HETEROCYCLES, Vol. 67, No. 2, 2006, pp. 763 - 768. © The Japan Institute of Heterocyclic Chemistry
Received, 25th July, 2005, Accepted, 14th October, 2005, Published online, 14th October, 2005. COM-05-S(T)40

PALLADIUM-CATALYZED ARYLATION OF DIISOPROPYL MALONATE APPLIED TO THE EFFICIENT SYNTHESIS OF THE SELECTIVE MMP INHIBITOR 5-(4-PHENOXYPHENYL)-5-[4-(2-PYRIMIDINYL)-1-PIPERAZINYL]BARBITURIC ACID

Stanley Hutchings, Wen Liu, and Roumen Radinov*

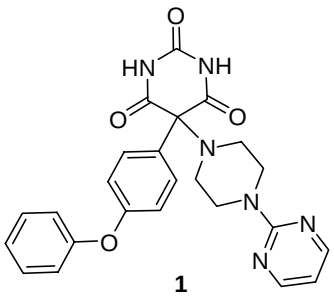
Chemical Synthesis – Process Research, Safety and Technical Sciences, Pre-Clinical Research and Development, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA

roumen.radinov@roche.com

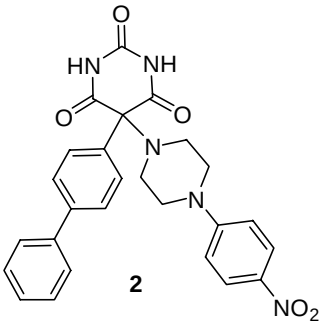
Dedicated to Professor Barry M. Trost on the occasion of his 65th birthday.

Abstract – An efficient synthesis of the highly selective MMP inhibitor 5-(4-phenoxyphenyl)-5-[4-(2-pyrimidinyl)-1-piperazinyl]barbituric acid is reported. The title compound was prepared in three steps and 72% overall yield from 4-bromophenyl phenyl ether *via* an improved arylation of diisopropyl malonate.

5-(4-Phenoxyphenyl)-5-[4-(2-pyrimidinyl)-1-piperazinyl]barbituric acid (**1**) belongs to a barbiturate-type of matrix metalloproteinase (MMP) inhibitors with increased selectivity for gelatinase B (MMP-9), which has been associated with an enhanced antitumor and antimetastatic activity.[1] *In vitro*, **1** is a more selective inhibitor of MMP-9 over MMP-1, MMP-7 and MMP-13 than the leading candidate in this class, compound (**2**),[2] and *ca.* 2000-fold more selective than the broad-spectrum MMP inhibitor batimastat. Treatment with **1** was also more effective than **2** in reducing the number and size of macroscopic liver metastases in T-cell lymphoma cells. Based on these results, **1** has been under consideration for the therapy of aggressive lymphomas.

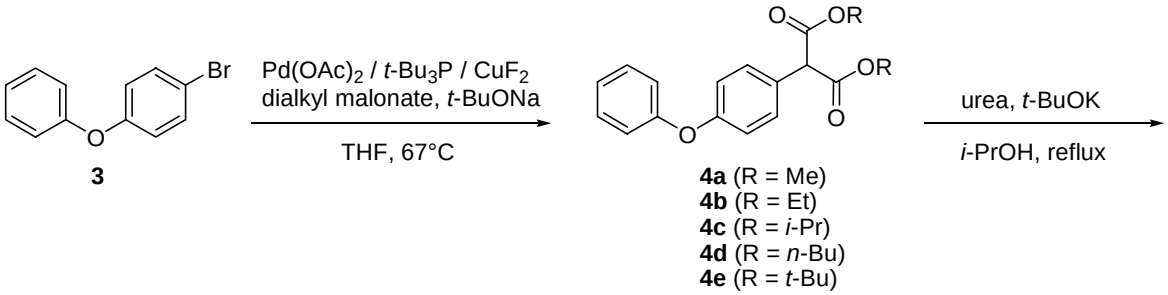


1



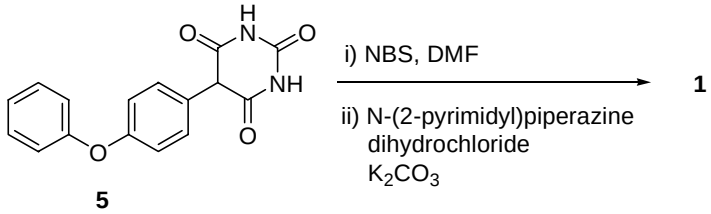
2

In its original preparation, 4'-phenoxyacetophenone was converted to **1** *via* a Willgerodt-Kindler rearrangement in seven steps and an overall yield of less than 30%. In the key step, condensation of methyl 4-phenoxyphenylacetate with dimethyl carbonate provided the requisite arylmalonate (**4a**) for the synthesis of 5-arylbarbituric acid (**5**).[3] Contemplating an efficient scalable synthesis of **1**, we describe in this report a more direct preparation based on the optimized coupling reaction of commercially available 4-bromophenyl phenyl ether (**3**) with a dialkyl malonate.



