

Antioxidant study of biaryls synthesized in the presence of Aliquat-336 activated by ultrasound

Said Khemais ¹, Houcine Labiadh ², Karima Lahbib ³ and Ridha Ben Salem ^{1,*}

¹ Physical Organic Chemistry Laboratory (UR11ES74), Science Faculty of Sfax, 3018 Sfax, Tunisia

² Unité de Recherche UR11ES30 de Synthèse et Structures de Nanomatériaux, Université de Carthage, Faculté des Sciences de Bizerte, 7021 Jarzouna, Tunisia

³ Laboratory of Heteroatom Organic Chemistry, Faculty of Sciences of Bizerte Jarzouna 7021, Tunisia

Abstract: In this work we describe the study of some Suzuki coupling reactions of an aryl halide with arylboronic acids. The reaction yields obtained were increased through sonochemical activation and in the presence of a phase transfer catalyst for a very short period of time. The isolated products obtained are highly pure. In this context, we propose the reaction mechanisms for these reactions in the presence of a catalyst. The synthesized compounds were screened for their antioxidant activity using the 1,1-diphenyl-2-picrylhydrazyl (DPPH), ferric reducing power (FRP) assay and ferrous ion chelating (FIC) methods. It was found that the synthesized biaryl compounds show an enhancing antioxidant activity.

Keywords: Coupling Reactions. Nickel Catalysts. Suzuki reaction. Sonochemical activation. Ultrasound. antioxidant.

Introduction

Coupling reactions are catalyzed with a palladium compound¹ or Ni-Pd bimetallic catalysts². The use of palladium catalysts to run the homocoupling reaction of aryl halides also has been reported in the literature³. However, the relatively low yield and the requirement of drastic reaction conditions for palladium catalyzed homocoupling reactions greatly limit its practical applications in organic synthesis. On the other hand, Ni catalysts have many advantages over the Pd catalyst; for example, they are more reactive and often cheaper than the Pd complexes. Ni-catalyzed reactions are more specific and are complementary to their Pd analogues. Their stability in air, ease of preparation and separation of the catalyst mixture from the product at the end of the reaction sequence are some of the advantages of Ni catalysts which have been found to be better catalysts than their Pd counterparts given Ni's smaller size compared to Pd and which is the reason why Ni catalysts have been used for coupling. They are effective, fairly simple to use and in general tolerate well the presence of other active groups. Palladium is especially important, when compared to the other transition metals typically used in these reactions, due to its exceptional ability to form carbon-carbon bonds. The first class of reactions catalyzed by nickel is coupling reactions. Indeed, the literature is full of examples. One can,

for example, perform a Kumada-Corriu coupling reaction using a nickel (II) complex⁴⁻⁶. However, Kumada-Corriu coupling is not the only coupling reaction that can be catalyzed using a nickel complex. In fact, the Suzuki-Miyaura coupling is also effectively catalyzed (with yields of over 90%) by the nickel (II) complex⁷. Ultrasounds generally show an acoustic wave with frequencies in the 20-100 MHz range⁸. This energy is enough to spark chemical reactions. However, the use of ultrasounds produced in the middle of the cavities^{8,9} can generate high local temperatures and pressures^{11,12} or very strong electric fields^{10,12}. In this respect, the sonication of the multiphase systems accelerates the reaction by guaranteeing a better contact between the different phases present¹³⁻¹⁵. In organic synthesis, many reactions have been re-analyzed using this unconventional activation technique. Biaryl is used as an intermediate for the production of a wide range of organic compounds (e.g. emulsifiers, optical brighteners, crop protection products, plastics), as a heat transfer medium alone or with diphenyl ether in heating fluids, as a dyestuff carrier for textiles and copying paper and as a solvent in pharmaceutical production. Aminodiaryls are used as rubber antioxidants and intermediates for the synthesis of organic compounds¹⁶. Biaryl derivatives are used as an intermediate for the synthesis of organic compounds including pharmaceuticals, antifungal agents¹⁷, optical brightening agents and dyes¹⁸. Biaryl

*Corresponding author : *Ridha Ben Salem*

Email address : ridha.bensalem@voila.fr

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(biphenyl) compounds are also used in luminescence chemistry, spectrophotometric analysis, molecular chemistry, and as a starting material for organometallic complexes¹⁹. In search of inexpensive and environmentally benign catalysts, tetraalkylammonium salts have been tested alternatively as catalysts for the Heck reaction^{20,21} in DMF/ water. In this paper, we have reported the synthesis of biaryl by Suzuki reaction in aqueous potassium carbonate under phase transfer catalysis using methyltriethylammonium chloride (Aliquat-336) as phase transfer agent.

