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Synthesis and Characterization of 4-substituted-3,4-dihydro-4-(2,4-dioxopentan-3-yl)-3-phenylbenzo[e][1,3] Oxazin-2-ones

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Abstract: Some substituted benzoxazine derivatives have been synthesized in simple two steps. The structures of the synthesized compounds were confirmed by NMR and Mass spectral data.
***Keywords*:** Imines, active methylene group, 1, 3-benzoxazines, one pot synthesis

1. Introduction

1,3-Benzodioxin-4-ones have been used (i) as protected forms of salicylic acid in the synthesis of salicylihalamide A and B, apicularen A1 and gustastatin, biologically active natural products and potential drug candidates and (ii) for the flash photolytic generation of α-oxo ketenes[1-6]. 1,3-benzoxazines is an important heterocycles due to their variety of biological activities[7-11]. Several successful attempts have been made and recorded in the literature demonstrating promising outcomes[12-14]. It was noted that condensation reactions could be operated without catalyst, but sometimes a catalyst such as TsOH or triethylamine was necessary. Recently, rhodium-catalyzed reactions of 2-(alkenyloxy) benzylamines which involve an allylic cleavage followed by regioselective carbonylation at the internal carbon atom have been developed as a new way to generate 3,4-dihydro-1,3- benzoxazines.

2. Results and discussions

The newly synthesized title compounds **5(a-e)** described in this communication were prepared according to the synthetic **Scheme I**.

The condensation reaction of salicylic aldehyde **1** and aniline **2** carried out in DCE at room temperature for 4h. 2-((phenylimino)methyl)phenol **3** was treated with phosphates and active methylene group containing compounds namely diethyl phosphonate, diethyl malonoate, ethylacetoacetate, acetyl acetone and nitro methane in DCE at 50 ^{o}C for 18h to produce diethyl (2-hydroxyphenyl) (phenylamino) methylderivatives **4(a-e)**. Compound **4** was cyclized with triphosgene to give 4-substituted-3,4-dihydro-4-(2,4-dioxopentan-3-yl)-3-phenylbenzo[e][1,3]oxazin-2-ones **5(a-e)** in 90-95% yield (**Scheme I**). The structures of the synthesized compounds were confirmed by ^{1}H NMR, and Mass data. The ^{1}H NMR data of all derivatives in the series are in agreement with the assigned structures. The mass spectra of compounds showed [M+H] peaks, in agreement with their molecular formula.

3. Experimental section

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS.

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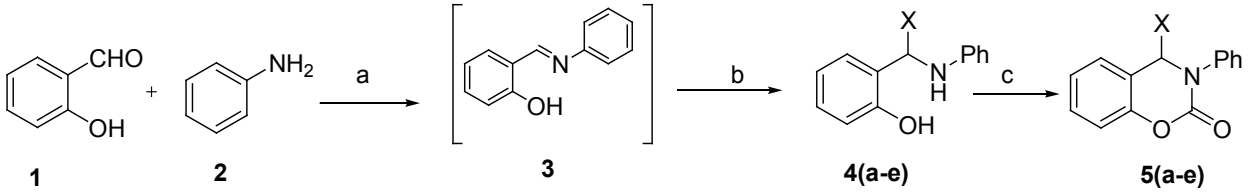


Scheme I. Synthesis of 4-substituted-3,4-dihydro-3-phenylbenzo[e][1,3] oxazin-2-one derivatives **5(a-e**)

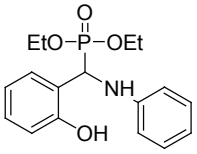
Reagents and Conditions: a) Titanium iso-propoxide, DCE, room temperature, 4 h; b) 1,3-diketone/nitro methane, 50 °C, 18 h; c) Triphosgene, room temperature, 1 h.

