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An Efficient Approach for the Synthesis of *N*-Phenylcarboxamido-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazine-4-ones

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An efficient synthesis of *N*-phenylcarboxamodo-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones is described by cyclization reaction of some 2-(benzylidene-amino)-benzoic acids with phenyl isocyanate under reflux conditions in $CHCl_3$. Higher yields of the products were produced in high purity with simple work-up.

Keywords: 1,2-Dihydro-3,1-benzoxazin-4-ones, Anthranilic acid, Phenyl isocyanate, Schiff base, Cyclization reaction

INTRODUCTION

The reactivity and chemical behavior of anthranilic acid and its derivatives make them as excellent starting materials in the synthesis of several types of nitrogen heterocycles such as 4*H*-3,1-benzoxazin-4-ones [1]. *N*-Substituted-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones are potential starting materials for the synthesis of biologically important heterocycles [2] such as 1,4-benzodiazepine-2,5-diones and indoxyls. Contrary to the parent compounds 4*H*-3,1-benzoxazin-4-ones [3], very few synthetic routes have ever been reported for 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones [4]. Herein, we wish to report an efficient protocol for the synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones using condensation reaction of anthranilic acid derivatives with aryl aldehydes and then, cyclization reaction of the obtained Schiff bases with phenyl isocyanate under mild reaction conditions.

EXPERIMENTAL

Apparatus

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^1H and 62.9 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal *TMS*, and coupling constants *J* are reported in Hz. Mass spectra were recorded with a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV.

General Reaction Procedure

A mixture of 0.001 mol of an anthranilic acid derivative **1** and 0.0012 mol of an aryl aldehyde was stirred in methanol for about 1 h in room temperature. The solvent was removed and then, the obtained Schiff bases **2** were washed with *n*-hexane and then dried. Then, to the solution of the Schiff bases **2** in 1 ml $CHCl_3$, 0.0015 mol (0.0025 mol in the cases of **2d**, **2f** and **2g**) phenyl isocyanate was added and the mixture was refluxed for the times as indicated in Table 1. After the removal of the solvent, the precipitate was washed with 2 ml of *n*-hexane (three times) and filtered to remove the residual of phenyl isocyanate. The raw products were washed with 10% $NaHCO_3$ and then with H_2O to remove the trace residual of **2** and then were dried in the air.

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2-Phenyl-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2a). M.p.: 166-168 ºC. IR (KBr): $\overline{\nu}$ = 3195, 1730, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 9.70 (s, 1H, NH), 7.77 (d, $^3J_{HH}$ = 7.2 Hz, 2H-Ar), 7.58-7.52 (m, 4H-Ar), 7.44 (s, 1H, CH), 7.36-7.29 (m, 6H-Ar), 7.19 (d, $^3J_{HH}$ = 7.0 Hz, 1H-Ar), 7.07 (d, $^3J_{HH}$ = 6.5 Hz, 1H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 162.5, 157.2, 153.2, 140.2, 139.3, 137.4, 135.7, 129.5, 129.1 (2C) ,126.8, 125.4, 124.1, 123.8, 120.6, 119.0, 85.1; EI-MS (70 eV): *m/z* (%) = 344 ($M^{+\cdot}$, 13).

2(3-Nitrophenyl)-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2b). M.p.: 165-169 ºC. IR (KBr): $\overline{\nu}$ = 3450, 1725, 1675 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 9.81 (s, 1H, NH), 8.16 (s, 1H-Ar), 7.93 (d, $^3J_{HH}$ = 7.2 Hz, 1H-Ar), 7.9-7.75 (m, 4H-Ar), 7.63 (s, 1H, CH), 7.55-7.48 (m, 3H-Ar), 7.44-7.30 (m, 4H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 162.0, 159.7, 153.1, 151.0, 149.9, 148.4, 139.8, 138.5, 137.2, 130.9, 129.2, 129.1, 125.7, 124.0, 121.6, 120.5, 119.9, 118.6, 84.4; EI-MS (70 eV): *m/z* (%) = 389 ($M^{+\cdot}$, 5).

