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Photochemistry of 7-azide-1-ethyl-3-carboxylate-6,8-difluoroquinolone: a novel reagent for photoaffinity labeling

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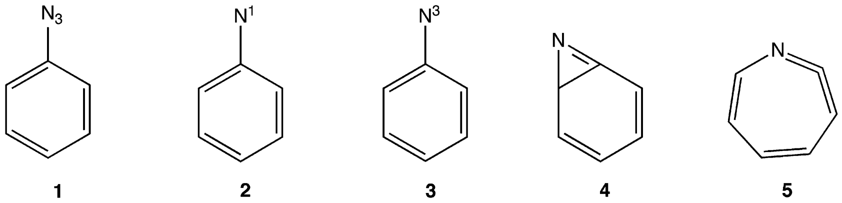
ABSTRACT

A novel reagent for photoaffinity labeling, 7-azido-1-ethyl-3-carboxylate-6,8-difluoroquinolone, was obtained by nucleophilic substitution of 1-ethyl-3-carboxylate-6,7,8-trifluoroquinolone. Photochemical reaction of this azide with diethyl amine gave 7-hydrazino-derivative as the major product. This compound was generated by singlet nitrene N–H insertion. In addition, 7-amino-1-ethyl-3-carboxylate-6,8-difluoroquinolone was also obtained.

The photochemical reaction of phenyl azide **1** has been described as wonderfully complex.[1–4] This reaction is initiated by the elimination of molecular nitrogen from phenyl azide to give a C_6H_5N fragment. At least four reactive intermediates have been associated with this fragment: singlet phenyl nitrene **2**, triplet phenyl nitrene **3**, benzazirine **4**, and 1,2-azacycloheptatetraene **5** (Scheme 1). The singlet phenyl nitrene **2** is considered the first intermediate formed upon photolysis of phenyl azide. Improved spectroscopic techniques have allowed direct observation of this short-lived intermediate.[5–7] It was also suggested[8] that singlet phenyl nitrene generates bicyclic benzazirine **4** which can undergo ring cleavage to 1,2-azacycloheptatetraene **5**. This latter intermediate has been trapped to give azepine type products.[9]

Aromatic azides are widely used in the biochemical technique called photoaffinity labeling (PAL).[10] This technique is used to identify amino acid residues present in the binding site of biological receptors. In this experiment, a light-sensitive moiety is appended to a natural substrate of an enzyme. Photolysis of the enzyme–substrate complex releases a reactive intermediate that, in an ideal experiment, will react with the first bond of the protein it encounters to form a robust new linkage between the reactive intermediate and the target biomolecule. Unfortunately, the trappable intermediate produced upon photolysis of phenyl azide is azacycloheptatetraene.[1–4] This intermediate is not the ideal species for an efficient PAL experiment since it reacts rather sluggishly.[11]

We have observed that the ring expansion of an aromatic singlet nitrene to 1,2-azacycloheptatetraene is strongly dependent on the substituents on the ring as well as the reaction temperature.[3,12] Singlet phenyl nitrene **2** undergoes intersystem crossing (ISC) to triplet nitrene **3** at 77 K while it undergoes ring expansion



Scheme 1.

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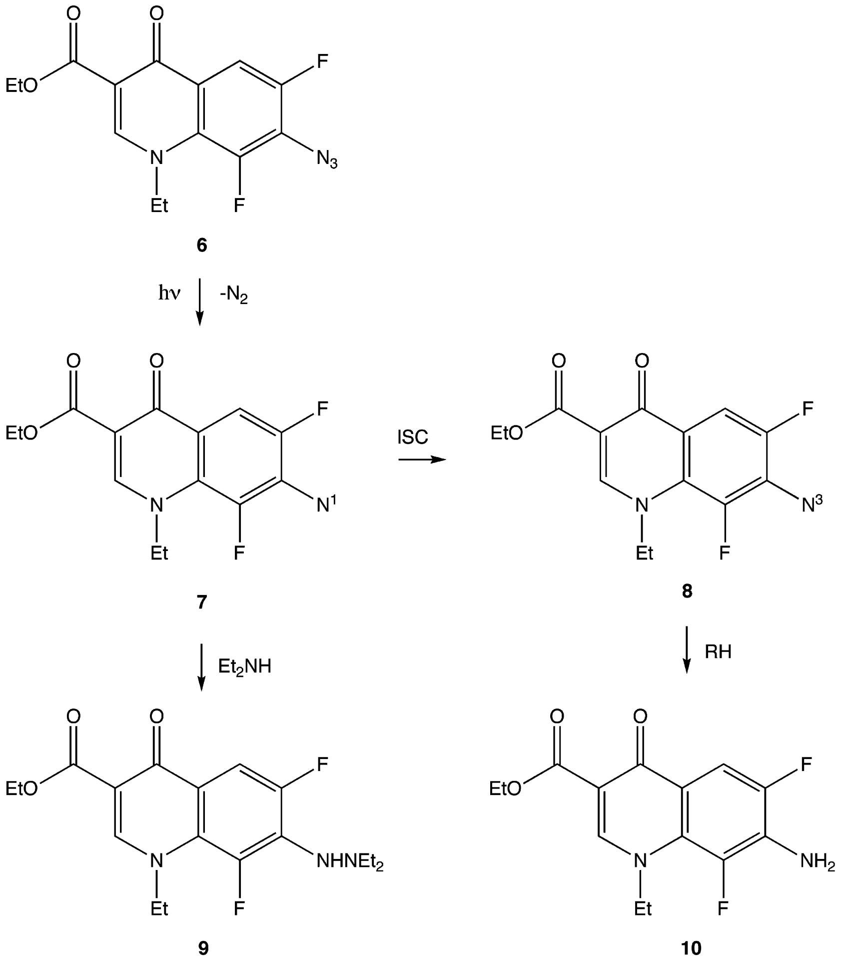

