AN EFFICIENT DOMINO SYNTHESIS OF FUNCTIONALIZED TETRAHYDROTHIENO[3,2-B]FURAN

Dr. B. Vinosha,[a,*] Dr. S. S.Sukumari[a] and Dr. R. Hariharan[b]

[a]PG and Research Department of Chemistry, Fatima College, Madurai, Tamilnadu, India 625018
[b]PG& Research Department of Chemistry, Pachaiyappa's College, Chennai, Tamilnadu, India 600030
*E-mail ID: vinosha.chemistry@fcmdu.edu.in

Abstract : An efficient domino protocol for the construction of functionalized tetrahydrothieno[3,2-b]furan from the reactions of 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones) with dihydrothiophen-3(2*H*)-one in the presence of DBU in ethanol is described under both thermal and microwave condition. The higher yields were obtained under Microwave condition compared to thermal condition. This transformation presumably occurs *via* domino Michael addition-proton exchange-annulation *via* intramolecular displacement sequence.

.*Keywords:* Domino reaction; tetrahydrothieno[3,2-b]furan; stereoselectivity; 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones); Michael addition

1. INTRODUCTION

Fused Furan and thiophene moieties[1-6] constitute an vital class of heteroaromatic compounds and exhibit a crucial role in synthetic organic chemistry. They exhibit a large variety of applications involving both the fields of natural products, pharmaceuticals and organic materials.[7–10.] Fused furan heterocyles exhibit potential biological activities and they exist in a number of commercially available pharmaceuticals.[11-13] Among fused furan heterocycles, [14]benzofuran [15-18] derivatives have been largely developed whereas for thieno[3,2-b]furan series very few examples are known.[19-23] These challenges have prompted the design of various multi -step to thieno[3,2-b]furan derivatives. Despite the several methods available toward the construction of thienofurans scaffolds, which requires hazardous chemicals, enzymes, and prolonged reaction time. Herein we report the expeditious and facile method for the formation of functionalized tetrahydrothieno[3,2-b]furan by a domino process of 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones)and dihydrothiophen-3(2*H*)-one in presence of DBU in a ratio of 1:1 in methanol medium without the need for time consuming steps.

2. Experimental Section

2.1 General Methods

The melting points are uncorrected. NMR spectra were recorded at 20°C on a Bruker AMX 300 instrument operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Solutions in $CDCl_3$ were approximately 0.05M and chemical shifts were referenced internally to TMS in δ scale (ppm). Two-dimensional NMR measurements, H,H-COSY and C,H-COSY, have also been performed using the above instrument. Standard Bruker software was used throughout. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS Analyser. A Biotage microwave synthesizer and a domestic microwave oven (IFB, model-electron of 750W capacity and microwave frequency of 2450 MHz) were employed for microwave irradiation.

General Procedure A: Conventional Heating

A solution of 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) (**1**, 1.0 mmol), dihydrothiophen-3(2H)-one (**2**, 1.0 mmol), and DBU (1.0 mmol) in MeOH (20 mL) was refluxed for 4 h. Upon completion by TLC analysis, the volatiles were removed under reduced pressure and the crude material was chromatographed on silica gel with petroleum ether–EtOAc (4:1) to give **3**.

General Procedure B: Microwave-Assisted Synthesis

A 10 mL quartz vial was charged with **1** (1.0 mmol), **2** (1.0 mmol), DBU (1.0 mmol), and MeOH (5 mL), then sealed and irradiated in a Biotage Initiator with microwave reactor. The program was set to 140 °C, 40 W, and 5 bar for the duration listed in Table 1. The reaction temperature plateaued at 140 °C within 2–5 min and was maintained for 20 min total. After cooling to rt by gas-jet over 5 min, the mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography with petroleum ether–EtOAc (4:1) to furnish **3**.

