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Palladium-Catalyzed Allylation of 3-Hydroxyisoxazole, 5-Isoxazolone and 5-Pyrazolone Systems*

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Abstract: Kinetic *vs.* thermodynamic control and steric hindrance are factors that determine the regioselectivity of the Pd(0)-catalyzed allylation of ambident heterocycles of the 3-hydroxyisoxazole, 5-isoxazolone and 5-pyrazolone series.

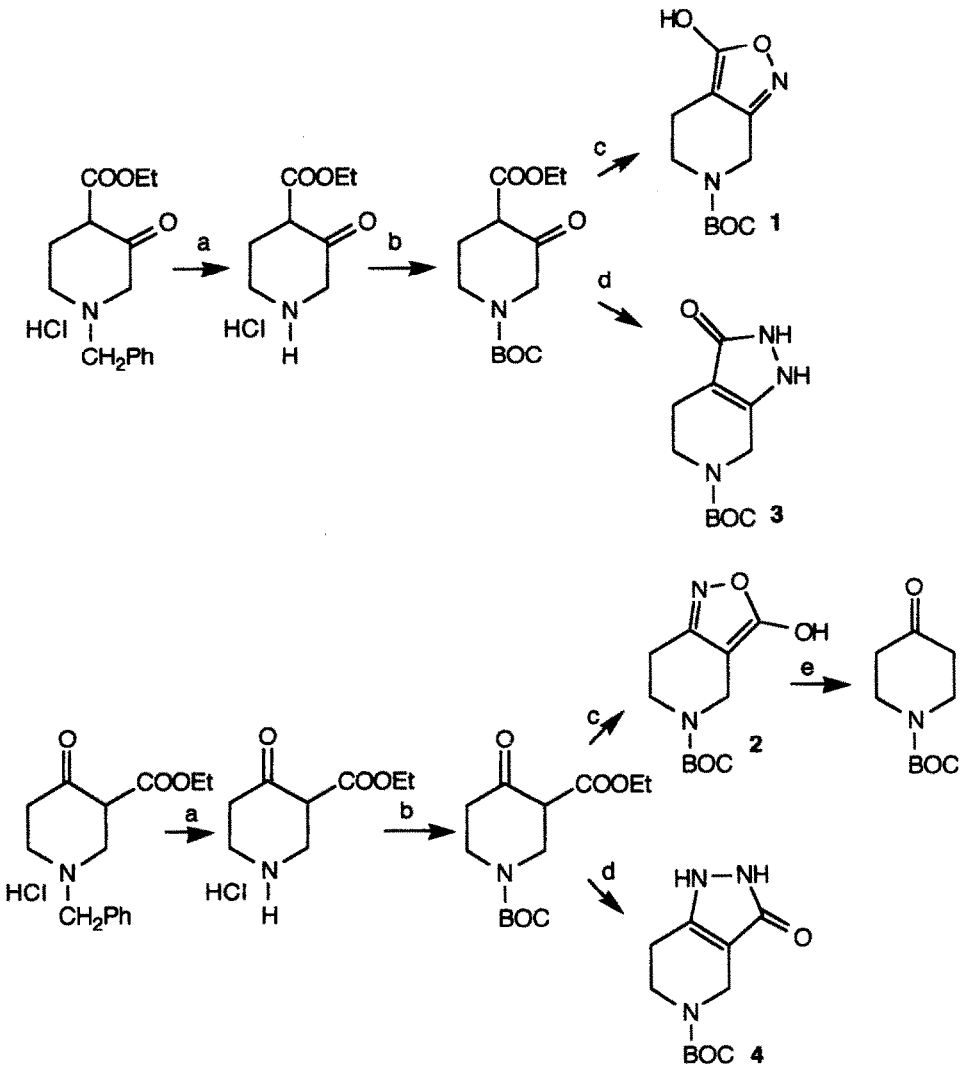
INTRODUCTION

The Pd(0)-catalyzed allylation of nucleophiles[1] has provided regioselective alkylation of heterocyclic ambident nucleophiles. Thus, regioselective N-9 allylation of purines at the imidazole part of the molecule, is a key step in the preparation of carbanucleosides.[2,3] Other ambident heterocyclic 5- and 6-membered rings possessing a tautomeric or mesomeric aromatic structure that have been allylated under Pd(0) catalysis include imidazole,[2b,3] 1,2,4-triazole,[4] indole (C-3 allylation under thermodynamic control and N-allylation under kinetic control),[5] tetronic acids (C-allylation under thermodynamic control),[6] ascorbic acid (vitamin C) (C-allylation),[7] 2-pyridones,[8] pyrimidin-2-ones (N-allylation under thermodynamic control),[2a,2h,9] pyridine-2,6-diones (C-allylation),[10] pyrimidine-2,4-dione (uracil) (N-1 and N-3 allylation),[2i,3,8,11] 5-methylpyrimidine-2,4-dione (thymine) (N-1 and N-3 allylation),[2g,2j,8,11] 6-methylpyrimidine-2,4-dione (6-methyluracil) (N-3 allylation),[8] citosine and 5-methylcytosine (N-1 allylation),[2g,2i] 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) (C-allylation under thermodynamic control)[12] and barbituric acid (C-allylation).[6] Remarkably, also heterocyclic ambident systems bearing a sulfur nucleophilic atom have been efficiently allylated on sulfur under Pd(0) catalysis,[4,8,13] i.e. 2-thioxothiazolidin-4-one (rhodanine), thiobenzoxazolone, thiobenzothiazolone, thiobenzimidazolone, 3(5)-mercapto-1,2-4-triazole, 2-thiopyridone, 2-mercaptopyrimidine, 6-methyl-2-thiouracil and 2-thiobarbituric acid.

From these studies some regioselectivity rules have emerged. For NHCO, NHCS and $COCH_2CO$ moieties, the preferred order of Pd-catalyzed allylation is $COCH_2CO$>NHCO>NHCS and within each system the regioselectivity is C>O, N>O, S>N. In general, non Pd-catalyzed standard alkylations produce mixtures of C- and O- and of N- and O- alkylation products and preferential S- over N- reaction under kinetic control.

C-allylation under Pd(0) catalysis of triacetic acid lactone is thermodynamically controlled[12] (reversible kinetically favoured O-allylation), whereas some experiments performed with S- and N-allylated derivatives of thiobenzimidazolone[4] suggest that in this case the major reactivity of S over N nucleophilic centres is kinetically controlled.

* Dedicated to the memory of Professor Ernest Colomer (Montpellier)



a.- H_2/Pd-C/3 atm; b.- i) $NaHCO_3/H_2O$, ii) $(BOC)_2O/HCCl_3$; c.- i) NH_2OH, 0°C ii)Conc. HCl; d.- NH_2NH_2/H_2O-EtOH; e.- H_2/Pt-C/EtOH

SCHEME I

In order to extend the knowledge of the Pd-catalyzed allylations of ambident nucleophiles we chose the title systems. They have two or more nucleophilic centres and present another interesting feature which deserves some comment. Indeed, some heterocyclic aminoacids presenting activity in neurotransmission processes contain a 3-hydroxyisoxazole moiety in their structure, i.e. ibotenic acid ((*RS*)-2-amino-2-(3-hydroxyisoxazol-5-yl)acetic acid),[14] AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid).[14] Also, muscimol (5-aminomethyl-3-hydroxyisoxazole) is active in neurotransmission.[15] Analogues of these compounds have

been synthesized for testing as neurotransmitters.[15,16] The 5-isoxazolone ring is also present in some aminoacids with agonist activity in glutamate receptors[17] and 5-pyrazolone containing aminoacids have been prepared as potential agonists or antagonists in glutamate receptors.[18] Moreover, bicyclic compounds with partial structures of 3-hydroxyisoxazole, 5-hydroxyisoxazole and 3- or 5-pyrazolone have been described and evaluated as conformationally restricted analogues of ibotenic acid, AMPA, NMDA (*N*-methyl-D-aspartic acid), 2-aminoadipic acid or GABA (γ-aminobutyric acid), i.e. 7-HPCA ((*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-7-carboxylic acid),[14,19] 5-HPCA ((*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-5-carboxylic acid),[16b,16c] 4-HPCA ((*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-4-carboxylic acid),[16c,20] 6-HPCA ((*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-6-carboxylic acid),[20] THIP (3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine),[15] iso-THIP (3-hydroxy-4,5,6,7-tetrahydroisoxazolo[3,4-*c*]pyridine,[15] THPO (3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine),[21] 3-hydroxy-4,5,6,7-tetrahydropyrazolo[5,4-*c*]pyridine and their 1- and 2-methyl derivatives.[15] Also, some alkylated derivatives of AMPA[22] and THPO[23] have been found active in neurotransmission processes.

