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Synthesis of 4-nitromethylene-1,4-dihydropyrimidine derivatives as pyrimidine nucleoside analogues

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ABSTRACT

The synthesis of 4-nitromethylene-1,4-dihydropyrimidine derivatives as pyrimidine nucleoside analogues was developed, starting from 3-nitropyran-2-one N-functionalized amidines. Primary amines were reacted with amidines yielding 4-nitromethylene-1,4-dihydropyrimidine derivatives. In an initial survey, several 4-nitromethylene-1,4-dihydropyrimidines turned into 4-nitromethylene-1,2,3,4-tetrahydropyrimidine derivatives under different reduction conditions. The reduction reaction also induced a change in the exocyclic double bond configuration from (*E*) to (*Z*), due to an intramolecular hydrogen bond.

1. Introduction

Nucleosides, fundamental building blocks of biological systems, are sequentially phosphorylated by kinases into nucleotides, and the resultant nucleotides are processed by polymerases and transformed into nucleic acids, the biopolymers carrying the cell genetic information.

It is plain that the search for nucleoside analogues, which act as selective inhibitors of kinases and polymerases has been the subject of intense study.

In recent years, several biological activities have been claimed for pyrimidine and purine analogues of natural bases. For instance, unnatural nucleoside analogues containing a modified pyrimidine nucleus have become prime candidates in the search for new antiviral and anticancer agents.[1]

A survey of the literature revealed that few reports deal with the synthesis of pyrimidine nucleosides having an extended conjugation system linked to C-4 in place of the amino or oxo substituents of naturally occurring nucleosides. These pyrimidine nucleoside analogues have been studied as potential cytidine deaminase (CDA) inhibitors to understand the CDA role in antitumour activity.[2]

Synthetic routes to substituted 4-methylene-dihydropyrimidine involve approaches based on either (i) the sulfur extrusion reaction of the corresponding C-4 alkylthio derivatives[3] or (ii) the 1,2,4-triazol-1-yl group displacement of the C-4 activated pyrimidines with malonate-type *C*-nucleophiles.[2b,4]

We are interested in pyrimidine nucleoside mimetics modified at the N-1 and C-2 positions, bearing an extended conjugation system on C-4, and possessing a set of groups able to act both as hydrogen bond donors and acceptors towards proteins and nucleic acids.

At the same time, the present study is included in a research program related to triacetic acid lactone amidines. Within this context, we recently developed[5] a new method for the synthesis of 4-dialkyaminopyridine derivatives by reacting secondary amines with acetamidines bearing the 3-nitro-2*H*-pyran-2-one group on N-1.

These acetamidines are characterized by three electrophilic centers: the amidine iminic carbon,[6] C-2 and C-6 of the pyran-2-one ring[7] in which the latter is highly susceptible to nucleophilic attack due to the extended conjugation, and the presence of an electron-withdrawing substituent at the C-3 position.[8]

Both open-chain intermediates, directly arising from the opening of 2*H*-pyran-2-one by nucleophiles, and the combined reactivity of the amidine iminic carbon exhibit a strong tendency to cyclize into a new heterocyclic system.[9]

Thus, the above observations and the described success in synthesizing 4-dialkyaminopyridine derivatives prompted us to exploit the behaviour of 3-nitro-2*H*-pyran-2-one acetamidines and primary amines with the purpose of building pyrimidine nucleoside mimetics bearing a NO_2 conjugated system on C-4.

We now wish to report an approach for the synthesis of C-4 substituted 4-nitromethylene-1,4-dihydropyrimidine derivatives

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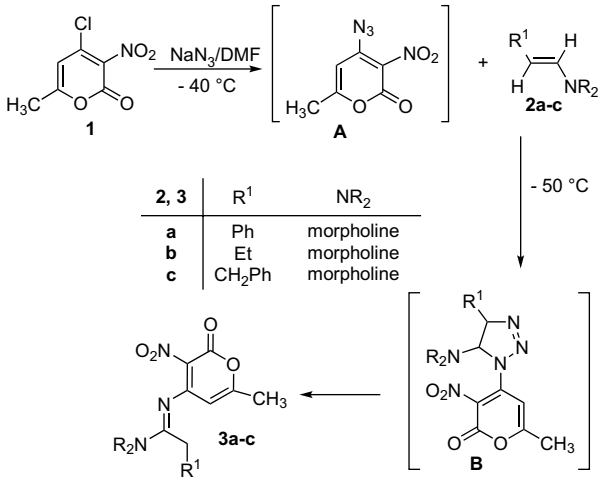
based on the combined nucleophilic feature of both the 3-nitro-2*H*-pyran-2-one moiety and the amidine imino group.

In order to study the polyfunctional character of the 4-nitromethylene-1,4-dihydropyrimidine derivatives we focused on a reduction reaction to explore the effects of the substituents.

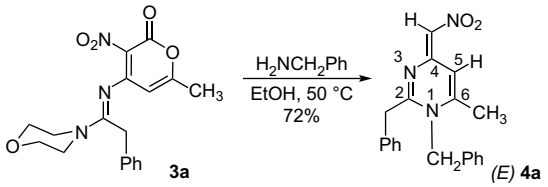
2. Results and discussion

4-Chloro-3-nitro-2*H*-pyran-2-one **1** was reacted with sodium azide and suitable enamines **2a–c** in a chilled DMF solution yielding amidines **3a–c**. The low inner temperature (−50 °C) avoided the known azide transformation into the 6-methyl-4*H*-pyrano[3,4-*c*][1,2,5]oxadiazol-4-one 3-oxide[5] and allowed the isolation of the amidines **3a–c**, as already described. The unsuccessful isolation of the 4,5-dihydro-triazole **B** is due to the electron-withdrawing effect of the N-1 substituent,[10] which facilitates the cleavage of the N1–N2 bond and promotes the amidine rearrangement (Scheme 1).



