Oxidation of Aromatic Lithium Thiolates into Sulfinate Salts: An Attractive Entry to Aryl Sulfones Labeled with Carbon-11

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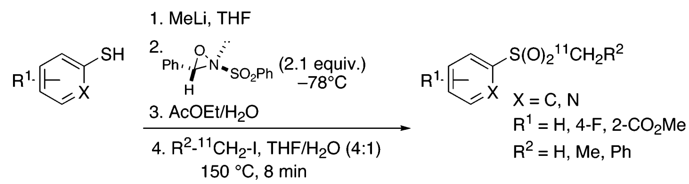

Aromatic ^{11}C-sulfones were synthesized by *S* alkylation of lithium arenesulfinates, which are readily available from the corresponding thiols by an oxaziridine-mediated oxidation reaction with [^{11}C]alkyl iodides in THF/H_2O (4:1) at 150 °C. The radiosyntheses, including purification by HPLC, were completed in an average of 35 min from the end of the bombardment with 55−76% overall radiochemical yields (decay corrected). The described procedure extends the range of accessible labeling methods.

Introduction

Positron emission tomography (PET) is a technique where organic molecules labeled with short-lived β^+-emitting nuclides may be used in various areas of clinical diagnosis and as tools in the drug-development process. To facilitate the incorporation of radionuclides into biologically interesting molecules, there is a need to improve and develop new synthetic methods.[1] The most frequently applied radionuclides in PET are ^{11}C and ^{18}F with half-lives of 20.3 and 110 min, respectively. The preparations of ^{11}C-labeled compounds are always a challenge, requiring the development of special synthetic procedures, taking into account the radioactivity, the short half-life of the radioisotope, and the use of submicromolar quantities of the labeled reactant. The synthesis time is a crucial parameter, and the reactions have to be rapid, efficient, selective, and preferably without any intermediate purification. Moreover, ^{11}C is available from the cyclotron only in forms of [^{11}C]CO_2 and [^{11}C]CH_4, which gives access to a limited number of labeled precursors (e.g., [^{11}C]HCN, [^{11}C]CO, [^{11}C]$COCl_2$, and [^{11}C]CH_3I).

The sulfone function is a key unit of a number of biologically active molecules and plays an important role in bringing about the activity of neuroactive drugs.[2] In the field of radiopharmaceuticals for PET, the neuroprotector hexapeptide Org 2766 **1**,[3] the presynaptic dopamine receptor antagonist (−)-OSU-6162 **2**,[4] the farnesyl transferase inhibitors **3**,[5] and the cyclooxygenase-2 (COX-2) inhibitors, such as TMI **4**,[6] incorporate a methylsulfonyl substituent labeled with ^{11}C (Figure 1).[7] In all cases, the labeling strategy based on the conventional route to sulfones involved methylation of the corresponding thiolate with synthetically well-established [^{11}C]methyl iodide,[8] followed by a double-oxidation reaction on the sulfur center. However, several drawbacks related to the constrains of the ^{11}C chemistry[1] can be pointed out: (i) the radioisotope was not incorporated at the final step, (ii) the oxidation reaction led to a complex mixture consisting of the desired compound, the analogous sulfoxide, and unidentified byproducts, (iii) isolation of the ^{11}C-sulfone from the reaction mixture was not straightforward, and (iv) the radiochemical yields were in all cases low to moderate (<37% decay corrected and calculated from [^{11}C]methyl iodide).

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(1) (a) Fowler, J. S.; Wolf, A. P. In *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*; Phelps, M., Ed.; Raven Press: New York, 1986; Chapter 9, pp 391−450. (b) Elsinga, P. H. *Methods* **2002**, *27*, 208−217. (c) Ferrieri, R. A.; Antoni, G.; Khilberg, T.; Långström, B. In *Handbook of Radiopharmaceuticals. Radiochemistry and Applications*; Welch, M. J., Redvanly, C. S., Eds.; Wiley: Chichester, 2003; pp 229−282.

