Convenient and Efficient Synthesis of Pyrazole-Based DHODase Inhibitors from 3-Aryl-4-cyanosydnone

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Abstract: Pyrazole-based DHODase inhibitors have been efficient and conveniently synthesized in 51–60% yield from 3-(*p*-aryl)-4-cyanosydnone via regioselective 1,3-diploar cycloaddition followed by an amidation and a Ritter reaction.

Key words: sydnones, 1,3-dipolar cycloaddition, propargylic ester, pyrazole, DHODase inhibitors

Helicobacter pylori is a gram-negative microaerophilic bacterium that infects up to 50% of the world's human population.[1] *Helicobacter pylori* resides in the acidic surroundings of the stomach, utilizing high urease enzyme activity to provide a locally alkaline environment. Inhibition of a key enzyme of the *de novo* pyrimidine biosynthetic pathway, dihydroorotate dehydrogenase[2] (DHODase), could selectively kill this *H. pylori* bacterium without affecting human cells or other bacterial species.[3] In 2000, Copeland et al.,[3] reported that pyrazole-based compounds **1** are potent and selective inhibitors of the dihydroorotate dehydrogenase of *H. pylori* (*H. pylori* DHODase) but do not inhibit the cognate enzymes from gram-positive bacteria or humans (Figure 1).

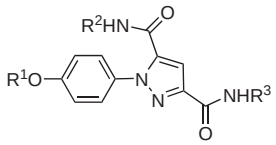

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Figure 1

There have been a few methods reported for the synthesis of the carboethoxy-pyrazole core. Ashton et al.[4] reported a regioselective synthesis of 1*H*-pyrazole-5-carboxylate from 2,4-diketo esters, but, in order to direct the initial attack of the arylhydrazine on the 4-carbonyl, the 2-carbonyl had to be protected. The pyrazole monoacid/monofuran cores were successfully synthesized by solution phase synthesis.[5] The furan was oxidized to a carboxylic acid with sodium periodate and ruthenium(III) chloride or potassium permanganate to provide the desired pyrazole acid/ester product.[6] A subsequent amidation step results in the pyrazole DHODase inhibitor **1**, which can be prepared in less than 50% yield. The core pyrazole **1** was also prepared on solid support, however, this methodology is generally performed only on a small scale.[7] We report the regioselective 1,3-dipolar cycloaddition of 3-aryl-4-cyanosydnone (**2** or **7**) to propargylic esters using the highly hindered diphenylmethyl propiolate. This provided only the diphenylmethyl 5-cyano-1-aryl-1*H*-pyrazole-3-carboxylate **5d** or **9** without any of the regioisomer **6**.[8] Subsequent amination and Ritter reactions provided a convenient and efficient access to pyrazole DHODase inhibitors.

Sydnones[9] undergo smooth cycloaddition with propargylic esters to give pyrazoles.[10–15] The reaction involves a 1,3-dipolar cycloaddition of the sydnones, which behave as cyclic azomethine imines. The initially formed cycloadducts readily release carbon dioxide to produce a mixture of five-membered regioisomeric pyrazoles. To optimize the ratio of regioisomers (**5**/**6**), 3-(*p*-ethoxyphenyl)-4-cyanosydnone **2** was treated with unsymmetrically substituted propargylic esters in chlorobenzene at reflux for 48 hours (Scheme 1). The reaction pathway involves a cycloaddition to a sydnone to give two N-bridged intermediates **3** and **4**. The regiochemistry of cycloaddition should be controlled by the steric effect of the bulky substituent R^2 of propargylic esters and the 4-cyano group of sydnone **2**. As the size of the R^2 substituent of propargylic esters was increased (Et, CH_2Ph, and *t*-Bu), the regioisomeric ratio (**5**/**6**) improved from 57:43 to 78:22 (Table 1). The structure assignment of the regioisomers (**5**/**6**) was made on the basis of their characteristic ^1H NMR spectrum. Particular attention was given to the chemical shift of the pyrazole proton. The ring proton in the 3-carboethoxy-substituted isomers (**5a**–**d**) appeared 1.2–1.3 ppm upfield relative to the 4-carboethoxy-substituted isomer (**6a**–**c**). However, when 3-(*p*-ethoxyphenyl)-4-cyanosydnone (**2**) was reacted with diphenylmethyl propiolate ($R^2 = CHPh_2$), only a single product, diphenylmethyl 5-cyano-1-(*p*-ethoxyphenyl)-1*H*-pyrazole-3-carboxylate (**5d**), was identified and isolated in 85% yield.

