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Improved synthesis of [^{11}C]SA4503, [^{11}C]MPDX and [^{11}C]TMSX by use of [^{11}C]methyl triflate

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Recently we have clinically used three new radioligands, [^{11}C]SA4503, [^{11}C]MPDX, and [^{11}C]TMSX, for mapping sigma$_1$, adenosine A_1, and adenosine A_{2A} receptors, respectively, in the human brain by positron emission tomography. These radioligands are synthesized by methylation of the respective demethyl precursor with [^{11}C]methyl iodide. Here we demonstrate the improved syntheses of these compounds by use of [^{11}C]methyl triflate, a highly reactive alternative to [^{11}C]methyl iodide.

Key words: carbon-11, methyl triflate, SA4503, MPDX, TMSX

INTRODUCTION

SYNTHESES of several ^{11}C-methylated compounds used in positron emission tomography (PET) have been improved by substituting [^{11}C]methyl triflate[1] ([^{11}C]CH_3OTf) for [^{11}C]methyl iodide ([^{11}C]CH_3I). Recently, the use of [^{11}C]CH_3OTf has been extended to the ^{11}C-methylation of amines, thiols, phenols, amides and carboxylic acids, and offered higher radiochemical yields that are carried out with smaller amounts of precursor for shorter reaction times at lower reaction temperature.[2–10]

In the present study, we investigated the use of [^{11}C]CH_3OTf to improve syntheses of three PET radioligands (Fig. 1) that were recently applied to clinical studies in our laboratory: for mapping sigma$_1$, adenosine A_1, and adenosine A_{2A} receptors in the brain, [^{11}C]SA4503 ([4-*O*-methyl-^{11}C]1-{3,4-dimethoxyphenethyl}-4-{3-phenylpropyl}piperazine),[11,12] [^{11}C]MPDX ([1-*N*-methyl-^{11}C]8-dicyclopropylmethyl-1-methyl-3-propylxanthine),[13,14] and [^{11}C]TMSX ([7-*N*-methyl-^{11}C]-(*E*)-8-{3,4,5-trimethoxystyryl}-1,3,7-trimethylxanthine)[15,16] were used respectively. These radioligands were synthesized previously by methylation of the respective demethyl precursor with [^{11}C]CH_3I.[11–16]

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MATERIALS AND METHODS

1-(3,4-Dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine (SA4503) was prepared by Santen Pharmaceutical Co., Ltd. (Osaka, Japan).[17] 4-*O*-Demethyl SA4503, 8-dicyclopropylmethyl-1-methyl-3-propylxanthine (MPDX), 8-dicyclopropylmethyl-3-propylxanthine (1-*N*-demethyl MPDX), (*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine (TMSX), and (*E*)-1,3-dimethyl-8-(3,4,5-trimethoxystyryl)xanthine (7-*N*-demethyl TMSX) were synthesized in our laboratory.[18–20] All other chemicals were obtained from commercial sources.

Preparation of [^{11}C]CH_3OTf

[^{11}C]CO_2 was produced by CYPRIS 370 cyclotron (Sumitomo Heavy Industries Ltd., Tokyo, Japan). [^{11}C]CH_3I was prepared from [^{11}C]CO_2 via [^{11}C]CH_3OH with an automated system as previously described.[21] [^{11}C]CH_3OTf was prepared by passing [^{11}C]CH_3I through a glass column [3.6 mm inner diameter (i.d.)] containing 200 to 300 mg silver triflate (Sigma-Aldrich Chem, Milwaukee, WI, USA) at 200°C with a N_2 flow of 30 m*l*/min.

Radiosynthesis of [^{11}C]SA4503, [^{11}C]MPDX, and [^{11}C]TMSX

[^{11}C]CH_3OTf was trapped in 0.25 m*l* solution of *N*,*N*-

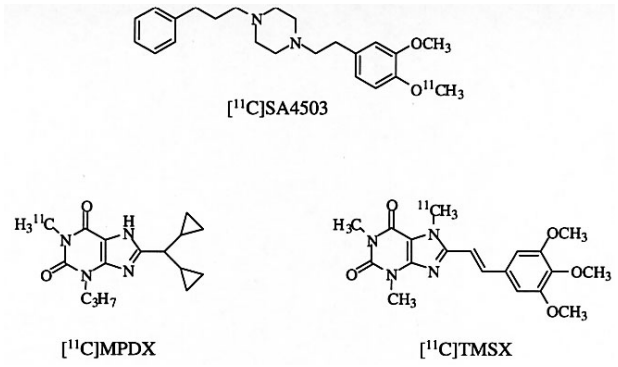

Fig. 1 Chemical structure of [^{11}C]SA4503, [^{11}C]MPDX, and [^{11}C]TMSX.

