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Reaction Coordinate

Synthesis and DFT studies of novel aryloxymaleimides via nucleophilic substitution of tosyloxy group

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Abstract: Maleimide skeleton distributes widely in a great many substances, and maleimides are very useful building blocks in organic synthesis and many related disciplines, like bioconjugation. As an excellent leaving group, tosyloxy (-OTs) group are very popular in organic synthesis; however, reports on use of -OTs group on maleimide scaffold are very rare. In this study, 3-tosyloxymaleimide was prepared from L-tartaric acid and used to react with various phenols or naphthols under PTC condition to give 3-aryloxymaleimides through nucleophilic substitutions. Yields of the reaction were not high due to a competitive transesterification reaction; however, this reaction would be practical if the side-reaction could be suppressed by appropriate reaction conditions. The reaction mechanism was investigated by theoretical computation. The intermediates and transition states of the reaction, as well as the potential barrier and reaction were discussed. Theoretical computations showed that this nucleophilic substitution is favorable both kinetically and thermodynamically, while electron-withdrawing groups on phenols are harmful to such reactions. This study will provide new knowledge and insights on the chemical properties of maleimide and tosyloxy group, as well as the related chemical reactions.

Keywords: Maleimide; Organic synthesis; Theoretical calculations; Density functional theory; Reaction mechanism

Introduction

Maleimide is a common scaffold of a variety of organic substances, and is also an important building block used in chemical synthesis. Maleimide and its derivatives can be easily prepared by condensation of maleic acid or maleic anhydride with amines, and are very useful in multiple area, especially in bioconjugation. (*I*) (*2*) (*3*) (*4*) (*5*) *p*-Toluenesulfonyloxy (-OTs, tosyloxy) is a common functional group widely used in organic synthesis, because it can be readily prepared from alcohols by tosylation with TsCl and act as an excellent leaving group in substitution reactions. (*6*) However, application of tosyloxy group on maleimide scaffolds were quite rarely reported. Till June 19, 2018, only 2 substances bearing a tosyloxy group on maleimide scaffolds and 2 related references had been reported (CAS RN 903578-02-9 (*7*) and 873939-14-1 (*8*)). In our previous studies, we unexpectedly found that *trans*-3,4-dihydroxypyrrolidine-2,5-dione may be converted to monotosyloxymaleimide under tosylation by TsCl/Et₃N. (*9*) Starting from the monotosyloxymaleimide, a number of monosubstituted maleimides were synthesized using nucleophilic substitution reactions under mild phase transfer catalysis (PTC) conditions. Density functional theory (DFT) was then used to investigate the mechanism of the reaction,

including the transition states and intermediates, intrinsic reaction coordinates (IRC), potential barriers, and the change of free energies; influencing factors of the reaction were also discussed.

Results and Discussion

Firstly, the commercially available L-tartaric acid was cyclized with *p*-methoxybenzylamine (PMB-NH₂) in xylene to give the L-tartarimide **1** (9) (10) (**Scheme 1**). Then **1** was treated with TsCl and Et₃N in CH₂Cl₂ to furnish the maleimide **2**. (9) The intermediate **3** was obtained through removal of *p*-methoxybenzyl (PMB) group of **2** by ceric ammonium nitrate (CAN) oxidation, and used as the starting material of synthesis of monosubstituted maleimides (**Scheme 2**).



Scheme 1. Reactions and conditions: (a) PMB-NH₂, xylene, reflux; (b) TsCl, Et₃N, CH₂Cl₂, 0^{0} C ~ rt; (c) CAN, MeCN-H₂O, reflux.

