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Triphosgene-Pyridine Mediated Stereoselective Chlorination of Acyclic Aliphatic 1,3-Diols†

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Abstract

We describe a strategy to chlorinate stereocomplementary acyclic aliphatic 1,3-diols using a mixture of triphosgene and pyridine. While 1,3-*anti* diols readily led to 1,3-*anti* dichlorides, 1,3-*syn* diols must be converted to 1,3-*syn* diol monosilylethers to access the corresponding 1,3-*syn* dichlorides. These dichlorination protocols were operationally simple, very mild, and readily tolerated by advanced synthetic intermediates.

Chlorosulfolipids are one of the major classes of naturally occurring organohalogens.¹ These natural products are essentially a long hydrocarbon chain containing multiple chlorine, sulfate, and/or hydroxy substituents along their aliphatic backbone. The inherent structural complexity exhibited by these biomolecules presents a significant challenge for total synthesis, thus prompting the development of contemporary strategies to access the intricate polychloride stereochemical arrays.² While the fundamental tactics undertaken by these studies generally focused on the stereoselective construction of vicinal dichloride structural motifs, stereocomplementary synthesis to access both diastereomers of unactivated, acyclic aliphatic 1,3-dichlorides essentially remained significant problems.^{2c,3} To bridge this gap of knowledge, this communication describes our unifying strategy for the production of both 1,3-*anti* and 1,3-*syn* dichlorides from their corresponding unreactive aliphatic 1,3-diols in a single synthetic operation and, most importantly, in a stereoselective manner.

Recently, we reported a new method to chlorinate sterically encumbered primary and secondary aliphatic alcohols via activation with triphosgene and pyridine.⁴ These operationally simple reactions were very clean, high yielding, and did not generate any chromatographically nuisance byproducts. As shown in Scheme 1, the mechanism of this reaction was proposed to proceed via an intermediacy of pyridinium carbamate ion **5**, which was presumably produced upon nucleophilic activation of chloroformate **4** with pyridine. Under the reaction conditions, the putative pyridinium carbamate intermediate **5** was susceptible to nucleophilic substitution by chloride ions at the carboxyl position to generate

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the target alkyl chlorides with an inversion of stereochemistry, while regenerating pyridine as the nucleophilic promoter and releasing CO₂ as the sole byproduct.

Our chlorination methodology naturally placed us in a strategic position to contribute a viable solution to the synthesis of alkyl 1,3-*anti* and 1,3-*syn* dichlorides. We proposed that these stereocomplementary compounds should be readily generated by subjecting the corresponding aliphatic 1,3-diol precursors to our triphosgene-pyridine activation. For proof of concept, we proceeded to explore the reactivity of 1,3-*anti* diol **6** and 1,3-*syn* diol **9**. We were cognizant that 1,3-diols are known to readily undergo carbonate cyclization with triphosgene and amine bases.⁵ Interestingly, treatment of 1,3-*anti* diol **6** with 1.0 equivalent of triphosgene and 4.0 equivalents of pyridine in dichloromethane at reflux produced 1,3-*anti* dichloride **7** in a quantitative yield, and cyclic carbonate byproduct **8** was detected only in a trace amount. This result suggested that in the presence of excess triphosgene and pyridine, 1,3-*anti* diol **6** rapidly underwent double chloroformylation, ultimately leading to dichlorination. In contrast, the use of 1,3-*syn* diol **9** produced cyclic carbonate **11** as the major product, indicating that monochloroformylation in 1,3-*syn* diol **9** was immediately captured by the facile 6-membered ring cyclization to form thermodynamically favorable chair conformation in cyclic carbonate **11**.

With these preliminary results in hand, we then explored the conversion of several exemplary 1,3-*anti* diols to 1,3-*anti* dichlorides in preparative scales. As depicted in Table 1, substrates bearing aromatic, allylic, and aliphatic groups as represented in 1,3-*anti* diols **12a** and **12b** afforded 1,3-*anti* dichlorides **13a** and **13b** in 90% and 65% yields, respectively. This dichlorination protocol was found to be compatible with structurally complex substrates, such as 1,3-*anti* diol **12c**. We found that primary TBS ether remained intact under the reaction conditions, and product **13c** was isolated in 80% yield. Our chemistry also enabled the production of synthetically daunting 1,3-dichloro compounds, most notably exemplified by the conversion of 1,3-*anti* β,γ -dihydroxyester **12d** to 1,3-*anti* β,γ -dichloroester **13d** in 73% isolated yield. The tolerability of this highly sensitive starting material and product under the reaction conditions underscore the mildness of our chlorination method. It is noteworthy that chlorination of these 1,3-*anti* diol substrates proceeded very cleanly. In fact, analysis of the crude reaction mixtures by both GC-MS and NMR essentially revealed quantitative conversion of the starting material to the corresponding 1,3-*anti* dichlorides without formation of any other byproducts.

