PREPARATION OF HETEROCYCLIC ENAMINES. USEFUL INTERMEDIATES IN THE SYNTHESIS OF 1,4-DIHYDROPYRIDINES

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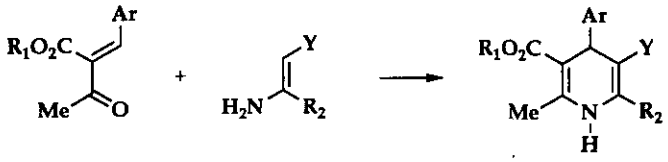
Abstract - Various heterocycles (4,5-dihydrooxazoles, 4,5-dihydro-4*H*-oxazines, and tetrazoles) can be readily metalated and condensed with a variety of organic nitriles to afford heterocyclic enamines (**2**). These enamines can be utilized in Hantzsch condensation reactions to prepare heterocyclic substituted 1,4-dihydropyridines (**3**) which are unavailable by standard routes.

1,4-Dihydropyridine carboxylic esters (**3**) represent a potent structural class of agents collectively known as "calcium entry blockers".[1] These compounds have been shown to be efficacious in the management of various cardiovascular disorders such as ischemic heart disease and hypertension.[2] The synthesis of 1,4-dihydropyridines is typically achieved through use of modified Hantzsch condensations between appropriately functionalized Knoevenagel derived adducts (**1**) and various enamines (**2**).[3] In most all published accounts, aminocrotonates (Y=CO_2R; R_2=Me) or their β-keto ester precursors serve as the acting enamine unit to furnish

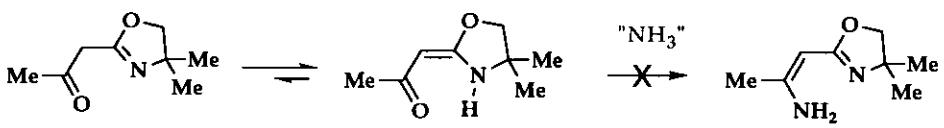


1 **2** **3**

the respective 1,4-dihydro-3,5-pyridinedicarboxylic (Hantzsch) esters (**3**).[4] For example, the synthesis of the antihypertensive agent Nitrendipine can be accomplished in high yield by condensation of Knoevenagel adduct (**1a**, R_1=Et; Ar=3-NO_2Ph) with methyl 3-aminocrotonate.

Our initial interest in this area primarily focused on the synthesis of various dihydropyridines with heterocyclic substitution at the C-5 position (**3**, Y=heterocycle).[5] These C-5 substitutions included heterocycles which could also serve as latent carboxylate appendages or carboxylic isosteres for possible therapeutic applications.[6] We wish to describe our chemistry for the construction of these dihydropyridines (**3**) through use of novel heterocyclic enamines (**2**, Y=oxazoline, oxazine, and tetrazole).

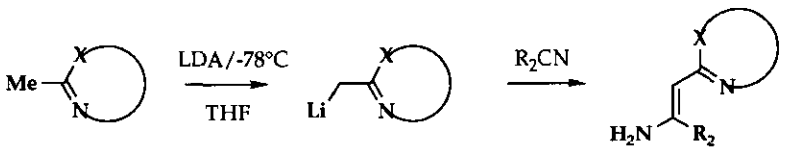
Meyers has previously demonstrated the synthetic versatility of oxazolines[7] and oxazines[8] as carboxylic acid synthons in a variety of metalation/homologation pathways. He reported the metalation of 4,5-dihydro-2,4,4-trimethyloxazole (**4a**) followed by treatment with ethyl acetate to afford 1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-2-propanone (**6a**) in good yield.[9] Our attempts at the utilization of the β-keto oxazoline (**6a**) as an enamine precursor under a variety of aminolysis and/or Hantzsch condensation conditions always gave a complex mixture of products. Meyers reported the β-keto oxazoline (**6a**) to exist as a tautomeric mixture with the enamino ketone (**6b**). The presence of this enamine tautomer probably accounts for the formation of other non-desired condensation products under the equilibrating Hantzsch conditions we employed.



