Protection of Functional Groups and Stannylation of Phenylalanine

S. A. METWALLY,*,† H. H. COENEN, and G. STÖCKLIN
Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, D-5170 Jülich, Federal Republic of Germany
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The protection of both amino and carboxylic acid groups in *p*-halogenated phenylalanine was done by using different reagents. The protected amino acid was stannylated by using hexamethyldistannane in the presence of tetrakis(triphenylphosphine)palladium as catalyst.

Substituted especially halogenated aromatic amino acids are generally prepared from appropriate, already substituted aryl derivatives, for example benzaldehydes.[1] Radiohalogenation with short lived isotopes, however, necessitates a fast introduction of the halogen, if possible in the last reaction step. *p*-Fluoro-L-phenylalanine labelled with the positron emitter fluorine-18 ($T_{1/2}$=110 min) was recently suggested as a potential tracer for measuring cerebral protein synthesis in vivo in man using positron emission tomography.[2] The direct electrophilic fluorination of L-phenylalanine leads to *p*-fluorophenylalanine, but only in low yields and the ortho- and meta-product which are also formed are difficult to separate.[2] Fluorodemetallation reactions on suitably metallated phenylalanine derivatives can provide a way to regioselective halogenation.

There are not many examples of complex biomolecules which were labelled by fluorodemetallation reactions.[3] However, a recent systematic study on simple aryltrimethyl compounds of group IVB showed that tin derivatives are most suitable for fluorodemetallation.[4] There are ample precedences in the literature for cleavage of aryl-tin bonds by halogens and interhalogens (I_2, Br_2, Cl_2, ICl, IBr). Given these facts, and the ease with which aromatic substrates can be metallated, and subsequently stannylated,[5,6] it occurred to us that such substances might be ideal substrates for fluorination using elemental fluorine.

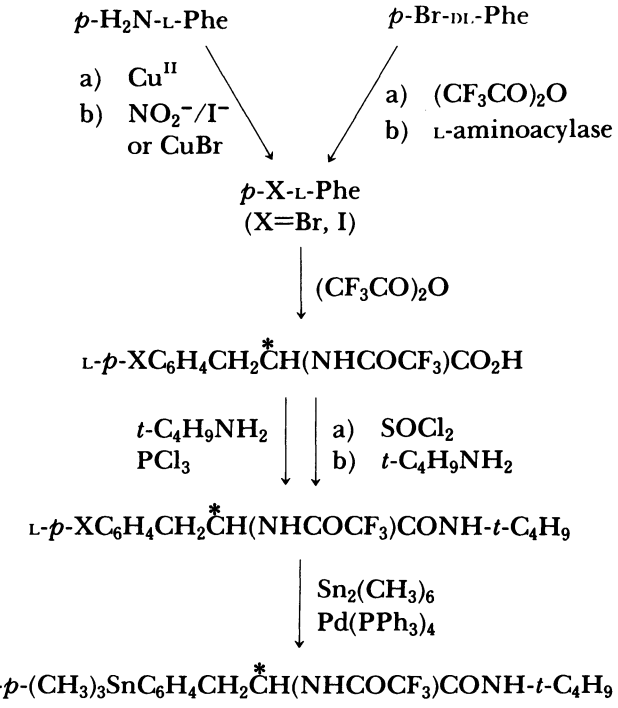
The aim of this work is the preparation of a suitable stannylated phenylalanines to be used for ^{18}F-fluorination. The need of a variety of amino- and carboxyl protecting groups which can be cleaved under relatively mild conditions to the corresponding amino acids is well recognized. The protection groups have to meet the following requirements in our specific case: The condensation and cleavage reactions have to proceed without racemization and the cleavage has to be fast with respect to the half life of fluorine-18. The protecting groups should not hinder the stannylation and fluorination.

Results and Discussion

The need of a *p*-stannylated derivative of phenylalanine for the direct regiospecific radiofluorination stimulated a search for suitable halogenated precursors with appropriate protecting groups for the metallation. In view of the necessary regiospecific labelling with fluorine-18, *p*-iodo- and *p*-bromo-L-phenylalanine were found useful intermediates which were prepared according to Scheme 1.

p-Iodo-L-phenylalanine was prepared from the commercially available L-*p*-aminophenylalanine by chelating the α-amino and the carboxyl group using copper(II) ions to form a stable copper complex[7] in which the aromatic amino group is free to react with appropriate reagents. The latter was diazotized by sodium nitrite-hydrochloric acid mixture to form the corresponding diazotized phenylalanine copper complex. The diazonium salt was transformed into the corresponding *p*-iodo-L-phenylalanine.

