ORGANIC LETTERS

2008
Vol. 10, No. 21
4859−4862

Solvent-Controlled Leaving-Group Selectivity in Aromatic Nucleophilic Substitution

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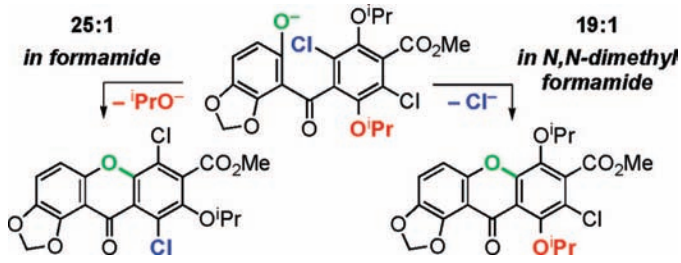
Received August 21, 2008

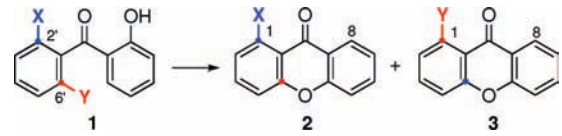
ABSTRACT



A solvent-controlled inversion of leaving group ability allows selective access to either of two internal substitution products in S_NAr reactions of substrates with competing leaving groups. Application of this principle in a selective synthesis of the highly functionalized xanthone core of the antibiotic FD-594 is presented.

In nucleophilic aromatic substitution reactions (S_NAr), a range of kinetic studies, turned into textbook-knowledge, has established the order of relative leaving-group ability: F, NO_2 > Cl > Br > I, which is inverse to that in aliphatic substitution.[1,2] Alkoxides are good leaving groups only in S_NAr reactions,[3] where OMe and Cl perform similarly, though their relative ordering depends on solvent and nucleophile.[2a] Competition between alkoxy and halogen leaving groups in S_NAr reactions is by no means esoteric; we show here that the base-induced cyclization of 2-hydroxybenzophenones[4] (**1**) with competing leaving groups X and Y (X, Y = halogen or alkoxide) in the 2′/6′-positions gives xanthones **2** and **3** (Scheme 1). The ratio **2**/**3** reflects the relative susceptibility for substitution under reaction conditions.

Scheme 1. Intramolecular Competition of Leaving Groups X/Y



In planning synthetic strategies toward naturally occurring oxygenated xanthones,[5] competing modes of cyclization of

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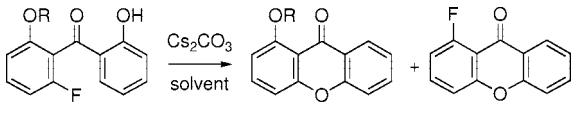
10.1021/ol801962a CCC: $40.75
Published on Web 10/09/2008

precursors **1** must be controlled. Here we present the concept of *solvent-dependent leaving-group ability* providing selectively access to either xanthone **2** or **3** from a single precursor **1**. Application of this principle to the synthesis of the highly oxygenated xanthone core of the antibiotic FD-594[6] showcases the synthetic utility of this approach.

A series of ortho-trisubstituted 2-hydroxybenzophenones **4a/b** and **5a/b** were obtained[7] for investigating the relative leaving-group ability of chloride or fluoride versus alkoxide in several solvents[8] (Tables 1 and 2). The fluorinated

Table 1. Competition of Fluoride/Alkoxide Leaving Groups[a]



4a (R = Me)
4b (R = ^{i}Pr)

6a (R = Me)
6b (R = ^{i}Pr)

7

entry	substrate	solvent	T (°C)	time (h)	**6/7**	yield (%)
1	**4a**	MeOH	85	1.4	100:0	99
2	**4a**	DMF	50	0.7	100:0	99
3	**4b**	MeOH	85	1.3	100:0	99
4	**4b**	DMF	rt	1	100:0	nd

