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SYNTHESIS OF 1-ARYL-1,4,5,6-TETRAHYDROPYRIMIDINES AND 1-ARYL-3-SUBSTITUTED 1,4,5,6-TETRAHYDROPYRIMIDINIUM SALTS

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Abstract- A synthetic approach to 1-aryl-1,4,5,6-tetrahydropyrimidines (**1**) is described, by ring closure of *N*-aryl-*N'*-formyl-1,3-propanediamines (**5**) with trimethylsilyl polyphosphate (PPSE). Quaternization of compounds (**1**) with methyl (or ethyl) iodide led to the corresponding cyclic amidinium salts (**2**), while treatment of compound (**1a**) with 2,4-dinitrochlorobenzene yielded an open chain product resulting from hydrolysis of the salt. An alternative method was employed for the synthesis of 1-aryl-1,4,5,6-tetrahydropyrimidinium salts bearing a branched alkyl or an aryl substituent on N3, not accessible through alkylation. Such compounds were obtained in high yields by dehydrogenation of the corresponding hexahydropyrimidines (**3**). The scope and limitations of both procedures are discussed.

INTRODUCTION

The synthesis of 1,4,5,6-tetrahydropyrimidines is a subject of interest due to the pharmacological activity of some members, which behave as anthelmintics[1] and antidepressants[2] among other actions. Typically, such properties arise from the affinity of the cyclic amidine system for several types of cholinergic receptors. Recently, Dunbar and coworkers have explored the use of some 2-unsubstituted tetrahydropyrimidines as selective M_1 agonists acting at the central nervous system, in the search of new therapeutical agents for the treatment of Alzheimer´s disease.[3]

Quaternary 1,4,5,6-tetrahydropyrimidinium salts (**2**) have been studied as N^5,N^{10}-methenyltetrahydrofolic acid models,[4] although less than the five-membered homologous dihydroimidazolium salts.[5] Recently, 2-

unsubstituted 1,4,5,6-tetrahydropyrimidinium salts have been used by Alder *et al.* for the synthesis of stable heteroatomic carbene complexes,[6] potentially useful as catalysts. They have also found application as models to evaluate the relative importance of steric and stereoelectronic effects in nucleophilic additions to nitrogen heterocycles.[7] Data in the literature are generally limited to 1-alkyl-tetrahydropyrimidines and symmetrically *N,N´*-dialkyl substituted tetrahydropyrimidinium salts, while *N*-aryl derivatives have been less studied. In previous work we reported the alkaline hydrolysis and reduction of 1,2-diaryl-3-methyltetrahydropyrimidinium salts[8,9] and 1-aryl-2-alkyltetrahydropyrimidines.[10] In connection to our investigation about nucleophilic additions and related stereoelectronic effects in such systems, we recently needed to prepare some 2-unsubstituted *N*-aryl-1,4,5,6-tetrahydropyrimidines and their salts. The classic synthesis of tetrahydropyrimidines involves the condensation of suitably substituted 1,3-diaminopropanes with carboxylic acid derivatives,[11] but for *N*-aryl derivatives the preparation of the diamines becomes a limiting factor. Furthermore, such procedures are often conditioned by the high temperatures and/or prolongued reaction times generally required for the cyclization.[12] In previous work we developed a method for the synthesis of 1,2-diaryl- and 1-aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines by ring closure of the corresponding *N*-acyl-*N´*-aryltrimethylenediamines.[10,13] In this work we extended the method to the synthesis of 2-unsubstituted derivatives (**1**) employing trimethylsilyl polyphosphate (PPSE). PPSE is a mild aprotic dehydrating agent and has been employed in Beckmann rearrangements,[14] nucleophilic substitutions,[15] aldol condensations[16] and in the synthesis of heterocyclic compounds, which include indoles,[17] isoquinolines,[17] coumarins[17] and dihydroisoquinolines among others.[18]

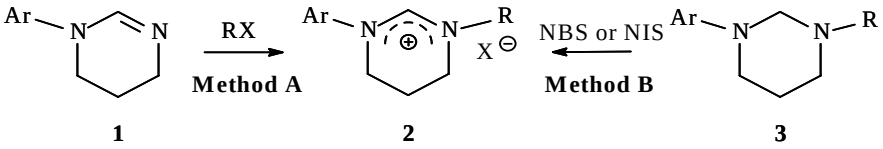
Quaternization of tetrahydropyrimidines (**1a,c-e**) with alkyl halides led to the corresponding *N*-aryl-*N´*-methyl- (or ethyl)-1,4,5,6-tetrahydropyrimidinium salts (**2a-e**) (Scheme 1, Method A). This method was only suitable for the introduction of nonbranched primary alkyl groups. Alternatively, compounds (**2f-k**) were synthesized by dehydrogenation of the corresponding hexahydropyrimidines (**3**) (Scheme 1, Method B). The scope and limitations of both procedures are discussed taking into account the availability and stability of the precursor heterocycles.

RESULTS AND DISCUSSION

The sequences employed for the synthesis of 1,4,5,6-tetrahydropyrimidines (**1**), hexahydropyrimidines (**3**) and tetrahydropyrimidinium salts (**2**) are depicted in Scheme 2.