We then continued our investigation towards solving the challenges associated with the dichlorination of 1,3-*syn* diols, particularly in controlling the rate of chlorination vs. carbonate cyclization. We envisioned that the competitive carbonate cyclization could be inhibited by simply masking one of the hydroxy groups in 1,3-*syn* diol to a monosilylether, *viz.* **14**. The rationale is illustrated in Scheme 3. Exposure of substrate **14** to triphosgene-pyridine should rapidly chlorinate the free secondary alcohol via pyridinium carbamate **15**. During this process, excess chloride ions liberated from decomposition of triphosgene should slowly cleave the silylether moiety to furnish putative chloroalcohol **16**.⁶ The ensuing *in situ* chloroformylation of the newly unmasked alcohol, followed by pyridine

activation should then form pyridinium carbamate **17** and furnish the desired 1,3-*syn* dichloride.

Table 2 describes a series of experiments to test this hypothesis. As shown in Entries 2–5, we prepared several monosilyl ethers **18**, ranging from trimethylsilyl ether, triethylsilyl ether, dimethylphenylsilyl ether, and diphenylmethylsilyl ether. Each of these substrates was subjected to identical dichlorination conditions, *i.e.* 1.0 equivalent of triphosgene, 4.0 equivalents of pyridine in dichloromethane (25 mM concentration based on starting material) at reflux. We identified that dimethylphenylsilyl ether was the most suitable functionality as it yielded the best ratio between 1,3-*syn* dichloride **10** and cyclic carbonate **11** (entry 4). Further reaction optimization revealed that the selectivity between dichlorination and carbonate cyclization was evidently modulated by the reaction concentration. As indicated in entries 4 and 6–8, increasing the reaction concentration up to 500 mM profoundly improved the selectivity to 99:1, favoring formation of 1,3-*syn* dichloride **10**.

Application of these optimized conditions towards several 1,3-*syn* diol substrates in preparative scale reactions is demonstrated in Table 3. For instance, the use of monosilylated 1,3-*syn* diols **19a** and **19b** readily generated 1,3-*syn* dichlorides **20a** and **20b**, respectively, in high yields. Exposure of advanced synthetic intermediate 1,3-*syn* diol monosilyl ether **19c** to the reaction conditions successfully produced the corresponding 1,3-*syn* dichloride **20c** in an excellent yield. Furthermore, we were also able to convert monosilylated 1,3-*syn* β,γ -dihydroxy ester **19d** to synthetically challenging and highly sensitive 1,3-*syn* dichloride **20d** in 92% yield using this methodology.⁷

Our success in the installation of 1,3-dichlorides inspired us to push this method towards the construction of stereocomplementary alkyl 1,3,5-trichlorides from the corresponding aliphatic triols. As shown in Scheme 4, 1,3,5-*anti* triol **21** was treated with 1.5 equivalents of triphosgene and 6.0 equivalents of pyridine in dichloromethane at reflux. Gratifyingly, the GC-MS and NMR analyses of the crude reaction mixture revealed a full conversion to 1,3,5-*anti* trichloride **22**, corresponding to 75% isolation yield. Similarly, when 1,3,5-*syn* triol **23** was reacted with identical molar equivalence of triphosgene-pyridine mixture at the optimal 500 mM concentration, the crude reaction mixture also indicated the complete consumption of the starting material to the corresponding 1,3,5-*syn* trichloride **24**. An attempt to isolate this sensitive compound using column chromatography resulted in 55% yield.

The relative stereochemistry of these acyclic chlorinated compounds was readily deduced by an analysis developed by Carman and Nougier,⁸ which involved a direct comparison of the ¹³C NMR signals of the 1,3-*anti* and 1,3-*syn* diastereomers. Carman and Nougier observed that in deuterated chloroform, the chemical shifts belonging to the 1,3-*anti* dichlorides, in particular those of the chlorinated carbon centers (C _{α} and C _{α'}) and their immediate neighboring carbons (C _{β} and C _{β'}), appeared more downfield in the ¹³C NMR spectrum by approximately 1 ppm than those produced by the comparable carbons in 1,3-*syn* dichlorides. Application of the Carman-Nougier analysis to our alkyl 1,3-dichloride products revealed similar patterns (Table 4). We indeed observed that the ¹³C NMR signals for both chlorinated carbons and their respective adjacent carbons for 1,3-*anti* dichlorides

13a–13d and **22** were consistently ~1 ppm more downfield than the signals from the corresponding 1,3-*syn* dichlorides **20a–20d** and **24**, respectively. These comparative chemical shifts data thus supported the stereoselectivity in our dichlorination reactions, *i.e.* 1,3-*anti* diols lead to 1,3-*anti* dichlorides, 1,3-*syn* diols lead to 1,3-*syn* dichlorides.