6a **6b** **2a**

To circumvent this problem, we envisioned that the direct preparation of the corresponding enamino oxazoline (**2a**) from oxazoline (**4a**) would preclude formation of **6b** and allow the construction of the corresponding heterocyclic substituted 1,4-dihydropyridine adducts (**3**). We have found that this direct preparation of heterocyclic enamines can be readily accomplished by a metalation/condensation sequence of the appropriate heterocycle (**4**) with organic nitriles. We have carried out the conversion using oxazoline (**4a**), 4,5-dihydro-2-methyloxazole (**4b**), 2-methyl-5,6-dihydro-4*H*-1,3-oxazine (**4c**), and 1,5-dimethyl-1*H*-tetrazole (**4d**) with a

variety of organic nitriles to afford the heterocyclic enamines (**2a** to **2j**) (Table 1). The overall transformation is illustrated below (X=O, NMe; R_2=alkyl, aryl, heteroaryl).

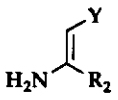


4 **5** **2**

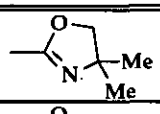
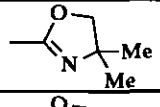
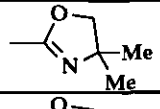
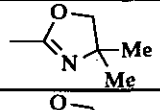
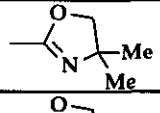
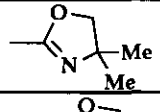
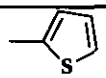
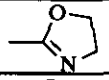
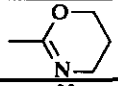
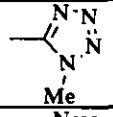
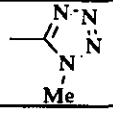
Thus treatment of a cold (-78°C), tetrahydrofuran (THF) solution of the appropriate heterocycle (**4**) with 1.1 eq. of lithium diisopropylamide (LDA) produced the corresponding lithio derivative (**5**). Condensation of **5** with *either an alkyl, aryl, or heteroaryl nitrile, followed by warming to room temperature and quenching* with an aqueous ammonium chloride solution furnished the various heterocyclic enamines (**2a** to **2j**) in yields ranging from 9 to 98%. These heterocyclic enamines were isolable compounds which could readily be purified by either distillation at reduced pressure or by recrystallization in alcoholic solvents. The enamines were hydrolytically stable at neutral or basic pH and in no cases were the β-keto hydrolysis products noticed on workup. It was observed, however, that in several cases (**2b**, **2f**, and **2g**) discoloration occurred on prolonged storage at room temperature. In these examples thermal decomposition was prevented by storage in a freezer.

The reaction proceeded well with all nitriles studied except acetonitrile (Entry 1) which afforded only a 9% yield of **2a** after distillation. Benzonitrile consistently afforded the highest yields of enamines (Entries 5 and 10) giving **2e** and **2j** in isolated yields of 92 and 98%, respectively. These results are probably attributable to the presence or lack of acidic α-protons which can be involved in *trans*-metalation chemistry with the intermediate lithio bases (**5**).[10] Indeed, when acetonitrile was employed as the nitrile, (Entry 1) 3-aminocrotononitrile[11] and the starting heterocycle (**4a**) were isolated as the major products. In this and another example (Entry 8) the heterocyclic enamines (**2a**) and (**2h**) could not be analytically purified even after repeated distillations due to the presence of these types of nitrile impurities. Attempted purification by silica gel chromatography only afforded the β-keto adducts (**6a**)[9] and (**6b**)[12] indicating facile hydrolysis of the enamines in acidic environments.

