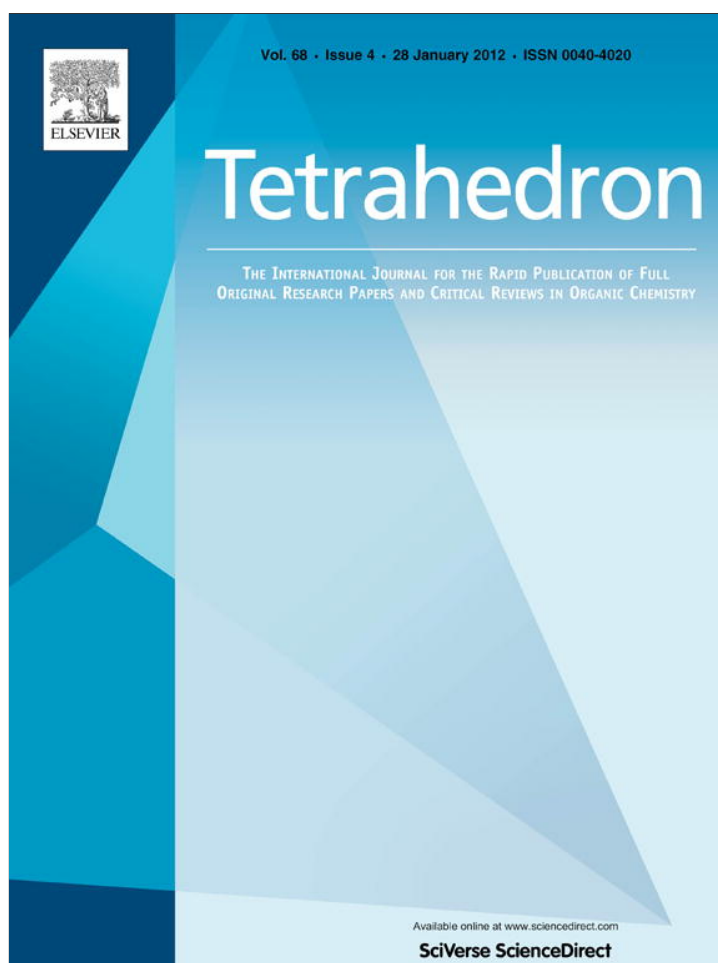


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Nucleophilic substitution approach towards 1,3-dimethylbarbituric acid derivatives—new synthetic routes and crystal structures

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ABSTRACT

We describe simple, convenient and high-yielding nucleophilic substitution reactions to synthesize new derivatives of 1,3-dimethylbarbituric acid (**1a**). Based on its active C5 position, condensing **1a** with sulfuryl chloride gives the corresponding 5,5-dichloro-1,3-dimethylbarbituric acid (**13**). The latter was reacted with silver nitrite and potassium cyanide to afford 5-chloro-5-nitro-1,3-dimethylbarbituric acid (**14**) and 5-cyano-1,3-dimethylbarbiturate (**17**), respectively. Furthermore, by employing the nucleophilic character of 2,3-dihydro-1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene (**8**) the obtained compounds **13** and **14** have been converted to 2-chloro-1,3-diisopropyl-4,5-dimethyl-1*H*-imidazol-3-ium-1,3-dimethyl-5-nitro-1,3-dimethylbarbiturate (**18**) and 1,3-dimethylbarbituric acid trimer (**21**), respectively. X-ray structures for compounds **13**, **14**, **17**, **18** and **21** were determined.

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1. Introduction

Barbituric acids (**1**) are heterocyclic derivatives of pyrimidine trione.^{1–3} They are well-known in medicinal chemistry as hypnotics, sedatives, anticonvulsants and anxiolytic agents.^{4–6} Recently, barbiturates have been used to induce anaesthesia in surgery procedures.⁷ C5-substituted and disubstituted barbituric acid and 2-thiobarbituric acids exhibit a wide spectrum of biological activity and some of them are useful drugs or agrochemicals.^{8,9} The C5 position in **1** is an active site since it could be acting as electrophilic and nucleophilic centres.^{10,11} As shown in Fig. 1, compounds **1–7** represent some known barbituric acid derivatives,^{12–16} which play an important role in pharmaceutical chemistry.

