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Visible-light-mediated Regioselective Synthesis of Novel Thiazolo[3,2-*b*][1,2,4]triazoles: Advantageous Synthetic Application of Aqueous Conditions

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Abstract

From a green chemistry perspective, sustainable irradiations as the power source and water as solvent have certainly grabbed the attention of chemists in recent times as these efforts reduce hazardous ecological imprints of organic synthesis. In the present work, we have established an efficient, up-front and green protocol for the regioselective synthesis of novel functionalized thiazolo[3,2-*b*][1,2,4]triazoles. The visible-light-mediated catalyst-free reaction of diversely substituted α-bromodiketones, generated *in situ* by the reaction of NBS and 1,3-diketones, with 3-mercapto[1,2,4]triazoles in aqueous conditions afforded thiazolo[3,2-*b*][1,2,4]triazole derivatives in excellent yields. The structure of the regioisomer has been confirmed explicitly by heteronuclear 2D-NMR [(^{1}H-^{13}C) HMBC, (^{1}H-^{13}C) HMQC] spectroscopic and X-ray crystallographic studies. Radical initiating and trapping experiments supported the free radical mechanism for the cyclization.

Keywords: visible-light, aqueous condition, regioselective, thiazolo[3,2-*b*][1,2,4]triazole, α-bromodiketones, 2D-NMR, X-ray crystallography

Introduction

Over the years, increasing environmental pollution and shortage of energy sources have encouraged researchers to explore green organic synthetic protocols to exterminate the dependency on non-renewable energy sources and polluting toxic solvents. Efforts have been made very recently towards the development of sustainable reaction media, especially, using water as solvent has aroused substantial attention in organic syntheses[1]. Organic transformations in aqueous conditions are always a preferable choice for chemists as water is a safe, cheap, non-toxic, non-polluting and non-flammable natural solvent available in abundance. A large variety of organic reactions have been established to take place in aqueous media[2], sometimes with exceptional improvements, such as rapid reaction rates and better selectivity compared to results obtained using traditional organic media. Indeed, water has emerged as a suitable "solvent" for selected transformations in organic chemistry regardless of prejudged beliefs of its unsuitable dissolution capabilities[3].

Light-induced organic transformations[4,5] include absorption of light by chemical substrates to excite electronically excited states from their ground states, where they undergo several physical and chemical transformations. In the recent past, a large number of environmentally benign chemical transformations[6] have been successfully established using visible-light strategies[7–9], as it is a clean, renewable, low-priced and widely available energy source[10].

Design and development of new models of heterocyclic systems with improved pharmacological and biological potential have been the continued pursuit of the synthetic community, as most of the pharmaceuticals, medicinal and agronomy chemicals have been derived from the heterocyclic moieties. Literature survey revealed that 1,2,4-triazoles and their fused heterocyclic derivatives[11–13] have perceived much attention due to their excellent biological and synthetic importance. The thiazole nucleus also acts as an important pharmacophore by interacting with the biological receptors with high affinity due to their ease of metabolism, high lipid solubility with hydrophilicity. 1,2,4-Trizoles nucleus fused with thiazole ring results in new heterocycles with improved biological activity. To the best of our knowledge there are three variants of thiazolotrizoles namely isothiazolo[3,2-*c*][1,2,4]triazole (I), thiazolo[2,3-*c*][1,2,4]triazole (II) and thiazolo[3,2-*b*][1,2,4]triazole (III) investigated in literature[14] **(Figure 1)**.

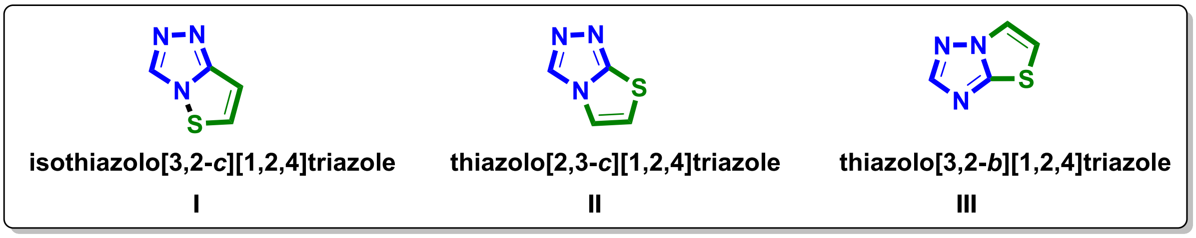


Figure 1. Different forms of thiazolotriazoles.

Out of these three isomers, thiazolo[3,2-*b*][1,2,4]triazole is the most impressive and commonly used scaffold as it is endowed with diverse biological activities such as antimicrobial[15–17], anticancer[18,19], analgesics[20,21], anti-inflammatory[22–24], anticonvulsant[22,26] , antioxidant[27], plant growth regulation[28], enzyme inhibitory[29,30] and platelet aggregation inhibitory activity[31]. Synthetic strategies[32] for thiazolo[3,2-*b*][1,2,4]triazoles involved mainly two routes: route **a** and **b** **(Figure 2)**. While route **a** includes the formation of a thiazole ring onto a triazole structure by the reaction of 3-mercapto-1,2,4-triazoles with α-functionalized ketones[33] or allyl bromide[34], or reaction with 1,4-diphenylbut-2-yne-1,4-dione[35] or one-pot reaction of mercaptotriazole, chloroacetic acid and aromatic aldehydes[26,36], route **b** involves the construction of the triazole ring onto the thiazole moiety[37] by the reaction 2-aminothiazoles with nitrile derivatives.

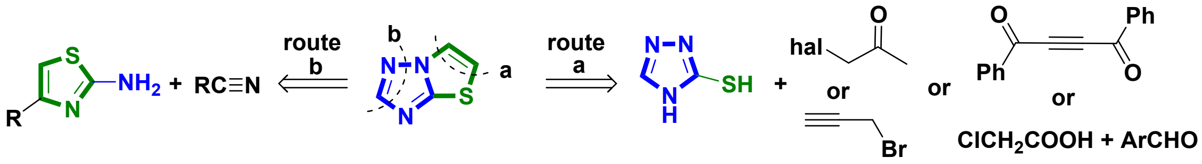


Figure 2. Literature reported retrosynthetic routes for construction of thiazolo[3,2-*b*][1,2,4]triazole core.

Our research group has been actively engaged in the designing and development of environment-friendly protocols[38] for the synthesis of diverse heterocyclic nuclei with bioactive profiles[39,40]. Presently, we are exploring the reaction of substituted unsymmetrical α-bromo-1,3-diketones with various binucleophiles[41,42] using several factors such as energy source, media and the reactivity of the substrate to get an insight of regioselective control of the reaction. In continuation of our research program, herein, we established a simple and green procedure (based on **route a)** for the regioselective synthesis of thiazolo[3,2-*b*][1,2,4]triazole by the reaction of 3-mercapto[1,2,4]triazole with several unsymmetrical 1,3-diketones using visible light as a source of energy in the aqueous medium. The structure of the single regioisomer obtained was unequivocally characterized by heteronuclear 2D-NMR [(^{1}H-^{13}C) HMBC, (^{1}H-^{13}C) HMQC] spectroscopic and X-ray crystallographic studies.