We also propose the study of the effect of the catalytic system and the ultrasonic activation on the evolution of the Suzuki coupling reaction to synthesize biaryls in the presence of Aliquat-336. The synthesized compounds were screened for their antioxidant activity.

Experimental Section

General procedure

Classical procedure without ultrasound

The aryl halide (0.5 mmol), Aliquat-336 (1.25 mmol), aryl boronic acid (0.75 mmol), K₂CO₃ (1.0 mmol) and the catalyst Ni(OAc)₂ (0.02 mmol) were placed in a Schlenk tube. Vacuum was applied for 30 min, and then argon was admitted. Water (1.5 mL) and N, N-dimethylformamide (1.5 mL) were added. The reaction was carried out at 100 °C for 5 h. After reaction, the mixture was cooled and the organic phase extracted (three times) with Hexane/Water (5:1). The extraction was dried on MgSO₄ and the solvent removed under vacuum. The coupling product was finally isolated by silica gel chromatography.

Ultrasonic irradiation

The ultrasonic probe was directly immersed in the reactor. An ultrasonic generator (Sonics VC 505 300 W) emits the sound vibration into the reaction mixture. Sonification was achieved at low frequencies of 20 kHz (amplitude of 50%) at room temperature for 5 min. The aryl halide (0.5 mmol), Aliquat-336 (1.25 mmol), boronic acid (0.75 mmol), K₂CO₃ (1.0 mmol) and the catalyst Ni(OAc)₂ (0.02 mmol) were placed in a reactor. Water (1.5 mL) and N, N-dimethylformamide (1.5 mL) were added. After reaction, the mixture was extracted (three times) with Hexane/Water (5:1). The extraction was dried on MgSO₄ and the solvent removed under vacuum. The coupling product was finally isolated by silica gel chromatography.

The yields of the reactions were determined by gas chromatography on a Shimadzu 2014-GC apparatus. The capillary column was DB-5 and the carrier gas was helium.

Characterization

All compounds were characterized by IR, ¹H NMR spectra, ¹³C NMR spectra and mass spectra. The IR spectra were recorded in KBr with a JASCO FT-IR-420 spectrometer, with a precision of ±2 cm⁻¹ in the 400-4000 cm⁻¹ range. The ¹H NMR spectra (400 MHz) and ¹³C NMR spectra (100 MHz) were obtained on a Bruker AC300 spectrometer using CDCl₃ as solvent and TMS as an internal standard. Chemical shifts are given in ppm.

The coupling products were analyzed by GC-MS (Hewlett-Packard computerized system consisting of a 5890 gas chromatograph coupled to a 5971A mass spectrometer using fused-silica capillary columns with polar stationary phase: Supelcowax 10 (60 m-0.2 mm-0.20 μm film thickness). GC-MS analyses were obtained using the following conditions: carrier gas He; flow rate 1 ml/min; split 1:20; injection volume 0.1 μl; injection temperature 250 °C; oven temperature programmed from 60 to 220 °C at 4 °C/min and holding at 220 °C for 30 min; the ionization mode used was electronic impact at 70 eV.

PL spectra were measured on a C₆PbI₄ thin film using a double monochromator U1000 equipped with a photomultiplier. The excitation wavelength was the 325 nm (3.815 eV) line of a Spectra-Physics beamlock 2085 argon laser.

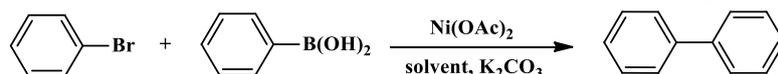
Melting points were recorded on a Reichert-Heizbank apparatus.

Results and Discussion

Chemistry

In this work, the study of some Suzuki reactions was analyzed using aryl halides and arylboronic acids. The isolated product was formed by magnetic stirring and in ultrasonic radiation in the presence of a phase transfer catalyst.

