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Highly selective synthesis of 2-substituted-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid derivatives using a novel protected dihydroxyfumarate ☆

Spencer D. Dreher,* Norihiro Ikemoto, Venita Gresham, Jinchu Liu, Peter G. Dormer, Jaume Balsells, David Mathre, Thomas J. Novak and Joseph D. Armstrong, III

Department of Process Research, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900, USA

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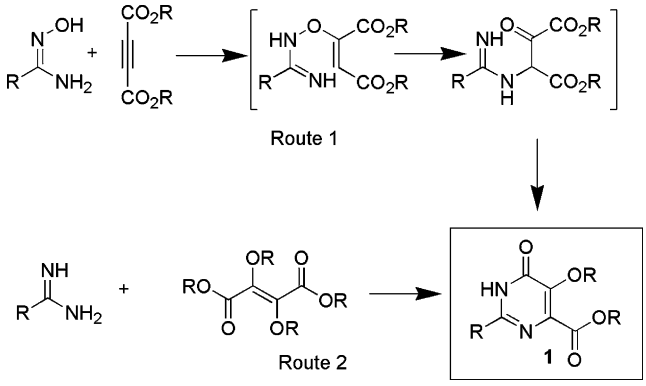
Abstract—A high yielding (50–96%) route to 2-substituted-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid derivatives has been developed using a rationally designed dihydroxyfumarate derivative. The fully unprotected pyrimidinone heterocycle was prepared in quantitative yield upon treatment with HCl.

Pyrimidines and pyrimidinones are diazine heterocycles that are important because of their well-documented biological activity,[1] and new or improved syntheses of these heterocycles are important to the field of drug design. 2-Substituted-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid (pyrimidinone) derivatives, **1**, are a class of compounds for which no simple, high-yielding general synthetic methodologies have been developed. The existing syntheses of these densely functionalized heterocycles suffer from very low yields due to poor regio- and chemoselectivity.[2,3] In the most developed synthetic route (Scheme 1, route 1), the desired pyrimidinones were prepared by the Michael reaction of N-hydroxy amidines and acetylynic diesters, followed by thermal Claisen rearrangement and amide condensation, typically in 30–40% overall yield.[2] Another route (route 2) that has been reported involves the condensation of dihydroxyfumarate derivatives with amidines to give the desired functionalized pyrimidinones.[3] The yields in this methodology are also reported to be low, but no systematic study has been applied to this chemistry.



Scheme 1.

We were interested in further examining the synthetic potential in the latter reaction sequence, the combination of dihydroxyfumarate derivatives with amidines. One primary concern was the regio-control in these condensations, as the fumarates' four contiguous electrophilic carbons could conceivably lead to five-, six- and seven-membered ring products. In addition, it has been reported that dihydroxyfumarate derivatives can fragment under basic conditions.[4] With these concerns in hand, we began to study the condensation of the readily available dimethoxy dihydroxyfumarate **3a**[5] with benzamidine HCl **2a**. When **3a** is mixed in MeOH at room temperature with benzamidine and NaOMe (as well as DBU or Et_3N), a trace amount (<10% by LCMS

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* Corresponding author. Tel.: +1-732-594-7669; fax: +1-732-594-1499; e-mail: spencer_dreher@merck.com

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analysis) of desired pyrimidinone **4a** was formed, with complete consumption of the starting materials. Amidine-incorporated products with lower than expected mass were obtained as the major products (by LCMS), presumably a result of base-promoted fragmentation of the dihydroxyfumarate by a retro-Claisen mechanism. In order to slow this fragmentation, we envisioned blocking one or both of the free hydroxyls with protecting groups that could be removed later under mild conditions. The benzyl protected dimethoxydihydroxyfumarate **3b** was prepared by Claisen condensation of methyl α-benzyloxy acetate and dimethyl oxalate.[6] When 1.5 equiv of **3b** was combined with benzamidine and DBU (3 equiv) in MeOH at 60 °C for 8 h, a reasonable 65% yield of **4b**, was obtained. A major side-product that was identified in the reaction mixture is the five-membered ring product **14**, which would arise from attack at the undesired methyl ester of **3b**. This led us to postulate that blocking this position as a bulky *tert*-butyl ester would result in better regioselectivity and higher yields. Compound **3c** was prepared by Claisen condensation of methyl α-benzyloxy acetate and methyl *tert*-butyl oxalate using LDA[6,7] in 72% yield after purification by silica-gel chromatography. Indeed, **3c** reacts cleanly with **2a** using NaOMe (3 equiv) in MeOH at room temperature, giving **4c** in 89% HPLC assay yield[8] and 84% isolated yield after crystallization. Only a trace of the five-membered ring analog **14** was present (<3 *A*% by HPLC) as the only side-product. A survey of bases found that DBU (3 equiv) was equally capable of promoting the reaction, and triethylamine (3 equiv) also gave the product, but at a lower rate and less cleanly (Table 1). Due to the higher cost of DBU, NaOMe was used as the standard base in the remaining experiments.

