Tetrahedron 66 (2010) 3795–3800

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of oxaspirobicyclic butenolides via a domino Michael addition/aldol reaction/γ-lactonization sequence

Mohammad Bagher Teimouri [a,*], Tayyebeh Abbasi [b]

[a] Petrochemical Department, Iran Polymer and Petrochemical Institute, PO Box 14965-115, Tehran 1497713115, Iran
[b] Department of Chemistry, University of Zanjan, PO Box 45195-313, Zanjan, Iran

ARTICLE INFO

Article history:
Received 2 January 2010
Received in revised form 24 February 2010
Accepted 15 March 2010
Available online 20 March 2010

Keywords:
Amine
Acetylenic ester
Alloxan
Barbiturate
γ-Butenolides
Multicomponent reaction

ABSTRACT

A three-component domino reaction approach between a primary amine, a dialkyl acetylenedicarboxylate, and 1,3-dimethylalloxan that affords novel oxaspirobicyclic γ-butenolidobarbiturate derivatives is reported. The reaction sequence consists of an initial Michael-addition of primary amines to dialkyl acetylenedicarboxylates, followed by aldol-like reaction with 1,3-dimethylalloxan, and then γ-lactonization to afford the products. This cascade reaction sequence represents a rapid and unprecedented route to the described biologically interesting molecules.

1. Introduction

Drugs belonging to the class of barbiturates have been used for more than a century as hypnotics and anticonvulsants.[1] Pharmaceutical industries market more than 50 barbiturate derivatives under various trade names,[2] and few people have not heard of the name of phenobarbital as the most widely used anticonvulsant worldwide and the earliest still in use. On the other hand, α,β-unsaturated γ-butyrolactones, also named, γ-butenolides, are important targets in organic synthesis, as these structures are found in a large variety of biologically active natural products.[3] γ-Butenolides with different substitution patterns are considered as potential insecticides, bactericides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antipsoriasis agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, etc.[4] Moreover, 4-alkoxycarbonyl-butenolides are also important synthetic building blocks. For example, (+)-nephrosteranic acid and related γ-lactones were prepared by diastereoselective hydrogenation of 5-alkyl-3-mesyloxy-4-ethoxycarbonyl-butenolides.[5] Isotetronic acid derivatives, containing a hydroxy group at carbon atom C-3 of the butenolide moiety, are also occurring in many natural products. It has been reported that 3-hydroxy-γ-butenolide and 3-amino-γ-butenolide scaffolds are responsible for the odor of some flowers.[6] This includes (+)-leptosphaerin[7] and compound WF-3681,[8] distomadine B,[9] various ascorbic acid (vitamin C) derivatives,[10] and many other pharmacologically relevant natural products.[11] Isotetronic acids have been used also as synthetic building blocks during the synthesis of (−)-tetrodotoxin,[12] 6-thiosialic, and neuraminic acids,[13–16] nactins,[17] and erythronolide A.[18] The butenolide structural unit is usually constructed by one of the following strategies:[4,19] (1) reaction of metal carbonyl complexes with alkynes;[20] (2) lactonization of 3-hydroxy-1-alkenyl carboxylic acids;[21] (3) selective partial reduction of cyclic anhydrides;[22] (4) regioselective oxidation of substituted furans;[23] (5) Pd-catalyzed carbonylative lactonization of 3-iodo-2(*Z*)-propenol;[24] (6) Pd-catalyzed carbonylative cyclization of 2-alkynols;[25] (7) radical cyclization of 2′-bromoalkyl 2-alkynoates;[26] (8) lactonization of 2,3-allenoates using a variety of electrophiles;[27] (9) cyclization of allenic acid precursors catalyzed by transition metal, such as Ag(I)[28a] and Au(III);[28b] (10) ring closing metathesis;[29] (11) phosphine-mediated reactions of ketones with methyl acetoxypropynoate[30] or acetylenic esters;[31] (12) cyclizations of oxalyl chloride with acetophenone derived silyl enol ethers[32] or 1,3-dicarbonyl compounds[33] 1,3-bis(silyloxy)alk-1-enes.[34]

Although, there are many ways to synthesize the γ-butenolide moiety, to the best of our knowledge up to now only two one-pot multicomponent approaches[31,35] have been published. The construction of multiple carbon–carbon and carbon–heteroatom bonds by tandem reactions represents an efficient approach to the synthesis of complex molecular structures from simple organic

* Corresponding author. Tel.: +98 21 44580000; fax: +98 21 44580032; e-mail address: m.teimouri@ippi.ac.ir (M.B. Teimouri).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.058

building blocks.[36,37] The variation and structural diversity of the target molecules in question had a strong impact on the development of synthetic methods.