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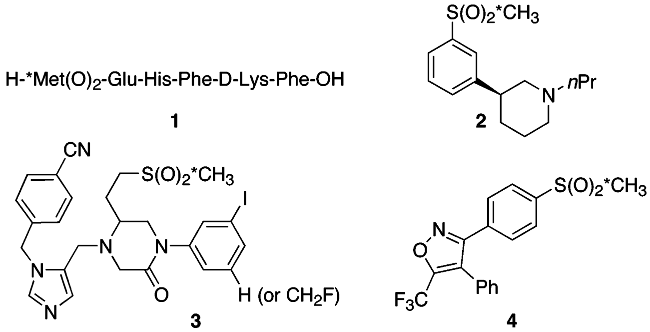
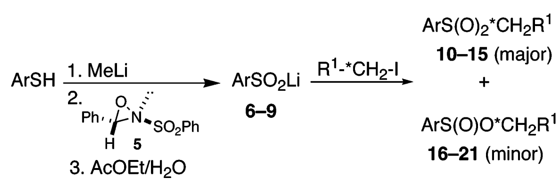


FIGURE 1. ^{11}C-Sulfones as PET tracers (*, labeled position).

In addition, strong oxidizing reagents (H_2O_2, *m*-CPBA, or oxone), required for a rapid reaction and used in large excess as compared to the ^{11}C-methyl sulfide, are not selective of the sulfone function and might not be appropriate in the case of polyfunctional molecules with sensitive groups.[9]

The main alternative route to sulfones involves the *S* alkylation of sulfinate salts.[9] This reaction has been used, for example, for the labeling with ^{14}C (β^- emitter, $t_{1/2} = 5730$ years) of methylsulfonylbenzene, starting from commercially available sodium benzenesulfinate (70% radiochemical yield after the reaction in DMF at room temperature for 3 days).[10] This strategy obviously reduces the number of radioactive steps. However, the limited availability and low nucleophilicity of the sulfinates[11] made this reaction uncommon toward more sophisticated targets and restrained any development in ^{11}C chemistry.

SCHEME 1. Sulfones via Lithium Sulfinates (*C = ^{12}C, ^{11}C)



In the course of our work concerning the reactivity of thiolates with *N*-sulfonyloxaziridines,[12] we have previously reported an original synthesis of lithium arenesulfinates and identified the benzaldehyde derivative **5** as the appropriate oxidizing agent (Scheme 1).[12b] The main features of this new reaction are a high efficiency, a remarkable chemoselectivity, a compatibility with a wide range of substrates, and the use of mild conditions.