Scheme 1. Synthesis of the amidines **3a–c**.

With the aim to synthesize 4-nitromethylene-1,4-dihydropyrimidine derivatives we performed a preliminary experiment by heating amidine **3a** in an ethanol solution at 50 °C with an equimolar amount of benzylamine (Scheme 2). In about 2 h the starting materials turned into the expected 1,4-dihydropyrimidine derivative **4a** in good yield (Table 1).

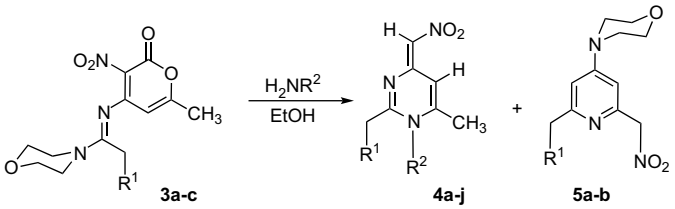


Scheme 2. Synthesis of 4-nitromethylene-1,4-dihydropyrimidine **4a**.

The structure of compound **4a** was initially deduced from spectroscopic data. The protons and carbons in the ^{1}H and ^{13}C NMR spectra were assigned using two-dimensional experiments performed in $CDCl_3$ solution. An HSQC experiment validated the attribution of CH_2–N (δ 5.08, 51.1), CH_2 on C-2 (δ 3.99, 42.1) and CH_3 on C-6 (δ 2.28, 20.7), and allowed the attribution of the signals related to the vinylic CH (δ 7.16, 118.4) and H-5 of the 1,4-dihydropyrimidine ring (δ 8.02, 109.7).[11] Quaternary carbons were assigned from the results of the HMBC experiments.

The high frequency signal related to H-5 (δ 8.02) shows that the CH-5 is cis-oriented to the nitro group.[12] Moreover, a NOESY experiment only displayed a correlation between the singlets at δ 2.82 (CH_3 linked to C-6) and 8.02, thus validating both the CH-5 attribution and the exocyclic double bond (*E*) configuration.

Table 1
Synthesis of 4-nitromethylene-1,4-dihydropyrimidine **4** and 4-morpholinopyridine **5** from amidines **3**



3	R^1
a	Ph
b	Et
c	CH_2Ph

4	R^1	R^2
a	Ph	CH_2Ph
b	Ph	Pr
c	Ph	4-CH_3OPh
d	Ph	CH_2CH_2OH
e	Ph	$C_6H_{10}OH$
f	CH_2Ph	CH_2Ph
g	Et	CH_2Ph
h	Et	CH_2CH_2OH
i	Et	$C_6H_{10}OH$
j	Ph	CH_2COOCH_3

5	R^1
a	Ph
b	Et

Amidines **3**	NH_2R^2	*t* (h)	Yields of isolated products (%)
3a	R^2=CH_2Ph	2	**4a** (72)
3a	R^2=$CH_2CH_2CH_3$	3	**4b** (60)
3a	R^2=4-CH_3OPh	20	**4c** (65)
3a	R^2=CH_2CH_2OH	2	**4d** (85)
3a	R^2=$C_6H_{10}OH$	8	**4e** (65), **5a** (5)
3c	R^2=CH_2Ph	4	**4f** (56)
3b	R^2=CH_2Ph	2	**4g** (71)
3b	R^2=CH_2CH_2OH	2	**4h** (72)
3b	R^2=$C_6H_{10}OH$	4	**4i**[a] (40), **5b** (35)
3a	R^2=CH_2COOCH_3	6	**4j**[b] (78)

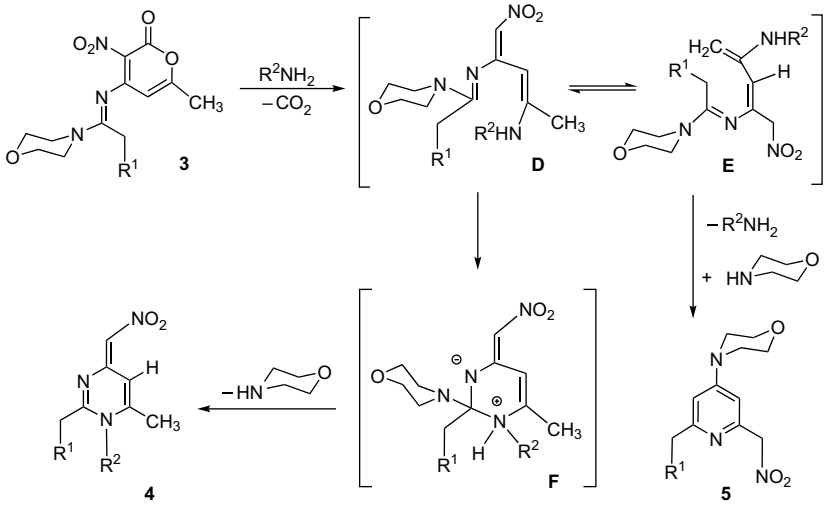
[a] After 48 h at room temperature the yield is 83%: see Section 2.
[b] CH_2Cl_2, 35 °C: see Section 4.

The formation of the substituted 1,4-dihydropyrimidine **4a** is rationalized as shown in Scheme 3.

