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Graphical Abstract

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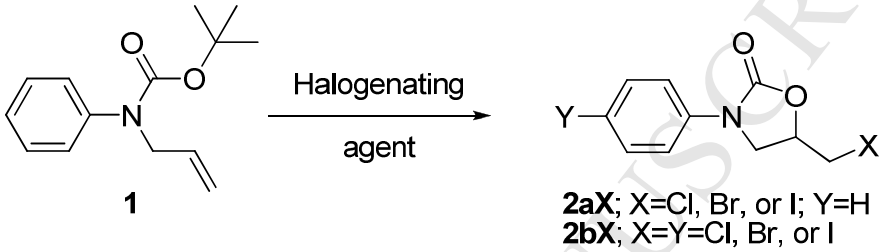

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2aX; X=Cl, Br, or I; Y=H
2bX; X=Y=Cl, Br, or I

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Direct synthesis of oxazolidin-2-ones from *tert*-butyl allylcarbamate via halo-induced cyclisation

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ABSTRACT

A novel synthetic pathway towards the 2-oxazolidinone derivatives involving the halo-induced cyclisation of *tert*-butyl allyl(phenyl)carbamate was successfully developed. Various halogenating reagents were evaluated under different reaction conditions for the reaction optimisation. Interestingly, the synthetic route to 2-oxazolidinone derivatives containing one halogen atom in the aliphatic site or two halogen atoms including the extra halogen atom substituted in the aryl group at the *para* position, were thoroughly established for all chloro-, bromo- and iodo compounds. Either halo-unsubstituted-aryl oxazolidinone or *p*-halo-substituted-aryl oxazolidinone could be selectively produced by selecting the appropriate choices of halogenated reagents and reaction conditions e.g. reaction time and temperature. Toloxatone, a commercial antidepressant, was successfully synthesized by using this developed method.

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1. Introduction

Oxazolidinones, 5-membered ring heterocyclic compounds, have been used and reported for their therapeutic effect against several diseases. They were recently developed as a new class of antibacterial drugs against methicillin resistant Staphylococcus aureus (MRSA), methicillin resistant Staphylococcus epidermitis (MRSE) and Vancomycin resistant enterococci (VRE).[1,2] Important examples are DuPont's compound DuP 721,[3-5] and its derivative, Linezolid (Zyvox®), the first commercial available oxazolidinone effective antibiotic being used as a long-term treatment for bacterial infection.[1] Toloxatone (Humoryl®) is a monoamine oxidase inhibitor (MAOI) used as an antidepressant medicine.[6] Furthermore, oxazolidinones are also an important class of chiral auxiliaries for asymmetric organic synthesis.[7-11] Considering these appealing properties, the methodological development of new synthetic routes for oxazolidinone building block has become an interesting topic over the years. Various cyclisations of appropriate precursors such as carbamate[12-15], amino alcohol,[14,15] amino alcohol carbamate,[16] epoxide,[17] β-lactam,[18] isocyanate,[19] amide,[20] and ketoamide[21] have been developed. The cyclisation of the carbamates can be achieved either in basic[14] or acidic [15] conditions (Figure 1).

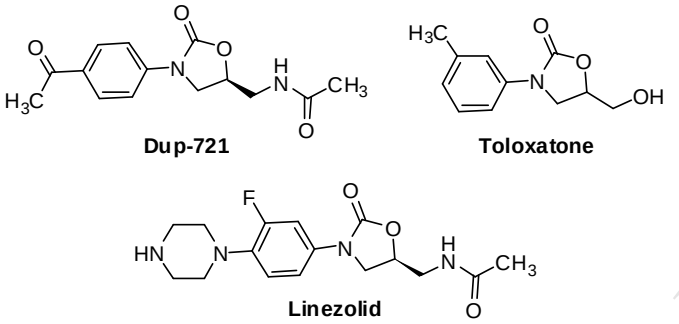
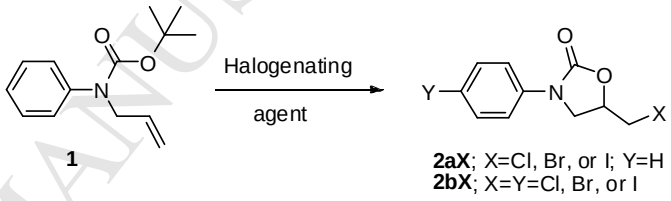


