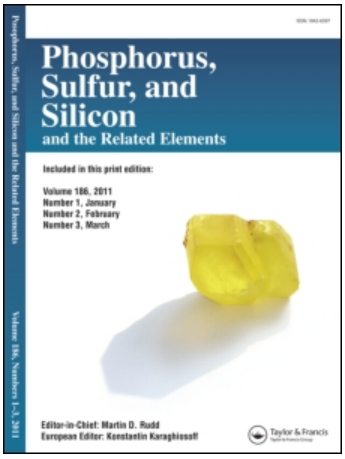


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Aromatic Chlorination with Thionyl Chloride. Applications in the Synthesis of Chlorinated Isoflavones

Otto Soidinsalo[a]; Kristiina Wähälä[a]
[a] Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, Finland

To cite this Article Soidinsalo, Otto and Wähälä, Kristiina(2007) 'Aromatic Chlorination with Thionyl Chloride. Applications in the Synthesis of Chlorinated Isoflavones', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 12, 2761 — 2767
To link to this Article: DOI: 10.1080/10426500701509485
URL: http://dx.doi.org/10.1080/10426500701509485

Phosphorus, Sulfur, and Silicon, 182:2761–2767, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701509485

Taylor & Francis
Taylor & Francis Group

Aromatic Chlorination with Thionyl Chloride. Applications in the Synthesis of Chlorinated Isoflavones

Otto Soidinsalo
Kristiina Wähälä
Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, Finland

*Genistein (**1**) undergoes selective chlorination on treatment with thionyl chloride to give first 8-chlorogenistein (**10**) and then 6,8-dichlorogenistein (**8**). Biochanin A (**18**) gives the 6,8-dichloro derivative **19**. A mechanism is suggested for the unexpected aromatic chlorinations.*

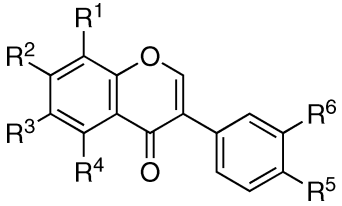
Keywords Biochanin A; chlorination; daidzein; genistein; thionyl chloride; isoflavone

INTRODUCTION

In connection with our recent work on isoflavonoid derivatives, a routine chlorination by thionyl chloride of a genistein (**1**) derivative carrying an *O*-(ω-carboxyalkyl) group in 7-position unexpectedly resulted in concomitant chlorination at C-8, as was clear from the EI mass spectrum and from the ^{1}H and ^{13}C NMR spectra augmented with ^{1}H-^{13}C HMQC and HMBC 2D measurements. Apart from an isolated example in the literature[1] of thionyl chloride apparently acting as a source of Cl^{+} towards hydroxy- and aminophenothiazines, chlorination of phenol derivatives by neat $SOCl_2$ is unknown. Phenol itself is reported[2] to give phenyl chlorosulfinate or diphenyl sulfite in high yield under reflux conditions. At lower temperatures *p*-chlorophenol was isolated at a level of a few percent in addition to much tarry residue. There is also a report[3] of a 3-hydroxypyrrole derivative undergoing chlorination by $SOCl_2$ at C-2. According to the mechanism suggested the reaction proceeds via the sulfinate ester, which delivers a chloride to C-2 and also produces sulfur monoxide.[3]

Received March 26, 2007; accepted June 12, 2007.
Otto Soidinsalo wishes to thank Dr. Jorma Matikainen for guidance in HRMS.
Address correspondence to Kristiina Wähälä, Laboratory of Organic Chemistry, Department of Chemistry, P.O. Box 55, University of Helsinki, 00014 Helsinki, Finland. E-mail: kristiina.wahala@helsinki.fi

As for isoflavones, a 1980 report[4] states that the parent isoflavone (**2**) does not react at all with thionyl chloride, while 7-hydroxyisoflavone (**3**) gives 7-chloroisoflavone (**4**), and 7-methoxyisoflavone (**5**) gives 6-chloro-7-methoxyisoflavone (**6**), both in moderate yields (Scheme 1). Although reaction mechanisms were not discussed in the paper, it seems likely that in some of the above reactions $SOCl_2$ functions as a Cl^- donor while in others it is a Cl^+ donor. Incidentally, chlorination of **3** using sulfuryl chloride gave[4] 6,8-dichloro-7-hydroxyisoflavone (**7**) and a chlorinated isoflavanone, while **5** gave chloroisoflavanones only. These isoflavanones result from the chlorination of the double bond in 2,3-position. In 2003, unidentified mono- and/or dichloroisoflavones were observed to result from the action of *hypochlorous acid* on isoflavones.[5] Very recently a Japanese group reported[6] the formation



