A SIMPLE APPROACH FOR THE SYNTHESIS OF 2,6-DIARYL-4-OXO-3,4-DIHYDROPYRIMIDINE-5-CARBONITRILES

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Abstract: A concise, facile and straightforward synthesis of 2,6-diaryl-4-oxo-3,4-dihydropyrimidine-5-carbonitriles **12a-h** is reported. The reaction for this preparation involves the condensation of ethyl α–cyanocinnamate and its *para* substituted analogs **8a**-e with arylamidines **9a-d** under very mild conditions. A probable mechanism of **12a-h** from **11a-h** is proposed. A preliminary pharmacological evaluation of compounds **12c, 12d, 12f** e **12h** has shown that these compounds possess analgesic activity.

Introduction

In our drug discovery program, we have been involved in the synthesis and antiinflammatory tests of 4-aminopyrimidine derivatives which gave encouraging results[1,2]. Because of this, we were motivated to continue looking for other pyrimidine compounds with a view to find more potent heterocycles. 4-Pyrimidinones appeared to be attractive candidates because various pyrimidinones exhibit a wide range of biological activities[3-9]. In 1985, Wierenga published a review about the antiviral and other bioactivities of pyrimidinones[2]. Our main objective was to have aryl groups at C-2 and C-6 positions and a carbonitrile at C-5. A literature search disclosed the existence of two such pyrimidinones 2,6-diphenyl-4-oxo-3,4-dihydropyrimidine-5-carbonitrile **1**[10] and 2-(*p*-chlorophenyl)-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile **2**[11].

The first one was obtained by the decomposition of 2,4-diphenyl-6-oxo-6*H*-1,3-thiazine-5-carbonitrile **3**, while the second one was prepared by condensation between cyanoacetamide and *N*-acylimidates as shown in Figure-1.

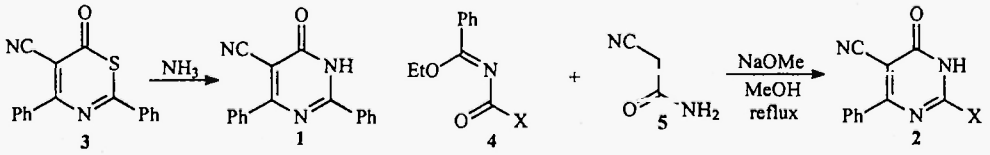


Figure-1: Synthesis of 2,6-diaryl-4-oxo-3,4-dihydropyrimidine-5-carbonitriles **1** and **2**.

Besides these two 4-oxo-pyrimidinones containing 2,6-diaryl-5-cyano groups, no other compounds of this series have been synthesized. To our knowledge, the pharmacological properties of substances **1** and **2** have not been tested. Because of this, we decided to extend this work and prepare **12a-h** under mild conditions, and evaluate their biological virtues, particularly the antiinflammatory and antitumor properties. This paper reports only the synthesis of **12a-h**.

Preliminary tests of compounds 12c, 12d, 12f e 12h **showed excellent analgesic effect in mice with contortions test induced by 0.8% of aqueous acetic acid (v/v). The analgesic effect was 79, 88, 77 e**

69%, respectively. No toxicity effects were observed with 50 mg/kg of the body weight. A complete account of the analgesic and antiinflammatory activities of 12a-h will be published at a later date.

Results and Discussions

There are many procedures involving the preparations of pyrimidinones[12,13], but we adopted the method of condensing substituted ethyl α-cyanocinnamates **8a-e** (Michael acceptors) and arylamidines **9a-d** (electron donors) as depicted in Figure 2. The first set of compounds were obtained through Knoevenagel condensation of an aromatic aldehyde with ethyl cyanoacetate in the presence of triethylamine[14]. The second set of compounds, arylamidines **9a-d** were acquired by the reaction of an imidate with ammonia[15]. The yields were better when the phenyl ring of arylamidine had electron donating group, but decreased when the electron withdrawing group was substituted in the same position.

