The amount of the organic solvent in the raw material liquid C is, for example, 50 parts by mass or more, preferably 100 parts by mass or more, and more preferably 150 parts by mass or more, and is, for example, 3000 parts by mass or less, preferably 2000 parts by mass or less, and more preferably 1000 parts by mass or less, relative to 100 parts by mass of the reaction substrate.

[0049]

The raw material liquid C may or may not contain a nitrogen-containing organic compound.

[0050]

A time (reaction time, retention time) during which the mixed solution of the solution containing phosgene prepared in the first flow reactor 21 and the raw material liquid C (reaction substrate) flows in the reactor unit 18 of the second flow reactor 22 may be appropriately set according to the type of the raw material liquid C and the flow velocity at which the mixed solution of the solution containing phosgene and the raw material liquid C flows in the second flow reactor 22, and is, for example, 0.5 seconds or more, preferably 0.6 seconds or more, more preferably 0.8 seconds or more, further preferably 1.0 second or more, and still further preferably 1.2 seconds or more, and is, for example, 15 minutes or less, preferably 10 minutes or less, and more preferably 5 minutes or less.

[0051]

The flow velocity at which the raw material liquid C flows in the feeding channel 14 and the flow velocity at which the mixed solution of the solution containing phosgene prepared in the first flow reactor 21 and the raw material liquid C (reaction substrate) flows in the reactor unit 18 of the second flow reactor 22 may be appropriately set according to the type of the raw material liquid C and a retention time in the reactor unit 18. Each flow velocity is, for example, 0.01 mL/min or more, preferably 0.1 mL/min or more, more preferably 0.5 mL/min or more, and is, for example, 5000 mL/min or less,

flow channels of the mixing units and the reactor units is preferably 1 mm^2 or more and 70 cm^2 or less, and more preferably 0.15 mm^2 or more and 30 cm^2 or less.

[0062]

The materials of the mixing units and the reactor units are not particularly limited and may be appropriately selected depending on needs for solvent resistance, pressure resistance, heat resistance, or the like. For example, a metal such as stainless steel, Hastelloy, titanium, copper, nickel and aluminum; a resin such as PEEK resin, silicone resin, and fluororesin; a glass; a ceramics; and SiC can be used.

[0063]

In the present invention, water may or may not coexist as needed. The coexistence of water can more reliably prevent a nitrogen-containing organic compound hydrochloride from precipitating. The nonexistence of water can prevent a side reaction caused by water. When water coexists, the concentration of water in all solvents including solvents contained in other raw material liquids described later (particularly, the concentration of water in the reaction solution of phosgene with a reaction substrate) is, for example, 10 wt% or less, preferably 5 wt% or less, and more preferably 1 wt% or less.

[0064]

A container for quenching the reaction solution is not limited to the tank 32 for post-treatment, and can be selected as appropriate according to the size of the apparatus. For example, a flask 33 as shown in the apparatus of FIG. 2 may be used.

According to the method of the present invention using the apparatuses as described above, a desired organic compound can be obtained in a high yield with a small amount of by-product.

[0065]

homogeneous solution, and the resulting solution was referred to as a raw material liquid A. To 53.1 g of tributylamine, 32.5 g of toluene was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid B. To 50.0 g of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 150.0 g of tetrahydrofuran was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid C. These solutions were reacted using the reaction apparatus 1 shown in FIG. 1 in the following manner.

The raw material liquid A and the raw material liquid B were transferred using diaphragm pumps (manufactured by KNF Co. Ltd.) 34a and 34b, respectively, at a rate of 39.5 ml/min and mixed by a T-shape mixer 15, and the resulting mixture was allowed to flow in a retention line 17 for 5 seconds to prepare a toluene solution of phosgene. Next, the raw material liquid C was transferred using a diaphragm pump (manufactured by KNF Co. Ltd.) 34c at a rate of 79.0 ml/min and mixed with the toluene solution of phosgene that was continuously flowing (79.0 ml/min) by another T-shape mixer 16, and the resulting mixture was allowed to flow in a retention line 18 for 10 seconds to perform a reaction. After the bottles containing the raw material liquid A, the raw material liquid B, and the raw material liquid C was emptied, the reagent in the flow channel was washed and flushed with toluene at the same rate. Note that the T-shape mixers 15 and 16 (inner diameter: 2.4 mm, material: stainless (SUS304)) and the retention lines 17 and 18 (inner diameter: 2.18 mm, outer diameter: 1/8 inch (about 3.18 mm), material: stainless (SUS304)) were placed in a constant-temperature bath 31 at 10°C to carry out this examination experiment. The reaction solution was continuously quenched while stirring with 250.0 g of 2N aqueous hydrochloric acid in a flask 32. After separation, 465.4 g of an organic layer containing 63.1 g of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinolinecarbonyl chloride was obtained (yield: 98%, RRT 0.81

