

The Reaction of Tetrasulfur Tetranitride with Benzyl Ketones.

Preparation of 3,4-Disubstituted-1,2,5-thiadiazoles (1)

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Received May 13, 1980

The reaction of tetrasulfur tetranitride (1) with various aryl and alkyl benzyl ketones (2a-o), oxindole (11), benzyl α -pyridyl ketone (12) and α -phenacylpyridine (13) afforded the corresponding 1,2,5-thiadiazoles (3a-n, 11 and 14). The scope and limitations of the above reaction were investigated and the evidences suggesting the radical anion mechanism are presented.

J. Heterocyclic Chem., **17**, 1681 (1980).

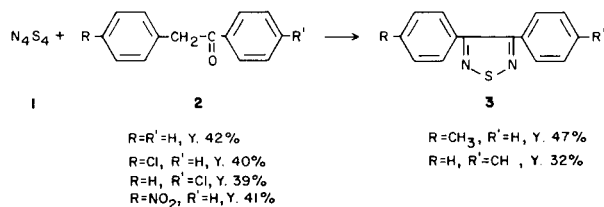
Some preparations of 1,2,5-thiadiazoles using tetrasulfur tetranitride (1) are reported; the reaction of 1 with aryloethanes such as ethylbenzene and 1,2-diphenylethane, gave the corresponding 1,2,5-thiadiazoles in low yields (4) and the reaction with acetylenes afforded 3,4-diaryl- and 3,4-diaroyl-1,2,5-thiadiazoles in good yields, respectively (5).

Recently, we have reported (6) that the reaction of benzyl ketones with 1 provided a new method for the preparation of 3,4-disubstituted-1,2,5-thiadiazoles. This method has an advantage of using easily accessible benzyl ketones as a starting material. It is the purpose of this contribution to give a more detailed scope of the reaction of 1 with benzyl ketones and to report some findings of mechanistic implication.

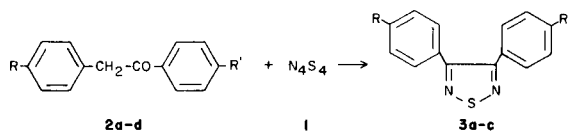
Results and Discussion.

Reaction of 1 with Desoxybenzoinz (2a-j).

It has previously reported (6) that the reaction of 1 with desoxybenzoinz having an electron-withdrawing group such as a chloro and nitro group at the 4- and 4'-position, gave 1,2,5-thiadiazoles in 39-41% yields, which are similar to that (42%) of the reaction of 1 with unsubstituted desoxybenzoinz. It was also found (6) that a electron-donating methyl group at the 4-position raised the yield (47%), while a methyl group at the 4'-position brought down the yield of 1,2,5-thiadiazole (32%).



In order to investigate the additivity of the above mentioned substituent effect, the reaction of 1 with desoxybenzoinz (2a-d) were carried out in refluxing toluene and the results are summarized in the Table 1.



The compound 3a was obtained in 49% yield as is expected in the reaction with 2a having a methyl and chloro group at the 4- and 4'-positions, respectively. However, the reaction with 2b having a methyl group at the 4'-position gave 3a in a better yield (44%) than the predicted one. When an equimolecular amount of 1 with 2c having two chloro groups was heated in toluene at reflux, 3b was obtained in 47% yield, accompanied by the recovery of 2c in 12% yield. The yield of 3b was increased up to 60% when two equivalent amounts of 1 were used.

Table 1

The Reaction of 1 with 4,4'-Disubstituted Desoxybenzoinz (2a-d)

Run	2	R	R'	Molar Ratio of 2/1	Products, Yields	Recovery of 2
1	a (7)	CH ₃	Cl	1/1	3a 49%	—
2	b (7)	Cl	CH ₃	1/1	3a 44%	—
3	c (8)	Cl	Cl	1/1	3b 47% (5)	12%
4	c	Cl	Cl	1/2	3b 60% (a)	—
5	d (9)	CH ₃	CH ₃	1/1	3c 28% (5)	14%
6	d	CH ₃	CH ₃	1/1.5	3c 28% (a)	1%

(a) Yields were calculated based upon 2.

