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Studies on Pyrimidine-annulated Heterocycles: A New Short Synthesis of 7,9-Dialkylcyclohepta[*b*]pyrimido-[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione Derivatives†

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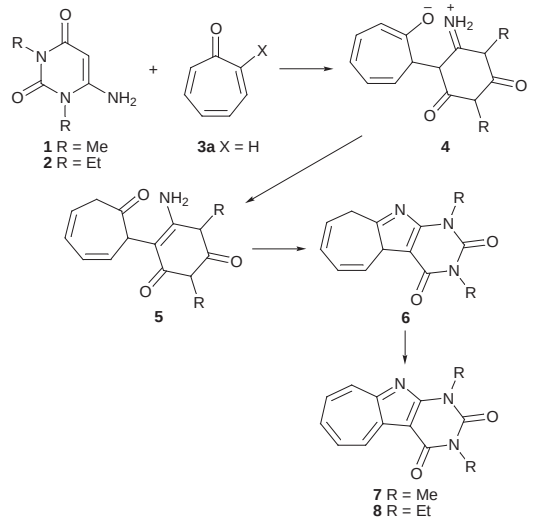
A new short synthesis of 7,9-dialkylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione derivatives consists of the reaction of 6-amino-1,3-dialkyluracils with tropone, 2-halotropones and 2,6-dibromotropone in an enamine-alkylation process, subsequent condensation of the amino group with carbonyl function, and aromatization under the reaction conditions.

Fused pyrimidines are important and common sources for the development of new potential therapeutic agents.[1] Among these, 5-deazaflavins (5-deazaisoalloxazine or 5-deazaalloxazine) have been studied in both enzymatic arid model systems to provide mechanistic insight into flavin-catalyzed reactions. Several routes for the preparation of 5-deazatlavins have been previously described.[2–8] We have been interested in exploiting the unique reactivities afforded by (vinylimino)-phosphoranes and related compounds in developing efficient routes for the preparation of fused heterocycles.[9–12] Since 1-azaazulene derivatives have also attracted much attention from the viewpoint of their pharmacological activities,[13] we have embarked on the exploration of methodology to synthesize versatile 1-azaazulenes. In this context, we now report a convenient reaction of 6-amino-1,3-dialkyluracils **1** and **2** with tropone, 2-halo- and 2,6-dibromotropones **3a**–**d** to provide cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10-(9*H*)-dione derivatives, which have an isomeric 5-deazaflavin skeleton, prepared through the reaction of 2-amino-1-azaazulene derivatives with aromatic isocyanates.[14]

The starting 6-amino-1,3-dialkyluracils **1** and **2** are prepared easily as described in the literature.[15] The reaction of uracils **1** and **2** with tropone **3a** (molar ratio of **1** or **2**/**3a**=0.5) in the presence of a catalytic amount of a dehydrogenating agent (10% Pd/C) under reflux in 1,4-dioxane leads directly to the 7,9-dimethyl- and 7,9-diethyl-cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-diones **7** and **8**, respectively (Scheme 1). The results are summarized in Table 1 (entries 1 and 2). The structural assignment of new compounds **7** and **8** was made on the basis of elemental analyses and spectral data. The mass spectra of **7** and **8** show the expected molecular ion peaks, and the IR spectra show two absorption bands in the region of 1700 and 1653 cm^{-1} and 1696 and 1653 cm^{-1} due to the two carbonyl groups, respectively, for **7** and **8**.[14] In the ^1H NMR spectra, the characteristic chemical shifts of H-1 are found at a low field of δ 9.37 (**7**) and 9.38 (**8**) as doublets, owing to the deshielding effect of the C-10 carbonyl group,[14] while the ^{13}C NMR spectra show two signals at δ 162.2 and 161.2 (**7**) and δ 161.3 and 161.9 (**8**) due to the carbon of the two carbonyl groups, respectively.



Scheme 1 *Reagents and conditions*: i, heat, Pd/C, 1,4-dioxane.

Table 1 Results for the reaction of uracils **1** and **2** with tropones **3a**–**d** with tripones **3a**–**d**

Entry	Uracil	Tropone	Reaction time[a]/h	Product (% yield)
1	**1**	**3a**	48	**7**(82)[b]
2	**2**	**3a**	17	**8**(76)[b]
3	**1**	**3b**	44	**7**(88)[c]
4	**1**	**3c**	30	**7**(50)[c]
5	**2**	**3b**	12	**8**(82)[c]
6	**1**	**3d**	48	**13**(60)[c]

[a]Reactions were carried out in 1,4-dioxane under reflux using a ratio of **1** or **2**/**3a**–**d** of 0.5. [b]Reactions were carried out in the presence of a catalytic amount of 10% Pd/C. [c]Reactions were carried out in the presence of NEt_3 and K_2CO_3.

