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Solvent-free regioselective synthesis of novel isoxazoline and pyrazoline *N*-substituted saccharin derivatives under microwave irradiation

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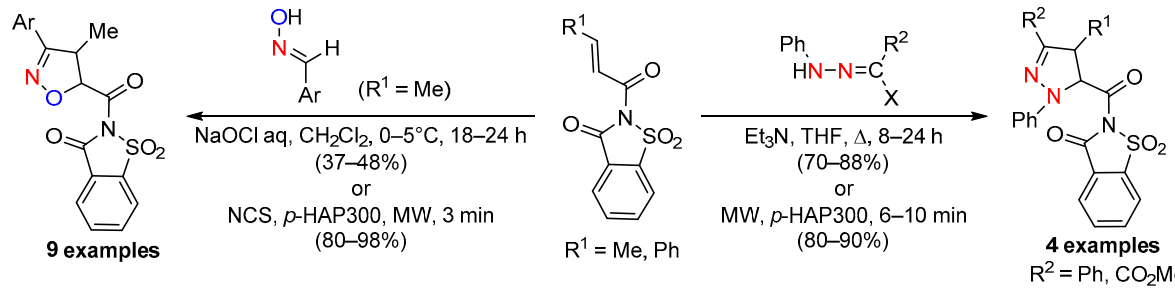


Novel isoxazoline and pyrazoline derivatives of *N*-substituted saccharin were synthesized in good yields by 1,3-dipolar cycloaddition of *N*-crotonoyl- or *N*-cinnamoylsaccharin as dipolarophile to arylnitrile oxides or nitrile imines using *p*-HAP300 as catalyst under solvent-free microwave conditions. In this process, the yields were significantly improved compared to classical conditions without alteration of the selectivity. The regioselectivity as well as the nonthermal specific microwave effect are discussed.

Keywords: arylnitrile oxide, nitrile imine, catalysis, 1,3-dipolar cycloaddition, microwave irradiation, solvent-free.

Compounds containing five-membered heterocyclic ring systems, such as isoxazoline and pyrazoline, continue to attract considerable interest due to the wide range of their biological activity. Isoxazoline derivatives have been reported to possess antimicrobial,[1,2] antituberculosis,[3] anti-inflammatory,[4] antiviral,[5] analgesic,[6] antitumor,[7] and antithrombotic activities.[8] Moreover, isoxazoline derivatives have played an important role in the theoretical development of heterocyclic chemistry and are also extensively used as intermediates in organic synthesis.[9] In similar way, pyrazolines have been reported to exhibit a variety of biological activities including anti-inflammatory,[10] antidepressant,[11] anticancer,[12] analgesic,[13] antioxidant,[14] antiinfective,[15] antifungal,[16] antihepatotoxic,[17] antinociceptive,[18] and pesticidal properties.[19] Furthermore, isoxazoline and pyrazoline are commonly used as advanced intermediates in organic synthesis or as basic scaffolds for modular synthesis of bioactive compounds because of their high chemical stability and their hydrogen-bonding ability.[5,10–12]

Several procedures were reported for the synthesis of such heterocycles. For example, isoxazolines are commonly prepared using 1,3-dipolar cycloaddition (1,3-DC) of alkenes to nitrile oxides, generated *in situ* by dehydrohalogenation of hydroxymoyl chlorides, or other cyclocondensation reactions.[20] In a similar way, various methods were reported for the synthesis of pyrazolines, such as the reaction of α,β-unsaturated carbonyl compounds with

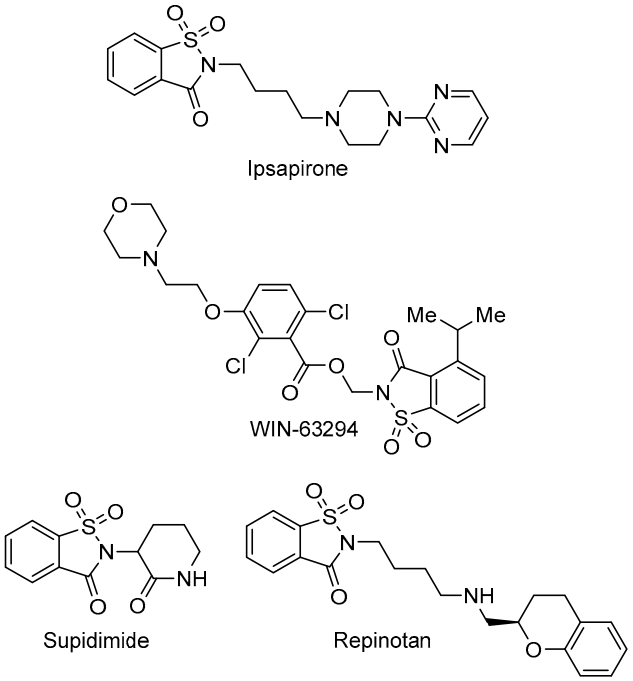


Figure 1. Chemical structures of biologically active compounds featuring *N*-substituted saccharin motif.

hydrazine or monosubstituted hydrazines.[21] Other examples based on 1,3-DC involving nitrile imines and alkenes have been reported to access the functionalized pyrazolines.[20a]

However, all these reported procedures have their own limitations. For example, the conventional heating of a nitrile oxide or nitrile imine with an alkene in cycloaddition reactions generally provide poor yields, side reactions, such as the dimerization or polymerization of 1,3-dipole and formation of by-products, poor regioselectivity, and a need of costly catalysts to improve the reaction.[22]

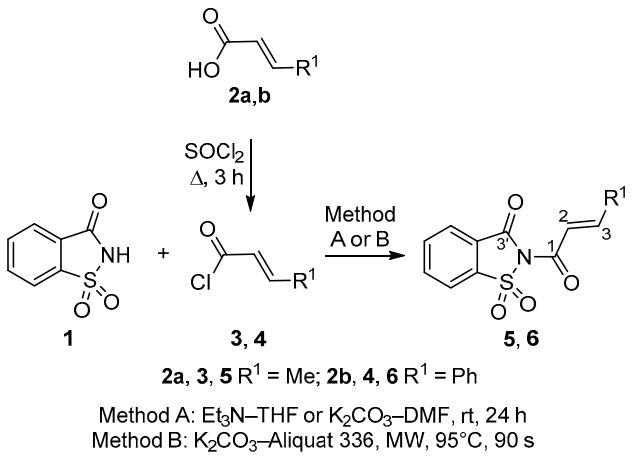
In continuation of our studies directed at the development of new procedures for the synthesis of functionalized heterocycles,[23] we report here an efficient regioselective synthesis of *N*-substituted saccharins, containing isoxazoline and pyrazoline moieties, using cycloaddition reaction between crotonamide dipolarophiles and nitrile oxide or nitrile imine under solvent-free microwave conditions. We chose to introduce saccharin moiety into the dipolarophile structures because of its unique chemical and biological properties.[24] Indeed, as a key structural element, *N*-substituted saccharin fragment is present in several biologically active compounds, such as ipsapirone, WIN-63294, supidimide, and repinotan (Fig. 1).[25]

The use of microwave activation in this case is motivated by the fact that 1,3-DC involves a polar transition state, which could make such reaction susceptible to MW activation.[26] Indeed, we recently reported several examples of dipolar cycloadditions in which MW irradiation was found to be extremely efficient in terms of yield, reaction time, and regioselectivity.[23e,g,27] The application of MW has become a powerful technique to accelerate organic reactions, the high heating efficiency giving significant rate enhancement, remarkable reduction in reaction times, and milder conditions.[28] The aim of this work is also to demonstrate the advantages obtained by the use of MW irradiation compared to the conventional heating in the synthesis of isoxazoline and pyrazoline adducts.

