SYNTHESIS OF TRITIUM AND CARBON-14 LABELED 4,5-BIS(4-METHOXYPHENYL)-2-(TRIFLUOROMETHYL)THIAZOLE

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SUMMARY

Tritium labeled 4,5-*bis*(4-methoxyphenyl)-2-(trifluoromethyl)thiazole (*1*) was synthesized with the tritium label located on the phenyl ring at the C-4 position of the thiazole ring and meta to the methoxy group. Anisole specifically labeled with tritium at C-3 was used to prepare tritium labeled *1* with specific activity of 53 μCi/mg in 53% overall radiochemical yield. The title compound *1* was also labeled with carbon-14 at the C-4 position of the thiazole ring. [^{14}C]Barium carbonate was used as the isotope source, and carbon-14 labeled compound *1* of 31.4 μCi/mg was obtained in 54% overall radiochemical yield. Deuterium and carbon-13 labeled starting materials and intermediates were used as models for preparing the tritium and carbon-14 labeled compounds, respectively.

Key Words: Synthesis, labeled 4,5-*bis*(4-methoxyphenyl)-2-(trifluoromethyl)thiazole, deuterium, tritium, carbon-13, carbon-14

INTRODUCTION

A number of non-steroidal antiinflammatory drugs, *e.g.*, aspirin (1), dipyridamole (2), flurbiprofen (3), and ibuprofen (4), are known to inhibit platelet aggregation. However the antiplatelet aggregation activity of these agents is low, and clinical demonstration of their antithrombotic utility has not been uniformly successful. A high-volume mouse pulmonary thromboembolism screen (5) was developed to identify compounds which inhibit collagen-induced platelet aggregation. One compound so identified was 4,5-*bis*(4-methoxyphenyl)-2-thiazoleacetic acid methyl ester (*2*). Its potency and unique structural features prompted an analog program which led to the synthesis of the trifluoromethylthiazole *1* (6), which possessed high potency against collagen-induced platelet aggregation, yet lacked effect on blood coagulation, and showed low toxicity and antiinflammatory activity. Compound *1* is currently under development as a potential antithrombotic agent with clinical utility. To provide tools

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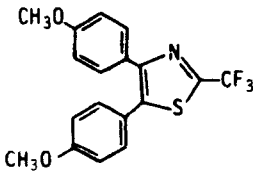
for studying its absorption, metabolic transformations, and excretion in test animals and man, we embarked on the synthesis of tritium and carbon-14 labeled *1*.



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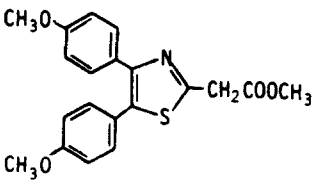

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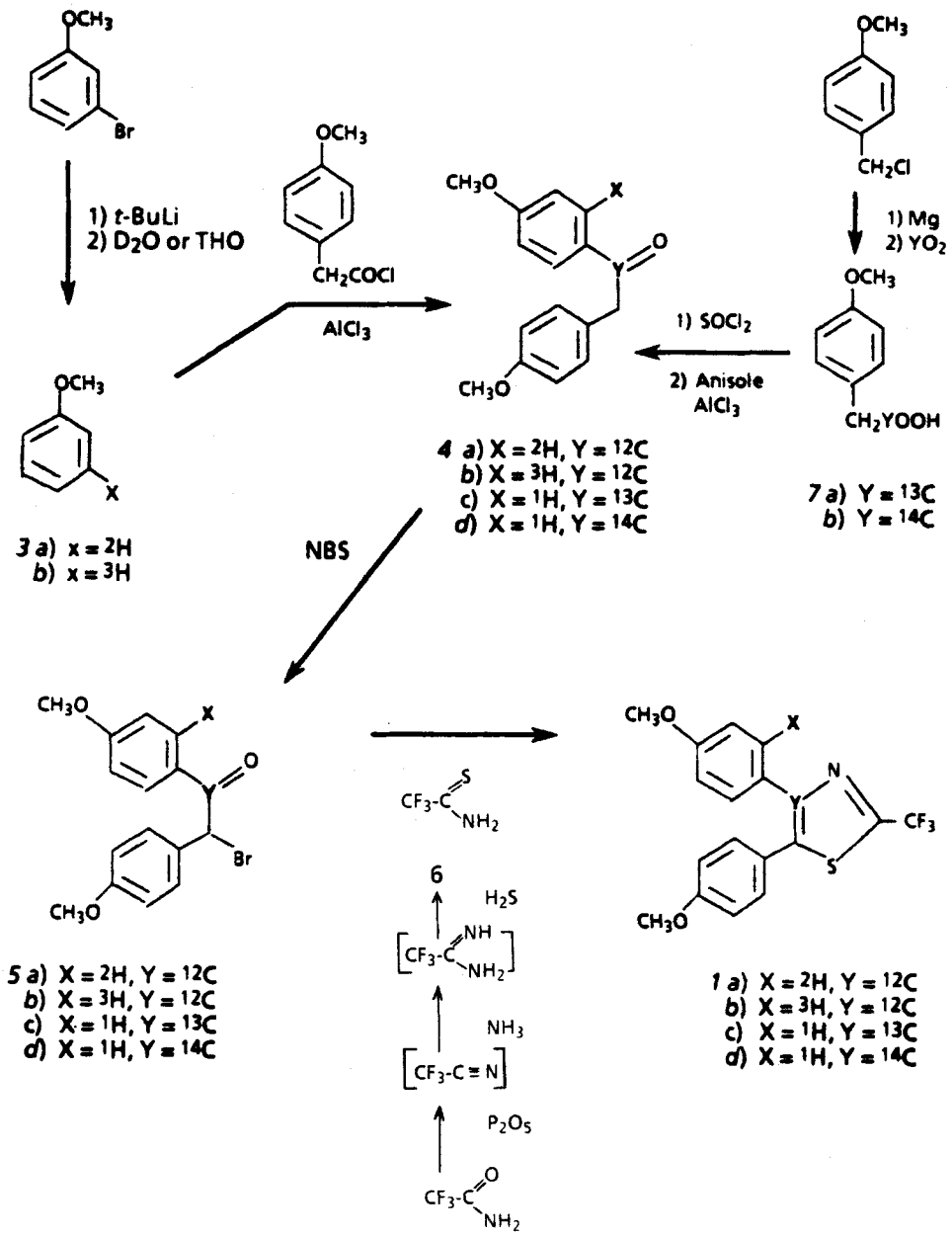
DISCUSSION AND RESULTS

