Palladium(0)-Catalyzed Reaction of 2-Bromo-7-methoxytropone with Arylboronic Acids: An Efficient Synthesis of 2-Aryl-7-methoxytropones[1]

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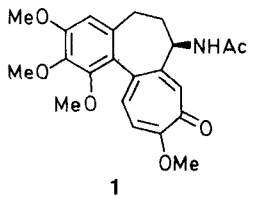
The palladium(0) catalyzed coupling of 2-bromo-7-methoxytropone (2-bromo-7-methoxy-2,4,6-cycloheptatriene-1-one, **4**) with substituted arylboronic acids **5a–f** provides an efficient and novel method for the synthesis of the corresponding 2-aryltropone **6a–f** in high yield.

The potent antimitotic effects as well as other physiological properties of colchicine **1** have prompted considerable synthetic and pharmacological investigations.[3] Colchicine itself has found only limited therapeutic use due to irreversible nature of its binding to tublin and attended toxic manifestations. However, reports[4–6] indicating that 5-aryl substituted tropones such as **2** and **3** which incorporate only some of the structural features of colchicine bind to tublin reversibly, but retain the antimitotic effects of colchicine, are of great importance since these observations offer the prospect of synthetic studies leading to therapeutically acceptable tropone derivatives.



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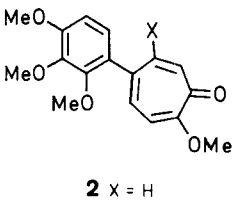
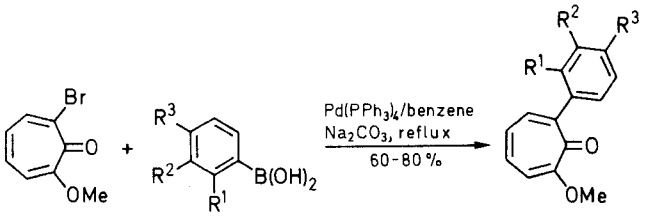


2 X = H
3 X = Cl

In the past, structure-activity investigations of aryltropones were hampered by the absence of efficient methods for their synthesis. An attempt at the synthesis of aryltropones employing a cycloaddition route was unsuccessful,[7] where as another cycloaddition strategy has met limited success.[8] The synthesis of 5-aryltropones using an interesting benzidine-type rearrangement[9] and the fascinating tropone synthesis of Boger[10] have not been applied to compounds such as **2** and **3**.

Recently we have developed a novel and efficient construction of 5-aryltropones by palladium(0) catalyzed coupling of 5-bromo-2-methoxytropone with arylboronic acids.[1] The palladium(0) catalyzed cross coupling of haloarenes with arylboronic acids[11,12] and other aryl organometallics leading to symmetrical and unsymmetrical biaryls[13–16] and a vinylic substitution of halotropones[17] under palladium(0) catalysis have been reported. However our work represents the first example of arylation of a halotropones with tetrakis(triphenylphosphine)palladium(0) as a catalyst. To date it also represents the most efficient method for the synthesis of colchicinoids such as **2**. We have continued to explore the generality of this reaction and in this paper we report its application to a facile synthesis of a variety of 2-aryl-7-methoxytropones. The procedure involves the reaction of 2-bromo-7-methoxytropone[18] **4** with substituted arylboronic acids **5a–f** using catalytic quantity of tetrakis(triphenylphosphine)palladium(0) (Scheme).

In all cases good yields of aryltropones **6a–f** were obtained. It is noteworthy that the procedure works well even with boronic acids containing a nitro- or bromo-substituents. In summary, it appears that palladium(0) catalyzed coupling of substituted arylboronic acids with 2-bromo-7-methoxytropone is an efficient and general method for the synthesis of arylated tropolones.



4 **5** **6**

5, 6	R^1	R^2	R^3
a	H	H	H
b	H	H	OMe
c	OMe	H	H
d	OMe	OMe	OMe
e	H	NO_2	H
f	H	H	Br

Scheme

Melting points are uncorrected and were recorded on Thomas Hoover capillary melting point apparatus. Infra-red spectra were recorded on Nicolet 5SXC FT-IR spectrometer. ^{1}H-NMR were recorded on GE (QE-300) spectrometer. HRMS was recorded on VG(ZAB-SE) spectrometer. 2-Bromo-7-methoxytropone **(4)** was synthesized according to literature procedure.[18] Phenylboronic and *p*-bromophenylboronic acids were purchased from Aldrich Chemical Co. Literature procedures were followed for the synthesis of *m*-nitrophenylboronic,[19] *o*-methoxyphenylboronic[20] and *p*-methoxyphenylboronic[21] acids. General procedure[22] employing the addition of aryllithium to tributylborate and hydrolysis of the boronic ester thus formed, was adopted for the synthesis of 2,3,4-trimethoxyphenylboronic acid.

