Concise Syntheses of the Oxo Derivatives of Benzo[c]phenanthridine Bases by N-Deformylated Cyclization Based on Vilsmeier–Haack Reaction

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Chelerythrine-type oxo[benzo[c]phenanthridine] bases were effectively synthesized by the action of 1,3-dimethoxybenzene on 2-(2-methoxycarbonylphenyl)-1-(N-methylformamido)napthalenes in the presence of phosphorus oxychloride. The N-deformylation based on the Vilsmeier–Haack reaction is also discussed.

Key words N-deformylation; phosphorus oxychloride; Vilsmeier–Haack reaction; benzo[c]phenanthridine synthesis; isoquinolone cyclization; selective demethylation

Recently we have reported the synthesis of chelerythrine (1), a quaternary benzo[c]phenanthridine alkaloid (quaternary base) with a benzene ring having four successive substituents (ring A) in its molecule, by the combination of the cesium fluoride-mediated Caisen rearrangement of an aryl propargyl ether and oxidative cleavage of the furan ring in the intermediary 2-methylarylfuran. However, the last step of the synthesis by N-deformylated cyclization of a 2-(2-formylphenyl)-1-(N-methylformamido)napthalene 2 under acidic conditions (p-toluenesulfonic acid/xylene) was not entirely satisfactory (46% yield at best). In the course of a synthetic study of decarine (3), we naturally occurring phenoic tertiary benzo[c]phenanthridine alkaloid (norbase) which has the same subtituent pattern as 1, we succeeded in establishing an effective cyclization method under mild conditions based on the Vilsmeier–Haack (V.H.) reaction. We report here the N-deformylation reaction and its application to the syntheses of the o xo derivative of a benzo[c]phenanthridine base (oxobase) 4 derived from 3 and oxochelerythrine (5).

Results and Discussion

The synthetic route developed for chelerythrine (1) was applied to decarine (3) by changing the methoxy group at the 7 position of the 2-methylbenzofuran substituent in a furanylformamide 6 to a benzoxyl group. Selective demethylation of the methyl ether function in the presence of the acid-sensitive methylenedioxy group was achieved by using trimethylsilyl iodide (TMSI). However, purification of the demethylated product 7 met difficulty because of low solubility of the product, in addition to the appearance of distinct spots on thin layer chromatography (TLC) due to the presence of geometrical isomers derived from the double bond nature of the tertiary amide structure in the naphthylformamide derivatives. Therefore the phenolic 7 was purified through its benzyl ether. Treatment of 6 with TMSI in quinoline at 180°C for 4 h followed by conventional benzylation gave a benzyl ether 8 in 55% yield. Although almost the same result was obtained when TMSI, formed in situ from trimethylsilyl chloride (TMSCl) and sodium iodide (NaI) in acetonitrile (MeCN), was used, prolonged heating for 5 d and also the use of a large excess of reagents (12–22 mol eq) were needed for the completion of demethylation. The furan ring in 8 was cleaved by successive oxidation with osmium tetroxide and periodic acid to give a crude acetate 9, which was then converted into the desired aldehydic formamide 11 upon hydrolysis and methylation.

Since acidic treatment of 11 according to the method described for chelerythrine only resulted in the formation of a complex mixture, we then attempted N-deformylation under non-acidic conditions (Table 1). Photolysis of 11 under neutral conditions also led to the formation of a complex mixture (run 1). On the other hand, treatment of 11 with either 70% aqueous potassium hydroxide in ethanol (run 2) or 10% sodium ethoxide in ethanol (run 3) followed by acidification with hydrochloric acid afforded the desired quaternary salt 12 isolated as its chloride, but the yield was low in each case. Our attention was then directed to the development of an N-deformylation reaction suitable for the preparation of 12.

