DIELS-ALDER REACTIONS OF 6-AZAPTERINS. AN ALTERNATIVE STRATEGY FOR THE SYNTHESIS OF 5,10-DIDEAZA-5,6,7,8-TETRAHYDROFOLIC ACID (DDATHF)

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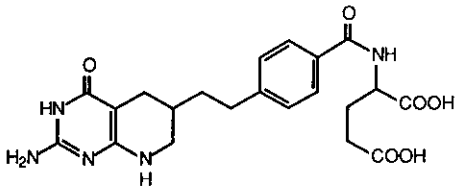
Abstract - Methyl 2-N-pivaloyl-5,10-dideazapteroate (**7**), a key intermediate in our recent unambiguous synthesis of the new antitumor agent, 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), has been synthesized by a novel inverse electron demand Diels-Alder reaction between 2-N-pivaloyl-7-methylthio-6-azapterin (**4**) and the pyrrolidine enamine of methyl p-(4-oxobutyl)benzoate, followed by Raney nickel desulfurization of the resulting 7-methylthio derivative (**5**).

We have recently described a novel and efficient regiospecific synthesis of 5-deazapterins by an intermolecular inverse electron demand Diels-Alder reaction between 2-N-pivaloyl-7-substituted-6-azapterins (fused 1,2,4-triazines) with enamines.[1] Furthermore, the cycloaddition reaction is regiospecific in that aldehyde enamines lead exclusively to 6-substituted-5-deazapterins. Despite the relative sluggishness of this reaction when the pyrrolidine enamine of butyraldehyde was employed, we were intrigued by the possibility that this methodology might be applied to the synthesis of **7**, which we have demonstrated in other work[2] to be a key intermediate in the synthesis of our extraordinarily active and selective antitumor agent, 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) (**1**).[3-8]



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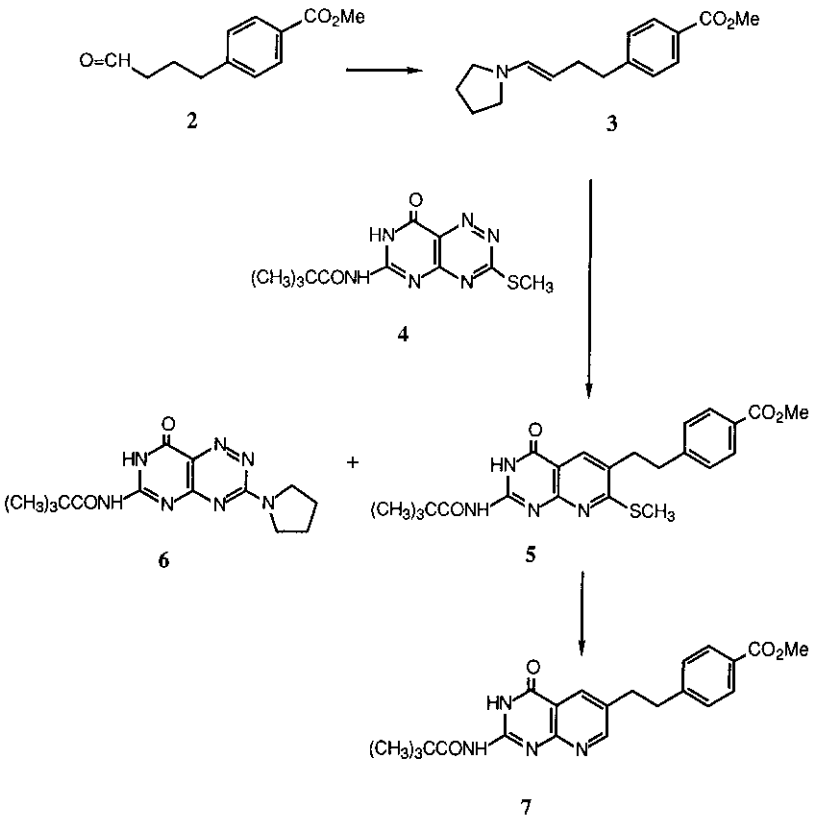
Thus, methyl p-(4-oxobutyl)benzoate **2**[9] was converted to its pyrrolidine enamine **3**, which was then heated in anhydrous dioxane with 2-N-pivaloyl-7-methylthio-6-azapterin (**4**)[1] overnight. Filtration of the cooled reaction mixture removed the precipitated byproduct **6**, the

product of displacement of the 7-methylthio substituent by pyrrolidine. Chromatography of the filtrate gave a modest yield of the Diels-Alder product **5**. The reaction pathway is presumed to be analogous to that described previously for such 6-azapterin cycloaddition reactions with enamines, which involves cycloaddition across positions 4a and 7 of the azadiene, with subsequent aromatization of the intermediate cycloadduct by loss of molecular nitrogen followed by pyrrolidine. The regiochemistry of this cycloaddition was confirmed by Raney nickel desulfurization of **5** to give methyl 2-N-pivaloyl-5,10-dideazapteroate (**7**) which was identical in every respect with an authentic sample synthetized independently by an unequivocal procedure.[2] Compound **7** has been previously utilized as a key intermediate for the preparation of DDATHF.[2]



