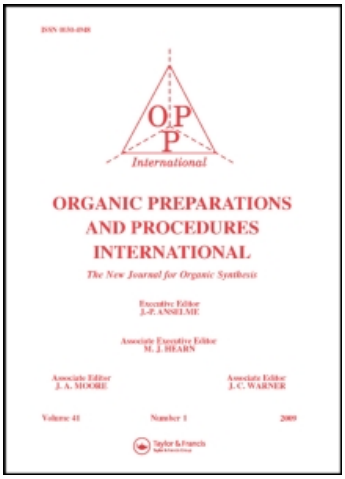

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A FACILE SYNTHESIS OF *o*-, *m*-, *p*-(TRIMETHYLSTANNYL)BENZYL CHLORIDES AND AMINES

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OPPI BRIEFS

A FACILE SYNTHESIS OF *o*-, *m*-, *p*-(TRIMETHYLSTANNYL)BENZYL CHLORIDES AND AMINES

Submitted by (10/06/97)

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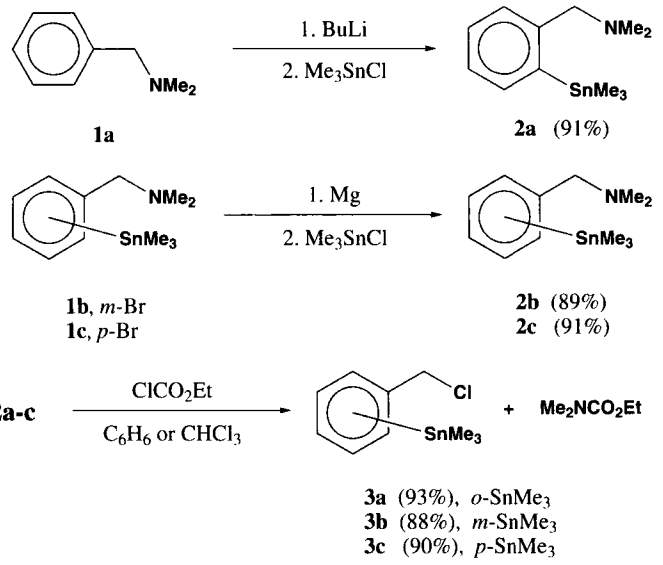
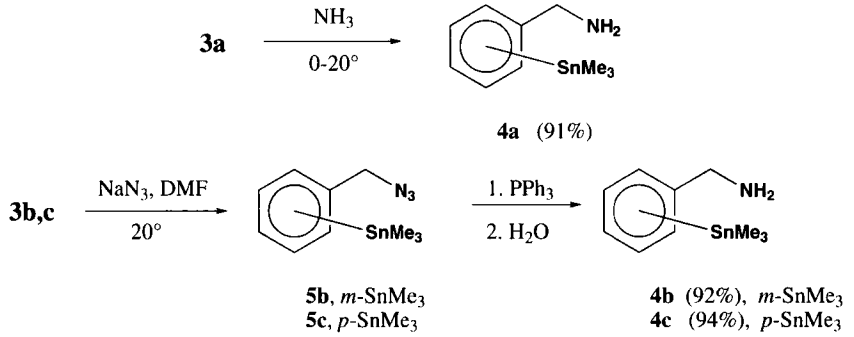
Bifunctional organotin compounds have a wide application in organic synthesis.[1-3] However, benzyl chlorides and benzylamines with trimethylstannyl substituents on the aromatic ring are unknown. We describe here a simple sequence of transformations which allows the preparation of these organometallic compounds in up to 100 grams quantities.

The readily available N,N-dimethylbenzylamine **1a**, *m*- and *p*-bromo-(N,N-dimethylbenzyl)amines **1b** and **1c** (which may be obtained quantitatively from the corresponding benzyl bromides) were used as starting materials. N,N-Dimethylbenzylamine (**1a**) was lithiated at the *ortho* position with butyllithium,[4] *m*- and *p*-bromo-N,N-dimethylbenzylamines (**1b** and **1c**) were converted into the corresponding Grignard reagents by reaction with magnesium. Subsequent treatment of the solutions of the metallated compounds with trimethyltin chlorides lead to the corresponding *o*-, *m*-, *p*-(trimethyltin)-substituted benzylamines **2a-c** in high yields.