Tetrahydropyrimidines (**1**) were synthesized by ring closure of the corresponding *N*-aryl-*N´*-formyltrimethylenediamines (**5**) (R'=H), themselves obtained by selective formylation of *N*-aryltrimethylenediamines (Scheme 2, Route a, step e).[19]

Scheme 1



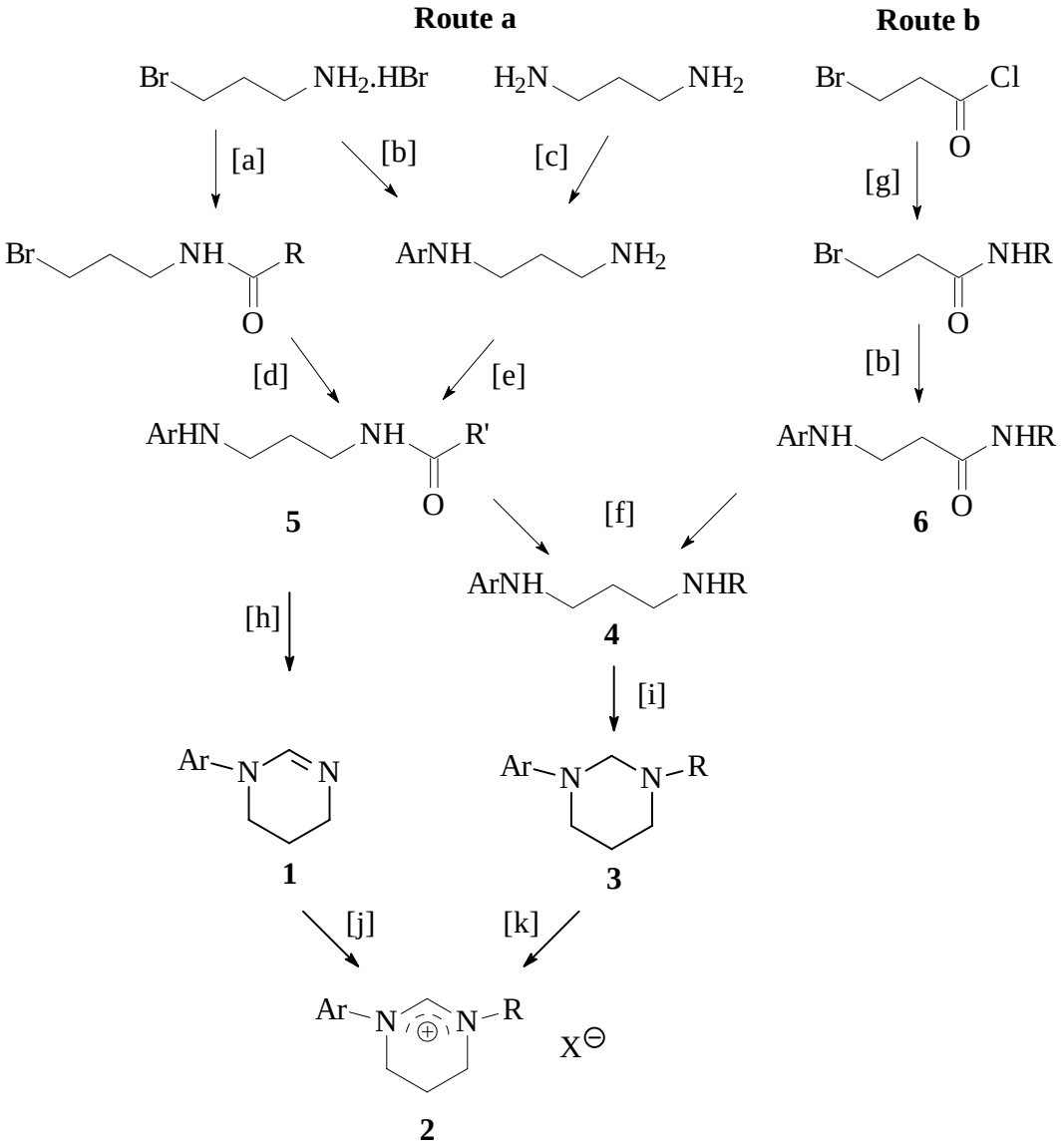
Compd. 1,2,3	Ar	R	X	Method
a	*o*-$CH_3C_6H_4$	CH_3	I	A
b	*o*-$CH_3C_6H_4$	C_2H_5	I	A
c	*p*-$CH_3OC_6H_4$	CH_3	I	A
d	*p*-ClC_6H_4	CH_3	I	A
e	*o*-$NO_2C_6H_4$	CH_3	I	A
f	*p*-ClC_6H_4	CH_3	Br	B
g	*p*-ClC_6H_4	C_2H_5	Br	B
h	*p*-ClC_6H_4	*iso*-C_4H_9	I	B
i	*p*-ClC_6H_4	*tert*-$C_4H_9CH_2$	Br	B
j	*p*-ClC_6H_4	*tert*-C_4H_9	Br	B
k	*p*-ClC_6H_4	C_6H_5	Br	B

