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Facile domino reactions for the stereoselective assembly of highly functionalized bis-(*trans*-2,3-dihydrofuranyl) sulfides

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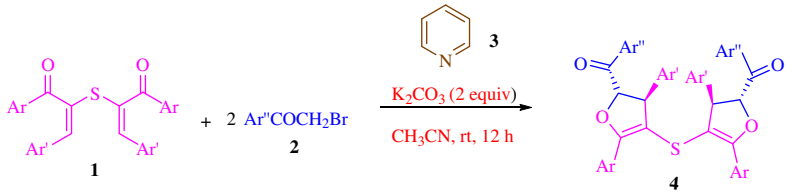
ABSTRACT

A facile stereoselective synthesis of a series of nineteen novel bis-(*trans*-2,3-dihydrofuranyl) sulfides from the reaction of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-ones) with substituted phenacyl bromides and pyridine in the presence of K_2CO_3 in acetonitrile via domino reactions is described. This transformation presumably occurs via pyridinium salt formation/ylide generation/Michael addition/intramolecular annulation domino sequence, involving the formation of two C–C and two C–O bonds and four stereocentres in a single step with complete stereoselectivity affording only one diastereomer.

Aryl sulfides are known to have broad significance in the pharmaceutical and material science arena, besides serving as important intermediates in organic synthesis. Their derivatives, viz. sulfoxides and sulfones are common functionalities in pharmaceutical agents like nonsteroidal anti-inflammatory agents,[1] selective M2 muscarinic receptor antagonists,[2] HIV protease inhibitors,[3] histone deacetylase inhibitors,[4] fatty acid amide hydrolase inhibitors,[5] etc. It is also pertinent to note that furans possess important biological activities such as anti-cancer,[6] anti-inflammatory,[7] analgesic,[8] anti-fungal[9] and anti-rheumatic.[10] They also find application as agrochemicals, pharmaceuticals, and in the food industry,[11] besides serving as potential intermediates in organic synthesis.[12] These applications stimulated widespread interest in the synthesis of furans.[13–16]

A perusal of the literature shows that no study has been reported yet on the synthesis of any compound belonging to bis(dihydrofuranyl) sulfides, while only one report exists on the synthesis of unsubstituted bis(3-tetrahydrofuranyl) sulfide.[17] This is the first time, the synthesis of a series of bis(2,3-dihydrofuranyl) sulfides has been realized (Scheme 1), that too with complete stereoselectivity affording solely one diastereomer **4**, despite the presence of four stereocentres. A plausible rationalization for the observed stereoselectivity has been provided (vide infra). These compounds bearing six aryl rings, offer great potential for generat-



Scheme 1. One pot synthesis of bis-(*trans*-2,3-dihydrofuranyl) sulfides **4**.

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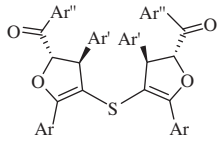
Table 1
Influence of base in acetonitrile on the yield of **4e**



Ar = Ar′ = Ph; Ar″ = *p*-ClC_6H_4

Entry	Base	mol (%)	Reaction time (h)	Yield of **4e** (%)
1	K_2CO_3[a]	100	12	39
2	K_2CO_3[a]	200	12	79
3	Et_3N[a]	200	12	73
4	DBU[a]	200	12	42
5	Pyridine	200	12	—[b]

[a] In these reactions, 200 mol % of pyridine was also employed.
[b] Product not obtained.

Table 2
Yield and melting point of bis-(*trans*-2,3-dihydrofuranyl) sulfides **4**

Compd	Ar	Ar′	Ar″	mp (°C)	Yield (%)[a]
4a	C_6H_5	C_6H_5	C_6H_5	160–162	73
4b	C_6H_5	*p*-ClC_6H_4	C_6H_5	204–206	72
4c	*p*-ClC_6H_4	C_6H_5	C_6H_5	194–196	70
4d	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	C_6H_5	228–230	80
4e	C_6H_5	C_6H_5	*p*-ClC_6H_4	239–241	79
4f	C_6H_5	*p*-ClC_6H_4	*p*-ClC_6H_4	212–214	71
4g	*p*-ClC_6H_4	C_6H_5	*p*-ClC_6H_4	240–242	78
4h	*p*-ClC_6H_4	*p*-ClC_6H_4	*p*-ClC_6H_4	246–248	72
4i	*p*-ClC_6H_4	*p*-FC_6H_4	*p*-ClC_6H_4	180–182	76
4j	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$	230–232	69
4k	C_6H_5	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	206–208	75
4l	*p*-ClC_6H_4	C_6H_5	*p*-$CH_3C_6H_4$	207–209	69
4m	*p*-ClC_6H_4	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	174–176	71
4n	*p*-ClC_6H_4	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	214–216	78
4o	C_6H_5	C_6H_5	2-Naphthyl	186–188	79
4p	C_6H_5	*p*-ClC_6H_4	2-Naphthyl	196–198	68
4q	*p*-ClC_6H_4	C_6H_5	2-Naphthyl	222–224	72
4r	*p*-ClC_6H_4	*p*-ClC_6H_4	2-Naphthyl	104–108	77
4s	*p*-ClC_6H_4	*p*-FC_6H_4	2-Naphthyl	230–232	74