It is well-known that oxygen or halogen atoms connecting to a double bond or an aromatic ring are somewhat inert to nucleophilic substitution due to the p- π conjugation. Typical methods of substituting OTs or halogen on aromatic rings include Ullmann reaction and its variations, like Ullmann condensation and Goldberg reaction, catalyzed by copper or palladium. As for maleimides, nucleophilic substitutions of halogen on maleimide without Cu or Pd catalysts have been reported (11) (12) (13); however, such studies on substitution of tosyloxy group are still absent. In this study, we used various phenols to displace the tosyloxy group of **3** to obtain the corresponding ethers (**4a**~**4k**) at the presence of K₂CO₃ under mild phase transfer catalysis (PTC) conditions (**Scheme 2**).



Scheme 2. Reactions and conditions: K₂CO₃, TBAB, CH₂Cl₂-H₂O, rt.

Generally, the reactions in Scheme 2 can be completed quickly at room temperature; however, yields of $4a \sim 4k$ are relatively low (Table 1), mainly due to a competitive transesterification reaction, i.e., transferring of tosyl from 3 to phenols, giving the corresponding aryl tosylates ($5a \sim 5k$). This side-reaction is unsurprising since enol esters are acylating reagents. For phenol derivatives ($4a \sim 4g$), the yields are between $24.3\% \sim 47.3\%$; for naphthol derivatives ($4h \sim 4k$), the yields differ greatly. The order of the yields is 4h > 4i > 4j > 4j > 4k; when the Ar-OH was 2-hydroxy-1-naphthalenecarbaldehyde, no ether product 4k was obtained, while the tosylate 5k became the only product. The lower yield of 4i is possibly due to the steric hindrance of bromine at C-1. The strong electron-withdrawing effect of formyl group of 6-hydroxy-2-naphthalenecarbaldehyde and 2-hydroxy-1-naphthalenecarbaldehyde probably lead to the poor yields of 4j and 4k by decreasing the nucleophilicity of naphthoxy anion; and for the latter, steric hindrance of formyl group is also likely to play a role in preventing the formation of 4k. The yield of by-products

5h~5k, however, are in ascending order. The reason we supposed is that the transesterification reaction might be not as sensitive to the effects of electron-withdrawing and steric hindrance as the major reaction is; since these two reactions are competitive, factors suppressing the major reaction will facilitate the side-reaction.

Name	Ar	Yield of	Yield of
		4a~4k	5a~5k
4a	phenyl	34.5%	35.3%
4b	\rightarrow	42.6%	37.7%
4c		43.0%	37.6%
4d		47.3%	36.4%
4 e	Н ₃ СО, <u>5</u>	24.3%	38.6%
4f		37.7%	19.1%
4g		38.7%	40.4%
4h	narr	44.7%	34.6%
4 i	Br	21.9%	55.7%
4j	Br Str	14.0%	64.3%
4k	онс	NA	70.0%

Table 1. Structure and yield of products 4a~4k and by-products 5a~5k.

The reaction mechanism of the formation of enol ether $4a \sim 4k$ was further investigated by theoretical computations using DFT. Possibly, this reaction may have a one-step SN_2 -like process, i.e., the attacking of phenoxy anion is concerted with the leaving of the tosyloxy anion, with a transition state (TS) (**6a** in **Scheme 3**) controlling the whole process. Alternatively, this reaction may be a two-step process, including an addition of phenoxy anion to form a tetrahedral intermediate **6a**, followed by an elimination of tosylate anion (**Scheme 3**). These two mechanisms can be discriminated by whether **6a** is a transition

state (one-step mechanism) or an intermediate (two-step mechanism). In quantum chemistry, this question can be expressed as whether **6a** is located at a first-order saddle point in the potential energy surface (PES), or a local minimum in the PES; the former indicates a transition state, while the latter indicates an intermediate.



Scheme 3. Proposed reaction mechanism of 3 with phenol.

