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Fluorescence labeling method for aryl halides with 4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenylboronic acid based on Suzuki coupling reaction

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Abstract

For the first time, fluorescence labeling methods for aryl halides with a fluorescent arylboronic acid was developed on the basis of a Suzuki coupling reaction. 4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenylboronic acid (DPA) was used as a fluorescence labeling reagent. In order to explore its analytical performance, the reaction conditions were optimized using simple bromobenzene derivatives. The reactivity was then investigated with chloro- and iodobenzene derivatives, and also bromobenzene derivatives with different position of substituents. The order of reactivity with DPA: iodobenzene > bromobenzene ≫ chlorobenzene derivatives, and *p*- > *m*- > *o*-substituted bromobenzenes. The detection limits of bromobenzene, 4-bromotoluene, and 4-bromoanisole ranged from 0.2 to 1.4 pmol/injection at a signal-to-noise ratio (S/N) of 3. The applicability of the method to biological samples was also evaluated using clofibrate as the analyte. The reaction was found not only to proceed well but also to be selective for clofibrate even in the presence of plasma components. The method allowed the sensitive detection of clofibrate in human plasma with the detection limit of 170 pmol/mL (260 fmol/injection) at a S/N = 3. The proposed method is highly selective and sensitive and thus would be useful for labeling of aryl halides that do not have other functional groups that could be labeled by currently available fluorescent labeling reagents.
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Keywords: Suzuki coupling reaction; Fluorescence labeling; Aryl halide

1. Introduction

Fluorescence labeling techniques characterized by high sensitivity and selectivity have frequently been utilized for the determination of trace levels of biologically important compounds on high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) [1]. However, most of the compounds to be analyzed are non-fluorescent or weakly fluorescent. Therefore, various fluorescence labeling reagents and methods have been developed for highly sensitive detection of bioactive compounds in biological samples [2,3]. Currently, there are many labeling reagents for a wide variety of functional groups, such as amino acids, alcohols, thiols, aldehydes, ketones, and carboxyl groups [1]. Although these reagents have been very useful for trace analysis, there remain analytes that are difficult to label. Thus new approaches to labeling reagents and methods are required. Aryl halides are such an example; a fluorescence labeling reagent and method for the analysis of aryl halides have not been reported to date although many compounds involving aryl halides in their structures have been used as pharmaceuticals and agricultural chemicals.

Recently, we reported several arylboronic acid derivatives as enhancers for the luminol-hydrogen peroxide–horseradish peroxidase chemiluminescence reaction [4]. Among these arylboronic acids, we have found that 4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenylboronic acid (DPA, a lophine

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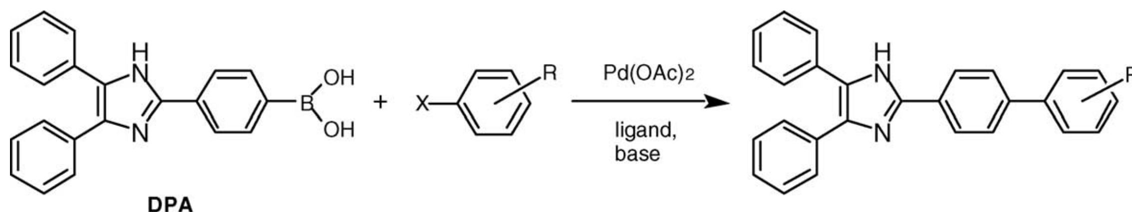

Fig. 1. Suzuki coupling reaction with DPA.