In previous work, cyclodehydration of *N*-aryl-*N´*-alkanoyl- (or aroyl)-trimethylenediamines (**5**) (R'= alkyl or aryl) was performed with PPE with good yields (reaction time: 5 hours).[10,13] Treatment of *N*-(*p*-chlorophenyl)-*N´*-formyl-1,3-propanediamine (**5**, R'=H, Ar=*p*-ClC_6H_4) with PPE for 10 hours led to a mixture of starting material and the corresponding amidine (**1d**) in low yields. The employment of PPSE in dichloromethane solution, instead, led to high yields of tetrahydropyrimidines (**1**). The observed difference was attributed to the virtually aprotic nature of PPSE and to an inherently superior dehydrating efficiency. Due to the absence of a 2-substituent, tetrahydropyrimidines (**1**) are labile towards hydrolysis,[20] so it seemed interesting to avoid aqueous work up of the reaction mixture. For this purpose, reaction of *N*-(*p*-chlorophenyl)-*N´*-formyl-1,3-propanediamine (**5**, R'=H, Ar=*p*-ClC_6H_4) was attempted with heterogeneized PPSE[21] in 1,2-dichloroethane, but starting materials were recovered after 10 hours reflux.

Hexahydropyrimidines (**3**) were synthesized by condensation of *N*-aryl-*N'*-alkyl- (or aryl)-1,3-propanediamines (**4**) with formaldehyde. The main limitation of such synthetic approach is the preparation of the required unsymmetrically *N,N´*-disubstituted 1,3-propanediamines. Such precursors were synthesized by two alternative sequences developed by us in previous work,[22,23] in which one of the

secondary amino groups is generated by aminolysis of a bromo derivative and the other by reduction of an amide.

Scheme 2



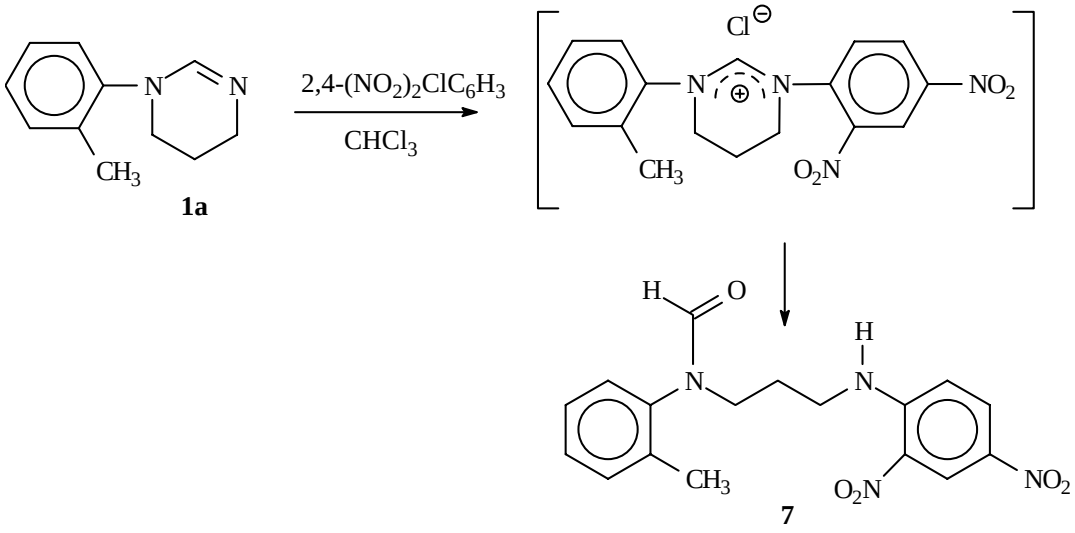
[a] RCOCl or $(RCO)_2O/OH^-$; [b] 2 $ArNH_2$, 100-120°C, 1 h; [c] *o*-chloronitrobenzene, 1 h, reflux; [d] 3 $ArNH_2$/toluene, 100-120°C, 1 h; [e] *p*-nitrophenyl formate/THF, -5°C, 30 min; [f] BH_3/THF, reflux, 3 h; [g] RNH_2/OH^-; [h] PPSE/Cl_2CH_2, reflux, 5 h; [i] formaldehyde/methanol, 30 min, rt; [j] RX, Cl_2CH_2, 2 h, reflux; [k] NBS or NIS/DME, 30 min, rt.

Diamines (**4g,h,i**) were synthesized following Route *a*, which involves reduction of *N*-acyl-*N´*-aryltrimethylenediamines (**5**) (R'= alkyl), themselves obtained either by aminolysis of the corresponding *N*-(3-bromopropyl)amides[22] or by selective monoacylation of *N*-aryl-1,3-propanediamines (Scheme 2).[19] Such method was only applicable to the synthesis of diamines in which the secondary amino group generated by reduction bears a primary alkyl substituent. Alternatively, diamines (**4f,j,k**) were

synthesized by a sequence which involves aminolysis of 3-bromopropanamides followed by reduction of the corresponding 3-arylaminopropanamides (**6**) (Scheme 2, Route b).[23] Condensation of *N*,*N'*-disubstituted 1,3-propanediamines (**4**) with formaldehyde in methanol led to the corresponding aminals with high yields. In contrast to tetrahydropyrimidines, the absence of a 2-substituent enhances the stability of hexahydropyrimidines (**3**) towards hydrolysis.