Over the last years our group (N. Kuhn) has studied reactions of nucleophilic carbenes with various electrophiles. In this context we became interested to react nucleophilic carbenes with barbituric acid derivatives having an electrophilic centre at C5. However, this would require an efficient and simple access to such compounds. Our results in this area are described in this paper.

Because of the strongly basic character of *N*-heterocyclic carbenes (**8**)^{17–19} (Fig. 2) they react immediately with *Bronsted* acids and have consequently been used as selective deprotonation reagents (compounds **9** and **10**).^{20,21} Furthermore, they are utilized as very useful nucleophiles to form stable charge transfer adducts (compounds **11** and **12**).^{22,23}



Fig. 1. Structures of some barbituric acid derivatives (R: H or alkyl).

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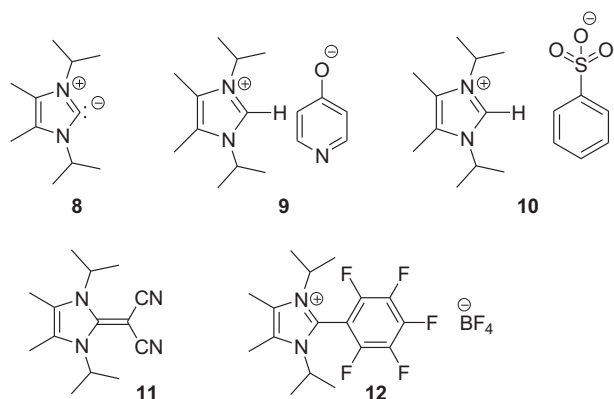


Fig. 2. Structures of some imidazole carbene derivatives.

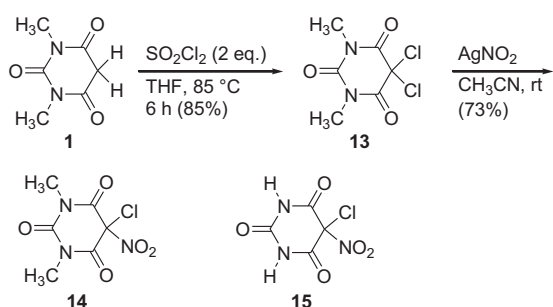
In this study, we have investigated the reaction of dichlorobarbituric acid **13** with 2,3-dihydro-1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene (**8**), nitrite and cyanide anions. We wish to describe herein a proposed mechanism for the synthesis of 1,3-dimethylbarbituric acid trimer (**21**). All the prepared compounds were confirmed by NMR, elemental analysis, mass spectrometry and single-crystal X-ray diffraction.

2. Results and discussion

2.1. Synthesis

It has long been known that nucleophilic substitution reactions of 1,3-dimethylbarbituric acid (**1a**) having one or two leaving groups at C5 give exclusive products in the C5 position.^{15,24,25} To achieve this target, this study describes novel synthetic procedures by employing various nucleophiles, the nature of the products formed was dependent on the character of the used nucleophiles. The preparation of 5,5-dichloro-1,3-dimethylbarbituric acid (**13**) has been explored previously^{26–28} but low product yields and limited access to starting materials have restricted the utility of some of these procedures. One of these methods is based on the reaction of synthesized tetramethyl alloxanthine with PCl₅ in *sym*-tetrachloroethane,²⁶ another route depends on electrochemical oxidation of **1a** at a pyrolytic graphite electrode by a single voltametric peak at pH 1 in the presence of chloride ion.²⁷ In addition, reaction of 6-chloro-1,3-dimethyluracil with chlorine gas in presence of acetic acid and acetic anhydride was also reported.²⁸

In our work, the preparation **13** was accomplished using a very simple and efficient one-pot methodology. To realize the strategy shown in Scheme 1, the two acidic hydrogen atoms at C5 in **1a** were readily substituted by chlorine atoms using 2 equiv of sulfuryl chloride affording the respective product **13** in very good yield (85%).