The hybrid-meta GGA functional M06-2X (14) (15) with basis set $6-31+G^{**}$ (16) (17) was selected for the DFT calculations including geometry optimization, vibration analysis, and calculation of intrinsic reaction coordinate (IRC). The M06-2X functional exhibits good performances in studies of organic reaction mechanism, including nucleophilic addition/substitution processes. (18) (19) The combination of M06-2X functional with the basis set $6-31G^{**}$ (or with diffusion functions) is usually adequate for theoretical studies of common organic systems (20) (21) (22) (23). For the optimized structure of stationary points, single point energies were recalculated using double-hybrid functional B2PLYP (24) and basis set ma-TZVP (def2-TZVP basis set (25) (26) with minimal diffuse function for heavy atoms (27) (28)) to yield higher accuracy.

The structure of **6a** was obtained by manually constructing an initial guessed structure followed by a geometry optimization. Vibration analysis of **6a** showed no imaginary frequencies, indicating **6a** is not a transition state, but an intermediate. Thus, transition states between the reactant and 6a (TS1) and between 6a and the product (TS3) were searched and IRCs were calculated for these transition states (see Data in Brief). Interestingly, **6a** has two distinct conformational isomers (IM1 and IM2), which were derived from IRC of TS1 and TS3, respectively, and were not interconvertible in geometry optimization (Figure 1). IM1 and IM2 just differ in the orientation of phenyl rings, i.e., the C-OPh torsion (5-1-28-29) and the O-Ph torsion (1-28-29-30). IM1 and IM2 were separated by a transition state (TS2), which has a unique imaginary frequency of 41.12*i*. We tried to find a transition state which directly connects the reactant to IM2, but failed. It seems that a nearly parallel position of the phenoxy anion with the maleimide ring facilitates the nucleophilic attacking and the formation of TS1 (Figure 2, structure of the reactant and TS1), probably due to the π - π interactions between the phenyl and maleimide ring, and leads to the formation of IM1. However, during the leaving of tosyloxy anion, the oxygen atom of the phenoxy group needs to reach the plane of maleimide ring, and therefore the weak interactions between the phenyl and maleimide ring in IM1 must be broken and then the phenyl rotates outward to form IM2, which allows the oxygen atom of the phenoxy group approaching the maleimide plane (Figure 2, structure of TS3 and the product). Nevertheless, the transition of IM1 to TS2 is just a conformational rotation with a potential energy barrier of only 3.2 KJ/mol, which is quite easy to accomplish.



Figure 1. Conformational isomers of 6a (IM1, TS2, and IM2).

TS1 has only one imaginary frequency (239.05*i*), which corresponds to the stretch of C···OPh bond (1.94 Å); bond length of C···OTs is 1.39 Å. The long C···OPh distance in TS1 indicates the transition state is closer to the reactant rather than to the product, and the phenoxy anion is easy to approach the carbon atom in reaction center to form the transition state. This is in consistent with the fact that the potential barrier from the reactant to TS1 is quite low (18.3 KJ/mol only). The only imaginary frequency of TS3 is 265.36*i*, corresponding to the stretch of C···OTs bond; bond length of C···OTs and C···OPh are 1.64 Å and 1.38 Å, respectively. The low barrier between IM2 and TS3 (2.5 KJ/mol) indicates that IM2 is very liable to decompose to form the product.

Table 2.	Gibbs free	energies	calculated	for reactant,	transition state	es, intermediate	s, and p	roduct	in the
			re	action of 3 w	vith phenol. ^{a)}				

	Single point	Thermal correction	Single point	Gibbs free	Relative
	energy (M06-	to	energy	energy	energy
	$2X)^{b}$	Gibbs free energy	(B2PLYP)		(KJ/mol)
Reactant	-1560.166119	0.220709	-1560.107793	-1559.887084	123.8
TS1	-1560.159162	0.221798	-1560.100791	-1559.878993	145.0
IM1	-1560.177945	0.224744	-1560.108957	-1559.884213	131.3
TS2	-1560.176740	0.225863	-1560.108790	-1559.882927	134.7
IM2	-1560.182231	0.224282	-1560.112709	-1559.888427	120.2
TS3	-1560.181288	0.224725	-1560.113655	-1559.888930	118.9
Product	-1560.219515	0.224045	-1560.158269	-1559.934224	0

