Synthesis of diaminomethylidene derivatives of tetronic acid

*M. A. Prezent** *and V. A. Dorokhov*†

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: vador@ioc.ac.ru

Methyl 4-chloro-3-oxobutanoate reacts with benzoylcyanamide in the presence of catalytic amounts of $Ni(acac)_2$ to give the corresponding ketene *N*-benzoylaminal, which is transformed in boiling AcOH into 3-[(amino)(benzoylamino)methylidene]tetrahydrofuran-2,4-dione. Debenzoylation of the latter in the presence of EtONa in EtOH yields a N,N-unsubstituted diaminomethylidene derivative of tetronic acid. Cyclization of the adduct of methyl 4-chloro-3-oxobutanoate with benzoylcyanamide in the presence of triethylamine follows a different pathway leading to methyl 2-amino-1-benzoyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate.

Key words: methyl 4-chloro-3-oxobutanoate, benzoylcyanamide, cyclization, diaminomethylidene derivative of tetronic acid.

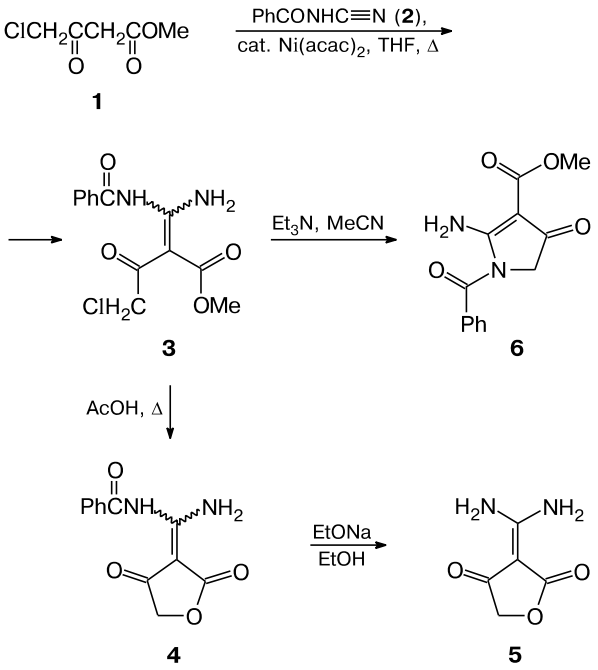
Derivatives of tetronic acid (4-hydroxyfuran-2(5*H*)-one) are known to be biologically important compounds found in a number of living organisms (fungi, algae, lichens, and tree fungi). They exhibit antiviral, anti-inflammatory, antibiotic, antitumor, and other types of biological activity (see recent reviews[1—4]) and are very popular as efficient reagents for the synthesis of various furan-containing compounds (see, *e.g.*, Refs 5—12).

Here we report on the synthesis of diaminomethylidene derivatives of tetronic acid that are new promising building blocks for the design of heterocyclic systems.

Earlier,[13—15] it has been found that β-oxo carboxylic acid esters easily react with cyanamides in the presence of catalytic amounts of $Ni(acac)_2$ to give the corresponding acyl(alkoxycarbonyl)ketene aminals, which were subsequently employed in various approaches to the synthesis of functionalized pyrimidines.[15—18]

Likewise, starting from methyl 4-chloro-3-oxobutanoate (**1**) and benzoylcyanamide (**2**), we obtained ketene aminal **3** in 70% yield (Scheme 1).

Scheme 1



The ^1H NMR spectrum of compound **3** in DMSO-d_6 shows one set of signals because the barrier to rotation about the C=C bond in such push-pull systems is very low.[13,15,19]

It is known that β-oxo carboxylic acid esters containing an appropriate substituent in the γ-position (Cl, Br, OH, or OAc) can be employed as the starting materials in the synthesis of tetronic acids (see Ref. 1). We found that ketene aminal **3** in boiling acetic acid undergoes cyclization into *N*-benzoyldiaminomethylidenetetronic acid **4**, which is debenzoylated under the action of EtONa in EtOH to give N,N-unsubstituted compound **5**. (Obviously, the formation of furandione **4** is preceded by hydrolysis of ester **3** to the corresponding acid.)

Crystalline products **4** and **5** are also α,α-dioxo ketene aminals, which is confirmed by spectroscopic data (IR, MS, and ^1H and ^{13}C NMR). As in the case of ketene aminal **3**, the ^1H NMR spectrum (DMSO-d_6) of compound **4** shows one set of signals. The spectrum of diami-

† Deceased.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1623—1625, August, 2012.

nomethylidenetetronic acid **5** contains no signals for aromatic protons.

Interestingly, the cyclization of ketene aminal **3** under basic conditions (in the presence of an equivalent amount of TEA) follows a different route leading to methyl 2-amino-1-benzoyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**6**); *i.e.*, the ring closure involves the fragments PhCONH and $ClCH_2$. The mass spectrum of compound **6** contains a molecular ion peak with *m/z* 260; the ^{1}H NMR spectrum (DMSO-d_6) show signals for MeO (δ 3.70) and for the aromatic protons of the benzoyl substituent.

