Advances in the Synthesis of 5- and 6-Substituted Uracil Derivatives

Javier I. Bardagí and Roberto A. Rossi

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INTRODUCTION

The uracil unit is one of the most important structures in life, being part of the building blocks of RNA and DNA and other natural products. Therefore, it is not surprising that uracil derivatives have important biological activity. Uracil-based compounds are used in the treatment of cancer (5-fluorouracil) and against infections of the HIV virus (AZT). Actions as antiviral and antitumoral agents are perhaps the most widely reported activity. However, other uracil derivatives have been synthesized which are herbicides, insecticides, bactericides, acaricides, etc. In addition, uracil units can be found in the chemistry of peptide nucleic acid (PNA) or as part of other fused systems with antiallergic, antihypertensive, cardiotonic, bronchodilator or antibronchitis activity.

The search for uracil derivatives has been carried out since the beginning of the last century and even today there is great interest in the development of new derivatives and strategies for synthesis so as to improve the yield of known compounds. To prepare uracils, there are three main synthetic strategies: a) building the uracil nucleus from acyclic precursors with appropriate substituents; b) modification of the structure of functionalized uracils or uracil itself by reaction with different reagents, as illustrated by the recent synthesis of 5-trifluoromethyluracil and uridines with oxiranyl and tetrahydrofuranyl substituents; c) functionalization of masked uracil moieties with reactions incompatible with the nucleus, for example the synthesis of 6-aryl and 6-acyluracils and 2'-deoxypseudouridine.

Combinations of these approaches are often found in the synthesis of target compounds with potential biological activities.

The present review will cover advances in the synthesis of 5- and 6-substituted uracils (Figure 1) over the last 8–10 years. It has been organized in terms of the type of union that links the uracil moieties to the substitution groups; fused systems will have a separate section.

Received June 23, 2009; in final form September 4, 2009.
Address correspondence to Robert A. Rossi, INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, ARGENTINA. E-mail: rossi@fcq.unc.edu.ar
I. Uracils with Carbon-based Substituent

1. C(Uracil)-C(sp³) Bonds

Chen et al. have synthesized 6-methyl (3) and 6-ethyluracils (7) using two different approaches as part of a study of polysubstituted uracils (Schemes 1 and 2). Uracil 3 was synthesized from a urea derivative 1 by reaction with diketene, to afford compound 2, which after reflux in acetic acid afforded uracil 3 (57% from 1). Later the authors developed a more efficient strategy by using diketene, trimethylsilyl chloride, and NaI in CH₃CN, obtaining 3 from 1 in one step in 95% yield.
6-Ethyluracil 7 was prepared from 1,3-dialkyl-6-chlorouracil 4 (Scheme 2)\(^9\) by reaction with the anion of diethylmalonate to give 5; the treatment of 5 with NaH and MeI afforded 6, which by hydrolysis and double decarboxylation induced by KOH gave 7 in 19% overall yield.

In a study of glutamate agonists and antagonists, Young and co-workers used their “ring switching” strategy to prepare a willardiine (Figure 2) isomer 2-(pyrimidin-2,4-dione-5-ylmethyl)-(2S)-glycine (9) from heterocycle 8 (Scheme 3).\(^{10}\)

A synthesis of 5-benzyluracils (13) from Baylis-Hillman adducts (10) was developed by Kim et al. (Scheme 4).\(^{11}\) Substitution of acetate by primary amines gave 11 in moderated yield which afforded ureas 12 after treatment with R\(^{\prime}\)NCO. Finally, in the presence of a base, 12 cyclized to afford uracil 13 in good yields.

Batra et al. synthesized 1,5-disubstituted uracils 17 using the same approach with a slight modification using BrCN instead of R\(^{\prime}\)NCO (Scheme 5).\(^{12}\) Recently, Cao and Huang developed a solid-phase synthetic strategy for the synthesis of uracil and 6-methyluracils bonded to different heterocycles through N1 or N3, starting from...
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\[ \text{Scheme 5} \]

\[ \text{14} \overset{\text{RNH}_2}{\xrightarrow{70-83\%}} \text{15} \overset{\text{NaH, PhCH}_3}{\xrightarrow{\text{rt 45}\degree}} \text{16} \overset{\text{Z=NHR}}{\xrightarrow{63-83\%}} \text{17} \overset{\text{R}_1=\text{Ph, 2-ClC}_6\text{H}_4}{\xrightarrow{75-84\%}} \]

\( \alpha,\beta\)-unsaturated esters and amines. A selenopolystyrene resin was used and good yields (41–75%) and moderate to good purity (64–96%) were obtained (Scheme 6). However, the inclusion of larger group at 6-position, like aryl or isopropyl, was not possible. As a result, this strategy seems to be an excellent option for variation of N1 and N3 substituent but it has a very limited utility in the synthesis of C5 or C6 derivatives.

\[ \text{Scheme 6} \]

\[ \text{R} = \text{allyl, propargyl} \] \[ \text{R}^2 = \text{alkyl, aryl} \]

