Nauk SSSR, Ser. Khim., 955 (1974).
(3) For examples see S. J. Cristol and J. K. Harrington, J. Org. Chem., 28, 1413 (1963); D. M. Lemal and A. J. Fry, ibid., 29, 1673 (1964); P. K. Freeman and D. G. Kuper, ibid., 30, 1047 (1965); J. W. Wheeler, R. H. Chung, Y. N. Vaishnav, and C. C. Shroff, ibid., 34, 545 (1969); G. Onloff and W. Pickenhagen, Helv. Chim. Acta, 54, 1789 (1971).
(4) R. K. Murray, Jr., T. K. Morgan, Jr., and K. A. Babiak, J. Org. Chem., 40, 1079 (1975); J. E. Baldwin and W. D. Foglesong, J. Am. Chem. Soc., 90, 4303 (1968).
(5) L. Friedman and H. Shechter, J. Am. Chem. Soc., 81, 5512 (1959); W. R. Moore, H. R. Ward, and R. F. Merret, ibid., 83, 2019 (1961).
(6) R. G. Bergman and V. J. Rajadhyaksha, J. Am. Chem. Soc., 92, 2163 (1970).
(7) H. J. Bayless, L. Friedman, F. B. Cook, and H. Shechter, J. Am. Chem. Soc., 90, 531 (1968), and references cited therein; R. H. Shapiro, J. H. Duncan, and J. C. Clopton, ibid., 89, 471 (1967).
(8) R. K. Murray, Jr., K. A. Babiak, and T. K. Morgan, Jr., J. Org. Chem., 40, 2463 (1975).

N- vs. C-Acylation of Metalated *O*-Methyllactims. Synthesis of 5,6,7,8-Tetrahydropyrido[2,3-*d*]-pyrimidines through C-Acylation by Nitriles[1]

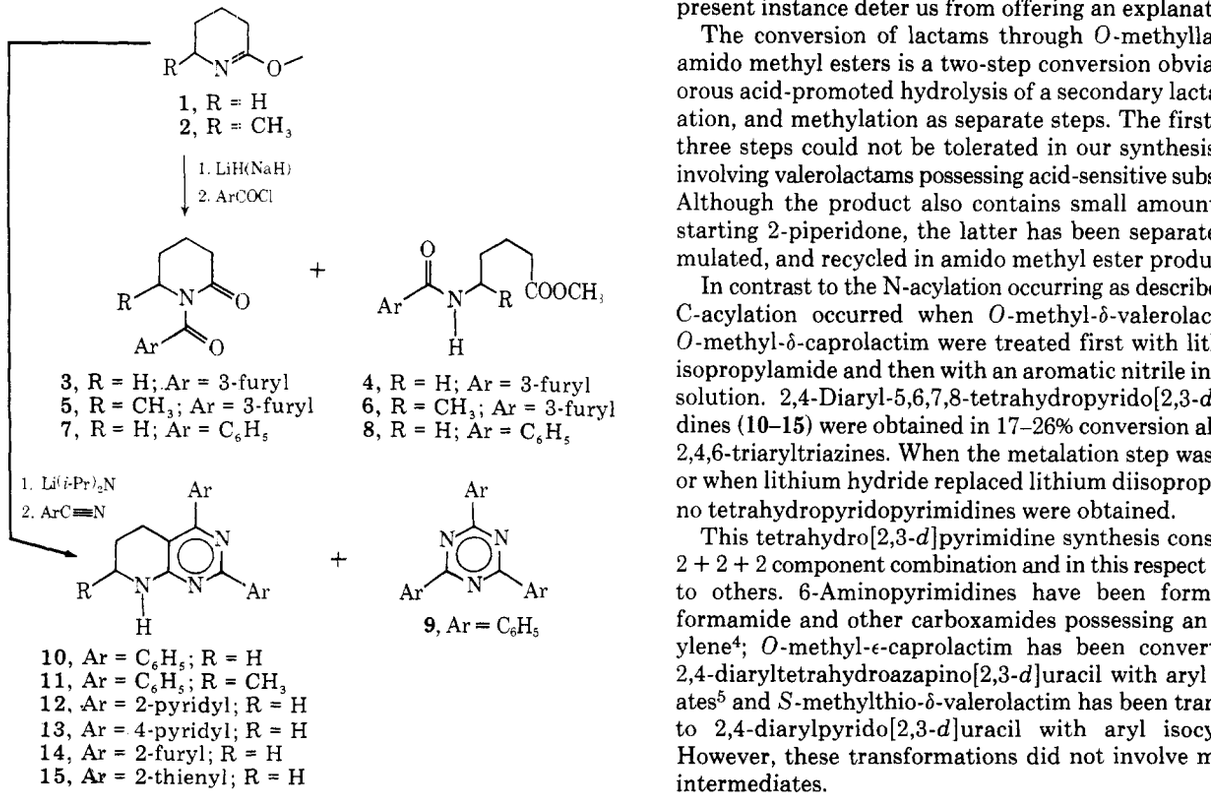
R. T. LaLonde,* A. El-Kafrawy, N. Muhammad, and J. E. Oatis, Jr.

