Manipal Journal of Pharmaceutical Sciences

Volume 1 | Issue 1 Article 6

1-7-2015

New Method for the Synthesis of 2, 3-dihydrobenzo[e] [1, 4] oxazepin-5(1H)-ones from Anthranilic acid, and Allyl halides or Allyl methanesulphonate

Sharada Prasanna Swain
spswain2013@gmail.com

Soumya Prakash Rout

ORIGINAL ARTICLE

New Method for the Synthesis of 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones from Anthranilic acid, and Allyl halides or Allyl methanesulphonate

Sharada Prasanna Swain[1*] and Soumya Prakash Rout[2]

1) National Central University, Department of Chemistry, Jhongli-32001, Taiwan.

2) Siksha 'O' Anusandhan University, School of Pharmaceutical Sciences, Bhubaneswar-751003, Odisha, India

ABSTRACT

Oxazepines and its bioisosteres are potent antipsychotic, anticancer agents, and heat shock protein 90 inhibitors. A new method for the synthesis of 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones from anthranilic acid and allyl halides or allyl methanesulphonate, by halolactonization is described. Anthranilic acid was reacted with halides or allyl methanesulphonate under basic condition, followed by addition of iodine or NBS at 25 ºC provided desired 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones.

Key words: Oxazepine, Halolactonization, Iodine, Anthranilic acid, Allyl halide.

INTRODUCTION

Oxazepines and its derivatives are an important class of heterocyclic compounds as they exhibit several biological activities such as β*Secretase* antagonism,[1] *glycogen phosphorylase* inhibition,[2] antipsychotic,[3] non-steroidal progesterone receptor antagonism,[4] heat shock protein 90 inhibition,[5] NMDA receptor antagonism for anticonvulsant activity,[6] inhibition of *stearoyl-CoA desaturase*.[7] There are several novel oxazepines which show potent anticancer activity by targeting *phosphoinositide 3-kinases*, *EGFR*, apoptosis proteins, *telomerase* enzyme[8-11]. The current authors are interested in design, synthesis and study of anticancer activity of novel oxazepine bioisosteres. The current authors have designed novel 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones as anticancer agents, and there are very few reported methods for synthesis of these molecules.

Singh et al. have described synthesis of benz-oxazepines from anthranilic acid and epoxides[12]. In order to make a library of compounds, varieties of epoxides are required, and all epoxides are not commercially available. So, epoxides should be prepared, and it takes two steps to prepare benzoxazepines. Herein, the current authors report a new method for synthesis of 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones from anthranilic acid, allyl halides or allyl methanesulphonate, and iodine or NBS by halolactonization. Halolactonization is an organic reaction for the synthesis of lactones by the addition of an oxygen, and iodine or bromine across a carbon-carbon double bond[13, 14].

* For Correspondence:
E-mail: spswain2013@gmail.com, spswain@cc.ncu.edu.tw

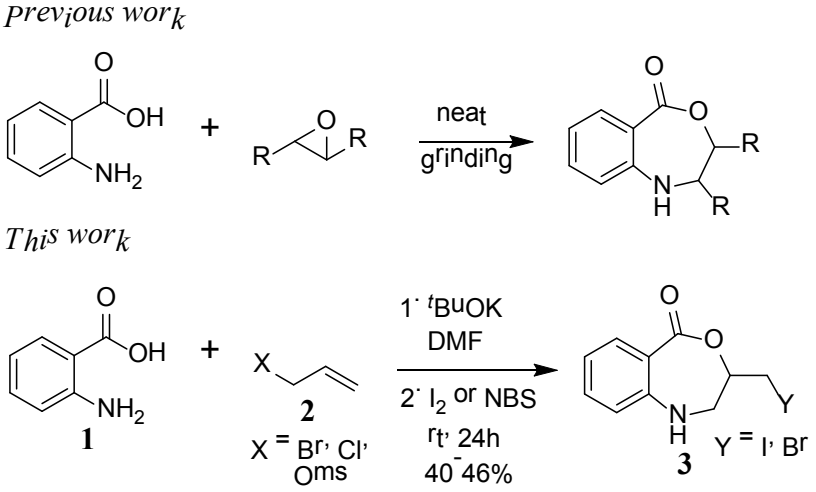
MATERIAL AND METHODS

All reactions were carried out in oven-dried glassware. Dry DMF, potassium *tert*-butoxide, iodine, *N*-bromosuccinimide (NBS), methane sulphonyl chloride were purchased from Loba Chemie. Anthranilic acid, allyl bromide, allyl chloride, allyl alcohol were purchased from Aldrich. Proton NMR spectra were recorded on a Bruker (300 MHz) spectrometer by use of $CDCl_3$ as the solvent. FTIR spectra were obtained by use of Perkin-Elmer spectrometer.