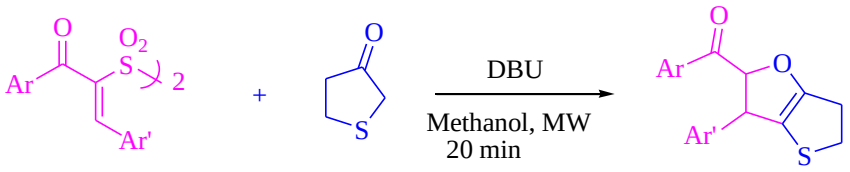
3. Results and Discussion

In the present study, the reaction of 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones) with dihydrothiophen-3(2*H*)-one in presence of DBU in a ratio of 1:1 in methanol medium under microwave irradiation and conventional thermal conditions afforded moderate yields of functionalized tetrahydrothieno[3,2-b]furan(Scheme 1). The mixture was irradiated in a sealed vial using a focused microwave reactor at 140 °C, 200 W, and 5 bar for 20 min (Table 1). After completion, the vial was cooled to room temperature and the crude residue was chromatographed on silica gel to isolate the product. For comparison, the reaction mixture was refluxed in MeOH at 80 °C for 4 h. Reaction progress in both methods was monitored by TLC.

The domino process delivered substituted tetrahydrothieno[3,2-b]furan (**3**) as the major product (Scheme). Pure functionalized tetrahydrothieno[3,2-b]furan was isolated after silica gel chromatography using EtOAc–petroleum ether [5:95 (v/v)].

Direct comparison of specific microwave effects, beyond thermal heating, was not feasible because the microwave and conventional experiments were conducted at different temperatures. Under the conditions employed, microwave irradiation gave functionalized tetrahydrothieno[3,2-b]furan in 72–78% yield within 20 min, whereas conventional heating required 4 h to afford 63–71% yield.

This protocol is operationally simple and uses readily available starting materials. To the best of our knowledge, this represents the first synthesis of functionalized tetrahydrothieno[3,2-b]furans, demonstrating the scope of the domino strategy.



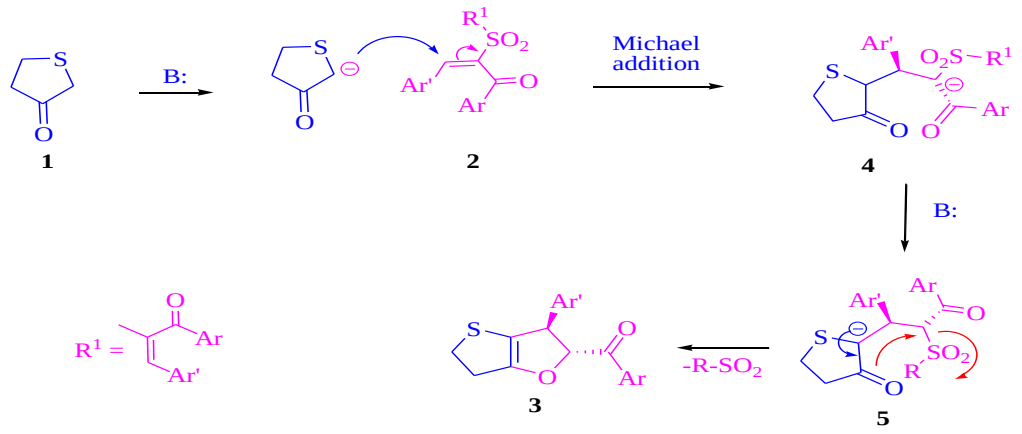
1 **2** **3**

Scheme 1: Synthesis of functionalized tetrahydrothieno[3,2-b]furans (3)

The proposed structures of the tetrahydrothieno[3,2-b]furans were corroborated by elemental analysis and 1D/2D NMR spectroscopy. Data for **3a** are discussed as a representative case.

