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Palladium(0)-Catalyzed Allylation of Uracils and 2-Thiouracils Drastic Effect of an Aqueous Reaction Medium on the Regioselectivity

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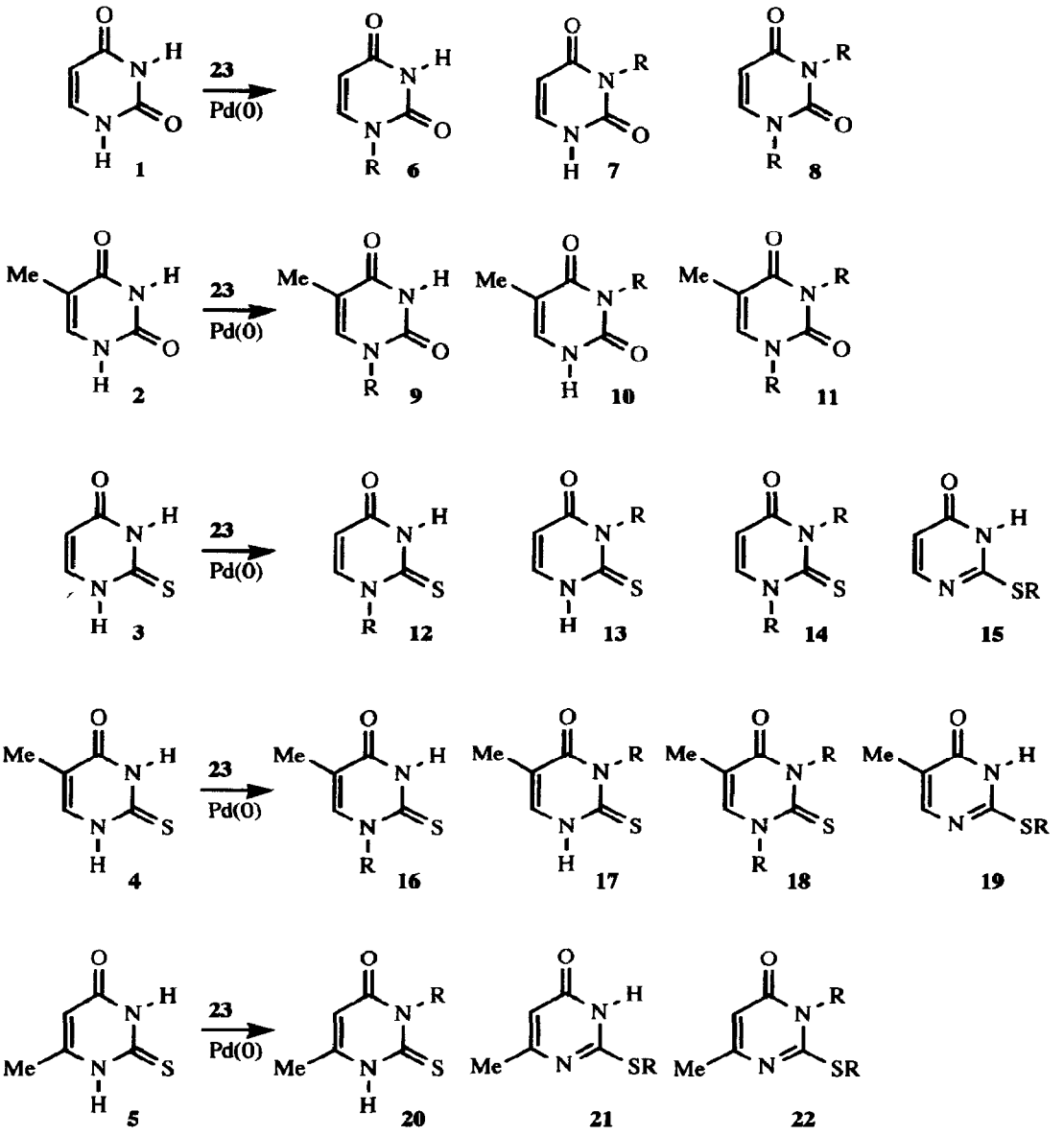
Abstract: Palladium(0)-catalyzed allylation of uracils in DMSO takes place at N-1 and at N-3. In sharp contrast, regiospecific allylation at N-1 is achieved in an organic-aqueous medium in the presence of palladium(II) acetate and the water-soluble sulfonated triphenylphosphine P(C_6H_4-*m*-SO_3Na)$_3$ (tppts). Similar reactions with 2-thiouracils are also drastically dependent on the solvent, taking place at N-1 and N-3 (in dioxane) or at sulfur (organic-aqueous medium). Probably reactions in the organic-aqueous medium are kinetically controlled whereas allylations in DMSO or refluxing dioxane are thermodynamically controlled.