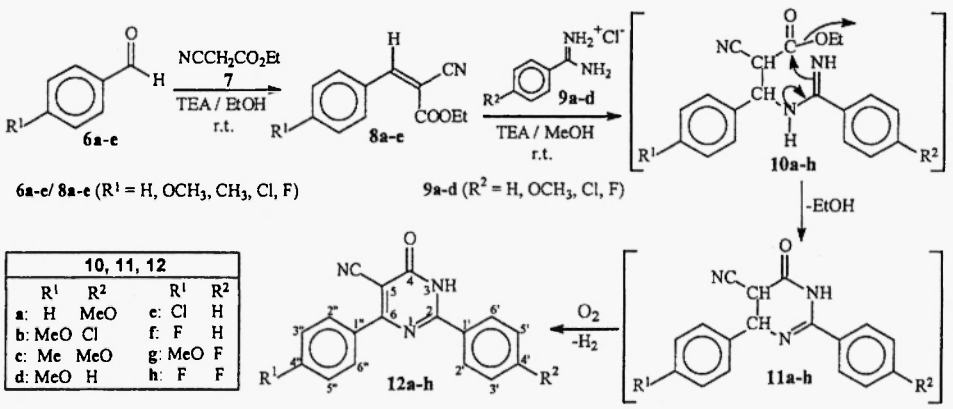


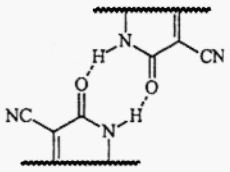
Figure-2: Synthetic pathways for compounds **12a-h**

Our future program focuses the Quantitative Structure Activity Relationships (QSAR) of these compounds, for which we need a large number of substituents in the *ortho*, *meta* and *para* positions on the phenyl group for evaluating such relationships. Therefore, we replaced one hydrogen atom by a fluorine atom at *para* position in one of the phenyl rings (**12g**) and also in both the phenyl rings at the same position (**12h**). This was done because the steric parameters of the fluorine and hydrogen atoms are not much different (van der Waal's radii are 1.35 Å and 1.24 Å, respectively)[16]. Since the electronegativities of both atoms are quite different, the pharmacological activities of fluorine-containing compounds sometimes exhibit enhanced biological properties[17].

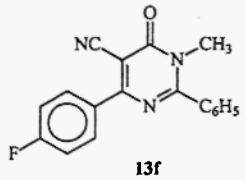
The infrared spectra of compounds **12a-h** exhibited absorptions at ~ 2220 (ν C≡N), ~ 1650 (ν C=O), ~ 1600 (ν C=N) and for the pyrimidine ring at ~ 1000 cm^{-1}, respectively. These data are consistent with the proposed structures[18,19].

The ^1H NMR spectra of **12a-h** also agreed with the structure. All compounds **12a-h** displayed a relatively broad signal around δ13.5 ppm. This is indicative of the strong intermolecular hydrogen bonding involving a dimeric structure **13**. An idea about the dimeric structure also came when we tried to *N*-methylate **12f** employing dimethyl sulfate and sodium hydroxide as a base. The *N*-methyl compound **13f** was obtained as a well-characterized crystalline compound, m.p. 173.2 °C[20]. Substantial decrease in m.p. of **13f** compared to

12f (m.p. (°C) > 300) strongly suggest an intermolecular hydrogen bonding between the two molecules of **12f**. The chemical shifts of the pyrimidines are compiled in the experimental part.



13



13f

The mechanism of formation of pyrimidinones **12a-h** seems interesting. The formation of 3,4,5,6-tetrahydropyrimidinones **11a-h** in principle should involve two steps: first, one of the nitrogen atoms of arylamidime **9a-d** should attack C-3 of **8a-e** to form the intermediate **10a-h** followed by the second step where the imino nitrogen atom attacks the carbonyl carbon atom of the ester part of **10a-h** with subsequent loss of an ethanol molecule. These intermediates suffer quick dehydrogenation during the reaction to furnish the final products **12a-h**. In general, is very difficult to isolate the intermediates **11a-h** under the experimental conditions.