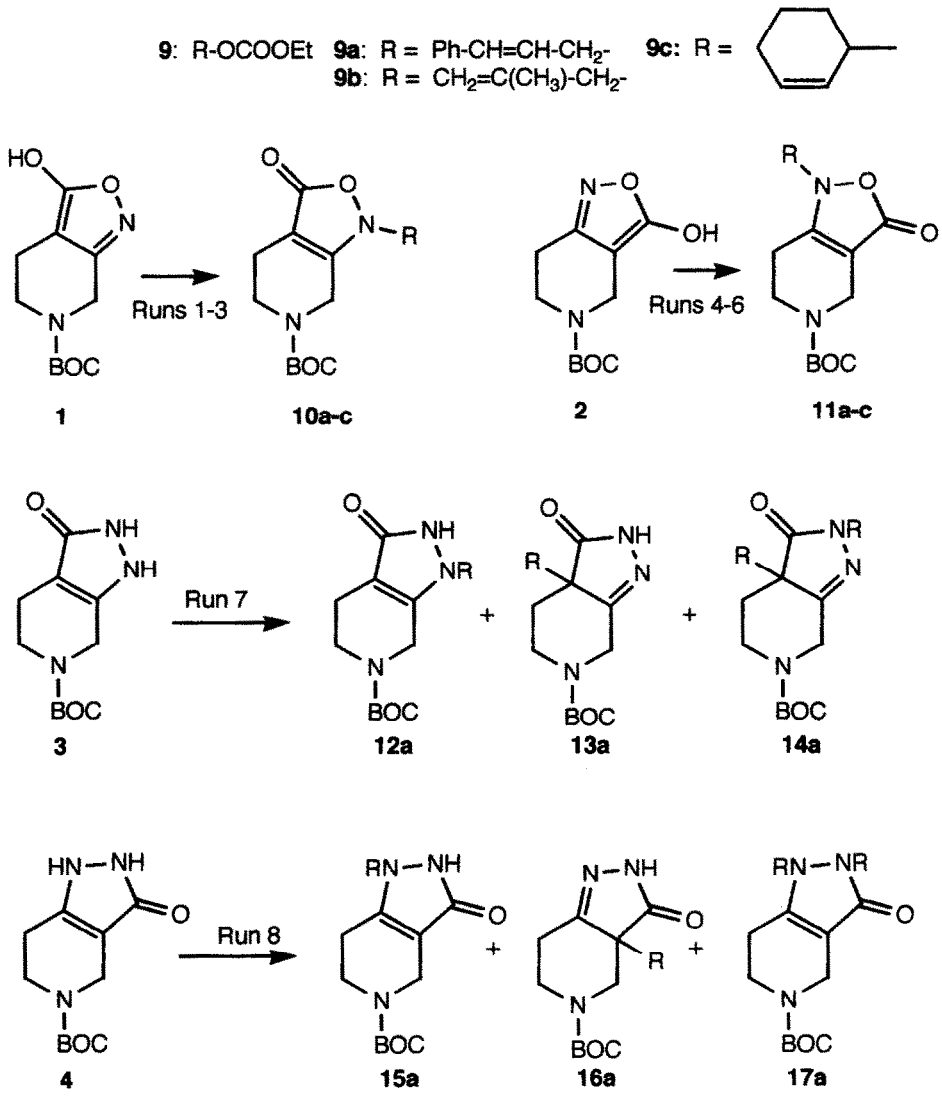
Alkylation of 3-hydroxyisoxazole[16a,d,e,22-24] and 5-pyrazolone[25] systems under basic conditions gives mixtures of N- and O-alkylated compounds. Only in the methoxymethylation[24b] of 3-hydroxy-4,5-dimethylisoxazole the N-alkylated derivative is exclusively obtained (thermodynamic control). Recently, the formation of a mixture of C-4 and N-methylated products arising from the reaction of substituted 5-isoxazolones with methyl iodide and triethylamine has been reported.[26] Alkylations of *N*-unsubstituted 5-pyrazolone systems have scarcely been described in the literature, and lead to N-1[27a] or N-2[27b] alkylated compounds.

RESULTS

In the course of a synthetic project we were interested in the preparation of compounds **1-4** (Scheme I) and the corresponding alkylated products in the 5-hydroxyisoxazole and pyrazolone rings. Following with our studies on the regioselective allylation of ambident heterocycles, we decided to carry on the Pd(0)-catalyzed allylation on these substrates and on simpler model molecules such as 3-hydroxy-5-methylisoxazole, **5**, 3-methyl-2-isoxazolin-5-one, **6**, 3-methyl-3-pyrazolin-5-one, **7**, and 4-methyl-2-pyrazolin-5-one, **8** (Scheme III).

Compound **1** was prepared as described in the literature[15] and **2** was obtained by an analogous procedure (Scheme I). Treatment of 1-*tert*-butoxycarbonyl-4-ethoxycarbonyl-3-piperidone and 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-piperidone with hydrazine afforded **3** and **4** respectively (Scheme I). Compounds **5** and **6** were prepared from ethyl acetoacetate and hydroxylamine. The regioselectivities of these reactions are dependent upon the pH conditions and the final acidification method.[28] This is not the case for β-ketoesters of cyclohexanone and piperidone series, where the ketone carbonyl group is more reactive and only 5-hydroxyisoxazoles are obtained.[28d,28c] However, we confirmed structure **2** by conversion into the known *N*-*tert*-butoxycarbonyl-4-piperidone by catalytic hydrogenation at atmospheric pressure.[28a]

The results of our allylation experiments are summarized in Schemes II and III and in Table 1. Allylation of bicyclic 5-hydroxyisoxazoles **1** and **2** with three allylating agents, cinnamyl ethyl carbonate, **9a**, ethyl 2-methylallyl carbonate, **9b**, and 2-cyclohexenyl ethyl carbonate, **9c** (runs 1-6, Table 1) afforded regioselectively N-alkylated compounds **10a-c** and **11a-c** (Scheme II). However, the reaction of 5-isoxazolone **6** (run 10, Table 1) with **9a** under analogous conditions showed poor regioselectivity, compounds **19a-22** being isolated (Scheme III). Ketone **22** should arise from **20a** by opening of the 5-isoxazolone ring, decarboxylation and hydrolysis of C=N bond. Treatment of bicyclic 5-pyrazolones **3** and **4** with **9a** under Pd(0) catalysis (runs 7 and 8, Table 1) gave monoallylated compounds at N-2 and C-4 centres (**12a** and **13a** from **3**; **15a** and **16a** from **4**) together with minor amounts of diallylated products (**14a** from **3** and **17a** from **4**) (Scheme II). Simple 5-pyrazolones **7** and **8** behaved differently giving rise to regioselective C-allylation when 1.2 equivalents of **9a** are used (runs 11 and 13, Table 1) (Scheme III). Even more, C-allylation does not stop at the monoalkylation step in the case of **7**, compound **23a** being the only isolated product. Reaction of **7** with 3.5 equivalents of **9a** afforded the triallylated derivative **24a** (run 12, Table 1), result that is in agreement with previous findings showing preferential Pd(0)-catalyzed N-allylation of amide systems.[4,8] Similarly, in **8** the second allylation took


9: R-OCOOEt 9a: R = Ph-CH=CH-CH2- 9b: R = CH2=C(CH3)-CH2- 9c: R =
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SCHEME II

place at N-1 to give **26a** together with a minor amount of **27** (run 14, Table 1). Finally, allylation of 3-hydroxy-5-methylisoxazole, **5**, with **9a** (run 9, Table 1) gave regioselectively the N-cinnamyl derivative **18a** as expected for an ambident amide system.