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

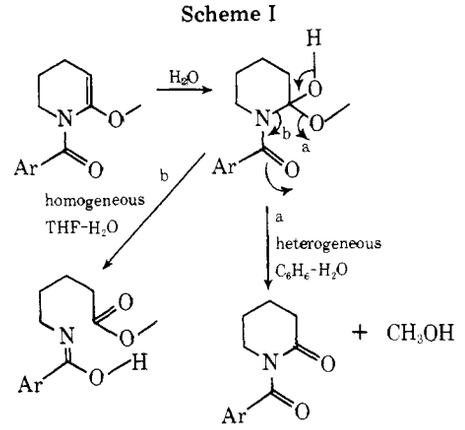
Received November 22, 1976

Our search for methods utilizing 2-piperidones as intermediates in the synthesis of piperidine alkaloids led us to examine the acylation of metalated *O*-methyl-δ-valerolactim (**1**) and *O*-methyl-δ-caprolactim (**2**), which were readily generated from the corresponding lactams.[2] The alkylations of metalated *O*-alkyllactims has been observed recently.[3] We report here the two different routes taken in the acylation of *O*-alkyllactims **1** and **2** by aroyl chlorides and aromatic nitriles and wish to emphasize the potential of one of these routes in the synthesis of 2,4-diaryl-5,6,7,8-tetrahydropyrido[2,3-*d*]-pyrimidines.

Treatment of **1** and **2** in benzene or tetrahydrofuran (THF) solution with alkali metal hydrides followed by the addition of the aroyl chloride gave mixtures containing N-acylated lactams, such as **3**, and amido methyl esters, such as **4**, in the yields and in relative amounts indicated in the Experimental Section. Omission of the metalation step resulted in the formation of both N-acylated lactams and amido methyl esters as before but in very low conversions. Metal hydrides were used as the base rather than lithium diisopropylamide, which was used in the C-acylations described below, in order to avoid the consumption of aroyl chloride through carboxamide formation. Lithium hydride suspended in THF and an acidic or basic aqueous treatment prior to workup favored the production of amido methyl esters (**4**, **6**, **8**) while sodium or lithium hydride suspended in benzene and a water, aqueous lithium hydroxide, or aqueous acidic treatment prior to workup favored *N*-acyllactam (**3**, **5**, **7**) formation. Scheme I



Scheme I



illustrates the two hydrolysis pathways which follow N-acylation and result from changing the acylation solvent from THF to benzene. The essential difference is that the homogeneous aqueous treatment carried out in THF strongly favored amido ester formation (path b) while the heterogeneous aqueous treatment carried out in benzene favored *N*-acyllactam formation (path a). The complexities of comparing homogeneous with heterogeneous systems in general and the need for considerably more experimental evidence in the present instance deter us from offering an explanation.

The conversion of lactams through *O*-methyllactims to amido methyl esters is a two-step conversion obviating vigorous acid-promoted hydrolysis of a secondary lactam, acylation, and methylation as separate steps. The first of these three steps could not be tolerated in our synthesis scheme involving valerolactams possessing acid-sensitive substituents. Although the product also contains small amounts of the starting 2-piperidone, the latter has been separated, accumulated, and recycled in amido methyl ester production.

In contrast to the N-acylation occurring as described above, C-acylation occurred when *O*-methyl-δ-valerolactim and *O*-methyl-δ-caprolactim were treated first with lithium diisopropylamide and then with an aromatic nitrile in benzene solution. 2,4-Diaryl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines (**10–15**) were obtained in 17–26% conversion along with 2,4,6-triaryltriazines. When the metalation step was omitted or when lithium hydride replaced lithium diisopropylamide, no tetrahydropyridopyrimidines were obtained.