6-Bromo-2-phenyl-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2c). Mp 215-220 ºC. IR (KBr): $\overline{\nu}$ = 3305, 1726, 1691 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) = 8.73 (bs, 2H, H-Ar and N-H), 7.75 (d, $^3J_{HH}$ = 7.7 Hz, 1H-Ar), 7.47-7.40 (m, 4H-Ar), 7.36 (d, $^3J_{HH}$ = 9.0 Hz, 1H-Ar), 7.28-7.22 (m, 5H, H-Ar and CH), 6.97-6.91 (m, 2H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 158.9, 157.3, 153.0, 151.9, 151.2, 141.8, 140.2, 138.2, 130.4, 129.2, 124.7, 123.8, 122.2, 120.2, 118.6, 114.3, 83.5; EI-MS (70 eV): *m/z* (%) = 424 [($M^{+\cdot}$+2), 8], 422 ($M^{+\cdot}$, 10).

2-(4-Chlorophenyl)-N-phenylcarboxamodo-6-(O-phenylcarbamoyl)-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2d). M.p.: 186-190 ºC. IR (KBr): $\overline{\nu}$ = 3475, 3320, 3185, 1749, 1718, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 11.24 (s, 1H, NH), 10.2 (s, 1H, NH), 7.70-7.10 (m, 17H, H-Ar and CH); ^{13}C NMR (DMSO-d_6): δ (ppm) = 158.9 (2C), 156.5, 151.5, 149.7, 139.9, 138.9 (2C), 129.2, 128.7, 128.0, 127.4, 126.3, 124.1, 119.8, 118.6, 115.7, 111.8, 82.7; EI-MS (70 eV): *m/z* (%) = 515 [($M^{+\cdot}$+2), 3], 513 ($M^{+\cdot}$, 8).

2-(4-Chlorophenyl)-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2e). M.p.: 146-151 ºC. IR (KBr): $\overline{\nu}$ = 3300, 1712, 1676 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 10.27 (s, 1H, NH), 7.94 (d, $^3J_{HH}$ = 6.7 Hz, 2H-Ar), 7.85-7.65 (m, 3H-Ar), 7.45-7.15 (m, 6H-Ar), 7.12-6.95 (m, 3H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 151.1 (2C), 149.8, 140.1, 138.5, 137.3, 129.2, 128.8, 128.5, 125.0, 124.7, 123.5, 119.9, 118.6, 114.8, 114.3, 85.0; EI-MS (70 eV): *m/z* (%) = 380 [($M^{+\cdot}$+2), 5], 378 ($M^{+\cdot}$, 14).

2-(2-Chlorophenyl)-N-phenylcarboxamodo-6-(O-phenylcarbamoyl)-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2f). M.p.: 158-160 ºC. IR (KBr): $\overline{\nu}$ = 3345, 3250, 1756, 1722, 1671 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 10.08 (bs, 1H, NH), 9.21 (s, 1H, NH), 8.54 (s, 1H-Ar), 7.73 (d, $^3J_{HH}$ = 7.2 Hz, 2H-Ar), 7.50-7.40 (m, 4H-Ar), 7.36-7.30 (m, 4H-Ar), 7.30-7.15 (m, 3H-Ar, CH), 7.04-7.00 (m, 1H-Ar), 6.85 (d, $^3J_{HH}$ = 7.2 Hz, 2H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 164.5, 160.0, 155.7, 154.7, 153.4, 150.8, 149.1, 142.3, 141.1, 138.9, 129.2, 129.1, 129.0, 128.9, 128.8, 127.8, 126.5, 126.3, 123.0, 121.4, 121.2, 119.4, 118.8, 85.3; EI-MS (70 eV): *m/z* (%) = 515 [($M^{+\cdot}$+2), 4], 513 ($M^{+\cdot}$, 11).

