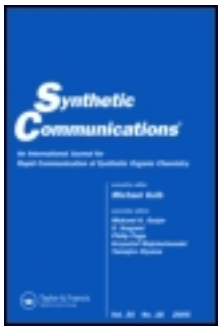

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An efficient synthetic approach to fluorescent oxazole-4-carboxylate derivatives

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Abstract

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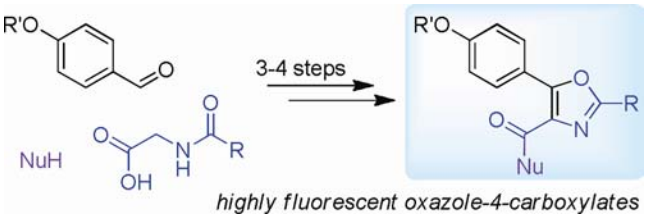

INTRODUCTION

Oxazoles represent an important class of heterocyclic compounds. [1,2] Oxazole moiety is found among biologically active compounds. [3–12] Oxazole derivatives are used as luminophores for scintillation [13] and as fluorescent labels. [14–17]

Known methods for synthesis of oxazole-4-carboxylates include metalation followed by the action of electrophile, [18] palladium-catalysed coupling reactions [19] and cyclization of brominated derivatives of dehydropeptides. [17, 20, 21]

RESULTS AND DISCUSSION

In the course of our systematic studies in the chemistry of arylideneimidazolones – chromophores of GFP-like fluorescent proteins [22, 23] we attempted to introduce halogen

substituent at vinylic position of the GFP chromophore (**A**, Scheme 1). This halogenated chromophore (**A**) would serve as a useful synthetic intermediate in the chemistry of chromophores of fluorescent proteins.

Among several synthetic approaches to **A** we examined the one outlined in Scheme 1. It is based on Erlenmeyer azlactone (**1**) formation from aldehyde and acylglycine with subsequent opening of azlactone cycle with nucleophile, bromination of the acylaminocinnamic acid **2** and finally, cyclization of vinylic bromides **3** upon the action of base. However, instead of the desired brominated imidazolinone **A** the final cyclization step produced only oxazoles **4**. Due to little information value of NMR spectra in case of highly substituted heterocycles we used X-ray analysis to confirm the structure of final products **4** (Fig. 1).

This undesired oxazole formation can be viewed as a useful synthetic method for preparation of a wide range of derivatives of 5-aryloxazole-4-carboxylic acids. The method makes it possible to introduce different aryl substituents at the position 5, aryl or alkyl substituents at position 2 of oxazole, and gives access not only to free carboxyl at position 4, but also to a range of its amide derivatives. The advantages of the synthetic strategy presented are: synthetic availability of a wide range of oxazolones **1**, [23] much better yields compared to an early report [21] and also avoiding palladium coupling and metalation procedures.

We characterized optical spectra of the chromophores obtained (Fig. 2 and Table 1). As expected, all chromophores possessed absorption maxima in UV region. At the same time, their emission peaks were in violet-blue region of the visible spectrum due to a large Stockes shift. The brightest fluorescence (quantum yield 0.82) was observed for **4b**. Chromophore **4a** with an ionizable hydroxyl group showed expected red shift of absorption and emission spectra upon deprotonation in basic conditions. Other chromophores (including **4d** possessing a carboxylic group) did not change absorption maxima in the pH range 2-12. Compared to **4b**, **4a** had considerably lower quantum yield (0.25), which further drastically decreased to 0.01 in the anionic state. Introduction of phenyl substituent in **4c** (compared to methyl in **4b**) resulted in a significantly red-shifted absorption, but practically did not change emission maximum.

We believe that 5-aryl-4-carboxyoxazole is a promising core for creation of new fluorescent dyes. This core can ensure high quantum yield of fluorescence and emission in the visible spectrum in spite of low size of the molecule. As spectral properties of these compounds are very sensitive to introduced substituents we expect that red shifted fluorophores can be obtained with this core structure.

EXPERIMENTAL

NMR spectra were recorded on Bruker Avance III 700 spectrometer. UV-vis spectra were recorded with a Varian Cary 100 spectrophotometer. Fluorescence excitation and emission spectra were recorded with a Varian Cary Eclipse fluorescence spectrophotometer.

