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

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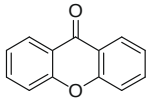
ABSTRACT

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 bio(pharmaco)logical 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 sites[6] 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 reagents[8] are used.



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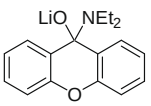
We report herein, a lithiation–methylation protocol developed in order to demonstrate the reactivity profile of **1** through various substitution patterns. Lithiation was chosen as a means to introduce functionalities. Either the ring or carbonyl oxygen atoms can act as potential coordination sites, 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.



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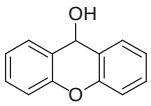

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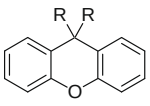

R= Me (**2**); OMe, (**5**); Cl, (**6**)

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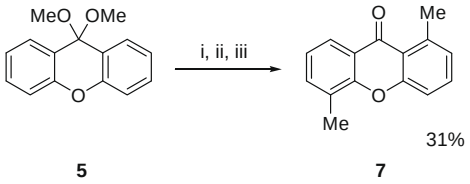
Aminoalkoxide **3** (prepared in situ) was used as an intermediate but work-up showed no appreciable conversion into **1**. Attempts to functionalize xanthydrol **4** were also in vain. In the light of these unsuccessful trials it was decided that **1** be protected as its ketal **5**,[9b] and then subjected to lithiation conditions. Since **1** is not a conventional ketone,[10] its ketal can only be obtained indirectly via 9,9-dichloroxanthene **6**[9] 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 **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 9,9-dimethylxanthene **2**[7b] 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-9*H*-xanthen-9-one **7** was isolated in 31% yield, (Scheme 1, Table 1, entry 1).



Scheme 1. Lithiation according to procedure A.[11] Reagents and conditions: (i) *t*-BuLi (6 equiv)/THP, −10 °C, 45 min; (ii) CH_3I and (iii) $H+/H_2O$.

When a lower excess of base was used C-4 lithiation was the predominating process and 4-methyl-xanthone **8**[12] was isolated by flash column chromatography as the major product (61%) (Scheme 2).

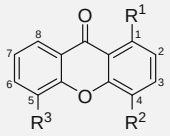
A mixture containing 1,5-dimethylxanthone **7** and 1-methylxanthone **9**[13] was formed along with **8** but only small quantities of each, enough for spectroscopic analysis, were obtained (Scheme 2, Table 1, entry 2).

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 $MgBr_2$ 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).

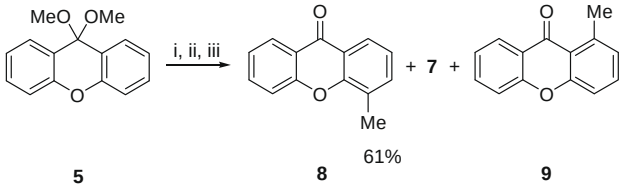
The use of a lower excess of LiCKOR (e.g., 1.5 equiv) led to a mixture of **8**, **10** and unreacted **1**. Following the established protocol, other functional groups were introduced with yields ranging from moderate to excellent (Table 1, entries 4–11).

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-

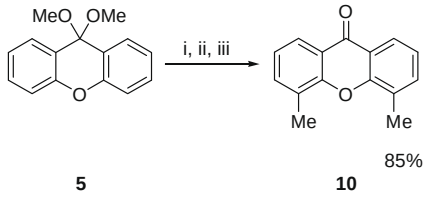
Table 1
Functionalization of xanthone (**1**) via lithiation of its dimethyl ketal (**5**) and subsequent electrophilic quench

Entry	Electrophile	Lithiation procedure[11]	Product				Yield[a] (%)
			R^1	R^2	R^3		
1	CH_3I	A	CH_3	H	CH_3	**7**	31
2	CH_3I	B	H	CH_3	H	**8**	61[b]
3	CH_3I	C	H	CH_3	CH_3	**10**	85
4	DMF	B	H	CHO[14]	H	**11**	50[c]
5	Et_2NCOCl	B	$CONEt_2$	H	H	**12**	27
			H	$CONEt_2$	H	**13**	38
			$CONEt_2$	H	$CONEt_2$	**14**	15
6	I_2	A	I	H	I	**15**	28
7	I_2	B	I	H	H	**16**	29
			H	I	H	**17**	34
			I	H	I	**18**	8
8	I_2	C	H	I	I	**19**	67
9	Me_3SiCl	A	$SiMe_3$	H	$SiMe_3$	**10**	41
10	Me_3SiCl	C	H	$SiMe_3$	$SiMe_3$	**20**	69
11	D_2O	C	H	D	D	**21**	89

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



Scheme 2. Lithiation according to procedure B.[11]Reagents and conditions: (i) *t*-BuLi (1.5 equiv)/THP, −13 °C, 30 min; (ii) CH_3I and (iii) $H+/H_2O$.



