## Synthesis of 3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazines and -1,4-benzothiazines under Phase-Transfer Catalysis

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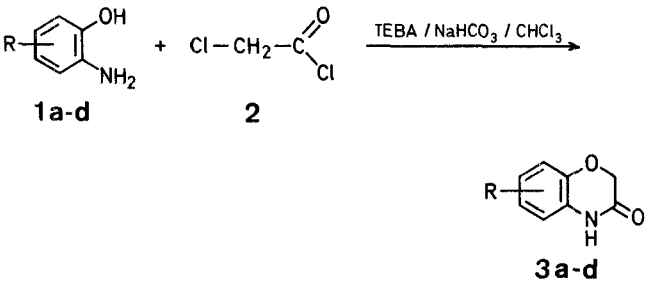
2*H*-1,4-Benzoxazin-3(4*H*)-ones (3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines) are compounds of considerable interest because of their pharmacological and antimicrobial properties. The previous syntheses of these compounds[1,2,3] suffer from one or more disadvantages such as low yields, long reaction times, and contamination of the end products with by-products. More recently, a one-step synthesis was reported[4]. In this synthesis, in which isobutyl methyl ketone is used as solvent and aqueous sodium hydrogen carbonate as base, the respective *o*-aminophenol is *N*-acylated with chloroacetyl chloride, followed by intramolecular *O*-alkylation.

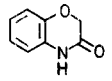
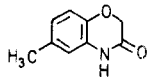
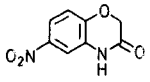
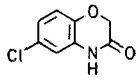
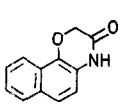
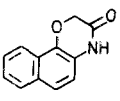
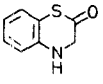
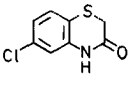
Since the use of phase-transfer catalysed *N*-acylation and *O*-alkylation has in many systems lead to excellent results, we assumed that the above described reaction, *N*-acylation and *in situ* intramolecular *O*-alkylation, might take place readily in ordinary solvents under phase-transfer catalysis conditions. Our results showed that by using benzyltriethylammonium chloride (TEBA) as phase-transfer catalyst the reaction of equimolecular amounts of *o*-aminophenol and chloroacetyl chloride in chloroform at 50–60 °C in the presence of solid sodium hydrogen carbonate gave 2*H*-1,4-benzoxazin-3(4*H*)-ones (**3a–d**; 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines) in good yields. With 2-amino-1-naphthol or 1-amino-2-napthol as aminophenols, the reaction afforded 3-oxo-3,4-dihydro-2*H*-naphtho[1,2-*b*]-1,4-oxazine (**4a**) and 2-oxo-2,3-dihydro-1*H*-naphtho[2,1-*b*][1,4]oxazine (**4b**), respectively.



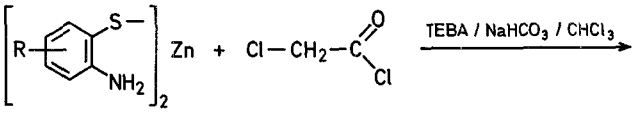

We found that this method has some advantages over the previously reported ones; the yields are high, the products are of excellent purity, and the use of special solvents such as methyl isobutyl ketone is not necessary.

The analogous reaction of *o*-aminobenzenethiols with chloroacetyl chloride leads to the formation of 2*H*-1,4-benzothiazin-3(4*H*)-ones (**6**; 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines). However, because of the instability of the aminobenzenethiols the reaction is more conveniently performed with the readily available zinc salts **5**.

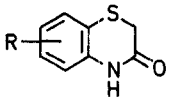
**Table.** 1,4-Benzoaxazine and 1,4-Benzothiazine Derivatives (**3**, **4**, **6**) prepared

| Product | Yield [%] | m.p. [°C] found | m.p. [°C] reported | I.R. (KBr) $\nu_{C=O}$ [cm$^{-1}$] | $^1$H-N.M.R. (DMSO-$d_6$/TMS$_{int}$) $\delta$ [ppm] |
|---|---|---|---|---|---|
| **3a**  | 89 | 171–172° | 172°[4] | 1690 | 5.02 (s, 2H); 7.36 (m, 4H); 10.18 (br. s, 1H) |
| **3b**  | 91 | 207–208° | 209°[4] | 1710 | 2.12 (s, 3H); 4.40 (s, 2H); 6.48–6.78 (m, 3H); 10.82 (br. s, 1H) |
| **3c**  | 87 | 234° | 233°[5] | 1715 | 4.69 (s, 2H); 7.03 (d, 1H); 7.62–7.82 (m, 2H); 10.92 (br. s, 1H) |
| **3d**  | 94 | 213–214° | 214°[4] | 1714 | 4.42 (s, 2H); 6.79 (m, 3H); 10.58 (br. s, 1H) |
| **4a**  | 85 | 246–247° | 247°[6] | 1725 | 4.62 (s, 2H); 6.88–7.70 (m, 6H); 10.75 (br. s, 1H) |
| **4b**  | 94.5 | 215–216° | $C_{12}H_9NO_2$[a] (199.2) | 1700 | 4.60 (s, 2H); 7.08–8.16 (m, 6H); 10.86 (br. s, 1H) |
| **6a**  | 82 | 181–182° | 181–181.5°[7] | 1670 | 3.51 (s, 2H); 7.02–8.09 (m, 4H); 10.54 (br. s, 1H) |
| **6b**  | 82 | 204–205° | 205–206°[8] | 1682 | 3.52 (s, 2H); 6.92–7.54 (m, 3H); 10.69 (br. s, 1H) |

[a] New compound: calc. C 72.35 H 4.55 N 7.03
found 72.04 4.40 7.01




**5a,b** **2**




**6a,b**

The structures of products **3**, **4**, and **6** were confirmed by microanalyses, I.R., and $^1$H-N.M.R. spectrometry.

**3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazines (3a–d), 3-Oxo-3,4-dihydro-2*H*-naphtho[1,2-*b*]-1,4-oxazine (4a), and 2-Oxo-2,3-dihydro-1*H*-naphtho[2,1-*b*][1,4]oxazine (4b); General Procedure:**
To a stirred solution of the *o*-aminophenol **1** (10 mmol) and benzyltriethylammonium chloride (2.28 g, 10 mmol) in chloroform (25 ml) is added finely powdered sodium hydrogen carbonate (3.36 g, 40 mmol). The resultant mixture is cooled in an ice-bath, then a solution of chloroacetyl chloride (**2**; 1.36 g, 12 mmol) in chloroform (5 mmol) is added dropwise over a period of 20 min. After the addition is completed the mixture is stirred at 0–5 °C for 1 h, then heated at 55 °C for 5 h. The solvent is removed and water (40 ml) is added. The crude product **3** or **4** is isolated by suction, washed with water, and recrystallised from ethanol.

**3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazines (6a,b):**
To a stirred mixture of the zinc salt of *o*-aminobenzenethiol **5** (5 mmol) and benzyltriethylammonium chloride (2.28 g, 10 mmol) in chloroform (25 ml) is added finely powdered sodium hydrogen carbonate (1.68 g, 20 mmol). The resultant mixture is cooled in an ice-bath, then a solution of chloroacetyl chloride (1.36 g, 12 mmol) in chloroform (5 ml) is added dropwise over a period of 20 min. When the addition is complete, the mixture is stirred at 0–5 °C for 1 h, then heated at 55 °C for 8 h. After removal of the solvent, 1 normal hydrochloric acid (40 ml) is added. The crude product is isolated by suction, washed with water, and recrystallised from ethanol.

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