In connection with our recent research on alloxans,[38] guided by observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biological profile remarkably, we investigated a three-component reaction of primary amines, dialkyl acetylenedicarboxylates, and 1,3-dimethylalloxan in dry CH_2Cl_2, which afforded oxaspirobicyclic γ-butenolides containing barbiturate moiety in high isolated yields.

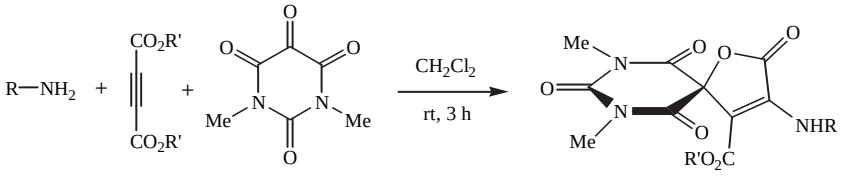
2. Results and discussion

We examined the reaction of the primary amines with dialkyl acetylenedicarboxylate in the presence of alloxan derivatives in dry CH_2Cl_2 at room temperature (25 °C) and we obtained the corresponding alkyl 3-(alkyl or arylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylates **4** in 88–96% yields; the full results are summarized in Table 1. ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of oxaspirobicyclic γ-butenolides **4**. No other product was detected by NMR spectroscopy.

The structures of the products **4a**–**k** were deduced from their elemental analyses and IR, ^1H NMR and ^{13}C NMR spectra. For example, the ^1H NMR spectrum of **4a** exhibited two single sharp lines readily recognized as arising from two equivalent N–CH_3 groups (δ_H 3.31 ppm) and methoxy protons along with three fairly broad singlets for the methylenes (δ_H 1.65 and 2.06 ppm) and methines (δ_H 2.09 ppm) of adamantyl moiety. A broad singlet (δ_H 7.07 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with D_2O. The chemical shift of the NH group indicates that this moiety must have participated in a six-membered intramolecular hydrogen bond formation with the vicinal carbonyl group.

The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct signals, which confirmed the proposed structure. The characteristic

Table 1
Three-component condensation reactions of primary amines, dialkyl acetylenedicarboxylates, and 1,3-dimethylalloxan in dry dichloromethane



1 **2** **3** **4**

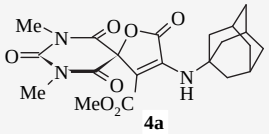
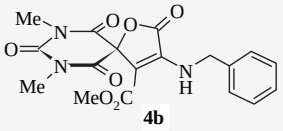
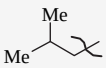
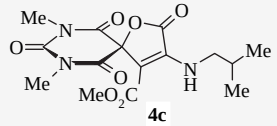
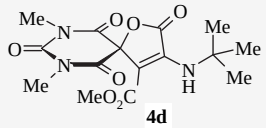
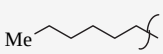
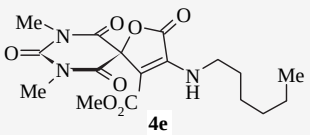
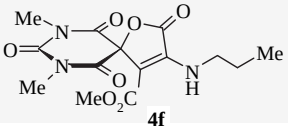
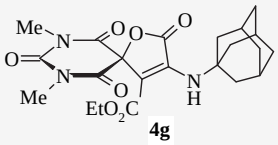
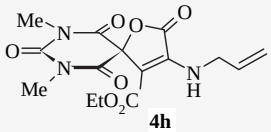
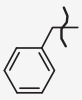
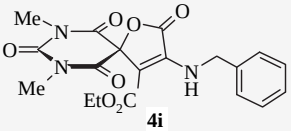
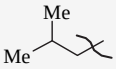
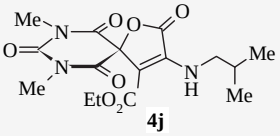
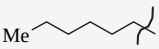
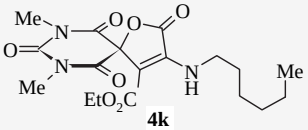
Entry	R	R′	Product	Yield[a] (%)
1		Me	 **4a**	96
2		Me	 **4b**	92
3		Me	 **4c**	95
4		Me	 **4d**	88
5		Me	 **4e**	88
6		Me	 **4f**	90