3-(Bromomethyl)-2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-one (3a):

To a stirred solution of anthranilic acid (137.2 mg, 1.01 mmol) in dry DMF (5.0 mL) at 0 °C potassium *tert*-butoxide (123.4 mg, 1.11 mmol) was added portion wise over 15 min. Then allyl bromide (122.1 mg, 1.01 mmol) was added to it and heated at 80 °C in an oil bath for 6 hours. The reaction flask was allowed to cool to room temperature, iodine (253.8 mg, 1.01 mmol) and sodium bicarbonate (168.1 mg, 2.01 mmol) were added to it, stirred for 18 hours at room temperature. The reaction was quenched with water, extracted with ethyl acetate (3 × 10 mL), and the combined

Scheme 1. Synthesis of 2, 3-Dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones from Anthranilic acid, and Allyl halides or Allyl methanesulphonate.



organic layers were washed with water, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude mass was purified by use of column chromatography on silica gel to provide compound **3a** (127.6 mg, 42%) as brown solid (15% EtOAc in *n*-hexanes, TLC R_f = 0.62). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (s, 1 H, NH), 8.16 (d, 1 H, *J* = 4.5 Hz, 1 × ArH), 7.62-7.59 (m, 2H, 2 × ArH), 6.57 (d, 1 H, *J* = 9.0 Hz, 1 × ArH), 4.77 (m, 1 H, CH), 3.93-3.86 (m, 4 H, CH_2); IR (neat) 3068 (ArH), 1692 (C=O), 1380 (C-N); Mass, calculated for $C_{10}H_{10}BrNO_2$ 254.99 and molecular ion (M+1) peak from LCMS was obtained at 255.99.

3-(Iodomethyl)-2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-one (3b):

To a stirred solution of anthranilic acid (137.2 mg, 1.01 mmol) in dry DMF (5.0 mL) at 0 °C potassium *tert*-butoxide (123.4 mg, 1.11 mmol) was added portion wise over 15 min. Then allyl bromide (122.1 mg, 1.01 mmol) was added to it, heated at 80 °C in an oil bath for 6 hours. The reaction flask was allowed to cool to room temperature, NBS (178.1 mg, 1.01 mmol) and sodium bicarbonate (168.1 mg, 2.01 mmol) were added to it, stirred for 18 hours at room temperature. The reaction was quenched with water, extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude mass was purified by use of column chromatography on silica gel to provide compound **3b** (114.7 mg, 45%) as yellow solid (15% EtOAc in *n*-hexanes, TLC R_f = 0.56). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 1 H, NH), 8.06 (d, 1 H, *J* = 4.8 Hz, 1 × ArH), 7.49-7.46 (m, 2H, 2 × ArH), 6.57 (d, 1 H, *J* = 9.0 Hz, 1 × ArH), 4.91 (m, 1 H, CH), 3.99-3.86 (m, 4 H, CH_2); IR (neat) 3060 (ArH), 1691 (C=O), 1380 (C-N); Mass, calculated for $C_{10}H_{10}INO_2$ 302.98 and molecular ion (M+1) peak from LCMS was obtained at 303.98.

2-(Allylamino) benzoic acid (5):[15]

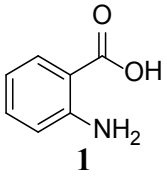
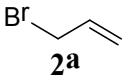
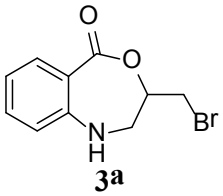
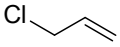
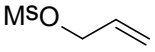
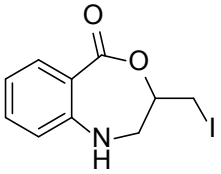
To a stirred solution of anthranilic acid (137.2 mg, 1.01 mmol) in dry DMF (5.0 mL) at 0 °C potassium *tert*-butoxide (123.4 mg, 1.11 mmol) was added portion wise over 15 min. Then allyl bromide (122.1 mg, 1.01 mmol) was added to it, heated at 80 °C in an oil bath for 6 hours. Then the reaction was quenched with water, extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude mass was purified by use of column chromatography on silica gel to provide compound **5** (99.2 mg, 56%) as white solid (30% EtOAc in *n*-hexanes, TLC R_f = 0.62). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, 1 H, *J* = 7.8 Hz, 1 × ArH), 7.39 (t, *J* = 7.2 Hz, 1 × ArH), 6.67-6.59 (m, 2H, 2 × ArH), 5.99-5.89 (m, 1H, CH=), 5.26-5.16 (m, 2H, =CH_2), 4.81 (s, 1 H, NH), 3.89 (d, *J* = 4.8 Hz, 2 H, CH_2).