2-(3-Chlorophenyl)-N-phenylcarboxamodo-6-(O-phenylcarbamoyl)-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2g). M.p.: 165-167 ºC. IR (KBr): $\overline{\nu}$ = 3320, 3140, 1750, 1703, 1681 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 10.28 (bs, 1H, NH), 9.78 (s, 1H, NH), 8.63 (s, 2H-Ar), 7.75-7.61 (m, 1H-Ar, CH), 7.60-7.40 (m, 6H-Ar), 7.35-7.20 (m, 4H-Ar), 7.14-6.92 (m, 4H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 161.8, 155.6, 153.3, 153.0, 151.6, 147.5, 140.1, 140.0, 139.6, 139.1, 138.7, 137.3, 132.4, 131.4, 129.8, 129.3, 129.2, 129.1, 129.0, 126.0, 122.3, 120.6, 118.7, 84.7; EI-MS (70 eV): m/z (%) = 559 [($M^{+\cdot}$+2), 9], ($M^{+\cdot}$, 8).

2-(3-Bromophenyl)-7-chloro-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2h). M.p.: 184-186 ºC. IR (KBr): $\overline{\nu}$ = 3315, 1711, 1667, 1613 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 10.44 (bs, 1H, NH), 8.58 (s, 1H-Ar), 8.01-7.90 (m, 3H-Ar), 7.75-7.30 (m, 2H-Ar), 7.50-7.30 (m, 4H-Ar, 1CH), 7.10-6.91 (m, 2H-Ar); ^{13}C NMR (DMSO-d_6): δ (ppm) = 171.4, 159.7, 153.3, 151.9, 151.2, 143.2, 141.8, 138.1, 137.5, 133.8, 130.4, 129.7, 129.3, 129.0, 128.9, 121.5, 120.3, 118.6, 83.6; EI-MS (70 eV): m/z (%) = 460 [($M^{+\cdot}$+4), 3], 458 [($M^{+\cdot}$+2), 5], 456 ($M^{+\cdot}$, 1).

2-(2-Chlorophenyl)-6,7-dimethoxy-N-phenyl-carboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2i). M.p.: 176-178 ºC. IR (KBr): $\overline{\nu}$ = 3410, 1711, 1689, 1600 cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) = 9.57 (s, 1H, NH), 7.51-7.46 (m, 4H-Ar) 7.28-7.21 (m, 6H, H-Ar and CH), 7.06 (s, 2H-Ar), 3.85 and 3.77 (2s, $2CH_3$); ^{13}C NMR (DMSO-d_6): δ (ppm) = 161.4, 155.2, 153.1, 147.1, 139.1, 135.4, 134.1,

133.4, 131.2, 129.0, 127.4, 123.9, 120.9, 110.8, 110.0, 107.4, 83.9, 56.6, 56.1; EI-MS (70 Ev): m/z (%) = 440 [($M^{+\cdot}$+2), 4], 438 ($M^{+\cdot}$, 12).