derivative) shows intense fluorescence. Lophine (2,4,5-triphenylimidazole), itself, is an efficient fluorescencer [5] and can chemiluminesce [6], and their derivatives possessing –COCl and –$CONHNH_2$ have been successfully applied to the labeling and highly sensitive detection of biologically important amines [7,8] and phenols [9], and carboxylic acids [10]. DPA appears to be a promising candidate for labeling of aryl halides by the use of Suzuki coupling reaction due to the fact that lophine derivatives are superior to some other commercially available labeling reagents on the fluorescence quantum yield and stability (Fig. 1) [7]. Suzuki coupling reaction is a palladium-catalyzed cross-coupling reaction of aryl halides with aryl boronic acids, which is one of the most versatile and powerful method for carbon–carbon bond formation [11–13]. In recent years, due to the mild reaction conditions [14–16], the tolerance of a broad range of functional groups [16,17], the use of available reagents [17], and the use of aqueous organic solvents [16,18,19], Suzuki coupling reaction has emerged in the field of organic synthesis and a considerable number of studies have been conducted on palladium source, ligand, solvent, temperature, and etc [17,20–22]. However, in these studies, the major focus was on the reaction yield for organic synthesis in simple reaction media and no attention has been given to its application in the field of analytical chemistry; the reactivities in the presence of complex organic and inorganic compounds in biological samples have not yet been elucidated.

In this paper we describe an analytical application of the Suzuki coupling reaction for the first time with the aim of labeling aryl halides with fluorescent arylboronic acid. For biomedical analysis, a highly selective and sensitive method is generally required. In view of these requirements, Suzuki coupling reaction is expected to have the following advantages: superior selectivity being derived from a small number of interfering compounds existing in biological samples, and altered sensitivity brought by the elimination of a halogen atom, which sometimes leads to unexpected quenching of fluorescence, from an analyte molecule during the coupling reaction. In this work, we first evaluated the scope and limitations of analytical performance of the proposed method by the use of a series of simple aryl halides (i.e., halogenobenzene derivatives) as analytes. Furthermore, applicability of the method with regard to the reactivity and selectivity was confirmed through the fluorescence labeling and HPLC determination of clofibrate (antihyperlipidemic drug) in a biological sample.

2. Experimental

2.1. Materials

DPA was synthesized in our laboratory according to the previous method [4]. Palladium(II) acetate, potassium fluoride (KF), *N*,*N*-dimethylformamide (DMF) and halogenobenzene derivatives obtained from Wako (Tokyo, Japan) were used as received. 2-(Dicyclohexylphosphino)biphenyl (DCPB) and 2-(di-*tert*-butylphosphino)biphenyl (DtPB) were purchased from Strem (Newburyport, MA, USA). Acetonitrile and dioxane of HPLC grade (Wako) were employed. Clofibrate was purchased from Sigma (St. Louis, MO, USA). Water was distilled and passed through a Pure Line WL21P system (Yamato, Tokyo, Japan). All other chemicals were the highest purity and quality available.

2.2. Apparatus

The HPLC system consisted of a Shimadzu LC-6A pump (Kyoto, Japan), a Rheodyne 7125 injector with a 20-μL loop, a Shimadzu RF-550 fluorescence detector, and a Rikadenki R-061 recorder (Tokyo, Japan). All the analytes were separated isocratically with a mobile phase at a flow-rate of 1.0 mL/min at ambient temperature and fluorescence intensity was monitored at 410 nm with an excitation of 320 nm. The HPLC separation of DPA derivatives of halogenobenzenes was performed on a Wakosil PAHs analytical column (250 mm × 4.6 mm I.D., 5 μm, Wako) with a mobile phase consisted of 4 mM phosphate buffer (pH 5.5) and acetonitrile (45:55, v/v). A DPA derivative of clofibrate was separated on a Capcell Pak C18 (250 mm × 4.6 mm I.D., 5 μm, Shiseido, Tokyo, Japan) with a mixture of water and acetonitrile (35:65, v/v) as mobile phase.

Uncorrected fluorescence spectra and intensities were measured with a 650-10S fluorescence spectrophotometer (Hitachi, Tokyo, Japan) using a 10-mm quartz cell with 10-nm bandwidth for both the excitation and emission monochromators.