^{a)} Geometry optimization, vibration analysis and IRC calculation were at M06-2X/6-31+G** level. For optimized structures, single point energies were recalculated at B2PLYP/ma-TZVP level. Each transition state has only one imaginary frequency, while others have no imaginary frequencies after geometry optimization. Frequency scale factor of 0.9670 (*29*) was used in calculating thermal correction values at 298.15K. Gibbs free energies were calculated by summing up single point energies (B2PLYP) and the thermal correction value. All energies, except Relative energy, are given in Hartree. ^{b)} The electronic energy barriers reported in the text were calculated using M06-2X single point energies reported here. The M06-2X single point energies of the reactant, intermediates, and product reported here are of the optimized structures, which are slightly different to the corresponding structures in the IRC (not optimized); so, the M06-2X single point energy barriers calculated from this Table are slightly different to the barriers read from the IRC.





Figure 2. Profile of free energies and structures of the stationary points along the reaction coordinate. For clearance, all hydrogen atoms are hidden and the tosyl group is displayed in line model.

The stationary points including transition states, intermediates, reactant and product were then geometryoptimized and calculated for Gibbs free energies (**Table 2**, **Figure 2**). Obviously, the free energy of TS3 is 1.3 KJ/mol lower than IM2 (for electronic energies, TS3 is just 2.5 KJ/mol higher); therefore, TS3 is not a real transition state when free energies are taken into account. The free energy barrier of TS2 is just 3.4 KJ/mol; therefore, conversion from the reactant to TS1 (with a free energy barrier of 21.2 KJ/mol to overcome) determines the speed of the whole reaction process. So, this reaction is quite easily to occur under room temperature. The overall free energy change of the whole reaction is -123.8 KJ/mol. Also, the free energy barrier between IM1 and TS1 is 13.7 KJ/mol, dramatically lower than the electronic energy barrier (49.3 KJ/mol), while the barrier of forward process changed less (21.2 KJ/mol in free energy, and 18.3 KJ/mol in electronic energy). The difference in thermal correction values of free energy of the reactant and IM1 is 10.6 KJ/mol, which is mainly contributed by the entropy difference. IM1 has a much lower entropy than the reactant; the T· Δ S item is -8.8 KJ/mol (T=298.15 K). The decrease of entropy would be attributed to the loss of degree of freedom and disorder upon the joining of two molecules into one.

The transition state of reaction of **3** with 2-hydroxy-1-naphthalenecarbaldehyde was also found and IRC was calculated using the same parameter settings (**Figure 3**). The only imaginary frequency of TS1 is 299.12*i*, corresponding to the stretch of the newly formed C···O bond (1.84 Å). This bond length is

significantly shorter than the TS1 of **4a** (1.94 Å), indicating that the naphthoxy anion will need to overcome much more resistance to reach a closer position to the center carbon atom to form the transition state. Obviously, the strong electron-withdrawing effect of the formyl group at *ortho*- position decreases the electronegativity of the oxygen atom, and therefore it needs to be much closer (than the phenoxy anion) to the center carbon atom to reach a balance with the leaving group (tosyloxy). This agrees with the fact that the potential barrier (37.6 KJ/mol, electronic energy) is significantly higher than that of **4a** (18.3 KJ/mol). The Gibbs free energy barrier of the forward process was calculated at the same computation level to **4a** (**Table 3**) to be 31.4 KJ/mol, higher than **4a** (21.2 KJ/mol), whereas the free energy barrier for the reverse process is 7.4 KJ/mol, lower than **4a** (13.7 KJ/mol). These data clearly demonstrated that formation of **4k** is more difficult than **4a**. Even so, such a reaction would be able to proceed easily at room temperature, assuming the absence of the competitive transesterification reaction, which is apparently very easier to proceed.



Figure 3. Comparison of transition state and IRC of 4a and 4k.