Table 1. Heterocyclic Enamines (2) from Metalation/Condensation Reactions of 4[a]

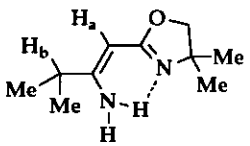


2

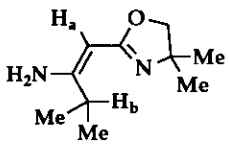
Entry	Enamine	Y	R_2	% Yield	mp/bp, °C
1	**2a**		Me	9	105-112/4 mm Hg
2	**2b**		Et	72	70-72/0.1 mm Hg
3	**2c**		i-Pr	77	58-61[b]
4	**2d**		t-Bu	40	132-133[c]
5	**2e**		Ph	92	75-75[d]
6	**2f**			70	69-70[e]
7	**2g**		Et	69	90-95/1 mm Hg
8	**2h**		Et	61	78-80/.07mm Hg
9	**2i**		Et	31	67-68[f]
10	**2j**		Ph	98	118-119[d]

[a] All reactions were carried out as described in the Experimental Section. [b] bp 80°C/0.1 mm Hg.
[c] Recrystallized from methanol. [d] Recrystallized from aqueous methanol. [e] bp 107°C/0.1 mm Hg.
[f] Recrystallized from ethanol.

Highfield ^1H nmr NOE experiments using a Bruker AM-360 spectrometer revealed enamine (**2c**) to predominantly exist in Z-isomeric form in $CDCl_3$ solution. Thus irradiation of the H_b resonance at 2.3 ppm resulted in an 8.2% enhancement of the vinylic H_a resonance at 4.4 ppm. Additionally, irradiation of the isopropyl methyl resonance at 1.1 ppm afforded a 5.2% NOE of H_a. Presumably hydrogen bonding interactions between the amino group and the ring sp^2 nitrogen atom dictate this configuration. Similar hydrogen bonding effects have been observed for aminocrotonates.[13]

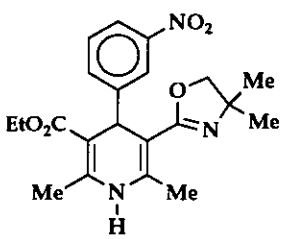


Z-2c

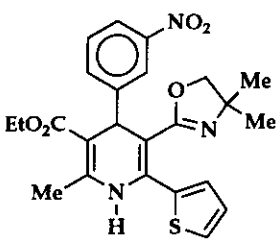


E-2c

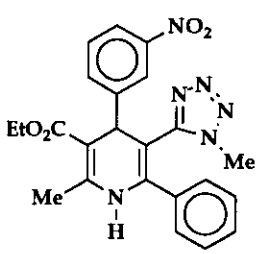
Use of these heterocyclic enamines in Hantzsch condensation reactions permitted the preparation of a wide variety of 1,4-dihydropyridine adducts.[5] For example, condensation of **1a**[14] with enamino oxazolines (**2a**), (**2f**), and (**2j**) yielded both simple and sterically hindered heterocyclic dihydropyridines (**3a**), (**3b**), and (**3c**) in yields of 52, 80, and 68%, respectively. Similarly, treatment of Knoevenagel adduct (**1b**, R_1=Et, Ar=3-CF_3Ph)[15] with enamine (**2h**) afforded the 1,3-oxazine substituted dihydropyridine (**3d**) in 61% yield. These dihydropyridine products were generally isolated by recrystallization from alcoholic solvents thus obviating the need for any chromatographic purification. Thus this enamine method allows convenient synthetic entry into a diverse number of C-5 and C-6 heterocyclic substituted 1,4-dihydropyridine ring systems.



