ortho-Hydroxylation of Aromatic Aldehydes: A Short Synthesis of 2-Hydroxypyrene-1-carbaldehyde

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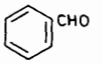
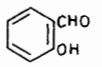
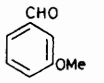
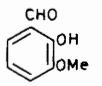
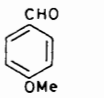
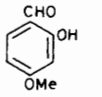
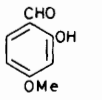
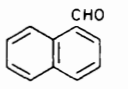
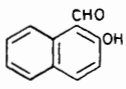
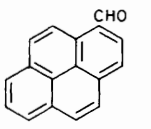
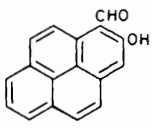
A new methodology for the *ortho*-hydroxylation of aromatic aldehydes *via ortho*-lithiated aromatic amino alkoxides provides easy access to 2-hydroxypyrene-1-carbaldehyde, a valuable precursor for biologically important pyrenofurans and pyrenocoumarins.

Aromatic *ortho*-hydroxy aldehydes are synthetic intermediates of great importance, particularly for the synthesis of oxygen heterocycles such as benzofurans, chromones, and coumarins.[1] In classical methods for the preparation of these compounds, the starting materials are phenols or phenol derivatives, which are *ortho*-formylated by known methods. We now report a new synthetic approach using an inverse order of functionalisation, *i.e.* from aldehydes as starting materials. This new method is based upon the oxidation of aryl-lithium species prepared by functional-group-directed metallation.[2] α-Amino alkoxides are aldehyde derivatives of high efficiency as *ortho*-metallation directors, particularly when *N,N,N'*-trimethylethylenediamine is used as the amine component.[3] We describe here the oxidation of α-amino alkoxides (**3**), with the regeneration of the aldehyde function by simple hydrolysis at the end of the process.

Conventional procedures can be used to prepare the lithiated intermediates, using commercial reagents.[3] A simpler method is derived from our development of the sonochemical Bouveault reaction[4] and the *in situ* generation of butyl-lithium reagents.[5] Thus, *N*-lithio-*N,N',N'*-trimethylethylenediamine is prepared by sonication of a solution of the amine, an excess of lithium, and 1-chlorobutane in anhydrous tetrahydropyran (THP). After addition of the aldehyde (**1**), lithiation of the amino alkoxide (**2**) can also be performed by *in situ* generation of butyl-lithium (n-, s-, or t-butyl), simply by

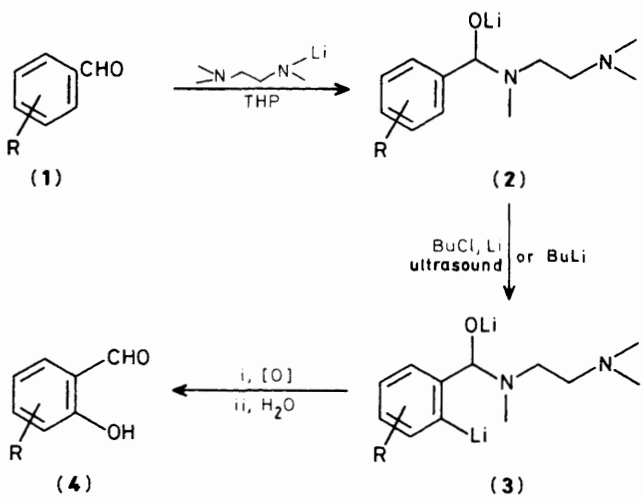
Table 1. *ortho*-Hydroxylation of aromatic aldehydes.

Starting aldehyde	Lithiation conditions	Products[a]	% Yields in different oxidation methods[b] O_2	$B(OBu^n)_3H_2O$	MoOPH
	Li/Bu^{s}Cl 45 min sonication, 20 °C		36	70	
	Li/Bu^{n}Cl 1 h sonication, 20 °C			35	
	Li/Bu^{s}Li 45 min sonication, 20 °C			26	
				25	
	Bu^{s}Li[c] 30 min, 20 °C		17	12	
	Bu^{s}Li[c] 1h, −60 °C		10	37	23

[a] Identified by comparison with authentic samples. [b] Yield of isolated product based on the initial aldehyde. [c] *In situ* generation of BuLi gives lower yields, as polycyclic aromatic systems react easily with metallic lithium to give radical anions.

