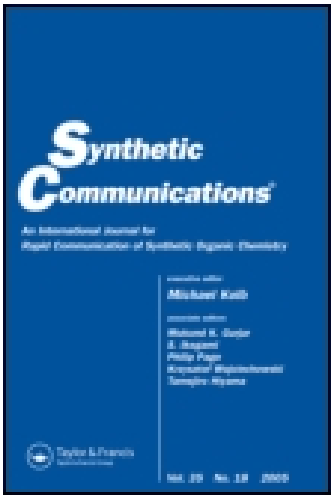

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Novel Methodology for the Preparation of 5-Substituted Tetrahydro[2,3-D]pyrimidines

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NOVEL METHODOLOGY FOR THE PREPARATION OF 5-SUBSTITUTED TETRAHYDRO[2,3-D]PYRIMIDINES

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Abstract

A convenient, concise route for the preparation of tetrahydropyrido[2,3-d]pyrimidines functionalized at the 5-position is presented starting from acyclic aldehydes. Key steps involve a high yielding Knoevenagel condensation, 1,4 conjugate addition with an allylcuprate and a pyrimidine annulation using guanidine hydrochloride. An improved synthesis of the starting aldehyde, ethyl 4-propalbenzoate is presented.

A general methodology has been developed for the synthesis of 5-substituted tetrahydropyrido[2,3-d]pyrimidines as illustrated by the synthesis of Compound **7** in Scheme 1.

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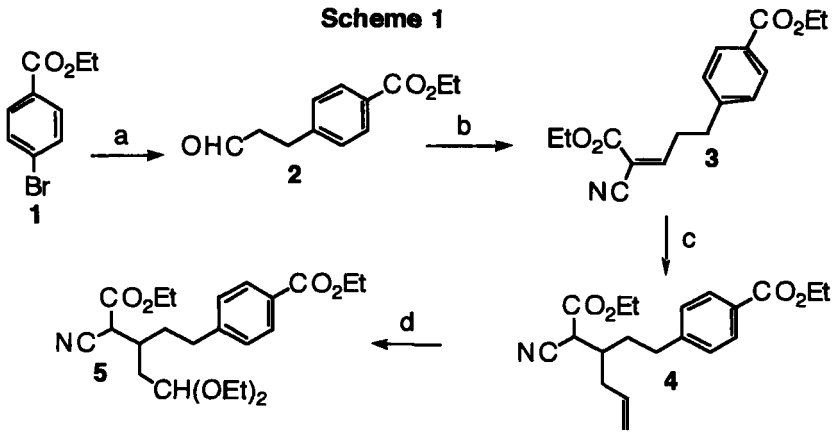
Scheme 1

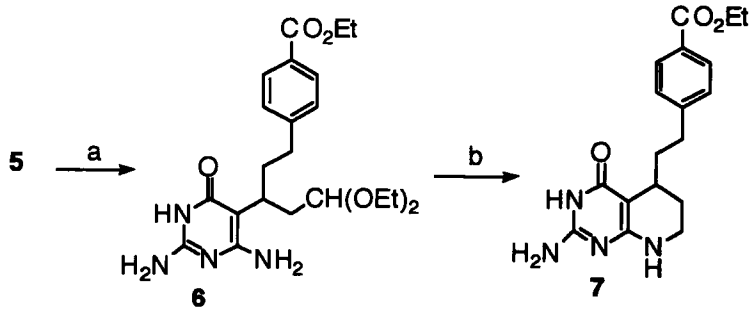


a) 5 mol % $Pd(OAc)_2$, Na_2CO_3, Bu_4NBr, DMF, 60 °C, 6 h, 82% b) ethyl cyanoacetate, basic alumina, neat, rt, 1 h, 64% c) 2.5 eq each of allyl magnesium bromide, LiBr, CuI; 1.0 eq. TMSCl, THF, -78 °C to rt, 2 h; TBAF, THF, rt, 30 min, 80% d) O_3, EtOH, -78 °C; Me_2S, -78 °C to rt, 12 h; cat. PTSA, reflux, 4 h, 71%

An improved synthesis of the known aldehyde **2**[1] was developed utilizing the palladium-catalyzed coupling of propargyl alcohol with ethyl 4-iodobenzoate under phase-transfer conditions[2].