2.3. Preparation of authentic DPA derivatives of halogenobenzenes

Iodobenzene (79.5 mg, 0.39 mmol), 4-iodotoluene (85.5 mg, 0.39 mmol) or 4-iodoanisol (91.5 mg, 0.39 mmol)

and DPA (150 mg, 0.39 mmol) were dissolved in DMF (8 mL). To this were added palladium(II) acetate (10.1 mg, 44.8 μmol), DCPB (8.0 mg, 5.8 μmol), and KF (0.087 mg, 1.50 μmol), and then the solution was purged with N_2 (5.0 mL/min) for 5 min. After heating at 100 °C for 100 min, the solution was filtered and concentrated to 2–3 mL by a rotary evaporator. The solution was then poured into water (ca. 20 mL) and allowed to stand at 4 °C overnight. The resulting precipitate was filtered, and a portion of the crude product was purified by chromatography on silica gel using CH_2Cl_2-2-PrOH (95:5) to give DPA derivatives of iodobenzene (DPA-benzene, m.p. 269–276 °C; EI-MS *m/z* 372; anal calcd. for $C_{27}H_{20}N_2$ ×3.8 H_2O: C, 73.55; H, 6.31; N, 6.35. Found: C, 73.34; H, 5.70; N, 5.95.), 4-iodotoluene (DPA-toluene, m.p. 248–255 °C; EI-MS *m/z* 386; anal calcd. for $C_{28}H_{22}N_2$ ×2.6 H_2O: C, 77.61; H, 6.33; N, 6.46. Found: C, 77.29; H, 5.80; N, 6.31.), and 4-iodoanisole (DPA-anisole, m.p. 198–206 °C; EI-MS *m/z* 402; anal calcd. for $C_{28}H_{22}N_2O$ ×1.3 H_2O: C, 78.96; H, 5.82; N, 6.58. Found: C, 78.90; H, 5.28; N, 7.10.) as pale yellow powders.

2.4. Fluorescence labeling procedure for halogenobenzenes

Halogenobenzenes as analytes, DPA, palladium(II) acetate, and DCPB were individually prepared by dissolving them in dioxane. KF was suspended in dioxane.

A test solution (100 μL) containing halogenobenzenes was mixed with 8.0 mM DPA solution (250 μL) in a screw-capped reaction vial (amber-colored glass, 3.5 mL; Pierce, Rockford, IL, USA). To this were successively added 50 μL each of 3.0 mM palladium(II) acetate solution, 1.5 mM DCPB solution, and suspension of 0.1 mM KF. After purging with N_2 (5.0 mL/min) for 5 s, the reaction mixture was heated at 100 °C for 45 min. After cooling, a 20-μL portion of the solution was injected onto the HPLC system.

2.5. Assay procedure for clofibrate in human plasma

A fifty-μL portion of plasma (spiked with an appropriate amount of clofibrate) was transferred into a glass stoppered centrifuge tube, and to this were added 200 μL of 20 mM phosphate buffer (pH 7.4) and 1.0 mL of ethyl acetate. The mixture was vortex-mixed for 1.5 min, sonicated for 1.0 min, and then centrifuged at 1400 × *g* for 15 min at 4 °C. The organic layer (0.85 mL) was collected in a screw-capped reaction vial and evaporated under a stream of N_2. The residue was reconstructed with 125 μL of DMF and then subjected to the following procedure for the fluorescence labeling.

For the labeling of clofibrate, DMF was employed to prepare each solution of DPA, palladium(II) acetate, and DCPB. Potassium hydroxide (KOH) as catalyst was prepared in water. To the DMF solution including clofibrate (125 μL), DMF solution of 12.5 mM DPA (100 μL), 3.0 mM palladium(II) acetate (50 μL), 1.5 mM DCPB (50 μL), and aqueous solution of 35 mM KOH (175 μL) were successively added and mixed well. After purging with N_2 (5.0 mL/min) for 5 s, the reaction mixture was heated at 100 °C for 45 min. After the neutralization with 120 mM hydrochloric acid (50 μL), a 20-μL portion of the resultant reaction mixture after passing through a membrane filter (0.45 μm, HLC-DISK 3, Kanto, Tokyo, Japan) was injected onto the HPLC system.