Scheme 3. Lithiation according to procedure C.[11]Reagents and conditions: (i) *t*-BuLi (3 equiv), *t*-BuOK (3 equiv)/THP, −13 °C, 30 min; (ii) CH_3I and (iii) $H+/H_2O$.

ently emanating from the ketal oxygen lone electron pairs may account for C-1 (C-8) substitution. Deuteration, however (Table 1, entry 11) suggests that the reaction may have well proceeded via a 4,5-dilithio species. During the lithiation there is competition among the lithiated species, the base and the electrophile. Whether a prelithiation complex[17] is involved, whose stability is compared against that of the transition state structure, in concert with the electrophile, or there is a stabilizing lithium-substituent interaction[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 annelation onto or cleavage of the xanthone structure, ultimately leading to diverse heterocycles.[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.

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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.

References and notes

1. For recent reviews, see: (a) Vieira, L. M. M.; Kijjoa, A. *Curr. Med. Chem.* **2005**, *12*, 2413. and references cited therein; (b) Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, *12*, 2447. and references cited therein; (c) Silva, A. M. S.; Pinto, D. C. G. A. *Curr. Med. Chem.* **2005**, *12*, 2481. and references cited therein; (d) Gales, L.; Damas, A. M. *Curr. Med. Chem.* **2005**, *12*, 2499. and references cited therein; (e) Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517. and references cited therein; (f) Riscoe, M.; Kelly, J. X.; Winter, R. *Curr. Med. Chem.* **2005**, *12*, 2539. and references cited therein; (g) Peras, V.; Nagem, T. J. *Phytochemistry* **1997**, *44*, 191. and references cited therein; (h) Peras, V.; Nagem, T. J.; De Oliveira, F. F. *Phytochemistry* **2000**, *55*, 683. and references cited therein; (i) Potterat, O. *Curr. Org. Chem.* **1997**, *1*, 415. and references cited therein.
2. (a) Bennett, G. J.; Lee, H. *Phytochemistry* **1989**, *28*, 967; (b) Afzal, M.; Al-Hassan, J. M. *Heterocycles* **1980**, *14*, 1173; (c) Sutanbawa, M. U. S. *Tetrahedron* **1980**, *36*, 1465; (d) Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C.; Boyad, M.; Thomsen, L. L.; Zhuang, L.; Denny, W. A. *J. Med. Chem.* **1991**, *34*, 2864. and references cited therein; (e) Jackson, W. T.; Boyd, R. J.; Froelich, L. L.; Gapinski, D. D.; Mallet, B. E.; Sawyer, J. S. *J. Med. Chem.* **1993**, *36*, 726; (f) Sun, L.; Liebeskind, L. S. *Tetrahedron Lett.* **1997**, *38*, 3663; (g) Hostettmann, K.; Hostettmann, M.. In *Methods in Plant Biochemistry*; Harborne, J. B., Ed.; Academic Press: London, 1989; Vol. l, p 493; (h) Sordat-Diserens, I.; Marston, A.; Hamburger, M.; Rogers, C.; Hostettmann, K. *Helv. Chim. Acta* **1989**, *72*, 1001; (i) Sordat-Diserens, I.; Humburger, M.; Rogers, C.; Hostettmann, K. *Phytochemistry* **1992**, *31*, 3589; (j) Ferrari, F.; Pasqua, G.; Moracelli, B.; Cimino, P.; Botta, B. *Nat. Prod. Res.* **2005**, *19*, 171.
3. Casillas, L. K.; Townsend, C. A. *J. Org. Chem.* **1999**, *64*, 4050. and references cited therein.
4. (a) Chandrasekhar, B.; Ramadar, S. R.; Ramana, D. V. *Tetrahedron* **2000**, *56*, 5947; (b) Sun, L.; Liebenskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 12473; (c) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081; (d) Kristensen, J. L.; Vedso, P.; Begtrup, M. *J. Org. Chem.* **2003**, *68*, 4091; (e) Thasana, N.; Ruchirawat, S. *Synlett* **2003**, 1037; (f) Hauser, F. M.; Dorch, W . A. *Org. Lett.* **2003**, *5*, 3753; (g) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551; (h) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288; (i) Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233.