The formation of compounds **7** and **8** is best explained by the mechanism depicted in Scheme 1. Analogous with the reaction of tropone with (vinylimino)phosphoranes[9] and β-amino enones,[10] the initial step is the enamine alkylation of **1** and **2** to the C-2 of tropone to give the intermediate **4**, which undergoes tautomerization to give ketone **5**. Intramolecular condensation to give the dihydroazaazulene **6** and subsequent aromatization in the presence of 10% Pd/C results in the formation of **7** and **8**.

We next observed that compounds **1** and **2** react with 2-chlorotropone **3b** and 2-bromotropone **3c** in the presence of K_2CO_3 and NEt_3 under reflux in 1,4-dioxane to give **7** and **8** in good yield in a single step (Scheme 2, Table 1, entries 3–5). Nucleophilic substitution onto a tropone carrying a mobile substituent is known to take place at C-2 (usual substitution) or at C-7 (abnormal substitution) to give 2-substituted tropones.[16] The present reaction of **1** and **2** with

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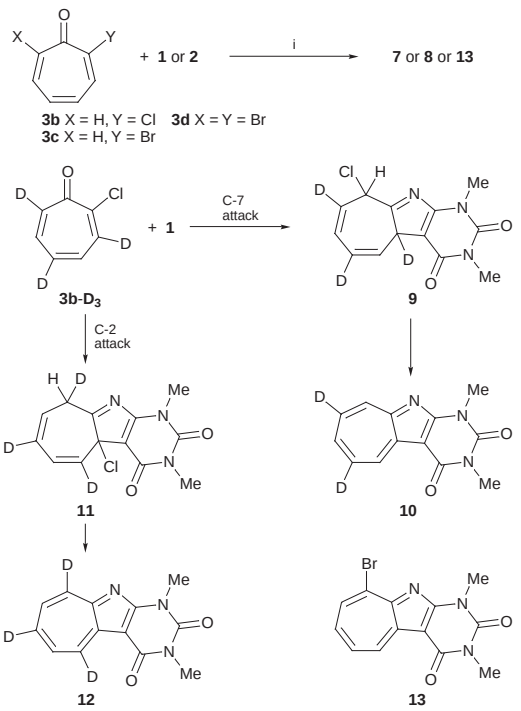

Scheme 2 *Reagents and conditions*: i, heat, NEt_3, K_2CO_3, 1,4-dioxane

3b,**c** does not seem to involve a straightforward displacement of the halide ion upon enamine alkylation. This was proved by labeling the troponoid ring with deuterium. Thus, the reaction of 2-chloro-3,5,7-trideuteriotropone **3b-D** with **1** resulted in the formation of a mixture of **10** and **12** in a ratio of 4:1 (Scheme 2). The structural assignment of the mixture of **10** and **12** was based on HRMS and ^{1}H NMR spectral data. Thus, the mechanistic pathways for the reaction of the tropone **3b-D** with **1** was deduced as shown also in Scheme 2. The initial enamine alkylation takes place at C-7 as well as at C-2, and the following hydrogen migration and condensation lead to the intermediates **9** and **11**. Elimination of DCl and HCl readily gives the final products **10** and **12**, respectively Thus, compounds **1** and **2** are expected to react with 2-halotropones **3b**,**c** in a similar way.

Similarly, the reaction of **1** with 2,7-dibromotropone **3d** proceeded to give functionalized 5-bromo-7,9-dialkylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione **13** in a single step (Scheme 2, Table 1, entry 6)

In conclusion, 6-amino-3,5-dialkyluracils are confirmed to react with tropone; 2-halotropones and 2,7-dihalotropones. The present reaction could serve as a convenient and efficient route to uracil annulated 1-azaazulene derivatives (the isomer of 1,3-dialkyl-5-deazaalloxazines), which may have utility as an oxidizing or reducing agent.

Experimental

General experimental details have been described previously.[12,17]

General Procedure for the Reaction of Uracils **1** *and* **2** *with Tropone* **3a**.—A mixture of **1** (47 mg, 0.33 mmol) or **2** (55 mg, 0.3 mmol), **3a** (32 mg, 0.6 mmol) and 10% Pd/C (3 mg) in 1,4-dioxane (3 cm^3) was heated under reflux for the period indicated in Table 1. The reaction mixture was filtered through Celite, the filtrate was concentrated, and the residue was purified by TLC on silica gel CH_2Cl_2–AcOEt, 1/1) to give the products, **7** and **8**.