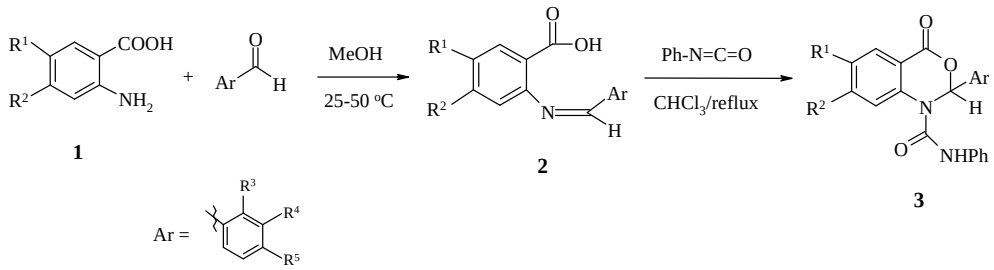
2-(4-Methoxyphenyl)-N-phenylcarboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2j). M.p.: 154-159 °C. IR (KBr): $\overline{\nu}$ = 3335, 1707, 1681, 1604; ^{1}H NMR (DMSO-d_6): δ (ppm) = 9.48 (bs, 1H, NH), 7.52-7.28 (m, 9H, H-Ar and CH), 6.86 (m, 3H-Ar), 3.70 (s, 3CH_3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 162.1, 159.7, 154.8, 153.3, 146.8, 139.3, 134.8, 129.4, 129.0, 128.1, 123.7, 120.7, 114.3, 111.3, 109.9, 107.7, 85.3, 56.6, 56.0, 55.5; EI-MS (70 eV): m/z (%) = 434 ($M^{+\cdot}$, 8).

2-(4-Chlorophenyl)-6,7-dimethoxy-N-phenyl-carboxamodo-1,2-dihydro-(4H)-3,1-benzoxazin-4-ones (2k). M.p.: 178-182 °C. IR (KBr): $\overline{\nu}$ = 3400, 1711, 1678, 1607; ^{1}H NMR (DMSO-d_6): δ (ppm) = 9.53 (s, 1H, NH), 7.70-6.90 (m, 12H and CH), 3.74 (2s, 2CH_3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 161.8, 154.9, 153.3, 146.9, 139.3, 136.8, 134.7, 133.8,129.0, 128.7, 123.8, 120.7, 119.7, 110.9, 109.0, 107.6, 84.8, 56.6, 56.0; EI-MS (70 Ev): m/z (%) = 440 [($M^{+\cdot}$+2), 9], 438 ($M^{+\cdot}$, 24).

RESULTS AND DISCUSSION

In continuation of our investigation on the synthesis of *N*-acetyl-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones [4a], the cyclization reaction of Schiff base **2** by phenyl isocyanate was studied. We observed that when the Schiff bases **2** were refluxed in $CHCl_3$ in the presence of phenyl isocyanate, a cyclization reaction occurred and *N*-(phenylcarboxamide)-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones **3** are obtained in high yield without use of any catalysts (Scheme 1).

The reaction conditions were mild with very simple work-up. Also, this method could be utilized for the synthesis of a variety of substituents on aromatic rings. Results are summarized in Table 1.

