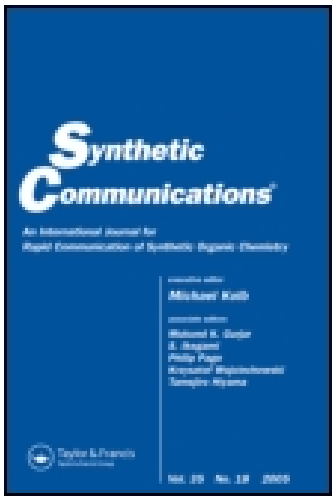

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5-Amino-2H-pyran-3(6H)-one, 1, a Convenient Intermediate in the Synthesis of Pyran Containing 1,4-Dihydropyridines

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5-Amino-2H-pyran-3(6H)-one, 1, a Convenient Intermediate in the Synthesis of Pyran Containing 1,4-Dihydropyridines

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ABSTRACT

5-Amino-2H-pyran-3(6H)-one, **1**, is a novel intermediate that is useful in the synthesis of pyran containing dihydropyridines. The synthesis and use of **1** will be discussed.

Key Words: 5-Amino-2H-pyran-3(6H)-one; Pyran; Dihydropyridines; Potassium channel blockers; Enamine.

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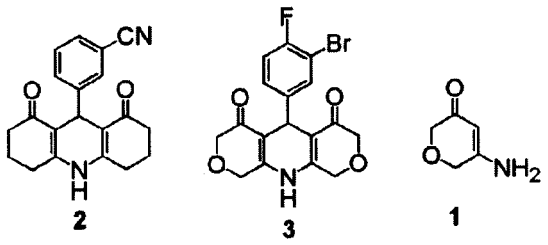
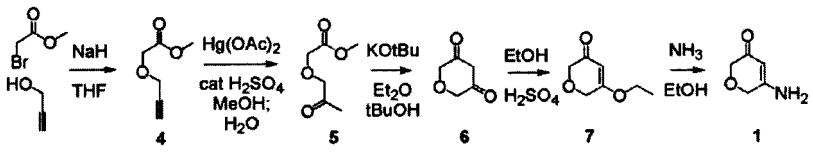


Figure 1. Structures of enamine **1** and DHPs **2** and **3.**

1,4-Dihydropyridines (DHPs) such as nifedipine are well known to have activity as calcium channel blockers. Recently, the acridinedione ZM244085, **2**, was reported as an ATP sensitive potassium (K_{ATP}) channel opener without calcium channel blocking activity (see Fig. 1).[1] During structure activity relationship studies investigating K_{ATP} channel openers for the treatment of overactive bladder, we discovered a series of novel pyran containing DHPs represented by structure **3**.[2] Enamine **1** was found to be a useful intermediate for the synthesis of this series. The synthesis and use of **1** to generate a wide range of pyran containing DHPs will be discussed.

Our synthesis of enamine **1** is shown in Sch. 1. A crucial intermediate for the synthesis of **1** as well as the pyran containing DHP series was pyran-3,5-dione, **6**. The reported synthesis of intermediate ketone **5** and cyclization to **6** by Teresawa and Okada was found to be inconvenient for larger scale.[3] A modification of a procedure reported by Morgan and Van Heyningen was used to generate **5**.[4] Propargyl alcohol was deprotonated with sodium hydride in THF and alkylated with methyl bromoacetate to provide acetylene **4** in 52% yield after distillation. Hydration of **4** catalyzed by mercury(II) acetate provided after distillation a 55% yield of ketone **5**. Conditions similar to those used by Ziegler and Bennett to synthesize 1-benzylpiperidine-3,5-dione were used to cyclize **5** to **6**.[5] The dropwise addition of **5** as a solution in ether to a mixture of potassium *tert*-butoxide in anhydrous ether provided, after



Scheme 1.