		R^1	R^2	R^3	R^4	R^5	R^6
1	genistein	H	OH	H	OH	OH	H
2	isoflavone	H	H	H	H	H	H
3	7-hydroxyisoflavone	H	OH	H	H	H	H
4	7-chloroisoflavone	H	Cl	H	H	H	H
5	7-methoxyisoflavone	H	OMe	H	H	H	H
6	6-chloro-7-methoxyisoflavone	H	OMe	Cl	H	H	H
7	6,8-dichloro-7-hydroxyisoflavone	Cl	OH	Cl	H	H	H
8	6,8-dichlorogenistein	Cl	OH	Cl	OH	OH	H
9	daidzein	H	OH	H	H	OH	H
10	8-chlorogenistein	Cl	OH	H	OH	OH	H
11	3′-chlorogenistein	H	OH	H	OH	OH	Cl
12	6-chlorogenistein	H	OH	Cl	OH	OH	H
13	3′,6-dichlorogenistein	H	OH	Cl	OH	OH	Cl
14	8-chloro-3′,4′,5,7-tetrahydroxyisoflavone	Cl	OH	H	OH	OH	OH
15	3′-chlorodaidzein	H	OH	H	H	OH	Cl
16	8-chlorodaidzein	Cl	OH	H	H	OH	H
17	3′,8-dichlorodaidzein	Cl	OH	H	H	OH	Cl
18	biochanin A	H	OH	H	OH	OMe	H
19	6,8-dichlorobiochanin A	Cl	OH	Cl	OH	OMe	H
20	glycitein	H	OH	OMe	H	OH	H
21	trimethoxygenistein	H	OMe	H	OMe	OMe	H

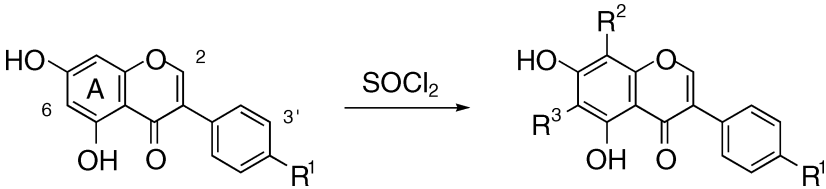
SCHEME 1

of 6,8-dichlorogenistein (**8**) in 10% yield from the HOCl chlorination of genistein (**1**), and of 3′,5′,8-trichlorodaidzein (65%) from a similar reaction of daidzein (**9**). Two *flavones* were reported[7] to give the 3-monochloro derivatives in low yield on treatment with $SOCl_2$, irrespective of the nature of substituents (6-methyl or 7-methoxy). The authors suggest a mechanism involving a flavylium chlorosulfite intermediate and elimination of sulfur monoxide.

Interestingly, a number of chlorinated hydroxyisoflavones are natural products in their own right, as metabolites of the parent hydroxyisoflavones, and possess antioxidant and other biological activity. Known examples include 8-chloro- and 6,8-dichlorogenistein[8] (**10** and **8**, respectively), 3′-chlorogenistein[5] (**11**), 6-chloro- and 3′,6-dichlorogenistein[9] (**12** and **13**, respectively), and 8-chloro-3′,4′,5,7-tetrahydroxyisoflavone[10,11] (**14**). Total synthesis from appropriate chloro-substituted monocyclic starting materials has been published[12] for **14** and, without any experimental or spectroscopic data, for **11** and the daidzeins **15**, **16**, and **17**, which however have not been identified as natural products.[5] As shown below, our examination of the genistein/$SOCl_2$ reaction provides an expedient laboratory synthesis of the bacterially produced[8] chlorinated genisteins **8** and **10**.

