Preparation of 7-Alkyl-2,3,6,7-tetrahydro-4-alkyl-2-oxo-1*H*-1,3-diazepine-5-carboxylates by Ring Expansion-Nucleophilic Addition

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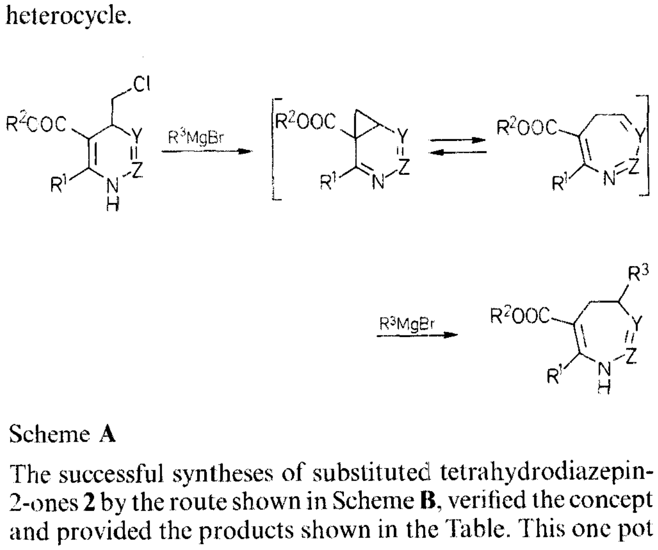
The preparation of ethyl 7-alkyl-2,3,6,7-tetrahydro-4-alkyl-2-oxo-1*H*-1,3-diazepine-5-carboxylates **2** by a one pot ring expansion-nucleophilic addition of ethyl 4-chloromethyl-1,2,3,4-tetraydro-6-alkyl-2-oxopyrimidine-5-carboxylates **1** is described.

Recently, we described the preparation of 4-aryl-4,5-dihydroazepines by an organometallic based ring expansion-nucleophilic addition sequence[1]. The three requirements for extension of this methodology to other heterocycles are as shown in Scheme **A**:

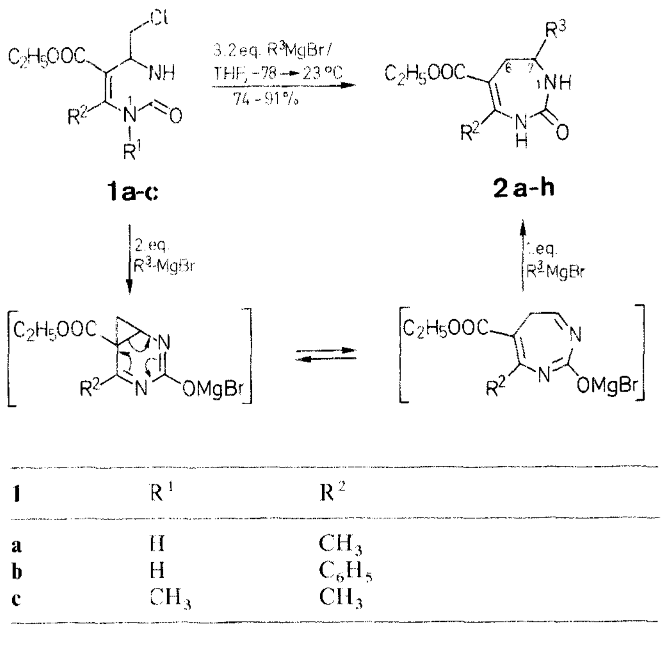
- an amino acrylate moiety contained in a six membered ring;
- a 4-α-halomethyl substituent; and
- a potential bi bond between Y and Z. One such heterocyclic system that falls into this category is the ethyl 4-chloromethyl-1,2,3,4-tetrahydro-6-alkyl-2-oxopyrimidine-5-carboxylates **1**, substrates reported to undergo ring-expansion induced by heteroatom bases[2]. Our previous success with the Grignard reagent-induced ring expansion-nucleophilic addition prompted our investigation of this heterocycle.



