Multicomponent tandem synthesis of oxospirobicyclic butenolidobarbiturates

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Novel oxospirobicyclic γ-butenolides containing barbiturate moiety have been synthesised by the Michael-addition of primary amines to dialkyl acetylenedicarboxylates followed by aldol-like reaction with alloxan derivatives, and then γ-lactonisation. Subsequent 1,4-addition of water and elimination of the amine group completes the sequence. This tandem reaction sequence represents a rapid and unprecedented route to the described biologically interesting molecules.

Keywords: amine, acetylenic ester, alloxan, barbiturate, γ-butenolide, multicomponent reaction

γ-Butenolides are ubiquitous integral parts of numerous pharmacologically relevant natural products.[1] This includes, for example, chlorotricolide,[2] securinine,[3] kallolide A,[4] pseudopterolide,[5] dysidiolide,[6] tonkinecin,[7] (±)-differolide.[8] The activity of these natural products has been attributed to the butenolide moiety.

3-Hydroxy-4-alkoxycarbonyl-γ-butenolides have been previously prepared mainly by base-mediated cyclisation reactions, namely, the reactions of pyruvates with aldehydes,[9] benzaldehyde with dimethyl methoxyfumarate,[10] acetophenones with formaldehyde and diethyl oxalate,[11] and by DABCO-mediated dimerisation of methyl 2,4-dioxopentanoate.[12] A different approach relies on the phosphine-mediated reaction of ketones with methyl acetoxypropynoate.[13] Also, the synthesis of spiro 3-methoxy-4-methoxycarbonyl-γ-butenolides based on PPh_3 mediated reactions of 1,2-quinones in refluxing benzene has been reported.[14] 5-Alkylidene-3-hydroxy-4-alkoxycarbonyl-butenolides have been prepared by cyclisation of 1,3-dicarbonyl compounds with oxalyl chloride.[15] Sonoda *et al*. reported the synthesis of 2,3-dioxo-2,3-dihydrofurans by cyclisation of acetophenone-derived silyl enol ethers with oxalyl chloride.[16] Although, there are many ways to synthesise the γ-butenolide moiety, to the best of our knowledge only two one-pot multicomponent approaches have been published.[14,17]

Indeed, our group has long had an interest in developing new reactions as well as expanding the scope of existing multicomponent reactions to rapidly access drug-like motifs. Our recent interest aimed at the development of efficient protocols for the preparation of biologically active heterocycles via multicomponent reactions,[18–21] has been guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biological profile remarkably. In this report the facile synthesis of some novel oxospirobicyclic γ-butenolides containing a barbiturate moiety is described.

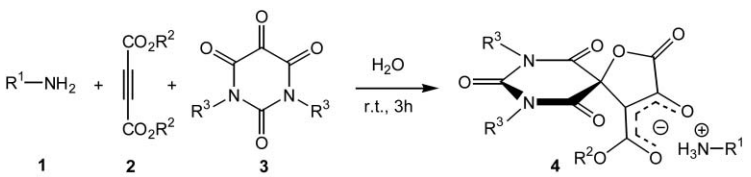
In the present investigation, a mixture of primary amine **1**, dialkyl acetylenedicarboxylates **2** and alloxan derivative **3** in a 1:1:1 molar ratio in water was vigorously stirred at room temperature for 3 h. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure, the residue was washed with diethyl ether and recrystallised from ethanol to afford corresponding alkyl or arylammonium 4-(alkoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro [4.5]dec-3-ene-3-olates **4** in excellent yields (Scheme 1, Table 1). Compounds **4a–q** are stable solids whose structures were established by FT-IR, ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis. The structure of **4m** was confirmed by a single-crystal X-ray analysis. (Fig. 1).

The scope and limitations of this simple process were explored by using two dialkyl acetylenedicarboxylates, two alloxan derivatives and a wide range of primary amines. A variety of structurally diverse amines underwent the one-pot reaction smoothly without using any catalyst to afford the corresponding spirocyclic butenolide derivatives in high yields.

Table 1 Three-component condensation reactions of primary amines, dialkyl acetylenedicarboxylates, and alloxan derivatives

Entry	R^1	R^2	R^3	Product	Yield[a] /%
1	Allyl	Methyl	H	**4a**	80
2	1-Adamantyl	Methyl	H	**4b**	96
3	*N*–Hexyl	Methyl	H	**4c**	91
4	Isobutyl	Methyl	H	**4d**	89
5	Benzyl	Methyl	H	**4e**	78
6	1-Adamantyl	Ethyl	H	**4f**	86
7	*n*-Propyl	Ethyl	H	**4g**	70
8	Allyl	Ethyl	H	**4h**	90
9	Allyl	Methyl	Methyl	**4i**	90
10	Isobutyl	Methyl	Methyl	**4j**	89
11	Phenyl	Methyl	Methyl	**4k**	87
12	1-Adamantyl	Methyl	Methyl	**4l**	97
13	Isobutyl	Ethyl	Methyl	**4m**	92
14	4-Hydroxyphenyl	Ethyl	Methyl	**4n**	91
15	Benzyl	Ethyl	Methyl	**4o**	97
16	*n*-Propyl	Ethyl	Methyl	**4p**	98
17	Phenyl	Ethyl	Methyl	**4q**	95

[a] Purified yield, which is >95% as determined by ^{1}H NMR.