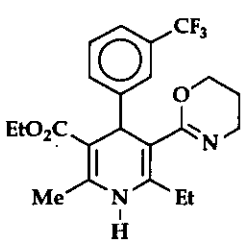
3a



3b



3c



3d

EXPERIMENTAL SECTION

General Methods. Ir spectra were recorded on either a Nicolet MX-1 FT or Beckman IR-9 spectrophotometer. ^{1}H Nmr spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer. Data are reported in the following manner: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, spt=septet, br=broadened, and m=unresolved multiplet), integration, coupling constant. ^{13}C Nmr spectra were recorded on a Varian FT-80A spectrometer at 22.5 MHz using an internal deuterium lock. Data are reported as follows: $[^{1}H]^{13}C$ chemical shifts and multiplicity as obtained from the coupled spectra (s=singlet, d=doublet, t=triplet, q=quartet). Melting points were determined by using a Thomas-Hoover capillary apparatus and are both uncorrected and uncalibrated. Starting oxazolines (**4a**), (**4b**), and tetrazole (**4d**) were purchased from Aldrich Chemical Co., Milwaukee, WI. Oxazine (**4c**) was prepared following literature accounts.[17] The tetrahydrofuran (THF) solvent used in all the metalation reactions was distilled under nitrogen from sodium benzophenone ketyl immediately prior to use.

General Procedure for the Preparation of Heterocyclic Enamines 2a to 2j.

To a stirred, 0°C, nitrogen atmosphere solution of diisopropylamine (5.56 g, 55.0 mmol) in 20 ml of dry THF was slowly added via syringe, n-butyllithium [24 ml, 55 mmol (2.3 *M* in n-hexane)]. After 10 min at 0°C, the solution was cooled to -78°C (dry ice - isopropanol) and a solution of 50.0 mmol of **4** in 50 ml of THF added slowly. After the addition was complete (c.a. 15 min), the yellow solution was stirred 2 h at -78°C. The appropriate nitrile (65 to 100 mmol) was quickly added and the solution was allowed to warm to room temperature and quenched with 10 ml of a saturated aq ammonium chloride solution. Ether (50 ml) and enough water to dissolve the remaining solids were added and the phases separated. The aqueous layer was extracted once with ether and the combined organic portions were washed with brine and dried over potassium carbonate. After filtration the solution was concentrated *in vacuo* to furnish the crude enamines which were purified by either Kugelrohr (bulb-to-bulb) distillation or by recrystallization from the indicated solvents as reported in Table 1. The following enamines were prepared using this procedure.

1-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-1-propen-2-amine (2a): ^{1}H Nmr ($CDCl_3$) δ 6.20 (br s, 2H), 4,34 (s, 1H), 3.78 (s, 2H), 1.88 (s, 3H), and 1.26 (s, 6H); ^{13}C nmr ($CDCl_3$) 164.1 (s), 154.2 (s), 80.5

(d), 77.1 (t), 66.6 (s), 28.9 (q), and 21.9 (q) ppm. An unsatisfactory C, H, and N analysis was observed for this compound.

1-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-1-buten-2-amine (2b): ^{1}H Nmr ($CDCl_3$) δ 6.25 (br s, 2H), 4.39 (s, 1H), 3.70 (s, 2H), 2.08 (q, *J*=7.2Hz, 2H), 1.22 (s, 6H), and 1.05 (t, *J*=7.2Hz, 3H); ^{13}C nmr ($CDCl_3$) 164.4 (s), 159.3 (s), 78.9 (d), 76.9 (t), 66.7 (s), 29.0 (q), 28.0 (t) and 12.3 (q) ppm. *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.26; H, 9.59; N, 16.66. Found: C, 63.91; H, 9.54; N, 16.47.

1-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-methyl-1-buten-2-amine (2c): ^{1}H Nmr ($CDCl_3$) δ 6.10 (br s, 2H), 4.40 (s, 1H), 3,78 (s, 2H), 2.32 (spt, *J*=7.0Hz, 1H), 1.27 (s, 6H), and 1.14 (d, *J*=7.0Hz, 6H); ^{13}C nmr ($CDCl_3$) 164.5 (s), 162.4 (s), 77.6 (t), 77.0 (t), 66.7 (s), 34.4 (d), 29.0 (q), and 21.3 (q) ppm. *Anal.* Calcd for $C_{10}H_{18}N_2O \cdot 0.05H_2O$: C, 65.58; H, 9.97; N, 15.30. Found: C, 65.33; H, 9.62; N, 15.03.

