UOPP #438055, VOL 41, ISS 6

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

Javier I. Bardagí and Roberto A. Rossi

QUERY SHEET

This page lists questions we have about your paper. The numbers displayed at left can be found in the text of the paper for reference. In addition, please review your paper as a whole for correctness.

There are no Editor Queries for this paper.

TABLE OF CONTENTS LISTING

The table of contents for the journal will list your paper exactly as it appears below:
Advances in the Synthesis of 5- and 6-Substituted Uracil Derivatives
Javier I. Bardagí and Roberto A. Rossi

Organic Preparations and Procedures International, 41:1–36, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940903378776

Taylor & Francis
Taylor & Francis Group

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

Javier I. Bardagí and Roberto A. Rossi

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, ARGENTINA

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

Javier I. Bardagí and Roberto A. Rossi

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, ARGENTINA

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.[1] 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.[2]

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[3] and uridines with oxiranyl and tetrahydrofuranyl substituents;[4] c) functionalization of masked uracil moieties with reactions incompatible with the nucleus, for example the synthesis of 6-aryl and 6-acyluracils[5] and 2′-deoxypseudouridine.[6] 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

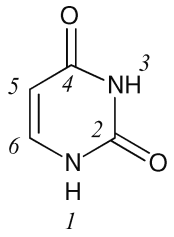
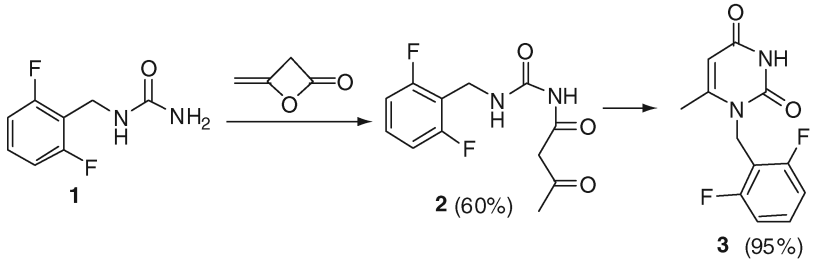


Figure 1

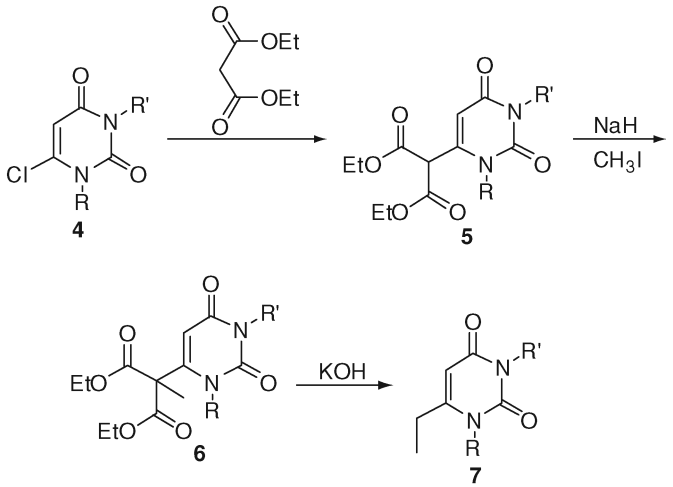
I. Uracils with Carbon-based Substituent

1. C(Uracil)-C(sp^3) 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**).[7] Later the authors developed a more efficient strategy by using diketene, trimethylsilyl chloride, and NaI in CH_3CN,[8] obtaining **3** from **1** in one step in 95% yield.



Scheme 1



Scheme 2

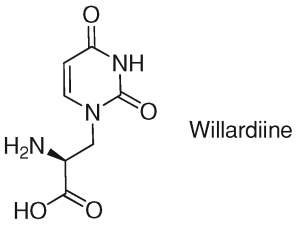
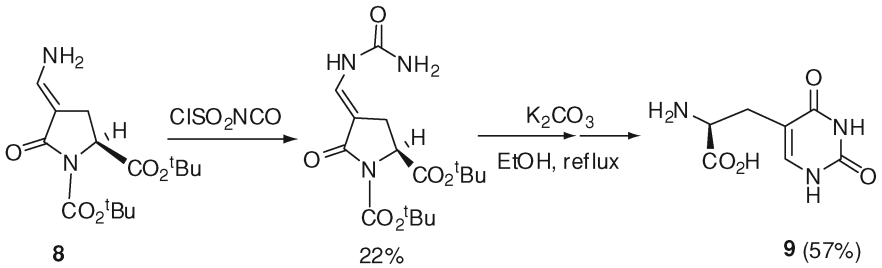


Figure 2

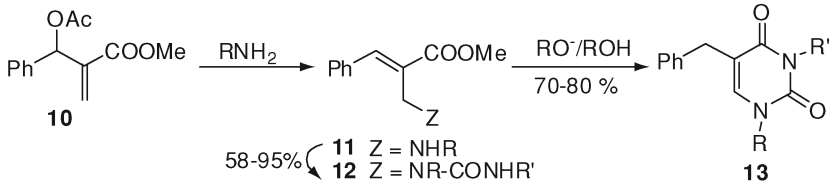
6-Ethyluracil **7** was prepared from 1,3-dialkyl-6-chlorouracil **4** (*Scheme 2*)[9] by reaction with the anion of diethylmalonate to give **5**; the treatment of **5** with NaH and MeI afforded **6**, which by hydrolysis and double decarboxylation induced by KOH gave **7** in 19% overall yield.

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-yl-methyl)-(2*S*)-glycine (**9**) from heterocycle **8** (*Scheme 3*).[10]



Scheme 3

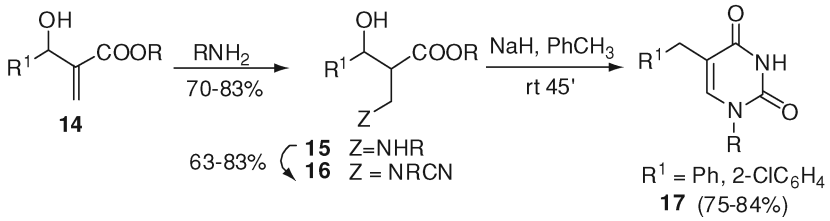
A synthesis of 5-benzyluracils (**13**) from Baylis-Hillman adducts (**10**) was developed by Kim *et al.* (*Scheme 4*).[11] Substitution of acetate by primary amines gave **11** in moderated yield which afforded ureas **12** after treatment with R′NCO. Finally, in the presence of a base, **12** cyclized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



Scheme 4

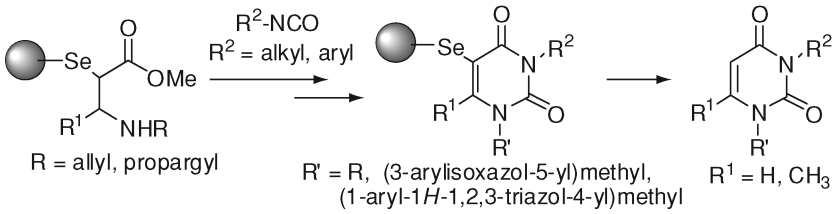
Batra *et al.* synthesized 1,5-disubstituted uracils **17** using the same approach with a slight modification using BrCN instead of R′NCO (*Scheme 5*).[12]

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



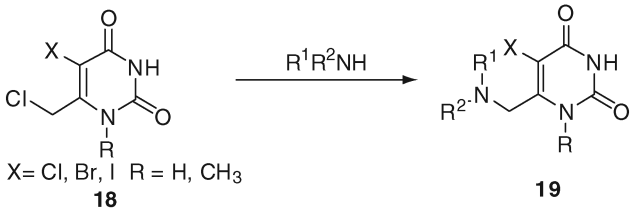
Scheme 5

α,β-unsaturated esters and amines.[13] 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 subtitutient but it has a very limited utility in the synthesis of C5 or C6 derivatives.



Scheme 6

Yano *et al.* have synthesized a family of 6-methylene-bridged uracil derivatives,[14,15] 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.

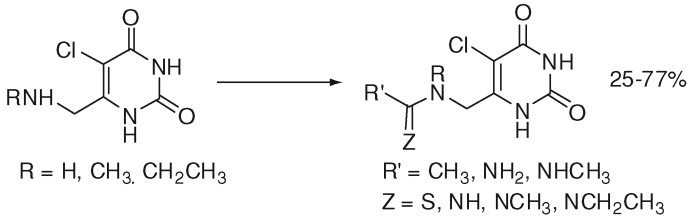


Scheme 7

Later on Corelli *et al.* published their microwave (MW) assisted synthesis of the same type of compounds in methanol as solvent,[16] starting from **18** (R = H, X = Cl)

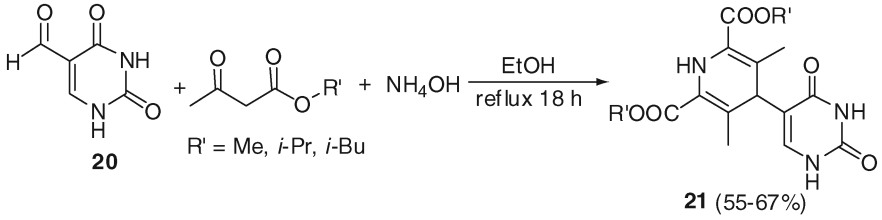
by reaction with different amines. Uracil **19a** (R^1 = H; R^2 = $(CH_2)_2NH_2$) was prepared from the protected **19b** (R^1 = H; R^2 = $(CH_2)_2$NH-Boc). Derivative **19c** (R^1 = H; R^2 = (CH_2)NHC(NH)NH_2) was also prepared from **19a** by reaction with *S*-methylisothiourea.

A series of guanidine, amidino and thioureido derivatives were synthesized from 6-aminomethyl-5-chlorouracil under different conditions (*Scheme 8*).[15]



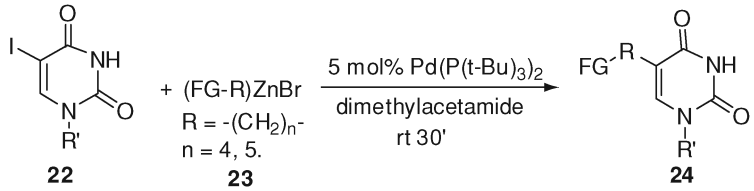
Scheme 8

5-Dihydropyrimidine-uracils (**21**) were synthesized by Knaus and co-workers[17] from 5-formyluracil (**20**) using a three-component Hantzsch reaction (*Scheme 9*).



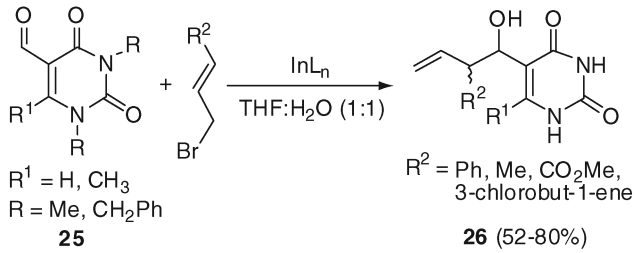
Scheme 9

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, -$OSiR_3$ (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).