Table 1 (*continued*)

Entry	R	R′	Product	Yield[a] (%)
7		Et	 **4g**	91
8		Et	 **4h**	89
9		Et	 **4i**	90
10		Et	 **4j**	91
11		Et	 **4k**	93

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

signal due to the spiro carbon was discernible at δ_C 106.1 ppm and four carbonyl groups were resonated at δ_C 150.3, 163.2, 164.8, and 164.9 ppm. Partial assignment of these resonances is given in Experimental section.

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1798, 1695, and 1628 cm^{-1} due to the carbonyls and the amino group at 3314 cm^{-1} as a weak band.

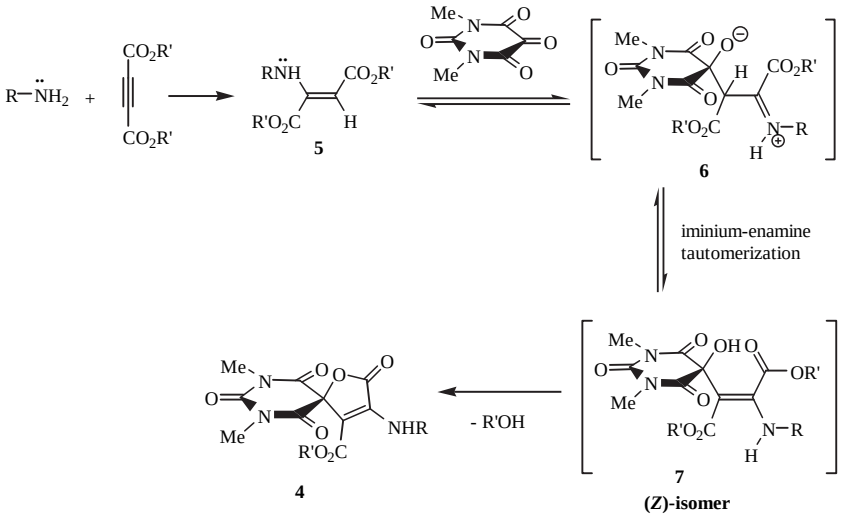
The scope and limitations of this three-component reaction were explored by using two dialkyl acetylenedicarboxylates and a wide range of primary amines. A variety of structurally diverse amines underwent the one-pot reaction smoothly without using any catalyst to afford the corresponding spirocyclic γ-butenolide derivatives in high yields. As shown in Table 1, the allylic, benzylic, hindered, and unhindered primary amines are used in this protocol with excellent results. Thus, a diverse set of biologically useful γ-butenolide products can be potentially prepared in one step by this method. However, the secondary amines, such as diethyl amine, morpholine, and thiomorpholine have not participated 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 1,3-dimethylalloxan and dimethyl acetylenedicarboxylates with each of these NH_2-containing compounds did not afford the desired barbiturate under the same reaction conditions.

A possible mechanism for the present reaction is shown in Scheme 1, which envisages a tandem sequence. On the basis of the well established chemistry of trivalent nitrogen nucleophiles, the successful nucleophilic attack by amines on a carbon atom is facilitated when the latter is conjugated with a carbonyl group, or when it is a part of an unsaturated bond otherwise activated. First, nucleophilic Michael-addition of the primary amine **1** to the β-carbon of the electron-deficient alkyne **2** generates the aminobutendioate **5** as an electron-rich enaminone.[39] The central carbonyl groups of the vicinal tri-carbonyl compounds, such as alloxan derivatives possess outstanding electrophilic (electron-pair-accepting) properties.[40] The polar reactions with carbanion-like (electron rich) species, such as enaminones give rise to nucleophilic addition reactions of carbonyl groups under exclusive C–C bond formation.[41] Subsequent nucleophilic aldol-like attack of aminobutendioate **5** to the central carbonyl group of the 1,3-dimethylalloxan **3** would yield iminium–oxyanion intermediate **6**, that can be tautomerized to hydroxy barbiturates **7**. γ-Lactonization of ***Z*-7** (compound **7** with the *Z*-configuration around the C=C double bond), would produce the oxaspirobicyclic γ-butenolidobarbiturates **4**.

