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Research Article

Base-catalyzed deuterium and tritium labeling of aryl methyl sulfones

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Summary

A method is presented for conveniently tritiating the aryl methyl sulfones of compounds identified as potent and selective inhibitors of human Cox-2 and as DP receptor antagonists. A base-catalyzed exchange reaction was conducted with deuterated water and the total deuterium incorporation, ranging from 46 to 99%, was calculated using mass spectrometry. Results from these exchanges were used as guidelines for tritium labeling giving specific radioactivities in the range of 28–120 mCi/mmol (1.03–4.43 GBq/mmol). Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: tritium; labeled compounds; methyl sulfone exchange; cyclooxygenase-2; DP receptor antagonists

Introduction

In the course of our work with compounds possessing anti-inflammatory properties, a number of classes of selective cyclooxygenase-2 inhibitors emerged.[1,2] Many of these derivatives were of sufficient potency to warrant further study and so requiring the determination of covalent protein binding and metabolic studies best carried out by incubations with radiolabeled substrates.[3] Labeling with carbon-14 could only be achieved by a total synthesis of each substrate. Furthermore, in our prostaglandin D_2 (DP) receptor antagonist program, many interesting compounds needed a short and efficient way to label them.[4] A common factor for all of these compounds was a methyl aryl sulfone moiety appearing to be essential for both the activity and selectivity.[5] In this aspect, tritium labeling of the methyl sulfones by exchange carried out on the final compounds or their immediate precursors seemed an easy alternative to many total syntheses.

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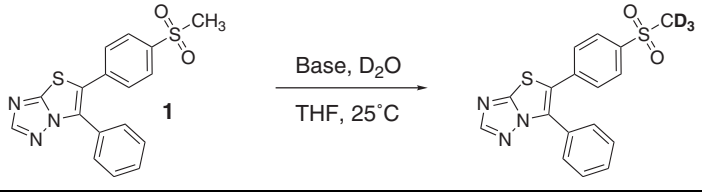
Results and discussion

Base-catalyzed deuterium exchange of acyclic and methyl aryl sulfones take place most rapidly at the α-methyl position.[6] Comparative deuterium exchange using Et_3N, KOH and DBU as bases was carried out on compound **1**. The results summarized in Table 1 show that the most effective base giving rise to the highest d_3 content as determined by mass spectrometry was found to be 1,8-diazabicyclo [5,4,0] undecen-7-ene (DBU). It can also be noted from Table 1 that deuterium exchange did occur using triethylamine as base and although only 37% d_3 content was observed over 7 days, the total isotope incorporation was 72.6%. Depending upon the isotope requirements, the sensitivity of the substrate to a stronger base and the recovery, triethylamine as a base-catalyst is viable to deuterate or tritiate α-methyl sulfones.

Preliminary exchanges using deuterium oxide and DBU as base were carried out on the desired substrates and these results were then used as guidelines for the tritium exchanges. The results for a selection of substrates are listed in Tables 2 and 3. All compounds **2**–**11** were labeled according to the typical procedure described in the Experimental Section. Because of the enolizable methylene on the cyclopentenone and its sensitivity to base, compound **7** was obtained via the exchange of its immediate alcohol precursor followed by an oxidation using pyridinium dichromate (PDC). For the indole compounds **8**–**11**, all the exchange reactions were performed on their free acids in order to avoid any deuterium or tritium incorporation α to the acid. The total

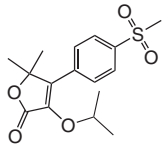
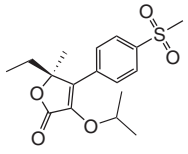
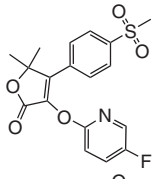
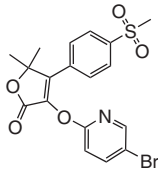
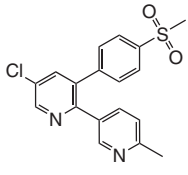
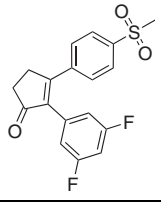
Table 1. Comparative study of the effect of base on the deuterium incorporation of compound 1



Entry	Base[a]	Time	Deuteration	Total incorporation (%)
1	50 µl Et_3N	7 days	17% d1 45% d2 37% d3	72.6
2	1 µl 15% KOH	7 days	0% d1 17% d2 82% d3	93.3
3	5 µl DBU	18 h	0% d1 0% d2 99.9% d3	99.9

[a] Base was added to a mixture of **1** and D_2O in THF.