3. Results and discussion

3.1. Fluorescence properties of DPA derivatives

Fluorescence spectra of authentic DPA derivatives of iodobenzenes were measured in CH_3CN–water (1:1, v/v). The excitation maxima of the DPA derivatives showed slight red-shifts compared with that of DPA (Table 1). Relative fluorescence intensities (RFI) of the DPA derivatives were larger than that of DPA, and the largest RFI was obtained with DPA–anisole.

3.2. Optimization of fluorescence labeling conditions

With regard to the relative reactivities of aryl chloride, bromide, and iodide with arylboronic acids in Suzuki coupling reaction, the general order of reactivity is reported to be as follows: –I > –Br ≫ –Cl [14]. In this study, the labeling reaction was optimized using a standard mixture of simple bromobenzene derivatives (i.e., bromobenzene, 4-bromotoluene and 4-bromoanisole). Dioxane, which is frequently used for Suzuki coupling reaction, was tentatively chosen as a solvent for the reaction. DPA concentration was investigated over the range 2–10 mM. The maximum reaction yield was obtained at concentration of 8 mM (Fig. 2A). As a catalyst system for Suzuki coupling reaction, we herein selected the combination of palladium(II) acetate, DCPB and KF on the basis the study by Wolfe et al. [17]. The peak heights obtained with DPA derivatives increased with an increase in palladium(II) acetate concentration, and reached a maximum and remained constant in the range of 3–5 mM; 3 mM was chosen. As shown in Fig. 2B, the addition of DCPB slightly improved the reactivity and 1.5 mM was employed for further experiments. KF concentration was varied over the range of 0–0.2 mM, and the maximum and constant peak height was observed at concentration of >0.05 mM. Reactions were performed at various temperature (25, 60, 80, 100, and 120 °C) and reaction times (15, 30, 45, 60, and 75 min.); the maximum

Table 1
Fluorescence excitation and emission wavelengths and relative fluorescence intensities of DPA and authentic DPA-derivatives

Compound	λ_{ex}	λ_{em}	RFI[a]
DPA	320	410	100
DPA–benzene	330	420	140
DPA–toluene	330	410	140
DPA–anisole	330	410	280

[a] RFI: relative fluorescence intensity.

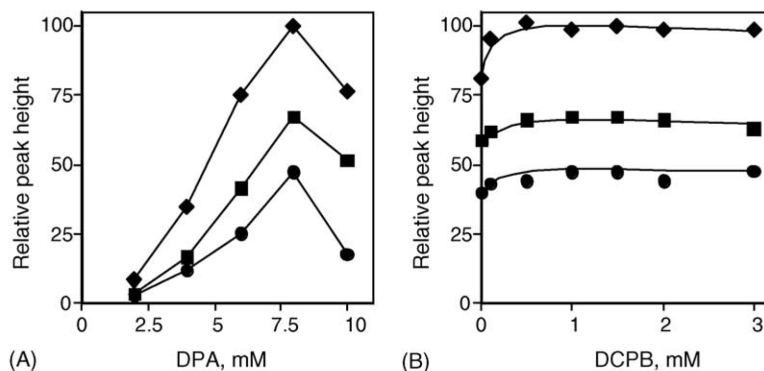

Fig. 2. Effects of (A) DPA and (B) DCPB concentrations on the peak heights. Labeling conditions: 0.09 mM KF was used. For the other experimental conditions, see text. Compounds: ♦, bromobenzene; ●, 4-bromotoluene; ■, 4-bromoanisole. Sample concentration: 10 pmol/injection for all compounds.