Scheme 1

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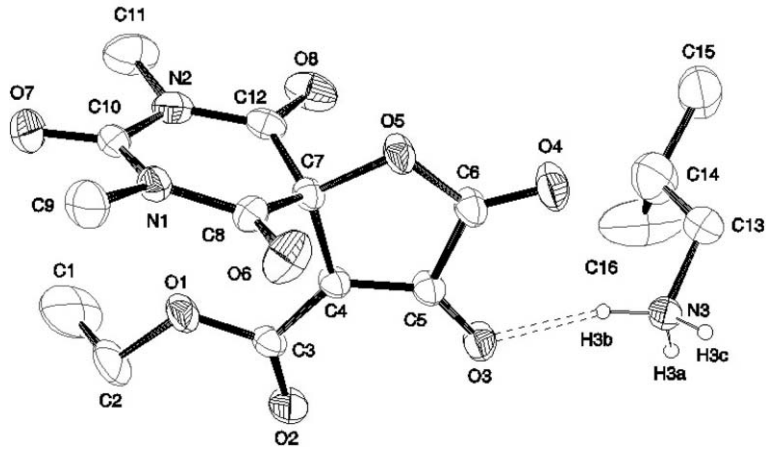
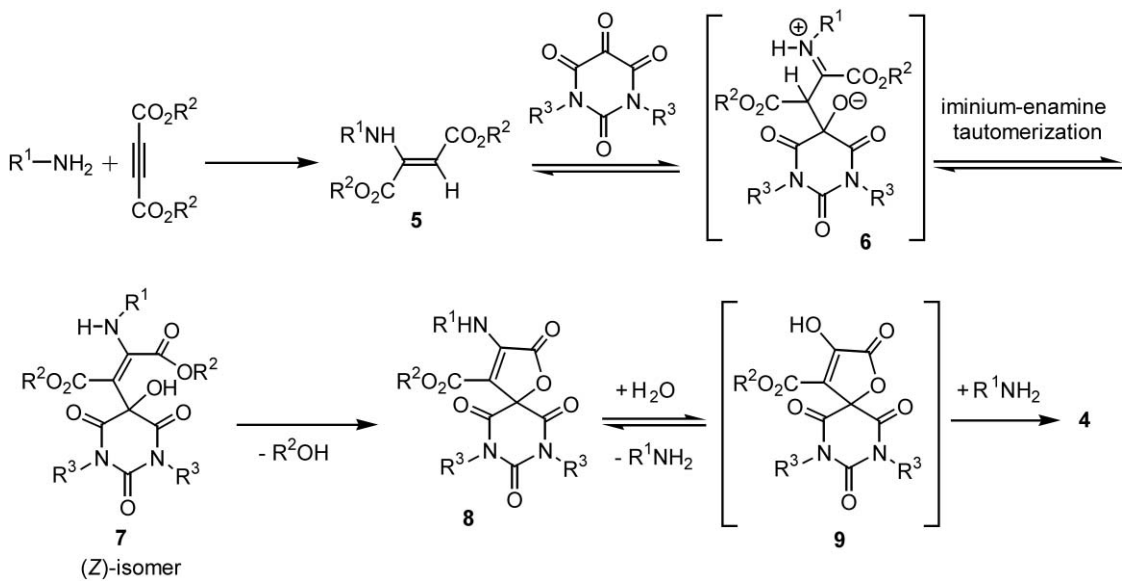


Fig. 1 ORTEP representation of compound **4m**.

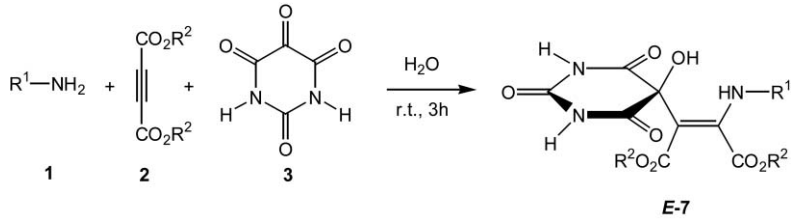
As shown in Table 1, the allylic, benzylic, hindered, and unhindered primary amines were used in this protocol with excellent results. Moreover, the aromatic primary amines give the corresponding barbiturates in good yields. Thus, a diverse set of biologically useful barbiturate products can be potentially prepared in one step by this method. However, secondary amines such as diethylamine, morpholine and thiomorpholine did not participate in the reaction. We also tried to take advantage of 25% aqueous ammonia, 50% aqueous hydroxylamine and phenylhydrazine as the amine component. Unfortunately, the reaction of alloxan and dimethyl acetylenedicarboxylate with each of these NH_2-containing compounds did not afford the desired barbiturate under the same reaction conditions.