Quaternization of tetrahydropyrimidines (**1**) with alkyl iodides yielded tetrahydropyrimidinium salts (**2a-e**) with high yields. The alkylation of tetrahydropyrimidines is thought to proceed through SN_2 mechanism and is thus adequate for the introduction of linear primary alkyl groups.[8,11] Quaternization of tetrahydropyrimidine (**1a**) was also attempted with an active aryl halide (2,4-dinitrochlorobenzene). The main product isolated from the reaction mixture was *N*-formyl-*N'*-(2,4-dinitrophenyl)-*N*-(*o*-tolyl)trimethylenediamine (**7**). This compound would originate in the hydrolysis of the corresponding 1,3-diaryltetrahydropyrimidinium salt, which could not be isolated (Scheme 3). Alternatively, the reaction was performed in the presence of equimolar amounts of sodium iodide. Literature indicates that addition of such reagent enhances SNAr reactions,[24] but, in our case, no difference was observed.

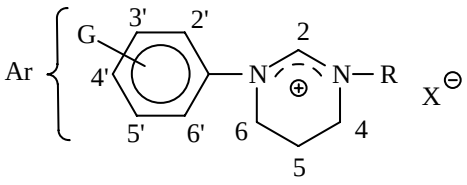
Scheme 3



Synthesis of tetrahydropyrimidinium salts (**2f,g,i-k**) was performed by dehydrogenation of hexahydropyrimidines (**3**) with *N*-bromosuccinimide (NBS) in dimethoxyethane (DME). For compound (**3h**), the reaction was conducted employing *N*-iodosuccinimide (NIS). Yields were comparably high, but NBS was more convenient due to the absence of colateral products arising from the decomposition of the reagent, which complicated the purification of the product in the case of NIS. Both reagents lead to better

results than mercuric acetate/EDTA where subsequent anion exchange is necessary.[25] ^{1}H NMR spectra of compounds (**2a-k**) are listed in Table 1.

Table 1



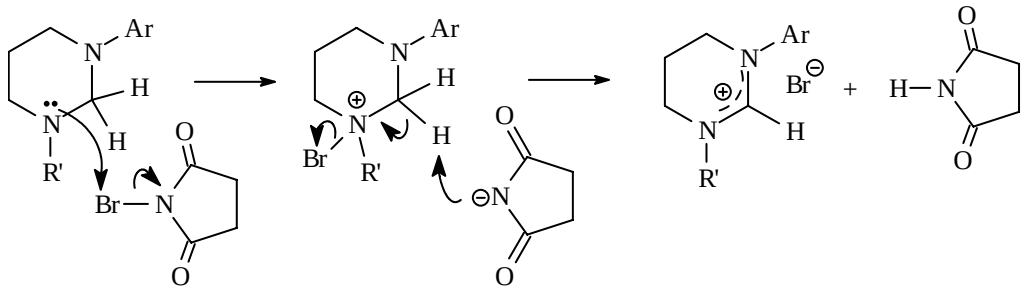
2

Compd.	G	X	R	CH_2 (4 and 6)	CH_2 (5)	CH (2)	Ar	R
2a	*o*-CH_3	I	CH_3	3.69 (t) [a] and 3.78 (t) [a]	2.40 (m)	8.17 (s)	3'-6': 7.27-7.33 (m) and 7.74 (d) [b] $ArCH_3$: 2.36 (s)	3.46 (s)
2b	*o*-CH_3	I	CH_2CH_3 (a) (b)	3.73 (t) [a] and 3.77-3.85 (m) [c]	2.40 (m)	8.19 (s)	3'-6': 7.26-7.34 (m) and 7.74 (d) [d] $ArCH_3$: 2.35 (s)	a: 3.77-3.85 (m) [c] b: 1.41 (t) [e]
2c	*p*-CH_3O	I	CH_3	3.53 (t) [a] and 3.83 (t) [a]	2.30 (m)	8.44 (s)	6.87 (dd) [f] and 7.46 (dd) [f] CH_3O: 3.74 (s)	3.41 (s)
2d	*p*-Cl	I	CH_3	3.58 (t) [d] and 3.94 (t) [g]	2.36 (m)	8.80 (s)	7.38 (dd) [h] and 7.57 (dd) [h]	3.47 (s)
2e	*o*-NO_2	I	CH_3	3.64 (t) [i] and 3.82 (t) [i]	2.41 (m)	8.15 (s)	4', 5': 7.83 (t) [j] and 7.65 (m) 3', 6': 8.65 (d) [j] and 8.13 (d) [k]	3.42 (s)
2f	*p*-Cl	Br	CH_3	3.59 (t) [d] and 3.91 (t) [d]	2.34 (m)	9.05 (s)	7.39 (dd) [f] and 7.56 (dd) [f]	3.52 (s)
2g	*p*-Cl	Br	CH_2CH_3 (a) (b)	3.60 (t) [l] and 3.89-3.94 (m) [c]	2.34 (m)	9.01 (s)	7.41 (d) [m] and 7.57 (d) [m]	a: 3.89-3.94 (m) [c] b: 1.36 (t) [n]
2h	*p*-Cl	I	$CH_2CH(CH_3)_2$ (a) (b) (c)	3.68 (t) [l] and 4.02 (t) [l]	2.46 (m)	8.34 (s)	7.48 (d) [m] and 7.52 (d) [m]	a: 3.61 (d) [j] b: 2.16 (m) c: 1.03 (d) [o]
2i	*p*-Cl	Br	$CH_2C(CH_3)_3$ (a) (b)	3.71 (t) [g] and 3.96 (t) [g]	2.33 (m)	8.74 (s)	7.37 (d) [p] and 7.61 (d) [p]	a: 2.67 (s) b: 1.01 (s)
2j	*p*-Cl	Br	$C(CH_3)_3$	3.73 (t) [q] and 3.96 (t) [q]	2.33 (m)	8.02 (s)	7.37 (d) [r] and 7.63 (d) [r]	1.56 (s)
2k	*p*-Cl	Br	C_6H_5	4.18 [i]	2.57 [i]	8.26 (s)	7.28-7.47 (m, 5 H) and 7.52-7.74 (m, 4 H)	