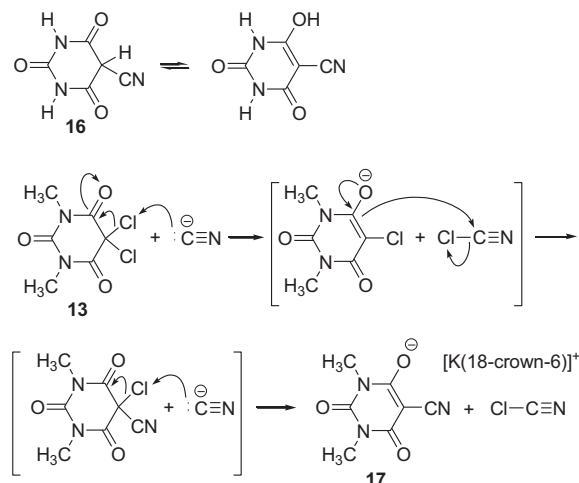


Scheme 1. Synthesis of dichlorobarbituric acid **13** and its reaction with silver nitrite.

2.1.1. The utility of 13 with ambident nucleophiles. 2.1.1.1. With nitrite anion to form compound 14. The 5,5-disubstituted barbituric acids were pursued further where compound **13** underwent nucleophilic substitution reactions with nitrite and cyanide.

In this work, the nucleophilic substitution of one Cl-atom in **13** was achieved under dry conditions by reacting **13** with silver nitrite in dry acetonitrile via an S_N2-like mechanism to afford compound **14**. In spite of an excess amount of nitrite anion, only one Cl-atom was replaced by a nitro group. The selection of acetonitrile was based on complete miscibility of both reactants, which may lead to high yield of product. On the other hand, dichloromethane solvent was employed in the purification step to get rid of the excess unreacted silver nitrite. Ziegler and Kappe and Biltz and Sedlat-scheck prepared the related compound **15** (Scheme 1) by reacting 5-nitrobarbituric acid with hydrogen peroxide and concentrated hydrochloric acid²⁹ or with chlorine in water.³⁰ However, in both procedures an aqueous medium was present in the reaction vessel, which led to a partial degradation of **15**.

Nucleophilic substitution by nitrite ion (ambident nucleophile) at a saturated carbon atom (sp³) can give both the nitro compound (RNO₂) as well as the nitrite ester (RONO).³¹ X-ray structural analysis of **14** shows the bonding to C5 is through nitrogen (*N*-attack) rather than oxygen (*O*-attack) to the carbon since the softer nitrogen of NO₂⁻ prefers to bind to a softer carbon in a tighter S_N2 transition state. According to Kornblum's rule, the more electronegative atom (hard base) in ambident nucleophiles reacts with a carbon atom (hard acid) if the reaction mechanism is S_N1-like (carbocation formed), while for the tetravalent carbon (softer acid) the less electronegative atom in the ambident nucleophiles will do. Since the active carbon (C5) in **13** is flanked between two carbonyl groups and attached to a high electronegative atom (Cl) it is difficult for the reaction to proceed via an S_N1 mechanism (formation of a carbocation) even though Ag⁺ is presented in the reaction mixture. We note that the mechanism might also proceed in a similar manner as illustrated in Scheme 2 (*vide infra*).



Scheme 2. The proposed mechanism for the formation of **17**.

2.1.1.2. With cyanide anion to form compound 15. Goutailler et al.³² proposed the formation of **16** (Scheme 2) as an intermediate in the photocatalytic degradation of dicyclanil. The molecule **16** was also prepared in low yield by heating of ethyl cyanoacetate with isocyanates in pyridine.³³

In the present work, 18-crown-6 was employed to increase the concentration of free cyanide anion, which substituted chlorine atom via carbon atom (*C*-attack) and consequently enhancing the

percent yield of **17**. The proposed mechanism for the synthesis of **17** is shown in Scheme 2.

As a part of current studies on 1,3-dimethylbarbituric acid and our interest in the chemistry of *N*-heterocyclic carbenes we next turned our attention to use *N*-heterocyclic carbenes as an efficient nucleophile. Accordingly, the 5-chloro-5-nitro-substituted barbituric acid derivative **14** was then subjected to further nucleophilic substitution with **8** in dry diethylether at $-78\text{ }^{\circ}\text{C}$ to produce compound **18** as colourless crystals in very good yield (86%) (Fig. 3). Actually, based on the nucleophilic character of the *N*-heterocyclic carbene either compound **19** or **20** was expected. The urea derivative **20** would be the result of nucleophilic attack to the C4 carbonyl group of **14**.³⁴ The absence of formation of these compounds may be attributed to steric repulsion between the oxygen atoms (O4 and O6) of the pyrimidine moiety with the isopropyl group of the nitrogen atoms in the imidazole moiety when imidazole carbene attempted to attack C5 in **14**.