Various reaction pathways are possible by mixing these polyfunctionalised starting materials; the thus-observed clean reaction is remarkable. The reaction might be explained by the mechanism shown in Scheme 2 in which a tandem sequence has been invoked to account for the generation of the butenolide and barbiturate moieties. The nucleophilic addition of amines to acetylenic esters has also been employed to afford enaminones.[22,23] Therefore, the first step may involve Michael addition of the primary amine to the acetylenic ester and formation of the aminobutendioate **5** as an electron-rich enaminone.[24] The central carbonyl groups of cyclic vicinal triones such as alloxan derivatives possess outstanding electrophilic properties.[25] The polar reactions with carbanion-like (electron rich) species such as enaminones give rise to nucleophilic addition reactions of carbonyl groups with exclusive C–C bond formation.[26] Subsequent nucleophilic (aldol-type) attack of aminobutendioate **5** to the central carbonyl group of the alloxan **3** would yield the iminium-oxyanion intermediate **6**, that can be tautomerised to hydroxy barbiturates **7**. γ-Lactonisation of ***Z*-7** (compound **7** with *Z*- configuration around the C=C double bond), would produce the spiro 3-aminobutenolide **8**. Indeed, the 3-alkylaminobutenolide **8** is an enaminone. Enaminones react with a variety of *O*-, *N*-, and *C*-nucleophiles to give the alkylamine substitution products. A typical reaction with an *O*-nucleophile is hydrolysis of (alkylamino)alkenoates to hydroxyalkenoates, these reactions are acid-catalysed and, probably proceed by an addition–elimination mechanism. The latter, after expulsion of the amine unit by 1,4-addition of water to **8** would provide the spiro 3-hydroxybutenolide **9**. The hydroxy group in compound **9** is very acidic because it is an enol form of a cyclic β-ketoester compound and especially augmented by the *vicinal* carbonyl group. The acid–base reaction between the enol **9** and the amine in reaction mixture leads to corresponding ammonium salt **4**.

As shown in Scheme 2, at least five distinct reactions occur in this one-pot process. All these steps take place in an ordered manner to provide the final compound with concomitant



Scheme 2



Scheme 2

creation of three bonds. Three irreversible steps (the formation of eneminone, lactonisation and the final acid–base reaction) cause the observed reaction sequence to be a unique and productive process.

In solution, 2-aminobutenedioates **5** can exist in (*Z*)- and/or (*E*)- isomeric forms. In most cases, the substituent at C-2 (*e.g.*, the alkyl or arylamino group) was found to be oriented *trans* with respect to the ester group or analogous structural element at C-4. So far, only a few examples of 2-aminobutenedioates with the opposite configuration around the C=C double bond, where the substituent at C-2 and the ester group are *cis* oriented, have been found.[27]

To our surprise, we found that the product of the reaction was dependent on the nature of the precursors. In some cases with alloxan (**3**, R^3 = H) as starting material, we obtained hydroxy barbiturates **7** (*E*-isomer) instead of spirocyclic butenolides **4** (Scheme 3, Table 2). The formation of hydroxy barbiturates **7** (in which the reaction stopped at the ***E*-7** production stage in some cases) is highly informative and provides clear-cut evidence for the existence of this type of intermediate in the reaction pathway.

The configuration of the C=C bond in the 2-aminobutenedioate moiety is the most significant factor that dictates the outcome of a given γ-lactonisation. In the (*E*) configuration, the direction of ester group is opposite to hydroxy group and this arrangement is not suitable for γ-lactonisation because a *trans* C=C bond contained within a five-membered ring is not energetically feasible. Our efforts to effect the cyclisation of hydroxy barbiturates **7** failed because of their *E*-configuration. In contrast, in the *Z*-configuration of **7,** the formation of spiro γ-butenolide **8** is highly favourable.

Some pieces of evidence are available to contribute towards a discussion of the mechanism of the tandem reaction. The key step in the synthesis is an efficient reaction of a primary amine with a dialkyl acetylenedicarboxylate to give a 2-alkylamino-2-butendioate derivative, which then reacts with an alloxan derivative. In order to confirm the mechanism outlined in Scheme 2, involving initial formation of a 2-alkylamino-2-butendioate intermediate, diethyl 2-(isobutylamino)-2-butendioate **5m**, a representative 2-alkylamino-2-butendioate, was synthesised separately by the condensation of isobutylamine and diethyl acetylenedicarboxylate. We then, examined the reaction of the product, diethyl 2-(isobutylamino)-2-butendioate, with one equivalent of 1,3-dimethylalloxan in water, and we obtained the product **4m** with 90% yield.

