Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Practical Preparation of Methyl 4-(Trimethylsilyl)-benzoate: An Intermediate in the Synthesis of SDZ 63135

John C. Amedio Jr [a], George T. Lee [a], Kapa Prasad [a] & Oljan Repic [a]
[a] Technical R & D, Chemical R & D, Sandoz Research Institute, Sandoz Pharmaceuticals Corp. East Hanover, New Jersey, 07936, USA
Published online: 23 Sep 2006.

To cite this article: John C. Amedio Jr, George T. Lee, Kapa Prasad & Oljan Repic (1995) A Practical Preparation of Methyl 4-(Trimethylsilyl)-benzoate: An Intermediate in the Synthesis of SDZ 63135, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:17, 2599-2612, DOI: 10.1080/00397919508011806

To link to this article: http://dx.doi.org/10.1080/00397919508011806

SYNTHETIC COMMUNICATIONS, 25(17), 2599-2612 (1995)

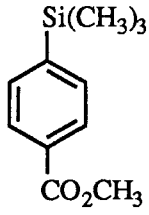
A PRACTICAL PREPARATION OF METHYL 4-(TRIMETHYLSILYL)BENZOATE: AN INTERMEDIATE IN THE SYNTHESIS OF SDZ 63135

John C. Amedio Jr.,* George T. Lee, Kapa Prasad and Oljan Repic

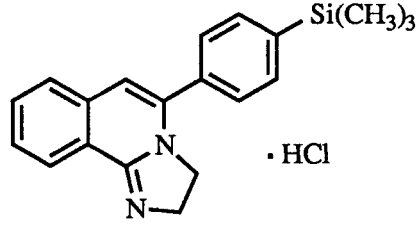
Technical R & D, Chemical R & D
Sandoz Research Institute, Sandoz Pharmaceuticals Corp.
East Hanover, New Jersey 07936, USA

Abstract: An improved synthesis of ester **1** is described utilizing a bromine-lithium exchange and a Grignard-mediated methoxycarbonylation reaction starting from 1,4-dibromobenzene. Compound **1** was converted to **2** through a condensation and dehydration sequence with an overall yield of 41.5%.

A practical and efficient synthesis of aryl methyl ester **1** was required to support kilogram scale preparations of the PAF receptor antagonist **2**, (SDZ 63135).[1,2]



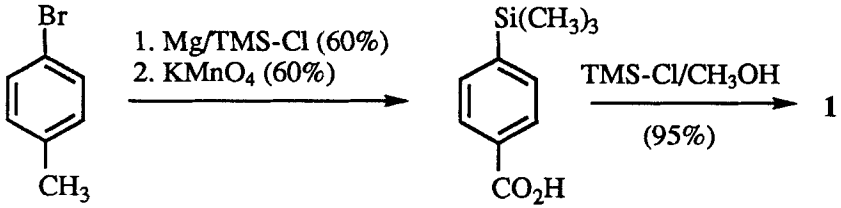
1



2

*To whom correspondence should be addressed.

The only representative approach to **1** involved silylation of the Grignard derived from *p*-bromotoluene, followed by potassium permanganate oxidation and esterification (chlorotrimethylsilane/ methanol or diazomethane) of the resultant acid **3** (Scheme I).[1,3]

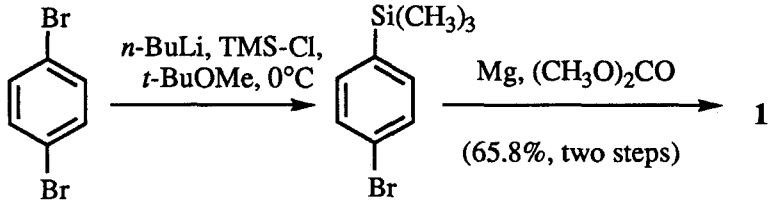


Scheme I

Indeed, this three-step sequence provided ester **1** in 34% overall yield. However, the utility of this pathway for large scale preparations of **1** was hampered by its modest yield and environmental concerns.[4] As a consequence, we developed a high yielding and more environmentally friendly route. Our approach utilized a singular lithium-halogen exchange from 1,4-dibromobenzene (*n*-BuLi, Me_3SiCl, *t*-BuOMe), followed by a Grignard mediated methoxycarbonylation reaction (Mg, $(CH_3O)_2CO$, THF) (Scheme II).