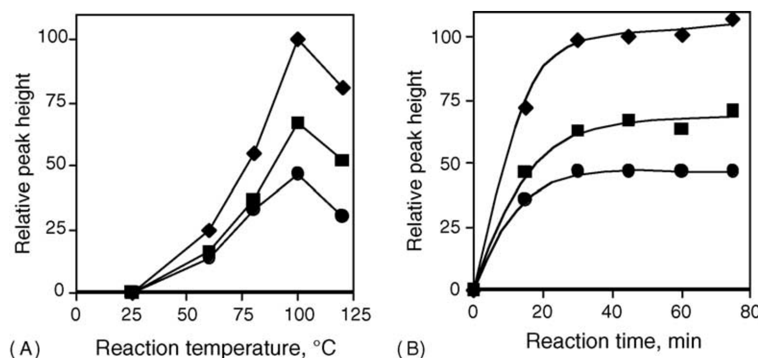

Fig. 3. Effects of (A) reaction temperature and (B) time on the peak heights. Experimental conditions, see text. Compounds: ♦, bromobenzene; ●, 4-bromotoluene; ■, 4-bromoanisole. Sample concentration: 10 pmol/injection for all compounds.

peak height could be obtained at 100 °C for 45 min as shown in Fig. 3.

3.3. Validation of the method

Fig. 4 illustrates the chromatograms of a reagent blank and a standard mixture of bromobenzenes obtained after the labeling procedure. The separation of DPA derivatives of bromobenzenes was achieved in 40 min by an isocratic elution. The retention times for the DPA derivatives in the reaction mixture were confirmed to be identical to those of corresponding authentic DPA derivatives (Fig. 4C).

Calibration curves were prepared with a standard mixture of bromobenzenes according to the labeling procedure and good linearities were observed between the fluorescence intensity as peak height and concentration of bromobenzenes up to 100 pmol/injection (Table 2). The detection limits of standard samples ranged from 0.2 to 1.4 pmol/injection at a signal-to-noise ratio (S/N) of 3. The reaction yields for bromobenzenes were determined by comparing the peak heights with authentic DPA derivatives: 45% for bromobenzene, 28% for bromotoluene and 20% for bromoanisole. On the synthetic studies concerning the reactivity of bromobenzenes with phenylboronic acid or its derivatives, the reaction yields were inconsistent depending on the conditions (i.e., solvents, palladium sources and phosphine ligands) [14,15]. Therefore, expanding study to involve the optimum combination of reagents will be effective to obtain higher reaction yields for bromobenzenes.

The repeatability of the proposed method was examined at the 40 pmol/injection levels for bromobenzenes. The relative standard deviations (RSD) for within-day ($n = 5$) and between-day ($n = 4$) runs were less than 6.1 and 7.2%, respectively, for all the analytes.

Table 2
Calibration curves, detection limits and reaction yields of the proposed method

Compound	Range (pmol/injection)	Equation[a]	r	Detection limit[b] (pmol/injection)	Reaction yield (%)
Bromobenzene	3–100	$y = 0.049x + 0.059$	0.996	1.4	45
4-Bromotoluene	3–100	$y = 0.023x - 0.021$	0.994	1.4	28
4-Bromoanisole	3–100	$y = 0.033x + 0.003$	0.997	0.2	20

[a] y, Peak height (cm); x, concentration (pmol/injection).
[b] S/N = 30.

