Tetrahedron 66 (2010) 9933–9937

Contents lists available at ScienceDirect

Tetrahedron

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

Novel heterocyclic β-nitroenamines-based on a one-pot three-component reaction: a facile synthesis of fully substituted 1*H*-pyrrolo[1,2-*a*]-fused-1,3-diazaheterocycles

Abdolali Alizadeh [a,*], Atieh Rezvanian [a], Yuan Deng [b]

[a] *Department of Chemistry, Tarbiat Modares University, PO Box 14115-175, Tehran 14115, Iran*
[b] *Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China*

ARTICLE INFO

Article history:
Received 12 August 2010
Received in revised form 27 September 2010
Accepted 18 October 2010
Available online 17 November 2010

Keywords:
1,*n*-Diamines
l,l-Bis(methylthio)-2-nitroethen
Diaroylacetylene
1*H*-Pyrrolo[1,2-*a*]-fused-1,3-diazaheterocycles
Multicomponent reaction

ABSTRACT

A one-pot multicomponent synthesis of a novel class of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazoles, 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidines, and 2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,3]diazepines, starting from simple and readily available inputs including diveres diamines, l,l-bis(methylthio)-2-nitroethen and diaroylacetylene, in excellent yields is described.

1. Introduction

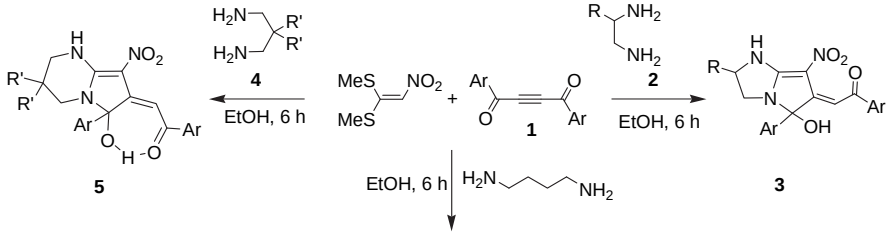
Heterocyclic compounds are important natural and synthetic materials. The remarkable ability of heterocyclic cores to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs and designed medicinal agents in medicinal chemistry.[1] In particular, nitrogen containing heterocycles are prevalent in many drugs,[2] thus synthetic chemists are increasingly motivated to discover new methods for rapid construction of pharmacologically important drug-like compounds.[3] Amongst them, the pyrroloimidazole, pyrrolopyrimidine, and pyrrolodiazepine scaffolds have been used for both synthetic and clinical studies. Pyrroloimidazoles are useful in the treatment of hypoalkemia, hypertension, and congestive heart failure.[4] Compounds containing the imidazole moiety have many pharmacological properties and play important roles in biochemical processes.[5] Pyrrolopyrimidine nucleoside derivatives are reported to have various biological activities, such as anti-HCV, anti-HIV type 1, and anti-HSV as well as being adenosine kinase, aurora-A kinase, and cAMP phosphodiesterase inhibitors.[6–9] Naturally occurring mycalisine A, cadeguomycin, and 2-deoxycadeguomycin[10,11] also posses a pyrrolo[2,3-*a*]pyrimidine moiety. A number of pyrrolopyrimidine derivatives structurally related to toyocamycin, sangivamycin, and the seco nucleosides of tubercidin have antiviral activity.[12,13] The diazepine nucleus is a pharmacophoric scaffold and many diazepines have recently received great attention, because of their wide range of therapeutic and pharmacological properties. Many members of the diazepine family are widely used as antianxiety, antidepressant, sedative, hypnotic, tranquilizing, anticonvulsant, antihistaminic, analgesic, and anti-inflammatory agents.[14,15]

The development of new approaches for the efficient construction of these heterocycles continues to be essential for accessing natural products and their structural analogues. Accordingly, and because of their scarce occurrence in exotic organisms, novel strategies for the synthesis of these *N*-heterocycles have received considerable attention in the past decades.[16] Heterocyclic enamines are versatile building blocks for the synthesis of various bicyclic and tricyclic structures bearing a bridgehead nitrogen atom. Among them, cyclic β-nitroenamines, which consist of push–pull ethylene systems with two donors (amine) at the two ends and an acceptor (nitro) at the other end of the ethylene, manifest themselves as common enamines in electrophilic reactions and could react with a variety of electrophiles, with electrophilic attack proceeding at either or both of two nucleophilic centers.[17–21] The high solubility of the nitroenamines in general

* Corresponding author. Tel.: +98 21 8800663; fax: +98 21 88006544; e-mail address: aalizadeh@modares.ac.ir (A. Alizadeh).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.10.052

organic solvents enables chemists to conduct reactions in the organic media accompanied by easy experimental manipulations and considerable safety. Although several nitroenamines have been known for a long time, apart from a few reactions,[22–24] they have not been used in organic synthesis. In the course of our research program into design of new routes for the synthesis of a variety of active biologically nitrogen heterocycles in our laboratory via one-pot synthesis and reactions of enamines,[25] we become interested in the application of l,l-bis(methylthio)-2-nitroethen for preparation of cyclic β-nitroenamines and their behavior in one-pot multi-component reaction. Our strategy to reach this goal is outlined in Scheme 1.