Figure 1. Oxazolidinone derivatives as commercial drugs

Halo-induced cyclisation is a unique method for the cyclisation of alkenes based on the intramolecular attack of a nucleophilic atom on an olefin preactivated by an electrophilic halogen[24]. It has been widely utilized in organic synthesis especially in the field of total syntheses of natural products. For example, *N*-iodosuccinimide (NIS) was used as an essential reagent for the crucial induced-intramolecular halo-etherification cyclisation step of the synthesis of the G-ring azaspiracid-1, marine metabolite responsible for human poisoning from the consumption of tainted shellfish.[25] The cyclisation reaction of 1,4-diaryl but-3-yn-1-ones was also reported to form halofurans by using *N*-bromosuccinimide (NBS) or NIS and iodine monochloride (ICl).[26] In the same manner, NBS or NIS, ICl, and iodine (I_2) could be used to activate the triple bond of (2-methoxyaryl) alkynones and hence induce the intramolecular cyclisation to form the corresponding iodochromone derivatives.[27] This type of synthetic method proved to represent not only an effective way for the synthesis of heterocyclic compounds, but also provides rapid and mild reaction conditions without any use of strong acid or base or harmful reagents. For instance, if halo-mediated cyclisation (iodolactonisation) was used to synthesize the corresponding pyrans from alkene starting material,[28] the similar processes using highly hazardous mercury(II) salts for the stoichiometric cyclisation used in the total synthesis of the antibiotic X-206 could have been avoided.[29]

To develop a simple methodology for the construction of the 2-oxazolidinone building block (Figure 1), we planned to utilise a halo-mediated cyclisation of readily accessible *N*-Boc-carbamate precursor. Recently, Robles-Machin reported the effective 5-exo intramolecular cyclisation by using the Boc group as the nucleophilic site to the Au-activated triple bond.[30] We, therefore, came up with the design of simple carbamate substrate **1** containing an allylic alkene site and the *N*-Boc unit for such a halo-induced cyclisation. In this work, we have successfully established the simple and convenient synthesis of the halogen containing 2-oxazolidinones **2** using allyl(phenyl)carbamate **1** as a precursor (Scheme 1). Various halogen generating reagents e.g. chlorine (Cl_2), bromine (Br_2), I_2, *N*-chlorosuccinimide (NCS), NBS, NIS, ICl, and a mixed solution of potassium iodide (KI) and potassium iodate (KIO_3) in acetic acid have been utilised. These reagents not only play a critical role in the cyclisation step to form the 2-oxazolidinone ring but also generate the halo substituted aromatic derivatives in which the substitution position is *para* depending on the reaction conditions. In order to systematically distinguish these two oxazolidinone products, **2aX** and **2bX** will be used to call 2-oxazolidinone containing one halogen atom (halo-substituted product) and 2-oxazolidinone containing two halogen atoms (dihalo-substituted product), respectively. Moreover, the **2bX** series has the potential advantage to be further functionalised by organometallic reagents to furnish a series of useful 2-oxazolidinone derivatives.

2. Results and Discussion



Scheme 1. Synthesis of halo-2-oxazolidinones **2aX** and **2bX** using various halogenating agents

The investigation of the halo-induced cyclisation was firstly accomplished by using a conventional halogenating reagent, e.g. Cl_2, Br_2, and I_2, compared to other halogenating sources (Scheme 1). In each condition, the halogen amount, solvent type and other related factors were systematically validated to obtain the optimized conditions for the synthesis of halo-substituted and dihalo-substituted 2-oxazolidinone compounds (**2aX** and **2bX**) (Table 1).