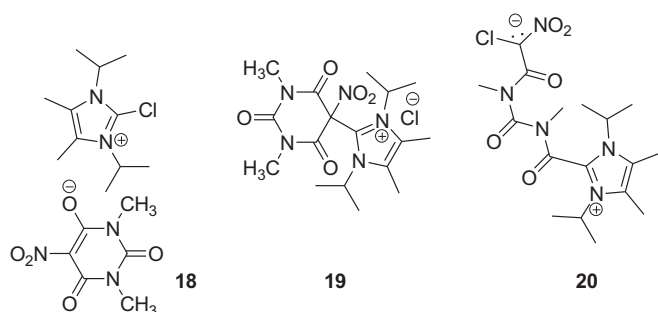
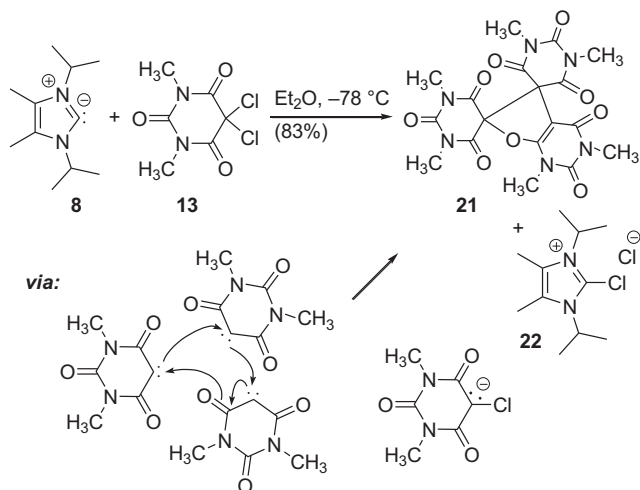


Fig. 3. Chemical structures of **18**, **19** and **20**.

In the reaction of dichloro compound **13** with carbene **8** an unexpected, formal trimerization of 1,3-dimethylbarbituric acid carbene was observed (Scheme 3). Formation of the trimeric form of 1,3-dimethylbarbituric acid was first reported by Poling et al.^{35,36} and Jursic and Stevens³⁷ They carried out the reaction by using an electro-oxidation method and by refluxing a solution of 5,5-dibromo-1,3-dimethylbarbituric acid with 1,3-dibarbituric in methanol for 4 days, respectively. None of them provided any proposed mechanism. In the current work, we were delighted to report a smooth one-pot synthesis of the trimer **21** by using *N*-heterocyclic carbenes. Thus, treating **13** with **8** in dry diethylether led to the formation of **21** in very good yield.



Scheme 3. The proposed mechanism for **21**.

As depicted in Scheme 3, we propose the formation of 1,3-dimethylbarbituric acid carbene intermediate in situ, which undergoes trimerization to reach a stable form. The mechanism might as well proceed via the monochloro anion. Washing the precipitate with dichloromethane is necessary to get rid of the 2-chloroimidazolium chloride (**22**). Interestingly, meldrum's acid **23** (the analogue of barbituric acid carbene) is dimerized to **24** (Fig. 4).³⁸ However, the target compound **21** was unambiguously identified by single-crystal X-ray diffraction (Fig 7).

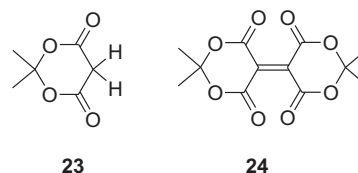


Fig. 4. The chemical structures of **23** and **24**.