Scheme A

The successful syntheses of substituted tetrahydrodiazepin-2-ones **2** by the route shown in Scheme **B**, verified the concept and provided the products shown in the Table. This one pot procedure, using a starting material prepared by condensation of urea, an alkyl acetoacetate, and 1,2-dichloroethyl ethylether[2], provides novel substituted heterocycles unavailable by other methods. All of the examples prepared to evaluate this methodology are both stable and crystalline.

A possible mechanism for the transformation of **1** to **2** is shown in Scheme **B** and is consistent with the following observations. The reaction requires three equivalents of Grignard reagent (two for deprotonation of acidic N-H and one as nucleophile) and produces the desired products regioselectively in good to excellent yields. The necessity of an available acidic proton on N-1 was demonstrated by the unsuccessful conversion of **1c** to the expected products upon exposure to Grignard reagents under the reaction conditions. The structures of **2** are supported by ^{1}H-NMR (360 MHz) which showed the expected chemical shifts, a doublet of doublet for the C-7 proton upon irradiation at 1-H, and two doublet of doublets for the C-6 methylene protons typical of an ABX type system.



1	R¹	R²
a	H	CH_3
b	H	C_6H_5
c	CH_3	CH_3

2	R²	R³
a	CH_3	C_6H_5
b	CH_3	$2\text{-}H_3CO\text{—}C_6H_4$
c	CH_3	$4\text{-}F_3C\text{—}C_6H_4$
d	CH_3	$3\text{-}F_3C\text{—}C_6H_4$
e	CH_3	$2\text{-}F_3C\text{—}C_6H_4$
f	CH_3	C_6F_5
g	C_6H_5	C_6H_5
h	C_6H_5	CH_3

Scheme **B**

Ethyl 2,3,6,7 Tetrahydro-2-oxo-1*H*-1,3-diazepine-5-carboxylates 2a-h; General Procedure:

To a stirred suspension of **1a** or **1b**[2] (10 mmol) in tetrahydrofuran (20 ml) cooled to −78 °C is added a 3 molar ethereal solution of phenylmagnesium bromide (10.7 ml, 32 mmol) or the other Grignard reagents indicated in the Table, prepared from the bromide and magnesium. After addition is complete, the cooling bath is removed and the reaction followed by TLC (silica gel). Complete reaction occurs after approximately 15 min at 23 °C and the excess Grignard reagent is quenched with saturated aqueous ammonium chloride solution. Extraction with chloroform (3 × 100 ml), drying with

Table. Ethyl 2,3,6,7-Tetrahydro-2-oxo-1*H*-1,3-diazepine-5-carboxylates **2** Prepared

