A Facile and Convenient Synthesis of *N*-Acetyl-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones from the Reaction of Anthranilic Acid Derivatives with Aryl Aldehydes

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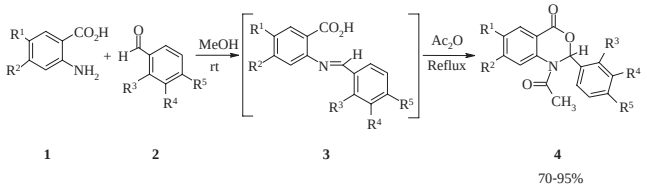
A facile and convenient synthesis of *N*-acetyl-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones has been reported by cyclization of some 2-(benzylideneamino)benzoic acids in acetic anhydride under reflux condition. High yields of the products were obtained in high purity with simple work-up.

4*H*-3,1-Benzoxazin-4-ones as an important class of heterocyclic compounds have been known for more than a century. They are valuable starting materials for the synthesis of a variety of heterocycles such as 2,3-disubstituted quinazolin-4(3*H*)-ones.[1–3] The chemistry of these compounds has been reviewed covering the period 1965–1998.[4] Contrary to the parent compounds 4*H*-3,1-benzoxazin-4-ones, very few synthetic routes have ever been published for N-substituted 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones.[5–8] They are potential starting material for synthesis of important heterocycles such as 1,4-benzodiazepine-2,5-diones and indoxyls.[9]

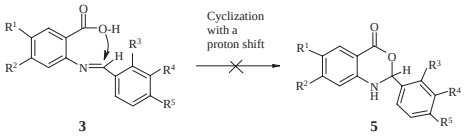
The previously reported method for the synthesis of *N*-acetyl-1,2-dihydro-3,1-benzoxazine-4-ones is the reaction of N-acylated anthranilic acids with paraformaldehyde in refluxing acetic acid.[7] Here, we wish to report a practical and convenient synthesis of the title compounds. Our experiments show that when an anthranilic acid derivative is condensed with an aryl aldehyde and then, the mixture is refluxed in acetic anhydride, the *N*-acetyl-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones **4** are produced in high yields (Scheme 1).

Also, we have observed that the intermediates **3** are stable in neutral media and even after 3 h reflux in toluene or DMF, no yield of **5** is obtained from direct cyclization of **3** via an intramolecular nucleophilic attack and a proton shift (Scheme 2).

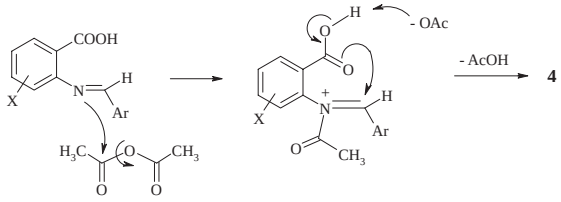
It seems that in the presence of acetic anhydride, acylation of the nitrogen occurs following with the intramolecular nucleophilic attack of the carboxyl oxygen to the iminium carbon.



Scheme 1.



Scheme 2.



Scheme 3.

The plausible mechanism has been shown in Scheme 3.

There is so far no report to study on the one-pot synthesis of **4** by using of a simple imine formation and cyclization. This method could also be utilized for the synthesis of a variety of substituents on the both aromatic rings. All experiments were carried out in one-pot without need to separation and purification of the compounds **3**. Results have been summarized in Table 1.

IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data give useful information for the structural assignment of the products. In IR spectra of compounds **4**, lactone and tertiary amid CO-stretching bands observe in about 1740 and 1690 cm^{-1} respectively. In ^{1}H NMR, the peak of C2-proton appears as singlet in aromatic region. The C2-peak in ^{13}C NMR observes in about δ 82.5. Also, in all cases molecular ion peaks with good abundances appear in mass spectra.[10]

Table 1. Synthesis of *N*-acetyl-2-aryl-1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones **4**[a]

Entry	R^1	R^2	R^3	R^4	R^5	Reflux in Ac_2O /h	Yield **4** /%[b]
1	H	H	H	H	H	2	84
2	Cl	H	H	H	H	2	81
3	OMe	OMe	H	H	H	1.5	88
4	H	H	H	Cl	H	3	87
5	H	H	H	NO_2	H	1	90
6	Cl	H	H	Cl	H	2	75
7	Cl	H	H	NO_2	H	1	80
8	OH	H	H	Cl	H	1	85[c]
9	OH	H	H	NO_2	H	1	85[c]
10	OMe	OMe	H	Cl	H	3	92
11	OMe	OMe	H	NO_2	H	1	95
12	H	CO_2H	H	Cl	H	3	78
13	H	CO_2H	H	NO_2	H	1	90
14	H	H	H	H	Me	3	73
15	Cl	H	H	H	Me	3	70
16	OH	H	H	H	Me	2	79[c]
17	OMe	OMe	OMe	H	H	2	94
18	OH	H	OH	H	H	1	83[c]
19	H	Br	OH	H	H	1	87[c]
20	Cl	H	OMe	H	H	2	79

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

In summary, the title compounds were synthesized by a condensation reaction of anthranilic acid derivatives with aryl aldehydes and then, concerted cyclization and acylation of the obtained imidic compound in acetic anhydride. The reactions were carried out in one-pot without separation and purification of the intermediate **3**. The reactions proceed in the absence of some types of basic or acidic catalyst. Good to high yields of the products were obtained in high purity with simple work-up.

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References and Notes

1 a) M. Alajarín, A. Vidal, M. M. Ortína, D. Bautista, *Synthesis* **2005**, 2426. b) H. M. F. Madkour, *Arkivok* **2004**, 36. c) S. M. Mosaad, K. I. Mohammed, M. A. Ahmed, S. G. Abdel-Hamide, *J. Appl. Sci.* **2004**, *4*, 302. d) C. Parkanyi, H. L. Yuan, B. H. E. Stromberg, A. Evenzahav, *J. Heterocycl. Chem.* **1992**, *29*, 749.

2 M. J. Kornet, T. Varia, W. Beaven, *J. Heterocycl. Chem.* **1983**, *20*, 1553.

3 L. A. Errede, J. J. MeBrady, H. T. Oien, *J. Org. Chem.* **1977**, *42*, 656 and references cited therein.

4 G. M. Coppola, *J. Heterocycl. Chem.* **1999**, *36*, 563.

5 L. Legrand, N. Lozach, *Bull. Soc. Chem. Fr.* **1967**, 2067.

6 P. Wiklund, J. Bergman, *Org. Biomol. Chem.* **2003**, *1*, 367.

7 P. Wiklund, J. Bergman, *Tetrahedron Lett.* **2004**, *45*, 969.

8 N. J. Hrib, J. G. Jurcut, D. E. Bregna, K. L. Burgher, H. B. Hartman, S. Kafca, L. L. Kerman, S. Kongsamut, J. E. Roehr, M. R. Szewczak, A. T. Woods-Kettelgerger, R. Corbett, *J. Med. Chem.* **1996**, *39*, 4044.

9 The compounds of this type can be ring opened by nucleophiles such as cyanide ion and the resulting *N*-cyanomethylanthranilic acids are potential starting material for synthesis of important heterocycles as 1,4-benzodiazepine-2,5-diones and 2-cyanoindoxyls: a) N. J. Hrib, J. G. Jurcut, D. E. Bregna, K. L. Burgher, H. B. Hartman, S. Kafca, L. L. Kerman, S. Kongsamut, J. E. Roehr, M. R. Szewczak, A. T. Woods-Kettelgerger, R. Corbett, *J. Med. Chem.* **1996**, *39*, 4044. b) K. Görlitzer, *Arch. Pharm.* **1975**, *308*, 700. c) P. Wiklund, M. Rogers-Evans, J. Brgman, *J. Org. Chem.* **2004**, *69*, 6371.