Palladium(0)-catalyzed allylation of nucleophiles is a powerful synthetic method[1] and control of the selectivities is a topic of great interest.[2] Thus, regioselective allylation of purines at N-9 in the imidazole ring has been used in the preparation of carbanucleosides[3] and nucleosides.[4] Pyrimidine derivatives are also allylated under palladium(0) catalysis; some of them give clear regioselective reactions: pyrimidin-2-ones at N,[3a,3g,5] 2-mercaptopyrimidine at S,[6,7] cytosine[3f,3k] and 5-methylcytosine[3k] at N-1. However some regioselectivity problems arise when two amide groups are present in the molecule, i.e. in the uracil family. Thus, uracil has been reported to react at N-1[3f,4] and at N1+N3,[7] and a similar behaviour has been described for 5-methyluracil (thymine): reaction at N1,[8] and at N-1+N-3.[3g,3h,3k,7] On the other hand, 6-methyluracil and 6-methyl-2-thiouracil react only at N-3 under palladium(0) catalysis,[7] although steric effects can militate against allylation at N-1. Finally 2-thiobarbituric acid allylates at C-5, and only when this position has been allylated twice, N-1 receives the third radical.[7]

In summary, more investigation to control the regioselectivity in the uracil and 2-thiouracil families was required. Moreover, uracils are scarcely soluble in organic media and highly polar solvents at high temperatures are required.[7] We knew from previous work that palladium(0)-catalyzed allylations can be thermodynamically controlled to afford products isomeric to those obtained under the usual alkylation conditions (alkyl halides and a base, kinetic control),[9] and that allylations can be driven in water using palladium associated with the trisodium salt of the tris(*m*-sulfophenylphosphine) P(C_6H_4-*m*-SO_3Na)$_3$ (or tppts).[10,11]

The logical outcome was to study the allylation of uracil **1** and thymine **2** in an organic-aqueous medium. Our allylation results are summarized in Scheme 1 and in the table. Palladium(0)-catalyzed reaction [$Pd(OAc)_2$/tppts)] of uracil **1** with cinnamyl acetate **23b** in water/acetonitrile in the presence of diazabicycloundecene (DBU) affords regioselectively 1-cinnamyluracil **6** in high yields (runs 2 and 3). It is remarkable that use of a large excess of **23b** results only in an improvement of the yield (compare runs 2 and 3), but not in diallylation. In sharp contrast, all N-allylation products **6-8** were isolated in the reaction of **1** with cinnamyl ethyl carbonate **23a** in hot DMSO (run 1).[7] Similar results were obtained with thymine **2** (compare runs 5 and 6).

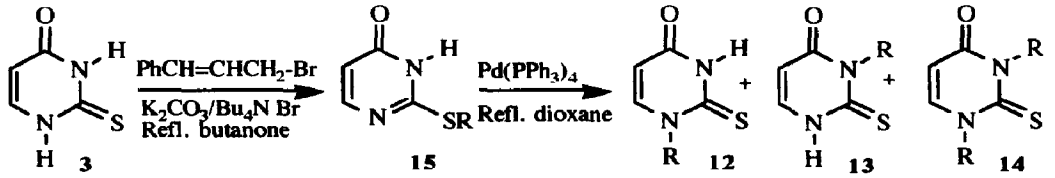


23a: PhCH=CH-CH_2-OCOOEt
23b: PhCH=CH-CH_2-$OCOCH_3$

SCHEME 1

Next, we studied the 2-thiouracil family. 2-Thiouracil **3** gave all possible N-allylation products **12-14** when treated with carbonate **23a** under $Pd(PPh_3)_4$ catalysis in refluxing dioxane. In the first experiment (run 7) large amounts of **3** were recovered and excess **23a** was required for a complete conversion of **3** (run 8) Again, the combination water-acetonitrile/cinnamyl acetate/DBU/$Pd(OAc)_2$/tppts permitted the isolation of a single compound, 2-cinnamylthiopyrimidin-4(6)-one **15** (run 9). Similar results were obtained with 2-thiothymine **4** (compare runs 10 and 11). 6-Methyl-2-thiouracil **5** affords 3-cinnamyl-6-methyl-2-thiouracil **20** albeit in low yield, as the only identified product of allylation under non-aqueous conditions (run 12).[7] Steric hindrance was invoked to explain the absence of attack at N-1. However, the organic-aqueous experimental conditions led to more than 90% yield of sulfide **21** (run 13).

