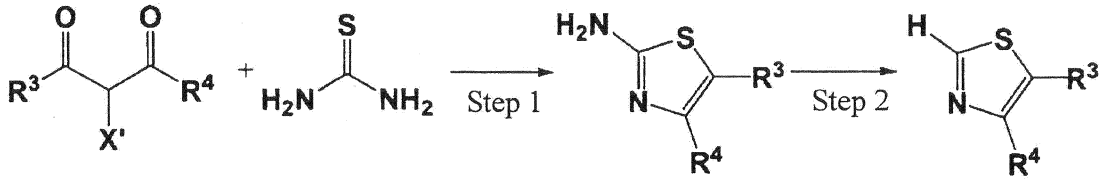
Society of Japan (Maruzen Co., Ltd.), pp. 187-205, and the like.

[0150]

Among the compounds represented by the formula (2), those having a thiazole ring as B are commercially available in some cases but they can be synthesized by referring, for example, to the following scheme:

[0151]

[Formula 16]



[0152]

In the reaction scheme described above, R^3 and R^4 are the same as defined in the formula (2) of the present invention. X' represents a halogen atom.

[0153]

The 2-aminothiazole derivative according to the thiazole cyclization reaction of Step 1 can be synthesized by referring to Pharmaceutical Chemistry Journal, 2007:41, pp. 105-108; Pharmaceutical Chemistry Journal, 2001:35, pp. 96-98; WO 2005/075435; WO 2005/026137; and the like. The reaction of Step 2 can be carried out by reference to Journal of Heterocyclic Chemistry, 1985:22, pp. 1621-1630; Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, 1982:1, pp. 159-164; and Bioorganic & Medicinal Chemistry Letters, 2008:18, pp. 6231-6235. In addition, the thiazole derivative represented by the formula (2) can be synthesized by referring to, for example, WO 2002/051849 and WO 2001/062250.

[0154]

Among the compounds represented by the formula (2), various compounds having a pyridine ring as B are commercially available. As well as being purchasable, synthetic

A-Solvent: 5% MeCN/95% H_2O + 0.05% TFA

B-Solvent: 95% MeCN/5% H_2O + 0.05%TFA

Gradient:

0-1 min	10% B-Solv.
1-7 min	10-50% B-Solv.
7-14 min	0-80% B-Solv.
14-16 min	80-100% B-Solv.
16-20 min	100% B-Solv.
20-22 min	100-10% B-Solv.
22-25 min	10% B-Solv.

The results in the present Example are shown in the following.

[0188]

~~[Table 9]~~

~~Experiment No~~

~~Reaction No.~~

~~Reaction Conditions~~

~~Solvent~~

~~Base~~

~~Ligand~~

~~Additive~~

~~Temperature~~

~~Reaction Time~~

~~Calculated Yield~~

~~[0189]~~

[Table 9]

Experiment No.	Reaction Conditions							HPLC area %					Calculated Yield % TM
	Solvent 0.3M	Base 2 eq.	Pd 0.1 eq.	Ligand 0.2 eq.	Additive 0.3 eq.	Temperature °C	Reaction Time hr	TM	A	B	C	D	
1	DME	K_2CO_3	$Pd(OAc)_2$	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.4 eq.)	-	120	24	63.0	4.1	21.6	N.D.	N.D.	98.8
2	NMP	K_3PO_4	$Pd(OAc)_2$	$P(t\text{-}Bu)_3 \cdot HBF_4$	-	120	24	20.8	8.2	62.1	3.7	N.D.	89.2
3	NMP	Cs_2CO_3	$Pd(OAc)_2$	$P(t\text{-}Bu)_3 \cdot HBF_4$	-	120	24	38.2	7.3	38.4	2.7	N.D.	95.0
4	Toluene	Cs_2CO_3	$Pd(OAc)_2$	PPh_3	-	120	24	19.5	6.4	59.6	5.6	N.D.	65.5
5	Toluene	Cs_2CO_3	$Pd(OAc)_2$	dppp	-	120	24	20.8	5.7	56.9	11.6	N.D.	65.8
6	Toluene	Cs_2CO_3	$Pd(OAc)_2$	dppe	-	120	24	20.5	5.4	55.5	13.5	N.D.	64.4
7	Toluene	Cs_2CO_3	$Pd(OAc)_2$	dppf	-	120	24	13.5	5.8	68.8	6.4	N.D.	61.7
8	Toluene	Cs_2CO_3	$Pd(OAc)_2$	dppb	-	120	24	24.9	6.0	53.7	7.8	N.D.	71.0
9	DME	Cs_2CO_3	$Pd(OAc)_2$	PCy_3	-	120	19	15.3	5.9	71.6	5.2	N.D.	90.0
10	EA	K_2CO_3	$Pd(OAc)_2$	PCy_3	PivOH	120	24	60.6	0.0	26.5	3.1	9.8	81.9
11	CPME	K_2CO_3	$Pd(OAc)_2$	PCy_3	PivOH	120	24	63.6	0.0	35.7	0.7	0.0	87.9
12	Toluene	K_2CO_3	$Pd(OAc)_2$	$P(n\text{-}Bu)_3$	PivOH	120	24	54.7	0.0	30.0	6.5	8.7	78.8
13	Toluene	K_2CO_3	$Pd(OAc)_2$	$P(n\text{-}Oct.)_3$	PivOH	120	24	55.4	0.0	28.7	7.9	8.1	79.0
14	Toluene	K_2CO_3	$Pd(OAc)_2$	PCy_3	PivOH	80	90	82.7	0.0	13.1	0.0	4.2	92.9