Scheme 10

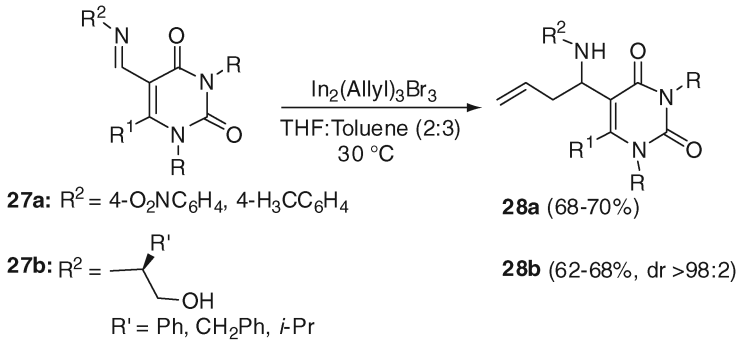
Kumar *et al*. employed an indium catalyst to prepare the 5-substituted uracils (**26** and **28**) from 5-formyluracils (**25**) and from the Schiff bases of **25** (*Scheme 11* and *12*).[19] Allylation of **25** with bromoallyl compounds in the presence of indium metal in a mixture of THF:H_2O (1:1) gave compound **26** in moderate to good yields (*Scheme 11*); diastereomeric



Scheme 11

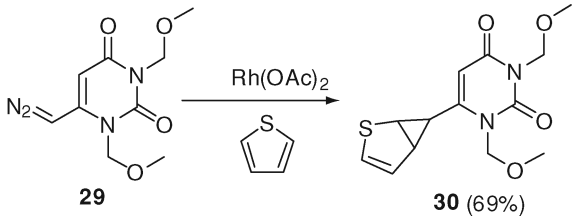
ratios of >99:1 were obtained in the best case. They suggest that the high diastereoselectivity of the reaction results from the complexation of the C-4 carbonyl oxygen of the uracil.

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 R^2 (**27b**) (*Scheme 12*).



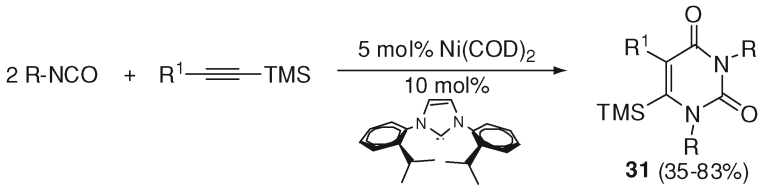
Scheme 12

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.[20]

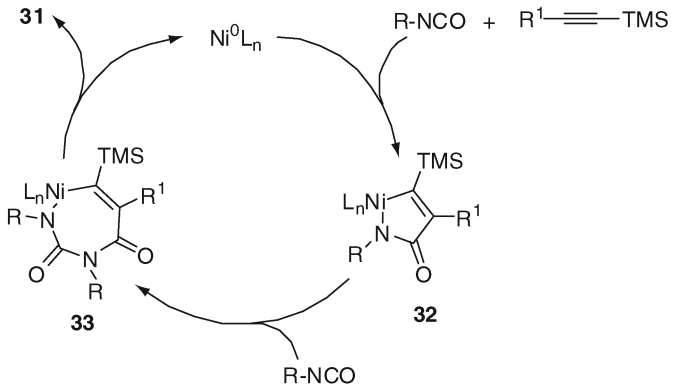


Scheme 13

The synthesis of tetrasubstituted uracils from one alkyne and two isocyanates using a Ni(0) catalyst was reported by Duong and Louie.[21] 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



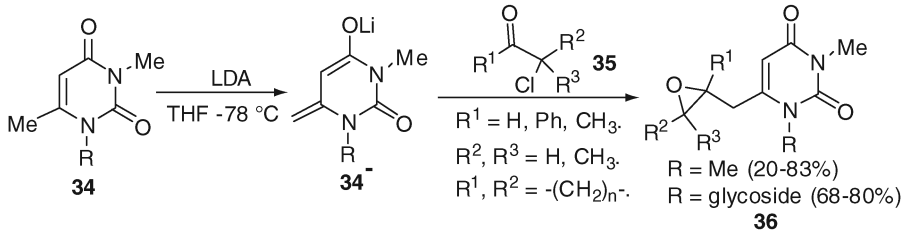
Scheme 14



Scheme 15

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.

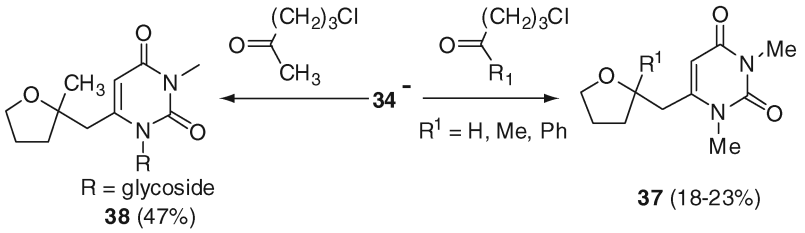
In search for new uracil derivatives, Saladino *et al.* synthesized a series of uracil and uridines with oxiranyl and tetrahydrofuranyl substituents (*Scheme 16–19*) and evaluated their biological activity toward the Sendai virus, finding potent and selective antiviral activity.[4] The authors used a metalation-alkylation sequence developed previosly[22] from **34**, which gave the anion $\mathbf{34}^-$ when treated with lithium diisopropylamide (LDA), and then the anion trapped with α-chloroketones **35** giving the oxiranyl methyl uracils **36** (*Scheme 16*).



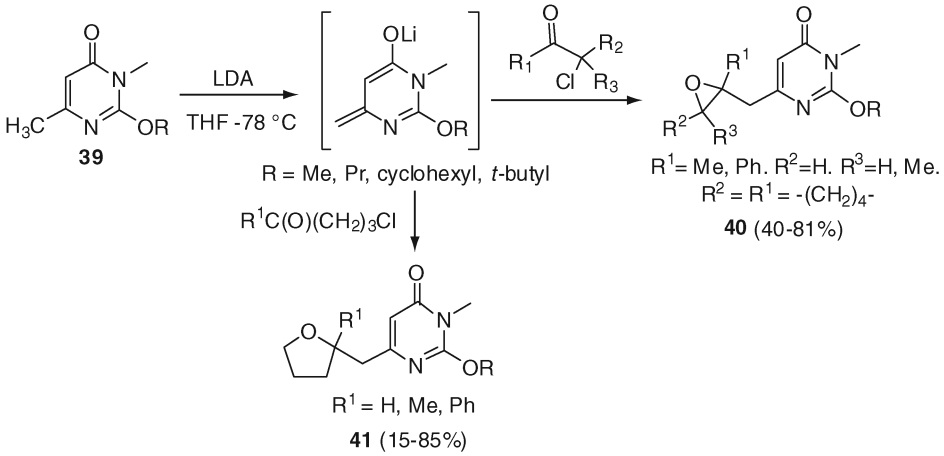
Scheme 16

The reaction of lithium enolate $\mathbf{34}^-$ (R = Me) with γ-chloroketones gave tetrahydrofuranylmethyl uracils (**37**); however, the yields were low (*Scheme 17*). The reaction of $\mathbf{34}^-$ (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*).



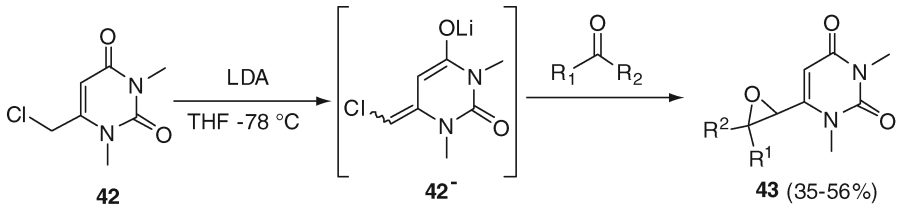
Scheme 17



Scheme 18

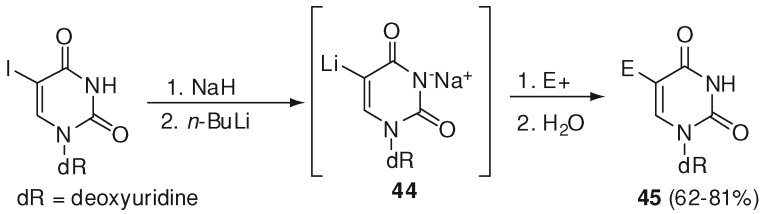
The use of 6-chloromethyl-1,3-dimethyluracil (**42**) instead of **39** allowed the preparation of 6-oxiranyl uracils **43** in acceptable yields after reaction with ketones (*Scheme 19*).

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, CH_3I, CD_3OD, TMSCl, PhCHO and CH_3SSCH_3 as electrophiles (E+, *Scheme 20*).[23]

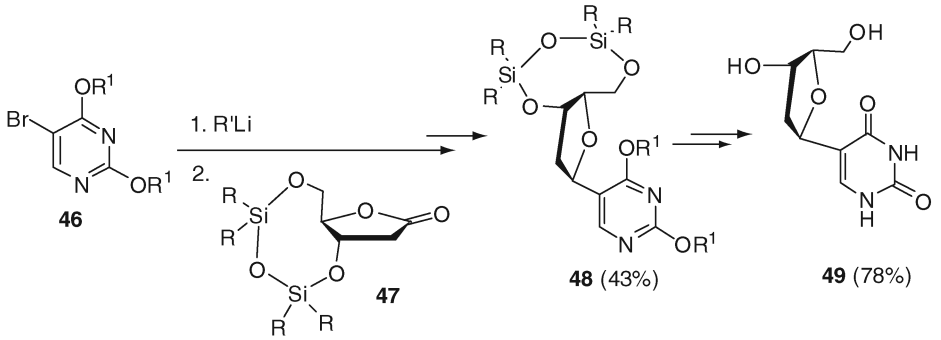


Scheme 19

Reese and Wu[6] 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*).



Scheme 20



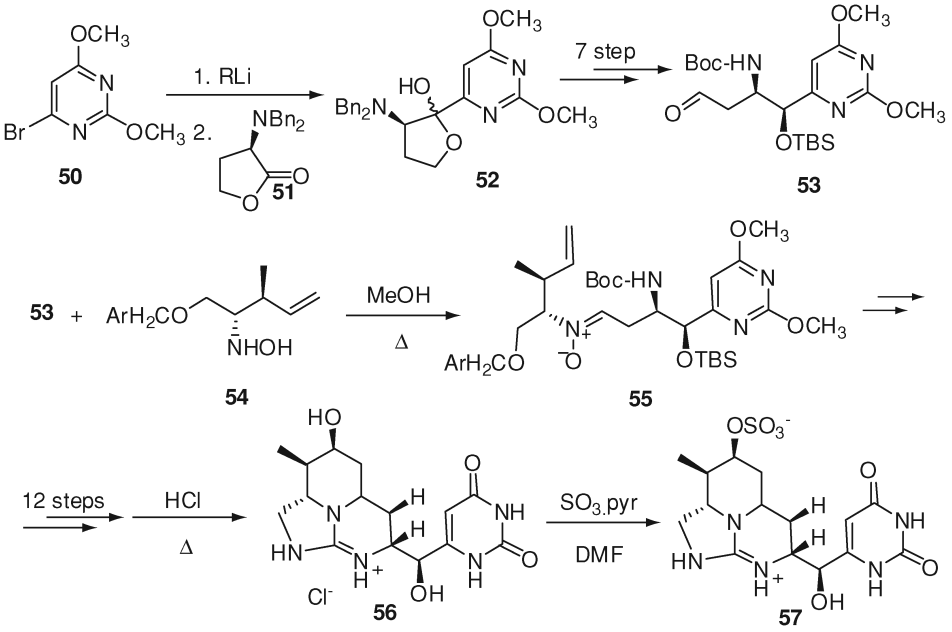
Scheme 21

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**.

