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ortho-Metalation/Chlorination of Benzoic Acid Derivatives: Preparation of [*benzene*-U-^{13}C]-*rac*-Clopidogrel ([*benzene*-U-^{13}C]-*rac*-SR25990C).

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SUMMARY

Directed *ortho*-lithiation is used to form [*benzene*-U-^{13}C]-2-chlorobenzaldehyde, the key building block for preparation of labelled racemic Clopidogrel ([*benzene*-U-^{13}C]-*rac*-SR25990C). Some practical observations are reported concerning the metalation of some derivatives of benzoic acid.

Keywords: 2-Chlorobenzaldehyde, ortho-Metalation, Strecker Synthesis, Plavix, Clopidogrel, SR25990

INTRODUCTION

Clopidogrel sulfate (Plavix™, SR25990C, **1**) is an orally active inhibitor of platelet aggregation, now marketed as an antithrombotic agent.[1,2] As part of studies of the metabolism of SR25990, a synthesis of stable isotopically-labelled SR25990 for use as a mass spectroscopic standard was required. Although Clopidogrel is a single enantiomer, the labelled racemate (**2**) would suffice as a standard; this was therefore the synthetic target, and was approached by means of a Strecker reaction, with [*benzene*-U-^{13}C]-2-chlorobenzaldehyde (**3**) as the pivotal intermediate. In turn, the obvious approach to **3** was by directed *ortho*-metalation and chlorination of a derivative of commercially available [*benzene*-U-^{13}C]-benzoic acid, and subsequent reduction.

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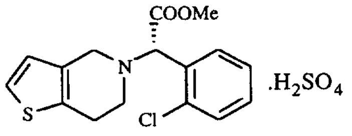

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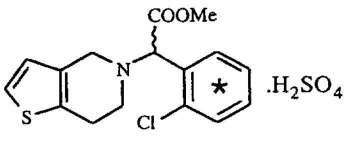

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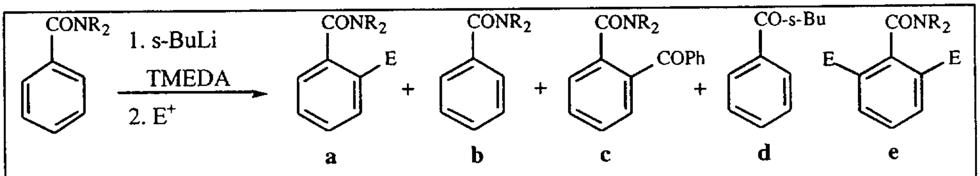
RESULTS AND DISCUSSION

The *ortho*-metalation of benzoic acid[3] and of a number of amides,[4] and subsequent chlorination with hexachloroethane is known. However, following the method described by Snieckus[4] for *ortho*-metalation of diethylbenzamide, no metalation was observed (Table 1). In view of this, the stability of *s*-butyllithium in the medium was examined; when *s*-butyllithium was added to one equivalent quantity of TMEDA in THF, 1,2-dimethoxyethane, or *tert*-butyl methyl ether and the base concentration checked by double titration, it was found that *s*-butyllithium was consumed within 15 minutes at -78°C.

Table 1. *ortho*-Metalation Reactions of Diethyl- and Diisopropylbenzamides[a]

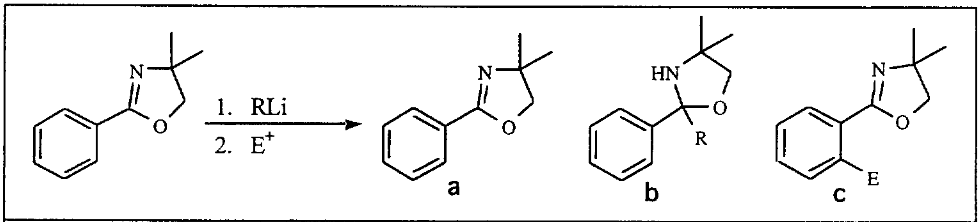


R	Conditions	E^+(E)	a (%)	b (%)	c (%)	d (%)	e (%)
Et	THF, -78°C	C_2Cl_6 (Cl)	-	78[b]	17[b]	-	-
Et	Toluene, -78°C	D_2O (D)	48	12	27	13	-
i-Pr	Toluene, -78°C	D_2O (D)	ca. 70	ca. 20	-	-	ca. 10
i-Pr	Toluene, -78°C	C_2Cl_6 (Cl)	68[c]	19	-	-	13

a. Yields and product identification by GC-MS. *b*. isolated yield. *c*. 40% isolated.

