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Novel one-pot synthesis of 1,3-dithiins and 1,3-thiazines under microwave irradiation

Ibadur R Siddiqui* & Pravin K Singh

Laboratory of Green Technology, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

E-mail: irspksjs@rediffmail.com

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A microwave induced expedited, high yielding three-component synthesis of 4,4′-bis[7″-aryl-5″-arylimino-2″,3″,5″,7″-tetrahydrothiazolo[4,5-*d*][1,3]dithiin-2″-thion-3″-yl)bibenzyls **3a-j** and 4,4′-bis[4″,7″-diaryl-2″,3″,4″,5″,7″-pentahydrothiazolo[4,5-*d*][1,3]thiazine-2″,5″-dithion-3″-yl]bibenzyls **4a-j** in one-pot involving Knoevenagel condensation followed by Michael addition is reported. The reaction is catalyzed by cheap and easily available NaCl under solvent-free conditions with excellent yield. The rate of the reaction has been found to be accelerated 213 fold as compared to the conventional method. The reaction is highly chemoselective and all the synthesized bibenzyl based 1,3-dithiins **3a-j** and 1,3-thiazines **4a-j** show promising antifungal activity.

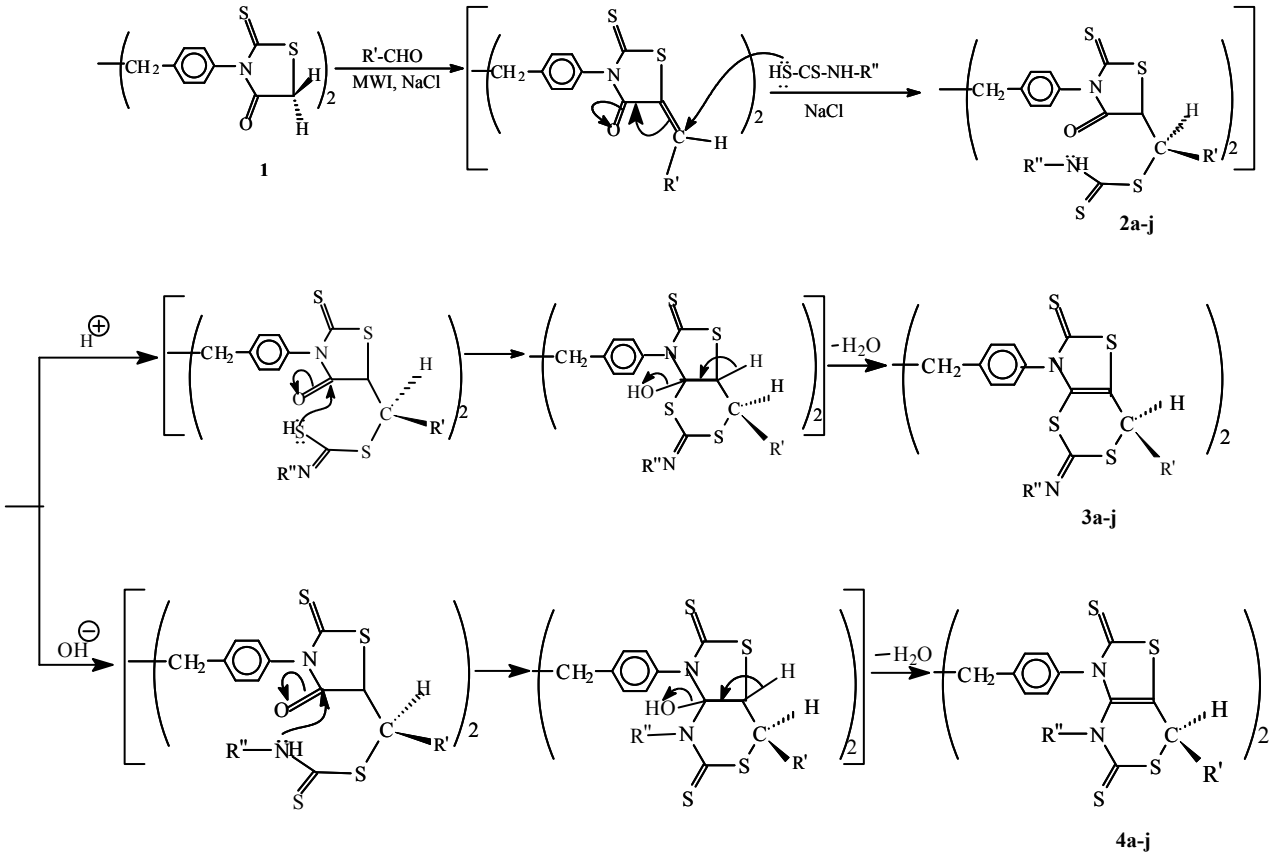
Keywords: Expedited, dithiins, thiazine, Knoevenagel condensation, Michael addition