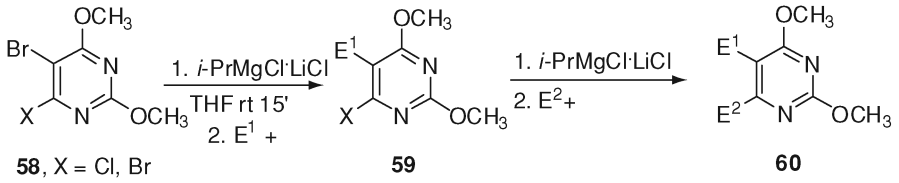
(−)-7-Epiculindospermopsin (**57**) is an example of a complex 6-substituted uracil derivative; the total synthesis of this compound was developed by White and Hanses.[24] They used a masked uracil nucleus, 2,4-dimethoxypyrimidine, which gave the uracil in the penultimate step of the synthesis. The synthesis 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** (*Scheme 22*). 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.[25] 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 (E^1+), 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 emyvirine **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.



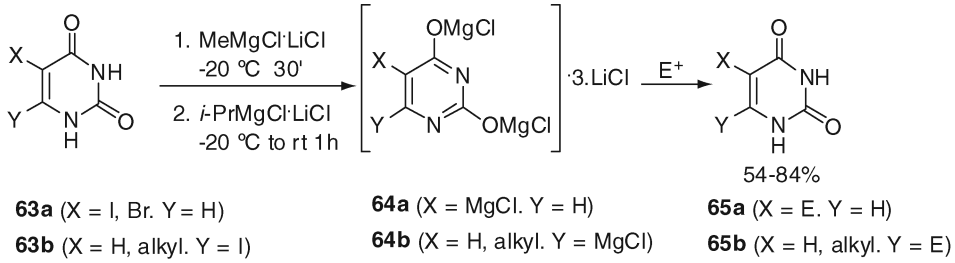
Scheme 22



Scheme 23

Scheme 24

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*).[26] 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 = CH_2Ph).

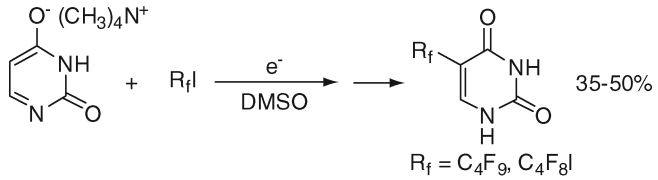


Scheme 25

158 *a. Perfluoroalkyl Compounds*

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

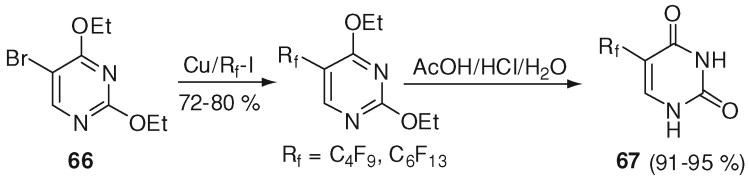
163 Savéant *et al.* have used an electrochemically-induced $S_{RN}1$ reaction to prepare 5-perfluoroalkyluracils in moderate yield (*Scheme 26*).[27]



Scheme 26

164

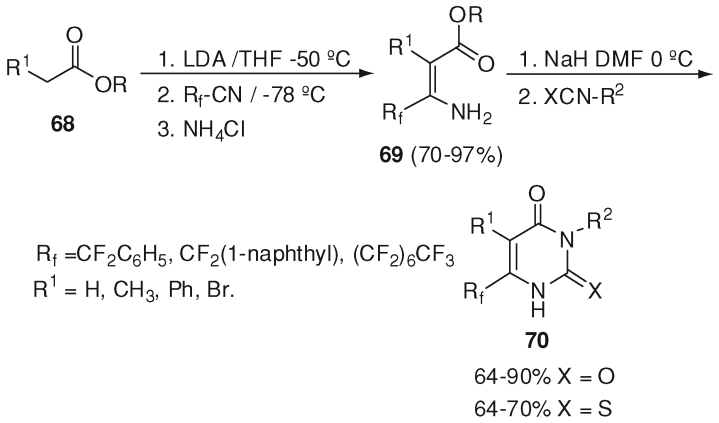
165 Strekowski *et al.*[28] synthesized 5-perfluoroalkyluracils **67** from 5-bromo-2,4-
166 diethoxypyrimidine (**66**) and iodoperfluoroalkanes in two steps (*Scheme 27*). They used
167 a known procedure which utilized a Cu-Bronze reagent to prepare uracils **67** with better
yield than those previously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



Scheme 27

168

169 6-Perfluoroalkyl uracils and thiouracils (3-aryl and 3-alkyl) have been prepared from
170 esters, perfluorinated nitriles, and iso(thio)cyanates (*Scheme 28*).[30] The first step of the
171 synthesis involves the reaction of the enolate of ester **68** with the nitriles to give fluorinated
172 β-enamino esters (**69**), which after treatment with NaH, reacts with iso- and isothiocyanates
173 to afford uracils **70** in good yields. The methodology seems to be useful to prepare even
174 5,6-disubstituted uracils.

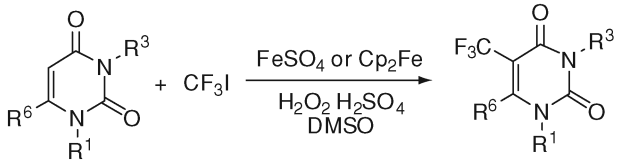


Scheme 28

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%).[30]

The fluorous synthesis with tagged ester (R = R_f, *Scheme 27*) was accomplished more recently.[31] The uracils **70** (R^1 = H, R_f = CF_2CH_2CH = CH_2, R^2 = aryl, alkyl) were obtained with good yields (52–99%).

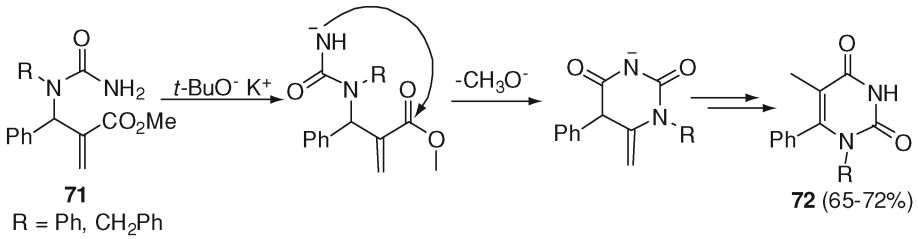
Recently, 5-trifluoromethyl uracils were synthesized from uracil and CF_3I in modest to excellent yields using a catalytic system of $FeSO_4$, H_2O_2 and H_2SO_4.[3] The authors were able to scale the synthesis to the use of 40 Kg of uracil. Using this approach to prepare 5-trifluoromethyl derivatives from substituted uracils was also successful (*Scheme 29*).



Scheme 29

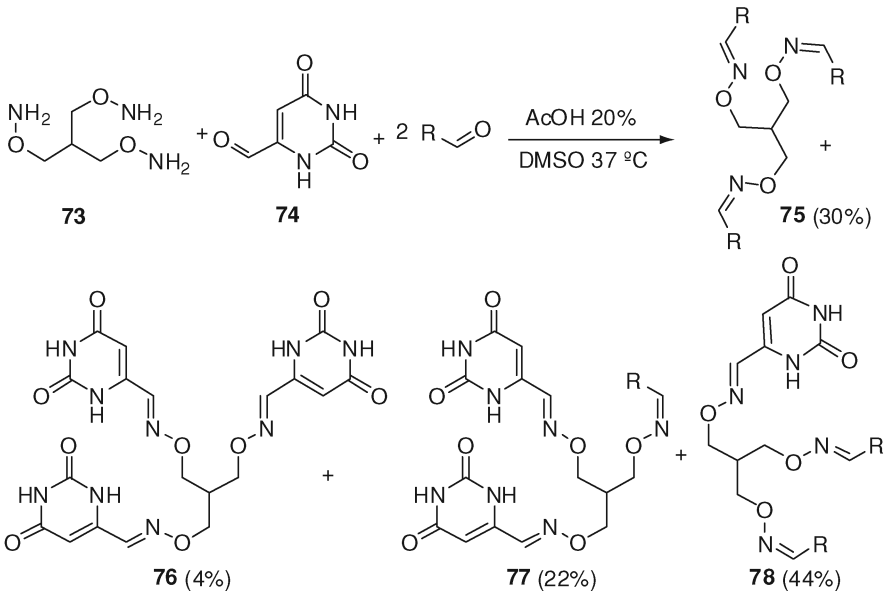
2. *C(Uracil)-C(sp^2) Bonds*

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*).[11]



Scheme 30

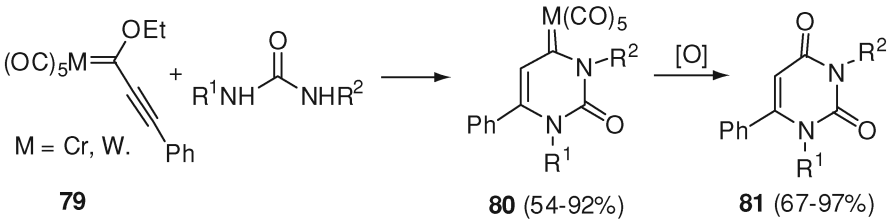
Searching for a rapid and economical screening of inhibition of human deoxyuridine triphosphate nucleotidohydrolase (dUTPasa) and human nuclear uracil DNA glycosylase (UNG2), Stivers *et al.* developed a strategy to prepare tris-uracil oximes from oxyamine **73**, 5-formyluracil (**74**) and aryl aldehydes (*Scheme 31*).[32] The synthesis involved reaction in DMSO at 37°C; a mixture of the homotrimeric (**75** and **76**) and heterotrimeric (**77** and **78**) compounds were obtained. More than two hundred aryl aldehydes were used and the mixtures were screened for active compounds without purification of the mixtures.



Scheme 31

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 **79** with substituted ureas, followed by oxidation of the metal carbonyl complex **80** to **81** (*Scheme 32*).[33–35]

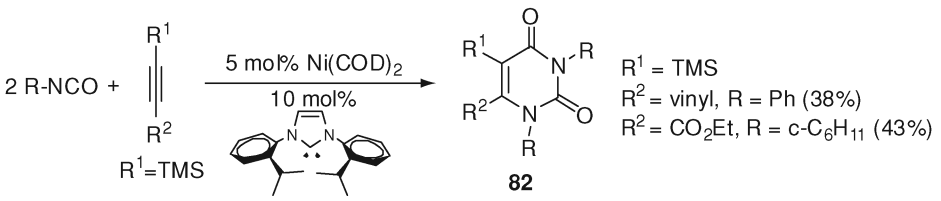
The synthesis of complexes **80** was accomplished at room temperature under MW irradiation with good yields that were better than with conventional heating,[33,34] with shorter reactions times (days to hours) and allowing the reactions to be performed, in some cases, without solvent. The authors studied several oxidants[35] to transform **80** into **81** and



Scheme 32

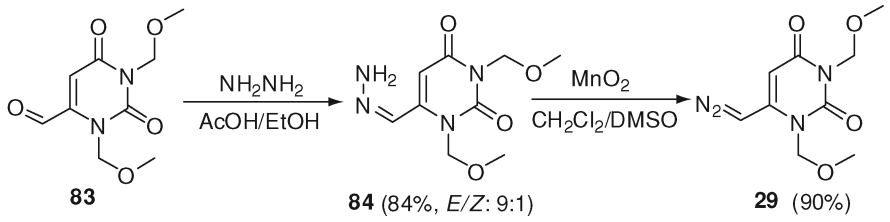
found that the use of TABF open to air[36] and *t*-butyl hydroperoxide were the most generally useful reagents.