[a] J=5.6 Hz, [b] J=7.4 Hz, [c] overlapping signals, [d] J=5.9 Hz, [e] J=7.3 Hz, [f] J_1=6.7 Hz, J_2= 2.2 Hz, [g] J=5.7 Hz, [h] J_1=6.8 Hz, J_2= 2.2 Hz, [i] broad signal, [j] J=7.7 Hz, [k] J=8.2 Hz, [l] J=5.8 Hz, [m] J=9.0 Hz, [n] J=7.2 Hz, [o] J=6.7 Hz, [p] J=8.8 Hz, [q] J=5.6 Hz, [r] J=8.7 Hz.

The mechanism usually accepted for the NBS dehydrogenation of nitrogen compounds involves the generation of intermediary succinimidoyl radicals.[26] To investigate the possible reaction pathway, dehydrogenation of compound (**3j**) was performed in the presence of butylhydroxytoluene (BHT) as radical scavenger. In such conditions the reaction was not inhibited and the corresponding tetrahydropyrimidinium salt (**2j**) was isolated. These findings indicate that an alternative ionic mechanism might be operating, perhaps one involving *N*-bromination of the aminal followed by deprotonation by succinimide anion (Scheme 4).

Scheme 4



CONCLUSIONS

Cyclization of *N*-aryl-*N´*-formyltrimethylenediamines (**5**) (R'=H) with PPSE provides a convenient method for the preparation of 1-aryl-1,4,5,6-tetrahydropyrimidines from easily available unexpensive starting materials. The reaction conditions and work-up are sufficiently mild to prevent hydrolytic cleavage of the tetrahydropyrimidine nucleus, so that this route seems applicable for the construction of this system in more complex molecules.

Quaternization of *N*-aryltetrahydropyrimidines provides easy access to the corresponding salts with a linear primary alkyl group in position 3. Due to the mechanism of the alkylation, such method cannot be employed for the synthesis of unsymmetrical *N,N´*-diaryl salts nor to derivatives containing a branched alkyl substituent attached to N3. Those derivatives can be obtained with high yields by dehydrogenation of the corresponding hexahydropyrimidines, accessible by condensation of suitably substituted 1,3-propanediamines with formaldehyde. Selectively *N,N´*-disubstituted 1,3-propanediamines, key intermediates in the preparation of the hexahydropyrimidines, can be synthesized with high yields by two alternative procedures depending on their substitution patterns.

N-Nitroaryl salts can only be prepared by alkylation, as the low nucleophilicity of the corresponding 1,3-diamines does not allow for the synthesis of the corresponding cyclic aminals by condensation reactions. Besides, nitrophenyltetrahydropyrimidines are the most stable towards hydrolysis among 2-H derivatives.

In the cases in which both procedures could in principle be employed, dehydrogenation of hexahydropyrimidines (**3**) was more efficient, leading to higher yields of the corresponding salts. This fact can be related to the higher relative stability of 2-unsubstituted hexahydropyrimidines in comparison with 2-H tetrahydropyrimidines.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer with deuteriochloroform as the solvent. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. J values are given in Hz. MS (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on aluminium alumina 60 F_{254} sheets or on aluminium silica gel 60 F_{254} sheets. Column chromatographies were performed either on silica gel 60 (230-400 mesh) or on aluminium oxide (neutral, grade I, 70-230 mesh), with typically 30-50 g of stationary phase *per gram* substance. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

***N*-Aryl-*N´*-formyl-1,3-propanediamines** (**5**) (R=H) were synthesized by formylation of the corresponding *N*-aryltrimethylenediamines. [19]

***N*-Alkyl-*N'*-(*p*-chlorophenyl)-1,3-propanediamines** (**4g-i**) were obtained by reduction of the corresponding *N*-aryl-*N'*-acyl-1,3-propanediamines (**5**). [22]

