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Chemoselective Removal of Dimeric 1,3-Diol Impurities Generated from Methyl Grignard Addition onto Esters

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Abstract:

In two separate cases, we have found that 1,3-diol dimeric impurities were common byproducts generated from the methyl Grignard addition onto esters to form the corresponding tertiary alcohols. These impurities proved difficult to purge by recrystallization as they tended to cocrystallize with the desired product. To avoid the necessity of chromatography, we developed a practical procedure for the chemoselective removal of these 1,3-diol impurities from crude tertiary alcohol by simply performing the recrystallization in the presence of phenylboronic acid. This straightforward method proved equally successful for two cases studied, and the procedure was later demonstrated on a multikilogram scale.

Introduction

During process development of **1**,[1] a side reaction was encountered during methyl Grignard addition onto an ester (**2**) that resulted in the formation of dimeric, diol byproducts (**3**).[2] The impurities proved difficult to purge and remained in final drug substance at unacceptably high levels (Scheme 1).

Sulfonamide **4**,[3] an advanced intermediate from another drug candidate, was experiencing identical difficulties associated with dimeric, diol impurities using similar Grignard methodology to form a tertiary alcohol from an ethyl ester (**5**) (Scheme 2).

These diol byproducts are the result of an alternate reaction pathway (Scheme 3) during which addition of methyl Grignard to an ethyl ester can involve enolization of an intermediate ketone, followed by Aldol-type generation of dimeric impurities.[4]

In both cases, purification for removal of these byproducts required chromatography. Herein, we wish to report a practical solution for the elimination of 1,3-diol dimeric impurities generated during methyl Grignard addition to esters.

Results and Discussion

In the synthesis of **1**, addition of 4 equiv of methyl Grignard to **2** in THF at −10 °C resulted in generation of >20% dimeric diol impurities (**3**).[2] The following optimizations led to an improved reaction profile. Reverse addition (substrate to an excess of Grignard) at room temperature resulted in increased Grignard attack, less enolization, and an improved reaction selectivity for the desired product over dimer (Table 1).

Table 1. **Impurity formation relative to equivalents of methylmagnesium bromide**

entry	equiv MeMgBr	% dimers
1	2.0	15
2	5.0	7
3	10.0	2

Table 2. **Attempted purification of 1**[a]

entry	comment	% of **1**	% dimers
1	crude	90.70	1.99
2	IPO	98.10	0.88
3	BuOH	96.25	1.25
4	EtOAc/hex	95.00	1.58
5	THF/hex	93.50	1.67
6	MEK	95.40	0.97
7	ACN	97.17	0.87
8	MTBE	93.30	1.53
10	pentane	88.17	2.81
11	hexanes	91.60	2.13
12	heptanes	91.90	1.94

[a] Performed by heating a suspension of **1** in 2 volumes (mL/g **1**) solvent.

With the impurity reduced to 2%, selective crystallizations were explored (Table 2).

Impurities typically crystallized along with the desired tertiary alcohol. No facile alternative to chromatography effectively delivered both acceptable purity and yield. Some crystallization conditions led to a reduction of the impurities, but not to within drug substance specifications (<0.1%) and with unacceptably low recovery of product (typically <60% yield). Other crystallizations delivered higher yield, but showed little purging ability or even favored enhancement of the dimeric impurities.

Cyclic boronates have been used as directing and protecting groups during synthesis,[5] to affect separation of cis from trans diols,[6] and as molecular sensors.[7] Although five-membered cyclic boronates may be formed from cis and trans

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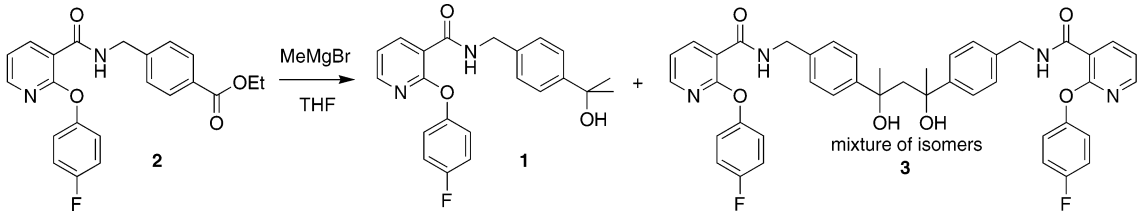
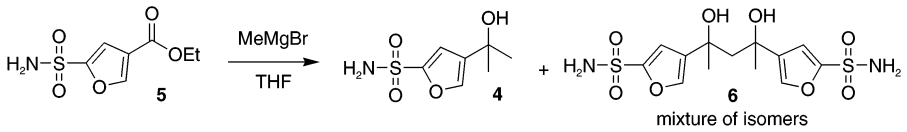
Scheme 1