[0189]

Abbreviations in the Table represent the following:

DME: Dimethoxyethane

NMP: N-Methylpyrrolidone

EA: Ethyl acetate

CPME: Cyclopentyl methyl ether

HBF_4: Tetrafluoroboric acid

dppp: 1,1'-Bis(diphenylphosphino)propane

dppe: 1,1'-Bis(diphenylphosphino)ethane

dppb: 1,1'-Bis(diphenylphosphino)butane

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

PCy3: Tricyclohexylphosphine

PivOH: Pivalic acid

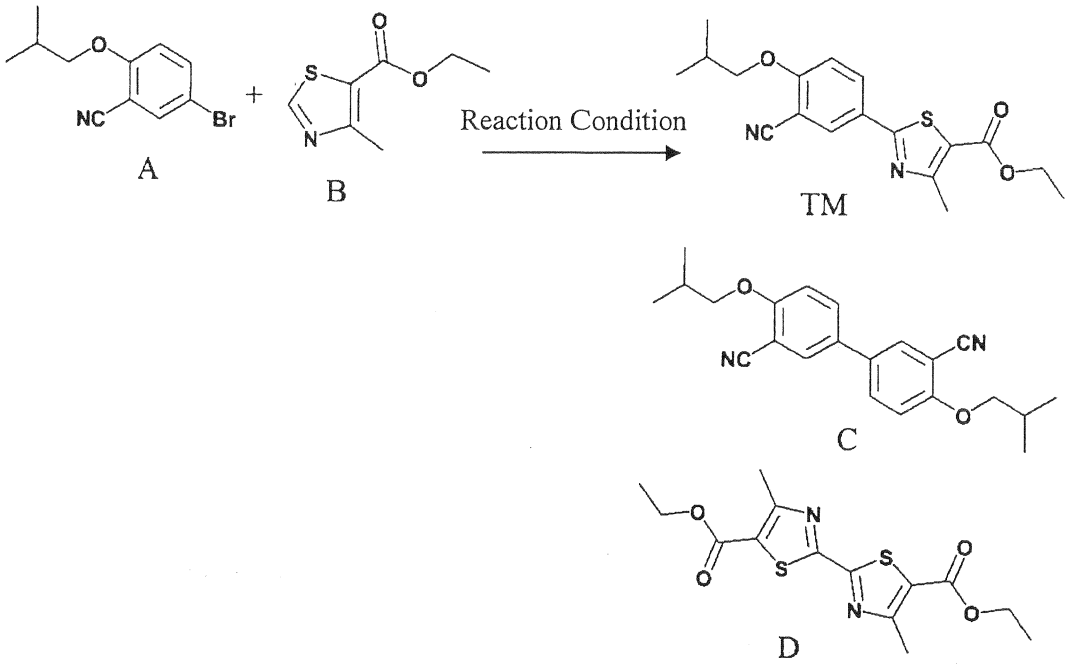
n-Oct.: n-Octyl

[Example 11]

Synthesis of ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate

[0190]