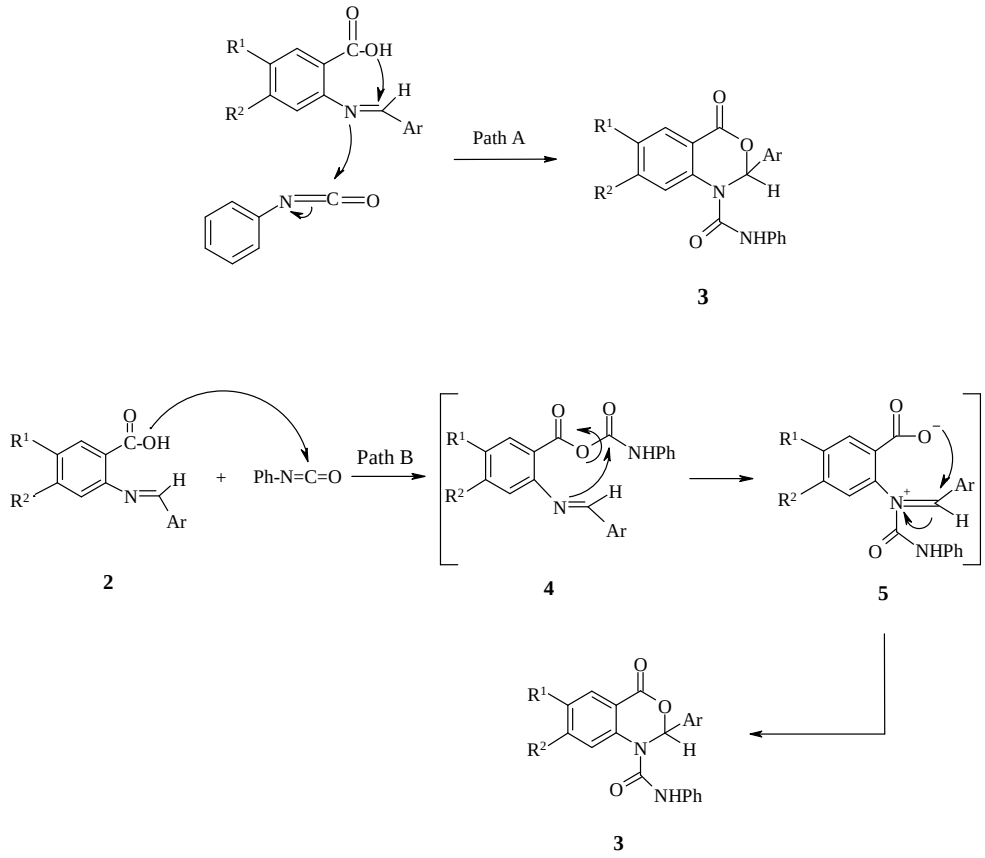


Scheme 1

Table 1. Synthesis of Compounds **3**[a] from the Cyclization Reaction of Schiff Bases **2** with Phenyl Isocyanate under Reflux Condition in $CHCl_3$

	R^1	R^2	R^3	R^4	R^5	Time (h)	Yield (%)[b]
a	H	H	H	H	H	2.0	90
b	H	H	H	NO_2	H	2.5	78
c	Br	H	H	H	H	3.0	75
d	OH	H	H	H	Cl	2.5	89
e	H	H	H	H	Cl	2.5	78
f	OH	H	Cl	H	H	2.5	89
g	OH	H	H	Br	H	2.5	90
h	H	Cl	H	Br	H	3.0	80
i	OMe	OMe	Cl	H	H	2.5	75
j	H	H	H	H	OMe	3.5	75
k	OMe	OMe	H	H	Cl	1.5	95

[a]In all cases, the products were identified and characterized by their physical and spectral data. [b]Isolated yields.



Scheme 2

Two plausible mechanisms are proposed for this cyclization reaction in Scheme 2. In the first pathway (Path A), the nucleophilic attack of imine to phenyl isocyanate occurs following with the intramolecular nucleophilic attack of the carboxyl oxygen to the imine carbon [4a]. In the second pathway (Path B), the nucleophilic attack of the carboxyl oxygen to phenyl isocyanate produces the intermediate **4**. The intramolecular transamidation of **4** produces the unstable zuitterionic intermediate **5** which cyclizes immediately to the desired compounds **3**. Pathway A seems to be the more liable route to cause the reaction.

The identification and characterization of the products were made by means of their physical and spectroscopic data. In IR spectra of compounds **3**, lactone and urea-like CO-stretching bands were observed in about 1730-1710 cm^{-1} and 1680-1650 cm^{-1}, respectively. In the cases of **2d**, **2f** and **2g** an additional CO-stretching was observed in about 1750 cm^{-1} because of carbamate formation. In ^{1}H NMR, the peak of C2-proton appeared as singlet in aromatic region; also, the appearance of C2-carbon peak in about 83-85 ppm in ^{13}C NMR was a good reason for the formation of 2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones **3**. In all cases, molecular ion peaks, in great abundance appeared in Mass-spectral.

CONCLUSIONS

In conclusion, the title compounds were synthesized by a condensation reaction of anthranilic acid derivatives with aryl aldehydes and then, cyclization reaction of the obtained Schiff bases took place with phenyl isocyanate. The reactions occurred under mild conditions in the absence of any catalyst. Good to high yields of the products were produced in high purity with simple work-up.

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