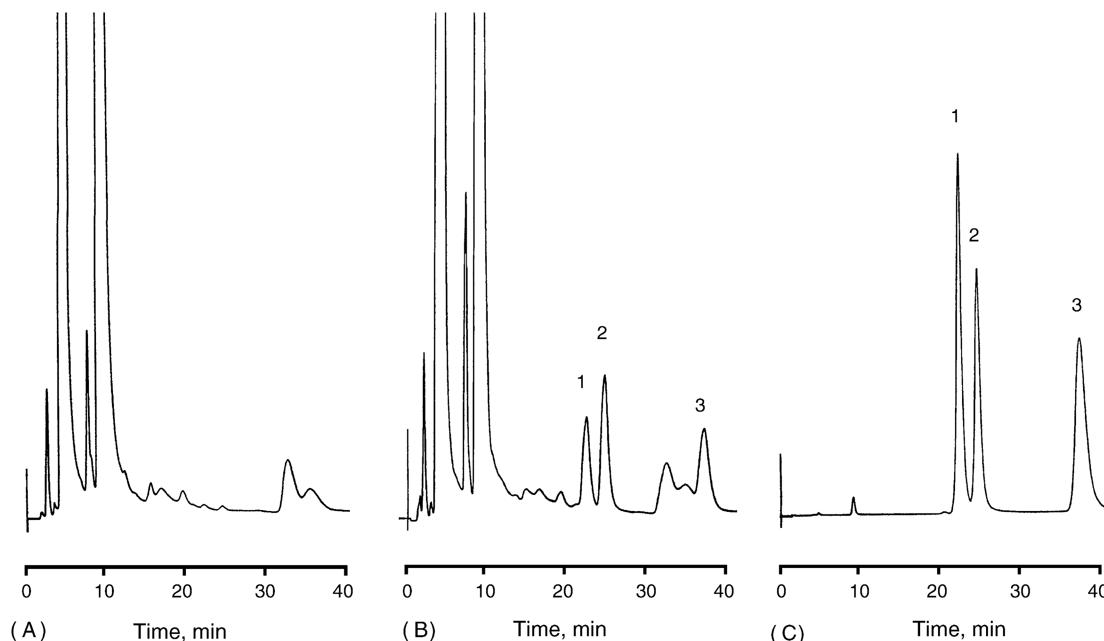

Fig. 4. Chromatograms of (A) reagent blank, (B) reaction mixture and (C) authentic DPA derivatives. Experimental conditions, see text. Peaks: 1, DPA derivative of 4-bromoanisole; 2, DPA derivative of bromobenzene; 3, DPA derivative of 4-bromotoluene. Sample concentration: 80 pmol/injection for all compounds.

DPA derivatives in the reaction mixture were fairly stable when stored in the screw-capped amber vial at 4 °C: 87–91% of initial peak heights remained after 5 weeks of storage.

3.4. Evaluation of reactivity of the proposed method

In order to confirm the reactivity of halogenobenzenes with DPA, the proposed method was applied to the labeling of corresponding iodobenzenes and chlorobenzenes. Fig. 5 represents results of the comparison. The order of increasing reactivity was iodobenzenes > bromobenzenes ≫ chlorobenzenes, which agreed well with the reported order of the reactivity [14].

The influence of different substituent positions was also examined on bromotoluene and bromoanisole. As shown in Fig. 6, *p*-substituted bromobenzenes indicated the highest reactivity. The reason that *o*-substituted bromobenzenes provided the lowest reactivity might be attributed to the steric hindrance during the transmetalation to palladium(II) halide [11].

In the above study, we presented the results on the reactivity of halogenobenzenes possessing electron-donating substituents. Although the labeling of halogenobenzenes with electron-withdrawing substituents such as carboxylic acid and aldehyde has also attempted, there was no conclusive proof that these compounds reacted with DPA to give fluorescent derivatives under the conditions examined for both the synthetic and HPLC analytical studies. Suzuki coupling of both electron-rich and -poor aryl bromides and chlorides were reported to proceed well with a catalyst composed of palladium(II) acetate/2-(di-*t*-butylphosphino)biphenyl (DtPB)/KF under non-aqueous conditions [17]. We also tested DtPB instead of DCPB, but the results were not improved. Although the difference of the reactivity remains as

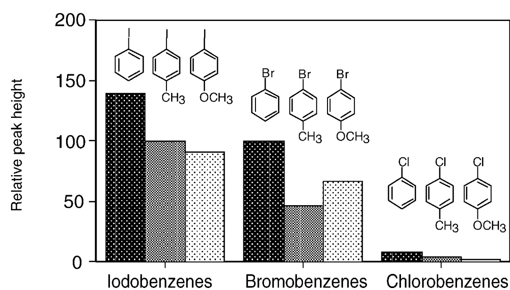

Fig. 5. Reactivity of iodo-, bromo-, and chlorobenzenes with DPA. Experimental conditions, see text. Sample concentration: 40 pmol/injection for all compounds.