1-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3,3-dimethyl-1-buten-2-amine (2d): ^{1}H Nmr ($CDCl_3$) δ 6.35 (br s, 2H), 4.47 (s, 1H), 3.76 (s, 2H), 1.25 (s, 6H), and 1.16 (s, 9H); ^{13}C nmr ($CDCl_3$) 165.7 (s), 164.8 (s), 77.0 (d), 76.9 (t), 66.7 (s), 35.3 (s), 29.0 (q), and 28.9 (q) ppm. *Anal.* Calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.28; N, 14.28. Found: C, 67.68; H, 10.31; N, 14.32.

α-[(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)methylene]benzenemethanamine (2e): ^{1}H Nmr ($CDCl_3$) δ 7.35 (m, 5H), 6.50 (br s, 2H), 4.82 (s, 1H), 3,80 (s, 2H), and 1.27 (s, 6H); ^{13}C nmr ($CDCl_3$) 164.3 (s), 155.4 (s), 133.2. (s), 129.4 (d), 128.6 (d), 126.0 (d), 81.5 (d), 77.2 (t), 66.6 (s), and 28.9 (q) ppm. *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.20; H, 7.46; N, 12.96. Found: C, 72.15; H, 7.56; N, 12.97.

α-[(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)methylene]-2-thiophenemethanamine (2f): ^{1}H Nmr ($CDCl_3$) δ 7.21 (m, 2H), 6.99 (t, *J*=4.0Hz, 1H), 6.30 (br s, 2H), 4.97 (s, 1H), 3,82 (s, 2H), and 2.28 (s, 6H); ^{13}C nmr ($CDCl_3$) 163.7 (s), 148.3 (s), 140.8 (s), 127.6 (d), 126.1 (d), 124.6 (d), 81.6 (d), 77.2 (t), 66.9 (s), and 28.8 (q) ppm. *Anal.* Calcd for $C_{11}H_{14}N_2OS$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.29; H, 6.27; N, 12.62.

1-(4,5-Dihydro-2-oxazolyl)-1-buten-2-amine (2g): ^{1}H Nmr ($CDCl_3$) δ 6.35 (br s, 2H), 4.43 (s, 1H), 3.97 (m, 4H), 2.16 (q, J=7.5Hz, 2H), and 1.12 (t, J=7.5Hz, 3H); ^{13}C nmr ($CDCl_3$) 167.0 (s), 160.0 (s), 78.8 (d), 65.3 (t), 54.4 (t), 29.1 (t), and 12.5 (q) ppm. *Anal.* Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.99. Found: C, 60.24; H, 8.71; N, 19.66.

1-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-1-buten-2-amine (2h): ^{1}H Nmr ($CDCl_3$) δ 6.30 (br s, 2H), 4.25 (s, 1H), 4.14 (t, *J*=5.4Hz, 2H), 3.48 (t, *J*=6.0Hz, 2H), 2.12 (q, *J*=7.2Hz, 2H), 1.88 (m, 2H), and 1.12 (t, *J*=7.2Hz, 3H); ^{13}C nmr ($CDCl_3$) 159.1 (s), 157.3 (s), 85.6 (s), 64.4 (t), 41.9 (t), 29.4 (t), 22.6 (t), and 12.5 (q) ppm. An unsatisfactory C, H, and N analysis was observed for this compound.

1-(1-Methyl-1*H*-tetrazol-5-yl)-1-buten-2-amine (2i): ^{1}H Nmr ($CDCl_3$) δ 6.40 (br s, 2H), 4.69 (s, 1H), 3.86 (s, 3H), 2.34 (q, *J*=7.6Hz, 2H), and 1.20 (t, *J*=7.6Hz, 3H); ^{13}C nmr ($CDCl_3$) 158.8 (s), 154.1 (s), 72.2 (d), 32.6 (q), 29.4 (t), and 12.6 (q) ppm. *Anal.* Calcd for $C_6H_{11}N_5$: C, 47.05; H, 7.24; N, 45.72. Found: C, 46.78; H, 7.19; N, 45.62.