IPC Code: Int.Cl.[8] C07D

1,3-Dithiins and 1,3-thiazines have long been recognized as a "privileged substructure" for drug design. Cephalosporins, which possessed 1,3-thiazine nucleus are presently in clinical use as antibiotics. 1,4-Dithiins and 1,4-oxathiins are commercial fungicides. Recently, various dithiins and thiazines have been synthesized by conventional method and evaluated[1-7] with a view to find pharmacological importance. Most of the methods[1-7] available for the construction of the 1,3-thiazine nucleus suffer from one or more drawbacks such as a longer reaction time and use of expensive and hazardous reagents and solvents[8-13]. Dithiocarbamates have been used as polyfunctional building blocks for the synthesis of various sulphur and nitrogen containing heterocycles of chemical and biological interest.

Reactions under solvent-free conditions using inorganic reagents are gaining much attention because of the mild reaction conditions, short reaction times, operational simplicity, formation of cleaner products[14,15] and special catalytic activity attributes under heterogeneous reaction conditions. The use of microwaves (MW) in organic synthesis has gained much attention in recent years because it offers several advantages such as rapid reaction rates and higher yields of cleaner products as a consequence of the selective absorption of microwave energy by polar molecules or polar intermediates formed during the course of the reaction[16]. The heating caused by microwave irradiation is a result of dipole rotation and ionic conductance[17]. Furthermore, with increasing environmental awareness, the development of environmentally benign synthetic methods have become desirable. Multicomponent synthesis have been documented and widely discussed, because they reduce both cost and time. In this respect multicomponent organic synthesis under solvent-free conditions in one-pot are important protocols because solvents are often toxic agents that pollute the environment.

Among the rational approaches involving drug discovery technology, combinatorial chemistry is one of the important tools for the design, discovery and optimization[18] of new and more effective drugs with lesser side effects. Primary manufacturing in the pharmaceutical industry involves the use of multistage batch processes to prepare relatively small to moderate quantity of complex chemical compounds. Consequently, there is a need for the development of a manipulatively easy, high yielding and environmentally benign solvent-free protocol for the synthesis of heterocyclic analogues of bibenzyl. In



Compd	R′	R″
3,4a	C_6H_5	C_6H_5
3,4b	*p*.$CH_3O.C_6H_4$	C_6H_5
3,4c	*m*,*p*.$(CH_3O)_2.C_6H_3$	C_6H_5
3,4d	*p*.Cl.C_6H_4	C_6H_5
3,4e	*p*.$NO_2.C_6H_4$	C_6H_5

Compd	R′	R″
3,4f	C_6H_5	*p*.$CH_3O.C_6H_4$
3,4g	*p*.$CH_3O.C_6H_4$	*p*.$CH_3O.C_6H_4$
3,4h	*m*,*p*.$(CH_3O)_2.C_6H_3$	*p*.$CH_3O.C_6H_4$
3,4i	*p*.Cl.C_6H_4	*p*.$CH_3O.C_6H_4$
3,4j	*p*.$NO_2.C_6H_4$	*p*.$CH_3O.C_6H_4$

Scheme I

this context organic reactions assisted by microwave especially under solvent-free conditions have attracted attention recently, because of their association with milder reaction conditions, enhanced yield, reduction in time and environment friendliness.

