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Regiospecific Substitution of *N*-Acyl-2,3-dihydro-4-pyridones at C-5 via Halogenation and Cross-Coupling.

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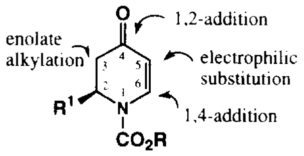
Abstract: *The C-5 position of N-Acyl-2-alkyl-2,3-dihydro-4-pyridones can be substituted by halogenation followed by a cross-coupling or carbonylation reaction.*

N-Acyl-2,3-dihydro-4-pyridones **1** are useful building blocks for alkaloid synthesis. These heterocycles can be readily prepared in one step by the addition of organometallics to 1-acyl salts of 4-methoxypyridine.[1,2] We recently developed a method for the enantioselective preparation of **1** by the addition of Grignard reagents[3] or metallo enolates[4] to homochiral 1-acylpyridinium salts such as **2**. The synthetic potential of enatiopure **1** has been demonstrated by us in the asymmetric syntheses of indolizidine,[4b] quinolizidine,[5] piperidine,[4b,6] and *cis*- and *trans*-decahydroquinoline[7] alkaloids. As part of a program centered on expanding the scope of the synthesis and synthetic utility of *N*-acyldihydropyridones, we have been investigating methods for introducing ring substituents in a regiospecific manner. Substituents can be introduced on **1** at C-6 through 1,4-addition reactions,[1,8] at C-4 by 1,2-addition with organocerium reagents,[9] and at C-3 via enolate alkylation.[8a,10] In this communication is reported the regiospecific substitution of **1** at C-5 using a halogenation and palladium-catalyzed cross-coupling sequence.



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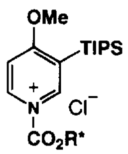
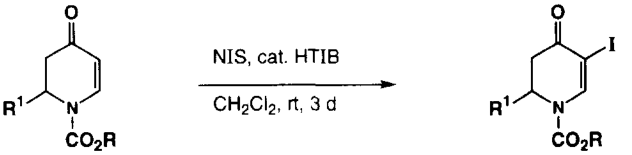


2

R* = (+)- *trans*-2-(α-cumyl)cyclohexyl (TCC)[11]

Dihydropyridone **1** (R = Me, R^1 = Ph) on treatment with NBS (1.0 eq, CH_2Cl_2, 0 °C→RT) gave a 93% yield of the desired C-5 brominated product. Although this was a simple method for the C-5 halogenation of **1**, subsequent attempts at palladium-catalyzed cross-coupling of the α-bromoenone failed. The sluggish reactivity of α-bromoenones in cross-coupling reactions has been observed.[12] We next turned our attention to the preparation of the α-iodo derivatives. The use of NIS was unsatisfactory as the yields were often low and variable. The procedure of Johnson and coworkers (I_2, pyridine, CCl_4),[13] which is effective for the preparation of various α-iodoenones, also gave poor results with **1**. Finally, the desired α-iodo-2,3-dihydro-4-pyridones were prepared in reproducibly high yield using NIS and a catalytic amount of [hydroxy(tosyloxy)iodo]benzene (HTIB)[14] as shown in Table I.



1 R, R^1 = Me, Ph

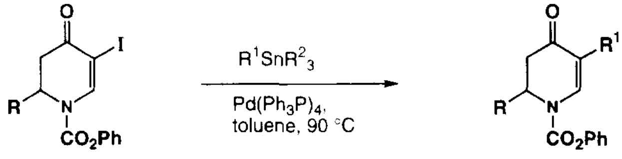
3 R, R^1 = Me, Ph

Table I. Preparation of 5-iodo-2,3-dihydro-4-pyridones **3**

R	R^1	Yield,[a,b] (%)
Ph	CH_3	84
Ph	Ph	79
CH_3	CH_3	98
CH_3	Ph	90

a) The reactions were performed on a 1.5-2.0-mmol scale. b) Yield of purified product obtained from radial PLC (silica gel, EtOAc, hexanes).