(2) (a) Kalir, R.; Kalir, H. H. Biological Activity of Sulfoxides and Sulfones. In *The Chemistry of Sulphur-containing Functional Group*; Patai, S., Rappoport, Z., Eds.; J. Wiley and Sons: Chichester, 1993; Chapter 16, pp 957−973. (b) Lamberth, C. *J. Sulfur Chem.* **2004**, *25*, 39−62. (c) Smith, P. H.; Chamberlain, K.; Sugars, J. M.; Bromilow, R. H. *Pestic. Sci.* **1995**, *45*, 357−361. (d) Tsuji, K.; Nakamura, K.; Ogino, T.; Konishi, N.; Tojo, T.; Ochi, T.; Seki, N.; Matsuo, M. *Chem. Pharm. Bull*. **1998**, *46*, 279−286. (e) Jones, P. B.; Parrish, N. M.; Houston, T. A.; Stapon, A.; Bansal, N. P.; Dick, J. D.; Townsend, C. A. *J. Med. Chem*. **2000**, *43*, 3304−3314. (f) Garg, R.; Kurup, A.; Mekapati, S. B.; Hansch, C. *Chem. Rev.* **2003**, *103*, 703−731. (g) Pinto, D. J. P.; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E.; Cacciola, J.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Luettgen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knabb, R. M.; Wong, P. C.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem*. **2001**, *44*, 566−578. (h) Hodson, S. J.; Bishop, M. J.; Speake, J. D.; Navas, F.; Garrison, D. T.; Bigham, E. C.; Saussy, D. L., Jr.; Liacos, J. A.; Irving, P. E.; Gobel, M. J.; Sherman, B. W. *J. Med. Chem*. **2002**, *45*, 2229−2239. (i) Salamon, E.; Mannhold, R.; Weber, H.; Lemoine, H.; Frank, W. *J. Med. Chem*. **2002**, *45*, 1086−1097. (j) Fletcher, S. R.; Burkamp, F.; Blurton, P.; Cheng, S. K. F.; Clarkson, R.; O'Connor, D.; Spinks, D.; Tudge, M.; van Niel, M. B.; Patel, S.; Chapman, K.; Marwood, R.; Shepheard, S.; Bentley, G.; Cook, G. P.; Bristow, L. J.; Castro, J. L.; Hutson, P. H.; MacLeod, A. M. *J. Med. Chem*. **2002**, *45*, 492−503. (k) Wada, C. K.; Holms, J. H.; Curtin, M. L.; Dai, Y.; Florjancic, A. S.; Garland, R. B.; Guo, Y.; Heyman, H. R.; Stacey, J. R.; Steinman, D. H.; Albert, D. H.; Bouska, J. J.; Elmore, I. N.; Goodfellow, C. L.; Marcotte, P. A.; Tapang, P.; Morgan, D. W.; Michaelides, M. R.; Davidsen, S. K. *J. Med. Chem*. **2002**, *45*, 219−232. (l) Campos, K. R.; Journet, M.; Lee, S.; Grabowski, E. J. J.; Tillyer, R. D. *J. Org. Chem.* **2005**, *70*, 268−274. (m) Patel, M. V.; Bell, R.; Majest, S.; Henry, R.; Kolasa, T. *J. Org. Chem.* **2004**, *69*, 7058−7065. (n) Thérien, M.; Gauthier, J. Y.; Leblanc, Y.; Léger, S.; Perrier, H.; Prasit, P.; Wang, Z. *Synthesis* **2001**, 1778−1779. (o) Giles, M. E.; Thomson, C.; Eyley, S. C.; Cole, A. J.; Goodwin, C. J.; Hurved, P. A.; Morlin, A. J. G.; Tornos, J.; Atkinson, S.; Just, C.; Dean, J. C.; Singleton, J. T.; Longton, A. J.; Woodland, A. J.; Teasdale, A.; Gregertsen, B.; Else, H.; Athwal, M. S.; Tatterton, S.; Knott, J. M.; Knott, J. M.; Thompson, N.; Smith, S. J. *Org. Process Res. Dev.* **2004**, *8*, 628−642. (p) Zhang, Y.-M.; Cockerill, S.; Guntrip, S. B.; Rusnak, D.; Smith, K.; Vanderwall, D.; Wood, E.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 111−114. (q) Masaki, H.; Mizuno, Y.; Tatui, A.; Murakami, A.; Koide, Y.; Satoh, S.; Takahashi, A. *Biorg. Med. Chem. Lett.* **2003**, *13*, 4085−4088. (r) Chang, S.-J.; Fernando, D.; Fickes, M.; Gupta, A. K.; Hill, D. R.; McDermott, T.; Parekh, S.; Tian, Z.; Wittenberger, S. J. *Org. Process Res. Dev.* **2002**, *6*, 329−335. (s) Lee, K. W.; Hwang, S. Y.; Kim, C. R.; Nam, D. H.; Chang, J. H.; Choi, S. C.; Choi, B. S.; Choi, H.-W.; Lee, K. K.; So, B.; Cho, S. W.; Shin, H. *Org. Process Res. Dev.* **2003**, *7*, 329−335. See also references cited in the following: (t) Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423−4425. (u) Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D. A. *Tetrahedron Lett.* **2004**, *45*, 3233−3236. (v) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608−5614. (w) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696−2700.

(3) Van Nispen, J. W.; Janssen, W. P. A.; Melgers, P. A. T. A.; Jansenn, P. S. L.; Jansen, J. F. G. A.; Vaalburg, W. *Int. J. Pept. Protein Res.* **1990**, *36*, 167−172.

(4) Neu, H.; Hartvig, P.; Torstenson, R.; Fasth, K. J.; Sonesson, C.; Waters, N.; Carlsson, A.; Tedroff, J.; Långström, B. *Nucl. Med. Biol.* **1997**, *24*, 507−511.