Yano et al. have synthesized a family of 6-methylene-bridged uracil derivatives, in the search for an inhibitor of thymidine phosphorylase (TP) better than 6-amino-5-chlorouracil, a known TP inhibitor. The authors were indeed able to obtain a more potent inhibitor of TP and with better properties (solubility and oral absorption). The synthesis of the aminomethyluracils (19) was accomplished through the reaction 5-halo-6-chloromethyluracils (18) with the appropriate amines (Scheme 7). Most of the reactions were carried with the amine in water as solvent and the yield obtained ranged from very low (1%) to excellent (93%); however, some reactions were not optimized in order to obtain the best yields possible. More than twenty-five amines were used, including acyclic and cyclic ones, diamines and aminoalcohols, among others.

\[ \text{Scheme 7} \]

Later on Corelli et al. published their microwave (MW) assisted synthesis of the same type of compounds in methanol as solvent, starting from 18 (\( R = \text{H, X = Cl} \))
by reaction with different amines. Uracil 19a (R¹ = H; R² = (CH₂)₂NH₂) was prepared from the protected 19b (R¹ = H; R² = (CH₂)₂NH-Boc). Derivative 19c (R¹ = H; R² = (CH₂)NH(NH)NH₂) was also prepared from 19a by reaction with S-methylisothiourea.

A series of guanidine, amidino and thioureido derivatives were synthesized from 6-aminomethyl-5-chlorouracil under different conditions (Scheme 8).

5-Dihydropyrimidine-uracils (21) were synthesized by Knaus and co-workers¹⁷ from 5-formyluracil (20) using a three-component Hantzsch reaction (Scheme 9).

Looking for a convenient synthesis of monofluorinated-alkyl uracils, Kung and co-workers have developed a direct alkylation of nucleosides at the 5-position.¹⁸ A Pd-catalyzed Negishi cross-coupling reaction of 22 and unactivated monosubstituted alkylzinc bromides (23) was used to prepared 5-alkyluracils 24 with moderate yield carrying -F (43–53%), esters, -CN, -OSiR₃ (29–39%) functional groups (FG) (Scheme 10). However, the method has the limitation of providing low yields of products (0–8%) when the alkyl chain is short (propyl, ethyl).

Kumar et al. employed an indium catalyst to prepare the 5-substituted uracils (26 and 28) from 5-formyluracils (25) and from the Schiff bases of 25 (Scheme 11 and 12).¹⁹ Allylation of 25 with bromoallyl compounds in the presence of indium metal in a mixture of THF:H₂O (1:1) gave compound 26 in moderate to good yields (Scheme 11); diastereomeric
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Scheme 11

Ratios of > 99:1 were obtained in the best case. They suggest that the high diastereoselectivity of the reaction results from the complexation of the C-4 carbonyl oxygen of the uracil. From the Schiff bases 27a, amines 28a were obtained in 68–70% yield. The authors were able to obtain a moderate yield and good diastereocontrol of the uracil 28b derived from chiral R2 (27b) (Scheme 12).

Scheme 12

More recently, Vasella et al. have used 6-(diazomethyl-1,3-bis(methoxymethyl)uracil 29 (see Scheme 34) to prepare 6-substituted uracil 30 (Scheme 13) by reactions with thiophene through a Rh(II) catalyst.

Scheme 13

The synthesis of tetrasubstituted uracils from one alkyne and two isocyanates using a Ni(0) catalyst was reported by Duong and Louie. They optimized the conditions to prepare 5-TMS-6-alkyl (methyl, t-butyl and i-propyl) uracils 31 in good yields (Scheme 14). The proposed mechanism involves an oxidative coupling between a molecule of alkyne and isocyanate which gives the nickel intermediate 32 (Scheme 15). Reaction with another
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molecule of isocyanate is suggested to give compound 33 which, after reductive elimination, gives uracil products 31 and the Ni(0) catalyst which continues the catalytic cycle. In search for new uracil derivatives, Saladino et al. synthesized a series of uracil and uridines with oxiranyl and tetrahydrofuranyl substituents (Scheme 16–19) and evaluated their biological activity toward the Sendai virus, finding potent and selective antiviral activity. The authors used a metalation-alkylation sequence developed previously from 34, which gave the anion 34$^-$ when treated with lithium diisopropylamide (LDA), and then the anion trapped with $\alpha$-chloroketones 35 giving the oxiranyl methyl uracils 36 (Scheme 16).

The reaction of lithium enolate 34$^-$ (R = Me) with $\gamma$-chloroketones gave tetrahydrofuranyl methyl uracils (37); however, the yields were low (Scheme 17). The reaction of 34$^-$ (R = glycoside) with 3-chloropropyl-methyl ketone afforded 38 in modest yield. With a similar approach, uracil precursor 39 afforded oxiranylmethyl derivative 40 and tetrahydrofuranylmethyl analogues 41 (Scheme 18).
The use of 6-chloromethyl-1,3-dimethyluracil (42) instead of 39 allowed the preparation of 6-oxiranyl uracils 43 in acceptable yields after reaction with ketones (Scheme 19). Lithiation of 5-iodo-2′-deoxyuridine sodium salt was accomplished by Suemune et al. to give compound 44, used to prepare different 5-substituted-2′-deoxyuridines (45) in good yield by reaction with MNP, CH₂I, CD₃OD, TMSCl, PhCHO and CH₃SSCH₃ as electrophiles (E+, Scheme 20).