Result and Discussion

Sherif et al[14] reported the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles *via* a one-pot reaction of 3-benzyl-1,2,4-triazole-5-thiol and aromatic ketones in acidified acetic acid (AcOH/H^+). However, when the reaction of α-bromo-1-phenylbutane-1,3-dione **3a** (generated *in situ via* solvent-free grinding of 1-phenylbutane-1,3-dione **1a** with NBS **2**) and 5-phenyl-4*H*-1,2,4-triazole-3-thiol **4a** was performed under identical conditions **(Figure 3)**, it led to the formation of a single product monitored on TLC. Spectral data of synthesized compound showed interesting outcomes as the peak of the methyl group from diketone was absent and a singlet of one proton intensity has been observed at δ 7.06 in ^{1}H NMR spectrum, which indicates the expulsion of the acetyl group from diketone. IR spectrum also displayed the missing peak of corresponding carbonyl stretch.

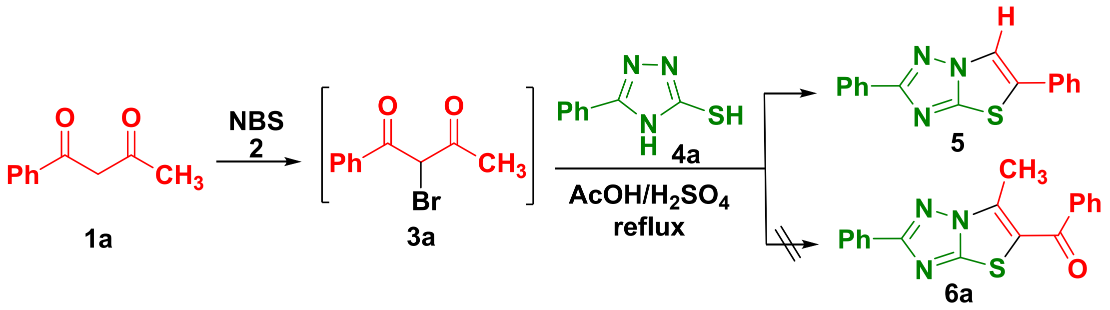


Figure 3. Unexpected synthesis of 2,5-diphenylthiazolo[3,2-*b*][1,2,4]triazole *via* reaction of *in situ* generated α-bromo-1-phenylbutane-1,3-dione with 5-phenyl-4*H*-1,2,4-triazole-3-thiol.

The structure of compound **5** was established as 2,5-diphenylthiazolo[3,2-*b*][1,2,4]triazole by comparing melting point and spectral data in the literature[19], where the desired synthesis had been achieved by the condensation of acetophenone with mercaptotriazole in refluxing acetic acid.

Therefore, we envisaged optimizing the reaction conditions for the novel highly substituted thiazolo[3,2-*b*][1,2,4]triazole derivatives through greener routes. We took α-bromo-1-phenylbutane-1,3-dione **3a** and 5-phenyl-4*H*-1,2,4-triazole-3-thiol **4a** as model substrates in different solvents (DCM, THF, CH_3CN, DMF, MeOH, EtOH and H_2O) and under solvent-free conditions **(Table 1)**. It was observed that the reaction proceeded smoothly in solvent-free conditions **(Table 1, entry 8)** as well as in polar protic solvents **(Table 1, entry 5-7)** at room temperature or using conventional heating. Unfortunately, the reaction yields in these conditions were not satisfactory. Influenced with the advantages of visible light, the reaction between **3a** and **4a** was investigated using various solvents under visible light irradiations **(Table 1, entry 9-13)**. Experimental studies showed that the reaction preceded efficiently in polar solvents H_2O, MeOH and EtOH under visible-light irradiations but the best results were obtained using H_2O as solvent (**Table 1**).

Previously, bromination of 1,3-diketones using NBS at room temperature has been reported by our research group[41] and others[43]. On exploring the reaction conditions for the bromination, we found that visible-light irradiation can be the best promoter. When 1-phenylbutane-1,3-dione **1a** was added with NBS **2** under visible light in aqueous conditions at room temperature, the reaction was completed within 15 minutes as monitored with TLC. The reaction product was isolated and the structure was established as α-bromo-1-phenylbutane-1,3-dione **3a** by matching the spectral and melting point data with literature[43]. α-Bromo-1,3-diketones **3a-j** was then treated with mercaptotriazoles to obtain the final product.

The reaction was also carried out in one-pot where **3a-j** were used *in situ* and condensed with 5-aryl-4*H*-1,2,4-triazole-3-thiol derivatives **4a-b** in similar aqueous conditions irradiated with visible-light to afford the target product with excellent yields. One-pot reaction yields were found better than the reaction proceeded in batch.

Table 1. Optimization of reaction conditions[a]

Entry	Solvent	Heat/Visible-light	Time	Yield (%)[b/c]
1.	DCM	Rt	6 hr	NR[d]
2.	THF	Reflux	4 hr	35/40
3.	CH_3CN	Reflux	5 hr	Trace
4.	DMF	Reflux	6 hr	NR[c]
5.	MeOH	Reflux	3 hr	60/67
6.	EtOH	Reflux	3 hr	65/72
7.	H_2O	Reflux	2 hr	40/54
8.	Solvent-free	Rt	1.5 hr	52/60
9.	MeOH	Visible-light	1 hr	70/75
10.	EtOH	Visible-light	50 min	74/80
11.	**H_2O**	**Visible-light**	**30 min**	**78/82**
12.	DMF	Visible-light	3 hr	20/25
13.	THF	Visible-light	2 hr	42/45

[a]Reaction conditions: a mixture of **3a** (2 mmol), and **4a** (2 mmol) in an appropriate solvent (10.0 mL) was processed in the indicated reaction condition. [b]Isolated yield of batch reaction. [c]Isolated yield of one-pot reaction. [d]N.R. = no reaction.

The reaction of trielectrophilic **(α_1, α_2, α_3)** unsymmetrical α-bromo-1,3-diketones **3** with trinucleophilic **(β_1, β_2, β_3)** 3-mercapto-1,2,4-triazoles **4** may led to produce four possible regioisomers; 5-aroyl-2-aryl-6-methylthiazolo[3,2-*b*][1,2,4]triazole **6**, 5-acetyl-2-aryl'-6-arylthiazolo[3,2-*b*][1,2,4]triazole **7**, 6-aroyl-3-aryl-5-methylthiazolo[2,3-*c*][1,2,4]triazole **8**, and 6-acetyl-3-aryl'-5-arylthiazolo[2,3-*c*][1,2,4]triazole **9** based on the electrophilicity difference of both the carbonyl groups **Figure 4**.

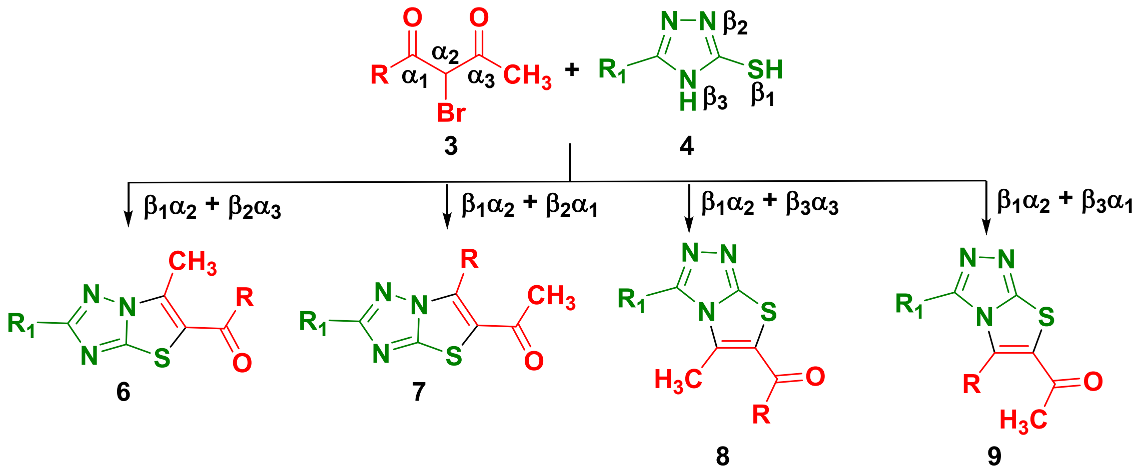


Figure 4. Possible regioisomeric structures.