After examination of a variety of conditions[3], it was found that Knoevenagel condensation of the aldehyde **2** and freshly distilled ethyl cyanoacetate proceeded smoothly using the aluminium oxide catalysis methodology described by Foucoud[4]. Conjugate addition of allylcuprate[5] to **3** using the excellent conditions described by Lipschutz[6] (allyl magnesium bromide and copper iodide with lithium bromide as the solublizing agent) with a slight excess of trimethylsilyl chloride[7] produced **4** in good yields on a multi-gram scale. Oxidative cleavage using either the Johnson-Lemieux system[8] or ozonolysis[9] and *in situ* protection of the resulting aldehyde as the diethyl acetal was found to be most conveniently performed on the acyclic derviative **4** as shown in Scheme 1. Attempted oxidative cleavage of the allyl group

Scheme 2



a) guanidine hydrochloride, NaOEt, EtOH, reflux, 6 h, 68%. b) $NaCNBH_3$, EtOH, pH 3-4 with conc. HCl, 16 h, 71%

after pyrimidne annylation with guanidine hydrochloride (not shown) resulted in oxidation of the pyrimidine ring.

Pyrimidine annulation of **5** with guanidine hydrochloride in basic boiling ethanol provided the diaminopyrimidne **6** in good yields (60 - 70 %) (Scheme 2). The one-step deprotection and reductive amination of compound **6** proceeded in good yields in wet acidic ethanol in the presence of sodium cyanoborohydride. In practice, this was conveniently performed on crude material so that the overall transformation of the acyclic derivative **5** to the tetrahydropyrido[2,3-d]pyrimidine **7** was essentially a one-pot operation.

Experimental Section

NMR spectra were recorded on a GE QE 300. Mass spectra were recorded on a Kratos MS 50TC mass analyzer. IR spectra were recorded on a Nicolet 730 FT spectrometer either as neat samples or as Kbr pellets. Copper iodide was purified by precipitation from potassium iodide solution and dried over phosphorus pentoxide at 100 °C for two days under reduced pressure. THF was distilled from

acetophenone sodium ketyl direcxtly before use. All other reagents were purchased from commercial suppliers and used as recieved.

Ethyl 4-propalbenzoate (2). Ethyl 4-bromobenzoate **1** (8.3 g, 36.22 mmol), allyl alcohol (3.16 g, 54.44 mmol), Na_2CO_3 (7.61 g, 71.80 mmol), $(Bu)_4NBr$ (11.78 g, 36.54 mmol), powdered 4 Å sieves (9.0 g), and $Pd(OAc)_2$ (407 mg, 1.813 mmol, 5 mol %) were added to dry, degassed DMF (60 ml) under an N_2 atmosphere and heated to 60 °C for 6 h. The reaction mixture was cooled to rt, diluted with EtOAc (100 ml) and filtered through a pad of Celite. The solvents were removed under reduced pressure. The residue was taken up in Et_2O (200 ml) and filtered again through Celite. The filtrate was washed with H_2O (4 x 50 ml), dried ($MgSO_4$) and condensed to give a pale brown oil which after chromatography on silica gel (6% EtOAc in hexanes) gave **2** (6.13 g, 29.72 mmol, 82%) as a colorless oil. The proton spectrum was consistent with published values[1]. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 6.88 Hz), 2.79 (t, 2H, J = 7.06 and 7.26 Hz), 2.96 (t, 2H, J = 7.06 and 7.26 Hz), 4.34 (q, 2H, 6.88 Hz), 7.24 (dd, 2H), 7.95 (dd, 2H), 9.79 (s, 1H).