Reese and Wu synthesized 5-(2-deoxy-β-D-ribofuranosyl)-2,4-dioxo-pyrimidine (2′-deoxypseudouridine, 49) as part of a study oriented to the synthesis of monomers for the antigen approach to oligonucleotide-based chemotherapy. In contrast to other synthesis of 49, 2-deoxy-D-ribose was used as the source of the sugar to prepare lactone 47 (Scheme 21).
Compound 46 was lithiated and allowed to react with 47 giving an acyclic compound, which after reduction and cyclization (under Mitsunobu conditions) afforded the protected product 48. The latter compound was deprotected to yield 49.

(−)-7-Epiculindospermopsin (57) is an example of a complex 6-substituted uracil derivative; the total synthesis of this compound was developed by White and Hanses. They used a masked uracil nucleus, 2,4-dimethoxypyrimidine, which gave the uracil in the penultimate step of the synthesis. The synthesis of 57 was developed from barbituric acid in 23 steps (0.6%). The authors proposed the synthesis of 57 from two fragments 53 and 54. Synthesis of 53 started with the preparation of 4-bromo-2,6-dimethoxypyrimidine 50 from barbituric acid (83%). 50 was then lithiated and allowed to react with 51 to give 52 in 97% yield, then 52 was transformed to 53 in 7 steps (34% from 52). The reaction of 53 and 54 afforded 55 in 60% yield. The nitrile oxide was transformed to 56 in 13 steps in 3.8% yield, the last step being the deprotection of the uracil with HCl. Finally, sulfation of 56 gave 57 (63%).

Boudet and Knochel used an improved bromine/magnesium exchange of 5-bromo-6-halo-2,4-dimethoxypyrimidine (58) to prepare 5,6-disubstituted uracils. The use of one equivalent of the magnesium reagent gave a regioselective substitution of the halogen in position 5, affording 6-halo-5-substituted-2,4-dimethoxypyrimidines (59) with good yields (70–91%) by reaction with different electrophiles (E₁+), such as aldehydes, acyl chlorides, allyl and benzyl bromide, TMSCl, and TsCN (Scheme 23). Access to 5,6-substituted uracils 60 was possible in two successive steps (69–81%) without the need to isolate 59.

Oxypurinol 61 and emivirine 62 (Scheme 24) were prepared as an application of this methodology, where hydrolysis with HCl in MeOH at reflux was used to convert the 2,4-dimethoxypyrimidines into uracils.
In the same type of studies with magnesium compounds, Kopp and Knochel synthesized uracils without the need to protect the acidic proton of uracil (Scheme 25). They prepared the tri-anion 64 from 5- and 6-iodouracils 63 and allowed it to react with different electrophiles (aldehydes, bromides, alkenes) obtaining good yields of the substitution products 65 (Scheme 25). The authors were able to synthetize a precursor (65) of emivirine 62 (X = i-Pr, Y = CH₂Ph).
a. Perfluoroalkyl Compounds

Perfluoroalkyl derivatives are an important class of the family of uracil compounds because of the special properties provided by fluoro atom. Compared to the synthesis of alkyl derivatives, perfluoro derivatives have been less explored, probably due to the difficulties found in the chemistry of perfluoroalkylated compounds.

Savéant et al. have used an electrochemically-induced $S_{RN1}$ reaction to prepare 5-perfluoroalkyluracils in moderate yield (Scheme 26).²⁷

Strekowski et al.²⁸ synthesized 5-perfluoroalkyluracils 67 from 5-bromo-2,4-diethoxyopyrimidine (66) and iodoperfluoroalkanes in two steps (Scheme 27). They used a known procedure which utilized a Cu-Bronze reagent to prepare uracils 67 with better yield than those previously reported.²⁹

6-Perfluoroalkyl uracils and thiouracils (3-aryl and 3-alkyl) have been prepared from esters, perfluorinated nitriles, and iso(thio)cyanates (Scheme 28).³⁰ The first step of the synthesis involves the reaction of the enolate of ester 68 with the nitriles to give fluorinated $\beta$-enamino esters (69), which after treatment with NaH, reacts with iso- and isothiocyanates to afford uracils 70 in good yields. The methodology seems to be useful to prepare even 5,6-disubstituted uracils.
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The good results obtained encouraged the authors to perform the synthesis of the same compounds through a solid-phase approximation. Linking the ester to a Wang resin (R = resin in Scheme 28) they were able to prepare 3-aryl and 3-alkyl-6-(difluorophenylmethyl)uracils in good yields (67–89%) with moderated to very good purity (65–99%); thiouracils were also prepared, but the yields and purity were lower (55–63% and 61–73%).

The fluorous synthesis with tagged ester (R = Rf, Scheme 27) was accomplished more recently. The uracils (R1 = H, Rf = CF2CH2CH = CH2, R2 = aryl, alkyl) were obtained with good yields (52–99%).

Recently, 5-trifluoromethyl uracils were synthesized from uracil and CF3I in modest to excellent yields using a catalytic system of FeSO4, H2O2 and H2SO4. The authors were able to scale the synthesis to the use of 40 Kg of uracil. Using this approach to prepare 5-trifluoromethyl derivatives from substituted uracils was also successful (Scheme 29).