***N*-Alkyl-*N'*-(*p*-chlorophenyl)-1,3-propanediamines** (**4f,j,k**) were obtained by reduction of the corresponding 3-arylaminopropanamides (**6**). [23]

1-Aryl-1,4,5,6-tetrahydropyrimidines (1). General procedure

A mixture of *N*-aryl-*N´*-formyl-1,3-propanediamine (**5**) (R'=H) (5 mmol) and a methylene chloride solution of trimethylsilyl polyphosphate[27] (25 mL) was heated under reflux for 5 h. The reaction mixture was allowed to cool and then extracted with water (5 x 25 mL). Acid solutions were made alkaline with solid $NaHCO_3$ in an ice-salt bath. The mixture was quickly extracted with methylene chloride (3 x 30 mL) and the organic layers were washed with water (10 mL) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* at rt and the crude bases purified by flash column chromatography on silica gel (methylene chloride-isopropylamine, 20:1) to afford compounds (**1a,c-e**). Yields, physical data and elemental analyses are as follows:

1-(*o*-Tolyl)-1,4,5,6-tetrahydropyrimidine (1a)

This compound was obtained as an oil (87%); ^{1}H NMR: δ 2.00 (m, 2, CH_2 5), 2.28 (s, 3, CH_3), 3.46 and 3.50 (m, 4, CH_2N), 7.07-7.26 (m, 5, aromatics and H 2); MS: m/z 174 ($M^{+\cdot}$). Anal. Calcd for $C_{11}H_{14}N_2$: C; 75.82, H; 8.10, N; 16.08. Found: C; 75.63, H; 8.15, N; 16.14.

1-(*p*-Methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (1c)

This compound was obtained as an oil (70%); ^{1}H NMR: δ 2.00 (m, 2, CH_2 5), 3.42 (t, J=5.5 Hz, CH_2N), 3.60 (t, J=5.6 Hz, CH_2N), 3.79 (s, 3, OCH_3), 6.94 (dd, J_1=6.7 Hz, J_2=2.3 Hz, 2, $CH_3OC_6H_4$, *meta* H), 7.01 (dd, J_1=6.7 Hz, J_2=2.3 Hz, 2, $CH_3OC_6H_4$, *ortho* H), 7.48 (br s, 1, H2); MS: m/z 190 ($M^{+\cdot}$). Anal. Calcd for $C_{11}H_{14}N_2O$: C; 69.45, H; 7.42, N; 14.72. Found: C; 69.36, H; 7.48, N; 14.79.

1-(*p*-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine (1d)

This compound was obtained as an oil (80%); ^{1}H NMR: δ 2.01 (m, 2, CH_2 5), 3.43 (t, J=5.2 Hz, CH_2N), 3.60 (t, J=5.8 Hz, CH_2N), 6.97 (dd, J_1=6.8 Hz, J_2=2.1 Hz, 2, ClC_6H_4, *ortho* H), 7.29 (dd, J_1=6.8 Hz, J_2=2.1 Hz, 2, ClC_6H_4, *meta* H), 7.57 (br s, 1, H2); MS: m/z 194 ($M^{+\cdot}$). Anal. Calcd for $C_{10}H_{11}N_2Cl$: C; 61.70, H; 5.70, N; 14.39. Found: C; 61.62, H; 5.74, N; 14.47.

1-(*o*-Nitrophenyl)-1,4,5,6-tetrahydropyrimidine (1e)

This compound was obtained in 81% yield; mp 45-46ºC (methylene chloride/hexane); ^{1}H NMR: δ 2.01 (m, 2, CH_2 5), 3.47 (t, J=5.6 Hz, CH_2N), 3.53 (t, J=5.6 Hz, CH_2N), 7.16 (br s, 1, H2), 7.28 (d, J=7.8 Hz, 1, $NO_2C_6H_4$, *ortho* H), 7.34 (t, J=8.0 Hz, 1, $NO_2C_6H_4$, *para* H), 7.61 (t, J=7.8 Hz, 1, $NO_2C_6H_4$, *meta* H), 7.89 (d, J=8.0 Hz, 1, $NO_2C_6H_4$, *meta* H); MS: m/z 205 ($M^{+\cdot}$). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C; 58.53, H; 5.40, N; 20.48. Found: C; 58.59, H; 5.36, N; 20.43.

