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Synthesis of 6-Substituted-4-Hydroxy-2-pyridinones via Intramolecular Ketene Trapping of Functionalized Enamine-Dioxinones

Bhavesh H. Patel,[†] Andrew M. Mason,[‡] and Anthony G. M. Barrett*[,†]

Department of Chemistry, Imperial College, London SW7 2AZ, U.K., and GlaxoSmithKline R&D, Gunnels Wood Road, Stevenage, Herts SG1 2NY, U.K.

agm.barrett@imperial.ac.uk

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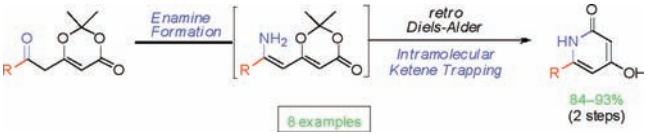
ABSTRACT



The synthesis of various 6-substituted-4-hydroxy-2-pyridinones is reported. The functionalized keto-dioxinones were constructed via a diethylzinc mediated crossed Claisen condensation reaction and subsequent enamine formation, thermolysis, and cyclization−aromatization providing the pyridinone unit.

The pyridinone structural motif is present in a range of natural products[1] and biologically active molecules,[2] with 6-substituted-4-hydroxy-2-pyridinones being key intermediates in their synthesis. Notably these heterocycles are used as templates in drug discovery,[2,3] used in the total synthesis of natural products including novel human chymase inhibitors produced by *Penicillium sp.*,[4] and employed in the preparation of related heteroaromatics.[5]

The synthesis of 4-hydroxy-6-methyl-2-pyridinone was first reported by Collie via treatment of triacetic lactone (4-hydroxy-6-methyl-2-pyrone) with ammonia.[6] Soon after, the same pyridinone was synthesized using a condensation reaction between a malonic ester and a β-aminocrotonate followed by decarboxylation.[7] Since then, several other routes with varying yields have been reported for the construction of 6-substituted-4-hydroxy-2-pyridinones. These include reactions of functionalized enamines with carbon suboxide (C_3O_2),[8] condensation of ethyl acetoacetate with benzonitrile followed by cyclization,[9] acid-mediated rearrangement of 2-amino-4-pyrones,[10] and reaction of Schiff's bases with diphenyl malonate and subsequent retro-ene reaction.[11]

Following on from our preceding work utilizing dioxinones,[12] we envisaged a versatile route toward 6-substituted-4-hydroxy-2-pyridinones **1** via cyclization of enamine-keto-ketenes **2** (Scheme 1). Such reactive intermediates **2** should be available from enamine-dioxinones **3**, which could be prepared from functionalized keto-dioxinones

[†] Imperial College.
[‡] GlaxoSmithKline R&D.

