Fluorescence Studies of some 1,2,3-Triazolo[1,5-*a*]pyridine and Imidazo[1,2-*a*]pyridine Esters and their Vinylogues

Elliot J. Latham and Stephen P. Stanforth*

Department of Chemical and Life Sciences,
University of Northumbria at Newcastle,
Newcastle upon Tyne, NE1 8ST, UK

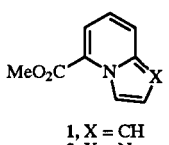
Received February 12, 1996

Dedicated to the memory of Professor Nicholas Alexandrou

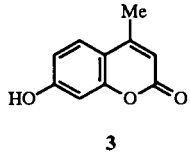
The relative fluorescence intensity of a number of 1,2,3-triazolo[1,5-*a*]pyridine esters **6** and **7** and imidazo-[1,2-*a*]pyridine esters **10** and **11** were determined and compared with methyl imidazo[1,2-*a*]pyridine-5-carboxylate **2** and 4-methylumbelliferone **3**.

J. Heterocyclic Chem., **33**, 991 (1996).

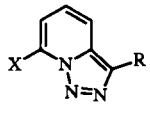
Recently we have reported our interest in nitrogen containing heterocycles which might be incorporated into fluorogenic reagents [1]. We were specifically interested in aza-substituted derivatives of the indolozine ester **1**, where the bridgehead nitrogen atom can be mesomerically associated with the ester substituent and we anticipated that heterocyclic molecules with this structural feature would probably be associated with useful fluorescent properties. Our interest in bicyclic heterocycles of this type was initially aroused when we observed that methyl imidazo[1,2-*a*]pyridine-5-carboxylate **2** was highly fluorescent [2]; the relative fluorescence intensity of heterocycle **2** was found to be 29% of 4-methylumbelliferone **3** in methanol solution (Table). The highly fluorescent nature of 7-arylimidazo[1,2-*a*]pyridine-5,6-dicarboxylates has been noted by other workers [3] and these molecules also have the bridgehead nitrogen atom mesomerically associated with the 5-ester group.



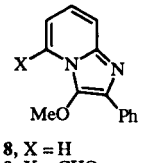
1, X = CH
2, X = N



3



4, X = H
5, X = CHO
6, X = CO_2Me
7, X = CH=$CHCO_2Me$



8, X = H
9, X = CHO
10, X = CO_2Me
11, X = CH=$CHCO_2Me$

In formulae **4-7**, **a**, R = H, **b**, R = Me; **c**, R = *t*-Bu; **d**, R = Ph

3-Substituted methyl 1,2,3-triazolo[1,5-*a*]pyridines-7-carboxylates **6** and their vinylogues **7** were chosen initially for preliminary studies as diaza analogues of indolizine **1** because these heterocycles **6** and **7** were readily prepared from the corresponding 4-substituted 1,2,3-triazolo[1,5-*a*]pyridine derivatives **4** as previously described by us. Thus, we have already reported the preparation of heterocycles **6b**, **6d**, **7a**, **7b** and **7d** [1] and we have now synthesised the *tert*-butyl derivative **7c** from 3-*tert*-butyl-1,2,3-triazolo[1,5-*a*]pyridine **4c** *via* 3-*tert*-butyl-1,2,3-triazolo[1,5-*a*]pyridine-7-carbaldehyde **5c** using similar methodology (see Experimental).

We have also prepared the methoxyimidazo[1,2-*a*]pyridine esters **10** and **11** in which the methoxy group can be mesomerically associated with the ester substituent. Compound **10** was synthesised by methylation of the corresponding acid [5] with dimethylsulfate. Regiospecific lithiation of compound **8** using a literature proceedure [5] and quenching the resulting lithio derivative with dimethylformamide (DMF) gave the aldehyde **9** together with unreacted compound **8**. The crude reaction mixture was heated with carbomethoxymethylenetriphenylphosphorane giving the vinylogous ester **11**.

The fluorescence excitation and emission maxima of 1,2,3-triazolo[1,5-*a*]pyridines and imidazo[1,2-*a*]-pyridines prepared for this study are recorded in the Table. Of the 1,2,3-triazolo[1,5-*a*]pyridines studied, only the vinylogous heterocycles **7** (with the exception of compound **7d**) showed relative fluorescence intensities comparable with or greater than the imidazo[1,2-*a*]pyridine ester **2**. The increase in relative fluorescence intensities of 1,2,3-triazolo[1,5-*a*]pyridines was pronounced along the

Table

Relative Fluorescence Intensities of Heterocycles in Methanol

Compound	λ_{max} excitation (nm)	λ_{max} emission (nm)	Relative Fluorescence Intensity (**3** = 100)
2	355	450	29
3	327	386	100
6b	350	469	1
6d	361	516	1
7a	352	458	44
7b	368	483	28
7c	369	481	25
7d	384	520	2
10	366	523	13
11	394	560	3

vinylogous series **6b** to **7b** whereas in contrast there was a decrease in relative fluorescence intensities along the vinylogous series of imidazo[1,2-*a*]pyridines **10** and **11**. This decrease has been attributed to steric interactions between the 3-methoxy group and the 5-alkenylester substituent which prevents the 5-alkenylester substituent achieving planarity with the heterocyclic ring. Phenyl substituted 1,2,3-triazolo[1,5-*a*]pyridines **6d** and **7d** both had low relative fluorescence intensities.