Table 1.- Allylation of Compounds **1-8**. Isolated Products and Allylation Preferences.

Run	**1-8** (mmol)	**9** (mmol)	mmol Pd[a]	mL THF[b]	Time	Products (%)[c]	Allylation
1	**1** (2.1)	**9a** (2.6)	0.2	40	12h	**10a** (83)	N > C, O
2	**1** (4.2)	**9b** (5.2)	0.21	40	12h	**10b** (71)	N > C, O
3	**1** (2.1)	**9c** (8.3)	0.1	40	72h	**10c** (48)	N > C, O
4	**2** (2.2)	**9a** (2.7)	0.2	40	48h	**11a** (47)	N > C, O
5	**2** (4.2)	**9b** (5.2)	0.2	50	24h	**11b** (85)	N > C, O
6	**2** (2.1)	**9c** (8.3)	0.1	40	48h	**11c** (37)	N > C, O
7	**3** (4.2)	**9a** (5.2)	0.3	40	12h	**12a**[*] (24); **13a** (9); **14a** (12)	HNC=CCO>HNCO N-2 and C-4 > O N-1 > O
8	**4** (0.83)	**9a** (1.14)	0.04	25	15h	**15a** (20); **16a** (55); **17a** (7)	HNC=CCO>HNCO N-2 and C-4 > O N-1 > O
9	**5** (1.0)	**9a** (1.25)	0.05	15	16h	**18a** (90)	N > O
10	**6** (5.0)	**9a** (6.25)	0.25	35	12h	**19a** (18); **20a** (8); **21a** (13); **22** (10)	C and N > O
11	**7** (4.4)	**9a** (5.5)[d]	0.2	40	12h	**23a** (14)	HNC=CCO>HNCO C > N-2, O
12	**7** (10.2)	**9a** (36.2)	0.5	40	12h	**24a** (69)	C > N-2, O N-1 > O
13	**8** (5.1)	**9a** (6.4)	0.3	40	12h	**25a** (94)	HNC=CCO>HNCO C > N-2, O
14	**8** (5.1)	**9a** (12.7)	0.4[e]	40	36h	**26a** (53); **27** (8)[f]	C > N-2, O N-1 > O

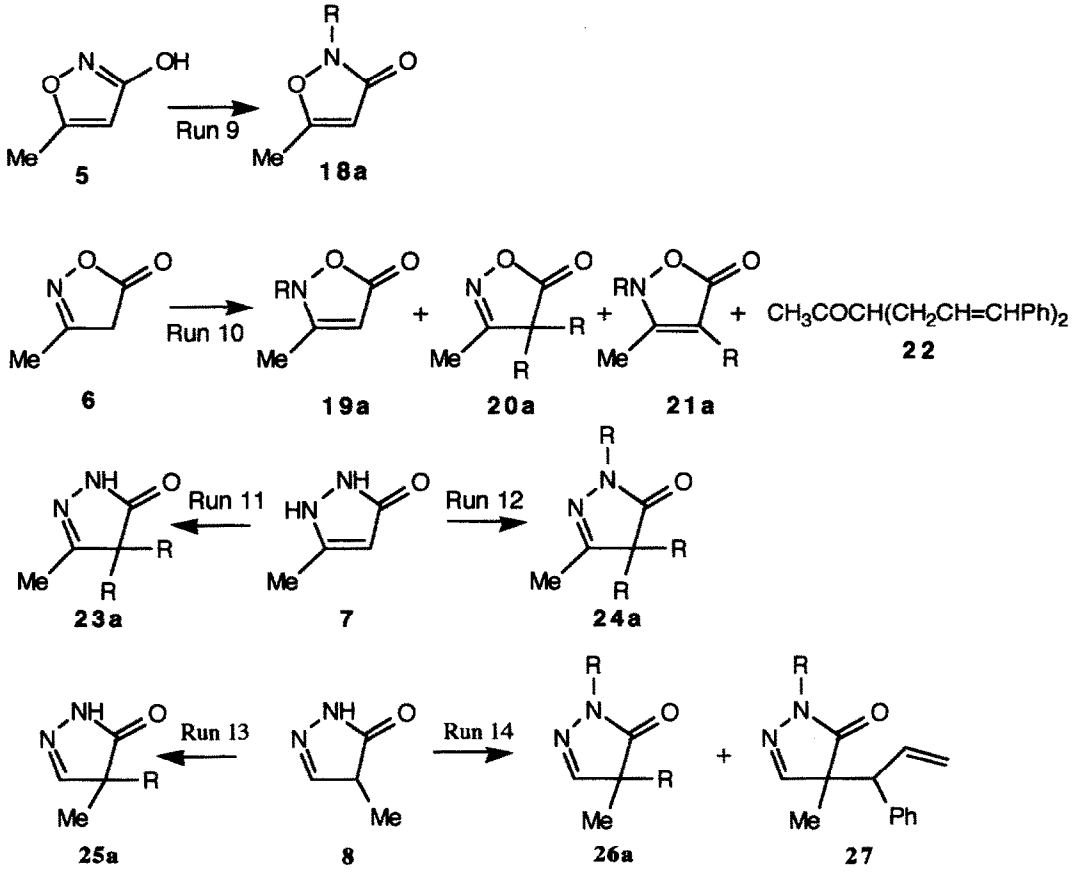
a) $Pd(PPh_3)_4$ in all cases. b) All the experiments were carried out in refluxing THF c) Non-optimized yields of chromatographically isolated products, based on **1-8**. d) Cinnamyl methyl carbonate was used in this run. e) The initial amount was 0.3 equivalents. After 12h at reflux temperature, additional 0.1 equivalents were added and the mixture refluxed for 24h. f) Diastereoisomeric mixture (GLC).

Possibly the steric hindrance at the nucleophilic carbon atom introduced by the piperidine ring is responsible for the observed different results between bicyclic (**1** and **2**) and monocyclic isoxazolones (**6**) and between bicyclic (**3** and **4**) and monocyclic pyrazolones (**7-8**).

For compounds **10-27** all N-CH_2 groups gave absorptions in the range δ 4.0-4.8 whereas C-CH2 groups gave signals at δ 2.5-3.0. Assignments of structures when regioisomers based on two different N atoms are possible, were made on the basis of the ^{13}C-NMR spectra with the program *Selective (Long-Range) Distortionless Enhancement by Polarization Transfer* (SDEPT).[29] Thus, by selective pulsing of the N-CH_2 protons of compound **12a** at δ 4.6 the coupled olefinic C-3 atom of the pyrazolone ring showed its signal enhanced by polarization transfer (SDEPT effect). Analogous results were obtained with compound **15a**. Should the cinnamyl chain have been on the other N atom, SDEPT effect for the carbonylic carbon atom of the pyrazolone ring would have been observed. Homonuclear NOE experiments confirmed also the assignment for structure **15a**.

In order to ascertain if the Pd(0)-catalyzed allylation of these systems is kinetically or thermodynamically controlled, some preliminary experiments were undertaken (Scheme IV). Conventional alkylation (cinnamyl bromide and potassium carbonate in refluxing acetone) of **5** led to **18a** and **28a**. Treatment of this mixture with

a catalytic amount of $Pd(PPh_3)_4$ in refluxing THF caused isomerization of **28a** to **18a**, indicating that Pd(0)-catalyzed *N*-allylation in 3-hydroxyisoxazole systems is thermodynamically controlled. For **7** the conventional alkylation gave a complex mixture from which compounds **23a**, **29a**, **30a** and **31a** were isolated. Isomerization of **30a** to **23a** under Pd(0) catalysis was observed; thus, thermodynamic control operates in Pd(0)-catalyzed *C*-allylation of 5-pyrazolone systems. A solution of **21a** in THF was also heated (80-140°C) with a catalytic amount of $Pd(PPh_3)_4$ affording **22**, presumably through intermediate **20a**. This result points to a thermodynamically controlled regioselective *C*-allylation of 5-isoxazolone systems although the required conditions were not reached in run 10. However, the instability of **20a** limits the synthetic usefulness of the method.