A less expensive way is the *N*-acylation of *p*-bromo-DL-phenylalanine with subsequent enzymatic deacylation of the L-enantiomer. The stereochemical purity of the *p*-halo-L-phenylalanines was tested by chiral TLC



L-Phe is a notation for L-phenylalanine.

L indicates the configuration of C* atom.

Scheme 1.

†On leave from Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.

plates and chiral HPLC (see Experimental).

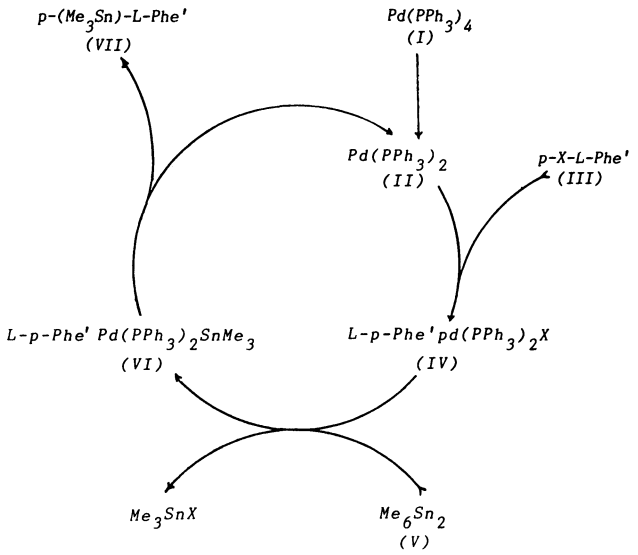
We have protected both the two functional groups by different types of blocking moieties: the carboxyl group was blocked by *t*-butylamide[8] or *t*-butyl ester[9] while the protecting groups for the amino function were trifluoroacetyl,[10] acetyl,[11] trityl,[12] and *o*-nitrobenzenesulfenyl groups.[11] Under the reaction conditions used, trifluoroacetyl and acetyl for the amino group and the conversion into *t*-butylamide for the carboxyl group proved to be the best protecting groups with respect to the requirements stated above (cf. Scheme 1). Hydrolysis of the protected amino acids was tested under various conditions, where hydroiodic acid (56% super pure) was found to be very suitable since the reaction was completed in the course of 15 min. Hydrochloric acid at different concentrations and temperatures failed to achieve such hydrolysis. The effect of protection for L-phenylalanine functional groups and also of the succeeding stannylation step on racemisation were tested after hydrolysis to the corresponding free L-phenylalanine. In this way the hydrolysis conditions were also checked for racemisation. It was noted that the amidation with *t*-butyl amine and PCl_3, given as an alternative in Scheme 1, was not as stated in the literature[8] and up to 10% of D-isomer was formed in some preparations.

Stannylation of the protected *p*-halophenylalanine was tried using different routes: a) Grignard reaction: Stannylation via Grignard reaction, using the known technique[13] did not give rise to stannylated products. b) Stannylation using an aryllithium intermediate:[14] The interaction of protected *p*-halophenylalanine with butyllithium followed by the reaction with trimethylstannyl chloride resulted in the formation of *p*-butylphenylalanine derivatives. c) Stannylation with Pd(0) catalysts: The stannylation was successful using hexamethyldistannane and protected *p*-iodo- or *p*-bromophenylalanine in presence of tetrakis(triphenylphosphine)palladium(0) as catalyst. This method was tested according to the wide application of this palladium catalyst in stannylation of simple organic compounds.[15–17] No stannylation for complex molecules such as protected phenylalanine was found in the literature. The features of this reaction can be summarized as follows:

a) *p*-Iodo-DL-phenylalanine (protected at both amino and carboxy group) behaves like simple iodo aromatic compounds[16] and gave a distinctly better yield than the *p*-bromo derivative.

b) The cleavage of hexamethyldistannane by the *p*-chloro-DL-phenylalanine derivative did not proceed even at 135 °C and 35 bar to any significant extent, and more drastic conditions led to decomposition of the catalyst.[18]

c) The completion of the reaction is clearly visualized since the catalyst serves as an indicator; as soon as *p*-halogenated-DL-phenylalanine derivative is consumed, Pd metal precipitates and the brown solution turns colorless.