1 : R=Me  
3 : R=H (des-N-methyl)  
12 : R=Ph  
Bn=CH2Ph

2 : R1=R2=Me  
9 : R1=Ac, R2=Bn  
10 : R1=H, R2=Bn  
11 : R1=Me, R2=Bn  
6 : R=Me  
7 : R=H  
8 : R=Bn

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The V. H. reaction\(^3\) is one of the most important methods for introduction of a formyl group into nucleophiles, such as electron-rich aromatic compounds, and a combination of \(N,N\)-dimethylformamide (DMF) and phosphorus oxychloride (POCl\(_3\)) has been most widely used as the formylating mixture. The iminium salt formed \textit{in situ} is regarded as the reactive species. Therefore it should be possible for this reactive species to act as a useful selective deformylating agent for the removal of a formyl group from tertiary formamides if the formamides are used in place of DMF. In other words the aldehydic formamide \(11\) could be converted into a secondary amine \(13\) by loss of the formyl group when treated with POCl\(_3\) in the presence of an appropriate nucleophile followed by alkaline hydrolysis. The amine \(13\) would provide a quaternary base \(12\) through spontaneous intramolecular iminium salt formation between the newly generated amine function and the aldehyde group in the phenyl substituent (Chart 1).

Since aminolysis of \(11\) in the presence of diethylamine as a nucleophile failed to give any isolable products, we then picked 1,3-dimethoxybenzene in place of diethylamine. Treatment of \(11\) with 1,3-dimethoxybenzene and POCl\(_3\) in chloroform at around 50 °C afforded the desired \(12\)\(^3\) in 50—60% yield, together with considerable amounts of undefined products in some cases. The inconsistent results forced us to investigate the V. H. type N-deformylation reaction with model amide compounds in order to establish the scope and limitations of the reaction (Table 2).

\(N\)-Methylformanilide, which can also be used as a formyl source in the V. H. formylation reaction, was deformedylated as expected to afford \(N\)-methylaniline in high yield (run 1).

The presence of a phenolic hydroxyl group did not interfere with the reaction (run 2). Ineffectively conversion was observed in the cases of \(N\)-methylacetanilide (run 3) and formanilide (run 4). Interestingly this reaction was applicable not only to an aliphatic tertiary amide (run 5), but also to a secondary one (run 6). Thus, this N-deformylation reaction was established as a useful reaction applicable to a variety of formamide compounds.

On the other hand, a phenolic formamide protected by a methoxymethyl group resulted in the formation of a

\[\text{Me}_2\text{NCHO or 11} \xrightarrow{\text{Nu-H}} \text{Me}_2\text{N-H or 12} \xrightarrow{\text{OH}} \text{Me}_2\text{NCHO} + \text{Me}_2\text{NCHO} \]

**Chart 1**

**Table 1. Cyclization of an Aldehydic Formamide 11 under Non-acidic Conditions**

<table>
<thead>
<tr>
<th>Run</th>
<th>Reagent/solvent</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hv in MeCN</td>
<td>r.t. 180</td>
<td>C.M.(^a)</td>
</tr>
<tr>
<td>2</td>
<td>70% KOH, reflux in EtOH</td>
<td>90 12: 28%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10% EtONa, reflux in EtOH</td>
<td>10 12: 25%</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) A complex mixture.

**Table 2. \(N\)-Deacylation by the Action of 1,3-Dimethoxybenzene on Carboxamides in the Presence of POCl\(_3\)\(^a\)**

<table>
<thead>
<tr>
<th>Substrate (A)</th>
<th>OMe</th>
<th>POCl(_3) (mol eq)</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product (B) yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run</td>
<td>n</td>
<td>R(_1) R(_2) R(_3)</td>
<td></td>
<td>Temp. (°C)</td>
<td>Time (d)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>H Me H</td>
<td>1.1</td>
<td>1.2</td>
<td>CH(_3)Cl(_2)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>OH Me H</td>
<td>2.0</td>
<td>2.1</td>
<td>CHCl(_3)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>H Me Me</td>
<td>2.0</td>
<td>2.1</td>
<td>CHCl(_3)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>H H H</td>
<td>1.1</td>
<td>1.2</td>
<td>CH(_3)Cl(_2)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>H Me H</td>
<td>2.0</td>
<td>1.2</td>
<td>CH(_3)Cl(_2)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>H H H</td>
<td>1.0</td>
<td>2.1</td>
<td>CHCl(_3)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>OMOM(^b) Me H</td>
<td>2.0</td>
<td>2.1</td>
<td>CHCl(_3)</td>
</tr>
</tbody>
</table>

\(a\) The conditions of alkaline hydrolysis are not given here.  
\(b\) A methoxymethyl ether.  
\(c\) A complex mixture.
complex mixture of insoluble products (run 7) under the same reaction conditions, suggesting that incomplete cyclization to a quaternary base 12 from 11 described above may be caused by the undesired partial deprotection of the benzyl group in 11 and/or 12 during the N-deformylation reaction. Proton nuclear magnetic resonance (1H-NMR) measurements of the reaction solution in the course of the reaction revealed no sign of debenzylation. This fact indicated that the presence of an aldehyde group in the phenyl substituent of 11 might be responsible for the unsatisfactory N-deformylated cyclization. Therefore, we changed the substrate from 11 to an ester derivative 14, which was expected to produce an oxobase 4 in this V. H. type N-deformylation reaction.