There remains a high possibility for the atmospheric oxygen molecule to cause the dehydrogenation of **11a-h** leading to the final products **12a-h**. In order to prove this, we carried out a reaction between **8e** and **9a** very carefully using dry nitrogen atmosphere and substituting triethylamine with anhydrous sodium carbonate to facilitate the work-up. The crude product isolated here was immediately subjected to ^{1}H NMR spectroscopy (R_f **12f** = 0.22; R_f **11f** = 0.36; hexane/ethyl acetate, 6:4). It was exciting to see two doublets at δ 4.93 and 4.97 ppm having J = 5.4Hz. These represent H-5 and H-6, respectively. This is reasonable because the molecular model of this compound shows a dihedral angle of ~140° between H-5 and H-6. This confirms the existence of the intermediate. In order to obtain **12a**, oxygen was bubbled to a solution of **11a** in acetone for an extended period of time, followed by the removal of acetone and recording the ^{1}H NMR spectrum again. This time, the spectrum showed the disappearance of both doublets, thus confirming the hypothesis that the atmospheric oxygen is responsible for the dehydrogenation.

Conclusions

We have achieved the synthesis of eight new 2,6-diaryl-4-oxo-3,4-dihydropyrimidinone carbonitriles **12a-h** in good to excellent yields, by condensing individually **8a-e** with **9a-d**. The intermediates **11a-h** are oxidized to **12a-h** during the reaction and none of them could be isolated easily. A probable mechanism of **12a-h** from **11a-h** has been proposed.

Experimental

Melting points were determined with a Thomas Hoover apparatus and are uncorrected. Infrared spectra (IR) were recorded with a Bruker spectrophotometer, model IFS66 (FT), using KBr pellets. Eletron-impact mass spectra (MS) were obtained using a Delsi-Nermag mass spectrometer, coupled to GC (HP 5890) at an ionization potential of 70 eV. Exact mass measurements were made with an Autospec-Micromass-EBE mass spectrometer. ^{1}H NMR spectra were measured at room temperature with a Varian 300 MHz spectrophotometer, model UNITY plus using DMSO-d_6 as solvent and TMS as an internal standard. Splitting

patterns are follows: s, singlet; d, doublet; dd, double doublet; dt, double triplet; m, multiplet; bs, broad singlet; Elemental analyses (C, H, N) were obtained using a Carlo Erba Elementary Analyser Model 1110.

General procedure for the synthesis of *2,6-diaryl-4-oxo-3,4-dihydro-pyrimidine-5-carbonitriles* **12a-h.**

A mixture of **8a-e** (7 mmol), arylamidine hidrochloride, **9a-d** (7 mmol) and triethylamine (5 drops) in methanol was stirred at room temperature for 16 to 24 hours. The solvent was evaporated under reduced pressure giving a solid mass. The solid was filtered and washed first with ethyl acetate and later with a little methanol and then crystallized from DMSO to give the corresponding pyrimidine derivatives **12a-h**.

2-(p-Anisyl)-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile **12a**, colourless crystals; yield = 73%; Mp (^{0}C) > 300; IR (ν cm^{-1}) = 3074, 2947 (C-H), 2220 (C=N), 1656 (C=O), 1604 (C=N), 975 (pyrimidinone ring); MS = Calcd.: 303.3196, Found: 303.10462; ^{1}H NMR (δ ppm) = 3.87 (s, OMe), 7.12 (d, H-3', H-5', J=9.0Hz,), 7.61 (m, H-3", H-4", H-5"), 8.02 (dd, H-2", H-6", J=7.5, 1.5Hz), 8.27 (d, H-2', H-6', J=9.0Hz), 13.54 (bs, NH); Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C 71.28%, N 13.85%, H 4.32%. Found: C 70.98%, N 14.18%, H 4.26%.

6-(p-Anisyl)-2-(p-chlorophenyl)-4-oxo-3,4-dihydropyrimidine-5-carbonitrile **12b**, colourless crystals; yield = 65%; Mp (^{0}C) > 300; IR (ν cm^{-1}) = 3071, 2959 (C-H), 2220 (C≡N), 1659 (C=O), 1606 (C=N), 1014 (pyrimidinone ring). MS = Calcd.: 337.7647, Found: 337.66301; ^{1}H NMR (δ ppm) = 3.82 (s, OMe), 7.04 (d, H-3", H-5", J=9.0Hz,), 7.47 (d, H-3', H-5', J=8.4Hz), 7.90 (d, H-2", H-6", J=8.7Hz), 8.32 (d, H-2', H-6', J=8.1Hz,), 13.73 (bs, NH); Anal. Calcd. for $C_{18}H_{12}N_3O_2Cl$: C 64.01%, N 12.44%, H 3.58%. Found: C 64.03%, N 12.68%, H 3.52%.

