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ACETYLENES. Part 2.[1] 2-METHYLPYRIMIDIN-4(3H)-ONES AND 4-AMINO-6-(1-HYDROXYALKYL)-2-METHYLPYRIMIDINES FROM ALKA-2,3-DIENOATES AND 4-HYDROXYALK-2-YNENITRILES, RESPECTIVELY.

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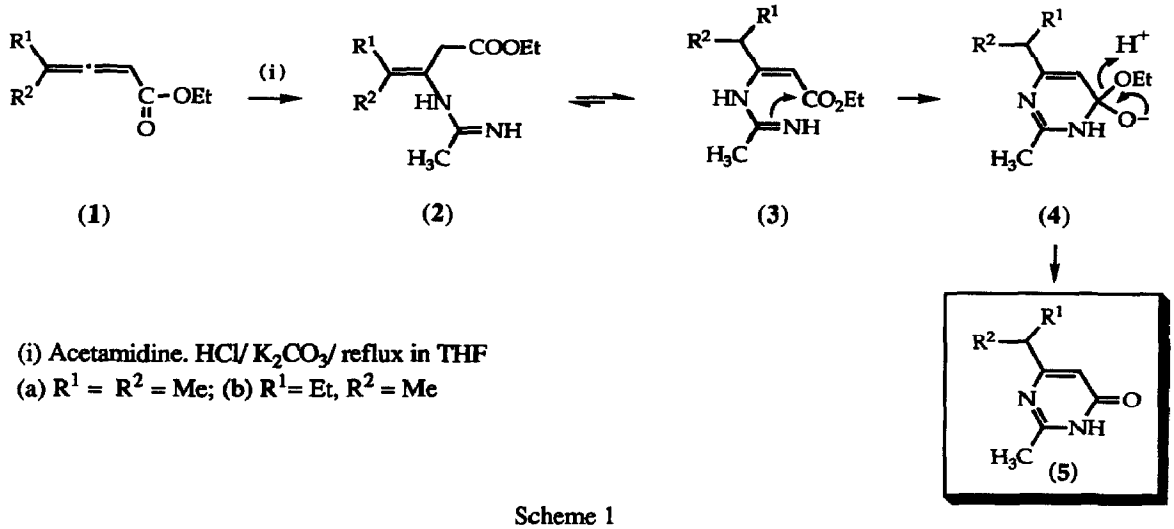
Abstract: Ethyl alka-2,3-dienoates and 4-tetrahydropyranyloxyalk-2-ynenitriles provide a 3-atom fragment when reacted with acetamidine in tetrahydrofuran, to furnish 2-methylpyrimidin-4(3H)-ones and 4-amino-2-methyl-6-(1-tetrahydropyranyloxyalkyl)pyrimidines, respectively (60 - 70%yield). The latter, with hydrochloric acid / ethanol, gave the corresponding 4-amino-6-(1-hydroxyalkyl-2-methylpyrimidines as their hydrochloride salts.

Established methods for the synthesis of 4-aminopyrimidines from [3 + 3]-atom fragments involve the use of an acrylonitrile, β-keto nitrile or a malonitrile with a guanidine, acetamidine, urea or thiourea derivative[3] (not every combination works in practice). The use of a β-aldehydo[4] or a β-keto ester[5] is routine for the synthesis of pyrimidin-4(3H)-ones. As an alternative approach we have established allenic and acetylenic nitriles as suitable 3-carbon atom donors for 4-aminopyrimidine (and 2,4-diaminopyrimidine) synthesis.[6] Here we extend our procedure to the synthesis of 2-methylpyrimidin-4(3H)-ones (**5**) and 4-amino-6-(1-hydroxyalkyl)-2-methylpyrimidines (**12**, R = H) from ethyl alka-2,3-dienoates (**1**) and 4-hydroxyalk-2-ynenitriles (**6**), respectively.

