь, является наиболее токсичным и менее доступным.

Ключевые слова: мочевины, гликольурилы, дизамещенные гликольурилы, N-алкилирование, гетероциклы.

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N-alkyl-substituted 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (glycolurils) are known to exhibit a broad spectrum of biological activity. In particular, 2,4,6,8-tetramethylglycoluril (Mebicar) and 2,6-diethyl-4,8-dimethylglycoluril (Albicar) are compounds having anxiolytic properties [1-3].

Thus, synthesis of new N-alkyl-substituted glycolurils or improvement in the well-known synthetic methods is permanently receiving interest among researchers.

The chemical structure of glycoluril represents an extremely attractive object for further targeted modification because glycoluril comprises four active nucleophilic sites through which substitution reactions may take place [4, 5].

The literature [6, 7] describes a method for preparing 2,6-dimethyl-4,8-*di*-*tert*-butylglycoluril via cyclocondensation of 1-methyl-3-*tert*-butylurea with glyoxal, in which case a racemic mixture is formed that consists of the three compounds: *cis*- and *trans*-isomers of dimethyl-*di*-*tert*-butylglycoluril and hydantoin. With that, the yield of *trans*-isomers was found to be threefold that of *cis*-isomers [8].

Glycoluril tetraderivatives can be not only bioactive but also highly energetic. Tetranitroglycoluril (SORGUIL) is produced by nitration of glycoluril through the formation of dinitroglycoluril (DINGU) [9, 10].

The present paper reports the results on the synthesis of tetrasubstituted glycolurils by the N-alkylation reaction in order to expand the series of tetrasubstituted glycolurils and examine their presumed biological activity in the PASS program.

Experimental

The work was performed with instruments of the Biysk Regional Center for Shared Use of Scientific Equipment of the SB RAS (IPCET SB RAS, Biysk).

Infrared spectra were recorded in KBr pellets on a FT-801 FTIR spectrometer under conditions of disturbed total internal reflection.

NMR spectra were taken on a Bruker Avance III 500 spectrometer operated at 400.13 MHz for ^{1}H and at 100.61 MHz for ^{13}C. The spectra were acquired from the solution in CD_3CN.

***General synthesis of di-tert-benzylglycoluril*:** To acetonitrile (20 mL) was added disubstituted glycoluril (0.0025 M), alkylating agent (0.01 M) (methyl iodide, ethyl bromide or benzyl chloride) and KOH (0.01 M). The reaction mass was heated to 75 °C and held for 3 h. Afterwards, the precipitated KHal salt was discarded and the solvent was withdrawn from the mother solution. The resulting solid residue was washed with diethyl ether and then with water to dissolve the residual salt, and then with diethyl ether again. The resultant powder was collected by filtration and dried under atmospheric pressure.

3a. 2,6-Dimethyl-4,8-*di-tert*-butyl-2,4,6,8-tetraaza[3.3.0]octane-2,7-dione: Yield 40%. Mp = 144−146 °C. **IR**, cm^{-1}: 2984, 2971, 2910, 2887, 1711, 1690. **^{1}H NMR** (400 MHz, CD_3CN) 5,17 (s, 2H, N-CH-N), 2,80 (s, 6H, CH_3), 1,44 (s, 18H, $C(\underline{CH_3})_3$. **^{13}C NMR** (100 MHz, CD_3CN) δ 158.87 (C=O), 69.94 (N-CH-N), 53.51 ($\underline{C}(CH_3)$), 28.34 (CH_3).

3b. 2,6-Diethyl−4,8-*di-tert*-butyl-2,4,6,8-tetraaza[3.3.0]octane-2,7-dione: Yield: 59%. Mp = 122−124 °C. **IR**, cm^{-1}: 3445, 3340, 3222, 2973, 2933,2875, 1686, 1655. **^{1}H NMR** (400 MHz, CD_3CN) 5.28 (s, 2H, N-CH-N), 3.17-3.23 (q, 4H, CH_2), 1.27 (s, 18H, CH_3), 1.02-1.05 (t, 6H, CH, CH_3). **^{13}C NMR** (100 MHz, CD_3CN) δ 158.95 (C=O), 67.92 (N-CH-N), 53.83 ($\underline{C}(CH_3)$), 35.21 ($C\underline{H_2}$-CH_3), 28.34 (CH_3), 11.75 (CH_2-$C\underline{H_3}$).