With 5-iodo-2,3-dihydro-4-pyridones **2** in hand, the Stille cross-coupling reactions[15] with vinyl- and phenyltributylytin were examined. The results are given in Table II. As shown, the yields are good for this conversion, and they are similar to the results obtained by Johnson and coworkers using carbocyclic α-iodoenones.[13]



3

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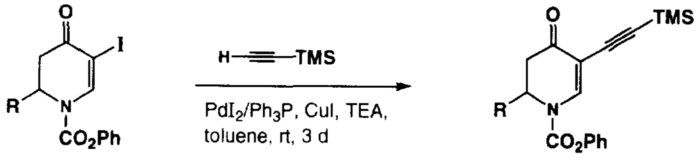
Table II. Stille coupling reactions of **3**

R	R^1	R^2	Yield,[a,b] (%)
CH_3	$CH=CH_2$	CH_3	79
CH_3	Ph	Bu	70
Ph	$CH=CH_2$	CH_3	70
Ph	Ph	Bu	61

a) The reactions were performed on a 0.2-0.5-mmol scale. b) Yield of purified product obtained from radial PLC (silica gel, EtOAc, hexanes)

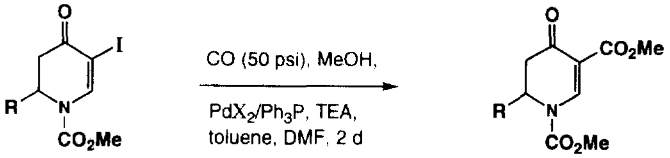
In the presence of a palladium catalyst and CuI, trimethylsilylacetylene undergoes coupling[16] with **3** to give the C-5 acetylenic derivative **5** in high yield (R = Me, 98 %; R = Ph, 78 %).



3 R = Me, Ph **5** R = Me, Ph

Palladium-catalyzed carboalkoxylation[17] reactions of dihydropyridones **3** were also performed. On treatment of **3** with carbon monoxide, methanol, TEA and a catalytic amount of a palladium-triphenylphosphine complex (Table III), esters **6** were formed in good yield (R = Me, 65 %; R = Ph, 67 %).

Oehlschlager and Dodd reported that 2-unsubstituted dihydropyridones like **6** (R = H) are very receptive towards conjugate addition of organocuprates.[18] It is expected that enantiopure dihydropyridone-esters **6** will be useful chiral building blocks for the asymmetric synthesis of complex, piperidine-containing alkaloids.



3 R = Me, Ph **6** R = Me, Ph

Table III. Carbonylation of dihydropyridone **3**

R	Catalyst	Temp.°C	Yield,[a,b] (%)
CH_3	PdI_2, 2 Ph_3P	60	46
CH_3	$PdCl_2(PPh_3)_2$	60	65
CH_3	$PdCl_2(PPh_3)_2$	100	50
Ph	$PdCl_2(PPh_3)_2$	60	67

a) The reactions were performed on a 0.3-0.5-mmol scale. b) Yield of purified product obtained from radial PLC (silica gel, EtOAc, hexanes)

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References and Notes

1. (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972. (c) Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121 and references cited therein.
2. For a review covering the addition of organometallics to 1-acylpyridinium salts, see: Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.
3. (a) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.
4. (a) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851. (b) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035.
5. Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807.
6. Comins, D. L.; Radi Benjelloun, N. *Tetrahedron Lett.* **1994**, *35*, 829.
7. (a) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838. (b) Comins, D. L.; Dehghani, A. *J. Org. Chem.* **1995**, *60*, 794.
8. (a) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (c) For intramolecular radical additions to C-4, see: Beckwith, A. L. J.; Joseph, S. P. Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.
9. Organocerium reagents undergo preferentially 1,2-addition: Comins, D. L.; Joseph, S. P.; Chen, X., Unpublished results.
10. (a) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetahedron Lett.* **1992**, *33*, 7635. (b) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732.
11. (a) Comins, D. L.; Salvador, J. M. *Tetrahedron Lett.* **1993**, *34*, 801. (b) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.
12. (a) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453. (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.
13. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic', M. R. *Tetrahedron Lett.* **1992**, *33*, 917.
14. (a) Angara, G. J.; Mc Nelis, E. *Tetrahedron Lett.* **1991**, *32*, 2099. (b) Bovonsombat, P.; Angara, G. J.; Mc Nelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787.
15. (a) Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645. (b) Stille, J. K. *Angew.Chem. Int. Ed. Engl.* **1986**, *25*, 508. (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
16. For this type of coupling with terminal alkynes, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Alami, M.; Ferri, F; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403 and references cited therein.
17. Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318.
18. Dodd, D. S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1991**, *32*, 3643.

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