As a result, 3-aryl-4-cyanosydnones **2** and **7** were treated with diphenylmethyl propiolate in chlorobenzene at reflux (ca. 130 °C) and the progress of the reaction was monitored by carbon dioxide evolution without isolating the bicyclic intermediate **8** (Scheme 2). After work-up

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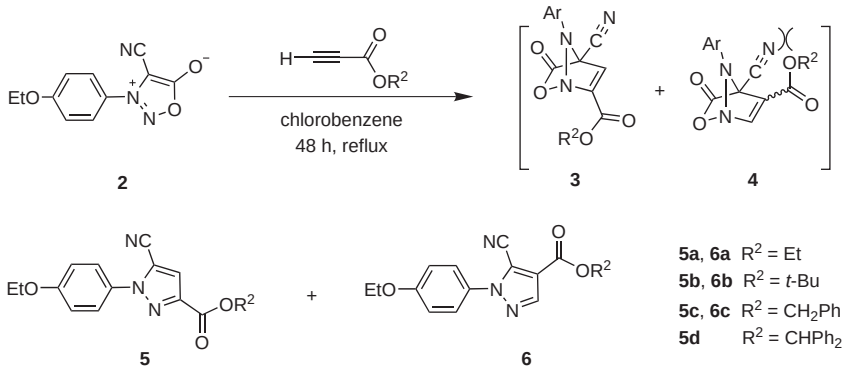


Scheme 1

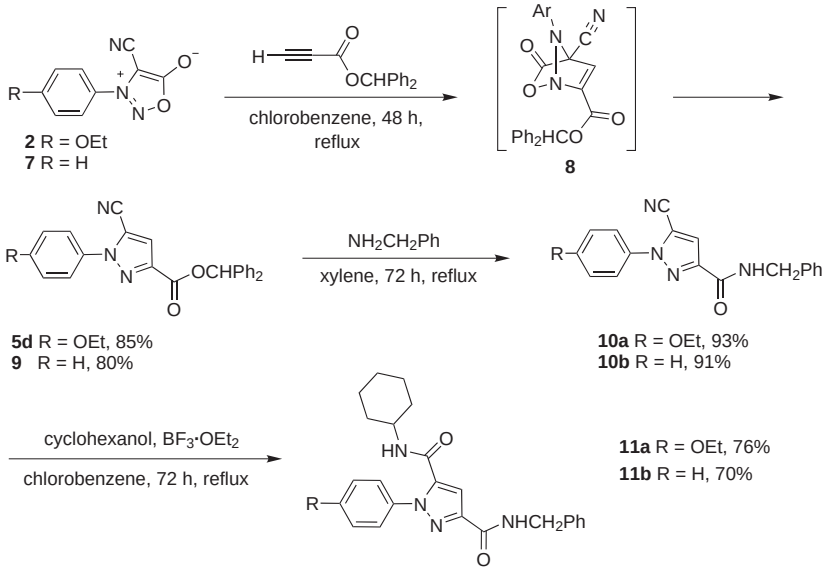
Table 1 1,3-Dipolar Cycloaddition of the Sydnone[a]

Entry	R^2	Regioisomeric ratio (%)[a]		Isolated yield of **5** and **6** (%)
		5a–d	**6a–c**	
1	Et	58	42	80
2	*t*-Bu	78	22	79
3	CH_2Ph	57	43	76
4	$CHPh_2$	ca. 100	–[c]	85[d]

[a] Sydnone **2**, unsymmetrically substituted propiolate, chlorobenzene, reflux, 48 h.
[b] The **5**/**6** ratios were determined by ^1H NMR spectroscopy.
[c] Not detected.
[d] Only **5d** was isolated.

and column chromatography, diphenylmethyl 5-cyano-1*H*-pyrazole-3-carboxylates **5d** and **9** were obtained as the single products in 85% and 80% yields, respectively. The carboxylic ester **5d** and acid **9** were directly converted to the corresponding secondary amides **10a** and **10b** in excellent yields (93% and 91%, respectively)[16,17] by treatment with benzylamine. We attempted to perform the Ritter reaction by treating compounds **10a** and **10b** with cyclohexanol in refluxing formic acid,[18] however, the resultant reaction mixture was complex and only provided a small amount of the expected N-alkylation products. The Ritter reaction was modified[19,20] by using boron trifluoride as a catalyst under aprotic and non-aqueous conditions. Compound **10a** or **10b** was added to a solution of cyclohexanol and boron trifluoride etherate in chlorobenzene and heated at reflux for 72 hours. After work-up and purification, the corresponding pyrazole DHODase inhibitor analogues **11a** and **11b** were obtained in 70% and 76% yields, respectively (Scheme 2).