Using Ni(0) as catalyst (see *Scheme 14*), Duong and Louie[21] 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** (R^1 = $SnBu_3$, R^2 = methyl, R = ethyl) was prepared using this approach and reaction with PhI in a Stille reaction ($Pd(PPh_3)_4$, CuI, DMF 60°C), gave 6-methyl-5-phenyl-1,3-diethyluracil in 75% yield in the two steps.



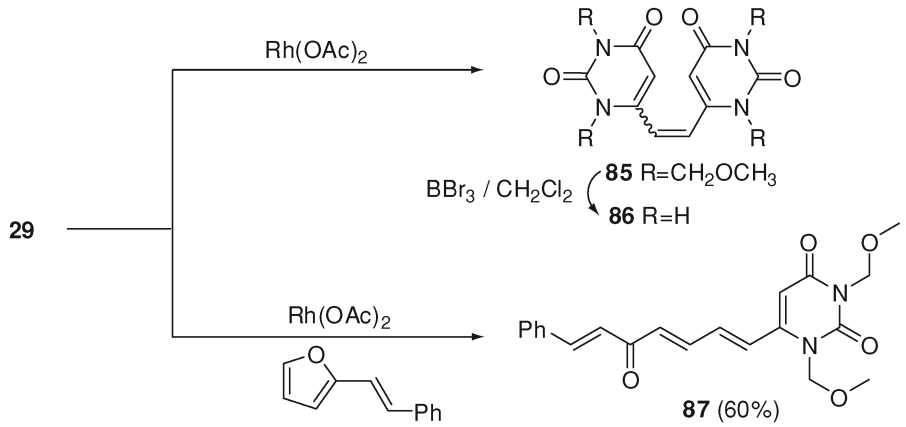
Scheme 33

Recently, Vasella *et al.* have prepared a versatile 6-diazomethyuracil derivative **29** (*Scheme 34*).[20] The synthesis started with 6-formyl-1,3-dimethoxymethyluracil (**83**) which, after reaction with NH_2NH_2, 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 MnO_2 to give compound **29** in 90% yield.



Scheme 34

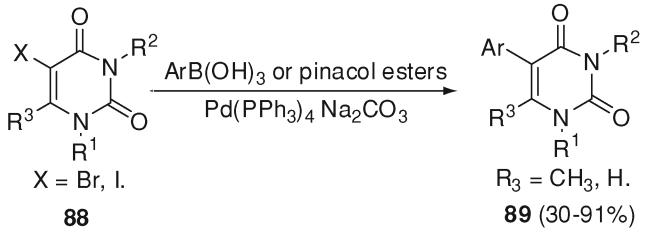
Reactions of compound **29** in the presence of $Rh(OAc)_2$ in CH_2Cl_2 afforded dimeric compounds **85** as a mixture of *Z* (45%) and *E* (22%) isomers (*Scheme 35*) through the formation of carbenoids. Deprotection of **85** with BBr_3 gave diuracil **86** in moderate yield (*Z* (52%) and *E* (58%)).



Scheme 35

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-naphtyl, 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.



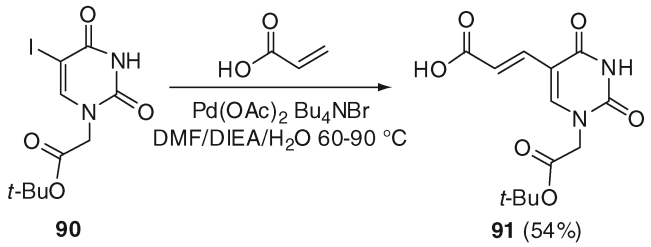
Scheme 36

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_2CO_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 ($RCH = CH_2B(OH)_2$) 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**, $R^1 = CH_2CH_2OCH_2P(O)(OR)_2$, $R^2 = R^3 = H$) with

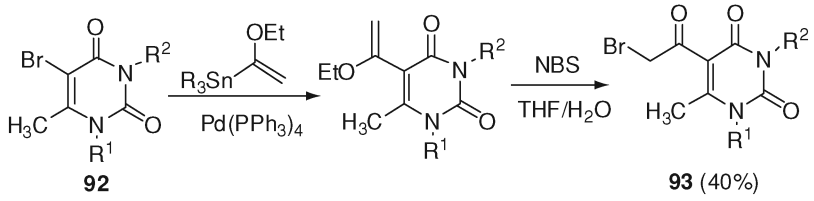
moderate isolated yield (24–58%) using the boronic acids of 1-naphtyl, 2-phenylvinyl, 4-fluorophenyl, 3-nitrophenyl, 2-furyl, phenyl, 3- and 4-pyridyl.[41]

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-tetrahydropyrimidin-5-yl)acrylic acid (**91**) from 1-(2-*t*-butoxy-2-oxoethyl)-5-iodouracil (**90**) (*Scheme 37*).[42] 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.



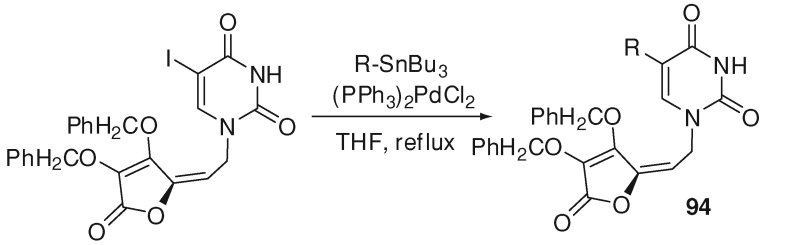
Scheme 37

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.[8]



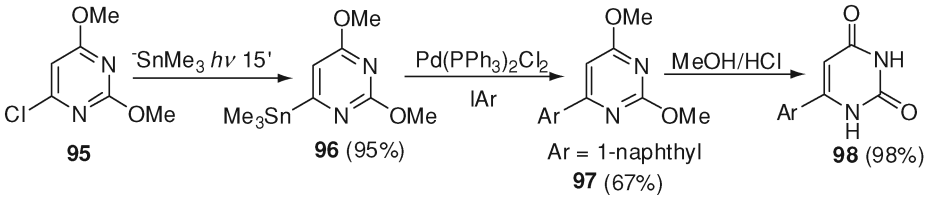
Scheme 38

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.[43] They utilized tributylstannanes to obtain compounds **94** in 31–43% yield (*Scheme 39*).



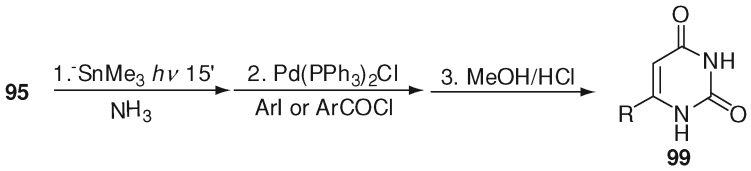
Scheme 39

6-Aryl and 6-acyl uracils were recently synthesized from the commercially available 6-chloro-2,4-dimethoxypyrimidine (**95**).[5] The photostimulated reaction of **95** with the anion $^{-}SnMe_3$ in liquid ammonia afforded stannane **96** in high yield through a $S_{RN}1$ reaction.[44] 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*).



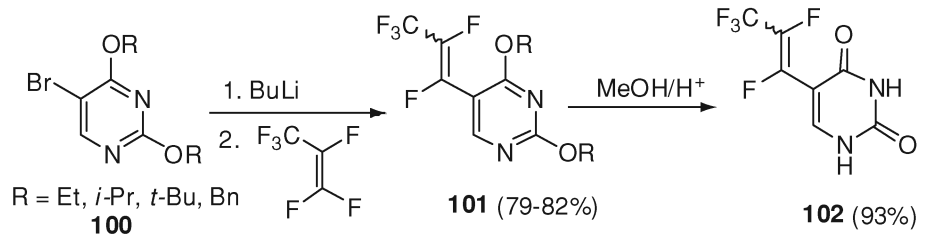
Scheme 40

When the three steps ($S_{RN}1$ 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 = 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 = ArCO), 6-benzoyl (54%) and 6-(2-chlorobenzoyl) uracils (49%) were obtained as isolated pure products.



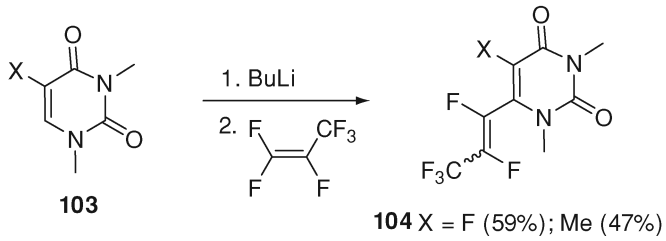
Scheme 41

Koroniak *et al.* have synthesized pentafluoropropenyl uracils using an addition-elimination approach.[45] 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 = Et) instead of **100**, to give 5,6-dipentafluropropenyl-2,4-diethoxypyrimidine; however, the yield was low (43%). Compound **101** (R = *t*-butyl) after hydrolysis gave uracil **102** in good yields (*Scheme 42*).



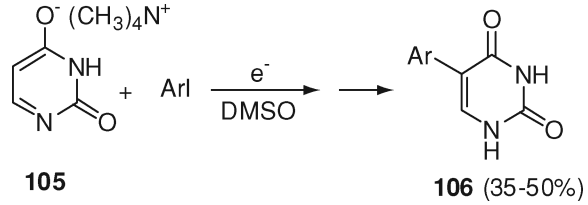
Scheme 42

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*)[45] but the reactions were not general, because no products were obtained from addition-elimination when X = H, Br, NO_2.



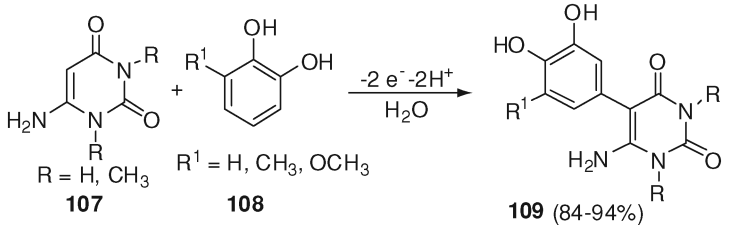
Scheme 43

Savéant *et al.*[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.