10 Substances were purchased commercially and used without more purification.

General reaction procedure: A mixture of 0.001 mol of an anthranilic acid derivative **1** and 0.0012 mol of an aryl aldehyde **2** was stirred in methanol for about 1 h at room temperature. The solvent was removed and then, the mixture was refluxed in 3 mL of acetic anhydride for the times as indicated in Table 1. After removal of the residue of acetic anhydride, the precipitate was washed with 3 mL of cold-water (three times) and filtered. The obtained products were dried in air and crystallized from methanol or ethanol. All new compounds afforded spectroscopic data. Selected spectral data:

Entry 6: Pale yellow crystals from ethanol, mp 137–139 °C. IR (KBr): ν (cm^{-1}) 1739, 1691. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 7.95 (s, 1H, arom. H), 7.61–7.50 (m, 2H, arom. H), 7.41(s, 1H, CH), 7.25–7.23 (m, 4H, arom. H), 2.51 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 169.6, 160.4, 137.6, 136.8, 135.2, 134.9, 132.4, 130.3, 130.0, 129.5, 126.2, 125.5, 124.2, 120.8, 83.1, 22.5. MS (EI): m/z (%) 339 [(M^+ + 4), 1], 337 [(M^+ + 2), 6], 335 (M^+, 9), 297 [(M^+ + 4) − H_2C=C=O, 7], 295 [(M^+ + 2) − H_2C=C=O, 48], 293 (M^+ − H_2C=C=O, 72), 216 ($C_{13}H_9{}^{37}ClN^+$, 16), 214 ($C_{13}H_9{}^{35}ClN^+$, 48), 155 ($C_7H_4{}^{37}ClNO^+$, 32), 153 ($C_7H_4{}^{35}ClNO^+$, 100), 139 ($C_6H_5{}^+$, 25).

Entry 9: White crystals from methanol, mp 165–168 °C. IR (KBr): ν (cm^{-1}) 1764, 1739, 1709, 1583, 1349. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 8.12 (s, 1H, arom. H), 7.74–7.71 (m, 2H, arom. H), 7.55–7.38 (m, 4H, arom. H), 7.52 (s, 1H, CH), 2.79 (s, 1H, CH_3COO), 2.27 (s, 3H, CH_3CON). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 170.0, 168.6, 161.0, 148.6, 148.3, 138.2, 136.1, 132.2, 130.2, 128.7, 125.2, 124.2, 123.3, 121.0, 120.9, 82.6, 22.5, 20.9. MS (EI): m/z (%) 370 (M^+, 10), 328 (M^+ − H_2C=C=O, 45), 286 ($C_{14}H_{10}N_2O_5{}^+$, 100), 241 ($C_{13}H_9N_2O_3{}^+$, 44), 195 ($C_{13}H_9NO^+$, 32), 177 ($C_{13}H_7N^+$, 35), 135 ($C_7H_3O_3{}^+$, 86).

Entry 11: Pale crystals from *n*-hexane/ethanol, mp 200–202 °C. IR (KBr): ν (cm^{-1}) 1717, 1687, 1524, 1340. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 8.13 (s, 1H, arom. H), 7.74–7.66 (m, 3H, arom. H), 7.51 (s, 1H, CH), 7.30 (s, 1H, arom. H), 6.90 (s, 1H, arom. H), 3.94 and 3.83 (2s, 6H, $2CH_3O$), 2.49 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 170.1, 161.0, 154.6, 148.5, 147.9, 138.7, 133.1, 132.2, 130.1, 123.9, 120.9, 111.8, 110.6, 106.8, 82.5, 56.6, 56.2, 22.7. MS (EI): m/z (%) 372 (M^+, 55), 330 (M^+ − H_2C=C=O, 100), 285 (M^+ − H_2C=C=O − COOH, 51), 221 ($C_{11}H_{11}NO_4{}^+$, 56), 206 ($C_{10}H_8NO_4{}^+$, 33), 179 ($C_9H_9NO_3{}^+$, 55).