In conclusion, we have reported a new multicomponent reaction, yielding pharmacologically relevant oxospirocyclic 3-hydroxy-4-alkoxycarbonyl-γ-butenolides containing two different pharmacophoric subunits, by a sequence of a 1,4-Michael addition, aldol-like reaction, lactonisation, 1,4-addition-elimination and an acid–base reaction. The one-pot multicomponent protocol has several distinct advantages over sequential multi-step procedures. These include superior atom economy, simplified workup procedures, greater efficiency and superior overall yields.

Table 2 Three-component reactions of primary amines, dialkyl acetylenedicarboxylates, and alloxan in water

Entry	R^1	R^2	Product	Yield[a] /%
1	4-Hydroxyphenyl	Methyl	***E*-7a**	92
2	4-Hydroxyphenyl	Ethyl	***E*-7b**	89
3	Phenyl	Ethyl	***E*-7c**	81
4	Isobutyl	Ethyl	***E*-7d**	95

[a]Purified yield, which is >95% as determined by ^{1}H NMR.

Experimental

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an elementar vario EL *III* instrument. FT-IR spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with $CDCl_3$ or CD_3SOCD_3 as solvents and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal reference. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were obtained from Aldrich, Merck, Fluka or Acros and were used without further purification.

Typical procedure for the preparation of **4a**

To a magnetically stirred solution of allylamine (0.057 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.143 g, 1.0 mmol) in water (5 mL) was added alloxan monohydrate (0.160 g, 1.0 mmol) at room temperature (25 °C) and stirring was continued for about 3 h. The completion of reaction was confirmed by TLC (EtOH/EtOAc 1:2). The solvent was removed under vacuum and the solid residue was washed with diethylether (3 mL) and was recrystallised from ethanol to give white powders (0.262 g, 80%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

Prop-2-en-1-ylammonium 4-(methoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4a**): M.p. 157–159 °C; IR (KBr) (ν_{max}, cm^{-1}): 3209, 3101 (N–H), 1792, 1746, 1717, 1690, 1615 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.34 (3 H, s, OCH_3), 3.42–3.49 (2 H, m, NCH_2), 5.25 (1 H, d, $^3J_{HH}$ = 10.4 Hz, =CH_2), 5.33 (1 H, d, $^3J_{HH}$ = 17.4 Hz, =CH_2), 5.78–5.87 (1 H, m, CH_2=CH–NCH_2), 8.07 (3 H, br s, –NH_3^+), 11.57 (2 H, br s, NHCONH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.6, 169.2, 164.3, 160.1, 150.2, 131.4, 120.2, 100.9, 77.1, 50.3, 41.5; Anal. Calcd for $C_{12}H_{13}N_3O_8$ (327.24): C, 44.04; H, 4.00; N, 12.84. Found: C, 43.84; H, 4.03; N, 12.74%.

Adamantan-1-ylammonium 4-(methoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4b**): White powder (0.405 g, 96%); M.p. 202–204 °C; IR (KBr) (ν_{max}, cm^{-1}): 3524, 3381, 3215 (N–H), 1778, 1730, 1717, 1687, 1636 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.54 and 1.62 (6 H, AB-system, $^3J_{HH}$ = 12.0 Hz, 3 × CH_2), 1.74 (6 H, s, 3 × CH_2), 2.05 (3 H, s, 3 × CH), 3.45 (3 H, s, OCH_3), 8.50–10.50 (5 H, br s, –NH_3^+ and NHCONH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.6, 169.3, 164.3, 160.1, 150.2, 100.6, 77.2, 56.5, 51.3, 50.2, 35.5, 28.9; Anal. Calcd for $C_{19}H_{23}N_3O_8$ (421.40): C, 54.15; H, 5.50; N, 9.97. Found: C, 53.96; H, 5.54; N, 9.92%.

Hexan-1-ylammonium 4-(methoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4c**): White powder (0.338 g, 91%); M.p. 191–193 °C; IR (KBr) (ν_{max}, cm^{-1}): 3214, 3112 (N–H), 1792, 1769, 1728, 1708, 1682 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.83 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 1.23–1.30 (6 H, m, $CH_2CH_2CH_2$), 1.45–1.53 (2 H, m, CH_2CH_3), 2.74 (2 H, t, $^3J_{HH}$ = 7.5 Hz, NCH_2), 3.30 (3 H, s, OCH_3), 7.74 (3 H, br s, –NH_3^+),11.52 (2 H, s, NHCONH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.6, 169.3,

165.3., 160.1, 150.2, 100.5, 77.2, 50.2, 39.4, 31.2, 27.4, 25.9, 22.3, 14.3; Anal. Calcd for $C_{15}H_{21}N_3O_8$ (371.34): C, 48.52; H, 5.70; N, 11.32. Found: C, 48.83; H, 5.74; N, 11.41%.

