Xanthone in synthesis: a reactivity profile via directed lithiation of its dimethyl ketal

Michal R. Odrowaz-Sypniewski a, Petros G. Tsoungas b,*, George Varvounis c, Paul Cordopatis a

a Department of Pharmacy, University of Patras, 265 00 Patras, Greece
b Ministry of Development, Messogion 14-16, 115 10 Athens, Greece
c Department of Chemistry, University of Ioannina, 451 10 Ioannina, Greece

ARTICLE INFO

Article history:
Received 13 March 2009
Revised 16 May 2009
Accepted 14 August 2009
Available online 21 August 2009

Keywords:
Xanthone
Lithiation
Methylation
Dimethyl ketal

ABSTRACT

Xanthone, as its dimethyl ketal, undergoes functionalization with a synthetically useful degree of regioselectivity using a lithiation protocol. The core structure is regenerated during the work-up. Monosubstitution at C-4 or C-1 and disubstitution at C-4 and C-5 or C-1 and C-5 are observed. The substitution pattern appears to be dependent upon the experimental conditions.

Xanthone 1 is a common structure in Nature. Many of its derivatives bearing methyl, hydroxy, methoxy or phenyl groups, or those possessing complex polycyclic frameworks, have been isolated from twenty families of higher plants, fungi and lichens. 1 It is also found in many natural products or other molecules exhibiting a broad spectrum of biopharmacological activities.2 Xanthone is usually assembled from its constituent fragments to form the middle pyranone ring.3 Other less commonly used methods have also been reported.4 Despite the numerous reports and continuous interest in the synthesis of 1, including linearly or angularly fused, carbocyclic or N,O-heterocyclic derivatives and their applications,5 its reactivity profile has not enjoyed equally deserved attention. Looking at the structure of 1, certain features are evident: (a) two benzene rings are fused to a pyran-4-one ring, (b) the benzene rings are identical, thus imparting symmetry elements to the structure, (c) C-1 (or C-8) and C-4 (or C-5) are acidic sites6 and (d) either or both rings are susceptible to electrophilic substitution, facilitated and directed by the pyran oxygen on the one hand, while hindered by the carbonyl group, on the other hand. Manipulation allows varying substitution patterns to be accessible. The advantage of this approach is to provide simpler, shorter and more efficient (in certain cases) access to derivatives of 1. During the synthesis of xanthone frameworks the core is usually constructed at a late stage of the reaction sequence. This, presumably, minimizes potential side reactions at the carbonyl group, which is known to be susceptible to reduction (partial or complete)7 or nucleophilic attack, if alkyl[aryl]lithium reagents8 are used.

We report herein, a lithiation–methylation protocol developed in order to demonstrate the reactivity profile of 1 through various substitution patterns. Lithiation was chosen as a means to introduce functionalities. Either the ring or carbonyl oxygen atoms can act as potential coordination sites, thus directing, in principle, metallation to all possible peri positions. Indeed, this approach has been applied to 9,9-dimethylxanthene 2.7a To be able to perform lithiation directly onto 1 would be an ideal one-step process with clear-cut advantages of synthetic value. A set of experiments were accordingly performed but the identity of the isolated products, their tedious isolation and their low yields discouraged further attempts along this line. Eventually, attention was focused on suitable protection of the carbonyl group such that, (a) it could be removed easily, ideally during the work-up stage, and (b) it would not interfere in the lithiation.

* Corresponding author. Tel.: +30 210 775 3050; fax: +30 210 771 3810.
E-mail address: pgt@gsrt.gr (P.G. Tsoungas).