2-Aryl-7-methoxytropones (2-Aryl-7-methoxy-2,4,6-cycloheptatriene-1-one, 6); General Procedure:

A solution of 2-bromo-7-methoxytropone (0.215 g, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.115 g, 0.1 mmol) in benzene (20 mL) is treated with aq 2 M Na_2CO_3 (1 mL) and ethanolic solution (1 mL) of arylboronic acid (**5**, 1.1 eq., 1.1 mmol) under inert atmosphere. The reaction mixture is warmed at reflux with stirring until TLC shows the absence of 2-bromo-7-methoxytropone. The reaction mixture is cooled to r.t. and 30% H_2O_2 (3 drops) is added. After stirring for 30 min, H_2O is added to the mixture and it is extracted with CH_2Cl_2 (2 × 25 mL). The organic layer is washed with water (2 × 5 mL), brine (10 mL) and dried (Na_2SO_4). Removal of solvent furnish a yellow solid which is charged on to the silica gel rotor plate of a Chromatotron. Elution with 40% EtOAc/hexane mixture furnishes **6** as a solid (Table).

Table. 7-Aryl-2-Methoxytropones **6a–f** Prepared

Product	Yield (%)	mp (°C)[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	Exact Mass calc. (Formula)[b]	Exact Mass found
6a	80	94–95	1592, 1563, 1500, 1364, 1275, 1223, 1166, 1090, 967, 756, 700	3.95 (s, 3H), 6.74 (d, 1H, J = 9.5), 6.86–6.92 (m, 1H), 7.01–7.07 (m, 1H), 7.31–7.48 (m, 6H)	213.0915, MH^+ ($C_{14}H_{13}O_2$)	213.0923
6b	76	111–112	1602, 1588, 1569, 1514, 1464, 1358, 1309, 1273, 1251, 1218, 1182, 1161, 1091, 973, 840, 821, 809, 762	3.84 (s, 3H), 3.95 (s, 3H), 6.73 (d, 1H, J = 9.5), 6.92 (d, 2H, J = 8.7), 6.84–7.05 (m, 2H), 7.45 (d, 2H, J = 8.7), 7.46 (d, 1H, J = 7.5)	242.0942 ($C_{15}H_{14}O_3$)	242.0940
6c	77	129–130	1615, 1601, 1581, 1500, 1406, 1359, 1283, 1239, 1223, 1172, 1124, 1049, 1023, 981, 810, 762	3.76 (s, 3H), 3.94 (s, 3H), 6.72 (d, 1H, J = 9.6), 6.81–6.88 (m, 1H), 6.94 (d, 1H, J = 8.3), 6.97–7.06 (m, 2H), 7.22 (dd, 1H, J_1 = 7.5, J_2 = 1.7), 7.3–7.4 (m, 2H)	242.0942 ($C_{15}H_{14}O_3$)	242.0941
6d	71	119–120	1591, 1572, 1505, 1459, 1411, 1359, 1301, 1274, 1239, 1215, 1162, 1093, 988, 910, 862, 806, 763	3.8 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.7 (d, 1H, J = 8.5), 6.72 (d, 1H, J = 9.6), 6.80–6.83 (m, 1H), 6.93 (d, 1H, J = 8.5), 6.98–7.05 (m, 1H), 7.36 (dd, 1H, J_1 = 8.8, J_2 = 1)	303.1232, MH^+ ($C_{17}H_{19}O_5$)	303.1233
6e	65	185–186	1597, 1568, 1518, 1344, 1273, 1218, 1095, 1078, 991, 736, 693	3.99 (s, 3H), 6.81 (d, 1H, J = 9.8), 6.92–6.98 (m, 1H), 7.12–7.19 (m, 1H), 7.5 (dd, 1H, J_1 = 8.9, J_2 = 1), 7.56 (t, 1H, J = 8.0), 7.81–7.85 (m, 1H), 8.19–8.23 (m, 1H), 8.32 (t, 1H, J = 2)	258.0766, MH^+ ($C_{14}H_{12}NO_4$)	258.0767
6f	60	100–101	1596, 1579, 1499, 1357, 1280, 1226, 1164, 1092, 1072, 973, 821, 787, 751	3.96 (s, 3H), 6.76 (d, 1H, J = 9.6), 6.86–6.92 (m, 1H), 7.04–7.11 (m, 1H), 7.34 (m, 1H), 7.35 (d, 1H, J = 8.5), 7.42 (dd, 1H, J_1 = 8.9, J_2 = 1.0), 7.51 (d, 1H, J = 8.5), 7.52 (m, 1H)	289.9942 ($C_{14}H_{11}{}^{79}BrO_2$)	289.9925

[a] All the compounds **6a–f** are crystallized from CH_2Cl_2/hexane mixture.
[b] Satisfactory microanalysis of products obtained: C ±0.38, H = ±0.27, N = ±0.24.

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