The analysis of ^{13}C NMR data for **13**, **14**, **17** and **18** indicated that the signal of C5 carbon is affected by the different substituents and its hybridization. Accordingly, in compounds **13** and **14**, the signals of C5 carbon resonate at 72.2 and 89.2 ppm, respectively; this downfield chemical shift is attributed to the presence of strong withdrawing groups at C5 position. This effect seems to be more pronounced with the NO_2 -group in compound **14**. Moreover, the distinction between the ^{13}C NMR signals for the corresponding C5 position of compounds **17** and **18** was easily accomplished due to the highly upfielded chemical shift (41.4 ppm) relative to (94.2 ppm), respectively.

2.2. X-ray crystallography

The chemical structures of compounds **13**, **14**, **17**, **18** and **21** were determined by X-ray diffraction analysis. The obtained compounds, besides **17**, which crystallized in the orthorhombic space group, crystallized in the monoclinic space group. The general view and atom-numbering scheme for the molecules are shown in Figs. 5–7.

In molecule **13** (Fig. 5a) the Cl atoms attached to the C1 position display some bond length disturbance [Cl(1)–C(1) 1.784(2) and Cl(2)–C(1) 1.747(2) Å]. The C(1)–C(4) bond length in **13** is considerably longer than the corresponding bond length in **1a** [1.53 vs 1.48 Å].³⁹ The bond angles in molecule **14** (Fig. 7b) clearly indicate sp^3 -hybridization of the C1-carbon [N(3)–C(1)–Cl(1) 110.8 (2)°]. The bond angle [Cl(1)–C(1)–N(3)] is larger than [Cl(1)–C(1)–Cl(2)] in molecule **13** by 5.1°. The geometry of the nitro group is as expected, having one shorter and one longer nitrogen–oxygen bond [N(3)–O(4) 1.210(4) Å] and [N(3)–O(5) 1.222(4) Å].

The corresponding bond lengths [C(14)–C(15) and C(15)–C(16)] in molecule **17** (Fig. 6a) are shortening to 1.415(5) and 1.417(5) Å, respectively. This fact is due to sp^2 -hybridization of C5. The bond lengths O(7)–K(1) [2.687(3) Å], C(13)–O(7) [1.229(5) Å] lie within the range of normal covalent distances. Similar geometric peculiarities of the nitro group are observed in molecule **18** (Fig. 6b) [N(5)–O(5) 1.189(5) and N(5)–O(4) 1.195(5)]. The sp^2 -hybridization of the C11-carbon was clear [C(12)–C(11)–N(5) 118.2(3)°]. The bond lengths and angles of the imidazolium cation are close to those reported in the literature.⁴⁰

Interestingly, the C–O bond lengths assigned for the carbonyl group located between two nitrogen atoms in compounds **13**, **14**, **17** and **18** reveal some important feature, for compounds **13** and **14** these bonds have approximately the same lengths (~ 1.200 Å), while the corresponding bond lengths in **18** and **17** are 1.213 and

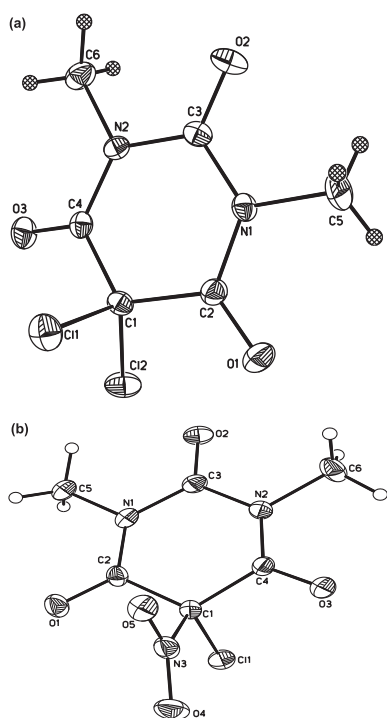


Fig. 5. View of compounds **13** (a) and **14** (b) in the crystal with atomic numbering scheme.

1.229 Å, respectively. This observation is attributed to the delocalization of negative charge in pyridinium ring in **17** and **18**; in addition, it is worthy to note that this bond in compound **17** is slightly longer due to the effect of strongly electron withdrawing group (CN) in compound **18**.