For 7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*), 10(9*H*)-dione **7**: yellow needles; mp 255– 256 °C (EtOH), δ_H(400 MHz) 3.52 (3H, s, Me-9) 3.83 (3H, s, Me-7), 7.92–8.06 (3H, m, H-2, H-3, H-4), 8.60 (1H, dd, *J* 8.6 1.5, H-5), 9.37 (H, d, *J* 8.7, H-1); δ_C (100.4 MHz) 27.9, 30.5, 99.9, 133.8, 134.3, 134.4, 135.4, 137.1, 145.8, 152.5, 160.0, 161.2, 162.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 and 1653; λ_{max}(MeCN)/nm (log ϵ) 243 (4.15), 298 (4,74), 360 (3,98), 437 (3.36); *m/z* 241 (M^+, 100%) (Found: C, 64.4; H, 4.3; N,17.3. $C_{13}H_{11}N_3O_2$ requires C, 64.72; H, 4.60; N,17.42%).

For 7,9-diethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione **8**: yellow powder mp 145–1469 °C (EtOH); δ_H (400 MHz) 1.33 (3H, t, *J* 7.1, Me), 1.47 (3H, t, *J* 7.1, Me), 4.20 (2H, q, *J* 7.1, CH_2), 4.46 (2H, q, *J* 7.1, CH_2), 7.95–8.00 (3H, m, H-2, H-3, H-4), 8.63 (H, d, *J* 9.5, H-5), 9.38 (H, dd, *J* 8.6, 2.4, H-1); δ_H (100.4 MHz) 13.4, 13.6, 36.4, 39.2, 76.7, 77.0, 77.3, 77.4, 100.2, 133.5, 134.2, 134.3, 135.2, 136.9, 145.8, 151.6, 159.9, 161.3, 161.9; $\nu_{max}(CHCl_3)/cm^{-1}$ 1696 and 1653; λ_{max}(MeCN)/nm (log ϵ) 244 (4.20), 298 (4.76), 360 (3.99), 435 (3.37): *m/z* 269 (M^+, 75%), 213 (100) (Found: C, 66.7; H, 5.6; N,15.5. $C_{15}H_{15}N_3O_2$ requires C, 66.90; H, 5.61; N, 15.61%).

General Procedure for the Reaction of Uracils **1** *and* **2** *with 2-Halotropones* **3b**–**d** *and* **3b-D**.—A solution of the uracil (0.3 mmol), 2-halotropone (0.6 mmol), K_2CO_3 (124 mg, 0.9 mmol) and NEt_3 (91 mg, 0.9 mmol) in 1,4-dioxane (3 mL) or in THF (3 cm^3) was heated under reflux for the period indicated in Table 1. After the reaction was complete, the reaction mixture was filtered through Celite and the filtrate purified by TLC on alumina (hexane–AcOEt, 1/1) to give the products.

For a mixture of 2,4-dideuterio- and 1,3,5-trideuterio-7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione **10** and **12**: *m/z* 244 (M^+, 46%), 243 (M^+, 100). **10**: δ_H (270 MHz) 3.53 (3H, s, Me), 3.84 (3H; s, Me), 7.92–8.08 (1H, m, H-3), 8.64 (1H, s, H-5) 9.39 (1H, s, H-1) (Found: M^+, 243.0978. $C_{13}H_9D_2N_3O_2$ requires M, 243.0977). **12**: δ_H (270 MHz) 3.53 (3H, s, Me), 3.84 (3H, s, Me), 7.92–8.08 (2H, m, H-2, H-4) (Found: M^+, 244.1014. $C_{13}H_8D_3N_3O_2$ requires M, 244.103.

For 5-bromo-7,9-dimethylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8-(7*H*), 10(9*H*)-dione **13**: yellow prisms; mp 253–254 °C (from EtOH); δ_H (300 MHz) 3.53 (3H, s, Me-9), 3.89 (3H, s, Me-7), 7.73 (1H, t, *J* 10.7, H-3), 7.95 (1H, t, *J* 10.7, H-2), 8.50 (1H, d, *J* 10.7 H-4), 9.38 (1H, d, *J* 10.7, H-1); $\nu_{max}(CHCl_3)/cm^{-1}$ 1702 and 1659; λ_{max}(MeCN)/nm (log ϵ) 225 (4.12), 259 (4.40), 303 (4.56), 367 (3.92), 440 (334), 505 (1.29); *m/z* 321 (M^+, 321, 63%), 114 (100) (Found: C, 48.7; H, 2.9; N, 13.1 $C_{113}H_{10}N_3OBr$ requires C, 48.77; H, 3.15; N,13.13%).

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