Tetrahedron Letters,Vol.29,No.35,pp 4385-4388,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

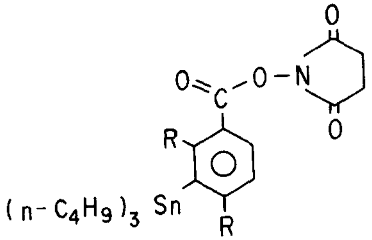
# SYNTHESIS OF N-SUCCINIMIDYL-2,4-DIMETHOXY-3-(TRI-N-BUTYLSTANNYL) BENZOATE VIA REGIO-SPECIFICALLY GENERATED LITHIUM 2,4-DIMETHOXY-3-LITHIOBENZOATE

Acharan S. Narula and Michael R. Zalutsky

Box 3808, Department of Radiology
Duke University Medical Center
Durham, NC 27710

Summary: Lithium 2,4-dimethoxy-3-lithiobenzoate can be efficiently generated from 2,4-dimethoxy-3-bromobenzoic acid in THF at -100°C.

In connection with a research project aimed at the synthesis of novel radiohalogenated organic conjugates for use in protein labeling, we required a regio-specific synthesis of N-succinimidyl-2,4-dimethoxy-3-(tri-n-butylstannyl)benzoate (1, R = $OCH_3$). Because we have recently shown[1] that N-succinimidyl-3-(tri-n-butylstannyl)benzoate (1, R = H) can be obtained via lithium m-lithiobenzoate (2, R = H), it is, therefore, conceivable that synthesis of 1(R = $OCH_3$) may rely on a suitable method for the generation[2] of lithium 2,4-dimethoxy-3-lithiobenzoate (2, R = $OCH_3$). This has now been accomplished, and the results discussed in this communication are noted in order to underline the importance of this work towards the regio-specific introduction of a halogen, e.g. Br or I, at Position 3 of 2-hydroxy-4-methoxybenzaldehyde (4). While we now have ready access to multigram quantitites of 3-bromo-2,4-dimethoxybenzoic acid, the true merit of our strategy is that it offers a general method for the synthesis of 1,2,3,4-substituted aromatic substrates where carbon 1 contains an electron withdrawing group (e.g. COOH), carbon 2 and 4 contain an electron donating group (e.g $OCH_3$) and carbon 3 contains a halogen (e.g. Br or I).



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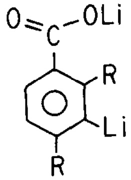

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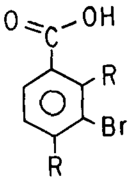

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### Synthesis of N-succinimidyl-2,4-dimethoxy-3-(tri-n-butylstannyl)benzoate (1, R = $OCH_3$) via lithium-2,4-dimethoxy-3-lithiobenzoate (2, R = $OCH_3$)

In view of the fact[3] that lithium 2,6-dimethoxybenzene can be readily prepared by metallation of 1,3-dimethoxybenzene with *n*-butyl lithium, one is likely to be tempted to generate 2(R = $OCH_3$) starting from the commercially available 2,4-dimethoxybenzoic acid. An inherent problem with this approach, however, is that the kinetics of metallation at C3-H are incompatible with the -COOH functionality in 2,4-dimethoxybenzoic acid. Since metal-halogen exchange can be effectively carried out at -100°C without substantial interference with the -COOH functionality (e.g. $2 \Rightarrow 3$; R = H); for our objective at hand, i.e. generation of 2(R = $OCH_3$), we required 2,4-dimethoxy-3-bromobenzoic acid (3, R = $OCH_3$). A four-step regio-specific synthesis of 2,4-dimethoxy-3-bromobenzoic acid starting from the readily available 2-hydroxy-4-methoxybenzaldehyde (4) is outlined below[4] (Fig. 1). The choice of 2-hydroxy-4-methoxybenzaldehyde as a starting material was dictated by the following considerations: (i) Position 1 contains an aldehydic function which can be readily converted