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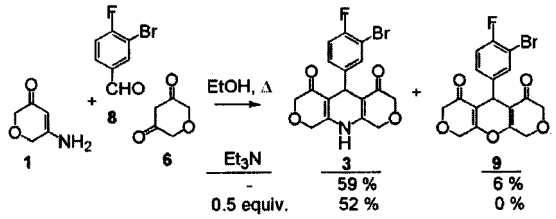

Scheme 2.

crystallization, a 31% yield of pure **6**. A synthesis of **6**, amenable to large scale, has recently been reported.[6]

We were unsuccessful at converting **6** directly into **1** under conditions which have been reported for the conversion of cyclohexane-1,3-dione to 3-aminocyclohex-2-enone.[7] Cyclopenten-1,3-dione, a molecule similar to **6** in that it is also relatively resistant to direct incorporation of ammonia, was successfully converted via an intermediate ethyl vinyl ether to the corresponding enaminone by Kikani et al.[8] This modification proved beneficial to us. Vinyl ether **7** was obtained by stirring **6** in ethanol in the presence of sulfuric acid at ambient temperature over night followed by a basic workup. Treatment of **7** with ammonia in ethanol at room temperature provided enaminone **1** in 77% overall yield from **6**.

The formation of symmetrical pyran **3** was examined using enamine **1**.[9]a Heating a mixture of **1**, **6** and 3-bromo-4-fluorobenzaldehyde **8** in ethanol for 60 hours provided a 10 : 1 mixture of **3** and pyran **9**[b] (Sch. 2). Repeating this reaction with 0.5 equivalents of triethylamine provided pure **3** in 52%.

Enamine **1** was found useful for synthesizing a variety of novel nonsymmetrical pyran containing DHPs. Reaction of cyclic 1,3-diones and β-keto sulfones of structure **10** with **1** in the presence of **8** provided ketone and sulfone containing DHPs respectively of general structure **12** (see Sch. 3 and Table 1). The addition of 0.5 equivalents of triethylamine to these Hantzsch reactions was beneficial in most cases by reducing the formation of symmetrical DHP **3** that complicated the purification of the nonsymmetrical

[a]We found that the DHP **3** could be obtained in only 33% by the method reported for the synthesis of **2**.

[b]Compound **9** was independently synthesized and isolated as a solid in 63% yield by heating two equivalents of **6** with one equivalent of **8** in EtOH for 60 hours at 80°C in a seated vessel. MS (DCI) m/z 412 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ4.14 (s, 4H), 4.60 (AB quart, 4H), 4.63 (s, 1H), 7.31 (m, 2H), 7.54 (dd, 1H).

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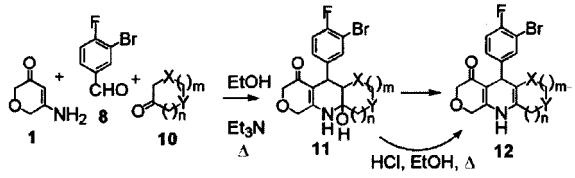

Scheme 3.

DHPs. Triethylamine is believed to be acting as an acid scavenger and thus reducing the conversion of **1** to **6**. The presence of **6** presumably results in the undesired Hantzsch reaction between **1**, **6** and **8** that leads to the formation of **3**.

The hemiaminal of structure **11** is believed to be an intermediate in the Hantzsch reaction involving **1**. In the case of sulfone **10a**, hemiaminal **11a** was the major product from the Hantzsch reaction. The presence of the triethylamine had prevented the in situ acid catalyzed dehydration of the hemiaminal to the DHP from occurring. Compound **11a** was smoothly converted to DHP **12a** by briefly heating in ethanol in the presence of HCl. The hemiaminal intermediates of DHPs possessing two carbonyl functionalities in conjugation with the DHP core were not isolated in the presence of triethylamine. Instead, the desired DHPs were obtained as a crystalline solid directly from the reaction mixtures.

As mentioned above, triethylamine was not beneficial in every case. Examples **10b** and **10c** provided low yields and complex reaction mixtures

Table 1. Pyran containing DHPs.