This tetrahydro[2,3-*d*]pyrimidine synthesis constitutes a 2 + 2 + 2 component combination and in this respect is similar to others. 6-Aminopyrimidines have been formed from formamide and other carboxamides possessing an α-methylene[4]; *O*-methyl-ε-caprolactim has been converted to a 2,4-diaryltetrahydroazapino[2,3-*d*]uracil with aryl isocyanates[5] and *S*-methylthio-δ-valerolactim has been transformed to 2,4-diarylpyrido[2,3-*d*]uracil with aryl isocyanates.[6] However, these transformations did not involve metalated intermediates.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Spectra were determined as follows: ^{1}H NMR at 60 MHz in $CDCl_3$, 2% Me_4Si (δ 0.00), on a Varian A-60A; IR on a Perkin-Elmer 137; mass spectra on a Hitachi Perkin-Elmer RMU6E using an indirect heated inlet; UV on a Beckman MVI. Gas–liquid chromatography was performed on 1.5% OV 101 on Chromosorb G, 5 ft × 0.25 in. column, back pressure 20 psi, and a column temperature of 200 °C. Retention time (t_R) is given in minutes. Elution chromatography was carried out on Woelm neutral alumina, activity 1, using the solvents indicated.

N-Acylations of *O*-Methyllactims. A. Conditions Favoring Amido Methyl Ester Formation. The following procedure for the conversion of *O*-methyl-δ-caprolactim (**2**) to **6** is typical of those favoring the amido methyl ester formation. Lithium hydride (13 mg) was suspended under nitrogen in 3 mL of THF freshly distilled from lithium aluminum hydride or sodium hydride. To this suspension was added 250 mg of **2** in 3 mL of THF over a period of 5 min. The heterogeneous mixture was heated to reflux for 3 h, cooled to 25 °C, and to it was added 256 mg of 3-furoyl chloride in 3 mL of THF. The resulting mixture was stirred for 88 h at 25 °C at the end of which time 3 mL of 6 N aqueous HCl was added over 15 min. The mixture was extracted with three 20-mL portions of CH_2Cl_2 and the combined extracts were dried ($MgSO_4$). Vacuum evaporation of the solvent gave an oil, which according to GLC contained 1% δ-caprolactam (t_R 1.2), 4% *N*-(3-furoyl)-δ-caprolactam (**5**) (t_R 3.0), and 95% methyl δ-(3-furamido)caproate. **6** (t_R 5.2 min). Elution from a column with ether gave 360 mg of an oil **6** (77% isolated): GLC t_R 5.2; IR (neat) 1740 ($COOCH_3$), 1640 (CONRH), 870 cm^{-1} (3-furyl); ^{1}H NMR δ 8.07 (m, 1 H, 3-furyl α-H), 7.45 (m, 1 H, 3-furyl α-H), 6.78 (m, 1 H, 3-furyl β-H), 3.65 (s, 3 H, OCH_3), 3.45 (m, 1 H, C-5 H), 2.36 (m, 2 H, C-2 H), 1.63 (m, 4 H, C-3 and C-4 H), 1.21 (d, 3 H, C-5 CH_3).

Anal. Calcd for $C_{12}H_{17}O_4N$: C, 60.18; H, 7.17; N, 5.85. Found: C, 60.08; H, 7.19; N, 5.86.

Similarly 560 mg of O-methyl-δ-valerolactim gave 800 mg of methyl δ-(3-furamido)valerate (72% isolated), **4** [mp 39–40 °C; GLC t_R 6.0; IR (neat) 1740 ($COOCH_3$), 1635 (CONHR), 870 cm^{-1} (3-furyl); ^{1}H NMR δ 7.96 (m, 1 H, 3-furyl α-H), 7.38 (m, 1 H, 3-furyl α-H), 6.67 (m, 1 H, 3-furyl β-H), 3.65 (s, 3 H, OCH_3), 3.37 (m, 2 H, C-5 H), 2.35 (m, 2 H, C-2 H), 1.65 (m, 4 H, C-3 and C-4 H)] which in the crude form contained 89% **4** (t_R 6.0), 6% *N*-(3-furoyl)-δ-valerolactam (**3**) (t_R 2.8), and 5% δ-valerolactam (t_R 2.2).