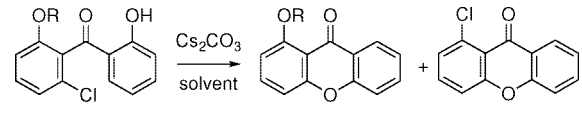
[a] General conditions for all tables: 10 mg of substrate/mL solvent; 1.5 equiv of Cs_2CO_3. T = reaction temperature; time = reaction time to complete conversion (TLC), unless otherwise indicated. Product ratios are derived from ^{1}H NMR of the crude mixture.

benzophenones **4a/b** gave the corresponding 1-alkoxyxanthones **6a/b** in almost quantitative yield with no trace of fluoroxanthone **7**, regardless of the alkoxy group or the solvent (Table 1).[9]

On the other hand, the chlorinated substrates **5** cyclized to give mixtures of alkoxyxanthones **6** and chloroxanthone **8** (Table 2). The product ratios are subject to a substantial *solvent effect*, which causes a remarkable reversal of the product selectivity. The magnitude of selectivity reversal is more pronounced for isopropyl ether **5b** (entry 7 vs 11) than for methyl ether **5a** (entry 1 vs 6).

The antibiotic FD-594[6] contains a highly substituted oxygenated xanthone core (the DEF rings), which we chose to disconnect to a key intermediate **9** for a projected total synthesis (Figure 1).[10]

Table 2. Competition of Chloride/Alkoxide Leaving Groups[a]



5a (R = Me)
5b (R = ^{i}Pr)

6a (R = Me)
6b (R = ^{i}Pr)

8

entry	substrate	solvent	T (°C)	time (h)	**6/8**
1	**5a**	MeOH	80	75	1:11[b]
2	**5a**	H_2O	100	27	1:8.6
3[c]	**5a**	formamide	80	30	1:7.7
4[d]	**5a**	THF	80	30	1:8.5
5	**5a**	DMF	45	5	1.7:1[e]
6	**5a**	DMPU	50	2.3	2.8:1
7	**5b**	MeOH	100[f]	20	1:8[g]
8[h]	**5b**	formamide	80−90	70	1:3.4
9[d]	**5b**	THF	80	30	1:5.5
10	**5b**	DMF	50	3	10:1
11	**5b**	DMPU	50	5	20:1

[a] General conditions: see Table 1. [b] 98% yield (90% **8** and 8% **6a**). [c] 97% conversion. [d] Heterogeneous reaction mixture in THF. [e] 99% yield (62% **6a** and 37% **8**). [f] Reaction in a sealed tube. [g] In addition, **6a** (3%) was also formed. [h] Conversion = 53%.

Scheme 2 shows a synthetic approach to xanthone **9**: ether protection and desymmetrization of terephthalate **10**[11] by saponification was followed by transformation to aldehyde

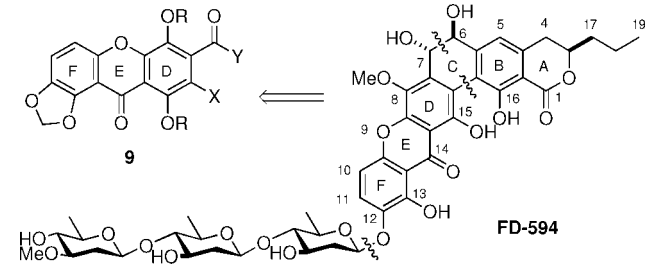


Figure 1. Structure of FD-594 and a derived xanthone core **9**.

11. Addition of lithioarene **12** to aldehyde **11** followed by oxidation/deprotection gave the cyclization precursor **14**.[12]

The cyclization of **14** with cesium carbonate as a base in different solvents gave a variable mixture of 1,4-dialkoxyxanthone **15** and 1,4-dichloroxanthone **16** (Table 3). The solvent effect on the leaving-group selectivity was even more pronounced than for the model compounds **5**. Either essentially pure **16** (entries 1−4) or **15** (entries 9 and 12) was obtained in suitable solvents. The reactions that are selective

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(7) These model compounds were prepared by (a) addition of metalated 3-alkoxyhalobenzenes to *O*-MOM-salicylaldehyde, (b) oxidation of the intermediary diarylmethanols, and (c) MOM-deprotection; see the Supporting Information.