(1) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168.
(2) Groutas, W. C.; Stanga, M. A.; Brubaker, M. J.; Huang, T. L.; Moi, M. K.; Carroll, R. T. *J. Med. Chem.* **1985**, *28*, 1106.
(3) Demuner, A. J.; Valente, V. M. M.; Barbosa, L. C. A.; Rathi, A. H.; Donohoe, T. J.; Thompson, A. L. *Molecules* **2009**, *14*, 4973.
(4) (a) Shimatani, T.; Hosotani, N.; Ohnishi, M.; Kumagai, K.; Saji, I. *J. Antibiot.* **2006**, *59*, 29. (b) Vegi, S. R.; Boovanahalli, S. K.; Sharma, A. P.; Mukkanti, K. *Tetrahedron Lett.* **2008**, *49*, 6297.
(5) (a) Findlay, J. A.; Krepinsky, J.; Shum, F. Y.; Tam, W. H. J. *Can. J. Chem.* **1976**, *54*, 270. (b) Hajdok, S.; Conrad, J.; Leutbecher, H.; Strobel, S.; Schleid, T.; Beifuss, U. *J. Org. Chem.* **2009**, *74*, 7230.
(6) (a) Collie, J. N. *J. Chem. Soc.* **1891**, *59*, 607. For other examples using a similar procedure, see:(b) Wislicenus, W.; Schöllkopf, K. *J. Prakt. Chem.* **1917**, *95*, 269. (c) Kato, T.; Yamamoto, Y.; Takeda, S. *Chem. Pharm. Bull.* **1973**, *21*, 1047. (d) Giddens, A. C.; Nielsen, L.; Boshoff, H. I.; Tasdemir, D.; Perozzo, R.; Kaiser, M.; Wang, F.; Sacchettini, J. C.; Copp, B. R. *Tetrahedron* **2008**, *64*, 1242.
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(8) Ziegler, E.; Hradetzky, F. *Monatsh. Chem.* **1964**, *95*, 1247.
(9) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(10) Kato, T.; Kubota, Y.; Tanaka, M.; Takahashi, H.; Chiba, T. *Heterocycles* **1978**, *9*, 841.
(11) Ito, K.; Miyajima, S. *J. Heterocyclic Chem.* **1992**, *29*, 1037.
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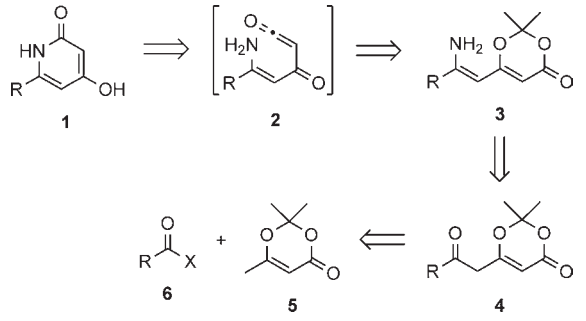
4, which in turn could be generated from the parent dioxinone **5** and commercially available acids **6** via *C*-acylation of the derived enolate.

Scheme 1. Retrosynthetic Strategy

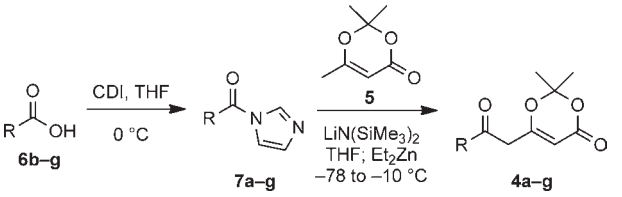


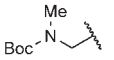
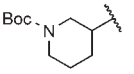
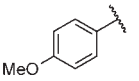
Herein, we report our initial results in the facile three-step synthesis of diversely substituted pyridinones **1** using a key intramolecular ketene trapping−cyclization−aromatization sequence.

The procedure for our previously reported synthesis of methyl keto-dioxinone **4a**[13] (Scheme 2) using a crossed Claisen condensation reaction was applied to the synthesis of other derivatives **4b**−**g** (Table 1). Acids **6b**−**g** were allowed to react with carbonyl diimidazole (CDI) at 0 °C to give imidazolides **7b**−**g** in 76−96% yield.[14] The lithium enolate of dioxinone **5** was treated with diethylzinc and following transmetalation,[15] to presumably a less basic alkylzincate species, allowed to react with imidazolides **7b**−**g** at −10 °C to provide the functionalized keto-dioxinones in 58−73% yield with no byproduct formation (Table 1). We successfully synthesized dioxinones with an isobutyl **4b** (entry 1) and benzyloxymethyl **4c** (entry 2) ketone. Furthermore, the protected amino-methyl-ketone **4d** (entry 3) and piperidine-3-ketone **4e** (entry 4) derivatives were efficiently applied in this chemistry. The 4-methoxy-phenyl **4f** (entry 5) and the inherently reactive furanyl **4g** (entry 6) derivatives were slightly less efficient in the *C*-acylation step. However, subsequent heterocyclization was comparably efficient to the other examples.

Initially we investigated the generation of methyl enamine-dioxinone **3a** from keto-dioxinone **4a** (Scheme 2). It was hoped that the dioxinone moiety would be stable upon treatment with ammonium acetate as this had previously been used to form β-enamine-esters from β-keto-esters.[16] Fortunately, in this case, heating was not required and

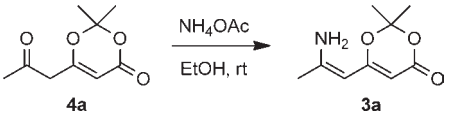
Table 1. Acyl Imidazolide Formation Followed by Claisen Condensation with Dioxinone **5**



entry	6	R	yield of 7[a] (%)	yield of 4[b] (%)
1	**b**		90	73
2	**c**		84	63
3	**d**		90	58
4	**e**		96	73
5	**f**		76	67
6	**g**		77	65

[a] Isolated yield of crude **7** following aqueous workup. [b] Isolated yield following chromatography.

