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Lithiation of 1,2,3-triazolo[1,5-*a*]pyridines **4b** and **4c** with lithium diisopropylamide (LDA) gave the corresponding lithio derivatives **5b** and **5c** from which esters **6b** and **6c** were obtained by treatment with carbon dioxide and then dimethyl sulfate. Lithio derivatives **5a-5c** reacted with DMF giving aldehydes **7a-7c**. Esters **9a-9c** were prepared from aldehydes **7a-7c** and carbomethoxymethylenetriphenylphosphorane.

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Derivatives of 4-methylumbelliferone **1** are commonly used as enzyme substrates because the different fluorescent properties of the coumarin ring in the substrate and product provide a means of monitoring enzymatic reactions [1,2]. Coumarin derivatives have also found use in other areas. For example the different fluorescent properties of bound and unbound macrocyclic coumarin derivatives have also recently been used as a method to detect metal ions [3,4]. We are interested in the synthesis of nitrogen containing heterocycles which might be incorporated into fluorogenic reagents in a similar way to coumarin derivatives. The synthesis and fluorescence properties of substituted imidazo[1,2-*a*]pyridines which possess an ester group at the 5-position have been reported [5,6] and we have observed that methyl imidazo[1,2-*a*]pyridine-5-carboxylate **2** [7] shows useful fluorescent properties [8]. This observation encouraged us to investigate the synthesis and fluorescent properties of aza substituted indolizines **3** because the bridgehead nitrogen lone pair of electrons in structures **2** and **3** can both be mesomerically associated with the ester group. This paper reports the synthesis of 1,2,3-triazolo[1,5-*a*]pyridines **6b** and **6c** as aza analogues of indolizine derivative **3** and

also the synthesis of the vinylogous esters **9a-9c**.

1,2,3-Triazolo[1,5-*a*]pyridines were chosen for preliminary studies because directed lithiation of derivatives **4** with LDA is known to give the corresponding lithio derivatives **5** which have been trapped with a variety of electrophiles [9]. We lithiated compounds **4b** and **4c** under similar conditions to those reported and trapped the lithio derivatives **5b** and **5c** with carbon dioxide. The resulting carboxylic acids were not characterised but were treated directly with dimethyl sulfate to give the esters **6b** and **6c**. The attempted preparation of ester **6a** by this method was however unsuccessful.

We next turned our attention to the synthesis of aldehydes **7a-7c** as precursors to the vinylogous esters **9a-9c**. Compound **4a** has been reported to react with LDA and then dimethylformamide (DMF) to give the alcohol derivative **8a** and not the expected aldehyde **7a** [9]. In our hands, this reaction yielded the aldehyde **7a** although the proton nmr spectrum of the crude reaction mixture indicated the presence of traces of the alcohol **8a**. Sodium borohydride reduction of the aldehyde **7a** gave the alcohol **8a** whose melting point was close to that previously reported [9]. Similarly, heterocycles **4b** and **4c** gave aldehyde derivatives **7b** and **7c** respectively. Aldehydes **7a-7c** all reacted smoothly with carbomethoxymethylenetriphenylphosphorane giving the esters **9a-9c**.

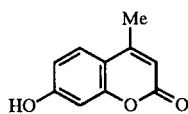
The esters **6b**, **6c** and **9a-9c** have been successfully prepared and their fluorescence properties are now being investigated.

## EXPERIMENTAL

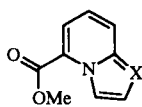
Proton nmr spectra were determined at 90 MHz in deuteriochloroform solution. Infra-red spectra were recorded as potassium bromide discs.

Methyl 1,2,3-Triazolo[1,5-*a*]pyridine-7-carboxylates **6b** and **6c**.

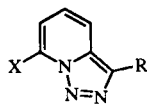
Compound **4b** (5.0 g) was lithiated in anhydrous ether solution at -40° for 6 hours with butyllithium (25 ml of a 1.6 M hexane solution) and diisopropylamine (4.3 g) using the method reported previously [9]. Compound **4c** (5.0 g) was similarly lithiated with butyllithium (25 ml of a 1.6 M hexane solution)