(5) (a) Eng, W.-S.; Hamill, T. G.; Francis, B. E.; Fioravanti, C.; Gibson, R. E.; Burns, H. D.; Ravert, H. T.; Mathews, W. B.; Dannals, R. F. *J. Labelled Compd. Radiopharm.* **1999**, *42* (Suppl. 1), S204−S206. (b) Burns, H. D.; Hamill, T. G.; Gibson, R. E. PCT Int. Appl. WO 78363, 2000. (c) Burns, H. D.; Eng, W.-S.; Gibson, R. E. PCT Int. Appl. WO 00654, 1999.

(6) Majo, V. J.; Prabhakaran, J.; Simpson, N. R.; Van Heertum, R. L.; Mann, J. J.; Kumar, S. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4268−4271. This paper describes also the labeling of the COX-2 inhibitors Etoricoxib and Rofecoxib.

(7) To our knowledge, radiosyntheses of **1**−**4** are the only reports describing the introduction of ^{11}C on the sulfone moiety. For a sulfone labeled with ^{18}F, see the following: (a) Isakson, P. C.; Seibert, K.; Talley, J. J. PCT Int. Appl. WO 14679, 1997. (b) Wüst, F. R.; Höhne, A.; Metz, P. *Org. Biomol. Chem.* **2005**, *3*, 503−507. (c) de Vries, E. F. J.; van Waarde, A.; Buursma, A. R.; Vaalburg, W. *J. Nucl. Med*. **2003**, *44*, 1700−1706. (d) McCarthy, T. J.; Sheriff, A. U.; Graneto, M. J.; Talley, J. J.; Welch, M. J. *J. Nucl. Med.* **2002**, *43*, 117−124. (e) Toyokuni, T.; Satyamurthy, N.; Herschman, H. R.; Phelps, M. E.; Barrio, J. R. PCT Int. Appl. WO 89013, 2003.

(8) Crouzel, C.; Långström, B.; Pike, V. W.; Coenen, H. H. *Appl. Radiat. Isot.* **1987**, *38*, 601−603.

(9) For information about syntheses of sulfones, see the following: (a) Ward, R. S.; Diaper, R. L. *Sulfur Rep.* **2001**, *22*, 251−275. (b) Simpkins, N. S. In *Sulphones in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1993; Vol. 10.

(10) Choudhry, S. C.; Serico, L.; Cupano, J. *J. Org. Chem.* **1989**, *54*, 3755−3757.

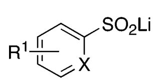
(11) The best approaches to sulfinic acid salts involve the treatment of aryllithium or Grignard reagents with SO_2 or the deprotection of appropriate sulfones. See, for example, the following: (a) *The Chemistry of Sulfinic Acids and their Derivatives-The Chemistry of Functional Groups*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1990. (b) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274−8276. (c) Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, *43*, 8479−8483. (d) Katritzky, A. R.; Rodriguez-Garcia, V.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 1849−1852. (e) Chan, W. Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537−4540. (f) De Vleeschauwer, M.; Gauthier, J. Y. *Synlett* **1997**, 375−377. (g) Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, *43*, 8479−8483. (h) Pinnick, H. W.; Reynolds, M. A. *J. Org. Chem.* **1979**, *44*, 160−161.

(12) (a) Sandrinelli, F.; Perrio, S.; Beslin, P. *J. Org. Chem.* **1997**, *62*, 8626−8627. (b) Sandrinelli, F.; Perrio, S.; Beslin, P. *Org. Lett.* **1999**, *1*, 1177−1180. (c) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M.-T. *Org. Lett.* **2002**, *4*, 3619−3622. (d) Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* **2004**, *69*, 6916−6919.