A survey of commercially available amidines demonstrated that the reaction is general (Table 1).[9] Standard alkyl (**2b–d**) and electron-poor (**2f**), electron-rich (**2g**), and basic (**2e**) aryl amidines gave excellent yields of the desired pyrimidinone heterocycles, and all were easily purified by crystallization from the crude reaction mixture. Amidine analogs containing *O*, N and S heteroatoms, such as O-methylisourea **2h**, 2-ethyl-2-thiopseudourea **2i** and 1,1-dimethylguanidine **2j** also reacted

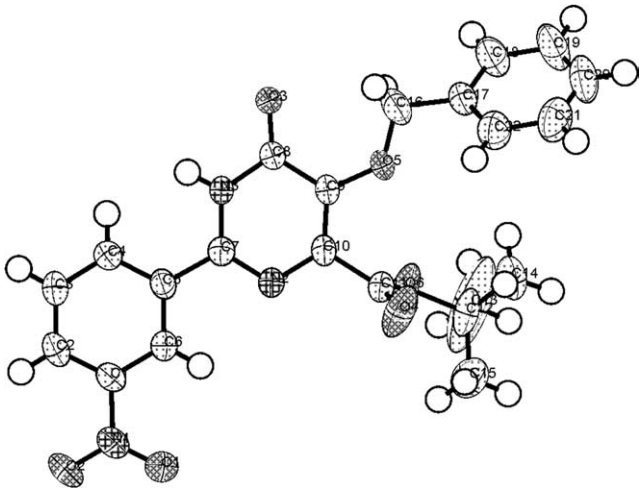
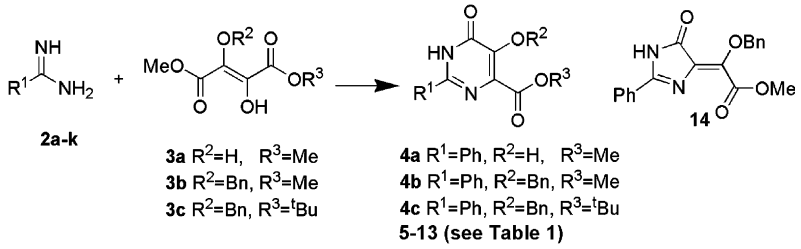


Figure 1.

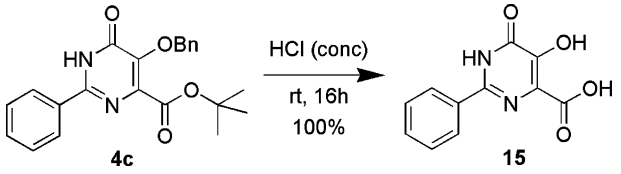


Scheme 2.

Table 1. Optimization and scope of dihydroxyfumarate/amidine condensation reactions (Scheme 2)

Amidines **1a–j**	Fumarate	Conditions	Product $R^1=$, $R^2=$, $R^3=$	Yield[a]
2a R^1 = Ph-, (HCl)	**3a**	NaOMe, Et_3N and DBU	**4a** Ph, H, Me	Trace
2a R^1 = Ph-, (HCl)	**3b**	DBU, 60 °C, 8 h	**4b** Ph, Bn, Me	65
2a R^1 = Ph-, (HCl)	**3c**	DBU, 60 °C, 8 h	**4c** Ph, Bn, ^{t}Bu	na (92)
2a R^1 = Ph-, (HCl)	**3c**	Et_3N, 60 °C, 24 h	**4c** Ph, Bn, ^{t}Bu	na (82)
2a R^1 = Ph-, (HCl)	**3c**	NaOMe, rt, 24 h	**4c** Ph, Bn, ^{t}Bu	84 (89)
2b R^1 = Me-, (HCl)	**3c**	NaOMe, rt, 24 h	**5** Me, Bn, ^{t}Bu	84
2c R^1 = H-, (HCl)	**3c**	NaOMe, rt, 24 h	**6** 6H, Bn, ^{t}Bu	93
2d R^1 = cyclopropyl-, (HCl)	**3c**	NaOMe, rt, 30 h	**7** Cyclopropyl-, Bn, ^{t}Bu	92
2e R^1 = 4-pyridine-, (HCl)	**3c**	NaOMe, rt, 30 h	**8** 4-Pyridine-, Bn, ^{t}Bu	96
2f R^1 = 3-NO_2Ph-, (HCl)	**3c**	NaOMe, rt, 48 h	**9** 3-NO_2Ph, Bn, ^{t}Bu	88
2g R^1 = 4-MeOPh-, (free base)	**3c**	NaOMe (2 equiv), rt, 30 h	**10** 4-MeOPh-, Bn, ^{t}Bu	94
2h R^1 = MeO-, (1/2H_2SO_4)	**3c**	NaOMe, rt, 36 h	**11** OMe, Bn, ^{t}Bu	50
2j R^1 = EtS-, (HBr)	**3c**	NaOMe or DBU	**12** EtS-, Bn, ^{t}Bu	Low
2k R^1 = Me_2N-, (H_2SO_4)	**3c**	NaOMe or DBU	**13** Me_2N-, Bn, ^{t}Bu	Low

na denotes that the compound was not isolated.
[a] HPLC assay yield in parentheses.