Synthesis of *N*-crotonoyl- and *N*-cinnamoylsaccharins as dipolarophiles. Several methods of the *N*-acylation of saccharin (**1**) have been described using either conventional heating or microwave irradiation in dry media and dimethylformamide as polar solvent. However, most of them have resulted in poor yields and a long reaction time, which could be ascribed in part to an inadequate solvent.[29]

In our work, we have carried out the synthesis of two *N*-acylsaccharins containing an α,β-unsaturated acyl group that could be used as dipolarophiles. The first reaction step consisted in treatment of crotonic acid (**2a**) and cinnamic acid (**2b**) with an excess of thionyl chloride without solvent (Scheme 1).[30] The corresponding acyl chlorides **3** and **4** were isolated in good yield after removal of the excess of thionyl chloride at moderate temperature (35–40°C) under reduced pressure (20 mmHg) to avoid the evaporation of the product. The products **3** and **4** were used in the subsequent step without additional purification. In the second reaction step, the acylation of saccharin (**1**) with acid chlorides **3** and **4** produced the desired dipolarophiles **5** and **6**, respectively (Scheme 1).

Scheme 1



In our previous work,[23d] DMF has been found to be an excellent solvent for the reaction of alkyl halides with saccharin (**1**) in basic media. Recently, several reported works have described the reaction of alkyl halides and sodium alkoxide using DMF as a good solvent.[31]

However, in our study, phase-transfer catalysis (PTC) combined with microwave irradiation was found to be an excellent methodology for preparing *N*-crotonoyl- and *N*-cinnamoylsaccharin derivatives **5** and **6** (method B, Scheme 1). Indeed, the results were compared with those obtained by conventional conditions (stirring at room temperature, method A). Moreover, PTC under classical condition has been successfully applied to the acylation of NH groups of amides, sultams, and lactams.[32] However, this method provided the products in moderate yields and, generally, an adequate control of both time and temperature of the reaction.

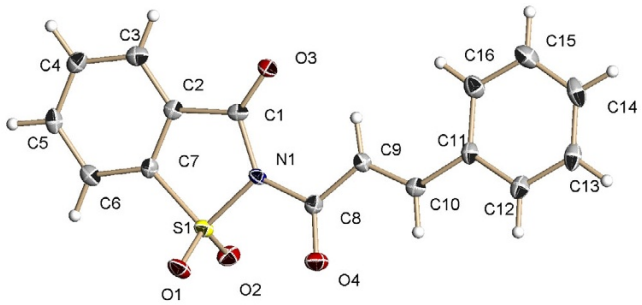


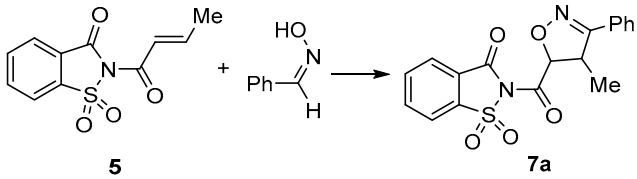
Figure 2. Molecular structure of *N*-cinnamoylsaccharin **6** with atoms represented as thermal vibration ellipsoids of 50% probability.

The preparation of *N*-acylsaccharin derivatives **5** and **6** proved to be more efficient under microwave irradiation (method B). It is worth noting that the reaction time was remarkably shortened from 24 h (DMF–K_2CO_3 or THF–Et_3N at room temperature) to 90 s (K_2CO_3–Aliquat 336) under PTC and microwave irradiation, and the yields were improved from 78–87 to 95–97%. In addition, under conventional heating at 95°C, the products **5** and **6** were obtained in low yield (40%) after 1 h with a significant degradation of the catalyst (Aliquat 336).

The structures of products **3**–**6** were elucidated by means of NMR spectroscopic techniques, IR spectra, and mass spectrometry, in the case of product **6**, also by single-crystal X-ray diffraction analysis. Compound **6** crystallizes from THF–H_2O as colorless needles in the orthorhombic *Pbca* space group. The asymmetric unit of this crystal reveals a structure (Fig. 2) that differs from the one described earlier[33] for crystals of compound **6** obtained as colorless prisms by crystallization from pure THF and that crystallized in the monoclinic *C*2/*c* space group.

Synthesis of isoxazoline derivatives of saccharin *via* 1,3-dipolar cycloaddition. The dipolarophiles **5** and **6** were then treated with different arylnitrile oxides (generated *in situ* by the action of an oxidant[34]) under classical conditions using aqueous sodium hypochlorite in biphasic medium (method C) or under microwave activation using NCS–Al_2O_3, NCS–*p*-HAP300 or NCS–natural phosphate (NP) in dry media (Table 1). Under these conditions, the best result for isoxazoline **7a** was obtained with NCS–*p*-HAP300 catalyst (method D). Recently we have reported that hydroxyapatite *p*-HAP300 ($Ca_{10}(PO_4)_6(OH)_2$) is a basic and efficient catalyst for the Knoevenagel condensation.[35b] This catalyst was prepared according to our previous reported procedure.[35] Furthermore, the use of *p*-HAP300 is particularly convenient for the 1,3-DC reaction compared to alumina and NP, since the former is efficiently recycled by simple heating at 300°C under reduced pressure for 20 min. Excellent preservation of basic capacity of the *p*-HAP300 catalyst was observed. The catalyst was reused after seven cycles and the reactivity was clearly conserved. We also performed the reactions without oxidant or without both catalyst and oxidant under both microwave and classical methods, and no reaction products were observed even after a long reaction time. With both methods C and D, dipolarophile **6** did not undergo the cycloaddition reactions; instead, the furoxan derivatives, products of dimerization of nitrile oxides, were isolated, which is consistent with literature reports.[36]

Table 1. Effect of catalyst in the MW solvent-free synthesis of isoxazoline **7a***



5 **7a**

Oxidant–Catalyst	Time, min	T_{MW}**, °C	Yield, %
–	4	122	–***
NCS–Al_2O_3	4	118	72
NCS–*p*-HAP300	3	115	80
p-HAP300	3	113	–***
NCS–NP	4	120	56 (40)*[4]

* The reactions were performed under MW irradiation without solvent using compound **5** (1.0 mmol) and benzaldoxime (1.2 mmol), NCS (1.2 mmol, if applicable), and catalyst (1.0 g).
** Temperature at the end of the reaction (infrared detection and a digital thermometric probe).
*** Incomplete reaction with unidentified products of degradation.
*[4] Yield of furoxan or 3,4-diphenyl-1,2,5-oxadiazole *N*-oxide (white crystalline solid, mp 114–116°C (mp 114–117°C)[36d]).

