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SULFANILIC ACID-CATALYZED GREEN SYNTHESIS OF 4-ARYLIDENE-2-PHENYL-5(4*H*)-OXAZOLONES

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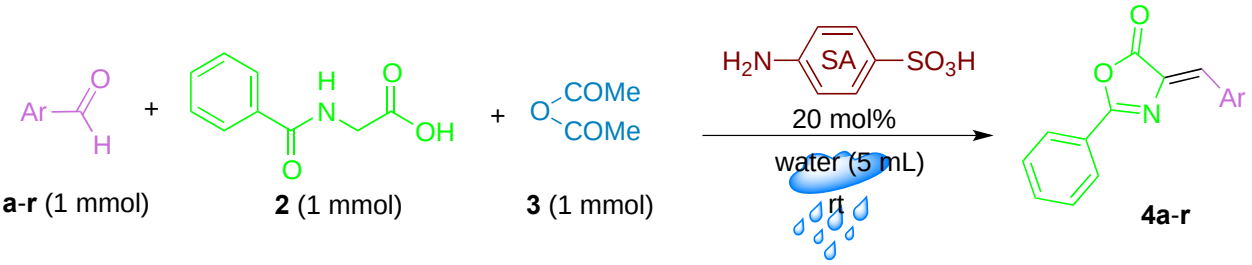
Abstract – This study is focused on the catalytic activity of sulfanilic acid (SA) in the straightforward synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones via condensation of aromatic aldehydes, hippuric acid, and acetic anhydride under green experimental conditions (water solvent). The catalyst could be recovered easily from the filtrate via evaporation of the solvent and reused many times. It was found that the method is clean, relatively rapid, and environmentally friendliness alternative for the synthesis of Erlenmeyer-Plöchl azlactones as well as no needed for heating, microwave and ultrasound irradiations. Furthermore, all of the substrates and catalyst are easily accessible and inexpensive.

4-Arylidene-2-phenyl-5(4*H*)-oxazolones (Erlenmeyer-Plöchl azlactones or oxazol-5(4*H*)-ones) are important small heterocycles with a five-membered ring as well as non-adjacent oxygen and nitrogen atoms.[1] Derivatives of azlactones were established to show a wide spectrum of biological activities such as antimicrobial, antiproliferative, tyrosinase inhibitory, antitubercular, antioxidant, anti-inflammatory, anti-HIV, anticonvulsant, and monoacylglycerol lipase (MAGL) inhibitory.[2] These heterocycles have been used as synthons for the design of electrophotographic photoreceptors, biosensors, photoswitches, organic light-emitting diodes, photonics, fluorophores, and in nonlinear optical materials.[3] Additionally, oxazol-5(4*H*)-one derivatives as valuable key intermediates have been widely applied to the synthesis of organic molecules, such as imidazolones,[4] *N*-benzoylamino-3-aryl acrylates,[5] oxazole-4-carboxamides,[6] α-amino acids,[7] optically active spiro-fused cyclohexanone/5-oxazolone derivatives,[8] peptides,[9] and a number of heterocyclic compounds.[10] So, survey new methods for the synthesis of this heterocyclic core is of particular interest from an organic chemist's point of view. One of the most popular ways to construct the azlactone unit is the cyclocondensation of *N*-substituted glycines with aldehydes in acetic anhydride and anhydrous sodium acetate as a basic catalyst (Erlenmeyer-Plöchl azlactone synthesis).[11] The cyclocondensation of aldehydes and hippuric acid as an *N*-substituted glycine can be catalyzed using

the plethora of catalysts and reagents including, metallic compounds,[12] organocatalysts,[13] ionic liquids,[14] and nanomaterials.[15] More recently, we used 5-sulfosalicylic acid as a catalyst for the synthesis of azlactones.[16]

The sulfanilic acid (SA) as a bi-functional acid-base catalyst is useful, inexpensive, commercially available, non-corrosive, stable, easy to handle, noninflammable, environmentally benign, and exists as grayish-white crystals or powder.[17,18] SA has been used as a catalyst toward synthesis of 1-amidoalkyl-2-naphthols,[18] 2-hydroxy-1-(4′-hydroxy-3′,5′-dinitrophenyl)-3-aryl-3-(arylamino)propan-1-one,[19] and 5-hydroxymethylfurfural.[18] Supported SA compounds have also been applied as the catalyst for the synthesis of 4,5-dihydropyrano[3,2-*c*]chromenes,[20] 4-*tert*-butylphenol,[21] benzimidazoles,[22] and quinoxalines.[23] To the best of our knowledge, so far, the SA has not been used as a catalyst to synthesis of this heterocyclic scaffold. This study describes the synthesis of azlactones in the presence of SA (Scheme 1).