Ethyl 2-cyano-5-(4-carboethoxyphenyl)pent-2-enoate (3). Ethyl 4-propalbenzoate (**2**) (1.05 g, 5.09 mmol) and ethyl cyanoacetate (0.624 g, 5.52 mmol) were combined neat in a 25 ml round bottom flask fitted with a magnetic stirring bar and a $CaCl_2$ drying tube. Alumina (1.54 g, Basic, Baker reagent, Brockman activity grade 1) was added slowly over 20 min while maintaining vigorous stirring with care taken to keep the reaction temperature below 10 °C. Stirring was continued for 30 min, the reaction mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The alumina was washed with additional CH_2Cl_2 (25 ml).

The CH_2Cl_2 layers were combined and evaporated under reduced pressure to give a pale yellow oil (1.57 g) that solidified on cooling. The material was recrystalized from hexanes to give **3** (1.45 g, 4.812 mmol, 64%) as large white prisims, mp 56 - 57°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 - 1.41 (m, 6H), 2.89 - 2.92 (m, 4H), 4.26 - 4.38 (m, 4H), 7.25 (dd, 2H), 7.61 (t, 1H), 8.01 (dd, 2H). MS m/z (relative intensity) 301 (8%), 257 (11%), 256 (58%), 255 (71%), 164 (47%), 163 (100%), 135 (61%). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.76; H, 6.39; N, 4.76.

Ethyl 2-cyano-3-[2-(4-carboethoxyphenyl)ethyl]hex-5-enoate (4). CuI (6.34 g, 33.28 mmol) and LiBr (2.89 g, 33.28 mmol, dried under reduced pressure at 150°C for 12 h), were stirred in dry THF (70 ml) at rt under an N_2 atmosphere until dissolution was complete (15 min). The solution was cooled to -78°C and allylmagnesium bromide (33.28 ml, 1.0M solution in THF) was introduced slowly dropwise while maintaining the reaction temperature below -70 °C. After 15 min at -78 °C, TMSCl (4.23 ml, 33.28 mmol) was added quickly followed immediately by dropwise addition of ethyl 2-cyano-5-(4-carboethoxyphenyl)pent-2-enoate (**3**) (3.34 g, 11.084 mmol) in dry THF (20 ml) while maintaining the reaction temperature below -65 °C. After 45 min at -78 °C, the reaction mixture was quenched with saturated NH_4Cl (75 ml), the pH was adjusted to 8 with NH_4OH (10-15 ml) and stirred at rt until all of the copper salts had dissolved (2-3 h). The reaction mixture was extracted with Et_2O (3 x 75), the ethereal solutions were combined, dried ($MgSO_4$) and condensed to give a pale brown oil. This was immediately taken up in dry THF (100 ml), cooled to 4 °C and TBAF (16.6 ml, 1.0M solution in THF) was added dropwise over 15 min. The reaction mixture was warmed to rt over 45 min. The solvents were removed under

reduced pressure and the crude residue was chromatographed over silica gel (4% EtOAc in hexanes) to give **3** (3.05 g, 8.88 mmol, 80%) as a colorless oil, consisting of an inseparable mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 - 1.41 (m, 6H), 1.74 - 1.81 (m, 2H), 2.17 - 2.45 (m, 3H), 2.59 - 2.77 (m, 2H), 3.43 - 3.66 (m, 1H), 4.15 - 4.23 (m, 4H), 5.04 - 5.19 (m, 2H), 5.60 - 5.66 (m, 1H), 7.18 - 7.21 (m, 2H), 7.91 - 8.04 (m, 2H); MS m/z (relative intensity) 343 (6.7%), 302 (9.9%), 298 (32.2%), 297 (21.9%), 256 (35.1%), 185 (28.4%), 142 (100%), 163 (54.8%). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 68.50; H, 7.26; N, 4.04.

