

## REACTIVITY OF HETEROAROMATIC ALDEHYDES WITH LOW VALENT TITANIUM

Luis Castedo\*, M. Magdalena Cid, Rosa Domínguez, Julio A. Seijas, and M. Carmen Villaverde  
 Departamento de Química Orgánica, Universidad de Santiago de Compostela,  
 Santiago de Compostela, Spain

Abstract- Behaviour of various aromatic heterocycles under dicarbonylic coupling with low valent titanium was studied. The results showed that the electron donating properties of the ring affect the degree of oxidation of the coupled compound.

In the course of a study on total synthesis of natural products we became interested in the preparation of azastilbenes. To carry out this synthesis, we chose the same methodology as used before for the synthesis of other stilbenes, mixed dicarbonylic coupling with low valent titanium;<sup>1</sup> this methodology has been extensively used for preparation of alkyl- and arylalkenes.<sup>2</sup> When we tried the synthesis of 4-azastilbenes by mixed coupling of 4-pyridinecarbaldehyde and benzaldehyde, we obtained a secondary product, 1,2-bis(4-pyridyl)ethane (1), due to the symmetrical coupling of two 4-pyridinecarbaldehyde units with a further reduction. When the 4,4'-diazastilbene was reacted with low valent titanium, reduced product was obtained after 1 h in 70% yield, this fast reduction of the stilbenic double bond agrees with the fact that no 4,4'-diazastilbene could be isolated from the coupling reaction. This result prompted us to study how heteroaromatic rings, with differing electron donating properties, behave under these reaction conditions. In the present paper we report the results obtained in the dicarbonylic coupling of the aromatic aldehydes shown in the Table 1. The structures of all compounds, known and new, were established from spectroscopic and analytical data, and comparison with the literature (Table 2).

The results obtained show that in pyridinecarbaldehydes the position of the nitrogen atom affects the reactivity of the compound in such a way as to determine the oxidation degree of the products. Thus when 4-pyridinecarbaldehyde was used, we obtained exclusively the reduced compound (1); with 3-pyridinecarbaldehyde no totally reduced compound, but a mixture of the glycol (2) and diazastilbene (3); and with 2-pyridinecarbaldehyde, a mixture of the glycol (4) and the reduced compound (5).

Of the five member heterocyclic nuclei investigated, only N-methylimidazole reacted like pyridyl nucleus; pyrrole, N-methylpyrrole and unsubstituted imidazolecarbaldehydes afforded complex mixtures and all the others gave the expected double-bonded coupled compound. However when the nitrogen atom was protected as urethane or acetamide<sup>9</sup> no reduction was observed. We hypothesized that only compounds with low electron density at the benzylic position give reduced products.

The fact that dicarbonylic coupling by means of low valent titanium works for the heteroaromatic compounds means that it may be possible to apply this methodology to the preparation of a number of pharmacologically active compounds with heteroaromatic rings in their structure.

### EXPERIMENTAL PART

All melting points are uncorrected and were recorded on a Kofler- Thermogeräte apparatus. <sup>1</sup>H-Nmr spectra were recorded on a Bruker WM-250 (250MHz) spectrometer; chemical shifts are reported in ppm relative to Me<sub>4</sub>Si ( $\delta = 0$  ppm), and coupling constants are in Hertz. Mass spectra (EI, 70 eV) were obtained on a Kratos MS-50 instrument. Flash chromatography was performed using Merck 230-400 mesh silica gel. All commercial aldehydes and 3-bromopyridine were purchased from Aldrich Chemical Co. Titanium trichloride and lithium aluminum

Table 1


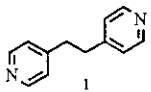

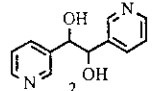
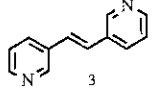

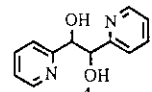
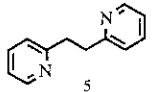

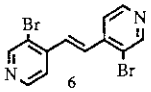

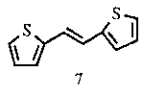

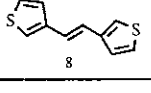

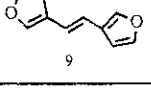

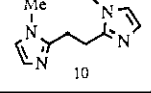




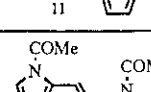

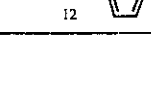
Starting material	Product	
	 1	
	 2	 3
	 4	 5
	 6	
	 7	
	 8	
	 9	
	 10	
	Complex mixture	
	Complex mixture	
	Complex mixture	
	 11	
	 12	

Table 2.