Table 2

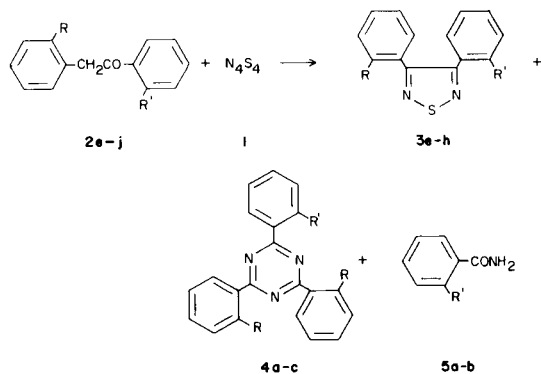
The Reaction of **1** with 2- or 2'-Substituted Desoxybenzions (**2e-j**)

Run	2	R	R'	Products, Yields	Recovery of 2
1	e (10)	CH ₃	H	3d , 3%	60%
2	f (8)	Cl	H	3e , 11%	56%
3	g (11)	NO ₂	H	3f , 18%	25%
4	h (12)	H	CH ₃	3d , 12%; 4a , 3% (13); 5a , 14% (14)	—
5	i (8)	H	Cl	3e , 46% 4b , +	—
6	j (15)	H	Br	3g , 18%; 4c , 4%; 5b , 15%	—

On the contrary, when two methyl groups were introduced in both 4- and 4'-positions as is the case of **2d**, the yield of 1,2,5-thiadiazole **3c** was considerably decreased.

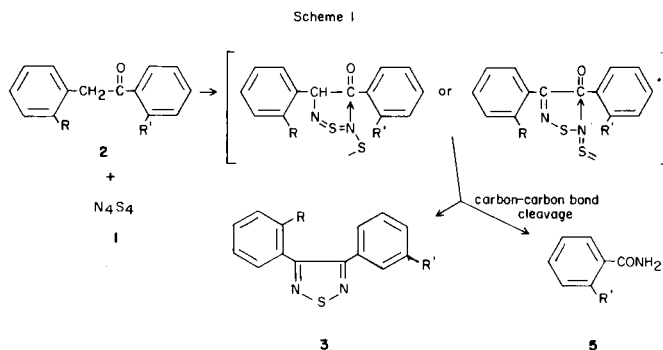
From the above results, it is concluded that the additivity of the substituent-effect observed in 4- or 4'-monosubstituted desoxybenzoin is not valid for 4,4'-disubstituted desoxybenzions (**2a-d**).

Next, the reaction of **1** with 2- or 2'-substituted desoxybenzions (**2e-j**) was studied and the results are summarized in the Table 2.



Surprisingly, **3d-f** were obtained in only poor yields, respectively, in the reaction with **2e-g** and a considerable amount of ketones (**2e-g**) were recovered though **1** was completely consumed. In the reaction with **2h** and **2j**, **3d** and **3g** were formed in poor yields. However, **2h** and **2j** were not recovered and the amides (**5a** and **5b**) which might be formed *via* carbon-carbon bond cleavage of **2h** and **2j**, were obtained together with a small amount of *s*-triazines (**4a** and **4c**). On the other hand, 2'-chloro-desoxybenzoin (**2i**) gave **3e** in 46% yield together with a trace amount of **4b**.

Thus, it is deduced that: (i) the attack of **1** on **2** occurs initially on the benzylic methylene and steric hindrance of the *ortho*-substituents of **2** interrupts the attack of **1**, resulting in the recovery of **2**; and (ii) methyl and bromo groups at the 2'-position obstruct the ring-closure of the intermediate and cause the carbon-carbon bond cleavage to yield the amides. These are depicted in Scheme 1.



The chloro group at the 2'-position of **2i** did not interrupt the reaction and this could be explained in the terms of van der Waals radius of the chloro group (1.80 Å) which is 0.10-0.15 Å smaller than those of methyl (2.0 Å) and bromo groups (1.95 Å) (**16**).

Reaction of **1** with Alkyl Benzyl Ketones (**2k-n**).

The reaction of **1** with alkyl benzyl ketones (**2k-n**) was investigated to demonstrate the usefulness of the above reaction for the preparation of 3-alkyl-4-aryl-1,2,5-thiadiazoles (**3h-k**) and the results are summarized in the Table 3.