Amidine **3a**, by reacting with a primary amine, underwent a nucleophilic attack at C-6 of the pyran-2-one ring, followed by ring opening to give the labile intermediate **D**. Subsequent nucleophilic addition to the amidine imino group provided 4-nitromethylene-1,4-dihydropyrimidine **4a**, due to secondary amine elimination. This result matches with previously reported data.[5] Indeed, the strong electron-withdrawing group at the C-3 position of the pyran-2-one moiety enhances the reactivity towards nucleophiles at the C-6 site.[8]

Continuing our research we attempted to extend the above protocol to variously substituted amidines. For this purpose amidines **3b**, **3c** were reacted with several amines and the results are summarized in Table 1.

In most cases the expected 1,4-dihydropyrimidine derivatives were obtained in satisfactory yield and in a short reaction time. Standard reaction conditions did not enable us to reach the 1,4-dihydropyrimidine derivative **4j**. When glycine methyl ester hydrochloride, previously deprotected by TEA in CH_2Cl_2 solution, was reacted with amidine **3a** in ethanol solution, at 50 °C or at room temperature, intractable mixtures were only recovered. However, the 1,4-dihydropyrimidine derivative **4j** was easily achieved by performing the reaction of the amidine **3a** with the deprotected glycine ester in CH_2Cl_2 solution at 35 °C (see Section 4).



Scheme 3. Suggested mechanism for the formation of **4** and **5**.

The amidines **3a**, **3b** reacted with *trans*-2-aminocyclohexanol under standard conditions (50 °C) also showed a different behaviour.

After 8 h, the reaction mixture of the amidine **3a** and *trans*-2-aminocyclohexanol provided the substituted 1,4-dihydropyrimidine **4e** and the 4-morpholinopyridine derivative **5a** in 65% and 5% yield, respectively. On the other hand, the reaction mixture, arising from the amidine **3b** (R^1=ethyl group) and *trans*-2-aminocyclohexanol, gave the expected 1,4-dihydropyrimidine derivative **4i** in 4 h in about 40% yield, in addition to a considerable amount of the substituted 4-morpholinopyridine **5b** (35%) as by-product. The structures of **5a**, **5b** were validated by comparing ^{1}H NMR (C_6D_6) spectra of authentic samples previously achieved.[5]

It can be reasonably assumed that the formation of **4** and **5** (Scheme 3) depends on the same transient intermediate **D**, through cyclization and morpholine loss. Morpholine elimination in the intermediate **F** gives rise to 1,4-dihydropyrimidine derivative **4i** and promotes the amine exchange in intermediate **E**. The amine competition, favoured by temperature, could explain the unsatisfactory yield of the 1,4-dihydropyrimidine **4i**.

Indeed, the expected 1,4-dihydropyrimidine **4i** was obtained as the only product in 48 h and with about 80% yield by conducting the reaction of **3b** and *trans*-2-aminocyclohexanol at room temperature.

The structures of the new compounds **4b**–**j** were validated by spectroscopic analysis and are in accordance with data previously reported for the 1,4-dihydropyrimidine derivative **4a**. All the analytical and spectroscopic data of compounds **4b**–**j** also supported the (*E*) steric arrangement previously observed for derivative **4a**.

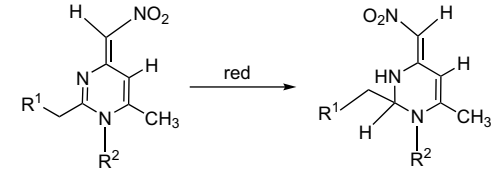
4-Nitromethylene-1,4-dihydropyrimidine derivatives **4** share with substituted amidines two nitrogen atoms at the 1,3-position of an allylic system. This atom set confers a strong basic character, thus allowing N-protonation to give amidinium cations stabilized by resonance.[13] This feature could reasonably provide derivatives **4** with additional binding properties towards proteins and nucleic acids.[14] Such imino conjugated nitromethylene substituted compounds can be thus considered a convenient starting material for further synthetic modifications, prompting us to explore further structural changes.

Therefore we carried out a preliminary study by undertaking reduction reactions of the 4-nitromethylene-1,4-dihydropyrimidines **4a** and **4d**.

Under different reaction conditions **4a** and **4d** always turned into 1,2,3,4-tetrahydropyrimidine derivatives **6a** and **6b**, respectively. Results are reported in Table 2 and yields are related to purified products.

As it can be seen in Table 2, the best results were achieved by reacting 1,4-dihydropyrimidine derivatives **4a**, **4d** with a large amount of $NaBH_4$, while the palladium on charcoal did not influence the reaction. Smaller amounts of $NaBH_4$ left some of the starting 1,4-dihydropyrimidine compound **4a** in an incomplete reaction. No better results were obtained by using $LiAlH_4$ for derivative **4a**, while the catalytic hydrogenation reaction carried out on **4d** allowed to isolate **6b** in low yield (about 20%), while no other identifiable compounds were isolated from the crude reaction product.

Table 2
Reaction of 1,4-dihydropyrimidines **4a** and **4d** with reducing agents: effect of the experimental condition on **6a**, **6b** yields



(*E*) **4a, 4d** (*Z*) **6a-b**

4	R^1	R^2
a	Ph	CH_2Ph
d	Ph	CH_2CH_2OH

6	R^1	R^2
a	Ph	CH_2Ph
b	Ph	CH_2CH_2OH

1,4-Dihydropyrimidine **4**	Experimental conditions	Yields of isolated products(%)
4a	$NaBH_4$ 4 equiv, MeOH	**6a** (30), **4a** (10)
4a	$NaBH_4$ 4 equiv, 0.1 equiv Pd10%C, MeOH	**6a** (30), **4a** (10)
4a	$NaBH_4$ 6 equiv, MeOH	**6a** (60)
4a	$NaBH_4$ 6 equiv, 0.1 equiv Pd10%C, MeOH	**6a** (55)
4a	$LiAlH_4$ 4 equiv, THF	**6a** (50)
4d	H_2/10%Pd/C, EtOH	**6b** (20)
4d	$NaBH_4$ 6 equiv, MeOH	**6b** (55)

Generally, the different adopted experimental conditions never affected the nature of the major product. In all the selected cases, the reduction occurred on the amidinic C-2=C-3 double bond, affording 4-nitromethylene-1,2,3,4-tetrahydropyrimidines **6a**, **6b** as the only detected products.