5	Ar	R'	Yield %
a	C_6H_5	H	78
b	*p*-Me-C_6H_4	H	83
c	C_6H_5	Me	74
d	*p*-Me-C_6H_4	Me	70

3	Ar	R	Yield %
a	C_6H_5	H	87
b	*p*-Me-C_6H_4	H	80
c	C_6H_5	Me	78
d	*p*-Me-C_6H_4	Me	84

6	Ar	Yield %
a	C_6H_5	86
b	*p*-Me-C_6H_4	82

Scheme 1. The reaction of diamine, l,l-bis(methylthio)-2-nitroethen and diaroylacetylene.

2. Results and discussion

The reaction between diamines (1,2-ethanediamine **2**, 1,3-propanediamine **4**, 1,4-butanediamine), l,l-bis(methylthio)-2-nitroethene, and diaroylacetylene in aqueous EtOH leads to the formation of pyrrolo[1,2-*a*]-fused-1,3-diazaheterocycles in excellent yields (Scheme 1).

The structures of compounds **3a**–**d**, **5a**–**d**, and **6a**–**b** (Fig. 1) were deduced from their elemental analysis, IR, and high-field ^{1}H, ^{13}C NMR spectra. The mass spectrum of **5b** displayed the molecular ion peak at *m*/*z* 405, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the OH and NH stretching frequency at 3338 and 3040 cm^{-1}. Absorption bands at 1653 and 1603 cm^{-1} are due to the C=O and NC=C groups. The ^{1}H NMR spectrum of **5b** showed five multiplets for CH_2 groups because these protons are diastereotopic (δ=1.87–1.90, 2.05–2.09, 2.83–2.88, 3.42–3.46, and 3.51–3.56 ppm), two sharp singlets for the two methyl groups (δ=2.27 and 2.36 ppm), four doublets for the aromatic moieties in the aromatic region of the spectrum (δ=7.07–7.79 ppm) and three singlets for CH, NH and OH groups (δ=8.13, 8.55 and 8.92 ppm). The most important difference between ^{1}H NMR spectrum of compounds **3**, **5**, and **6** is due to the chemical shift of their OH group. For example, compound **3a** can not orient for an intramolecular hydrogen bonding and thus OH appears as a broad bond at 1.59 ppm while for **5b**, intramolecular hydrogen bond causes that OH group resonances at down field (8.92 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **5b** showed 19 distinct resonances in agreement with the suggested structure.

Finally, the structures of **5b** and **6b** were further confirmed by X-ray crystallographic analysis (Fig. 1).

Although we have not established the mechanism of reaction experimentally, a possible explanation is proposed in Scheme 2.

Two isomers *Z* and *E* for all products were expected, but when the different 1,*n*-diamines were applied in the reaction, only one of the two possible isomers (*E* or *Z*) was obtained stereospecifically for each of them. The ^{1}H and ^{13}C NMR, and IR spectral data of the crude product clearly indicated the structures of all these products.

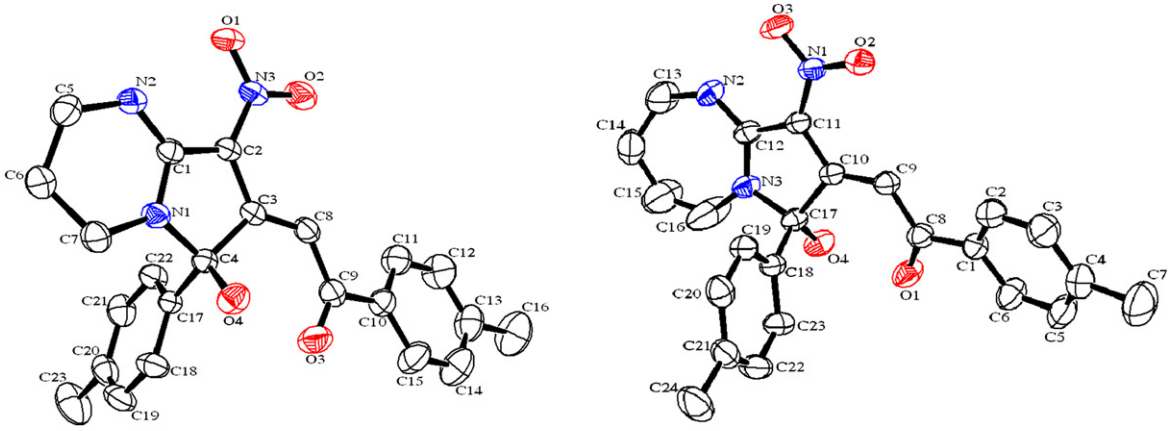
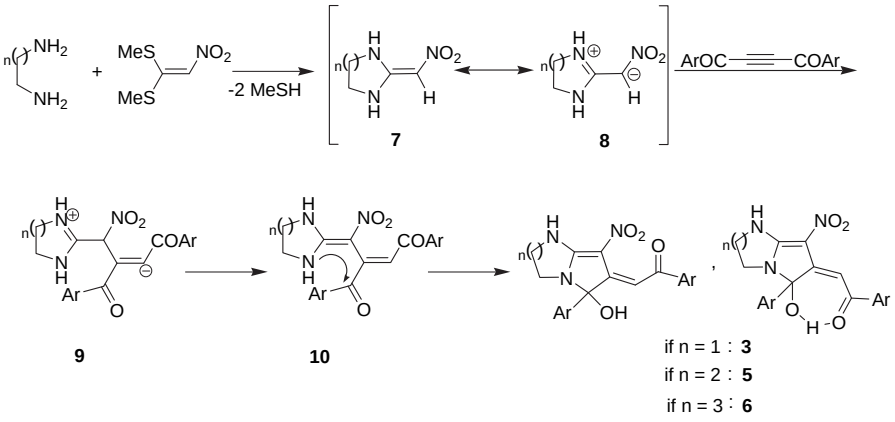


Fig. 1. The molecular structure of compound **5b** and **6b**.



