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C-Methylation of Phenols, Tyrosine Derivatives, and a Tyrosine Containing Peptide

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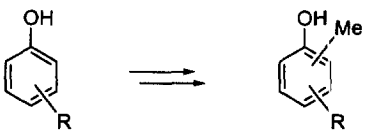
Abstract: A two step procedure is reported for the efficient C-methylation of phenolic compounds using a Stille reaction. This procedure requires no phenol protection and is tolerant to a wide variety of functional groups.

Keywords: Stille reaction, methylation, phenols.

Methods that allow easy and general access to C-methylated phenols are of interest due to the prominence of these derivatives in various natural products [1] and pharmaceuticals [2]. Ongoing investigations of quinone methides for various bioalkylating processes in our laboratories called for an efficient means for the C-methylation of numerous phenols [3]. We report a two step procedure that allows the efficient synthesis of *ortho* and *para* methylated phenol derivatives. This procedure requires no phenol protection and is tolerant to a variety of other functional groups.

Several procedures have been reported for the C-methylation of phenols (Scheme 1). A majority of these reports use the reduction of benzylic alcohols [4], aldehydes [5], benzonitriles [6], and Mannich bases [7] to produce the desired methyl groups. These procedures are limited

Scheme 1.



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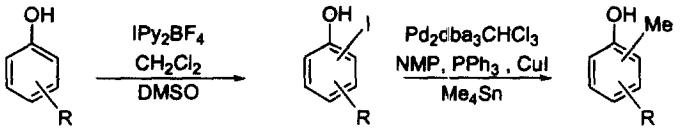
to phenols without competing reducible functionality. Directed *ortho* metalation has also been utilized for the C-methylation of phenols [8]. Phenols with base sensitive functionality are precluded from use under these conditions. Macdonald and coworkers have reported a procedure for the direct *ortho* methylation of unprotected phenols using a modified Simmons-Smith reagent [9]. They found this procedure to be incompatible with electron deficient substrates. Metal oxide catalyzed reactions of phenols and methanol under high temperature and pressure has also been reported to produce C-methylated products [10]. This method is limited to relatively simple, volatile phenolic substrates.

Methylations have also been performed on protected phenolic substrates using a Stille [11] or Negishi [12] coupling reaction. These approaches have proven to be more tolerant to a broad array of functional groups. We report an extension of the co-catalytic, palladium-copper Stille reaction [13] to convert various phenols including tyrosine, tyrosine analogs, and tyrosine containing peptides to their corresponding C-methylated derivatives. This method has proven effective in the presence of other redox active functional groups and without the need for protection of the phenol.

Phenols **1a-f** (Table 1) were converted to the desired methylated analogs by a two step procedure (Scheme 2). The phenols were first iodinated using Barluenga's reagent (IPy_2BF_4) to afford triiodo- or diiodophenols **2a-f** in excellent yields [14]. The iodophenols were converted to the methylated derivatives **3a-f** [17] via a co-catalytic, palladium-copper Stille reaction [13]. Entries 1 and 2 are examples of phenols carrying electron withdrawing, reducible functional groups. Substrates **1a** and **1b** were cleanly iodinated and efficiently converted to the corresponding trimethylphenols **3a** and **3b** in 81% and 88% overall yields, respectively. The C-methylation of phthaloyl-protected tyramine **1c** (entry 3) showed no sign of competitive iodination and was cleanly dimethylated to afford **3c** in 76% overall yield. Phthaloyl-protected octopamine **1d** (entry 4) was efficiently iodinated and dimethylated with no evidence of 1,6-elimination of the benzylic alcohol detected under the reaction conditions. This provided **3d** in 87% overall yield. Protected tyrosine **1e** (entry 5) was cleanly converted to the 3,5-dimethyl analog **3e** by the two step procedure in 73% overall yield. This approach simplifies access to the known 3,5-dimethyltyrosine derivative [15].

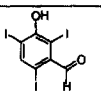
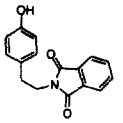
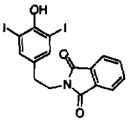
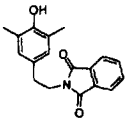
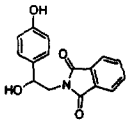
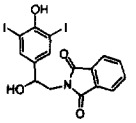
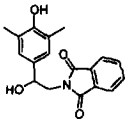
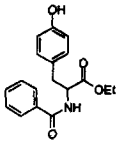
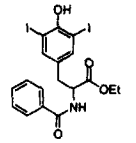
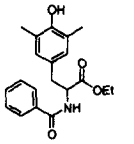
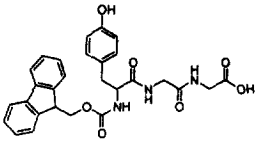
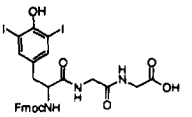
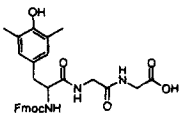
To examine this two step methylation in the context of a peptide derivative, we chose Fmoc-protected, truncated enkephalin **1f** (entry 6). Both the iodination and methylation of **1f** were accomplished with no sign of side reactions to afford **3f** in 75% overall yield. To our knowledge this is the first example of a tyrosine C-methylation in a peptide.

Scheme 2.