### Scheme 28

The synthesis of 5-methyl-1,6-diphenyluracil and 5-methyl-6-phenyl-1-(phenylmethyl)uracil (72) was performed from the Baylis-Hilman adducts 10 described in Section I.1 (Scheme 4) through cyclization of the urea 71 (Scheme 30).
Searching for a rapid and economical screening of inhibition of human deoxyuridine triphosphate nucleotidohydrolase (dUTPasa) and human nuclear uracil DNA glycosylase (UNG2), Stivers et al. developed a strategy to prepare tris-uracil oximes from oxyamine and 5-formyluracil and aryl aldehydes (Scheme 31). The synthesis involved reaction in DMSO at 37°C; a mixture of the homotrimeric and heterotrimeric compounds were obtained. More than two hundred aryl aldehydes were used and the mixtures were screened for active compounds without purification of the mixtures.

As part of a study on the reactions of metal (Cr, W) carbene complexes, Ricart et al. synthesized monoalkyl (1 or 3) and 1,3-dialkyl-6-phenyluracils via reaction of carbenes with substituted ureas, followed by oxidation of the metal carbonyl complex to (Scheme 32). The synthesis of complexes was accomplished at room temperature under MW irradiation with good yields that were better than with conventional heating with shorter reactions times (days to hours) and allowing the reactions to be performed, in some cases, without solvent. The authors studied several oxidants to transform into and
found that the use of TABF open to air and t-butyl hydroperoxide were the most generally useful reagents.

Using Ni(0) as catalyst (see Scheme 14), Duong and Louie prepared 6-carbonyl and 6-vinyl-5-(trimethylsilyl)uracils (82) from one alkyne and two isocyanates (Scheme 33) in moderate yields (38–43%). Although the synthesis of 5,6-diphenyl derivatives was not possible, the stannane 82 (R1 = SnBu3, R2 = methyl, R = ethyl) was prepared using this approach and reaction with PhI in a Stille reaction (Pd(PPh3)4, CuI, DMF 60°C), gave 6-methyl-5-phenyl-1,3-diethyluracil in 75% yield in the two steps.

Recently, Vasella et al. have prepared a versatile 6-diazomethyuracil derivative 29 (Scheme 34). The synthesis started with 6-formyl-1,3-dimethoxymethyluracil (83) which, after reaction with NH2NH2, gave hydrazone 84 in 84% as a mixture of E/Z isomers in a ratio of 9:1. This mixture was allowed to react with MnO2 to give compound 29 in 90% yield.

Reactions of compound 29 in the presence of Rh(OAc)2 in CH2Cl2 afforded dimeric compounds 85 as a mixture of Z (45%) and E (22%) isomers (Scheme 35) through the formation of carbenoids. Deprotection of 85 with BBr3 gave diuracil 86 in moderate yield (Z (52%) and E (58%)).
Reactions induced by Rh(OAc)$_2$ in the presence of different carbenophiles afforded 6-
substituted and fused compounds (see Scheme 13 and Scheme 70–72). When 2-styrylfuran
was used as the carbenophile, ketone 87 was obtained as a mixture of four $E/Z$ isomers.
However when the reaction was allowed to equilibrate during seven days, it afforded
($E,E,E$)-87 in 60% (Scheme 35).

From 2003 to 2005, a series of polysubstituted uracils were synthesized by Chen et al.
in a study of gonadotropin receptor antagonists. They used a Pd-catalyzed Suzuki-Miyaura
reaction to synthesize 5-aryluracils (89) from 5-halouracils (88) (Scheme 36). Aldehyde,
amino, methylaryl as well as chiral structures were used as substituents in positions 1 and
3 in substrate 88. Boronic acids or pinacol esters of 1-naphthyl, 2-dibenzofuranyl$^{37}$ and
phenyl with OCH$_3$, OH, OCF$_3$, OPh, alkyl,$^{37,38,39}$ F, Cl, SCH$_3$, OR and alkenyl groups as substituents$^{37,39}$ were used to obtain moderate to good product yields.

Agrofoglio et al.$^{40}$ have developed a strategy to prepare 5-(2-furyl) and 5-(2-thiophenyl)
acyclo-nucleosides (89, $R^1$ = acyclic diol, $R^2 = R^3 = H$) from 5-iodouracil. They used a
catalytic system (Pd(OAc)$_2$ AsPh$_3$, K$_2$CO$_3$ in THF) to introduce the aryl moiety and the
products were obtained in good yields (68–94%). The synthesis with an alkenyl boronic
acid (RCH = CH$_2$B(OH)$_2$) was also tested (52–60%); however, the competition with a
Heck reaction led to a mixture of isomers impossible to separate.

More recently, Pomeisl et al. employed the same approach to synthesize 5-aryl-1-(2-
phosphomethoxy)ethyl uracil (89, $R^1$ = CH$_2$CH$_2$OCH$_2$P(O)(OR)$_2$, $R^2 = R^3 = H$) with
moderate isolated yield (24–58%) using the boronic acids of 1-naphtyl, 2-phenylvinyl, 4-fluorophenyl, 3-nitrophenyl, 2-furyl, phenyl, 3- and 4-pyridyl. As part of a study within the development of labeled PNA, Oquare and Taylor used a Heck reaction to prepare (E)-3-(1-(2-t-butoxy-2-oxoethyl)-2,4-dioxo-1,2,3,4-tetrahydroprymidin-5-yl)acrylic acid (91) from 1-(2-t-butoxy-2-oxoethyl)-5-iodouracil (90) (Scheme 37). This reaction was a key step in a synthesis of a PNA monomer derived from uracil, produced in 6 steps and 30% overall yield from commercial 5-iodouracil.