To explain these results we performed some complementary experiments (Scheme 2). Thus, sulfide **15**, independently prepared, was isomerized to a mixture of **12-14** (ratio determined by ^{1}H-NMR) under experimental conditions similar to those of runs 7 and 8, whereas **13** remained unaltered under the same conditions. From this the hypothesis emerges that sulfide **15** (and for that matter **19** and **21**) is the product of kinetic control whereas N-allylated **12-14** are due to the thermodynamic control (isomerization from S- to N-) although kinetic control operates within the set of N-allylated products (no isomerization from N- to N-). The interpretation of the results in the uracil series is not so clear, but two points are remakable in runs 2 and 3: a) the monoreaction, even in the presence of a four-fold excess of allylating agent, can be related to the precipitation of **6** in the reaction media; and b) the regioselectivity, more difficult to explain. It might be that water favours the more compact transition state in which the ordered structure of the solvent is minimally disturbed.



Ratio **12:13:14** = 3.6:1.7:1.0

SCHEME 2

Table.- Reaction of Uracils and Thiouracils with Cinnamyl Derivatives **23** under Palladium(0) Catalysis

Run	**1-5** (mmol)	**23** (mmol)	Pd/phosphine (mmol Pd)[a]	Solvent (mL)	Temp (°C)	Time (h)	Products[12] (%)
1[b]	**1** (9.0)	**23a** (9.0)	B (0.4)	DMSO (20)	105	5.5	**6**(38), **7**(7), **8**(9)
2	**1** (2.23)	**23b** (6.69)[c]	A (0.08)	H_2O/MeCN (17/2)	60	24	**6**(65)
3	**1** (2.23)	**23b** (8.92)[c]	A (0.08)	H_2O/MeCN (17/2)	60	24	**6**(80)
4	**1** (2.23)	**23a** (2.48)	A (0.08)	H_2O/MeCN (60/2)	60	24	**6**(8)
5[b]	**2** (4.0)	**23a** (4.0)	B (0.2)	DMSO (20)	105	45	**9**(30), **10**(14), **11**(7)
6	**2** (1.98)	**23b** (7.92)[c]	A (0.08)	H_2O/MeCN (17/2)	60	24	**9**(53)
7	**3** (8.0)	**23a** (8.0)	B (0.4)	Dioxane (20)	Refl.	16	**3**(24), **12**(48), **13**(14), **14**(9)
8	**3** (6.0)	**23a** (12.0)	B (0.3)	Dioxane (20)	Refl.	20	**12**(20), **13**(23), **14**(40)
9	**3** (1.6)	**23b** (8.0)[c]	A (0.05)	H_2O/MeCN (17/2)	60	24	**15**(43)
10	**4** (5.0)	**23a** (5.0)	B (0.25)	Dioxane (20)	Refl.	48	**16**(23), **17**(17), **18**(4), **19**(6)
11	**4** (0.9)	**23b** (4.4)[c]	A (0.03)	H_2O/MeCN(17/2)	60	24	**19**(55)
12[b]	**5** (8.0)	**23a** (9.6)	C (0.4)	Dioxane (20)	Refl.	144	**20**(30)
13	**5** (1.76)	**23b** (7.04)[c]	A (0.07)	H_2O/MeCN (18/2)	60	24	**21**(92), **22**(4)

[a] A: $Pd(OAc)_2$/tppts (1/9-10); B: $Pd(PPh_3)_4$; C: $Pd(acac)_2/PPh_3$ (1/4). [b] Ref. 7. [c] 1 equivalent DBU was used

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References

1 (a) Trost, B.M.; Verhoeven, T.R. "Organopalladium Compounds in Organic Synthesis and in Catalysis", vol. *8*, chapter 57 in *Comprehensive Organometallic Chemistry*. Ed. by Sir Wilkinson, G., Stone, F.G.A. and Abel, E.W. Pergamon Press, **1982**.
(b) Heck, R.F. *Palladium Reagents in Organic Synthesis;* Academic Press: London. **1985**.
(c) Godleski, S.A. "Nucleophiles with Allyl-Metal Complexes", Vol *4*, chapter 3.3 in *Comprehensive Organic Synthesis*. Ed by Trost, B.M. and Fleming I. Pergamon Press, **1991**.