5. (a) Ghosh, C. K.; Sahana, S.; Patra, A. *Tetrahedron* **1993**, *49*, 4127; (b) Lecheter, R. M.; Yue, T.-Y.; Cheung, K.-K. *J. Chem. Soc., Chem. Commun.* **1993**, 159; (c) Gabutt, C. D.; Hepworth, J. D.; Urquhart, M. W. J.; Vazquez de Miguel, L. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1547; (d) Kristensen, J. L.; Vedso, P.; Begtrup, M. *Tetrahedron* **2002**, *58*, 2397; (e) Tisdale, E. J.; Kochman, D. A.; Theodorakis, E. *Tetrahedron Lett.* **2003**, *44*, 281; (f) Kolokythas, G.; Pouli, N.; Marakos, H.; Pratsinis, H.; Kletsas, D. *Eur. J. Med. Chem.* **2006**, *41*, 71; (g) Henry, K. M.; Townsend, C. A. *J. Am. Chem. Soc.* **2005**, *127*, 3300; (h) Henry, K. M.; Townsend, C. A. *J. Am. Chem. Soc.* **2005**, *127*, 3724.
6. Based on a report (Abrams, S. R. *J. Labelled Compds. Radiopharm.* **1978**, *24*, 941) **1** can be deuterated at C-1 and C-4 by the K, but not the Li salt, of *N*,*N*,*N*′,*N*′-d^4-1,3-diaminopropane. C-4 proved to be the most readily deprotonated site.
7. (a) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902; (b) McWilliams, K.; Kelly, J. W. *J. Org. Chem.* **1996**, *61*, 7408; (c) Galt, R. H. B.; Horbury, J.; Matusiak, Z. S.; Pearce, R. J.; Shaw, J. S. *J. Med Chem.* **1989**, *32*, 2357; (d) Gilman, H.; Diehl, J. *J. Org. Chem.* **1961**, *26*, 4817; (e) Coelho, P. J.; Carvalho, L. M.; Silva, J. C.; Oliveira-Campos, A. M. F.; Samat, A.; Guglielmetti, R. *Helv. Chim. Acta* **2001**, *84*, 117; (f) Clayden, J.; Kenworthy, M. N.; Youssef, L. H.; Helliwell, M. *Tetrahedron Lett.* **2000**, *41*, 5171.
8. (a) Halton, B.; Cooney, M. J.; Boese, R.; Maulitz, A. H. *J. Org. Chem.* **1998**, *63*, 1583; (b) Martin, J. C.; Smith, R. G. *J. Am. Chem. Soc.* **1964**, *86*, 2252.
9. (a) Reese, C. B.; Song, Q.; Yan, H. *Tetrahedron Lett.* **2001**, *42*, 1789; (b) Reese, C. B.; Yan, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1807.
10. Ho, D. K.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M. *J. Org. Chem.* **1987**, *52*, 342.
11. *General lithiation procedure according to methods A and B*: 9,9-Dimethoxyxanthene (**5**) (500 mg, 2 mmol) was dissolved in dry tetrahydropyran (2 mL) (method A); (4 mL) (method B). After cooling to −10 °C (method A); −40 °C (method B), *t*-BuLi solution (7.0 mL, of 1.7 mol/L, 12 mmol) (method A); (1.76 mL, of 1.7 mol/L, 3 mmol) (method B) in hexanes was added over a period of 2 min, while the temperature was maintained between −10 and 0 °C (method A); −40 and −30 °C (method B). Stirring was continued at 0 to 10 °C over 45 min (method A); at −40 to −30 °C over 30 min (method B). Next, the reaction mixture was quenched with the appropriate electrophile while the temperature was maintained as given above, then poured into water (50 mL), acidified to pH 3 with aqueous HCl and extracted with ethyl acetate (3 × 15 mL). The products were isolated by flash column chromatography on silica.*General lithiation procedure according to method C*: 9,9-Dimethoxyxanthene (**5**) (500 mg, 2 mmol) and *t*-BuOK (6 mmol) were dissolved in dry tetrahydropyran (6 mL). After cooling to −40 °C, *t*-BuLi solution (3.5 mL, of 1.7 mol/L, 6 mmol) in hexanes was added over a period of 2 min, and the temperature was maintained between −40 and −30 °C. The rest of the procedure was identical with procedure B.
12. Blake, J. A.; Gagnon, E.; Lukeman, M.; Scaiano, J. *Org. Lett.* **2006**, *8*, 1057.
13. Pickert, M.; Frahm, A. W. *Archiv. Pharm.* **1998**, *331*, 177.
14. Valenti, P.; Chiarini, A.; Gasperi, F.; Budriesi, R. *Arzneim. Forsch.* **1990**, *40*, 122.
15. Schnurch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046.
16. (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *J. Org. Chem.* **2005**, *70*, 1501; (b) Palmer, B. D.; Boyd, M.; Denny, W. A. *J. Org. Chem.* **1990**, *55*, 438; (c) Mortier, J.; Nguyen, T.-H.; Tilly, D.; Castanet, A.-S. *ARKIVOC* **2007**, *6*, 47.
17. Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
18. Van Eikema, N. J. R.; Schleyer, P. V. R. *Tetrahedron* **1994**, *50*, 5903.
19. These features may also prove useful in studies of remote stereocontrol relayed through the ring, see: Clayden, J.; Lund, A.; Vallverdú, L.; Helliwell, M. *Nature* **2004**, *431*, 966.