Scheme 37

The synthesis of 5-bromoacetyl uracils 93 from 92 has been accomplished in 40% yield (Scheme 38) using a Stille reaction. The ultimate goal was the synthesis of 5-thiazolyl uracils from 93 derivatives, but somewhat surprisingly, the yield of this transformation was not reported. Mintas et al. have also used this strategy to prepare 5-aryl and 5-alkenyl uracils substituted with a derivative of L-ascorbic acid at N1. They utilized tributylstannanes to obtain compounds 94 in 31–43% yield (Scheme 39).

Scheme 38

Scheme 39
6-Aryl and 6-acyl uracils were recently synthesized from the commercially available 6-chloro-2,4-dimethoxypyrimidine (95). The photostimulated reaction of 95 with the anion $\text{SnMe}_3$ in liquid ammonia afforded stannane 96 in high yield through a $\text{S}_{\text{RN1}}$ reaction. Compound 96 was employed in a Stille reaction with 1-iodonaphthalene affording pyrimidine 97 in good yields. Finally the target uracil 98 was obtained by hydrolysis in quantitative yield (Scheme 40).

When the three steps ($\text{S}_{\text{RN1}}$ reaction-cross coupling reaction-hydrolysis) were performed in a one-pot reaction without the need to purify intermediates 96 and 97 (Scheme 41), 6-substituted uracils 99 ($R = \text{1-naphthyl, 4-chlorophenyl, 3-chlorophenyl, 2,3,4,5,6-pentafluorophenyl}$) were obtained (43–57%) in isolated pure products. When the electrophile was a benzoyl chloride (99, $R = \text{ArCO}$), 6-benzoyl (54%) and 6-(2-chlorobenzoyl) uracils (49%) were obtained as isolated pure products.

Koroniak et al. have synthesized pentafluoropropenyl uracils using an addition-elimination approach. The (2,4-dimethoxypyrimidin-5-yl)lithium compound derived from 100 allowed the preparation of 5-pentafluoropropenyl-2,4-dialkoxypyrimidine ($E$ and $Z$ mixture, 101) by reaction with commercial hexafluoropropene. Substitution on position 6 was possible from 101 ($R = \text{Et}$) instead of 100, to give 5,6-dipentafluoropropenyl-2,4-dieethoxyxypirimidin; however, the yield was low (43%). Compound 101 ($R = \text{t-butyl}$) after hydrolysis gave uracil 102 in good yields (Scheme 42).
From 1,3-dimethyl-5-substituted uracils (103) the authors were able to prepare 6-pentafluorouracil (104) with 47–59% yield for X = F, Me (Scheme 43) but the reactions were not general, because no products were obtained from addition-elimination when X = H, Br, NO2.

\[ \begin{align*} 
103 \xrightarrow{\text{BuLi}} & \quad 104 \\
X & \quad X = F (59\%); \text{Me (47\%)}
\end{align*} \]

Scheme 43

Savéant et al.\textsuperscript{46,47} have synthesized 5-aryluracils (106) by the reaction of uracil anion (105) with aryl iodides, using an electrochemical approach (Scheme 44, see also Scheme 26). The reactions were postulated to occur through an S\_RN\_1 reaction and the yields were moderate, where 1-imidazolyl and benzene compounds with NO\_2, CN, COPh, CF\_3, F as substituents were introduced.

\[ \text{O'} (\text{CH}_3)_4 \text{N}^+ + \text{ArI} \xrightarrow{\text{e}^-} \text{DMSO} \rightarrow \text{Ar} \quad \text{106 (35-50\%)} \]

Scheme 44

Using another electrochemical reaction Davarani et al.\textsuperscript{48} have recently synthesized catechol-uracil derivatives (109) in very good yields from 6-aminouracils 107 and catechols 108 (Scheme 45). The reactions proceed through an electrochemical oxidation of catechols followed by a Michael addition and were regioslective, giving only substitution in position 4 of the catechols.

\[ \text{R} = \text{H, CH}_3; \text{R}' = \text{H, CH}_3, \text{OCH}_3 \]

\[ \text{107} + \text{108} \xrightarrow{-2 \text{e}^--2\text{H}^+} \text{H}_2\text{O} \rightarrow \text{109 (84-94\%)} \]

Scheme 45
3. C(Uracil)-C(sp) Bonds

The Sonogashira coupling of terminal alkynes has been used to obtain modified nucleosides.\(^4^9\), \(^5^0\) Recently, Hudson \textit{et al.}\(^5^1\), \(^5^2\) adopted this approach to prepare 5-alkynyl derivatives with an ester group at N1 or as part of a PNA monomer (Scheme 46). The authors were able to prepare compounds 110 from 5-iodouracil in modest yield (38–53\%) through the reaction of different alkynes. The synthesis also was performed with the uracil-PNA unit linked to an insoluble polymer support.\(^5^1\)

\[ \text{R}^1 \text{C≡C} + \text{I}\text{N} \overset{\text{Pd(PPh}3\text{)}2\text{Cl}_2 \text{or Pd(PPh}3\text{)}4, \text{Cul, NEt3, DMF or THF, rt or 50°C 2-16 h}}{\rightarrow} \text{R}^1 \text{C≡C} \]

\[ \text{R}^1 \text{C≡C-N} \overset{\text{9H-fluoren-2-yl (84\% R'}}{\rightarrow} \text{R}^1 \text{C≡C-N} \]