In the ^{1}H NMR spectrum of **3a**, H-2 and H-3 resonate as doublets at δ 4.40 and 5.66 ppm, respectively (J = 11.1 Hz), and display a COSY cross-peak confirming their vicinal relationship. HMBC correlations (Figure 1-3) from both H-2 and H-3 to C-3a at δ 70.4 ppm support the fused bicyclic framework. The C-6 methylene protons appear as a triplet at δ 1.52 ppm (J = 6.9 Hz) with HMBC to C-5 at δ 23.2 ppm, while the C-5 methylene protons at δ 2.07 ppm (J = 6.9 Hz) correlate to C-6 at δ 40.5 ppm.

A proposed pathway for the assembly of tetrahydrothieno[3,2-b]furans is outlined in Scheme 2. Initial conjugate addition of the cyclothiopentanone **1** enolate to 2,2′-sulfonylbis(1,3-diarylprop-2-en-1-ones) **2** generates adduct **4**. Proton transfer gives **5**, which then undergoes intramolecular cyclization with expulsion of the sulfonyl group to furnish the product.



1 **2** **4** **5** **3**

Scheme 2: Probable mechanism for the formation of functionalized tetrahydrothieno[3,2-b]furans (**3**)

Table 1: Reaction of 2,2'-sulfonylbis(1,3-diaryl-prop-2-en-1-one) (1)
With dihydrothiophen-3(2*H*)-one

S. No.	Ar	Ar'	Product	Yield (%)[a]	
				Thermal[b]	MW[c]
1	C_6H_5	C_6H_5	**3a**	63	72
2	C_6H_5	*p*-ClC_6H_4	**3b**	69	76
3	*p*-ClC_6H_4	C_6H_5	**3c**	65	72
4	*p*-$CH_3C_6H_4$	C_6H_5	**3d**	68	73
5	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	**3e**	71	78

[a]Isolated yield after purification by column chromatography
[b]Heated under reflux in ethanol for 4 h.
[c]Irradiated in ethanol at 140 ^{0}C at 200 W power level and 5 bar pressure for 20 min.

phenyl(3-phenyl-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)methanone (3a):
Isolated as white solid.m.p.=204-206ºC;^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.52(t, 2H, , *J* =6.9Hz), 2.07(t, 2H, *J* =6.9Hz), 4.40(d, 1H, *J*=11.1Hz), 5.66(d, 1H, *J* =11.1Hz), 7.10(d, 2H, *J*=6.9Hz), 7.23-7.54(m, 5H), 7.93(d, 2H, *J*=7.8Hz), 7.66(t, 1H, *J*=7.8Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ_C23.2,40.5, 48.8, 53.5, 70.4, 127.2, 127.8, 128.4, 128.6, 130.8, 133.5, 136.1, 137.5, 194.3, 213.2. Anal. Calcd for $C_{19}H_{16}O_2S$: C, 74.00; H, 5.23; O, 10.38; Found C, 74.16; H, 5.29.

(3-(4-chlorophenyl)-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)(phenyl)methanone (3b):
Isolated as white solid.^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.56 (s, 2H), 3.28(s, 2H), 5.20(d, 1H, *J*=10.5Hz), 6.37(d, 1H, *J* =10.5Hz), 7.19-7.44(m, 7H), 7.48(d, 2H, *J*=7.2Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ_C34.0, 49.6, 56.7,59.7, 82.8, 127.4,128.1, 128.2,128.6,128.9,129.3,133.5,136.2,137.4, 190.3..Anal. Calcd for $C_{19}H_{15}ClO_2S$ C, 66.56; H, 4.41; Found C, 66.48; H, 4.35.

(4-chlorophenyl)(3-phenyl-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)methanone (3c):
Isolated as white solid.^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.42(s, 2H), 1.94(s, 2H), 4.37(d, 1H, *J*=6.9Hz), 5.44(d, 1H, *J* =6.9Hz), 7.26-7.65(m, 7H), 7.86(d, 2H, *J*=8.4Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C23.2, 48.8, 53.4, 69.8, 127.4,127.9,129.0,129.9,130.7,134.3,137.2,140.1,193.1 .Anal. Calcd for $C_{19}H_{15}ClO_2S$: C, 66.56; H, 4.41;. Found C, 66.48; H, 4.52.