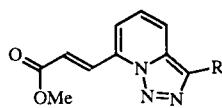
**1**



**2** X = N  
**3** X = CH



**4** X = H  
**5** X = Li  
**6** X = CO<sub>2</sub>Me  
**7** X = CHO  
**8** X = CH<sub>2</sub>OH



**9**

In formulae **4-9**: a, R = H; b, R = Me; c, R = Ph

and diisopropylamine (2.9 g). The ethereal solution of lithio derivatives **5b** and **5c** were poured onto solid carbon dioxide and the excess carbon dioxide was allowed to evaporate giving a solid. Dichloromethane and water were then added and the aqueous layer was neutralised by addition of dilute hydrochloric acid with constant swirling. The organic layer was dried (magnesium sulfate) and evaporated. A mixture of the resulting solid, acetone, potassium carbonate and an equimolar quantity of dimethyl sulfate were heated at reflux for 4 hours. The reaction mixture was filtered and the filtrate was added to water and dichloromethane. The organic layer was dried (magnesium sulfate) and evaporated yielding the esters **6b** (10%) and **6c** (10%) after column chromatography over silica gel (eluent, ethyl acetate). The attempted preparation of ester **6a** by this method was unsuccessful.

Compound **6b** was obtained as a yellow powder, mp 146-148° (from methanol); ir:  $\nu$  3080, 2950, 1730, 1625, 1450, 1280 and 755  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.89 (1H, d,  $J = 11$  Hz, ArH), 7.78 (1H, t,  $J = 11$  Hz, ArH), 7.70 (1H,  $J = 11$  Hz, ArH), 4.10 (3H, s,  $-\text{CO}_2\text{Me}$ ) and 2.66 (3H, s,  $-\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_9\text{H}_9\text{N}_3\text{O}_2$ : C, 56.5; H, 4.75; N, 22.0. Found: C, 56.45; H, 4.7; N, 21.85.

Compound **6c** was obtained as yellow plates, mp 118-120° (from methanol); ir:  $\nu$  3080, 2920, 1710, 1625, 1490, 1150 and 765  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  8.22 (1H, dd,  $J = 9$  and 1.5 Hz, ArH), 8.01-7.69 (2H, m, ArH), 7.69-7.29 (5H, m, ArH) and 4.12 (3H, s,  $-\text{CO}_2\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2$ : C, 66.4; H, 4.4; N, 16.6. Found: C, 66.65; H, 4.35; N, 16.4.

#### 1,2,3-Triazolo[1,5-*a*]pyridine-7-carbaldehydes **7a-7c**.

To an ethereal solution of lithio derivatives **5a-5c**, prepared as described above from compounds **4a-4c** respectively, was added DMF at  $-40^\circ$ . The mixture was allowed to warm to room temperature with stirring and allowed to stand overnight. Dichloromethane and water was added and the aqueous layer was neutralised by addition of dilute hydrochloric acid with constant swirling. The organic layer was dried (magnesium sulfate) and evaporated giving the crude aldehydes **7a-7c**.

#### Compound **7a**.

Compound **4a** (2.0 g) was lithiated with butyllithium (8 ml of a 2.5 *M* solution in hexane) and diisopropylamine (2.0 g) and the resulting lithio derivative **5a** was quenched with DMF (1.45 g) giving compound **7a**, 1.45 g (58%) as a rust colored powder, mp 95-99° (from toluene); ir:  $\nu$  3060, 1690 and 1520  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  12.00 (1H, s,  $-\text{CHO}$ ), 8.30 (1H, s, ArH), 8.05 (1H, dd,  $J = 8$  and 1.5 Hz, ArH), 7.72 (1H, dd,  $J = 7$  and 1.5 Hz, ArH) and 7.42 (1H, dd,  $J = 8$  and 7 Hz, ArH) ppm.

#### Compound **7b**.

Compound **4b** (2.0 g) was lithiated with butyllithium (8 ml of a 2.5 *M* solution in hexane) and diisopropylamine (1.9 g) and the resulting lithio derivative **5b** was quenched with DMF (1.3 g) giving compound **7b**, 0.86 g (36%) as a tan colored powder, mp 102-105° (from toluene); ir:  $\nu$  3080, 2915, 1690, 1625 and 1525  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  11.00 (1H, s,  $-\text{CHO}$ ), 7.90 (1H, dd,  $J = 9$  and 1.5 Hz, ArH), 7.66 (1H, dd,  $J = 7$  and 1.5 Hz, ArH), 7.38 (1H, dd,  $J = 9$  and 7 Hz, ArH) and 2.70 (3H, s,  $-\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_8\text{H}_7\text{N}_3\text{O}$ : C, 59.6; H, 4.4; N, 26.1. Found: C, 60.0; H, 4.55; N, 25.9.