Scheme 44

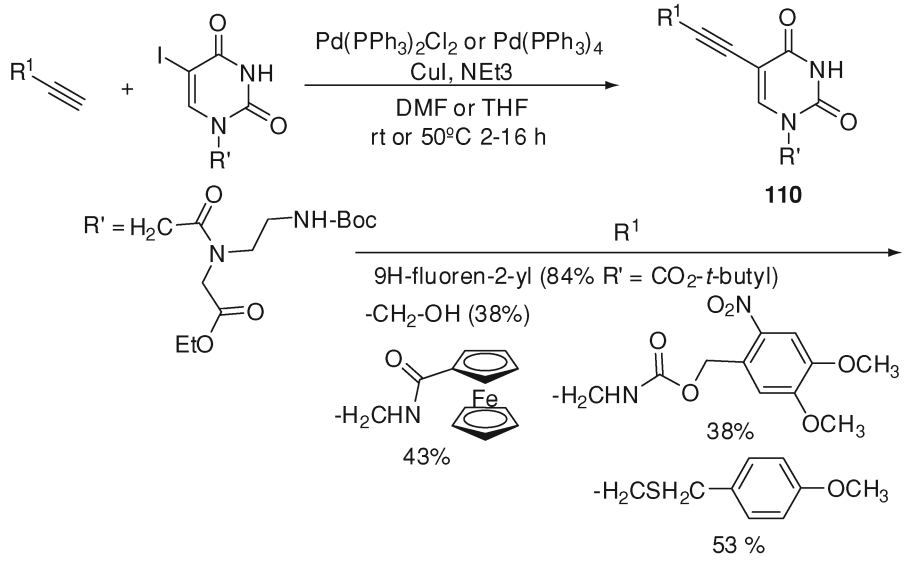
Using another electrochemical reaction Davarani *et al.*[48] have recently synthesized catechol-uracil derivatives (**109**) in very good yields from 6-aminouracils **107** and catechols **108** (*Scheme 45*). The reactions proceed through an electrochemical oxidation of catechols followed by a Michael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



Scheme 45

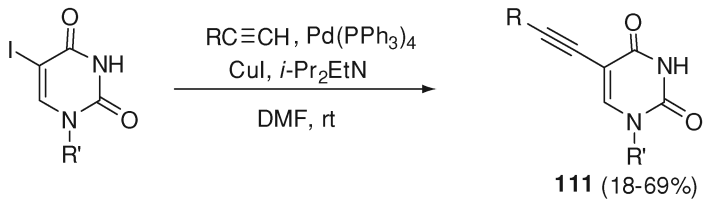
3. C(Uracil)-C(sp) Bonds

The Sonogashira coupling of terminal alkynes has been used to obtain modified nucleosides.[49, 50] Recently, Hudson *et al.*[51, 52] 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.[51]



Scheme 46

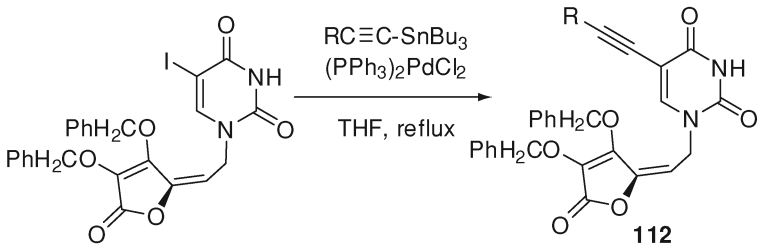
Under similar experimental conditions, Mintas *et al.* reported the synthesis of fourteen 5-alkynyl nucleoside analogues (**111**) in moderate to good yield from (*Z*)- and (*E*)-1-[4′-(*N*-phthalimido)-2′-butenyl]-5-iodouracil (*Scheme 47*).[53]



R = -(CH2)3CH3, -(CH2)4CH3, -(CH2)5CH3, -(CH2)7CH3
-(CH2)2Ph, 4-PhBr, 4-PhCH3, 4-Ph(CH2)3CH3, 4-Ph(CH2)4CH3

Scheme 47

The Stille reaction has been also used by Mintas *et al.* to prepare 5-alkynyl derivatives.[43] They employed a set of tributylstannanes to prepare compounds **112** (R = H (44%), R = Me (33%) yields, *Scheme 48*).

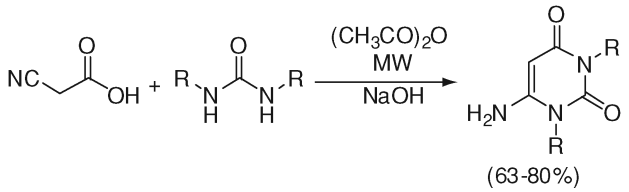


Scheme 48

4. C(Uracil)-Heteroatom Bonds

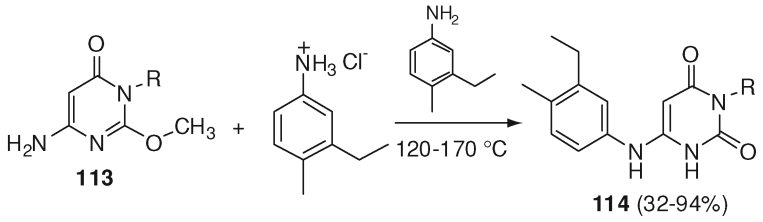
a. C(Uracil)-N Bonds

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*).[54]



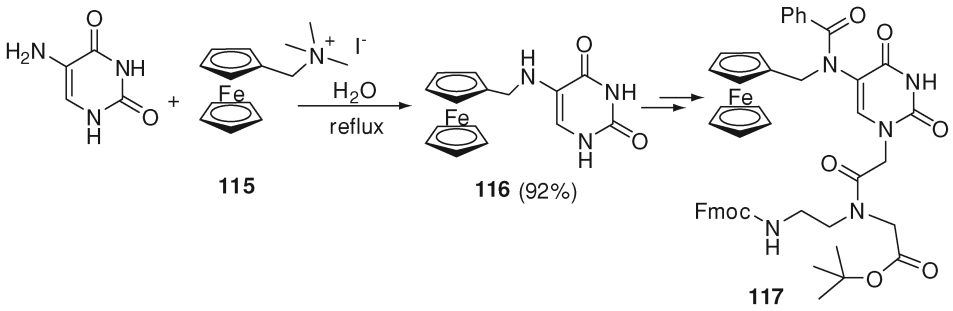
Scheme 49

Although, the synthesis of many 6- and 5-(*N*-substituted) uracils has been developed in the 1970s,[55,56] 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.[57]



Scheme 50

With a similar approach Spiccia *et al.*[58] 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*). From



Scheme 51

this compound the authors could prepare PNA monomer **117** (15% from **115**) and analyzed its electrochemical properties.

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, BPh_4, $SbCl_6$, 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 I_2/nitric acid, ICl, $Br_2/(AcO)_2O$, Br_2/H_2O, Br_2/DMF, Cl_2, NXS, CAN/halogen source, among others.[60–62]

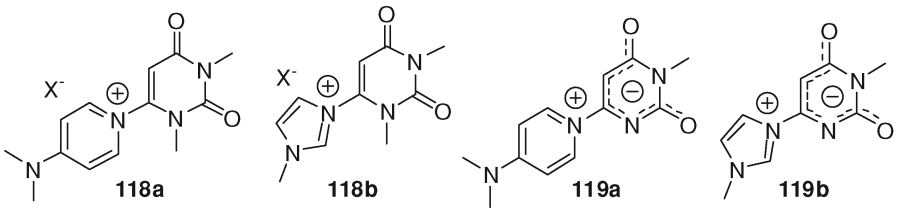


Figure 3

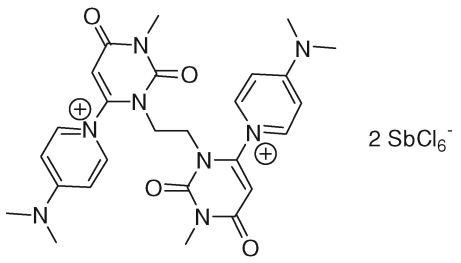
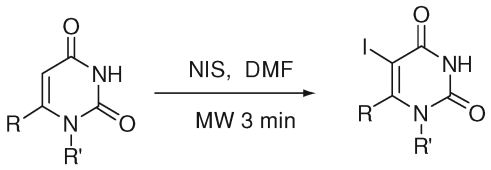


Figure 4

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*).[63] 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

c. C(Uracil)-Other Heteroatom Bonds

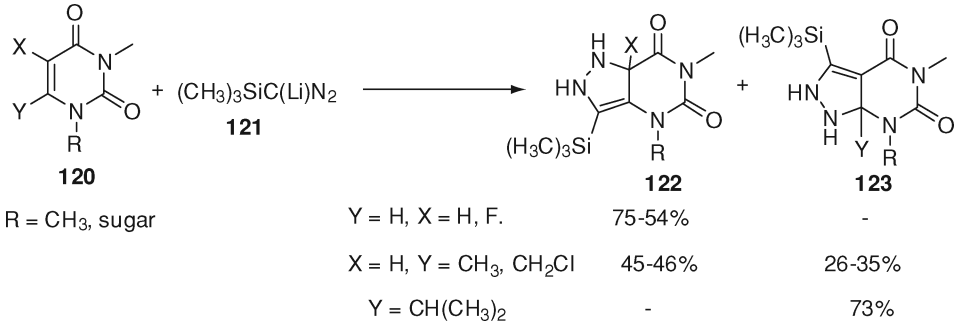
Using the methodology described in Section I.1 (*Scheme 25*), Kopp and Knochel also prepared 5-pheny(methyl)sulfanyluracil and 5-trimethylsilyluracil in good yields (64–77%).[26] Doung and Louie (Section I.1, *Scheme 14*) synthesized 5-trimethylsilyl-6-alkyl-1,3-aryluracils with variable yields (17–83%).[21] Suemune *et al.* (Section I.1, *Scheme 20*) have synthesized 5-trimethylsilyl- and 5-(methylthio)-2′-deoxyuridine in good yields (62–85%).[23]

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)N_2 (**121**) or diazomethane.[64,65] 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

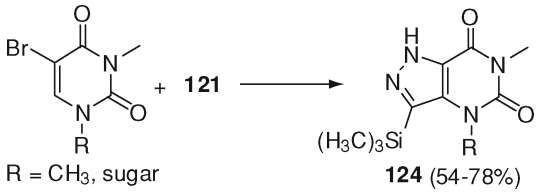


Scheme 53

products is attributed to nucleophilic attack at C6 and subsequent cyclization. When X = NO_2, 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-Δ^1-pyrazolino[4,3-d]pyrimidin-5,7-dione regioisomer analogue to **122**.

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**.

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*).

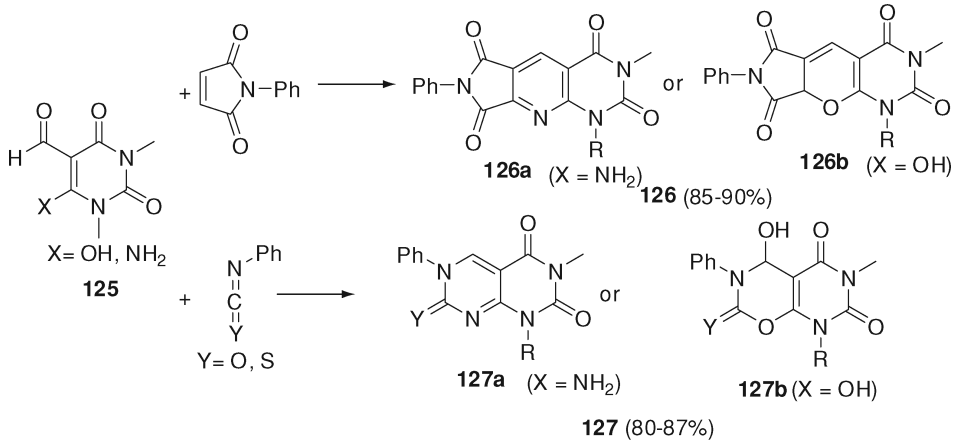


Scheme 54

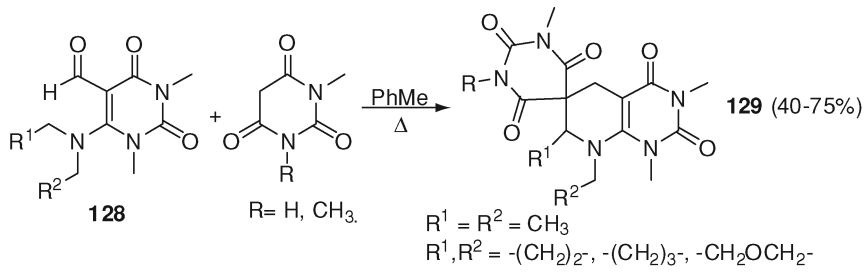
Bhuyan and co-workers have synthesized various complex fused uracils by means of different approaches.[66–68] From *N,N*-dimethyl-5-formylbarbituric acid or 6-amino-1,3-dimethyluracil (**125**), pyrano-(**126a**) and pyrido[2,3-*d*]pyrimidine (**126b**) and (thio)oxazino[4,5*d*]pyrimidine (**127a** and **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]

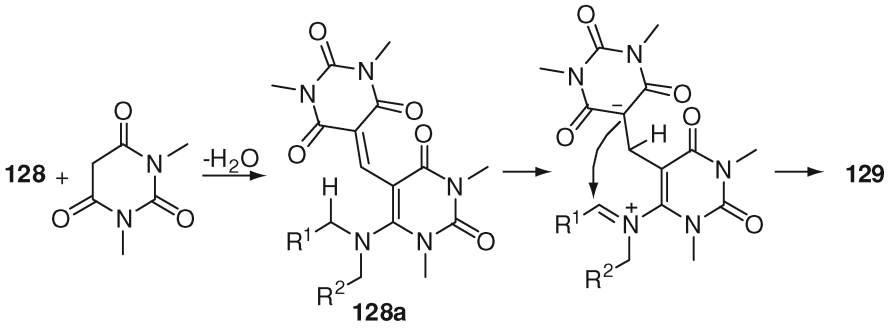
A hypothetical mechanism was proposed but poorly demonstrated: after Knoevenagel condensation to give product **128a** an internal redox process occurred to generate a 1,6-dipole through a 1,5-H shift. Cyclization of the zwitterion formed gave the final product (*Scheme 57*).



