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METALATED AROMATIC CARBOXYLIC ACIDS: IMPROVED SYNTHESIS OF SDZ HUL412

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Abstract: Synthesis of aryl methyl ester **2** is described utilizing a metalation-condensation and a metalation-alkylation sequence starting from the dianion of p-toluic acid generated in an aprotic solvent medium.

In our efforts to find a practical and efficient method toward a commercial synthesis of the 5-aryl-substituted-imidazo[2,1-a] isoquinoline **1** (SDZ HUL412)[1], a PAF receptor antagonist[2], kilogram quantities of aryl methyl ester **2** were required. To this end, two alternative routes were investigated. The first involved the use of a metalation-condensation sequence, and the second a metalation-alkylation pathway. Both approaches required the formation of a metalated p-toluic acid (Tables I and II). In the present paper, we describe an efficient method for the generation of such a species and its role in the synthesis

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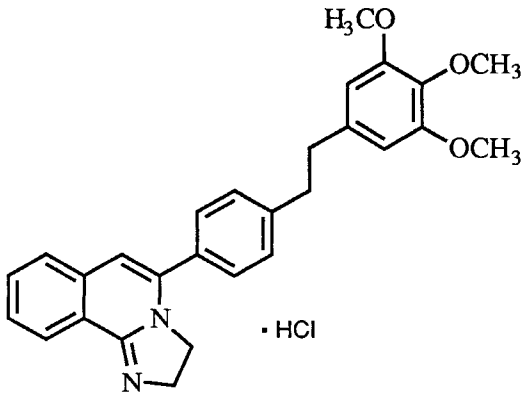
of a compound of pharmaceutical interest. Thus, we have extended the scope of aromatic carboxylic acid dianions.[3-5]



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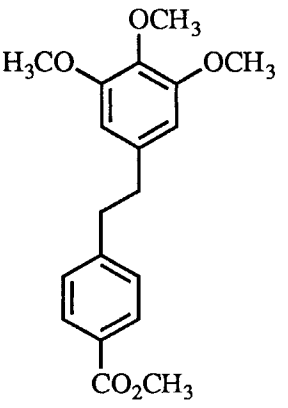
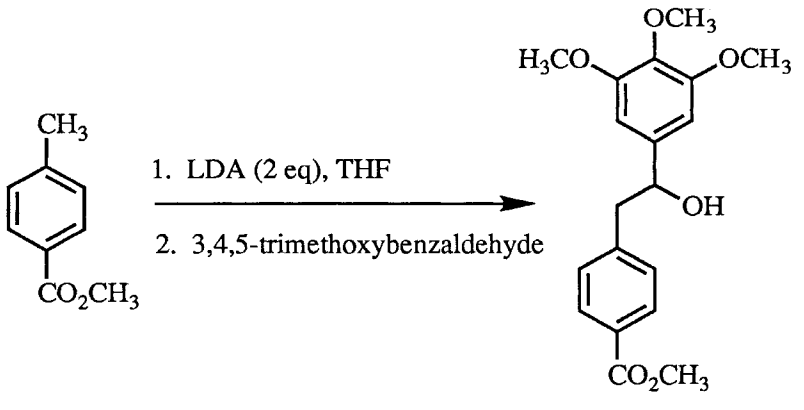


2

Originally, we explored the formation of p-toluic acid dianion using previously reported conditions[3-5] and its reaction with 3,4,5-trimethoxybenzaldehyde. On multi-gram quantities, these procedures provided alcohol **3** in low yields (16-20%) (Scheme 1).

Scheme 1:

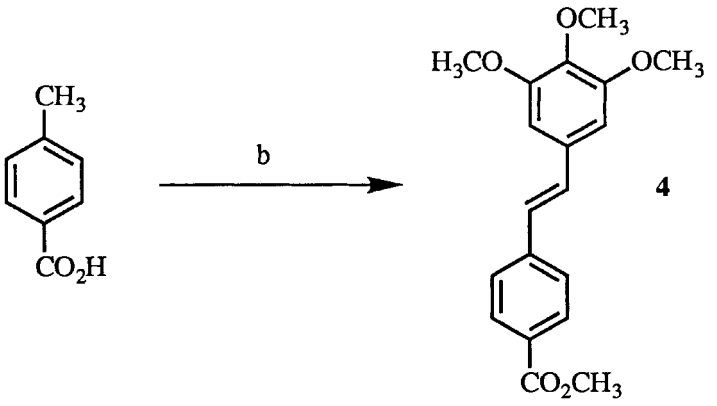


3

Based on the assumption that incomplete dianion formation, due to insolubility of the required intermediate, may be responsible for the low yield[6], we attempted to improve the reaction conditions by the addition of a polar aprotic solvent.[7] Indeed, the yield was substantially superior under these circumstances. Table I summarizes the condensation between the dianion of p-toluic acid (generated in a THF/aprotic solvent environment and LDA) with 3,4,5-trimethoxybenzaldehyde (metalation-condensation).

The yields reported were determined after recrystallization of the methyl ester **4**, prepared by esterification (conc. sulfuric acid, methanol, reflux) and dehydration (p-TsOH, toluene, reflux) of the crude condensation product **3**. Although the sequence involving hexamethylphosphoric triamide (HMPA) proved most favorable (66%, Table I, entry 1), safety concerns excluded its use in large-scale plant operations.[8] Attempts at using catalytic amounts of polymer-bound HMPA (a solid variant of the reagent) resulted in lower yields (38%, Table I, entry 4). Among alternatives studied, it was found that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was the most effective HMPA substitute (42%, Table I, entry 2). The yields proved to be independent of THF/DMPU ratio (Table I, entries 2 and 3) in the range investigated. The purified olefinic methyl ester **4** was processed to the desired ester **2** under the standard hydrogenation prescription (H_2, 10% Pd-C, EtOAc, 89% yield, see experimental section). The four-step

Table I[a]



4

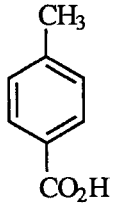
Entry	Solvent	4 (Yield)
1	THF/HMPA (5:1)	66%
2	THF/DMPU (3:1)	42%
3	THF/DMPU (2:1)	40%
4	THF/HMPA[c]	38%
5	THF/TMEDA (3.3:1)	30%
6	THF/TDA-1[d] (3:1)	30%

a. All reactions were carried out with 2.4 equiv. of LDA. b. i. LDA, solvent, 3,4,5-trimethoxybenzaldehyde. ii. sulfuric acid, methanol, reflux. iii. p-TsOH, toluene, reflux. c. HMPA bound on polystyrene crosslinked with 2% divinylbenzene. d. Soula, G. *J. Am. Chem. Soc.* 1985, **50**, 3717.

sequence (condensation-esterification-dehydration-hydrogenation) provided the desired methyl ester **2** in 37% overall yield.[9]

In order to further develop the strategy towards **2**, it seemed possible to avoid the hydrogenation of **4** to **2** by reacting the dianion

Table II



1. LDA, solvent, 3,4,5-trimethoxybenzyl chloride
2. TMS-Cl, methanol

2

Entry	Equiv. LDA	Conc.	Solvent[a]	Yield
1	2.5	0.50 M	THF/DMPU	68%
2	2.5	1.00 M	THF/DMPU	55%
3	2.5	0.26 M	THF/DMPU	45%
4	2.2	1.00 M	THF/TDA-1	42%
5	2.2	0.50 M	THF/HMPA[b]	40%

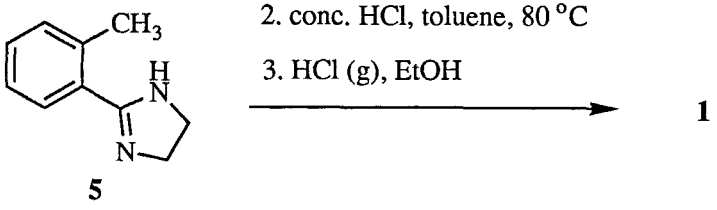
a. Entries 1-4 were carried out in a 3:1 solvent ratio. b. HMPA bound on polystyrene crosslinked with 2% divinylbenzene.

from p-toluic acid with a suitable alkylating reagent (Table II).[3-5] Using similar conditions developed in the condensation sequence, we were able to achieve moderate to good yields of product **2**. Table II summarizes the alkylation of p-toluic acid dianion with 3,4,5-trimethoxybenzyl chloride.[10] The yields reported are for the methyl ester **2**, formed by chlorotrimethylsilane-methanol esterification of the crude acid.