2.1. Chlorination conditions

In the initial attempt, the synthesis of chloro-substituted 2-oxazolidinone **2Cl** was executed by using the cyclisation reaction of **1** with Cl_2 gas in dichloromethane (Table 1). When 2.2 eq. of Cl_2 was used, only chloro-substituted product **2aCl** was obtained in 31% yield (entry 1). In the case of the excessive use of Cl_2, not only the halo-mediated intramolecular cyclisation proceeded, but also the electrophilic aromatic substitution (S_EAr) at the *para* position occurred to yield dichloro-substituted product **2bCl** in 47% yield (entry 2). Due to the low yielding reaction, uncontrollability of the exact amount of Cl_2 used and high corrosiveness of Cl_2 gas, the chloro-induced cyclisation was then carried out by using NCS as an alternative Cl^+ ion source. With 2.2 eq of NCS, CH_2Cl_2 was initially used as solvent but failed to provide any substituted product, demonstrating the bad combination of NCS and CH_2Cl_2. Therefore, the solvent was changed to CH_3CN, the reaction could be improved to produce **2aCl** at room temperature and at reflux conditions (entries 3-4). However, the amount of recovered starting materials was as high as 70% and also the required longer reaction time suggests a low reactivity of NCS in this reaction. This is not unexpected when

we consider that the N-Cl bond dissociation energy (ΔH_{f298}= 389 kJ/mol) is higher than that (ΔH_{f298}= 243 kJ/mol) of the Cl-Cl bond.[31] As the yield of **2aCl** was satisfactory, the amounts of NCS were raised to 5.0 eq in order to gain dichloro-substituted product **2b**, however, the reaction gave only **2aCl** again in moderate yield (entry 5). For the activation of this N-Cl bond, 20% mol of CF_3COOH (TFA) was added, and the reaction proceeded under reflux, dichloro-substituted product **2bCl** was exclusively obtained (entry 6).

2.2. Bromination conditions

Following the Cl case, the first trial for the Br case was to use Br_2 as a brominating agent due to its availability and inexpensiveness. Using only 1.0 eq. of Br_2, **2aBr** we could selectively produce only bromo-substituted 2-oxazolidinone in moderate yield (entry 7). The dibromo-substituted compound **2bBr** could be selectively produced in excellent yields by using 2.2 eq. of Br_2 (entry 8). The better yields compared to that of excessive use of Cl_2 might be due to its higher electrophilicity and the relatively weaker bond (ΔH_{f298}= 194 kJ/mol) of Br_2.[31] After that, Br_2 was changed to an alternative brominating source (NBS) to avoid the potentially hazardous situation that may arise from its toxicity, difficult handling, and harmfulness. In the same manner, the use of NBS, which possesses the weaker *N*-halogen bond (ΔH_{f298}= 276 kJ/mol) compared to that of NCS (ΔH_{f298}= 389 kJ/mol), may provide the better solution for the synthesis of dibromo-substituted 2-oxazolidinone.[31] Even though the reaction time had to be extended to 24 hours due to the lower reactivity of NBS, with 2.2 eq. it could satisfactorily and efficiently produce bromo-substituted **2aBr** in excellent yield (entry 9). The addition of 5.0 eq. of NBS in CH_3CN was attempted, and **2bBr** was selectively obtained but only in 68% yield (entry 10). The addition of 10% TFA also became useful to enhance the reactivity of the cyclisation and the S_EAr, as the control of the NBS amount (5.0 eq.) could regioselectively and efficiently provide **2bBr** in 99% yield (entry 11). It is worth noting here that in this case 10 mol % of TFA and room temperature are efficient enough for the **2bBr** formation because of the weaker *N*-halogen bond.

2.3. Iodination conditions

For the easiness of further functionalisation reasons, as seen in various organometallic carbon-carbon coupling reactions,[32] the scaffold development of *p*-iodo-aryl-2-oxazolidinone **2bI** is extremely attractive as it has a high potential to open a new useful and convenient pathway for oxazolidinone derivatization. When the less electrophilic iodine (I_2) was used either at room temperature or 50 ^oC, only the iodo-substituted 2-oxazolidinone **2aI** was obtained always in moderate to good yields without the occurrence of the aromatic iodo-substitution (53-88%, entries 12-15). A similar result was obtained when using NIS at room temperature for 24 hours which provided **2aI** in CH_3CN in 93% yield (entry 16). The fact that reaction under dark conditions with excess amount of I_2 also created **2aI** in 88% yield (entry 15) suggested that this reaction proceeds via a non-radical mechanistic pathway. Although the addition of TFA seemed to have some enhanced effects on the reaction to furnish **2bI**, there was still some **2aI** produced (entry 17). Moreover, this information also mechanistically proves that an NXS can generate only one X^+. Increasing the amount of NIS up to 5.0 eq. in the presence of TFA led to the good conversion of starting material to the diiodo-substituted 2-oxazolidinone **2bI** in high yield (74%, entry 18).