Ethyl 2-cyano-3-(2,2-ethoxyethyl)-5-(4-carboethoxyphenyl)-pentanoate (5). Ethyl 2-cyano-3-[2-(4-carboethoxyphenyl)ethyl]hex-5-enoate (**4**) (3.0 g, 8.736 mmol) in dry EtOH (250 ml) in an open flask was cooled to -78 °C and ozone was bubbled through until a blue color persisted (25-30 min). The reaction mixture was purged with oxygen for 15 min, Me_2S (1.21 ml, 16.49 mmol) was added and the reaction mixture allowed to warm slowly to rt overnight. A catalytic amount of PTSA (150 mg) was added and the reaction mixture was allowed to stir a further 24 h at rt before being quenched with H_2O (50 ml) and extracted with Et_2O (2 x 75 ml). The ethereal layers were combined, washed with 5% Na_2CO_3 (50 ml), dried ($MgSO_4$), condensed to a pale viscous oil which was chromatographed over silica gel (10% EtOAc in hexanes) to give **5** (2.602 g, 6.21 mmol, 71%), a viscous, colorless oil. The proton NMR indicated this material to be a mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 - 1.41 (m, 12H), 1.73 - 1.87 (m, 3H), 2.31 - 2.40 (m, 1H), 2.58 - 2.80 (m, 2H), 3.40 - 3.77 (m, 3H), 4.10 - 4.52 (m, 8H), 7.21 (dd, 2H), 7.98 (dd, 2H). MS m/z (relative

intensity) 419 (2%), 374 (83%), 328 (88%), 270 (60%), 215 (68%), 177 (100%). HRMS m/z calcd for $C_{23}H_{33}NO_6$ 419.2308, found: 419.2311. Anal cald. for $C_{23}H_{33}NO_6$: C, 65.87; H, 7.88; N, 3.34. Found: C, 65.71; H, 7.81; N, 3.29.

5-[2-(4-Carboethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-5-deazapterin (7). Na (0.193 g, 8.39 mmol) was dissolved in dry EtOH (6 ml) under an N_2 atmosphere and guanidine hydrochloride (0.667 g, 6.98 mmol) was added followed by ethyl 2-cyano-3-(2,2-ethoxyethyl)-5-(4-carboethoxyphenyl)-pentanoate (**5**) (1.17 g, 2.792 mmol) in dry EtOH (2 ml) as before. The reaction mixture was heated at reflux for 9 h, cooled to rt and neutralized with AcOH. The volatiles were removed under reduced pressure and the amber gum triturated with warm H_2O (15 ml). The H_2O was decanted and the residue dried under high vacuum for 3 h. Chromatography over silica gel (4% MeOH-CH_2Cl_2) gave **6** (0.820 g, 1.896 mmol, 68 %) as a pale yellow powder. ^1H NMR (300 MHz, DMSO-d_6) d 1.02 - 1.13 (m, 6H), 1.28 (t, 3H), 2.41 - 2.54 (m, 3H), 3.41 (t, 1H), 4.22 - 4.31 (m, 6H), 7.51 (br, 4H), 7.82 (AA'BB', 4H), 10.2 (br, 1H).

Crude **6** (0.820 g, 1.896 mmol) was suspended in 95% EtOH (25 ml) and 1N HCl (5.7 ml. 3.0 equiv.) was added with stirring at rt. After 2 h, $NaCNBH_3$ (0.0717 g, 1.141 mmol) was added in small portions. Stirring was continued at rt for 24 h, the reaction was diluted with H_2O (50 ml), neutralized with 6N NaOH, cooled to 4 °C and filtered to give a pale solid which after chromatography over silica gel (3% MeOH-CH_2Cl_2) gave **7** (0.461 g, 1.347 mmol, 71% from 16, 48% from 15) as a white powder: mp 187 - 191 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, 3H), 1.31 - 1.48 (m, 3H), 1.70 - 1.84 (m, 2H), 2.44 - 2.80 (m, 3H), 3.08 - 3.12 (m, 2H), 4.12 (q, 2H), 5.92 (br, 2H), 6.32 (br, 1H), 7.28 (dd, 2H), 7.84

(dd, 2H), 9.72 (br, 1H). MS m/z (relative intensity) 342 (17%), 297 (10%), 179 (13%), 167 (8%), 166 (76%), 169 (100%). HRMS m/z calcd for $C_{18}H_{22}N_4O_3$ 342.1692, found: 342.1685. Anal cald. for $C_{18}H_{22}N_4O_3$: C, 63.16; H, 6.43; N, 16.37. Found: C, 63.21; H, 6.38; N, 16.32.

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