The synthesis of tritium labeled 4,5-*bis*(4-methoxyphenyl)-2-(trifluoromethyl)-thiazole (*1b*) is outlined in Scheme 1. Lithiation of 3-bromoanisole followed by quenching with tritiated water introduced tritium into a non-exchangeable position (meta to the methoxy group) in the phenyl ring. The meta position of the tritium label in [3-^{3}H]anisole (*3b*) in relation to the methoxy group was supported by the nuclear magnetic resonance (NMR) spectrum of the deuterated analog *3a* prepared in the same manner from 3-bromoanisole and deuterium oxide. Friedel-Crafts acylation of *3a* and *3b* with 4-methoxyphenylacetyl chloride afforded deuterium and tritium labeled 1,2-*bis*(4-methoxyphenyl)ethanone, *4a* and *4b* respectively. The assignment of the position of the deuterium label in *4a* (and by analogy the tritium label in *4b*), in the phenyl ring adjacent to the carbonyl carbon and at the position ortho to the carbonyl group, was based on the proton and carbon-13 NMR spectra of *4a*. Bromination of 1,2-bis(4-methoxyphenyl)ethanone was previously carried out with bromine (6,7). We found that N-bromosuccinimide (NBS) was a superior bromination agent for this transformation, and afforded significantly higher yields of deuterium and tritium labeled bromoketones *5a* and *5b* from *4a* and *4b* .

Previously described procedures (6) for the reaction between 1,2-*bis*-arylethanones and trifluorothioacetamide (*6*) afforded 4,5-*bis*-arylthiazoles in approximately 30%

Scheme 1. Synthesis of Tritium and Carbon-14 Labeled 4,5-*Bis*(4-methoxyphenyl)-2-(trifluoromethyl)thiazole



yields only. These procedures involved subjecting trifluorothioacetamide, whether added to the reaction mixture or generated *in situ*, to prolonged heating, which appeared incompatible with its tendency to dimerize and polymerize at elevated temperatures. We prepared *6* from trifluoroacetonitrile* according to known procedures (9). It proved to be stable and could be stored without ill effects at 0°C for several weeks. The condensation of *6* with labeled bromoketones *5a* and *5b* proceeded readily at room temperature, and deuterium and tritium labeled 4,5-*bis*(4-methoxyphenyl)-2-(trifluoromethyl)thiazoles *1a* and *1b* were obtained in yields of up to 69% when 1.5 equivalents of *6* were used. With a two-fold excess of 6, yields of thiazole of up to 78% were realized. The assignment of the label positions in the thiazoles as shown in Scheme 1 is based on the known mode of addition of thioamides to α-haloketones (10), *i.e.*, attack by sulfur occurs at the α-carbon bearing the halogen, with attachment of nitrogen to the carbonyl carbon. This situates the deuterium or tritium label in the phenyl ring at the C-4 position of the thiazole ring. This assignment was further supported by subesquent experiments, described below and in the Experimental Section, involving carbon-13 labeled intermediates and thiazole *1c*.

The synthesis of carbon-14 labeled 4,5-*bis*(4-methoxyphenyl)-2-(trifluoromethyl)-thiazole (*1d*) began with the Grignard reaction of 4-methoxybenzyl magnesium chloride with [^{14}C]carbon dioxide according to known procedures (11,12). The resulting 4-methoxyphenyl[1-^{14}C]acetic acid (*7b*), obtained in 85% radiochemical yield, was converted to the corresponding acid chloride which was used to acylate anisole to afford 1,2-*bis*(4-methoxyphenyl)-[1-^{14}C]ethan-1-one (*4d*) in 81% yield. Bromination with NBS produced the bromoketone *5d*, which on treatment with trifluorothioacetamide (6) gave carbon-14 labeled thiazole *1d*. The assignment of label position in *1d* at C-4 was confirmed by carrying out a parallel synthesis of carbon-13 labeled thiazole *1c*, starting with carboxylation of 4-methoxybenzyl magnesium chloride with [^{13}C]carbon dioxide. The 1,2-*bis*(4-methoxyphenyl)ethanone labeled with carbon-13 at

* Trifluoroacetonitrile was either prepared on ~0.2 mole scale according to the procedure of Gilman and Jones (8), or obtained from a commercial source (Pfalz and Bauer).

the carbonyl carbon (compound *4c*) was brominated and treated with trifluorothioacetamide to give a thiazole, whose ^{13}C-NMR spectrum showed isotopic enrichment exclusively at C-4 adjacent to nitrogen.