Isobutylammonium 4-(methoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4d**): White powder (0.305 g, 89%); M.p. 167–169 °C (dec); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3220, 3198, 3150 (N–H), 1794, 1731, 1722, 1648, 1618 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, $^3J_{HH}$ = 6.2 Hz, CH(CH_3)$_2$), 1.80-1.83 (1 H, m, C*H*(CH$_3$)$_2$), 2.61 (2 H, d, $^3J_{HH}$ = 6.4 Hz, NCH_2CH), 3.47 (3 H, s, OCH_3), 8.10–10.50 (5 H, br s, –NH_3^+ and N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.6, 169.0, 164.2, 160.1, 150.2, 101.4, 77.1, 50.4, 46.3, 26.9, 20.2; Anal. Calcd for $C_{13}H_{17}N_3O_8$ (343.28): C, 45.48; H, 4.99; N, 12.24. Found: C, 45.76; H, 5.02; N, 12.29%.

Benzylammonium 4-(methoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4e**): White powder (0.294 g, 78%); M.p. 176–179 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3495, 3205, 3103 (N–H), 1792, 1750, 1715, 1683, 1619 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.43 (3 H, s, OCH_3), 4.01 (2 H, s, NCH_2), 7.35–7.44 (5 H, m, C$_6H_5$), 8.11 (3 H, br s, –NH_3^+), 11.50 (2 H, br s, N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.6, 169.3, 164.3, 160.1, 150.2, 134.5, 129.3, 129.1, 128.9, 100.9, 77.2, 50.3, 42.9; Anal. Calcd for $C_{16}H_{15}N_3O_8$ (377.30): C, 50.93; H, 4.01; N, 11.14. Found: C, 51.16; H, 4.03; N, 11.18%.

Adamantan-1-ylammonium 4-(ethoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4f**): White powder (0.374 g, 86%); M.p. 255–254 °C (dec); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3360, 3250, 3180 (N–H), 1802, 1750, 1737, 1712. 1620 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.06 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH$_2$CH_3), 1.53 and 1.61 (6 H, AB-system, $^2J_{HH}$ = 12.0 Hz, 3 × CH_2), 1.75 (6 H, s, 3 × CH_2), 2.03 (3 H, s, 3 × C*H*), 3.91 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.90 (3 H, br s, –NH_3^+), 11.59 (2 H, br s, N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.5, 169.2, 163.3, 160.6, 150.2, 101.2, 77.1, 58.5, 51.2, 40.3, 35.6, 28.8, 14.7; Anal. Calcd for $C_{20}H_{25}N_3O_8$ (435.42): C, 55.17; H, 5.79; N, 9.65. Found: C, 55.50; H, 5.84; N, 9.59%.

Propan-1-ylammonium 4-(ethoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4g**): White powder (0.240 g, 70%); M.p. 178–180 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3272, 3190, 3124 (N–H), 1788, 1742, 1722, 1647, 1610 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.86 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH$_2$CH_3), 1.06 (3 H, t, $^3J_{HH}$ = 7.0 Hz, OCH$_2$CH_3), 1.47–1.55 (2 H, m, CH_2CH$_3$), 2.74 (2 H, t, $^3J_{HH}$ = 7.4 Hz, NCH_2), 3.91 (2 H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 8.00–11.00 (5 H, br s, –NH_3^+ and N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 158.3, 157.1, 149.5, 145.6, 79.4, 79.0, 30.4, 27.3, 27.3, 25.0, 24.8; Anal. Calcd for $C_{13}H_{17}N_3O_8$ (343.28): C, 45.48; H, 4.99; N, 12.24. Found: C, 45.60; H, 5.03; N, 12.35%.

Prop-2-en-1-ylammonium 4-(ethoxycarbonyl)-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4h**): White powder (0.307 g, 90%); M.p. 154–156 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3289, 3163 (N–H), 1798, 1740, 1713, 1679, 1624 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.07 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_3CH$_2$), 3.43 (2 H, d, $^3J_{HH}$ = 5.9 Hz, NCH_2), 3.90 (2 H, t, $^3J_{HH}$ = 7.0 Hz, OCH_2), 5.26 (1 H, d, $^3J_{HH}$ = 9.4 Hz, =CH_AH$_B$), 5.33 (1 H, d, $^3J_{HH}$ = 16.1 Hz, =CH$_A$$H_B$), 5.80–5.85 (1 H, m, -C*H*=CH$_2$), 8.50–11.00 (5 H, br s, –NH_3^+ and N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.5, 169.3, 163.4, 160.7, 150.2, 131.5, 120.2, 100.8, 77.1, 58.4, 41.5, 14.7; Anal. Calcd for $C_{13}H_{15}N_3O_8$ (341.27): C, 45.75; H, 4.43; N, 12.31. Found: C, 45.65; H, 4.46; N, 12.24%.