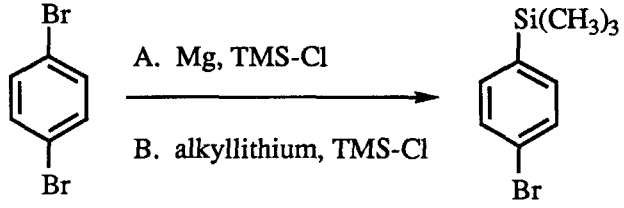
Earlier reports[5,6] describe the preparation of **4** from 1,4-dibromobenzene via Method A or Method B (Scheme III).

Method A afforded **4** in 52-55% yield, while Method B yielded **4** in 47–92%. The potential for high yield yet lack of reproducibility reported in



4

Scheme II

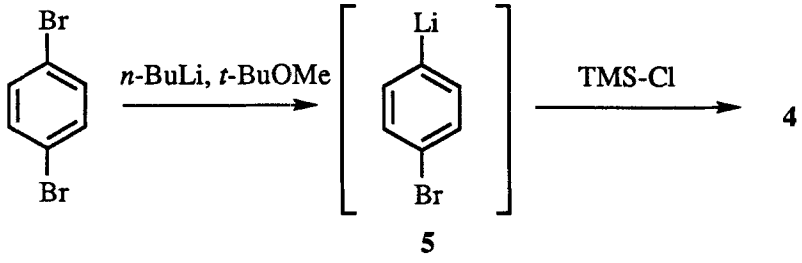


4

Scheme III

Method B led us to further develop this methodology. Prior literature reports stated that 1,4-dibromobenzene in diethyl ether was treated with *n*-butyllithium or *t*-butyllithium to effect a bromine-lithium exchange. Addition of chlorotrimethylsilane, followed by an acidic work-up then afforded **4**. Our objective was to clearly define conditions for obtaining **4** reproducibly in high yield utilizing an acceptable "ethereal" solvent[7] and *n*-butyllithium as the base.[8] We first turned our attention to using alternate ether solvents (tetrahydrofuran or *t*-butyl methyl ether). Treatment of 1,4-dibromobenzene in tetrahydrofuran with n-butyllithium

Table I[a]

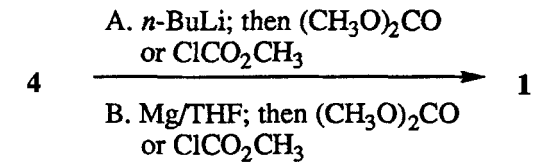


Entry	(5 to 4) Reaction time	Purity (%)	4 Yield (%)
1	4.0 hr.	98	96
2	1.5 hr.	98	92
3	0.5 hr.	91	91
4	0.25 hr.	89	85

a. Purity and yields were determined on crude reaction mixtures. Yields were based on comparison with pure reference standard **4** by HPLC.

at 0 °C, followed by addition of chlorotrimethylsilane, provided no desired product. However, use of the solvent *t*-butyl methyl ether provided successful bromine-lithium exchange and silylation in high yield (Table I).

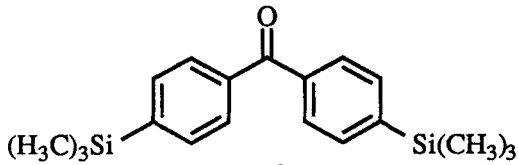
Under entry 1 and 2 conditions compound **4** needed no further purification (see Experimental Section); when the reaction time was reduced below 1.5 hours (entries 3 and 4), a purification was required.



Scheme IV

With bromosilane **4** in hand, we attempted a direct methoxycarbonylation under conditions C or D (Scheme IV).