EXPERIMENTAL SECTION

Specific and total activity determinations were carried out on a Packard Tri-Carb liquid scintillation spectrometer Model 2425, using the external standard method. Diotol (Burdick & Jackson) was used as the counting cocktail. Thin-layer chromatographic analysis (TLC) was done using 2.5 cm x 10 cm glass plates, precoated with a 250 μm layer of Silica Gel GF (Analtech). Radioactive zones on developed plates were detected with a Packard Model 7720/21 Radiochromatogram Scanner equipped with a Model 7222 Thin Layer Chromatography Scanner. Ultraviolet spectra were obtained on a Cary Model 15 spectrometer, infrared spectra on a Digilab Model 14D Fourier transform spectrometer, and mass spectral analyses were obtained using a Varian Model CH-5. The proton magnetic resonance spectra (^{1}H-NMR) were obtained using a Varian A60A or a Varian HFT-80 spectrometer, while the carbon-13 nuclear magnetic resonance spectra (^{13}C-NMR), were produced with a Varian CFT-20 or a Varian CFT-80A spectrometer. Melting points were determined in capillary tubes with a Thomas-Hoover Unimelt apparatus and were uncorrected.

[3-^{3}H]Anisole (*3b*)

3-Bromoanisole (Aldrich), 1.9 ml, 15.0 mmol, was added dropwise with stirring from a syringe to a cold (-78°) mixture of 19 ml of 1.9M *t*-butyllithium in pentane and 40 ml of freshly distilled tetrahydrofuran (THF). After 10 minutes of stirring at -78°C, the yellow color of the mixture dissipated and white precipitates appeared. A 0.2 ml sample of tritiated water (ICN Radiochemicals, nominally 5 Ci/ml) was added from a syringe, followed by 0.2 ml of water. The mixture was allowed to warm to room temperature and partitioned with 100 ml of water and 10 ml of pentane. The organic phase was washed with 100 ml of brine and dried over sodium sulfate. The dry solution was fractionally distilled, first at atmospheric pressure to remove pentane and THF,

then at reduced pressure, to give 1.30 g (79.3% yield) of *3b*, bp 85-7°C at 80 torr, sp. act. 175 μCi/mg. The radiochemical yield was 227.5 mCi, or 45.5% of theory.

[3-^{2}H]Anisole (*3a*)

The procedure was the same as that described for *3b*. From 2.4 ml of 3-bromoanisole (19 mmol), 20 ml of 1.9 M *t*-butyllithium in pentane, 150 ml of freshly distilled THF, and 1.0 ml of deuterium oxide, there was obtained 1.67 g (78%) of *3a*, bp 80-83°C at 80 torr; TLC (CCl_4, Rf 0.32) identical to a standard sample of anisole; mass spectrum: m/z (rel. intensity), 109 (25.4) molecular ion, 108 (4.5), 94 (8.5) M^+-CH_3, 79 (53.7) M^+-CH_2O, 66 (100) C_5H_4O; ^{1}H-NMR: $CDCl_3$ δ, 7.24 (dd, 1H, J = 8.5 Hz, J = 8.0 Hz, *meta* H), 6.88 (m, 3H, *ortho* and *para* H), 3.73 (s, 3H, O-CH_3); ^{13}C-NMR: ppm, 159.59 (C_1), 129.35 (C_5), 129.07 (C_3, $J_{^{13}C-^2H}$ = 24.4 Hz), 120.44 (C_4), 113.83 (C_2,C_6), 54.89 (O-CH_3).

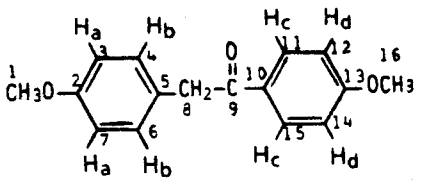
1-(4-Methoxy[2-^{3}H]phenyl)-2-(4-methoxyphenyl)ethan-1-one (*4b*)

A mixture of 24.9 g (150 mmol) of 4-methoxyphenylacetic acid and 35 ml (450 mmol) of thionyl chloride was refluxed for 2 hours. The crude mixture was fractionally distilled to give 27.0 g (97% yield) of 4-methoxyphenylacetyl chloride, an orange-red liquid, bp 107-110°C at 2 torr. A solution of 2.26 (12.25 mmol) of 4-methoxyphenylacetyl chloride, and 1.30 g (11.9 mmol) of *3b* in 30 ml of carbon disulfide was cooled in an ice bath. With good stirring, 3.33 g (25 mmol) of anhydrous aluminum chloride was added in portions. The deep red reaction mixture was stirred at room temperature for 3.5 hours, and poured into a mixture of 300 ml of crushed ice and 20 ml of 6N HCl solution. The white precipitates which resulted were dissolved in 150 ml of CH_2Cl_2 and the mixture partitioned. The aqueous phase was extracted with 100 ml of CH_2Cl_2, and the combined organic layers were washed with 150 ml of 1N NaOH, folowed by 150 ml of brine, and dried over Na_2SO_4. The dry solution was concentrated and chromatographed on 325 g of silica gel packed in and eluted with 1.5% v/v MeOH/CH_2Cl_2 at 5 ml per minute and fractions of 15 ml each were collected. The pooling of fractions 68-135 yielded 2.59 g of crude *4b* . The material was crystallized from 15 ml of hot EtOH and 20 ml of H_2O to yield 2.56 g of *4b* (84%), mp 111-111.5°C,

sp. act. 75.6 μCi/mg or 19.4 mCi/mmol, radiochromatographically homogeneous by TLC (1% v/v MeOH/CH_2Cl_2, R_f 0.50).