Similar observations have been reported by Stanetty and Mihovilovic,[5] and the base-induced cleavage of tetrahydrofuran to give acetaldehyde enolate and ethylene,[6] and of 1,2-dimethoxyethane to give methyl vinyl ether and methoxide,[7] are well known. A similar process can reasonably be postulated for cleavage of TBME. This process was avoided by using toluene as the reaction solvent. Under these conditions, metalation occurred but was both slow and incomplete, with the result that significant amounts of starting material remained, with which a proportion of lithiated species reacted to give a benzophenone. Moreover, the process was complicated by nucleophilic addition of *s*-butyllithium to the amide and by bis-metalation (Table 1). Side-reactions were suppressed effectively by using diisopropylbenzamide as the substrate (Table 1). However, metalation still did not proceed to completion and attempts to separation of the product from starting material were unsuccessful. Better results were obtained using the oxazoline **4** (in unlabelled form, Table 2),[8] in which case the efficiency of metalation was sufficient that it was not necessary to complex the base with TMEDA.

Table 2. *ortho*-Metalation of unlabelled **4**.[a]

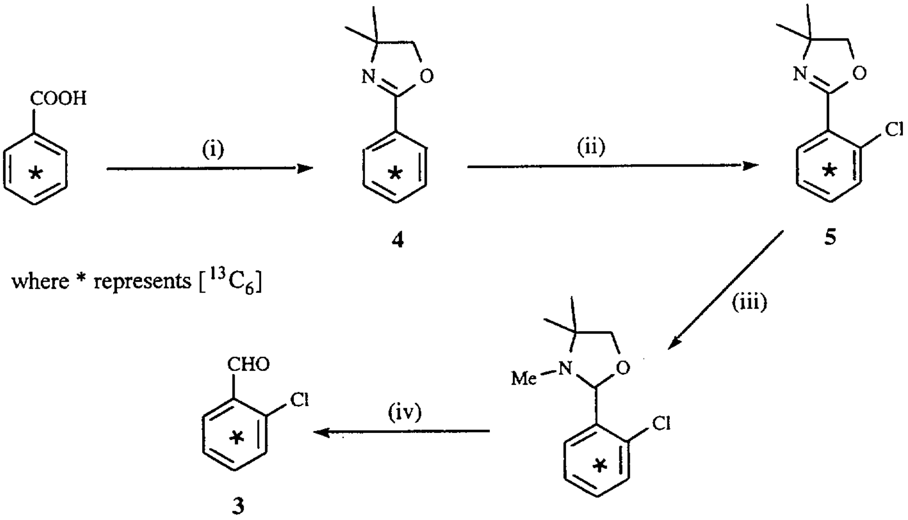


RLi	conditions	E+ (E)	**a** (%)	**b** (%)	**c** (%)
BuLi	Et_2O, 0°C	D_2O (D)	-	34	66
i-Pr_2NLi	THF, -78°C	D_2O (D)	100	0	0
s-BuLi	Toluene, -78°C	D_2O (D)	0	3	97
		C_2Cl_6 (Cl)	43	3	54

a. Yields and product identification by GC-MS.

Given the efficiency of the metalation of **4**, the yield of chlorinated product was disappointing. In the absence of any other proton source, it can only be surmised that excess *s*-butyllithium reacts with hexachloroethane more rapidly than does the *ortho*-metalated intermediate, and that the resulting 2-chlorobutane is a better electrophile (as a proton source) than is hexachloroethane. Suppression of this process was, however, difficult since the addition of a smaller amount of base resulted in incomplete lithiation and, where the reaction time was extended, a significantly increased level of the undesired addition product. Nevertheless, this appeared to be the best method available.