The selection of the solvent in a sonochemical reaction is crucial because the cavitation intensity varies with the solvent and depends on its nature. The intensity of cavitation in water is always a maximum and the cavitation intensity in other solvents is compared to that in water²². The effect of solvents and adding water as the co-solvent on the coupling Suzuki reaction (Table 1) was studied.

Table 1. Effect of different solvents on the Suzuki reaction in the presence of ultrasound

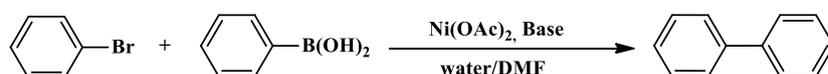
Entry	Solvent	ϵ to 25°C	μ (10^{-30} cm ⁻¹)	Yield(%) ^b
1	Toluene	2.38	11.20	5
2	THF	7.58	5.90	13
3	CH ₃ CN	35.94	5.70	26
4	H ₂ O	87	0.00	90
5	DMF	36.7	10.80	55
6	DMA	37.8	2.82	40
7	NMP	15.45	4.09	45
8	DMSO	46.7	4.3	50
9	MeOH	32.7	1.71	3
10	H ₂ O/DMF (1 :1)	-	-	97
11	H ₂ O/DMF (1 :4)	-	-	85
12	MeOH/H ₂ O (1 :1)	-	-	65

^a Reaction conditions: (0.5 mmol) of bromobenzene (0.75 mmol) of phenylboronic acid (1 mmol) of K₂CO₃, (0.05 mol%) of Ni(OAc)₂.

^b Conversion to coupled product determined by GC, based on aryl halides; average of two runs.

These results showed a conversion of 40-50% after 15 min for the reaction of polar aprotic solvents such as N,N-dimethylformamide (DMF), N, N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP) and dimethylsulfoxide (DMSO) (Table 1, entries 1-4). The reaction in ethereal, alcoholic, and non-polar solvents was sluggish (Table 1, entries 1, 2 and 9). However, the addition of water as a polar co-solvent to the aprotic solvents greatly improved the

rate of reaction. The addition of water to DMF led to a very rapid increase in the reaction rate: the reaction was complete after 5 minutes and 8 minutes when the water to DMF ratios were 1: 1 and 1: 4 respectively (Table 1, entries 10, 11). The results suggest that the water to DMF ratio plays an important role in the Ni (II)-catalyzed Suzuki reaction.

Table 2. Effect of different bases on the Suzuki reaction

Entry	Base	Yield(%) ^{ab}
1	K ₂ CO ₃	97
2	Na ₂ CO ₃	96
3	Et ₃ N	90
4	Cs ₂ CO ₃	75
5	KOH	73
6	NaOAc	61

^a Reaction conditions: (0.5 mmol) of bromobenzene, (0.75 mmol) of phenylboronic, (1 mmol) of base, (0.05 mol%) of Ni(OAc)₂, (1.5mL) of water and (1.5 mL) of DMF, 5 h, 100°C.

^b Conversion to coupled product determined by GC, based on aryl halides; Average of two runs.

To examine the effect of a base on the reaction, a series of bases were used for the coupling between bromobenzene and phenylboronic acid. The most common and inexpensive bases, such as K₂CO₃, Na₂CO₃ and Et₃N, were found to be more effective (Table 2). Surprisingly, Cs₂CO₃ was found to be less effective in the present system although it is a common base for several nickel Suzuki reactions^{23,24}. Similarly, it was found that the commonly used NaOAc was also less effective in the studies performed although it is an efficient base for Pd/NiFe₂O₅ Suzuki-type catalytic reactions²⁵. This may be due to the relatively lower basic nature of phosphinite compared to phosphines.

The reaction mechanism starts with the reduction of the Ni (II) precursor to form Ni (0). It turns out that the presence of Aliquat-336 plays an important role in the reduction of nickel (II) and in the stabilization and solubilization of nickel (0). During the reaction process, several reduction and oxidation catalytic cycles of palladium take place. The solubilization is provided by the formation of an [R₄N]₂[NiArBrCl₂]-type ionic complex. The formation of this complex leads to the release of an R₃N amine which plays the basic role required to finish the catalytic cycle of the Suzuki reaction.