An important feature of this sequence is the rapidity of the double-oxidation reaction at very low temperatures (−78 °C) in contrast, for example, to oxaziridine-mediated oxidations of sulfides to sulfones.[13] By way of comparison, the oxidation of methyl phenyl sulfide with 2.5 equiv of the same reagent took more than 3 days to go to completion at room temperature. We also demonstrated that lithium sulfinates, after isolation as stable solids, could be converted in high yields into the corresponding sulfones by *S* alkylation with alkyl halides and with a phase-transfer catalyst (*n*-Bu_4NBr) in toluene/acetone/H_2O (3:3:4) for 24 h (Scheme 1, *C = ^{12}C). Sulfinic esters resulting from the competing *O* alkylation were rarely detected.[14] These results led us to consider this oxidation/alkylation methodology to be very attractive for the ^{11}C labeling of a sulfone function. Described herein is the synthesis of various model aromatic sulfones labeled with ^{11}C using ^{11}C-alkyl iodides.

Results and Discussion

The starting aromatic sulfinates **6**−**9** were prepared from the appropriate thiols according to the previously reported sequence: deprotonation with MeLi (1.1 equiv) in THF to generate the lithium thiolates and then oxidation at a low temperature (−78 °C) with *N*-sulfonyloxaziridine **5** (2.1 equiv).[12b] After the workup, including extraction into the aqueous phase, lithium sulfinates **6**−**9** were isolated quantitatively as pure stable white solids (Scheme 1). This synthesis was compatible with a variety of substituents on the phenyl ring and also with the pyridine heterocycle.



X	R^1	
C	H	**6**
C	4-F	**7**
C	2-CO_2Me	**8**
N	H	**9**

The reaction of the simple benzenesulfinate **6** with [^{11}C]CH_3I to afford methylsulfonylbenzene [^{11}C]**10** was chosen as a typical example for the optimization of the alkylation conditions. The protocol we used was as follows. After the reduction of [^{11}C]CO_2 with LAH and a reaction with HI, [^{11}C]CH_3I was distilled into the reaction medium containing sulfinate **6**. The closed reactor was then heated at 150 °C for 5 min, the solvents and the unreacted [^{11}C]CH_3I were removed by evaporation, and the radioactivity of the residue was counted. After dilution in a petroleum ether/ethyl acetate (7:3) mixture, an aliquot of the crude product was subjected to TLC and HPLC analyses. In all experiments, the desired sulfone [^{11}C]**10** was the sole radioactive compound detected and obtained with a radiochemical purity higher than 95%. Crude radiochemical yields (decay corrected to the end of bombardment (EOB) and from [$^{11}CCO_2$]) were ranging from 33 to 75% and were strongly dependent on the reaction medium (Table 1).

In the previously reported toluene/acetone/H_2O (3:3:4) system[12b] containing *n*-Bu_4NBr, the sulfone [^{11}C]**10** was formed in a radiochemical yield not exceeding 43% (entry 1). The replacement of toluene with THF was beneficial, and [^{11}C]**10** was produced in 67% radiochemical yield (entry 3). The removal of acetone had no significant effect (entry 4). It is noteworthy that this cosolvent was found to be essential in nonradioactive chemistry.[15] The use of water in THF appears as an important parameter, probably related to the solubility of the sulfinate salt in the solvent. When trace amounts of H_2O were added (entry 8), [^{11}C]**10** was isolated in 48% radiochemical yield. A significant improvement was observed when the reaction was carried out in THF containing 25% H_2O (entry 5, radiochemical yield: 72%). Acetonitrile and, to a large extent, ethyl alcohol in combination with H_2O in a 4:1 ratio yielded the sulfone [^{11}C]**10** with lower radiochemical yields (53 and 33%, respectively, entries 9 and 10). In DMF (entries 11 and 12), [^{11}C]**10** was obtained in 68−71% radiochemical yields, similar to those found in THF/H_2O (4:1). For an efficient and rapid evaporation, the THF/H_2O (4:1) mixture was preferred and kept in the further studies. To reduce the number of reagents, the need for