Once the most suitable conditions have been found, we extended the 1,3-DC reaction of dipolarophile **5** to other arylnitrile oxides (Scheme 2). The reactions were carried out in a single-mode cavity with focused MW irradiation and were monitored by TLC (method D). For the purpose of comparison, the reactions were carried out also under the conventional conditions (method C). The results are summarized in Table 2.

The isoxazoline products **7a**–**i** were obtained in moderate yields (37–48%) under classical conditions (two-phase system, 18–24 h at 0–5°C), while rather high yields (80–98%) were achieved with the use of the microwave irradiation in a solvent-free system (3 min at 103–118°C). No products **7a**–**i** were isolated with classical heating under same reaction conditions (3 min, final temperature, and atmospheric pressure) determined under microwave irradiation.

In general, according to literature reports, the regiochemistry of 1,3-DC is governed by both steric and electronic factors that often led to a mixture of two regioisomers. It is noteworthy that in our case all cycloadditions with various nitrile oxides and dipolarophile **5** afforded one regioisomer (Scheme 2, Table 2), which was confirmed by NMR spectra. For example, the ^{1}H NMR spectrum of regioisomer **7a** showed a doublet centered at 4.64 ppm for the stereogenic center 5-CH and a multiplet at 2.44–2.51 ppm for the 4-CH proton. The aromatic proton exhibited a multiplet at 7.72–8.67 ppm. The ^{13}C NMR spectrum of compound **7a** exhibited a signal at 12.2 ppm corresponding to the CH_3 carbon and two peaks at 46.1 and 71.3 ppm assigned to the isoxazoline carbons C-5 and C-4. The C=N and two carbonyl carbons resonated at 156.0, 166.7, and 173.2 ppm, respectively. This regiocontrolled process can

Scheme 2

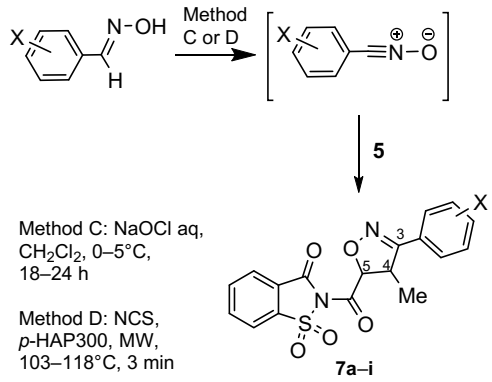


Table 2. Synthesis conditions and yields of compounds **7a–i**

Compound	X	Classical conditions		Microwave irradiation	
		Time, h	Yield, %	T_{MW}**, °C	Yield, %
7a	H	2	38 (54)*	115	80
7b	4-Cl	2	41	110	87
7c	4-NO_2	1	45	105	90
7d	3-NO_2	1.5	38	103	84
7e	4-MeO	1	45	113	92
7f	4-Me	1.5	40	110	85
7g	2,4,6-Me_3	1.5	38	110	82
7h	4-F	1.5	48	118	98
7i	4-Me_2N	2	37	109	89

* Yield of the isolated furoxan.
** Temperature at the end of the reaction (infrared detection).

be explained by the highly disfavored steric hindrance between the nitrile oxide and dipolarophile **5** as outlined in Figure 3.[37] Interestingly, no post-isomerization was observed in contrast to the previously reported works.[36c,38]

Surprisingly, all reactions carried out under the same conditions with dipolarophile **6** (X = H) did not work at all, even at prolonged reaction times and forced conditions. This result may be also explained by both unfavorable steric (proximity of aryl and phenyl groups of nitrile oxide and dipolarophile, respectively) and electronic factors (repulsive interaction between the carbonyl of saccharin and oxygen anion of nitrile oxide) as given in Figure 4. In addition, we noticed during this work that the dipolarophile **6** has no reactivity in the cycloaddition reaction with nitrile oxides, which could be ascribed to the highly disfavored steric effects and the poor reactivity of compound **6** due to the hyperconjugation.

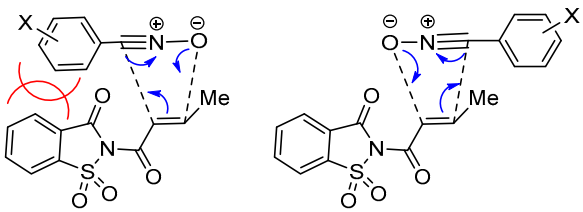


Figure 3. The control of regioselectivity by steric effects of the 1,3-DC of compound **5** to nitrile oxides.

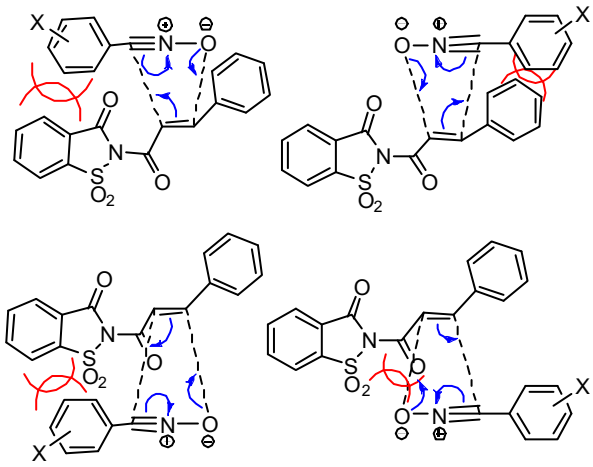


Figure 4. Disfavored approach in the 1,3-DC of compound **6** to nitrile oxides.

It is important to note that the use of MW in this cycloaddition reaction highly disfavored the dimerization process of arylnitrile oxides, and this observation has been rarely mentioned.[23a,39] Finally, the structures of all cycloadducts **7a–i** were confirmed through ^{1}H and ^{13}C NMR, MS, and IR analyses.

Synthesis of pyrazoline derivatives of saccharin *via* 1,3-dipolar cycloaddition. We have developed the synthesis of novel *N*-substituted saccharin derivatives **8–11** containing pyrazoline moiety *via* 1,3-DC of some nitrile imines (generated *in situ* by the action of base on the hydrazonoyl halides[40]) with dipolarophiles **5** and **6** under both microwave irradiation and conventional methods. The reaction was carried out either by reflux in anhydrous THF in the presence of triethylamine as base or under microwave activation using *p*-HAP300 as solid support in dry media. The reaction afforded, in each case, only one isolated product as evidenced by TLC analysis (Scheme 3). The end of the reaction was indicated by the appearance of the pyrazolines **8–11** identified by their intense fluorescence (λ_{max} 365 nm). The obtained results are shown in Table 3.

