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Synthesis and redox properties of novel alkynyl flavins

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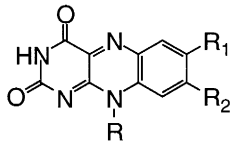
Abstract

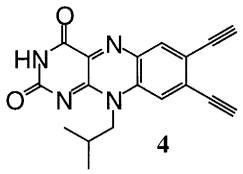
The synthesis of C7 and/or C8 alkynyl flavins is described. The yields range from 14–48% over six steps. The reduction potentials of these compounds are in good agreement with the values expected based on the Hammett substituent coefficients.

Keywords: alkynes; electrochemistry; enediyne; flavins.

Flavoenzymes are an ubiquitous and diverse class of biological redox catalysts.[1] The redox activity centers of these enzymes are derivatives of riboflavin (vitamin B_2, **1a**), which consists of an isoalloxazine ring system substituted with methyl groups at C7 and C8 and a ribityl group at N10. A plethora of models have been prepared to better understand flavin redox properties and to serve as structural and mechanistic probes.[2] The synthesis of modified flavins with different redox potentials has allowed the possibility of altering enzyme function. In particular, 8-cyano-8-desmethyl-riboflavin (**1b**)[3] has been used as a new catalyst for the enzymatic oxidation of carbonyl compounds.[4] Recently, our group has been interested in biomolecules appended with *o*-alkynyl substituents.[5] Such molecules possess potential applications as molecular probes or as anticancer agents via thermal or photochemical Bergman cyclization.[6,7] Here we wish to disclose the synthesis and redox properties of C7 and/or C8 alkynyl flavin derivatives (**4**–**6**).



1a : R = ribityl; R_1, R_2 = CH_3
1b : R = ribityl; R_1 = CH_3, R_2 = CN
2 : R = isobutyl; R_1, R_2 = H
3 : R = isobutyl; R_1, R_2 = CH_3



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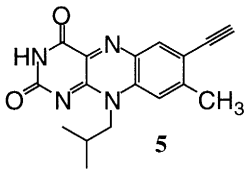

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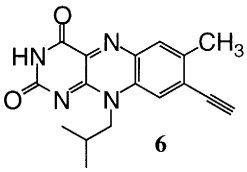

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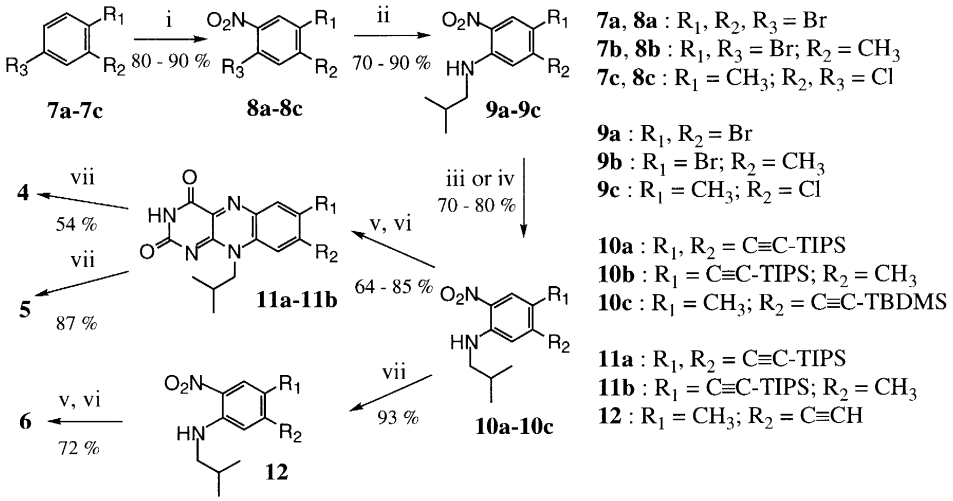
The synthesis of flavin analogues **4**–**6** is depicted in Scheme 1. Nitration of **7a**–**c** followed by nucleophilic substitution with isobutylamine afforded **9a**–**c** in good yields.[8] Coupling **9a**–**c** with TIPS- or TBDMS-protected acetylene and using $Pd(PPh_3)_4$ as a catalyst in diisopropylamine gave **10a**–**c**. Reduction of the nitro group in **10a** and **10b** was accomplished with zinc in 30% aqueous NH_4OH–THF,[9] and the crude *N*-isobutyl-*o*-phenylenediamines were used without further purification. Condensation of the diamine with alloxane in acetic acid gave **11a–b**. Unprotected **4** and **5** were prepared by removal of the silyl groups with tetrabutylammonium fluoride with 14 and 48% overall yield, respectively, from **7a–b**. Compound **6** was prepared by silyl deprotection of **10c** prior to reduction and condensation with alloxane (43% overall yield from **7c**). Flavin analogues **2**[10] and **3**,[11] prepared for comparison, were synthesized according to the literature procedures[12] from commercially available 3,4-dimethyl-5-nitroaniline and 1-chloro-2-nitrobenzene, respectively.