As shown in Scheme 1, at least three distinct reactions (Michael addition, stereocontrolled aldol-type reaction and lactonization) occur in this one-pot process. All these steps take place in an ordered manner to provide the final compound with concomitant creation of three chemical bonds. Two irreversible steps (the formation of eneminone and lactonization) cause the observed reaction sequence to be a unique and a productive process.

In solution, 2-aminobutenedioates can exist in (*Z*)- and/or (*E*)-isomeric forms with respect to C=C double bond. 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.[42]

The configuration of the 2-aminobutenedioate moiety concerning the orientation around the C=C bond is the most



Scheme 1. Multicomponent synthesis of barbiturate-containing oxaspirobicyclic butenolides **4**; a possible reaction sequence.

significant key factor that dictates the outcome of a given γ-lactonization. In the (*E*) configuration, the ester group is opposite to hydroxy group and this arrangement is not suitable for γ-lactonization because a trans C═C bond-containing a five-membered ring cannot be formed, energetically. While, the *Z*-configuration of **7** in the formation of spiro γ-butenolide **4** is highly desirable.

Some pieces of evidence are available to contribute toward a discussion of the mechanism of the tandem reaction. The key step in the synthesis is an efficient component reaction of a primary amine with a dialkyl acetylenedicarboxylate to give a 2-alkylamino-2-butendioate derivative, which then reacts with alloxan derivatives. In order to confirm the route mechanism of the reaction in Scheme 1, via the formation of 2-alkylamino-2-butendioate intermediate in the first stage of the reaction, diethyl 2-(isobutylamino)-2-butendioate **7j** as a representative of 2-alkylamino-2-butendioate was synthesized separately by the condensation of isobutylamine and diethyl acetylenedicarboxylate. Then, we examined the reaction of the isolated diethyl 2-(isobutylamino)-2-butendioate with one equivalent amount of 1,3-dimethylalloxan in water, and we obtained the product **4j** with 93% yield.

3. Conclusion

The present work describes a tandem protocol for the synthesis of new alkyl 3-(alkyl or arylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylates via a Michael addition, stereocontrolled aldol-type reaction, and γ-lactonization sequence. A library of novel oxaspirobicyclic γ-butenolidobarbiturates bearing two biologically interesting sub-structures can be rapidly accessed using this methodology. 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.

4. Experimental

4.1. General

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 $CDCl_3$ 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, F_{254}) and visualized with UV light. All chemical reagents were obtained from Merck, Fluka or Acros and were used without further purification.

4.2. Typical procedure for preparation of methyl 3-(1-adamantylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (4a)

To a magnetically stirred solution of 1-adamantylamine (0.151 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.143 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added 1,3-dimethylalloxan (0.170 g, 1.0 mmol) at room temperature (25 °C). The reaction mixture was then stirred for 3 h. The solvent was removed under reduced pressure and the residue was treated with diethylether (5 mL) to give **4a** as a white powder (0.414 g, 96%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes. Mp 200–202 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3314 (N–H), 1798, 1695, 1628, (C═O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.65 and 2.06 (12H, 2br s, 6C*H*$_2$ of adamantyl), 2.09 (3H, br s, 3CH of adamantly), 3.31 (6H, s, 2NC*H*$_3$), 3.64 (3H, s, OC*H*$_3$), 7.07 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 164.9, 164.8, 163.2, 150.3, 143.9, 106.1, 77.9, 54.9, 52.0, 42.7, 35.6, 29.7, 29.4. Anal. Calcd for $C_{21}H_{25}N_3O_7$ (431.44): C, 58.46; H, 5.84; N, 9.74%. Found: C, 58.29; H, 5.80; N, 9.82%.