Although the exocyclic double bond of the 4-nitromethylene-1,4-dihydropyrimidines **4a**, **4d** had the (*E*) configuration, the 4-nitromethylene-1,2,3,4-tetrahydropyrimidines **6a**, **6b** were exclusively detected as the (*Z*) isomers.

The structure assignment for compounds **6a**, **6b** is based on the literature data available for similar substitution patterns,[15] and on the spectroscopic data collected for the 1,2,3,4-tetrahydropyrimidine derivative **6a**.

The ^{1}H NMR spectrum of 1,2-dibenzyl-6-methyl-4-(nitromethylene)-1,2,3,4-tetrahydropyrimidine **6a** ($CDCl_3$ at 300 MHz) showed two doublets at δ 3.77 and 4.54 (J=16.5 Hz), two sets of signals at δ 3.03 and 3.16 (J=13.1, 7.1, 6.5 Hz)[16] and a complex multiplet at δ 4.86. Three singlets at δ 2.09, 4.96, 6.58 and an exchangeable proton signal at δ 9.91, related to the NH, were also observed. The latter signal was also validated by the IR ($CHCl_3$) stretching at 3254 cm^{-1}.

The protons, carbons and the exocyclic double bond stereochemistry assignments were made by two-dimensional NMR experiments. An HSQC experiment allowed the attribution of the CH-2 (δ 4.86, 69.8), the CH-5 (δ 4.96, 92.5) and the nitromethylene proton (C=C*H*–NO_2, δ 6.58, 106.6).

The quaternary carbon was assigned from the results of an HMBC experiment.

The NOESY experiment displayed spatial proximity between the H-2 (δ 4.86) and both the CH_2 linked to C-2 (δ 3.03 and 3.16) and benzyl CH_2 on N-1 (δ 3.77 and 4.54) as well as with the NH exchangeable proton at δ 9.91. A positive Overhauser effect proved the spatial proximity of the CH-5 (δ 4.96) to the methyl group (δ 2.09) on C-6 as well as to the exocyclic H signal (δ 6.58), thus validating the double bond (*Z*) configuration.

^{1}H and ^{13}C NMR data recorded in C_6D_6 (see Section 4) and related 1,2,3,4-tetrahydropyrimidine derivative **6a** supported in all cases the reported structure.

The experimental results can be rationalized as depicted in Scheme 4.

Both catalytic hydrogenation and chemical reduction by $NaBH_4$ gave rise to the labile intermediate **G** as the (*E*) isomer. Ethanol or methanol, polar solvents, favouring the tautomeric equilibrium[17] between species **G** and **H**, promoted the achievement of the (*Z*) isomer.

Imino amidine bond reduction is uncommon up to date,[18] and hitherto available reactions involve reductive cleavage of amidines.[18a] The reported results highlight the weight of the NO_2 group over both the reduction site of the 1,4-dihydropyrimidine compounds **4** and the stereochemistry of the resulting 1,2,3,4-tetrahydropyrimidine derivatives **6**. The conjugated nitromethylene group enhances the reactivity at the imino bond, favouring the reduction reaction. The exclusive formation of the (*Z*) isomer is due to a strong stabilization by an intramolecular hydrogen bond, and it is known to occur with other β-amino derivatives of nitroolefins.[4,19,15b]

3. Conclusions

We have described the preparation of 4-nitromethylene-1,4-dihydropyrimidine derivatives **4** as pyrimidine nucleoside analogues through a one-pot reaction between amidines **3** and primary amines, adding further proof of the utility of substituted 2*H*-pyran-2-one acetamidines as building blocks in organic synthesis.

We have reported the preparation of several 4-nitromethylene-1,2,3,4-tetrahydropyrimidine derivatives **6** through reduction reactions of the derivatives **4**.

4. Experimental

4.1. General

Melting points were determined using a Buchi 510 (capillary) or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured using Perkin–Elmer FT-IR 16 P.C. (Nujol) and Perkin–Elmer FT-IR 'Spectrum One' (KBr, $CHCl_3$ spectroscopic grade) spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 MHz or on a Bruker Avance 300 or on Bruker Avance 500 spectrometer in $CDCl_3$ solution, unless otherwise stated. Chemical shifts are expressed in parts per million from internal standard tetramethylsilane (δ) and coupling constants (J) are given in hertz. Mass spectroscopy data (MS) were obtained by electron impact ionization (EI) (70 eV) on ThermoQuest MD 800 or by electrospray ionization (ESI) on ThermoFinnigan 'LCQ Advantage'. Column chromatography was performed on Kieselgel 60 (Merck) 0.063–0.200 mm with eluants and ratios indicated below.