Under solvent-free MW conditions, the four pyrazolines **8–11** were obtained as single regioisomers with good yields (80–90%) within short reaction times (6–10 min). They were also obtained under conventional reflux conditions (8–24 h) in almost as good yields (70–88%). Similar results were previously reported by our group when using KF–Al_2O_3 or basic alumina as promoters under solvent-free microwave conditions, for the *in situ* generation of nitrile imines from hydrazonoyl halide.[41] The structures of all the pyrazolines **8–11** were established from their NMR, MS, and IR data. For instance, the identity of the isomer of compound **8** obtained was confirmed by its ^{1}H NMR spectrum, the one doublet of the proton 5-CH was observed downfield at 5.28 ppm, *trans*-coupled to the proton 4-CH. The observed deshielding of the proton 5-CH can be explained by the electronegative substituent effects of the pyrazoline nitrogen atom and the carbonyl group.

Finally, to highlight the specific microwave effects, the reactions for the synthesis of products **7a–i** and **8–11** were

Scheme 3

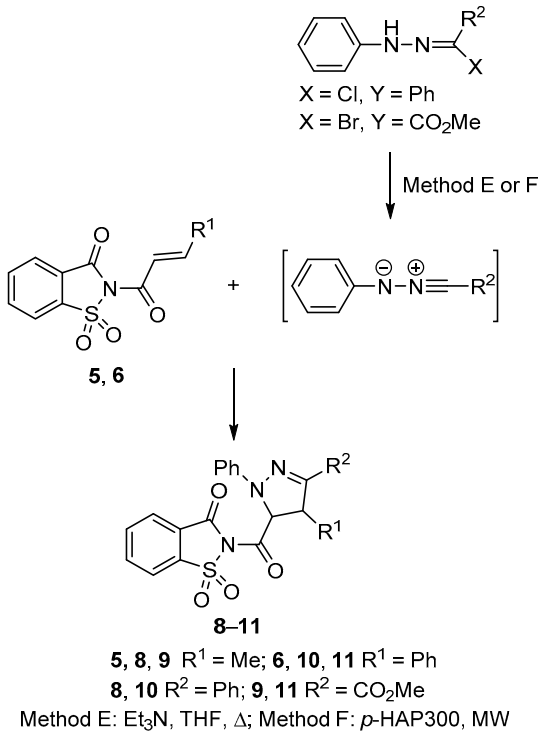
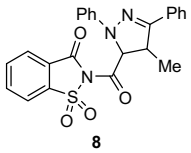
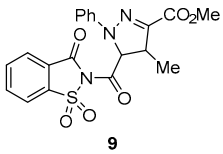
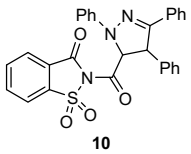
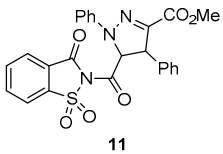


Table 3. Synthesis conditions and yields of compounds **8**–**11**

Compound	Microwave irradiation			Classical conditions		
	Time, min	T_{MW}*, °C	Yield**, %	Time, h	Yield, %	Yield**, %
 **8**	6	140	90	11	88	10
 **9**	6	142	89	8	75	10
 **10**	10	115	87	24	76	8
 **11**	10	120	80	24	70	5

* Temperature at the end of the reaction (infrared detection).

** Yield of isolated product obtained with classical heating under same reaction conditions (10 min, final temperature, and atmospheric pressure) as used under microwave irradiation for the synthesis of the same product.

carried out using a preheated oil-bath applied to the same respective reaction mixtures for the similar time, pressure, vial size, and temperature (as measured at the end of MW irradiation) as those during the microwave experiments. The products **8**–**11** were obtained with 5–10% isolated yield under conventional heating conditions, which could suggest that the effect of microwave irradiation is not purely thermal. Indeed, the nonthermal MW effects can be explained by considering the development of polarities ground state and transition state. Indeed, as the polarity is enhanced with the reaction progress, the dipole–dipole stabilization by the electric field is increased and, consequently, a positive MW effect is expected.[23d,26a]

In conclusion, we have reported an efficient and green method for the synthesis of novel isoxazoline- and pyrazoline-containing *N*-substituted saccharins using a cooperative effect of solvent-free MW activation and *p*-HAP300 catalysis. The process involves a regiospecific [3+2] cycloaddition between *N*-crotonoyl or *N*-cinnamoyl-saccharin as dipolarophile, obtained by the *N*-acylation of saccharin under both classical heating and MW irradiation conditions, to arylnitrile oxides and nitrile imines. The best results were observed under MW irradiation and assigned to the rapid heating and the specific MW effects. The total regiocontrol of the 1,3-dipolar cycloaddition of nitrile oxides and nitrile imines with dipolarophiles was not altered by using MW irradiation as the source of energy, compared to the classical conditions. Also we noticed that the *N*-cinnamoyl saccharin did not take part in the cycloaddition reaction with nitrile oxides, which could be ascribed to the highly disfavored steric effects and the poor reactivity of this dipolarophile due to the hyperconjugation.

Experimental

IR spectra were recorded on a Bruker Vertex 70 instrument in KBr pellets or neat between two NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 and 75 MHz, respectively) using TMS as internal standard. Mass spectra were recorded on a Brucker Daltonics Esquire 3000+ instrument equipped with an atmospheric pressure ionization ion source. High-resolution mass spectra were recorded on a ThermoFisher Q Exactive Plus Hybrid Quadrupole-Orbitrap Mass Spectrometer using positive ion electrospray ionization mode. The spectral data for compounds have been performed at the 'UATRS (Unites d'Appui Technique à la Recherche Scientifique)-CNRST, Rabat, Morocco. Melting points were determined on a Kofler block and are uncorrected. The reactions were monitored by TLC performed on silica gel plates GF254. Spots on chromatograms were detected under UV light (254 nm and 365 nm) and also by iodine vapors. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). The microwave-assisted reactions were carried out in a CEM Discover, single-mode cavity with focused MW heating (MW power supply 0–300 W in 1 W increments, IR temperature sensor, open or closed vessel mode, pressure range 0–20 bar, 10-ml or 80-ml vials). Starting materials, reagents, and solvents were obtained from commercial

sources and used as received unless otherwise indicated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Other solvents were purified by standard procedures. NP used in this work was obtained in the Khouribga region (Morocco), and the structure of the material is similar to that of fluoroapatite ($Ca_{10}(PO_4)_6F_2$).[42]

***N*-Acylation of saccharin (1)** (General method). A. Conventional method. Freshly prepared acyl chloride **3** or **4** (1.1 mmol) and triethylamine (0.13 ml, 0.10 g, 1.0 mmol) or potassium carbonate (0.14 g, 1.0 mmol) were added to saccharin (**1**) (0.18 g, 1.0 mmol) in anhydrous THF or DMF (8 ml), respectively. The mixture was stirred at room temperature for 24 h. In the case of K_2CO_3–DMF, the mixture was processed by ice water (5 times the volume), and the formed solid precipitate was isolated by filtration under vacuum. In the case of Et_3N–THF, the solvent was removed under vacuum, and the residue was dissolved in CH_2C1_2 (20 ml) and washed with water (2×20 ml), the organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The solid residue in all cases was recrystallized from THF–H_2O, 4:1.