(8) Solvent effects on leaving-group order in S_NAr reactions have been documented through kinetic measurements; see ref 2a.

(9) In case of reaction in methanol, this result is in accordance to an earlier report: Horne, S.; Rodrigo, R. *J. Org. Chem.* **1990**, *55*, 4520–4522.

(10) This disconnection is based on the synthetic strategy already used for the total syntheses of the benanomicin−pradimicin antibiotics: (a) Tamiya, M.; Ohmori, K.; Kitamura, M.; Kato, H.; Arai, T.; Oorui, M.; Suzuki, K. *Chem.—Eur. J.* **2007**, *13*, 9791–9823. (b) Ohmori, K.; Tamiya, M.; Kitamura, M.; Kato, H.; Oorui, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3871–3874. (c) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229–1232.

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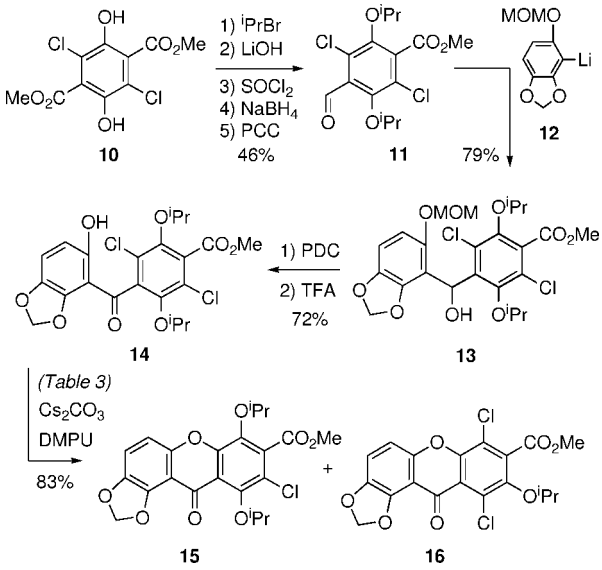
(12) See the Supporting Information for details of this synthesis.

(13) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, Germany, 1988.

Scheme 2. Synthesis of the FD-594 Xanthone Core[12]



for **16** are slower than those leading primarily to **15** (compare entry 3 vs 9). The presence of the radical scavengers 2,6-di-*tert*-butylcresole or sodium *meta*-nitrobenzenesulfonate did not affect the outcome in DMF. The reaction in toluene was unaffected by the presence of either $[Cu(MeCN)_4]PF_6$ or $Pd(OAc)_2$/dppf.

When the chemoselectivity of cyclization (measured as logarithm of the product ratio **15/16**) is plotted as a function of solvent polarity $E_T^N(30)$,[13] the data points for a range of solvents lie approximately on a straight line, but several dipolar aprotic solvents with strong donor capabilities cluster together in a separate region (Figure 2).

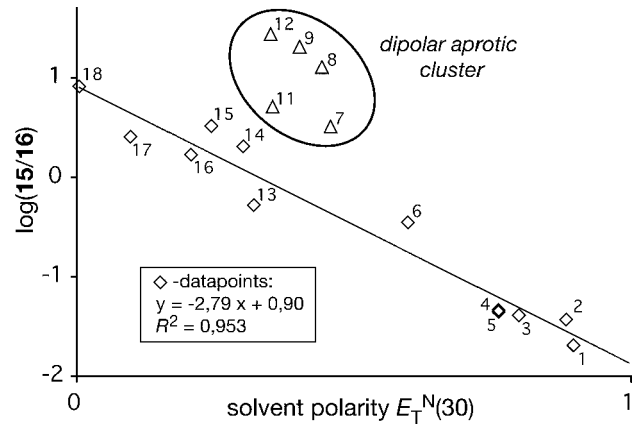


Figure 2. Product selectivity in the reaction **14** → **15** + **16** as a function of solvent polartiy. Data points are the entries of Table 3.