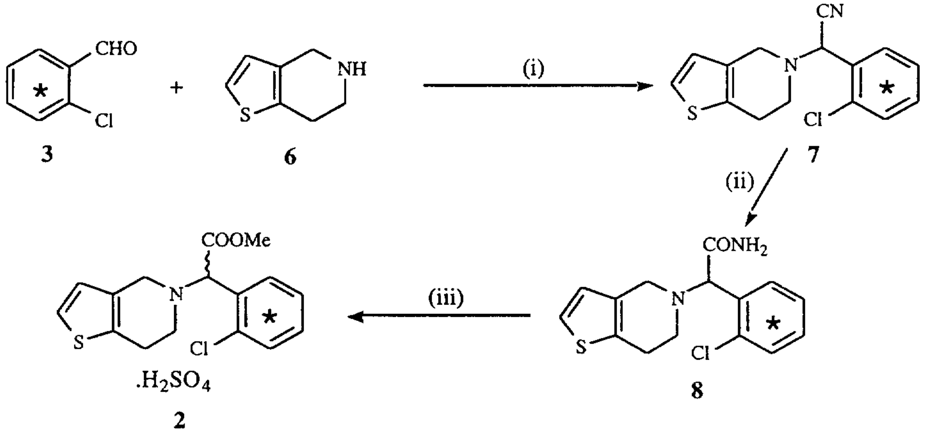
The route used to prepare [*benzene*-U-^{13}C]-2-chlorobenzaldehyde (**3**) is shown in Scheme 1. [*benzene*-U-^{13}C]-Benzoic acid was converted to the oxazoline **4** using the literature method.[9] Lithiation and chlorination of **4** gave **5** in 60% yield after separation from unreacted starting material. An advantage of the chosen approach was that **5** could be reduced,[10] and the resulting oxazolidine hydrolysed readily to give **3** directly. This product, although isolated, was not purified since chromatographic loses were significant and better overall results were obtained by carrying out the Strecker synthesis directly using the crude material.



Scheme 1. Preparation of [*benzene*-U-^{13}C]-2-Chlorobenzaldehyde (**3**)
Reagents: (i) a.. $SOCl_2$; b. $H_2NCMe_2CH_2OH$; c. $SOCl_2$.
(ii) a. *s*-BuLi, toluene, -78°C. b. C_2Cl_6, -40°C to R.T.
(iii) a. MeI, R.T.; b. $NaBH_4$, EtOH, R.T. (iv) 2N HCl, R.T.

Assembly of the desired material was carried out using Strecker methodology as planned: treatment of labelled aldehyde **3** with the thienopyridine **6** and acetone cyanohydrin gave the nitrile **7** in 31% overall yield from **5**. Despite the poor overall yield, the last process appeared relatively clean, with the only impurities detected by

GC-MS of the crude product being small quantities of adducts formed from **6** and acetone cyanohydrin which were not isolated. Conversion of the resulting nitrile **7** to the final product **2** required a two-step process; saponification of **7** was not an option, since a retro-Strecker reaction occurred in preference to hydrolysis, but hydrochloric acid-promoted hydrolysis gave the amide **8** in quantitative yield. Methanolysis of **8** proceeded directly to the ester **2**, which was isolated as its sulfate. This step required strongly acidic conditions and the yield was only modest (although most of the unreacted starting material was recovered); alternative methods, using Meerwein's reagent[11] and dimethylformamide dimethyl acetal[12] were examined but these represented no improvement upon the method used. The process as described provides [*benzene*-U-^{13}C]-*rac*-SR25990 (**2**) in an overall 7% yield from labelled benzoic acid.



Scheme 2. Elaboration of [*benzene*-U-^{13}C]-2-Chlorobenzaldehyde to **2**
Reagents: (i) acetone cyanohydrin, $MgSO_4$, 45°C, toluene.
(ii) HCl, MeOH, R.T. (iii) a. 2 eq. H_2SO_4, MeOH, reflux; b. H_2SO_4, Et_2O, R.T.

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded using a Jeol GSX-270 instrument. Gas chromatography and mass spectrometry were performed using a Hewlett-Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5970MSD) on a capillary column (HP-1, 23 m x 0.2 mm x 0.33 μm), using decane as an internal standard for quantitative measurements. High-resolution mass spectra were recorded using a VG Autospec magnetic sector instrument at the University of York. Reagents were obtained commercially, [*benzene*-U-^{13}C]-benzoic acid in particular being obtained from Cambridge Isotope Laboratories.