Scheme 1. *Reagent*: (i) $NaNO_3$ (1.5 equiv.), H_2SO_4, 3 h, 40°C; (ii) *i*$BuNH_2$ (5 equiv.), Et_3N (1.5 equiv.), THF, 10–20 h, Δ; (iii) TIPS-C≡CH (2.5 equiv.), $Pd(PPh_3)_4$ (10% w/w), *i*Pr_2NH, 3–10 h, 120–140°C; (iv) TBDMS-C≡CH (1.5 equiv.), $Pd(PPh_3)_4$ (10% w/w), *i*Pr_2NH, 3 h, 120°C; (v) Zn (dust, 5 equiv.), 30% aq. NH_4OH–EtOH, 5 h, rt; (vi) alloxane (1.2 equiv.), boric acid (1.5 equiv.), AcOH, 12 h, rt; (vii) TBAF (2.5 equiv.), THF, 1 h, 0°C

The redox properties of flavins **2**–**6** were examined by cyclic voltammetry (CV) in dichloromethane.[11,13] The observed reduction potentials[14] of the flavin analogues along with ΔE values are summarized in Table 1. Bis(desmethyl)flavin, **2**, was taken as the base value and had a reduction potential of −709 mV($E_{1/2}$°). The redox potential of compound **4** was determined as −559 mV, 150 mV more positive than **2**. The mono C7/C8 alkynyl flavins, **5** and **6**, showed reduction potentials of 4 mV and 41 mV more positive than **2**, respectively. As expected, the electron-withdrawing properties of the alkynyl moiety moved the potential to more positive values. Those substituent effects corresponded favorably with the electron-withdrawing effect based on the Hammett σ values.[15]

In conclusion, the first ethynylflavin analogues (**4**–**6**) were synthesized with 14–48% overall yield in six steps. These compounds exhibit electrochemical properties consistent with previous studies. These compounds may find further utility as handles for other electroactive and functional moieties by the rich coupling chemistry available to terminal acetylenes. Investigations into the synthesis of riboflavins containing enediynes are in progress.

Table 1
Reduction potentials (mV) of flavins **2**–**6**[a]

flavin	$E_{1/2}$ (mV)[b]	ΔE (mV)[c]	σ_{m+p}[16]
2	- 709	0	0
3	- 791	-82	-0.24
4[17]	- 559	+150	0.44
5[18]	- 705	+4	0.04
6[18]	- 668	+41	0.16

[a] Flavins **2-6** (10^{-3} M) in CH_2Cl_2, TBAP (10^{-1} M) vs Ag/AgCl, scan rate 100 mV/s [b] $E_{1/2} = (E_p^c + E_p^a)/2$
[c] $\Delta E = E_{1/2}$ (**3-6**) – $E_{1/2}^o$

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14. A standard three-electrode cell with a glassy carbon working electrode, Ag/AgCl reference electrode, and platinum wire counter electrode were used.
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17. Characterization of compound **4**; mp 280 (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br, NH), 8.42 (s, 1H), 7.73 (s, 1H), 4.60 (br, 2H), 3.74 (s, 1H), 3.51 (s, 1H), 2.44 (m, 1H), 1.08 (d, 6H, J=6.7 Hz); ^{13}C NMR (100 MHz, DMSO-D_6) δ

159.3, 155.4, 151.1, 140.0, 135.0, 134.1, 133.0, 129.1, 121.1, 120.6, 89.1, 86.1, 81.1, 79.9, 50.2, 26.6, 19.5; FAB-MS calcd 318.3, found 319 (M+1). Cyclization of **4** in DMSO with 100 equiv. of 1,4-cyclohexadiene was examined. The ^{1}H NMR spectrum of the reaction products did show the presence of new aromatic hydrogens consistent with Bergman cyclization. Further kinetic experiments, including the redox dependant cyclization, are in progress.

18. All new compounds gave satisfactory spectral data (^{1}H NMR, ^{13}C NMR, FAB-MS).