*4.2.1. Methyl 3-(benzylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4b**).* White powder (0.356 g, 92%); mp 136–138 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3355 (N–H), 1790, 1690, 1640 (C═O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 3.28 (6H, s, 2NC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 4.92 (2H, d, $^3J_{HH}$=4.8 Hz, NHC*H*$_2$), 6.93 (1H, br s, N*H*), 7.26–7.30 (5H, m, C_6H_5); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.6, 164.6, 162.8, 150.2, 141.6, 137.6, 128.9, 127.9, 127.5, 105.6, 65.8, 52.1, 46.2, 29.4. Anal. Calcd for $C_{18}H_{17}N_3O_7$ (387.34): C, 55.81; H, 4.42; N, 10.85%. Found: C, 55.97; H, 4.47; N, 10.72%.

*4.2.2. Methyl 3-(isobutylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4c**).* White powder (0.336 g, 95%); mp 112–114 °C; IR (KBr) ($\nu_{max,}$ cm^{-1}): 3365 (N–H), 1792, 1762, 1692, 1636 (C═O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 0.92 (6H, d, $^3J_{HH}$=6.6 Hz, CH(C*H*$_3$)$_2$), 1.80 (1H, m, C*H*(CH$_3$)$_2$), 3.31 (6H, s, 2NC*H*$_3$), 3.57 (2H, m, NHC*H*$_2$CH), 3.65 (3H, s, OC*H*$_3$), 6.90 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.3, 164.7, 163.0, 150.2,

142.7, 104.6, 76.8, 52.0, 49.4, 29.8, 29.4, 19.6. Anal. Calcd for $C_{15}H_{19}N_3O_7$ (353.32): C, 50.99; H, 5.42; N, 11.89%. Found: C, 51.14; H, 5.34; N, 11.95%.

*4.2.3. Methyl 3-(tert-butylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4d**).* White powder (0.310 g, 88%); mp 157–159 °C; IR (KBr) (ν_{max}, cm^{-1}): 3318 (N–H), 1799, 1694, 1627 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 1.48 (9H, s, C(CH_3)$_3$), 3.33 (6H, s, 2NCH_3), 3.66 (3H, s, OCH_3), 7.24 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 164.7, 163.2, 150.2, 143.8, 106.1, 77.8, 54.4, 51.9, 30.5, 29.4. Anal. Calcd for $C_{15}H_{19}N_3O_7$ (353.32): C, 50.99; H, 5.42; N, 11.89%. Found: C, 51.48; H, 5.45; N, 11.78%.

*4.2.4. Methyl 3-(hexylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4e**).* White powder (0.336 g, 88%); mp 180–182 °C; IR (KBr) (ν_{max}, cm^{-1}): 3346 (N–H), 1797, 1706, 1668, 1637 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 0.81, (3H, t, $^3J_{HH}$=6.0 Hz, CH_2CH_3), 1.25 and 1.54 (8H, 2 m, 4 CH_2), 3.28 (6H, s, 2NCH_3), 3.62 (3H, s, OCH_3), 3.69 (2H, m, NHCH_2), 6.66 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.3, 164.8, 163.0, 150.3, 142.3, 104.5, 76.8, 51.9, 42.6, 31.5, 31.1, 29.3, 26.1, 22.4, 13.9. Anal. Calcd for $C_{17}H_{23}N_3O_7$ (381.38): C, 53.54; H, 6.08; N, 11.02%. Found: C, 53.38; H, 6.04; N, 10.94%.

*4.2.5. Methyl 3-(propylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4f**).* White powder (0.305 g, 90%); mp 98–100 °C; IR (KBr) (ν_{max}, cm^{-1}): 3357 (N–H), 1792, 1761, 1689 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 0.95 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 1.59–1.64 (2H, m, $CH_2CH_2CH_3$), 3.33 (6H, s, 2NCH_3), 3.67 (3H, s, OCH_3), 3.71 (2H, m, NHCH_2CH_2), 6.69 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 164.9, 164.8, 163.0, 150.3, 142.6, 104.2, 77.7, 52.0, 44.2, 29.42, 24.1, 10.9. Anal. Calcd for $C_{14}H_{17}N_3O_7$ (339.30): C, 49.56; H, 5.05; N, 12.38%. Found: C, 49.15; H, 5.02; N, 12.29%.