X = Br, I
Ph = phenyl
Phe' = protected phenylalanine

Scheme 2.

It can be assumed that the first step in the stannylation reaction is the dissociation of the catalyst (I) into bis(triphenylphosphine)palladium (II) possibly complexed with the solvent. Oxidative addition of (II) to the protected *p*-iodo- or *p*-bromo-DL-phenylalanine (III) gives iodo- or bromo-DL-phenylalanine bis(triphenylphosphine)palladium (IV). This complex interacts with hexamethyldistannane (V) under substitution of the halogen substituent by the trimethylstannyl group to yield Phe' $Pd(PPh_3)_2SnMe_3$ (VI) which dissociates to the *p*-stannylated phenylalanine derivative (VII) and the bis(triphenylphosphin)palladium (II). The reaction cycle is shown in Scheme 2 and is similar to the selective ketone synthesis from acid chlorides and tetraalkylstannane catalysed by $[PdCl(PhCH_2)(PPh_3)_2]$.[19]

Dichlorobis(triphenylphosphine)palladium also was found to initiate the reaction of hexamethyldistannane (V) with *p*-iodo- or *p*-bromo-DL-phenylalanine derivatives, but the catalyst was not active as Pd(0) complex. This is implied by the fact that with the divalent complex the reaction went to only 20% completion at 115 °C in 20 h. The present system thus may furnish the only convenient method for aromatic amino acid stannylation.

Experimental

Melting points are uncorrected. The ^1H NMR measurements were performed on an 80 MHz Brucker spectrometer (WP 80), using TMS as internal standard and $CDCl_3$ or D_2O as solvents. Mass spectra were recorded at 70 eV on an AEI MS 12 mass spectrometer using a direct insertion technique and a probe temperature ranging between 150 and 200 °C. IR spectra were recorded in KBr on a Perkin-Elmer model 20

spectrophotometer. Hexamethyldistannane was prepared according to published procedures.[20] The substituted phenylalanines and the palladium catalyst were from Aldrich (Steinheim, FRG). Other solvents and reagents were from Merck (Darmstadt, FRG), unless otherwise noted.

Synthesis of *p*-Iodo-L-phenylalanine: *p*-Amino-L-phenylalanine hydrochloride hydrate (0.5 g) was dissolved in water (15 ml) and boiled under reflux for 45 min with an excess (1 g) of black copper oxide. The excess copper oxide was filtered off and the solution was concentrated and cooled to give green crystals of the *p*-amino-L-phenylalanine copper complex (0.45 g). It was dissolved in dilute hydrochloric acid (20 ml) and cooled to 0 °C. Cold soldium nitrite solution (0.06 g in 5 ml of water) was added and the resulting diazonium salt was kept in ice for 30 min. The solution was boiled under reflux with potassium iodide (0.2 g) and the copper complex was decomposed by hydrogen sulphide and the precipitated copper sulphide was removed by filtration. *p*-Iodo-L-phenylalanine was isolated by the addition of sodium acetate and identified by TLC.

Synthesis of *p*-Bromo-L-phenylalanine: *N*-Trifluoroacetyl-*p*-bromo-DL-phenylalanine was prepared as described below and 0.5 g was dissolved in phosphate buffer (pH 7—7.2) and 12 mg $CaCl_2$ and 1 ml aminoacylase solution (*N*-acylamino acid amidohydrolase EC 3.5.1.14, 3.2 mol dm^{-3}, 25 U mg^{-1}) added. The solution was kept at 38 °C for 20 h then acidified (pH 3). The precipitated enzyme was separated by centrifugation. The supernatant is adjusted to pH 5.5—6 and concentrated until the free L-amino acid starts to crystalize. After cooling for several hours the *p*-bromo-L-phenylalanine is filtered off, washed with H_2O and ethanol, and identified by TLC.