dimethylformamide (DMF) or acetone containing 0.25 mg precursor (4-*O*-demethyl SA4503, 1-*N*-demethyl MPDX or 7-*N*-demethyl TMSX) and base (5 to 10 μl 0.1 to 5 M NaOH, 1 mg NaH or 10 mg Cs_2CO_3) at a room temperature or at −17 to −12°C by blowing compressed air through a thermal converter, and then heated for 0 to 3 min at 120°C. After adding a mixture of 0.65 m*l* 0.1 M HCl and 0.65 m*l* mobile phase used for preparative high-performance liquid chromatography (HPLC), the reaction mixture was applied to HPLC separation. The HPLC conditions used were YMC-Pack ODS-A columns [10 mm i.d. × 250 mm length (column A) and 20 mm i.d. × 250 mm length (column B), YMC Co. Ltd., Kyoto, Japan]; a mobile phase: a mixture of acetonitrile and 50 mM acetic acid/ammonium acetate (1/1) [35/65 for [^{11}C]SA4503, 45/55 for [^{11}C]MPDX and 50/50 for [^{11}C]TMSX, v/v]; a flow rate of 5 m*l*/min for column A and of 15 m*l*/min for column B; and a UV detector at 280 nm for [^{11}C]SA4503 or 260 nm for [^{11}C]MPDX and [^{11}C]TMSX. The retention times were 6.5 min and 8.5 min for 4-*O*-demethyl SA4503 and [^{11}C]SA4503, respectively (Fig. 2); 4.7 min, 7.9 min, and 8.8 min for 1-*N*-demethyl MPDX, [^{11}C]MPDX, and [7-*N*-methyl-^{11}C]8-dicyclopropylmethyl-7-methyl-3-propylxanthine ([^{11}C]7-isomer), respectively (Fig. 2); and 4.7 min and 7.2 min for 7-*N*-demethyl TMSX and [^{11}C]TMSX, respectively (Fig. 2). All procedures for the synthesis of [^{11}C]TMSX were performed under the dim light to prevent isomerization from the (*E*)-form of [^{11}C]TMSX to (*Z*)-form.[16]

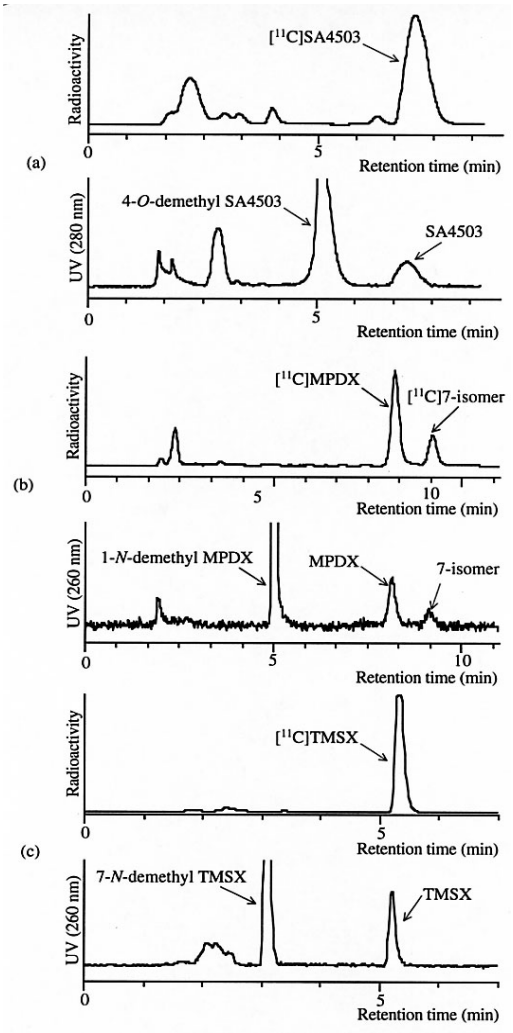

Fig. 2 HPLC separation of [^{11}C]SA4503 (a), [^{11}C]MPDX (b), and [^{11}C]TMSX (c). Column: YMC-Pack ODS-A [(a) and (c): 10 mm i.d. × 250 mm length, and (b): 20 mm i.d. × 250 mm length]; mobile phase, (a): acetonitrile/(50 mM acetic acid/ammonium acetate, 1/1) (35/65, v/v), (b): acetonitrile/water (45/55, v/v), and (c): acetonitrile/water (50/50, v/v); flow rate, (a) and (c): 5 m*l*/min and (b): 15 m*l*/min.