*4.2.6. Ethyl 3-(1-adamantylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4g**).* White powder (0.405 g, 91%); mp 189–191 °C; IR (KBr) (ν_{max}, cm^{-1}): 3318 (N–H), 1799, 1685, 1625 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 1.11 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 1.61 and 1.65 (6H, AB-system, $^3J_{HH}$=14.6 Hz, 3CH_2 of adamantyl), 2.05 (6H, s, 3CH_2 of adamantyl), 2.08 (3H, s, 3 CH of adamantly), 3.30 (6H, s, 2NCH_3), 4.07 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2), 7.29 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 164.9, 164.8, 162.8, 150.2, 144.0, 106.5, 77.9, 60.7, 54.8, 42.7, 35.8, 29.7, 29.3, 14.1. Anal. Calcd for $C_{22}H_{27}N_3O_7$ (445.46): C, 59.32; H, 6.11; N, 9.43%. Found: C, 59.08; H, 6.16; N, 9.37%.

*4.2.7. Ethyl 3-(allylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4h**).* White powder (0.313 g, 89%); mp 139–141 °C; IR (KBr) (ν_{max}, cm^{-1}): 3222 (N–H), 1787, 1687, 1609 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 1.16 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 3.35 (6H, s, 2NCH_3), 4.12 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2), 4.41 (2H, dd, $^3J_{HH}$=6.2, 6.1 Hz, NHCH_2CH=), 5.21 (1H, d, $^3J_{HH}$=10.5 Hz, =CH_AH$_B$), 5.24 (1H, d, $^3J_{HH}$=18.4 Hz, =CH$_A$H$_B$), 5.86–5.95 (1H, m, CH_2=C*H*–CH_2), 6.82 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 164.8, 164.7, 162.4, 150.2, 142.3, 133.8, 117.28, 105.9, 76.7, 61.0, 44.6, 29.4, 14.1. Anal. Calcd for $C_{15}H_{17}N_3O_7$ (351.31): C, 51.28; H, 4.88; N, 11.96%. Found: C, 51.45; H, 4.83; N, 12.05%.

*4.2.8. Ethyl 3-(benzylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4i**).* White powder (0.361 g, 90%); mp 118–120 °C; IR (KBr) (ν_{max}, cm^{-1}): 3331 (N–H), 1794, 1700, 1640 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 1.11 (3H, t, $^3J_{HH}$=7.0 Hz, CH_2CH_3), 3.34 (6H, s, 2NCH_3), 4.09 (2H, q, $^3J_{HH}$=7.0 Hz, OCH_2), 4.97 (2H, d, $^3J_{HH}$=6.1 Hz, NHCH_2), 7.01 (1H, br s, N*H*), 7.24–7.34 (5H, m, C$_6H_5$); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.6, 164.7, 162.5, 150.2, 142.2, 137.4, 129.0, 128.0, 127.6, 105.8, 77.3, 61.0, 46.3, 29.4, 14.0. Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.37): C, 56.86; H, 4.77; N, 10.47%. Found: C, 56.73; H, 4.81; N, 10.52%.

*4.2.9. Ethyl 3-(isobutylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4j**).* White powder (0.334 g, 91%); mp 174–176 °C; IR (KBr) (ν_{max}, cm^{-1}): 3341 (N–H), 1799, 1703, 1668, 1638 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 0.96 (6H, d, $^3J_{HH}$=6.7 Hz, CH(CH_3)$_2$), 1.16 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 1.83 (1H, m, C*H*(CH_3)$_2$), 3.35 (6H, s, 2NCH_3), 3.61 (2H, dd, $^3J_{HH}$=6.7, 6.7 Hz, NHCH_2CH), 4.12 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2), 6.85 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.4, 164.8, 162.8, 150.2, 142.9, 60.8, 49.5, 30.5, 29.7, 29.4, 24.9, 19.6, 14.1. Anal. Calcd for $C_{16}H_{21}N_3O_7$ (367.35): C, 52.31; H, 5.76; N, 11.44%. Found: C, 52.20; H, 5.71; N, 11.58%.