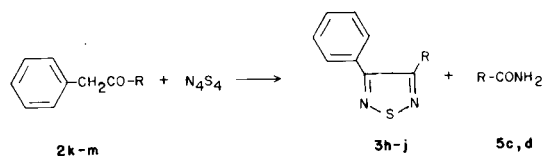


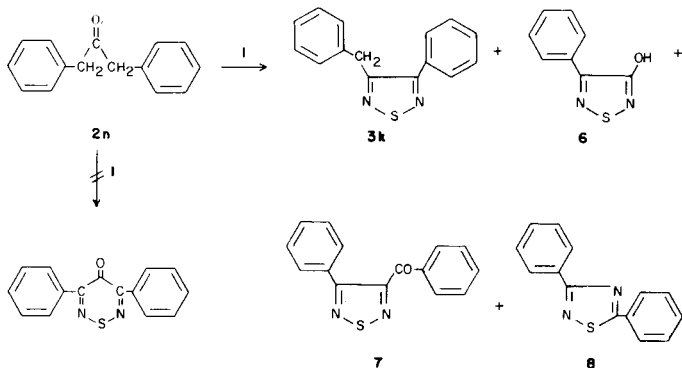
Table 3

The Reaction of **1** with Alkyl Benzyl Ketones (**2k-n**)

Run	2	R	Products, Yield %	Recovery of 2
1	k	<i>n</i> -C ₃ H ₇	3h , 20%	5%
2	l	iso-C ₃ H ₇	3i , 19%; 5c , 9% (17)	—
3	m	<i>n</i> -C ₄ H ₉	3j , 30%; 5d , 20% (18)	18%
4	n	PhCH ₂	3k , 32%; 6 , 14% (19); 7 , 2%; 8 , + (20)	—

Though 3-methyl-4-phenyl-1,2,5-thiadiazole was produced in good yield as was previously reported (6), 3-ethyl-4-phenyl-1,2,5-thiadiazole was not obtained in a significant yield and a large amount of resinous materials was formed. In the reaction with **2** having longer carbon chain such as *n*-propyl, isopropyl and *n*-butyl (**2k-m**), the expected 1,2,5-thiadiazoles (**3h-j**) were obtained in 20, 19 and 30% yields, respectively. The amides **5c** and **5d** were formed in the reaction with **2l** and **2m**; however, the pathway of the formation of these amides is obscure.

The reaction of **1** with dibenzylketone (**2n**) was expected to give **3k** and/or 1,2,6-thiadiazine-4-one. The products isolated were 1,2,5-thiadiazoles, **3k**, **6** (19) and **7** in 32, 14 and 2% yields, respectively, accompanied with a trace amount of 3,5-diphenyl-1,2,4-thiadiazole (**8**) (20); however, 1,2,6-thiadiazine-4-one was not formed. The pathways of the formation of **6**, **7** and **8** is not known.

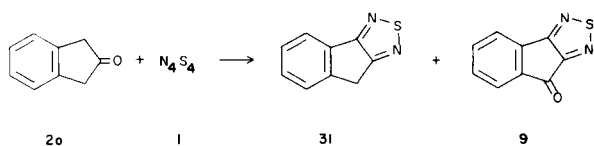


In summary, the reaction of **1** with alkyl benzyl ketones seems to be a practical method for the preparation of 3-alkyl-4-aryl-1,2,5-thiadiazoles, though 3-ethyl-4-phenyl-1,2,5-thiadiazole was not obtained.

Reaction of **1** with Some Benzyl Ketones (**2o**, **10**, **12** and **13**).

It has been previously reported (6) that the reaction of **1** with cyclic benzyl ketones such as acenaphthenone and 2-indanone (**2o**) afforded acenaphtheno[1,2-*c*]-1,2,5-thiadiazole and indeno[2,3-*c*]-1,2,5-thiadiazole (**3l**) in 7 and 20% yields, respectively.

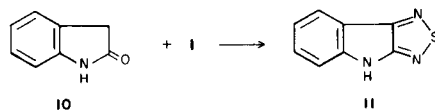
In the reaction with **2o**, **9** was found to be formed as a by-product in 4% yield.