Table 3. Gibbs fre	ee energy changes	s in the reaction	of 3 with 2-hydroxy-	1-naphthalenecarbaldehyde. ^{a)}
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	Single point	Thermal	Single point	Gibbs free	Relative
	energy (M06- 2X)	correction to Gibbs free energy	energy (B2PLYP)	energy	energy (KJ/mol)
Reactant	-1827.0553572	0.272080	-1826.9746736	-1826.7025936	0
TS1	-1827.0410351	0.271086	-1826.9617225	-1826.6906365	31.4
IM1	-1827.0525356	0.272069	-1826.965520	-1826.6934510	24.0

^{a)} All parameter settings in the calculation were the same to those in **Table 2**.

Conclusion

In this study, nucleophilic displacement reactions of tosyloxy group on maleimide scaffold was explored. The nucleophiles were different phenols and naphthols, and the reactions were carried out at the presence of K_2CO_3 under mild PTC conditions. Usage of tosyloxy group on maleimides was very rarely reported, and this study is attempting to provide a preliminary exploratory research and to discover the potential issues in such reactions. The reaction mechanism and influencing factors were explored by theoretical computations using DFT, based on the experimental results. The free energy barrier and free energy of reaction showed that these nucleophilic substitution reactions were favorable both thermodynamically and

kinetically. However, the yield of the reactions were low to moderate, primarily attributed to the competitive transesterification reaction. Nevertheless, this reaction still could be of practical value if suitable reaction conditions are found to suppress the undesirable transesterification reaction. Further computational and experimental studies in this area are still underway and will be reported upon new progress.

Experimental Details

1. Chemical synthesis

General methods: **1** and **2** were prepared according to our previous studies. (9) CAN were from Aladdin Chemical Reagents (Shanghai, China). Phenols and naphthols were purchased from Aladdin Chemical Reagents or IVKeyan (Shanghai, China). Other reagents were from Fuyu Fine Chem (Tianjin, China). Boiling range of petroleum ether used in this study is 60-90 ^oC. Pre-coated silica gel GF254 plates (Qingdao Haiyang Chemical, Qingdao, China) were used in TLC. Preparative column chromatography was performed using silica gel (100-200 mesh). NMR spectra were recorded on Bruker Avance III-400 or AscendTM 600 spectrometers. HRMS spectra were determined using Bruker Daltonics maXis UHR-TOF with ESI ionization source.

1.1. 3-Tosyloxymaleimide (3)

2 (19.10 g, 49.3 mmol) and CAN (93.73 g, 171 mmol) were suspended in MeCN-H₂O (279 ml : 31 ml), and the mixture was stirred and refluxed until TLC (4:1, petroleum ether-EtOAc) showed the reaction had completed. The mixture was cooled down to room temperature, to which water (800 ml) was slowly added. The mixture was then left overnight to allow the product to precipitate. After filtration, the obtained solid was subject to column chromatography (8:1, petroleum ether-EtOAc) to furnish **3** (9.52 g, 35.6 mmol) as a light yellow powder. Yield: 72.2%. ¹H NMR (600 MHz, CDCl₃): 2.49 (s, 3H, PhCH₃), 6.30 (d, 1H, J=1.2, H-4), 7.34 (br, 1H, NH), 7.43 (m, 2H, Ar-H), 7.90 (m, 2H, Ar-H); ¹³C NMR (400 MHz, CDCl₃): 21.9, 110.3, 128.8, 130.5, 130.8, 147.5, 149.3, 163.7, 167.4; HRMS m/z: $[M+NH_4]^+$ calculated 285.0540, found 285.0540; $[M+Na]^+$ calculated 290.0094, found 290.0091.