In conclusion, we have developed an efficient method to control the regioselectivity of the 1,3-dipolar cycloaddition of bulky diphenylmethyl propiolate with 3-aryl-4-cyanosydnone (**2** or **7**), which was applicable to the synthesis of DHODase inhibitor analogues **11a** and **11b**. The cyclized 5-cyano-1-aryl-1*H*-pyrazole-3-carboxylate (**5d** or **9**) was obtained as a single isomer. After amidation and Ritter reaction, compounds **5d** and **9** were converted to compounds **11a** and **11b** in 51% and 60% yields, respectively, from 3-(*p*-aryl)-4-cyanosydnone **2** and **7**.



Scheme 2 Synthesis of the pyrazole-based DHODase inhibitors.

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(8) **1,3-Dipolar Cycloaddition; General Procedure.** Ethyl, *tert*-butyl, benzyl, or diphenylmethyl propiolate (0.25 g, 2.0 equiv) was added to a solution of 3-(*p*-ethoxyphenyl)-4-cyanosydnone (**2**, 0.23 g, 1.0 equiv) in chlorobenzene (10 mL) and heated to reflux under N_2 for 48 hours. After the reaction was complete, the reaction mixture was concentrated under reduced pressure to remove chlorobenzene. The residue was dissolved in CH_2Cl_2 (2.0 mL) and purified by gravity column chromatography (silica, EtOAc–hexanes, 15:85) to provide the corresponding products **5a**–**d** and **6a**–**c**.
5d: IR (KBr): 3031 (s), 2980 (s), 2229 (m, CN), 1726 (m, C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (t, *J* = 10.4 Hz, 3 H, CH_3), 3.98 (q, *J* = 10.4 Hz, 2 H, CH_2), 6.92 (d, *J* = 7.7 Hz, 2 H, ArH), 7.08 (s, 1 H, Ph_2CH), 7.15 (s, 1 H, pyrazole-H), 7.20–7.35 (m, 8 H, ArH), 7.41 (d, *J* = 7.7 Hz, 2 H, ArH), 7.47–7.54 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.66, 63.95, 77.92, 110.11, 115.15, 115.65, 117.82, 124.92, 124.97, 127.22, 128.15, 128.57, 128.62, 130.95, 139.53, 139.59, 144.21, 159.65, 159.99; Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.65; H, 5.12; N, 9.96.
9: IR (KBr): 3020 (s), 2985 (s), 2932 (m, C=N), 1736 (m, C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.90 (d, *J* = 7.7 Hz, 2 H, ArH), 7.07 (s, 1 H, Ph_2CH), 7.13 (s, 1 H, pyrazole-H), 7.21–7.37 (m, 8 H, ArH), 7.41 (d, *J* = 7.7 Hz, 2 H, ArH), 7.47–7.54 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 77.89, 110.11, 115.13, 115.64, 117.80, 124.90, 124.95, 126.45, 127.19, 128.15, 128.56, 128.59, 130.92, 139.49, 139.55, 144.20, 159.97; Anal. Calcd for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08. Found: C, 75.92; H, 4.56; N, 11.12.