1a-r (1 mmol) **2** (1 mmol) **3** (1 mmol) **4a-r**

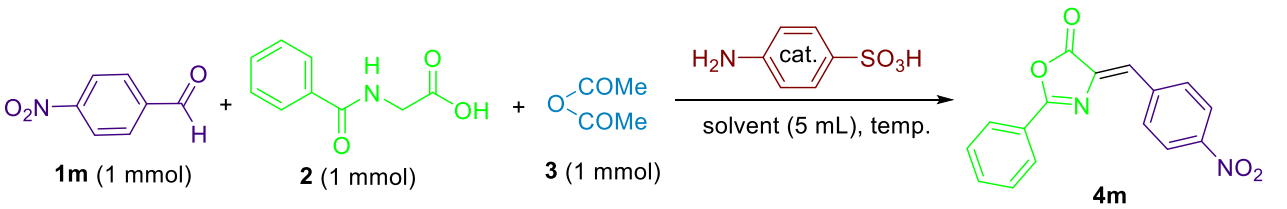
Ar: C_6H_5 (**1a**; **4a**), 4-Me-C_6H_4 (**1b**; **4b**), 4-HO-C_6H_4 (**1c**; **4c**), 3-HO-C_6H_4 (**1d**; **4d**), 2-HO-C_6H_4 (**1e**; **4e**), 4-MeO-C_6H_4 (**1f**; **4f**), 3-MeO-C_6H_4 (**1g**; **4g**), 4-Me_2N-C_6H_4 (**1h**; **4h**), 2,4-$(MeO)_2$-C_6H_3 (**1i**; **4i**), 2-Cl-C_6H_4 (**1j**; **4j**), 4-Cl-C_6H_4 (**1k**; **4k**), 2,4-diCl-C_6H_3 (**1l**; **4l**), 4-NO_2-C_6H_4 (**1m**; **4m**), 3-NO_2-C_6H_4 (**1n**; **4n**), 2-NO_2-C_6H_4 (**1o**; **4o**), 2-thienyl (**1p**; **4p**), 3-thienyl (**1q**; **4q**), 5-methylthiophen-2-yl (**1r**; **4r**)

Scheme 1. Room temperature synthesis of azlactones (**4a-r**) using sulfanilic acid (SA) catalyst

In order to optimize the reaction conditions, in preliminary experiments, 4-nitroaniline (**1m**, 1 mmol) was treated with hippuric acid (**2**, 1 mmol) and acetic anhydride (**3**, 1 mmol) in water solvent (the model reaction). Various amounts of catalyst loading including 5, 10, 15, 20, and 25 mol% were studied in water. It was found that 20 mol% is the best effective loading (Table 1, entries 1-5). Afterwards, the model reaction was also studied in a series of solvents such as EtOH, EtOAc, CH_2Cl_2, MeCN, MeOH, Ph-Me, and EtOH-H_2O (4:1 v/v) at rt and led to lower yields (Table 1, entries 6-12). Hence, H_2O is found to be the best solvent for this reaction. Furthermore, the reaction in solvent-free conditions produced a moderate yield of product (Table 1, entry 13). It was found that run the model reaction at other temperature conditions gave 87-96% yield of the products (Table 1, entries 14-19). In entry 17 (Table 1), the reaction time is very short, and reaction yield is excellent. In entry 4 (Table 1), it does not require heating, so it saves energy. Therefore, the conditions in entry 4 are superior to those in entry 17. As a

result, after screening above-mentioned experiments, it was found that the best results were obtained with 20 mol% SA in water at rt.