Protection of *p*-Halo-DL-phenylalanines: *N*-Trifluoroacetyl-*p*-halo-DL-phenylalanine. The following is a representative and modified procedure to that known in the literature.[11] Dry *p*-bromo-DL-phenylalanine (0.96 g) was dissolved in a 10—15 fold amount of dry trifluoroacetic acid (warming if necessary). The solution was cooled in an ice-salt bath to −10 °C. Trifluoroacetic anhydride (1.2 mol) (0.929 g; 0.61 ml) was added gradually in the course of a few minutes. The temperature was increased to 10 °C and left for 30 min. The reaction mixture was dried under vacuum at a maximum temperature of 30 °C using a well cooled receiver. The nonreacted amino acid was removed by dissolving the residue in dry ether followed by filtration and evaporation of ether. The solid was recrystallized from benzene to give colorless needles of *N*-trifluoroacetyl-*p*-bromo-DL-phenylalanine, mp 152 °C yield 1.25g. IR 1680—1730 (-COOH, C=C) 3100 cm^{-1} (sec. amide), ^1H NMR ($CDCl_3$) δ=7.3—7.8 (q, 4 aromatic H); MS M^+: 329 and 331. Calcd for $C_{11}H_9NO_3BrF_3$: C, 38.82; H, 2.64; N, 4.11%. Found: C, 38.85; H, 2.71; N, 4.32%.

***N*-Trifluoroacetyl-*p*-chloro-DL-phenylalanine.** Colorless needles from benzene, mp 114 °C, yield 90%. Found: C, 44.82; H, 3.26; N, 4.64%. Calcd for $C_{11}H_9NO_3F_3Cl$: C, 44.74; H, 3.05; N, 4.74%.

***N*-Trifluoroacetyl-*p*-iodo-DL-phenylalanine.** Colorless needles from benzene, mp 148 °C, yield 83%. Found: C, 34.28; H, 2.64; N, 3.75%. Calcd for $C_{11}H_9NO_3F_3I$: C, 34.10; H, 2.32; N, 3.61%.

***N*-Trifluoroacetyl-*p*-bromo-DL-phenylalanine *t*-Butylamide:** The following are typical general procedures: a) *N*-Trifluoroacetyl-*p*-bromo-DL-phenylalanine (1 g) is dissolved in dry pyridine (10 ml) by warming if necessary. *t*-Butylamine (1.31 ml) is added and the mixture is cooled in an ice bath. Phosphorus trichloride (0.13 ml) in 5 ml dry pyridine is added gradually to the cold reaction mixture. The solution is heated under reflux for 3 h, followed by concentration to one third and poured on ice-cold water. The solid product was filtered, washed with water until pyridine free and dried. It was crystallized from ethanol into colorless needles of *N*-trifluoroacetyl-*p*-bromo-DL-phenylalanine *t*-butylamide, mp 127 °C, yield 0.5 g. b) Alternatively: 25 ml $SOCl_2$ were added to *N*-trifluoroacetyl-*p*-bromo-L-phenylalanine (4.75 g) and kept for 3 h at 40 °C. Subsequently, the excess of $SOCl_2$ was evaporated. The residual acid chloride was dissolved in 30 ml CH_2Cl_2 and *t*-butylamine added dropwise until alkaline reaction (2.2 ml). The CH_2Cl_2 solution was extracted 4 times with water and then dried over Na_2SO_4. After evaporation to dryness the residue was recrystallized from ethanol. Yield 1.4 g, 26%.

***N*-Trifluoroacetyl-*p*-chloro-DL-phenylalanine *t*-Butylamide:** Colorless needles from ethanol mp 132 °C, yield 55%. ^1H NMR ($CDCI_3$) δ=1.17 (s, 9H), 4.25 (d, 2H), 5.25 (t, 1H), 7.37—7.75 (q, 4 aromatic H). Found: C, 51.84; H, 4.66; N, 8.12%. Calcd for $C_{15}H_{16}ClN_2O_2F_3$: C, 51.72; H, 4.59; N, 8.04%.

***N*-Trifluoroacetyl-*p*-iodo-L-phenylalanine *t*-Butylamide:** Colorless needles from ethanol mp 129 °C, yield 50%. ^1H NMR ($CDCl_3$) δ=1.15 (s, 9H), 4.25 (d, 2H), 5.31 (t, 1H), 7.35—7.70 (q, 4 aromatic H). Found: C, 34.28; H, 2.68; N, 3.82%. Calcd for $C_{15}H_{16}IN_2O_2$: C, 34.10; H, 2.32; N, 3.61%.