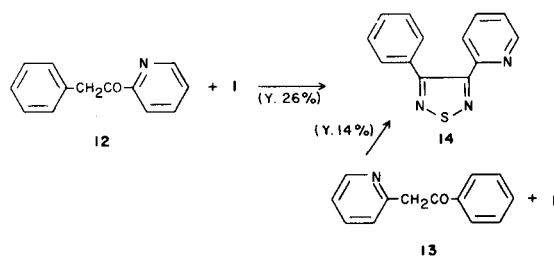
The compound **9** corresponds to the oxidation product of **3l**. Thus, the reaction of **3l** with **1** was carried out in refluxing toluene for 24 hours. No formation of **9** was detected and **3l** was recovered in 75% yield. The pathway

of the formation of **9** is not clear.

As is previously reported (6), phenylacetamide did not react with **1** in refluxing toluene. It is of interest that oxindole (**10**) (21), cyclic benzylamide, reacted with **1** to afford 1,2,5-thiadiazolo[3,4-*c*]indole (**11**), though the yield was poor and a large amount of unreacted **10** was recovered.



Pyridyl 1,2,5-thiadiazole (**14**) was prepared in 26 and 14% yields, respectively, as shown below, accompanied by a large amount of tarry materials. The difference of the yields might be due to the stability of the starting ketone [**12** (**22**) and **13**].

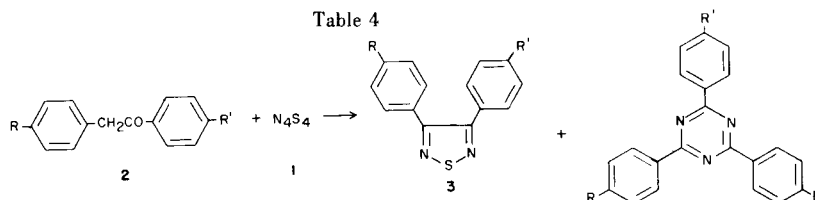


Effect of Additives on the Reaction of Tetrasulfur Tetranitride (**1**) with Desoxybenzoin (**2p-r**).

It was suggested by V. Bertini, *et al.* (8), that the initiation of reaction of **1** with 9,10-dihydrophenanthrene and tetrahydronaphthalene, giving the corresponding 1,2,5-thiadiazoles, originated with a free radical, which abstracted one hydrogen atom from the benzylic position, thus bringing about a sequence of reactions.

In this context, we have investigated the reaction of **1** with **2** under the following reaction conditions: (i) under the introduction of air; (ii) in the presence of *p*-hydroquinone under nitrogen atmosphere; and (iii) in the presence of *m*-dinitrobenzene. The results are summarized in the Table 4. When air was introduced during the reaction, yields of **3m-o** were remarkably brought down and unreacted **2p-r** were recovered. Since **1** was recovered in 52% yield after being heated at reflux for 24 hours in toluene with air-introduction, the decrease of the yield is not due to the decomposition of **1**. The addition of *p*-hydroquinone slightly effects the reaction and **3m** was obtained in 36% yield, while the yield of **3m** was also decreased significantly by the addition of *m*-dinitrobenzene which is known as a radical anion scavenger (25).

From these results, we now suppose that the reaction of **1** with benzyl ketone might proceed *via* a radical anion intermediate, though its structure is not clear.



2	R	R'	Products, Yields		Recovery of 2	Additives
			3	4		
2p	H	H	3m, 14% (6)	4d, 3.5%	6	O ₂
2q	H	4-CH ₃ (23)	3n, + (6)	—	27	O ₂
2r	4-Cl (24)	H	3o, — (6)	4e, +	32	O ₂
2p	H	H	3m, 36%	4d, 2%	—	HQ (a)
2p	H	H	3m, 29%	4d, 3%	—	<i>m</i> -DNB (b)
2p	H	H	3m, 17.5%	—	—	<i>m</i> -DNB

(a) *p*-Hydroquinone. (b) *m*-Dinitrobenzene.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured on a Nippon Bunko IR-A-102 spectrophotometer as potassium bromide pellets or as liquid films on sodium chloride plates. ¹H-nmr spectra were recorded on a Nippon Denshi JEOL FT-100 nmr spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer at 70 eV and on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system, respectively.