*4.2.10. Ethyl 3-(hexylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate (**4k**).* White powder (0.368 g, 93%); mp 94–96 °C; IR (KBr) (ν_{max}, cm^{-1}): 3337 (N–H), 1798, 1702, 1665, 1637 (C=O); ^1H NMR (400.1 MHz, $CDCl_3$): δ_H 0.74 (3H, br s, CH_2CH_3), 0.84 (3H, br s, OCH_2CH_3), 1.15–1.19 (8H, m, 4 CH_2), 1.44–1.46 (2H, br s, CH_2), 3.17 (6H, s, 2NCH_3), 3.62 (2H, m, NHCH_2), 3.95 (2H, q, $^3J_{HH}$=6.8 Hz, OCH_2), 6.76 (1H, br s, N*H*); ^{13}C NMR (100.7 MHz, $CDCl_3$): δ_C 165.3, 164.8, 162.5, 150.2, 142.6, 104.7, 77.5, 60.6, 42.4, 31.2, 30.7, 29.0, 26.0, 22.3, 13.9, 13.8. Anal. Calcd for $C_{18}H_{25}N_3O_7$ (395.40): C, 54.68; H, 6.37; N, 10.63%. Found: C, 54.46; H, 6.30; N, 10.52%.

Acknowledgements

We would like to thank Iran Polymer and Petrochemical Institute (IPPI) Research Council for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.03.058.

References and notes

1. Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229.
2. *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 9th ed.; Delgado, J. N., Remers, W. A., Lippincott, J. B., Eds.; Wolters Kluwer Health: Philadephia, PA, 1991.
3. (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (b) Pattenden, G. *Prog. Chem. Nat. Prod.* **1979**, *35*, 133; (c) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* **1987**, *51*, 1; (d) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287; (e) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; (f) Brückner, R. *Chem. Commun.* **2002**, 141; (g) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679; (h) Langer, P. *Synlett* **2006**, 3369; (i) Ito, N. *Pure Appl. Chem.* **1991**, *63*, 13; (j) Branchadell, V.; Orti, J.; Ortuno, R. M.; Oliva, A.; Font, J.; Bertran, J.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 2190; (k) Chia, Y.; Chang, F.; Wu, Y. *Tetrahedron Lett.* **1999**, *40*, 7513.
4. Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387 and references therein.
5. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *22*, 4097.
6. Dong, Y.; Pai, N. N.; Ablaza, S. L.; Yu, S.-X.; Bolvig, S.; David, A.; Forsyth, D. A.; Le Quesne, P. W. *J. Org. Chem.* **1999**, *64*, 2657.
7. Pallenberg, A. J.; White, J. D. *Tetrahedron Lett.* **1986**, *27*, 5591.
8. Namiki, T.; Nishikawa, M.; Itoh, Y.; Uchida, I.; Hashimoto, M. *Tetrahedron Lett.* **1987**, *28*, 1400.
9. Pearce, A. N.; Appleton, D. R.; Babcock, R. C.; Copp, B. R. *Tetrahedron Lett.* **2003**, *44*, 3897.
10. Toyoda-Ono, Y.; Maeda, M.; Nakao, M.; Yoshimura, M.; Sugiura-Tomimori, N.; Fukami, H. *J. Agric. Food Chem.* **2004**, *52*, 2092.
11. (a) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 647; (b) Anderson, J. R.; Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 215; (c) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1982**, *21*, 695; (d) Keates, S. E.; Loewus, F. A.; Helms, G. L.; Zink, D. L. *Phytochemistry* **1998**, *49*, 2397; (e) Lin, W.-H.; Fang, J.-M.; Cheng, Y. S. *Phytochemistry* **1999**, *50*, 653; (f) Enders, D.; Dyker, H.; Leusink, F. R. *Chem.—Eur. J.* **1998**, *4*, 311 and references cited therein.
12. Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