Allyl methanesulphonate (2c):[16]

The allyl methanesulphonate was prepared by following reported procedure.[16] To a stirred solution of allyl alcohol (581.4 mg, 10.01 mmol), trimethylamine (3.1 g, 30.03 mmol) in dry dichloromethane (20.0 mL) at 0 °C methane sulphonyl chloride (1.3 g, 11.01 mmol) was added drop wise over 10 min, and stirred at room temperature for 3 hours. Then the reaction was washed with water, dried over $MgSO_4$, filtered, and evaporated under vacuum to provide compound **2c** (1.3 g, 92%).

RESULTS AND DISCUSSION:

Table 1. Reaction of Anthranilic acid with Different Allyl substrates

Entry	Anthranilic acid	Allyl compound	Halo compound	Benzo-oxazepines	Reaction time (h)	Yield (%)
1	 **1**	 **2a**	NBS	 **3a**	24	42
2	**1**	 **2b**	NBS	**3a**	24	40
3	**1**	 **2c**	NBS	**3a**	20	44
4	**1**	**2a**	I_2	 **3b**	24	45
5	**1**	**2b**	I_2	**3b**	24	45
6	**1**	**2c**	I_2	**3b**	20	46

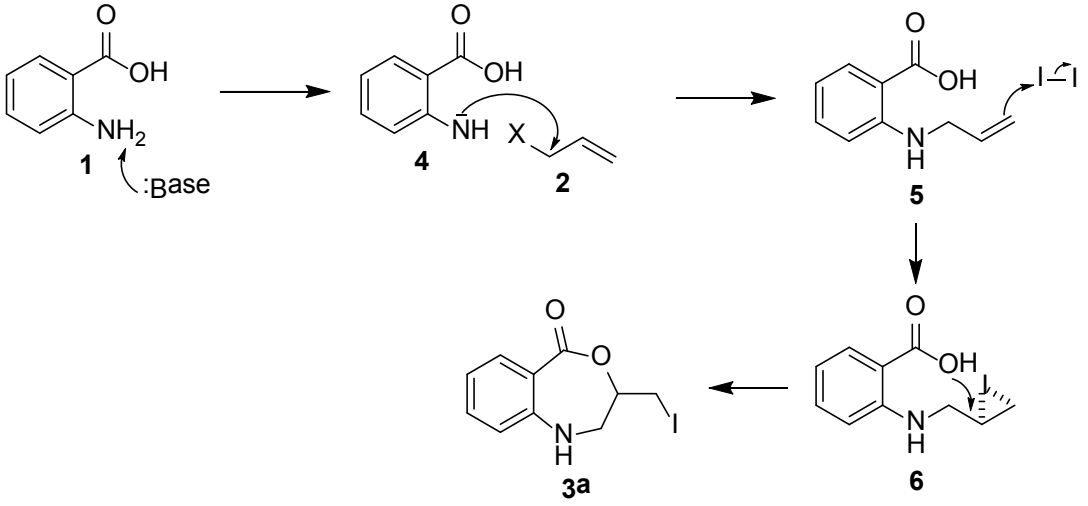


Figure 1. Plausible Mechanism of Halolactonization

The authors started initial study by using potassium *tert*-butoxide as base for abstraction of amine proton of anthranilic acid at 0 ºC. The deprotonation was carried out at lower temperature in order to get higher quantity of desired anion **4**, as carboxylic acid proton may also get abstracted. The reaction was then heated for substitution reaction with allylbromide, which was monitored by TLC, until the starting material was finished. Once, the *N*-allylation was over, the reaction was allowed to cool to room temperature. Then NBS was added and stirred at room temperature (rt), as bromohydrin can be easily formed at room temperature. The desired compound **3a** was obtained with moderate yield 42%. The authors have also replaced the bromo leaving group by chloro and OMs functional group. The allyl chloride **2b** provided lower yield, whereas allyl methanesulphonate **2c** gave higher yield (46%), and reaction time was reduced. Then authors tried to replace the NBS by iodine. The reaction also worked well with iodine, and provided the desired compound **3b** in 45% yield.

Published by Impressions@MAHE, 2015

Iodolactonization and bromolactonization[13] are familiar reactions in organic synthesis for synthesis of lactones from allenic acids. The authors tried to apply iodolactonization concept to prepare desired benzo-oxazepines **3**. NBS and Iodine successfully formed halohydrin intermediate **6**, and then it underwent intramolecular cyclization to form the fused 7-membered ring compounds **3**.