RESULTS AND DISCUSSION

We find that the reaction of genistein (**1**) in neat $SOCl_2$ proceeds highly selectively and gives 70% yield of 8-chlorogenistein (**10**), which is readily identified by its EI mass spectrum and ^1H and ^{13}C NMR spectra. Its identity is further confirmed by HMQC and HMBC experiments (Scheme 2). The spectra were also in agreement with those reported



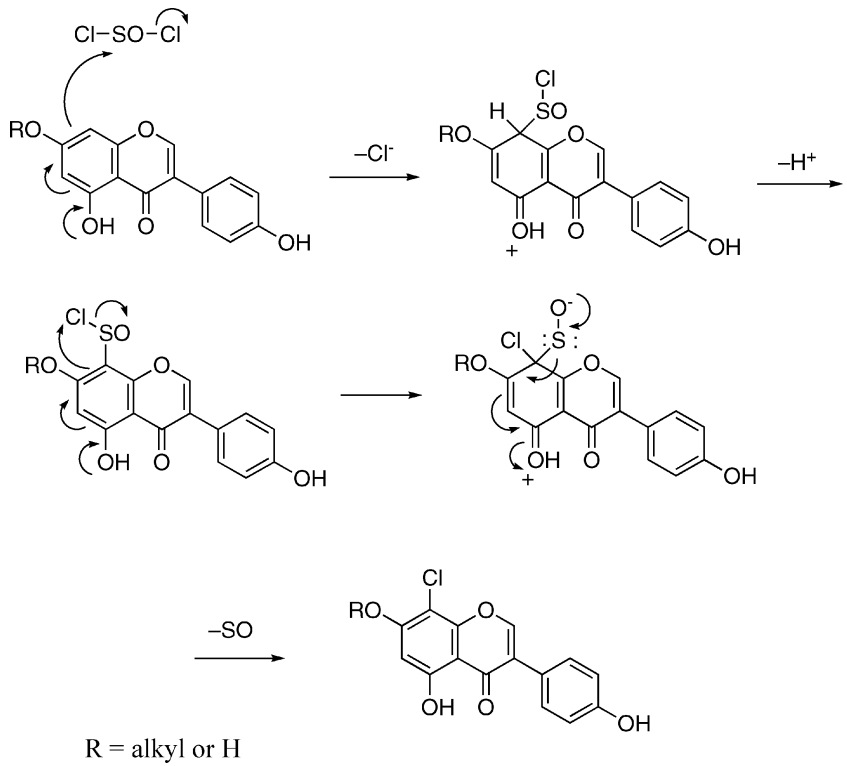
1 genistein $R^1 = OH$
8 6,8-dichlorogenistein $R^1 = OH$, $R^2 = R^3 = Cl$
18 biochanin A $R^1 = OMe$
10 8-chlorogenistein $R^3 = H$, $R^1 = OH$, $R^2 = Cl$
19 6,8-dichlorobiochanin A $R^1 = OMe$, $R^2 = R^3 = Cl$

SCHEME 2

in the literature[8] for the fermentation broth product. The reason for the high selectivity at the position 8 may be explained by the *para* addition with respect to the OH group. Continued reaction with added fresh $SOCl_2$ gives 6,8-dichlorogenistein (**8**) in 60% yield, with the spectral data again in conformity with the (^{13}C incomplete) earlier data.[8] We found that the addition of fresh $SOCl_2$ was necessary in order to achieve the dichlorinated compound. Attempts to speed up the reaction by employing a higher temperature or microwave irradiation did not prove beneficial. Also chlorination with thionyl chloride in the presence of dimethyl sulfoxide[13] only resulted in complex mixtures of various chlorinated products.

With biochanin A (**18**), only the dichlorinated product **19** was obtained whereas daidzein (**9**) and glycitein (**20**) just gave intractable mixtures with $SOCl_2$. Experiments with simple model compounds such as resorcinol, phloroglucinol, and trihydroxyacetophenone yielded complex mixtures of various chlorinated products according to GC-MS, whereas no reaction was observed with 4-hydroxyacetophenone. Additionally, genistein (**1**) was also reacted with sulfuryl chloride, but no selectively chlorinated products could be detected by ^1H NMR. Further experiments were conducted with genistein trimethyl ether (**21**) and $SOCl_2$ to discount the possibility that the chlorinations observed require the presence of a free hydroxy group at the phenolic ring A. Monochlorination of **21** was detected by LC-MS after stirring the reaction mixture at room temperature for 30 min. According to ^1H NMR and LC-MS, chlorination occurs at ring A, but without positional selectivity, giving an inseparable mixture of chlorinated compounds.