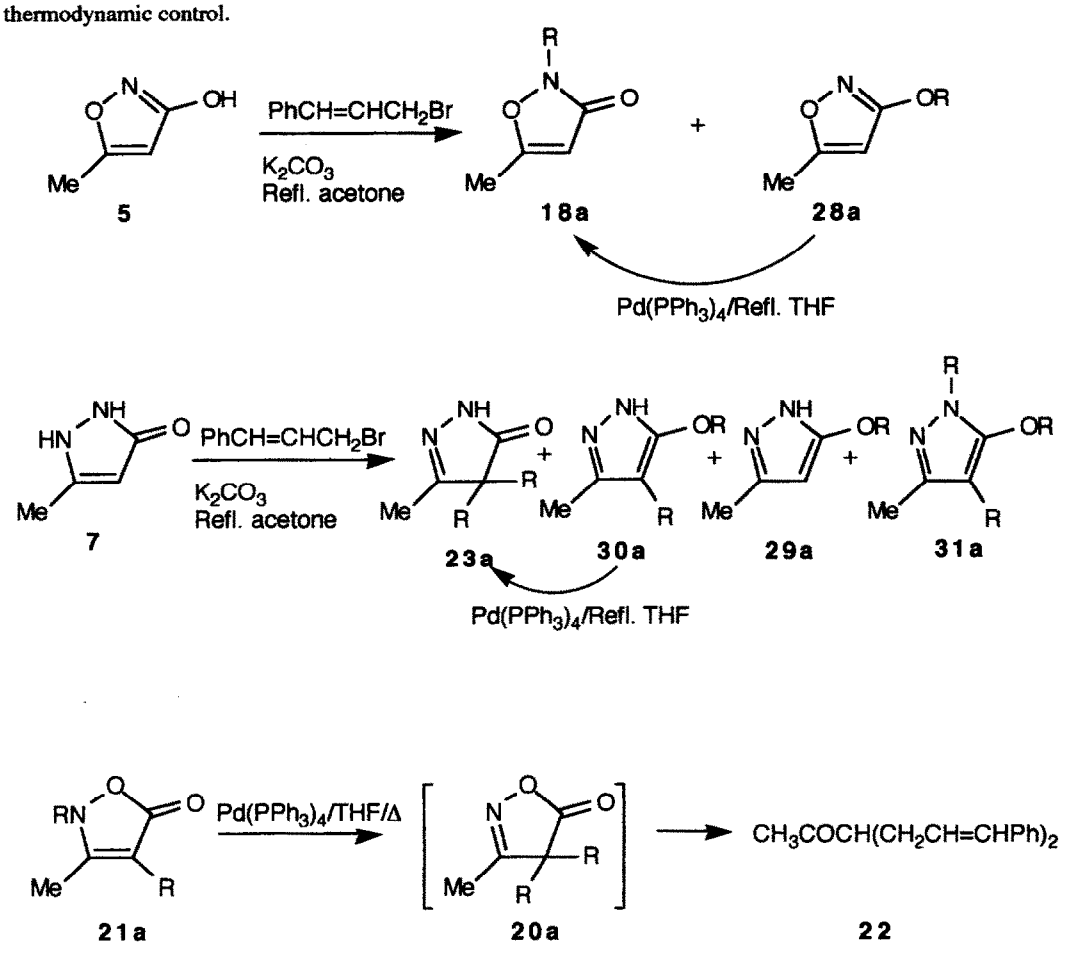
SCHEME III

CONCLUSION

a) Thermodynamically controlled regioselective Pd(0)-catalyzed allylation of sterically free 5-pyrazolones occurs at C-4. When C-4 is common to a second fused-ring, also allylations at N-1 and N-2 are observed.

b) Kinetically controlled Pd(0)-catalyzed allylation of sterically free 3-methyl-5-isoxazolone is not regioselective, both N-2 and C-4 being attacked. If C-4 is common to a second fused-ring only regioselective allylation at N-2 occurs.

c) Pd(0)-Catalyzed allylation of 5-methyl-3-hydroxyisoxazole occurs regioselectively at N-2 under thermodynamic control.



SCHEME IV

EXPERIMENTAL

Compound **1** was obtained as described.[15] Compounds **7** and **8** are commercially available. Allylic carbonates **9a-c** were prepared by standard procedures. ^{1}H-NMR (^{13}C-NMR) spectra were registered at 250 or 400 MHz (62.5 or 100 MHz).

3-Ethoxycarbonyl-4-piperidone hydrochloride. 10% Pd-C (1.003 g) was added to a solution of *N*-benzyl-3-ethoxycarbonyl-4-piperidone hydrochloride (10.006 g, 33.6 mmole) in ethanol-water 1:1 (200 mL) and the mixture was hydrogenated at room temperature under pressure (3 atm). After 24h the mixture was filtered through celite and the solvent evaporated, yielding 3-ethoxycarbonyl-4-piperidone hydrochloride (6.830 g, 33.0 mmole, 99%) which was washed with ethanol; m.p. 164-6°C (lit.[21a] m.p. 168-72°C); IR(KBr): 2955-2448, 1683, 1624 cm^{-1}; ^{1}H-NMR (d_6-DMSO+ $CDCl_3$): 1.34 (t, J = 9.0 Hz, 3H), 2.76 (t, J = 3.0 Hz, 2H), 3.38 (m, 3H), 3.85 (m, 2H), 4.30 (q, J = 9.0 Hz, 2H), 10.0 (broad s, 1H), 12.0 (s, 1H).

N-tert-Butoxycarbonyl-3-ethoxycarbonyl-4-piperidone. To a mechanically stirred suspension of 3-ethoxycarbonyl-4-piperidone hydrochloride (6.802 g, 32.7 mmole) in $CHCl_3$ (50 mL), a solution of sodium hydrogenocarbonate (2.804 g, 32.7 mmole) in water (25 mL) and sodium chloride (5.700 g, 98.2 mmole) were added. Then, a solution of di-*tert*-butyl dicarbonate (7.150 g, 32.7 mmole) in $CHCl_3$ (20 mL) was slowly added and the mixture kept under reflux for 12 h. The organic layer was separated and the aqueous phase extracted with chloroform. The combined organic layers were dried with anhydrous sodium sulfate and the solvent evaporated, yielding *N-tert*-butoxycarbonyl-3-ethoxycarbonyl-4-piperidone as an oil (8.480 g, 31.3 mmole, 96%) which crystallized spontaneously; m.p. 52-4°C; IR(film): 1701, 1666, 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.3 (t, J = 9.0 Hz, 3H), 1.5 (s, 9H), 2.4 (t, J = 5.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.06 (s, 2H), 4.2 (q, J = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$): 13.7, 13.8, 27.7, 28.2, 36.3, 44.6, 55.3, 60.2, 60.5, 79.0, 79.3, 95.6, 153.3, 167.8, 169.6, 169.8, 202.6. Anal.: Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.40; H, 7.78; N, 5.16.

5-*tert*-Butoxycarbonyl-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridine, **2**. *N-tert*-Butoxycarbonyl-3-ethoxycarbonyl-4-piperidone (8.005 g, 29.5 mmole) was added stepwise at 0°C over a stirred solution prepared from hydroxylamine hydrochloride (2.050 g, 29.5 mmole), sodium hydroxide (2.034 g, 50.2 mmole) and water (25 mL). The stirred mixture was kept at this temperature for one hour, then concentrated hydrochloric acid was added until pH *ca* 2 and the solution extracted with chloroform. Compound **2** crystallized on partial evaporation of the organic solvent (until about 5 mL) (4.045 g, 16.8 mmole, 59%); m.p. 142-4°C; IR(KBr): 3128-2873, 1727, 1689, 1652, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 2.6 (t, J = 5.0 Hz, 2H), 3.7 (t, J = 5.0 Hz, 2H), 4.2 (s, 2H). Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.84; H, 6.68; N, 11.59.