3

4a (R = Me)
4b (R = Et)
4c (R = *i*-Pr)
4d (R = *n*-Bu)
4e (R = *t*-Bu)



5 **1**

Palladium / *t*-Bu_3P complexes have recently been reported to catalyze the coupling of aryl bromide (**3**) with diethyl malonate (2 mol% of $Pd(dba)_2$, 4 mol% of *t*-Bu_3P, sodium hydride as the base and THF as the solvent at 70°C for 8 h).[4] Arylmalonate (**4b**) was subsequently isolated by chromatography in 89% yield on a 1 mmol scale. However, our initial evaluation indicated the reaction to be problematic upon scale up. Incomplete conversion of **3** was generally obtained under a variety of reaction conditions, producing a number of byproducts along with the desired arylation product (**4b**). The best conditions, in our hands, required 5 mol% of palladium catalyst and an elevated temperature of *ca.* 100 °C in THF in a sealed vessel in order to complete the reaction of **3** with diethyl malonate within 16 h on a 60-gram scale. Lowering the amount of catalyst below 5 mol% led to increased amounts of byproducts.

The crude aryl malonate (**4b**) was submitted without purification to the condensation with urea as previously described for the synthesis of **2**.[5] Then, the 5-arylbarbituric acid (**5**) was isolated by crystallization in 65% yield over the two steps from **3**, and the synthesis of **1** was accomplished in 49% overall yield from **3**. However, this product was found to contain *ca.* 300 ppm of palladium requiring additional purification.

We, subsequently, found that the addition of a catalytic amount of copper(II) fluoride (*ca.* 1 equiv. to Pd) and the use sodium *tert*-butoxide as the base promoted the reaction of **3** with diethyl malonate (*ca.* 1.2 equiv. each). This modification allowed us to reduce the P/Pd ratio to 1.3 and to lower the reaction temperature. Thus, the bimetallic catalyst system of 4.4 mol% of palladium(II) acetate, 4.9 mol% of CuF_2, and 5.7 mol% *t*-Bu_3P gave a clean and complete conversion of **3** to **4b** at *ca.* 67°C in THF. The yield of 5-arylbarbituric acid (**5**) was consequently increased to 79%, which allowed the preparation of **1** in an improved 64% overall yield on a 1-kg scale. However, our efforts to reduce the palladium loading further to the 1 mol% level by changing the reaction conditions (i.e., ligand, palladium source, base, solvent, temperature, additives etc.) once again proved unsuccessful.

Finally, a breakthrough occurred when a more sterically hindered malonate ester was employed for the coupling with aryl bromide (**3**). The outcome of the reaction using malonate esters of increasing steric bulk is presented in the Table. The lowest catalyst loading and the highest purity was achieved for arylmalonate (**4c**) using diisopropyl malonate. Thus, a similar conversion was achieved with diisopropyl malonate using only 0.56 mol% palladium loading, as compared to a 4.4 mol% palladium loading with diethyl malonate. Dimethyl malonate was clearly inferior, and di-*tert*-butyl malonate did not offer any advantage over diisopropyl malonate. Dibutyl malonate was better than diethyl but worse than diisopropyl malonate. Based on these results, diisopropyl malonate was selected as the nucleophile of choice for the arylation, and the synthesis of **1** was accomplished using a 1 mol% palladium loading as described below.

A solution of **3**, palladium(II) acetate (1 mol%), copper(II) fluoride (1 mol%), *t*-Bu_3P (1.3 mol%), sodium *tert*-butoxide (1.21 equiv.) and diisopropyl malonate (1.26 equiv.) was heated in THF (2 vol) to 67°C for 15 h. The reaction mixture was diluted with heptane, quenched by the addition of 3M HCl, filtered and concentrated, and then diluted with methyl *tert*-butyl ether (MTBE).

Table. Palladium Catalyzed Coupling Reaction with Dialkyl Matonates[a)]

Pd mol%	Product (%) in the reaction mixture as estimated by HPLC				
	4a	**4b**	**4c**	**4d**	**4e**
4.44	-	94	**-**	**-**	-
2.23	23	86	**97**	94	-
1.11	-	82	**97**	88	-
0.56	-	-	**95**	82	-
0.20	-	-	**55**	9	52

a) $Pd(OAc)_2$ / *t*-Bu_3P / CuF_2 (1:1.3:1), dialkyl malonate (1.26 equiv.), *t*-BuONa (1.21 equiv.), THF, 67°C, 16 h.