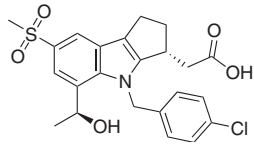
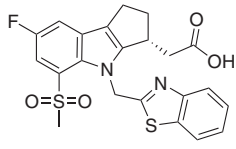
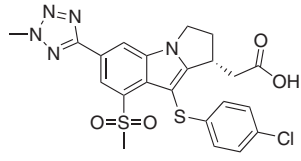
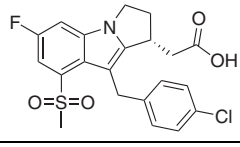
Table 2. Deuterium and tritium exchanges on inhibitors of human Cox-2

Compound	Substrate	Deuteration	Tritiation
2		0.2% d0 2.6% d1 0% d2 97.2% d3	SA = 68 mCi/mmol 3.9 mCi
3		3.2% d0 0.6% d1 1.4% d2 94.8% d3	SA = 85 mCi/mmol 4.0 mCi
4		2.3% d0 0.6% d1 13.9% d2 83.2% d3	SA = 75 mCi/mmol 3.4 mCi
5		0% d0 0% d1 2.8% d2 97.2% d3	SA = 62 mCi/mmol 2.8 mCi
6		3.9% d0 3.0% d1 6.1% d2 87.0% d3	SA = 75 mCi/mmol 5.0 mCi
7[a]		2.6% d0 3.1% d1 15.0% d2 79.3% d3	SA = 95 mCi/mmol 6.2 mCi

[a] Labeled as the cyclopenten-1-ol.

deuterium incorporation ranged from 90.3 to 99.1% for compounds **2**–**7**[7] and from 46.1 to 98.7% for compounds **8**–**11**. The differences observed for the d_0, d_1, d_2 and d_3 values in Tables 2 and 3 reflect the relative exchange rates and all the compounds could have equilibrated to a higher d_3 content with an appropriate monitoring of the reaction time. However, the amount of labeling obtained from our typical exchange procedure was much more than sufficient to meet all of the covalent binding and metabolic studies requirements.

Table 3. Deuterium and tritium exchanges on DP receptor antagonist compounds

Compound	Substrate	Deuteration	Tritiation
8		16.9% d0 39.2% d1 32.5% d2 11.4% d3	SA = 28 mCi/mmol 1.0 mCi
9		0.0% d0 2.6% d1 0.0% d2 97.4% d3	SA = 120 mCi/mmol 0.7 mCi
10		5.9% d0 26.1% d1 50.2% d2 17.8% d3	SA = 58 mCi/mmol 3.1 mCi
11		6.5% d0 9.8% d1 25.1% d2 58.6% d3	SA = 75 mCi/mmol 1.7 mCi

Tritiation was realized using tritiated water and DBU to afford radiolabeled compounds **2**–**11** having specific radioactivities in the range of 28–120 mCi/mmol. We have shown experimentally in house by radiometric HPLC that if tritium is lost, a radioactive peak corresponding to tritiated water would be detected in the solvent front of the HPLC chromatogram.[8] Using this analytical procedure, we had no evidence with selected tritiated methyl sulfones that a water peak was formed in standard microsomal incubations.[9] This indicated that no back exchange of tritium and no metabolism at the site of tritiation was taking place.