Hydrogenation of **2**. 10% Pt-C (0.010 g) Was added to a solution of **2** (0.642 g, 2.7 mmole) in ethanol (10 mL) and the mixture hydrogenated at room temperature and atmospheric pressure, following the progress of the reaction by thin layer chromatography. The mixture was filtered over celite and the solvent was evaporated to yield 1-*tert*-butoxycarbonyl-4-piperidone as an oil which crystallized from ethyl acetate-hexane 1:1 (0.458 g, 2.3 mmole, 86%); m.p. 73-5°C (lit.[30] m.p. 70-2°C). ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 2.4 (t, J = 6.0 Hz, 4H), 3.7 (t, J = 6.0 Hz, 4H).

6-*tert*-Butoxycarbonyl-3-oxo-2,3,4,5,6,7-hexahydropyrazolo[3,4-*c*]pyridine, **3**. A mixture of *N-tert*-butoxycarbonyl-4-ethoxycarbonyl-3-piperidone[15] (3.000 g, 11.1 mmole), hydrazine hydrate (0.610 g, 12.2 mmole) and ethanol (12 mL) was heated at 70°C for 3 h, then left at room temperature for 12 h. By cooling at -20°C for 24 h, compound **3** precipitated (1.709 g, 7.2 mmole, 64%); m.p. 230-2°C; IR(KBr): 2977-2576, 1692, 1619, 1592, 1550 cm^{-1}; ^{1}H-NMR (d_6-DMSO): 1.4 (s, 9H), 2.3 (t, J = 5.0 Hz, 2H), 3.4 (broad s, 2H), 3.50 (t, J = 5.0 Hz, 2H), 4.3 (s, 2H); ^{13}C-NMR (d_6-DMSO): 28.2, 40.6, 41.2, 42.4, 79.3, 96.9, 138.1, 154.2, 157.3. Anal.: Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.18; H, 7.12; N, 17.51.

5-*tert*-Butoxycarbonyl-3-oxo-2,3,4,5,6,7-hexahydropyrazolo[4,3-*c*]pyridine, **4**. It was prepared in 81% yield from *N-tert*-butoxycarbonyl-3-ethoxycarbonyl-4-piperidone as for **3**; m.p. 215-6°C (dec); IR(KBr): 2978-2602, 1705, 1611, 1535 cm^{-1}; ^{1}H-NMR (d_6-DMSO): 1.4 (s, 9H), 2.5 (t, J = 5.0 Hz, 2H, partially masked by d_6-DMSO), 3.5 (t, J = 5.0 Hz, 2H), 4.1 (s, 2H); ^{13}C-NMR (d_6-DMSO): 21.8, 28.0, 39.8, 40.5, 78.9, 96.4, 138.5, 154.2, 156.5. Anal.: Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.16; H, 7.21; N, 17.48.

3-Hydroxy-5-methylisoxazole, **5**. Ethyl acetoacetate (3.005 g, 23.1 mmole) was slowly added at 0°C over a stirred solution prepared from hydroxylamine hydrochloride (1.606 g, 23.1 mmole), sodium hydroxide (1.938 g, 48.5 mmole) and water (30 ml). The stirred mixture was kept at 0°C for one hour, then concentrated hydrochloric acid (10 mL) was added stepwise. The acidic solution was maintained 15 min at room temperature and heated at 90°C for 30 min. After reaching room temperature the solution was extracted with diethyl ether, the organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to give **5** (0.543 g, 5.5 mmole, 24%), which was purified by sublimation (55°C / 20 mm Hg); m.p. 79-81°C (lit.[28c] m.p. 83-4°C);

IR(KBr): 3010-2500, 1634, 1529 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.3 (s, 3H); 5.7 (s, 1H), 10.6 (broad s, 1H); ^{13}C-NMR ($CDCl_3$): 13.9, 57.9, 93.7, 170.3.

3-Methyl-2-isoxazolin-5-one, **6**. A mixture of ethyl acetoacetate (3.064 g, 23.05 mmole), hydroxylamine hydrochloride (1.652 g, 23.05 mmole), potassium carbonate (1.592 g, 11.52 mmole), ethanol (20 mL) and water (20 mL) was stirred at room temperature for 12 h. The solution was extracted with diethyl ether, dried and evaporated to give a 1:5 mixture of **6** and the intermediate oxime (*syn* and *anti* isomers) (signals in the ^{1}H-NMR ($CDCl_3$) at δ 1.15 (t, J = 7.0 Hz), 1.87 (s), 1.89 (s), 3.13 (s), 3.31(s), 4.09 (q, J = 7.0 Hz)). A solution of this mixture in ethanol/water 1:1 (30 mL) was acidified with HCl until pH about 2 and heated at 80°C until consumption of oximes (GLC). After reaching room temperature, the solution was extracted with chloroform, and the organic layer was dried and evaporated to afford **6** (0.990 g, 10.0 mmole, 42%), which was purified by microdistillation at reduced pressure (85-90°C (oven temperature)/0.1 mm Hg) (lit.[31] b.p.92-4°C/ 0.6 mm Hg); IR(KBr): 1809, 1732 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.05 (s, 3H), 3.35 (s, 2H).

6-*tert*-Butoxycarbonyl-1-cinnamyl-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[3,4-*c*]pyridine, **10a** (Run 1 Table 1) (General Procedure). A degassed solution of tetrakis(triphenylphosphine)palladium(0) (0.126 g, , 0.2 mmole) and cinnamyl ethyl carbonate, **9a**, (0.540 g, 2.6 mmole) in anhydrous THF (10 mL) was added over a degassed solution of **1** (0.504 g, 2.1 mmole) in anhydrous THF (30 mL). The mixture was refluxed under argon for 12 h, following the progress of the reaction by thin layer chromatography. The solvent was evaporated and the residue was chromatographed through a column of silica-gel under pressure. Elution with hexane-ethyl acetate 1:1 afforded **10a** as an oil (0.620 g, 1.7 mmole, 84%); IR(film): 1742, 1695, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.4 (s, 9H), 2.2 (t, J = 5.0 Hz, 2H), 3.5 (t, J = 5.0 Hz, 2H), 4.1 (d, J = 7.5 Hz, 2H), 4.3 (s, 2H), 6.2 (dt, J = 16.0 Hz, J = 7.5 Hz, 1H), 6.5 (d, J = 16.0 Hz, 1H), 7.2 (s, 5H); ^{13}C-NMR ($CDCl_3$): 28.3, 40.0, 42.0, 54.6, 63.6, 81.0, 119.6, 126.4, 126.7, 127.6, 128.5, 128.6, 135.5, 136.3, 161.5, 169.7. Anal.: Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.10; H, 6.83; N, 6.76.

All other compounds were prepared as for **10a** under the particular conditions described in Table 1.

6-*tert*-Butoxycarbonyl-1-(2-methyl-2-propen-1-yl)-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[3,4-*c*]pyridine, **10b** (Run 2, Table 1). M.p. 82-4°C (from diethyl ether-hexane); IR(KBr): 1735, 1693, 1646 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 1.8 (s, 3H), 2.4 (dt, J = 5.0 Hz, J = 1.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.0 (s, 2H), 4.3 (t, J = 1.0 Hz, 2H), 5.0 (m, 2H); ^{13}C-NMR ($CDCl_3$): 18.9, 20.2, 28.2, 40.5, 41.1, 58.0, 80.9, 99.6, 115.9, 137.8, 154.4, 160.7, 169.3; MS(m/e): 294(M, 1), 237(89), 221(10), 57(100), 55(86). Anal.: Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.25; H, 7.53; N, 9.40.