1-(4-Methoxy[2-^{2}H]phenyl)-2-(4-methoxyphenyl)ethan-1-one *(4a)*

The procedure used was the same as that described for *4b*. To a solution of 3.32 g (18.0 mmol) of 4-methoxyphenylacetyl chloride and 1.91 g (17.5 mmol) of *3a* in 30 ml of carbon disulfide was added 4.8 g (36 mmol) of anhydrous aluminum chloride. The crude product was chromatographed on 320 g of silica gel packed in and eluted with 1.5% v/v MeOH/CH_2Cl_2. The eluate was collected in 15 ml fractions at 5 ml per minute. Pooling of fractions 41-100 gave 3.65 g of crude product, which was crystallized from 17 ml of hot EtOH and 15 ml of H_2O to yield 3.61 g of *4a* (81%), mp 111-111.5°C, chromatographically homogeneous by TLC (1% v/v MeOH/CH_2Cl_2, Rf 0.50; 20% v/v EtOAc/Hexane, R_f 0.3), mass spectrum: m/z (re. intensity), 257 (6.7) mono-deuterated molecular ion, no di-deuterated material, 136 (100) $C_8H_6DO_2$ + ; 121 (10) C_8H_9O + ; ^{1}H-NMR*: $CDCl_3$ δ, 3.75 (s, 3H, Ar-OCH_3), 3.80 (s, 3H, Ar-OCH_3), 4.1 (s, 2H, Ar-CH_2-CO), 6.8 (d, 2H, H_a), 7.15 (d, 2H, H_b), 6.9 (m, 2H, H_d), 7.95 (d, 1H, H_c); ^{13}C-NMR*: $CDCl_3$, ppm 163.48 (C_{16}), 158.50 (C_2), 130.85 (C_{11}), 130.4 (t, $J_{^{13}C-^2H}$ ~ 25 Hz, C_{15}), 130.36 (C_4C_6), 129.63 (C_{10}), 127.03 (C_5), 114.10 (C_3C_7), 113.76, 113.67 ($C_{12}C_{14}$), 55.37, 55.16 (C_1C_{16}), 44.30 (C_8).



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4-Methoxyphenyl[1-^{14}C]acetic Acid (*7b*)

4-Methoxybenzylmagnesium chloride was prepared with modified known methods (12,13). To a stirred, refluxing mixture of 0.547 g (22.5 mmol) of magnesium turnings

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* For numbering assignments in *4a*, see structure *8*.

and 75 ml of dry, freshly distilled tetrahydrofuran*, was added dropwise 3.52 g (22.5 mmol) of 4-methoxybenzyl chloride (Aldrich). Within a few minutes, the reaction started, and refluxing was continued for 1 hour to completely consume the magnesium. A 4.0 ml aliquot of the mixture was acidified and back titrated with NaOH and found to be 0.188M.

The Grignard reagent solution was cooled to -50°C** in an acetonitrile-ethanol/dry ice bath while [^{14}C]carbon dioxide was generated from 0.358 g of barium [^{14}C]carbonate (Amersham, batch #239, nominally 57.9 mCi/mmol) and 1.432 g of carrier barium carbonate, by the dropwise addition of 6 ml of 6N $HClO_4$ to the solids. The [^{14}C]carbon dioxide was fed to the Grignard solution by a constant stream of nitrogen. After all of the acid was added, the generator was warmed to a light reflux to degas the solution, while under the nitrogen purge. The cold excess Grignard reagent was then quenched by the addition of 25 ml of 6N H_2SO_4 and warming the reaction mixture to room temperature. The THF was removed *in vacuo*, and the residue extracted with 3 x 25 ml of ether. The concentrated extract was dissolved in 25 ml of 1N NaOH and washed with 2 x 30 ml of ether. The aqueous solution was then acidified with 5 ml of 18N H_2SO_4 and extracted 3 x 25 ml with ether. The extract was washed with brine and dried over Na_2SO_4. The dry extract was concentrated to a white crystalline solid, 1.279 g (85% yield), mp. 86.5-87°C, sp. act. 68.8 μCi/mg (11.43 mCi/mmol), radiochromatographically homogeneous by TLC (97:2:0.5 v/v CH_2Cl_2: MeOH:HOAc, $R_f = 0.33$).

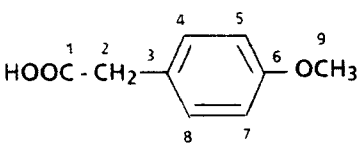
4-Methoxyphenyl[1-^{13}C]acetic Acid *(7a)*

The procedure used was the same as that described for *7b*. A 0.22M solution of 4-methoxybenzylmagnesium chloride, prepared from 0.608 g (25 mmol) of magnesium turnings and 3.915 g (25 mmol) of 4-methoxybenzyl chloride in 80 ml of dry, freshly distilled THF, was cooled to -50°C, and treated with the $^{13}CO_2$ generated from 1.974 g

* Tetrahydrofuran was found to be the solvent of choice in this preparation. Use of ether led to extensive coupling of the Grignard reagent.

** The Grignard reagent must be cooled to -50°C to avoid formation of an acidic side product which was readily detectable by ^{13}C-NMR (173.8 ppm).