General Procedure for the Reaction of Sulfur Nitride (1) with Benzyl Ketones (2a-o), Oxindole (10), Benzylpyridyl Ketone (12) and Phenacylpyridine (13).

After an equimolecular mixture of sulfur nitride (1, 5 mmoles) and 2a-o, 10, 12 or 13 in 20 ml. of toluene was heated at reflux for 24 hours, it was allowed to cool to room temperature. An insoluble material containing tars and unidentified inorganic compounds was filtered off and the filtrate was evaporated *in vacuo* to leave the residue, which was extracted with hot benzene (20 ml. × 3). The extract was condensed to about 10 ml. and the condensate was subjected to column chromatography on alumina using at first hexane (A), then benzene (B), chloroform (C) and methanol (D), in case of the reaction of 2a-m, 2o, 10, 12 and 13, or on silica gel (Wako gel, C-300) using at first hexane (A) and then a 9:1 mixture of hexane and benzene (E) in case of the reaction with 2n.

Sulfur, 4a-c and 4e were obtained from the fraction A. The compounds 3a-j, 3l-o, 4d and unreacted 2 were obtained from the fraction B. The compounds 5a, 5b, 9 and 10 were isolated from the fraction C. Unreacted 10, and amides 5c and 5d were obtained from the fraction D. The compounds 3k, 6, 7 and 8 were isolated from the fraction E. The compound 14 was eluted by a 1:3 mixture of ethyl acetate and chloroform.

3-*p*-Chlorophenyl-4-*p*-tolyl-1,2,5-thiadiazole (3a).

This compound was obtained as colorless plates (hexane), m.p. 72-74°; ms: *m/e* 288, 286.

Anal. Calcd. for C₁₅H₁₁ClN₂S: C, 62.82; H, 3.87; N, 9.77. Found: C, 62.80; H, 3.77; N, 9.70.

3-Phenyl-4-*o*-tolyl-1,2,5-thiadiazole (3d).

This compound was obtained as colorless prisms (methanol), m.p. 73-74°; ¹H-nmr: δ 1.89 (s, 3H), 7.1-7.5 ppm (m, 9H); ms: *m/e* 252.

Anal. Calcd. for C₁₅H₁₂N₂S: C, 71.40; H, 4.89; N, 11.10. Found: C, 71.37; H, 4.99; N, 10.88.

3-*o*-Chlorophenyl-4-phenyl-1,2,5-thiadiazole (3e).

This compound was obtained as colorless prisms (ethanol), m.p. 88-88.5°; ms: *m/e* 274, 272.

Anal. Calcd. for C₁₄H₉ClN₂S: C, 61.65; H, 3.33; N, 10.27. Found: C, 61.72; H, 3.32; N, 10.19.

3-*o*-Nitrophenyl-4-phenyl-1,2,5-thiadiazole (3f).

This compound was obtained as colorless needles (hexane), m.p. 100-101°; ms: *m/e* 283.

Anal. Calcd. for C₁₄H₉N₃O₂S: C, 59.36; H, 3.20; N, 14.83. Found: C, 59.59; H, 3.31; N, 14.61.

3-*o*-Bromophenyl-4-phenyl-1,2,5-thiadiazole (3g).

This compound was obtained as colorless needles (hexane), m.p. 73.5-75.5°; ms: *m/e* 318, 316.

Anal. Calcd. for C₁₄H₉BrN₂S: C, 53.00; H, 2.86; N, 8.83. Found: C, 53.02; H, 2.93; N, 8.72.

3-Propyl-4-phenyl-1,2,5-thiadiazole (3h).

This compound was obtained as pale brown oil; ¹H-nmr: δ 0.88 (t, 3H), 1.81 (m, 2H), 2.97 (m, 2H), 7.3-7.7 ppm (m, 5H); ms: *m/e* 204.

Anal. Calcd. for C₁₁H₁₂N₂S: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.65; H, 5.84; N, 13.54.

3-Phenyl-4-isopropyl-1,2,5-thiadiazole (3i).

This compound was obtained as colorless prisms (methanol), m.p. 36-36.5°; ¹H-nmr: δ 1.34 (d, 6H), 3.47 (sep, 1H), 7.4-7.6 ppm (m, 5H); ms: *m/e* 204.