Stannylbenzylamines (**2a-c**) react with ethyl chloroformate in benzene at 60-80° to afford the substituted benzyl chlorides **3a-c**. The high stability of the C-Sn bond under these severe conditions should be noted. These compounds are stable and can be distilled *in vacuo* without decomposition even in the case of the *o*-substituted chloride (**3a**). The latter compound (**3a**) was converted to benzylamine **4a** by treatment with an excess of liquid ammonia at room temperature; no trace of polyalkylated product could be detected.



The best method for the transformation of *m*- and *p*-(trimethylstannyl)benzyl chlorides **3b,c** into amines **4b,c** proceeds through the corresponding azides obtained by treatment with sodium azide in DMF followed by subsequent reduction of the azides **5b,c** with triphenylphosphine without additional purification.



The compounds obtained (**3** and **4**) may be used both in heterocyclization reactions with participation of *o*-isomers and in palladium-catalyzed (Stille) homo-coupling reactions.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker WP-200 SV (200 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. Elemental analyses were performed by the Analytical Division of the Institute of Organoelement Compounds.

***o*-(Trimethylstannyl) N,N-Dimethylbenzylamine (2a).**- To a hexane solution of *n*-BuLi (52 mL, 1.92 M, 0.1 mol) under an argon atmosphere were added 30 mL of ether with stirring and then N,N-dimethylbenzylamine (20 g, 0.15 mol) in one portion. The reaction mixture was refluxed for 3 h,

cooled to 10° and then a solution of Me_3SnCl (21 g, 0.105 mol) in diethyl ether (40 mL) was added to the stirred suspension. The mixture was refluxed for 2 h, and then kept for 12 h at 20°. The reaction mixture was washed with a solution of NaCl (40 g) in water (200 mL), and the organic layer was isolated. The aqueous layer was extracted with ether (3 x 30 mL) and the combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and the residue was distilled *in vacuo*, affording *o*-(trimethylstannyl)benzylamine (27.3 g, 91%), bp. 94-96° (1 Torr).

^{1}H NMR: δ 0.26 (s, 9H); 2.19 (s, 6H); 3.42 (s, 2H); 7.16-7.34 (m, 4H).

Anal. Calcd. for $C_{12}H_{21}Sn$: C, 48.37; H, 7.10; N, 4.70. Found: C, 48.18; H, 7.05; N, 4.56

***m*- and *p*-(Trimethylstannyl)-N,N-dimethylbenzylamine (2b,c)**.- To magnesium turnings (2 g, 0.082 mol) in THF (50mL) was added with stirring, 15% of the volume of the solution of benzylamines **1b** or **1c** (17.4 g, 0.081 mol) in THF (10 mL) in one portion. After several minutes, the reaction started and the remaining solution of the aryl bromide was added in such a way as to ensure a gentle reflux of the reaction mixture. After the addition was complete, the reaction mixture was refluxed one more hour and then cooled to 10°. Then a solution of trimethyltin chloride (16 g, 0.08 mol) in THF (20 mL) was added dropwise under stirring. The solution was refluxed for 2 h and allowed to stand for 12 h at 20°. The reaction mixture was washed with 10% aqueous NaCl (60 mL), the organic layer was separated, and the aqueous layer was extracted with ether (2x30 mL). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue was distilled *in vacuo* to yield **2b** (21.11g, 89%), bp. 96-98° (1 Torr), or **2c** (21.8g, 91%), bp. 98-100° (1 Torr).

^{1}H NMR of **2b**: δ 0.25 (s, 9H); 2.14 (s, 6H); 3.38 (s, 2H); 7.18-7.41 (m, 4H); ^{1}H NMR of **2c**: δ 0.27 (s, 9H); 2.15 (s, 6H); 3.35 (s, 2H); 7.20-7.33 (dd, 4H, J = 7.8 Hz).