Scheme 46

Under similar experimental conditions, Mintas \textit{et al.} reported the synthesis of fourteen 5-alkynyl nucleoside analogues (111) in moderate to good yield from (Z)- and (E)-1-[4'-\((N\text{-phthalimido})\)-2'-butenyl]-5-iodouracil (Scheme 47).\(^5^3\)

\[ \text{R} \overset{\text{RC≡CH, Pd(PPh}3\text{)}4, \text{Cul, i-Pr}2\text{EtN, DMF, rt}}{\rightarrow} \text{R} \]

\[ \text{R} = -(\text{CH}_2)_3\text{CH}_3, -(\text{CH}_2)_4\text{CH}_3, -(\text{CH}_2)_5\text{CH}_3, -(\text{CH}_2)_7\text{CH}_3, -(\text{CH}_2)_2\text{Ph}, 4-\text{PhBr}, 4-\text{PhCH}_3, 4-\text{Ph}(\text{CH}_2)_3\text{CH}_3, 4-\text{Ph}(\text{CH}_2)_4\text{CH}_3 \]

Scheme 47

The Stille reaction has been also used by Mintas \textit{et al.} to prepare 5-alkynyl derivatives.\(^4^3\) They employed a set of tributylstannanes to prepare compounds 112 (R = H (44\%), R = Me (33\%) yields, Scheme 48).
4. C(Uracil)-Heteroatom Bonds

a. C(Uracil)-N Bonds

Uracils linked to amines are perhaps the most studied heteroatom-substituted derivatives due to the fact that many synthetic and natural compounds of this type exhibit a diverse range of biological activities. The synthesis of 6-aminouracils from condensation of 2-cyano acetic acid with urea and \( N \)-alkylureas was developed by Traube in 1900, but the reaction times were long and the yields poor. Recently, Devi and Bhuyan have improved this synthesis by performing the reaction without solvent under MW irradiation, obtaining good yields of 6-aminouracils (Scheme 49).

Although, the synthesis of many 6- and 5-(N-substituted) uracils has been developed in the 1970s, Wright and co-workers synthesized 6-(3-ethyl-4-methylanilinyl)-3-alkyluracils (114) using a modified method from 6-amino pyrimidinone (113) with good yields (Scheme 50). Concomitant deprotection of the imido group happened to give uracil directly.

With a similar approach Spiccia et al. have recently synthesized a PNA monomer attached to a ferrocenyl moiety. From dimethyl(ferrocenyl-methyl) ammonium salt 115, the reaction with 5-aminouracil, uracil 116 was obtained in good yield (Scheme 51).
In a detailed study of the reaction of 6-chlorouracils with pyridines and 1-methylimidazole, Schmidt and Kindermann synthesized uracilates, uracilium salts 118, and uracilylbetaines 119 (Figure 3).59 Reaction of 6-chloro-1,3-dimethyluracil with both heterocycles produced uracilium salts 118 in good yield (65–67%); derivatives of pyridine 18a could be isolated with different anions (X = Cl, BPh4, SbCl6, I, OTf).

The use of 6-chloro-3-methyluracil could give mesomeric uracil betaines 119 (58–79%) for the reaction with the same amines (Figure 3). The reaction of 119 with 1,2-dichloroethane afforded 1,1′-(3,3′-(ethane-1,2-diyl)bis(1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4,3-diyl))bis(4-(dimethylamino)pyridinium) (Figure 4) in 88% yield.

### b. Synthesis of 5,6-Halogen Derivatives

In many cases, halogens as substituents in uracil derivatives lead to interesting biological activity and/or improved biological properties. Additionally, most of the substitution on the uracil nucleus is performed by substitution of the halogen on 5- or 6- (or 5,6-) halouracils by different functional groups. For this reason, various syntheses of 5- and 6-halogen uracils have been studied and the search for better conditions is of current interest. 5- and 6-Halogenuracils have been synthesized by I2/nitric acid, ICl, Br2/(AcO)2O, Br2/H2O, Br2/DMF, Cl2, NXS, CAN/halogen source, among others.60–62
Recently, in a search for a more friendly approach to the iodination of pyrimidine-2,4-diones, Botta et al. synthesized 5-iodouracils from uracils (Scheme 52). With N-iodosuccinimide (NIS) as the iodine source and three minutes MW irradiation, excellent yields of substitution products (97–98%) were obtained. The use of an unprotected nucleoside gave a yield of 65%. The authors tested the methodology in solid-supported chemistry and obtained good results, demonstrating the applicability of solid-phase organic synthesis for pyrimidones and nucleosides.

Scheme 52

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c. C(Uracil)-Other Heteroatom Bonds

Using the methodology described in Section I.1 (Scheme 25), Kopp and Knochel also prepared 5-phenyl(methyl)sulfanyluracil and 5-trimethylsilyluracil in good yields (64–77%). Doung and Louie (Section I.1, Scheme 14) synthesized 5-trimethylsilyl-6-alkyl-1,3-aryluracils with variable yields (17–83%). Suemune et al. (Section I.1, Scheme 20) have synthesized 5-trimethylsilyl- and 5-(methylthio)-2′-deoxyuridine in good yields (62–85%).