Scheme 2. A plausible mechanism for the formation of products **3a**–**d**, **5a**–**d** and **6a**,**b**.

3. Conclusion

In summary, we have discovered a novel, mild, and straightforward procedure for the synthesis of a new class of substituted *N*-heterocyclic derivatives from the three-component reaction between nitroenamines, derived from the addition of various diamines to l,l-bis(methylthio)-2-nitroethen, and diaroylacetylene, in aqueous media. Depending on the ring size of the cyclic nitroenamines, various new pyrrolo[1,2-*a*]imidazoles, pyrrolo[1,2-*a*]pyrimidines, and pyrrolo[1,2-*a*][1,3]diazepines have been prepared. Good yields of the products, the ready availability of the starting materials and the reaction's simplicity of the process recommend this as a useful method.

4. Experimental

4.1. General

The diamines, and l,l-bis(methylthio)-2-nitroethene were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Diaroylacetylene was prepared according to published procedures.[26,27] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.13 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer, absorbencies are reported in cm^{-1}.

4.2. General synthesis procedure: (for example 5b)

A solution of l,l-bis(methylthio)-2-nitroethene (0.162 g, 1 mmol) and 1,3-propanediamine (0.074 g, 1 mmol) in ethanol (5 mL) was magnetically stirred for 4 h at reflux. Then a solution of 1,4-bis(4-methylphenyl)-2-butyne-1,4-dione (0.26 g, 1 mmol) in ethanol (3 mL) was added dropwise at rt and the mixture was stirred for 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck 230–240 mesh) column chromatography using hexane–EtOAc (5:1).

*4.2.1. 2-[5-Hydroxy-7-nitro-5-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-yliden]-1-phenyl-1-ethanone (**3a**).* Yellow powder, mp=120–124 °C (decomp.), 0.327 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3345 (OH), 3048 (NH), 1649 (NC=C), 1623 (C=O), 1600, 1577 and 1525 (Ph), 1553 and 1394 (C–NO_2), 1263 (C–N), 1171 (C–O). Anal. calcd for $C_{20}H_{17}N_3O_4$ (363.37): C, 66.11; H, 4.72; N, 11.56%. Found: C, 66.17; H, 4.63; N, 11.32%. MS (EI, 70 eV): *m*/*z* (%)=357 (4), 343 (58), 331 (12), 313 (72), 297 (50), 284 (138), 226 (10), 105 (137), 77 (96), 51 (27). δ_H (500.1 MHz, $CDCl_3$): 1.59 (1H, s, OH), 3.04 (1H, q, $^3J_{HH}$=10.2 Hz, CH_2), 3.79 (1H, td, $^2J_{HH}$=10.2 Hz, $^3J_{HH}$=4.7 Hz, CH_2), 4.04 (1H, td, $^2J_{HH}$=10.2 Hz, $^3J_{HH}$=4.7 Hz, CH_2), 4.18 (1H, q, $^3J_{HH}$=10.2 Hz, CH_2), 7.28–7.35 (2H, m, 2CH of Ph), 7.39 (2H, t, ^3J=7.9 Hz, 2CH of Ph), 7.49 (2H, d, ^3J=7.1 Hz, 2CH of Ph), 7.54 (2H, d, ^3J=7.2 Hz, 2CH of Ph), 7.90 (2H, d, ^3J=7.9 Hz, 2CH of Ph), 8.06 (1H, s, C=C*H*), 8.37 (1H, s, NH). δ_C (125.7 MHz, $CDCl_3$): 41.4 (CH_2NH), 48.4 (CH_2N), 91.3 (COH), 108.4 (C=*C*H), 110.1 (C–NO_2), 125.3 (2CH of Ph), 128.4 (2CH of Ph), 128.5 (2CH of Ph), 128.6 (2CH of Ph), 129.0 (CH of Ph), 132.9 (CH of Ph), 137.71 (C_{ipso}–COH), 138.6 (C_{ipso}–CO), 159.0 (*C*=CH), 163.5 (NHCN), 191.8 (CO).