[a] Obtained yield after filtration.

ing a library of densely functionalized sulfides and their derivatives, sulfoxides and sulfones, which could, in turn, be attractive for investigating biological and material properties. This transformation occurring via one pot domino reactions furnishing good yields of **4** (considering the number of steps involved) stems as a part of our recently embarked research on the synthesis of novel heterocycles employing domino, multicomponent, and green transformations.[18]

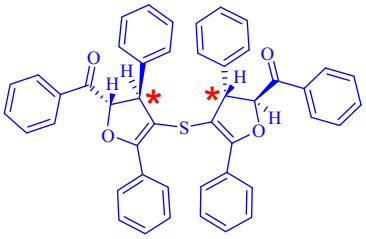


Figure 2. Possible diastereomer of **4** (viz. **4′**) differing in relative configurations at starred carbons [not formed].

In this work, the bis-(*trans*-2,3-dihydrofuranyl) sulfides **4** were obtained in good yields from the pseudo three-component reaction of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-ones) **1** with phenacyl bromide **2** and pyridine **3** in the presence of K_2CO_3 in CH_3CN at room temperature (Scheme 1). The data presented in Table 1 show that (i) the reaction fails to occur when pyridine alone, in the absence of any added base and that (ii) the base added and its quantity, in addition to pyridine, influences the yield of **4** significantly. It is also found that a maximum yield of the product was obtained, when 1 mol of (*Z*,*Z*)-2,2′-thiobis(1,3-diaryl-prop-2-en-1-ones) was reacted with 2 mol each of phenacyl bromide, K_2CO_3, and pyridine in acetonitrile solvent (Table 1).

Consequently, all subsequent reactions were performed typically by reacting a mixture of (*Z*,*Z*)-2,2′-thiobis(1,3-diaryl-prop-2-en-1-ones) (1 mmol) **1**, phenacyl bromide (2 mmol) **2,** and pyridine (2 mmol) **3** in the presence of K_2CO_3 (2 mmol) in acetonitrile at room temperature[19] for 12 h. The solid product upon filtration, washing with petroleum ether and recrystallization from dichloromethane–ethanol mixture afforded bis-(*trans*-2,3-dihydrofuranyl) sulfides **4** in good yields in a pure state (68–80%) (Scheme 1, Table 2).

The structure of **4** is in accord with the results of elemental analyses and ^1H, ^{13}C, and 2D NMR spectroscopic data as illustrated for **4d**. In the ^1H NMR spectrum of **4d** (Fig. 1), the methyl group of the *p*-tolyl ring appears as a singlet at 2.32 ppm, which showed (i) HMBC with *ipso* carbon of the *p*-tolyl ring at 137.5 ppm and (ii) C,H-COSY correlation with the carbon signal at 21.1 ppm. The hydrogens, H-2 and H-3, related by a H,H-COSY correlation, appeared as doublets, respectively at 5.75 and 4.10 ppm (J = 4.2 Hz) revealing their *trans*-relationship. These hydrogens showed HMBCs (Fig. 1) with C-4 at 105.8 ppm and C-5 at 154.2 ppm and also showed, respectively C,H-COSY correlations with the carbon signals at 86.2 and 56.0 ppm enabling their assignments to C-2 and C-3. The H-3 showed HMBCs with the carbonyl carbon at 194.4 ppm and C-2 at 86.2 ppm. The H-2 showed HMBCs with C-3 at 56.0 ppm. Two diastereomeric structures, **4** and **4′** (Fig. 2), differing in their relative configurations at the benzylic carbons of the

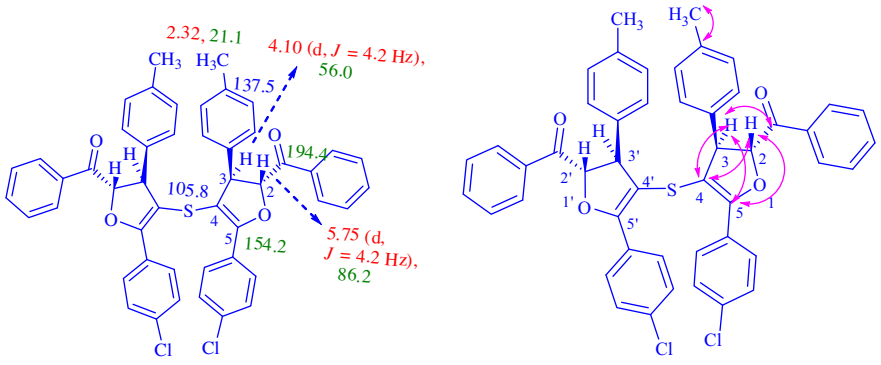


Figure 1. Selected HMB correlations and chemical shifts in **4d**.