α-[(1-Methyl-1*H*-tetrazol-5-yl)methylene]benzenemethanamine (2j): ^{1}H Nmr ($CDCl_3$) δ 7.45 (m, 5H), 6.42 (br s, 2H), 5.16 (s, 1H), and 3.87 (s, 3H); ^{13}C nmr ($CDCl_3$) 154.4 (s), 153.9 (s), 137.5 (s), 129.7 (d), 128.5 (d), 126.4 (d), 73.2 (d), and 32,5 (q). *Anal.* Calcd for $C_{10}H_{11}N_5$: C, 59.69; H, 5.52; N, 34.81. Found: C, 59.67; H, 5.56; N, 34.67.

Ethyl 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate Hydrochloride (3a).

A solution of **1a** (4.98 g, 18.8 mmol) and enamine (**2a**) (2.90 g, 18.8 mmol) in 20 ml of ethanol was refluxed for 18 h. A solution of 100 ml of 10% aqueous HCl (v/v) was added and the resulting solution allowed to reflux for 15 min. On cooling to ice-bath temperatures, crystallization occurred. The mixture was filtered and the yellow solid then recrystallized from aqueous ethanol to yield 4.25 g (52%) of **3a** as a yellow solid: mp 236°C (decomp.); ir (KBr) 2980, 1700, 1650, 1605, 1590, 1530, 1480, 1445, 1350, 1260, 1240, 1125 and 1025 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 10.50 (br s, 1H), 8.25 (m, 1H), 8.10 (m, 1H), 7.74 (m, 2H), 5.20 (s, 1H),

4.53 (s, 2H), 4.08 (q, *J*=7.5 Hz, 2H), 2.45 (s, 3H), 2.36 (s, 3H), 1.47 (s, 3H), 1.24 (s, 3H), and 1.20 (t, *J*=7.5 Hz, 3H); ^{13}C nmr (DMSO-d_6) 168.8 (s), 165.8 (s), 154.3 (s), 147.6 (s), 147.5 (s), 145.0 (s), 133.9 (d), 129.9 (d), 121.9 (d), 121.8 (d), 104.1 (s), 90.9 (s), 81.5 (t), 60.9 (s), 59.9 (t), 37.7 (d), 25.9 (q), 25.7 (q), 19.2 (q), 17.8 (q), and 14.0 (q) ppm. *Anal.* Calcd. for $C_{21}H_{25}N_3O_5$•HCl: C, 57.87; H, 6.02; N, 9.65. Found: C, 57.71; H, 6.23; N, 9.62.

Ethyl 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-1,4-dihydro-2-methyl-4-(3-nitrophenyl)-6-(2-thienyl)-3-pyridinecarboxylate Hydrochloride (3b).

A solution of **1a** (6.58 g, 25.0 mmol) and enamine (**2f**) (5.55 g, 25.0 mmol) in 50 ml of ethanol was refluxed overnight (19 h). The reaction mixture was concentrated *in vacuo* and the residue taken up in 100 ml of 10% aq HCl (v/v) and heated on a steam bath for 10 min. After cooling, the solution was extracted with chloroform. The combined organic layers were washed with water and brine and dried over anhydrous magnesium sulfate. Filtration, concentration *in vacuo*, and recrystallization of the residue from ethanol:ether afforded 10.1 g (80%) of **3b** as a yellow solid: mp 143-145°C; ir (KBr) 2950, 1700, 1585, 1525, 1470, 1440, 1350, 1230, 100, and 715 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 12.00 (br s, 1H), 10.62 (br s, 1H), 8.29 (m, 1H), 7.99 (m, 3H), 7.63 (m, 2H), 7.22 (dd, *J*=3.6 and 4.8 Hz, 1H), 5.40 (s, 1H), 4.31 (s, 2H), 4.14 (q, *J*=6.4 Hz, 2H), 2.41 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H), and 1.26 (t, *J*=6.4Hz, 3H); ^{13}C nmr ($CDCl_3$) 168.1 (s), 165.8 (s), 147.8)s), 147.1 (s), 146.9 (s), 145.4 (s), 134.0 (s), 132.8 (s), 132.0 (s), 131.3 (s), 130.0 (s), 127.8 (s), 121.9 (d), 121.8 (d), 105.2 (s), 90.0 (s), 81.3 (t), 61.6 (s), 60.1 (t), 37.8 (d), 25.7 (q), 25.4 (q), 17.8 (q), and 14.1 (q) ppm. *Anal.* Calcd for $C_{24}H_{25}N_3O_5S$•HCl: C, 57.20; H, 5.21; N, 8.34. Found: C, 57.17; H, 5.31; N, 8.06.