*4.2.2. 2-[5-Hydroxy-5-(4-methylphenyl)-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-yliden]-1-(4-methylphenyl)-1-ethanone (**3b**).* Yellow powder, mp=100–105 °C (decomp.), 0.332 g, yield: 85%. IR (KBr) (ν_{max}, cm^{-1}): 3353 (OH), 3065 (NH), 1650 (NC=C), 1602 (C=O), 1610, 1567 and 1515 (Ar), 1539 and 1389 (C–NO_2), 1275 (C–N), 1176 (C–O). Anal. calcd for $C_{22}H_{21}N_3O_4$ (391.42): C, 67.51; H, 5.41; N, 10.74%. Found: C, 67.48; H, 5.47; N, 10.68%. MS (EI, 70 eV): *m*/*z* (%)=391 (M^+, 4), 387 (27), 328 (41), 312 (73), 234 (59), 178 (63), 149 (58), 91 (74), 69 (100), 43 (93). δ_H (500.1 MHz, $CDCl_3$): 1.59 (1H, s, OH), 2.28 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.05 (1H, q, $^3J_{HH}$=10.1 Hz, CH_2), 3.79 (1H, td, $^2J_{HH}$=10.2 Hz, $^3J_{HH}$=4.7 Hz, CH_2), 4.04 (1H, td, $^2J_{HH}$=10.2 Hz, $^3J_{HH}$=4.6 Hz, CH_2), 3.79 (1H, q, $^3J_{HH}$=10.1 Hz, CH_2), 7.11 (2H, d, $^3J_{HH}$=8.0 Hz, 2CH of Ar), 7.19 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.39 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.82 (2H, d, $^3J_{HH}$=8.0 Hz, CH of Ar), 8.04 (1H, s, C=C*H*), 8.42 (1H, s, NH). δ_C (125.7 MHz, $CDCl_3$): 21.0 (CH_3), 21.5 (CH_3), 41.3 (CH_2NH), 48.3 (CH_2N), 91.4 (COH), 108.6 (C=*C*H), 110.8 (C–NO_2), 125.3 (2CH of Ar), 128.9 (2CH of Ar), 129.1 (2CH of Ar), 129.1 (2CH of Ar), 134.8 (C_{ipso}–COH), 136.0 (C_{ipso}–Me), 138.8 (C_{ipso}–CO), 143.7 (C_{ipso}–Me), 158.6 (*C*=CH), 163.4 (NHCN), 191.9 (CO).

*4.2.3. 2-[5-Hydroxy-2-methyl-7-nitro-5-phenyl-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-yliden]-1-phenyl-1-ethanone (**3c**).* Yellow powder, mp=110–114 °C (decomp.), 0.347 g, yield: 92%. IR (KBr) (ν_{max}, cm^{-1}): 3271 (OH), 3062 (NH), 1657 (NC=C), 1619 (C=O), 1595, 1576 and 1522 (Ph), 1545 and 1382 (C–NO_2), 1266 (C–N), 1176 (C–O). Anal. calcd for $C_{21}H_{19}N_3O_4$ (377.40): C, 66.83; H, 5.07; N, 11.13%. Found: C, 66.75; H, 5.11; N, 11.17%. MS (EI, 70 eV): *m*/*z* (%)=377 (M^+, 6), 344 (22), 297 (7), 234 (6), 105 (31), 91 (24), 77 (31), 57 (35), 43 (100). δ_H (500.1 MHz, $CDCl_3$): 1.59 (1H,s, OH), 1.45 (3H, d, $^3J_{HH}$=6.1 Hz, CH_3), 3.44–3.52 (1H, m, CH), 3.71 (1H, t, $^3J_{HH}$=10.4 Hz, CH_2), 4.08 (1H, t, $^3J_{HH}$=9.7 Hz, CH_2), 7.26–7.53(10H, m, 10CH of Ph), 8.03 (1H, s, C=C*H*), 8.46 (1H, s, NH). δ_C (125.7 MHz, $CDCl_3$): 18.8 (CH_3), 48.0 (CH), 52.4 (CH_2N), 92.2 (COH), 108.3 (C=*C*H), 111.5 (C–NO_2), 125.3 (2CH of Ph), 128.4 (2CH of Ph), 128.5 (2CH of Ph),

128.6 (2CH of Ph), 128.9 (1CH of Ph), 132.7 (1CH of Ph), 137.4 (C_{ipso}–COH), 138.5 (C_{ipso}–CO), 159.5 (*C*=CH), 163.5 (NHCN), 191.7 (CO).

*4.2.4. 2-[5-Hydroxy-2-methyl-5-(4-methylphenyl)-7-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]imidazol-6(5H)-yliden]-1-(4-methylphenyl)-1-ethanone (**3d**).* Yellow powder, mp=100–105 °C (decomp.), 0.352 g, yield: 87%. IR (KBr) (ν_{max}, cm^{-1}): 3340 (OH), 3053 (NH), 1653 (NC=C), 1604 (C=O), 1590, 1566 and 1520 (Ar), 1563 and 1348 (C–NO_2), 1285 (C–N), 1177 (C–O). Anal. calcd for $C_{23}H_{23}N_3O_4$ (405.45): C, 68.13; H, 5.72; N, 10.36%. Found: C, 68.22; H, 5.59; N, 10.34%. MS (EI, 70 eV): *m*/*z* (%)=405 (M^+, 9), 387 (8), 359 (32), 286 (13), 257 (17), 178 (31), 149 (55), 119 (32), 69 (100), 57 (89), 43 (84). δ_H (500.1 MHz, $CDCl_3$): 1.45 (3H, d, $^3J_{HH}$=6.1 Hz, CH_3), 1.53 (1H, s, OH), 2.29 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.47–3.52 (1H, m, CH), 3.70 (1H, t, $^3J_{HH}$=10.4 Hz, CH_2), 4.06 (1H, t, $^3J_{HH}$=9.7 Hz, CH_2), 7.12 (2H, d, $^3J_{HH}$=8.2 Hz, 2CH of Ar), 7.18 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.41 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH of Ar), 7.81 (2H, d, $^3J_{HH}$=8.1 Hz, CH of Ar), 8.01 (1H, s, C=*CH*), 8.50 (1H, s, NH). δ_C (125.7 MHz, $CDCl_3$): 18.7 (CH_3), 21.0 (CH_3), 21.6 (CH_3), 52.4 (CH), 55.6 (CH_2N), 92.3 (COH), 108.0 (C=*C*H), 114.0 (C–NO_2), 125.3 (2CH of Ar), 128.9 (2CH of Ar), 129.0 (2CH of Ar), 129.1 (2CH of Ar), 134.5 (C_{ipso}–COH), 136.0 (C_{ipso}–Me), 138.8 (C_{ipso}–CO), 143.6 (C_{ipso}–Me), 159.1 (*C*=CH), 163.5 (NHCN), 191.2 (CO).