Scheme 3.

to give the desired pyrimidines (by LCMS analysis), but less cleanly. Compound **8a** could be crystallized in moderate yield, but **9a** and **10a** could not be isolated by crystallization due to the low yields.[10]

Unambiguous structural determination for the pyrimidinone heterocycles was obtained by X-ray crystal structure of the 3-nitrophenyl analogue **9** (Fig. 1).[11] In addition, both protecting groups were removed from **4c** in one step under acidic conditions to give the core pyrimidine heterocycle, 2-phenyl-5,6-dihydroxy-pyrimidine-4-carboxylic acid **15**, in quantitative yield (Scheme 3).

In summary, a general synthetic method has been developed that allows access to C2 alkyl- and aryl-substituted pyrimidinones **1** in high yield and purity. By understanding the inherent problems of retro-Claisen fragmentation and regioselectivity of this reaction, a dihydroxyfumarate derivative with an appropriate protecting scheme was devised that constrained its reactivity to the desired path. A simple procedure for deprotection was then found to enable further derivatization.

References and notes

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7. Typical procedure: preparation of 2-benzyloxy-3-hydroxy-fumarate 4-*tert*-butyl ester 1-methyl ester (**3c**). LDA was generated by addition of *n*-BuLi (60 mL, 2.5 M in hexanes, 150 mmol) to diisopropylamine (21.0 mL, 150 mmol) in THF (60 mL) at 0 °C, and aged for 10 min. In a separate flask, a mixture of methyl *tert*-butyl oxalate (24.0 g, 150 mmol) and methyl α-benzyloxy acetate (18.0 g, 100 mmol) in THF (240 mL) was cooled to −78 °C. The LDA was then added quickly by cannula, and the resulting mixture stirred for 1 h at −78 °C, then warmed to room temperature over 1 h. The mixture was then quenched with cold aqueous HCl (200 mL, 1 M), and the reaction was diluted with EtOAc (200 mL). The layers were separated, and the aqueous was back-washed with EtOAc (2×100 mL). The resulting organics were dried ($MgSO_4$), filtered and stripped, then purified by column chromatography on silica-gel (eluents 1–60% EtOAc/hexanes) to give 22.2 g (72%) of **3c** as a mixture of enol/ketone tautomers and the ketone hydrate. ^1H and ^{13}C NMR are complex due to keto-enol tautomers and the ketone hydrate. NMR spectra confirming these structures are provided in the Supplementary materials. The purified product is a single spot by TLC analysis. We recommend that fumarate reagent **3c** be used directly after chromatographic purification, due to decomposition, which can reduce yields in the heterocycle formation. Compound **3c** can be stored for several days in a −20 °C freezer, with minimal decomposition.
8. The yield was determined by quantitative HPLC by comparison with a known amount of a purified standard.
9. Typical procedure: preparation of 5-benzyloxy-6-hydroxy-2-cyclopropyl-pyrimidine-4-carboxylic acid *tert*-butyl ester (**7**). To a solution of cyclopropane-1-carboximidamide HCl **2d** (1.21 g, 10.0 mmol) and **3c** (4.60 g, 15.0 mmol) in MeOH (16.6 mL) at 0 °C, was added NaOMe (6.8 mL, 25 wt% solution in MeOH, 30 mmol). The mixture was warmed to room temperature, then stirred for 30 h. After dilution with MeOH (5 mL) and cooling to 0 °C, 1 N HCl (40 mL) was added and the product was precipitated from the mixture. The solid was washed with 10 mL of cold 9:1 H_2O/MeOH and dried giving 3.14 g of **7** (92% isolated yield) of >98% pure (HPLC area percent purity at 210 nm) as a white crystalline solid, mp 164.0–164.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 12.98 (1H, br s), 7.46–7.49 (2H, m), 7.30–7.38 (m, 3H), 5.24 (2H, s), 1.89–1.95 (1H, m), 1.52 (9H, s), 1.24–1.29 (2H, m), 1.05–1.10 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) 164.3, 159.7, 159.5, 145.7, 139.4, 137.3, 128.6, 128.3 (two peaks), 82.6, 73.4, 27.9, 13.5, 10.0.
10. The pyrimidinones could not be purified in good yield by silica-gel chromatography due to streaking of the products on the column.
11. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 236303. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).