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(17) **Amidation; General Procedure.** Benzylamine (8.0 mmol) was added to a solution of 3-aryl-4-cyanosydnone (**5d** or **9**, 2.0 mmol) in xylene (15 mL) and the resulting solution was heated to reflux for 72 h under N_2. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove xylene. The residue was dissolved in CH_2Cl_2 (2.0 mL) and purified by column chromatography (silica, EtOAc–hexanes, 4:1) to provide the corresponding product **10a** or **10b** in 93% and 91% yields, respectively.
10a: Mp 142–144 °C; IR (KBr): 3331 (s, NH), 2237 (m, CN), 1655 (m, C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (t, *J* = 6.8 Hz, 3 H, CH_3), 4.10 (q, *J* = 6.8 Hz, 2 H, CH_2), 4.44 (d, *J* = 6.3 Hz, 2 H, NCH_2), 7.13 (d, *J* = 9.0 Hz, 2 H, ArH), 7.20–7.26 (m, 1 H, ArH), 7.29–7.31 (m, 4 H, ArH), 7.66 (s, 1 H, pyrazole-H), 7.71 (d, *J* = 9.0 Hz, 2 H, ArH), 9.14 (t, *J* = 6.3 Hz, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.83, 43.51, 65.01, 111.99, 116.38, 117.03, 117.28, 126.94, 128.15, 128.67, 169.59, 131.97, 140.63, 148.63, 160.70, 160.93; Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.40; H, 5.35; N, 16.02.
10b: Mp 95–96 °C; IR (KBr): 3281 (s, NH), 2232 (m, CN), 1649 (m, C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.45 (d, *J* = 6.2 Hz, 2 H, NCH_2), 7.20–7.27 (m, 1 H, ArH), 7.29–7.31 (m, 4 H, ArH), 7.55–7.65 (m, 3 H, ArH), 7.77 (s, 1 H, pyrazole-H), 7.79 (d, *J* = 9.0 Hz, 2 H, ArH), 9.18 (t, *J* = 6.2 Hz, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 43.52, 11.94, 116.90, 117.83, 125.17, 128.18, 128.68, 129.61, 131.05, 131.21, 139.03, 140.55, 148.98, 160.90; Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.54; H, 4.74; N, 18.44.

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(20) **Ritter Reaction; General Procedure** A solution of cyclohexanol (4.0 mmol) and $BF_3{\cdot}OEt_2$ (4.0 mmol) in chlorobenzene was stirred at r.t. for 0.5 h. Compound **10a** or **10b** (1.0 mmol) was added to the reaction mixture, which was heated to reflux for 72 h. The solution was neutralized with Et_3N and the reaction mixture was concentrated under reduced pressure to remove chlorobenzene. The residue was dissolved in CH_2Cl_2 (2.0 mL) and purified by column chromatography (silica, EtOAc–hexanes, 1:4) to provide the corresponding product **11a** or **11b** as light-yellow solids in 76% and 70% yields, respectively.
11a: Mp 146–148 °C; IR (KBr); 3322 (s, NH), 2929 (m), 2852 (m), 1647 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.09–1.21 (m, 4 H), 1.33 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.52–1.73 (m, 6 H), 3.57 (m, 1 H, NCH), 4.09 (q, *J* = 10.1 Hz, 2 H, CH_2), 4.42 (d, *J* = 5.9 Hz, 2 H, NCH_2), 6.99 (d, *J* = 8.6 Hz, 2 H, ArH), 7.22 (d, *J* = 8.6 Hz, 2 H, ArH), 7.30 (d, *J* = 3.7 Hz, 4 H, ArH), 7.33 (s, 1 H, ArH), 7.36 (s, 1 H, pyrazole-H), 8.47 (d, *J* = 7.7 Hz, 1 H, NH), 8.89 (t, *J* = 5.9 Hz, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.02, 25.06, 25.55, 32.45, 42.47, 48.54, 63.88, 108.50, 114.58, 126.68, 127.15, 127.72, 128.66, 133.18, 139.35, 140.10, 146.33, 158.28, 158.72,

161.22; Anal. Calcd for $C_{26}H_{30}N_4O_3$: C, 69.93; H, 6.77; N, 12.55. Found: C, 69.79; H, 6.85; N, 12.40.

11b: Mp 142–143 °C; IR (KBr): 3281 (s, NH), 2927 (s), 1644 (m, C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.07–1.29 (m, 4 H), 1.53–1.75 (m, 6 H), 3.59 (m, 1 H, NCH), 4.44 (d, *J* = 6.1 Hz, 2 H, NCH_2), 7.20–7.25 (m, 2 H, ArH), 7.30 (d, *J* = 4.2 Hz, 4 H, ArH), 7.42–7.46 (m, 4 H, ArH), 7.51 (s, 1 H, pyrazole-H), 8.54 (d, *J* = 7.8 Hz, 1 H, NH), 8.92 (t, *J* = 6.1 Hz, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.91, 26.39, 33.26, 43.37, 49.49, 109.67, 126.01, 128.08, 128.60, 129.56, 129.67, 130.04, 140.36, 140.86, 140.96, 147.57, 159.24, 162.10; Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.42; H, 6.60; N, 13.77.