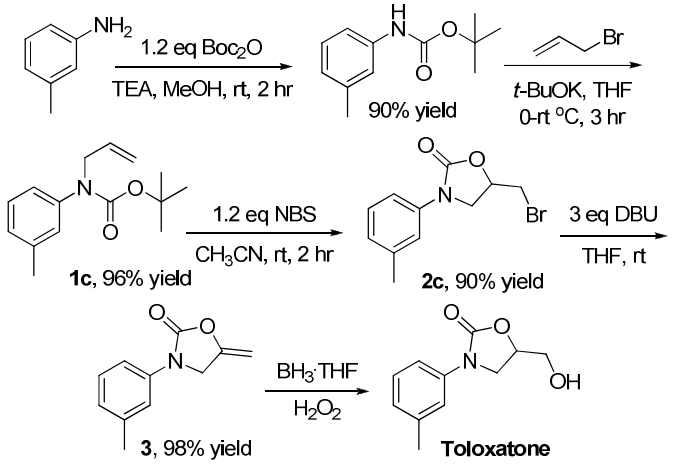
As the yield of *p*-iodo-aryl-2-oxazolidinone **2bI** was not fully satisfied, several iodinating agents were also attempted herein for the reaction optimisation.[33] Firstly, when ICl was used as an I^+ ion source in $CHCl_3$/MeOH in the presence of $CaCO_3$ at room temperature for 24 hours, the amount of ICl seemed to play an important role in this reaction.[34] Treatment of only 1.2 eq. of ICl, iodo-substituted 2-oxazolidinone **2aI** solely occurred in good yield (71%, entry 19). However, in the case of 5.0 eq. of ICl, the reaction gave only the *p*-I-aryl product **2bI** in excellent yield (96%, entry 20). In order to obtain the desired iodonium ions for the iodination reaction, a mixed solution of KI and KIO_3 in acetic acid was found to be an effective and convenient method. When the amount of KI/KIO_3 is 1.2 eq., the iodo-substituted product **2aI** was observed in excellent yield (91%, entry 21), but once the amount of KI/KIO_3 was increased to 2.2 eq. in refluxing acetic acid, the diiodo-substituted 2-oxazolidinone scaffold product **2bI** could be solely obtained in excellent yield (89%, entry 22) due to the highly reactive iodonium ions.

2.4. Proof of Mechanistic Pathway

AIBN (10 mol %) was selected as radical initiator in order to prove whether the reaction mechanism for this process proceeds via an electrophilic or radical pathway (entry 23). The reaction resulted in solely chloro-substituted oxazolidinone **2aCl** in excellent yield (86%), demonstrating that the first chloro-induced cyclisation might occur through both electrophilic and radical pathways, as the yield was improved up to nearly 40% compared to that of the condition without AIBN. In NBS and NIS cases, the reaction gave exclusively the bromo- and iodo-substituted products **2aI**, also proving evidence for the possible involvement of a radical process (both in 99%, entries 24 and 25).

2.5. Application in Toloxatone synthesis

As seen in many applications of the syntheses of oxazolidinone drugs literally reported,[35-37] the utility of this protocol has also been exemplified by the synthesis of toloxatone (Figure 1) as shown in Scheme 2. The key step in the synthesis of toloxatone is the halo-induced cyclisation of *tert*-butyl allyl(phenyl)carbamate **1c**, which could successfully produce oxazolidinone **2c** in excellent yield. The equivalents of NBS were reduced to 1.2 eq., otherwise the disubstituted product could be generated as well due to the presence of an additional activating group on the benzene ring. After that, toloxatone was prepared by DBU induced E2 reaction followed by hydroboration in THF. This synthetic pathway has the advantage of being higher yielding compared to that reported in the literature.[38]