Scheme 55



Scheme 56

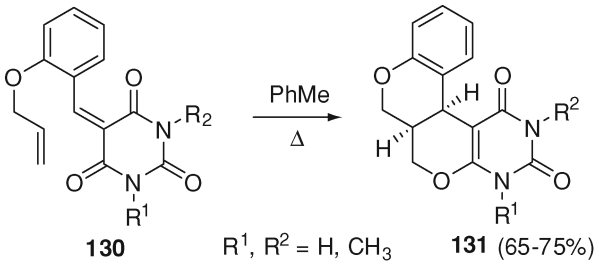


Scheme 57

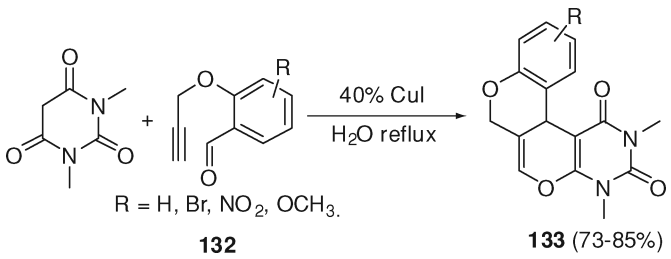
A stereoselective intramolecular hetero Diels-Alder reaction of compound **130** (*Scheme 58*), prepared from barbituric acids and salicylaldehyde, allowed the preparation of the fused system **131** in good yield with less than 5% of the *trans*-stereoisomer.[68]

A similar approach was used by Gross *et al.*[69] 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

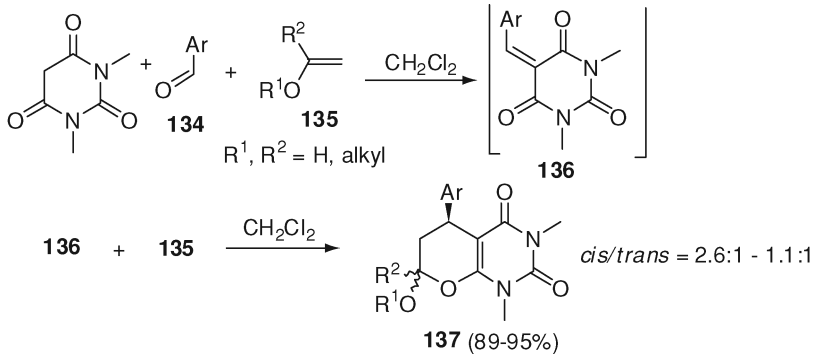


Scheme 58



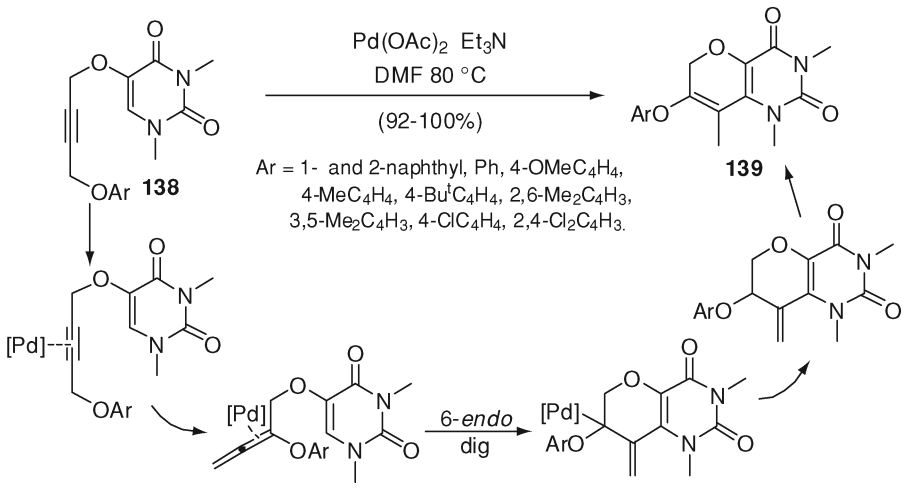
Scheme 59

396 enol ethers **135**. The goal of the authors was to prepare compounds **137** *via* a three-
397 component one-pot synthesis, as shown in *Scheme 60*, giving the desired products in excellent yields.[2]

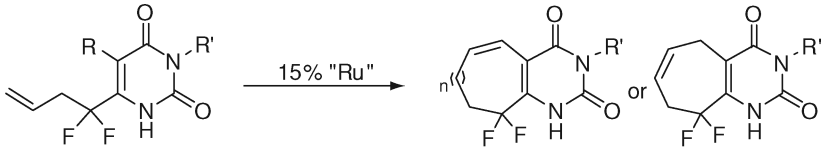


Scheme 60

398
399 Pyrano[3,2-*c*]pyrimidines-2,4-diones (**139**) have been synthesized in excellent
400 yields (92–100%) *via* Pd-catalyzed reaction from 5-substituted-1,3-dimethyuracils (**138**)
401 (*Scheme 61*).[70] The proposed mechanism involves an uncommon [1,3]aryloxy migration,
402 followed by a 6-*endo dig* cyclization.
403 Using the same methodology described in Section I.1.a, (*Scheme 28*), Fustero and
404 co-worker synthesized the 5,6-disubstituted uracils **140a** in order to prepare C5-C6 fused
405 uracils **141** through an intramolecular olefin metathesis (*Scheme 62*).[71] Compound **141a**

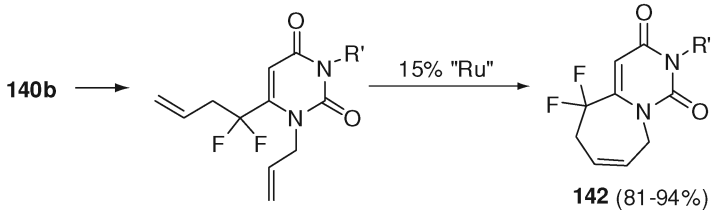


Scheme 61



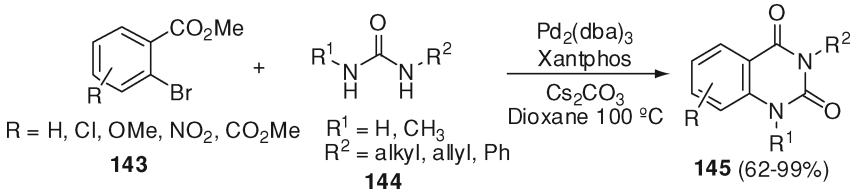
Scheme 62

406 was obtained for n = 0 but by using different Ru catalysts the authors could control, the
407 reaction obtaining **141a** (n = 1) or **141b** as a single product from **140a** (n = 1).
408 As shown in *Scheme 63*, the preparation of N1-C6 fused-uracils **142** was also possible
from **140b**.



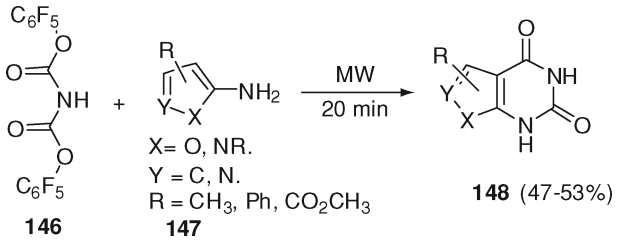
409 **Scheme 63**

410 Through a well-known Pd-catalyzed arylation, Woodward *et al.* have synthesized
411 uracils fused to a phenyl group in good yields from reaction of 2-bromobenzoic methyl
412 esters (**143**) and substituted ureas (**144**) (*Scheme 64*).[72] Both electron-donating as well
413 as electron-withdrawing substituents in the phenyl moiety are tolerated. In addition, a
414 regioselective reaction was obtained with monosubstituted ureas **144** (R^1 = H) to obtain
415 N3 alkyl uracils **145** (R^1 = H).
416 From substituted phenylamines, Rivkin *et al.*[73] prepared analogues of **145**, mono and
417 disubstituted in the phenyl ring, using *bis*(pentafluorophenyl) imidodicarbonate (**146**) in a



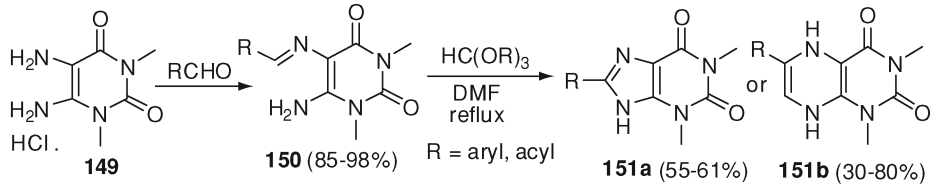
Scheme 64

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



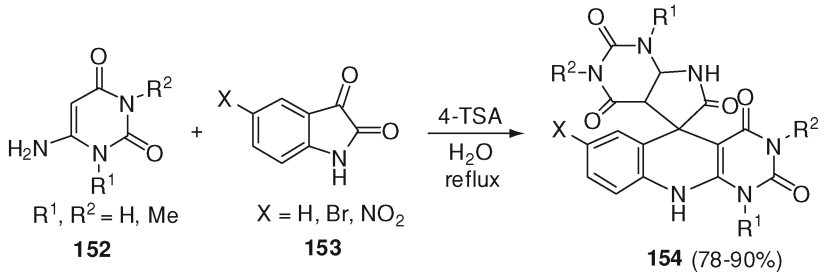
Scheme 65

421
422 Xanthine (**151a**) or pteridine (**151b**) derivatives were obtained in moderate to good
423 yields from 5,6-diamino-1,3-dimethyluracil (**149**). The synthetic sequence involves the
424 preparation of enamines **150** from aldehydes and subsequent reaction with different one-
425 carbon sources (triethyl orthoformate, orthoacetate or orthobenzoate). Depending on the ortho ester used, **151a** or **151b** was obtained (*Scheme 66*).[74]