Anal. Calcd. for C₁₁H₁₂N₂S: C, 64.57; H, 5.92; N, 13.71. Found: C, 64.46; H, 5.92; N, 13.53.

3-*n*-Butyl-4-phenyl-1,2,5-thiadiazole (3j).

This compound was obtained as pale brown oil; ¹H-nmr: δ 0.92 (t, 3H), 1.16 (m, 2H), 1.80 (m, 2H), 3.00 (t, 2H), 7.4-7.6 ppm (m, 5H); ms: *m/e* 218.

Anal. Calcd. for C₁₂H₁₄N₂S: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.75; H, 6.25; N, 13.25.

2-(*o*-Chlorophenyl)-4,6-diphenyl-1,3,5-triazine (4b).

This compound was obtained as colorless needles (ethanol), m.p. 130.5-133°; ms: *m/e* 345, 343.

Anal. Calcd. for C₂₁H₁₄ClN₃: C, 73.36; H, 4.10; N, 12.22. Found: C, 73.63; H, 4.35; N, 12.02.

2-(*o*-Bromophenyl)-4,6-diphenyl-1,3,5-triazine (4c).

This compound was obtained as colorless needles (methanol), m.p. 135-137.5°; ms: *m/e* 389, 387.

Anal. Calcd. for C₂₁H₁₄BrN₃: C, 64.97; H, 3.63; N, 10.82. Found: C,

65.34; H, 3.84; N, 10.94.

2,4-Bis(*p*-chlorophenyl)-6-phenyl-1,3,5-triazine (**4e**).

This compound was obtained as colorless needles (hexane), m.p. 246-248°; ms: m/e 382, 380, 378.

Anal. Calcd. for C₂₁H₁₃Cl₂N₃: C, 61.65; H, 3.33; N, 10.20. Found: C, 61.69; H, 3.34; N, 10.20.

3-Hydroxy-4-phenyl-1,2,5-thiadiazole (**6**).

This compound was obtained as colorless plates (hexane), m.p. 170-171°; [lit. (19), 166-168°]; ir (potassium bromide): ν OH 3200-2400 cm⁻¹; ms: m/e 178 (M⁺), 135 (PhCNS), 103 (PhCN).

Anal. Calcd. for C₈H₆N₂OS: C, 53.92; H, 3.39; N, 15.72. Found: C, 54.10; H, 3.76; N, 15.70.

3-Benzoyl-4-phenyl-1,2,5-thiadiazole (**7**).

This compound was obtained as colorless prisms (hexane-ethanol), m.p. 81-82°; ir (potassium bromide): ν CO 1660 cm⁻¹; ms: m/e 266 (M⁺), 163 (M⁺-PhCN), 161 (M⁺-PhCO), 105 (PhCO), 103 (PhCN).

Anal. Calcd. for C₁₅H₁₀N₂OS: C, 67.49; H, 3.64; N, 10.60. Found: C, 67.66; H, 3.79; N, 10.52.

4-Oxoindeno[1,2-c]-1,2,5-thiadiazole (**9**).

This compound was obtained as yellow needles (hexane), m.p. 113°; ir (potassium bromide): ν CO 1730 cm⁻¹; ms: m/e 188.

Anal. Calcd. for C₉H₄N₂OS: C, 57.45; H, 2.14; N, 14.89. Found: C, 57.25; H, 2.06; N, 14.92.

1,2,5-Thiadiazolo[3,4-*b*]indole (**11**).

This compound was obtained as yellow needles (hexane-ethanol), m.p. 159-161°; ir (potassium bromide): ν NH 3200 cm⁻¹; ms: m/e 175.

Anal. Calcd. for C₈H₅N₃S: C, 54.86; H, 2.88; N, 23.99. Found: C, 54.84; H, 2.90; N, 23.83.

3-Phenyl-4-pyridyl-1,2,5-thiadiazole (**14**).

This compound was obtained as colorless needles (hexane), m.p. 63-64°; ms: m/e 225.

Anal. Calcd. for C₁₃H₉N₃S: C, 65.25; H, 3.79; N, 17.57. Found: C, 65.31; H, 3.91; N, 17.57.

Acknowledgement.

Financial support of this work by a Grant-in-Aid (No. 455388) from the Ministry of Education, Japan, is gratefully acknowledged.

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