1 2 3

Table 1. Phenols, Iodinated Intermediates, and Methylated Products.

entry	compound	starting phenol 1	iodophenol 2	% yield 2	methylated phenol 3[b]	% yield 3
1	**a**			98		83
2	**b**			96[a]		92
3	**c**			97		78
4	**d**			95		92
5	**e**			99		74
6	**f**			93		81

[a] BMTA ICl_2 was used for iodination [16].

[b] All products have been fully characterized [17].

A representative example of the palladium-copper, co-catalytic methylation of an iodophenol is given by the conversion of **2d** to **3d**. Iodophenol **2d** (500 mg, 934 μmol) was added to a high-pressure reaction tube containing N-methylpyrrolidinone (1.5 ml). $Pd_2dba_3CHCl_3$ (27 mg, 26 μmol) and triphenylphosphine (50 mg, 191 μmol) were added to the stirring solution and gently heated to ~50 °C for 10 min. Copper(I) iodide (17 mg, 91 μmol) was added to the stirring solution and again heated to ~50 °C for 10 min. After cooling to room temperature, tetramethyl tin (285 μL, 2.06 mmol) was added neat to the stirring solution. The tube was

sealed and heated to 65 °C overnight with stirring. Aqueous workup and ethyl acetate extraction followed by drying ($MgSO_4$) and concentration afforded the crude product. Flash chromatography provided **3d** (268 mg, 861 μmol) in 92% yield [17].

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17. **3a**: ^{1}H NMR (270 MHz, acetone-d_6) δ 10.52 (s, 1H), 7.46 (s, 1H), 6.89 (s, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (68 MHz, acetone-d_6) δ 193.4, 151.8, 131.9, 131.7, 131.2, 130.2, 126.8, 18.9, 16.3, 11.1; MS (EI) *m/z* (relative intensity) 164 (M^+, 100), 163 (91), 135 (49), 121 (18), 107 (8), 91 (34), 77 (17). **3b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.88 (s, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (68 MHz, $CD_3OD/CDCl_3$, (1:1)) δ 151.2, 133.0, 130.7, 129.8, 128.2, 117.8, 110.8, 19.4, 16.4, 14.4; MS (EI) *m/z* (relative intensity) 161 (M^+, 100), 146 (98), 118 (10), 116 (12), 91 (10), 77 (10). **3c**: ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.84-7.77 (m, 4H), 6.70 (s, 2H), 3.70 (app. t, J = 7.7 Hz, 2H), 2.70 (app. t, J = 7.7 Hz, 2H), 2.07 (s, 6H); ^{13}C NMR (68 MHz, DMSO-d_6) δ 168.2, 152.2, 134.9, 132.1, 128.94, 128.88, 124.7, 123.5, 39.7, 33.5, 17.1; MS (EI) *m/z* (relative intensity) 295 (M^+, 23), 160 (12), 148 (100), 135 (77), 91 (16), 77 (14). **3d**: ^{1}H NMR (270 MHz, CD_3OD/acetone-d_6, (1:7)) δ 7.80-7.77 (m, 4H), 6.97 (s, 2H), 4.85 (dd, J = 9.1, 4.3 Hz, 1H), 3.91 (dd, J = 13.7, 9.1 Hz, 1H), 3.65 (dd, J = 13.7, 4.3 Hz, 1H), 2.16 (s, 6H); ^{13}C NMR (68 MHz, CD_3OD/acetone-d_6, (1:7)) δ 169.0, 153.5, 134.9, 133.8, 133.0, 127.0, 124.6, 123.7, 71.2, 46.5, 16.7; MS (EI) *m/z* (relative intensity) 311 (M^+, 6), 295 (13), 160 (17), 151 (100), 148 (72), 135 (54), 77 (23). **3e**: ^{1}H NMR (270 MHz, CD_3OD) δ 7.75-7.71 (m, 2H), 7.56-7.49 (m, 1H), 7.47-7.40 (m, 2H), 6.80 (s, 2H), 4.70 (dd, J = 8.8, 6.1 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.09 (dd, J = 13.7, 6.1 Hz, 1H), 2.95 (dd, J = 13.7, 8.8 Hz, 1H), 2.15 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.4, 167.3, 152.0, 134.0, 131.9, 130.0, 128.6, 127.2, 126.7, 123.8, 61.8, 53.9, 37.2, 16.3, 14.3; MS (EI) *m/z* (relative intensity) 341 (M^+, 4), 268 (10), 220 (26), 135 (89), 105 (100), 77 (52). **3f**: ^{1}H NMR (270 MHz, CD_3OD) δ 7.77 (d, J = 7.3 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.3 Hz, 2H), 7.31-7.22 (m, 2H), 6.81 (s, 2H), 4.37-4.11 (m, 4H), 3.95-3.76 (m, 4H), 2.98 (dd, J = 13.7, 6.3 Hz, 1H), 2.79 (dd, J = 13.7, 8.8 Hz, 1H), 2.15 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.1, 170.6, 169.1, 155.8, 150.4, 142.4, 139.8, 127.5, 126.4, 126.0, 125.4, 123.4, 122.9, 118.1, 65.4, 55.9, 47.4, 40.7, 39.0, 35.3, 14.0; HRMS-FAB (*m/z*) $[M + Na]^+$ calcd for $C_{30}H_{31}N_3NaO_7$, 568.2054; found, 568.2049.