Prod- uct	Yield <sup>a</sup> (%)	mp(°C) (solvent)	Molecular formula or lit. mp (°C)	Eluent	<sup>1</sup> H-nmr (CDCl <sub>3</sub> /TMS) δ(ppm), J (Hz)	ms (EI): m/z (%)	Microanalyses
1	25	oil <sup>3</sup>	---	EtOAc:Hexane 1:1	2.93(s, 2H, CH <sub>2</sub> ); 7.06(d, J=5.9, 2H, H-3 and H-5); 8.47(d, J=5.9, 2H, H-2 and H-6)	184(M <sup>+</sup> , 65), 106(100)	
2	16(24)	169-170 (CH <sub>2</sub> Cl <sub>2</sub> )	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> :MeOH 95:5	3.90(br s, 1H, OH); 4.75(s, 1H, HCOH); 7.22(m, 1H, ArH); 7.53(m, 1H, ArH); 8.25(d, J=1.4, 1H, H-2); 8.38(m, 1H, H-6)	217(M <sup>+</sup> +1, 100), 149(19), 108(23)	Calc : C 66.70; H 5.55; N 12.96 Found : C 66.93; H 5.41; N 13.05
3	2(28)	71 (CH <sub>2</sub> Cl <sub>2</sub> )	90 <sup>4</sup>	CH <sub>2</sub> Cl <sub>2</sub> :MeOH 95:5	7.15(s, 1H, HC=C); 7.33(m, 1H, ArH); 7.87(m, 1H, ArH); 8.53(dd, J=6.4 and 1.6, 1H, H-6); 8.75(d, J=1.8, 1H, H-2)	182(M <sup>+</sup> , 100), 181(90), 154(32)	
4	10(35)	96 (CH <sub>2</sub> Cl <sub>2</sub> )	92-93 <sup>5</sup>	CH <sub>2</sub> Cl <sub>2</sub> :MeOH 95:5	5.16(s, 1H, HCOH); 5.44(br s, 1H, OH); 7.14(m, 1H, ArH); 7.65(m, 1H, ArH); 7.48(d, J=7.9, 1H, H-3); 8.44(m, 1H, H-6)	217(M <sup>+</sup> +1, 100), 154(79), 137(61)	
5	24(26)	oil <sup>6</sup>	---	CH <sub>2</sub> Cl <sub>2</sub> :MeOH 95:5	3.24(s, 2H, CH <sub>2</sub> ); 7.11(m, 2H, ArH); 7.55(dd, J=7.7 and 7.6, 1H, ArH); 8.55(m, 1H, H-6)	184(M <sup>+</sup> , 50), 106(100)	
6	30	oil	C <sub>12</sub> H <sub>10</sub> Br <sub>2</sub> N <sub>2</sub>	EtOAc:Hexane 1:1	3.05(s, 2H, CH <sub>2</sub> ); 7.08(d, J=4.9, 1H, H-5); 8.40(d, J=4.9, 1H, H-6); 8.70(s, 1H, H-2)	342(M <sup>+</sup> , 21), 182(100), 171(15)	Calc : C 42.10; H 2.92; N 8.19 Found: C 42.13; H 3.10; N 7.98
7	91	130-132 (Cl <sub>2</sub> CH <sub>2</sub> )	129-131 <sup>7</sup>	crystallization	6.97-7.04(m, 2H, H-3 and H-4); 7.05(s, 1H, HC=C); 7.17(d, J=5.1, 1H, H-5)	192(M <sup>+</sup> , 100), 191(56)	
8	93	133-135 (CH <sub>2</sub> Cl <sub>2</sub> )	148-150 <sup>8</sup>	crystallization	6.97(s, 1H, HC=C); 7.22(m, 1H, H-4); 7.29(m, 2H, H-5 and H-2)	192(M <sup>+</sup> , 93), 191(100)	
9	45	174 (EtOH)	136-139 <sup>8</sup>	Hexane	6.59(m, 1H, H-4); 6.67(s, 1H, HC=C); 7.38(m, 1H, H-5); 7.47(m, 1H, H-2)	160(M <sup>+</sup> , 13), 131(94), 77(100)	
10	(42)	164 (CH <sub>2</sub> Cl <sub>2</sub> )	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> :MeOH 95:5	3.17(s, 2H, CH <sub>2</sub> ); 3.46(s, 3H, Me); 6.78(d, J=1.2, 1H, ArH); 6.93(d, J=1.2, 1H, ArH)	190(M <sup>+</sup> , 54), 175(77), 95(100)	Calc : C 63.16; H 7.37; N 29.47 Found: C 63.29; H 7.37; N 29.40
11	30	105 (EtOAc)	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	EtOAc:Hexane 1:3	1.39(t, J=7.1, 3H, CH <sub>3</sub> ); 4.42(q, J=7.1, 2H, CH <sub>2</sub> ); 6.19(t, J=3.5, 1H, H-3); 6.55(dd, J=1.6 and 3.5, 1H, H-4); 7.28(dd, J=1.6 and 3.3, 1H, H-5); 7.57(s, 1H, HC=C)	302(M <sup>+</sup> , 100), 157(93)	Calc : C 63.58; H 5.96; N 9.27 Found: C 63.10; H 6.20; N 9.52
12	50	187 (EtOAc)	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	EtOAc:Hexane 1:3	2.56(s, 3H, CH <sub>3</sub> ); 6.24(t, J=3.4, 1H, H-3); 6.57(dd, J=1.4 and 3.4, 1H, H-4); 7.08(dd, J=1.4 and 3.3, 1H, H-5); 7.60(s, 1H, HC=C)	242(M <sup>+</sup> , 76), 158(74), 157(100)	Calc : C 69.42; H 5.78; N 11.57 Found: C 69.90; H 5.76; N 11.73