In conclusion, we have developed a general tactic for the synthesis of stereocomplementary aliphatic 1,3-*anti* and 1,3-*syn* dichlorides, enabled by our triphosgene-pyridine chlorination conditions. The mild nature of this highly stereoselective method readily tolerated sensitive functional groups, allowing for the construction of synthetically challenging complex molecules. Extension of the strategy to vicinal diols and synthetic application towards chlorosulfolipid natural products are currently underway in our laboratory.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and References

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stereocomplementary 1,2- vs. 1,3-dichlorides

multiple examples

synthetic challenge

Figure 1.
Examples of Chlorosulfolipid Natural Products

Scheme 1.

Triphosgene-Pyridine Promoted Chlorination of Secondary Alcohols.

Conditions:

triphosgene (1.0 equiv), pyridine (4.0 equiv), CH₂Cl₂, 0°C → reflux, 12 hrs

Scheme 2.

Initial Studies of Triphosgene-Pyridine Chlorination with 1,3-Diols.^[a,b]

[a] Starting materials are racemic with >20:1 dr. [b] The ratio of dichloride and cyclic carbonate products was determined via GC-MS analyses of the crude reaction mixtures.

Scheme 3.
Chlorination Strategy with 1,3-*syn* Diol Monosilylether.

Scheme 4. Chlorination of Stereocomplementary 1,3,5-Triols.^[a,b]

[a] Starting materials are racemic with >20:1 dr. [b] Products were isolated as a single diastereomer with presumed stereochemical inversion.

Table 1Chlorination of 1,3-*anti* Diols.

entry	starting material ^[a]	product ^[b]	yield ^[c]
1	 12a	 13a	90%
2	 12b	 13b	65%
3	 12c	 13c	80%
4	 12d	 13d	73%

^[a] Starting materials are racemic with >20:1 dr.^[b] Products were isolated as a single diastereomer with presumed stereochemical inversion.^[c] Yields are based on product isolation after flash column chromatography.

Table 2Screening and Reaction Optimization with 1,3-*syn* Diol Monosilylether.

entry	-R	conc. (mM) ^[a]	dichloride 10 : carbonate 11 ^[b]
1	-H	25	34:66
2	-SiMe ₃	25	65:35
3	-SiEt ₃	25	32:68
4	-SiMe₂Ph	25	80:20
5	-SiMePh ₂	25	65:35
6	-SiMe ₂ Ph	5	69:31
7	-SiMe ₂ Ph	100	80:20
8	-SiMe₂Ph	500	99:1

^[a] Concentration was based on starting material **18**.

^[b] The ratio of dichloride **10** and cyclic carbonate **11** was determined via GC-MS analyses of the crude reaction mixtures.

Table 3Chlorination of 1,3-*syn* Diol Monosilylether.

$\text{R}_1-\text{CH}(\text{OH})-\text{CH}(\text{OR})-\text{R}_2 \xrightarrow[\text{CH}_2\text{Cl}_2 (500 \text{ mM}), 0^\circ\text{C} \rightarrow \text{reflux}]{\text{triphosgene (1.0 equiv)}, \text{pyridine (4.0 equiv)}} \text{R}_1-\text{CH}(\text{Cl})-\text{CH}(\text{Cl})-\text{R}_2$

 $\text{R} = \text{SiMe}_2\text{Ph}$

entry	starting material ^[a]	product ^[b]	yield ^[c]
1	<p>19a</p>	<p>20a</p>	76%
2	<p>19b</p>	<p>20b</p>	82%
3	<p>19c</p>	<p>20c</p>	94%
4	<p>19d</p>	<p>20d</p>	92%

^[a] Starting materials are racemic with >20:1 dr.^[b] Products were isolated as a single diastereomer with presumed stereochemical inversion.^[c] Yields are based on product isolation after flash column chromatography.

Table 4

Carman-Nougier ^{13}C NMR Analyses.^[a]

entry	compound	relative stereochemistry	chemical shifts (ppm)			
			C $_{\beta}$	C $_{\alpha}$	C $_{\alpha'}$	C $_{\beta'}$
1		1,3- <i>anti</i> (13a)	45.0	60.5	59.2	42.8
		1,3- <i>syn</i> (20a)	44.1	59.8	58.3	41.1
			0.9	0.7	0.9	1.7
2		1,3- <i>anti</i> (13b)	45.0	60.8	60.7	38.7
		1,3- <i>syn</i> (20b)	44.1	60.0	59.9	37.1
			0.9	0.8	0.8	1.6
3		1,3- <i>anti</i> (13c)	45.0	60.6	60.0	36.7
		1,3- <i>syn</i> (20c)	44.0	60.0	59.2	35.2
			1.0	0.6	0.8	1.5
4		1,3- <i>anti</i> (13d)	44.8	59.9	55.4	44.8
		1,3- <i>syn</i> (20d)	43.9	59.4	54.7	43.6
			0.9	0.5	0.7	1.2
5		1,3- <i>anti</i> (22)	44.9	60.0	57.3	41.1
		1,3- <i>syn</i> (24)	44.0	59.3	56.5	39.8
			0.9	0.7	0.9	1.3

^[a]Chemical shifts are reported relative to residual CHCl_3 as an internal reference (77.0 ppm).