B. Microwave synthesis. Saccharin (**1**) (0.18 g, 1.0 mmol) and acyl chloride **3** or **4** (1.0 mmol) were placed in a pyrex tube (length 6 cm, diameter 2 cm). Then K_2CO_3 (0.14 g, 1 mmol) and Aliquat 336 (0.05 mmol) were added, and the obtained mixture was activated by MW irradiation for 90 s at 95°C. The residue was dissolved in CH_2C1_2 (5 ml) and then filtered through a pad of Celite 545 to remove Aliquat 336. The solvent was evaporated under reduced pressure, and the residue was recrystallized from THF–H_2O, 4:1.

2-(But-2-enoyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (5). Yield 78% (method A, DMF–K_2CO_3), 78% (method A, THF–Et_3N), 95% (method B). White crystals. Mp 182–184°C (THF). R_f 0.38 (hexane–AcOEt, 6:4). IR spectrum (KBr), ν, cm^{-1}: 3038 (CH_3 ν), 1697 (C=C *trans* ν), 1626 (C=O σ), 1458 (CH_3 σ as); 1362 (CH_3 σ sy), 1357 (SO_2 ν sy), 1325 (=C–H *trans* σ), 1056 (SO_2 ν as), 972 (=C–H *trans* δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.03 (3H, d, *J* = 7.1, CH_3); 7.07 (1H, d, *J* =15.2, 2-CH); 7.41–7.46 (1H, m, 3-CH); 7.15–7.90 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.9 (C-4); 122.4 (C-2); 126.3; 134.9; 135.8; 143.3; 151.0 (C-3); 157.7; 162.9 (C-1,3'). Mass spectrum, *m*/*z* (I_{rel}, %): 274 $[M+Na]^+$(100), 290 $[M+K]^+$ (35), 541 $[2M+K]^+$ (18). Found, *m*/*z*: 252.0331 $[M+H]^+$. $C_{11}H_{10}NO_4S$. Calculated, *m*/*z*: 252.0326.

2-Cinnamoyl-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (6). Yield 87% (method A, DMF–K_2CO_3), 87% (method A, THF–Et_3N), 97% (method B). White crystals. Mp 234–236°C (THF–H_2O, 4:1) (mp 232–234°C, THF[33a]). R_f 0.30 (hexane–AcOEt, 6:4). IR spectrum (KBr), ν, cm^{-1}: 1695 (C=C *trans* ν), 1694 (C=O σ), 1347 (SO_2ν sy), 1319 (=C–H *trans* σ), 1036 (SO_2ν as), 997 (=C–H *trans* δ), 764–680 (=C–H 5H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43–7.58 (3H, m, H Ar); 7.70 (1H, d, *J*= 16.0, 2-CH); 7.65–7.78 (2H, m, H Ar); 7.92–7.95 (1H, m, H Ar); 7.98 (2H, d, *J* = 7.5, H Ar); 8.07 (1H, d, *J*= 16.0, 3-CH); 8.17 (1H, d, *J*= 7.6, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 117.0; 121.0; 122.4 (C-2); 125.5; 126.7; 128.5 (2C); 129.0 (2C); 131.8; 134.0; 135.1; 137.0; 155.8 (C-3); 158.1; 161.5. Mass spectrum, *m*/*z* (I_{rel}, %): 336 $[M+Na]^+$ (100), 352 $[M+K]^+$ (40), 649 $[2M+Na]^+$ (12). Found, *m*/*z*: 314.0488 $[M+H]^+$. $C_{16}H_{12}NO_4S$. Calculated, *m*/*z*: 314.0480.

***p*-HAP300 catalyst** was prepared by following the procedure reported in previous studies.[35] The porous calcium hydroxyapatite particles (*p*-HAP300) were prepared by a modified chemical wet method reported elsewhere.[35a] $Ca(OH)_2$ (0.5 M) was dissolved in deionized water at 25°C and mixed with a $NH_4H_2PO_4$ (0.6 M) solution at room temperature in a mixture of EtOH–H_2O, 1:1. The reagents were introduced at molar ratio Ca/P 1.67. The suspension was aged for 12 h, filtered, and dried at 100°C overnight and then heated under the flow of air for 3 h at 300°C in a muffle furnace.

Synthesis of isoxazolines 7a–i (General method). C. Conventional method. A mixture of *N*-crotonoylsaccharin **5** (0.25 g, 1.0 mmol) and arylaldoxime (1.2 mmol) was dissolved in CH_2Cl_2 (15 ml). The solution was then cooled to 0–5°C, and excess of 3.6% aqueous sodium hypochlorite solution (15 ml) was added dropwise under vigorous stirring for 18–24 h. The reaction was monitored by TLC. After completion of the reaction, the organic phase was separated and washed many times with water, then dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by recrystallization from ethanol (products **7a**,**f**,**h**) or by column chromatography (products **7b**–**e**,**g**,**i**) using hexane–AcOEt, 8:2 or 6:4, as eluent.

D. Microwave synthesis. A mixture of *N*-crotonoylsaccharin **5** (0.25 g, 1.0 mmol) and arylaldoxime (1.2 mmol) was dissolved in CH_2Cl_2 (20 ml) and added with stirring to a mixture of NCS (0.16 g, 1.2 mmol) and *p*-HAP300 (1.0 g) at room temperature. The mixture was first stirred at room temperature for 2 min, and then the solvent was evaporated under reduced pressure. The resulting solid residue was irradiated by microwaves for 3 min to complete the reaction (TLC). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and the product was extracted by CH_2Cl_2 or acetonitrile (2×10 ml). The catalyst was removed by filtration and washed with CH_2Cl_2 or acetonitrile (10 ml), and the solvent was evaporated under reduced pressure to obtain the solid product. The crude product was purified by recrystallization from EtOH or by column chromatography using hexane–AcOEt, 8:2 or 6:4, as eluent. Isoxazoline product **7a** was obtained also by using various heterogeneous catalysts (NCS–Al_2O_3, NCS–*p*-HAP300 or NCS–NP) and also in neat conditions (without catalyst) under microwave irradiation.