Oxazolones **1a-c** were prepared by literature procedures. [23]

GENERAL PROCEDURE FOR PREPARATION OF ACYLAMINOCINNAMIC ACIDS 2

2a: To a suspension of **1a** (2.45 g, 10.0 mmol) in dry acetonitrile (50 mL) cyclohexylamine (1.49 g, 15.0 mmol) was added. The mixture was stirred for 30 minutes, while white precipitate was formed. Then the reaction mixture was cooled to 0^{o}C and filtered, precipitate was washed by small amount of acetonitrile and diethyl ether. Yield 2.65 g (77%). Mp 224-227^{o}C

^{1}H NMR (DMSO-d_6) δ 9.33 (br. s, 1H), 7.69 (d, 1H, J=7.67Hz), 7.56 (d, 2H, J=8.11Hz), 7.14 (d, 2H, J=8.11Hz), 6.90 (s, 1H), 3.61 (m, 1H), 2.27 (s, 3H), 1.98 (s, 3H), 1.72-1.68 (m, 4H), 1.59 (m, 1H), 1.27 (m, 4H), 1.12 (m, 1H).

^{13}C NMR (DMSO-d_6) δ 20.76 (CH_3), 22.79 (CH_3), 24.78 (2xCH_2), 25.20 (CH_2), 32.18 (2xCH_2), 48.19 (CH), 121.76 (2xCH), 125.55 (CH), 130.26 (2xCH), 130.60, 131.94, 150.09, 164.08, 168.96, 169.13.

HRMS (ESI) calcd for $C_{19}H_{24}N_2O_4$ 344.1736, found 344.1742.

GENERAL PROCEDURE FOR BROMINATED ACYLAMINOCINNAMIC ACIDS 3

3a: To a solution of **2a** (1.58 g, 5.0 mmol) in dry dichloromethane (50 mL) $NaHCO_3$ (1.68 g, 20.0 mmol) was added. Then a solution of bromine (1.0g, 6.3 mmol) in dichloromethane (10 mL) was added with stirring. After the addition was complete the mixture was stirred for additional 30 minutes, filtered, diluted with 100 mL of dichloromethane, washed with 5% Na_2SO_3 (50 mL), water (2x50mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The resulting white solid was washed with small amount of diethyl ether giving 1.85 g (88%) of **3a** containing **4a** as a trace impurity. Mp 221-224^oC.

H NMR (DMSO-d_6) δ 9.38 (br. s, 1H), 7.66 (d, 1H, J=7.89Hz), 7.33 (d, 2H, J=8.55Hz), 7.08 (d, 2H, J=8.33Hz), 3.26 (m, 1H), 2.26 (s, 3H), 1.99 (s, 3H), 1.49 (m, 2H), 1.42 (m, 1H), 1.30 (m, 2H), 1.06 (m, 2H), 0.94 (m, 1H), 0.77 (m, 2H).

^{13}C NMR (DMSO-d_6) δ 20.72 (CH_3), 22.39 (CH_3), 24.27 (2xCH_2), 25.03 (CH_2), 32.18 (2xCH_2), 47.50 (CH), 113.05, 121.34 (2xCH), 130.37 (2xCH), 134.66, 135.59, 150.47, 161.32, 167.91, 168.86.

HRMS (ESI) calcd for $C_{19}H_{23}BrN_2O_4$ 422.0841, found 422.0848.

GENERAL PROCEDURE FOR PREPARATION OF OXAZOLES 4

4a: A solution of **3a** (0.847 g, 2.0mmol) in wet DMF (30 mL DMF and 5 mL water) was refluxed with K_2CO_3 (0.69 g, 5.0 mmol) for 1-2 minutes. The solvent was removed in vacuo, the mixture was dissolved in 100 mL DCM, acidified with 5% HCl, washed with

water (2x50 mL), brine and dried over Na_2SO_4. The solution was concentrated *in vacuo* to give a white solid, which was purified by column chromatography: ($CHCl_3$:EtOH=20:1). Yield 440 mg, (73%). Mp 202-204^oC.

^1H NMR (DMSO-d_6) δ 9.90 (s, 1H), 8.06 (d, 2H, J=8.33Hz), 7.75 (d, 1H, J=7.89Hz), 6.85 (d, 2H, J=8.55Hz), 3.74 (m, 1H), 2.47 (s, 3H), 1.78 (m, 2H), 1.71 (m, 2H), 1.58 (m, 1H), 1.38-1.27 (m, 4H), 1.13 (m, 1H).