We\(^9\) have already established a general and practical transformation of norbases into the corresponding oxobases through dihydrobenzof[c]phenanthridine bases, quaternary bases and 6-cyano-5, 6-dihydrobenzof[c]phenanthridine bases (Ψ-cyanides) by four reaction steps: reductive N-alkylation, dehydrogenation, cyanation and oxidation. In order to prepare an authentic sample the quaternary base 12\(^8\) was firstly converted into the oxobase 4 in high yield by treatment with potassium cyanide followed by air-oxidation of the formed Ψ-cyanide 15 under basic conditions.

Oxidation\(^10\) of 11 with sodium chloride–hydrogen peroxide in sodium hydrogen phosphate buffer solution followed by methylation afforded the methyl ester 14 in good yield. Application of the newly developed N-deformylation reaction to 14 gave the oxobase 4 in 95% yield, and this could be easily debenzylated by catalytic hydrogenation to yield a phenolic oxobase 16. Independently, the same treatment of the methyl ester 17 afforded oxochelerythrine (5), also in high yield (Chart 2). Thus, we have succeeded in establishing a useful and convenient route for the preparation of chelerythrine-type oxobenzof[c]phenanthridine alkaloids by applying the V. H. type N-deformylation reaction.

**Experimental**

All melting points were measured on a micro melting-point hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded for Nujol mulls on a Hitachi 260-10 or JASCO IR-700 spectrophotometer. 1H-NMR spectra were recorded in CDCl3 solution with a JEOL JNM GX-270 or GSX-400 or -500s spectrometer, unless otherwise stated, with tetramethylsilane as an internal reference. Electron-impact mass spectra (EIMS) were recorded on a Hitachi M-60 spectrometer with direct inlet system. For column and flash chromatography, Silica gel 60 (70–230 mesh ASTM; Merck) and Silica gel 60 (230–400 mesh ASTM; Merck) were used, while for TLC and preparative TLC (PLC), DC-Fertigplatten Sil-G 25 UV254 (Macherey-Nagel) and Silica gel GF254 (Merck) were used. In general, the extract was washed with brine, dried over magnesium sulfate, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise stated.

![Chart 2](image-url)
(5H, m, CH2-PH), 7.73 (1H, d, J = 5.4 Hz, 4-H), 8.10 and 8.29 (total 1H, s, NCH3). MS m/z: 465 (94%, M+), 91 (100%). Anal. Calcd for C28H28N6O4: C, 74.82; H, 4.88; N, 3.01. Found: C, 74.64; H, 4.88; N, 2.89.

Direct Preparation of the Benzyl Ether 6 from the Methyl Ether 6: (a) Through Demethylation with TMSI in Quinoline TMSI (0.27 ml, 1.87 mmol) was added to a solution of 6 (0.499 g, 1.28 mmol) in quinoline (7.5 ml) at 100 °C under argon and the mixture was stirred at 180 °C. After 16 h, additional TMSI (0.17 ml, 0.44 mmol) was added, and the reaction mixture was stirred at the same temperature for 0.5 h. After work-up as above, the crude 7 (0.448 g) was benzylated using K2CO3 (0.355 g, 2.57 mmol), benzyl chloride (0.22 ml, 1.93 mmol) and DMF (15 ml) to give 8 (0.327 g, 55%).

(b) Through Demethylation with TMSI-Cl in MeCN TMSI (0.27 ml, 1.87 mmol) was slowly added to a suspension of 6 (0.600 g, 1.57 mmol) and NaCl (0.34 g, 0.015 mol) in MeCN (3 ml) at 0 °C. The mixture was added to a suspension of NaOH (0.29 g, 0.01 mol) in water (3 ml) at 0 °C. After 0.5 h, 8 (0.327 g, 55%) was isolated and the crude product was recrystallized from chloroform-methanol.

A mixture of the acid, dimethyl sulfate and potassium carbonate in DMF was stirred at room temperature for 10 min. Work-up gave an ester formamide, which was recrystallized from chloroform–methanol.