However, surprisingly, the reaction yielded only a single regioisomeric product in water under visible-light irradiations within 30 minutes as indicated by TLC. IR spectrum of **6a** displayed a single absorption band at 1628 cm^{-1} due to stretching of the C=O group indicating the complete consumption of 1,3-diketone. Likewise, ^{13}C-NMR studies showed a peak at δ 188.5 corresponding to the carbonyl group incorporated in the product. ^{1}H-NMR studies demonstrated a single peak at δ 2.71 ppm validating one methyl group and ten protons in the chemical shift (δ) range of phenyl ring confirmed the successful condensation of two reactants to form (6-methyl-2-phenylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(phenyl)methanone **6a**.

Under the optimized reaction conditions, a study on the substrate scope of 1,3-diketones and 3-mercaptotriazole was carried out and summarized in **Table 2.** It was concluded from the results that a wide range of unsymmetrical 1,3-diketones substituted with *ortho-*/*meta-*/*para-*/heteroaryl substituents exhibited great compatibility to this one-pot reaction protocol. 1,3-Diketones tethered with electron-releasing substituents irrespective of their position on aryl ring afforded the desired products in better yields in comparison to the electron-withdrawing substituents. Substitutions at *para-* position of aryl ring **(6g, 6p)** resulted in improved yields than the comparable yields of *ortho-* and *meta-* derivatives **(6h-i, 6q)**. Mercaptotriazole with electron-donating groups, such as 4-methoxy, also afforded the corresponding triazolothiazole **(6j-r)** in excellent yield (77% and 94%). However the reaction of mercaptotriazoles with electron withdrawing group (such as -NO$_2$) did not completed even after irradiation of 5 hours.

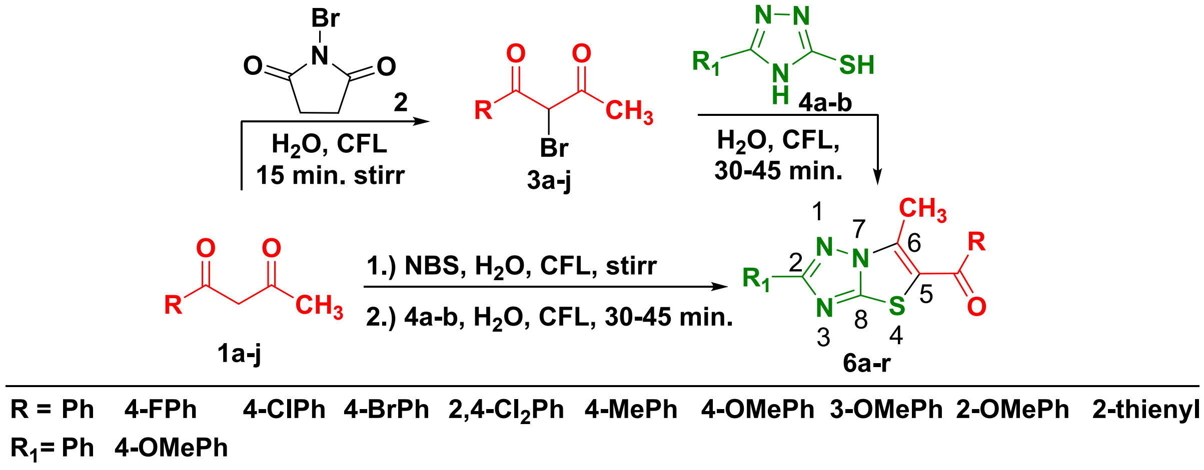
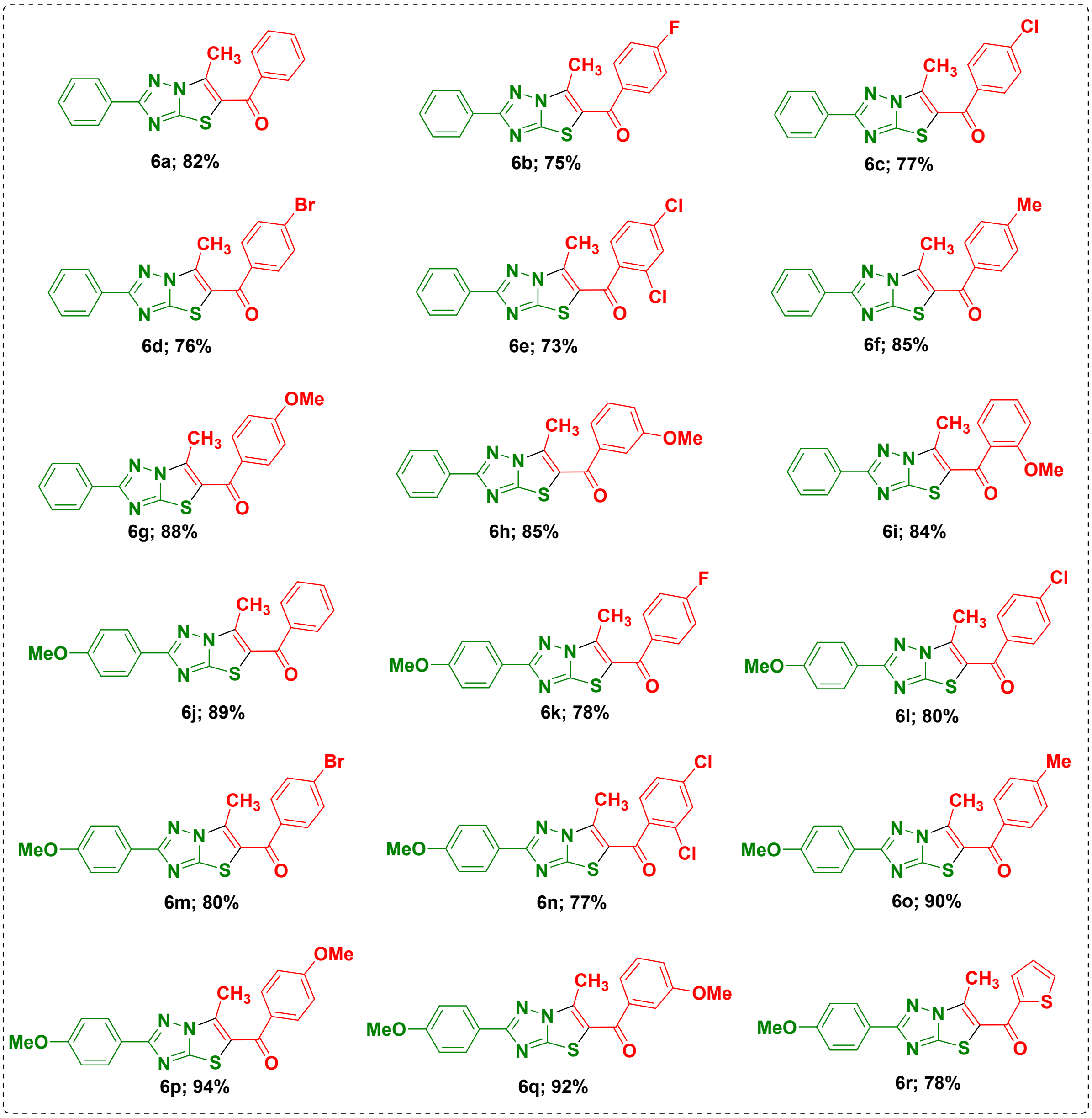


Figure 5. Regioselective synthesis of 5-aroyl-2-aryl-6-methylthiazolo[3,2-*b*][1,2,4]triazole.