We found the alkylation to be concentration dependent (compare entries 1-3, Table II). The most efficient reaction conditions consisted of p-toluic acid dianion formation in a 0.50 M THF/DMPU solution, providing the ester **2** in 68% yield (entry 1, Table II). Increasing the

concentration to 1.00 M in THF/DMPU resulted in 55% product formation (entry 2, Table II). For large scale applications, the 1.00 M solvent system was utilized since the dilution factor was more environment friendly. Decreasing the concentration below 0.50 M gave a substantial decrease in yield (entry 3, Table II). The three-step sequence (chlorination-alkylation-esterification) provided ester **2** in 40% overall yield.[11] The synthesis of compound **1** was completed by the condensation of imidazoline **5** dianion with methyl ester **2**, followed by dehydration of the resulting tertiary alcohol and subsequent salt formation (Scheme 2).[1,12]

Scheme 2:



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Herein we report the formation of a metalated aromatic carboxylic acid and its utility in large scale preparation of a compound of pharmaceutical interest.

Experimental

4-[2-(3,4,5-trimethoxyphenyl)ethenyl]benzoic acid, methyl ester 4: A 5-L, 4-necked round-bottomed flask, equipped with a mechanical stirrer, addition funnel, thermometer and cooling bath was

charged with THF (600 mL), DMPU (200 mL) and diisopropylamine (113.0 mL, 808.0 mmol). The solution was cooled between -65 and -60 °C, and over a period of 40 minutes n-butyllithium (505.0 mL of a 1.6 M solution in hexanes, 808.0 mmol) was added while maintaining an internal temperature of -60 to -55 °C. The solution was stirred for 15 minutes after the addition. p-Toluic acid (50.0 g, 367.0 mmol), dissolved in THF/DMPU (100/30 mL), was added over a period of 20 minutes while maintaining an internal temperature below -55 °C. The mixture was warmed to -40 to -35 °C and allowed to stir for an additional 1.5 hours. 3,4,5-Trimethoxybenzaldehyde (70.9 g, 404.0 mmol), dissolved in THF/DMPU (100/30 mL), was added over a period of 20 minutes while maintaining an internal temperature of -40 to -35 °C. After the addition was complete, the cooling bath was removed and the reaction mixture was warmed to 0-5 °C. Stirring was allowed for 1.0 hour. Water (500 mL) was added and the solution was stirred for an additional 15 minutes. Ethyl acetate (1.0 L) was added and stirring was continued for 15 minutes. The layers were separated and the aqueous layer was extracted further with ethyl acetate (2 x 500 mL). The aqueous layer was acidified with 6 M aq. HCl (pH 3) and extracted with ethyl acetate (3x 500 mL). The combined organic extracts were washed with water (3 x 500 mL) and concentrated under reduced pressure (25-30 mm Hg, 40-45 °C bath temp.). The residue was diluted with methanol (300 mL) and conc. sulfuric acid (10.0 mL). The mixture was refluxed for 15 hours. After cooling to 22-23 °C, the solvent was removed under

reduced pressure (25-30 mm Hg, 40-45 °C bath temp.), the crude residue was diluted with toluene (300 mL) and p-TsOH (catalytic amount) was added. The mixture was refluxed for 1.0 hour and then cooled to 22-23 °C and washed with saturated aqueous sodium bicarbonate solution (150 mL). The organic layer was concentrated under reduced pressure (25-30 mm Hg, 40-45 °C bath temp.) to give a crude paste, which was dissolved in isopropanol (500 mL) and cooled to 0-5 °C under rapid stirring. After 5.0 hours the solids were collected by suction filtration, washed with cold isopropanol (200 mL) and dried (25-30 mm Hg, 22-23 °C for 24 hours) to give 50.1 g (42%) of **4**. ^{13}C NMR (75 mHz) δ ($CDCl_3$): 166.8, 153.4, 141.7, 132.4, 131.2, 129.9, 128.8, 126.9, 126.2, 104.0, 103.9, 56.1, 51.9. ^{1}H NMR (300 mHz) δ ($CDCl_3$): 7.99 (d, 2H, J=8.3 Hz), 7.52 (d, 2H, J=8.3 Hz), 7.13-6.96 (q, 2H, J=16.3, 35.7 Hz), 6.74 (s, 2H), 3.89 (two overlapping singlets, 9H), 3.87 (s, 3H). IR (KBr, cm^{-1}): 2941, 2839, 1715, 1606, 1578, 1421, 1345, 848, 813. MS (NH_3/DCI): m/z=329 (M+1). $C_{19}H_{20}O_5$ Calc. C: 69.50; H: 6.14. Found: C: 69.82; H: 6.17.