*4.2.5. 2-[6-Hydroxy-8-nitro-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-7(6H)-yliden]-1-phenyl-1-ethanone (**5a**).* Yellow powder, mp=130–134 °C (decomp.), 0.332 g, yield: 88%. IR (KBr) (ν_{max}, cm^{-1}): 3301 (OH), 3085 (NH), 1665 (NC=C), 1615 (C=O), 1595, 1586 and 1521 (Ph), 1565 and 1391 (C–NO_2), 1286 (C–N), 1192 (C–O). Anal. calcd for $C_{21}H_{19}N_3O_4$ (377.40): C, 66.83; H, 5.07; N, 11.13%. Found: C, 66.76; H, 5.00; N, 11.15%. MS (EI, 70 eV): *m*/*z* (%)=377 (M^+, 37), 331 (100), 286 (9), 256 (21), 105 (69), 91 (9), 77 (57), 57 (17), 43 (14). δ_H (500.1 MHz, $CDCl_3$): 1.87–1.90 (1H, m, CH_2), 2.06–2.09 (1H, m, CH_2), 2.81–2.86 (1H, m, CH_2), 3.43–3.45 (1H, m, CH_2), 3.53–3.56 (2H, m, CH_2), 7.24–7.31 (2H, m, 2CH of Ph), 7.36 (2H, t, ^3J=7.6 Hz, 2CH of Ph), 7.46 (2H, d, ^3J=7.5 Hz, 2CH of Ph), 7.51 (2H, d, ^3J=7.5 Hz, 2CH of Ph), 7.86 (2H, d, ^3J=7.6 Hz, 2CH of Ph), 8.14 (1H, s, C=*CH*), 8.51 (1H, s, NH), 8.93 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 19.6 (CH_2), 36.2 (CH_2NH), 38.3 (CH_2N), 93.1 (COH), 107.6 (C=*C*H), 111.8 (C–NO_2), 125.6 (2CH of Ph), 128.1 (2CH of Ph), 128.3 (2CH of Ph), 128.6 (2CH of Ph), 128.9 (1CH of Ph), 132.6 (1CH of Ph), 138.3 (C_{ipso}–COH), 138.68 (C_{ipso}–CO), 154.4 (*C*=CH), 154.7 (NHCN), 192.2 (CO).

*4.2.6. 2-[6-Hydroxy-6-(4-methylphenyl)-8-nitro-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-7(6H)-yliden]-1-(4-methylphenyl)-1-ethanone (**5b**).* Yellow powder, mp=120–124 °C (decomp.), 0.385 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3338 (OH), 3040 (NH), 1653 (NC=C), 1603 (C=O), 1593, 1575 and 1519 (Ph), 1561 and 1383 (C–NO_2), 1285 (C–N), 1178 (C–O). Anal. calcd for $C_{23}H_{23}N_3O_4$ (405.45): C, 68.13; H, 5.72; N, 10.36%. Found: C, 68.02; H, 5.74; N, 10.33%. MS (EI, 70 eV): *m*/*z* (%)=405 (M^+, 28), 359 (83), 286 (6), 270 (17), 194 (6), 149 (8), 119 (53), 84 (89), 69 (18), 49 (100). δ_H (500.1 MHz, $CDCl_3$): 1.87–1.90 (1H, m, CH_2), 2.05–2.09 (1H, m, CH_2), 2.27 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.83–2.88 (1H, m, CH_2), 3.42–3.46 (1H, m, CH_2), 3.51–3.56 (2H, m, CH_2), 7.07 (2H, d, $^3J_{HH}$=8.05 Hz, 2CH of Ar), 7.17 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.38 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.79 (2H, d, $^3J_{HH}$=8.2 Hz, CH of Ar), 8.13 (1H, s, C=*CH*), 8.55 (1H, s, NH), 8.92 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 19.7 (CH_2), 21.0 (CH_3), 21.6 (CH_3), 36.1 (CH_2NH), 38.2 (CH_2N), 93.1 (COH), 107.8 (C=*C*H), 112.2 (C–NO_2), 125.5 (2CH of Ar), 128.8 (2CH of Ar), 128 (2CH of Ar), 129.0 (2CH of Ar), 135.5 (C_{ipso}–COH), 136.1 (C_{ipso}–Me), 138.6 (C_{ipso}–CO), 143.5 (C_{ipso}–Me), 154.3 (*C*=CH), 154.4 (NHCN), 191.8 (CO). Crystal data for **5b** $C_{23}H_{23}N_3O_4$ (CCDC 778304): M_W=405.5, triclinic, space group *P*–1, *a*=5.9788(4) Å, *b*=10.8688(7) Å, *c*=17.1068(12) Å, α=77.991(1) β=88.607(1), γ=78.278(1), *V*=1064.57(12) Å,[3] *Z*=2, D_c=1.265 mg/m^3, *F* (000)=273, crystal dimension 0.12×0.20×0.48 mm, radiation, Mo Kα (λ=0.71073 Å), 1.96≤2θ≤25.20, intensity data were collected at 295(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of −6≤*h*≤7, −12≤*k*≤12, −20≤*l*≤20; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2635 observed reflections with *R* (into)= 0.0768 by a full-matrix least-squares technique converged to *R*=0.0509 and Raw=0.1524 [$I>2\sigma(I)$]. Complete crystallographic data (excluding structural factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 778304. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.com.ac.uk].