Table 2. Substrate Scope



6a; 82% **6b; 75%** **6c; 77%**

6d; 76% **6e; 73%** **6f; 85%**

6g; 88% **6h; 85%** **6i; 84%**

6j; 89% **6k; 78%** **6l; 80%**

6m; 80% **6n; 77%** **6o; 90%**

6p; 94% **6q; 92%** **6r; 78%**

After completing the synthesis of (2-aryl'-6-methyl-thiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone, we envisaged to assign unambiguous regioisomeric structure of the reaction product by heteronuclear 2D NMR experiments [(^{1}H-^{13}C) HMBC and (^{1}H-^{13}C) HMQC]. 2D NMR spectra exposed definitive evidence to support the structure of the regioisomeric product as **6a** and **6j**.

The (^{1}H-^{13}C) HMBC as well as (^{1}H-^{13}C) HMQC of compounds (6-methyl-2-phenylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(phenyl)methanone **6a** shown cross peak of carbonyl carbon at δ 188.5 with a 2''/6''-H proton (δ 7.80-7.82) of aryl ring signifies the presence of carbonyl carbon with aryl ring, henceforth eliminating the possibility of regioisomers with acetyl group **7** and **9**. Possibility for the formation of thiazolo[2,3-*c*][1,2,4]triazole **8** can also be ruled out as the HMBC spectrum of **6a** does not show any correlated peak of methyl group protons at 6th position (δ 2.71) with C-2 carbon (δ 168.3). Thus, the structure can indisputably assigned as (6-methyl-2-phenylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(phenyl)methanone **6a**. Similar correlation results of (^{1}H-^{13}C) HMQC and (^{1}H-^{13}C) HMBC were observed for compound **6j** as shown in **Figure 6**.

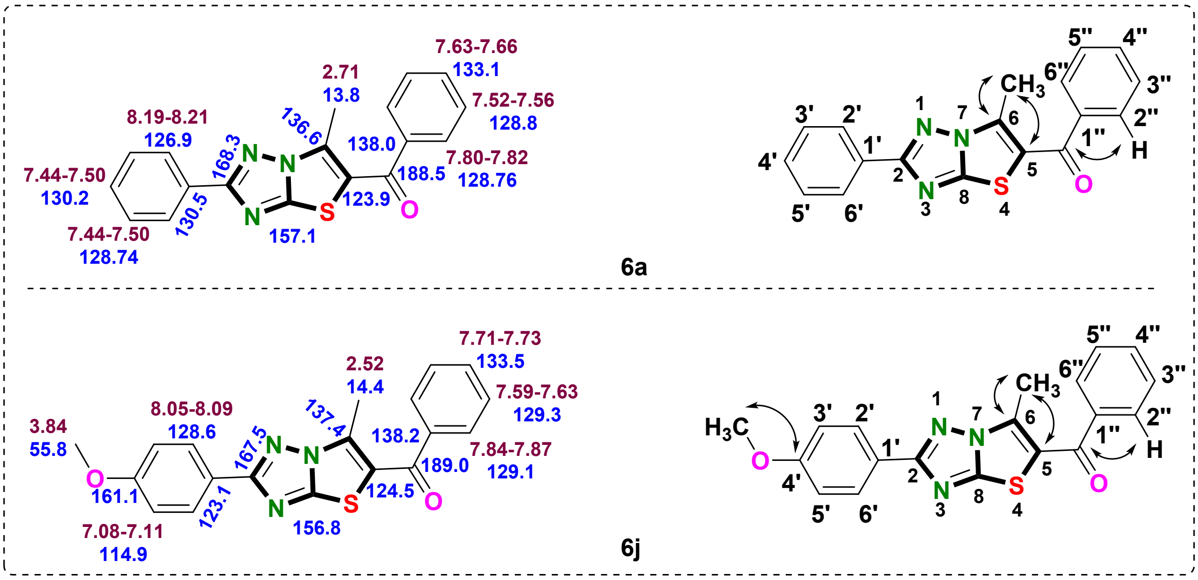


Figure 6. ^{1}H (in violet) and ^{13}C (in blue) chemical shifts of compound **6a** and **6j** and correlation depiction.

X-ray Crystallographic studies

X-ray crystallography gave the final validation of the structure as (2-(4-methoxyphenyl)-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(phenyl)methanone **6j** isomer. Efforts were made to grow crystals of several samples by gradual evaporation of solvents (ethanol+chloroform+

petroleum ether) at room temperature but only **6j** was successfully furnished into a colourless needle-shaped single crystal.

The crystalline structure of compound **6j** was studied by single X-Ray diffraction. Compound **6j** crystallized in monoclinic $P2_1/n$ space group, containing one molecule per asymmetric unit. **Figure 7** displays the ORTEP plot for **6j** with the labeling scheme of corresponding asymmetric units.

Compound **6j** appears as the regioisomer thiazolo[3,2-*b*][1,2,4]triazole (III) as depicted in the ORTEP plot, according to the bond distances and the angle data summarized in the **supplementary data**. The molecule shows a planar fragment formed by the fused thiazolo-triazole ring and the R_1 substituent, 4-MeOPh in this case, while the phenyl group R twists, as deduced from the data. In that sense, taking the fused rings as the reference, the dihedral angle that forms those with the phenyl substituent is 55.8(2)º and 3.8(2)º with the phenyl group. These results are in accordance with an electronic delocalization along with them, as deduced from the bond distances and the angle data. The methoxy group is nearly enclosed in this plane, being the corresponding O2 and C22 the farthest atoms with a distance from the main plane of 0.185(3) and 0.245(3) Å, respectively. On the contrary, the ketonic O1, in the middle of the fused and the phenyl rings, point out in the same direction as the sulphur atom to minimize the steric hindrance, probably due to the bending of phenyl substituents and the methyl on C6. The ketonic O1 atom keeps out from the main plane with a distance of 0.354(3) Å. The sulphur atom is asymmetric, situated in the thiazole ring in both compounds, as deduced from the data.

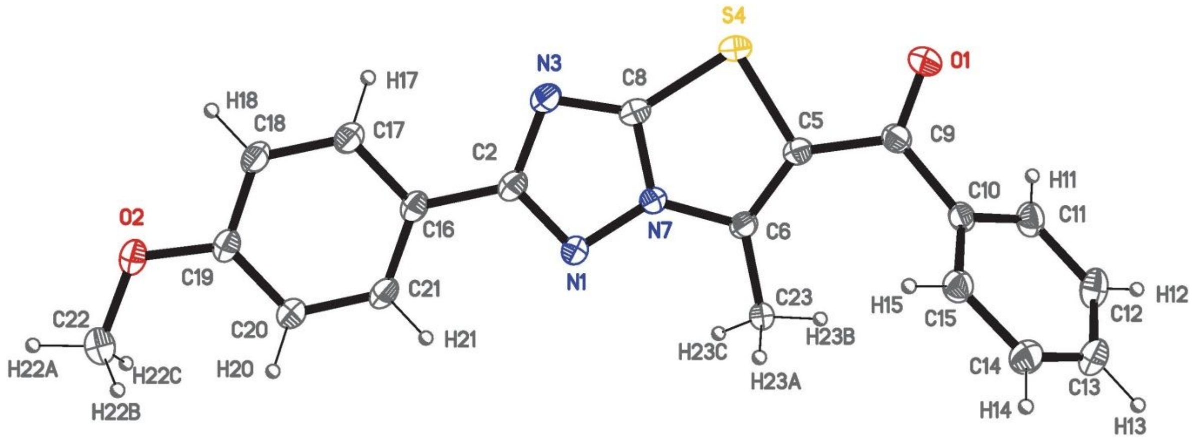


Figure 7. ORTEP plot showing the labeling scheme for compound **6j**.