Scheme 2



Scheme 3

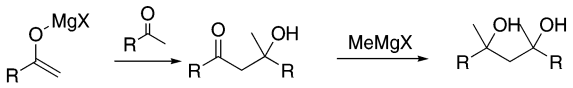


Table 3. **Recrystallization in the presence and absence of phenylboronic acid**

entry	comment	% of **1**	% dimers
1	crude	89.73	2.57
2	toluene	96.83	1.20
3	toluene + $PhB(OH)_2$	98.39	0.03

vicinal diols, angle strain frequently leads to easy hydrolysis.[8] 1,3-Diols can accommodate both cis and trans isomers in formation of strainless, six-membered cyclic boronates. Since boronic acids readily react with 1,3-diols to generate cyclic boronates, we surmised that it might be possible to selectively derivatize the dimeric diol impurities from the Grignard reaction. This could potentially differentiate the impurity to be removed from the desired tertiary alcohol, allowing for purification via crystallization. Phenylboronic acid could provide the requisite boronate, imparting additional lipophilicity to the derivatized dimeric diol impurity for greater solubility in the crystallization solvent.

On the basis of this hypothesis, the crude **1** containing ~3% dimers was heated to solution at reflux in toluene in the presence of 10 mol % phenylboronic acid for 1 h. After cooling to ambient temperature and stirring for 1 h, the resulting solids were filtered and analyzed. Much to our delight, only 0.03% dimers remained in the isolated product, and the dimeric byproducts were found in the mother liquor as their phenyl boronic esters.[9,10] A control experiment (Table 3) was performed in the absence of phenylboronic acid, with the resultant solid product still containing 1.2% dimeric, diol byproducts.

Sulfonamide **4**, an advanced intermediate from another drug candidate, was experiencing identical difficulties associated with dimeric, diol impurities (vide supra). Approximately 3% of 1,3-diol dimeric impurities (**5**) remained in the bulk **4** produced, was carried forward to drug substance, and could not be removed without chromatography. A solvent adjustment was required to accommodate the characteristics of this new compound (in THF), but the purification method proved to be equally applicable. Derivatization in THF, followed by a displacement into diisopropyl ether gave marked improvement in overall purity, reduced the dimeric impurities, and eliminated the need for chromatography (Table 4). This procedure was successfully exemplified on a pilot plant scale to purify 79 kg of **4** (Scheme 4).

Table 4. **Results of phenylboronic acid purification as applied to 4 on pilot plant scale**

entry	comment	% of **4**	% dimers
1	crude	93.82	2.99
2	THF/IPE	96.52	2.40
3	THF/IPE + $PhB(OH)_2$	99.06	0.07

Conclusion

We have developed a useful, selective method for removal of 1,3-diol dimeric impurities encountered during methyl Grignard attack upon esters. Phenylboronic acid preferentially forms cyclic boronic esters, which solubilize 1,3-diol dimeric impurities, allowing for easy purification of tertiary alcohol products via simple crystallization. In addition, solid-supported boronic acid reagents[11] may conceivably allow for separation of diol impurities when crystallization of desired alcohol is not feasible.