2-[(4-Methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)-carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7a). Yellow crystals. Mp 115–117°C (hexane–Et_2O, 4:1). R_f 0.25 (hexane–AcOEt, 4:1). IR spectrum (KBr), ν, cm^{-1}: 3063 (CH_3 ν), 1769 (C=N σ), 1593 (C=O σ), 1328 (SO_2 ν sy), 1074 (ν SO_2 as), 783–693 (=C–H 5H adj δ). ^{1}H NMR

spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.58 (3H, d, *J* = 7.1, CH_3); 2.44–2.51 (1H, m, 4-CH); 4.64 (1H, d, *J* = 7.7, 5-CH); 7.72–7.81 (3H, m, H Ar); 7.95–8.02 (1H, m, H Ar); 8.13–8.34 (4H, m, H Ar); 8.59–8.67 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.2 (CH_3); 46.1 (C-4); 71.3 (C-5); 126.1; 126.3; 126.5; 127.6 (2C); 127.9 (2C); 130.8; 131.0; 131.2; 132.7; 138.8; 156.0 (C=N isoxazoline); 166.7 (C=O saccharin); 173.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 393 $[M+Na]^+$ (100), 763 $[2M+Na]^+$ (10). Found, *m*/*z*: 371.0699 $[M+H]^+$. $C_{18}H_{15}N_2O_5S$. Calculated, *m*/*z*: 371.0696.

2-{[3-(4-Chlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7b). Yellow crystals. Mp 165–167°C (hexane–CH_2Cl_2, 4:1). R_f 0.62 (hexane–AcOEt, 6:4). IR spectrum (KBr), ν, cm^{-1}: 2925 (CH_3 ν), 1650 (C=N σ), 1590 (C=O σ), 1400 (SO_2 ν sy), 1092 (SO_2 ν as), 837 (=C–H 2H adj δ), 756 (C–Cl ν). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.59 (3H, d, *J* = 7.2, CH_3); 2.48–2.55 (1H, m, 4-CH); 4.65 (1H, d, *J* = 7.6, 5-CH); 7.80–7.89 (2H, m, H Ar); 7.97–8.14 (5H, m, H Ar); 8.20–8.23 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.0 (CH_3); 45.2 (C-4); 71.0 (C-5); 125.2; 125.3; 125.6; 125.8; 126.7; 128.5 (2C); 129.9 (2C); 130.4; 134.4; 137.9; 156.0 (C=N); 166.7 (C=O saccharin); 173.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 427 $[M+Na]^+$ (100), 831 $[2M+Na]^+$ (15). Found, *m*/*z*: 405.0309 $[M+H]^+$. $C_{18}H_{14}ClN_2O_5S$. Calculated, *m*/*z*: 405.0305.

2-{[4-Methyl-3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7c). Yellow solid. Mp 215–217°C (EtOH). R_f 0.79 (hexane–AcOEt, 3:2). IR spectrum (KBr), ν, cm^{-1}: 2875 (CH_3 ν), 1700 (C=N σ), 1582 (C=O σ), 1526–1350 (C–NO_2 ν), 1351 (SO_2 ν sy), 1100 (SO_2 ν as), 856 (=C–H 2H adj δ). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm (*J*, Hz): 1.50 (3H, d, *J* = 7.2, CH_3); 2.39–2.47 (1H, m, 4-CH); 4.56 (1H, d, *J* = 7.8, 5-CH); 7.40–7.51 (3H, m, H Ar); 7.62–7.73 (2H, m, H Ar); 7.96–8.19 (3H, m, H Ar). ^{13}C NMR spectrum (CD_2Cl_2), δ, ppm: 10.6 (CH_3); 44.5 (C-4); 70.3 (C-5); 118.3; 125.4; 125.5; 125.7; 126.8; 128.6 (2C); 129.7 (2C); 130.5; 134.3; 137.2; 156.0 (C=N isoxazoline); 166.7 (C=O saccharin); 173.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 438 $[M+Na]^+$ (100), 853 $[2M+Na]^+$ (10). Found, *m*/*z*: 416.0557 $[M+H]^+$. $C_{18}H_{14}N_3O_7S$. Calculated, *m*/*z*: 416.0547.

2-{[4-Methyl-3-(3-nitrophenyl)-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7d). Yellowish solid. Mp 125–127°C (hexane–MeOH, 4:1). R_f 0.75 (hexane–AcOEt, 3:2). IR spectrum (KBr), ν, cm^{-1}: 2994 (CH_3 ν), 1700 (C=N σ), 1591 (C=O σ), 1534–1351 (C–NO_2 ν), 1351 (SO_2 ν sy), 1100 (SO_2 ν as), 740, 835 (=C–H 3H adj δ). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.40 (3H, d, *J*= 7.3, CH_3); 2.27–2.35 (1H, m, 4-CH); 4.45 (1H, d, *J*= 7.9, 5-CH); 7.40–7.45 (1H, m, H Ar); 7.68–7.76 (2H, m, H Ar); 7.83–7.90 (2H, m, H Ar); 7.99–8.11 (2H, m, H Ar); 8.16–8.20 (1H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 10.2 (CH_3); 44.1 (C-4); 69.9 (C-5); 117.9; 124.9; 125.3; 125.5; 126.4; 128.2 (2C); 129.6 (2C); 130.0; 134.1; 137.6; 155.6 (C=N isoxazoline); 166.3 (C=O saccharin); 172.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 438 $[M+Na]^+$(100), 454 $[M+K]^+$ (28), 853 $[2M+Na]^+$ (19). Found, *m*/*z*: 416.0560 $[M+H]^+$. $C_{18}H_{14}N_3O_7S$. Calculated, *m*/*z*: 416.0547.

2-{[3-(4-Methoxyphenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7e). Viscous product. R_f 0.63 (hexane–AcOEt, 4:1). IR spectrum (neat), ν, cm^{-1}: 2959–2929 (CH_3 ν), 1720 (C=N σ), 1607 (C=O σ), 1337 (SO_2 ν sy), 1104 (SO_2 ν as), 836 (=C–H 2H adj δ). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 7.4, CH_3); 2.00–2.08 (1H, m, 4-CH); 3.69 (3H, s, OCH_3), 4.25 (1H, d, *J* = 7.7, 5-CH); 6.85–6.98 (2H, m, H Ar); 7.75–7.93 (5H, m, H Ar); 8.15–8.20 (1H, m, H Ar). ^{13}C NMR spectrum (CD_2Cl_2), δ, ppm: 13.5 (CH_3); 45.5 (C-4); 60.0 (OCH_3); 73.3 (C-5); 115.1; 126.4; 127.3; 127.5; 128.8 (2C); 128.9 (2C); 130.7; 132.2; 139.8; 140.5; 157.0 (C=N isoxazoline); 167.7 (C=O saccharin); 174.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 423 $[M+Na]^+$ (100). Found, *m*/*z*: 401.0815 $[M+H]^+$. $C_{19}H_{17}N_2O_6S$. Calculated, *m*/*z*: 401.0802.