(10.0 mmol) of barium [^{13}C]carbonate (Stohler Isotope, 90% ^{13}C enrichment) and 6.0 ml of 6N $HClO_4$, to give 1.5106 g (91% yield from $BaCO_3$) of *7a*, mp 86-87°C, a single zone by TLC (97:2:0.5 v/v CH_2Cl_2:MeOH:HOAc, $R_f = 0.33$), mass spectrum m/z (rel. intensity): 167 (31.3) M^+, 121 (100) M^+-$^{13}CO_2H$; calculated from molecular ion cluster: 92% ^{13}C enrichment; λ max (EtOH) nm (ε): 226 (8800), 276 (1600), 383 (1400); infrared spectrum (Nujol mull) cm^{-1}: 3070, 2720, 2660, 2560 (Acid-OH), 1700 ($^{12}C=O$), 1678, 1657 ($^{13}C=O$), 1615, 1585, 1515 (C=C), 1305, 1245, 1185 (C-O, other); calculated for $C_9H_{10}O_3$: C, 65.05%, H, 6.07%; found: C, 64.97%, H, 6.15%; ^{1}H-NMR:$CDCl_3$ δ, 3.54 (d, 2H, $J_{C-H} = 7.75$ Hz, ^{13}C-CH_2-Ar), 3.75 (S, 3H, Ar-OCH_3), 6.85 (d, 2H, J = 8.5 Hz, Ar-H), 7.15 (d, 2H, J = 8.5 Hz, Ar-H), 11.3 (S, 1H, CO_2H); ^{13}C-NMR*, $CDCl_3$ ppm: 178.39 (C_1), 158.94 (C_6), 130.45 (D, $J_{C-C-C-C} = 1.6$ Hz, C_4,C_8), 125.48 (D, $J_{C-C-C} = 3.0$ Hz, C_3), 114.14 (C_5,C_7), 55.19 (C_9), 40.17 (D, $J_{C-C} = 55.4$ Hz, C_2).



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1,2-*Bis*(4-methoxyphenyl)[1-^{14}C]ethan-1-one (*4d*)

Anisole (Eastman) was acylated with the acid chloride derived from *7b* according to the procedure described above for preparing tritium labeled *4b*. A mixture of 1.279 g of 4-methoxy[1-^{14}C]acetic acid (*7b*) (7.69 mmol) and 3.0 ml of thionyl chloride (41 mmol) was refluxed gently for 2.0 hours. The solution was concentrated and the crude acid chloride was dissolved in 16 ml of carbon disulfide with 1.25 ml of anisole (11.54 mmol) and cooled in an ice bath. Slowly and with good stirring, 2.13 g of aluminum chloride (16.0 mmol) was added. The deep red solution was stirred at room temperature for 3.0 hours. The mixture was poured over ~100 ml of crushed ice containing 10 ml of 6N HCl. The resulting two-phased mixture was briefly concentrated

* For number assignments in *7a*, see structure *9*.

to remove the CS_2 and extracted with 2 x 30 ml of CH_2Cl_2. The extract was washed with saturated NaCl solution and dried over Na_2SO_4. The dry extract was concentrated and chromatographed on a column containing 180 g of silica gel packed in 1.5% v/v $MeOH/CH_2Cl_2$. The column was eluted with the same solvent mixture at a flow rate of 4.66 ml/min, and the eluate was collected in 14 ml fractions. Fractions 39-79 were pooled and concentrated to give 1.768 g of crude *4d* which was recrystallized from 12 ml of hot cyclohexane and 3.5 ml of hot ethyl acetate to yield 1.595 g of *4d* (81%), mp. 110.5-111.5°C, sp. act. 44.9 μCi/mg (11.5 mCi/mmol), radiochromatographically homogeneous by TLC (1% v/v $MeOH/CH_2Cl_2$, $R_f = 0.47$; 3% v/v $EtOAc/CH_2Cl_2$, $R_f = 0.51$; 25% v/v EtOAc/hexane, $R_f = 0.33$).

1,2-*Bis*(4-methoxyphenyl)[1-^{13}C]ethan-1-one (*4c*)

The procedure was the same as the one described above for preparing *4d* from *7b*. From 1.115 g (6.71 mmol) of 4-methoxyphenyl[1-^{13}C]acetic acid (*7a*), there was obtained 1.583 g of crude material which was recrystallized from 10 ml of hot cyclohexane and 3 ml of ethyl acetate to yield 1.481 g of *4c* (86%), mp. 110-111°C, homogeneous by TLC (1% v/v $MeOH/CH_2Cl_2$, $R_f = 0.48$; 3% v/v $EtOAc/CH_2Cl_2$, $R_f = 0.52$; 25% v/v EtOAc/hexane, $R_f = 0.33$), mass spectrum m/z (rel. intensity): 257 (1.37) M^+ 136 (100) $C_7{}^{13}C_1H_7O_2{}^+$, calculated to be 92-95% enriched in ^{13}C from the 135, 136, 137 ion cluster; λmax (EtOH) nm (ε): 220 (20,250), 275 (18,350); calculated for $C_{16}H_{16}O_3$: C, 74.98%; H, 6.29%; found: C, 74.97%, H, 6.39%; IR (Nujol mull), cm^{-1}: 1680 (^{12}C = 0), 1640 (^{13}C = 0), 1615, 1600, 1585, 1520, 1510 (C = C), 1270, 1250, 1070, 1025 (C-O); ^{1}H-NMR*:$CDCl_3$ δ, 3.73 (S, 3H, Ar-OCH_3), 3.80 (S, 3H, Ar-OCH_3), 4.13 (d, 2H, $J_{C\text{-}C\text{-}H} = 6.1$ Hz,-CH_2-^{13}CO), 6.81 (d, 2H, $J_{cd} = 8.8$ Hz, H_a), 6.88 (d, 2H, $J_{ab} = 8.8$ Hz, H_d), 7.16 (D, 2H, $J_{cd} = 8.8$ Hz, H_b), 7.96 (dd, 2H, $J_{ab} = 8.8$ Hz, $J_{C\text{-}C\text{-}C\text{-}H} = 3.5$ Hz, Hc); ^{13}C-NMR*:$CDCl_3$ ppm, 196.38 (C_9), 163.53 (C_{13}), 158.56 (C_2), 130.90 (d, $J_{C\text{-}C\text{-}C} = 3.2$ Hz, C_{11},C_{15}), 130.39 (d,$J_{C\text{-}C\text{-}C\text{-}C} = 1.3$ Hz, C_4H_6), 129.73 (d, calc. $J_{C\text{-}C} = 56$ Hz, C_{10}), 127.07 (d, $J_{C\text{-}C\text{-}C} = 2.3$ Hz, C_5), 114.17 (C_3,C_7), 113.79 (d, $J_{C\text{-}C\text{-}C\text{-}C} = 4.2$ Hz, C_{12},C_{14}), 55.34, 55.13 (C_{16},C_1), 44.33 (d, $J_{C\text{-}C} = 40.8$, C_8).