Experimental

General

All reagents and solvents were commercially available and were used directly without any purification. Reactions were performed in a well-ventilated fumehood and evaporations carried out on a Buchi evaporator *in vacuo*. TLCs were performed on Merck kGaA F_{254} precoated silica plates. Analytical HPLCs were performed on a Waters instrument equipped with a Zorbax C_{18} column (4.6×150 mm) and peak detection was done simultaneously by UV

(254 nm, Waters 996 Photodiode Array detector) and a liquid scintillation flow monitor (Packard Radiomatic 150 TR Flow Scintillation Analyzer). Radioactivity measurements were performed on a Beckmann Coulter LS6000SC liquid scintillation counter using Ultima Gold XR (Packard Bioscience #6013119). Deuterium incorporation was calculated based on the intensities of protonated molecules and their isotopic peaks using a linear matrix program on a Micromass Quattro LC (electrospray mode) coupled with a Waters 2790 HPLC. A Bruker 500 MHz NMR instrument was also used to calculate the deuterium incorporation as well as to determine the site of incorporation. The tritium exchange reactions were carried out in closed 4 ml vials. The mixtures were also extracted in these same vials with the top organic layers being pipetted off leaving behind the tritiated water and minimizing exposure risks.

Typical procedure for deuterium or tritium exchanges. To a solution of the substrate (20 mg) in THF (500 µl) containing DBU (5 µl) was added deuterium oxide (200 µl, 99.9 at% D) or tritiated water (200 µl, 80 mCi/mmol). The mixture was stirred in a closed vial at room temperature for 18 h. To the mixture was added ethyl acetate (2 ml) and 1 N HCl (1 ml) containing saturated brine (3 drops) (the substrates containing pyridines were not washed with 1 N HCl. Three dilute brine washes were effective in removing all the DBU). The mixture was stirred for 30 s and most of the top layer removed and transferred to a new vial. The bottom layer was re-extracted with ethyl acetate (1 ml) twice and the combined extracts twice washed with dilute brine (1 ml) (these two extra water washings effectively removed most of the residual tritiated water). The combined organics were dried (Na_2SO_4) and the solutions pipetted off from the salts. The clear solutions were concentrated and pumped on to obtain exact weights (the tritium-labeled products were mostly of sufficient purity by TLC and HPLC to proceed with protein binding assays and metabolic studies. If not, a short chromatography on silica gel using a mixture of ethyl acetate and hexane would easily remove any baseline material and front running peroxide inhibitor originally contained in the THF solvent. The exchanges also work well in acetonitrile). Typical yields of the labeled products were between 15 and 19 mg each. The total deuterium incorporation was calculated using the isotopic profiles from MS (for example, compound **3**: $1/3 \times 0.6\% + 2/3 \times 1.4\% + 3/3 \times 94.8\% = 95.9\%$ total incorporation). The tritiated products were dissolved in acetonitrile (5 ml) and these stock solutions were counted by liquid scintillation and their specific activities calculated before storing at $-78^{\circ}C$. Results are listed in Tables 2 and 3.

3-Isopropoxy-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5 H)-one (**2**)

Total deuterium incorporation calculated by MS: 98.6%. ^1H NMR (500 MHz, Acetone-d_6): δ 8.10–8.02 (m, 4 H), 5.21–5.15 (m, 1 H), 3.20 (s, 3 H), 1.69

(s, 6 H), 1.29 (s, 3 H), 1.27 (s, 3 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 167.00, 142.74, 142.17, 141.21, 136.36, 129.95, 128.35, 83.92, 74.25, 44.12, 26.76, 22.80. Mass spectrum for $C_{16}H_{20}O_5S$: (M-H) 323.2.

(5S)-5-Ethyl-3-isopropoxy-5-methyl-4-[4-(methylsulfonyl)phenyl]furan-2(5 H)-one (**3**)

Total deuterium incorporation calculated by MS: 95.9%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.10–8.02 (m, 4 H), 5.28–5.22 (m, 1 H), 3.20 (s, 3 H), 2.05 (q, J = 7.4 Hz, 2 H), 1.69 (s, 3 H), 1.29 (d, J = 6.0 Hz, 6 H), 0.81 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 167.30, 142.21, 140.72, 138.28, 129.71, 128.42, 86.42, 74.29, 44.11, 31.84, 25.87, 22.80, 22.78, 7.86. Mass spectrum for $C_{17}H_{22}O_5S$: (M-H) 337.1.