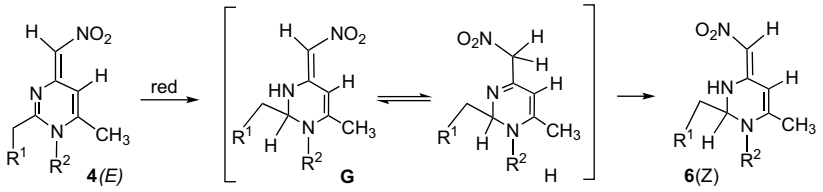
Materials. Enamines **2a**,[20] **2b**,[21] **2c**[22] are known compounds. 4-Chloro-3-nitro-2*H*-pyran-2-one **1** and amidines **3a**–**c** have already been described.[5]

4.2. Deprotection procedure for *trans*-2-aminocyclohexanol hydrochloride

To a vigorously stirred solution of NaOMe in MeOH (0.070 g, 3 mmol of Na in 6 mL of MeOH) was added *trans*-2-aminocyclohexanol hydrochloride (0.365 g, 2.4 mmol).The mixture was stirred for 1 h at room temperature. The precipitated NaCl was removed by filtration through Celite and the filter cake was rinsed with MeOH (5 mL). The solvent was removed under reduced pressure to provide *trans*-2-aminocyclohexanol, which was sufficiently pure for the next step.

4.3. General procedure for the synthesis of 4-(nitromethylene)-1,4-dihydropyrimidine 4a–i

Amidines **3a**–**c** (2 mmol) suspended in ethanol (20 mL) with an equimolar amount of the suitable amine were put in a preheated oil bath at 50 °C. The reaction mixture was heated for the reaction times indicated in Table 1 until disappearance (TLC monitoring) of the starting amidine.



Scheme 4. Suggested mechanism for the formation of **6**.

The workup of the reaction mixture was strongly dependent on amine and amidine used. Therefore we describe separately the workup of the reaction mixtures obtained.

Method A. The mixture was cooled to room temperature to give a solid product, which was recrystallized from ethanol to afford pure the 1,4-dihydropyrimidine derivatives **4a** or **4d**, respectively.

Method B. The solvent was removed in vacuo and the crude residue was purified through a short silica gel column (eluant indicated later) affording 1,4-dihydropyrimidine derivatives **4b** as a thick orange oil and **4c**, **4f**, **4g**, **4h** afterwards recrystallized from $^{i}Pr_2O$. The crude reaction mixtures arising from amidines **3a** and **3b** reacting with *trans*-2-aminocyclohexanol were instead separated by silica gel column (eluant indicated later) giving a first fraction containing the compounds **4e** and **4i**, and a second fraction containing the pyrimidine derivatives **5a** and **5b**,[5] respectively, as a minor product. Both derivatives **4e** and **4i** were crystallized as indicated. ^{1}H NMR (C_6D_6) for **5a** and **5b** were in accordance with the corresponding data of authentical samples previously obtained.[5]

4.3.1. (E)-1,2-Dibenzyl-6-methyl-4-(nitromethylene)-1,4-dihydropyrimidine ***4a***

Yellow powder from ethanol, mp 150 °C; IR ν_{max} (KBr) 1629 (C=N), 1546 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz) δ 2.28 (3H, s, CH_3), 3.99 (2H, s, CH_2C$_6$H$_5$), 5.08 (2H, s, NCH_2C$_6$H$_5$), 6.98–7.44 (10H, m, ArH), 7.16 (1H, s, HC=), 8.02 (1H, s, H-5); ^{13}C NMR (75 MHz) δ 20.7 (CH_3), 42.1 (CH_2C$_6$H$_5$), 51.1 (NCH_2C$_6$H$_5$), 109.7 (CH-5), 118.4 (HC=), 125.2, 128.2, 128.5, 129.0, 129.7, 130.1 (ArCH), 134.1, 134.5 (ArCqu), 151.9 (C-6), 156.1 (C-4), 159.6 (C-2); (EI): *m*/*z* (% relative intensity) 333 [M$^+$] (15), 287 [M$^+$−NO_2] (12), 197 (13), 91 (100). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.85; H, 5.74; N, 12.44.

4.3.2. (E)-2-Benzyl-6-methyl-4-(nitromethylene)-1-propyl-1,4-dihydropyrimidine ***4b***

AcOEt/cyclohexane, 8:2; thick orange oil; IR ν_{max} (KBr) 1630 (C=N), 1553 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz) δ 0.86 (3H, t, *J*=7.3 and 7.7 Hz, CH_3CH$_2$), 1.48 (2H, sex, *J*=7.3 and 7.7 Hz, CH$_3$CH_2), 2.31 (3H, s, CH_3), 3.68–3.80 (2H, m, CH_2N), 4.08 (2H, s, CH_2C$_6$H$_5$), 6.93 (1H, s, HC=), 7.15–7.31 (5H, m, ArH), 7.84 (1H, s, H-5); ^{13}C NMR (50 MHz) δ 11.2 (*C*H$_3$CH$_2$CH$_2$), 20.3 (CH_3), 23.6 (CH$_3$*C*H$_2$CH$_2$), 42.0 (*C*H$_2$C$_6$H$_5$), 50.0 (CH$_3$CH$_2$*C*H$_2$*N*), 110.0 (CH-5), 117.3 (HC=), 128.0, 128.5, 129.0, 129.4 (ArCH), 134.7 (ArCqu), 151.7 (C-6), 156.5 (C-4), 159.0 (C-2); ESI-MS: *m*/*z* (% relative intensity): 308 [M+Na] (100), 286 [M+1] (92), 242 [M+1−46, NO_2] (39). Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.17; H, 6.61; N, 14.62.