The diaminomethylidene derivatives of tetronic acid (**4**) and (**5**) we obtained for the first time are of certain interest as potential reagents for heterocyclic synthesis. In this context, N,N-unsubstituted aminal **5** seems to be more promising because such α,α-dioxo ketene aminals are highly efficient in heterocyclization processes.[18]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75 MHz, respectively) at 25 °C. Mass spectra were measured on a Kratos MS-30 instrument (EI, 70 eV). IR spectra were recorded on a Specord M-82 instrument (KBr pellets).

Benzoylcyanamide was prepared as described earlier.[20] Nickel acetylacetonate (Aldrich) was recrystallized from MeOH and dried *in vacuo*. Methyl 4-chloro-3-oxobutanoate (Aldrich), commercial anhydrous ethanol, glacial acetic acid, acetonitrile, and THF were also used.

Methyl 2-[(amino)(benzoylamino)methylidene]-4-chloro-3-oxobutanoate (3). A solution of cyanamide **2** (1.46 g, 10 mmol), methyl 4-chloro-3-oxobutanoate (1.5 g, 10 mmol), and $Ni(acac)_2$ (0.128 g, 0.5 mmol) in THF (20 mL) was refluxed for 1 h and concentrated. The residue was recrystallized from MeOH. The yield of compound **3** was 2.07 g (70%), m.p. 121—122 °C (MeOH). Found (%): C, 52.66; H, 4.44; N, 9.47. $C_{13}H_{13}ClN_2O_4$. Calculated (%): C, 52.63; H, 4.41; N, 9.44. IR, ν/cm^{-1}: 3350—3150 (NH), 1684, 1648, 1632 (CO). MS, *m/z*: 296 $[M]^+$, 247 $[M - CH_2Cl]^+$. ^{1}H NMR (DMSO-d_6), δ: 3.80 (s, 3 H, MeO); 4.70 (s, 2 H, CH_2CO); 7.60—7.80 (m, 3 H, Ph); 8.00 (d, 2 H, Ph, *J* = 7.0 Hz); 9.90, 10.30, 14.35 (all s, 3 H, 3 NH).

3-[(Amino)(benzoylamino)methylidene]tetrahydrofuran-2,4-dione (4). A solution of ketene aminal **3** (2.07 g, 7 mmol) in acetic acid (10 mL) was refluxed for 1 h and concentrated. The residue was recrystallized from MeOH. The yield of furandione **4** was 1.46 g (85%), m.p. 210—211 °C (MeOH). Found (%): C, 58.37; H, 4.48; N, 11.33. $C_{12}H_{10}N_2O_4$. Calculated (%): C, 58.54; H, 4.09; N, 11.38. IR, ν/cm^{-1}: 3370—3170 (NH), 1696, 1668, 1652 (CO). MS, *m/z*: 246 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 4.60 (s, 2 H, CH_2); 7.65 (t, 2 H, Ph, *J* = 7.0 Hz); 7.75 (m, 1 H, Ph); 7.95 (d, 2 H, Ph, *J* = 7.0 Hz); 8.50—10.00 (br.s, 2 H, NH_2); 11.50—12.50 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 71.2 (C(5)); 81.7 (C(3)); 127.5 (*o*-Ph); 129.3 (*m*-Ph); 131.1 (*ipso*-Ph); 134.1 (*p*-Ph); 156.7 (NH_2—C—NH_2); 167.4 (C=OPh); 173.5 (C(2)); 194.9 (C(4)).

3-(Diaminomethylidene)tetrahydrofuran-2,4-dione (5). Benzoyl derivative **4** (1.46 g, 6 mmol) was added to a solution of metallic sodium (0.138 g, 6 mmol) in ethanol (20 mL). The reaction mixture was stirred at room temperature for 5 h, neutralized with HCl (0.216 g) in ethanol (10 mL), and concentrated. The residue was recrystallized from acetonitrile, washed with a small amount of water, and dried. The yield of compound **5** was 0.477 g (56%), m.p. >300 °C (MeCN). Found (%): C, 42.47; H, 4.45; N, 19.42. $C_5H_6N_2O_3$. Calculated (%): C, 42.26; H, 4.25; N, 19.71. IR, ν/cm^{-1}: 3420, 3300 (NH), 1620, 1600 (CO). MS, *m/z*: 142 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 4.30 (s, 2 H, CH_2); 7.50 (br.s, 2 H, NH_2); 7.80 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 70.4 (C(5)); 80.0 (C(3)); 159.6 (NH_2—C—NH_2); 174.5 (C(2)); 193.3 (C(4)).