3-[(5-Fluoropyridin-2-yl)oxy]-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5 H)-one (**4**)

Total deuterium incorporation calculated by MS: 92.7%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.06 (d, J = 2.9 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 2 H), 7.91 (d, J = 8.3 Hz, 2 H), 7.75–7.71 (m, 1 H), 7.17–7.15 (m, 1 H), 3.15 (s, 3 H), 1.76 (s, 6 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 165.84, 158.89, 158.39, 156.91, 149.81, 143.16, 138.31, 135.15, 134.98, 134.77, 129.88, 128.70, 128.67, 128.53, 113.08, 84.98, 44.06, 26.37. Mass spectrum for $C_{18}H_{16}FNO_5S$: (M + H) 378.1.

3-[(5-Bromopyridin-2-yl)oxy]-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5 H)-one (**5**)

Total deuterium incorporation calculated by MS: 99.1%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.43 (d, J = 2.4 Hz, 1 H), 8.22–8.18 (m, 3 H), 8.08 (d, J = 8.5 Hz, 2 H), 7.28 (d, J = 8.7 Hz, 1 H), 3.32 (s, 3 H), 2.21–2.21 (m, 1 H), 1.93 (s, 6 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 165.71, 161.32, 150.17, 148.80, 143.61, 143.19, 137.93, 134.99, 129.87, 128.68, 115.41, 113.80, 85.09, 44.04, 26.32. Mass spectrum for $C_{18}H_{16}BrNO_5S$: (M + H) 440.0.

5-Chloro-6′-methyl-3-[4-(methylsulfonyl)phenyl]-2,3′-bipyridine (**6**)

Total deuterium incorporation calculated by MS: 92.1%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.54 (d, J = 2.3 Hz, 1 H), 8.20 (d, J = 2.0 Hz, 1 H), 7.76 (m, 3 H), 7.40–7.36 (m, 3 H), 6.94 (d, J = 8.0 Hz, 1 H), 2.96 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 158.97, 153.65, 150.71, 148.70, 144.42, 141.79, 138.79, 138.05, 136.68, 132.45, 131.43, 131.33, 128.40, 122.95, 44.17, 24.21. Mass spectrum for $C_{18}H_{15}ClN_2O_2S$: (M + 2 H) 360.2.

2-(3,5-Difluorophenyl)-3-[4-(methylsulfonyl)phenyl]cyclopent-2-en-1-one (**7**)

Total deuterium incorporation calculated by MS: 90.3%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.95 (d, J = 8.3 Hz, 2 H), 7.66 (d, J = 8.3 Hz, 2 H), 7.01–6.95 (m, 1 H), 6.84–6.78 (m, 2 H), 3.18–3.16 (m, 2 H), 3.14 (s, 3 H), 2.70–2.68 (m, 2 H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 168.77, 164.73, 164.62, 162.77, 162.66, 143.03, 141.64, 139.79, 136.64, 129.68, 128.40, 113.29, 103.96, 44.03, 35.29, 30.63. Mass spectrum for $C_{18}H_{14}F_2O_3S$: (M) 348.2.

[(3R)-4-(4-Chlorobenzyl)-5-[(1S)-1-hydroxyethyl]-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid (**8**)

Total deuterium incorporation calculated by MS: 46.1%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.95 (d, J = 2.0 Hz, 1 H), 7.79 (d, J = 2.0 Hz, 1 H), 7.32 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.0 Hz, 2 H), 5.92 (d, J = 15.2 Hz, 1 H), 5.65 (d, J = 15.2 Hz, 1 H), 5.19 (q, J = 6.5 Hz, 1 H), 3.62–3.58 (m, 1 H), 3.07 (s, 3 H), 3.01–2.98 (m, 1 H), 2.85–2.81 (m, 1 H), 2.65 (d, J = 8.7 Hz, 1 H), 2.40–2.38 (m, 1 H), 1.45 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (125 MHz, Acetone-d_6): δ 173.3, 152.0, 141.1, 139.4, 133.3, 132.6, 129.7, 127.8, 126.4, 121.7, 118.8, 117.3, 64.6, 50.3, 45.0, 39.1, 36.5, 36.2, 24.6, 23.5. Mass spectrum for $C_{23}H_{24}ClNO_5S$: (M + H) 462.8.