Conversion of 4 to 2 (hydrogenation):[13]

A 2.0-L Paar hydrogenation flask, flushed with nitrogen, was charged with 10% palladium on carbon (6.5 g), ethyl acetate (325 mL) and **4** (63.0 g, 0.19 mol). The flask was flushed with hydrogen gas, then filled to 1 atmosphere (about 15 psi) with hydrogen gas. Agitation was allowed for 1.0 hour (or until the hydrogen absorption was complete).

The flask was evacuated several times with nitrogen. The reaction mixture was filtered through Celite (10.0 g), and the filter cake was washed three times with ethyl acetate (a total of 90 mL). The filtrate was concentrated under reduced pressure (20-30 mm Hg, 40-45 °C bath temp) to give a stirrable residue. 2-Propanol (50 mL) was added and the mixture was concentrated under reduced pressure (20-30 mm Hg, 40-45 °C bath temp) to give a mobile oil, which was diluted with 2-propanol (250 mL). The mixture was warmed to 75-80 °C in order to dissolve the oil completely. The solution was allowed to cool to 0-5 °C slowly as crystallization occurred. The suspension was stirred for 30 minutes at 0-5 °C. The solids formed were collected by suction filtration and washed with two 25-mL portions of cold (0-5 °C) 2-propanol. The solids were dried in a vacuum oven (40 °C) to a constant weight to obtain 55.6 g of **2** (88.0% yield).

3,4,5-Trimethoxybenzyl chloride:[10]

A 12-L, 4-necked round-bottomed flask, equipped with a mechanical stirrer, thermometer, addition funnel and cooling bath was charged with 3,4,5-trimethoxybenzyl alcohol (500 g, 2.53 mol) and toluene (1.5 L). The solution was cooled to 0-5 °C, and concentrated hydrochloric acid (831 mL) was added rapidly (exothermic). The reaction was stirred for 75 minutes at 10-15 °C. Water (1.0 L) was added, and stirring was continued for 10 minutes. The layers were separated, and the organic phase was washed with saturated aqueous sodium bicarbonate (500 mL).

The organic layer was concentrated under reduced pressure (25-30 mm Hg, 35-40 °C bath temp.) to give a mobile oil. This was taken up in absolute ethanol (250 mL) and cooled to 0-5 °C. Hexane (1.0 L) was added over 30 minutes. After the addition, stirring was continued for 1.0 hour as crystallization occurred. The solids formed were collected by suction filtration and washed with hexane (250 mL). The solids were dried in vacuo (25-30 mm Hg, 30-35 °C) to a constant weight to give 401.0 g (73%) of 3,4,5-trimethoxybenzyl chloride. Spectral analysis has been reported.[10] CAUTION: Irritant! Handle according to safety procedures outlined in Material Safety Data Sheet.

4-[2-(3,4,5-trimethoxyphenyl)ethyl]-benzoic acid, methyl ester 2: A 5-L, 4-necked round-bottomed flask, equipped with a mechanical stirrer, addition funnel, thermometer and cooling bath was charged with THF (685 mL), DMPU (228 mL) and diisopropylamine (93 mL, 0.918 mol). The solution was cooled between -65 to -60 °C, and, over a period of 40 minutes, n-butyllithium (574 mL of a 1.6 M solution in hexanes, 0.918 mol) was added while maintaining an internal temperature of -60 to -55 °C. The solution was stirred for 15 minutes, and p-toluic acid (50.0 g, 0.376 mol), dissolved in THF (250 mL), was added over a period of 40 minutes while maintaining an internal temperature below -55 °C. The mixture was warmed between -40 to -35 °C and allowed to stir for an additional 4.5 hours. 3,4,5-Trimethoxybenzyl chloride (87.5 g, 0.381 mol), dissolved in THF (250