As regards the reaction mechanism in the $SOCl_2$-mediated aromatic chlorination, obviously the intermediacy of Cl^+ is implied. This in itself is unusual, as normally $SOCl_2$ is a source of Cl^-. This means that the oxidation state of sulfur must be reduced in the process. We tentatively suggest the reaction route depicted in Scheme 3, which produces sulfur monoxide, and which is reminiscent but different from the mechanism of the flavone chlorinations mentioned above.[7] Sulfur monoxide has been suggested as a product in certain other redox reactions of thionyl chloride[14–16] but detection of SO has not been possible owing to its ready disproportionation[17] to SO_2 and elemental sulfur. In our reactions, we have not isolated elemental sulfur but a slight turbidity of the solvent $SOCl_2$ was observed, possibly indicating the presence of S_8. An alternative is that initial attack of the phenolic ring might occur directly on chlorine instead on sulfur. Also in this case the eliminated S(O)Cl would easily form SO and Cl^-. Finally, mechanisms involving the initial formation of a phenolic sulfinate ester[3] are excluded as already mentioned.



R = alkyl or H

SCHEME 3

CONCLUSION

Genistein (**1**) and biochanin A (**18**) were selectively chlorinated with thionyl chloride yielding the monochlorinated compound **10**, as well as the dichlorinated analogues (**8** and **19**). Other factors possibly contributing to the reaction were also investigated, such as activation with DMSO, the use of higher reaction temperature and microwave irradiation. However, these methods did not yield satisfactory results as the selectivity of the chlorination reaction was lost. A plausible mechanism for the selective chlorination of 5-hydroxyisoflavones by $SOCl_2$ is suggested.

EXPERIMENTAL

NMR spectra were measured with a Varian Gemini 2000 or with a Bruker Avance 500 spectrometer using TMS as internal standard.

Chemical shifts are given as δ values and coupling constants in Hz. Mass spectra were obtained with a JEOL JMS SX102 mass spectrometer at 70 eV. LC-MS(ESI+) was performed on a HP 1100 instrument equipped with Mariner ESI-TOF. Melting points were determined in open capillary tubes with a GWB melting point apparatus and are uncorrected. TLC was performed on Merck RP-18 F_{254s} plates. MPLC was performed with a Buchi sepacore instrument using 40 × 150 mm RP-18 packed columns, mobile phase MeCN : H_2O (70 : 30), 0.1% HCOOH, and a flow rate of 50 mL/min.

General Synthetic Procedure

The isoflavone (ca. 0.36 mmol) was dissolved in freshly distilled thionyl chloride (15 mL). The solution was stirred in a flask equipped with a $CaCl_2$ tube at room temperature for 7 d. The orange solution was slowly added into ice-water (200 mL) **CAUTION**. The precipitate formed was filtered off, washed with water (20 mL), dried *in vacuo* and purified by MPLC. For 6,8-dichlorogenistein, the 7-day treatment was repeated twice before quench. For 6,8-dichlorobiochanin A, a single 7-day repetition was sufficient.

8-Chlorogenistein (10)

White solid; 78 mg (70%); m.p. 243–245°C from EtOH/H_2O. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.44 (s, 1H, 6-H), 6.83 (d, J = 8.4 Hz, 2H, 3′-H, 5′-H), 7.39 (d, J = 8.4 Hz, 2H, 2′-H, 6′-H), 8.49 (s, 1H, 2-H), 9.61 (s, 1H, 4′-H), 11.68 (s, 1H, 7-OH), 12.93 (s, 1H, 5-OH); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 97.2 (C-8), 99.1 (C-6), 105.2 (C-4a), 115.2 (C-3′, C-5′), 120.9 (C-1′), 122.7 (C-3), 130.4 (C-2′, C-6′), 153.0 (C-8a), 154.3 (C-2), 157.8, (C-4′), 160.0 (C-5), 160.2 (C-7), 180.4 (C-4). MS: m/z 304, 186, 118. HRMS: calcd. for $C_{15}H_9ClO_5$: 304.0139; found: 304.0130.