Prompted by the above reports and in continuation of the work on the development of new synthetic routes for potential bioactive compounds[19,25], an expeditious method has been devised for the synthesis of bibenzyl based 1,3-dithiins **3a-j** and 1,3-thiazines **4a-j** under microwave irradiation (**Scheme I**) in the presence of cheap and easily available NaCl.

Results and Discussion

It is noteworthy that all the bibenzyl based 1,3-dithiins and 1,3-thiazines are new. After some preliminary experimentation it was found that the envisaged microwave induced cyclocondensation of **2a-j** under acidic conditions to **3a-j** 1,3-dithiins (79-90% yield) and under basic conditions to **4a-j** 1,3-thiazines (82-94% yield) is more effective. However, the use of conventional thermal heating was far less effective resulting in relatively low yields (56%) of **3a-j** and **4a-j**. That the effect of microwaves may not be purely thermal is supported by the fact that only 56% conversion over 20 hr at the same bulk of temperature (90°C) employing conventional heating in an oil-bath was effected.

In conclusion, an expeditious multi-component synthetic route has been developed for the synthesis of 1,3-dithiin **3a-j** and 1,3-thiazine **4a-j** by cyclo-condensation of the intermediate 4,4′-bis[perhydro-

Table I — Analytical and spectral data of bibenzyl based 1,3-dithiin **3a-j** and 1,3-thiazines **4a-j**