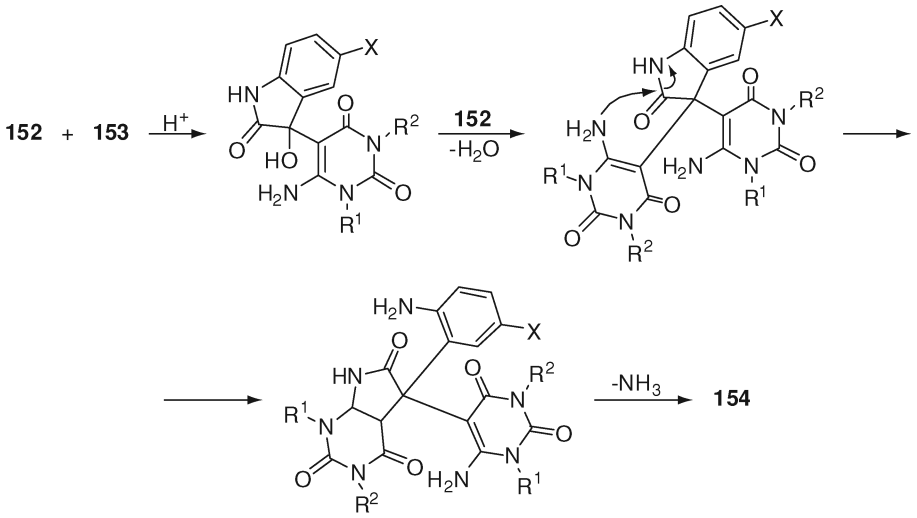


Scheme 66

426
427 Spiro[pyrimido-[4,5-*d*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]pentanones (**154**)
428 were synthesized by Bazgir *et al.* from 6-aminouracils (**152**) and 5-substituted indoline-
429 2,3-diones (**153**) (*Scheme 67*), using water as solvent and 4-toluenesulfonic acid (4-TSA)
430 as catalyst. The complex polyheterocyclic compounds **154** were obtained in very good
431 yields (78–90%).[75]
432 Although a mechanism could not be established with certainty, a possible route was
433 proposed as depicted in *Scheme 68*.
434 It has been shown that the replacement of one carbon atom by nitrogen is a good
435 strategy to obtain new potential antitumor compounds from known anticancer drug.[76–78]

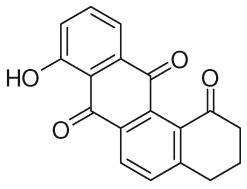


Scheme 67



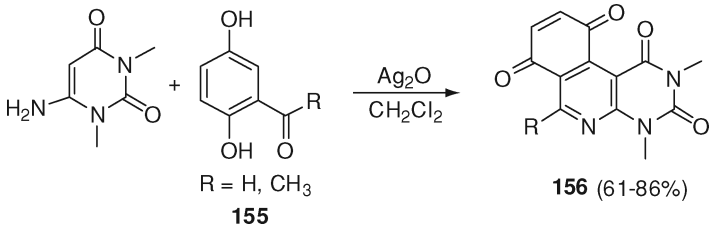
Scheme 68

436 In line with this, Valderrama and Vásquez proposed the synthesis of *aza*-analogues of
437 angucyclinone (*Figure 5*).
438 The authors synthesized quinones **156** in good yields from hydroquinone **155** and
439 6-amino-1,3-dimethyluracil using Ag_2O in CH_2Cl_2 at room temperature (*Scheme 69*).[79]
440 From compounds **156**, adducts **157** and **158** (*Figure 6*) were synthesized through a
441 cycloaddition reaction with different dienes. Angucyclinone **159** analogues from 157 were
442 finally obtained with good yields by mild hydrolysis with hydrochloric acid followed by
443 oxidation with PCC of the alcohol intermediaries.



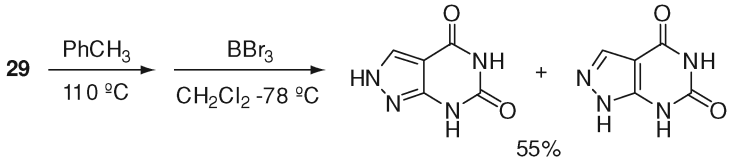
benz[a]anthraquinone chromophore of angucycline andangucyclinones

Figure 5



Scheme 69

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 carbenophiles by an intramolecular reaction.[20] Thermolysis of **29** in toluene gave 1:1 mixture 1*H*- and 2*H*-pyrazolo[4,3-*d*]uracil in 55% yield after deprotection with BBr_3 (*Scheme 70*).



Scheme 70

The reaction of **29** with 2-methoxypropene in the presence of $Rh_2(AcO)_4$ (*Scheme 71*) gave a cyclopropane derivative (*endo/exo*) from addition to the double bond, which after treatment with $AlClMe_2$ gave the cyclopenta[*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*).[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.

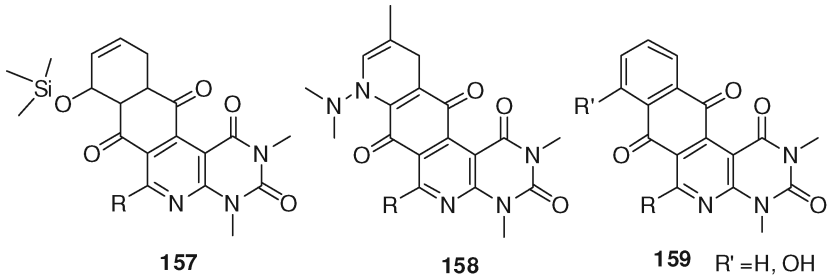
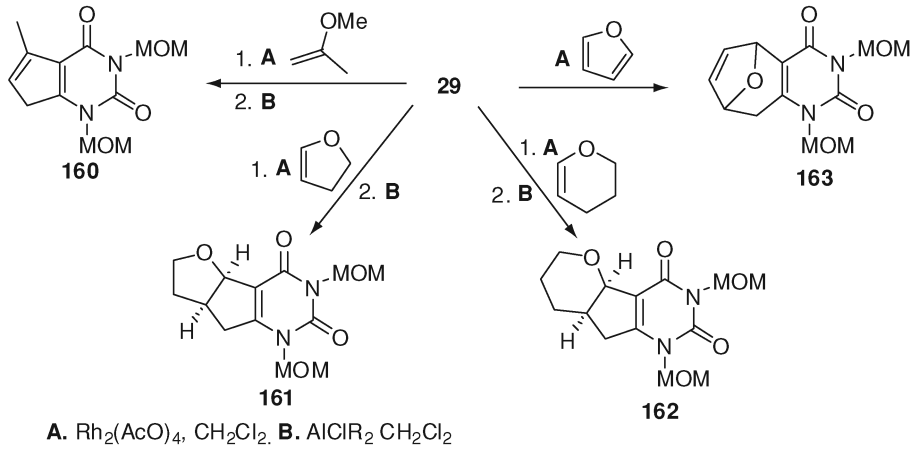
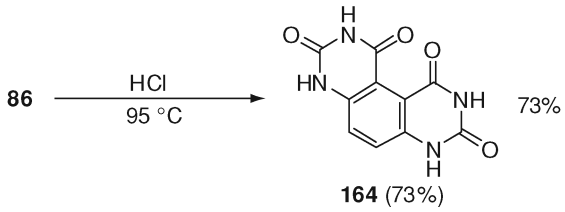


Figure 6

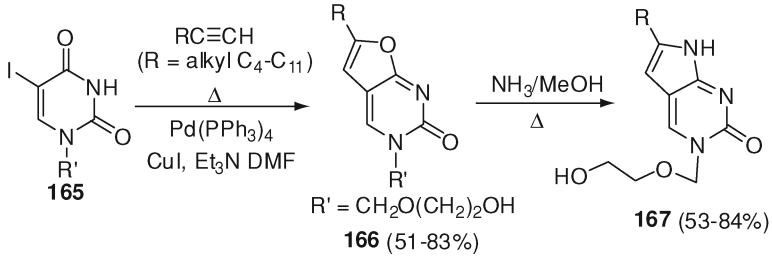


Scheme 71

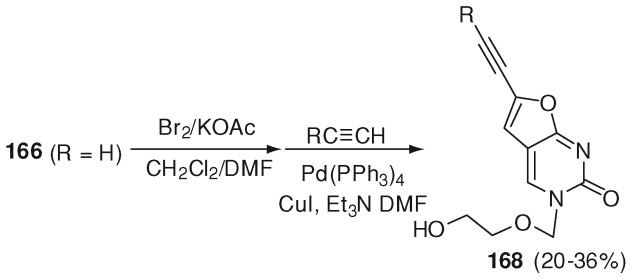


Scheme 72

Robins and co-workers extended their work in the synthesis and the biological evaluation of furo[2,3-*d*]pyrimidin-2(3*H*)-one and synthesized derivatives **166** (*Scheme 73*).[80,81] N1 substituted uracils were synthesized in moderate to good yields (51–83%) from 5-iodouracils **165** ($R' = CH_2O(CH_2)_2OH$), and different alkynes. The authors performed a Sonogashira coupling following a Cu(I)-promoted cyclization in a two step one pot procedure.[80] 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%).



Scheme 73



Scheme 74

Access to pyrrolo derivatives **167** was possible from **166** ($R' = CH_2O(CH_2)_2OH$) 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*).[80]

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
$S_{RN}1$: Unimolecular Radical Nucleophilic Substitution
TABF: Tetrabutylammonium fluoride
THF: Tetrahydrofuran
TMSCl: Trimethylchlorosilane
TMS: Trimethylsilyl
TP: Thymidine phosphorylase
MNP: $(CH_3)_3C\text{-}N{=}O$
4-TSA: 4-Toluene sulfonicacid
Xantphos: 2,2′-Oxy*bis*(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.

References

1. M. Lagoja, *Chem. Biodiv.*, **2**, 1 (2005).
2. A. Palasz, *Monatsh. Chem*, **139**, 1397 (2008).
3. D. Uraguchi, K. Yamamoto, Y. Ohtsuka, K. Tokuhisa and T. Yamakawa, *Appl. Catal., A*, **348**, 137 (2008).
4. R. Saladino, C. Crestini, A. T. Palamara, M. C. Danti, F. Manetti, F. Corelli, E. Garaci and M. Botta, *J. Med. Chem.*, **44**, 4554 (2001).
5. J. I. Bardagí and R. A. Rossi, *J. Org. Chem.*, **73**, 4491 (2008).
6. C. B. Reese and Q. Wu, *Org. Biomol. Chem.*, **1**, 3160 (2003).
7. Z. Guo, Y. Zhu, F. C. Tucci, Y. Gao, R. S. Struthers, J. Saunders, T. D. Gross, Q. Xie, G. J. Reinhartb and C. Chen, *Bioorg. Med. Chem. Lett.*, **13**, 3311 (2003).
8. M. W. Rowbottom, F. C. Tucci, P. J. Connors, Jr., T. D. Gross, Y. Zhu, Z. Guo, M. Moorjani, O. Acevedo, L. Carter, S. K. Sullivan, Q. Xie, A. Fisher, R. S. Struthers, J. Saundersa and C. Chen, *Bioorg. Med. Chem. Lett.*, **14**, 4967 (2004).
9. Y. Zhu, T. D. Gross, Z. Guo, P. J. Connors, Jr., Y. Gao, F. C. Tucci, R. S. Struthers, G. J. Reinhart, J. Saunders, T. K. Chen, A. L. K. Bonneville and C. Chen, *J. Med. Chem.*, **46**, 2023 (2003).
10. A. Dinsmore, P. M. Doyle, P. B. Hitchcock and D. W. Young, *Tetrahedron Lett.*, **41**, 10153 (2000).
11. C. G. Lee, S. Gowrisankar and J. N. Kim, *Bull. Korean Chem. Soc.*, **26**, 3, 481 (2005); *Chem. Abstr.*, **143**, 440139 (2005).
12. S. Nag, G.P. Yadav, P. R. Maulik and S. Batra, *Synthesis*, **6**, 911 (2007).
13. J. Cao and X. Huang, *J. Comb. Chem.*, **10**, 526 (2008).
14. S. Yano, H. Kazuno, N. Suzuki, T. Emura, K. Wierzba, J. Yamashita, Y. Tada, Y. Yamada, M. Fukushima and T. Asao, *Bioorg. Med. Chem.*, **12**, 3431 (2004).
15. S. Yano, H. Kazuno, N. Suzuki, T. Emura, K. Wierzba, J. Yamashita, Y. Tada, Y. Yamada, M. Fukushima and T. Asao, *Bioorg. Med. Chem.*, **12**, 3443 (2004).
16. F. Corelli, M. Botta, A. Lossani, S. Pasquini, S. Spadari and F. Focher, *Il Farmaco*, **59**, 987 (2004).
17. A. Fassihi, C. Velazquez and E. E. Knaus, *J. Heterocyclic Chem.*, **41**, 263 (2004).
18. A. Chacko, W. Qu and H. Kung, *J. Org. Chem.*, **73**, 13, 4874 (2008).
19. S. Kumar, V. Kumar, S. Singh and S. S. Chimni, *Tetrahedron Lett.*, **42**, 30, 5073 (2001).
20. F. Zhang, A. Kulesza, S. Rani, B. Bernet and A. Vasella, *Helv. Chim. Acta*, **91**, 1201 (2008).
21. H. A. Duong and J. Louie, *Tetrahedron*, **62**, 7552 (2006).
22. M. Botta, R. Saladino, G. Delle Monache, G. Gentile and R. Nicoletti, *Heterocycles*, **43**, 1687 (1996).
23. M. Aso, T. Kaneko, M. Nakamura, N. Koga and H. Suemune, *Chem. Commun.*, 1094 (**2003**).