*4.2.7. 2-[6-Hydroxy-3,3-dimethyl-8-nitro-6-phenyl-1,2,3,4,-tetrahydropyrrolo[1,2-a]pyrimidin-7(6H)-yliden]-1-phenyl-1-ethanone (**5c**).* Yellow powder, mp=220–225 °C (decomp.), 0.364 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3315 (OH), 3056 (NH), 1667 (NC=C), 1615 (C=O), 1600, 1577 and 1523 (Ph), 1553 and 1391 (C–NO_2), 1288 (C–N), 1177 (C–O). Anal. calcd for $C_{23}H_{23}N_3O_4$ (405.451): C, 68.13; H, 5.72; N, 10.36%. Found: C, 68.17; H, 5.69; N, 10.43%. MS (EI, 70 eV): *m*/*z* (%)=405 (M^+, 6), 387 (8), 362 (67), 344 (65), 330 (24), 270 (18), 161 (17), 91 (100), 57 (21), 43 (25). δ_H (500.1 MHz, $CDCl_3$): 0.82 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.54 (1H, d, $^3J_{HH}$=12.3 Hz, CH_2), 3.14 (2H, AB_q, $^3J_{HH}$=12.4 Hz, CH_2), 3.20 (1H, d, $^3J_{HH}$=12.3 Hz, CH_2), 7.26–7.31 (2H, m, 2CH of Ph), 7.37 (2H, t, ^3J=7.8 Hz, 2CH of Ph), 7.47 (2H, d, ^3J=7.5 Hz, 2CH of Ph), 7.52 (2H, d, ^3J=7.5 Hz, 2CH of Ph), 7.86 (2H, d, ^3J=7.8 Hz, 2CH of Ph), 8.15 (1H, s, C=*CH*), 8.40 (1H, s, NH), 8.87 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 24.0 (CH_3), 24.3 (CH_3), 27.6 (Me_2C), 47.6 (CH_2NH), 50.0 (CH_2N), 92.9 (COH), 107.8 (C=CH), 111.7 (C–NO_2), 125.7 (2CH of Ph), 128.0 (2CH of Ph), 128.3 (2CH of Ph), 128.6 (2CH of Ph), 128.8 (CH of Ph), 132.6 (CH of Ph), 138.5 (C_{ipso}–COH), 138.7 (C_{ipso}–CO), 153.6 (*C*=CH), 154.9 (NHCN), 192.1 (CO).

*4.2.8. 2-[6-Hydroxy-3,3-dimethyl-6-(4-methylphenyl)-8-nitro-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-7(6H)-yliden]-1-(4-methylphenyl)-1-ethanone (**5d**).* Yellow powder, mp=180–184 °C (decomp.), 0.364 g, yield: 84%. IR (KBr) (ν_{max}, cm^{-1}): 3296 (OH), 3028 (NH), 1658 (NC=C), 1606 (C=O), 1594, 1579 and 1534 (Ph), 1563 and 1344 (C–NO_2), 1276 (C–N), 1176 (C–O). Anal. calcd for $C_{25}H_{27}N_3O_4$ (433.50): C, 69.27; H, 6.28; N, 9.69%. Found: C, 69.33; H, 6.21; N, 9.62%. MS (EI, 70 eV): *m*/*z* (%)=433 (M^+, 9), 387 (28), 293 (9), 236 (5), 119 (27), 99 (17), 85 (46), 71 (67), 57 (100), 43 (66). δ_H (500.1 MHz, $CDCl_3$): 0.82 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.54 (1H, d, $^3J_{HH}$=12.7 Hz, CH_2), 3.08 (1H, d, $^3J_{HH}$=13.30 Hz, CH_2), 3.18 (2H, d, $^3J_{HH}$=12.6 Hz, CH_2), 7.07 (2H, d, $^3J_{HH}$=8.0 Hz, 2CH of Ar), 7.16 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.39 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar), 7.78 (2H, d, $^3J_{HH}$=8.0 Hz, CH of Ar), 8.14 (1H, s, C=*CH*), 8.45 (1H, s, NH), 8.89 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 21.0 (CH_3), 21.6 (CH_3), 24.0 (CH_3), 24.3 (CH_3), 27.6 (Me_2C), 47.6 (CH_2NH), 50.0 (CH_2N), 93.0 (COH), 108.0 (C=*C*H), 111.6 (C–NO_2), 125.6 (2CH of Ar), 128.7 (2CH of Ar), 128.8 (2CH of Ar), 129.0 (2CH of Ar), 135.6 (C_{ipso}–COH), 136.1 (C_{ipso}–Me), 138.6 (C_{ipso}–CO), 143.5 (C_{ipso}–Me), 153.5 (*C*=CH), 154.6 (NHCN), 191.7 (CO).