Ethyl 1,4-Dihydro-2-methyl-5-(1-methyl-1*H*-tetrazol-5-yl)-4-(3-nitrophenyl)-6-phenyl-3-pyridine-carboxylate (3c).

A solution of **1a** (6.58 g, 25.0 mmol) and **2j** (5.03 g, 25.0 mmol) in 50 ml of ethanol was refluxed for 23 h. The reaction mixture was concentrated *in vacuo* and the residue then recyrstallized from acetonitrile:ethanol to give 7.62 g (68%) of **3c** as a yellow solid: mp 193-194°C; ir (KBr) 3320, 2985, 1675, 1530, 1490, 1350, 1235, 1095, 775, and 700 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 9.43 (br s, 1H), 8.20 (m, 1H), 8.10 (m, 1H), 7.75 (m, 2H), 7.37 (m, 5H), 4.98 (s, 1H), 4.03 (q, *J*=6.8 Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H), and 1.14 (t, *J*=6.8 Hz, 3H); ^{13}C nmr (DMSO-d_6) 166.5 (s), 154.1 (s), 149.1 (s), 148.2 (s), 148.0 (s), 141.2 (s), 134.3 (d),

133.4 (s), 129.9 (d), 129.0 (d), 128.6 (d), 122.0 (d), 121.6 (d), 98.8 (s), 94.6 (s), 59.3 (t), 43.6 (d), 33.4 (q), 18.7 (q), and 14.1 (q) ppm. *Anal.* Calcd for $C_{23}H_{23}N_6O_4$: C, 61.88; H, 4.97; N, 18.83. Found: C, 61.77; H, 4.98; N, 18.76.

Ethyl 5-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-6-ethyl-1,4-dihydro-2-methyl-4-[3-(trifluoromethyl)-phenyl]-3-pyridinecarboxylate (3d).

A solution of **1b** (5.71 g, 19.9 mmol) and enamine (**2h**) (3.10 g, 20.1 mmol) in 50 ml of ethanol were refluxed overnight. Removal of the volatiles *in vacuo* and recrystallization from isopropyl ether:hexane yielded 5.13 g (61%) of **3d** as a pale yellow solid: mp 92-94°C; ir (KBr) 1674, 1653, 1623, 1499, 1328, 1210, 1162, 1124, 1099, and 1074 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.40 (m, 4H), 5.96 (bs, 1H), 5.15 (s, 1H), 4.15 (m, 4H), 3.39 (t, *J*=5.8 Hz, 2H), 2.48 (q, *J*=7.3 Hz, 2H), 2.31 (s, 3H), 1.75 (m, 2H), 1.17 (t, *J*=7.1 Hz, 3H), and 1.13 (t, *J*=7.3 Hz, 3H); ^{13}C nmr ($CDCl_3$) 167.9 (s), 156.5 (s), 149.1 (s), 146.7 (s), 131.1 (d), quartet at 129.8, *J*=31.6 Hz (s), 128.4 (d), quartet at 124.7, *J*=273.6 Hz (s), quartet at 122.6, *J*=4.0 Hz (d), 107.4 (s), 100.4 (s), 64.4 (t), 59.5 (t), 42.5 (t), 41.2 (d), 24.9 (t), 22.0 (t), 19.6 (q), 14.2 (q), and 13.0 (q) ppm. *Anal.* Calcd for $C_{22}H_{25}F_3N_2O_3 \cdot 0.15\ H_2O$: C, 62.15; H, 6.00; N, 6.59. Found: C, 62.07; H, 6.00; N, 6.43.