Scheme 2. Formation of Enamine-Dioxinone **3a**



complete conversion to the methyl enamine-dioxinone was achieved with ammonium acetate in ethanol at room temperature.[17]

Keto-dioxinones **4a**−**h**[18] were successfully converted to the enamine-dioxinone derivatives **3a**−**h** (Scheme 3).[19] Direct thermolysis of these intermediates proceeded by addition to toluene at reflux to generate the

(13) Patel, B. H.; Mason, A. M.; Patel, H.; Coombes, R. C.; Ali, S.; Barrett, A. G. M. *J. Org. Chem.* **2011**, *76*, 6209.

(14) Compounds **7b**−**g** were characterized by ^{1}H and ^{13}C NMR spectroscopy, and HRMS for those that were stable, and then used immediately in the next step; commercially available **7a** was used.

(15) Morita, Y.; Masaaki, S.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

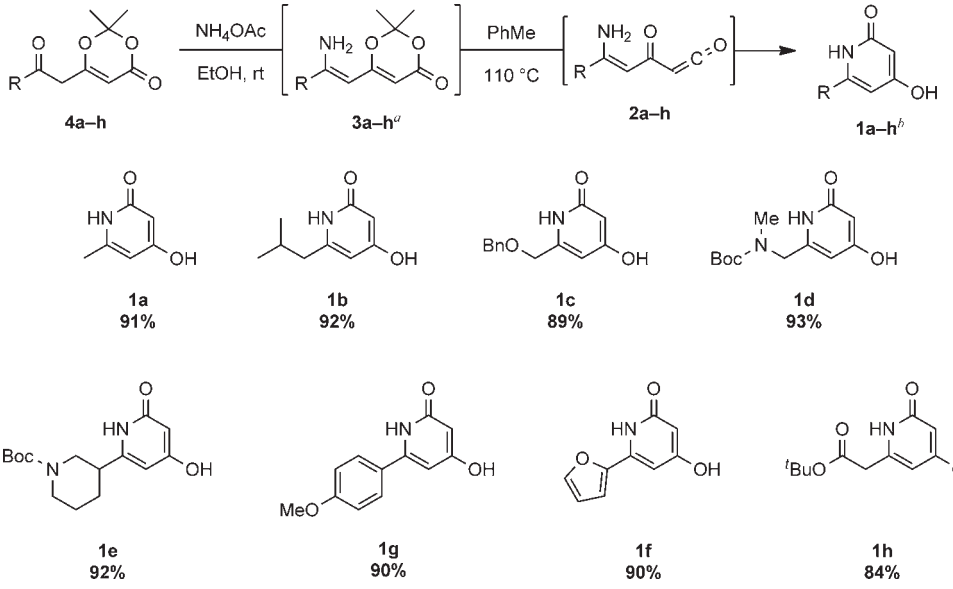
(16) (a) Perlman, N.; Etinger, M.; Niddam-Hildesheim, V.; Abramov, M. *WO Patent* **2009**, 064476. (b) Tang, W.; Wu, S.; Zhang, X *J. Am. Chem. Soc.* **2003**, *125*, 9570.

(17) Formation of the enamine-dioxinones was confirmed by ^{1}H NMR spectroscopy in d_6-acetone; enamine-dioxinones were not purified by chromatography due their instability and hydrolysis back to the keto-derivative in the presence of silica.

(18) For procedure to prepare keto-dioxinone **4h**, see analogous procedure for allyl ester keto-dioxinone: Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.

(19) It was essential to store the enamine-dioxinones in the freezer and use as soon as possible in the subsequent step. A'one-pot' procedure using keto-dioxinone **4a** and NH_4OAc in PhMe (0.012 M) was attempted; however, this gave a mixture of pyridinone and pyranone products (2:1, 84%).