The five-membered ring in compound **21** is in an envelope conformation, whereas one of the barbiturate rings is almost planar while the others show much larger deviations from planarity (Fig. 7). However, the bond distances and angles of the trimer are in agreement with those observed in the previous reported data.³⁶

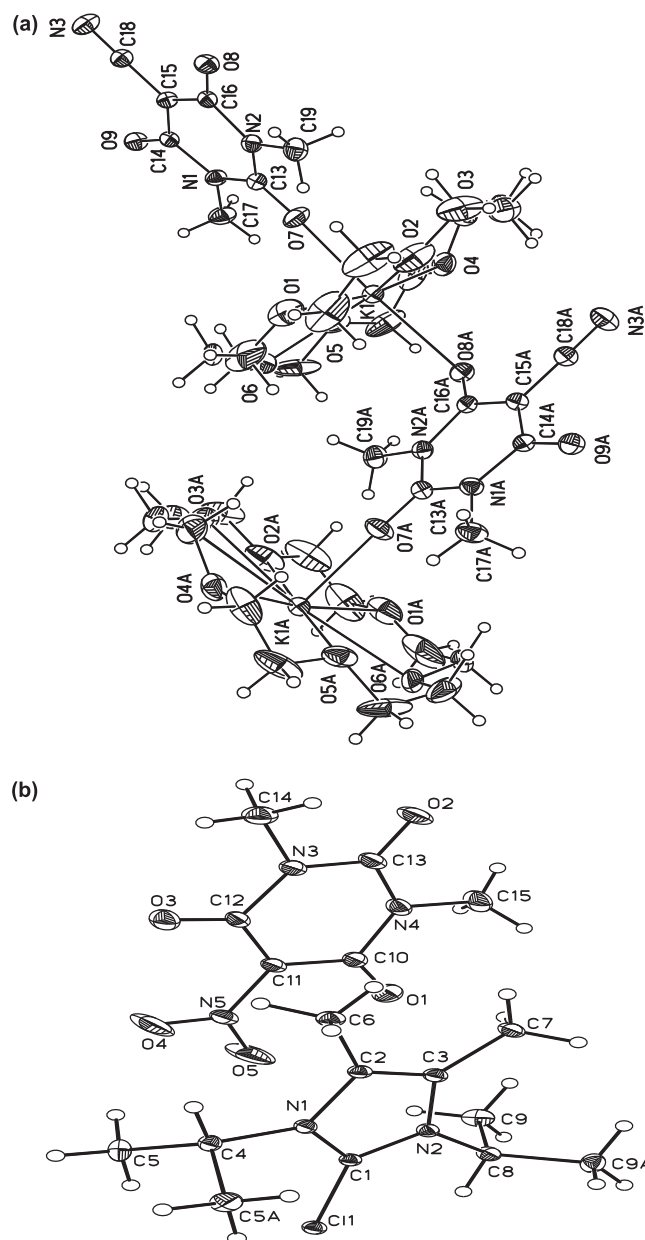
3. Conclusion

In summary, a facile synthesis of a series of 1,3-dimethylbarbituric acid derivatives in very good yields via nucleophilic substitution strategy is reported. Synthetic utility of the nucleophilic attack of different nucleophiles onto 5,5-dichloro-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**13**) has been highlighted. The reactions demonstrated broad substrate scope and good substitution tolerance. Furthermore, we have presented a new procedure for the synthesis of 1,3-dimethylbarbituric acid trimer (**21**) by employing the strongly nucleophilic character of *N*-heterocyclic carbenes with a proposed mechanism. Compared to the well-established protocol, it is noteworthy that this process is sufficiently rapid, efficient and purification of the trimer involves simple crystallisation from a suitable solvent. In view of extensive use of barbituric acid derivatives in medicinal chemistry, the compounds prepared in the present study and the methodology developed here may find useful applications in bio-organic and medicinal chemistry.