Derivative **6j** pack in columns along the *b* axis to minimize the steric hindrance of the molecule, showing only weak contacts between the O1 oxygen and aromatic hydrogen atoms of neighboring molecules, leading to the final packing shown in **Figure 8.**

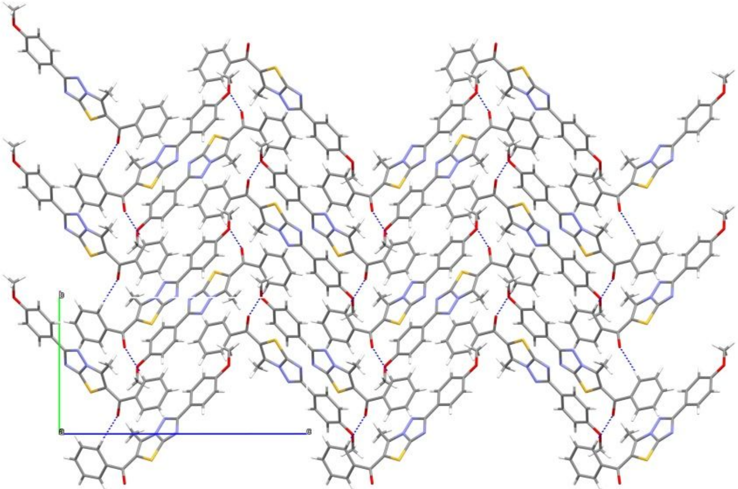


Figure 8. View of the crystal packing of **6j**

Mechanism involved

The possible mechanistic route[9,42,44] for the regioselective synthesis of (2-aryl'-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone **6a-r** is outlined in **Figure 9**. To begin with, the visible-light assisted homonuclear fission of S-H bond of 3-mercapto-[1,2,4]triazoles **4** and C-Br bond of α-bromodiketone **3** to generate the free radicals **10** and **11**, respectively, which mutually share their electron to form s-alkylated open chain structure **12**. Bromine free radical then facilitates the homolytic cleavage of β_3-N-H bond, which shifts to generate a new N-β_2 triazole radical (more nucleophilic due to α-effect), which combined with the less sterically hindered carbonyl carbon and the oxygen atom was supported by the hydrogen free radical. The intramolecular combination of these free radicals generated the (2-aryl'-6-hydroxy-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone **13** which undergoes dehydration to yield (2-aryl'-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone **6** as the exclusive product, show compatibility to our previous results[42].

To further support the plausible reaction mechanism, radical initiating and trapping experiments were carried out. Under the standard conditions, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction mixture. It has been found that the reaction was inhibited, with the yields of product **6a** being only 20%, while in presence of free radical initiator; benzoyl peroxide, the condensation reaction was improved in terms of reaction yields (**6a**;90%) and reaction rate. These results indicate that a free radical pathway is involved.

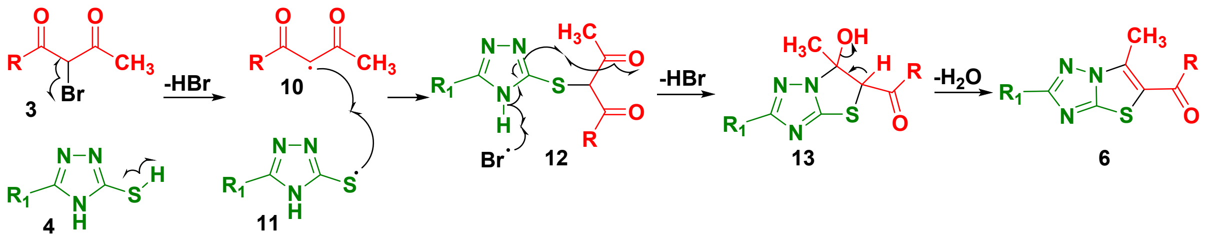


Figure 9. A plausible mechanism for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles **6a-r**.

Conclusion:

In conclusion, we have developed a highly efficient synthetic protocol for the regioselective synthesis of (2-aryl'-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone **6a-r**. Synthesis involves one-pot [3+2] cyclo-condensation of 1,3-diketones **1** with 3-mercapto-[1,2,4]triazoles **4** in presence of N-bromosuccinimide (NBS) **2** in water by stirring under visible-light irradiations. Single regioisomeric products were obtained in excellent yields and the structure of the regioisomers has been confirmed unequivocally by the laborious multinuclear NMR [(^{1}H ^{13}C) HMBC, (^{1}H ^{13}C) HMQC] spectroscopy. X-ray crystallographic studies validate the exclusive formation of single regioisomer as (2-aryl'-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone. A plausible mechanism involving free radical participation has also been proposed. This methodology reported herein offers an environmentally friendly way for the synthesis of functionalized thiazolo[3,2-*b*][1,2,4]triazoles. Studies engaged with the exploration of their biological applications are currently in progress.

Experimental:

General Methods: An electrical digital Melting Point Apparatus (MEPA) was used to examine melting points in open capillaries and are not corrected. Analytical TLC was performed using Merck Kieselgel 60 F254 silica gel plates and visualized under UV light (254 nm). The visible-light source with a lumen range of 2700-7000K (power 27 W) was placed 5 cm away from the reaction mixture. A borosilicate glass conical was used to experiment. IR spectra were recorded on Buck Scientific IR M-500 spectrophotometer in KBr pellets (υ_{max} in cm^{-1}), ^{1}H (500 Hz) and ^{13}C NMR (125 Hz) spectra for the analytical purpose were recorded on a Bruker instrument, using $CDCl_3$ as a solvent and the chemical shifts are expressed in parts per million (ppm) and coupling constant *J* in Hz with TMS as internal standard. High-resolution mass spectra (HRMS) were measured in ESI^{+} mode at MRC, MNIT, Jaipur. 2D correlation spectra, (^{1}H-^{13}C) gs-HMQC and (^{1}H-^{13}C) gs-HMBC of samples were carried out at IIT, Mandi.

General method of Synthesis

3-Mercapto-1,2,4-triazoles[30] and 1,3-diketones[41,45] were prepared according to literature procedures. Commercially available NBS was used without any purification.

General method for preparation of (2-aryl'-6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)(aryl)methanone (6)

To a stirred solution of 1,3-diketone (**1**, 1.0 eq) in distilled water, 0.178 g of NBS (**2,** 1.0 eq) was added under visible-light irradiations. Reaction contents were allowed to stir for about 15 minutes. Subsequently, 3-mercapto-1,2,4-triazole (**3**, 1.0 eq) was added to the reaction mixture and stirred for further 30-40 minutes under the same reaction conditions till the finishing point was monitored on TLC. Excess water was distilled off under reduced pressure using a rotatory evaporator, the reaction product was neutralized with an aqueous solution of sodium bicarbonate and extracted with ethyl acetate. Solid obtained after evaporation of ethyl acetate was recrystallized with ethanol, filtered and dried to obtain the product in 73-94% yields.