Table 3. Cyclization of **14** to **15/16** in a Range of Solvents[a]

entry	solvent	$E_T^N(30)$[b]	T (°C)	time (h)	**15/16**
1	CF_3CH_2OH[c]	0.898	80	70	1:50
2	EtOH (aq)[d]	0.885[e]	80	7.5	1:27.5
3	formamide	0.799	50	24	1:25
4	MeOH	0.762	80	14	1:22
5	MeOD	0.762	80	13	1:23
6	[bmim]PF_6[f]	0.60[g]	50	2.3	1:2.9
7	MeCN	0.460	50	2	3.2:1
8	DMSO	0.444	rt	8	12:1
9	DMF	0.404	45	0.5	19:1
10	DMF	0.404	rt	<20	16:1
11	acetone	0.355	50	2	5:1
12	DMPU	0.352	50	0.7	25:1
13	^{t}AmOH	0.321	90	18	1:1.95
14	pyridine	0.302	50	2	2:1
15	diglyme	0.244	50	3	3.2:1
16	THF	0.207	80	1.7	1.65:1
17	toluene	0.099	130	2.3	2.5:1
18	c-C_6H_{12}	0.006	90	18	8:1

[a] General conditions: see Table 1. [b] Solvent polarity parameter.[13] [c] 6 equiv of Cs_2CO_3, conversion = 40%. [d] H_2O/EtOH = 2:1. [e] Interpolated value. [f] *N*-Butyl-*N*′-methylimidazolium hexafluorophosphate. [g] Value ($E_T(30)$ ≈ 50 kcal/mol) calculated from lit.[14] diglyme = $O(C_2H_4OMe)_2$; DMPU = *N*,*N*′-dimethylpropylidene urea; ^{t}AmOH = 2-methyl-2-butanol.

The mechanism of nucleophilic aromatic substitution (S_NAr) includes two steps, namely, the nucleophilic attack on the aromatic system (transition state T_1) and extrusion of the leaving group (T_2).[2a] For moderate nucleophiles such as those centered on oxygen or nitrogen, attack to the aromatic ring (T_1) is usually rate-limiting, which explains the curious leaving-group order: F, OR > Cl > Br, paralleling the electrophilicity of the *ipso*-carbon to welcome the incoming nucleophile.[1,2]

In reactions with polarizable, kinetically fast nucleophiles, T_2 is rate-determining,[2a] and the classical leaving-group order is observed (Cl > F > OR). In cyclizations to xanthones, the entropically favored nucleophilic attack may outweigh the low nucleophilicity of phenolate, such that T_1 and T_2 become similar in energy. Dipolar aprotic solvents increase the nucleophilicity of phenoxide; T_1 is further lowered in energy, T_2 becomes rate-limiting, and we observe fast reactions with high selectivity for the halogen-leaving groups (Cl, F > OR). In other solvents, increasing solvent polarity will decrease the phenoxide nucleophilicity by solvation (increasing T_1) and better solvate the leaving group (decreasing T_2). This simple picture explains the observed reversal of the *leaving group order* in the cyclization of 2-chloro-6-alkoxy-2′-hydroxybenzophenones as a change of the rate-determining step from T_1 (polar solvents) to T_2 (nonpolar solvents).

Fluorinated substrates do not show this ambiguity because fluorine is a superior leaving group over alkoxide in both transition states. Choice of fluorine as the leaving group ensures selective ring closure, but this option will often be out of reach due to the difficulty of introducing aromatic fluorine into advanced synthetic intermediates.[15]

We conclude that, in synthetic routes where alkoxy and chlorine leaving groups compete for an internal nucleophile

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in an S_NAr reaction, the relative leaving-group order can be controlled by a solvent effect. The finding is relevant to the synthesis of highly functionalized and nonsymmetrically substituted xanthones and may be of more general importance in the case of S_NAr reactions with competing leaving groups.

Acknowledgment. This work is dedicated to the memory of the late Charles Mioskowski. L.H. thanks the Japan Society for the Promotion of Science (JSPS) for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and substance characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801962A