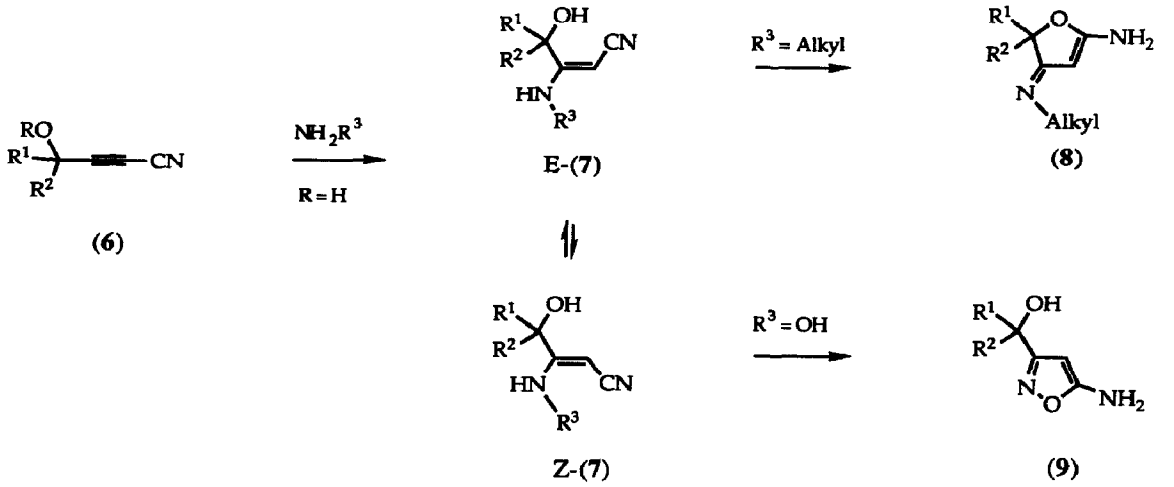
We have found ethyl alka-2,3-dienoates[7] **1a,b** to undergo Michael addition of acetamidine, presumably to the unconjugated enaminic ester **2**,[8] followed by isomerisation to the conjugated adduct **3**. Intramolecular nucleophilic attack at the ethoxycarbonyl group of **3** led to the 2-methylpyrimidin-4(3H)-ones (**5**) in excellent yield. As an example, ethyl 4-methylpenta-2,3-dienoate **1a** with an equivalent of acetamidine hydrochloride and potassium carbonate at 50 ^{0}C in tetrahydrofuran (THF) for 7h, gave 2-methyl-6-(1-methylethyl)pyrimidin-4-(3H)-one (**5a**) in 60% yield (preparative thin layer chromatography from silica gel with ethyl acetate as eluent). Spectroscopic data[9] included δ_H ($CDCl_3$) 6.19 (=CH), δ_C 106.59 (C-5), 158.07 (C-6), 166.14 (C-2) and 175.41 (C-5), characteristic of the pyrimidin-4(3H)-one ring system.[10]

The reaction of the 4-hydroxyalk-2-ynenitriles **6** (R = H) with primary amines is known to give the 5-amino-3-imino-2,3-dihydrofurans **8** in greater than 90% yield.[11] 4-Hydroxyalk-2-ynenitriles **6** (R = H) with hydroxylamine are known to give the 5-aminoisoxazoles **9** in ca. 85% yield via the adduct Z-**7** with no detection of the corresponding furan.[12] The latter cyclization mode parallels that for pyrimidine synthesis (Scheme 3).



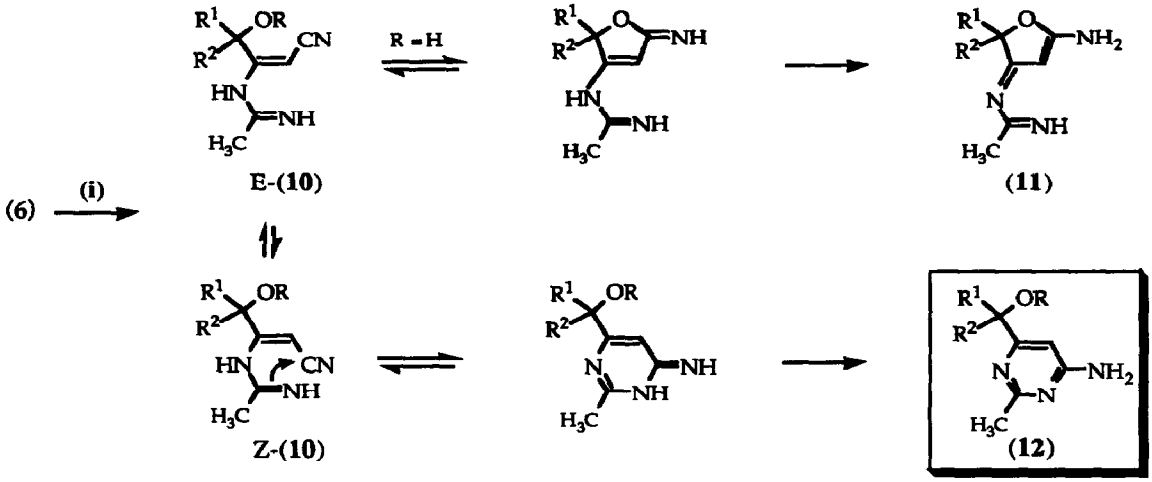
(i) Acetamidine. HCl/ K_2CO_3/ reflux in THF
(a) $R^1 = R^2 = Me$; (b) $R^1 = Et$, $R^2 = Me$