(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)(phenyl)methanone (6a)

White crystals;

M. Pt. 115 ºC; Yield: 82%; IR (KBr) ν_{max} (cm^{-1}): 1628 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.21 – 8.19 (m, 2H, 2',6'-H), 7.82 – 7.80 (m, 2H, 2",6"-H), 7.67 – 7.63 (m, 1H, 4"-H), 7.56 – 7.52 (m, 2H, 3",5"-H), 7.50 – 7.44 (m, 3H, 3',4',5'-H), 2.71 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 188.5, 168.3, 157.1, 138.0, 136.6, 133.1, 130.5, 130.2, 128.8, 128.7, 128.7, 126.9, 123.9, 13.8.

HRMS (ESI): m/z calcd for $C_{18}H_{13}N_3OS$: 319.0779; found: 320.0781 [M+1]$^+$;

Elemental analysis: Calcd. for $C_{18}H_{13}N_3OS$: C, 67.71; H, 4.07; N, 13.16% Found: C, 67.68; H, 4.06; N, 13.13%.

(4-fluorophenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6b)

Buff coloured solid;

M.Pt. 151 °C; Yield 75%; IR (KBr) ν_{max} (cm^{-1}): 1643 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.22 – 8.19 (m, 2H, 2',6'-H), 7.90 – 7.86 (m, 2H, 2",6"-H), 7.51 – 7.46 (m, 3H, 3",4',5"-H), 7.25 – 7.21 (m, 2H, 3',5'-H), 2.75 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 187.0, 168.5, 166.8, 164.7, 157.0, 136.7, 134.3, 131.7, 131.6, 130.4, 128.8, 127.0, 123.4, 116.1, 13.9.

^{19}F NMR (376 MHz, CDCl$_3$) δ: -103.9.

HRMS (ESI): m/z calcd for $C_{18}H_{12}FN_3OS$: 337.0685; found: 338.0689 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{18}H_{12}FN_3OS$: C, 64.09; H, 3.56; N, 12.46% Found: C, 64.08; H, 3.55; N, 12.44%.

(4-chlorophenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6c)

Creamy white solid;

M. Pt. 173.5 ºC; Yield: 77%; IR (KBr) ν_{max} (cm^{-1}): 1643 (C=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.19 (m, 2H, 2',6'-H), 7.80 – 7.77 (m, 2H, 2",6"-H), 7.55 – 7.52 (m, 2H, 3",5"-H), 7.51 – 7.47 (m, 3H, 3',4',5'-H), 2.75 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.2, 168.4, 157.0, 139.7, 136.9, 136.3, 130.4, 130.3, 130.2, 129.2, 128.7, 127.0, 123.3, 13.9.

HRMS (ESI): m/z calcd for $C_{18}H_{12}ClN_3OS$: 353.0390; found: 354.0392 $[M+1]^+$; 356.0365 $[M+1+2]^+$, (3:1);

Elemental analysis: Calcd. for $C_{18}H_{12}ClN_3OS$: C, 61.10; H, 3.39; N, 11.88% Found: C, 61.08; H, 3.35; N, 11.86 %.

(4-bromophenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6d)

Brownish solid;

M. Pt. 181 ºC; Yield: 76%; IR (KBr) ν_{max} (cm^{-1}): 1643 (C=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.19 (m, 2H, 2',6'-H), 7.72 – 7.68 (m, 4H, 2",3",5",6"-H), 7.51 – 7.47 (m, 3H, 3',4',5'-H), 2.76 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.5, 168.6, 157.1, 137.0, 136.8, 132.3, 130.5, 130.4, 130.4, 128.9, 128.4, 127.1, 123.4, 14.0.

HRMS (ESI): m/z calcd for $C_{18}H_{12}BrN_3OS$: 396.9884; found: 397.9888 $[M+1]^+$; 399.9876 $[M+1+2]^+$, (1:1);

Elemental analysis: Calcd. for $C_{18}H_{12}BrN_3OS$: C, 54.40; H, 3.02; N, 10.57% Found: C, 54.38; H, 3.00; N, 10.52%.

(2,4-dichlorophenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6e)

Brown crystals;

M. Pt. 169 ºC; Yield: 73%; IR (KBr) ν_{max} (cm^{-1}): 1636 (C=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.20 – 8.17 (m, 2H, 2',6'-H), 7.55 (d, 1H, ^4J=1.2 Hz, 3"-H), 7.50 – 7.46 (m, 3H, 3',4',5'-H), 7.44 (dd, 1H, ^3J=8.2 Hz, ^4J=1.2 Hz, 5"-H), 7.40 (d, 1H, ^3J=8.2 Hz, 6"-H), 2.57 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.2, 168.7, 157.6, 137.8, 137.8, 136.6, 132.0, 130.5, 130.3, 129.3, 128.8, 127.9, 127.1, 125.6, 115.7, 13.0.

HRMS (ESI): m/z calcd for $C_{18}H_{11}Cl_2N_3OS$: 387.0000; found: 388.0004 $[M+1]_+$, 389.9991 $[M+1+2]_+$, 391.9982 $[M+1+4]_+$ (9:6:1);

Elemental analysis: Calcd. for $C_{18}H_{11}Cl_2N_3OS$: C, 55.67; H, 2.83; N, 10.82% Found: C, 55.62; H, 2.81; N, 10.78 %.

(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)(p-tolyl)methanone (6f)

White solid;

M. Pt. 153 ºC; Yield: 85%; IR (KBr) ν_{max} (cm^{-1}): 1636 (C=O);

^1H NMR (500 MHz, $CDCl_3$) δ = 8.20 (dd, 2H, ^3J=7.7 Hz, ^4J=1.5 Hz, 2',6'-H), 7.74 (d, 2H, ^3J=8.0 Hz, 2",6"-H), 7.50 – 7.44 (m, 3H, 3',4',5'-H), 7.34 (d, 2H, ^3J=8.0 Hz, 3",5"-H), 2.72 (s, 3H, 4"-Me), 2.47 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.3, 168.3, 157.1, 144.4, 136.3, 135.4, 130.7, 130.3, 129.6, 129.2, 128.8, 127.1, 124.1, 21.9, 14.0.

HRMS (ESI): m/z calcd for $C_{19}H_{15}N_3OS$: 333.0936; found: 334.0940 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{15}N_3OS$: C, 68.46; H, 4.50; N, 12.61% Found: C, 68.43; H, 4.49; N, 12.58 %.

(4-methoxyphenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6g)

Creamy white solid;

M. Pt. 124 ºC; Yield: 88%; IR (KBr) ν_{max} (cm^{-1}): 1636 (C=O);

^1H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.19 (m, 2H, 2',6'-H), 7.88 – 7.84 (m, 2H, 2",6"-H), 7.50 – 7.45 (m, 3H, 3',4',5'-H), 7.03 – 7.00 (m, 2H, 3",5"-H), 3.91 (s, 3H, 4"-OMe), 2.73 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.0, 168.1, 163.9, 156.9, 135.7, 131.6, 130.6, 130.4, 130.2, 128.8, 127.0, 123.9, 114.1, 55.6, 13.9.

HRMS (ESI): m/z calcd for $C_{19}H_{15}N_3O_2S$: 349.0885; found: 350.0890 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.32; H, 4.29; N, 12.03% Found: C, 65.29; H, 4.25; N, 12.00 %.

(3-methoxyphenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6h)

Whitish solid;

M. Pt. 126 ºC; Yield: 85%; IR (KBr) ν_{max} (cm^{-1}): 1632 (C=O);

^1H NMR (500 MHz, $CDCl_3$) δ = 8.22 – 8.19 (m, 2H, 2',6'-H), 7.51 – 7.46 (m, 3H, 3',5',5"-H), 7.44 (d, 1H, ^3J=7.9 Hz, 4'-H), 7.41 – 7.38 (m, 1H, 6"-H), 7.32 (s, 1H, 2"-H), 7.20 – 7.16 (m, 1H, 4"-H), 3.88 (s, 3H, 3"-OMe), 2.74 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.4, 168.4, 159.9, 157.2, 139.4, 136.9, 130.6, 130.3, 129.9, 128.8, 127.0, 123.9, 121.3, 119.6, 113.2, 55.6, 14.0.