Experimental Section

General Procedures. The ^1H and ^{13}C NMR spectra were recorded on a Varian Innova 400 spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside, N.Y.). Melting points were obtained from a Thomas-Hoover Uni-Melt capillary apparatus and are uncorrected. Samples were analyzed using reversed-phase HPLC on a Hewlett-Packard (HP1100). The

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(8) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31−80.
(9) Characterization via preparative TLC and APcI MS.
(10) Boron content of **1** after treatment was measured at 437 ppm, which was reduced to 20 ppm by a re-slurry in 5 mL of toluene/g of **1** in 89% yield.
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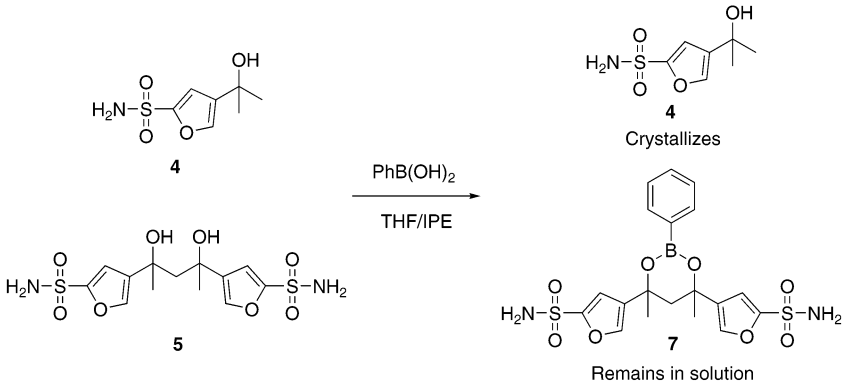
Scheme 4



mobile phase buffer consisted of 50 mM KH_2PO_4 with 25 mM decanesulfonic acid, sodium salt. The buffer was brought to a pH of 2.5 with phosphoric acid. The mobile phase consisted of 75% buffer, 15% acetonitrile, and 10% methanol. An Inertsil CN-3 column, 4.6 × 150 × 3 μm^3, was used for the separation. The system flow rate was set at 2.0 mL/min, and the column temperature was maintained at 40 °C. The samples were evaluated at a wavelength of 219 nm. Boron analysis was evaluated using an Agilent ICP-MS (Inductively Coupled Plasma Mass Spectrometer). Samples were initially prepared in 5 mL of HNO_3 (trace metal grade) and 5 mL of 30% H_2O_2. These solutions were then digested in a microwave labstation provided by Milestone. The samples were heated using a 50-min temperature gradient that ranged from ambient to 225 °C. Once fully digested, the samples were then diluted with 0.5% HNO_3. Values were compared versus a standard Boron curve generated using Plasma Emission Standards supplied by E. M. Science. Standard concentrations ranged from 0.01 to 100 ppm. Mass spectra were obtained on a Waters Micromass ZMD mass spectrometer using APcI with a 50:50 water/acetonitrile mobile phase. HPLC mass spectra were obtained on a Hewlett-Packard HP-1100 series LC/MSD, using a gradient from 0.01% formic acid in 98:2 water/acetonitrile to 0.005% formic acid in acetonitrile for mobile phase. A Phenominex C18−HC column, 30 × 2.00 mm^2, 5 μm, was used for separation.

Crystallization of 2-(4-Fluoro-phenoxy)-*N*-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide (1). To a 50-mL round-bottom flask was added 4.97 g (13.07 mmol, 1.0 equiv) of solid **1** (containing 2.6% dimeric diol byproducts) and 25 mL of toluene. The flask was heated to solution and held at reflux for 20 min. The solution was allowed to slowly cool to ambient temperature over 1 h, at which point solids precipitated. After a 90-min granulation, the solids were filtered, washed once with 5 mL of toluene, and then placed in a vacuum oven until dry. Obtained 3.2 g of **1** with 96.8% overall purity and 1.20% dimeric diol impurities **(3)** remaining.

Purification of 2-(4-Fluoro-phenoxy)-*N*-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide (1). To a 50-mL round-bottom flask was added 4.97 g (13.07 mmol, 1.0 equiv) of solid **1** (containing 2.6% dimeric diol byproducts), 25 mL of toluene, and 159 mg (1.3 mmol, 10 mol %) of phenylboronic acid. The flask was heated to solution and held at reflux for 20 min. The solution was allowed to slowly cool to ambient temperature over 1 h, at which point solids precipitated. After a 90-min granulation the solids were filtered, washed once with 5 mL of toluene, and then placed in a vacuum oven until dry. Obtained 3.13 g of **1** with 98.4% overall purity and 0.03% dimeric diol impurities **(3)** remaining.