Anal. Calcd. for $C_{12}H_{21}NSn$: C, 48.37; H, 7.10; N, 4.70

Found for **2b**: C, 48.21; H, 7.02; N, 4.54

Found for **2c**: C, 48.23; H, 7.04; N, 4.55

***o*-,*m*-,*p*-(Trimethylstannyl)benzyl Chlorides (3a-c)**.- To a solution of ethyl chloroformate (11.6 g, 0.107 mol) in benzene (100 mL) with stirring and cooling with cold water, the appropriate benzylamine **2a-c** (28.31 g, 0.095 mol) was added dropwise. The reaction mixture was stirred for 2hrs at 60-65° in the case of **2a** or refluxed for 6-7hrs (**2b,c**). The solution was concentrated *in vacuo* and the residue was distilled *in vacuo*. In all cases the first fraction was ethyl N,N-dimethylcarbamate, bp. 35-37° (8 Torr), and then the respective benzyl chlorides **3a-c**. Yield of **3a**, bp. 90° (1 Torr): 25.15 g (93%); **3b**, bp. 98-100° (1 Torr): 24.07g (88%); **3c**, bp.100-101° (1 Torr): 24.10g (90%).

^{1}H NMR of **3a**: δ 0.15 (s, 9H); 4.45 (s, 2H); 7.16-7.36 (m, 4H); ^{1}H NMR of **3b**: δ 0.19 (s, 9H); 4.52 (s, 2H); 7.28-7.51 (m, 4H); ^{1}H NMR of **3c**: δ 0.09 (s, 9H); 4.50 (s, 2H); 7.19-7.40 (dd, 4H, J = 7,7 Hz).

Anal. Calcd. for $C_{10}H_{15}ClSn$: C, 41.50; H, 5.23; Cl, 12.25

Found for **3a**: C, 41.29; H, 5.19; Cl, 12.18

Found for **3b**: C, 41.32; H, 5.19; Cl, 12.14

Found for **3c**: C, 41.36; H, 5.17; Cl, 12.13

***o*-(Trimethylstannyl)benzylamine (4a)**.- In a 300 mL steel cylinder (for the processes under pressure) cooled to -50° was placed liquid ammonia (220 mL) and then benzyl chloride (**3a**, 12 g, 0.04 mol) was cautiously poured in. The cylinder was sealed and allowed to warm up to 0° and shaken every 10 minutes. The reaction vessel was maintained at 0° for 6-8 h and shaken every half hour and then left for 20 h at 20°. It was cooled to -60°, opened and cautiously poured into ether (200 mL) with stirring and cooling at -60° in 1-L flask fitted with an efficient condenser. Ammonia was allowed to evaporate, and after the reaction mixture had warmed up to 0°, NH_4Cl was filtered. The ethereal solution was concentrated *in vacuo* and the residue was distilled *in vacuo* to afford 10.17 g (91%) of *o*-(trimethylstannyl)benzylamine, bp. 92-94° (1Torr).

^{1}H NMR: δ 0.18 (s, 9H); 1.22 (s, 2H); 3.94 (s, 2H); 7.17-7.41(m, 4H).

Anal. Calcd. for $C_{10}H_{17}NSn$: C, 44.49; H, 6.35; N, 5.19. Found: C, 44.32; H, 6.32; N, 5.10