doi:10.1016/j.tetlet.2009.08.050
Aminoalkoxide 3 (prepared in situ) was used as an intermediate but work-up showed no appreciable conversion into 1. Attempts to functionalize xanthodrol 4 were also in vain. In the light of these unsuccessful trials it was decided that 1 be protected as its ketal 5,8 and then subjected to lithiation conditions. Since 1 is not a conventional ketone,9 its ketal can only be obtained indirectly via 9,9-dichloroxanthene 6 by reaction with sodium methoxide. While 6 is stable enough to handle, it is also extremely labile to acidic hydrolysis to regenerate the xanthone core structure. By using acidic hydrolysis to regenerate the xanthone core structure. By using 5, the acidity at C-1 (or C-8) is removed, but at the same time, a coordination centre is introduced at the same position despite the tetrahedral arrangement at C-9. In preliminary experiments lithiation conditions similar to those used for the lithiation of xanthone 7 were applied (Scheme 1). After quenching with excess methyl iodide, 1,5-dimethylxanthone 7 was obtained accompanied by large quantities of tars. As the yield of the isolated product 7 was not satisfactory, a set of experiments was performed in the hope of improving the yield and to better control the lithiation leading to monosubstitution. The parameters varied were temperature, base (n-BuLi, sec-BuLi, t-BuLi), molar ratio of base to 5 and reaction time. In our hands, very low temperatures (−78 °C), and long reaction times as often applied in lithiations did not favour functionalization of 5. However, at higher temperatures, deprotonation appeared to be quite fast. Around −10 °C, after relatively short reaction times (45 min) and using a sixfold excess of t-BuLi in tetrahydropyran (THP) and quenching with an excess of methyl iodide, 1,5-dimethyl-9H-xanthene-9-one 7 was isolated in 31% yield, (Scheme 1, Table 1, entry 1).

When a lower excess of base was used C-4 lithiation was the predominating process and 4-methyl-xanthone 8 was isolated by flash column chromatography as the major product (61%) (Scheme 2).

A mixture containing 1,5-dimethylxanthone 7 and 1-methylxanthone 9 was formed along with 8 but only small quantities of each, enough for spectroscopic analysis, were obtained (Scheme 2, Table 1, entry 2).

The results indicate that: (a) the primary substitution site is C-4 (C-5) and the secondary site is C-1, (C-8), (b) double deprotonation occurs sequentially and the product ratio depends mainly on base stoichiometry. Attack of the base at C-1 (C-8) is, we believe, driven by coordination of lithium with the methoxy groups. To test this hypothesis and suppress the process, a Lewis acid such as MgBr2 was used as an additive during lithiation. This approach did not improve the regioselectivity. However, another modification of the reaction conditions partially solved our problems. Use of the super base LICKOR (t-BuLi/t-BuOK) has a strong effect on the regioselectivity of the substitution pattern. Accordingly, primary substitution is directed at C-4 and secondary substitution occurs this time at C-5. No substitution at C-1 (C-8) was observed. Thus when three equivalents of LICKOR was used, the yield of 4,5-dimethylxanthone 10 exceeded 80% (Scheme 3, Table 1, entry 3).

The use of a lower excess of LICKOR (e.g., 1.5 equiv) led to a mixture of 8, 10 and unreacted 1. Following the established protocol, other functional groups were introduced with yields ranging from moderate to excellent (Table 1, entries 4–11).

Although the aforementioned substitution pattern is generally followed, the regioselectivity of reactions following procedure B was seriously affected, for example, the halogenation. This may tentatively be attributed to halogen-lithium exchange,15 rather than sequential lithiation. Inconsistency in reactivity patterns has been reported in the literature for a number of lithiation reactions.16 The observed results, in our hands, with the probable exception of halogenation, may well be the outcome of carbanion generation in sequence. The pyran oxygen, through its acidifying effect, facilitates carbanion generation predominantly at C-4 and/or C-5 while the coordinating effect of its lone pair directs the lithiation at those positions. Weaker coordinating interactions, appar-