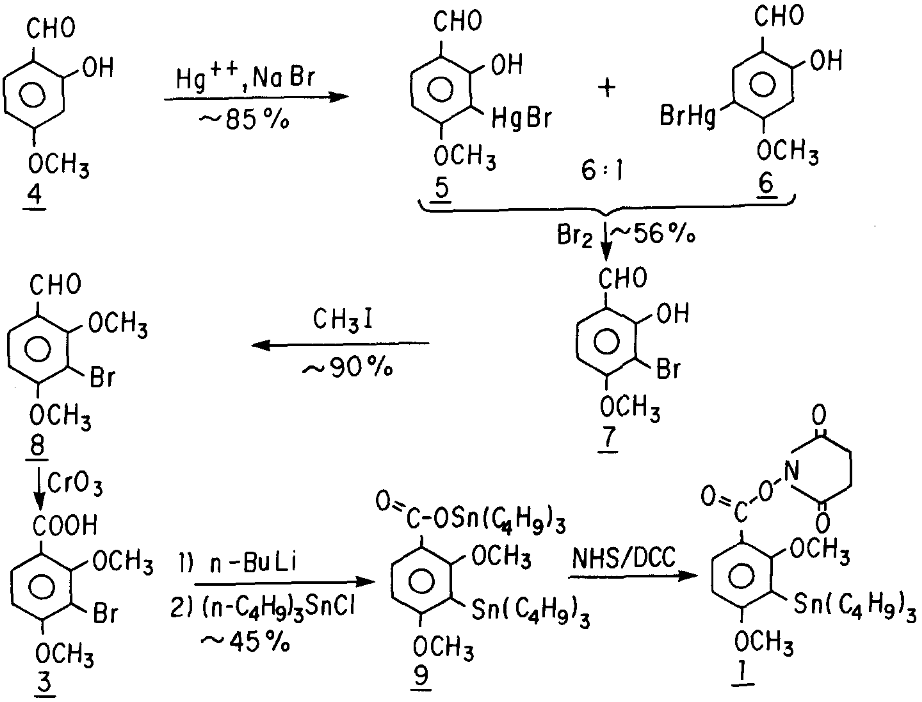

Figure 1: Synthesis of N-Succinimidyl-2,4-dimethoxy-3-(Tri-n-butylstannyl)Benzoate (1)

to a COOH group; and (ii) Position 2 contains an OH group which can offer co-ordination to a $Hg^{++}$ salt and, therefore, can be expected to direct the electrophilic reagent [e.g. $Hg(OAc)_2$] to the ortho position.[5]

Indeed, treatment of 2-hydroxy-4-methoxybenzaldehyde with mercuric acetate in refluxing alcohol containing $\sim$ 1% acetic acid followed by treatment with aq. NaBr gave in over 85% yield a 6:1 mixture of organo-mercury compounds 5 and 6 m.p. $\sim$ 200°C, [$^1$H-NMR: (300 MHz $CDCl_3$, $\delta$ ): compound 5: 3.90 (s, 3H, C4-$OCH_3$), 6.70 and 7.55 (pair of doublets, Jab = 8Hz, C5-H and C6-H), 9.80 (s, 1H, HC=O) and 11.33 (s, 1H, $\phi$-OH); compound 6: 3.80 (s, 3H, C4-$OCH_3$), 6.50 (s, 1H, C3-H), 7.46 (s, 1H, C6-H), 9.70 (s, 1H, HC=O) and 11.64 (s, 1H, $\phi$--OH).] The ratio of two compounds from this reaction was obtained from the integration of the phenolic and aldehydic signals assigned above. Treatment of the above mixture of organo-mercury compounds (5 and 6) with 1 equivalent of bromine in $CHCl_3$ containing a small amount of acetic acid gave, after usual work-up and purification over silica gel (elution with 30% EtOAc in hexane), in $\sim$ 56% yield the pure 3-bromo-2-hydroxy-4-methoxybenzaldehyde (7), m.p. 115-117°C [$^1$H-NMR: (300 MHz, $CDCl_3$, $\delta$ ): 4.0 (s, 3H, C4-$OCH_3$), 6.50 and 7.52 (pair of doublets, Jab = 8Hz, C5-H and C6-H), 9.75 (1H, s, HC=O), 11.96 (1H, s, $\phi$-OH). Mass: m/e 230, 232 $C_8H_7O_3Br$ ($M^+$, 88.8%, 86.9%). Methylation of the phenolic OH in 7 with $MeI/K_2CO_3$, proceeded readily to give 3-bromo-2,4-dimethoxybenzaldehyde (8), m.p. 80° [$^1$H-NMR: (300MHz, $CDCl_3$, $\delta$ ): 4.0 (s, 2 x 3H, C2 and C4 - $OCH_3$), 6.82 and 7.84 (pair of doublets, Jab = 8Hz, C5-H and C6-H), 10.30 (s, 1H, HC=O. Mass: m/e 244, 246 ($C_9H_9O_3Br$ ($M^+$, 63.3%, 61.5%). Jones oxidation of 8 gave in 83% yield 2,4-dimethoxy-3-bromobenzoic acid [3, R = $OCH_3$; m.p. 175-177°C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ ): 4.0 & 4.04 (s, 2 x 3H, C2 and C4 $OCH_3$), 6.83 and 8.81 (pair of doublets, Jab = 8Hz, C5-H & C6-H), 10.8 (bs, 1H, COOH); Mass: m/e 260, 262 $C_9H_9O_4Br$ ($M^+$, 100%, 97.3%).