(3-phenyl-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)(*p*-tolyl)methanone (3d):Isolated as white solid.m.p.=204-206ºC;^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.58(s, 3H), 2.42(t, 2H, , *J*=4.8Hz), 3.31(t, 2H, *J*=7.2Hz), 5.21(d, 1H, *J*=9.4Hz), 6.36(d, 1H, *J* =9.4Hz), 7.13(d, 2H, *J*=7.8Hz), 7.27-7.18(m, 5H), 7.41(d, 2H, *J*=6.6Hz), 7.66(t, 1H, *J*=7.8Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C21.6, 56.7, 82.8, 95.0, 128.1, 128.6, 128.8, 129.0, 129.1, 129.4, 134.8, 136.3, 144.5, 189.6. Anal. Calcd for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63. Found C, 74.45; H, 5.59.

(3-(4-chlorophenyl)-2,3.5,6-tetrahydrothieno[3,2-b]furan-2-yl)(*p*-tolyl)methanone: (3e): Isolated as white solid.^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.59(s, 3H), 2.36(s, 2H), 3.29(s, 2H), 5.20(d, 1H, *J*=6Hz), 6.25(d, 1H, *J* =6Hz), 7.34-7.14(m, 5H), 7.66(d, 2H, *J*=8.1Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C21.7, 56.9, 75.4, 82.2, 95.0, 128.9, 129.2, 129.5, 134.6, 134.9, 145.0, 189.3.Anal. Calcd for $C_{20}H_{17}ClO_2S$: C, 67.31; H, 4.80. Found C, 67.38; H, 4.75.