<sup>a</sup> Yield using method A. Yield with method B is shown in brackets.

hydride were purchased from Fluka Chemical Co. Lithium and dimethoxyethane were purchased from Merck-Schuchardt. 3-Bromo-4-pyridinecarbaldehyde was obtained from 3-bromopyridine.<sup>10</sup> Solvents were dried by distillation from sodium benzophenone ketyl prior to use.

#### General procedure for carbonyl coupling

**Method A.** To a slurry of  $\text{TiCl}_3$  (1.6 g, 11 mmol, 4 eq.) under an argon atmosphere in dry DME (20 ml) in a dried round-bottomed flask equipped with a magnetic stirrer and a refluxing condenser, lithium pieces (262 mg, 38 mmol, 14 eq.) are added and the mixture is refluxed for 2 h. A solution of the carbonyl compound (2.7 mmol, 1 eq.) in DME (10 ml) is added. The mixture is refluxed for 15 h. After cooling to room temperature, the mixture is filtered, a saturated aqueous solution of  $\text{K}_2\text{CO}_3$  (50 ml) was added, the organic layer was separated and the aqueous layer was extracted with chloroform (5 x 40 ml). The combined organic phases are dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford the crude product. This is purified either on a silica gel flash column using the eluents listed in the Table 2, or by crystallization.

**Method B.** A dried round-bottomed flask equipped with a magnetic stirrer and a refluxing condenser is loaded with  $\text{TiCl}_3$  (1.7 g, 11 mmol, 4 eq.) and dried THF (30 ml). The mixture is cooled to  $0^\circ\text{C}$  and  $\text{LiAlH}_4$  (1.7 g, 44 mmol, 16 eq.) is added. The mixture is then refluxed for 1 h, the carbonyl compound (2.75 mmol, 1 eq.) is added, and the reflux is continued for 15 h. After the mixture was cooled to room temperature, a saturated aqueous solution of  $\text{K}_2\text{CO}_3$  (50 ml) is added and the mixture is extracted with chloroform (5 x 50 ml). The combined organic layers are dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum to afford the crude product, which is purified by flash chromatography using the eluents listed in the Table 2.

#### ACKNOWLEDGEMENTS

We thank the Comision Asesora and Xunta de Galicia for financial support and Xunta de Galicia for a grant to M. M. Cid.

#### REFERENCES

1. a) I. Ben, L. Castedo, J. M. Saá, J. A. Seijas, R. Suau, and G. Tojo, *J. Org. Chem.*, 1985, **50**, 2236.  
b) J. A. Seijas, A. R. de Lera, M. C. Villaverde, and L. Castedo, *J. Chem. Soc., Chem. Comm.*, 1985, 839.
2. a) J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, 1978, **43**, 3255.  
b) J. Pons and M. Santelli, *Tetrahedron*, 1988, **44**, 4295.
3. J. Vansant, S. Toppet, G. Smets, J. P. Declercq, G. Germain, and M. Van Meerssche, *J. Org. Chem.*, 1980, **45**, 1565.
4. P. Y. White and L. S. Summers, *Aust. J. Chem.*, 1977, **30**, 1153.
5. M. Imuta and H. Ziffer, *J. Org. Chem.*, 1978, **43**, 3530.
6. G. R. Newkome, V. K. Gupta, C. R. Taylor, and F. R. Fronczek, *Organometallics*, 1984, **3**, 1549.
7. J. Nakayama, S. Murabayashi, and M. Hoshino, *Heterocycles*, 1986, **24**, 2639.
8. R. V. Hoffman, G. G. Orphanides, and H. Shechter, *J. Am. Chem. Soc.*, 1978, **100**, 7927.
9. K. Nickisch, W. Klose, and F. Bohlmann, *Chem. Ber.*, 1980, **113**, 2036.
10. E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 3291.

Received, 22nd February, 1990