Prop-2-en-1-ylammonium 4-(methoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4i**): White powder (0.320 g, 90%); M.p 178–180 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3255 (N–H), 1780, 1700, 1679, 1631 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.34 (3 H, s, OCH_3), 3.43 (6 H, s, 2 NCH_3), 5.27 (1 H, d, $^3J_{HH}$ = 10.4 Hz, =CH_AH$_B$), 5.34 (1 H, d, $^3J_{HH}$ = 17.4 Hz, =CH$_A$$H_B$), 5.80-5.87 (1 H, m, CH$_2$=C*H*–), 8.04 (3 H, br s, –NH_3^+); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.3, 168.3, 164.3, 160.2, 151.3, 131.4, 120.3, 101.2, 77.9, 50.3, 41.5, 29.1; Anal. Calcd for $C_{14}H_{17}N_3O_8$ (355.30): C, 47.33; H, 4.82; N, 11.83. Found: C, 47.15; H, 4.79; N, 11.77%.

Isobutylammonium 4-(methoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4j**): White powder (0.330 g, 89%); M.p. 175–177 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3254 (N–H), 1780, 1700, 1680, 1632 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, $^3J_{HH}$ = 6.7 Hz, CH(CH_3)$_2$), 1.80–1.83 (1 H, m, C*H*(CH$_3$)$_2$), 2.62 (2 H, d, $^3J_{HH}$ = 5.4 Hz, NCH_2CH), 3.13 (6 H, s, 2 NCH_3), 3.42 (3 H, s, OCH_3), 7.91 (3 H, br s, –NH_3^+); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.3, 168.1, 164.2, 160.1, 151.2, 101.7, 77.8, 50.4, 46.3, 29.1, 26.9, 20.3; Anal. Calcd for $C_{15}H_{21}N_3O_8$ (371.34): C, 48.52; H, 5.70; N, 11.32. Found: C, 48.30; H, 5.64; N, 11.24%.

Phenylammonium 4-(methoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4k**): White powder (0.340 g, 87%); M.p 174–176 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3249, 3174 (N–H), 1790, 1700, 1692, 1601 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.14 (6 H, s, 2 NCH_3), 3.46 (3 H, s, OCH_3), 6.88 (3 H, br s, –NH_3^+), 7.15–7.18 and 7.33–7.37 (5 H, 2 m, C$_6H_5$); ^{13}C NMR (100.7 MHz, DMSO-d_6): 170.5, 167.3, 163.7, 157.9, 151.1, 136.5, 130.0, 125.6, 121.4, 104.8, 77.7, 51.0, 29.2; Anal. Calcd for $C_{17}H_{17}N_3O_8$ (391.33): C, 52.18; H, 4.38; N, 10.74. Found: C, 52.47; H, 4.35; N, 10.67%.

Adamantan-1-ylammonium 4-(methoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4l**): White powder (0.436 g, 97%); M.p. 199–201 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3150 (N–H), 1772, 1700, 1688, (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.54 and 1.62 (6 H, AB-system, $^2J_{HH}$ = 12.0 Hz, 3 CH_2 of adamantyl), 1.74 (6 H, s, 3 CH_2 of adamantyl), 2.05 (3 H, s, 3C*H* of adamantyl), 3.13 (6 H, s, 2 NCH_3), 3.43 (3 H, s, OCH_3), 7.87 (3 H, br s, –NH_3^+); ^{13}C NMR 100.7 MHz, DMSO-d_6): δ_C 171.3, 168.3, 164.3, 160.1, 151.3, 101.3, 77.8, 51.3, 50.3, 40.4, 35.5, 29.1, 28.8; Anal. Calcd for $C_{21}H_{27}N_3O_8$ (449.45): C, 56.12; H, 6.05; N, 9.35. Found: C, 56.22; H, 6.01; N, 9.29%.

Isobutylammonium 4-(ethoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4m**): White powder (0.355 g, 92%); M.p. 162–164 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3256, 3230 (N–H), 1789, 1718, 1678, 1627 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.88 (6 H, d, $^3J_{HH}$ = 6.7 Hz, CH(CH_3)$_2$), 1.00 (3 H, t, $^3J_{HH}$ = 7.1 Hz, OCH$_2$CH_3), 1.82 (1 H, m, C*H*(CH$_3$)$_2$), 2.62 (2 H, d, $^3J_{HH}$ = 6.9 Hz, NCH_2CH), 3.14 (6 H, s, 2 NCH_3), 3.87 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.89 (3H, s, –NH_3^+); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.1, 168.2, 163.1, 160.9, 151.2, 101.6, 77.7, 58.4, 46.3, 29.1, 26.9, 20.2, 14.7; Anal. Calcd for $C_{16}H_{23}N_3O_8$ (385.36): C, 49.87; H, 6.02; N, 10.90. Found: C, 50.16; H, 5.98; N, 10.96%.