2 Frost, C.G.; Howarth, J.; Williams, J.M.J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-1122.

3 (a) Trost, B.M.; Kuo, G-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621-622.
(b) Coe, D.M.; Hilpert, H.; Noble, S.A.; Peel, M.R.; Roberts, S.M.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1991**, 312-314.
(c) Saville-Stones, E.A.; Lindell, S.D.; Jennings, N.S.; Head, J.C.; Ford, M.J. *J. Chem Soc.,Perkin Trans. I* **1991**, 2603-2604.
(d) Roberts, S.M.; Shoberu, K.A. *J. Chem. Soc., Perkin Trans. I* **1991**, 2605-2607.
(e) Peel, M.R.; Sternbach, D.D.; Johnson, M.R. *J. Org. Chem.* **1991**, *56*, 4990-4993.
(f) Liotta, F.; Unelius, C.R.; Kozak, J.; Norin, T. *Acta Chem. Scand.* **1992**, *46*, 686-688.
(g) Gundersen, L-L.; Benneche, T.; Rise, F.; Gogoll, K.; Undheim, K. *Acta Chem. Scand.* **1992**, *40*, 761-771.
(h) Coe, D.M.; Roberts, S.M.; Storer, R. *J. Chem. Soc., Perkin Trans. I* **1992**, 2695-2704.
(i) Ramesh, K.; Wolfe, M.S.; Lee, Y.; Vander Velde, D.; Borchardt, R.T. *J. Org. Chem.* **1992**, *57*, 5861-5868.
(j) Gundersen, L-L.; Benneche, T.; Undheim, K. *Tetrahedron Lett.* **1992**, *33*, 1085-1088.
(k) Jähne, G.; Müller, A.; Kroha, H.; Rösner, M.; Holzhäuser, O.; Meichsner, C.; Helsberg, M.; Winkler, I.; Riess, G. *Tetrahedron Lett.* **1992**, *33*, 5335-5338.
(l) MacKeith, R.A.; McCague, R.; Olivo, H.F.; Palmer, C.F.; Roberts, S.M. *J. Chem. Soc., Perkin Trans. I*, **1993**, 313-314.
(m) Merlo, V.; Reece, F.J.; Roberts, S.M.; Gregson, M.; Storer, R. *J. Chem. Soc., Perkin Trans. I* **1993**, 1717-1718.
(n) Da Silva, A.D.; Coimbra, E.S.; Fourrey, J-L.; Machado, A.S.; Robert-Géro, M. *Tetrahedron Lett.* **1993**, *34*, 6745-6748.
(o) Koga, M.; Schneller, S.W. *J. Org. Chem.* **1993**, *58*, 6471-6473.
(p) Siddiqi, S.M.; Chen, X.; Schneller, S.W. *J. Med. Chem.* **1994**, *37*, 551-554.

4 Bollit, V.; Chaguir, B.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 2481-2484.

5 (a) Keilen, G.; Benneche, T.; Undheim, K. *Acta Chem. Scand., Ser. B.* **1987**, *41*, 577-580.
(b) Falck-Pedersen, M.L.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 251-258.
(c) Falck-Pedersen, M.L.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, *47*, 63-67.

6 Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099-8102.

7 Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1457-1464.

8 Coe, D.M.; Orr, D.C.; Roberts, S.M.; Storer, S. *J. Chem. Soc., Perkin Trans. I* **1991**, 3378-3379.

9 (a) Moreno-Mañas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5328-5335.
(b) Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *J. Org. Chem.* **1990**, *55*, 4925-4928.
(c) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *Tetrahedron* **1994**, *50*, 515-528.

10 (a) Safi, S.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025-2028.
(b) Blart, E.; Genet, J.P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505-514.

11 (a) Genet, J.P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715-717.
(b) Genet, J.P.; Blart, E.; Savignac, M.; Lemeune, S.; Paris, J.M. *Tetrahedron Lett.* **1993**, *34*, 4189-4192

12 Products **6-11** and **20** were known.[7] Assignments of structures to isomers **12** and **13** and to **16** and **17** were made by SDEPT-1D experiments.[13] Sulfides **15**, **19** and **21** were prepared independently as for **15** (Scheme 2). They presented signals for the S-CH_2 group at δ 3.95-3.98 (H-NMR) and 32.2-32.3 (13C-NMR) far away from the N-CH_2 signals (> 4.95 and > 46.6). Mp's (°C) **12**: 225-6; **13**: 180-1; **14**: 91-2; **15**: 201-2; **16**: 166-7; **17**: 159-160; **18**: 161-2; **19**: 211-2; **21**: 164-5. New products **12**, **14-19** and **21** gave good elemental analyses.

13 (a) Parella, T.; Sánchez-Ferrando, F.; Virgili, A. *Bull. Magn. Reson.* **1992**, *14*, 263-266.
(b) Parella, T.; Sánchez-Ferrando, F.; Virgili, A. *Magn. Reson. Chem.* **1994**, in press.

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