Treatment of **4** with *n*-BuLi in tetrahydrofuran, followed by addition of dimethyl carbonate or methyl chloroformate under variable reaction conditions (stoichiometry, temperature), gave low yields of methyl ester **1**. We were unable to inhibit the formation of ketone **6**.

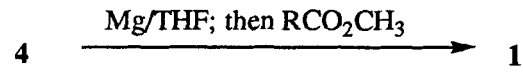


6

However, the corresponding Grignard reagent was found to be a better choice of nucleophile. In this case the ketone formation was minimized (Table II).

The methoxycarbonylation reaction with methyl chloroformate resulted in a 50% overall yield of purified **1** (entry 1). Due to the high toxicity of methyl chloroformate and its lachrymator character, an alternative

Table II[a,b]



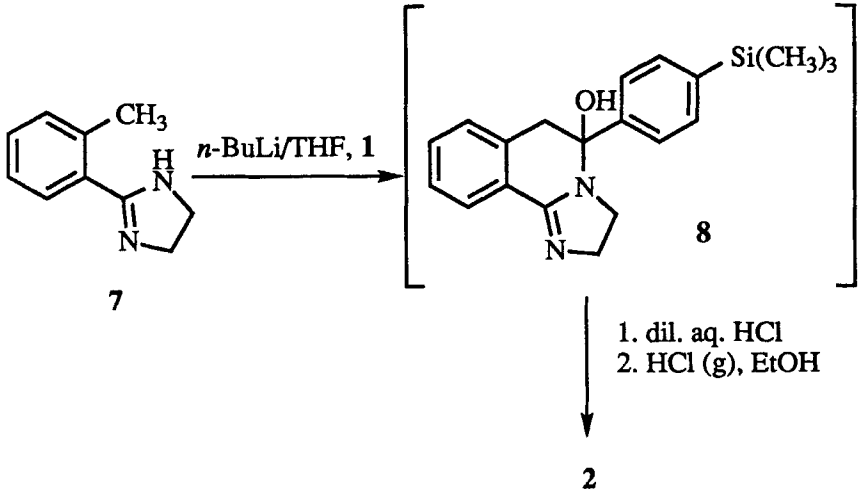
Entry	R (Equiv.)	Yield (%)
1	Cl (1.05)	50.0
2	CH_3O (1.5)	60.0
3	CH_3O (2.45)	65.8
4	CH_3O (3.06)	62.3

a. Yields based on 1,4-dibromobenzene. Compound **1** was isolated by short path vacuum distillation (see Experimental Section).
b. All reactions were carried out at –25 to 65 °C, with the exception of entry 4 (—25 to 22 °C).

electrophile was required. The less toxic dimethyl carbonate proved effective (entries 2–4).[9] An increase in the quantity of dimethyl carbonate resulted in an increase in yield (entries 2 and 3). Thus, this two-step process from 1,4-dibromobenzene provided **1** in 65.8% yield requiring one distillation and utilizing relatively non-toxic reagents in comparison to earlier syntheses (three steps, 34% overall yield and three purification steps)[1]. This material was then utilized to prepare SDZ 63135, **2**, through a condensation and dehydration sequence with 4,5-dihydro-2-(2-methylphenyl)-1H-imidazole **7** (Table III):[1,12]

Reaction of lithio **7** with **1** in THF, followed by dehydration in dilute

Table III



Entry	Equiv. of *n*-BuLi	Condensation temperature (°C)	% Yield of **2**
1	2.3	–60 to –55	66.4
2	3.3	–60 to –55	52.0
3	2.3	–5 to –15	38.0
4	2.3	23 to 25	25.8

acid and HCl salt formation with HCl gas, afforded **2** in 66% yield. The critical step was determined to be formation of **8** and was found to be quite sensitive to temperature and stoichiometry.