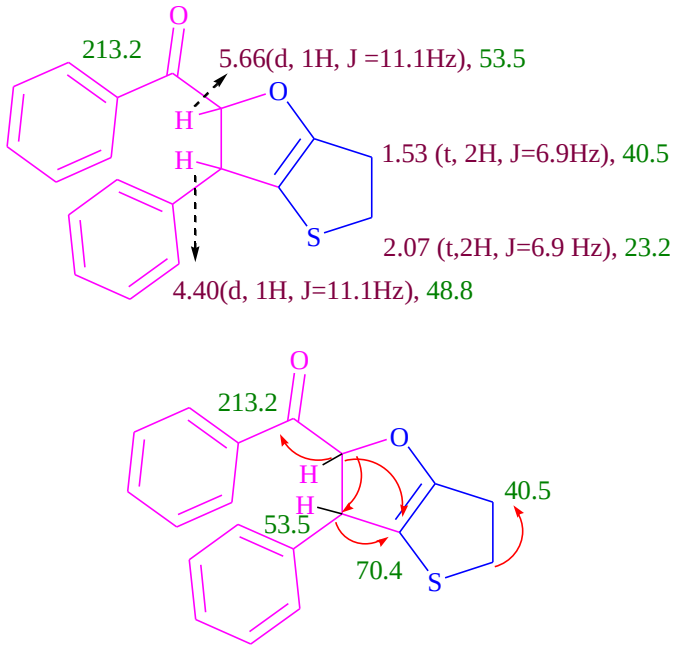


Fig 1. Selected HMBCs and chemical shifts in **3a**

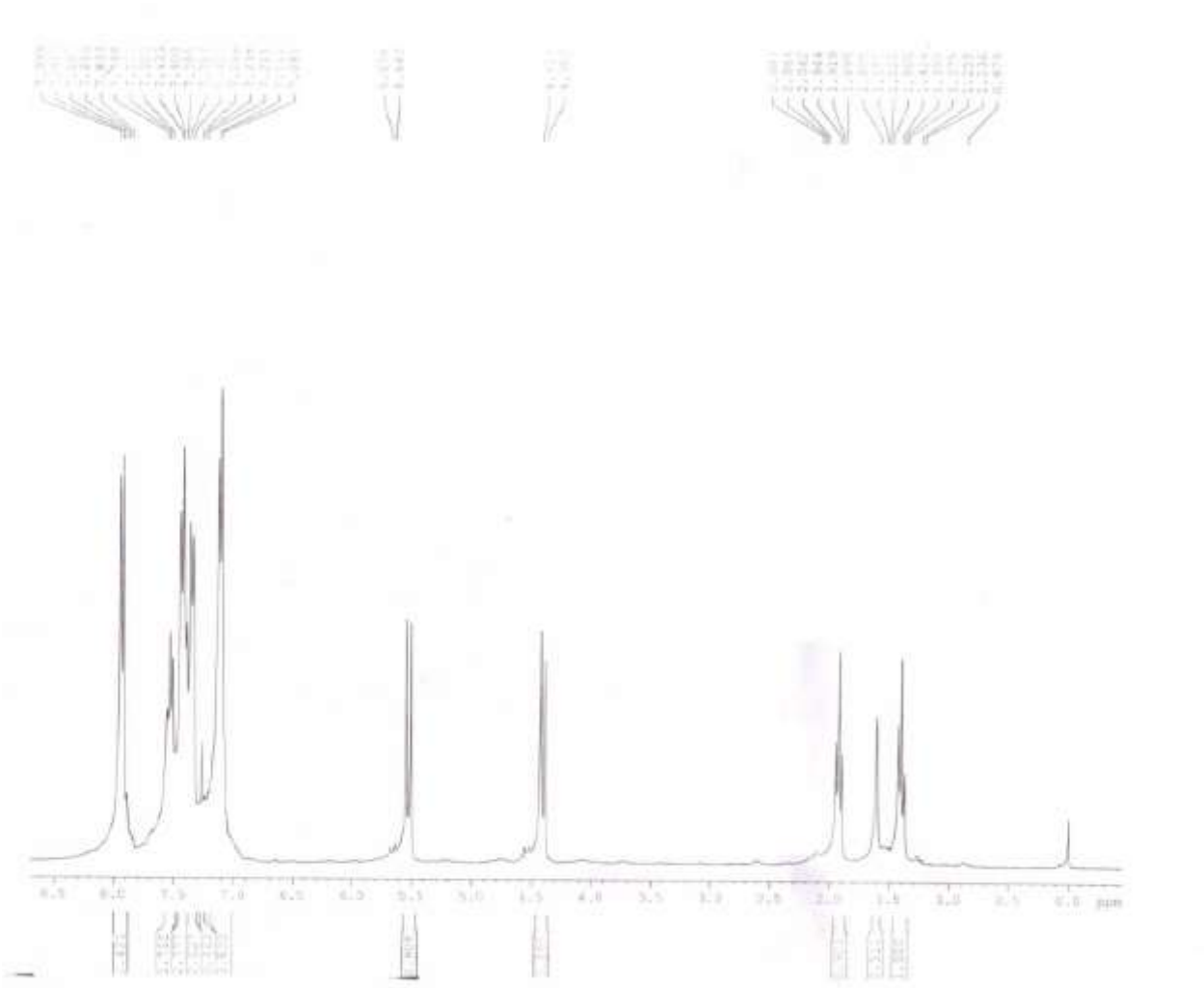


Fig 2. ^{1}HNMR Spectrum of phenyl(3-phenyl-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)methanone (3a)