Scheme 2. Synthesis of Toloxatone

In summary, a simple and facile halo-induced intramolecular cyclisation method was thoroughly developed. The target halo- or dihalo-2-oxazolidinone products **2aX** and **2bX** were obtained

in excellent yields by treating *tert*-butyl allyl(phenyl)carbamate **1** with various halogenating reagents, Cl_2, NCS for chlorinating agents, Br_2, NBS for brominating agents, I_2, NIS, ICl, and KI/KIO_3 for iodinating agents. The condition optimisation was accomplished by varying factors, e.g. amount of reagent, solvent, temperature and reaction time. After optimisation, these two halo-2-oxazolidinone scaffolds (**2aX** and **2bX**) could be regioselectively produced. In general, the cyclisation reaction to yield **2aX** prefers the relatively less reactive halonium ion (NCS, NBS, NIS, and I_2), but on the other hand, the relatively more reactive halonium ion (Cl_2, Br_2, KI/KIO_3) tend to perform through both the cyclisation reaction and S_EAr furnishing dihalo-substituted-2-oxazolidinone **2bX**. However, along the optimisation process, the addition of TFA as a catalyst in the NCS, NBS, or NIS case could provoke the S_EAr to selectively produce dihalo-substituted-2-oxazolidinone **2bX**. By adding AIBN as radical initiator, the main mechanism of this reaction was proved to be by the electrophilic pathway with some enhanced effect by the radical pathway in the case of NCS. For the further functionalisation point of view, the rather interesting scaffold development of diiodo-substituted-2-oxazolidinone **2bX** has a high potential to open a new useful and convenient gateway for oxazolidinone derivatization. This developed method was also successfully introduced to the synthesis of toloxatone, a commercial antidepressant.

Table 1. Synthesis of halo-2-oxazolidinones **2aX** and **2bX** using various halogenating agents under various reaction conditions

Entry	Halogen source	Reaction conditions				Isolated yield (%)	
		Solvent	Catalyst	Temp.	Time	**2aX**	**2bX**
1	Cl_2 (2.2 eq)	CH_2Cl_2	-	rt	1 h	31	-
2	Cl_2 (excess)	CH_2Cl_2	-	rt	1 h	-	47
3	NCS (2.2 eq)	CH_3CN	-	rt	48 h	25	-
4	NCS (2.2 eq)	CH_3CN	-	reflux	48 h	32	-
5	NCS (5.0 eq)	CH_3CN	-	rt	48 h	47	-
6	NCS (5.0 eq)	CH_3CN	TFA 20%	reflux	48 h	-	99
7	Br_2 (1.0 eq)	CH_2Cl_2	-	rt,	1 h	44	-
8	Br_2 (2.2 eq)	CH_2Cl_2	-	rt,	1 h	-	81
9	NBS (2.2 eq)	CH_3CN	-	rt	24 h	99	-
10	NBS (5.0 eq)	CH_3CN	-	rt	24 h	-	68
11	NBS (5.0 eq)	CH_3CN	TFA 10%	rt	24 h	-	99
12	I_2 (3.0 eq)	CH_3CN	-	rt	24 h	53	-
13	I_2 (3.0 eq)	$CH_3C_6H_4$	-	50 ^oC	24 h	64	-
14	I_2 (excess)	$CH_3C_6H_4$	-	50 ^oC	24 h	81	-
15*	I_2 (excess)	$CH_3C_6H_4$	-	50 ^oC	24 h	88	-
16	NIS (2.2 eq)	CH_3CN	-	rt	24 h	93	-
17	NIS (2.2 eq)	CH_3CN	TFA 10%	rt	24 h	46	41
18	NIS (5.0 eq)	CH_3CN	TFA 10%	rt	24 h	-	74
19	ICl (1.2 eq)	$CHCl_3$/MeOH	$CaCO_3$	rt	24 h	71	-
20	ICl (5.0 eq)	$CHCl_3$/MeOH	$CaCO_3$	rt	24 h	-	96
21	KI/KIO_3 (1.2 eq)	AcOH	-	rt	3 h	91	-
22	KI/KIO_3 (2.2 eq)	AcOH	-	rt	3 h	-	89
23	NCS (2.2eq)	CH_3CN	AIBN	reflux	48 h	86	-
24	NBS (2.2 eq)	CH_3CN	AIBN	reflux	24 h	99	-
25	NIS (2.2 eq)	CH_3CN	AIBN	reflux	24 h	99	-

*Processed under dark condition

3. Conclusion

We have developed an efficient and high-yielding of oxazolidinone derivatives by halo-induced cyclisation of *tert*-butyl allyl(phenyl)carbamate by using various halogenating agents. The synthesis of toloxatone has been successfully achieved using the developed method.