6-*tert*-Butoxycarbonyl-1-(2-cyclohexen-1-yl)-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[3,4-*c*]pyridine, **10c** (Run 3, Table 1). Oil; IR(KBr): 1744, 1705, 1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 1.5-2.0 (m, 6H), 2.4 (t, J = 5.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.1 (m, 1H), 4.4 (s, 2H), 5.5 (m, 1H), 6.1 (m, 1H); ^{13}C-NMR ($CDCl_3$): 19.0, 20.3, 24.3, 25.4, 28.2, 40.0, 41.0, 58.9, 80.9, 123.1, 134.4, 160.7, 170.1; MS(m/e): 321(M+1, 4), 320(M, 2), 81(100).

5-*tert*-Butoxycarbonyl-1-cinnamyl-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[4,3-*c*]pyridine, **11a** (Run 4, Table 1). M.p. 122-3°C (from diethyl ether); IR(KBr): 1726, 1685, 1607 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.4 (s, 9H), 2.5 (dt, J = 5.0 Hz, J = 1.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.1 (t, J = 1.0 Hz, 2H), 4.3 (d, J = 6.3 Hz, 2H), 6.1 (dt, J = 16.2 Hz, J = 6.3 Hz, 1H), 6.8 (d, J = 16.2 Hz, 1H), 7.3 (s, 5H); ^{13}C-NMR ($CDCl_3$): 22.8, 28.2, 38.5, 39.0, 53.6, 80.6, 100.0, 120.0, 126.5, 128.3, 128.5, 135.5, 135.7, 154.4, 162.6, 168.3; MS(m/e): 299(M-57, 11), 117(100), 57(20). Anal.: Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.40; H, 6.76; N, 7.84.

5-*tert*-Butoxycarbonyl-1-(2-methyl-2-propen-1-yl)-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[4,3-*c*]pyridine, **11b** (Run 5, Table 1). M.p. 75-6°C (from diethyl ether); IR(KBr): 1723, 1660, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.4 (s, 9H), 1.7 (s, 3H), 2.5 (dt, J = 5.0 Hz, J < 1.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.0 (broad s, 2H), 4.1 (t, J < 1.0 Hz, 2H), 4.9 (m, 2H); ^{13}C-NMR ($CDCl_3$): 20.1, 22.6, 28.2, 38.4, 39.2, 56.8, 80.5, 97.5, 115.5, 138.1, 154.4, 161.8, 168.1; MS(m/e): 294(M, 6), 238(19), 57(100), 55(70). Anal.: Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.40; H, 7.45; N, 9.40.

5-*tert*-Butoxycarbonyl-1-(2-cyclohexen-1-yl)-3-oxo-1,3,4,5,6,7-hexahydroisoxazolo[4,3-*c*]pyridine, **11c** (Run 6, Table 1). Oil; IR(KBr): 1738, 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.46 (s, 9H), 1.46-2.10 (m, 6H), 2.5 (t, J = 5.0 Hz, 2H), 3.7 (t, J = 5.0 Hz, 2H), 4.16 (m, 3H), 5.5 (m, 1H), 6.0 (m, 1H).

6-*tert*-Butoxycarbonyl-1-cinnamyl-3-oxo-2,3,4,5,6,7-hexahydropyrazolo[3,4-*c*]pyridine, **12a** (Run 7, Table 1). M.p. 179-81°C (from diethyl ether); IR(KBr): 2999, 2975, 2859, 2658, 1700, 1687, 1525 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 2.5 (t, J = 5.0 Hz, 2H), 3.6 (t, J = 5.0 Hz, 2H), 4.4 (s, 2H), 4.6 (d, J = 6.0 Hz, 2H), 6.2 (dt, J = 15.8 Hz, J = 6.0 Hz, 1H), 6.5 (d, J = 15.8 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): 19.4, 28.3, 39.9, 40.5, 41.8, 80.2, 99.6, 123.4, 126.6, 127.8, 128.4, 133.4, 136.1, 137.3, 154.8, 158.8; MS(m/e): 356(M+1, 3), 355(M, 11), 298(93), 117(100), 57(55). Anal.: Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.59; H, 7.09; N, 11.82. Found: C, 67.64; H, 7.08; N, 11.81.

6-*tert*-Butoxycarbonyl-3a-cinnamyl-3-oxo-3,3a,4,5,6,7-hexahydropyrazolo-2*H*-[3,4-*c*]pyridine, **13a** (Run 7, Table 1). M.p. 67-9°C (from diethyl ether); IR(KBr): 3253, 2977, 1699 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.3 (s, 9H), 1.6 (m, 1H), 1.9 (dt, J = 5.8 Hz, J = 2.9 Hz, 1H), 2.6 (dd, J = 13.9 Hz, J = 6.2 Hz, 1H), 2.7 (dd, J = 13.9 Hz, J = 8.4 Hz, 1H); 3.1 (t, J = 12.4 Hz, 1H), 3.6 (d, J = 14.2 Hz, 1H), 4.0 (broad absorption, 1H), 4.6 (d, J = 14.5 Hz, 1H), 5.8 (dt, J = 15.7 Hz, J = 7.3 Hz, 1H), 6.4 (d, J = 15.7 Hz, 1H); 7.1 (m, 5H), 8.5 (s, 1H); MS(m/e): 356(M+1, 3), 355(M, 9), 299(27), 117(37), 57(100). Anal.: Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.59; H, 7.09; N, 11.82. Found: C, 67.05; H, 7.06; N, 11.32.

6-*tert*-Butoxycarbonyl-2,3a-dicinnamyl-3-oxo-3,3a,4,5,6,7-hexahydropyrazolo-2*H*-[3,4-*c*]pyridine, **14a** (Run 7, Table 1).M.p. 143-4°C (from diethyl ether); IR(KBr): 1707, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.3 (s, 9H), 1.7 (dt, J = 13.5 Hz, J = 4.9 Hz, 1H), 2.0 (d, J = 13.5 Hz, 1H), 2.7 (dd, J = 13.5 Hz, J = 7.3 Hz, 1H), 2.8 (dd, J = 13.5 Hz, J = 7.3 Hz, 1H), 3.3 (t, J = 12.0 Hz, 1H), 3.7 (d, J = 14.6 Hz, 1H), 4.0 (broad absorption, 1H), 4.2 (dd, J = 15.3 Hz, J = 6.9 Hz, 1H), 4.6 (dd, J = 15.3 Hz, J = 5.8 Hz, 1H), 4.8 (broad d, J = 14.6 Hz, 1H), 5.8 (dt, J = 15.3 Hz, J = 7.3 Hz, 1H), 6.0 (dt, J = 15.7 Hz, J = 6.5 Hz, 1H), 6.4 (d, J = 15.3 Hz, 1H), 6.5 (d, J = 15.7 Hz, 1H), 7.1 (m, 10H); ^{13}C-NMR ($CDCl_3$): 28.2, 32.6, 35.3, 43.4, 45.8, 52.0, 80.6, 121.4, 123.3, 126.1, 126.4, 127.6, 128.3, 128.5, 133.5, 134.6, 136.3, 154.2, 159.2, 176.1; MS(m/e): 472 (M, 1), 415(5), 117(100), 57(18). Anal.: Calcd. for $C_{29}H_{33}N_3O_3$: C, 73.70; H, 7.25; N, 8.89. Found: C, 73.85; C, 7.04; N, 8.80.

5-*tert*-Butoxycarbonyl-1-cinnamyl-3-oxo-2,3,4,5,6,7-hexahydropyrazolo[4,3-*c*]pyridine, **15a** (Run 8, Table 1). M.p. 186-7°C (from diethyl ether); IR(KBr): 3180, 1682 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 2.6 (broad s, 2H), 3.67 (broad s, 2H), 4.3 (broad s, 2H), 4.86 (d, J = 6.1 Hz, 2H), 6.4 (m, 1H), 6.7 (d, J = 15.9 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): 28.4, 39.2, 39.8, 50.1, 65.8, 80.0, 98.7, 123.8, 126.4, 127.9, 128.4, 132.7, 135.8, 138.6, 154.9, 157.7; MS(m/e): 356(M+1, 2), 355(M, 5), 299(22), 298(43), 117 (60), 57(100). Anal.: Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.59; H, 7.09; N, 11.82. Found: C, 67.40; H, 7.06; N, 11.69.