Compound	X	Y	m	n	Product[a]	Yield (%)
10a[10]	SO_2	CH_2	0	1	**12a**[b]	59
10b[10]	SO_2	CH_2	1	1	**12b**[c]	77
10c	C=O	CH_2	0	1	**12c**[d]	32
10d	C=O	CH_2	1	1	**12d**	48
10e[11]	C=O	NH	0	2	**12e**[c]	52
10f[5]	C=O	NBn	1	1	**12f**[e]	39
10g[12]	C=O	S	1	1	**12g**	39
6	C=O	O	1	1	**3**	52

[a]Unless noted otherwise, products were collected by filtration directly from the reaction mixture.
[b]Hemiaminal of structure **10a** was isolated.
[c]Triethylamine was not used.
[d]Ammonium acetate used in place of triethylamine.
[e]Product was purified by chromatography.

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using triethylamine. In the case of **10b**, the use of no base provided the highly crystalline**12b** in 77%. Ammonium acetate in place of triethylamine proved beneficial in the case of **10c** wherein **12c** was isolated pure in 32%.

Compound **1** is a useful reagent for generating pyran containing DHPs. We have demonstrated its use for generating both symmetrical as well as nonsymmetrical pyran containing DHPs.

EXPERIMENTAL

Proton NMR spectra were obtained on a General Electric QE 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Thin layer chromatography (TLC) was performed using 250 μm silica gel 60 glassbacked plates with F_{254} as indicator.

Methyl propynyloxyacetate (4). A mechanically stirred suspension of sodium hydride (60% dispersion in mineral oil) (50 g, 1.25 mol) in tetrahydrofuran (800 mL) at 0°C under nitrogen was treated dropwise with a solution of propargyl alcohol (84 g, 1.5 mol) in tetrahydrofuran (175 mL), stirred at 0°C for 1 hour, treated with a solution of methyl bromoacetate (199 g, 1.3 mol) in tetrahydrofuran (250 mL) over 15 minutes, stirred at 0°C for 30 minutes, stirred at ambient temperature for 2 hours, and treated with 2 M HCl (800 mL). The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, concentrated and distilled (bp 75 − 85°C at 20 torr) to provide 83 g (52%) of **4**: ^{1}H NMR ($CDCl_3$) δ2.49 (t, 1H), 3.77 (s, 3H), 4.22 (s, 2H), 4.32 (d, 2H).

Methyl (2-oxopropoxy)acetate (5). A solution of **4** (53 g, 0.40 mol) in methanol (0.4 L) was treated with mercury(II) acetate (14 g, 0.04 mol), treated with concentrated sulfuric acid (2 mL), refluxed for 20 minutes, cooled to ambient temperature, concentrated under vacuum to a volume of 150 mL, treated with 1 M HCl (150 mL) and extracted with dichloromethane (5 × 100 mL). The combined dichloromethane layers were dried ($MgSO_4$), filtered, concentrated and distilled (72–78°C at 0.7–0.5 torr) to provide 33.3 g (55 %) of **5**: ^{1}H NMR ($CDCl_3$) δ2.18 (2, 3H), 3.77 (s, 3H), 4.20 (s, 2H), 4.21 (s, 2H).

Pyran-3,5-dione (6). A solution of **5** (50 g, 0.34 mol) in anhydrous ether (1.0 L) was added dropwise over 2 hours to a mechanically stirred solution of potassium *tert*-butoxide (1 M in tert-butanol, 340 mL) in anhydrous ether (500 mL). The mixture was treated with 2 M HCl (200 mL) and the layers were

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separated. The aqueous layer was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated (keeping the water bath temperature below 30°C). This crude product which crystallized on standing was treated with 1 : 1 hexane : ethyl acetate (200 mL). The crystals were collected by filtration, washed with 1 : 1 hexane : ethyl acetate (100 mL) and dried under vacuum to provide 12.2 g (31%) of **6**: ^{1}H NMR (DMSO-d_6) δ 4.07 (s, 4H), 5.32 (s, 1H), 11.9 (bs, 1H).