(4-Hydroxyphenyl)ammonium 4-(ethoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4n**): White powder (0.384 g, 91%); M.p. 170–172 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3241, 3100 (N–H), 1792, 1709, 1664, 1641 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.98 (3 H, t, $^3J_{HH}$ = 7.1 Hz, OCH$_2$CH_3), 3.14 (6 H, s, 2 NCH_3), 3.86 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 6.79 and 7.12 (4 H, 2 d, $^3J_{HH}$ = 8.7 Hz, C$_6H_4$OH), 9.00–10.50 (4 H, br s, –NH_3^+ and OH); ^{13}C NMR (100.7 MHz, DMSO-*d*6): δ_C 170.9, 168.0, 163.0, 160.4, 157.2, 151.2, 124.5, 123.8, 116.5, 102.5, 77.7, 58.6, 29.1, 14.7; Anal. Calcd for $C_{18}H_{19}N_3O_9$ (421.35): C, 51.31; H, 4.55; N, 9.97. Found: C, 51.23; H, 4.57; N, 10.04%.

Benzylammonium 4-(ethoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4o**): White powder (0.407 g, 97%); M.p. 179–181 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3258 (N–H), 1776, 1713, 1698, 1619 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.99 (3 H, t, $^3J_{HH}$ = 7.1 Hz, OCH$_2$CH_3), 3.14 (6 H, s, 2 NCH_3), 3.85 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.02 (2 H, s, NCH_2), 7.34–7.44 (5 H, m, C$_6H_5$), 8.32 (3 H, br s, –NH_3^+); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.1, 168.3, 163.2, 160.9, 151.2, 134.5, 129.3, 129.0, 128.9, 101.3, 77.8, 58.3, 42.9, 29.1, 14.5; Anal. Calcd for $C_{19}H_{21}N_3O_8$ (419.38): C, 54.41; H, 5.05; N, 10.02. Found: C, 54.20; H, 5.00; N, 9.97%.

Propan-1-ylammonium 4-(ethoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4p**): White powder (0.364 g, 98%); M.p. 173–175 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3447, 3241 (N–H), 1785, 1706, 1677, 1623 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 0.86 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH$_2$CH_3), 1.00 (3 H, t, $^3J_{HH}$ = 7.1 Hz, OCH$_2$CH_3), 1.53 (2 H, m, CH_2CH$_3$), 2.73 (2 H, t, $^3J_{HH}$ = 7.4 Hz, NCH_2), 3.14 (6 H, s, 2 NCH_3), 3.87 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.90 (3 H, br s, –NH_3^+);^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.1, 168.2, 163.1, 161.0, 151.2, 101.7, 77.7, 58.5, 41.1, 29.1, 20.91, 14.70. 11.3; Anal. Calcd for $C_{15}H_{21}N_3O_8$ (371.34): C, 48.52; H, 5.70; N, 11.32. Found: C, 48.23; H, 5.67; N, 11.27%.

Phenylammonium 4-(ethoxycarbonyl)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-en-3-olate (**4q**): White powder (0.385 g, 95%); M.p 168–170 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3229 (N–H), 1790, 1692, 1670, 1622 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.00 (3 H, t, $^3J_{HH}$ = 6.3, CH$_2$CH_3), 3.16 (6 H, s, 2 NCH_3), 3.91 (2 H, q, $^3J_{HH}$ = 6.5, OCH_2), 5.98 (3 H, br s, –NH_3^+), 7.16-7.17 and 7.32–7.34 (5 H, 2 m, C$_6H_5$); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 170.3, 167.3, 162.6, 158.6, 151.0, 136.6, 129.9, 125.5, 121.5, 105.1, 77.6, 59.3, 29.2, 14.5; Anal. Calcd for $C_{18}H_{19}N_3O_8$ (405.35): C, 53.33; H, 4.72; N, 10.37. Found: C, 53.56; H, 4.70; N, 10.31%.