* See structure *8* for designation of protons and carbon atoms in compound *4c*.

2-Bromo-1-(4-methoxy[2-^{3}H]phenyl)-2-(4-methoxyphenyl)ethan-1-one (*5b*)

A mixture of 2.50 g of *4b* (9.75 mmol) and 20 ml of CCl_4 was warmed until the solids dissolved. N-bromosuccinimide* (1.85 g, 9.85 mmol) was added and the mixture heated with stirring. When reflux started, 0.035 g (0.14 mmol) of benzoyl peroxide was added and the reflux was continued for 30 minutes. The mixture was cooled, decolorized with activated charcoal and filtered. The filtrate was concentrated to an oil and crystallized from 5 ml of benzene and 25 ml of hexane to yield 2.93 g of *5b* (90%), mp. 104-5°C, sp. act. 57.1 μCi/mg or 19.1 mCi/mmol, two radioactive zones by TLC (identical to a standard sample of 2-bromo-1,2-bis(4-methoxyphenyl)-ethan-1-one, compound unstable on silica gel, 20% v/v EtOAc/hexane, R_f 0.23 major, R_f 0.1 minor; 1:4:5 v/v EtOAc: hexane: CH_2Cl_2, R_f 0.6 major, R_f 0.27 minor.

2-Bromo-1-(4-methoxy[2-^{2}H]phenyl)-2-(4-methoxyphenyl)ethan-1-one (*5a*)

The procedure used was the same as that for *5b*. A mixture of 2.66 g *4a* (10.4 mmol), 1.87 g of NBS (10.5 mmol) and 23 ml of CCl_4 was refluxed for 30 minutes. The crude product was crystallized from 5 ml of benzene and 25 ml of hexane to give 3.177 g of *5a* (91%), mp. 104-5, identical to a standard sample of 2-bromo-1,2-bis(4-methoxyphenyl)ethan-1-one by TLC.

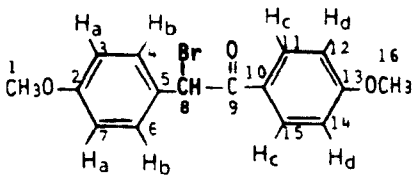
1,2-*Bis*(4-methoxyphenyl)-2-bromo[1-^{14}C]ethan-1-one (*5d*)

A mixture of 1.594 g of *4d* (6.22 mmol) and 1.217 g of NBS (6.84 mmol) was refluxed in 13 ml of CCl_4. When refluxing started, 0.042 g of benzoyl peroxide (0.17 mmol) was added all at once. After 20 min of reflux, 0.061 g (0.34 mmol) of NBS was added, and reflux continued for 20 minutes until all of the NBS was consumed. The succinimide was filtered off and the filtrate concentrated. The residual crude *5d* was used without purification in the cyclization reaction to produce carbon-14 labeled thiazole *1d*.

* A sample of N-bromosuccinimide from Aldrich Chemical Co. was recrystallized from hot water to afford white crystals.

1,2-*Bis*(4-methoxyphenyl)-2-bromo[1-^{13}C]ethan-1-one (*5c*)

Similarly as above, *5c* was obtained in 79% yield from *4c* after recrystallization from benzene and hexane, mp. 104-105°C; identical to a standard sample of 1,2-*bis*(4-methoxyphenyl)-2-bromoethan-1-one by TLC [silica gel, 1:4:5 v/v EtOAc: n-hexane:CH_2Cl_2, R_f = 0.59 (major), 0.22 (minor)]; calculated for $C_{16}H_{15}BrO_3$: C, 57.33%; H, 4.51%; Br, 23.84%; found: C, 56.96%, H, 4.74%; Br, 23.89%; mass spectrum: m/z (rel. intensity), 337 (0.19), 335 (0.20) M^+, 256 (5.3) M^+-Br, 136 (100) $C_7{}^{13}C_1H_7O^+$, 92% enrichment ^{13}C calculated from the 135, 136, 137 ion cluster; IR (Nujol mull), cm^{-1}: 1680 (^{12}C = O), 1640 (^{13}C = O), 1605, 1575, 1510 (C = C), 1265, 1255, 1180, 1165, 1035, 1025, 980 (C-O, other), 855, 835, 810, 785, 735, 675, 635 (-CH, other); ^{1}H-NMR*:$CDCl_3$ δ, 3.76 (S, 3H, Ar-OCH_3), 3.82 (S, 3H, Ar-OCH_3), 6 36 (d, 1H, $J_{C\text{-}C\text{-}H}$ = 2.4 Hz, -CH-Br), 6.86 (d, 2H, J_{cd} = 8.9 Hz, H_a), 6.88 (d, 2H, J_{ab} = 9.1 Hz, H_d); 7.47 (d, J_{cd} = 8.8 Hz, H_b), 7.95 (dd, 2H, J_{ab} = 9.04 Hz, $J_{C\text{-}C\text{-}C\text{-}H}$ = 3.6 Hz, H_c), ^{13}C-NMR*:$CDCl_3$ ppm, 189.65 (C_9), 163.91 (C_{13}), 160.14 (C_2), 131.48 (d, $J_{C\text{-}C\text{-}C}$ = 2.7 Hz, C_{11},C_{15}), 130.51 (d, $J_{C\text{-}C\text{-}C\text{-}C}$ = 1.3 Hz, C_4,C_6), 128.30 (C_5), 126.88 (d, $J_{C\text{-}C}$ = 56.8 Hz, C_{10}), 114.43 (C_3,C_7), 114.04 (d, $J_{C\text{-}C\text{-}C\text{-}C}$ = 4.4Hz, C_{12},C_{14}), 55.47, 55.24 (C_{16},C_1), 51.37 (d, $J_{C\text{-}C}$ = 43.2 Hz, C_8).