Re-slurry of 2-(4-Fluoro-phenoxy)-*N*-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide (1) for Removal of Boron Content. 1 (500 mg, 1.31 mmol, 1.0 equiv containing 437 ppm boron) and toluene (2.5 mL) were added to a round-bottom flask and stirred at ambient temperature for 36 h. Toluene (1.5 mL) was added to aid in mobility, and the slurry was filtered. The solid cake was washed once with 1.2 mL of toluene. **1** was obtained (446 mg, 89% yield), containing 20 ppm boron content. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (m, 1H), 8.23 (m, 1H), 8.16 (m, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.13−7.03 (m, 5H), 4.65 (d, J = 5.5 Hz, 2H), 2.80 (brs, 1H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.74, 161.55, 160.43, 150.14, 148.92, 142.69, 136.58, 127.48, 125.15, 123.73, 123.64, 119.77, 116.91, 116.79, 116.55, 72.41, 43.83, 31.97. Analysis calculated for $C_{22}H_{21}FN_2O_2$: C, 69.46; H, 5.56; N, 7.36. Found: C, 69.75; H, 5.87; N, 7.45.

2,4-Bis-(4-(2-sulfonamido)furanyl)-2,4-dihydroxypentane (6). Chromatographic isolation provided a small sample of 2,4-bis-(4-(2-sulfonamido)furanyl)-2,4-dihydroxypentane, **5**. ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.54 (s, 4), 7.51 (s, 2), 6.83 (s, 2), 5.36 (s, 2), 2.13 (q, 2), 1.35 (s, 6). ^{13}CMR (400 MHz, DMSO-d_6): δ 151.54, 141.23, 136.62, 112.91, 70.27, 53.12, 31.25. LC/MS: *m*/*e* 393 (M^{-1}, negative ion).

Purification of 4-(1-Hydroxy-1-methyl-ethyl)-furan-2-sulfonamide (4). To a 500-mL round-bottom flask was added 50.00 g (243.62 mmol) of **4** (HPLC purity: 93.81% desired alcohol, 2.99% diol impurity) and 150 mL of THF. The mixture was stirred for 20 min to ensure maximum dissolution. The hazy solution was then filtered over 7.5 g of Celite to remove residual ash, the Celite was rinsed once with 150 mL of THF, and the combined filtrate was added to a 1000 mL of round-bottom flask, followed by 1.53 g (12.17 mmol, 0.05 equiv) of 97% phenylboronic acid. The solution was distilled until a total volume of 125 mL was reached. Diisopropyl ether (IPE; 250 mL) was added and THF was displaced until there was 225 mL of total pot volume. IPE (225 mL) was added, and displacement continued until there

was 375 mL total pot volume. IPE (125 mL) was added, and displacement continued until there was 375 mL of total pot volume. The contents were cooled to 20−25 °C, and the slurry was allowed to granulate at 20−25 °C for 24 h. The solids were filtered at 20−25 °C, followed by a wash with 100 mL of IPE. There was 44.75 g (218.04 mmol, 90% yield) of eggshell-colored solid after drying. HPLC purity: 99.3% desired alcohol (**4**), 0.07% diol impurities (**5**).

Re-slurry of 4-(1-Hydroxy-1-methyl-ethyl)-furan-2-sulfonamide (4) for Removal of Boron Content. 4 (1.0 g, 4.87 mmol, 1.0 equiv, containing 49 ppm boron) and IPE (5.0 mL) were added to a round-bottom flask and stirred at ambient temperature for 36 h. The slurry was filtered. The solid cake was washed once with 3.0 mL of IPE. This obtained 959 mg (96% yield) of **4** with undetectable boron content. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (s, 3H), 6.95 (s, 1H), 5.08 (brs, 1H), 1.38 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 152.33, 140.90, 137.22, 112.83, 67.26, 31.61. Anal. calcd for $C_{22}H_{21}FN_2O_2$: C, 40.97; H, 5.40; N 6.82. Found: C, 41.20; H, 5.45; N, 6.79.

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