HRMS (ESI): m/z calcd for $C_{19}H_{15}N_3O_2S$: 349.0885; found: 350.0888 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.32; H, 4.29; N, 12.03% Found: C, 65.28; H, 4.28; N, 12.02 %.

(2-methoxyphenyl)(6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6i)

Creamy solid;

M. Pt. 142 ºC; Yield: 84%; IR (KBr) ν_{max} (cm^{-1}): 1632 (C=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.21 – 8.17 (m, 2H, 2’,6’-H), 7.56 – 7.51 (m, 1H, 6”-H), 7.50 – 7.45 (m, 3H, 3’,4’,5’-H), 7.40 (dd, 1H, ^3J=7.5 Hz, ^4J=1.6 Hz, 4”-H), 7.12 – 7.08 (m, 1H, 5”-H), 7.03 (d, 1H, ^3J=8.4 Hz, 3”-H), 3.82 (s, 3H, 2”-OMe), 2.57 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.3, 168.2, 165.0, 157.3, 156.7, 136.5, 132.9, 130.5, 130.2, 128.7, 128.4, 126.9, 124.1, 121.0, 111.5, 55.7, 12.8.

HRMS (ESI): m/z calcd for $C_{19}H_{15}N_3O_2S$: 349.0885; found: 350.0889 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.32; H, 4.29; N, 12.03% Found: C, 65.30; H, 4.27; N, 12.01 %.

(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)(phenyl)methanone (6j)

Whitish crystals,

M. Pt. 178.5 ºC; Yield: 89%; IR (KBr) ν_{max} (cm^{-1}): 1622 (C=O);

^{1}H NMR (500 M*Hz*, $CDCl_3$) δ: 8.09-8.05 (m, 2H, 2',6'-H), 7.87 – 7.84 (m, 1H, 2'',6''-H), 7.73-7.71 (m, 1H, 4''-H), 7.63-7.59 (m, 2H, 3'',5''-H), 7.11-7.08 (m, 2H, 3',5-H), 3.84 (s, 3H, 4'-OMe), 2.52 (s, 3H, 6-Me).

^{13}C NMR (125 M*Hz*, $CDCl_3$) δ: 189.0, 167.5, 161.1, 156.8, 138.2, 137.4, 133.5, 129.3, 129.1, 128.6, 124.5, 123.1, 114.9, 55.8, 14.4

HRMS (ESI): m/z calcd for $C_{19}H_{15}N_3O_2S$: 349.0885; found: 350.0891 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.32; H, 4.29; N, 12.03% Found: C, 65.30; H, 4.24; N, 12.02%.

(4-fluorophenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6k)

Buff coloured solid;

M.Pt. 229.5 °C; Yield 78%; IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, 2H, ^3J=10 Hz, 2',6'-H), 7.90 – 7.86 (m, 2H, 2'',6''-H), 7.25 – 7.19 (m, 2H, 3'',5''-H), 7.01 (d, 2H, ^3J=10 Hz, 3',5'-H), 3.88 (s, 3H), 2.75 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 174.4, 168.4, 161.3, 136.7, 134.3, 131.5, 131.4, 128.5, 123.0, 122.9, 116.2, 116.0, 114.1, 55.3, 13.9.

^{19}F NMR (376 MHz, DMSO-d^6) δ: -105.5.

HRMS (ESI): m/z calcd for $C_{19}H_{14}FN_3O_2S$: 367.0791; found: 368.0795 $[M+1]^+$;

Elemental analysis: Calcd. for $C_{19}H_{14}FN_3O_2S$: C, 62.12; H, 3.81; N, 11.44% Found: C, 62.10; H, 3.78; N, 11.41%.

(4-chlorophenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6l)

Creamy white solid;

M. Pt. 181.5 ºC; Yield: 80%; IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O);

^1H NMR (500 MHz, $CDCl_3$) δ = 8.15 – 8.12 (m, 2H, 2',6'-H), 7.79 – 7.76 (m, 2H, 2'',6''-H), 7.54 – 7.50 (m, 2H, 3'',5''-H), 7.01 – 6.98 (m, 2H, 3',5'-H), 3.87 (s, 3H, 4'-OMe), 2.73 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 168.4, 161.3, 157.0, 139.6, 136.9, 136.3, 130.2, 129.1, 128.5, 123.0, 122.9, 114.1, 55.3, 13.9.

HRMS (ESI): m/z calcd for $C_{19}H_{14}ClN_3O_2S$: 383.0495; found: 384.0494 $[M+1]^+$; 386.0468 $[M+1+2]^+$, (3:1);

Elemental analysis: Calcd. for $C_{19}H_{14}ClN_3O_2S$: C, 59.45; H, 3.65; N, 10.95% Found: C, 59.41; H, 3.64; N, 10.92 %.

(4-bromophenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6m)

Creamy white solid;

M. Pt. 189 ºC; Yield: 80%; IR (KBr) ν_{max} (cm^{-1}): 1636 (C=O);

^1H NMR (500 MHz, $CDCl_3$) δ = 8.16 – 8.13 (m, 2H, 2',6'-H), 7.71 – 7.68 (m, 4H, 2'',3'',5'',6''-H), 7.02 – 6.99 (m, 2H, 3',5'-H), 3.88 (s, 3H, 4'-OMe), 2.74 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.8, 168.8, 161.8, 157.4, 137.4, 137.2, 132.5, 130.7, 128.9, 128.6, 123.4, 123.3, 114.5, 55.8, 14.4.

HRMS (ESI): m/z calcd for $C_{19}H_{14}BrN_3O_2S$: 426.9990; found: 427.9992 $[M+1]^+$; 429.9973 $[M+1+2]^+$, (1:1);

Elemental analysis: Calcd. for $C_{19}H_{14}BrN_3O_2S$: C, 53.39; H, 3.27; N, 9.83% Found: C, 52.34; H, 3.26; N, 9.81 %.

(2,4-dichlorophenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6n)

Brown solid;

M. Pt. 190.5 ºC; Yield: 77%; IR (KBr) ν_{max} (cm^{-1}): 1632 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.14 – 8.10 (m, 2H, 2',6'-H), 7.55 (d, 1H, ^4J=1.5 Hz, 3''-H), 7.44 (dd, 1H, ^3J=8.5 Hz, ^4J=1.5 Hz, 5''-H), 7.40 (d, 1H, ^3J=8.5 Hz, 6''-H), 7.01 – 6.97 (m, 2H, 3',5'-H), 3.87 (s, 3H, 4'-OMe), 2.55 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 186.1, 168.6, 161.4, 157.5, 137.7, 136.6, 134.0, 131.9, 130.4, 129.2, 128.6, 127.9, 125.1, 122.8, 114.1, 55.3, 12.9.

HRMS (ESI): m/z calcd for $C_{19}H_{13}Cl_2N_3O_2S$: 417.0106; found: 418.0108 [M+1]$_+$, 420.0995 [M+1+2]$_+$, 424.0978 [M+1+4]$_+$ (9:6:1);

Elemental analysis: Calcd. for $C_{19}H_{13}Cl_2N_3O_2S$: C, 54.54; H, 3.11; N, 10.04% Found: C, 54.50; H, 3.10; N, 10.02 %.