RESULTS AND DISCUSSION

The radiochemical yields of the three radioligands are summarized in Table 1.

Firstly ^{11}C-methylation of three demethyl precursors with [^{11}C]CH_3OTf was investigated in DMF containing aqueous NaOH, which was frequently used in the ^{11}C-methylation with [^{11}C]CH_3OTf.[4,5,9] Compared with the methylation with [^{11}C]CH_3I, the use of [^{11}C]CH_3OTf slightly improved the radiochemical yields of [^{11}C]SA4503 and [^{11}C]MPDX but not of [^{11}C]TMSX in the presence of 5 μmol NaOH/5 μl water. When trapping [^{11}C]CH_3OTf at low temperature (−17 to −12°C) followed by heating at 120°C for 1 min, the radiochemical yield of [^{11}C]SA4503 was greatly improved (56.2 ± 2.3%). For the increased radiochemical yield the heating at 120°C for 1 min was essential. On the other hand, the same procedure did not improve the radiochemical yields of [^{11}C]MPDX and [^{11}C]TMSX. The increased yield of [^{11}C]SA4503 may be partially explained by the trapping efficiency of [^{11}C]CH_3OTf in a DMF at low temperature: 86% at low temperature (−17 to −12°C) and 74% at a room temperature, however, the different effects between [^{11}C]SA4503 and the other two compounds are mainly explained by

Table 1 Radiochemical yields of [^{11}C]SA4503, [^{11}C]MPDX and [^{11}C]TMSX

	Reagent	Precursor	Solvent	Base	Trap[$]	Reaction	Radiochemical yield (%)[#]	
[^{11}C]SA4503	[^{11}C]CH_3OTf	0.25 mg	0.25 m*l* DMF	5 μmol NaOH	room	–	33.5 ± 9.3 (n = 3)	
					room	120°C, 1 min	35.6 ± 8.0 (n = 3)	
				10 μmol NaOH	room	–	22.0	
				5 μmol NaOH	cooling	–	1.5	
					cooling	120°C, 1 min	56.2 ± 2.3 (n = 3)	
				1 mg NaH	cooling	120°C, 1 min	13.0	
	[^{11}C]CH_3I	0.20 mg	0.20 m*l* DMF	1–2 mg NaH	cooling	120°C, 1 min	20–31*	
								[^{11}C]7-isomer (%)[§]
[^{11}C]MPDX	[^{11}C]CH_3OTf	0.25 mg	0.25 m*l* DMF	1 μmol NaOH	room	–	0.44	41.9
				5 μmol NaOH	room	–	34.3 ± 7.6 (n = 3)	15.4 ± 5.8 (n = 3)
				10 μmol NaOH	room	–	25.0	13.0
				25 μmol NaOH	room	–	8.9	16.9
				5 μmol NaOH	cooling	120°C, 1 min	24.2	9.6
			0.25 m*l* Acetone	10 μmol NaOH	room	–	1.1	59.5
			0.25 m*l* DMF	1 mg NaH	room	120°C, 1 min	14.8	8.6
	[^{11}C]CH_3I	1 mg	0.30 m*l* DMF	1 mg NaH	cooling	120°C, 1 min	19–30**	0.35–1.6
[^{11}C]TMSX	[^{11}C]CH_3OTf	0.25 mg	0.25 m*l* DMF	5 μmol NaOH	room	–	24.8	
				10 μmol NaOH	room	–	12.0	
				5 μmol NaOH	cooling	120°C, 1 min	23.6	
				10 mg Cs_2CO_3	room	–	55.3 ± 5.2 (n = 3)	
					room	120°C, 1 min	46.7 ± 13 (n = 3)	
					room	120°C, 3 min	52.1	
					cooling	120°C, 1 min	25.8	
	[^{11}C]CH^{3}I	0.50 mg	0.25 m*l* DMF	5–10 mg Cs_2CO_3	cooling	120°C, 3 min	25–46***	

[#] The decay corrected radiochemical yields based on [^{11}C]CH_3OTf or [^{11}C]CH_3I used.

[$] [^{11}C]$CH_3OTf$ or [^{11}C]CH_3I was trapped in the solvent at room temperature or at −17 to −12°C by blowing compressed air through a thermal converter.