1,3-Disubstituted hexahydropyrimidines (3). General procedure

A solution of 1,3-propanediamine (**4**) (5 mmol) in methanol (40 mL) was treated with 40% aqueous formaldehyde (0.4 mL, 5.5 mmol). The solution was stirred at rt for 30 min, after which it was treated with 20% aqueous sodium carbonate (20 mL). The mixture was extracted with methylene chloride (3 x 50 mL) and the organic layers were washed with water (10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude products were purified by column chromatography on neutral alumina using chloroform as mobile phase, to yield compounds (**3f-k**). Yields, physical data and elemental analyses of new compounds are as follows:

1-(*p*-Chlorophenyl)-3-(2,2-dimethylpropyl)hexahydropyrimidine (3i)

This compound was obtained in 89% yield; mp 48-49°C (ethanol/water); ^{1}H NMR: δ 0.90 (s, 9, CH_3), 1.73 (m, 2, CH_2 5), 2.23 (s, 2, C*H*$_2$ *tert*-C_4H_9), 2.75 (t, J=5.4 Hz, 2, CH_2 4), 3.18 (t, J=5.6 Hz, 2, CH_2 6), 3.89 (s, 2, CH_2 2), 6.83 (d, J=6.8 Hz, 2, ClC_6H_4, *ortho* H), 7.19 (d, J=6.8 Hz, 2, ClC_6H_4, *meta* H); MS: m/z 266 ($M^{+\cdot}$). Anal. Calcd for $C_{15}H_{23}N_2Cl$: C; 67.52, H; 8.69, N; 10.50. Found: C; 67.65, H; 8.63, N; 10.43.

3-*tert*-Butyl-1-(*p*-chlorophenyl)hexahydropyrimidine (3j)

This compound was obtained as an oil (86%); ^{1}H NMR: δ 1.25 (s, 9, CH_3), 1.75 (m, 2, CH_2 5), 2.75 (t, J=5.5 Hz, 2, CH_2 4), 3.21 (t, J=5.5 Hz, 2, CH_2 6), 3.99 (s, 2, CH_2 2), 6.87 (d, J=6.9 Hz, 2, ClC_6H_4, *ortho* H), 7.17 (d, J=6.9 Hz, 2, ClC_6H_4, *meta* H); MS: m/z 252 ($M^{+\cdot}$). Anal. Calcd for $C_{14}H_{21}N_2Cl$: C; 66.52, H; 8.37, N; 11.08. Found: C; 66.44, H; 8.39, N; 11.15.

1-(*p*-Chlorophenyl)-3-phenylhexahydropyrimidine (3k)

This compound was obtained as an oil (87%); ^{1}H NMR: δ 1.84 (m, 2, CH_2 5), 3.38-3.49 (m, 4, CH_2 4 and 6), 4.61 (s, 2, CH_2 2), 6.90-7.32 (m, 9, aromatics); MS: m/z 272 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{17}N_2Cl$: C; 70.45, H; 6.28, N; 10.27. Found: C; 70.28, H; 6.31, N; 10.36.

1,3-Disubstituted 1,4,5,6-tetrahydropyrimidinium iodides (2)

Method A. General procedure

A mixture of 1,4,5,6-tetrahydropyrimidine (**1**) (5 mmol) and alkyl iodide (6 mmol) in anhydrous methylene chloride (50 mL) was refluxed protected from moisture. The reaction was monitored by TLC (chloroform:methanol 9:1) until disappearance of the starting material. The solution was evaporated *in vacuo* and the residue purified by flash column chromatography (silica gel, chloroform:methanol 9:1) to yield compounds (**2a-e**). ^{1}H NMR spectra of compounds (**2a-e**) are given in Table 1. Yields, physical data and elemental analyses are as follows:

3-Methyl-1-(*o*-tolyl)-1,4,5,6-tetrahydropyrimidinium iodide (2a)

This compound was obtained as an oil (74%); MS: m/z 189 ($M^{+\cdot}$-I). Anal. Calcd for $C_{12}H_{17}N_2I$: C; 45.58, H; 5.42, N; 8.86. Found: C; 45.66, H; 5.37, N; 8.94.

3-Ethyl-1-(*o*-tolyl)-1,4,5,6-tetrahydropyrimidinium iodide (2b)

This compound was obtained as an oil (70%); MS: m/z 203 ($M^{+\cdot}$-I). Anal. Calcd for $C_{13}H_{19}N_2I$: C; 47.29, H; 5.80, N; 8.48. Found: C; 47.44, H; 5.77, N; 8.42.

1-(*p*-Methoxyphenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (2c)

This compound was obtained as an oil (72%); MS: m/z 205 ($M^{+\cdot}$-I). Anal. Calcd for $C_{12}H_{17}N_2OI$: C; 43.39, H; 5.16, N; 8.43. Found: C; 43.50, H; 5.11, N; 8.37.

1-(*p*-Chlorophenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (2d)

This compound was obtained in 77% yield; mp 97-98^{o}C (anhydrous isopropanol); MS: m/z 209 ($M^{+\cdot}$-I). Anal. Calcd for $C_{11}H_{14}N_2ClI$: C; 39.25, H; 4.19, N; 8.32. Found: C; 39.42, H; 4.13, N; 8.24.

1-(*o*-Nitrophenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (2e)

This compound was obtained in 75% yield; mp 202-203^{o}C (anhydrous isopropanol); MS: m/z 220 ($M^{+\cdot}$-I). Anal. Calcd for $C_{11}H_{14}N_3O_2I$: C; 38.06, H; 4.06, N; 12.10. Found: C; 38.17, H; 4.01, N; 12.01.