Table 1. Optimization of the reaction conditions for the synthesis of 4-(4-nitrobenzylidene)-2-phenyl-oxazol-5(4*H*)-one (**4m**)



Entry	Catalyst loading/mol%	Solvent	Temp./°C	Time/min.	Isolated yields/%
1	5	H_2O	rt	55	65
2	10	H_2O	rt	52	75
3	15	H_2O	rt	48	80
4	**20**	**H_2O**	**rt**	**32**	**97**
5	25	H_2O	rt	35	90
6	20	EtOH	rt	73	95
7	20	EtOAc	rt	94	85
8	20	CH_2Cl_2	rt	75	89
9	20	MeCN	rt	95	87
10	20	MeOH	rt	90	96
11	20	Ph-Me	rt	70	86
12	20	EtOH:H_2O (1:1)	rt	45	73
13	20	no solvent	rt	120	70
14	20	H_2O	40	21	91
15	20	H_2O	50	12	88
16	20	H_2O	60	9	87
17	20	H_2O	70	3	96
18	20	H_2O	80	3	91
19	20	H_2O	reflux	3	90

Bold letters and numbers (row 4) in the table have shown the optimized reaction conditions.

Having optimized reaction conditions, we proceeded to develop the scope of the reaction with a wide range of aryl/heteroaryl aldehydes. All these reactions carried out smoothly giving corresponding azlactones in good to excellent yields (Table 2). Generally, products are formed in Z-isomer.[3] It appears that the electronic nature of the substituents at the phenyl rings has no noteworthy effect on the synthesis of this heterocycles. In another attempt, the reusability of the catalyst was also examined for the synthesis of **4m**. After completion of the reaction, the solid product was filtered off and washed with water. The catalyst was recovered from filtrate by evaporation and reused in the next reactions and, the product **4m** was obtained in 94%, 89%, 85%, and 80% isolated yields in four successive runs, respectively.

In conclusion, in this study, a series of azlactones were successfully synthesized using SA catalyst in good to excellent yields under green conditions at rt. The advantages of the current method are

commercial access to starting materials, green, efficient, experimental simplicity, safe, and high yields, which these features attractive from a chemist's point of view.

Table 2. The synthesis of azlactones (**4a-r**) catalyzed by SA based on the optimized reaction conditions according to the Scheme 1

Entry	Structure of Erlenmeyer-Plöchl azlactones; Ar	Time (min)	Isolated yields (%)	Mp (°C)	
				Found	Reported[15-17,25]
1	C_6H_5 (**4a**)	45	87	167-169	168-169
2	4-Me-C_6H_4 (**4b**)	60	87	145-147	144-145
3	4-HO-C_6H_4 (**4c**)	60	90	170-172	172-173
4	3-HO-C_6H_4 (**4d**)	45	85	145-147	144-145
5	2- HO-C_6H_4 (**4e**)	55	82	165-168	168-170
6	4-MeO-C_6H_4 (**4f**)	53	87	160-161	165-166
7	3-MeO-C_6H_4 (**4g**)	54	85	100-102	101-102
8	4-Me_2N-C_6H_4 (**4h**)	45	96	210-212	213-214
9	2,4-diMeO-C_6H_3 (**4i**)	60	86	158-160	151-152
10	2-Cl-C_6H_4 (**4j**)	60	84	168-169	163-164
11	4-Cl-C_6H_4 (**4k**)	35	87	188-189	198
12	2,4-diCl-C_6H_3 (**4l**)	33	84	165-167	163-164
13	4-NO_2-C_6H_4 (**4m**)	32	97	174-175	177-178
14	3-NO_2-C_6H_4 (**4n**)	45	96	171-173	167-168
15	2-NO_2-C_6H_4 (**4o**)	40	89	164-165	158-159
16	2-thienyl (**4p**)	40	75	172-174	173-175
17	2-furyl (**4q**)	45	80	171-173	169-170
18	5-methylthiophen-2-yl (**4r**)	50	80	144-147	145-147

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, except liquid aldehydes, which were distilled before use. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE DRX spectrometer. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light. Elemental microanalyses were performed on Elementar Vario EL III analyzer at Damghan University, Damghan, Iran. All of the targeted products are reported in the literature and are characterized by comparison of their spectral and physical data by literature descriptions.