5-*tert*-Butoxycarbonyl-3a-cinnamyl-3-oxo-3,3a,4,5,6,7-hexahydropyrazolo-2*H*-[4,3-*c*]pyridine, **16a** (Run 8, Table 1). M.p. 172-3°C (from diethyl ether); IR(KBr): 1693 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.5 (s, 9H), 2.6 (m, 6H), 4.3 (broad absorption, 1H), 4.5 (broad absorption, 1H), 5.8 (dt, J = 7.3 Hz, J = 15.6 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 7.2 (m, 5H), 8.8 (s, 1H); ^{13}C-NMR ($CDCl_3$): 28.3, 34.9, 45.6, 50.0, 54.0, 81.0, 121.7, 126.2, 127.5, 128.3, 134.4, 154.6, 163.5, 177.0; MS(m/e): 356(M+1, 2), 355(M, 7), 299(20), 117(34), 57(100). Anal.: Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.59; H, 7.09; N, 11.82. Found: C, 67.58; H, 7.11; N, 11.82.

5-*tert*-Butoxycarbonyl-1,2-dicinnamyl-3-oxo-2,3,4,5,6,7-hexahydropyrazolo[4,3-*c*]pyridine, **17a** (Run 8, Table 1). M.p. 147-50°C (from diethyl ether); IR(KBr): 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.4 (s, 9H), 2.6 (s, 2H), 3.6 (s, 2H), 4.3 (s, 2H), 4.6 (d, J = 5.5 Hz, 2H), 4.8 (d, J = 5.8 Hz, 2H), 6.2 (dt, J = 15.9 Hz, J = 5.8 Hz, 1H), 6.4 (m, 2H), 6.6 (d, J = 15.9 Hz, 1H), 7.25 (m, 10H). Anal.: Calcd. for $C_{29}H_{33}N_3O_3$: C, 73.86; H, 7.05; N, 8.91. Found: C, 73.77; H, 7.14; N, 8.83.

2-Cinnamyl-5-methylisoxazolin-3-one, **18a** (Run 9, Table 1). M.p. 39-41°C (from diethyl ether/pentane); IR(film): 1721, 1679, 1631 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.19 (d, J = 1.0 Hz, 3H), 4.5 (dd, J = 6.5 Hz, J = 1.0 Hz, 2H), 5.5 (d, J = 1.0 Hz, 1H), 6.1 (dt, J = 15.7 Hz, J = 6.5 Hz, 1H), 6.55 (broad d, J = 15.7 Hz, 1H), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$): 13.2, 47.9, 98.1, 121.6, 126.3, 127.9, 128.2, 128.4, 131.8, 131.9, 134.2, 170.0. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 71.83; H, 6.10; N, 6.10.

2-Cinnamyl-3-methylisoxazolin-5-one, **19a** (Run 10, Table 1). M.p. 60-1°C (from diethyl ether); IR(KBr): 1716, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.2 (s, 3H), 4.3 (dd, J = 6.6 Hz, J = 1.1 Hz, 2H), 5.1 (s, 1H), 6.1 (dt, J = 16.0 Hz, J = 6.6 Hz, 1H), 6.6 (broad d, J = 16.0 Hz, 1H), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$): 12.3, 52.5, 91.1, 120.0, 126.5, 128.4, 128.6, 135.4, 164.15, 170.8. Anal.: Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.50; H, 6.14; N, 6.50.

4,4-Dicinnamyl-3-methylisoxazolin-5-one, **20a** (Run 10, Table 1). M.p. 124-6°C (from diethyl ether); IR(KBr): 1785 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 2.55 (ddd, J = 14.2 Hz, J = 7.7 Hz, J = 1.1 Hz, 2H), 2.75 (ddd, J = 14.2 Hz, J = 7.3 Hz, J = 1.5 Hz, 2H), 5.8 (apparent dt, J = 15.5 Hz, J = 7.5 Hz, 2H), 6.5 (broad d, J = 15.5 Hz, 2H), 7.2 (m, 10H); ^{13}C-NMR ($CDCl_3$): 12.3, 37.8, 55.9, 120.5, 126.37, 126.40, 128.5, 135.5, 136.0, 167.75, 179.5. Anal.: Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.69; H, 6.45; N, 4.16.

2,4-Dicinnamyl-3-methylisoxazolin-5-one, **21a** (Run 10, Table 1). M.p. 60-3°C (from pentane); IR(KBr): 1724, 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.0 (s, 3H), 3.0 (d, J = 5.8 Hz, 2H), 4.2 (dd, J = 6.6 Hz, J = 1.5 Hz, 2H), 6.1 (m, 2H), 6.3 (d, J = 15.7 Hz, 1H), 6.5 (d, J = 16.0 Hz, 1H), 7.2 (m, 10H); ^{13}C-NMR ($CDCl_3$): 11.1, 25.3, 30.9, 53.3, 102.6, 120.0, 125.9, 126.6, 127.1, 128.3, 128.4, 128.7, 130.7, 135.6, 136.9, 161.8, 171.3. Anal.: Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.66; H, 6.42; N, 4.26.

3-Cinnamyl-6-phenyl-5-hexen-2-one, **22** (Run 10, Table 1). Oil. B.p. 210-20°C (oven temp.)/ 0.1 mmm Hg. IR(film): 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 2.4 (m, 2H), 2.5 (m, 2H), 2.8 (m, 1H), 6.1 (dt, J = 15.7 Hz, J = 7.3 Hz, 2H), 6.4 (d, J = 15.7 Hz, 2H), 7.2 (m, 10H); ^{13}C-NMR ($CDCl_3$): 29.8, 34.45, 52.7, 126.05, 126.8, 127.2, 128.5, 132.3, 137.15, 210.95; MS(m/e): 272(M-17, 13), 247(M-43, 3), 173(30), 117(31), 115(45), 91(97), 43(100).

4,4-Dicinnamyl-3-methyl-2-pyrazolin-5-one, **23a** (Run 11, Table 1). M.p. 176-8°C (from diethyl ether); IR(KBr): 3165, 3085, 3027, 1710, 1677 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 2.6 (dd, J = 13.7 Hz, J = 7.6 Hz, 2H), 2.7 (dd, J = 13.7 Hz, J = 7.3 Hz, 2H), 5.8 (apparent dt, J = 15.6 Hz, J = 7.6 Hz, 2H), 6.44 (d, J =15.6 Hz, 2H), 7.2 (m, 10H), 8.44 (s, 1H); ^{13}C-NMR ($CDCl_3$): 14.3, 37.5, 56.8, 122.0, 126.2, 127.5, 128.4, 134.1, 136.5, 162.1, 178.6. Anal.: Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.97; H, 6.76; N, 8.44.

1,4,4-Tricinnamyl-3-methylpyrazolin-5-one, **24a** (Run 12, Table 1). M.p. 144-5°C (from diethyl ether); IR(KBr): 1702 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.0 (s, 3H), 2.45 (dd, J = 13.4 Hz, J = 7.3 Hz, 2H), 2.66 (dd, J = 13.4 Hz, J = 7.3 Hz, 2H), 4.3 (d, J = 6.1 Hz, 2H), 5.75 (dt, J = 15.6 Hz, J = 7.3 Hz, 2H), 5.9 (dt, J = 15.6 Hz, J = 6.1 Hz, 1H), 6.39 (d, J = 15.6 Hz, 2H), 6.43 (d, J = 15.6 Hz, 1H), 7.1 (m, 15H); ^{13}C-NMR ($CDCl_3$): 14.1, 37.6, 45.7, 58.2, 122.0, 123.5, 126.1, 126.3, 127.3, 127.4, 128.3, 128.4, 133.1, 134.1, 136.1, 136.4, 161.0, 175.3. Anal.: Calcd. for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77; N, 6.27. Found: C, 83.27; H, 6.72; N, 6.26.