(a) 2-(4-Benzoyloxy-3-methoxy-2-methoxycarbonylphenyl)-6,7-methylenedioxy-1-(N-methylformimidoo)napthalene (14) For oxidation of 11 (0.070 g, 0.15 mmol), MeCN (2 ml), a solution of sodium phosphate monobasic dihydrate (0.005 g, 0.03 mmol) in water (0.1 ml), 30% (v/v) H2O2 (0.7 ml) and a solution of sodium chloride (0.022 mmol) in water (0.1 ml) were used. Work-up afforded a carboxylic acid (0.072 g, quant.) as colorless prisms, mp 265–267 °C. IR νmax cm−1: 1716, 1632 (CO).

For esterification of the acid (0.050 g, 0.10 mmol), dimethyl sulfate (0.011 ml, 0.11 mmol), K2CO3 (0.034 g, 0.24 mmol) and DMF (2 ml) were used. Work-up gave 14 (0.047 g, 92%) as colorless prisms, mp 179–180 °C. IR νmax cm−1: 3359, 1719, 1670 (CO). Anal. Calcd for C29H26N2O6: C, 70.35; H, 4.98; N, 2.80. Found: C, 70.28; H, 4.97; N, 2.85.

(b) 2-(3,4-Dimethoxy-2-methoxycarbonylphenyl)-6,7-methylenedioxy-1-(N-methylformimidoo)napthalene (17) For oxidation of 2 (0.080 g, 0.20 mmol), MeCN (2 ml), a solution of sodium phosphate monobasic dihydrate (0.006 g, 0.04 mmol) in water (0.1 ml), 30% hydrogen peroxide (0.01 ml) and a solution of sodium chloride (0.028 g, 0.31 mmol) in water (0.1 ml) were used. Work-up afforded an acid (0.079 g, 94%) as colorless prisms, mp 281–283 °C. IR νmax cm−1: 1716, 1632 (CO).

For esterification of the acid (0.072 g, 0.19 mmol), dimethyl sulfate (0.022 ml, 0.21 mmol), K2CO3 (0.063 g, 0.45 mmol) and DMF (1 ml) were used. Work-up gave 17 (0.073 g, 92%) as colorless prisms, mp 201–203 °C. IR νmax cm−1: 1730, 1667 (CO). IR νmax cm−1: 3280–3000 (3H × 2.5), br, NMe), 3.01 (3H × 3.5), s, NMe), 3.55 and 3.38 (3H, s, OMe), 3.91, 3.92 and 3.94 (3H, s, OMe × 2), 6.05 and 6.08 (each 1H × 2.5), d, J = 0.9 Hz, OCH3, 6.09 (2H × 3.5, s, OCH3), 6.87 (1H, d, J = 8.5 Hz, S-H), 6.99 and 6.98 (1H, d, J = 8.5 Hz, 6-H), 6.98 and 7.05 (1H, total 1H, s, H8), 7.16 and 7.18 (1H, total 1H, s, H8), 7.22 and 7.24 (total 1H, d, J = 8.5 Hz, 4-H), 7.63 and 7.65 (total 1H, d, J = 8.5 Hz, 5.8), 8.10–8.20 (1H × 3.5, br, NCHO), 8.33 (1H × 2.5, s, NCHO). MS m/z: 499 (100%, M+), 223 (100%). Anal. Calcd for C30H24N2O6: C, 65.24; H, 5.06; N, 3.31. Found: C, 65.02; H, 4.89; N, 3.89.

8-Benzylxy-6-cyano-7-methoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[e]phenanthridine (15) According to the reported methoda a mixed solution of 12 (0.280 g, 0.66 mmol) in water (56 ml) and MeOH (28 ml) was treated with potassium cyanide (0.101 g, 1.55 mmol) at 50°C for 1.5 h. Work-up gave 15 (0.227 g, 70%) as colorless prisms (from chloroform-methanol), mp 235–237 °C. IR νmax cm−1: 3280–3000 (3H × 2.5), br, NMe), 3.01 (3H × 3.5), s, NMe), 3.55 and 3.38 (3H, s, OMe), 3.91, 3.92 and 3.94 (3H, s, OMe × 2), 6.05 and 6.08 (each 1H × 2.5), d, J = 0.9 Hz, OCH3, 6.09 (2H × 3.5, s, OCH3), 6.87 (1H, d, J = 8.5 Hz, S-H), 6.99 and 6.98 (1H, d, J = 8.5 Hz, 6-H), 6.98 and 7.05 (1H, total 1H, s, H8), 7.16 and 7.18 (1H, total 1H, s, H8), 7.22 and 7.24 (total 1H, d, J = 8.5 Hz, 4-H), 7.63 and 7.65 (total 1H, d, J = 8.5 Hz, 5.8), 8.10–8.20 (1H × 3.5, br, NCHO), 8.33 (1H × 2.5, s, NCHO). MS m/z: 499 (514, 100%), 223 (100%). Anal. Calcd for C30H23N2O6: C, 65.24; H, 5.06; N, 3.31. Found: C, 65.02; H, 4.89; N, 3.89.