^{13}C NMR (DMSO-d_6) δ 13.19 (CH_3), 24.76 (2xCH_2), 25.05 (CH_2), 32.15 (2x CH_2), 47.56 (CH), 115.06 (2xCH), 118.10, 127.43, 129.27 (2xCH), 151.25, 157.84, 158.61, 160.01.

HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found 300.1468.

Please see the Supplementary Information, available online, for complete experimental and spectral details.

ACKNOWLEDGMENT

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ACCEPTED MANUSCRIPT

Table 1. Spectral properties of **4a-d**.

Chromophore	Water				EtOH	
	Absorbance max, nm	Extinction coefficient, $M^{-1}cm^{-1}$	Emission max, nm	Fluorescence quantum yield	Absorbance max, nm	Extinction coefficient, $M^{-1}cm^{-1}$
4a	290	19000	400	0.25	300	26000
4a anion [a]	322	24000	460	0.01	340	31000
4b	291	18000	395	0.82	298	27000
4c	333	12000	393	0.15	317	25000
4d	309	24000	411	0.65	315	17000

[a] In the presence of 10 mM NaOH.

Scheme 1. Synthesis of oxazoles (**4**) via Erlenmeyer azlactones. Attempt to synthesize halogenated GFP chromophore derivative (**A**)

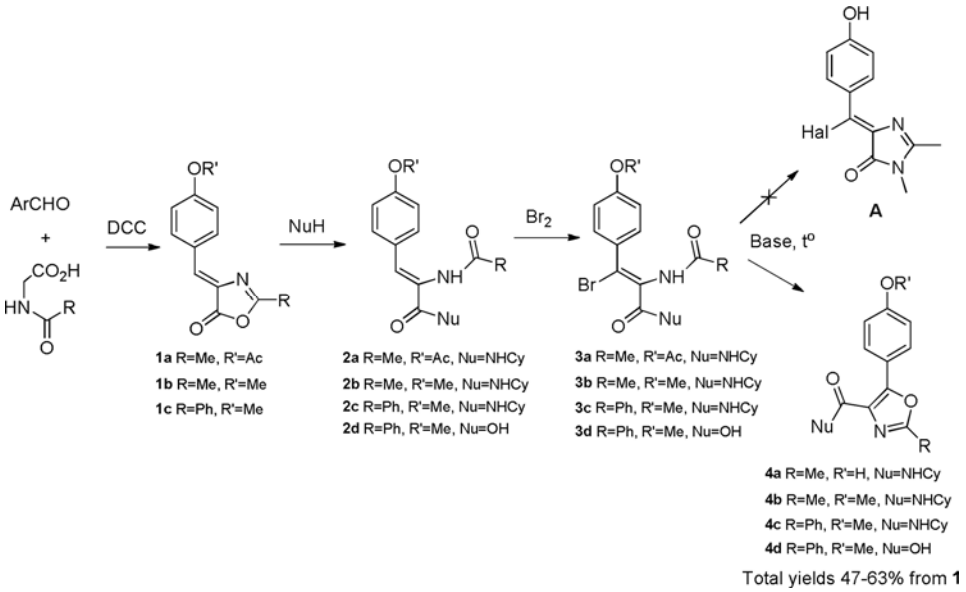

Figure 1. Structure of 4b by X-ray crystallography.

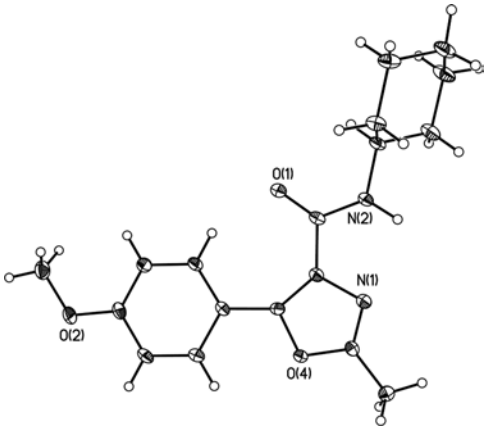

Figure 2. Absorbance and fluorescence spectra of oxazoles **4a-d** in water.