Scheme 1



Scheme 2

The reaction of equivalent amounts of the 4-hydroxynitrile **6a** (R = H) and acetamidine gave products indicating competitive cyclization modes via the acetamidino adducts E,Z-**10a** (R = H).[13] The 4-amino-6-(1-hydroxyalkyl)-2-methylpyrimidine **12a** (R = H) (Table, entry 5), a 5-amino-3-keto-2,3-dihydrofuran (a hydrolysis product of **11**) and an oxazolidin-2-one were isolated, all in very low yield. To specifically promote pyrimidine formation, the 4-tetrahydropyranyloxyalk-2-ynenitrile derivatives **6a-c** (R = Thp) were used. These, with an equivalent of acetamidine hydrochloride and sodium carbonate in refluxing THF (5, 5, and 50h, respectively), gave the 4-amino-2-methylpyrimidines **12a-c** (R = Thp) in 60 - 70% recrystallized yield. Supportive spectroscopic data for these pyrimidines[14] included δ_H 6.46 - 6.81 and δ_C ca. 100.2 ppm., indicative



(i) Acetamidine. HCl / Na_2CO_3 / reflux THF
(a) R^1 = Me, R^2 = Et; (b) R^1 = R^2 = Et; ; (c) R^1 = Me, R^2 = t-Bu

Scheme 3

of the pyrimidine unsubstituted aromatic 5-position (see Table). Treatment of **12a,b** (R = Thp) with HCl / EtOH gave the corresponding 6-(1-hydroxyalkyl)pyrimidines **12a,b**[15] (R = H) in ca. 80% yield as their hydrochloride salts. Acidification of the pyrimidine **12c** (R = Thp) (EtOH / HCl), evaporation, then neutralisation of the residue (dilute NaOH) followed by chloroform extraction gave the free base **12c** (R = H) in 61% recrystallized yield.

#	COMPD #	mp/deg C	YIELD/%	UV / nm (EtOH)	IR / 1/cm (from KBr disks)	H / ppm
1	5a	133 - 134	60	272 (4651), 223 (6686)	3100, 1660, 1600	6.19
2	5b	85 - 87	70	274 (4125), 223 (6349)	3130, 1660, 1600	6.15
3	12a(R=Thp)~	132 - 134	60	232 (12400), 271 (5000)	3320, 3140, 1670, 1595	6.46, 6.70
4	12a(R=H)*	216 - 218	78	232 (9500), 259 (6400)	3210,3140, 1660, 1640, 1605, 1505	6.76
5	12a(R=H)	106	11	231 (10700), 270 (4500)	3420, 3320, 3150, 1655, 1605, 1560	6.17
6	12b(R=Thp)	158 - 159	69	232 (12500), 271 (5000)	3400, 3160, 1660, 12555	6.65
7	12b(R=H)*	212 - 214	80	230 (10800), 266 (5600)	3210, 3140, 1660, 1640, 1605, 1505	6.73
8	12c(R=Thp)~	115	63		3315, 3145, 1660, 1595, 1555	6.36, 6.81
9	12c(R=H)	218	61	232 (13000), 271 (5000)	3140, 3310, 3180, 1650, 1600, 1555	6.12

* = Hydrochloride salt, ^1H from $CDCl_3$ / DMSO-d_6; ~ = Two diasterioisomeric pairs.