(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)(p-tolyl)methanone (6o)

Creamy white solid;

M. Pt. 178 ºC; Yield: 90%; IR (KBr) ν_{max} (cm^{-1}): 1630 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15 – 8.11 (d, 2H, ^3J= 10 Hz, 2',6'-H), 7.73 (d, 2H, ^3J= 10 Hz, 2'',6''-H), 7.33 (d, 2H, ^3J= 10 Hz, 3'',5''-H), 6.99 (d, 2H, ^3J=10 Hz, 3',5'-H), 3.87 (s, 3H, 4'-Me), 2.70 (s, 3H, 4''-Me), 2.46 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 188.2, 168.1, 161.2, 157.0, 144.1, 136.2, 135.3, 129.4, 129.0, 128.4, 123.6, 123.1, 114.1, 55.3, 21.7, 13.9.

HRMS (ESI): m/z calcd for $C_{20}H_{17}N_3O_2S$: 363.1041; found: 364.1044 [M+1]$^+$;

Elemental analysis: Calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.11; H, 4.68; N, 11.57% Found: C, 66.10; H, 4.65; N, 11.55 %.

(4-methoxyphenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6p)

White solid;

M. Pt. 198.5 ºC; Yield: 94%; IR (KBr) ν_{max} (cm^{-1}): 1628 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 – 8.12 (m, 2H, 2',6'-H), 7.87 – 7.83 (m, 2H, 2'',6''-H), 7.03 – 6.98 (m, 4H, 3',5',3'',5''-H), 3.91 (s, 3H, 4''-OMe), 3.87 (s, 3H, 4'-OMe), 2.72 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 186.9, 168.0, 163.7, 161.2, 156.9, 135.7, 131.5, 130.5, 128.4, 123.4, 123.2, 114.1, 114.0, 55.6, 55.3, 13.8.

HRMS (ESI): m/z calcd for $C_{20}H_{17}N_3O_3S$: 379.0991; found: 380.0994 [M+1]$^+$;

Elemental analysis: Calcd. for $C_{20}H_{17}N_3O_3S$: C, 63.32; H, 4.48; N, 11.08% Found: C, 63.29; H, 4.45; N, 11.04 %.

(3-methoxyphenyl)(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)methanone (6q)

Creamy white solid;

M. Pt. 157.5 ºC; Yield: 92%; IR (KBr) ν_{max} (cm^{-1}): 1630 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.16 – 8.12 (m, 2H, 2',6'-H), 7.46 – 7.43 (m, 1H, 5''-H), 7.40 – 7.38 (m, 1H, 6''-H), 7.31 (dd, 1H, ^4J=2.5 Hz, ^4J=1.5 Hz, 2''-H), 7.18 (ddd, 1H, ^3J=8.2 Hz, ^4J=2.5 Hz, ^4J=1.0 Hz, 4''-H), 7.01 – 6.98 (m, 2H, 3',5'-H), 3.88 (s, 3H, 4'-OMe), 3.87 (s, 3H, 3''-OMe), 2.73 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ = 188.4, 168.4, 161.4, 159.9, 157.2, 139.4, 136.9, 129.9, 128.6, 123.5, 123.2, 121.2, 119.5, 114.2, 113.2, 55.6, 55.4, 14.0.

HRMS (ESI): m/z calcd for $C_{20}H_{17}N_3O_3S$: 379.0991; found: 380.0993 [M+1]$^+$;

Elemental analysis: Calcd. for $C_{20}H_{17}N_3O_3S$: C, 63.32; H, 4.48; N, 11.08% Found: C, 63.31; H, 4.43; N, 11.07 %.

(2-(4-methoxyphenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl)(thiophen-2-yl)methanone (6r)

Dark Brown solid;

M. Pt. 171 ºC; Yield: 78%; IR (KBr) ν_{max} (cm^{-1}): 1622 (C=O);

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.14 (d, 2H, ^3J=9.0 Hz, 2',6'-H), 7.91 (d, 1H, ^3J=4.0 Hz, 5''-H), 7.78 (d, 1H, ^3J=4.0 Hz, 3''-H), 7.24 – 7.20 (m, 1H, 4''-H), 7.00 (d, 2H, ^3J=9.0 Hz, 3',5'-H), 3.87 (s, 3H, 4'-OMe), 2.91 (s, 3H, 6-Me).

^{13}C NMR (125 MHz, CDCl$_3$) δ 178.7, 168.3, 161.3, 156.4, 143.4, 137.1, 134.9, 133.6, 128.4, 128.3, 123.1, 120.6, 114.1, 55.3, 13.6.

HRMS (ESI): m/z calcd for $C_{17}H_{13}N_3O_2S_2$: 355.0449; found: 356.0454 [M+1]$^+$;

Elemental analysis: Calcd. for $C_{17}H_{13}N_3O_2S_2$: C, 57.46; H, 3.66; N, 11.83% Found: C, 57.43; H, 3.65; N, 11.80 %.

X-ray crystallography

Single crystal X-ray diffraction experiments were carried out for compound **6j** in the "CAI de Difracción de Rayos X, UCM". An adequate crystal was mounted on a Bruker Smart CCD diffractometer using Cu-Kα radiation (λ= 1.54178 Å).

Data were collected at 298 K over a reciprocal space hemisphere using the 'Bruker APEX-II CCD' diffractometer software. The cell parameters were determined and refined by least-squares fit of all the reflections collected. The structure was solved by intrinsic phasing using the SHELXT solution program[46] and refined by full matrix least squares on F^2 using the SHEXL refinement package[47] running in the Olex2 environment[48]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included with fixed isotropic contributions at their calculated positions determined by molecular geometry and refined riding on the corresponding carbon atoms.

Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Centre, via www.ccdc.cam.ac.uk/data_request/cif, on quoting the depository number 2099149 (compound **6j**).

Table 3. Crystal and refinement data for **6j**.

Crystal Data	**6j**
CCDC code	2099149
Empirical formula	$C_{19}H_{15}N_3O_2S$
Formula wt.	349.40
Temperature/K	297.0
Crystal system.	monoclinic
Space group	$P2_1/n$
a/Å	8.5191(2)
b/Å	10.3297(2)
c/Å	18.8853(4)
α /°	90.0
β /°	96.6638(8)
γ /°	90.0
V/Å^3	1650.67(6)
Z	4
D_c / g/cm^3	1.410
μ / mm^{-1}	1.894
F(000)	728.0
2θ range/°	9.43 to 144.376
index ranges	-10,-12,-23 to 10, 12, 22
reflections collected	36441
unique reflections [Rint]	3269 [Rint = 0.0471]
completeness to theta	99.9%

data/restraints/params	3269/0/228
Goodness-of-fit on F^2	1.061
R1 (reflns obsd) $[I>2\sigma(I)]$ [a]	0.0468 (3030)
*w*R2 (all data) [b]	0.1324

[a] $R1=\Sigma||F_o|-|F_c||/\ \Sigma|F_o|$ [b] $wR2=\{\Sigma[w(F_o^2-F_c^2)^2]/\ \Sigma[w(F_o^2)^2]\}$

Associated content

The Supporting Information includes additional experimental data, ^1H, ^{13}C, HMBC, HMQC, HRMS spectra and X-ray crystallographic studies results) for final compounds.

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Author contributions

R.A. contributed to the conceptualization and development of the methodology, reviewed the manuscript, and supervised the project. P.K. and M.H. performed the experimental analysis and M.C.T. characterized the synthesized regioisomer through X-ray crystallographic studies. P.K., M.H. and M.C.T. wrote the manuscript. All authors contributed to the discussion and in improving the writing of the manuscript.

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Competing interests

The authors declare no competing interest.

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