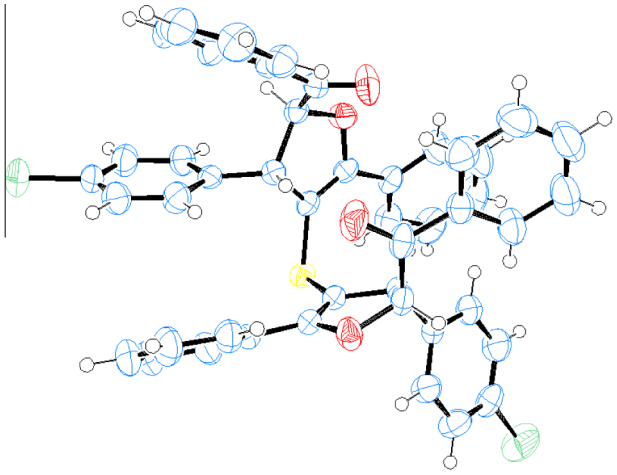


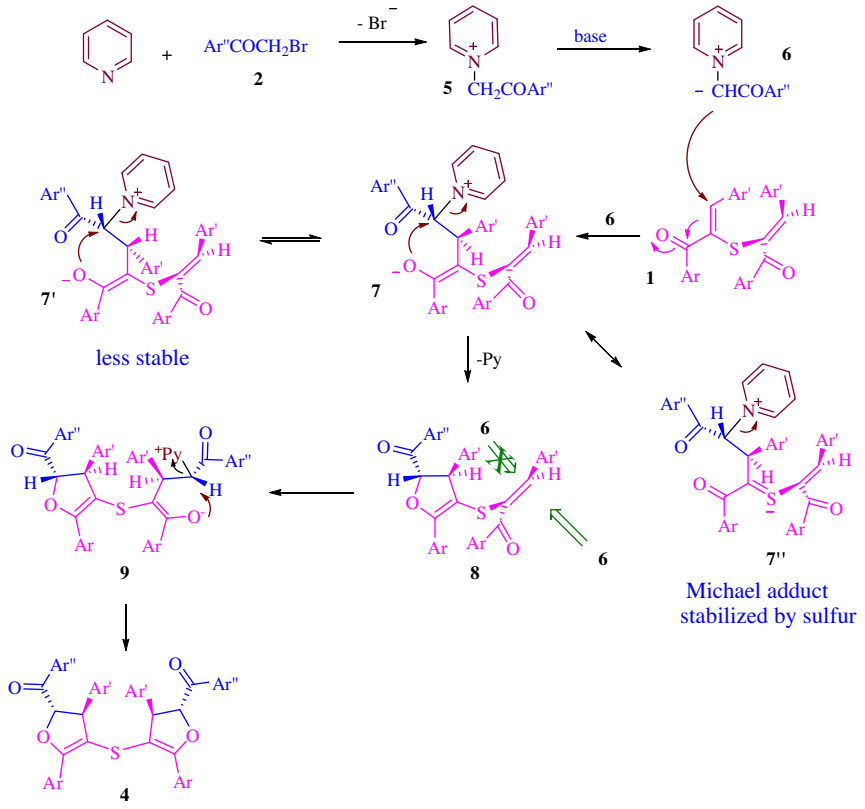
Figure 3. ORTEP diagram of **4b**.

dihydrofuranyl rings are in accord with ^{1}H, ^{13}C NMR, and HRMS mass spectra. Further distinction among them (**4** and **4′**) is enabled by an X-ray crystallographic study of a single crystal of **4b**[20] (Fig. 3), which discloses that the product has the relative stereochemistry at stereocentres shown in structure **4** (Fig. 1).