adding the corresponding chlorobutane, which reacts with the remaining lithium under sonication.†

Three different oxidation methods for the lithiated intermediate (**3**) were tested. Oxidation with molecular oxygen[1] often gave low to medium yields of product (**4**). More successful was a two-step one-pot condensation of the lithio species (**3**) with tributyl borate, followed by oxidation of the carbon–boron bond with 30% hydrogen peroxide.[6] The third method was the direct oxidation of (**3**) with oxodiperoxy(pyridine)(hexamethylphosphoramidemolybdenum) (MoOPH).[7] As seen in Table 1, various aromatic aldehydes can be *ortho*-hydroxylated in yields depending on the structure and the oxidation method.[1] The more interesting applications are probably to be found in the chemistry of polycyclic aromatic hydrocarbons, as



Scheme 1

† *Typical procedure.* Generation of the *ortho*-lithiated intermediates (**3**). A mixture of *N,N,N'*-trimethylethylenediamine (0.245 g, 2.4 mmol) 1-chlorobutane (0.222 g, 4.4 mmol) and of lithium (dispersion containing 2% Na; 0.084 g, 0.012 g atom) in anhydrous THP (4 ml) under argon was sonicated during 15 min in an ultrasonic cleaning bath. The aldehyde (**1**) (2 mmol) was added and the mixture was stirred during 15 min at 20 °C. The corresponding chlorobutane (4 mmol) was then added and sonication was continued for 30–60 min.

Oxidation with 30% H_2O_2 *via* the boronic ester. Tri-n-butyl borate (1.1 ml, 4 mmol) was added to the stirred solution of (**3**) at 0 °C. Stirring was continued from 1 h, then AcOH (1 ml) was added all at once, followed slowly by 30% H_2O_2 (0.5 ml). After 5 min stirring, standard work-up, chromatography, and/or crystallisation afforded the desired pure product. Oxidations with molecular oxygen or MoOPH were performed by bubbling O_2 or adding solid MoOPH[6] (1.3 g, 3 mmol) to the stirred solution of (**3**) at 0 °C.

exemplified by the easy preparation of 2-hydroxypyrene-1-carbaldehyde. This is a starting material for the synthesis of pyrenofurans, which exhibit exceptional mutagenic activities,[8] and pyrenocoumarins, which are inhibitors of tumour induction.[9] We have recently described the only previously known method (to our knowledge) for the preparation of this compound. From pyrene itself it necessitates seven steps, and an overall yield of *ca.* 14% is obtained.[8] The present method requires only one step from the commercial pyrene-1-carbaldehyde and proceeds in an overall yield of 37%.

This method represents the first direct access to *ortho*-hydroxy aldehydes from aromatic aldehydes. It will be useful for converting readily available starting materials into compounds with substitution patterns difficult to obtain otherwise.

Received, 26th April 1988; Com. 8/01648H

References

1 A. Mustafa, 'Benzofurans,' in 'The Chemistry of Heterocyclic Compounds,' Wiley Interscience, New York, 1974; G. P. Ellis, 'Chromenes, Chromanones and Chromones,' in 'The Chemistry of Heterocyclic Compounds,' Wiley Interscience, New York, 1977.
2 K. A. Parker and K. A. Koziski, *J. Org. Chem.*, 1987, **52**, 674, and references therein.
3 D. L. Comins and J. D. Brown, *J. Org. Chem.*, 1984, **49**, 1078.
4 J. Einhorn and J. L. Luche, *Tetrahedron Lett.*, 1986, **27**, 1791, 1793.
5 J. Einhorn and J. L. Luche, *J. Org. Chem.*, 1987, **52**, 4124.
6 P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34; M. Ivao, J. N. Reed, and V. Snieckus, *J. Am. Chem. Soc.*, 1982, **104**, 5531.
7 N. J. Lewis, S. Y. Gabhe, and M. R. De La Mater, *J. Org. Chem.*, 1977, **42**, 1479.
8 P. Demerseman, J. Einhorn, J. F. Gourvest, and R. Royer, *J. Heterocycl. Chem.*, 1985, **22**, 39.
9 R. G. Harvey, C. Cortez, T. P. Ananthanarayan, and S. Schmolka, *Tetrahedron Lett.*, 1987, **28**, 6137.