II. Fused Systems

1. C5-C6 Polycyclic Uracils

In a search for new uracils, Botta and Saladino et al. have synthesized fused pyrazole derivatives, through the reaction 5- and 6-substituted uracil with lithium trimethylsilyldiazomethane TMSC(Li)N₂ (121) or diazomethane. The authors used N1,N3-alkylated uracils and N3-alkylated uridines and found umpolung of reactivity of 121 in reaction with C6 derivatives.

When unsubstituted or 5-fluorouracils 120 (X = H, F; Y = H) were allowed to react with 121, products 122 were obtained in good yield (Scheme 53); the formation of the
products is attributed to nucleophilic attack at C6 and subsequent cyclization. When X = NO2, CN or CHO, poor yields or no cyclic product 122 were obtained; however, in the case of the nitro compound using diazomethane instead of 121 gave an acceptable yield (39–45%) of 3a,7a-dihydro-4,6-dimethyl-7a-nitro-Δ1-pyrazolino[4,3-d]pyrimidin-5,7-dione regioisomer analogue to 122.367

With C6 substituted uracils (120, X = H), the reaction with 121 gave a mixture of 122 and pyrazolidine 123 (Scheme 53), due to attack of 121 to C5 instead of C6. The use of an isopropyl group at C6 allowed the preparation of 123 in good yield without the formation of 122.371 The reaction with halogen (other than fluorine) was only successful when X = Br, giving fused uracil derivatives 124 after loss of hydrogen bromide (Scheme 54).

Scheme 54

Bhuyan and co-workers have synthesized various complex fused uracils by means of different approaches.66–68 From N,N-dimethyl-5-formylbarbituric acid or 6-aminoo-1,3-dimethyluracil (125), pyrano-(126a) and pyrido[2,3-d]pyrimidine (126b) and (thio)oxazino[4,5-d]pyrimidine (127a and 127b) were prepared through a MW-assisted solid-phase (Scheme 55). Using maleimide or phenyl isothiocyanate as dienophiles, the authors showed that MW-assisted reactions gave better yields than conventional thermal reactions.66

More recently, access to fused-spiro uracils (129) from 6-(N,N-dialkylamino)-5-formyluracil (128) and barbituric acids was demonstrated (Scheme 56).67 A hypothetical mechanism was proposed but poorly demonstrated: after Knoevenagel condensation to give product 128a an internal redox process occurred to generate a 1,6-dipole through a 1,5-H shift. Cyclization of the zwitterion formed gave the final product (Scheme 57).
Synthesis of 5- and 6-Substituted Uracil Derivatives

Scheme 55

A stereoselective intramolecular hetero Diels-Alder reaction of compound 130 (Scheme 58), prepared from barbituric acids and salicylaldehyde, allowed the preparation of the fused system 131 in good yield with less than 5% of the trans-stereoisomer. A similar approach was used by Gross et al. to prepare 133 in very good yields (Scheme 59) from 1,3-dimethyl barbituric acid and aldehydes 132. A domino Knoevenagel-hetero-Diels-Alder reaction was used and although a catalytic amount of CuI is required to activate the alkyne, the reactions have the advantage of using water as solvent.

An intermolecular variation of this hetero-Diels-Alder reaction was used to prepare pyrano[2,3-d]pyridine-2,4-dione 137 from 5-arylidene-1,3-dimethylbarbituric acid 136 and...
enol ethers 135. The goal of the authors was to prepare compounds 137 via a three-component one-pot synthesis, as shown in Scheme 60, giving the desired products in excellent yields.\(^2\)
was obtained for \( n = 0 \) but by using different Ru catalysts the authors could control, the reaction obtaining \( 141a \) (\( n = 1 \)) or \( 141b \) as a single product from \( 140a \) (\( n = 1 \)).

As shown in Scheme 63, the preparation of N1-C6 fused-uracils \( 142 \) was also possible from \( 140b \).

Through a well-known Pd-catalyzed arylation, Woodward \textit{et al.} have synthesized uracils fused to a phenyl group in good yields from reaction of 2-bromobenzoic methyl esters (\( 143 \)) and substituted ureas (\( 144 \)) (Scheme 64).\textsuperscript{72} Both electron-donating as well as electron-withdrawing substituents in the phenyl moiety are tolerated. In addition, a regioselective reaction was obtained with monosubstituted ureas \( 144 \) (\( R_1 = H \)) to obtain N3 alkyl uracils \( 145 \) (\( R_1 = H \)).

From substituted phenylamines, Rivkin \textit{et al.}\textsuperscript{73} prepared analogues of \( 145 \), mono and disubstituted in the phenyl ring, using \textit{bis}(pentafluorophenyl) imidodicarbonate (\( 146 \)) in a
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Scheme 64

solvent-free MW reaction; the yields were moderate to good (44–78%). The use of other heteroaromatic amines (147) allowed the authors to prepare compound 148 in moderate yield (Scheme 65). The synthesis of one disubstituted uracil was carried out from (2E)-3-amino-3-(4-bromophenyl)acrylonitrile in 84% yield.