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REFERENCES

1. (a). D.J. Triggle, D.A. Langs, and R.J. Janis, *Med. Res. Rev.*, **1989**, *9*, 123; (b). H. Meyer, S. Kazda, and P. Belleman, *Ann. Rep. Med. Chem.*, **1983**, *18*, 79; and (c). S. Goldmann and J. Stotefuss, *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 1559.
2. (a). W.G. Naylor and J.D. Horowitz, *Pharmac. Ther.*, **1983**, *20*, 203; and (b). P.M. Vanhoutte and R.A. Cohen, *Am. J. Cardiol.*, **1983**, *52*, 99A.

3. (a). G.A. Sausins and G. Duburs, *Heterocycles*, **1988**, *27*, 269; (b). J. Prous, P. Blancafort, J. Castaner, M.N. Serradell, and N. Mealy, *Drugs of the Future*, **1981**, 6, 427; (c). D.M. Stout and A.I. Meyers, *Chem. Rev.*, **1982**, *82*, 223; (d). J, Kuthan and A. Kurfurst, *Ind. Eng. Chem. Prod. Res. Dev.*, **1982**, *21*, 191; and (e). F. Bossert, H. Meyer, and E. Wehinger, *Angew. Chem., Int. Ed. Engl.*, **1981**, *20*, 762.

4. Examples of these types of agents include Nifedipine (Ar=2-NO_2Ph; R_1=Me; R_2=Me; Y=CO_2Me) and Nitrendipine (Ar=3-NO_2Ph; R_1=Et; R_2=Me; Y = CO_2Me).

5. G.S. Poindexter and D.L. Temple, *U.S. Patent* **1983**, 4,414,213, (*Chem. Abstr.*, **1984**, *100*, 121,050h).

6. C.A. Lipinski, *Ann. Rep. Med. Chem.*, **1986**, *21*, 283.

7. A.I. Meyers and E.D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, **1976**, *15*, 270.

8. A.I. Meyers and N. Nazarenko, *J. Org. Chem.*, **1973**, *38*, 175.

9. A.I. Meyers, D.L. Temple, R.L. Nolen, and E.D. Mihelich, *J. Org. Chem.*, **1974**, *39*, 2778.

10. B.J. Wakefield, "The Chemistry of Organolithium Compounds," Pergammon Press, Oxford, England, **1974**, pp. 116-121.

11. 3-Aminocrotononitrile was isolated as a colorless solid: mp 77-79°C; ir (KBr) 2180 cm^{-1}; ^{13}C nmr (DMSO-d_6) 163.4 (s), 122.6 (s), 60.3 (d), and 19.0 (q) ppm.

12. 1-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-2-butanone (**6b**) was isolated as a colorless oil: ^1H nmr($CDCl_3$) δ 11.35 (bs, 1H), 4.69 (s, 1H), 4.22 (t, *J*= 5.4 Hz, 2H), 3.40 (t, *J* = 6.3 Hz, 2H), 2.15 (m, 2H), 2.11 (q, *J* = 7.2 Hz, 2H), and 1.09 (t, *J* = 7.2 Hz, 3H).

13. (a). A.G. Sanchez and M.T. Aldave, *J. Chem. Soc.*, **1968**, 2570; and (b). S.A. Glickman and A.C. Cope, *J. Am. Chem. Soc.*, **1945**, *67*, 1017.

14. V.H. Meyer, F. Bossert, E. Wehinger, K. Stopel, and W. Vater, *Arzneim.-Forsch/Drug Res.*, **1981**, *31*, 407.

15. Ethyl 3-oxo-2-[[3-trifluoromethyl)phenyl]methylene]butanoate (**1b**, mp 45-48°C) was prepared using standard Knoevenagel condensation conditions.[16]

16. G. Jones, *Org. Reactions*, **1967**, *15*, 204.

17. I.B. Butt, D.G. Neilson, K.M. Watson, and Zakir-Uikh, *J. Chem. Soc., Perkin Trans I*, **1977**, 2328.

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