2-{[4-Methyl-3-(4-methylphenyl)-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7f). White crystals. Mp 142–144°C (hexane–MeOH, 4:1). R_f 0.63 (hexane–AcOEt, 4:1). IR spectrum (KBr), ν, cm^{-1}: 2994–2980 (CH_3 ν), 1700 (C=N σ), 1591 (C=O σ), 1351 (SO_2 ν sy), 1100 (SO_2 ν as), 812 (=C–H 2H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 7.2, CH_3); 2.10–2.17 (1H, m, 4-CH); 2.45 (3H, m, CH_3 Ar); 4.35 (1H, d, *J* =7.7, 5-CH); 7.10–7.22 (2H, m, H Ar); 7.69–7.80 (2H, m, H Ar); 7.94–8.06 (3H, m, H Ar); 8.15–8.20 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.2 (CH_3); 24.0 (CH_3 Ar); 47.1 (C-4); 72.9 (C-5); 126.4; 127.1; 127.4; 127.6; 128.8 (2C); 129.0 (2C); 130.5; 132.2; 139.8; 140.5; 157.0 (C=N isoxazoline); 167.7 (C=O saccharin); 174.25 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 407 $[M+Na]^+$ (100). Found, *m*/*z*: 385.0862 $[M+H]^+$. $C_{19}H_{17}N_2O_5S$. Calculated, *m*/*z*: 385.0853.

2-[4-Methyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7g). White crystals. Mp 135–137°C (hexane–CH_2Cl_2, 9:1). R_f 0.61 (hexane–AcOEt, 4:1). IR spectrum (KBr), ν, cm^{-1}: 2994–2980 (CH_3 ν), 1668 (C=N σ), 1589 (C=O σ), 1350 (SO_2 ν sy), 1098 (SO_2 ν as), 825 (=C–H δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.09 (3H, d, *J* = 6.8, 4-CH_3); 2.30 (3H, s, CH_3); 2.45–2.52 (1H, m, 4-CH); 2.48 (6H, s, 2CH_3); 4.44 (1H, d, *J* =7.5, 5-CH); 7.00 (2H, s, H Ar); 7.81–7.95 (3H, m, H Ar); 8.16–8.22 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.8 (isoxazoline CH_3); 21.1 (2CH_3); 22.1 (CH_3); 48.1 (C-4); 75.2 (C-5); 122.9; 123.0; 126.2; 127.5 (2C); 128.1 (2C); 134.5; 136.3; 136.6; 140.2; 140.5; 157.2 (C=N isoxazoline); 170.0 (C=O saccharin); 174.5 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 435 $[M+Na]^+$ (100). Found, *m*/*z*: 413.1170 $[M+H]^+$. $C_{21}H_{21}N_2O_5S$. Calculated, *m*/*z*: 413.1167.

2-{[3-(4-Fluorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]carbonyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7h). Yellow crystals. Mp 110–112°C (hexane–CH_2Cl_2, 4:1). R_f 0.62 (hexane–AcOEt, 3:2). IR spectrum (KBr), ν, cm^{-1}: 2930 (CH_3 ν), 1680 (C=N σ), 1598 (C=O σ), 1402 (SO_2 ν sy), 1096 (SO_2 ν as), 838 (=C–H 2H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.10 (3H, d, *J* = 7.8, CH_3); 2.47–

2.55 (1H, m, 4-CH), 4.62 (1H, d, J = 8.1, 5-CH); 7.40–7.55 (2H, m, H Ar); 7.78–7.96 (5H, m, H Ar); 8.17–8.23 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.5 (CH_3); 46.2 (C-4); 73.2 (C-5); 120.2; 123.3; 125.0; 126.7; 128.0; 128.8 (2C); 129.5 (2C); 130.8; 135.6; 140.3; 160.7 (C=N); 165.2 (C–F); 170.0 (C=O saccharin); 174.5 (C=O isoxazoline). Mass spectrum, m/z (I_{rel}, %): 411 $[M+Na]^+$ (100), 799 $[2M+Na]^+$ (20). Found, m/z: 389.0609 $[M+H]^+$. $C_{18}H_{14}FN_2O_5S$. Calculated, m/z: 389.0603.

2-({3-[4-(Dimethylamino)phenyl]-4-methyl-4,5-dihydroisoxazol-5-yl}carbonyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (7i). Yellowish solid. Mp 212–214°C (EtOH). R_f 0.73 (hexane–AcOEt, 3:2). IR spectrum (KBr), ν, cm^{-1}: 2993–2981 (CH_3 ν), 1670 (C=N σ), 1600 (C=O σ), 1349 (SO_2 ν sy), 1097 (SO_2 ν as), 830 (=C–H 2H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.11 (3H, d, J = 6.8, CH_3); 2.50–2.56 (1H, m, 4-CH); 3.03 (6H, s, $N(CH_3)_2$); 4.50 (1H, d, J = 7.7, 5-CH); 6.88–7.01 (2H, m, H Ar); 7.78–7.89 (2H, m, H Ar); 7.96–8.11 (3H, m, H Ar); 8.20–8.26 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.9 (CH_3); 40.1 ($N(CH_3)_2$); 47.4 (C-4); 75.2 (C-5); 112.9; 120.3; 122.5; 123.2; 127.5 (2C); 128.4 (2C); 136.3; 140.0; 140.2; 152.2; 160.2 (C=N); 169.5 (C=O saccharin); 173.8 (C=O). Mass spectrum, m/z (I_{rel}, %): 436 $[M+Na]^+$ (100). Found, m/z: 414.1134 $[M+H]^+$. $C_{20}H_{20}N_3O_5S$. Calculated, m/z: 414.1120.

Synthesis of pyrazolines 8–11 (General method). E. Conventional method. Triethylamine (0.28 ml, 2.0 mmol) was added to a solution of hydrazonoyl halide (2.0 mmol) and dipolarophile **5** or **6** (2.0 mmol) in THF (10 ml) at room temperature. The mixture was refluxed for 8–24 h and then filtered. The mixture was dried over anhydrous sodium sulfate and then filtered. The solvent was then evaporated under vacuum to give dark-brown oil. The crude product was purified by column chromatography using hexane–AcOEt, 8:2 or 6:4, as eluent.

F. Microwave synthesis. A mixture of hydrazonoyl halide (2.0 mmol) and dipolarophile **5** or **6** (2.0 mmol) was dissolved in CH_2Cl_2 (20 ml), and the solution was added with stirring to *p*-HAP300 (2 g) at room temperature. The mixture was first stirred at room temperature for 2 min, and the solvent was evaporated under vacuum, then the resulting solid was exposed to microwave irradiation with a power of 80 W to complete the reaction (as monitored by TLC). The reaction mixture was cooled, removed from vial, and washed with CH_2Cl_2 (2×20 ml). The organic solvent was dried over anhydrous sodium sulfate and then filtered. The solvent was then evaporated under vacuum to give a dark-brown crude oil which was purified by column chromatography using hexane–AcOEt, 8:2 or 6:4, as eluent.