4. Experimental section

4.1. General synthetic procedure of 2aX and 2bX s

Compound **1** (100 mg, 0.429 mmol) was dissolved in organic solvent (10 mL) and then the halogenating agent was added into the solution under nitrogen atmosphere. In case of Cl_2, the mixture was neutralised with saturated $NaHCO_3$. In case of NCS and NBS, cold water was added to the mixture until the solution turned turbid. In the case of Br_2, I_2, NIS, and KI/KIO_3, saturated aqueous solution $Na_2S_2O_3$ was added to the mixture until the orange or dark brown solution turned to a colorless solution which was then neutralised with saturated $NaHCO_3$. In the case of ICl, the mixture was added to 40% $NaHSO_3$ until a dark brown solution turned to a colorless solution. After that, the mixture in each case was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO4, filtered and evaporated in vacuo to yield the crude product as a pale yellow oil. Purification was accomplished by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15) to produce **2aX** or/and **2bX** as a white solid.

5-(Chloromethyl)-3-phenyloxazolidin-2-one (2aCl): Obtained as a yellow solid, m.p. 72-74 ^oC; R_f (40% EtOAc/Hexane) 0.33; n_{max} (liquid film) 3600–3100 (br), 3029, 2957, 1731, 1594, 1501, 1479, 1408 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* 7.8 Hz, Ar-H_{ortho}), 7.37 (2H, t, *J* 7.6 Hz, Ar-H_{meta}), 7.16 (1H, t, *J* 7.4, Ar-H_{para}), 4.90-4.84 (1H, m, NCH_2CHCH_2Cl), 4.18 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2Cl$), 3.97 (1H, dd, *J* 5.5, 9.0 Hz, $NCH_AH_BCHCH_2Cl$), 3.81-3.72 (2H, m, NCH_2CHCH_2Cl); δ_C (100 MHz, $CDCl_3$) 153.9, 137.7, 129.2, 124.3, 118.3, 70.8, 48.1, 44.5; HRMS: MNa^+, found 234.0354. $C_{10}H_{10}ClNNaO_2$ requires 234.0292.

5-(Bromomethyl)-3-phenyloxazolidin-2-one (2aBr): Obtained as a yellow solid, m.p. 76-78 ^oC; R_f (40% EtOAc/Hexane) 0.40; n_{max} (liquid film) 3600–3100 (br), 3034, 2917, 1755, 1594, 1504, 1480, 1410; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.3 Hz, Ar-H_{ortho}), 7.38 (2H, t, *J* 7.3 Hz Ar-H_{meta}), 7.16 (1H, t, *J* 7.5 Hz, Ar-H_{para}), 4.89-4.83 (1H, m, NCH_2CHCH_2Br), 4.19 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2Cl$), 3.94 (1H, dd, *J* 6.0, 9.0 Hz, $NCH_AH_BCHCH_2Br$), 3.56 (2H, dd, *J* 7.5, 10.5 Hz, NCH_2CHCH_2Br); δ_C (100 MHz, $CDCl_3$) 153.9, 137.7, 129.2, 124.3, 118.4, 70.6, 49.3, 32.6; HRMS: MNa^+, found 277.9750. $C_{10}H_{10}BrNNaO_2$ requires 277.9787.

5-(Iodomethyl)-3-phenyloxazolidin-2-one (2aI): Obtained as a yellow solid, m.p. 96-98 ^oC; R_f (40% EtOAc/Hexane) 0.45; n_{max} (liquid film) 3600–3100 (br), 3041, 2916, 1742, 1602, 1504, 1473, 1403; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.0 Hz, Ar-H_{ortho}), 7.38 (2H, t, *J* 8.0 Hz, Ar-H_{meta}), 7.15 (1H, t, *J* 7.5 Hz, Ar-H_{para}), 4.77-4.70 (1H, m, NCH_2CHCH_2I), 4.16 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2I$), 3.78 (1H, dd, *J* 6.0, 9.0 Hz, $NCH_AH_BCHCH_2I$), 3.45 (1H, dd, *J* 4.0, 10.5 Hz, $NCH_2CHCH_AH_BI$), 3.35 (1H, dd, *J* 8.0, 10.5 Hz, $NCH_2CHCH_AH_BI$); δ_C (100 MHz, $CDCl_3$) 154.0, 137.7, 129.0, 124.3, 118.3, 71.1, 50.9, 36.2; HRMS: MNa^+, found 325.9623. $C_{10}H_{10}INNaO_2$ requires 325.9648.