10

2,2,2-Trifluorothioacetamide (*6*)

Ten ml of 2,2,2-trifluoroacetylnitrile (Pfaltz & Bauer) was condensed into a flask equipped with an ethanol/dry ice condenser and cooled in a bath of the same mixture. Liquid ammonia (~30 ml) was condensed into the flask. The cooling bath was removed and the mixture was allowed to reflux and eventually evaporate at room temperature.

* See structure *10* for designation of protons and carbon atoms in compound *5c*.

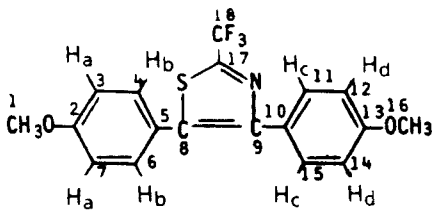
The residue was dissolved in 25 ml of dry ether and hydrogen sulfide gas was bubbled through the liquid for 1.25 min. A light precipitate which formed was removed by filtration and the filtrate was concentrated *in vacuo* to give 12.32 g of yellow oil which was redissolved in 15 ml of dry ether for storage in the freezer, ^{13}C-NMR:$CDCl_3$ ppm, 187.47 (q, $J_{C\text{-}C\text{-}F}$, 36.2 Hz, -$CSNH_2$), 117.41 (q, $J_{C\text{-}F}$ = 280.2 Hz, -CF_3). (Note: Ether is strongly bound to the material. After the $CDCl_3$ solution was twice concentrated, the ether was not removed.) The material was stable after 2 weeks of storage in the freezer. Crystalline *6* was obtained when neat, liquid *6* was cooled at 0°C, mp. 45-6°C; homogeneous by TLC (CH_2Cl_2, R_f = 0.30, 02% v/v EtOAc in hexane, R_f 0.25); mass spectrum: M/z (rel. intensity) 129 (100) molecular ion, 65 (15) M^+ -CH_2NS, 60 (42) M^+-CF_3; infrared spectrum: Nujol mull, cm-^{1} 3360, 3300, 3180, (NH), 2560 (SH), 1640 (C = N), 1215, 1150 (C-F); λ_{max} in dioxane, nm (ε) 255 (1150), 308 (6000); due to instability at high temperatures and volitility, a reliable elemental analysis was unobtainable.

4-(4-Methoxy[2-^{3}H]phenyl)-5-(4-methoxyphenyl)-2-(trifluoromethyl)thiazole (*1b*)

A mixture of 1.46 g of *5b* (4.35 mmol), 0.86 g of *6* (6.6 mmol) and 13 ml of CH_3CN was stirred for 18 hours at room temperature in a stoppered flask. The mixture was partitioned with 50 ml of water and 50 ml of ether. The aqueous layer was extracted with 50 ml of ether, and the combined organic phases were washed with 50 ml of brine and dried over Na_2SO_4. The dry extract was concentrated and chromatographed on 150 g of silica gel packed in and eluted with 20% v/v EtOAc/ hexane at 4.4 ml/min and fractions of 11 ml each were collected. Fractions 33-51 were pooled and concentrated to an oil which was crystallized from 2 ml of pentane to yield 1.10 g (69%) of *1b*, mp. 55-56°C; sp. act. 53 μCi/mg or 19.4 mCi/mmol, total activity 53.6 mCi; radiochromatographically homogeneous by TLC (20% v/v EtOAc/ hexane, R_f 0.45, CH_2Cl_2 R_f 0.60, 1:4:5 v/v EtOAc:hexane:CH_2Cl_2 R_f 0.74; λ_{max} in ethanol nm (ε) 229 (19,600), 263 (15,150), 316 (8.200); infrared spectrum: same as reference standard; calculated for $C_{18}H_{14}F_3NO_2S$ (MW 365.30): C, 59.17%, H, 3.86%, N, 3.83%; found: C, 59.19%, H, 3.93%, N, 3.94%.

4-(4-Methoxy[2-^{2}H]phenyl)-5-(4-methoxyphenyl)-2-(trifluoromethyl)thiazole (*1a*)

The procedure used was the same as that described for *1b*. A mixture of 3.14 g of *5a* (9.34 mmol), 1.87 g of *6* (14.5 mmol), and 25 ml of CH_3CN was stirred at room temperature for 20 hours. The reaction mixture was heated for two hours at 60°C, worked up as described above, and chromatographed first on 150 g of silica gel with 20% v/v EtOAc/hexane, then on 60 g of silica gel with CH_2Cl_2. The product was crystallized from 2 ml of pentane to give 1.847 g of *1a* (55%); m.p. 56-57°C; radiochromatographically homogeneous by TLC (20% v/v EtOAc/hexane R_f 0.42, CH_2Cl_2 R_f 0.62, 1:4:5 EtOAc:hexane: CH_2Cl_2 R_f 0.68); mass spectrum: m/z (rel. intensity), 366 (100) molecular ion, ca. 98% deuterium incorporation from isotope array, 351 (16) M^+-CH_3; λ_{max} in ethanol, nm (ε): 229 (19,100), 263 (15,100), 317 (8,200); ^{1}H-NMR*: $CDCl_3$ δ, 4.80 (s, 2H, Ar-OCH_3), 4.85 (s, 3H, Ar-OCH_3), 6.87 (m, 4H, aromatic H_a, H_d), 7.27 (d, 2H, J = 9 Hz, H_b), 7.47 (d, 1H, J = 9 Hz, H_c).