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9. All compounds gave high resolution mass spectrum (HRMS) and/or elemental analysis and spectroscopic data consistent with the assigned structures; As an example: 2-Methyl-6(1-methylethyl)pyrimidin-4(3H)-one-**5a** (60%) mp. 133 - 134 ^{0}C (HRMS gave M^+ 152.1950, $C_8H_{12}N_2O$ requires M^+ 152.1961) δ_H ($CDCl_3$) 2.20 [6H, d, $(CH_3)_2CH$], 2.48 (3H, s, CH_3-C=N), 2.75 [1H, m, $(CH_3)_2CH$], 6.19 (1H, s, =CH), δ_C 20.91 [$(CH_3)_2CH$], 21.33 (CH_3-C=N), 35.49 [$(CH_3)_2CH$], 106.59 (=CH), 158.07 (C-6), 166.14 (C-2), 175.41 (C=O), m/z 152 (M^+, 46%), 137 (100), 124 (25), 96 (28), 81 (2), 68 (13) and 54 (5).
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14. 4-Amino-6-(1-ethyl-1-tetrahydropyranyloxypropyl)-2-methylpyrimidine-**12b** (R = Thp) (69%) mp. 158 -159^{0}C. (Found: C, 64.41; H, 8194; N, 15.10: $C_{15}H_{25}O_2N_3$ requires C, 64.48; H, 9.02; N, 15.04) ν_{max} (KBr) 3400, 3160, (NH_2), 1660 (C=N) and 1555, δ_H (250 MHz, $CDCl_3$) 0.60 (3H, t, CH_3CH_2), 0.64 (3H, t, CH_3CH_2), 1.56 [10H, m, $(CH_3CH_2)_2$, $OCH(CH_2)_3$], 2.47 (3H, s, CH_3-C=), 3.50 (1H, m, OCH-H, axial), 4.10 1H, m, OCH-H, equatorial), 4.83 (1H, m, OCH), 5.10 (2H, s, exchanges with D_2O, NH_2), 6.65 (1H, s, =CH), δ_C (250 MHz, $CDCl_3$) 7.9 (CH_3CH_2), 8.1 (CH_3CH_2), 20.7 (CH_2), 25.5 (CH_2), 25.9 (CH_3-C=), 29.1 (CH_2), 31.4 (CH_2), 32.4 (CH_2), 63.6 (CH_2O), 84.9 (MeCEt), 93.6 (CH, anomeric), 100.2 (=CH), 163.5 (C), 166.8 (C), 171.5 (C), m/z 279 (M^+, <3%), 194 (8%), 179 (38), 167 (13) and 166 (100%).
15. 4-Amino-6-(1-ethyl-1-hydroxypropyl)-2-methylpyrimidine hydrochloride-**12b** (R = H) 4-amino-6-(1-ethyl-1-tetrahydropyranyloxypropyl)-2-methylpyrimidine (0.53g, 1.2 mmol) was dissolved in ethanol (30 ml, 95%) and conc. HCl adeded (0.1 ml). This was shaken manuallly for 10 min and the solvent removed (rotatory evaporator). The oily residue crystallised immediately on standing. Recrystallization from ethanol / chloroform gave 4-amino-6-(1-hydroxypropyl)-2-methylpyrimidine (0.21g, 80%) mp 212 - 214 ^{0}C (Found: C, 51.46; H, 7.88; N, 18.20; Cl, 15.70, $C_{10}H_{18}N_3Cl$ requires C, 51.83, H, 7.83; N, 18.30; Cl, 15.30. HRMS gave m/z 194.1239, M^+ - H_2Cl requires m/z 194.1294) ν_{max} (KBr) 3210, 3140, broad (NH_2, OH), 1660 (C=N), 1605 (C=C) and 1505 cm^{-1}, δ_H (250 MHz, $CDCl_3$, DMSO-d_6) 0.75 [6H, t, $(CH_3CH_2)_2$, 1.74 - 1.88 [2H, m, $(CH_3CH\text{-}H)_2$], 1.96 - 2.11 2H, m, $(CH_3CH\text{-}H)_2$], 2.63 (3H, s, CH3-C=), 5.47 (1H, s, exchanges with D_2O, OH), 6.73 (1H, s, =CH), 8.67, 8.89 (2H in total, exchanges with D_2O, NH_2), 13.49 (1H, s, exchanges with D_2O, $-NH_2.HCl$), δ_C (250 MHz, $CDCl_3$, DMSO-d_6) 7.5 [$(CH_3CH_2)_2$], 21.5 (CH_3-C=), 32.2 [$(CH_3CH_2)_2$], 75.4 (Et_2C), 98.8 (=CH), 162.6 (C), 164.6 (C), 166 (C), m/z 194 (<1%), 180 (10), 167 (49), 166 (100), 153 (31), 152 (34), 110 (34) and 68 (17%).

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