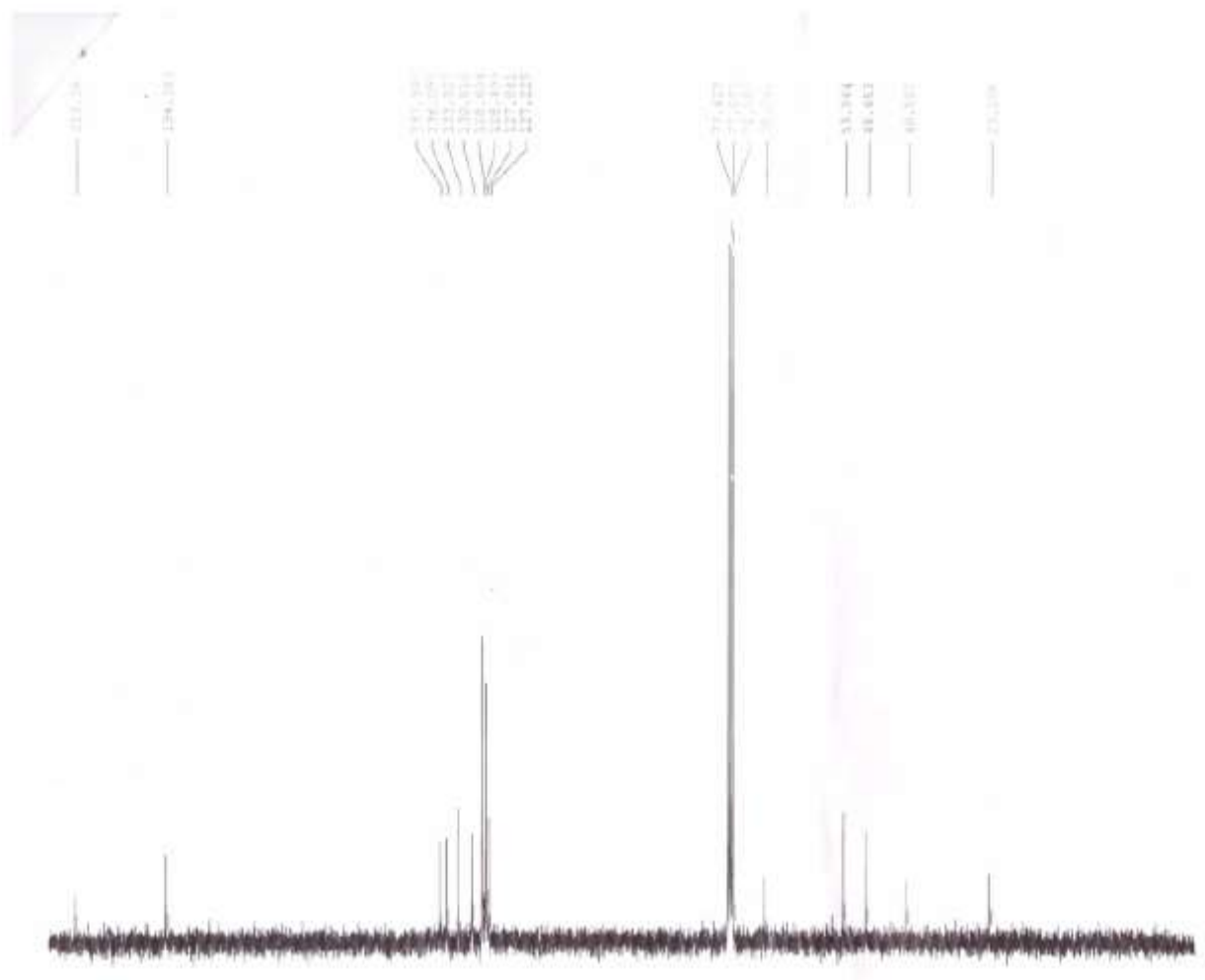


Fig 3. ^{13}C NMR Spectrum of phenyl(3-phenyl-2,3,5,6-tetrahydrothieno[3,2-b]furan-2-yl)methanone (3a)

Conclusion

The present work describes an efficient and facile protocol for the predominant formation of functionalized tetrahydrothieno[3,2-b]furans in moderate yields from the domino reactions of 2,2'-sulfonylbis(1,3-diarylprop-2-en-1-ones) and dihydrothiophen-3(2*H*)-one in presence of DBU in a molar ratio of 1:1 in methanol medium via a Michael addition-enolisation and displacement sequence.

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