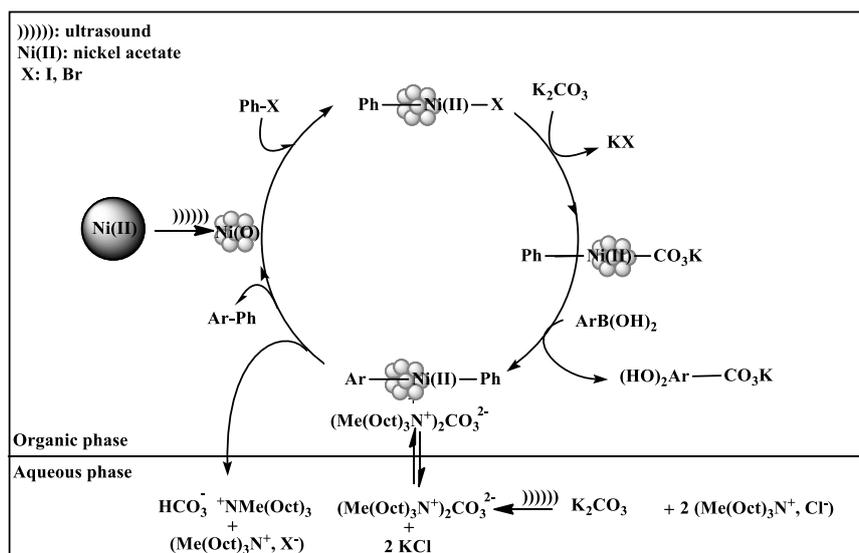
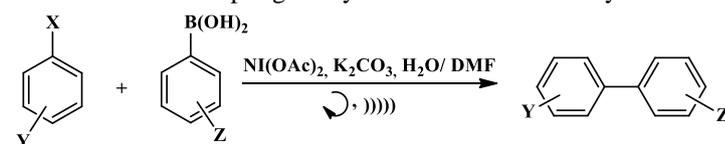


Figure 1. Sonochemical activation of Suzuki coupling in the presence of Aliquat-336

In order to increase the yield of the Suzuki coupling reaction, bi-activation with the Aliquat-336

phase transfer catalyst bias associated with ultrasonic radiation was used.

Table 3. Suzuki coupling of aryl halides and various arylboronic acids



Entry	X	Y	Z	Coupling product	Lit.	Yield(%) ^{ac}	Yield(%) ^{bc}
1	I	H	H	1a	35,36	78	91
2	I	4-Me	H	1a	35,36	75	87
3	Br	4-Me	H	2a	35,36	70	82
4	Br	4-OMe	H	3a	35,36,37	74	87
5	Br	3-OMe	H	4a	35	71	82
6	Br	2-OMe	H	5a	35	71	77
7	Br	2-Me	H	6a	35	62	72
8	Br	4-CHO	H	7a	40	70	80
9	Br	4-CN	H	8a	42	74	86
10	Rr	4-NO ₂	H	9a	35	74	88
11	Br	4-OMe	4-OMe	10a	37	69	85
12	Br	4-Me	4-Me	11a	38	74	88
13	Br	4-CN	4-CN	12a	38	68	83
14	Br	2-Me	2-Me	13a	41	60	75
15	Br	4-Cl	4-Cl	14a	38	74	90
16	Br	4-COMe	H	15a	35	78	91
17	Br	3-COMe	H	16a	35	70	86
18	Br	2-COMe	H	17a	41	65	83

^a Reaction conditions: Catalyst (0.02 mmol), Aliquat-336 (1.25 mmol), aryl halide, (0.5 mmol) arylboronic acid (0.75 mmol), K₂CO₃, (1 mmol), water (1.5 mL), DMF (1.5 mL), 5 h, 100°C

^b Catalyst (0.02 mmol), Aliquat-336 (1.25 mmol) aryl halide, (0.5 mmol) arylboronic acid, (0.75 mmol), K₂CO₃ (1 mmol), water (1.5 mL), DMF (1.5 mL), ultrasonic irradiation 5 min