13. Mack, H.; Brossmer, R. *Tetrahedron* **1998**, *54*, 4521.
14. Mack, H.; Brossmer, R. *Tetrahedron Lett.* **1992**, *33*, 1867.
15. Lafont, D.; Hoch, M.; Schmidt, R. R. *J. Carbohydr. Chem.* **1986**, *5*, 601.
16. Holmquist, L. *Acta Chem. Scand.* **1971**, *25*, 712.
17. Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017.
18. Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564.
19. Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353.
20. (a) Deshong, P.; Sidler, D. R. *Tetrahedron Lett.* **1987**, *28*, 2233; (b) Doyama, K.; Joh, T.; Onitsuka, K.; Shiohara, T.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1987**, 649.
21. Tanikaga, R.; Hosoya, K.; Kaji, A. *Synthesis* **1987**, 389.
22. Urove, G. A.; Welker, M. E. *Organometallics* **1988**, *7*, 1013.
23. (a) Cottier, L.; Descotes, G.; Nigay, H.; Parron, J.; Gregoire, V. *Bull. Soc. Chim. Fr.* **1986**, 844; (b) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.
24. Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.
25. (a) Yu, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684; (b) Xiao, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422.
26. Clough, J. M.; Pattenden, G.; Wight, P. G. *Tetrahedron Lett.* **1989**, *30*, 7469.
27. (a) Gill, G. B.; Idris, M. S. H. *Tetrahedron Lett.* **1985**, *26*, 4811; (b) Marshall, A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367; (c) Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075; (d) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942; (e) Chen, G.; Fu, C.; Ma, S. *Tetrahedron* **2006**, *62*, 4444.
28. (a) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796; (b) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431.
29. (a) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247; (b) Michaut, M.; Santelli, M.; Parrain, J.-L. *J. Organomet. Chem.* **2000**, *606*, 93; (c) Langer, P.; Albrecht, U. *Synlett* **2002**, 1841; (d) Li, Y.; Zhang, T.; Li, Y.-L. *Tetrahedron Lett.* **2007**, *48*, 1503; (e) Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 4648.
30. Nozaki, K.; Sato, N.; Ikeda, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 4516.
31. (a) Nair, V.; Nair, J. S.; Vinod, A. U.; Rath, N. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3129; (b) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis* **2000**, 1713.
32. Murai, S.; Hasegawa, K.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 636.
33. (a) Saalfrank, R. W.; Lutz, T. *Angew. Chem. Int. Ed.* **1990**, *29*, 1041; (b) Saalfrank, R. W.; Lutz, T.; Hoerner, B.; Guendel, J.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1991**, *124*, 2289.
34. Dede, R.; Michaelis, L.; Fuentes, D.; Yawer, M. A.; Hussain, I.; Fischer, C.; Langer, P. *Tetrahedron* **2007**, *63*, 12547.
35. Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875.
36. Ho, T.-L. *Tandem Organic Reactions*; John Wiley: New York, NY, 1992.
37. (a) Philip, J.; Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195; (b) Jeffrey, D.; Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.
38. (a) Teimouri, M. B.; Abbasi, T.; Mivehchi, H. *Tetrahedron* **2008**, *64*, 10425; (b) Teimouri, M. B.; Abbasi, T.; Ahmadian, S.; Poor Heravi, M. R.; Bazhrang, R. *Tetrahedron* **2009**, *65*, 8120.
39. (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104; (b) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433; (c) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem.* **2006**, *118*, 8278; (d) Azizian, J.; Hatamjafari, F.; Karimi, A. R.; Shaabanzadeh, M. *Synthesis* **2006**, 765; (e) Cao, H.; Wang, X.; Jiang, H.; Zhu, Q.; Zhang, M.; Liu, H. *Chem.—Eur. J.* **2008**, *14*, 11623; (f) Cao, H.; Jiang, H.-F.; Qi, C.-R.; Yao, W.-J.; Chen, H.-J. *Tetrahedron Lett.* **2009**, *50*, 1209; (g) Zhu, Q.; Jiang, H.; Li, J.; Zhang, M.; Wang, X.; Qi, C. *Tetrahedron* **2009**, *65*, 4604; (h) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron* **2009**, *65*, 5251.
40. Rubin, M. B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121.
41. Schank, K.; Lieder, R.; Lick, C.; Glock, R. *Helv. Chim. Acta* **2004**, *87*, 869.
42. (a) Zhu, Q.; Jiang, H.; Li, J.; Zhang, M.; Wang, X.; Qi, C. *Tetrahedron* **2009**, *65*, 4604; (b) Cao, H.; Wang, X.; Jiang, H.; Zhu, Q.; Zhang, M.; Liu, H. *Chem.—Eur. J.* **2008**, *14*, 11623; (c) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.