Scheme 2.

to **5** at room temperature. It was observed that polyfluorinated singlet nitrenes have interesting bimolecular chemistry.[13,14] In several papers, Platz[2,4,6,7] and Keana[15] have demonstrated that polyfluorinated aryl azides might be useful as photoaffinity labeling reagents. Furthermore, we have reported that two fluorine substituents ortho to the nitrene group retard ring expansion and allow bimolecular capture of singlet phenyl nitrene,[16,17] which is the ideal reaction for a PAL experiment.[11] Our experimental results were in good agreement with theoretical studies by Karney and Borden,[18,19] and laser flash photolysis experiments by Platz and collaborators.[20] We recently reported the synthesis and thermochemical reaction of 7-azido-1-ethyl-3-carboxylate-6,8-difluoroquinolone with amines.[21] However, thermochemical conditions are not suitable for PAL.[22] In this Letter, we report the photochemistry of this azide in diethyl amine.

Irradiation of 7-azido-1-ethyl-3-carboxylate-6,8-difluoroquinolone **6** (Scheme 2) in chloroform containing diethylamine gave a hydrazine derivative **9** in good yield.[23] In addition to this, 7-amino-1-ethyl-3-carboxylate-6,8-difluoroquinolone **10** was also obtained.[24] The mechanism for this photochemical reaction is presented. Upon photolysis, azide **6** gave a singlet nitrene **7** that generated the hydrazino-derivative by selective N–H insertion with diethyl amine.[21] In the reaction mixture, a small amount of 7-amino-1-ethyl-3-carboxylate-6,8-difluoroquinolone **10** was also obtained. This latter compound is most likely due to triplet nitrene reaction with a C–H bond in the solvent. A triplet nitrene could be generated by means of an intersystem crossing mechanism (ISC) induced by the presence of the ketone group in the azide structure.[2]

In a typical experiment, a chloroform solution of the arylazide containing diethylamine (2.0 M) was irradiated with 350 nm light in a Southern New England Rayonet photoreactor for 48 h. The reaction mixture was purged with N_2 during the irradiation. The solvent was removed to yield a brown solid. The solid was purified by column chromatography with silica gel using a mixture of ethyl acetate/hexane.

In conclusion, photochemistry of 7-azido-1-ethyl-3-carboxylate-6,8-difluoroquinolone in diethylamine gives 60% yield of singlet nitrene insertion product. Therefore, this azide could be a convenient reagent for photoaffinity labeling.

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23. *Hydrazine* **9**. White solid; yield 60%; mp: 192–194 °C, ^{1}H NMR ($CD_3SO_2CD_3$, ppm) 8.67 (1H, s, vinyl H), 7.99 (1H, dd, aromatic H), 4.45 (2H, q, OCH_2), 4.43 (2H, q, NCH_2), 4.22 (4H, q, CH_2), 1.39 (6H, t, CH_3), 1.27 (6H, t, CH_3); ^{19}F NMR ($CD_3SO_2CD_3$, ppm) −137.68 (1F, d), −152 (1F, d); IR (cm^{-1}) 3455 (N–H), 1651 (broad peak, C=O), 1057 (C–F); exact mass for $C_{18}H_{23}F_2N_3O_3$: 367.1707 amu, observed: 367.1711 amu.
24. *Amine* **10**. Brown solid; yield 20%; mp: 200–202 °C, ^{1}H NMR ($CD_3SO_2CD_3$, δ ppm) 8.70 (1H, s, vinyl H), 8.15 (1H, dd, aromatic H), 4.37 (4H, br q, $2CH_2$), 1.32 (3H, br t, CH_3), 1.26 (3H, br t, CH_3); ^{19}F NMR ($CD_3SO_2CD_3$, ppm) −135.09 (1F, d), −139.06 (1F, d); IR (cm^{-1}) 3425 (NH_2), 1714 (C=O, ester) 1651 (C=O, cetona), 1134 (C–F); exact mass for $C_{14}H_{14}F_2N_2O_3$: 296.0972 amu, observed: 296.0975 amu.