***m*- and *p*-(Trimethylstannyl)benzylamines (4b,c)**.- To a stirred suspension of NaN_3 (9.5 g, 0.146 mol) in dry DMF (55 mL), compound **3b** or **3c** (36.75 g, 0.127mol) was added dropwise. After the slightly exothermic reaction ceased, the reaction mixture was stirred for 5 h at 20°, and then left overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and after 1 h it was filtered through a thin layer of silica gel, which was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* (10 Torr, t < 65°). When almost all DMF was distilled off, the liquid residue was kept for 10-15 minutes at 60-65° (1 Torr). The practically pure azides **5b,c**, were used without further purification. To a solution of azide **5b** or **5c** in THF (100 mL), was added dropwise a solution of PPh_3 (36.3 g, 0.14 mol) in THF (100 mL). An exothermic reaction with evolution of N_2 began after one minute and then the rate of addition was adjusted so as to keep the temperature below 35°. When the addition was complete, the solution was warmed to 45-50° for 1 h (evolution of N_2 stopped), cooled to 30° and water (5 mL) was added in one portion. The solution was stirred for 1 h and kept for 12 h at 20°. The solvent was distilled off *in vacuo*, the residue was diluted with 200 mL of pentane-ether 1:1, Ph_3PO was filtered and washed with the same solution. The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and the residue was distilled *in vacuo* to afford benzylamines **4b** (31.5g, 92%), bp. 98° (1 Torr), or **4c** (32.2g, 94%), bp. 100° (1 Torr).

^{1}H NMR of **4b**: δ 0.24 (s, 9H); 1.43 (s, 2H); 3.88 (s, 2H); 7.22-7.41 (m, 4H); ^{1}H NMR of **4c**: δ 0.26 (s, 9H); 1.48 (s, 2H); 3.95 (s, 2H); 7.33-7.56 (dd, 4H, J = 7.8 Hz); ^{1}H NMR of **5b**: δ 0.16 (s, 9H); 4.50 (s, 2H); 7.57-7.79 (m, 4H); ^{1}H NMR of **5c**: δ 0.17 (s, 9H); 4.45 (s, 2H); 7.52-7.75 (dd, 4H, J = 7.8Hz).

Anal. Calcd. for **4b,c**: C, 44.49; H, 6.35; N, 5.19

Found for **4b**: C, 44.31; H, 6.29; N, 5.08

Found for **4c**: C, 44.34; H, 6.33; N, 5.08

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A NOVEL ROUTE TO 4-ARYLIDENE-2-PHENYL-5(4H)-OXAZOLONES

Submitted by M. Kidwai* and R. Kumar
(09/09/97)

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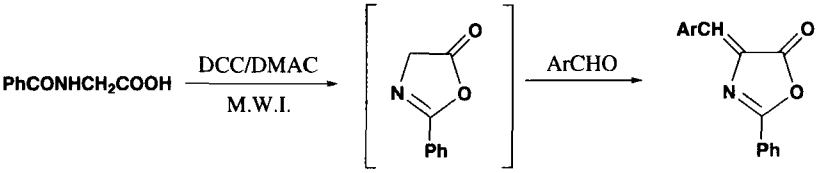
Current interest in our laboratory[1] in the use of microwave[2] energy led us to investigate it use for the synthesis of azlactones which are important synthons for biologically active molecules.[3,4] A literature survey showed that arylidene oxazolones have been prepared by the condensation of hippuric acid with aromatic aldehydes in the presence of catalyst such as acetic anhydride and sodium acetate,[5] potassium carbonate,[6] zinc chloride[7] and N-chloroacetyl-benzamide-sodium acetate.[8] The reactions involve cyclodehydration of hippuric acid to its azlactone followed by condensation of methylene group of the azlactone with the aromatic aldehyde.[7] We now report a new convenient method for the synthesis of azlactones.

Arylaldehydes along with hippuric acid when subjected to microwave irradiation (MWI) at 2450 MHz for 1.5-2.0 min using N,N-dimethylacetamide (DMAC) as a suitable energy transfer solvent and N,N-dicyclohexylcarbodiimide (DCC) as a condensing agent.

A shortcoming of classical preparation of aromatic azlactones from phenolic aldehydes with acetic anhydride and sodium acetate[5] is that the hydroxy group are always acetylated and also 1-1.5 h heating is required.[7] In comparison, the reaction using microwave energy is completed in just 1.5-2.0



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min without affecting the phenolic hydroxyl groups and provide good to excellent yields of products compared to 48-60% yields using conventional heating. The analytical and spectral data of products (**1a-j**) are in agreement with those reported in literature.[7,9,10] Thus the present method is superior to