Scheme 65

Xanthine (151a) or pteridine (151b) derivatives were obtained in moderate to good yields from 5,6-diamino-1,3-dimethyluracil (149). The synthetic sequence involves the preparation of enamines 150 from aldehydes and subsequent reaction with different one-carbon sources (triethyl orthoformate, orthoacetate or orthobenzoate). Depending on the ortho ester used, 151a or 151b was obtained (Scheme 66).74

Scheme 66

Spiro[pyrimido-[4,5-d]quinoline-5,5′-pyrrolo[2,3-d]pyrimidine]pentanones (154) were synthesized by Bazgir et al. from 6-aminouracils (152) and 5-substituted indoline-2,3-diones (153) (Scheme 67), using water as solvent and 4-toluenesulfonic acid (4-TSA) as catalyst. The complex polyheterocyclic compounds 154 were obtained in very good yields (78–90%).75 Although a mechanism could not be established with certainty, a possible route was proposed as depicted in Scheme 68.

It has been shown that the replacement of one carbon atom by nitrogen is a good strategy to obtain new potential antitumor compounds from known anticancer drug.76–78
In line with this, Valderrama and Vásquez proposed the synthesis of aza-analogues of angucyclinone (Figure 5).

The authors synthesized quinones 156 in good yields from hydroquinone 155 and 6-amino-1,3-dimethyluracil using Ag₂O in CH₂Cl₂ at room temperature (Scheme 69). From compounds 156, adducts 157 and 158 (Figure 6) were synthesized through a cycloaddition reaction with different dienes. Angucyclinone 159 analogues from 157 were finally obtained with good yields by mild hydrolysis with hydrochloric acid followed by oxidation with PCC of the alcohol intermediaries.

Figure 5
Using the versatile diazo compound 29 (see Scheme 34), Vasella et al. have also prepared different fused uracils through a Rh(II)-promoted reaction with different carbeneophiles by an intramolecular reaction.\textsuperscript{20} Thermolysis of 29 in toluene gave a 1:1 mixture of 1\textit{H}- and 2\textit{H}-pyrazolo[4,3-\textit{d}]uracil in 55% yield after deprotection with BBr\textsubscript{3} (Scheme 70).

The reaction of 29 with 2-methoxypropene in the presence of Rh\textsubscript{2}(AcO)\textsubscript{4} (Scheme 71) gave a cyclopropane derivative (\textit{endo}/\textit{exo}) from addition to the double bond, which after treatment with AlClMe\textsubscript{2} gave the cyclopenta[\textit{d}]pyrimidine 160 in 55% yield. The reaction of dihydrofuran and dihydropyran afforded tricyclic uracils 161 and 162 in 51% and 88% yields respectively, through the same reaction sequence. The use of furan gave 163 in 73% yield without the need of Al(III) catalysis.

The acid-catalyzed intramolecular cyclization of 86 prepared from 29 (see Scheme 35), gave fused-diuracil 164 in 73% yield (Scheme 72).\textsuperscript{20}

2. Other Polycyclic Uracils

Uracil derivatives fused at C5-O4 or C6-N1 are less common than the fused uracils previously described; however, some efforts have also been made to develop new synthetic strategies for this family of compounds.
Robins and co-workers extended their work in the synthesis and the biological evaluation of furo[2,3-d]pyrimidin-2(3H)-one and synthesized derivatives 166 (Scheme 73). N1 substituted uracils were synthesized in moderate to good yields (51–83%) from 5-iodouracils 165 (R' = CH₂O(CH₂)₂OH), and different alkynes. The authors performed a Sonogashira coupling following a Cu(I)-promoted cyclization in a two step one pot procedure. The synthesis of free uracil 166 (R' = H) was also done using the same approach, but in two consecutive steps and lower yields (step one 50–80%, step two 28–34%).
Access to pyrrolo derivatives 167 was possible from 166 (R’ = CH₂O(CH₂)₂OH) after treatment with ammonia in methanol (Scheme 73).

Compound 166 (R = H) was also synthesized; however, the yield was low (30%). This compound was used to prepare alkynyl derivatives 168 by performing a bromination and a Sonogashira coupling with different alkynes but again the yields were low (Scheme 74).

III. Glossary

Cp: Cyclopenta-2,4-dien-1-ide
DIEA: N,N-Diisopropylethylamine
DMA: Dimethylacetamide
DMF: N,N-Dimethylformamide
DMSO: Dimethyl sulfoxide
dR: Deoxyuridine
FG: Functional group
LDA: Lithium diisopropylamide
L: Ligand
MW: Microwave
NXS: N-Halosuccinimide
PCC: Pyridinium chlorochromate
PNA: Peptide nucleic acid
SRN1: Unimolecular Radical Nucleophilic Substitution
TABF: Tetrabutylammonium fluoride
THF: Tetrahydrofuran
TMSCl: Trimethylchlorosilane
TMS: Trimethylsilyl
TP: Thymidine phosphorylase
MNP: (CH₃)₃C=N
4-TSA: 4-Toluene sulfonic acid
Xantphos: 2,2’-Oxybis(2,1-phenylene)bis(diphenylphosphine)

Acknowledgements

This work was supported in part by the Agencia Córdoba Ciencia, the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), SECYT, Universidad Nacional de
Córdoba, and FONCYT, Argentina. J. I. B. gratefully acknowledges receipt of a fellowship from CONICET.

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