5-Amino-6H-pyran-3-one (1). A solution of compound **6** (0.5 g, 4.4 mmol) in ethanol (10 mL) was treated with conc. H_2SO_4 (5 drops), stirred at ambient temperature over night, concentrated to a volume of approximately 3 mL, diluted with ether (50 mL), washed with saturated sodium bicarbonate solution (15 mL), washed with brine, dried ($MgSO_4$) and concentrated to provide 0.52 g of the intermediate ethyl vinyl ether as a low melting point white solid. This solid was treated with a solution of ammonia in ethanol (10 mL), stirred over night at ambient temperature and concentrated to provide 0.38 g (77%) of **1** as a off white solid: MS (DCI/NH_3) m/z 114 $(M + H)^+$, 131 $(M + NH_4)^+$; ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 2H), 4.19 (s, 2H), 5.01 (s, 1H), 7.01 (bs, 2H). Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.20; H, 6.09; N, 12.25.

9-(3-Bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b] thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide (12a). A mixture of compound **1** (1.5 g, 13 mmol), aldehyde **8** (3.2 g, 16 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (**10a**)[10] (1.8 g, 13 mmol) and triethylamine (0.93 mL, 6.6 mmol) in ethanol (20 mL) was stirred in a sealed tube at 80°C for 60 hours, cooled and concentrated to dryness. The residue was treated with ethanol (50 mL), treated with 1 M HCl (in diethyl ether, 5 mL), heated to reflux for 5 minutes and kept at ambient temperature for 3 hours. The resulting solid was collected by filtration, washed with ethanol and dried under vacuum for 16 hours to provide **12a** (3.2 g, 59 %): mp > 260°C; MS (ESI(+)) m/z 414 $(M + H)^+$, 431 $(M + NH_4)^+$; MS (ESI(−)) m/z 412 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33–3.42 (m, 2H), 4.03 (s, 2H), 4.49 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H); Anal. Calcd for $C_{16}H_{13}NO_4SFBr$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.25; H, 3.24; N, 3.26.

General Example for Synthesis of Pyran Containing DHPs

5-(3-Bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b : 4,3-e]pyridine-4,6(7H,9H)-dione (3). A mixture of enaminone **1** (113 mg, 1.00 mmol), aldehyde **8** (255 mg, 1.25 mmol), compound **6** (114 mg,

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1.0 mmol) and triethylamine (70 μL, 0.50 mmol) in ethanol (2 mL) was stirred for 60 hours at 80°C in a seated vessel and allowed to stand at ambient temperature for 24 hours. The solid was collected by filtration, washed with ethanol and dried under vacuum to provide 206 mg (52%) of **3**: mp > 250°C; MS (APCI(−)) m/z 392 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 4H), 4.41–4.60 (AB qu, 4H), 4.94 (s, 1H), 7.19–7.32 (m, 2H), 7.42 (dd, 1H), 10.12 (br s, 1H); Anal. Calcd for $C_{17}H_{13}BrFNO_4 \cdot 0.5\ H_2O$: C, 50.64; H, 3.49; N, 3.47. Found: C, 50.66; H, 3.56; N, 3.90.

10-(3-Bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H,5H-pyrano[3,4-b]thiopyrano[2,3-e]pyridin-9(8H)-one 1,1-dioxide (12b). Substituting **10b**[10] for **6** without triethylamine provided **12b** (77%). MS (ESI(+)) m/z 428 $(M+H)^+$, 445 $(M+NH_4)^+$; MS (ESI(−)) m/z 426 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 2.22 (m, 2H), 2.41–2.56 (m, 1H), 2.64 (dt, 1H), 3.09–3.35 (m, 2H), 4.02 (s, 2H), 4.43 (AB q, 2H), 5.06 (s, 1H), 7.25 (m, 2H), 7.41 (dd, 1H), 9.67 (bs, 1H); Anal. Calcd for $C_{17}H_{15}NO_4SFBr$: C, 47.68; H, 3.53; N, 3.27. Found: C, 47.36; H, 3.65; N, 3.06.