***p*-Halogeno-DL-phenylalanine *t*-Butyl Ester:** The following is a typical procedure: A large amount of concentrated sulfuric acid (about 1 ml per 1 g of amino acid) is added to a suspension of the amino acid in diethylene glycol dimethyl ether (5 to 10 ml per 1 g of amino acid), an equal volume of liquid isobutene (liquified by passing the gaseous isobutene in a wide glass tube immersed in Dry Ice-acetone mixture) was added and the mixture was shaken overnight in a pressure gold-lined steal bottle. The solution was cautiously poured into excess 2 M (1 M=1 mol dm^{-3}) sodium hydroxide and the ester was extracted under vacuum to leave an oil (all of the three *p*-halogenophenylalanines). Addition of dilute hydrochloric acid resulted in the immediate precipitation of the ester hydrochloride. The nonreacted amino acid precipitates soon after extraction from the aqueous layer. The yield was almost quantitative and 5 g of *p*-chloro-DL-phenylalanine, for example, gave 5.9 g of the *t*-butyl ester hydrochloride and 0.7 g of *p*-chlorophenylalanine was isolated from the aqueous layer. Trials to carry the reaction in presence of concentrated sulfuric acid without solvent failed.

***p*-Chloro-DL-phenylalanine *t*-Butyl Ester Hydrochloride:** Colorless flakes from water mp 221 °C (decomp) ^1H NMR (D_2O) δ=1.38 (s, 9H), 4.5 (d, 2H), 5.25 (t, 1H), 7.25—7.8 (q, 4 aromatic H). Found: C, 53.74; H, 6.68; N, 4.88%. Calcd for $C_{13}H_{19}NCl_2O_2$: C, 53.60; H, 6.52; N, 4.81%.

***p*-Bromo-DL-phenylalanine *t*-Butyl Ester Hydrochloride:** Colorless flakes from dil ethanol mp 214 °C (decomp). ^1H NMR (D_2O) δ=1.35 (s, 9H), 4.57 (d, 2H), 5.3 (t, 1H), 7.25—7.75 (q, 4 aromatic H). Found: C, 46.64; H, 5.76; N, 4.22%. Calcd for $C_{13}H_{19}BrClNO_2$; C, 46.42; H, 5.65; N, 4.16%.

***p*-Iodo-DL-phenylalanine *t*-Butyl Ester Hydrochloride:** Colorless flakes from water mp 233 °C (decomp) ^1H NMR (D_2O) δ=1.38 (s, 9H), 4.55 (d, 2H), 5.3 (t, 1H), 7.3—7.8 (q, 4 aromatic H). Found: C, 40.86; H, 5.12; N, 3.78%. Calcd for

$C_{13}H_{19}NClIO_2$: C, 40.73; H, 4.96; N, 3.95%.

***t*-Butyl Esters of *N*-Acetyl-, *N*-Nitrobenzesulfenyl, and *N*-Trityl-*p*-halogeno-DL-phenylalanine:** The following is a general method: Either 0.01 mol of acetyl chloride, *o*-nitrobenzenesulfenyl chloride or trityl bromide was added to a solution of 0.01 mol of *p*-halogeno-DL-phenylalanine *t*-butyl ester hydrochloride in 25 ml of dry chloroform and 2.8 ml of triethylamine. After being left at room temperature for 6 h, the solution was successively washed with water, dilute acetic acid, aqueous potassium hydrogencarbonate solution, and again with water. It was dried over sodium sulfate and evaporated under vacuum to dryness. The crude products were usually crystallized from ethanol, methanol, or ethyl acetate-petroleum ether.

***N*-Acetyl-*p*-chloro-DL-phenylalanine *t*-Butyl Ester:** Colorless needles from toluene, mp 123 °C, yield 47%. ^{1}H NMR ($CDCl_3$) δ=1.38 (s, 9H), 2.1 (s, 3H), 4.87 (d, 2H), 5.18 (t, 1H), 7.25—7.75 (q, 4 aromatic H). Found: C, 60.58; H, 6.82; N, 4.64%. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.6; H, 6.73; N, 4.71%.