The MTBE solution was washed consecutively with 3M HCl, 1M $KHCO_3$ and brine and concentrated. The crude aryl malonate (**4c**) thus obtained, was treated with urea and potassium *tert*-butoxide in isopropanol, and the crystalline barbituric acid (**5**) was isolated in 84% yield from **3**. One-pot bromination and amination of **5** provided **1**, which was isolated by crystallization from aqueous ethanol in an improved 72% overall yield from **3**. As a result of the lower catalyst loading used in the preparation of **4c**, the heavy metal content was reduced to *ca.* 150 ppm in **4c**, *ca.* 20 ppm in **5**, and less than 1 ppm in **1** without additional purification.

In summary, an efficient three-step synthesis of the barbituric acid derivative (**1**) was achieved from commercially available 4-bromophenyl phenyl ether (**3**) using an improved arylation with diisopropyl malonate.

EXPERIMENTAL

5-(4-Phenoxyphenyl)barbituric Acid (5). To a mixture of $Pd(OAc)_2$ (135 mg, 0.6 mmol), CuF_2 (60 mg, 0.6 mmol), *t*-Bu_3P (90% grade, 220 µL, 0.8 mmol), *t*-BuONa (6.98 g, 73 mmol) and THF (30 mL) were added consecutively 4-bromophenyl phenyl ether (**3**, 10.5 mL, 60 mmol) and diisopropyl malonate (14.4 mL, 76 mmol). The clear solution was heated to 67 °C for 15 h. The suspension was allowed to cool to ambient temperature and diluted with hexane (30 mL), and then the reaction mixture was quenched by the addition of 3M HCl (7.5 mL, 22.5 mmol). The mixture was filtered through Celite and the filter pad was rinsed with hexane-THF 1:1 (100 mL). The combined filtrates were concentrated under reduced pressure and the residue was dissolved in MTBE. The resulting solution was washed with 3M HCl (2x25 mL), 1M $KHCO_3$ (2x25 mL) and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 24.0 g of crude **4c** as a yellow oil. To this crude product were added urea (6.41 g, 107 mmol) and isopropanol (127 mL). The mixture was heated to 80 °C and a 1M solution of *t*-BuOK in THF (152 mL, 152 mmol) was added slowly over 3 h while distilling off *ca.* 60 mL of solvent to maintain a reflux temperature between

78-86 °C. After the addition was complete, the mixture was heated to reflux (*ca.* 78-79 °C) for an additional 14 h. The mixture was allowed to cool to ambient temperature and a mixture of conc. HCl (14.9 mL, 178 mmol) and water (35 mL) was slowly added. The mixture was stirred for an additional 10 min, then concentrated under reduced pressure to remove the organic solvents. The resulting aqueous mixture was diluted with water (100 mL) and the precipitate was collected by filtration and washed with water (70 mL). The wet solid was suspended in ethyl acetate (70 mL) and the mixture was heated to reflux for 10 min to remove residual water by azeotropic distillation, and then diluted with hexane (35 mL). After cooling to 25 °C, the solid was collected by filtration, washed with ethyl acetate – hexane 1:1 (2x40 mL) and dried by suction to give 15.0 g (84.4% yield) of **5** as a white solid.

5-(4-Phenoxyphenyl)-5-[4-(2-pyrimidinyl)-1-piperazinyl]barbituric Acid (1). A solution of **5** (10.0 g, 34 mmol) in DMF (30 mL) was cooled to 10 °C , and a solution of NBS (6.20 g, 34 mmol) in DMF (15 mL) was added over 16 min, while maintaining the temperature of the reaction mixture between 5 and 10 °C. The addition funnel was rinsed with DMF (5 mL) and the rinse was added to the reaction mixture. After stirring at 5-10 °C for 20 min, 1-(2-pyrimidyl)piperazine dihydrochloride (8.08 g, 34 mmol) was added in one protion, followed by potassium carbonate (9.34 g, 68 mmol). After stirring for 1 h at 5-10 °C, the mixture was allowed to warm to 25 °C and then stirred for an additional 20 h. The mixture was diluted with ethyl acetate (25 mL) and a solution of citric acid (6.49 g, 34 mmol) in water (75 mL) was added slowly, while maintaining the temperature at 24-28 °C. After completion of the addition, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2x35 mL). The combined organic extracts were washed with water (50 mL), and the solvent was exchanged with ethanol by distillation (bp 77 °C). The solution was concentrated to *ca.* 40 mL and water (10 mL) was added. The mixture was heated to reflux for 5 min, and then allowed to cool to 20 °C over 40 min. The solid was collected by filtration, washed with 70% aq ethanol (2x25 mL) and dried by suction. The resulting solid was further dried at 56 °C/70 mmHg to give 13.2 g (85.3% yield) of **1** as an off-white solid.

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