1.2. General procedure of synthesis of 3-aryloxymaleimide (4a~4k)

3 (300 mg, 1.12 mmol), Ar-OH (2.04 mmol), and TBAB (50 mg) were dissolved in CH_2Cl_2 (15 ml), to which a K_2CO_3 aqueous solution (K_2CO_3 300 mg in H_2O 2.5 ml) was added. The mixture was stirred vigorously at room temperature until TLC (4:1, petroleum ether-EtOAc) showed the reaction had completed. The mixture was then diluted by CH_2Cl_2 (15 ml) and washed by water (25 ml × 3) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated and subject to a silica gel column chromatography (15:1 ~ 7:1, petroleum ether-EtOAc) to give the desired 3-aryloxymaleimides (**4a**~**4k**) and the by-products aryl tosylates (**5a**~**5k**). (For 4-(2-methoxyethyl)phenol, **5e** was firstly eluted by 10:1 petroleum ether-acetone, and then **4e** was collected using 7:1 petroleum ether-EtOAc.)

3-Phenoxymaleimide (**4a**): white solid, yield 34.5%. ¹H NMR (600 MHz, CDCl₃): 5.31 (d, 1H, J=1.8, H-4), 7.19-7.21 (m, 2H, Ar-H), 7.31-7.34 (m, 1H, Ar-H), 7.45-7.48 (m, 2H, Ar-H), 7.67 (br, 1H, NH); ¹³C NMR (400 MHz, CDCl₃): 100.5, 119.8, 127.0, 130.4, 153.8, 159.6, 165.4, 169.3; HRMS: $m/z [M+Na]^+$ calculated 212.0318, found 212.0319.

Phenyl tosylate (5a) (30) (31) (32): white solid, yield 35.3%.

3-(4-*tert***-Butylphenoxy)maleimide (4b)**: white solid, yield 42.6%. ¹H NMR (600 MHz, CDCl₃): 1.34 (s, 9H, *t*-Bu), 5.33 (d, 1H, J=1.2, H-4), 7.10-7.12 (m, 2H, Ar-H), 7.23 (br, 1H, NH), 7.43-7.46 (m, 2H, Ar-H); ¹³C NMR (400 MHz, CDCl₃): 30.3, 33.6, 99.3, 118.1, 126.2, 149.0, 150.5, 158.7, 164.4, 168.4; HRMS: m/z [M+Na]⁺ calculated 268.0944, found 268.0947.

4-tert-Butylphenyl tosylate (5b) (33): white solid, yield 37.7%.

3-(4-Isopropylphenoxy)maleimide (4c): white solid, yield 43.0%. ¹H NMR (400 MHz, CDCl₃): 1.26 (d, 6H, J=6.8, CH₃×2), 2.95 (m, 1H, CHMe₂), 5.32 (s, 1H, H-4), 7.09-7.12 (m, 2H, Ar-H), 7.27-7.31 (m, 2H, Ar-H), 7.60 (br, 1H, NH); ¹³C NMR (400 MHz, CDCl₃): 24.0, 33.7, 100.3, 119.5, 128.2, 147.7, 151.8, 159.8, 165.5, 169.5; HRMS: m/z [M+Na]⁺ calculated 254.0788, found 254.0793.

4-Isopropylphenyl tosylate (5c) (*33*): colorless liquid, yield 37.6%.

3-(3,4-Dimethylphenoxy)maleimide (4d): white solid, yield 47.3%. ¹H NMR (400 MHz, CDCl₃): 2.27 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 5.29 (s, 1H, H-4), 6.91 (m, 1H, Ar-H), 6.96 (m, 1H, Ar-H), 7.18 (m, 1H, Ar-H), 7.58 (br, 1H, NH); ¹³C NMR (400 MHz, CDCl₃): 19.3, 20.0, 100.2, 116.7, 120.6, 131.1, 135.4, 139.1, 151.8, 159.9, 165.5, 169.6; HRMS: m/z [M+Na]⁺ calculated 240.0631, found 240.0637.

3,4-Dimethylphenyl tosylate (5d) (*33*) : white solid, yield 36.4%.