[§] Radiochemical yields of [7-*N*-methyl-^{11}C]8-dicyclopropylmethyl-7-methyl-3-propylxanthine.

* Ref. 11, ** Ref. 13, *** Ref. 15

different reactivity of each demethyl precursor with [^{11}C]CH_3OTf. The N-H bond in both 1-*N*-demethyl-MPDX and 7-*N*-demethyl TMSX has weaker than the phenolic O-H bond in 4-*O*-demethyl SA4503. Therefore, methylation of 1-*N*-demethyl-MPDX and 7-*N*-demethyl TMSX with [^{11}C]CH_3OTf may occur faster at lower temperature than that of 4-*O*-demethyl SA4503. When the amounts of NaOH over 5 μmol were increased, the radiochemical yields of the three compounds were reduced. A large excess of NaOH and/or the amounts of water included in the solution might affect the rate of nucleophilic substitution.

Secondly we investigated the effects of substitution of [^{11}C]CH_3OTf for [^{11}C]CH_3I in the original reaction conditions. In the presence of NaH (1 to 2 mg, 42 to 83 μmol) as a base in DMF, the use of [^{11}C]CH_3OTf resulted in slightly lower radiochemical yields of [^{11}C]SA4503 and [^{11}C]MPDX than that of [^{11}C]CH_3I. The anhydrous condition may not be suitable for the methylation with [^{11}C]CH_3OTf, although it was essential for the methylation of [^{11}C]SA4503 and [^{11}C]MPDX with [^{11}C]CH_3I.[11,13] On the other hand, in the synthesis of [^{11}C]TMSX in a DMF containing Cs_2CO_3 the use of [^{11}C]CH_3OTf greatly improved radiochemical yield compared with the use of [^{11}C]CH_3I: 55.3 ± 5.2%, vs. 25 to 46%.[15] Heating the mixture was not necessary.

Thirdly it is reported that the radiochemical yield of [^{11}C]WAY-100635 in acetone as a solvent of precursor was higher than that in DMF.[10] Therefore, we investigated the effect of acetone as solvent on the radiosynthesis of only [^{11}C]MPDX, because 4-*O*-demethyl SA4503 and 7-*N*-demethyl TMSX were scarcely dissolved in acetone. In acetone the radiochemical yield of [^{11}C]MPDX became negligible (1.1%), whereas that of [^{11}C]7-isomer was very high (59.5%). The summed radiochemical yield of [^{11}C]MPDX and [^{11}C]7-isomer in acetone was the highest among all conditions investigated. Polarity of the solvent greatly affected to stereoselectivity of nucleophilic reaction. As for the stereoselectivity, the base used is also the other factor. The ratio of [^{11}C]MPDX ([^{11}C]1-isomer) and [^{11}C]7-isomer was differently affected by the amounts of NaOH in the range of 1 to 25 μmol in DMF. In the previous study we found that methylation with [^{11}C]CH_3I in DMF containing Cs_2CO_3 or K_2CO_3 resulted in the largest ratio of [^{11}C]7-isomer to [^{11}C]MPDX.[13] When the precursor was treated with NaH in anhydrous DMF, dehydrogation easily occurred at 1-*N*-position, but not 7-*N*-position of xanthine, which resulted in much selective synthesis of [^{11}C]MPDX by use of [^{11}C]CH_3I.[13]

Thus, the substitution of [^{11}C]CH_3OTf for [^{11}C]CH_3I

produced higher radiochemical yields of all three radioligands investigated. It is pointed out that HPLC separation of three radioligands was not improved by use of [^{11}C]CH_3OTf, because the amounts of unexpected by-products produced were not so much in each reaction with [^{11}C]CH_3OTf or [^{11}C]CH_3I. In the syntheses of [^{11}C]MPDX and [^{11}C]TMSX by using [^{11}C]CH_3OTf the amount of respective precursor (0.25 mg) used was smaller than those in the previous syntheses using [^{11}C]CH_3I, although the amounts were not optimized in the previous syntheses.[13,15] A 1 to 3 min shorter reaction time may be another advantage in the syntheses of [^{11}C]MPDX and [^{11}C]TMSX. As the other advantage of the use of [^{11}C]CH_3OTf, an anhydrous condition is not required in the syntheses of [^{11}C]SA4503 and [^{11}C]MPDX, as a compared with previous syntheses using [^{11}C]CH_3I and NaH.[11,13] In conclusion, the radiochemical yields of [^{11}C]SA4503, [^{11}C]MPDX and [^{11}C]TMSX were improved by the use of [^{11}C]CH_3OTf.

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