4.3.3. (E)-2-Benzyl-1-(4-methoxyphenyl)-6-methyl-4-(nitromethylene)-1,4-dihydropyrimidine ***4c***

AcOEt/cyclohexane, 7:3; beige amorphous powder from $^{i}Pr_2O$, mp 118 °C; IR ν_{max} (KBr) 1639 (C=N), 1553 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 1.31 (3H, s, CH_3), 3.13 (s, 3H, OCH_3), 3.55 (2H, s, CH_2C$_6$H$_5$), 6.40 and 6.54 (4H, *J*=8.8 Hz, ArH), 6.80–7.02 (5H, m, ArH), 7.63 (1H, s, HC=), 8.08 (1H, s, H-5); ^{13}C NMR (50 MHz) δ 21.4 (CH_3), 42.1 (*C*H$_2$C$_6$H$_5$), 55.9 (OCH_3), 108.0 (CH-5), 118.3 (HC=), 115.3, 127.4, 128.7, 128.8, 129.2 (ArCH), 129.8, 134.9 (ArCqu), 152.3 (C-6), 156.3 (C-4), 159.5 (Ar*C*OCH$_3$), 160.8 (C-2); ESI-MS: *m*/*z* (% relative intensity): 350 [M+1] (100), 304[M+1−46, NO_2] (4). Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.64; H, 5.33; N, 12.12.

4.3.4. (E)-2-(2-Benzyl-6-methyl-4-(nitromethylene)pyrimidin-1(4H)-yl)ethanol ***4d***

Deep yellow powder from ethanol, mp 205 °C; IR ν_{max} (KBr) 3308 (OH), 1624 (C=N), 1547 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.47 (3H, s, CH_3), 3.62–3.72 (2H, m, CH_2OH), 4.05–4.12 (2H, m, CH_2N), 4.27 (s, 2H, CH_2C$_6$H$_5$), 5.25 (1H, t, *J*=5.5 Hz, OH exchangeable), 6.76 (1H, s, HC=), 7.19–7.39 (5H, m, ArH), 7.86 (1H, s, H-5); ^{13}C NMR (50 MHz, DMSO-d_6) δ 21.2 (CH_3), 41.1 (*C*H$_2$C$_6$H$_5$), 50.8 (NCH_2), 60.2 (HOCH_2), 109.2 (CH-5), 115.3 (HC=), 127.7, 129.3, 129.4 (ArCH), 136.0 (ArCqu), 155.5 (C-6), 157.2 (C-4), 161.0 (C-2); ESI-MS: *m*/*z* (% relative intensity): 310 [M+Na] (18), 288 [M+1] (100), 242 [M+1−46, NO_2] (45). Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.56; H, 5.92; N, 14.52.

4.3.5. (E)-2-(2-Benzyl-6-methyl-4-(nitromethylene)pyrimidin-1(4H)-yl)cyclohexanol ***4e***

EtOAc/methanol, 95:5; deep yellow powder from ethanol, mp 238 °C; IR ν_{max} (KBr) 3399 (OH), 1627 (C=N), 1551 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.60–2.20 (8H, m, CH_2 CH_2 CH_2 CH_2), 2.55 (3H, s, CH_3), 3.86–4.00 (1H, m, C*H*OH), 4.06–4.38 (1H, m, C*H*N-1), 4.17 and 4.54 (2H, 2×d, *J*=15.4 Hz, $CH_2C_6H_5$), 5.45 (1H, d, *J*=5.5 Hz, OH exchangeable), 6.81 (1H, s, HC=), 7.16–7.40 (5H, m, ArH), 7.81 (1H, s, H-5); ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.7 (CH_3), 24.2, 25.8, 30.2, 36.4 (4×CH_2), 43.7 ($CH_2C_6H_5$), 69.3 (C*H*N-1), 69.5 (C*H*OH), 111.1 (CH-5), 115.2 (HC=), 129.0, 129.6, 129.7 (Ar–CH), 136.2 (ArCqu), 155.2 (C-6), 156.7 (C-4), 162.0 (C-2); ESI-MS: *m*/*z* (% relative intensity): 364 [M+Na] (28), 342 [M+1] (100), 296 [M+1−46, NO_2] (30). Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.89; H, 6.68; N, 12.20.

4.3.6. (E)-1-Benzyl-6-methyl-4-(nitromethylene)-2-phenethyl-1,4-dihydropyrimidine ***4f***

CH_2Cl_2/Et_2O, 1:1; pale nut crystals from $^{i}Pr_2O$, mp 125 °C; IR ν_{max} (Nujol) 1625 (C=N), 1552 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz) δ 2.27 (3H, s, CH_3), 2.89–2.97 and 3.03–3.11 (4H, 2×m, *CH*$_2$*CH*$_2$C$_6$H$_5$), 5.07 (s, 2H, NCH_2C$_6$H$_5$), 6.90–7.42 (11H, m, ArH+HC=), 7.95 (1H, s, H-5); ^{13}C NMR (50 MHz) δ 20.6 (CH_3), 32.7 (*C*H$_2$CH$_2$C$_6$H$_5$), 35.8 (CH$_2$*C*H$_2$C$_6$H$_5$), 50.8 (NCH$_2$C$_6$H$_5$), 109.5 (CH-5), 117.5 (HC=), 125.1, 126.7, 128.7, 128.8, 129.9 (10×ArCH), 133.9, 140.2 (ArCqu), 152.0 (C-6), 156.4 (C-4), 160.3 (C-2); ESI-MS: *m*/*z* (% relative intensity): 348 [M+1] (100), 302 [M+1−46, NO_2] (100). Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.43; H, 6.16; N, 12.07.