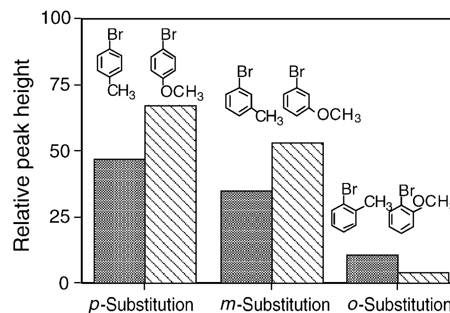

Fig. 6. Reactivity of *o*-, *m*-, and *p*-substituted bromobenzenes with DPA. Experimental conditions, see text. Sample concentration: 50 pmol/injection for all compounds.

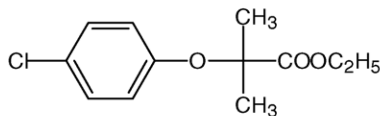

Fig. 7. Structure of clofibrate.

a matter to be elucidated, the correct combination of solvent, base and ligand is extremely important for Suzuki coupling reaction [17], and thus further optimization will be required on the labeling of aryl halides with electron-withdrawing substituents.

3.5. HPLC-fluorescence determination of clofibrate in human plasma

As mentioned above, it was found that the labeling of halogenobenzenes with DPA proceeded stoichiometrically to give fluorescent derivatives. We next evaluated the applicability of the proposed method to a real sample with biological matrix. As an analyte, clofibrate (a well known antihyperlipidemic drug, Fig. 7) was selected for the reason that it is not fluorescent and does not have any effective functional group to be labeled by available methods, and thus has been measured generally by UV absorption [23]. Before the determination of clofibrate in human plasma, labeling condition was further optimized to alternate the reactivity of a chlorobenzene moiety of clofibrate with DPA.

The influence of organic solvent on the reactivity was examined using dioxane, DMF, tetrahydrofurane, acetonitrile, acetone, and dimethylsulfoxide. Among the solvent tested, only dioxane and DMF gave the significant fluorescent peaks on HPLC; DMF showing 10 times higher peak than dioxane was used in the present study. Because Suzuki coupling reaction is known to proceed in the presence of water, its effect on the reactivity was investigated in the range of water content from 0 to 50% in the reaction mixture; the peak height reached maximum at 35–40% and then decreased. KOH, trisodium phosphate, dipotassium hydrogenphosphate and KF were compared as a base in the reaction. Of these bases, KOH and trisodium phosphate were equally the most effective (Fig. 8). Both KOH and trisodium phosphate gave the maximum and constant yields with the same concentration range of 20–40 mM; 35 mM of KOH was employed for further experiments. On the DPA concentration, 12.5 mM giving the maximum yield was selected. Palladium(II) acetate concentration was varied over the range of 0–5 mM, and the maximum peak height was observed at the concentration over 1 mM. The addition of DCPB in the reaction mixture faintly improved the reaction yield, and 1.5 mM was used. Reaction temperature and time affected the reactivity of clofibrate with the same tendency for bromobenzenes as shown in Fig. 3; the reaction at 100 °C for 45 min was recommended.

For the effective extraction of clofibrate from plasma sample, commonly used liquid-liquid extraction was investigated as a sample pretreatment by using 50 μL-plasma spiked with

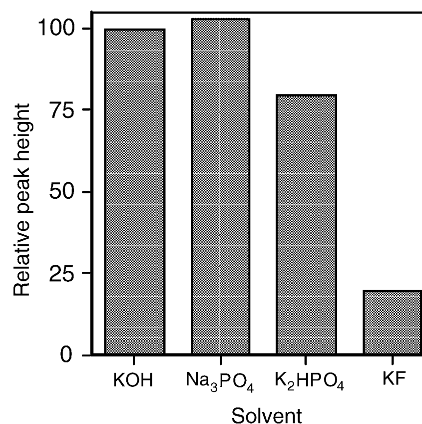

Fig. 8. Reactivity of clofibrate with DPA in the presence of various bases. Experimental conditions, see text. Sample concentration: 910 pmol/injection for all compounds.