mL), was added over 40 minutes while maintaining an internal temperature of -40 to -35 °C. After the addition was complete, the cooling bath was removed, and the reaction mixture was warmed to 20-22 °C. Stirring was allowed for 16 hours. Water (500 mL) was added, and the solution was stirred for 15 minutes. The layers were separated, and the aqueous phase was washed with two 500-mL portions of ethyl acetate. The aqueous phase was acidified with 2 N aqueous hydrochloric acid (approx. 500 mL) and extracted with two 500-mL portions of ethyl acetate. The ethyl acetate extractions were combined and concentrated under reduced pressure (25-30 mm Hg, 40-45 °C bath temp.) until approximately 700 mL of solvent was collected. The pot residue was diluted with methanol (400 mL), and the distillation was continued until 300 mL of solvent was collected. The residue was diluted with additional methanol (300 mL) and chlorotrimethylsilane (93 mL). The mixture was refluxed for 3.0 hours (internal temperature of 55-65 °C) and then cooled to an internal temperature of 20-22 °C. Following dilution with ethyl acetate (500 mL), a solution consisting of saturated aqueous sodium bicarbonate (200 mL) diluted with saturated aqueous sodium chloride (400 mL) was added and stirred for 15 minutes. The layers were separated, and the organic layer was washed with an additional saturated aqueous sodium bicarbonate (200 mL). The organic layer was concentrated under reduced pressure (25-30 mm Hg, 40-45 °C bath temp.) to give a mobile oil. The residue was diluted with 2-propanol (250 mL), cooled to 0-5 °C and stirred for 16 hours. The

solids formed were collected by suction filtration at 0-5 °C and washed with cold 2-propanol. The wet solids were dried in vacuo (25-30 mm Hg, 25-30 °C) for 24 hours (or until a constant weight) to give 66.7 g of **2** (55% yield). ^{13}C NMR (75 MHz) $\delta(CDCl_3)$: 166.9, 153.0, 146.9, 136.7, 129.6, 128.4, 127.9, 105.5, 60.7, 56.0, 51.8, 37.8, 37.6 ppm. ^{1}H NMR (300 MHz) $\delta(CDCl_3)$: 7.95 (d, 2H, J= 8.3 Hz), 7.24 (d, 2H, J= 8.3 Hz), 6.35 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.80 (s, 6H), 3.0-2.8 (m, 4H). IR (KBr, cm^{-1}): 2912, 2904, 2838, 2824, 1719, 1606, 1595, 1590, 1508, 1458, 1423, 1339, 1310, 1247, 1164, 1123, 1101, 1008, 848, 766. MS (NH_3/DCI): m/z = 331 (M+1). $C_{19}H_{22}O_5$ calc. C: 69.07; H: 6.71. Found: C: 69.14; H: 6.77.

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8. HMPA is a known carcinogen (see reference 7 and citations therein).
9. The overall yield determined from Table I, entry 1 is 59%.
10. Early studies were carried out with commercially available 3,4,5-trimethoxybenzyl chloride (Fluka). Because of the high cost of this reagent, an in-house syhthesis was developed (see experimental section). For reported preparations of this reagent see: Otsuka Pharmaceuticals Co. LTD., Japan Patent #58032839, 1983. b) Garzio, A.; Vitladino, G.; Bottazzi, A.; Pelagalli, D.; Coccoli, C. US Patent #4273931, 1981. c) French Patent # 2228064. d) Abdel-R.M.; Aboul-Enein, M.N.; Taha, R.M. *J. Chem. U.A.R. 1968, 11(3), 401.* The reactions presented in Table II were conducted with 3,4,5-trimethoxybenzyl chloride prepared in-house.

11. The overall yield of methyl ester **2** determined from Table II, entry 2 is 50%.
12. Further development of this reaction sequence for large scale applications is currently under investigation and the results will be reported at a later date.
13. The authors wish to thank Mr. Jerome Linder for his contribution in the hydrogenation reaction (**4** to **2**).

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