impurity: 0 area% vs product area). No crystals precipitated during the reaction, and the reaction solution was a clear solution.

[0074]

Example 6

To 28.4 g of triphosgene, 78.0 g of toluene was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid A. To 53.1 g of tributylamine, 32.5 g of toluene was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid B. To 50.0 g of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 150.0 g of tetrahydrofuran was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid C. These solutions were reacted using the reaction apparatus 1 shown in FIG. 1 in the following manner.

The raw material liquid A and the raw material liquid B were transferred using diaphragm pumps (manufactured by KNF Co. Ltd.) 34a and 34b, respectively, at a rate of 39.5 ml/min and mixed by a T-shape mixer 15, and the resulting mixture was allowed to flow in a retention line 17 for 5 seconds to prepare a toluene solution of phosgene. Next, the raw material liquid C was transferred using a diaphragm pump (manufactured by KNF Co. Ltd.) 34c at a rate of 79.0 ml/min and mixed with the toluene solution of phosgene that was continuously flowing (79.0 ml/min) by another T-shape mixer 16, and the resulting mixture was allowed to flow in a retention line 18 for 10 seconds to perform a reaction. After the bottles containing the raw material liquid A, the raw material liquid B, and the raw material liquid C was emptied, the reagent in the flow channel was washed and flushed with toluene at the same rate. Note that the T-shape mixers 15 and 16 (inner diameter: 4.8 mm, material: stainless (SUS304)) and the retention lines 17 and 18 (inner diameter of tube: 4.0 mm, outer diameter of tube: 6.0 mm, material: stainless (SUS304)) were placed in a

constant-temperature bath 31 at 10°C to carry out this examination experiment. The reaction solution was continuously quenched while stirring with 250.0 g of 2N aqueous hydrochloric acid in a flask 32. After separation, 457.4 g of an organic layer containing 63.9 g of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinolinecarbonyl chloride was obtained (yield: 97%, RRT 0.81 impurity: 0 area% vs product area). No crystals precipitated during the reaction, and the reaction solution was a clear solution.

[0075]

Reference Example 1 (Examination 1 of Required Retention Time)

To 7.37 g of triphosgene, 49.4 g of toluene was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid A. Next, to 13.81 g of tributylamine, 42.9 g of toluene was added to prepare a homogeneous solution, and the resulting solution was referred to as a raw material liquid B (corresponding to a raw material liquid D in FIG. 3). These solutions were reacted using a reaction apparatus 3 shown in FIG. 3 in the following manner. Note that the reaction apparatus 3 is the same as the reaction apparatus 2 of FIG. 2 except that the second flow reactor 22 is not provided. The same components are indicated by the same reference numerals, and the descriptions thereof are omitted. The outlet of the reaction tube and a React IR15 were connected, and the reaction conversion rate was calculated by means of inline analysis.

The raw material liquid A and the raw material liquid B (corresponding to a raw material liquid D in FIG. 3) were transferred using syringe pumps (manufactured by YMC Co. Ltd.) 35a and 35d and mixed by a T-shape mixer 15 (inner diameter: 0.5 mm, material: polytetrafluoroethylene (PTFE)), and the resulting mixture was allowed to flow in a retention line 17 (inner diameter: 0.5 mm, material: polytetrafluoroethylene (PTFE)) to prepare a toluene solution of phosgene. Note that the T-shape mixers 15 and the retention lines 17 were