

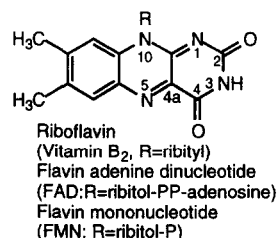
Model Systems for Flavoenzyme Activity. A Versatile Synthesis of N(3)-Alkylated Flavins

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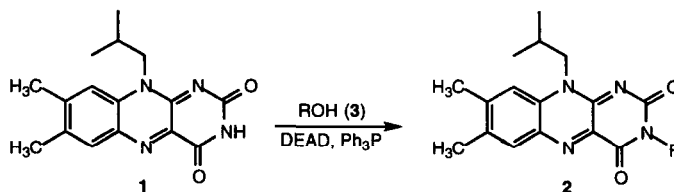
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Abstract: Reaction of isoalloxazines (flavins) with primary and secondary alcohols using Mitsunobu conditions provides flavins alkylated at the N(3) position. This method provides a versatile and divergent synthesis of both primary alkyl flavins, and the difficult to synthesize secondary alkyl flavins. © 1997 Elsevier Science Ltd.

Riboflavin (Vitamin B₂) is a required nutritional supplement in mammalian diets. Flavins, in the form of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) serve as redox cofactors in a huge variety of biological transformations and electron transfer processes.¹ The diverse and vital processes mediated by flavin cofactors has made structural analogs the focus of enzyme inhibitor design and synthesis.² Additionally, flavin derivatives have been widely used in our research^{3a} and others³ as synthetic models for flavoenzyme processes.


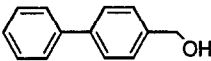
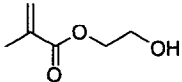


While a wide variety of flavins have been synthesized via a number of routes,^{2,3,4} there is currently no general method for the synthesis of N(3) alkyl flavins. To provide a versatile synthesis of these systems, we have investigated the coupling of N(10) isobutyl flavin **1** with primary and secondary alcohols using the Mitsunobu reaction (Scheme 1).⁶ Reaction of flavin **1** with alcohols **3** in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine⁷ provided N(3) alkyl flavins **2a-g** in moderate to very good yield (Table 1). This reaction was general, allowing coupling of flavin **1** to hindered alcohols **3c** and **3f**, and the reactive methacrylate derivative **3g**.



Scheme 1. N(3) alkylation of N(10)-isobutyl flavin **1**

Table 1. Preparation of N(3)-alkyl flavins **2**

Alcohol 3	Product	Time	Yield (%)	Mp (°C)
CH ₃ CH ₂ OH	2a	2 hr	61	219-220
CH ₃ (CH ₂) ₅ OH	2b	18 hr	52	142-146.5
(CH ₃) ₂ CHOH	2c	2 hr	68	179-189
C ₆ H ₅ CH ₂ OH	2d	6 hr	64	192.5-196
	2e	18 hr	29	73-83
	2f	8 hr	59	260-263
	2g	3 hr	37	95-101

In summary, an efficient and general method for the N(3) alkylation of flavins has been developed. Application of these flavins as model systems for flavoenzyme behavior is currently underway, and will be reported in due course.

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References and Notes

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- (7) General procedure for the preparation of N(3)-alkylated flavins: To a suspension of flavin **1** (0.2 mmol) and PPh₃ (0.22 mmol) in dry THF (500 µL) was added the corresponding alcohol **3** (0.6 mmol) then DEAD (0.22 mmol) dropwise at 0° C. The relatively high reagent concentration is required for the success of the reaction. The mixture was stirred at 0°C for two hours, then allowed to proceed at room temperature until the reaction was complete by TLC (2:1 EtOAc:AcCN). The reaction mixture was concentrated *in vacuo*, then the residue applied to a silica gel flash column, which was eluted with 2:1 EtOAc:Hexane to provide flavins **2a-g** as yellow solids.

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