A Convenient Synthesis of Naphth[2',3':5,6]- and [1',2':5,6]-1,3-oxazino[3,2-b]benzimidazoles and Benzoxazolo[3,2-b][1,3]quinazolone

Mechanism of Thiophosgene Heteroeyelisation [1]

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Heteroeyelisation, 6-Oxonaphth[2',3':5,6]-1,3-oxazino[3,2-b]benzimidazole, 6-Oxonaphth[1',2':5,6]-1,3-oxazino[3,2-b]benzimidazole

Reaction of thiophosgene or phosgene on 2'-aminonaphthanilides (2, 5) gave the corresponding 2-substituted-6-oxonaphth[2',3':5,6]-1,3-oxazino[3,2-b]benzimidazoles (3) and 6-oxonaphth[1',2':5,6]-1,3-oxazino[3,2-b]benzimidazoles (6) respectively. The mechanism of such reactions has been studied by carrying reaction between 2'-hydroxyanthranilide (7a) and thiophosgene in acidic and basic media.

The utility of thiophosgene to synthesize a variety of heterocyclic molecules is well established [2]. In continuation of our earlier interest in building polynuclear heterocyclic systems by reaction of thiophosgene on 2'-aminoalicylanilides [3], the synthesis of 2-substituted-6-oxonaphth[2',3':5,6]-1,3-oxazino[3,2-b]benzimidazoles (3) and 2-substituted-6-oxonaphth[1',2':5,6]-1,3-oxazino[3,2-b]benzimidazoles (6) and benzoxazolo[3,2-b][1,3]quinazol-5-one (10) using thiophosgene and phosgene in a single step has been carried out and the mechanism of such reactions is discussed in the present communication.

The starting materials for the synthesis of 3 and 6 were substituted 2'-nitronaphthanilides (1 and 4) made by treating 2-hydroxy-3-naphthoic acid and 1-hydroxy-2-naphthoic acid respectively with 2-nitroanilines in presence of phosphorus trichloride. Hydrogenation of 1 and 4 using Raney-nickel catalyst gave 2'-amino-2-hydroxy-3-naphthanilides (2) and 2'-amino-1-hydroxy-2-naphthanilides (5) respectively. Treatment of 2 and 5 with thiophosgene in presence of triethylamine yielded the corresponding 6-oxonaphth[2',3':5,6]-1,3-oxazino[3,2-b]benzimidazoles (3) and 6-oxonaphth[1',2':5,6]-1,3-oxazino[3,2-b]benzimidazoles (6) respectively in good yield. Use of phosgene in place of thiophosgene in the above reaction gave identical products and the yield in both the cases are comparable.

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**Chemical Structures**

1a: \( R = \text{NO}_2, R' = \text{H} \)
1b: \( R = \text{NO}_2, R' = \text{Cl} \)
2a: \( R = \text{NH}_2, R' = \text{H} \)
2b: \( R = \text{NH}_2, R' = \text{Cl} \)

3a: \( R' = \text{H} \)
3b: \( R' = \text{Cl} \)

4a: \( R = \text{NO}_2, R' = \text{H} \)
4b: \( R = \text{NO}_2, R' = \text{Cl} \)
5a: \( R = \text{NH}_2, R' = \text{H} \)
5b: \( R = \text{NH}_2, R' = \text{Cl} \)

6a: \( R' = \text{H} \)
6b: \( R' = \text{Cl} \)
The mechanism of such reactions has been discussed in our earlier communication [3]. However, in the light of our present investigations it has now been established that these thiophosgene induced heterocyclisations follow different courses when the reactions are carried out in presence of an acid or a base.

Reaction of 2'-hydroxyanthranilide \(7\alpha\) [4] with thiophosgene in presence of triethylamine did not afford the expected benzoxazolo[3,2-b][1,3]quinazol-5-one \(10\), prepared earlier by reaction of anthranilic acid with 2-chlorobenzoxazole [5], instead 3-(2-aminobenzoyl)benzoxazole-2-thione \(8\) was obtained. This is because of the formation of the phenoxide anion by triethylamine which, being a better nucleophile than an aromatic amine, attacks thiophosgene preferentially to give \(8\). When a solution of \(8\) in dilute hydrochloric acid and acetic acid was stirred at room temperature, it smoothly cyclised to afford \(10\).

\[
\begin{align*}
\text{NH}_2 & \quad \text{H} \quad \text{OR} \\
\text{CSCI} \quad \text{Et}_3 & \quad \text{N} \\
\text{CSCI} \quad \text{H}^+ & \quad \text{H}^+ \\
\text{N} & \quad \text{N} \\
\text{SH} & \quad \text{OR} \\
\text{N} & \quad \text{N} \\
\text{SH} & \quad \text{OR} \\
\end{align*}
\]

Treatment of \(7\alpha\) with thiophosgene in acidic conditions directly yields the cyclic product \(10\) and no intermediates could be isolated. This is due to the preferential attack by amino group, now a stronger nucleophile than a phenolic OH in acidic medium, on thiophosgene thereby yielding the isothiocyanate \(11\alpha\) which undergoes spontaneous ring closure to give \(12\alpha\). The formation of \(12\alpha\) follows an immediate attack of OH to yield \(9\) which suffers loss of a molecule of hydrogen sulfide to give \(10\).