5-(Chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (2bCl): Obtained as a white solid, m.p. 107-109 ^oC; R_f (40% EtOAc/Hexane) 0.40; δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 9.0 Hz, Ar-H_{ortho}), 7.34 (2H, d, *J* 9.0 Hz, Ar-H_{meta}), 4.93-4.85 (1H, m, NCH_2CHCH_2Cl), 4.15 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2Cl$), 3.95 (1H, dd, *J* 5.7, 9.0 Hz, $NCH_AH_BCHCH_2Cl$), 3.80-3.73 (2H, m, NCH_2CHCH_2Cl); δ_C (100 MHz, $CDCl_3$) 153.7, 136.3, 129.5, 129.1, 119.4, 70.8, 47.9, 44.5; HRMS: MNa^+, found 267.9960. $C_{10}H_9Cl_2NNaO_2$ requires 267.9903.

5-(Bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one (2bBr): Obtained as a pale brown solid, m.p. 90-91 ^oC; R_f (40% EtOAc/Hexane) 0.37; n_{max} (liquid film) 3600–3100 (br), 3102, 2961, 1754, 1498, 1417, 1403; δ_H (400 MHz, $CDCl_3$) 7.49-7.41 (4H, m, Ar-H_{ortho}, Ar-H_{meta}, Ar-H_{para}), 4.90-4.84 (1H, m, NCH_2CHCH_2Br), 4.15 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2Br$), 3.90 (1H, dd, *J* 6.0, 9.0 Hz, $NH_AH_BCHCH_2Br$), 3.65 (1H, dd, *J* 4.0, 10.8 Hz, $NCH_2CHCH_AH_BBr$), 3.57 (1H, dd, *J* 7.3, 10.8 Hz, $NCH_2CHCH_AH_BBr$); δ_C (100 MHz, $CDCl_3$) 153.7, 136.8, 132.0, 119.7, 70.5, 49.0, 32.5; HRMS: MNa^+, found 357.8845. $C_{10}H_9Br_2NNaO_2$ requires 357.9818.

5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (2bI): Obtained as a dark brown solid, m.p. 95-97 ^oC; R_f (40% EtOAc/Hexane) 0.40; n_{max} (liquid film) 3600–3100 (br), 3095, 2914, 1747, 1487, 1417, 1394; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* 8.5 Hz, Ar-H_{meta}), 7.32 (2H, d, *J* 8.5 Hz, Ar-H_{ortho}), 4.70-4.80 (1H, m, NCH_2CHCH_2I), 4.15 (1H, t, *J* 9.0 Hz, $NCH_AH_BCHCH_2I$), 3.76 (1H, dd, *J* 6.0, 9.0 Hz, $NCH_AH_BCHCH_2I$), 3.50 (1H, dd, *J* 3.8, 10.0 Hz, $NCH_2CHCH_AH_BI$), 3.35 (1H, dd, *J* 8.5, 10.0 Hz, $NCH_2CHCH_AH_BI$); δ_C (100 MHz, $CDCl_3$) 153.7, 137.9, 137.5, 120.0, 87.8, 71.1, 50.6; HRMS: MNa^+, found 451.8568. $C_{10}H_9I_2NNaO_2$ requires 451.8615.

4.2. Synthesis of Toloxatone

According to the general synthetic procedure, **2c** was synthesized from **1c** (100 mg, 0.404 mmol) and NBS (86.3 mg, 1.2 eq) in CH_3CN 10 mL at room temperature in 2 hours as yellow oil.

***tert*-Butyl-*m*-tolylcarbamate**: Obtained as a white needle-like crystal, m.p. 138-140 ^oC; R_f (40% EtOAc/Hexane) 0.66; δ_H (400 MHz, $CDCl_3$) 7.33 (1H, s, Ar-H), 7.21 (1H, t, *J* 8.0 Hz, Ar-H), 7.11 (1H, d, *J* 8.0 Hz, Ar-H), 6.87 (1H, d, *J* 8.0 Hz, Ar-H), 6.45 (1H, s, NH), 2.35 (3H, s, Ar-CH_3), 1.54 (9H, s, $OC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 152.8, 138.9, 138.2, 128.8, 123.8, 119.2, 115.6, 80.4, 28.9, 21.5.

