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Efficient synthesis of 2,6-disubstituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters

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Abstract

A general procedure is described for the preparation of 6-substituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters (6-substituted-5-hydroxy-3(2*H*)-pyridazinone-4-carboxylic acid ethyl esters). These compounds are shown to undergo selective alkylation at the 2-position in moderate to good yields (19–77%) to afford 2,6-disubstituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters (2,6-disubstituted-5-hydroxy-3(2*H*)-pyridazinone-4-carboxylic acid ethyl esters).
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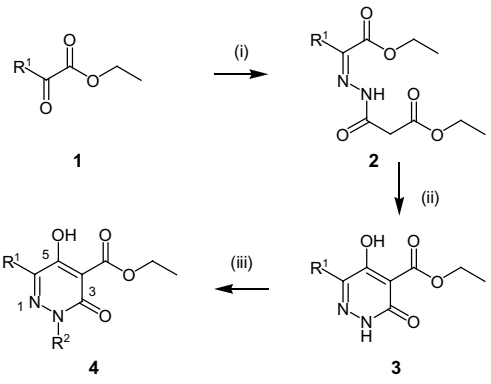
Keywords: Pyridazinone; Dieckmann cyclization; Selective alkylation; α-Keto-ester; α-Hydrazono-ester

3(2*H*)-Pyridazinones (3-oxo-2,3-dihydro-pyridazines) are an important class of biologically active molecules with many potential therapeutic applications. For example, these molecules have been previously reported to be platelet aggregation inhibitors,[1] α-adrenoceptor antagonists,[2] and antisecretory/antiulcer agents.[3] We previously reported a versatile synthesis to prepare 2,6-disubstituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters (**4**),[4] in which the 2-substituent was introduced in the first step of the synthetic sequence. Herein we report a novel synthesis of the same heterocycles that regioselectively introduces the 2-substituent in the final step, allowing facile variation at this position.

Our retrosynthetic strategy employed the condensation of a variety of α-keto-esters with commercially available hydrazinocarbonyl-acetic acid ethyl ester followed by an intramolecular Dieckmann cyclization to afford 6-substituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters (**3**). We envisioned the di-anions of these cyclized intermediates undergoing selective alkylation with electrophiles at the 2-position to provide the title compounds (**4**) (Scheme 1). Similar N-alkylations of



Scheme 1. Reagents and conditions: (i) Hydrazinocarbonyl-acetic acid ethyl ester, DMSO, 0.4% TFA (v/v), 70 °C, 16 h; (ii) NaOAc, DMF, 150 °C, 30 min, −2 h; (iii) NaH, DMF, 25 °C, 10 min followed by addition of electrophiles, then heating (if needed).

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3(2*H*)-pyridazinones have been reported to proceed in the presence of KOH under phase transfer conditions,[5] with metallic sodium in absolute ethanol,[6] and with NaH in DMF.[7] However, to the best of our knowledge, there are no reported examples of the regioselective alkylation of 3(2*H*)-pyridazinones containing unprotected hydroxyl groups at the 5-position.

We initially evaluated the feasibility of forming the cyclized intermediates (**3**). The condensation of aryl- and alkyl-α-keto-esters (**1**) with hydrazinocarbonyl-acetic acid ethyl ester proceeded in DMSO containing 0.4% TFA (v/v) at 70 °C overnight to afford the hydrazone intermediates **2a**–**h** (Table 1). In all cases, analysis of the reaction mixtures by LC–MS indicated two distinct products with the desired mass, presumably the *E* and *Z* hydrazone isomers. Purification by flash column chromatography yielded either a major hydrazone product (⩾10:1 mixture of isomers; suggesting isomerization on silica gel) or an inseparable, near-equal mixture of isomers.[12] Heating the purified hydrazones, either as inseparable mixtures or major isomers, in the presence of 2 equiv of NaOAc in DMF at 150 °C, afforded the desired cyclized intermediates **3a**–**h** in less than 2 h (Table 1). In cases where near-equal mixtures of hydrazone isomers were cyclized, the disappearance of both isomers was observed suggesting their in situ isomerization under the reaction conditions. In most cases, the products could be isolated in pure form by addition of aqueous 1 M HCl to the cooled reaction mixture followed by filtration of the resulting precipitate.