This successful demonstration of the effectiveness of the above Diels-Alder methodology for the construction of complex target molecules in the 5-deazapterin series has encouraged us to examine other 6-azapterin substrates as electron-deficient azadienes. We are currently examining replacement of the 7-methylthio substituent (which suffers displacement by pyrrolidine in the course of the Diels-Alder reaction, and furthermore is difficult to remove from the cycloadduct by reductive desulfurization) with a 7-alkoxycarbonyl group (which activates the azadiene towards inverse-electron demand cycloaddition, and should be readily removed through eventual decarboxylation).

EXPERIMENTAL

Methyl 2-N-Pivaloyl-7-methylthio-5,10-dideazapteroate (5).

A mixture of methyl p-(4-oxobutyl)benzoate (**2**) (13.27 g, 64.3 mmol), pyrrolidine (6.86 g, 96.5 mmol) and *ca* 10 g of anhydrous magenesium sulfate in 100 mL of anhydrous tetrahydrofuran was stirred vigorously under N_2 for 3 h. The mixture was then filtered and the filtrate concentrated. To the resulting enamine **3** was added 2-N-pivaloyl-7-methylthio-6-azapterin (**4**) (5.74 g, 19.5 mmol) in 150 mL of anhydrous 1,4-dioxane. The reaction mixture was refluxed with stirring under N_2 for 36 h, cooled to room temperature, and the precipitated solid **6** collected by filtration; yield 3.05 g (61%), mp >300 °C [^{1}H NMR (d_6-DMSO) δ 1.19 (2, 9 H), 1.91-2.04 (m, 4 H), 3.43-3.49 (m, 2 H), 3.73-3.81 (m, 2 H). HRMS Calcd for $C_{14}H_{19}N_7O_2$ (M^+), 317.1600, found 317.1604]. The filtrate was concentrated under reduced pressure and the residual solid triturated with chloroform. A small amount of insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography, eluting with 2% methanol/methylene chloride, to give 3.54 g (12%) of **5** as a white microcrystalline solid; mp 180-182 °C; ^{1}H Nmr ($CDCl_3$) δ 12.00 (bs, 1 H), 8.30 (bs, 1 H), 8.04 (s, 1 H), 7.98 (d, J = 7.0 Hz, 2 H), 7.71 (s, 3 H), 7.30 (d, J = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.04 (m, 4 H), 1.34 (s, 9 H). HRMS Calcd for $C_{23}H_{26}N_4O_4S$ (M^+) m/z 454.1675, found 454.1648. Anal. Calcd for $C_{23}H_{26}N_4O_4S$: C, 60.78; H, 5.77; N, 12.33; S, 7.05. Found: C, 60.87; H, 6.01; N, 12.12; S, 6.86.

Methyl 2-N-Pivaloyl-5,10-dideazapteroate (7).

A mixture of methyl 2-N-pivaloyl-7-methylthio-5,10-dideazapteroate (**5**) (0.11 g, 0.24 mmol) and *ca* 1.0 g of Raney nickel (Aldrich, washed with water followed by ethanol) in 20 mL of ethanol was stirred vigorously at room temperature under N_2 for 5 days. The mixture was filtered through Celite, which was washed well with ethanol. Evaporation of the filtrate and purification by preparative thin layer chromatography, eluting with 2% methanol/methylene chloride, gave 0.02 g (20%) of a white microcrystalline solid; mp 237-238 °C. Ir (KBr) ν_{max} 3200, 2980, 1710, 1670, 1600, 1450, 1290, 1140 and 800 cm^{-1}; ^{1}H Nmr (d-TFA, DMSO-d_6) δ 8.55 (s, 1 H), 8.13 (s, 1 H), 7.57 (d, J = 8.3 Hz, 2 H), 6.86 (d, J = 8.3 Hz, 2 H), 3.57 (s, 3 H), 2.87 (t, J = 6.9 Hz, 2 H), 2.76 (t, J = 6.9 Hz, 2 H), 0.96 (s, 9 H). HRMS Calcd for $C_{22}H_{24}N_4O_4$ (M^+) 408.1797, found 408.1807. Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.78; H, 6.15; N, 13.64.

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9. J. I. DeGraw, H. Tagawa, P. H. Christie, J. A. Lawson, E. G. Brown, R. L. Kisliuk, and Y. Gaumont, J. Heterocyclic Chem., 1986, *23*, 1. We have developed a much improved synthesis of this key intermediate which is described in ref. 2.

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