^c All isolated yields, average of two runs

In this context, the results shown in Table 3 highlight that under optimized conditions at room temperature, the coupling of aryl halides with nickel catalyzed arylboronic acids, where they are activated by the Aliquat-336 phase transfer catalyst under ultrasonic radiation, tend to improve the yield

compared to conventional conditions. For example, adding the Aliquat-336 phase transfer catalyst leads to a remarkable activity (Table 3) which improves the yield^{20,21,26,27}. The positive effect of ultrasound on the yield of the coupling halides with aryl boronic acids bearing different substituents has also been

demonstrated. The effect of the substituents of the aryl boronic acid in this reaction has been investigated. The p-bromotoluene reacts with a set of aryl boronic acids which produces the corresponding biphenyl with moderate to excellent conversions (entries 2, 3, 12, 87, 82, 88%). This process was also tolerant of ortho-substituents as evidenced by the successful coupling of phenylboronic acid with 2-bromotoluene (entries 7, 14, 72, 75%). As for the non-activated substrate p-bromoanisole, the use of deactivated electron rich aryl bromide (e.g. entry 4, 11) as well as activated, electron-poor ones (entries 8-10, 13 and 16) also resulted in high yields²⁸. Generally, these coupling reactions can be satisfactorily carried out at room temperature.

Biological activity

All analyses were performed using a *UV spectrophotometer (6005)*. The result is presented as IC_{50} (the concentration of test product required for scavenging 50% of the radical).

Statistical analysis

Results are expressed as the mean \pm standard error of the mean (SEM). Statistical differences were evaluated by one-way analysis of variance (ANOVA) followed by Turkey's HSD test when significant differences were observed ($p < 0.05$). All analyses were performed using STATISTICA version 5.00 (Stat Soft- France, Tulsa, OK, USA) for Windows.

DPPH radical scavenging activity

The most common methods for determining antioxidant activity in a practical, rapid and accurate manner are those that involve a radical chromophore, simulating the reactive oxygen species (ROS). The free radical DPPH, purple in color that absorbs at 517 nm, is one of the most widely used radical chromophores for in vitro evaluation of antioxidant activity. The DPPH radical scavenging assay employed here is as described by Braca et al²⁹.

The reduction capability of the DPPH radical is determined by the decrease in absorbance at 517 nm induced by antioxidants. Ascorbic acid (AA) is the reagent used as standard. The sample is able to reduce the stable radical DPPH to the yellow-colored diphenylpicrylhydrazine. Experimentally, various dilutions of the compound methanolic solution or standard (0.001-1 mg/mL, in triplicate) were added to the DPPH solution (0.035 mg/mL). The absorbance of the mixture was taken at 517 nm with methanol as blank. A control sample with no added test compounds was also analyzed. Radical scavenging activity was expressed as a percentage and calculated using the formula: % Scavenging = $[(A_{cont} - A_{test})/A_{cont}] * 100$, where A_{cont} is the absorbance of the control, and A_{test} is the absorbance of the sample in the presence of the test compound. The result was presented as IC_{50} (the concentration of test compound required for scavenging 50% of the DPPH radical). It was found

that the aryl compound has a DPPH radical scavenging activity with an IC_{50} of 3.644 ± 0.018 mg/mL compared to ascorbic acid (IC_{50} : 0.039 ± 0.002 mg/mL), Figure 3.

Ferric reducing power (FRP)

A direct correlation has been observed between the antioxidant activity and reducing power of certain compounds. The reducing power of the extract was determined according to the method of Oyaizu³⁰ and compared with that of ascorbic acid. Substances which have a reducing potential, react with potassium ferricyanide (Fe^{3+}) to form potassium ferrocyanide (Fe^{2+}), which then reacts with ferric chloride to form a ferric ferrous complex that has a maximum absorption at 700 nm. Experimentally, a methanolic solution of the compounds (1 mL) at various concentrations (0.001-1 mg/mL) was mixed with a phosphate buffer (0.2 M) and potassium ferricyanide (1%). The mixture was incubated at 50 °C for 20 min. Aliquots of trichloroacetic acid (10%) were added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer (2.5 mL) was mixed with distilled water and a freshly-prepared ferric chloride solution (0.1%). The absorbance was measured at 700 nm. Ascorbic acid was used as standard. A control sample was prepared without adding a standard or test compound. Increased absorbance of the reaction mixture indicates an increase in reducing power. The percentage increase in the reducing power was calculated using the following formula: Increase in reducing power (%) = $[(A_{test} - A_{cont})/A_{cont}] * 100$, where A_{test} is the absorbance of the sample in the presence of the compound and A_{cont} is the absorbance of the control. The result was expressed as IC_{50} which corresponds to the concentration of the extract necessary to reduce 50% of the ferric ferrous complex. The results show that the aryl compound showed a good reducing power with IC_{50} at 1.12 ± 0.016 mg/mL compared to the ascorbic acid (IC_{50} : 0.0035 ± 0.00004 mg/mL), Figure 3.