Educts		Product No.	Yield [%][a]	m.p. [°C]	Molecular Formula[b]	IR (Nujol) ν[cm^{-1}]	^{1}H-NMR (CDCl$_3$/TMS)[c] δ[ppm]
Pyrimidine	R^3 in R^3—MgBr						
1a	C_6H_5	**2a**	91	192–193.5	$C_{15}H_{18}N_2O_3$ (274.3)	3290, 3190, 1670, 1645, 1610	1.18 (t, J = 7.5 Hz, 3H); 2.27 (s, 3H); 2.94 (dd, J = 7.5, 15.0 Hz, 1H); 3.04 (dd, J = 2.0, 15.0 Hz, 1H); 4.06 (q, J = 7.5 Hz, 2H); 4.63 (dd, J = 2.0, 7.5 Hz, 1H); 5.57 (br s, 1H); 6.93 (br s, 1H); 7.25–7.40 (m, 5H)
1a	2-H_3CO—C_6H_4	**2b**	87	189–190	$C_{16}H_{20}N_2O_4$ (304.3)	3360, 3240, 1695, 1670, 1620	1.14 (t, J = 7.2 Hz, 3H); 2.26 (s, 3H); 2.96 (dd, J = 2.0, 15.0 Hz, 1H); 3.08 (dd, J = 7.5, 15.0 Hz, 1H); 3.85 (s, 3H); 4.00, 4.03 (dq, J = 7.0, 12.0 Hz, 1H each); 5.03 (dd, J = 7.5, 2.0 Hz, 1H); 5.33 (br s, 1H); 6.40 (br s, 1H); 6.86 (d, J = 7.5 Hz, 1H); 6.95 (t, J = 6.0 Hz, 1H); 7.22–7.28 (m, 2H)
1a	4-F_3C—C_6H_4	**2c**	83	165–167	$C_{16}H_{17}F_3N_2O_3$ (342.3)	3380, 3240, 1700, 1680, 1630	1.13 (t, J = 7.2 Hz, 3H); 2.27 (s, 3H); 3.03 (m, 2H); 4.02 (q, J = 7.2 Hz, 2H); 4.77 (m, 1H); 5.55 (br s, 1H); 6.62 (br s, 1H); 7.40, 7.62 (d, J = 8.0 Hz, 2H each)
1a	3-F_3C—C_6H_4	**2d**	85	175–177	$C_{16}H_{17}F_3N_2O_3$ (342.3)	3300, 3180, 1675, 1650, 1610	1.14 (t, J = 7.5 Hz, 3H); 2.26 (s, 3H); 3.01 (dd, J = 3.0, 15.0 Hz, 1H); 3.08 (dd, J = 6.0, 15.0 Hz, 1H); 4.01 (q, J = 7.5 Hz, 2H); 4.77 (dd, J = 3.0, 6.0 Hz, 1H); 5.57 (br s, 1H); 6.62 (br s, 1H); 7.45–7.58 (m, 4H)
1a	2-F_3C—C_6H_4	**2e**	86	207–209	$C_{16}H_{17}F_3N_2O_3$ (342.3)	3360, 3240, 1695, 1675, 1620	1.13 (t, J = 7.5 Hz, 3H); 2.33 (s, 3H); 2.86 (dd, J = 9.0, 15.0 Hz, 1H); 3.11 (br d, J = 15.0 Hz, 1H); 4.03 (m, 2H); 5.04 (br d, J = 9.0 Hz, 1H); 5.35 (br s, 1H); 6.83 (br s, 1H); 7.42 (m, 1H); 7.59 (d, J = 4.5 Hz, 2H); 7.65 (d, J = 7.5 Hz, 1H)
1a	C_6F_5	**2f**	76	254–255.5	$C_{15}H_{13}F_5N_2O_2$ (364.3)	3350, 3240, 1700, 1670, 1630	1.02 (t, J = 7.5 Hz, 3H); 2.18 (s, 3H); 2.80 (br d, J = 14.0 Hz, 1H); 3.06 (dd, J = 7.5, 14.0 Hz, 1H); 3.91 (m, 2H); 4.93 (m, 1H); 7.50 (br s, 1H); 8.68 (br s, 1H)
1b	C_6H_5	**2g**	77	168–170[d]	$C_{20}H_{20}N_2O_3$ (336.4)	3240, 3100, 1695, 1680, 1630	0.65 (t, J = 7.5 Hz, 3H); 3.02 (dd, J = 3.0, 15.0 Hz, 1H); 3.22 (dd, J = 6.0, 15.0 Hz, 1H); 3.56 (q, J = 7.5 Hz, 2H); 4.88 (dd, J = 3.0, 6.0 Hz, 1H); 7.27–7.43 (m, 10H); 8.03 (br s, 1H); 8.23 (br s, 1H)
1b	CH_3	**2h**	74	131–134	$C_{15}H_{18}N_2O_3$ (274.3)	3330, 3240, 1695, 1660, 1630	0.66 (t, J = 7.5 Hz, 3H); 1.12 (d, J = 6.0 Hz, 3H); 2.52 (dd, J = 7.5, 15.0 Hz, 1H); 2.74 (dd, J = 3.0, 15.0 Hz, 1H); 3.58 (m, 1H); 3.69 (q, J = 7.5 Hz, 2H); 7.12 (br s, 1H); 7.23 (m, 2H); 7.32–7.42 (m, 3H); 8.04 (br s, 1H)

[a] Yield of isolated analytical sample.

[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.27, N ±0.35.

[c] Recorded at 360 MHz; **2f**–**h** in DMSO-d_6; value for 7-H reported with irradiation at 1-H.

[d] Softens and decomposes at 136 °C.

magnesium sulfate, filtration and concentration at reduced pressure affords **2**, which is homogeneous by TLC (silica gel, 1 % methanol in ether) as a white solid which is washed with cold anhydrous ether (100 ml) or recrystallized from ethyl acetate/hexane to provide the analytical samples (Table).

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