Table 1
Synthesis of 6-substituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters (**3**)[17,18]

Entry	R^1	Products **2**[a] (Isolated yield, %)[b]	Products **3** (Isolated yield, %)[c]
1		**2a** (85)	**3a** (80)
2[8]		**2b** (84)	**3b** (82)
3		**2c** (86)	**3c** (74)
4[9]		**2d** (20)[d]	**3d** (60)
5[10]		**2e** (73)	**3e** (51)
6		**2f** (33)[d]	**3f** (85)
7[11]		**2g** (65)	**3g** (95)[e]
8[9]		**2h** (68)	**3h** (38)

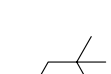
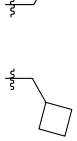
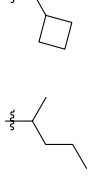
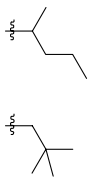
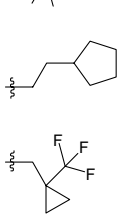
[a] ⩾10:1 Mixture of *E* and *Z*-isomers unless otherwise noted.
[b] Isolated yields after flash column chromatography.
[c] Isolated yields after precipitation from the crude reaction mixtures unless otherwise noted.
[d] Near-equal mixture of *E* and *Z*-isomers.
[e] Purified by concentrating the cooled reaction mixture and passing the residue through a plug of silica gel, eluting with 100% EtOAc, followed by concentration in vacuo to afford a brown solid.

With the cyclized intermediates (**3**) in hand, we investigated methods that would afford selective derivatization of the 2-position. Initial attempts to alkylate **3a** with isoamyl bromide using KOH and TBAB in benzene[5] failed to give any desired product. Alternatively, treatment of **3a** with 2.2 equiv of NaH in DMF followed by 1.1 equiv of isoamyl bromide and heating at 80 °C for 3 h afforded the N-alkylated product in 74% yield. The site of alkylation was confirmed by matching the ^{13}C NMR spectral data for the isolated product with the corresponding data for the identical 3(2*H*)-pyridazinone that was prepared through an unambiguous, independent synthesis.[13]

Encouraged by this result, we explored the ability of this method to selectively derivatize cyclized pyridazinones **3a**–**h** with a variety of alkylating agents (Table 2). The use of primary and secondary alkyl halides typically afforded the desired products in good yields, regardless of the R^1 substituent present on the pyridazinone ring (entries 1–12). A double alkylation product, presumably the enol ether, was observed (estimated yield of 80% based on LC–MS of the crude reaction mixture) from the alkylation of **3f** at 80 °C, contributing to the lower yield of the mono-alkylated pyridazinone (entry 6). However, the formation of this di-alkylated product was suppressed by performing the reaction at room temperature (entry 7). Utilizing the same conditions, the alkylation of **3g**, **3h**, and **3a** proceeded at room temperature in moderate yields (entries 8–10). Neopentyl iodide (entry 13) required a higher temperature and longer reaction time to give the coupled product and did so in reduced yield. Tosylates were tolerated as electrophiles (entries 14 and 15) with yields comparable to those obtained for similar alkyl halides. Pyridyl and benzyl bromides (entries 16–19) coupled, but with lower yields. Again, a double alkylation product, presumably the enol ether, was obtained during the alkylation of **3e** with benzyl bromide (entry 20), contributing to the lower yield of the mono-alkylated pyridazinone. The formation of this di-alkylated product was suppressed by utilizing benzyl chloride as the electrophile (entry 21).