4.3.7. (E)-1-Benzyl-6-methyl-4-(nitromethylene)-2-propyl-1,4-dihydropyrimidine ***4g***

CH_2Cl_2/Et_2O, 1:1; pale nut powder from $^{i}Pr_2O$, mp 148 °C; IR ν_{max} (Nujol) 1620 (C=N), 1540 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz) δ 0.94 (3H, t, *J*=7.0 Hz, *CH*$_3$CH$_2$), 1.62–1.82 (2H, m, CH$_3$*CH*$_2$), 2.29 (3H, s, CH_3), 2.56–2.64 (2H, m, CH_2 on C-2), 5.19 (2H, s, NCH_2C$_6$H$_5$), 7.04 (1H, s, HC=), 6.97–7.07 and 7.34–7.42 (5H, 2×m, ArH), 7.94 (1H, s, H-5); ^{13}C NMR (50 MHz) δ 13.8 (*C*H$_3$), 20.3 (CH$_3$*C*H$_2$CH$_2$), 20.6 (CH_3), 36.3 (*C*H$_2$ on C-2), 50.9 (NCH_2C$_6$H$_5$), 109.5 (CH-5), 117.3 (HC=), 125.1, 128.7, 129.8 (ArCH), 134.1 (ArCqu), 152.2 (C-6), 156.7 (C-4), 161.2 (C-2); ESI-MS: *m*/*z* (% relative intensity): 308 [M+Na] (100), 286 [M+1] (12), 240 [M+1−46, NO_2] (100). Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.45; H, 6.62; N, 14.60.

4.3.8. (E)-2-(6-Methyl-4-(nitromethylene)-2-propylpyrimidin-1(4H)-yl)ethanol ***4h***

CH_3CN/CH_3OH, 95:5; pale orange powder from $^{i}Pr_2O$, mp 143 °C; IR ν_{max} (Nujol) 1620 (C=N), 1540 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.94 (3H, t, *J*=7.3 Hz, *CH*$_3$CH$_2$CH$_2$), 1.66 (2H, sex, *J*=7.3 and 7.7 Hz, CH$_3$*CH*$_2$CH$_2$), 2.47 (3H, s, CH_3), 2.83 (2H, t, *J*=7.7 Hz, CH_2 on C-2), 3.64–3.72 (2H, m, CH_2OH), 4.11–4.17 (2H, m, CH_2N), 5.16 (1H, t, *J*=5.5 Hz, OH exchangeable), 6.75 (1H, s, HC=), 7.84 (1H, s, H-5); ^{13}C NMR (50 MHz, DMSO-d_6) δ 14.1 (*C*H$_3$CH$_2$CH$_2$), 20.4 (CH$_3$*C*H$_2$CH$_2$), 21.3 (CH_3), 36.1 (*C*H$_2$ on C-2), 50.3 (*NCH*$_2$), 60.1 (HO*C*H$_2$), 108.8 (CH-5), 115.1 (HC=), 155.1 (C-6), 157.3 (C-4), 162.3 (C-2); ESI-MS: *m*/*z* (% relative intensity): 262 [M+Na] (32), 240

[M+1] (100), 194 [M+1−46, NO_2] (23). Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.18; H, 7.27; N, 17.42.

*4.3.9. (E)-2-(6-Methyl-4-(nitromethylene)-2-propylpyrimidin-1(4H)-yl)cyclohexanol **4i***

Yellow powder from ethanol, mp 178 °C; IR ν_{max} (Nujol) 3330 (OH), 1620 (C=N), 1550 (NO_2) cm^{-1}; ^1H (300 MHz, DMSO-d_6) δ 0.94 (3H, t, J=7.3 Hz, $CH_3CH_2CH_2$), 1.25–1.42 (2H, m, CH_2 ring), 1.71–1.81 and 1.99–2.07 (8H, 2×m, CH_2 CH_2 CH_2 ring+CH_3CH_2), 2.58 (3H, s, CH_3 on C-6), 2.87 (2H, t, J=7.3 Hz, CH_2 on C-2), 4.06 (1H, s, CHOH), 4.17 (1H, m, CH-N1), 5.12 (1H, s, OH exchangeable), 6.76 (1H, s, HC=), 7.73 (1H, s, H-5); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.2 (CH_3), 21.4 (CH_2), 22.9 (CH_3 on C-6), 24.3, 26.1, 30.6, 36.5 (4×CH_2 ring), 37.8 (CH_2 on C-2), 68.3 (CHN-1), 69.6 (CHOH), 110.0 (CH-5), 114.7 (HC=), 155.8 (C-6), 156.9 (C-4), 162.9 (C-2); ESI-MS: m/z (% relative intensity): 316 [M+Na] (100), 294 [M+1] (29), 248[M+1−46, NO_2] (15). Anal. Calcd for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.45; H, 8.03; N, 14.21.

4.4. Reaction of amidine 4a with glycine methyl ester hydrochloride: synthesis of (*E*)-methyl 2-(2-benzyl-6-methyl-4-(nitromethylene)pyrimidin-1(4*H*)-yl)acetate 4j

TEA (5.6 mL, 4 mmol) was added to a stirred suspension of glycine methyl ester hydrochloride (0.502 g, 4 mmol) in CH_2Cl_2 (15 mL). After an additional 30 min stirring, amidine **3a** (0.715 g, 2 mmol) was then added in CH_2Cl_2 (15 mL) solution. The reaction mixture was heated at 35 °C for 6 h until disappearance (TLC monitoring) of the starting compound **3a**, then quenched with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with H_2O (60 mL), dried with Na_2SO_4 and then evaporated in vacuo. The crude residue was purified through a short silica gel column (CH_2Cl_2/acetone/Et_2O, 7:2:1) affording **4j**. Yield 78%, yellow crystals, mp 145 °C; IR ν_{max} (KBr) 1736 (C=O), 1638 (C=N), 1560 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ 2.23 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 4.03 (2H, s, $CH_2C_6H_5$), 4.55 (2H, s, NCH_2COOCH_3), 7.11 (1H, s, HC=), 7.18–7.40 (5H, m, ArH), 7.90 (1H, s, H-5); ^{13}C NMR (50 MHz) δ 20.3 (CH_3), 42.4 ($CH_2C_6H_5$), 49.0 (NCH_2COOCH_3), 53.4 (OCH_3), 108.9 (CH-5), 118.6 (HC=), 128.0, 128.7, 129.4 (ArCH), 133.6 (ArCqu), 151.2 (C-6), 155.4 (C-4), 158.7 (C-2), 166.7 (C=O); ESI-MS: m/z (% relative intensity): 338 [M+Na] (100), 316 [M+1] (10), 270 [M+1−46, NO_2] (26). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.88; H, 5.45; N, 13.15.