Ferrous ion chelating (FIC) activity

It has been reported that chelating agents are effective as secondary antioxidants because they reduce the redox potential thereby stabilizing the oxidized form of the metal ion.

The FIC ability of the extract was determined according to the method of Singh and Rajini³¹. A methanolic solution of the test compound (1.0 mL) at various concentrations (0.001-1 mg/mL) was added to 1.0 mL of $FeSO_4$ (0.1 mM) and 1.0 mL of ferrozine (0.25 mM). The tubes were shaken well and left to stand for 10 min. The absorbance was measured at 562 nm. The ability of each sample to chelate ferrous ions was calculated relative to the control consisting of only iron ferrozine, using the following formula: % FIC = $[(A_{cont} - A_{test})/A_{cont}] * 100$, where A_{cont} is the absorbance of the control, and A_{test} is the absorbance of the sample in the presence of the compound.

The aryl compound showed a high ferrous ion chelating ability with IC_{50} at 2.40 ± 0.18 mg/mL

compared to the ascorbic acid (IC_{50} : 0.0057 ± 0.0002 mg/mL), Figure 3.

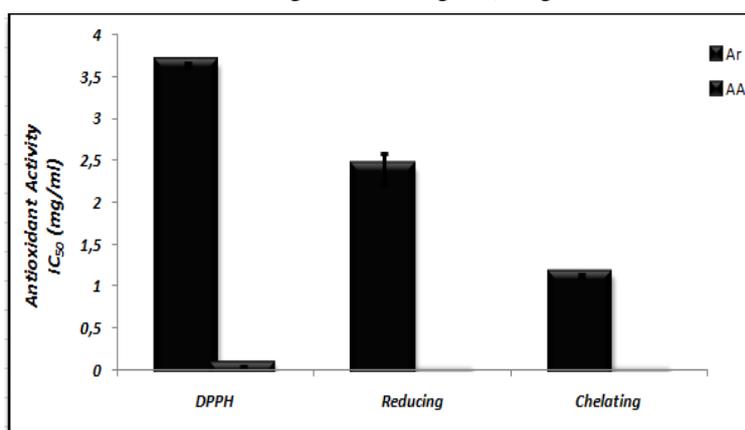


Figure 3. Antioxidant activity of biaryl-synthesized compounds (Ar: biaryl, AA: Ascorbic acid, IC_{50} mg/mL)

These results have made the link between the synthesized Biaryl compounds and antioxidant activities. They have opened the way to analyzing the complex relationship between free iron and ROS which are responsible for the oxidation of key proteins involved in signal transduction of apoptosis.

It was found that biphenyl compounds show an enhancing antioxidant activity with the DPPH, FRP and FIC methods. These results are further confirmed by those of El-Wakil et al. (2006)³², which show that the presence of aminodiphenyl groups could enhance antioxidant proprieties. This biological activity has also been highlighted by the presence of a hydroxyl group in the aromatic ring which could be an electron donor to exert direct antioxidant activity by the scavenging effect³³. These results also emphasize the ability of biaryl compounds, as iron chelators, to exert a secondary antioxidant effect by chelating the bivalent iron necessary for the formation of hydroxyl radicals and preventing the Fenton reaction³⁴.

Conclusions

Firstly, Ni (II) in the presence of Aliquat-336 has been studied in a water-DMF mixture showing high catalytic activity in the Suzuki reaction with short reaction times. Secondly, the ability of the synthesized biaryl compounds as antioxidant agents has been studied using different *in vitro* methods. It has been found that biphenyl compounds show an enhancing antioxidant activity.

Acknowledgements

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Experimental Section

All spectral data and melting points of synthesized compounds compare favourably with those cited in the literature (Table 3).

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