An experimental evidence to the above fact was brought forward by treating 2'-methoxyanthranilide \(7\beta\) [6] with thiophosgene when 2-mercapto-3-(2-methoxyphenyl)quinazol-4-one \(12\beta\) [7] was isolated from the reaction mixture. The formation of \(12\beta\) can be explained by initial formation of the isothiocyanate \(11\beta\) in presence of an acid. These results show that the reaction of thiophosgene in basic medium follows a mechanism involving a benzoxazole-2-thione \(8\), as in the formation of \(10\), benzoxazine-2-thione \(3\) or naphthoxazine-2-thione (as in the formation of \(3\) and \(6\)) and not an isothiocyanate \(11\) or benzimidazole-2-thione as reported earlier [3] which holds true for reactions done in acidic media.

**Experimental**

4'-Chloro-2'-nitro-2-hydroxy-3-naphthanilide \(1\beta\)

\(\text{PCl}_3\) (3 ml) was added dropwise to a refluxing solution of 2-hydroxy-3-naphthoic acid \(18.8\) g, 0.1 mole) and 4-chloro-2-nitroaniline \(17.2\) g, 0.1 mole) in xylene \(200\) ml). After the addition was over, refluxing was continued for \(1\) h. Excess of \(\text{PCl}_3\) was decomposed by adding water in the reaction mixture and solvent removed by steam distillation. The product was filtered, washed with hot water \((2 \times 200\) ml), dried and crystallised from acetone; yield \(25.5\) g \((75\%)\), m.p. \(218\) °C.

**Analysis for \(C_{17}H_{11}ClN_3O_4\)**

Calcd C 59.64 H 3.21 N 8.18, Found C 59.63 H 2.80 N 8.10.

Other nitro compounds prepared in a similar manner are (m.p., yield given) - \(1\alpha\) \((180\) °C, 55\%), \(4\alpha\) \((190\) °C, 69\%) [8], and \(4\beta\) \((225\) °C, 62\%) [8].

2'-Amino-4'-chloro-2-hydroxy-3-naphthanilide \(2\beta\)

A mixture of \(1\beta\) \((3.12\) g, 0.01 mole) and Raney-nickel (about \(1.5\) g) in ethanol \(125\) ml) was hydrogenated at \(2.5\) kg/cm\(^2\) for \(12\) h. The catalyst was filtered off and solvent removed from filtrate to get a solid which was crystallized from ethanol; yield \(2.75\) g \((88\%)\), m.p. \(215\) °C.

**Analysis for \(C_{17}H_{13}ClN_2O_2\)**

Calcd C 65.38 H 4.16 N 8.97, Found C 65.40 H 4.50 N 9.00.

The following amines were made by similar reduction of the corresponding nitro compounds - (m.p., yield given) – \(2\alpha\) \((290\) °C, 80\%), \(5\alpha\) \((210\) °C, 80\%) [8], \(5\beta\) \((206\) °C, 80\%) [8].
A solution of thiophosgene (1.4 ml, 0.015 mole) in acetone (20 ml) was added dropwise to a stirred solution of 2b (4.70 g, 0.015 mole) in acetone (80 ml). Stirring was continued for 1 h and then the clear solution refluxed for 3 h. The solvent was removed from the reaction mixture and the residual solid crystallized from acetone, yield 4.0 g (83%), m.p. > 350 °C. Mass-M+ at m/e = 320.

Analysis for C14H10ClN2O2
Caled C 67.42 H 2.80 N 8.73
Found C 67.30 H 3.00 N 8.39.

The other compounds synthesized in a similar manner are (m.p., yield given) – 3a (312 °C, 81%), 6a (192 °C, 73%), and 6b (200 °C, 75%).

6-Oxonaphth[1',2':5,6]-1,3-oxazino[3,2-b]-benzimidazole (6a)
A solution of phosgene (1.5 g, 0.015 mole) in dry toluene (25 ml) was added dropwise to an ice-cooled and stirred solution of 5a (2.8 g, 0.01 mole) in dry acetone (100 ml). Stirring was continued for 1 h at the same temperature and then the reaction mixture refluxed gently for 3 h. Solvent was removed from the reaction mixture and the residue crystallized from acetone, yield 2.25 g (77%), m.p. 192 °C. Mass-M+ at m/e = 286.

Analysis for C19H12N2O2
Caled C 75.52 H 3.49 N 7.79
Found C 75.80 H 3.30 N 7.80.

A solution of thiophosgene (0.88 ml, 0.01 mole) in dry chloroform (10 ml) was added dropwise to a stirred solution of 7a (2.2 g, 0.01 mole) and triethylamine (2.8 ml, 0.02 mole) in dry chloroform (50 ml) at 0 °C. Stirring was continued for 1 h and the reaction mixture refluxed for 6 h. The solvent was removed in vacuo, the residue washed with water and crystallized from tetrahydrofuran, yield 1.3 g (50%), m.p. 235 °C. IR, νmax (KBr) cm⁻¹: 3200 (NH₂, asymmetric stretching), 3120 (NH₂, symmetric stretching), 1660 (C=O), 1610 (NH₂, bending), 1190 (C=S).

Analysis for C14H10N2O2S
Caled C 62.22 H 4.44 N 10.37
Found C 62.01 H 4.28 N 10.05.

2-Mercapto-3-(2-methoxyphenyl)quinazol-4-one (12b)
A solution of thiophosgene (0.45 ml, 0.005 mole) in chloroform (5 ml) was added dropwise to a stirred solution of 7b (1.2 g, 0.005 mole) in 10 ml acetic acid and 5 ml 10% hydrochloric acid at room temperature. Stirring was continued for 12 h, the organic layer separated, washed once with water, dried (Na₂SO₄) and solvent removed in vacuo. The residual solid was crystallized from benzene-hexane, yield 1.2 g (84%), m.p. 252 °C (lit. [7], m.p. 253 °C).

Analysis for C15H12N2O2S
Caled C 63.38 H 4.22 N 9.85
Found C 63.08 H 4.06 N 9.64.

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