General procedure for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (4a-r). The appropriate aldehyde (**1**, 1 mmol), hippurric acid (**2**, 1 mmol), acetic anhydride (**3**, 1 mmol), water (5 mL),

and SA as a catalyst (20 mol%) was stirred at rt. After completion of the reaction as indicated by TLC (hexane:EtOAc; 70:30) analysis, the reaction mixture allowed to stand for 5 h at rt. The resulting precipitated products were filtered off, washed with ice water and dried at rt. The crude products were purified by recrystallization from absolute EtOH, if required. The filtrate containing the catalyst was used as such for exploring the reusability of the catalyst. Representative spectral date is as follows:

(*Z*)-4-(4-Nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (4m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H, -CH=) 7.59 (dd, J = 4.7, 10.9 Hz, 2H, Ar-H), 7.70-7.74 (m, 1H, Ar-H), 8.25 (dd, J = 1.2, 8.6 Hz, 2H, Ar-H), 8.34-8.36 (m, 2H, Ar-H), 8.28-8.33 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.8, 122.3, 127.4, 128.9, 129.4, 129.8, 131.1, 131.3, 142.1, 146.8, 160.5, 166.4; Anal. Calcd for $C_{16}H_{10}N_2O_4$: C 65.31, H 3.43, N 9.52. Found: C 65.29, H 3.40, N 9.49.

(Z)-4-(4-Methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (4f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 7.9-7.19 (d, J = 8.2 Hz, 2H, Ar-H), 7.33 (s, 1H, -CH=), 7.52 (d, J = 8.2 Hz, 2H, Ar-H), 7.71-7.77 (m, 2H, Ar-H), 8.11 (dd, J = 7.4, 1H, Ar-H), 8.32 (d, J = 7.2, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.5 (OCH_3), 114.6, 126.5, 127.6, 128.1, 128.6, 132.1, 133.3, 135.6 (-CH=), 142.5 (C_{Ar}-O), 144.3 (C-N), 161.2 (C=N), 182.2 (C=O).

(Z)-4-(3-Methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (4g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (s, 3H, OCH_3), 7.03 (d, J = 8.4 Hz, 1H, Ar-H), 7.18 (s, 1H, -CH=), 7.32 (m, 2H, Ar-H), 7.41-7.44 (m, 1H, Ar-H), 7.53 (d, J = 8.4 Hz, 1H, Ar-H), 7.82 (s, 1H, Ar-H), 8.9-8.07 (m, 2H, Ar-H), 8.42 (dd, J = 7.4, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.4 (OCH_3), 115.4, 117.2, 122.6, 127.7, 128.0, 132.3, 133.3, 133.5, 134.3, 135.9 (-CH=), 145.4 (C-N), 155.2 (C_{Ar}-O), 159.5 (C=N), 18.5 (C=O), Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.13; H, 4.67; N, 5.04.

(Z)-4-(4-(Dimethylamino)benzylidene)-2-phenyloxazol-5(4*H*)-one (4h). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.12 (s, 6H, NMe_2), 6.74 (d, J = 9.6 Hz, 2H, Ar-H), 9.13 (d, J = 3.6 Hz, 2H, Ar-H), 7.22 (s, 1H, -CH=), 8.15 (d, J = 7.8 Hz, 2H, Ar-H), 7.52 (d, J = 7.2 Hz, Ar-H), 7.57 (d, J = 7.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.1 (NMe_2), 111.7, 121.7, 128.7, 128.8, 131.9, 132.31, 133.4, 134.8, 134.9, 152.2 (C-NMe_2), 160.5 (C=N), 168.8 (C=O); Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.93; H, 5.50; N, 9.59.

(Z)-4-((5-Methylthiophen-2-yl)methylene)-2-phenyloxazol-5(4*H*)-one (4r). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.63 (s, 3H, CH_3), 6.89 (s, 1H, H-4 of thiophene), 7.44 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.62 (s, 1H, H-3 of thiophene), 8.18 (s, 1H, -CH=), 8.20 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.2 (CH_3), 125.6, 126.0, 126.8, 127.6, 128.2, 129.0, 133.1 (C-2 of thiophene), 136.0 (C-3 of thiophene), 136.4 (C-N), 151.4 (C-5 of thiophene), 160.6 (C=N), 167.2 (C=O); Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.88; H, 4.10; N, 5.18; S, 11.92.

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