[Formula 30]



[0191]

To a test tube-type reaction vessel (10 mL) were added ethyl 4-methylthiazole-5-carboxylate (85.5 mg, 0.5 mmol), 5-bromo-2-isobutoxybenzonitrile (127.1 mg, 0.5 mmol) obtained in Reference Example 3, a palladium species, a ligand, a base (1.0 mmol), an additive (0.15 mmol), and a solvent (1.7 mL). Thereafter, the reaction vessel was filled with nitrogen, heated to 120°C under airtight seal, and the reaction mixture was stirred. After the reaction was complete, a portion of the reaction mixture was diluted with DMSO and the solution obtained was measured by HPLC. The total HPLC area % of the compounds A to D and TM was set as 100% and the calculated yield of the target material was computed from the HPLC area % of the target material. The results are shown in Table 10.

[0192]

[0192]

High Performance Liquid Chromatography:

Analytical System: G1315A Hewlett Packard Series 1100

Software: ChemStation for LC 3D

Experimental Conditions:

Column: Phenomenex Luna Phenyl-Hexyl 5um 4.6 × 100 mm

Flow: 1.0 mL/min

Wavelength: 240nm

Temperature: 40°CA-Solvent: 5%MeCN/95%H_2O + 0.05%TFA

B-solvent: 95%MeCN/5%H_2O + 0.05%TFA

Gradient:

0-1 min	10% B-Solv.
1-14 min	10-70% B-Solv.
14-24 min	70-80% B-Solv.
24-25 min	80-100% B-Solv.
25-30 min	100% B-Solv.
30-32 min	100-10% B-Solv.
32-35 min	10% B-Solv

~~[0193]~~

~~[Table 10]~~

~~Experiment No.~~

~~Reaction Condition~~

~~Solvent~~

~~Base~~

~~Ligand~~

[Table 10]

Experiment No.	Reaction Conditions							HPLC area %					Calculated Yield % TM
	Solvent 0.3M	Base 2 eq.	Pd	Ligand	Additive 0.3 eq.	Temperature °C	Reaction Time hr	TM	A	B	C	D	
1	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.1 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.2 eq.)	-	120	5.5	31.4	39.2	29.4	N.D.	N.D.	26.5
2	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.1 eq.)	XPhos (0.2 eq.)	-	120	5.5	31.5	38.0	30.6	N.D.	N.D.	26.5
3	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.1 eq.)	RuPhos (0.2 eq.)	-	120	5.5	39.4	35.7	24.9	N.D.	N.D.	34.0
4	Toluene	K_2CO_3	$Pd(OPiv)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	-	120	15	90.1	3.1	4.1	0.7	2.1	90.7
5	Toluene	$KHCO_3$	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	-	120	15	41.0	34.6	24.1	0.0	0.3	35.7
6	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	-	120	15	46.0	30.3	22.2	0.8	0.7	40.9
7	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	AcOH	120	15	47.5	29.6	21.9	0.6	0.4	42.1
8	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	PivOH	120	15	79.3	10.3	8.2	0.3	1.9	77.1
9	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	$EtCO_2H$	120	15	62.7	20.0	15.7	0.6	0.9	57.9
10	Toluene	K_2CO_3	$Pd(OAc)_2$ (0.02 eq.)	$P(t\text{-}Bu)_3 \cdot HBF_4$ (0.04 eq.)	$i\text{-}PrCO_2H$	120	15	93.4	1.0	3.8	0.6	1.2	93.7
11	Toluene	K_2CO_3	$Pd(P(t\text{-}Bu)_3)_2$ (0.1 eq.)	-	-	120	6	8.9	50.2	40.9	0.0	0.0	7.1
12	Toluene	K_2CO_3	$(Pd(P(t\text{-}Bu)_3)Br)_2$ (0.1 eq.)	-	-	120	6	11.9	49.7	36.8	1.6	0.0	9.8
13	Toluene	K_2CO_3	$Pd(P(t\text{-}Bu)_3)_2$ (0.1 eq.)	-	PivOH	120	6	90.7	0.1	6.7	0.0	2.5	91.4
14	Toluene	K_2CO_3	$(Pd(P(t\text{-}Bu)_3)Br)_2$ (0.1 eq.)	-	PivOH	120	6	78.0	10.5	0.5	3.5	7.5	87.0