*Preparation of **E–7a**; typical procedure*

To a magnetically stirred solution of 4-aminophenol (0.110 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.143 g, 1.0 mmol) in water (5 mL) was added alloxan (0.160 g, 1.0 mmol) at room temperature (25 °C) and stirring was continued for about 3 h. The completion of reaction was confirmed by TLC (EtOAc-hexane 2:1). The resulting solid was removed by filtration, washed with water (5 mL) and diethylether (3 mL) and dried at 80 °C in air to give ***E*-7a** as a white powder (0.362 g, 92%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

Dimethyl (2E)-2-[(4-hydroxyphenyl)amino]-3-(5-hydroxy-2,4,6-trioxohexahydroprimidin-5-yl)but-2-enedioate (***E*-7a**): M.p. 158–160 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3544, 3434, 3324 (N–H and O–H), 1767, 1743, 1707, 1676, 1627 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.63 and 3.67 (6 H, 2 s, 2 OCH_3), 6.80 and 6.99 (4 H, 2 d, $^3J_{HH}$ = 8.7 Hz, C_6H_4OH), 7.44 (2 H, br s, 2 OH), 7.98 (1 H, s, C_6H_4N*H*); 9.13 and 9.93 (2 H, 2 s, N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 173.7, 168.5, 161.1, 160.7, 158.5, 152.2, 150.2, 128.4, 123.8, 116.5, 110.0, 78.4, 53.9, 52.4; Anal. Calcd for $C_{16}H_{15}N_3O_9$ (393.30): C, 48.86; H, 3.84; N, 10.68. Found: C, 49.07; H, 3.86; N, 10.73%.

Diethyl (2E)-2-[(4-hydroxyphenyl)amino]-3-(5-hydroxy-2,4,6-trioxohexahydroprimidin-5-yl)but-2-enedioate (***E*-7b**): White powder (0.375 g, 89%); M.p. 189–191 °C (dec); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3430, 3380, 3306 (N–H and O–H),1749, 1737, 1707, 1687, 1652 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.03 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 1.12 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 4.02-4.15 (4 H, 2 q, $^3J_{HH}$ = 7.1 Hz, 2 OCH_2), 6.82 and 6.99 (4 H, 2 d, $^3J_{HH}$ = 8.7 Hz, C_6H_4OH), 7.42 and 7.47 (2 H, 2 s, 2 O*H*), 7.97 (1 H, s, C_6H_6N*H*), 9.07 and 9.92 (2 H, 2 s, N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 173.8, 168.7, 160.5, 160.1, 158.6, 152.2, 150.1, 128.7, 123.8, 116.4, 109.9, 78.4, 63.1, 66.9, 14.2, 13.9; Anal. Calcd for $C_{18}H_{19}N_3O_9$ (421.35): C, 51.31; H, 4.55; N, 9.97. Found: C, 51.04; H, 4.51; N, 9.93%.

Diethyl (2E)-2-anilino-3-(5-hydroxy-2,4,6-trioxohexahydroprimidin-5-yl)but-2-enedioate (***E*-7c**): White powder (0.328 g, 81%); M.p. 177–179 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3549, 3384, 3316 (N–H and O–H), 1800, 1726, 1711, 1668, 1635 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.01 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 1.12 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 4.02–4.14 (4 H, m, 2 OCH_2), 6.64 and 6.63–7.51 (5 H, m, C_6H_5), 8.03 (1 H, s, O*H*), 9.12 (1 H, br s, C_6H_5N*H*), 11.36 (1 H, s, N*H*CONH), 11.92 (1 H, br s, NHCON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 173.3, 168.9, 160.5, 160.0, 152.2, 150.4, 133.0, 130.1, 126.9, 115.6, 110.8, 78.6, 63.2, 61.1, 14.2, 13.8; Anal. Calcd for $C_{18}H_{19}N_3O_8$ (405.38): C, 53.33; H, 4.72; N, 10.37. Found: C, 53.59; H, 4.68; N, 10.30%.

Diethyl (2E)-2-(5-hydroxy-2,4,6-trioxohexahydropyrimidin-5-yl)-3-(isobutylamino)but-2-enedioate (***E*-7d**): White powder (0.366 g, 95%); M.p. 176–178 °C (dec); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3220, 3104 (N–H and O–H), 1797, 1723, 1706 (C=O); ^{1}H NMR (400.1 MHz, DMSO- d_6): δ_H 0.88 (6 H, d, $^3J_{HH}$ = 6.7 Hz, CH(CH_3)$_2$), 1.06 (3 H, t, $^3J_{HH}$ = 6.8 Hz, OCH_2CH_3), 1.80–1.84 (1 H, m, C*H*(CH$_3$)$_2$), 2.61 (2 H, d, $^3J_{HH}$ = 7.0 Hz, CH_2CH), 3.34 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 3.91 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.00–10.00 (4 H, br s, O–H, NH and N*H*CON*H*); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ_C 171.4, 169.1, 163.3, 160.8, 150.2, 101.3, 77.1, 65.4, 58.6, 46.4, 26.8, 20.2, 15.6, 14.6; Anal. Calcd for $C_{16}H_{23}N_3O_8$ (385.37): C, 49.87; H, 6.02; N, 10.90. Found: C, 49.93; H, 5.98; N, 10.86%.

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