4.5. Reaction of the 4-(nitromethylene)-1,4-dihydropyrimidines 4a, 4d with $NaBH_4$: synthesis of compounds 6a, 6b

To a stirred suspension of **4a** (0.333 g, 1 mmol) or **4d** (0.287 g, 1 mmol) in MeOH (25 mL) at 0 °C was added, in portions, $NaBH_4$ (0.227 g, 6 mmol). The reaction mixture was stirred at room temperature until disappearance (about 2 h, TLC monitoring) of starting compounds **4a** or **4d**. The mixture was quenched with water and extracted with CH_2Cl_2 (4×30 mL). The combined organic layers were washed with H_2O (80 mL), dried with Na_2SO_4 and then evaporated in vacuo. The crude residue was purified through a short silica gel column (eluant indicated later) affording the corresponding 4-(nitromethylene)-1,4-dihydropyrimidine derivatives **6a** or **6b**, respectively, in pure form. Isolated yields of the products **6a** and **6b** are listed in Table 2.

*4.5.1. (Z)-1,2-Dibenzyl-6-methyl-4-(nitromethylene)-1,2,3,4-tetrahydropyrimidine **6a***

CH_2Cl_2/acetone, 8:2; yellow crystals, mp 153–154 °C; IR ν_{max} ($CHCl_3$) 3254 (NH), 1593 (C=C), 1542 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ 2.09 (3H, s, CH_3), 3.03 and 3.16 (2H, 2×dd, J=13.1, 7.1, 6.5 Hz, $CH_2C_6H_5$), 3.77 and 4.54 (2H, 2×d, J=16.5 Hz, $NCH_2C_6H_5$), 4.86 (1H, m, H-2), 4.96 (1H, s, H-5), 6.58 (1H, s, HC=), 7.08–7.40 (10H, m, ArH), 9.91 (1H, br s exchangeable, NH); ^1H NMR (500 MHz, C_6D_6) δ 1.36 (3H, s, CH_3), 2.69 and 2.87 (2H, 2×dd, J=12.9, 7.7, 5.8 Hz, $CH_2C_6H_5$), 3.25 and 3.86 (2H, 2×d, J=16.6 Hz, $NCH_2C_6H_5$), 4.36–4.40 (1H, m, H-2), 4.44 (1H, s, H-5), 6.80 (1H, s, HC=), 6.85–7.26 (10H, m, ArH), 10.05 (1H, br s exchangeable, NH); ^{13}C NMR (75 MHz) δ 20.2 (CH_3), 37.6 ($CH_2C_6H_5$), 54.0 ($NCH_2C_6H_5$), 69.8 (CH-2), 92.5 (CH-5), 106.6 (HC=), 126.9, 127.8, 128.6, 129.2, 129.6, 129.9 (10×ArCH), 135.3, 136.0 (ArCqu), 151.9 (C-6), 154.5 (C-4); ^{13}C NMR (125.7 MHz, C_6D_6) δ 18.7 (CH_3), 37.3 ($CH_2C_6H_5$), 53.5 ($NCH_2C_6H_5$), 69.5 (CH-2), 92.1 (CH-5), 106.8 (HC=), 126.3, 126.9, 127.7, 128.9, 129.7 (10×ArCH), 135.8, 136.7 (ArCqu), 150.5 (C-6), 151.7 (C-4); ESI-MS: m/z (% relative intensity): 358 [M+Na] (100), 336 [M+1] (92), 289 [M+1−46, NO_2] (100). Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.75; H, 6.44; N, 12.35.

*4.5.2. (Z)-2-(2-Benzyl-6-methyl-4-(nitromethylene)-3,4-dihydropyrimidin-1(2H)-yl) ethanol **6b***

CH_3CN/MeOH, 95:5; orange thick oil; IR ν_{max} ($CHCl_3$) 3271 (NH), 3018 (OH), 1593 (C=C), 1547 (NO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.06 (3H, s, CH_3), 2.73–2.88 (1H, m, CH_2N), 2.88–3.04 (2H, m, $CH_2C_6H_5$), 3.06–3.43 (2H+1H, m, CH_2OH and CH_2N), 4.89 (1H, br s exchangeable, OH), 4.95 (1H, s, H-5), 5.19 (1H, s, H-2), 6.42 (1H, s, HC=), 7.15–7.35 (5H, m, ArH), 9.63 (1H, br s exchangeable, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.1 (CH_3), 36.6 ($CH_2C_6H_5$), 52.6 (CH_2N), 60.5 (CH_2OH), 69.2 (CH-2), 91.5 (CH-5), 105.2 (HC=), 127.5, 129.2, 130.5 (ArCH), 136.7 (ArCqu), 152.0 (C-6), 156.3 (C-4); ESI-MS: m/z (% relative intensity): 290 [M+1] (100), 243 [M+1−46, NO_2] (35). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.37; H, 6.53; N, 14.43.

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