2-[(4-Methyl-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (8). Viscous oil. R_f 0.74 (hexane–AcOEt, 4:1). IR spectrum (neat), ν, cm^{-1}: 1635 (C=N σ), 1582 (C=O σ), 1456 (CH_3 σ as), 1364 (CH_3 σ sy), 1331 (SO_2 ν sy), 1073 (SO_2 ν as), 700–634 (=C–H 5H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.30 (3H, d, J = 7.2, CH_3); 3.12–3.18 (1H, m, 4-CH); 5.28 (1H, d, J = 7.1, 5-CH); 7.27–7.78 (14H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.9 (CH_3); 30.8 (C-4); 53.4 (C-5); 20.1; 121.5; 123.5; 127.6; 128.5; 129.1; 129.3; 129.5; 131.5; 132.1; 132.3; 133.1; 141.5; 143.8; 154.0 (C=N pyrazoline); 169.8 (C=O saccharin); 176.3 (C=O). Mass spectrum, m/z (I_{rel}, %): 468 $[M+Na]^+$ (100), 484 $[M+K]^+$ (24), 929 $[2M+K]^+$ (5). Found, m/z: 446.1174 $[M+H]^+$. $C_{24}H_{20}N_3O_4S$. Calculated, m/z: 446.1167.

Methyl 5-[(1,1-dioxido-3-oxo-1,2-benzothiazol-2(3*H*)-yl)carbonyl]-4-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (9). Viscous oil. R_f 0.65 (hexane–AcOEt, 4:1). IR spectrum (neat), ν, cm^{-1}: 1635 (C=N σ), 1580 (C=O σ), 1456 (CH_3 σ as), 1364 (CH_3 σ sy), 1331 (SO_2 ν sy), 1073 (SO_2 ν as), 705–638 (=C–H 5H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.55 (3H, d, J = 7.5, CH_3); 3.18–3.24 (1H, m, 4-CH); 3.75 (3H, s, OCH_3); 5.58 (1H, d, J = 7.3, 5-CH); 7.07–7.15 (1H, m, H Ar); 7.32–7.46 (3H, m, H Ar); 7.70–7.88 (4H, m, H Ar); 7.96–8.01 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.0 (CH_3); 31.5 (C-4); 51.0 (OCH_3); 58.6 (C-5); 118.1; 120.8; 122.9; 123.8; 127.6; 129.1; 134.2; 136.5; 141.5; 142.2; 153.6 (C=N pyrazoline); 164.7 (C=O ester); 169.7 (C=O saccharin); 176.3 (C=O). Mass spectrum, m/z (I_{rel}, %): 450. $[M+Na]^+$ (100), 466 $[M+K]^+$ (31). Found, m/z: 428.0925 $[M+H]^+$. $C_{20}H_{18}N_3O_6S$. Calculated, m/z: 428.0913.

2-[(1,3,4-Triphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)carbonyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (10). Viscous oil. R_f 0.65 (hexane–AcOEt, 6:4). IR spectrum (neat), ν, cm^{-1}: 1634 (C=N σ), 1581 (C=O σ), 1332 (SO_2 ν sy), 1072 (SO_2 ν as), 700–658 (=C–H 5H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 3.10 (1H, d, J = 7.4, 4-CH); 5.27 (1H, d, J = 14.7, 5-CH); 7.26–7.75 (19H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 45.8 (C-4); 53.4 (C-5); 120.1; 123.4; 126.0; 127.9; 128.0; 128.2; 128.4; 128.5, 128.6; 128.7; 129.0; 130.0; 131.0; 131.9; 132.2; 133.0; 154.1 (C=N pyrazoline); 170.6 (C=O saccharin); 172.9 (C=O). Mass spectrum, m/z (I_{rel}, %): 530 $[M+Na]^+$ (100), 546 $[M+K]^+$ (15). Found, m/z: 508.1330 $[M+H]^+$. $C_{29}H_{22}N_3O_4S$. Calculated, m/z: 508.1324.

Methyl 5-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazole-2-carbonyl)-1,4-diphenyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (11). Viscous oil. R_f 0.68 (hexane–AcOEt, 3:2). IR spectrum (neat), ν, cm^{-1}: 1633 (C=N σ), 1580 (C=O σ), 1330 (SO_2 ν sy), 1075 (SO_2 ν as), 689–648 (=C–H 5H adj δ). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 3.68 (3H, s, OCH_3); 4.27 (1H, d, J = 15.0, 4-CH); 5.24 (1H, d, J = 7.0, 5-CH); 7.00–7.19 (3H, m, H Ar); 7.31–7.64 (7H, m, H Ar); 7.82–7.97 (3H, m, H Ar); 8.16–8.22 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 47.7 (C-4); 52.3 (CH_3); 53.7 (C-5); 119.1; 120.3; 122.4; 124.0; 126.0; 127.8; 128.0; 128.4; 129.2; 134.5; 136.0; 140.2; 140.6; 143.8; 152.1 (C=N pyrazoline); 163.9 (C=O ester); 170.6 (C=O saccharin); 175.1 (C=O). Mass spectrum, m/z (I_{rel}, %): 512 $[M+Na]^+$ (100), 528 $[M+K]^+$ (23). Found, m/z: 490.1081 $[M+H]^+$. $C_{25}H_{20}N_3O_6S$. Calculated, m/z: 490.1070.

X-Ray structural analysis of compound 6. The crystals were obtained by by slow evaporation of solution of compound **6** in THF–H_2O, 4:1, at room temperature in open air. A crystal of suitable size for X-ray diffraction analysis was coated with dry perfluoropolyether, mounted

on glass fiber, and fixed in a cold nitrogen stream (100 K) to the goniometer head. Data collection was performed on a Bruker-Nonius X8Apex-II CCD diffractometer, using monochromatic radiation λ(MoKα) 0.71073 Å, by means of ω- and φ-scans with a width of 0.50 deg. The data were reduced (SAINT)[43] and corrected for absorption effects by the multiscan method (SADABS).[44] The structures were solved by direct methods (SIR-2002)[45] and refined against all F^2 data by full-matrix least-squares techniques (SHELXTL-6.12)[46] minimizing $w(F_o^2–F_c^2)^2$. All the non-hydrogen atoms were refined anisotropically, while C–H hydrogen atoms were placed in geometrically calculated positions using a riding model and refined with isotropic temperature factors (U_{iso} values fixed at 1.2 times the U_{eq} values of the corresponding attached carbon atoms). X-ray data for compound **6** have been deposited at the Cambridge Crystallographic Data Center (deponent CCDC 1448385).

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