24. J. D. White and J. Hansen, *J. Org. Chem.*, **70**, 1963 (2005).

25. N. Boudet, and P. Knochel, *Org. Lett.*, **8**, 17, 3737 (2006).

26. F. Kopp and P. Knochel, *Org. Lett.*, **9**, 9, 1639 (2007).

27. M. Médiebielle, J. Pinson and J. M. Savéant, *Tetrahedron Lett.*, **33**, 7351 (1992).

28. M. A. Ismail, H. H. Zoorob and L. Strekowski, *Arkivoc*, part x, 1 (2002).

29. D. Cech, R. Wohfeil, G. Etzold, *Nucleic Acid Res.*, **2**, 2183 (1975)

30. S. Fustero, J. Piera, J. F. Sanz-Cervera, S. Catalán and C. Ramírez de Arellano, *Org. Lett.*, **6**, 1417 (2004).

31. S. Fustero, S. Catalán, S. Flores, D. Jiménez, C. del Pozo, J. L. Aceña, J. F. Sanz-Cervera, and S. Mérida, *QSAR Comb. Sci.*, **25**, 753 (2006).

32. Y. Jiang, S. Chung, D. J., Krosky and J. T. Stivers, *Bioorg. Med. Chem.*, **14**, 5666 (2006).

33. R. Polo, J. M. Moretó, U. Schick and S. Ricart, *Organometallic*, **17**, 2135 (1998).

34. A. Spinella, T. Caruso, U. Pastore and S. Ricart, *J. Organomet. Chem.*, **684**, 266 (2003).

35. G. D. Sala, A. Artillo, S. Ricart and A. Spinella, *J. Organomet. Chem.*, **692**, 1623 (2007).

36. Barluenga's protocol based on fluoride ion. J. Barluenga, F. Andina, M. A. Fernández-Rodriguez, P. Garcia-Garcia, I. Merino and E. Aguilar, *J. Org. Chem.*, **69**, 7352 (2004).

37. Z. Guo, Y. Zhu, T. D. Gross, F. C. Tucci, Y. Gao, M. Moorjani, P. J. Connors, Jr., M. W. Rowbottom, Y. Chen, R. S. Struthers, Q. Xie, J. Saunders, G. Reinhart, T. K. Chen, A. L. K. Bonneville and C. Chen, *J. Med. Chem.*, **47**, 1259 (2004).

38. F. C. Tucci, Y. Zhu, Z. Guo, T. D. Gross, P. J. Connors, Jr., R. S. Struthers, G. J. Reinhart, J. Saundersa and C. Chen, *Bioorg. Med. Chem. Lett.*, **13**, 3317 (2003).

39. Z. Guo, Y. Chen, C. Q. Huang, T. D. Gross, J. Pontillo, M. W. Rowbottom, J. Saunders, S. Struthers, F. C. Tucci, Q. Xie, W. Wade, Y. Zhu, D. Wua and C. Chen, *Bioorg. Med. Chem. Lett.*, **15**, 2519 (2005).

40. F. Amblard, S. P. Nolan, R. F. Schinazi and L. A. Agrofoglio, *Tetrahedron*, **61**, 537 (2005).

41. K. Pomeisl, A. Holý and R. Pohl, *Tetrahedron Lett.*, **48**, 3065 (2007).

42. B. Y. Oquare and J. S. Taylor, *Bioconjugate Chem.*, **19**, 2196 (2008).

43. T. Gazivoda, S. Raić-Malić, M. Marjanović, M. Kralj, K. Pavelić, J. Balzarini, E. De Clercq and M. Mintas, *Bioorg. Med. Chem.*, **15**, 749 (2007).

44. For reviews, see: R. A. Rossi, A. B. Pierini, A. B. Peñéñory, *Chem. Rev.* **103**, (2003), and R. A. Rossi, *Photoinduced Aromatic Nucleophilic Substitution;* Chapter 16, "*Synthetic Organic Photochemistry"*, p 495, Marcel Dekker, New York (2005).

45. H. Wójtpwicz-Rachel, M. Migas and H. Koroniak, *J. Org. Chem.*, **71**, 8842 (2006).

46. M. Médebielle, M. A. Oturan, J. Pison and J. M. Savéant, *Tetrahedron Lett.*, **34**, 3409 (1993).

47. M. Médebielle, M. A. Oturan, J. Pison and J. M. Savéant, *J. Org. Chem.*, **61**, 1331 (1996).

48. S. S. H. Davarani, N. S. Fumani, H. Arvin-Nezhad and F. Moradi, *Tetrahedron Lett.*, **49**, 710 (2008).

49. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 4467 (1975).

50. F. W. Hobbs Jr., *J. Org. Chem.*, **54**, 3420 (1989).

576 51. R. H. E. Hudson, G. Li and J. Tse, *Tetrahedron Lett.*, **43**, 1381 (2002).

577 52. F. Wojciechowski and R. H. E. Hudson, *Nucleos. Nucleot. Nucl.*, **26**, 1199 (2007).

578 53. T. Gazivoda, S. Raić-Malić, V. Krištafor, D. Makuc, J. Plavec, S. Bratulić, S. Kraljević-Pavelić,
579 K. Pavelić, L. Naesens, G. Andrei, R. Snoeck, J. Balzarini and M. Mintas, *Bioorg. Med. Chem.*,
580 **16**, 5624 (2008).

581 54. I. Devi and P. J. Bhuyan, *Tetrahedron Lett.*, **46**, 5727 (2005).

582 55. C. Zhi, Z. Long, J. Gambino, W. Xu, N. C. Brown, M. Barnes, M. Butler, W. LaMarr and G. E.
583 Wright, *J. Med. Chem.*, **46**, 2731 (2003).

584 56. N. C. Brown, J. Gambino and G. E. Wright, *J. Med. Chem.*, **20**, 1186 (1977).

585 57. C. Zhi, Z. Long, A. Manikowski, N. C. Brown, P. M. Tarantino, K. Holm, E. J. Dix, G. E.
586 Wright, K. A. Foster, M. M. Butler, W. A. LaMarr, D. J. Skow, I. Motorina, S. Lamothe and
587 R. Storer, *J. Med. Chem.*, **48**, 7063 (2005).

588 58. G. Gasser, M. J. Belousoff, A. M. Bond and L. Spiccia, *J. Org. Chem.*, **71**, 7565 (2006).

589 59. A. Schnudt and M. K. Kindermann, *J. Org. Chem.*, **62**, 3910 (1997).

590 60. J. Asakura and M. Robins, *J. Org. Chem.*, **55**, 4928 (1990).

591 61. M. Elshehry, J. Balzarini and C. Meier, *Synthesis*, **5**, 841 (2009).

592 62. S. Boncel, A. Gondela and K. Walczak, *Curr. Org. Synth.*, **5**, 365 (2008) and reference therein.

593 63. L. Paolini, E. Petricci, F. Corelli and M. Botta, *Synthesis*, **2**, 1039 (2003).

594 64. R. Saladino, L. Stasi, C. Crestini, R. Nicoletti and M. Botta, *Tetrahedron*, **53**, 7045 (1997).

595 65. R. Saladino, L. Stasi, R. Nicoletti, C. Crestini and M. Botta, *Eur. J. Org. Chem.*, 2751 (**1999**).

596 66. I. Devi, H. N. Borah and P. J. Bhuyan, *Tetrahedron Lett.*, **45**, 2405 (2004).

597 67. B. Baruah and P. J. Bhuyan, *Tetrahedron Lett.*, **45**, 243 (2009).

598 68. I. Devi and P. J. Bhuyan, *Tetrahedron Lett.*, **45**, 7727 (2004).

599 69. M. J. Khoshkholgh, S. Balalaie, H. R. Bijanzadeh, F. Rominger and J. H Gross, *Tetrahedron*
600 *Lett.*, **49**, 6965 (2008).

601 70. K. C. Majumdar, B. Sinha, B. Chattapadhyay and K. Ray, *Tetrahedron Lett.*, **49**, 4405
602 (2008).

603 71. S. Fustero, S. Catalán, J. Piera, J. F. Sanz-Cervera, B. Fernández and J. L. Aceña, *J. Org. Chem.*,
604 **71**, 3910 (2006).

605 72. M. C. Willis, R. H. Snell, A. J. Fletcher and R. L. Woodward, *Org. Lett.*, **8**, 22, 5089 (2006).

606 73. S. M. Chicetti, S. P. Ahearn and A. Rivkin, *Tetrahedron Lett.*, **49**, 6081 (2008).

607 74. O. I. El-Sabbagh, M. E. El-Sadek, S. El-Kalyoubi and I. Iamail, *Arch. Pharm. Chem. Life Sci.*,
608 **340**, 1 (2007).

609 75. R. Ghahremanzadeh, S. C. Azimi, N. Gholami and A. Bazgir, *Chem. Pharm. Bull.*, **56**, 1617
610 (2008).

611 76. H. Lee, S.-I. Lee, and S.-I.Yang, *Bioorg. Med. Chem. Lett.*, **8**, 2991 (1998).

612 77. G. Tudor, P. Gutierrez, A. Aguilera-Gutierrez, and E. A. Sausville, *Biochem. Pharmacol.*, **65**,
613 1061 (2005).

614 78. J. A. Valderrama, M. F. González, P. Colonelli, and D. Vásquez, *Synlett*, **2006**, 2777.

615 79. J. A. Valderrama and D. Vásquez, *Tetrahedron Lett.*, **49**, 703 (2008).

616 80. Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. Clercq and M. J. Robins, *J. Med. Chem.*, **48**,
617 4690 (2005).

618 81. Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. Clercq and M. J. Robins, *Can. J. Chem.*, **84**,
619 580 (2006).