A plausible mechanism depicted in Scheme 2 involves the formation of phenacylpyridinium salt **5** in the first step, which is subsequently deprotonated to yield the pyridinium ylide, **6**. The Michael addition of this pyridinium ylide **6** to (*Z*,*Z*)-2,2′-thiobis(1,3-diaryl-prop-2-en-1-ones) **1** affords pyridinium enolates **7**, which undergo annulation to form **8**. Similar domino reactions involving the other α,β-unsaturated C=C bond of **8** with pyridinium ylide **6** ultimately affords *trans*(4,4′-thiobis(3,5-diaryl-2,3-dihydrofuran-4,2-diyl))bis(arylmetha-nones) **4**. Presumably, the sulfur atom of **1** with its low-lying vacant D-orbitals and the consequent –*R*-effect stabilizes the transition state of Michael addition and facilitates the formation of the Michael adduct (Scheme 2). On the contrary, in the nitrogen analog of **1**, the nitrogen by its +*R*-effect could diminish the electrophilicity and render the Michael addition difficult. This conclusion is supported by the fact that the reaction of a model compound comprising one α,β-unsaturated carbonyl moiety with nitrogen at α-position, viz. (*Z*)-1,3-diaryl-2-(*N*-methylanilino)-2-propen-1-ones with phenacyl bromide and pyridine under the reaction conditions employed for the synthesis of **4** failed to furnish the analogous furan derivatives.

It is pertinent to note that only one stereoisomer, **4** is formed, despite the presence of four stereocentres showing that the reaction is highly stereoselective. The *trans*-relationship between the Ar′ and COAr″ groups in the dihydrofuran ring of **8** is ascribable to the facile annulation via displacement of pyridine from the Michael adduct **7**, while the *cis* stereochemical relationship requires annulation via the other possible Michael adduct **7′**, a diastereomer of **7**, that could be present in the equilibrium mixture, which would have gauche interactions between aryl ring with aroyl as well as pyridinium ring rendering **7′** difficult to react. This *trans*-relationship between the Ar′ and COAr″ is also in accord with higher stability of **4** relative to its diastereoisomer with Ar′ and COAr″ in *cis*-relationship. The reaction of **8** with **6** furnishing **4** with the *trans*-relationship between Ar′ and COAr″ in the second dihydrofuranlyl ring is also explicable similarly.

The relative configuration of the two benzylic carbon (Ar′CH) stereocentres, one in each dihyrofuranyl ring, as shown on structure **4** is not readily apparent. This is tentatively ascribable to the preferred attack of the phenacylpyridinium ylide **6** on **8** from the less hindered side as shown in Scheme 2 affording intermediate **9**, which upon annulation via substitution furnishes **4**.



Scheme 2. Plausible mechanism for the stereoselective formation of bis-(*trans*-2,3-dihydrofuranyl) sulfides **4**.

In conclusion, we have described a facile synthesis of *trans*-(4,4′-thiobis(3,5-diaryl-2,3-dihydrofuran-4,2-diyl))bis(arylmethanones) from pseudo three-component domino reactions of (*Z*,*Z*)-2,2′-thiobis(1,3-diaryl-prop-2-en-1-ones), substituted phenacyl bromides, and pyridine. This transformation occurs via two C–C and two C–O bond formations and the generation of four stereocentres in a completely stereoselective manner with the exclusive formation of one diastereomer.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.088.

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19. *General procedure for the synthesis of (4,4′-thiobis(3,5-diaryl-2,3-dihydrofuran-4,2-diyl))bis(arylmethanones) (**4**)*
A mixture of (*Z*,*Z*)-2,2′-thiobis(1,3-diaryl-prop-2-en-1-ones) **1** (1 mmol) with α-phenacyl bromides **2** (2 mmol), pyridine **3** (2 mmol), and K_2CO_3 (2 mmol) in acetonitrile was stirred at room temperature for 12 h. The solid precipitated from the reaction mixture was filtered, washed with petroleum ether (2 ml), and recrystallized from dichloromethane–ethanol mixture (3:2 (v/v), 5 ml) to give *trans*-(4,4′-thiobis(3,5-diaryl-2,3-dihydrofuran-4,2-diyl))bis(arylmethanones) **4** in good yields. Spectroscopic data for a representative compound **4d** are given below.
*4,4′-Thiobis(5-(4-chlorophenyl)-3-p-tolyl-2,3-dihydrofuran-4,2-diyl)bis-(phenylmethanone) (**4d**)*. Obtained as white solid; yield: 80%; mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.32 (s, 6H, CH_3), 4.10 (d, 2H, *J* = 4.2 Hz, H-3), 5.75 (d, 2H, *J* = 4.2 Hz, H-2), 6.95 (br s, 8H, ArH), 7.18 (d, 4H, *J* = 8.7 Hz, ArH), 7.41 (t, 4H, *J* = 7.8 Hz, ArH), 7.59 (t, 2H, *J* = 7.8 Hz, ArH), 7.67 (d, 8H, *J* = 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.1, 56.0, 86.2, 105.8, 127.9, 128.0 (2C), 128.6, 128.8, 129.1, 129.3, 133.6, 134.8, 137.2, 137.5, 154.2, 194.4. Anal. Calcd for $C_{48}H_{36}Cl_2O_4S$: C, 73.93; H, 4.65; Found: C, 73.81; H, 4.71.
20. Crystallographic data (excluding structure factors) for compound **4b** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 814421. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].