Anal. Calcd for $C_{11}H_{15}O_4N$: C, 58.60; H, 6.72; N, 6.21. Found: C, 58.46; H, 6.41; N, 6.11.

B. Conditions Favoring *N*-Acyllactam Formation. The procedure was the same as described in part A above except that THF was replaced by benzene and the 6 N aqueous HCl treatment was replaced by lithium hydroxide. Thus from 54 mg of lithium hydride, in 10 mL of benzene, and 1.0 g of **2**, in 2 mL of benzene, after heating to reflux 3 h followed by cooling to 25 °C and the addition of 1.02 g of 3-furoyl chloride, in 5 mL of benzene, further heating to reflux for 1 h and stirring at 25 °C for 19 h and subsequent addition of 5 mL of 12% lithium hydroxide over 15 min followed by workup gave an oil which was chromatographed from a column of silica gel by eluting with benzene–ethyl acetate (85:15) to produce 1.2 g (75%) of *N*-(3-furoyl)-δ-caprolactam (**5**): mp 36–37 °C; GLC t_R 3.0; IR (neat) 1700, 1670 (imide), and 870 cm^{-1} (3-furyl); ^{1}H NMR δ 7.95 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.54 (m, 1 H, 3-furyl β-H), 4.48 (m, 1 H, C-6 H), 2.60 (m, 2 H, C-3 H), 1.91 (m, 4 H, C-4 and C-5 H), 1.30 (d, 3 H, C-6 CH_3).

Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.74; H, 6.34; N, 6.75. Found: C, 63.52; H, 6.34; N, 6.64.

Similarly, 1.0 g of *O*-methyl-δ-valerolactim with 424 mg of sodium hydride (a 50% dispersion in oil) in benzene and 1.15 g of 3-furoyl chloride gave, after a water treatment, which replaced the lithium hydroxide treatment mentioned above, a solid, which on sublimation, produced 1.20 g (70%) of *N*-(3-furoyl)-δ-valerolactam (**3**): mp 81–82 °C; GLC t_R 2.8; IR (KBr) 1700, 1670 (imide), and 870 cm^{-1} (3-furyl); ^{1}H NMR δ 7.95 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.54 (m, 1 H, 3-furyl β-H), 3.75 (m, 2 H, C-6 H), 2.60 (m, 2 H, C-3 H), 1.91 (m, 4 H, C-4 and C-5 H).

Anal. Calcd for $C_{10}H_{11}O_3N$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.19; H, 5.76; N, 7.26.

Also 300 mg of *O*-methyl-δ-valerolactim with 20 mg of lithium hydride in benzene and 380 mg of benzoyl chloride gave, after treatment with 0.4 N aqueous HCl to pH 7.5, which replaced the lithium hydroxide treatment mentioned above, 500 mg of solid which consisted of 67% *N*-benzoyl-δ-valerolactam (**7**), GLC t_R 5.2, and 32% methyl δ-benzamidovalerate (**8**), GLC t_R 10.7. Products **7** and **8** were identified by GLC comparison with authentic samples of **7**, prepared from valerolactam and benzoyl chloride, and **8**, prepared from δ-aminovaleric acid and benzoyl chloride followed by esterification of the resulting δ-benzamidovaleric acid with diazomethane. ^{1}H NMR of the 67–32% mixture showed δ 7.2–7.6 (m, phenyl H), 3.55 (s, OCH_3), 3.7 (m, CH_2NCO), 2.1–2.6 (m, CH_2CON).