TABLE 1. Radiosynthesis of Sulfone [^{11}C]10[a] According to Scheme 1: Influence of the Reaction Conditions

entry	solvent[b]	*n*-Bu_4NBr[c]	*T* (°C)	time (min)	yield[d] (%)
1	toluene/acetone/H_2O (3:3:4)	yes	150	5	43 ± 3
2	toluene/acetone/H_2O (3:3:4)	no	150	5	43 ± 4
3	THF/acetone/H_2O (3:3:4)	yes	150	5	67 ± 4
4	THF/H_2O (1:1)	yes	150	5	69 ± 3
5	THF/H_2O (4:1)	yes	150	5	72 ± 2
6	THF/H_2O (4:1)	no	150	5	74 ± 1
7	THF/H_2O (4:1)	no	150	8	86 ± 2
8	THF/traces of H_2O[e]	yes	150	5	48 ± 3
9	CH_3CN/H_2O (4:1)	yes	150	5	53 ± 2
10	EtOH/H_2O (4:1)	yes	150	5	33 ± 5
11	DMF	yes	80	5	71 ± 5
12	DMF	yes	120	5	68 ± 4

[a] A total of 5 mg of the sulfinate salt **6**. [b] A total of 500 μL. [c] A total of 2 mg. [d] Crude radiochemical yield calculated from the amount of radioactivity of $^{11}CH_3I$ and the radioactivity of the crude product obtained after the evaporation of the volatile compounds and before HPLC purification (decay corrected to EOB, mean values of three to five runs). Radiochemical purities higher than 95% determined by radioTLC. [e] A total of 0.06 mL of H_2O in 0.5 mL of THF.

TABLE 2. Radiosynthesis of ^{11}C-Sulfones [^{11}C]10−15[a,b] According to Scheme 1

entry	sulfinate	^{11}C-alkyl iodide	^{11}C-sulfone	yield (%)	
				crude[c]	isolated[d]
1	**6**	$^{11}CH_3I$	[^{11}C]**10**	86 ± 2	76 ± 3
2	**6**	$Ph^{11}CH_2I$	[^{11}C]**11**	75 ± 1	62 ± 3
3	**7**	$^{11}CH_3I$	[^{11}C]**12**	73 ± 2	65 ± 2
4	**7**	$CH_3{}^{11}CH_2I$	[^{11}C]**13**	70 ± 3	59 ± 4
5	**8**	$^{11}CH_3I$	[^{11}C]**14**	77 ± 1	62 ± 3
6	**9**	$^{11}CH_3I$	[^{11}C]**15**	73 ± 2	66 ± 5

[a] A total of 5 mg of the sulfinate salts **6**−**9**. [b] In THF/H_2O (4:1) at 150 °C for 8 min. [c] Radiochemical yield calculated from the amount of radioactivity of the ^{11}C-alkyl iodides and the radioactivity of the crude product obtained after the evaporation of the volatile compounds and before HPLC purification (decay corrected to EOB, mean values of 3−5 runs). Radiochemical purities higher than 95% determined by radioTLC. [d] Radiochemical yield (decay corrected to EOB, mean values of 3−5 runs) calculated from the amount of radioactivity of the ^{11}C-alkyl iodides and the radioactivity of the ^{11}C-sulfone purified by HPLC (radiochemical purities higher than 99% determined by radioTLC).

(13) Davis, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, *19*, 5171−5174.

(14) Sulfinates are ambident nucleophiles. With soft electrophiles such as alkyl halides the alkylation occurs predominantly at sulfur to give sulfones: (a) Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* **2005**, *7*, 1223−1225. (b) Srivastava, P. K.; Field, L. *Phosphorus Sulfur Relat. Elem.* **1985**, *25*, 161−165. (c) Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.-G. *J. Chem. Res.* **2004**, 267−269.

(15) (a) Crandall, J. K.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327−1329. (b) Deguin, B.; Roulet, J.-M.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 6197−6200.