*4.2.9. 2-[7-Hydroxy-9-nitro-7-phenyl-2,3,4,5-tetrahydropyrrolo[1,2-a][1,3]diazepin-8-(7H)-yliden]-1-phenyl-1-ethanone (**6a**).* Yellow powder, mp=200–205 °C (decomp.), 0.352 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3263 (OH), 3051 (NH), 1645 (NC=C), 1612 (C=O), 1604, 1572 and 1515 (Ph), 1564 and 1360 (C–NO_2), 1286 (C–N), 1197 (C–O). Anal. calcd for $C_{22}H_{21}N_3O_4$ (391.42): C, 67.51; H, 5.41; N, 10.74%. Found: C, 67.36; H, 5.44; N, 10.62%. MS (EI, 70 eV): *m*/*z* (%)= 391 (M^+, 55), 345 (100), 286 (23), 268 (35), 119 (22), 105 (99), 91 (16), 77 (30), 55 (24), 41 (9). δ_H (500.1 MHz, $CDCl_3$): 1.62–1.72 (1H, m, CH_2), 1.82–1.94 (2H, m, CH_2), 1.98–2.09 (1H, m, CH_2), 3.11–3.15 (1H, m, CH_2), 3.58–3.65 (3H, m, CH_2), 7.27–7.31 (2H, m, 2CH of Ph), 7.36 (2H, t, ^3J=7.7 Hz, 2CH of Ph), 7.47 (2H, d, ^3J=7.7 Hz, 2CH of Ph),

7.52 (2H, d, ^3J=7.3 Hz, 2CH of Ph), 7.84 (2H, d, ^3J=7.3 Hz, 2CH of Ph), 8.13 (1H, s, C=C*H*), 8.71 (1H, s, NH), 9.98 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 26.0 (CH_2), 27.0 (CH_2), 43.0 (CH_2NH), 44.2 (CH_2N), 93.6 (COH), 107.7 (C=*C*H), 111.5 (C–NO_2), 125.8 (2CH of Ph), 128.0 (2CH of Ph), 128.3 (2CH of Ph), 128.6 (2CH of Ph), 128.8 (CH of Ph), 132.6 (CH of Ph), 138.7 (C_{ipso}–COH), 138.9 (C_{ipso}–CO), 154.7 (*C*=CH), 160.0 (NHCN), 192.3 (CO).

*4.2.10. 2-[7-Hydroxy-7-(4-methylphenyl)-9-nitro-2,3,4,5-tetrahydropyrrolo[1,2-a][1,3]diazepin-8-(7H)-yliden]-1-(4-methylphenyl)-1-ethanone (**6b**).* Yellow powder, mp=200–205 °C (decomp.), 0.398 g, yield: 95%. IR (KBr) (ν_{max}, cm^{-1}): 3335 (OH), 3052 (NH), 1648 (NC=C), 1602 (C=O), 1600, 1564 and 1515 (Ph), 1558 and 1381 (C–NO_2), 1286 (C–N), 1179 (C–O). Anal. calcd for $C_{24}H_{25}N_3O_4$ (419.48): C, 68.72; H, 6.01; N, 10.02%. Found: C, 68.53; H, 5.99; N, 10.08%. MS (EI, 70 eV): *m*/*z* (%)=419 (M^+, 22), 387 (28), 373 (39), 310 (46), 236 (29), 91 (71), 57 (96), 43 (100). δ_H (500.1 MHz, $CDCl_3$): 1.63–1.72 (1H, m, CH_2), 1.85–1.94 (2H, m, CH_2), 2.01–2.07 (1H, m, CH_2), 2.26 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.10–3.14 (1H, m, CH_2), 3.56–3.62 (3H, m, CH_2), 7.06 (2H, d, $^3J_{HH}$=7.7 Hz, 2CH of Ar), 7.16 (2H, d, $^3J_{HH}$=7.7 Hz, 2CH of Ar), 7.39 (2H, d, $^3J_{HH}$=7.8 Hz, 2CH of Ar), 7.77 (2H, d, $^3J_{HH}$=7.8 Hz, CH of Ar), 8.12 (1H, s, C=C*H*), 8.75 (1H, s, NH), 9.98 (1H, s, OH). δ_C (125.7 MHz, $CDCl_3$): 21.0 (CH_3), 21.56 (CH_3), 26.0 (CH_2), 27.0 (CH_2), 43.0 (CH_2NH), 44.1 (CH_2N), 93.6 (COH), 107.8 (C=CH), 112.9 (C–NO_2), 125.7 (2CH of Ar), 128.7 (2CH of Ar), 128.8 (2CH of Ar), 129.0 (2CH of Ar), 136.0 (C_{ipso}–COH), 136.1 (C_{ipso}–Me), 138.5 (C_{ipso}–CO), 143.5 (C_{ipso}–Me), 154.5 (*C*=CH), 159.8 (NHCN), 191.9 (CO). Crystal data for **6b** $C_{24}H_{25}N_3O_4$ (CCDC 778303): M_W=419.44, triclinic, space group *P*–1, *a*=6.4600 (3) Å, *b*=10.4517(4) Å, *c*=15.7074(7) Å, α=90.0550(10), β=95.1650 (10), γ=90.9930(10), *V*=1056.06(8) $Å^3$, *Z*=2, Dc=1.306 mg/m^3, *F* (000)=436, crystal dimension 0.28×0.23×0.15 mm, radiation, Mo Kα (λ=0.71073 Å), 1.30≤2θ≤25.20, intensity data were collected at 295 (2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-7\leq h\leq 7$, $-12\leq k\leq 12$, $-18\leq l\leq 18$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 3055 observed reflections with *R* (into)=0.0705 by a full-matrix least-squares technique converged to *R*=0.0574 and Raw=0.1648 [$I>2\sigma(I)$]. Complete crystallographic data (excluding structural factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 778303. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.com.ac.uk].