3-(4-(2-Methoxyethyl)phenoxy)maleimide (4e): white solid, yield 24.3%. ¹H NMR (400 MHz, CDCl₃): 2.91 (t, 2H, J=6.8, PhCH₂), 3.37 (s, 3H, OCH₃), 3.63 (t, 2H, J=6.8, OCH₂), 5.32 (d, 1H, J=1.6, H-4), 7.10-7.13 (m, 2H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.40 (br, 1H, NH); ¹³C NMR (400 MHz, CDCl₃): 35.5, 58.8, 73.1, 100.4, 119.6, 130.7, 138.1, 152.2, 159.7, 165.3, 169.2; HRMS: m/z [M+Na]⁺ calculated 270.0737, found 270.0737.

4-(2-Methoxyethyl)phenyl tosylate (5e) (34): colorless liquid, yield 38.6%.

3-(2,3,5-Trimethylphenoxy)maleimide (4f): white solid, yield 37.7%. ¹H NMR (600 MHz, CDCl₃): 2.08 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 5.13 (d, 1H, J=1.2, H-4), 6.76 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 7.15 (br, 1H, NH); ¹³C NMR (600 MHz, CDCl₃): 11.7, 20.0, 20.9, 100.5, 117.7, 124.5, 129.3, 136.9, 139.3, 152.1, 159.8, 165.1, 169.1; HRMS: m/z [M+Na]⁺ calculated 254.0788, found 254.0786.

2,3,5-Trimethylphenyl tosylate (5f) (35): white solid, yield 19.1%.

3-(5,6,7,8-Tetrahydro-2-naphthoxy)maleimide (4g): white solid, yield 38.7%. ¹H NMR (600 MHz, CDCl₃): 1.79-1.83 (m, 4H, H-6', H-7'), 2.77 (t, 4H, J=6.0, H-5', H-8'), 5.31 (d, 1H, J=1.2, H-4), 6.87-6.90 (m, 2H, Ar-H), 7.11 (m, 1H, Ar-H), 7.28 (br, 1H, NH); ¹³C NMR (600 MHz, CDCl₃): 22.7, 22.9, 28.9, 29.5, 100.3, 116.6, 119.7, 130.8, 135.9, 139.6, 151.5, 159.9, 165.3, 169.2; HRMS: m/z [M+Na]⁺ calculated 266.0788, found 266.0791.

5,6,7,8-Tetrahydro-2-naphthyl tosylate (5g) (33) : colorless liquid, yield 40.4%.

3-(1-Naphthoxy)maleimide (4h): dark red solid, yield 44.7%. ¹H NMR (600 MHz, CDCl₃): 5.19 (d, 1H, J=1.8), 7.31-7.33 (m, 1H), 7.49-7.51 (m, 1H), 7.55-7.59 (m, 3H), 7.82-7.83 (m, 1H), 7.92-7.96 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): 101.1, 116.0, 120.9, 125.3, 125.4, 127.1, 127.2, 127.3, 128.2, 135.0, 149.8, 159.8, 165.2, 169.1; HRMS: m/z [M+Na]⁺ calculated 262.0475, found 262.0473.

1-Naphthyl tosylate (5h) (33) : white solid, yield 34.6%.

3-(1,6-Dibromo-2-naphthoxy)maleimide (4i): white solid, yield 21.9%. ¹H NMR (400 MHz, DMSO-*d*₆): 5.65 (s, 1H, H-4), 7.78-7.80 (m, 1H, Ar-H), 7.93-7.96 (m, 1H, Ar-H), 8.17-8.21 (m, 2H, Ar-H), 8.48-8.49

(m, 1H, Ar-H), 11.09 (br, 1H, NH); ¹³C NMR (100 MHz, DMSO- d_6): 102.8, 113.1, 120.9, 121.9, 129.2, 130.1, 131.0, 131.3, 132.1, 133.9, 149.8, 158.1, 166.7, 171.0; HRMS: m/z [M+Na]⁺ calculated 419.8664, found 419.8665.