In summary, we have discovered an efficient method for the synthesis of 2,6-substituted-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-4-carboxylic acid ethyl esters. Variation of substituents at the 6-position is achieved via the use of readily accessible α-keto-esters. Variation of the 2-position substituents, introduced in the last step by selective alkylation, allows significant diversification of the pyridazinone products due to the widely accessible set of available

Table 2
Alkylation of pyridazinones **3** with various electrophiles[19]

Entry	R^1	R^2	X	Temperature (°C)	Time (h)	Yield[a] (%)
1			Br	80	3	74
2			Br	80	3	76
3			Br	80	3	73
4			Br	80	1	61
5			Br	80	1	77
6			Br	80	1	20[b]
7			Br	25	6	61
8			Br	25	3	41
9			Br	25	2	53
10			I	25	16	87
11			Br	80	5	73
12			Br	80	5	61
13			I	110	16	25
14			OTs[14]	80	5	52
15			OTs[15]	80	7	35
16			Br[c]	80	5	46

(*continued on next page*)

Table 2 (*continued*)

Entry	R^1	R^2	X	Temperature (°C)	Time (h)	Yield[a] (%)
17			Br	80	5	47
18			Br	80	3	59
19			Br	80	3	61
20			Br	80	3	19
21			Cl	80	3	66

[a] Isolated yield unless otherwise noted.
[b] Estimated yield based on LC–MS of the crude reaction mixture.
[c] The hydrobromide salt of the alkylating agent, 2-bromomethyl-pyridine, was employed, necessitating the use of 3.2 equiv of NaH.

alkylating agents. Over-alkylation was observed in two cases but could be suppressed by either reducing the reaction temperature or using a weaker electrophile.

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9. The required α-keto-esters were obtained following a modified procedure from Zhu, L.; Wehmeyer, R.; Rieke, R. *J. Org. Chem.* **1991**, *56*, 1445. The corresponding alkyl zinc halide (1.2 mmol) was combined with CuI (1.2 mmol) in THF (3 mL) at −25 °C and stirred at 0 °C for 20 min. The mixture was cooled to −20 °C and chloro-oxo-acetic acid ethyl ester (1 mmol) was added. The mixture was warmed to 25 °C over 1 h. The reaction was quenched by the addition of saturated NH_4Cl and the product was extracted into Et_2O. Concentration in vacuo followed by flash column chromatography afforded the desired α-keto-ester.
10. The required α-keto-ester was obtained in 53% yield by following the procedure described by Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513 (replacing chloro-oxo-acetic acid methyl ester with chloro-oxo-acetic acid ethyl ester).
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14. The required tosylate was obtained by treatment of 2-cyclopentyl-ethanol with tosyl chloride (1.1 equiv), Et_3N (1.3 equiv) and DMAP (0.1 equiv) in CH_2Cl_2 (5 mL/mmol of the alcohol) at room temperature for 16 h. The mixture was washed with 1 M HCl and the organic phase passed through a plug of silica gel, eluting with 100% CH_2Cl_2. Concentration in vacuo afforded the desired tosylate.
15. The required tosylate was obtained from (1-trifluoromethyl-cyclopropyl)-methanol[16] under the same conditions described above.[14] However, it was necessary to heat the reaction mixture to 45 °C for 16 h.
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17. *Representative procedure for the preparation of compounds* **2**. [(2-Ethoxycarbonyl-acetyl)-hydrazono]-thiophen-2-yl-acetic acid ethyl ester (**2a**): Oxo-thiophen-2-yl-acetic acid ethyl ester (2 g, 10.86 mmol) was dissolved in anhydrous DMSO (54.3 mL). Hydrazinocarbonyl-acetic acid ethyl ester (1.75 g, 11.95 mmol) was added followed by TFA (0.2 mL). The flask was evacuated and filled with nitrogen. The mixture was heated at 70 °C for 16 h. Upon cooling to 25 °C, the mixture was diluted with EtOAc and washed with 0.1 M HCl (three times). The organic phase was further washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash column chromatography (10–15% EtOAc/hexanes) afforded **2a**