#### Compound **7c**.

Compound **4c** (0.75 g) was lithiated with butyllithium (2 ml of a 2.5 *M* solution in hexane) and diisopropylamine (0.51 g) and the resulting lithio derivative **5c** was quenched with DMF (1.3 g) giving compound **7c**, 0.50 g (58%) as a tan colored powder, mp 152-156° (from toluene); ir:  $\nu$  3050, 1700, 1615 and 1530  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  11.00 (1H, s,  $-\text{CHO}$ ), 8.28 (1H, dd,  $J = 8$  and 1.5 Hz, ArH), 8.08-7.80 (2H, m, ArH) and 7.79-7.16 (5H, m, ArH) ppm.

Aldehydes **5a** and **5c** failed to give satisfactory microanalysis but their structures were confirmed by their transformations into compounds **8a**, **9a** and **9b** (see below).

#### 7-Hydroxymethyl-1,2,3-triazolo[1,5-*a*]pyridine **8a**.

A mixture of aldehyde **7a** (0.075 g) and sodium borohydride (0.05 g) in methanol (10 ml) was heated at reflux for 1 hour. The mixture was allowed to cool to room temperature and evaporated. Water and dichloromethane were added to the residue. The organic layer was dried (magnesium sulfate) and evaporated giving the alcohol **8a**, 0.03 g (40%), mp 126-128° (from toluene), lit mp 127-129° [9].

#### Methyl *trans*-1,2,3-Triazolo[1,5-*a*]pyridine-7-propenoates **9a-9c**.

A mixture of the aldehyde **7a-7c** and carbomethoxymethylenetriphenylphosphorane in dichloromethane was stirred at room temperature for 3 hours under a nitrogen atmosphere. The mixture was evaporated and the esters **9a-9c** were isolated by column chromatography over silica gel (eluent, ethyl acetate for compound **9a**, petroleum ether:ethyl acetate, 1:1 for compounds **9b** and **9c**).

#### Compound **9a**.

Aldehyde **7a** (0.20 g) and carbomethoxymethylenetriphenylphosphorane (1.0 g) gave compound **9a**, 0.17 g (62%) as a fawn colored powder, mp 149-152° (from toluene); ir:  $\nu$  3100, 3010, 2960, 1725, 1640, 1615, 1435 and 1230  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  8.20 (1.5H, m, ArH +  $-\text{CH}=\text{CH}-$ ), 8.00 (0.5H, s,  $-\text{CH}=\text{CH}-$ ), 7.88-7.75 (1H, m, ArH), 7.40-7.20 (3H, m, ArH +  $-\text{CH}=\text{CH}-$ ) and 3.90 (3H, s,  $-\text{CO}_2\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$ : C, 59.1; H, 4.5; N, 20.7. Found: C, 59.2; H, 4.35; N, 20.65.

#### Compound **9b**.

Aldehyde **7b** (0.15 g) and carbomethoxymethylenetriphenylphosphorane (0.7 g) gave compound **9b**, 0.15 g (74%) as yellow needles, mp 162-164° (from toluene); ir:  $\nu$  3105, 3005, 2950, 1710, 1640, 1615, 1430 and 1230  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  8.05 (1H, d,  $J = 18$  Hz,  $-\text{CH}=\text{CH}-$ ), 7.80-7.54 (2H, m, ArH), 7.24 (2H, m, ArH +  $-\text{CH}=\text{CH}-$ ), 3.90 (3H, s,  $-\text{CO}_2\text{Me}$ ) and 2.70 (3H, s,  $-\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$ : C, 60.8; H, 5.1; N, 19.35. Found: C, 60.6; H, 4.8; N, 19.4.

#### Compound **9c**.

Aldehyde **7c** (0.25 g) and carbomethoxymethylenetriphenylphosphorane (0.8 g) gave compound **9c**, 0.28 g (90%) as a yellow powder, mp 186-188° (from toluene); ir:  $\nu$  3100, 3050, 2960, 1720, 1635, 1610, 1430 and 1235  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  8.20-7.20 (10H, m, ArH +  $-\text{CH}=\text{CH}-$ ) and 3.88 (3H, s,  $-\text{CO}_2\text{Me}$ ) ppm.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2$ : C, 68.8; H, 4.2; N, 15.05. Found: C, 68.45; H, 4.4; N, 15.2.

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