Treatment of 3(R = $OCH_3$) with 2.2 eq. of n-BuLi in THF at -100°C under argon, followed by warming to -80°C for 30 min generated the desired dilithio-anion 2(R = $OCH_3$), which was quenched with $\sim$ 2.5 eq. of tri-n-butyl tin chloride. The desired tri-n-butylstannyl-2,4-dimethoxy-3(tri-n-butylstannyl)benzoate (9) was isolated from the neutral fractions by silica gel chromatography (eluant: 10% ether in $CHCl_3$, yield $\sim$ 45%). Because of the labile nature of the tri-n-butyl tin ester, this product was directly converted to N-succinimidyl-2,4-dimethoxy-3-(tri-n-butylstannyl)benzoate 1, R = $OCH_3$), essentially in the same manner as described previously for the synthesis of N-succinimidyl-3-(tri-n-butylstannyl) benzoate (1, R = H). The assigned structure for 1 (R = $OCH_3$) was in full agreement with its spectral data: $^1$H-NMR: (300 MHz, $CDCl_3$, $\delta$ ); 0.90-1.48 (typical m, 27H, 3 x n-$C_4H_9$); 2.91 (s, 4H, -CO-$CH_2$-$CH_2$-CO); 3.76 (s, 3H, $OCH_3$); 3.88 (s, 3H, $OCH_3$); 6.66 and 8.12 (pair of doublets, Jab = 8Hz, C5-H & C6-H). FAB-Mass: m/e 512 [($C_{25}H_{39}O_6Sn$) - ($C_4H_9$)] ($M^+$ - 57, 40%), 455 ($M^+$ - $C_4H_4NO_3$, 66%), 285 [(455 - 3 x $C_4H_9$) + H, 32%], 165 [(285 - Sn), 100%].

The efficiency of our procedure to generate lithium 2,4-dimethoxy-3-lithiobenzoate is appealing and, in order to further enhance the synthetic utility of this reagent, we are currently investigating its reaction with several different types of electrophiles.

## Acknowledgements

This work was supported in part by a contract from Abbott Laboratories, Chicago, IL, and NCI Grant No. CA42324. The authors wish to thank Betsy Von Biberstein and Sarah Caldwell for excellent technical assistance.

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4. Although 2,4-dimethoxy-3-bromo-benzoic acid is a relatively simple aromatic substrate, its synthesis has not been reported in the literature. However, we do note that a 1:1 mixture of methyl-5-bromo-2-hydroxy-4-methoxybenzoate and methyl-3-bromo-2-hydroxy-4-methoxybenzoate can be obtained via bromination ortho to the phenol hydroxy group of methyl-2-hydroxy-4-methoxybenzoate in the presence of $TiCl_4$. T.M. Cresp, M.V. Sargent, J.A. Elix and D.P.H. Murphy, J. Chem. Soc. Perkin I, 340 (1973).

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(Received in USA 3 June 1988)