This process provided **1** in 41.5% overall yield utilizing four operations, compared to a 11.5% overall yield in five synthetic transformations as previously reported.[1]

Experimental

(4-Bromophenyl)trimethylsilane 4: A 3-L, 4-necked round-bottomed flask, equipped with a mechanical stirrer, thermometer, addition funnel, nitrogen inlet and cooling bath, was charged with 1,4-dibromobenzene (200 g, 0.848 mol) and *t*-butyl methyl ether (850 mL). The solution was cooled to 0–5 °C and *n*-butyllithium (530 mL of a 1.6 M solution in hexanes, 0.848 mol) was added over a period of 35 minutes while maintaining an internal temperature of 5–10 °C. The reaction contents were stirred for 15 minutes. Chlorotrimethylsilane (108 mL, 0.848 mol) was added over a period of 20 minutes while maintaining an internal temperature of 15–18 °C. The mixture was warmed to 20–22 °C and allowed to stir for 1.5 hours. A solution of saturated aqueous ammonium chloride (200 mL) in water (200 mL) was added over a period of 15 minutes while maintaining an internal temperature of 22–23 °C. The solution was stirred for 15 minutes and the layers were separated. The organic layer was filtered by suction through Celite (150 g). The filtrate was concentrated under reduced pressure (40–45 °C bath temperature, 25–30 mm Hg) to give 182.4 g of **4** (92.0% yield, 98.0% purity, no purification).[10] ^{1}H NMR ($CDCl_3$, 300 mHz): δ 7.47 (d, J=8.3 Hz, 2H), 7.36 (d, J=8.3 Hz, 2H), 0.24 (s, 9H); ^{13}C NMR (see ref. 5e, $CDCl_3$, 75 mHz): δ 139.1, 135.2, 131.1, 123.7, –0.99; IR (cm^{-1}): 2957, 1574, 1479, 1376, 1250, 1066, 1011, 841, 719; MS *m/z* (NH_3/DCI): 246/248 (M+ NH_4^+).

Methyl 4-(Trimethylsilyl)benzoate 1: A 5-L, 4-necked round-bottomed flask, equipped with a mechanical stirrer, thermometer, addition funnel, nitrogen inlet, heating mantle and cooling bath, was charged with magnesium turnings (40.0 g, 1.66 mol) and iodine (0.2 g). The flask was warmed to 60–65 °C, and a solution of 1,2-dibromoethane (2.6 mL) dissolved in tetrahydrofuran (500 mL) was added over a period of 2 minutes while maintaining an internal temperature of 53–58 °C. The mixture was stirred for 5 minutes. An aliquot (40 mL) consisting of 4-(bromophenyl)trimethylsilane **4** (388.0 g, 1.66 mol, 98.0 % purity) in tetrahydrofuran (300 mL) was added over a period of 2 minutes while maintaining an internal temperature of 55–60 °C. The mixture was warmed to 60–65 °C, and the remainder of the above solution was added over a period of 30 minutes while maintaining an internal temperature of 60–65 °C. The reaction mixture was cooled to −30 to −35 °C, and a solution of dimethyl carbonate (428.0 mL, 5.08 mol, 3.06 equiv.) in tetrahydrofuran (290 mL) was added[11] over a period of 10 minutes while maintaining an internal temperature of −25 to −27 °C. The reaction mixture was warmed to −10 to −12 °C over a period of 20 minutes and stirred for an additional 30 minutes. The reaction contents were stirred to 22–23 °C over a period of 45 minutes and allowed to stand for 16 hours. A solution of concentrated hydrochloric acid (180 mL) diluted in water (620 mL) was added over a period of 15 minutes while maintaining an internal temperature of 23–30 °C (exothermic, cooling necessary). Heptane (700

mL) was added over a period of 5 minutes while maintaining an internal temperature of 20–25 °C. The mixture was stirred for 10 minutes. The layers were separated (aqueous layer pH = 1), and the organic layer was washed with water (240 mL), saturated aqueous sodium bicarbonate (240 mL) and water (240 mL) (aqueous pH = 7.0–7.5 after final wash). The organic layer was concentrated under reduced pressure to give 333.0 g of a residue. The residue was short-path distilled under reduced pressure (78–83 °C pot temperature, 78–90 °C head temperature, 0.75–0.65 mm Hg) to provide 233.0 g of **1** (62.3% from 1,4-dibromobenzene). ^{1}H NMR ($CDCl_3$, 300 mHz): δ 8.05 (d, J=8.3 Hz, 2H), 7.6 (d, J=8.3 Hz, 2H), 3.95 (s, 3H), 1.5 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 mHz): δ 167.1, 146.7, 133.5, 130.3, 128.5, 51.5, -1.2; IR (cm $^{-1}$): 2955, 1725, 1436, 1386, 1282, 1263, 1250, 1189, 1122, 1094, 1021, 836, 823, 743, 717; MS: *m/z* (NH_3/DCI) 226 (M + NH_4^+).