2-(p-Anisyl)-4-oxo-6-(p-tolyl)-3,4-dihydropyrimidine-5-carbonitrile **12c**, colourless crystals; yield = 62%; Mp (^{0}C) > 300; IR (ν cm^{-1}) 3080, 2950 (C-H), 2220 (C≡N), 1654 (C=O), 1607 (C=N), 1029 (pyrimidinone ring); MS = Calcd.: 317.3464, Found: 317.11887; ^{1}H NMR (δ ppm) = 2.41 (s, Me), 3.87 (s, OMe), 7.12 (d, H-3", H-5", J=9.0Hz,), 7.40 (d, H-2", H-6", J=7.8Hz), 7.95 (d, H-3', H-5', *J*=7.8Hz), 8.26 (d, H-2', H-6', J=8.4Hz), 13.42 (bs, NH); Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C 71.91%, N 13.24%, H 4.76%. Found: C 71.84%, N 13.46%, H 4.66%.

6-(p-Anisyl)-4-oxo-2-(phenyl)-3,4-dihydropyrimidine-5-carbonitrile **12d**, colourless crystals; yield = 57%, Mp (^{0}C) > 300; IR (ν cm^{-1}) = 3081, 2955 (C-H), 2220 (C≡N), 1658 (C=O), 1604 (C=N), 1025 (pyrimidinone ring); MS = Calcd.: 303.3196, Found: 303.10087; ^{1}H NMR (δ ppm) = 3.87 (s, OMe) 7.16 (dd, H-2", H-6", J=8.1Hz), 7.63 (m, H-3', H-4', H-5'), 8.11 (d, H-3", H-5", J=8.1Hz), 8.24 (dd, H-2', H-6', J=8.7, 0.6Hz), 13.56 (bs, NH); Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C 71.28%, N 13.85%, H 4.32%. Found: C 71.13%, N 14.02%, H 4.46%.

6-(p-Chlorophenyl)-4-oxo-2-(phenyl)-3,4-dihydropyrimidine-5-carbonitrile **12e**, colourless crystals; yield = 90%; Mp (^{0}C) > 300; IR (ν cm^{-1}) = 3085, 2957 (C-H), 2220 (C≡N), 1660 (C=O), 1594 (C=N), 973 (pyrimidinone ring). MS = Calcd.: 307.7385; Found: 307.05258; ^{1}H NMR (δ ppm) = 7.64 (m, H-3', H-4', H-5', H-2", H-6"), 8.07 (d, H-3", H-5", J=8.7Hz), 8.24 (dd, H-2', H-6', J=8.1, 1.5Hz), 13.78 (bs, NH); Anal. Calcd. for $C_{17}H_{10}N_3OCl$: C 66.35%, N 13.65%, H 3.28%. Found: C 66.30%, N 13.59%, H 3.14%.

6-(p-Fluorophenyl)-4-oxo-2-(phenyl)-3,4-dihydropyrimidine-5-carbonitrile **12f**, colourless crystals; yield = 95%, Mp (^{0}C) > 300; IR (ν cm^{-1}) = 3066, 2947 (C-H), 2220 (C≡N), 1677 (C=O), 1596 (C=N), 950 (pyrimidinone ring); MS (m/z %) = 289 M$^+$(100); 262 (37); 187 (41); ^{1}H NMR (δ ppm) = 7.57 (m, H-3", H-5",

H-3', H-4', H-5'), 8.17 (dd, H-2", H-6", J=8.0, 1.5Hz), 8.25 (d, H-2', H-6', J=7.8Hz), 13.80 (bs, NH); Anal. Calcd. for $C_{17}H_{10}FN_3O$. $½H_2O$: C 67.99%, N 13.99%, H 3.69%. Found: C 67.69%, N 13.89%, H 3.78%.