8-Benzylxy-7-methoxy-5-methyl-2,3-methylenedioxybenzo[e]phenanthridine (6(5H)-one (4) According to the reported methoda a solution of 3 (0.155 g, 0.49 mmol) in hexamethylphosphoramide (11 ml) was treated with sodium hydride (52.9%, 0.155 g, 3.42 mmol) at room temperature for 5.5 h. After work-up, purification of the crude product
by PLC with benzene-ethyl acetate (2:1, v/v) gave 4 (0.176 g, 82%) as colorless prisms (from chloroform-methanol), mp 190–192°C. IR (KBr, cm⁻¹): 1640 (C=O). ¹H-NMR (60 MHz) δ: 3.87 (3H, s, NMe), 4.11 (3H, s, OMe), 5.22 (2H, s, OCH₂Ph), 6.04 (2H, s, OCH₂O), 7.09 (1H, s, 1-H), 7.30–7.70 (8H, m, ArH). 7.86 (1H, d, J = 9.0 Hz, 10- or 11-H), 7.90 (1H, d, J = 9.1 Hz, 11- or 10-H). Anal. Calcd for C₁₇H₁₄NO₇: C, 73.79; H, 4.82; N, 3.19. Found: C, 73.56; H, 4.84; N, 3.17.

N-Decacylation of Carboxamides A 30% solution (w/v) of a carboxamide in either chloroform or dichloromethane was treated with 1,3-dimethoxybenzene and POCl₃ under the conditions shown in Table 2. When the starting material was no longer detectable on TLC, the reaction mixture was treated with 5% aqueous sodium hydroxide in ethanol at room temperature. After extraction, the extract was repeatedly washed with 5% hydrochloric acid. The washings were combined and basified with 5% aqueous sodium hydroxide. Work-up gave the corresponding amine.

(a) The Oxabase 4 As above, a solution of 14 (0.040 g, 0.08 mmol) in chloroform (0.5 ml) was treated with 1,3-dimethoxybenzene (0.014 ml, 0.09 mmol) and POCl₃ (0.01 ml, 0.10 mmol) at 40°C for 1 d. After hydrolysis, recrystallization of the crude product from chloroform-methanol gave 4 (0.034 g, 95%) as colorless prisms, mp 189–190°C. This product was identical with the sample prepared above.

(b) Oxocheletrythrine (5) As above, a solution of 17 (0.050 g, 0.12 mmol) in chloroform (0.5 ml) was treated with 1,3-dimethoxybenzene (0.017 ml, 0.13 mmol) and POCl₃ (0.013 ml, 0.14 mmol) at 60°C for 1 d. After hydrolysis, recrystallization of the crude product from chloroform-methanol gave 5 (0.040 g, 93%) as colorless prisms, mp 192–194°C (lit.

8-Hydroxy-7-methoxy-5-methyl-2,3-methylenedioxybenzo[c]phenanthridin-6(5H)-one (16) A suspension of 4 (0.050 g, 0.14 mmol) and 5% Pd-C (0.056 g) in ethanol (50 ml) was hydrogenated at room temperature and atmospheric pressure until the reaction ceased. After removal of the catalyst by filtration, the filtrate was evaporated. Recrystallization of the residue afforded colorless prisms (0.035 g, 88%), mp 225–228°C. IR (KBr, cm⁻¹): 3200 (OH), 1630 (CO). ¹H-NMR (CDCl₃ + CD₂OD) δ:

References and Notes
11. The ¹H-NMR spectrum showed a complex signal pattern due to the presence of a tautomeric ring-opened phenolic ketone.