*[*benzene*-U-^{13}C]-2-(2-Chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole* (**5**). Oxazole **4** (prepared using the method of Shono *et al.*[9] from [*benzene*-U-^{13}C]-benzoic acid in 82% yield; 2.19 g, 12 mmol) in anhydrous toluene (10 ml) was added during 15 min under nitrogen at -78°C to a solution of *sec*-butyllithium (1.3M in hexanes; 11.1 ml, 14 mmol). After 30 min, hexachloroethane (8.6 g, 36 mmol) in toluene (20 ml) was added by means of a cannula following which the mixture was allowed to warm to room temperature during 40 min. The reaction was quenched with aqueous ammonium chloride and re-extracted with toluene (3 x 50 ml), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. The crude material was purified by chromatography on silica gel in hexane - ethyl acetate (85:15) followed by preparative HPLC of the mixed fractions in the same system to give **5** (1.5 g, 58%). $\delta_H(CDCl_3)$ 1.39 (6H, s), 4.12 (2H, s), 7.0-7.2 (2H, m), 7.5-7.75 (2H, m), 8.1-8.4 (1H, m).

*[*benzene*-U-^{13}C]-*rac*-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetonitrile* (**7**). A solution of **5** (1.50 g, 8.3 mmol) in methyl iodide (3.1 ml) was heated at reflux for 16 h. Upon cooling, excess methyl iodide was removed under vacuum and the pale yellow solid was redissolved in anhydrous ethanol (15 ml). Sodium borohydride (461 mg, 12 mmol) was added in portions during 10 min, and the mixture stirred for 2 h. Ethanol was removed under reduced pressure, water (25 ml) was added followed, after 30 min, by 2N hydrochloric acid (50 ml). After a further 30 min, the mixture was extracted with toluene (3 x 25 ml), and the combined extracts were washed with aqueous sodium hydrogencarbonate (40 ml) and dried ($MgSO_4$). To this solution of **3** were added **6** (1.40 g, 10 mmol),[2] anhydrous magnesium sulfate (1.4 g) and, after 5 minutes, acetone cyanohydrin (850 mg, 10 mmol). The suspension was stirred under nitrogen at 45°C for 48 h, following which volatile materials were removed under vacuum, and the residue purified by

column chromatography on silica gel in hexane - ethyl acetate (85:15) followed by crystallisation from hexane to give **7** (744 mg, 31%). $\delta_H(CDCl_3)$ 2.75-3.05 (4H, m), 3.64 (1H, d), 3.79 (1H, d), 5.29 (1H, m), 6.79 (1H, d), 7.07 (1H, d), 6.95-8.1 (4H, m); *m/z* (EI) 294/296 ($M^{+\cdot}$), 156, 110 (100%).

*[*benzene-*U-^{13}C]-*rac-*2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetamide* (**8**): A solution of **7** (729 mg, 2.5 mmol) in anhydrous methanol (10 ml) saturated with hydrogen chloride was stirred for 48 h. Volatile material was removed under vacuum and the residue was azeotropically dried with dichloromethane. The residue was partitioned between aqueous sodium hydrogencarbonate and dichloromethane. The aqueous phase was re-extracted with dichloromethane and the combined organic fractions were dried ($MgSO_4$) and concentrated to give **8** (729 mg, 94%). $\delta_H(CDCl_3)$ 2.8-3.0 (4H, m), 3.59 (1H, d), 3.69 (1H, d), 4.91 (1H, m), 6.07 (1H, m), 7.06 (1H, m), 6.8-8.0 (4H, m); *m/z* (EI) 312/314 ($M^{+\cdot}$), 268/270 (100%), 138.

*Methyl [*benzene-*U-^{13}C]-*rac-*(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]-pyridin-5-yl)acetate Sulfate* (**2**). A solution of **8** (729 mg, 2.3 mmol) in methanol containing sulfuric acid (1 ml) was heated at reflux for 144 h. The solvent volume was reduced under vacuum, and the mixture partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The aqueous phase was re-extracted with ethyl acetate and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue in hexane - ether (85:15) on silica gel gave the free base of **2** (366 g, 50%) followed by **8** (190 mg, 26%). Addition of a 1 g/l solution of sulfuric acid in ether to a stirred solution of the free base of **2** in ether, followed by filtration after 10 min gave **2**. δ_H (CD_3OD) 3.7-3.85 (2H, m), 2.87 (3H, s), 4.1-4.55 (2H, m), 5.87 (1H, q), 6.80 (1H, d), 7.2-7.45 (2H, m), 7.40 (1H, d), 7.8-8.05 (2H, m); *m/z* (FAB^+) 328, 330 ($[MH]^+$), 286, 154 (100%), 137, 136. HRMS 328.0869; calc. for $C_{10}{}^{13}C_6H_{17}ClNO_2S$ 328.0870

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