6-(p-Anisyl)-2-(p-fluorophenyl)-4-oxo-3,4-dihydropyrimidine-5-carbonitrile **12g**, colourless crystals; yield = 70%; Mp (^{0}C) = 299-301; IR (ν cm^{-1}) = 3041, 2937 (C-H), 2218 (C≡N), 1645 (C=O), 1580 (C=N), 995 (pyrimidinone ring); MS (*m/z* %) = 321 M^+(100), 293 (62), 201 (85); ^{1}H NMR (δ ppm) = 3.87 (s, OMe), 7.12 (d, H-2", H-6", J=8.6Hz), 7.43 (d, H-3", H-5", J=8.6Hz), 8.10 (d, H-3', H-5', J=8.6Hz), 8.31 (d, H-2', H-6', J=8.6Hz); Anal. Calcd. for $C_{18}H_{12}FN_3O_2$. $½H_2O$: C 65.45%, N 12.72%, H 3.97%. Found: C 65.15%, N 13.03%, H 4.22%.

2,6-Bis-(p-fluorophenyl)-4-oxo-3,4-dihydropyrimidine-5-carbonitrile **12h**, colorless crystals; yield = 42%; Mp (^{0}C) = 302-304; IR (ν cm^{-1}) = 3072, 2937 (C-H), 2218 (C≡N), 1666 (C=O), 1600 (C=N), 1004 (pyrimidinone ring); MS (*m/z* %) = 309 M^+(66), 281 (22); 188 (48); ^{1}H NMR (δ ppm) = 7.43 (m, H-2", H-3", H-5", H-6"), 8.11 (d, H-3', H-5', J=8.2Hz), 8.31 (d, H-2', H-6', J=8.3Hz), 13.74 (sl, NH); Anal. Calcd. for $C_{17}H_9F_2N_3O$. $¼H_2O$: C 65.07%, N 13.39%, H 3.05%. Found: C 65.16%, N 13.19%, H 3.14%.

General procedure for the synthesis of *6-(p-fluorophenyl)-3-methyl-4-oxo-2-(phenyl)-3,4-dihydropyrimidine-5-carbonitrile* **13f**.

To a mixture of 300mg (1mmol) of **12f** and an aqueous solution of sodium hydroxide (10N, 10mL) was added dimethylsulfate (2.0mL) dropwise at 60^{0}C. The reaction was monitored by TLC and allowed to react until consumption of the starting material. The solids were filtered, washed with distilled water and dried under vacuum. The residue was eluted on a silica gel column using a mixture of hexane/ethyl acetate (6:4 v/v). The first product (R_f = 0.8) was **13f**. The fractions were combined, solvent evaporated and the solid dried under vacuum.

6-(p-Fluorophenyl)-3-methyl-4-oxo-2-(phenyl)-3,4-dihydropyrimidine-5-carbonitrile **13f**, white crystals, yield = 38%; Mp (^{0}C) = 173; IR (ν cm^{-1}) = 3093 (C-H), 2229 (C≡N), 1612 (C=O), 1562 (C=N); MS (*m/z* %) = 305 M^+(100), 202 (66), 173 (62), 103 (18); ^{1}H NMR (δ ppm) = 4.28 (s, NMe), 7.25 (m, H-3", H-5"), 7.54 (m, H-3', H-4', H-5'), 8.22 (dt, H-2", H-6", J=2.1, 5.4Hz), 8.57 (dd, H-2', H-6', J=6, 1.8Hz); Anal. Calcd. for $C_{18}H_{12}FN_3O$: C 70.81%, N 13.76%, H 3.96%. Found: C 70.50%, N 14.05%, H 4.10 %.

Acknowledgements

We gratefully acknowledge the Brazilian National Research Council (CNPq) for financial support. One of us (F.J.B. M. Jr.) is thankful to the Education Ministry of Brazil (CAPES) for a fellowship. We also wish to thank the Analytical Center of the Fundamental Chemistry Department, Federal University of Pernambuco, Recife, for I.R. and ^{1}H MNR spectra, and to Prof. Carlos Roque and Mrs. Kesia Peixoto (both of the UNICAMP, São Paulo, Brazil) for obtaining the mass spectra of all compounds.

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Received on August 22, 2005.