Compd	Yield[a] (%) (Time, h)	Yield[b] (%) (Time, s)	m.p. (°C)	Mol. formula	^{1}H NMR δ (400 MHz, $CDCl_3$)	Calcd % (Found) C	H	N	MS (M^+) m/z
3a	48 (5.20)	82 (123)	163	$C_{48}H_{34}N_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 6.76 (s, 2H, ArCH), 7.22-8.10 (m, 28H, ArH)	62.44 (62.41	3.71 3.70	6.07 6.05)	922
3b	53 (5.50)	84 (155)	167	$C_{50}H_{38}N_4O_2S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.23-7.89 (m, 26H, ArH).	61.07 (61.00	3.89 3.90	5.70 5.68)	982
3c	53 (5.40)	80 (160)	159	$C_{52}H_{42}N_4O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 4.15 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.22-8.10 (m, 24H, ArH)	59.86 (59.84	4.06 4.03	5.37 5.37)	1042
3d	52 (5.30)	86 (150)	174	$C_{48}H_{32}N_4S_8Cl_2$	2.85 (s, 4H, acyclic CH_2CH_2), 6.76 (s, 2H, ArCH), 7.25-7.99 (m, 26H, ArH)	58.10 (58.06	3.25 3.23	5.65 5.66)	990
3e	54 (6.00)	90 (60)	183	$C_{48}H_{32}N_6O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 6.76 (s, 2H, ArCH), 7.22-7.73 (m, 26H, ArH)	56.89 (56.68	3.18 3.14	8.29 8.28)	1012
3f	53 (5.45)	89 (158)	191	$C_{50}H_{38}N_4O_2S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.23-7.87 (m, 26H, ArH).	61.07 (61.00	3.89 3.88	5.70 5.70)	982
3g	51 (5.35)	83 (167)	183	$C_{52}H_{42}N_4O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 12H, OCH_3), 6.76 (s, 2H, ArCH), 7.22-7.88 (m, 24H, ArH).	59.86 (59.85	4.06 4.05	5.37 5.35)	1042
3h	50 (5.20)	79 (165)	187	$C_{54}H_{46}N_4O_6S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 12H, OCH_3), 4.15 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.22-7.79 (m, 22H, ArH).	58.78 (58.77	4.20 4.17	5.08 5.06)	1102
3i	52 (5.38)	81 (155)	194	$C_{50}H_{36}N_4O_2S_8Cl_2$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.22-7.85 (m, 24H, ArH).	57.07 (57.04	3.45 3.43	5.32 5.30)	1050
3j	52 (5.40)	87 (155)	185	$C_{50}H_{36}N_6O_6S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.76 (s, 2H, ArCH), 7.22-7.67 (m, 24H, ArH).	55.95 (55.93	3.38 3.36	7.83 7.81)	1072
4a	52 (5.00)	89 (176)	176	$C_{48}H_{34}N_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 6.73 (s, 2H, ArCH), 7.22-7.86 (m, 28H, ArH).	62.44 (62.45	3.71 3.70	6.07 6.05)	922
4b	53 (6.00)	83 (120)	182	$C_{50}H_{38}N_4O_2S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.24-7.92 (m, 26H, ArH).	61.07 (61.07	3.89 3.89	5.07 5.04)	982
4c	49 (6.10)	82 (132)	168	$C_{52}H_{42}N_4O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 4.15 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.21-7.98 (m, 24H, ArH).	59.86 (59.84	4.06 4.07	5.37 5.38)	1042
4d	51 (5.35)	87 (76)	183	$C_{48}H_{32}N_4S_8Cl_2$	2.85 (s, 4H, acyclic CH_2CH_2), 6.73 (s, 2H, ArCH), 7.12-7.99 (m, 26H, ArH).	59.10 (59.12	3.25 3.26	5.65 5.63)	990
4e	53 (6.50)	89 (63)	191	$C_{48}H_{32}N_6O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 6.73 (s, 2H, ArCH), 7.02-7.96 (m, 26H, ArH).	56.89 (56.90	3.18 3.20	8.29 8.30)	1012
4f	51 (5.25)	91 (144)	187	$C_{50}H_{38}N_4O_2S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.12-7.87 (m, 26H, ArH).	61.07 (61.10	3.89 3.90	5.70 5.69)	982
4g	50 (5.27)	90 (143)	189	$C_{52}H_{42}N_4O_4S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 12H, OCH_3), 6.73 (s, 2H, ArCH), 7.21-7.98 (m, 24H, ArH).	59.86 (59.89	4.06 4.05	5.37 5.35)	1042
4h	51 (6.10)	82 (96)	191	$C_{54}H_{46}N_4O_6S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 12H, OCH_3), 4.15 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.20-7.96 (m, 22H, ArH).	58.78 (58.80	4.20 4.18	5.08 5.06)	1102
4i	40 (3.30)	84 (89)	197	$C_{50}H_{36}N_4O_2S_8Cl_2$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.22-7.89 (m, 24H, ArH).	57.07 (57.04	3.45 3.44	5.32 5.30)	1050
4j	54 (6.10)	94 (54)	196	$C_{50}H_{36}N_6O_6S_8$	2.85 (s, 4H, acyclic CH_2CH_2), 4.13 (s, 6H, OCH_3), 6.73 (s, 2H, ArCH), 7.21-7.98 (m, 24H, ArH).	55.95 (55.96	3.38 3.36	7.83 7.82)	1072

Table I — Antifungal screening results of compounds **3a-j** and **4a-j**

Compd	Average % inhibition after 96 h against					
	F. oxysporum			*P. citrinum*		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
3a	50	41	35	56	39	33
3b	94	76	39	95	80	40
3c	83	47	34	88	40	35
3d	95	53	41	93	77	49
3e	91	80	42	92	56	36
3f	61	50	44	46	43	34
3g	82	43	34	87	40	37
3h	38	35	33	67	50	36
3i	92	70	49	97	67	45
3j	78	65	40	73	56	38
4a	90	78	54	89	74	35
4b	87	67	45	81	62	33
4c	100	81	59	100	79	53
4d	85	62	41	88	69	45
4e	100	93	80	98	92	48
4f	90	81	60	78	73	40
4g	89	72	63	75	60	34
4h	87	71	64	85	70	33
4i	99	93	78	100	95	77
4j	100	90	80	98	96	80
Dithane M-45	100	96	90	100	98	90
Griseofulvin	100	95	92	100	99	91