Entry 12: Pale crystals from methanol, mp 215–218 °C. IR (KBr): ν (cm^{-1}) 3450–2250, 1735, 1700, 1685. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 11.23 (bs, 1H, COOH), 8.11–7.83 (m, 3H, arom. H), 7.31 (s, 1H, CH), 7.28–7.21 (m, 4H, arom. H), 2.50 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 171.1, 168.4, 162.4, 138.2, 136.2, 135.6, 132.1, 132.0, 130.6, 128.5, 127.3, 126.9, 126.0, 124.6, 123.4, 82.6, 22.6. MS (EI): m/z (%) 347 [(M^+ + 2), 2], 345 (M^+, 5), 305 [(M^+ + 2) − H_2C=C=O, 22], 304 [(M^+ + 2) − H_2C=C=O − H, 30], 303 [(M^+ + 2) − H_2C=C=O, 80], 302 (M^+ − H_2C=C=O − H, 71), 261 ($C_{14}H_{10}{}^{37}Cl\ NO_2{}^+$, 8), 259 ($C_{14}H_{10}{}^{35}ClNO_2{}^+$, 23), 163 ($C_8H_5NO_3{}^+$, 100).

Entry 17: Pale yellow crystals from *n*-hexane/ethanol, mp 172–175 °C. IR (KBr): ν (cm^{-1}) 1720, 1684. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 7.47 (s, 1H, arom. H), 7.45–7.30 (m, 3H, arom. H and CH), 6.94 (s, 1H, arom. H), 6.90–6.82 (m, 2H, arom. H), 3.98, 3.95, and 3.87 (3s, 9H, $3CH_3O$), 2.43 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 159.6, 159.5, 159.4, 156.4, 156.3, 149.5, 149.0, 142.8, 125.3, 125.2, 120.1, 111.2, 109.0, 107.3, 82.3, 56.4, 56.3, 56.2, 21.2. MS (EI): m/z (%) 357 (M^+, 42), 315 (M^+ − H_2C=C=O, 100), 270 (M^+ − H_2C=C=O − COOH, 57), 206 ($C_{10}H_8NO_4{}^+$, 39), 179 ($C_9H_9NO_3{}^+$, 48), 107 ($C_7H_7O^+$, 64).

Entry 19: White crystals from *n*-hexane/ethanol, mp 80–82 °C. IR (KBr): ν (cm^{-1}) 1763, 1742, 1689. ^{1}H NMR (250.1 MHz) in $CDCl_3$: δ 8.12 (d, $^4J_{HH}$ = 2.5 Hz, 1H, arom. H), 7.63 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, arom. H), 7.33–7.08 (m, 5H, arom. H and CH), 6.99 (d, $^3J_{HH}$ = 8.7 Hz, 1H, arom. H), 2.33 (s, 1H, CH_3COO), 2.30 (s, 3H, CH_3CON). ^{13}C NMR (62.9 MHz) in $CDCl_3$: δ 169.5, 168.8, 160.7, 148.4, 148.3, 137.6, 137.3, 132.5, 130.6, 127.4, 126.3, 126.0, 123.9, 121.8, 120.2, 82.3, 22.3, 21.0. MS (EI): m/z (%) 405 [(M^+ + 2), 3], 403 (M^+, 4), 361 [(M^+ + 2) − H_2C=C=O, 45)], 359 (M^+ − H_2C=C=O, 45), 319 [(M^+ + 2) − $2H_2C$=C=O, 99)], 315 (M^+ − $2H_2C$=C=O, 100), 199 ($C_7H_4{}^{81}BrNO^+$, 48), 197 ($C_7H_4{}^{79}BrNO^+$, 49), 93 ($C_6H_5O^+$, 65).

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