3c. 2,6-Dibenzyl−4,8-*di-tert*-butyl-2,4,6,8-tetraaza[3.3.0]octane-2,7-dione: Yield 83%. Mp = 223−225 °C. **IR,** cm^{-1}: 3062, 3028, 2968, 2934, 2892, 1704 (C=O), 1687 (C=O). **^{1}H NMR** (400 MHz, CD_3CN) 7.39-7.19 (m, 10H, Ph); 5.43 (s, 2H, N-CH-N), 4.79 (*J*= 17.3 Hz, d, 2H, CH_2-Ph), 4.75 (*J*= 17.3 Hz, d, 2H, CH_2-Ph), 1.30 (s, 18H, CH_3). **^{13}C NMR** (100 MHz, CD_3CN) δ 159.14 (C=O), 138.11 (*i*-Ph), 128.60 (*m*-Ph), 126.16 (*o,p*-Ph), 68.41 (N-CH-N), 54.08 ($\underline{C}(CH_3)$), 43.73 (CH_2-Ph), 28.27 (CH_3).

4a. 2,6-Dimethyl-4,8-diisopropyl-2,4,6,8-tetraza[3.3.0]octane-2,7-dione: Yield 34%. **IR,** cm^{-1} 2976, 2942, 2884,1698 (C=O). **^{1}H NMR** (400 MHz, CD_3CN) 5.11 (s, 2H, N-CH-N), 3.77-3.73 (m, 2H, CH), 1.88 (s, 6H, CH_3), 1.30-1.22 (m, 12H, CH_3). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 159.17 (C=O), 70.78 (N-CH-N), 46.67 (CH), 20.58 (CH_3), 19.35 (CH_3).

4b. 2,6-Diethyl-4,8-diisopropyl-2,4,6,8-tetraaza[3.3.0]octane-2,7-dione: Yield 51%. **IR,** cm^{-1}:2974, 2937, 2881, 1693 (C=O). **^{1}H NMR** (400 MHz, CD_3CN) 5.16 (s, 2H, N-CH-N), 3.69-3.66 (m, 2H, $\underline{C}H(CH_3)_2$), 3.51-3.09 (m, 4H, CH_2), 1.07-1.35 (18H, CH_3). **^{13}C NMR** (100 MHz, CD_3CN) δ 158.66 (C=O), 68.16 (N-CH-N), 47.26 (CH), 36.60 (CH_2), 19.63, 19.91 (CH_3), 11.97 (CH_3).

4c. 2,6-Dibenzyl-4,8-diisopropyl-2,4,6,8-tetraaza[3.3.0]octane-2,7-dione: Yield 58%. **IR,** cm^{-1}: 3320, 3172, 2976, 2934, 2892, 1714 (C=O), 1688 (C=O). **^{1}H NMR** (400 MHz, CD_3CN) 7.40-7.24

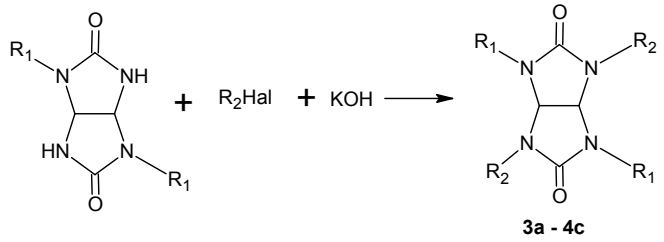
(m, 10H, Ph); 5.06 (s, 2H, N-CH-N), 4.72 (*J*= 16.4 Hz, d, 2H, CH_2-Ph), 4.35 (*J*= 16.4 Hz, d, 2H, CH_2-Ph), 3.43-3.45 (m, 2H, CH), 1.22 (s, 12H, CH_3). **^{13}C NMR** (100 MHz, CD_3CN) δ 158.94 (C=O), 137.69 (*i*-Ph), 128.60 (*m*-Ph), 127.19 (*o,p*-Ph), 69.29 (N-CH-N), 48.05 (CH), 45.55 (CH_2-Ph), 19.46 (CH_3).