4. Experimental section

4.1. General

Commercially available reagents were purchased from Aldrich and were used without further purification. All reactions were performed in purified solvents under argon. 2,3-Dihydro-1,3-



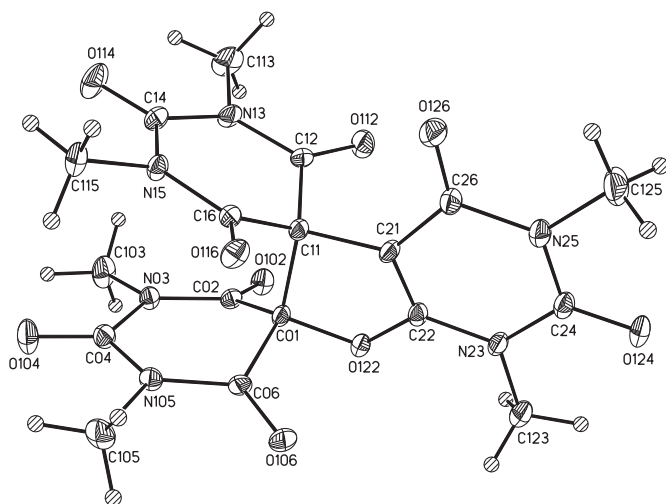


Fig. 7. View of the trimer in **21** with atomic numbering scheme.

1,3-dimethylbarbituric acid (**1a**) (1.40 g, 9.0 mmol) in THF (25 mL) was refluxed at 85 °C for 6 h. After cooling to room temperature, the solvent was removed in vacuo and the residue recrystallised from CH₂Cl₂/diethylether to give dichloro compound **13** (1.72 g, 85%) as colourless crystals. δ_{H} (250 MHz, CDCl₃) 3.30 (s, 6H, 1,3-Me); δ_{C} (62.5 MHz, CDCl₃) 30.7 (1,3-Me), 149.1 (C2), 72.2 (C5), 161.7 (C4,6). Anal. Calcd for C₆H₆Cl₂N₂O₃: C 32.02, H 2.69, N 12.45. Found C 32.25, H 2.51, N 12.68. MS (FAB), m/z : 225 [93, M⁺], 191 [100, M⁺–Cl] and further fragments.

4.2.2. 5-Chloro-1,3-dimethyl-5-nitro-2,4,6(1H,3H,5H)-pyrimidinetrione (**14**). To a solution of **13** (0.80 g, 3.6 mmol) in acetonitrile (30 mL), silver nitrite was added (1.25 g, 8.1 mmol) in one portion at room temperature. The reaction mixture was allowed to stir at room temperature overnight. Thereafter, the solvent was evaporated in vacuo and the residue dissolved in CH₂Cl₂ (15 mL) and filtered off. The CH₂Cl₂ filtrate was evaporated under reduced pressure whereby a powder residue was obtained. It was purified by crystallisation from CH₂Cl₂/diethylether to afford **14** (0.62 g, 73%) as colourless crystals. δ_{H} (250 MHz, CDCl₃) 3.34 (s, 6H, 1,3-Me); δ_{C} (62.5 MHz, CDCl₃) 30.6 (1,3-Me), 149.2 (C2), 89.2 (C5), 159.1 (C4,6). Anal. Calcd for C₆H₆ClN₃O₅: C 30.59, H 2.57, N 17.84. Found C 30.78, H 2.43, N 17.62. MS (FAB), m/z : 189 [6, M⁺–NO₂], 161 [100, M⁺–NO₂–2Me] and further fragments.

4.2.3. Potassium 5-cyano-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate 1,4,7,10,13,16-hexaoxacyclooctadecane (**17**). To a mixture of potassium cyanide (0.35 g, 5.4 mmol) and 18-crown-6 (0.93 g, 3.5 mmol) in CH₂Cl₂ (15 mL), a solution of **13** (0.40 g, 1.8 mmol) in CH₂Cl₂ (15 mL) was added. After being stirred at room temperature overnight, the reaction mixture was concentrated in vacuo. The resulting residue was recrystallised from CH₂Cl₂/diethylether to give **17** (0.48 g, 55%) as yellow crystals. δ_{H} (250 MHz, CDCl₃) 3.51 (s, 6H, 1,3-MeB), 3.65 (s, 12H, crown ether); δ_{C} (62.5 MHz, CDCl₃) 30.6 (1,3-MeB), 41.4 (C5B), 109.4 (CN), 154.3 (C2B), 165.1 (C4,6B). Anal. Calcd for C₁₉H₃₀N₃O₉K: C 47.19, H 6.25, N 8.69. Found C 47.43, H 6.24, N 8.98. MS (FAB), m/z : 180 [100, M⁺] and further fragments.