***N*-Acetyl-*p*-bromo-DL-phenylalanine *t*-Butyl Ester.** Colorless needles from benzene, mp 138 °C, yield 55%. ^{1}H NMR ($CDCl_3$) δ=1.37 (s, 9H), 2.2 (s, 3H), 4.82 (d, 2H), 5.2 (t, 1H), 7.32—7.75 (q, 4 aromatic H). Found: C, 56.78; H, 6.36; N, 4.48%. Calcd for $C_{15}H_{20}BrNO_3$: C, 56.60; H, 6.28; N, 4.40%.

***N*-Acetyl-*p*-iodo-DL-phenylalanine *t*-Butyl Ester:** Colorless needles from benzene, mp 127 °C, yield 63%. ^{1}H NMR ($CDCl_3$) δ=1.38 (s, 9H), 2.3 (s, 3H), 4.86 (d, 2H), 5.2 (t, 1H), 7.32—7.8 (q, 4 aromatic H). Found: C, 46.52; H, 5.28; N, 3.64%. Calcd for $C_{15}H_{20}NO_3I$: C, 46.27; H, 5.14; N, 3.59%.

Stannylation of *p*-Halo-*N*-acetyl- or *N*-Trifluoroacetyl-L-phenylalanine *t*-Butylamide: The following is a general procedure for the stannylation of protected *p*-halophenylalanines: A mixture of hexamethyldistannane (39 mmol), *p*-bromo- or *p*-iodo-*N*-trifluoro- or *N*-acetyl-L-phenylalanine *t*-butylamide (2.5 mmol), tetrakis(triphenylphosphine)palladium(0) (1.3×10^{-4} mol) and dioxane (50 ml) was heated under reflux for 5 h whereby palladium metal was precipitated as fine black powder. The mixture was cooled and filtered, and the filtrate was evaporated under vacuum to a residue. This was taken up in ether or benzene and the solution was washed several times with water and dried over $MgSO_4$. The solvent was removed to leave the product which was crystallized from benzene.

***N*-Acetyl-*B*-[4-(trimethylstannyl)phenyl]-L-alaine *t*-Butylamide.** White crystals, yield 15—20%. ^{1}H NMR ($CDCl_3$) δ=7.6 (p, 4H, aryl H), 0.34 (s, with Sn satellites, 9H, $SnMe_3$), 1.18 (s, 9H, *t*-butyl H), 2.06 (s, 3H), 2.06 (s, 3H). The mass spectrum showed the expected parent ion at m/z 410. Found: C, 52.74; H, 7.54; N, 3.48; Sn, 28.94%. Calcd for $C_{18}H_{30}O_2N_2Sn$: C, 52.68; H, 7.31; N, 3.41; Sn, 28.78%.

***N*-Trifluoroacetyl-*B*-[4-(trimethylstannyl)phenyl]-L-alanine *t*-Butylamide.** White crystals, yield 15—20%. ^{1}H NMR ($CDCl_3$) δ=7.8 (q, 4H, aryl H), 0.32 (s, with Sn satellites, 9H, $SnMe_3$), 1.18 (s, 9H, *t*-butyl H), the mass spectrum indicated the expected parent ion at m/z 464. Found: C, 46.64; H, 5.88; N, 3.14; Sn, 25.86%. Calcd for $C_{18}H_{27}O_2NSnF_3$: C, 46.55; H, 5.81; N, 3.01; Sn, 25.43%.

Chromatographich Analysis of Enantiomeric Purity: The enantiomeric purity of all phenylalanine derivatives prepared were checked in form of the free amino acid on chiral TLC plates or by means of chiral HPLC. In the case of protected compounds blocking groups were previously hydrolised. Typically 5 to 10 mg of the compound were heated for 20 min in 2 ml 56% pure HI at 140 °C in a closed reaction vial. The chiral TLC plates from Macherey-Nagel (Düren, FRG) were developed with methanol-H_2O-acetonitrile 50:50:200 (v/v/v). For chiral HPLC a column from serva (Heidelberg, FRG) (Si-100 Polyol, Chrial Pro Cu, 5 µm, 4×250 mm) was used with a 1 mM $CuSO_4$ solution as eluant and a flow of 4 ml min^{-1}.

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