5-[4-Trimethylsilyl)phenyl]-2,3-dihydroimidazo[2,1-a] isoquinoline hydrochloride 2: A 3-L, 4-necked round-bottomed flask, equipped with a cooling bath, thermometer, mechanical stirrer, nitrogen inlet and addition funnel, was charged with 4,5-dihydro-2-(2-methylphenyl)-1H-imidazole[12] (80.0 g, 0.492 mol, 1.05 equiv.) and tetrahydrofuran (765 mL). The contents were cooled between –10 to –8 °C, and *n*-butyllithium (450 mL, 1.13 mol, 2.41 equiv. of a 2.5 M solution in hexanes) was added at such a rate that the internal temperature

did not exceed –5 °C (exothermic). The reaction contents were stirred between –5 and –10 °C for 10 minutes, then cooled between –60 and –65 °C. Methyl 4-(trimethylsilyl)benzoate **1** (103.0 g, 0.466 mol) dissolved in tetrahydrofuran (185 mL) was added over a period of 25–30 minutes while maintaining an internal temperature of –60 to –55 °C. The reaction mixture was stirred between –60 to –55 °C for 1.0 hour. Concentrated hydrochloric acid (323 mL) diluted in water (323 mL) was added over a period of 5 minutes (exothermic). The mixture was stirred to 22–23 °C, then heated to 43–53 °C for 30 minutes. The mixture was cooled to 22–23 °C, and concentrated ammonium hydroxide (323 mL) was added over a period of 20 minutes while maintaining an internal temperature of 25–35 °C (exothermic). Heptane (150 mL) was added and stirring was continued for 10 minutes. The layers were separated and the organic layer was washed with water (2 x 150 mL). The organic layer was concentrated under reduced pressure (55–65 °C bath temperature, 25–30 mm Hg) until 1.30 L of solvent was collected. The residue was diluted with absolute ethanol (900 mL) and heated to 30–35 °C. The mixture was cooled to 22–24 °C, and HCl gas (44.0 g) was bubbled through the solution over a period of 15 minutes while maintaining an internal temperature of 28–35 °C (exothermic). The suspension was cooled to 22–24 °C and stirred for 45 minutes. The solids were collected by suction filtration and washed with cold (5 °C) absolute ethanol (2 x 75 mL). The solids were suspended in water/ethanol (10/400 mL) and heated to 43–53 °C for 10 minutes. The

suspension was cooled to 0–5 °C and stirred for 15 minutes. The solids were collected by suction filtration and washed with cold (5 °C) absolute ethanol (50.0 mL), dried in vacuo until a constant weight to give 110.0 g of **2** (66.4 % yield). ^{1}H NMR ($CDCl_3$/DMSO 300 mHz): δ 8.8 (d, J=8.2 Hz, 1H), 7.91-7.71 (m, 2H), 7.70 (s, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.57 (d, J=8.1 Hz, 2H), 7.0 (s, 1H), 4.6 (ddd, J=9.6, 8.2, 2.6 Hz, 2H), 4.20 (ddd, J=9.6, 8.2, 2.6 Hz, 2H), 2.56 (bs), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$/DMSO 75 mHz): δ 161.4, 147.9, 145.1, 141.9, 139.9, 138.5, 137.2, 133.6, 132.6, 119.6, 117.0, 54.9, 48.2, 3.5; IR (cm^{-1}): 3505-3365 (b), 3023, 2952, 1648, 1601, 1581, 1410, 1298, 1248, 1158, 1102, 854, 839, 823, 760; MS *m/z* (MH^+): 319; Calculated for $C_{20}H_{23}N_2ClSi$: C: 67.68, H: 6.53, N: 7.89, Cl: 9.99. Found: C: 67.79, H: 6.66, N: 7.87, Cl: 9.99.