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4,5-*Bis*(4-methoxyphenyl)-2-(trifluoromethyl)[4-^{14}C]thiazole (*1d*)

A 2.75 ml aliquot of *6* in ether (0.82 g/ml, 9.6 mmol) was concentrated and dissolved in 20 ml of CH_3CN, along with the crude *5d*. The solution was stirred in a stoppered flask for 18 hours at room temperature. A second aliquot of *6*, 0.5 ml (1.8 mmol), was concentrated and added to the reaction mixture, which was stirred for 24 hours more. The mixture was then filtered to remove a fine precipitate, and the filtrate concentrated *in vacuo*. The residue was chromatographed on 200 g of silica gel packed in and eluted with 20% v/v EtOAc/hexane. Fractions of 13 ml each were collected at a flow rate of 3.9 ml/min. Fractions 23-57 were pooled and concentrated to give 1.924 g

* See structure *11* for designation of protons in compound *1a*.

of a colorless oil. The oil was crystallized by dissolving in 3 ml of n-pentane, cooling in an ice bath for 1 minute, and seeding. Crystals formed quickly, and were filtered and dried under high vacuum at room temperature to give 1.771 g of *1d* (78% from *5d*), mp. 55-56°C, sp. act. 31.38 μCi/mg (11.47 mCi/mmol), total activity, 55.6 mCi, overall radiochemical yield 53.5% from $Ba^{14}CO_2$, a single radioactive zone by TLC (25% v/v EtOAc/hexane, $R_f = 0.45$; CH_2Cl_2, $R_f = 0.60$; 1:4:5 v/v EtOAc:hexane:CH_2Cl_2, $R_f = 0.75$); λ_{max} in EtOH nm (ε): 229 (21,000), 264 (15,400), 317 (8,450); infrared spectrum: same as reference standard; ^{1}H-NMR* $CDCl_3$ δ: 3.80 (S, 3H, Ar-OCH_3), 3.83 (S, 3H, Ar-OCH_3), 6.81 (d, 2H, $J_{ab} = 9.0$ Hz, H_d), 6.87 (d, 2H, $J_{cd} = 8.9$ Hz, H_a), 7.29 (D, 2H, $J_{cd} = 8.9$ Hz, H_b), 7.46 (d, 2H, $J_{ab} = 8.9$ Hz, H_c).

4,5-*Bis*(4-methoxyphenyl)-2-(trifluoromethyl)[4-^{13}C]thiazole (*1c*)

Similarly, from *5c* and *6* in ether, *1c* was obtained in 70% yield, m.p. 55-56°C, homogeneous by TLC (25% v/v EtOAc/ hexane, $R_f = 0.45$; CH_2Cl_2, $R_f = 0.60$; 1:4:5 v/v EtOAc:hexane: CH_2Cl_2, $R_f = 0.75$); calculated for $C_{18}H_{14}F_3NO_2S$: C, 59.17%; H, 3.86%; N, 3.83%; S, 8.78%; found: C, 59.27%; H, 4.05%; N, 3.74%; S, 8.98%; λmax in EtOH nm (ε): 229 (19,900), 263 (15,100), 316 (8.300); mass spectrum: m/z (rel. intensity), 366 (100) M^+, 351 (12.7) M^+-CH_3, 90% ^{13}C enrichment calculated from the molecular ion cluster 365, 366, 367; IR (Nujol mull), cm^{-1}: 1605, 1575, 1515 (C = C, C = N), 1250, 1175, 1140, 1030 (CF_3, C-O, other), 835 (-CH); ^{1}H-NMR* $CDCl_8$ δ: 3.73 (S, ^{3}H, Ar-OCH_3), 3.78 (S, ^{3}H, Ar-OCH_3), 6.76 (d, ^{2}H, $J_{cd} = 9.0$ H_z, H_a), 6.82 (d, 2H, $J_{ab} = 9.0$ Hz, H_d), 7.25 (d, 2H, $J_{cd} = 9.0$ Hz, H_b), 7.44 (dd, $J_{ab} = 9.0$ Hz, $J_{C\text{-}C\text{-}H} = 3.9$ Hz, H_c); ^{13}C-NMR*:$CDCl_3$ ppm, 160.37, 159.78 (C_2,C_{13}), 150.63 (C_9), 135.29 (d, $J_{C\text{-}C} = 67.4$ Hz, C_8), 131.03 (C_4,C_6), 130.36 (d, $J_{C\text{-}C\text{-}C} = 1.7$ Hz, H_{11},C_5), 126.19 (d, $J_{C\text{-}C} = 67.51$, C_{10}), 122.65 (d, $J_{C\text{-}C\text{-}C} = 1.9$ Hz,C_5); 114.59 (C_3,H_7), 113.92 (d, $J_{C\text{-}C\text{-}C\text{-}C} = 4.6$Hz, C_{12},C_{14}), 55.30, 55.24 (C_1,C_{16}), 120.03 (dq, $J_{C\text{-}F} = 271.8$ Hz, $J_{C\text{-}N = C\text{-}C} = 9$ Hz, C_{18}), 152.2 (q, $J_{C\text{-}C\text{-}F} = 40$ Hz, C_{17}).

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* See structure *11* for proton designations in compounds *1d* and *1c*.

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