***tert*-Butyl allyl(*m*-tolyl)carbamate (1c)**: Obtained as a pale yellow oil; R_f (40% EtOAc/Hexane) 0.70; δ_H (400 MHz, $CDCl_3$) 7.34 (1H, s, Ar-H), 7.23 (1H, t, *J* 8.0 Hz, Ar-H), 7.05 (1H, d, *J* 8.0 Hz, Ar-H), 7.01 (1H, d, *J* 8.0 Hz, Ar-H), 5.98-5.89 (1H, m, $NCH_2CH=CH_2$), 5.20-5.14 (2H, m, $NCH_2CH=CH_2$), 4.21 (2H, d, *J* 4.0 Hz, $NCH_2CH=CH_2$), 2.40 (3H, s, Ar-CH_3), 1.47 (9H, s, $OC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 154.6, 142.8, 138.4, 134.4, 128.3, 127.0, 126.5, 123.4, 116.2, 80.2, 53.0, 28.3, 21.

5-(Bromomethyl)-3-*m*-tolyloxazolidin-2-one (2c): Obtained as a yellow solid, m.p. 75-77 ^oC;; R_f (40% EtOAc/Hexane) 0.39; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, s, Ar-H), 7.35-7.27 (2H, m, Ar-H), 7.00 (1H, d, *J* 8.0 Hz, Ar-H), 4.91-4.84 (1H, m, NCH_2CHCH_2Br), 4.16 (1H, t, *J* 8.0 Hz, $NCH_AH_BCHCH_2Br$), 3.90 (1H, dd, *J* 8.0, 9.0 Hz, $NCH_AH_BCHCH_2Br$), 3.62 (1H, dd, *J* 3.9, 10.6 Hz, $NCH_2CHCH_AH_BBr$), 3.55 (1H, dd, *J* 7.6, 10.6 Hz, $NCH_2CHCH_AH_BBr$) 2.43 (3H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 153.9, 139.1, 137.7, 129.0, 125.3, 119.2, 115.6, 70.6, 49.5, 32.5, 21.6.

5-Methylene-3-*m*-tolyloxazolidin-2-one (3): Obtained as a pale yellow solid, m.p. 73-75 ^oC; R_f (40% EtOAc/Hexane) 0.56; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, s, Ar-H), 7.25-7.18 (2H, m, Ar-H), 6.91 (1H, d, *J* 8.0 Hz, Ar-H), 4.79-4.75 (1H, m, $C=CH_AH_B$), 4.58-4.54 (2H, m, $NCH_2C=CH_2$), 4.37-4.33 (1H, m, $C=CH_AH_B$), 2.30 (3H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 153.9, 139.1, 137.7, 129.0, 125.3, 119.2, 115.6, 70.6, 49.5, 32.5, 21.6; HRMS: MNa^+, found 212.1019. $C_{11}H_{11}NNaO_2$ requires 212.0682.

5-(Hydroxymethyl)-3-*m*-tolyloxazolidin-2-one (Toloxatone): Obtained as a white solid, m.p. 75-76 ^oC; R_f (40% EtOAc/Hexane) 0.06; δ_H (400 MHz, $CDCl_3$) 7.30 (1H, s, Ar-H),

7.23 (1H, t, *J* 8.0 Hz, Ar-H), 7.16 (1H, d, *J* 8.0 Hz, Ar-H), 6.88 (1H, d, *J* 7.2 Hz, Ar-H), 4.69-4.62 (1H, m, NCH_2CHCH_2), 3.98-3.85 (3H, m, NCH_2CHCH_2OH and $NCH_2CHCH_AH_BOH$), 3.66 (1H, d, *J* 6 Hz, $NCH_2CHCH_AH_BOH$), 2.29 (3H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 154.9, 138.7, 138.0, 129.0, 125.0, 119.1, 115.6, 72.6, 62.9, 46.6, 29.7; HRMS: MH^+, found 208.1305. $C_{11}H_{14}NO_3$ requires 208.0974.

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