Scheme 3. Enamine Formation and Pyridinone Synthesis via Intramolecular Ketene Trapping[a]



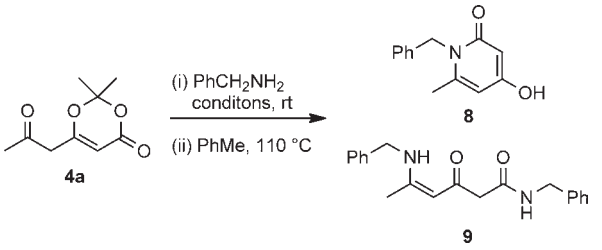
[a] Analysis by ^{1}H NMR spectroscopy showed disappearance of the CH_2 protons (singlet peak at ~4.1−3.3 ppm) α to the ketone, and the appearance of the CH enamine proton (singlet peak at ~4.6−4.4 ppm), and an upfield shift of the dioxinone CH proton (singlet peak from ~5.5−5.3 ppm to ~4.9−4.7 ppm).[b] Isolated yield.

enamine-acyl-ketenes **2a**−**h** *in situ*,[20] which underwent intramolecular cyclization to give the aromatic pyridinones **1a**−**h** (Scheme 3). High dilution was essential to avoid intermolecular reaction, and slow addition to toluene at reflux was optimal in ensuring clean conversion.[21]

The pyridinones **1a**−**h** were isolated as solids following trituration, without the need for chromatography, in 84−93% yield (Scheme 3). Protected alcohol, amine, and ester functionalities were all successfully applied in the transformation (see **1c**−**e,h**) thereby allowing for the incorporation of alternative groups away from the pyridinone ring, in analogue synthesis.

Keto-dioxinone **4a** was allowed to react with benzylamine in a similar fashion.[22] However, under reaction conditions in ethanol used in the synthesis of enamines **3**, subsequent trapping gave only acyclic adduct **9** and none of the desired *N*-benzyl-pyridinone **8** (Table 2, entry 1). Even with the use of stoichiometric amounts of the amine (Table 2, entries 2 and 3), byproduct **9** was obtained presumably due to the presence of water in the reaction mixture. This was overcome by preparation of the enamine in the presence of molecular sieves in dichloromethane and subsequent intramolecular trapping, which gave the pyridinone **8** in 75% yield over the two steps (Table 2, entry 4).

Table 2. Synthesis of *N*-Benzyl-4-hydroxy-6-methyl-2-pyridinone **8**



entry	$PhCH_2NH_2$ (equiv)	conditions	yield of **8**[a] (%)	yield of **9**[a] (%)
1[b]	2.5	EtOH	0	82
2[b]	1.0	EtOH	0	45
3[c]	1.0	–	0	48
4[b,d]	1.0	MS 4 Å, CH_2Cl_2	75	0

[a] Isolated yield following trituration with Et_2O. [b] Initial treatment with benzylamine and subsequent thermolysis. [c] Addition of **4a** to a mixture of $PhCH_2NH_2$ and PhMe at reflux. [d] EtOAc was added to solubilize the enamine dioxinone.

In conclusion, we have extended the use of dioxinones to develop a general methodology for the synthesis of 6-substituted-4-hydroxy-2-pyridinones in 45−64% overall yield from inexpensive starting materials, with only one purification required. Enamine-dioxinones were successfully used as cyclization precursors containing both electrophilic and nucleophilic entities. Further applications are in

(20) Hyatt., J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

(21) Typical experimental procedure: Keto-dioxinone **4a**−**h** (0.60 mmol) and NH_4OAc (0.23 g, 3.00 mmol) were stirred in absolute EtOH (2.5 mL). After 2−3 h, the solvent was evaporated, EtOAc (10 mL) added, and the resultant solid filtered. The solvent was evaporated to provide crude enamine-dioxinone **3a**−**h**, which in PhMe (5 mL) were added to PhMe (50 mL) at reflux over 30 min. After 4 h, the solvent was evaporated and the residue triturated with Et_2O (25 mL) to provide the desired pyridinone **1a**−**h**.

(22) We thank one of the referees for suggesting this experiment.

progress toward the synthesis of alternative pyridinone derivatives and will be reported in due course.

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Supporting Information Available. Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra corresponding to all isolated and purified compounds. This material is available free of charge via the Internet at http://pubs.acs.org.