Acknowledgements: We thank Dr. M. J. Shapiro and Dr. E. Fu and their groups for spectroscopic measurements.

References

1. a) Houlihan, William; Cheon, Seung, H., United States Pat. 4992428A, 1991. b) Houlihan, William, United States Pat. 4910206A, 1990. c) Houlihan, William, World Pat. 8800587, 1988.
2. Danhauser-Riedl, Susanne et al., Cancer Res. 1991, *51(1)*, 43.
3. For literature preparations of methyl (4-trimethylsilyl)benzoate **1**, see: a) Yamamoto, K.; Hayashi, A.; Suzuki, S.; Tsuji, Jiro,

Organometallics, 1987, *6*, 974. b) Picard, J.P. et al., J. Org. Chem., 1979, *44(3)*, 420. c) Eaborn, C.; Jackson, P.M., J. Chem. Soc B, 1969, 21.

4. The generation of MnO_2 created waste disposal problems.

5. For literature preparations of (4-bromophenyl) trimethylsilane **4**, see: a) Reimann, E.; Langwieler, I., Archiv. Pharm., 1975, *11(308)*, 888. b) Moerlein, S.M., J. Organomet. Chem., 1987, *319*, 29. c) Glyde, E.; Taylor, R., J. Chem. Soc. Perkin Trans. I, 1973, 1632. d) Effenberger, F.; Haebich, D., Liebigs Ann. Chem. 1979, 842. e) Schraml, J.; Chvalovsky, V.; Maegi, M.; Lippmaa, E., Coll. Czech. Chem. Comm., 1975, *140* , 897. f) Gilman, H.; Melvin, H.W.; Goodman, J.J., J. Am. Chem. Soc., 1954, *76*, 3219. g) Chvalovsky, V.; Bazant, V., Coll. Czech. Chem. Comm., 1951, *16*, 580. h) Jones, R.G.; Gilman, H., Org. Reactions, 1951, *6*, 339. i) Roberts, J.D.; McElhill, E.A.; Armstrong, R., J. Am. Chem. Soc., 1949, *71*, 2923. j) Burkhard, C.A., J. Am. Chem. Soc., 1946, *68*, 2103.

6. For lithium-bromine exchange reactions with 1,4-dibromobenzene, see: a) Stephens, E.B.; Kinsey, K.E.; Davis, J.F.; Tour, J.M., Macromolecules, 1993, *26*, 3519. b) Tour, J.M.; Stephens, E.B., Poly. Mater. Sci. Eng. 1991, *64*, 223. c) Tour, J.M.; Stephens, E.B., J. Am. Chem. Soc., 1991, *113*, 2309. d) Brandsma, L.; Verkruijsse, H.D., "Preparative Polar Organometallic Chemistry", Springer-Verlag Berlin, 1987, volume 1, page 190.

7. Diethyl ether is not acceptable for large scale preparations due to its extremely low flashpoint.
8. *t*-Butyllithium is pyrophoric and prohibited for use in our pilot plant operations.
9. For methoxycarbonylation of an aryl magnesium bromide, see: Whitmore, F.C.; Loder, D.J., Org. Synth., Coll. Vol. II, 282.
10. Bromosilane **4** can be purified by short path distillation: 105–115 °C, 25–30 mm Hg (Lit.: 74–76 °C, 2.5 mm, see ref. 5h).
11. Reverse addition gave a lower yield (39%).
12. For the preparation of **7**, see: a) Houlihan, W.J.; Parrino, V.A., J. Org. Chem., 1982, *47(26)*, 5177. b) Piskov, V.B.; Kasperovich, V.P.; Yakovleva, L.M., Khim. Geterotsikl. Soedin., 1976, *8*, 1112. c) Houlihan, W.J., Ger. Offen. 2549088, 1976.

(Received in the USA 24 January 1995)