(2.89 g, 9.25 mmol, 85% yield) as a faintly yellow oil that crystallized to a beige, waxy solid upon standing. ^{1}H NMR (400 MHz, $CDCl_3$, 10:1 mixture of isomers observed, data for major isomer reported): $\delta = 1.28$ (t, 3H, $J = 6.9$ Hz), 1.47 (t, 3H, $J = 7.1$ Hz), 3.80 (s, 2H), 4.22 (q, 2H, $J = 7.1$ Hz), 4.47 (q, 2H, $J = 7.1$ Hz), 7.03 (t, 1H, $J = 4.2$ Hz), 7.33 (d, 1H, $J = 4.4$ Hz), 7.60 (d, 1H, $J = 3.7$ Hz), 11.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 14.3, 40.7, 61.5, 62.9, 127.5, 128.1, 129.0, 130.9, 138.2, 160.5, 166.9, 168.5. MS (ESI): $m/z = 313.1$ [M+H$^+$] (100%). Anal. Calcd for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97. Found: C, 49.83; H, 5.38; N, 9.01.

18. *Representative procedure for the preparation of compounds* **3**. 5-Hydroxy-3-oxo-6-thiophen-2-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (**3a**): [(2-Ethoxycarbonyl-acetyl)-hydrazono]-thiophen-2-yl-acetic acid ethyl ester (**2a**) (1 g, 3.2 mmol) was dissolved in DMF (16 mL) and NaOAc (0.525 g, 2.55 mmol) was added. The flask was evacuated and filled with nitrogen. The mixture was heated at 150 °C for 30 min. Upon cooling to 25 °C, 1 M HCl (32 mL) was added and the product precipitated. After stirring for 5 min, the solid was collected by filtration, washed with 1 M HCl and dried in vacuo for 16 h to afford **3a** as a light beige powder (0.68 g, 2.55 mmol, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.29$ (t, 3H, $J = 7.3$ Hz), 4.30 (q, 2H, $J = 7.3$ Hz), 7.12 (dd, 1H, $J = 5.4$, 3.8 Hz), 7.62 (d, 1H, $J = 3.8$ Hz), 7.80 (d, 1H, $J = 4.6$ Hz), 13.00 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.0$, 61.6, 107.6, 127.5, 127.8, 127.8, 135.7, 137.1, 158.3, 158.5, 166.2. MS (ESI): $m/z = 267.1$ [M+H$^+$] (100%), 533.2 [2M+H$^+$] (25%). Anal. Calcd for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.52. Found: C, 49.48; H, 4.09; N, 10.67.

19. *Representative procedure for the preparation of compounds* **4**. 5-Hydroxy-2-(3-methyl-butyl)-3-oxo-6-thiophen-2-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (Table 2, entry 1): 5-Hydroxy-3-oxo-6-thiophen-2-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (**3a**) (0.2 g, 0.751 mmol) was suspended in anhydrous DMF (3.75 mL). A 60% suspension of NaH in mineral oil (0.066 g, 1.65 mmol) was added. The mixture was stirred in a sealed vial for 10 min with occasional venting. 1-Bromo-3-methyl-butane (0.125 g, 0.826 mmol) was added and the mixture stirred at 80 °C for 3 h. Upon cooling to 25 °C, the mixture was diluted with EtOAc and washed with 1 M HCl (three times). The organic phase was further washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash column chromatography (100% CH_2Cl_2) afforded the desired product (Table 2, entry 1, 0.186 g, 0.553 mmol, 74% yield), as a yellow waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (d, 6H, $J = 6.2$ Hz), 1.50 (t, 3H, $J = 7.1$ Hz), 1.64–1.76 (m, 3H), 4.22 (t, 2H, $J = 7.1$ Hz), 4.53 (q, 2H, $J = 7.0$ Hz), 7.10 (dd, 1H, $J = 4.9$, 3.6 Hz), 7.38 (d, 1H, $J = 4.0$ Hz), 7.88 (d, 1H, $J = 4.6$ Hz), 13.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.3$, 22.6, 25.9, 37.3, 50.8, 63.1, 103.2, 127.3, 127.6, 128.2, 134.8, 135.8, 156.5, 163.7, 171.4. MS (ESI): $m/z = 337.2$ [M+H$^+$] (100%). Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 57.13; H, 6.38; N, 8.49.