~~Additive~~

~~Temperature~~

~~Reaction Time~~

~~Calculated Yield~~

[0193]

Abbreviations in the Table represent the following:

AcOH: acetic acid

$EtCO_2H$: propionic acid

i-$PrCO_2H$: 2-methylpropanoic acid

[0194]

[Example 12]

Synthesis of ethyl 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate

[0195]

[Formula 31]

[0197]

High Performance Liquid Chromatography:

Analytical System: G1315A Hewlett Packard Series 1100

Software: ChemStation for LC 3D

Experimental Conditions:

Column: Phenomenex Luna Phenyl-Hexyl 5 um 4.6 × 100 mm

Flow: 1.0 mL/min

Wavelength: 240 nm

Temperature: 40°C

A-Solvent: 5%MeCN/95%H_2O + 0.05%TFA

B-solvent: 95%MeCN/5%H_2O + 0.05%TFA

Gradient:

0-1 min	10%	B-Solv.
1-14 min	10-70%	B-Solv.
14-24 min	70-80%	B-Solv.
24-25 min	80-100%	B-Solv.
25-30 min	100%	B-Solv.
30-32 min	100-10%	B-Solv.
32-35 min	10% B-Solv.	

~~[0198]~~

~~[Table 11]~~

~~Experiment No.~~

~~Reaction Conditions~~

~~Solvent~~

[Table 11]

Experiment No.	Reaction Conditions							HPLC area %					Calculated Yield %
	Solvent 0.3M	Base 2 eq.	Pd 0.02 eq.	Ligand 0.04 eq.	Additive 0.3 eq.	Temperature °C	Reaction Time hr	TM	A	B	C	D	TM
1	Xylene	-	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	-	120	5	1.1	59.2	39.5	0.0	0.2	0.9
2	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	-	120	5	31.0	40.5	27.4	0.3	0.8	26.7
3	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	PivOH	120	5	74.6	13.2	9.1	0.0	3.1	72.5
4	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$CyPrCO_2H$	120	5	28.7	42.5	28.7	0.0	0.1	24.3
5	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$tetraMeCyPrCO_2H$	120	5	45.5	32.5	19.1	0.0	2.8	41.6
6	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$(CH_3CH_2)_2CHCO_2H$	120	5	61.8	21.2	12.7	0.5	3.8	59.4
7	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$CyPnCO_2H$	120	5	52.0	28.2	18.7	0.0	1.1	46.8
8	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$1\text{-}ad\text{-}CO_2H$	120	5	49.9	29.5	20.1	0.0	0.6	44.4
9	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$CyPenteneCO_2H$	120	5	37.0	37.1	25.7	0.0	0.3	31.8
10	Xylene	K_2CO_3	$Pd(OAc)_2$	$(t\text{-}Bu)_2PCy$	$3\text{-}THFCO_2H$	120	5	50.5	29.0	20.1	0.0	0.3	44.9
11	Xylene	K_2CO_3	$PdCl_2$	$(t\text{-}Bu)_2PCy$	PivOH	120	5	86.2	6.1	5.6	0.0	2.1	85.2

~~Base~~

~~Ligand~~

~~Additive~~

~~Temperature~~

~~Reaction Time~~

~~Calculated Yield~~

[0198]

Abbreviations in the Table represent the following:

$CyPrCO_2H$: cyclopropanecarboxylic acid

$tetraMeCyPrCO_2H$: 2,2,3,3-tetramethylcyclopropanecarboxylic acid

$CyPnCO_2H$: cyclopentanecarboxylic acid

$1\text{-}ad\text{-}CO_2H$: 1-adamantanecarboxylic acid

$CyPenteneCO_2H$: 3-cyclopentenecarboxylic acid

$3\text{-}THFCO_2H$: tetrahydrofuran-3-carboxylic acid

[Industrial Applicability]

[0199]

The novel coupling process of the present invention, wherein a phenyl derivative represented by the formula (1) and a heterocyclic derivative represented by the formula (2) are coupled in the presence of a transition metal compound to obtain a phenyl-substituted heterocyclic derivative represented by the formula (3), is useful for producing a xanthine oxidase inhibitor, which is a therapeutic agent for hyperuricemia, or an intermediate thereof in a process involving aw small number of steps and, consequently, in high yield and at low cost.