Attempted synthesis of 1-(*o*-tolyl)-3-(2,4-dinitrophenyl)- 1,4,5,6-tetrahydropyrimidinium chloride

A mixture of 1-(*o*-tolyl)-1,4,5,6-tetrahydropyrimidine (**1a**) (0.174 g, 1 mmol) and 2,4-dinitrochlorobenzene (0.202 g, 1 mmol) in anhydrous methylene chloride (10 mL) was refluxed protected from moisture. The reaction was monitored by TLC (chloroform:methanol 9:1) until disappearance of the starting material. The solution was evaporated *in vacuo* and the residue purified by column chromatography (silica gel, chloroform:methanol 9:1) to yield *N*-formyl-*N'*-(2,4-dinitrophenyl)-*N*-(*o*-tolyl)trimethylenediamine (**7**) (0.215 g, 60%); mp 154-156ºC (ethanol); ^{1}H NMR: δ 1.97 (m, 2, $CH_2CH_2CH_2$), 2.28 (s, 3, $CH_3C_6H_4$), 3.52 (q, J=6.6 Hz, 2, CH_2N-2,4$(NO_2)_2C_6H_3$), 3.82 (t, J=6.7 Hz, 2, CH_2NCHO), 6.89 (d, J=9.6 Hz, 1, $CH_3C_6H_4$, *ortho* H), 7.10 (d, J=7.2 Hz, 1, aromatic), 7.29-7.34 (m, 3, aromatics), 8.18 (s, 1, CHO), 8.26 (d, J= 9.6 Hz, 1, 2,4$(NO_2)_2C_6H_3$, *meta* H), 8.80 (br s, 1, NH), 9.14 (s, 1, 2,4$(NO_2)_2C_6H_3$, *meta* H); MS: m/z 358 ($M^{+\cdot}$). Anal. Calcd for $C_{17}H_{18}N_4O_5$: C; 56.98, H; 5.06, N; 15.63. Found: C; 57.11, H; 5.01, N; 15.54.

Method B. General procedure

NBS (or NIS) (5 mmol) was added to a solution of hexahydropyrimidine (**3**) (5 mmol) in anhydrous dimethoxyethane (50 mL). The solution was stirred until complete conversion of the hexahydropyrimidine (approximately 30 min), as evidenced by TLC (alumina, chloroform). The solution was concentrated *in vacuo*, the residue was washed with methanol and then with ether and purified by flash column chromatography (silica gel, chloroform:methanol 9:1) to yield compounds (**2f-k**). ^{1}H NMR spectra of compounds (**2f-k**) are given in Table 1. Yields, MS and elemental analyses are as follows:

1-(*p*-Chlorophenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium bromide (2f)

This compound was obtained as an oil (89%); MS: m/z 209 ($M^{+\cdot}$-Br). Anal. Calcd for $C_{11}H_{14}N_2BrCl$: C; 45.62, H; 4.87, N; 9.67. Found: C; 45.44, H; 4.91, N; 9.76.

1-(*p*-Chlorophenyl)-3-ethyl-1,4,5,6-tetrahydropyrimidinium bromide (2g)

This compound was obtained as an oil (87%); MS: m/z 223 ($M^{+\cdot}$-Br). Anal. Calcd for $C_{12}H_{16}N_2BrCl$: C; 47.47, H; 5.31, N; 9.23. Found: C; 47.28, H; 5.37, N; 9.31.

1-(*p*-Chlorophenyl)-3-(2-methylpropyl)-1,4,5,6-tetrahydropyrimidinium iodide (2h)

This compound was obtained as an oil (87%); MS: m/z 251 ($M^{+\cdot}$-I). Anal. Calcd for $C_{14}H_{20}N_2ClI$: C; 44.40, H; 5.32, N; 7.40. Found: C; 44.57, H; 5.26, N; 7.49.

1-(*p*-Chlorophenyl)-3-(2,2-dimethylpropyl)-1,4,5,6-tetrahydropyrimidinium bromide (2i)

This compound was obtained as an oil (86%); MS: m/z 265 ($M^{+\cdot}$-Br). Anal. Calcd for $C_{15}H_{22}N_2BrCl$: C; 52.11, H; 6.41, N; 8.10. Found: C; 51.94, H; 6.44, N; 8.19.

3-*tert*-Butyl-1-(*p*-chlorophenyl)-1,4,5,6-tetrahydropyrimidinium bromide (2j)

This compound was obtained as an oil (81%); MS: m/z 251 ($M^{+\cdot}$-Br). Anal. Calcd for $C_{14}H_{20}N_2BrCl$: C; 50.70, H; 6.08, N; 8.45. Found: C; 50.87, H; 6.02, N; 8.32.

1-(*p*-Chlorophenyl)-3-phenyl-1,4,5,6-tetrahydropyrimidinium bromide (2k)

This compound was obtained as an oil (80%); MS: m/z 350 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{16}N_2BrCl$: C; 54.65, H; 4.59, N; 7.97. Found: C; 54.84, H; 4.54, N; 9.85.

Dehydrogenation of compound (**3j**) (0.252 g, 1 mmol) with NBS (0.192 g, 1 mmol) was performed in the presence of butylhydroxytoluene (0.220 g, 1 mmol) in dimethoxyethane (15 mL). After usual work-up and purification, compound (**2j**) was isolated in 76% yield (0.252 g).

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