4′′-oxo-2′′-thioxothiazol-5′′-yl-[arylmethyl]-*N*-aryl-dithiocarbamate-3′′-yl)bibenzyls **2a-j** (formed *in situ*) in one-pot, under microwave irradiation and solvent-free conditions. It reduces both cost and time. Chemo-selectivity of the cyclocondensation under acidic and basic conditions is rationalized on the basis of hard and soft acids and bases (HSAB) principle. During the cyclocondensation of **2a-j** in acidic medium[20], the hard proton protonates the hard carbonyl oxygen, leading to the formation of **3a-j** *via* intramolecular nucleophilic attack by thionic S of dithiocarbamate moiety, while the cyclocondensation of **2a-j** in basic medium[21] furnishes N, S- ambident anion, the terminal N of which attacks the carbonyl carbon to yield the corresponding **4a-j**.

The isomeric compounds **3a-j** and **4a-j** clearly differ in their IR spectra. **3a-j** exhibited a strong band attributed to $\nu_{C=N}$ around 1681–1686 cm^{-1}, whereas **4a-j** were devoid of this band. Consolidation of steps has proved to be effective for realizing an environmentally benign process, enabling elimination of toxic intermediates from the environment through *in-situ* generation followed by consumption and it may find applications in organic synthesis.

Antifungal Screening

All the synthesized compounds **3a-j** and **4a-j** were screened for their antifungal activity (**Table II**) against *Fusarium oxysporum* and *Penicillium citrinum* by agar growth technique[23] at 10, 100 and 1000 ppm concentration using griseofulvin and dathane M-45 [a mixed maganous and zinc salt of N,N-ethylenebis-(dithiocarbamic acid)] as standards. The test fungi were inoculated in the centre of the petridishes and incubated at 28±1°C for 96 hr. After this time, the percent inhibition of the mycelial growth compared with that in control dishes was recorded. Most of the screened compounds showed promising fungicidal activity at 1000 ppm concentration with both the test fungi, *Fusarium oxysporum* and *Penicillium citrinum* (**Table I**). Among the tested compounds **3b**, **3d**, **3e**, **3i**, **4c**, **4e**, **4i** and **4j** displayed best antifungal activity, comparable with griseofulvin and dithane M-45. These compounds completely inhibit the mycelial

growth of the test fungi in tested as well as reinoculated dishes and hence **3b**, **3d**, **3e**, **3i**, **4c**, **4e**, **4i** and **4j** were fungicidal and not fungistatic. This demonstrates that the presence of 1,3-dithiins and 1,3-thiazines moieties with bibenzyl nucleus resulted in appreciable enhancement of fungitoxicity of these compounds.[19,24] Presumably this is due to the appropriate orientation of lock and key mechanism of drug action.

Experimental Section

All aromatic aldehydes, silica gel and neutral alumina were obtained from Aldrich and Fluka Chemicals and used as such without further purification. ^{1}H NMR spectra were recorded on a Bruker 40^{o}C (400 MHz) FT spectrometer in $CDCl_3$ using TMS as internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer at 70 eV. IR spectra in KBr were recorded on a Perkin-Elmer 577 infrared spectrometer. Elemental analyses were carried out using a Coleman automatic carbon, hydrogen and nitrogen analyzer. An unmodified domestic household microwave oven (Padmini Essentia, Model Brownie) operating at 2450 MHz was used at a power output of 600 W for all the experiments. m.p.'s were determined in open glass capillaries and are uncorrected.