EXPERIMENTAL

Proton nmr were determined at 90 MHz in deuteriochloroform solution. Infra-red spectra were recorded as potassium bromide discs.

Fluorescence spectra were determined using a Hitachi F-4000 fluorescence spectrophotometer. Solutions (1.3-2.3 x 10^{-6} molar) were prepared by dilution of stock solutions which were prepared from accurately weighed heterocycles in spectroscopic grade methanol. The relative fluorescence intensities of heterocycles were determined and adjusted to constant concentration by application of an appropriate scaling factor since fluorescence intensity is linearly related to concentration in dilute solutions [6].

Methyl *trans*-3-*tert*-Butyl-1,2,3-triazolo[1,5-*a*]pyridine-7-propenoate **7c**.

Compound **7c**, mp 163-165° (from toluene) was prepared as a yellow powder from compound **4c** *via* aldehyde **5c** in a similar way to other 1,2,3-triazolo[1,5-*a*]pyridine-7-propenoates [1] in 7% overall yield. The crude aldehyde **5c** was used directly in the preparation of compound **7c** and was not characterised. Compound **7c** had; ir: υ 3068, 2973, 1720, 1637, 1610 and 1231 cm^{-1}; ^1H nmr: δ 8.12-7.64 (3H, m, ArH + -CH=CH-), 7.32-7.15 (2H, m, ArH + -CH=CH-), 3.85 (3H, s, $-CO_2Me$) and 1.60 (9H, s, $-CMe_3$) ppm.

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.8; H, 6.6; N, 16.2. Found: C, 64.7; H, 6.7; N, 16.35.

Methyl 3-Methoxy-2-phenylimidazo[1,2-*a*]pyridine-5-carboxylate **10**.

A stirred mixture of 3-methoxy-2-phenylimidazo[1,2-*a*]pyridine-5-carboxylic acid [5] (0.5 g), potassium carbonate (1.03 g) and dimethylsulfate (0.24 g) in acetone (10 ml) was heated under reflux for 3 hours. The mixture was allowed to cool to room temperature, poured into water and extracted with dichloromethane. The combined organic extracts were washed with water, dried (magnesium sulfate) and evaporated. The residue was purified by column chromatography over silica gel (eluent, ethyl acetate) giving compound **10**, 0.15 g (29%) as a pale yellow powder, mp 91-93° (from hexane); ir: υ 3076, 2998, 2949, 1731, 1564 and 1280 cm^{-1}; ^1H nmr: δ 8.06 (2H, dd, J = 8 and 1.5 Hz, ArH), 7.76-7.20 (4H, m, ArH), 7.08 (2H, t, J = 3.5 Hz, ArH), 4.01 (3H, s, -OMe) and 3.85 (3H, s, -OMe) ppm.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.1; H, 5.0; N, 9.9. Found: C, 68.0; H, 4.9; N, 10.0.

Methyl *trans*-3-Methoxy-2-phenylimidazo[1,2-*a*]pyridine-5-propenoate **11**.

Compound **8** (0.5 g) was lithiated according to the published proceedure [5]. The mixture was quenched in the cold with DMF (0.16 g) and was then allowed to warm to room temperature. The mixture was poured into water, extracted with ether and the combined organic extracts were washed with water and dried (magnesium sulfate). The residue was purified by column chromatography over silica gel (eluent, ethyl acetate) giving 0.5 g of a 1:1 mixture of compound **8** and aldehyde **9** by ^1H nmr spectroscopy. This mixture (0.25 g) and carbomethoxymethylenetriphenylphosphorane (0.67 g) in dry toluene (10 ml) was heated at reflux for 4.5 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temperature, evaporated and the residue purified by column chromatography over silica gel (eluent, petroleum ether bp 40-60°:ethyl acetate, 2:1) giving compound **11** as a yellow powder, 0.13 g (43%), mp 171-173.5° dec (from heptane); ir: υ 3069, 2940, 1713, 1636, 1562 and 1208 cm^{-1}; ^1H nmr: δ 8.69 (1H, d, J = 16 Hz, -CH=CH-), 8.20-8.02 (2H, m, ArH), 7.64-7.00 (6H, m, ArH), 6.50 (1H, d, J = 16 Hz, -CH=CH-) and 3.86 (6H, s, 2 x -OMe) ppm.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 69.8; H, 5.0; N, 8.9.

Acknowledgements.

We warmly thank Synthetic Chemicals Ltd., for financial assistance and Mr. Lance S. Fuller of Synthetic Chemicals Ltd., for encouragement. We also thank Dr. Arthur James for useful advice and discussions.

REFERENCES AND NOTES

[1] E. J. Latham and S. P. Stanforth, *J. Heterocyclic Chem.*, **32**, 787 (1995).

[2] A. P. Shawcross and S. P. Stanforth, unpublished results.

[3] H. -J. Knölker, R. Boese and R. Hitzemann, *Chem. Ber.*, **123**, 327 (1990).

[4] B. Abarca, A. Asensio, R. Ballesteros, J. Bosch, G. Jones, F. Mojarrad, M. R. Metni and C. M. Richardson, *J. Chem. Res. (M)*, 0346 (1990).

[5] A. J. Guildford, M. A. Tometzki and R. W. Turner, *Synthesis*, 987 (1983).

[6] G. G. Guilbault, Practical Fluorescence, Theory, Methods and Techniques, Dekker, New York, 1973.