1,6-Dibromo-2-naphthyl tosylate (5i): white solid, yield 55.7%. ¹H NMR (600 MHz, CDCl₃): 2.44 (s, 3H), 7.30 (m, 2H), 7.48 (m, 1H), 7.62 (m, 1H), 7.68 (m, 1H), 7.80 (m, 2H), 7.96 (m, 1H), 8.02 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): 21.8, 116.3, 121.3, 122.9, 128.0, 128.8, 129.3, 129.9, 130.1, 131.3, 131.4, 132.7, 133.5, 145.3, 145.9; HRMS: m/z $[M+NH_4]^+$ calculated 473.9192, found 473.9196.

3-(6-Formyl-2-naphthoxy)maleimide (4j): white solid, yield 14.0%. ¹H NMR (600 MHz, DMSO- d_6): 5.77 (d, 1H, J=1.2, H-4), 7.66-7.68 (m, 1H, Ar-H), 7.96-7.98 (m, 1H, Ar-H), 8.03 (m, 1H, Ar-H), 8.12 (m, 1H, Ar-H), 8.32 (m, 1H, Ar-H), 8.66 (m, 1H, Ar-H), 10.16 (s, 1H, CHO), 10.95 (br, 1H, NH); ¹³C NMR (400 MHz, DMSO- d_6): 102.6, 117.1, 121.0, 123.9, 129.4, 130.9, 133.0, 134.4, 134.8, 137.3, 154.2, 158.2, 167.1, 171.4, 193.4; HRMS: m/z [M+H]⁺ calculated 268.0604, found 268.0601.

6-Formyl-2-naphthyl tosylate (5j): white solid, yield 64.3%. ¹H NMR (600 MHz, CDCl₃): 2.45 (s, 3H, CH₃), 7.22-7.24 (m, 1H, Ar-H), 7.31-7.33 (m, 2H, Ar-H), 7.54 (m, 1H, Ar-H), 7.74-7.75 (m, 2H, Ar-H), 7.83-7.85 (m, 1H, Ar-H), 7.93-7.97 (m, 2H, Ar-H), 8.31 (m, 1H, Ar-H), 10.14 (s, 1H, CHO); ¹³C NMR (150 MHz, CDCl₃): 21.8, 120.2, 122.6, 123.9, 128.5, 129.1, 130.0, 131.1, 131.5, 132.2, 133.9, 134.5, 136.7, 145.8, 149.5, 191.8; HRMS: m/z [M+H]⁺ calculated 327.0686, found 327.0686.

1-Formyl-2-naphthyl tosylate (5k) (36): white solid, yield 70.0%.

2. Theoretical computation

All theoretical computations were performed using Gaussian 09 (*37*). SMD implicit solvent model (*38*) of dichloromethane was used in all calculations. Geometry optimization, vibration analysis, and IRC calculation were done at M06-2X/6-31+G** level; single point energies were recalculated for the optimized structures using functional B2PLYP and basis set def2-TZVP (with minimal diffuse function for heavy atoms). Gibbs free energies were obtained by summing up the single point energy (B2PLYP level) with the thermal correction value. The frequency scale factor of 0.9670 (*29*) was used in calculation of the thermal correction values. Imaginary frequencies of transition states reported here have not been scaled. IRCs were calculated using LQA method, and the Hessian matrix was recalculated every 5 steps. The step size of IRC was 0.05 Bohr; 300 steps at maximum in each direction were calculated, and all IRCs completed within 300 steps.

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Data in Brief

The NMR spectra of the novel aryloxymaleimide compounds and the computational data (including coordinates of the stationary points and IRCs) may be found in Data in Brief.

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ACCEPTED MANUSCRIPT

Nucleophilic substitutions of tosyloxy group on maleimide can occur easily Transesterification is a significant side-reaction when phenols are used This substitution reaction is favorable both kinetically and thermodynamically Electron-withdrawing groups on phenols are harmful to the substitution reaction

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