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Lithiation procedure11</th>
<th>Product</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>R1</td>
<td>R2</td>
</tr>
<tr>
<td>1</td>
<td>CH3I</td>
<td>A</td>
<td>CH3</td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>CH3I</td>
<td>B</td>
<td>H</td>
<td>CH3</td>
</tr>
<tr>
<td>3</td>
<td>CH3I</td>
<td>C</td>
<td>H</td>
<td>CHO</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>B</td>
<td>CONEt2</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>Et2NCl</td>
<td>B</td>
<td>CONEt2</td>
<td>H</td>
</tr>
<tr>
<td>6</td>
<td>I2</td>
<td>A</td>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>I2</td>
<td>B</td>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>Me3SiCl</td>
<td>A</td>
<td>H</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>Me3SiCl</td>
<td>C</td>
<td>SiMe3</td>
<td>H</td>
</tr>
<tr>
<td>10</td>
<td>Me3SiCl</td>
<td>C</td>
<td>H</td>
<td>SiMe3</td>
</tr>
<tr>
<td>11</td>
<td>D3O</td>
<td>C</td>
<td>H</td>
<td>D</td>
</tr>
</tbody>
</table>

* Yield refers to isolated product. Flash chromatography was used for product separation.
* Products of C1-monosubstitution and C1, C5-disubstitution isolated but not quantitatively (just enough material to record the NMR spectrum).
* Products of C1-monosubstitution and C1, C5-disubstitution observed in the 1H NMR spectrum of the crude reaction mixture, but not isolated.

Scheme 1. Lithiation according to procedure A.11 Reagents and conditions: (i) t-BuLi (6 equiv)/THP, −10 °C, 45 min; (ii) CH3I and (iii) H+H2O.
Reagents and conditions: (i) t-BuLi (1.5 equiv)/THP, –13 °C, 30 min; (ii) CH\textsubscript{3}I and (iii) H\textsubscript{2}O\textsubscript{2}.

Scheme 2. Lithiation according to procedure B.\textsuperscript{13} Reagents and conditions: (i) t-BuLi (3 equiv), t-BuOK (3 equiv)/THP, –13 °C, 30 min; (ii) CH\textsubscript{3}I and (iii) H\textsubscript{2}O\textsubscript{2}.

Reagents and conditions: (i) t-BuLi (3 equiv), t-BuOK (3 equiv)/THP, –13 °C, 30 min; (ii) CH\textsubscript{3}I and (iii) H\textsubscript{2}O\textsubscript{2}.

Current Medicinal Chemistry, 2005, 12, 2481.
and references cited therein; (g) Peras, V.; Nagel, T. J. Phytocchemistry 1997, 44, 191.
and references cited therein; (h) Peras, V.; Nagel, T. J.; De Oliveira, F. F. Phytocchemistry 2000, 55, 683.
and references cited therein.

References and notes

and references cited therein; (g) Peras, V.; Nagel, T. J. Phytocchemistry 1997, 44, 191.
and references cited therein; (h) Peras, V.; Nagel, T. J.; De Oliveira, F. F. Phytocchemistry 2000, 55, 683.
and references cited therein.


and references cited therein.


6. Based on a report (Abrams, S. R. J. Labelled Compds. Radiopharm. 1978, 24, 9411) that can be verified at C-1 and C-4 by the KBr tecate. Nevertheless, the technical aspects of the transition state structure, in concert with the electrophile, or there is a stabilizing lithium-substituent interaction\textsuperscript{18} at the rate-limiting transition structure, is in question.

In conclusion, the reactivity profile of 1 has been investigated via directed lithiation of its ketal 5. The protocol developed allows mono or disubstitution, directly and with synthetically useful regioselectivity, the latter being dependent upon the nature of the electrophile. Disubstitution offers the advantage of incorporating identical functionalities in one-step. The synthetic utility of the protocol rests upon two elements of tactical significance: (a) the use of xanthone, masked as its dimethyl ketal, rapidly regenerating the core structure upon work-up, and (b) manipulation of the reaction conditions leading to regioselectivity. The substitution patterns so obtained provide access to various transformations such as annellation or cleavage of the xanthone structure, ultimately leading to diverse heterocycles.\textsuperscript{19} In this respect, the protocol is a valuable addition to the existing armory of indirect approaches to xanthone derivatives. Further work along this line is in progress and will be reported in due course.

Acknowledgements

Financial support from the General Secretariat of Research and Technology through the Programme ENTER and elemental analyses from Dr. L. Leontiadis’s Laboratory, ‘Demokritos’ Research Centre are gratefully acknowledged.

Supplementary data

Supplementary data (experimental procedures and full characterization of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.050.