4.2.4. 2-Chloro-1,3-diisopropyl-4,5-dimethyl-1H-imidazol-3-ium 1,3-dimethyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate (**18**). A solution of **8** (0.80 g, 4.4 mmol) in diethylether (10 mL) was cooled to –78 °C, then added to a solution of **14** (1.04 g 4.4 mmol) in diethylether (25 mL). Thereafter, the reaction mixture was allowed to stir at room temperature overnight. The precipitate was

then filtered off and dried in vacuo. The product was purified by crystallisation from CH₂Cl₂/diethylether to give **18** (1.58 g, 86%) as colourless crystals. δ_{H} (250 MHz, CDCl₃) 3.06 (s, 6H, 1,3-MeB), 1.43 (d, $J=6.8$ Hz, 12H, 1,3-CHMe₂), 2.16 (s, 6H, 4,5-Me), 4.78 (sept, 2H, CHMe₂); δ_{C} (62.5 MHz, CDCl₃) 30.6 (1,3-MeB), 151.6 (C2B), 114.2 (C5B), 158.2 (C4,6B), 9.8 (4,5-Me), 20.2 (1,3-CHMe₂), 52.6 (1,3-CHMe₂), 126.3 (C4,5), 127.9 (C2). Anal. Calcd for C₁₇H₂₆ClN₅O₅: C 49.10, H 6.30, N 16.84. Found C 49.39, H 6.02, N 16.71. MS (FAB), m/z : 215 [100, M⁺], 173 [14, M⁺–C₃H₇], 136 [23, M⁺–(C₃H₇), –Cl] and further fragments.

4.2.5. 5,6-Dihydro-1,3-dimethyl-5,6-bis-[1',3'-dimethyl]-2',4',6'-trioxypyrimid (5',5') yl[2,3-d] uracil (**21**). A solution of **8** (0.53 g, 2.9 mmol) in diethylether (10 mL) was cooled to –78 °C, then was added to **13** (0.65 g, 2.9 mmol) in diethylether (25 mL). After that, the reaction mixture was allowed to stir at room temperature overnight, and then the precipitate was filtered off, washed with CH₂Cl₂ and dried in vacuo. The product was purified by crystallisation from CH₂Cl₂/diethylether to give **21** (1.11 g, 83%) as colourless crystals. δ_{H} (250 MHz, DMSO-*d*₆) 3.26–3.29–3.52 (s,s,s, 6,9,3H,1,3-MeB). Anal. Calcd for C₁₈H₁₉N₆O₉: C 46.76, H 3.92, N 18.18. Found C 46.91, H 3.60, N 18.52. MS (FAB), m/z : 215 [100, M⁺], 173 [18, M⁺–C₃H₇], 136 [20, M⁺–(C₃H₇), –Cl] and further fragments.

4.3. X-ray crystallographic data

Suitable crystals for crystallographic investigations of **13**, **14**, **17** and **18** were obtained by slow diffusion of ether into CH₂Cl₂ solution. A crystal of **21** was obtained by slow evaporation of a solution of 15.0 mg of **21** in methanol (5 mL). X-ray measurements for synthesized compounds were carried out on a glass fibre with epoxy cement at room temperature. Preliminary examination and data collection were performed with a Stoe CAD4 and IPDS 2 diffractometer with graphite-monochromated Mo K α radiation ($\lambda=0.71073$ Å) and Cu K α radiation ($\lambda=1.54184$ Å). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXS-97⁴² and SHELXTL V5.1 (NT). Details for the structure solutions and refinements are given in Table 1 (Supplementary data).

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Supplementary data

Supplementary crystallographic data associated with this article (CCDC 842202, CCDC 842203, CCDC 842204, CCDC 842205 and CCDC 842380) can be found free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. In addition, crystal data and structure refinement for C₆H₆Cl₂N₂O₃ (**13**), C₆H₆ClN₃O₅ (**14**), C₁₉H₃₀N₃O₉K (**17**), C₁₇H₂₆ClN₅O₅ (**18**), and C₁₈H₁₉N₆O₉ (**21**) are contained in the Supplementary data. Supplementary data related to this article can be found online at [doi:10.1016/j.tet.2011.11.093](https://doi.org/10.1016/j.tet.2011.11.093).

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