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.052.

References and notes

1. (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon: Oxford, 1990; Vol. 2, Chapter 7.1; (b) Erlanson, D. A.; Mc Dowell, R. S.; O'Brien, T. *J. Med. Chem.* **2004**, *47*, 3463.
2. Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.
3. Padwa, A. *Prog. Heterocycl. Chem.* **1994**, *6*, 36.
4. (a) Ksander, G.M.; Meredith, E.; Monovich, L.H.; Papillon, J.; Firooznia, F.; Hu, Q. WO 024945, 2007. (b) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725.
5. Lambardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182.
6. Varaprasad, C. V. N. S.; Ramasamy, S. K.; Girardet, J. L.; Gunic, E.; Lai, V.; Zhong, Z.; An, H.; Hong, Z. *Bioorg. Chem.* **2007**, *35*, 25.
7. Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 899.
8. Moriarty, K. J.; Koblish, H. K.; Garrabrant, T.; Maisuria, J.; Khalil, E.; Ali, F.; Petrounia, L. P.; Crysler, C. S.; Maroney, A. C.; Johnson, D. L.; Galemmo, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5778.
9. Klump, S.; Frey, M.; Kleefeld, G.; Sauer, A.; Eger, K. *Biochem. Pharmacol.* **1989**, *38*, 949.
10. Wade, A. E.; Krawczyk, S. H.; Townsend, B. L. *Tetrahedron Lett.* **1988**, *29*, 4073.
11. Edstrom, E. D.; Wei, Y. *Tetrahedron Lett.* **1994**, *35*, 8989.
12. Gupta, P. K.; Daunert, S.; Nassiri, M. R.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1989**, *32*, 402.
13. Gupta, P. K.; Nassiri, M. R.; Coleman, L. A.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1989**, *32*, 1420.
14. (a) Schutz, H. *Benzodiazepines*; Springer: Heidelberg, 1982; (b) Smalley, R. K. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 4, p 600; (c) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, p 166; (d) De Baun, J.R.; Pallos, F.M.; Baker, D.R. U.S. Patent 3,978,227, 1976; *Chem. Abstr.* **1977**, *86*, 5498d; (e) Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747.
15. (a) Zellou, A.; Cherrah, Y.; Hassar, M.; Essassi, E.-M. *Ann. Pharm. Fr.* **1998**, *56*, 169; (b) Savelli, F.; Boido, A.; Mule, A.; Piu, L.; Alamanni, M. C.; Pirisino, G.; Satta, M.; Peana, A. *Farmaco* **1989**, *44*, 125; (c) Srivastava, V. K.; Satsangi, R. K.; Kishore, K. *Arzneim. Forsch.* **1982**, *32*, 1512; (d) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164; (e) Failli, A. A.; Shumsky, J. S.; Steffan, R. J.; Caggiano, T. J.; Williams, D. K.; Trybulski, E. J.; Ning, X.; Lock, Y.; Tanikella, T.; Hartmann, D.; Chan, P. S.; Park, C. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 954; (f) Hadac, E. M.; Dawson, E. S.; Darrow, J. W.; Sugg, E. E.; Lybrand, T. P.; Miller, L. J. *J. Med. Chem.* **2006**, *49*, 850.
16. Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099.
17. Kagabu, S.; Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 362.
18. Rajappa, S. *Tetrahedron* **1999**, *55*, 7065.
19. Komoto, I.; Seko, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2957.
20. Nazarenko, K. G.; Shvidenko, K. V.; Pinchuk, A. M.; Tolmachev, A. A. *Monatsh. Chem.* **2005**, *136*, 211.
21. Aoki, I.; Tabuchi, T.; Minamida, I. U.S. Patent 5,122,527, 1992.
22. (a) Rajappa, S. *Tetrahedron* **1981**, *37*, 1453; (b) Efremov, D. A.; Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M. *Nitroalkenes*; John Wiley: New York, NY, 1994.
23. Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. *Nitroalkenes, Conjugated Nitro Compounds*; Wiley: New York, NY, 1994; p 210.
24. Nishiwaki, N.; Mizukawa, Y.; Terai, R.; Tohda, Y.; Ariga, M. *ARKIVOC* **2000**, *1*, 115.
25. (a) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *Tetrahedron* **2010**, *66*, 6924; (b) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *Tetrahedron* **2008**, *64*, 351; (c) Alizadeh, A.; Rezvanian, A. *Synthesis* **2008**, *11*, 1747; (d) Alizadeh, A.; Rezvanian, A.; Bijanzadeh, H. R. *Synthesis* **2008**, *5*, 725; (e) Alizadeh, A.; Babaki, M.; Zohreh, N.; Rezvanian, A. *Synthesis* **2008**, *23*, 3793; (f) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *Helv. Chim. Acta* **2007**, *90*, 2414.
26. Skattebol, L.; Jones, E. R. H.; Whiting, M. C. *Organic Syntheses Collective, IV*; Wiley: New York, NY, 1963; p 792.
27. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. *J. Chem. Soc.* **1946**, 39.