C-Acylations of *O*-Methyllactims. 2,4-Diaryl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (10). The conversion of *O*-methyl-δ-valerolactim (1) to 2,4-diphenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**10**) by the procedure described below is typical of the procedures used to prepare all of the 2,6-diaryl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines. To a hexane–ether solution of lithium diisopropylamide (2.7 mmol) at −78 °C under N_2 was added 260 mg (2.7 mmol) of 1 in 6 mL of ether, freshly distilled from lithium aluminum hydride. The mixture was stirred at −78 ° for 2 h, at the end of which time the mixture was allowed to come to 25 °C and the solvent was removed at reduced pressure. Benzene (10 mL), freshly distilled from sodium hydride, was added and then 560 mg (5.4 mmol) of benzonitrile in 5 mL of benzene was added. The resulting dark orange mixture was refluxed for 1 h. After workup and subsequent chromatography with ether–hexane (1:9) was obtained 200 mg of unconverted benzonitrile, 140 mg of 1,3,5-triphenyltriazine, and 200 mg of **10** (26%): mp 176–177 °C; IR (CCl_4) 3500, 3250 (NH), 1590, 1550, 1440, 1410 cm^{-1}; ^{1}H NMR δ 1.75 (br m, 2 H, C-6 H), 2.78 (br m, 2 H, C-5 H), 3.28 (br m, 2 H, C-7 H), 6.25 (br s, 1 H, NH, absent on D_2O addition), 7.2–8.6 (m, 10 H, phenyl H); mass spectrum *m/e* (rel intensity) 287 (100) (M^+), 286 (90); UV (EtOH) $\epsilon_{243nm(max)}$ 40 800 $\epsilon_{271(sh)}$ 21 200, $\epsilon_{314(sh)}$ 6980; UV (EtOH, H$^+$) $\epsilon_{258(max)}$ 38 300, $\epsilon_{290(sh)}$ 20 100.

Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.92; N, 14.63. Found: C, 79.25; H, 6.08; N, 14.55.

The quantities of reactants and product, percentage yield, and the melting point for each of the remaining members of the series, **11–15** are given below. In all cases, except in the preparation of **11**, 2.7 mmol of the lithiated *O*-methyllactim was employed.

2,4-Diphenyl-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**11**): lithium diisopropylamide (2.7 mmol), 200 mg of **2** (1.57 mmol), and 560 mg of benzonitrile (5.4 mmol) gave after the standard treatment and elution chromatography of the product (ether–hexane, 1:10), 200 mg of benzonitrile and then 50 mg of 1,3,5-triphenyltriazine; continued elution (ether) gave 80 mg (17%) of white, crystalline **11**, mp 118–120 °C.

2,4-Di(2-pyridyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**12**): a 550-mg quantity of 2-cyanopyridine (5.5 mmol) gave after the standard treatment and product recrystallization from anhydrous ethyl ether 200 mg (26%) of white, crystalline **12**, mp 158–159 °C, which in acetone solution produced an immediate violet colored solution with aqueous ferrous sulfate.

2,4-Di(4-pyridyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**13**): a 550-mg quantity of 4-cyanopyridine (5.5 mmol) gave after the standard treatment and product recrystallization from ethanol 200 mg (26%) of white, crystalline **13**, mp 188–190 °C.

2,4-Di(2-furyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**): a 500-mg quantity of 2-furonitrile (5.5 mmol) gave after the standard treatment and product recrystallization from ethanol 170 mg of **14** (23%), mp 167–170 °C.

2,4-Di(2-thienyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**15**): a 590-mg quantity of 2-thienonitrile (5.4 mmol) gave after the standard treatment and product recrystallization from ethanol 200 mg of **15** (25%), mp 171–172 °C, which in acetone solution gave a deep yellow precipitate with aqueous mercuric acetate.

Registry No.—**1**, 5693-62-9; **2**, 61586-88-7; **3**, 61586-89-8; **4**, 61586-90-1; **5**, 61586-91-2; **6**, 61586-92-3; **7**, 4252-56-6; **8**, 17079-25-3; **10**, 61586-93-4; **11**, 61586-94-5; **12**, 61586-95-6; **13**, 61586-96-7; **14**, 61586-97-8; **15**, 61586-98-9; 3-furoyl chloride, 26214-65-3; benzoyl chloride, 98-88-4; benzonitrile, 100-47-0; 2-cyanopyridine, 100-70-9; 2-furonitrile, 617-90-3; 2-thienonitrile, 1003-31-2.

Supplementary Material Available. Full spectral data and elemental analyses for the 2,6-diaryl-5,6,7,8-tetrahydropyrido[2,3-*d*]-pyrimidines (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Support of this work by the National Institutes of Health, U.S. Public Health Service (Grant AI 10188), is gratefully acknowledged.
(2) H. Lüssi, *Chimia*, **27**, 65 (1973).
(3) B. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, **97**, 7152 (1975).
(4) K. Morita, S. Kobayashi, H. Shimadzu, and M. Ochiai, *Tetrahedron Lett.*, 861 (1970).
(5) R. Richter and H. Ulrich, *Chem. Ber*, **106**, 374 (1973).
(6) U. Kraatz, *Justus Liebigs Ann. Chem.*, 412 (1976).