X = diethyl phosphonate, diethyl malonoate, ethylacetoacetate, acetyl acetone, nitro methane

4. General experimental procedure for synthesis of 4(a-e)

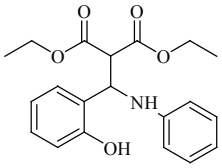
To a stirred solution of salicylaldehyde (0.01 mmol) in dichloroethane (10 mL) at room temperature was added aniline (0.01mmol) and stirred for 15 min. followed by addition titanium iso propoxide (0.02 mmol) and stirred the reaction at same temperature for 4 h. After completion of starting material (Checked by TLC) 1,3-diketone (0.02 mol) was added at room temperature and stirred at 50°C for 18 h. After completion of reaction, reaction mixture was poured into ice cold water, extracted with dichloromethane, washed with water and brine solution. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered and concentrated under reduced pressure, to obtain crude product and crude product was purified by column chromatography, required product was eluted at 2-5% methanol in chloroform to obtain respective compounds **4(a-e)**. The Yields of the products varied between 85 to 92%.

2((2-Hydroxyphenyl-2phenylamino))-1-methylphosphonate 4a



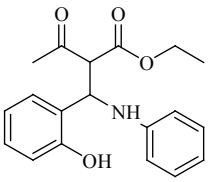
Pale yellow solid, Yield: 90%; M.p: 193 – 197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.14-7.31 (m, 5H), 6.66-6.97 (m, 4H), 4.93 (d, *J* = 6.0 Hz, 1H), 3.95-4.15 (q, *J* = 6.4 Hz, 4H), 3.05 (brs, 1H) 1.24-1.48 (t, 6H); ESI-MS: m/z (rel. abund.%) 336 $[M+H]^+$.

2((2-Hydroxyphenyl-2phenylamino))-1-diethyl 2-methylmalonate 4b



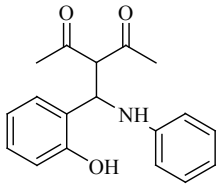
Brown solid; Yield: 82%; mp: 180-185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.13-7.35 (m, 5H), 6.46-6.87 (m, 4H), 3.54 (d, *J* = 6.0 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.24-4.18 (m, 4H), 3.27 (brs, 1H) 1.28-1.32 (t, 6H); ESI-MS: m/z (rel.abund.%) 358 $[M+H]^+$.

2((2-Hydroxyphenyl-2phenylamino))-1-methyl-3-oxobutanoate 4c



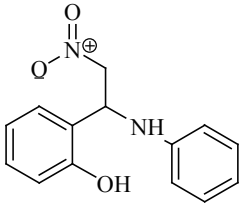
Off white solid; Yield: 85%; mp: 187-192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.21-7.29 (m, 5H), 6.48-6.98 (m, 4H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.25-4.11 (q, *J* = 6.8 Hz, 2H), 3.78 (d, *J* = 6.2 Hz, 1H), 3.25 (brs, 1H) 2.08 (s, 3H), 1.28-1.32 (t, *J* = 6.0 Hz, 3H); ESI-MS: m/z (rel.abund.%) 328 $[M+H]^+$.

2((2-Hydroxyphenyl-2phenylamino))-1- methylpentane-2,4-dione 4d



Off-white solid; Yield: 92%; mp: 176-182 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (s, 1H), 7.22-7.27 (m, 5H), 6.46-6.96 (m, 4H), 4.74 (d, *J* = 6.4 Hz, 1H) ,3.81 (d, *J* = 6.4 Hz, 1H), 3.25 (brs, 1H) 2.09 (s, 6H); ESI-MS: m/z (rel. abund.%) 298 $[M+H]^+$.

2((2-Hydroxyphenyl-2phenylamino))-1-nitroethane 4e

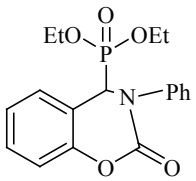


Yellow solid; Yield: 92%; mp: 165-170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.24-7.29 (m, 5H), 6.48-6.97 (m, 4H), 5.05-4.79 (d, 2H) ,3.91 (d, 1H), 3.25 (brs, 1H); ESI-MS: m/z (rel.abund.%) 258.3 (M^+)