10 nmol/mL clofibrate. As a solvent for extraction, 1 mL of ethyl acetate, diethyl ether and chloroform were compared and the maximum recovery was obtained with ethyl acetate. The recovery of clofibrate reached constant (ca. 76%) with more than 1 mL of ethyl acetate and thus was selected.

The calibration curve for clofibrate using spiked plasma was obtained by plotting peak heights against concentrations in plasma. A linear relationship was obtained in the concentration range 1–300 nmol/mL. The regression equation and correlation coefficient were as follows: $y = 1.12x - 0.37$ ($r = 0.998$); y is the peak height (cm) and x as the concentration in plasma in nmol/mL. The detection limit of clofibrate in human plasma was 170 pmol/mL (260 fmol/injection, S/N = 3), which was 30 times lower than that by the conventional HPLC–UV method [23].

The method was validated using spiked plasma (5 nmol/mL) on the repeatability for within-day ($n = 3$) and

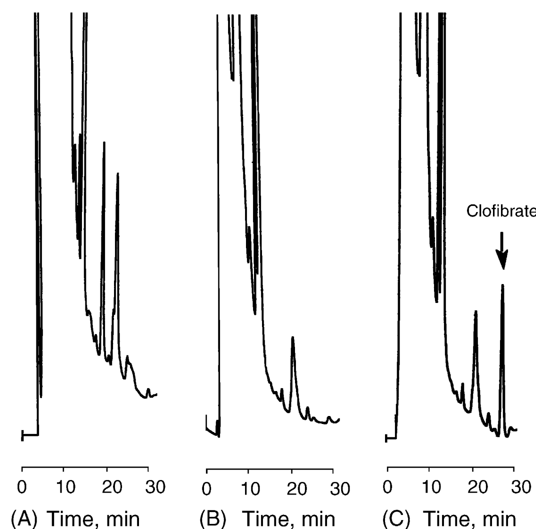

Fig. 9. Chromatograms of (A) reagent blank, (B) control plasma, and (C) plasma spiked with clofibrate. Experimental conditions, see text. Clofibrate concentration: 250 nmol/mL.

between-day ($n = 3$) runs being less than 11.6 and 12.7% as RSD, respectively.

Fig. 9 represents the chromatograms of a reagent blank, a human plasma control and the plasma spiked with clofibrate. The peak for clofibrate was completely separated from reagent peaks within 30 min. As might have been expected, the chromatogram for plasma sample did not give any interfering peak that is derived from an intrinsic component in plasma.

4. Conclusions

An analytical application of Suzuki coupling reaction has been demonstrated for the labeling of aryl halides with the fluorescent arylboronic acid, DPA, for the first time. We have explored the analytical performance of the proposed method by using a series of simple aryl halides, varying the halogen and other aryl substituents. The applicability to biological samples was also demonstrated with clofibrate as the analyte. The reaction was found to proceed well even in the presence of plasma components. Furthermore, the present method was sufficiently selective toward aryl halides and plasma components were not an obstacle to the separation and detection of the analyte. This method, however, is affected by kinds and position of substituents on the aryl halides. Aryl chlorides are also less reactive in comparison with bromides and iodides. Since Suzuki coupling reaction have a great choice on catalysts, bases, ligands and reaction media, careful selection of these factors might cover these shortcomings. The present method should be very useful for labeling of aryl halides lacking other functional groups that might be labeled by known fluorescent labeling reagents. Recent studies on Suzuki coupling reaction show rapid progress with regard to the reaction yields. Thus the application of the Suzuki labeling method should continue to be more widely applicable to an increasingly diverse range of analytical applications in biomedical, biochemical and environmental studies.

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