Results and discussion

The starting disubstituted glycolurils were prepared by cyclization of monosubstituted urea with glyoxal by the reported procedure [11]. The general protocol for the study is illustrated in Fig. 1.

Figures 2−4 show the product yield plotted against the reaction temperature and time and molar ratio of starting components by the example of the synthesis of dibenzyl-*di-tert*-butylglycoluril.

As is seen in Fig. 2, the target product yield at 25 °C and 35 °C was as low as 9 and 21%, respectively, whereas the temperature rise to 45 °C resulted in a threefold increase in the yield. The maximum yield of dibenzyl-*di-tert*-butylglycoluril of 83% calculated as *di-tert*-butylglycoluril was achieved when the reaction temperature was 75 °C, which is close to the solvent boiling point.



№	R_1	R_2
3a	$C(CH_3)_3$	CH_3
3b	$C(CH_3)_3$	C_2H_5
3c	$C(CH_3)_3$	Bn
4a	$CH(CH_3)_2$	CH_3
4b	$CH(CH_3)_2$	C_2H_5
4c	$CH(CH_3)_2$	Bn

Fig. 1. General scheme for the study of the N-alkylation reaction of disubstituted glycolurils

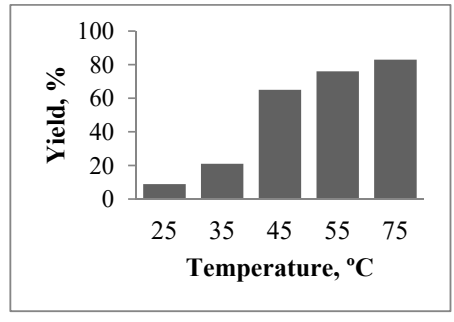


Fig. 2. Yield of **3c** plotted against reaction temperature

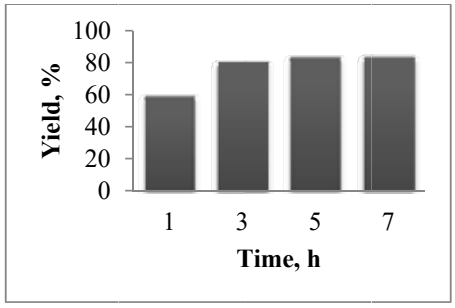


Fig. 3. Yield of **3c** plotted against reaction time

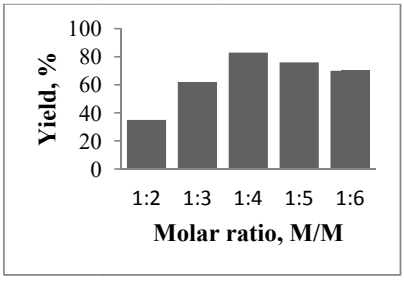


Fig. 4. Yield of **3c** plotted against molar ratio of di-tert-butylglycoluril to benzyl chloride

The reaction time increment from 1 to 3 h sharply enhanced the product yield (Fig. 3), and the further rise in reaction time almost did not favor an increase in the target product yield. Thus, the holding time of 3 h was more appropriate.

The experimental results demonstrated that the 1:4 M/M molar ratio of *di-tert*-butylglycoluril to benzyl chloride was optimum. It is seen in Fig. 4 that the product yield declined as the alkylating agent concentration in the initial mixture was raised to 1:6 M/M. It was also found that benzyl chloride should be used as the alkylating agent because it gave a higher yield of the target product than benzyl bromide, and its application is more preferable owing to its lower toxicity and greater availability compared to benzyl bromide.

It can be inferred from the aforesaid that the following conditions are required for the maximum yield of dibenzyl-*di-tert*-butylglycoluril: 1:4 molar ratio of the reactants, temperature 75 °C and time 3 h. In this case, the target product yield was 83%.

Conclusions

Never-before-seen glycoluril tetraderivatives were synthesized herein and dimethyl-*di-tert*-butylglycoluril was derived by the new method. High-yielding conditions were determined by the example of dibenzyl-*di-tert*-butylglycoluril: 1:4 M/M molar ratio of *di-tert*-butylglycoluril to benzyl chloride, temperature 75ºC and time 3 h.

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