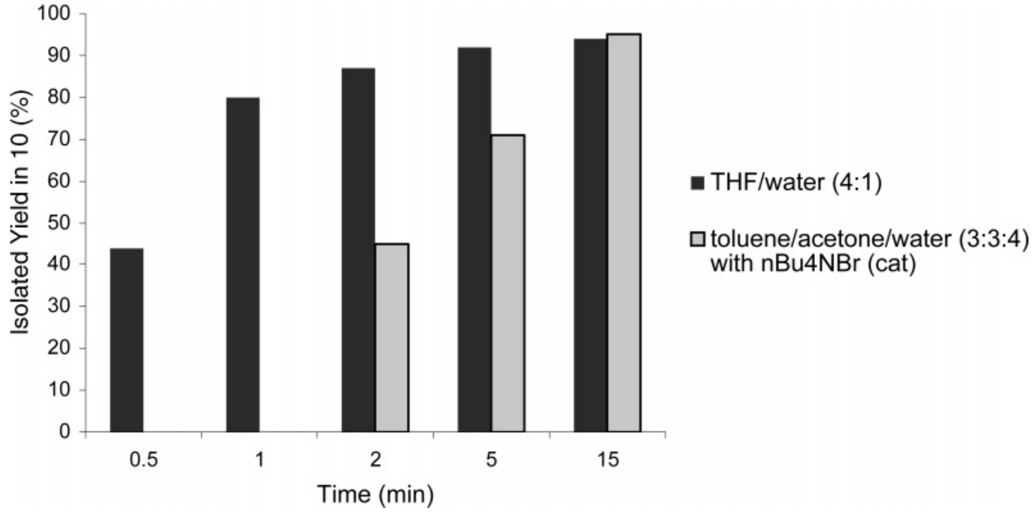


FIGURE 2. Reaction of lithium sulfinate **6** with unlabeled methyl iodide in a closed reactor at 150 °C: comparison of the solvent effect.

n-Bu_4NBr was examined under initial and newly established conditions. In both cases, the phase-transfer agent was found to be useless (compare entries 2 and 6 with entries 1 and 5, respectively). In summary, from a practical point of view, the retained conditions were heating the sulfinate salt and the alkyl halide at 150 °C in THF/H_2O (4:1). Under these conditions, the radiochemical yield in [^{11}C]**10** reached 86% after 8 min of reaction (entry 7).

The synthesis was extended to a range of aromatic sulfones [^{11}C]**11**−**15** (Table 2). [1-^{11}C]Ethyl iodide[16] and [1-^{11}C]benzyl iodide[17] were obtained according to described procedures that consisted of trapping [^{11}C]CO_2 with a Grignard reagent to generate the corresponding carboxylate, reduction into the alcoholate with LAH, and then a reaction with HI. ^{11}C alkylations of sulfinates **6**−**9** always led to sulfones [^{11}C]**10**−**15** in radiochemical yields higher than 70% and eventually were contaminated by the unreacted [^{11}C]alkyl iodides that were not removed by evaporation. The sole nonradioactive compounds present in the crude reaction mixture were the starting sulfinates **6**−**9** (taken in excess compared to the [^{11}C]alkyl iodide). The removal of the salts was efficiently carried out before or after the evaporation of the volatile compounds. In the former case, the reaction mixture was passed through a Sep-PaK C-18, followed by elution with petroleum ether/ethyl acetate (7:3). In the latter case, the radioactive residue dissolved in petroleum ether/ethyl acetate (7:3) was directly filtrated onto $MgSO_4$. Subsequent purification by HPLC was very easy. Sulfones [^{11}C]**10**−**15** were obtained according to an online procedure, including HPLC purification in 55−76% radiochemical yields [decay corrected to EOB and calculated from ^{11}C-alkyl iodides] and in a 30−40 min total time synthesis. The analogous sulfinic esters [^{11}C]**16**−**21**, which could be a result of an *O* alkylation, were never detected. Characterization of radioactive products carried out by TLC and HPLC involved the synthesis of authentic samples for coelution with the radioactive compounds. Sulfones **10**−**15** were prepared by lithium sulfinate alkylation, and sulfinic esters **16**−**21** were prepared according to literature methods (see Supporting Information).

To confirm the accelerating effect found in the THF/H_2O (4:1) medium as compared to that of the phase-transfer conditions with toluene/acetone/H_2O (3:3:4), the conversion of sulfinate **6** into sulfone **10**, by heating with unlabeled methyl iodide (1.2 equiv) at 150 °C in a closed reactor, was evaluated at different times (Figure 2). Total conversions were reached after 15 min with both solvent sytems. In contrast, after 2 min, the yield of **10** obtained for the two-solvent system reached 87%, whereas it did not exceed 45% in the three-solvent mixture.