5. General experimental procedure for synthesis of 3,4-dihydro-3-phenylbenzo[e][1,3] oxazin-2-one derivatives 5(a-e)

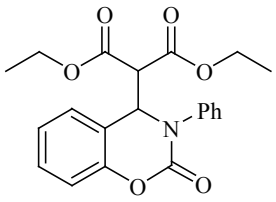
To a stirred solution of **4(a-e)** (0.01 mol) in chloroform (10 mL) was added triphosgene (0.012 mol) as dropwise at 0°C and stirred the reaction at room temperature for 30 min. After completion of reaction, reaction mixture was poured into ice water, extracted with chloroform washed the combined organics with *aq*.$NaHCO_3$ solution, followed by water and brine solution. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered and concentrated under reduced pressure, to obtain crude product and crude product was purified by column chromatography, required product was eluted at 50-60% pet ether in ethyl acetate to obtain respective compounds **5(a-e)**. The Yields of the products varied between 80 to 90%.

Diethyl 3,4-dihydro-2-oxo-3-phenyl-2H-benzo[e][1,3] oxazin-4-yl-4-phosphonate 5a



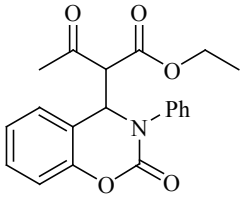
Off brown solid; Yield: 82%; mp: 228-235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15-7.52 (m, 9H), 5.12 (s, 1H), 4.01 (q, *J* = 6.0 Hz, 4H) 1.15 (t, *J* = 6.8 Hz, 6H); ESI-MS: m/z (rel.abund.%) 362 $[M+H]^+$.

Diethyl 2-(3,4-dihydro-2-oxo-3-phenyl-2H-benzo[e][1,3] oxazin-4-yl)malonate 5b



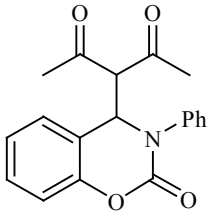
Off white solid; Yield: 90%; mp: 240-245 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 7.15-7.36 (m, 5H), 6.45-6.88 (m, 4H), 3.55(d, *J* = 6.0 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.24-4.18 (m, 4H), 1.28-1.32 (t, 6H); ESI-MS: m/z (rel.abund.%) 353 $[M+H]^+$.

Ethyl 2-(3,4-dihydro-2-oxo-3-phenyl-2H-benzo[e][1,3] oxazin-4-yl)-3-oxobutanoate 5c



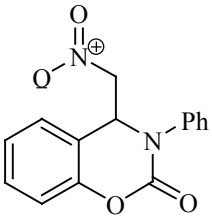
Off white solid; Yield: 85%; mp: 237-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 7.18-7.41 (m, 5H), 6.43-6.90 (m, 4H), 5.02 (d, *J* = 6.2 Hz, 1H), 3.49 (d, *J* = 6.2 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H), 1.28 (t, *J* = 6.8 Hz, 3H); ESI-MS: m/z (rel.abund.%) 353 $[M+H]^+$.

3,4-Dihydro-4-(2,4-dioxopentan-3-yl)-3-phenylbenzo[e][1,3] oxazin-2-one 5d



White solid; Yield: 80%; mp: 228-235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 7.21-7.39 (m, 5H), 6.39-6.84 (m, 4H), 3.80 (d, *J* = 6.0 Hz, 1H), 4.82 (dd, 1H), 2.32 (t, *J* = 6.8 Hz, 6H); ESI-MS: m/z (rel.abund.%) 324 $[M+H]^+$.

3,4-Dihydro-4-(nitromethyl)-3-phenylbenzo[e][1,3] oxazin-2-one 5e



Yellow solid; Yield: 87%; mp: 210-215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 7.19-7.38 (m, 5H), 6.36-6.86 (m, 4H), 4.83 (dd, 2H), 3.82 (d, *J* = 6.0 Hz, 1H); ESI-MS: m/z (rel.abund.%) 294 $[M+H]^+$.

6. Conclusion

In conclusion, the present paper describes the synthesis from commercially available salicylaldehyde and aniline as starting materials in two steps. It is observed that within the series of title compounds obtained in good yields.

7. Authors' contributions

BRK carried out the total experimental work under the guidance of ELN. SG and MTC performed the statistical

analysis and drafted the manuscript. All authors read and approved the final manuscript.

8. Acknowledgements

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9. Competing interests

The authors declare that they have no competing interests.

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