4,4′-bis[7′′-aryl-5′′-arylimino-2′′, 3′′, 5′′, 7′′-tetrahydrothiazolo[4,5-*d*][1,3]dithiin-2′′-thion-3″-yl]bibenzyls 3a-j]

Method A (Thermal method). A mixture of 4,4′-bis(rhodanin-3″-yl)bibenzyl 1 (25 mmole) (Ref. 22), and aromatic aldehyde (50 mmole) in glacial acetic acid was refluxed for 2 hr. The reaction mixture was then cooled and poured into water. The solid obtained was mixed with acidified solution (HCl, 5N) of *N*-aryldithiocarbamic acid (50 mmole) in dioxan (60 mL). This homogeneous mixture was concentrated to half of its volume, cooled and poured into water. The solid obtained was treated with conc. H_2SO_4 (17 mL) drop by drop and refluxed for 30 min, cooled and poured into ice-water. This solution was neutralized with NH_4OH. Purification by crystallization from EtOH gave pure **3a-j**.

Method B (Microwave irradiation method). A mixture of 4,4′-bis(rhodanin-3″-yl)bibenzyl **1** (2.5 mmole) (Ref. 22), aromatic aldehyde (5 mmole), *N*-aryldithiocarbamic acid (5 mmole), NaCl (0.5 mmole) and H_2SO_4 (0.25 mL, 1 *N*) was taken in a 100 mL pyrex conical flask capped with a funnel and subjected to microwave irradiation for the specified time (**Table II**), to give 4,4′-bis[7′′-aryl-5′′-aryl-imino-2′′,3′′,5′′,7′′-tetrahydrothiazolo[4,5-*d*][1,3]di-thiin-2′′-thion-3″-yl]bibenzyls **3a-j**. The completion of the reaction was checked by TLC using benzene:MeOH (7:3 v/v). The reaction mixture was cooled and extracted with acetone (3 × 20 mL). The extracts were concentrated under reduced pressure. The crude products were purified by flash chromatography (benzene:MeOH, 8:2 v/v).

4,4′-bis[4′′,7′′-diaryl-2′′,3′′,4′′,5′′,7′′-pentahydro-thiazolo[4,5-*d*][1,3]thiazine-2′′,5′′-dithion-3″-yl]-bibenzyls 4a-j

Method A (Thermal method). A mixture of 4,4′-bis(rhodanin-3″-yl)bibenzyl 1 (25 mmole) (Ref. 22), and aromatic aldehyde (50 mmole) in glacial acetic acid was refluxed for 2 hr. The reaction mixture was cooled and poured into water. The solid obtained was mixed with acidified solution (HCl, 5*N*) of *N*-aryldithiocarbamic acid (50 mmole) in dioxan (60 mL). This homogeneous mixture was concentrated to half of its volume, cooled and poured into water. The solid obtained was refluxed with 10 % aq. NaOH (20 mL) for 30 min. The mixture was cooled and poured into water. The *p*H was adjusted to between 5-6 with 5 *N* HCl. The precipitate was filtered and purified by recrystallization from EtOH to gave pure 4a-j.

Method B (Microwave irradiation method). A mixture of 4,4′-bis(rhodanin-3″-yl)bibenzyl **1** (2.5 mmole) (Ref. 22), the aromatic aldehyde (5 mmol) *N*-aryldithiocarbamic acid (5 mmole), NaCl (0.5 mmoe) and NaOH (0.25 mL, 1 *N*) was taken in a 100 mL pyrex conical flask capped with a funnel and subjected to microwave irradiation for the specified time (**Table II**), to give 4,4′-bis[4′′,7′′-diaryl-2′′,3′′,4′′,5′′,7′′-pentahydrothiazolo[4,5-*d*][1,3]thia-zine-2′′,5′′-dithion-3″-yl] bibenzyls **4a-j**. The completion of the reaction was checked by TLC using benzene:MeOH (8:2 v/v). The reaction mixture was cooled and extracted with acetone (3 × 20 mL). The extracts were concentrated under reduced pressure. The crude products were purified by flash chromatography (benzene : MeOH, 8:2 v/v).

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