Methyl 2-amino-1-benzoyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (6). A mixture of ketene aminal **3** (2.07 g, 7 mmol) and triethylamine (0.71 g, 7 mmol) in MeCN (10 mL) was refluxed for 2 h and kept for 16 h. The precipitate that formed was filtered off, washed with water, and dried. The yield of compound **6** was 1.36 g (75%), m.p. 230—232 °C (MeCN). Found (%): C, 59.87; H, 4.95; N, 10.83. $C_{13}H_{12}N_2O_4$. Calculated (%): C, 60.00; H, 4.65; N, 10.76. IR, ν/cm^{-1}: 3544—3220 (NH), 1700, 1680, 1660 (CO). MS, *m/z*: 260 $[M]^+$, 229 $[M - MeO]^+$, 155 $[M - PhCO]^+$. ^{1}H NMR (DMSO-d_6), δ: 3.70 (s, 3 H, MeO); 4.00 (s, 2 H, CH_2); 7.30—7.70 (m, 3 H, Ph); 7.95 (d, 2 H, Ph, *J* = 7.0 Hz); 8.50—9.30 (br.s, 2 H, NH_2).

References

1. D. Tejedor, F. Garcia-Tellodo, *Org. Prep. Proc. Int.*, 2004, **36**, 33.
2. A. L. Zagrafos, D. Georgiadis, *Synthesis*, 2006, 3157.
3. R. Schobert, A. Schlenk, *Bioorg. Med. Chem.*, 2008, **16**, 4203.
4. G. Athanasellis, O. Igglesi-Markopoulou, J. Markopoulos, *Bioinorg. Chem. Appl.*, 2010, Article ID 315056.
5. K. Görlitrer, U. Bartke, *Pharmazie*, 2002, **57**, 672.
6. N. Sydorenko, R. P. Hsung, O. S. Darwish, J. M. Hahn, J. Lui, *J. Org. Chem.*, 2004, **69**, 6732.
7. S. A. Savina, V. M. Lyubchanskaya, L. M. Alekseeva, A. S. Shashkov, V. G. Granik, *Russ. Chem. Bull.* (*Int. Ed.*), 2007, **56**, 2298 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2007, 2220].
8. Y. Bourdreux, E. Bodio, C. Willis, C. Billaud, T. Le Gall, C. Mioskowski, *Tetrahedron*, 2008, **64**, 8930.
9. N. G. Kozlov, S. L. Bondarev, A. P. Kadutskii, L. I. Basalaeva, F. S. Pashkovskii, *Zh. Org. Khim.*, 2008, **44**, 1041 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2008, **44**, 1031].
10. A. Shaabany, E. Soleimani, A. Sarvary, A. H. Rezayan, *Bioorg. Med. Chem. Lett.*, 2008, 3968.
11. A. Shaabany, A. Sarvary, S. Keshipour, A. H. Rezayan, R. Ghadari, *Tetrahedron*, 2010, **66**, 1911.
12. F. Shi, N. Ma, Y. Zhany, G. Zhang, B. Jiang, S. Tu, *Synth. Commun.*, 2010, **40**, 235.
13. V. A. Dorokhov, M. F. Gordeev, Z. K. Dem´yanets, M. N. Bochkareva, V. S. Bogdanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1989, **38**, 1654 [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1806].
14. V. A. Dorokhov, Z. K. Dem´yanets, *Russ. Chem. Bull.* (*Engl. Transl.*), 1993, **42**, 384 [*Izv. Akad. Nauk*, *Ser. Khim.*, 1993, 419].

15. V. A. Voronkova, A. V. Komkov, V. A. Dorokhov, *Russ. Chem. Bull.* (*Int. Ed.*), 2009, **58**, 351 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 347].
16. V. L. Gein, S. G. Pitirimova, O. V. Vinokurova, Yu. S. Andreichikov, A. V. Komkov, V. S. Bogdanov, V. A. Dorokhov, *Russ. Chem. Bull.* (*Engl. Transl.*), 1994, **43**, 1398 [*Izv. Akad. Nauk*, *Ser. Khim.*, 1994, 1475].
17. V. A. Dorokhov, M. A. Prezent, V. S. Bogdanov, *Russ. Chem. Bull.* (*Engl. Transl.*), 1994, **43**, 1550 [*Izv. Akad. Nauk*, *Ser. Khim.*, 1994, 1638].
18. V. A. Dorokhov, V. A. Voronkova, A. V. Komkov, S. V. Baranin, L. S. Vasil´ev, *Russ. Chem. Bull.* (*Int. Ed.*), 2010, **59**, 1035 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2010, 1012].
19. J. Sandstrom, *Topics in Stereochemistry*, Eds H. L. Alinger, E. L. Elial, S. H. Wilen, John Wiley, New York, 1983, **14**, p. 83.
20. V. S. Plugin, S. L. Kuznetsova, Yu. E. Sapozhnikov, *Zh. Org. Khim.*, 2008, **44**, 461 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2008, **44**].

Received October 19, 2011;
in revised form March 27, 2012