In summary, the authors have developed a new mild reaction for the synthesis of 2, 3-dihydrobenzo[*e*] [1, 4] oxazepin-5(1*H*)-ones from commercially available anthranilic acid, and allyl halides or allyl methanesulphonate. This reaction provides halo substituted compounds, which can be functionalized by nucleophilic substitution reaction. This method will be used to prepare a library of compounds for several biological activity studies.

ACKNOWLEDGEMENTS

The authors acknowledge SOA University, Bhubaneswar for providing laboratory facilities and other necessary support for analysis.

REFERENCES

1. Blass B. 5-Amino-oxazepine and 5-amino-thiazepine compounds as β-*Secretase* antagonists and methods of use. ACS Med Chem Lett 2012; 3: 873−4.
2. Schweiker SS, Loughlin WA, Lohning AS, Petersson MJ, Jenkins ID. Synthesis, screening and docking of small heterocycles as *Glycogen Phosphorylase* inhibitors. Eur J Med Chem 2014; 84: 584-94.
3. Jain MS, Surana SJ. Synthesis and evaluation of antipsychotic activity of 11-(40-(N-arylcarboxamido/ N-aryl-a-phenyl-acetamido)-piperazinyl)-dibenz [b, f] [1, 4]-oxazepine derivatives Arab J Chem 2013; http://dx.doi.org/10.1016/j.arabjc.2013.07.033.
4. Zhang P, Kern JC, Terefenko EA, Fensome A, Unwalla R, Zhang Z. 7-Aryl 1,5-dihydro-benzo[e][1,4]oxazepin-2-ones and analogs as non-steroidal progesterone receptor antagonists. Bioorg Med Chem 2008; 16: 6589–600.
5. Neubert T, Numa M, Ernst J, Clemens J, Krenitsky P, Liu M. Discovery of novel oxazepine and diazepine carboxamides as two new classes of heat shock protein 90 inhibitors. Bioorg. Med. Chem. Lett. 2015; 25: 1338–42.
6. Sahu M, Nerkar AG, Chikhale HU, Sawant SD. In Silico screening, synthesis and pharmacological screening of quinazolinones containing oxazepinone ring as NMDA receptor antagonists for anticonvulsant activity: part –I. J. of Young Pharm. 2015; 1: 21-7.
7. Deng Y, Yang Z, Shipps Jr. GW, Lo S-M, West R, Hwac J. Discovery of liver-targeted inhibitors of *stearoyl-CoA desaturase* (SCD1). Bioorg Med Chem Lett 2013; 23: 791–6.
8. Yin Y, Zhang Y-Q, Jin B, Sha S, Wua X, Sangani CB et al. 6,7-Dihydrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4] oxazepine derivatives as selective inhibitors of PI3K. Bioorg Med Chem 2015; 23: 1231–40.
9. Chen X, Du Y, Sun H, Wang F, Kong L, Sun M. Synthesis and biological evaluation of novel tricyclic oxazine and oxazepine fused quinazolines. Part 1: Erlotinib analogs. Bioorg Med Chem Lett 2014; 24: 884 - 7.
10. Donnell AF, Michoud C, Rupert KC, Han X, Aguilar D, Frank KB et al. Benzazepinones and benzoxazepinones as antagonists of inhibitor of apoptosis proteins (IAPs) selective for the second Baculovirus IAP Repeat (BIR2) domain. J Med Chem 2013; 56: 7772−87.
11. Liu X-H, Jia Y-M, Song B-A, Pang Z-X, Yang S. Design and synthesis of novel 2-methyl-4,5-substitutedbenzo[f]-3,3a,4,5-tetrahydro-pyrazolo[1,5-d][1,4]oxazepin-8(7H)-one derivatives as *telomerase* inhibitors. Bioorg Med Chem Lett 2013; 23: 720–3.
12. Singh AK, Chawla R, Yadav LDS. Click reaction of epoxides with anthranilic acids using neat grinding to access benzoxazepines. Synthesis 2012; 44: 2353-8.
13. Nolsøe JMJ, Hansen TV. Asymmetric iodolactonization: an evolutionary account. Eur J Org Chem 2014; 3051–65.
14. Mphahlele MJ. Molecular iodine-mediated cyclization of tethered heteroatom-containing alkenyl or alkynyl systems. Molecules 2009; 14: 4814-37.
15. Hidemasa H, Yuusaku Y. Palladium-catalyzed mono-N-allylation of unprotected anthranilic acids with allylic alcohols in aqueous media. J Org Chem 2011; **76**: 8433-9.
16. Gryparis C, Efe C, Raptis C, Lykakis IN, Stratakis M. Cyclization of 1,6-Enynes Catalysed by Gold Nanoparticles Supported on TiO2: Significant Changes in Selectivity and Mechanism, as Compared to Homogeneous Au-Catalysis. Org Lett 2012; 14: 2956-9.