[(3R)-4-(1,3-Benzothiazol-2-ylmethyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid (**9**)

Total deuterium incorporation calculated by MS: 98.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.17 (s, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 7.92 (d, J = 8.1 Hz, 1 H), 7.69 (dd, J = 2.4, 8.4 Hz, 1 H), 7.56 (dd, J = 2.4, 9.5 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 6.57 (d, J = 19.2 Hz, 1 H), 6.12 (d, J = 19.2 Hz, 1 H), 3.58–3.51 (m, 1 H), 3.33 (s, 3 H), 2.95–2.89 (m, 1 H), 2.79–2.69 (m, 3 H), 2.38 (dd, J = 10.2, 16.1 Hz, 1 H), 2.27–2.21 (m, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 172.89, 169.53, 156.38, 154.49, 153.02, 152.58, 134.50, 132.59, 129.30, 126.56, 126.22, 125.18, 122.55, 122.31, 121.66, 110.75, 110.41, 49.67, 44.00, 38.11, 35.52, 22.51. Mass spectrum for $C_{22}H_{19}FN_2O_4S_2$: (M + H) 459.3.

[(1R)-9-[(4-Chlorophenyl)thio]-8-(methylsulfonyl)-6-(2-methyl-2H-tetrazol-5-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl]acetic acid (**10**)

Total deuterium incorporation calculated by MS: 65.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.30 (bs, 1H), 8.52 (dd, J = 1.4, 11.2 Hz, 2H), 7.27–7.25 (m, 2H), 7.00 (d, J = 8.7 Hz, 2H), 4.54–4.50 (m, 1H), 4.48 (s, 3H), 4.41–4.35 (m, 1H), 3.64–3.58 (m, 1H), 3.39 (s, 3H), 2.97 (dd, J = 16.8, 3.3 Hz, 1H), 2.92–2.86 (m, 1H), 2.57 (dd, J = 10.0, 16.8 Hz, 1H), 2.40–2.33 (m, 1H). ^{13}C NMR (125 MHz, Acetone-d_6): δ 172.4, 163.7, 158.4, 139.0, 134.4, 132.3, 129.7, 129.2, 128.7,

126.5, 120.5, 119.0, 114.4, 90.0, 44.9, 44.2, 36.0, 34.9, 32.8, 30.7. Mass spectrum for $C_{22}H_{20}ClN_5O_4S_2$: (M + H) 517.0.

[(1R)-9-(4-Chlorobenzyl)-6-fluoro-8-(methylsulfonyl)-2,3-dihydro-1H-pyrrolo [1,2-a]indol-1-yl]acetic acid (**11**)

Total deuterium incorporation calculated by MS: 78.6%. ^{1}H NMR (500 MHz, Acetone-d_6): δ 12.0 (bs, 1H), 7.54–7.50 (m, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 4.63 (d, J = 17.4 Hz, 1H), 4.49 (d, J = 17.2 Hz, 1H), 4.36–4.30 (m, 1H), 4.26–4.22 (m, 1H), 3.63–3.57 (m, 1H), 2.95–2.87 (m, 1H), 2.74 (s, 3H), 2.71 (d, J = 3.7 Hz, 1H), 2.60–2.52 (m, 1H), 2.48–2.42 (m, 1H). ^{13}C NMR (126 MHz, Acetone-d_6): δ 172.80, 158.22, 156.40, 150.72, 142.31, 135.44, 133.84, 131.85, 130.91, 129.05, 128.96, 124.81, 110.64, 104.46, 102.95, 44.19, 37.57, 34.84, 30.97. Mass spectrum for $C_{21}H_{19}ClFNO_4S$: (M + H) 436.3.

Conclusion

In summary, we have developed an efficient synthesis of labeling aryl methyl sulfones by using deuterated or tritiated water and DBU in a base-catalyzed exchange reaction. Mass spectrometry was used successfully to calculate the deuterium incorporation which ranged from 46 to 99%. Many potent Cox-2 and DP compounds were labeled with tritium in order to evaluate their metabolic behavior as well as to determine their covalent protein binding affinity. All tritiated compounds **2**–**11** were easily obtained in good-to-excellent chemical yields with specific activities ranging from 28 to 120 mCi/mmol.

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