4-Cinnamyl-4-methyl-2-pyrazolin-5-one, **25a** (Run 13, Table 1). M.p. 59-61°C (from diethyl ether); IR(KBr): 3200-2800, 1723, 1683 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.26 (s, 3H), 2.50 (m, 2H), 5.95 (dt, J = 15.2 Hz, J = 7.6 Hz, 1H), 6.43 (d, J = 15.2 Hz, 1H), 7.2 (m, 6H), 9.0 (broad s, 1H); ^{13}C-NMR ($CDCl_3$): 18.3, 38.2, 51.1, 122.4, 126.1, 127.4, 128.3, 134.3, 136.4, 156.2, 179.8. Anal.: Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.82; H, 6.64; N, 13.04.

1,4-Dicinnamyl-4-methylpyrazolin-5-one, **26a** (Run 14, Table 1). M.p. 84-6°C (from diethyl ether); IR(KBr): 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.2 (s, 3H), 2.6 (m, 2H), 4.3 (dd, J = 15.6 Hz, J = 6.7 Hz, 1H), 4.5 (dd, J = 15.6 Hz, J = 5.8 Hz, 1H), 5.9 (dt, J = 15.9 Hz, J = 7.6 Hz, 1H), 6.1 (apparent dt, J = 15.3 Hz, J = 6.7 Hz, 1H), 6.4 (d, J = 15.3 Hz, 1H), 6.5 (d, J = 15.9 Hz, 1H), 7.2 (m, 11H); ^{13}C-NMR ($CDCl_3$): 18.2, 38.0, 45.3, 51.7, 122.1, 123.0, 125.7, 127.0, 127.9, 128.0, 132.6, 133.7, 135.6, 136.0, 154.5, 175.7. Anal.: Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.17; H, 6.74; N, 8.53.

1-Cinnamyl-4-methyl-4-(1-phenyl-2-propen-1-yl)pyrazolin-5-one, **27** (Run 14, Table 1). Diastereoisomeric mixture (from GC/MS). Only the major isomer is observed in the ^{1}H-NMR. M.p. 76-8°C (from diethyl ether); IR(KBr): 1707 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.3 (s, 3H), 3.57 (d, J = 9.8 Hz, 1H), 3.97 (ddd, J = 15.6 Hz, J = 6.9 Hz, J = 1.2 Hz, 1H), 4.23 (ddd, J = 15.6 Hz, J = 5.8 Hz, J = 1.4 Hz, 1H), 5.25 (dd, J = 16.0 Hz, J = 1.4

Hz, 1H), 5.28 (dd, J = 10.2 Hz, J = 1.1 Hz, 1H), 5.41 (ddd, J = 15.7 Hz, J = 6.9 Hz, J = 5.8 Hz, 1H), 6.11 (dt, J = 16.0 Hz, J = 10.0 Hz, 1H), 6.4 (d, J = 15.7 Hz, 1H), 7.1 (m, 10H), 7.4 (s, 1H); MS(m/e) (major isomer): 330(M, 5), 117(100), 91(10). Anal.: Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.72; H, 6.62; N, 8.46.

Alkylation of **5** with cinnamyl bromide. Formation of 3-cinnamyloxy-5-methylisoxazole, **28a**, and its isomerization under Pd(0) catalysis. A mixture of **5** (0.338 g, 3.4 mmole), potassium carbonate (2.356 g, 17.4 mmole), cinnamyl bromide (0.672 g, 3.41 mmole) and acetone (30 mL) was refluxed for 12 h. The solid was filtered off, the filtrate was dried with anhydrous sodium sulfate and the solvent evaporated to yield a 1.25:1.0 mixture (^{1}H-NMR) of **18a** and **28a** (0.675 g) (**28a** showed ^{1}H-NMR ($CDCl_3$): 2.3 (d, J = 0.7 Hz, 3H), 4.8 (dd, J = 6.2 Hz, J = 1.1 Hz, 2H), 5.6 (q, J = 0.7 Hz, 1H), 6.4 (dt, J = 16.0 Hz, J = 6.2 Hz, 1H), 6.7 (broad d, J = 16.0 Hz, 1H)). This crude residue was taken in anhydrous THF (20 mL), then $Pd(PPh_3)_4$ (0.213 g, 0.184 mmole) was added and the mixture refluxed for 48 h. A solid was filtered off (0.103 g, 0.2 mmole) and identified as cinnamyltriphenylphosphonium bromide. The filtrate was evaporated and the residue filtered through silica-gel to yield **18a** (0.464 g, 2.1 mmole).

Alkylation of **7** with cinnamyl bromide. Formation of 4-cinnamyl-5-cinnamyloxy-3-methylpyrazole, **30a**. A mixture of **7** (2.067 g, 20.4 mmole), potassium carbonate (14.087 g, 101.9 mmole), cinnamyl bromide (4.828 g, 24.5 mmole) and acetone (70 mL) was refluxed for 12 h. The solid was filtered off, the filtrate was dried with anhydrous sodium sulfate and the solvent evaporated. The residue (4.303 g) was chromatographed through silica-gel under pressure eluting with hexane-ethyl acetate 2:1. From recrystallization of the eluted fractions, the following compounds were obtained:

23a (0.330 g, 1.0 mmole, 5%).

5-Cinnamyloxy-3-methylpyrazole, **29a** (0.137 g, 0.6 mmole, 3%): m.p. 150-2°C (from diethyl ether); IR(KBr): 3200-2500, 1567, 1543, 1501 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 4.5 (dd, J = 5.5 Hz, J = 1.0 Hz, 2H), 5.3 (s, 1H), 6.1 (dt, J = 16.1 Hz, J = 5.5 Hz, 1H), 6.3 (d, J = 16.1 Hz, 1H), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$): 11.2, 50.2, 91.15, 124.0, 126.55, 127.8, 128.4, 132.3, 136.2, 140.3, 161.6. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.62; H, 6.69; N, 12.73.

4-Cinnamyl-5-cinnamyloxy-3-methylpyrazole, **30a** (0.032 g, 0.1 mmole): m.p. 158-61°C (from diethyl ether); IR(KBr): 3059-2500, 1529, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 3.2 (d, J = 5.1 Hz, 2H), 4.6 (dd, J = 4.8 Hz, J < 1.0 Hz, 2H), 6.2 (m, 2H), 6.3 (d, J = 16.1 Hz, 1H), 6.4 (d, J = 16.1 Hz, 1H), 7.2 (m, 10H). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.84. Found: C, 79.52; H, 6.68; N, 8.64.

1,4-Dicinnamyl-5-cinnamyloxy-3-methylpyrazole, **31a** (0.750 g, 1.7 mmole, 8%); m.p. 120-1°C (from diethyl ether); IR(KBr): 1495, 1451 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H), 3.2 (d, J = 5.1 Hz, 2H), 4.6 (d, J = 4.0 Hz, 2H), 4.8 (d, J = 5.8 Hz, 2H), 6.3 (m, 5H), 6.7 (d, J = 16.0 Hz, 1H), 7.2 (m, 15H).

An 1.00:1.75 (^{1}H-NMR) mixture (0.107 g) of **23a** and **30a**. Another fraction containing a mixture of alkylated compounds could not be resolved.

Pd(0)-Catalyzed isomerization of **30a** to **23a**. An 1.00:1.75 mixture of **23a** and **30a** (0.107 g), anhydrous THF (15 mL) and $Pd(PPh_3)_4$ (0.013 g, 0.02 mmole) was refluxed for 24 h and then heated at 120°C in a closed reactor for 20 h.The composition after this treatment was 2.25:1.00 (^{1}H-NMR monitoring). Further addition of $Pd(PPh_3)_4$ (up to 0.423 g) and heating at 140°C for 60 h produced total conversion into **23a**.

Pd(0)-Catalyzed isomerization of **21a**. A solution of **21a** (0.106 g, 0.32 mmole), $Pd(PPh_3)_4$ (0.040 g, 0.034 mmole) in anhydrous THF (35 mL) was heated at 80-140°C in a sealed reactor for 100 h. Evaporation of the solvent and filtration of the residue through silica-gel afforded **22** (0.065 g, 0.22 mmole).

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