5-(3-Bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[b]pyrano-[4,3-e]pyridine-4,6(1H,3H)-dione (12c). Substituting **10c** for **6** and substituting NH_4OAc for Et_3N provided **12c** (32%): MS (ESI(+)) m/z 378 $(M+H)^+$, 395 $(M+NH_4)^+$; MS (ESI(−)) m/z 376 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 2.31 (t, 2H), 2.59 (dt, 1H), 2.73 (dt, 1H), 4.04 (s, 2H), 4.53 (AB q, 2H), 4.71 (s, 1H), 7.22 (m, 2H), 7.43 (dd, 1H), 10.36 (bs, 1H); Anal. Calcd for $C_{17}H_{13}NO_3FBr$: C, 53.99; H, 3.46; N, 3.70. Found: C, 53.68; H, 3.63; N, 3.63.

5-(3-Bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano[3,4-b]-quinoline-4,6(3H,7H)-dione (12d). Substituting **10d** for **6** provided **12d** (48%): MS (ESI(+)) m/z 392 $(M+H)^+$; MS (ESI(−)) m/z 390 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 1.76–2.01 (m, 2H), 2.25 (t, 2H), 2.43–2.64 (m, 2H), 4.01 (s, 2H), 4.48 (AB q, 2H), 4.90 (s, 1H), 7.20 (m, 2H), 7.39 (dd, 1H), 9.82 (bs, 1H); Anal. Calcd for $C_{18}H_{15}HO_3FBr$: C, 55.12; H, 3.85; N, 3.57. Found: C, 54.99; H, 4.04; N, 3.49.

10-(3-Bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b]-[1,6]naphthyridine-1,9(5H,8H)-dione (12e). Substituting **10e**[11] for **6** without Et_3N provided **12e** (52%): MS (APCI(+)) m/z 393 $(M+H)^+$; MS (APCI(−)) m/z 391 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 2.38–2.60 (m, 2H), 3.18–3.26 (m, 2H), 4.00 (s, 2H), 4.45 (AB q, 2H), 4.95 (s, 1H), 7.14 (s, 1H), 7.16–7.28 (m, 2H), 7.41 (dd, 1H), 9.59 (s, 1H); Anal. Calcd for $C_{17}H_{14}N_2O_3FBr$: C, 51.93; H, 3.59; N, 7.12. Found: C, 51.68; H, 3.83; N, 7.10.

8-Benzyl-5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano-[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione (12f). Substituting **10f**[5] for **6** provided, after concentration of the reaction mixture and chromatography of

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the residue on silica gel using 5% MeOH in CH_2Cl_2, **12f** (39%). MS (ESI(+)) m/z 483 $(M + H)^+$, 505 $(M + NH_4)^+$; MS (ESI(−)) m/z 481 $(M-H)^-$; ^{1}H NMR ($CDCl_3$) δ3.06 (dd, 1H), 3.17 (d, 1H), 3.29 (d, 1 H), 3.39 (d, 1 H), 3.60 (d, 1 H), 3.68 (d, 1 H), 3.98 (d, 1 H), 4.13 (d, 1 H), 4.33 (AB q, 2 H), 5.09 (s, 1 H), 6.99 (t, 1 H) 7.26–7.37 (m, 6 H), 7.46 (dd, 1 H).

5-(3-Bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-pyrano[3,4-b]thiopyrano[4,3-e]pyridine-4,6(7H,9H)-dione (12g). Substituting **10g**[12] for **6** provided **12g** (39%): MS (ESI(+)) m/z 410 $(M + H)^+$, 427 $(M + NH_4)^+$; MS (ESI(−)) m/z 408 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ3.12 (d, 1H), 3.50 (d, 2H), 3.81 (dd, 1H), 4.03 (s, 2H), 4.48 (AB q, 2H), 4.97 (s, 1H), 7.20 (ddd, 1H), 7.26 (t, 1H), 7.40 (dd, 1H), 9.98 (bs, 1H); Anal. Calcd for $C_{17}H_{13}NO_3SFBr$: C, 49.77; H, 3.19; N, 3.41. Found: C, 49.43; H, 3.28; N, 3.21.

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