In conclusion, we have described an unprecedented access to aromatic sulfones labeled with ^{11}C. It involves the conversion of thiophenols into lithium sulfinates by an oxidation methodology, followed by a rapid *S* alkylation in THF/H_2O (4:1) with ^{11}C-alkyl iodides. This sequence was found as an attractive alternative to the conventional route to ^{11}C-sulfones (i.e., formation of a ^{11}C-thioether with subsequent sulfur oxidation), according to the sulfinate access under mild conditions, the efficiency of the radioactive alkylation step, and the easiness of the final purification.

Experimental Section

General Procedure for the Synthesis of Lithium Sulfinates 6−9. To a cooled (−78 °C) solution of the aromatic thiol (1 mmol) in THF (1.5 mL) was added dropwise MeLi (0.69 mL of a 1.6 N solution in Et_2O, 1.1 mmol). After stirring the solution at −78 °C for 15 min, a solution of *N*-sulfonyloxaziridine **5** (548 mg, 2.1 mmol) in THF (1.2 mL) was added dropwise very slowly (exothermic reaction). The reaction mixture was warmed to −40 °C (15 min), and around this temperature, the mixture became cloudy. The solution was then stirred at −10 °C (ice/NaCl bath) for 15 min, and AcOEt (30 mL) was added. The sulfinate salt was extracted with *distilled* H_2O (3 × 3 mL). The combined aqueous extracts were washed with AcOEt (4 × 30 mL), concentrated, and dried overnight under high vacuum to provide quantitatively the pure sulfinate salt.[18] Further purification was not required.

General Procedure for the Synthesis of ^{11}C-Alkylaryl Sulfones [^{11}C]10−15. ^{11}C-Alkyl iodide was trapped at 0 °C in a THF/H_2O

(16) (a) Kawamura, K.; Elsinga, P. H.; Kobayashi, T.; Ishii, S.-I.; Wang, W.-F.; Matsuno, K.; Vaalburg, W.; Ishiwata, K. *Nucl. Med. Biol.* **2003**, *30*, 273−284. (b) Slegers, G.; Sambre, J.; Goethals, P.; Vandecasteele, C.; Van Haver, D. *Appl. Radiat. Isot.* **1986**, *37*, 279−292.

(17) (a) Guillouet, S.; Barre, L.; Gourand, F.; Lasne, M.-C.; Rault, S. *J. Labelled Compd. Radiopharm.* **1996**, *38*, 367−371. (b) Fasth, K.-J.; Hoernfeldt, K.; Långström, B. *Acta Chem. Scand.* **1995**, *49*, 301−304. (c) Musachio, J. L.; Mathews, W. B.; Ravet, H. T.; Carroll, F. I.; Dannals, R. F. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 49−57. (d) Fasth, K. J.; Långström, B. *Acta Chem. Scand.* **1990**, *44*, 720−725. (e) Dannals, R. F.; Långström, B.; Ravert, H. T.; Wilson, A. A.; Wagner, H. N., Jr. *Appl. Radiat. Isot.* **1988**, *39*, 291−295.

(4:1) solution (total volume, 500 μL) containing the sulfinates **6**−**9** (5 mg). The reactor was closed, and the reaction mixture was heated to 150 °C for 8 min. After cooling at 0 °C for 1 min, the radioactivity was counted and the volatile compounds were evaporated under a flow of N_2. The residue was diluted in a petroleum ether/ethyl acetate (7:3) mixture (500 μL), and the radioactivity was measured again. The crude mixture was filtrated through $MgSO_4$, analyzed by radioTLC, and injected onto a semipreparative LC. The collected fraction was analyzed by radioTLC, and the radioactivity was counted to assess identity and radiochemical purity. As a result of the low amounts of radioactivity used, no measurement of specific radioactivity was attempted.

(18) The weight of the sulfinate salt was slightly superior because of remaining water.

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Supporting Information Available: General methods of Experimental Section and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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