6,8-Dichlorogenistein (8)

White solid; 75 mg, 60%; m.p. 280–282°C from MeCN/H_2O. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.84 (d, J = 7.8 Hz, 2H, 3′-H, 5′-H), 7.41 (d,J = 7.8 Hz, 2H, 2′-H, 6′-H), 8.56 (s, 1H, 2-H), 9.41 (s, 1H, 4′-H), 11.64 (s, 1H, 7-OH), 13.69 (s, 1H, 5-OH); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 98.8 (C-8), 104.2 (C-6), 105.1 (C-4a), 115.1 (C-3′, C-5′), 120.4 (C-1′), 122.6 (C-3), 130.2 (C-2′, C-6′), 150.9 (C-8a), 154.5 (C-2), 155.6 (C-5), 155.7 (C-7), 157.7 (C-4′) 180.0 (C-4). MS: m/z 338, 220, 118. HRMS: calcd. for $C_{15}H_8Cl_2O_5$: 337.9749; found: 337.9743.

6,8-Dichlorobiochanin A (19)

White solid; 80 mg, 65%; m.p. 201–203°C from MeCN/H_2O. ^{1}H NMR (300 MHz, acetone-d_6): $\delta = 3.84$ (s, 3H, 4′-OMe), 7.00 (d, $J = 8.4$ Hz, 2H, 3′-H, 5′-H), 7.57 (d, $J = 8.4$ Hz, 2H, 2′-H, 6′-H), 8.39 (s, 1H, 2-H), 10.12 (s, 1H, 7-OH), 13.72 (s, 1H, 5-OH); ^{13}C NMR (75 MHz, acetone-d_6): $\delta =$ 55.2 (4′-OMe), 98.8 (C-8), 104.2 (C-6), 105.1 (C-4a), 113.8 (C-3′, C-5′), 122.1 (C-1′), 122.3 (C-3), 130.2 (C-2′, C-6′), 150.8 (C-8a), 154.8 (C-2), 155.6 (C-5), 155.7 (C-7), 159.4 (C-4′) 179.9 (C-4). MS: *m/z* 352, 220, 132. HRMS: calcd. for $C_{16}H_{10}Cl_2O_5$: 351.9905; found: 351.9881.

REFERENCES

[1] M. Fujimoto, *Bull. Chem. Soc. Jpn*., **32,** 480 (1959).
[2] W. E. Bissinger and F. E. Kung, *J. Am. Chem. Soc.*, **70,** 2664 (1948).
[3] D. H. Kim and A. A. Santilli, *Tetrahedron Lett.*, 2441 (1971).
[4] J. R. Merchant and G. Martyres, *J. Heterocyclic Chem.*, **17,** 1331 (1980).
[5] J. K. Prasain, R. Patel, M. Kirk, L. Wilson, N. Botting, V. M. Darley-Usmar, and S. Barnes, *J. Mass Spectrom.*, **38,** 764 (2003).
[6] R. Kuruto-Niwa, T. Ito, H. Goto, H. Nakamura, R. Nozawa, and Y. Terao, *Environmental Toxicology and Pharmacology*, **23,** 121 (2007).
[7] J. R. Merchant and D. V. Rege, *Tetrahedron*, **27,** 4837 (1971).
[8] I. O. Anyanwutaku, E. Zirbes, and J. P. N. Rosazza, *J. Nat. Prod.*, **55,** 1498 (1992).
[9] W. A. König, C. Krauss, and H. Zähner, *Helv. Chim. Acta*, **60,** 2071 (1977).
[10] K. Komiyama, S. Funayama, Y. Anraku, A. Mita, Y. Takahashi, S. Õmura, and H. Shimasaki, *J. Antibiot.*, **42,** 1344 (1989).
[11] S. Funayama, Y. Anraku, A. Mita, K. Komiyama, and S. Õmura, *J. Antibiot.*, **42,** 1350 (1989).
[12] A. L. Tökes, *J. Antibiot.*, **43,** 1332 (1990).
[13] H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **29,** 97 (1964).
[14] G. Büchi and G. Lukas, *J. Am. Chem. Soc.*, **86,** 5654 (1964).
[15] E. Koenigs and H. Greiner, *Ber*., **64,** 1049 (1931).
[16] Y. Okumura, *J. Org. Chem.*, **28,** 1075 (1963).
[17] P. W. Schenk, *Z. Anorg. Allg. Chem.*, **211,** 150 (1933).