Proceedings

Lewis acid-mediated mono- and bis-addition of C-nucleophiles to 1,3-dioxolan-4-ones.

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Abstract: The reactions of 1,3-dioxolan-4-ones, readily available from α-hydroxy acids and aldehydes, with C-nucleophiles are described. Two possible reaction pathways resulting in O-substituted acids and tri-(hetero)arylmethanes are shown.

Keywords: 1,3-dioxolan-4-one; oxocarbenium cation; C-nucleophile; 1-alkyne; Si-containing nucleophiles.

1. Introduction

The reactions of oxocarbenium cations with different types of C-nucleophiles is a convenient tool for building carbon-carbon bonds [1]. Many examples of the generation of oxocarbenium cations from different types of five-, six-, and seven-membered ring acetals and related compounds have been reported [2].

1,3-Dioxolan-4-ones are readily available building blocks obtained by the condensation of carbonyl compounds with α-hydroxy carboxylic acids, including natural ones, such as malic, lactic, and mandelicacids [3]. 1,3-Dioxolan-4-ones (the so-called Seebach chiral templates [4]) have found widespread application in the preparation of chiral compounds. Also, it was shown that 1,3-dioxolan-4-onescan be used in alkylation [5], aldol addition [6], Michael [7], and Mannich reactions [8]. However, few examples of C-nucleophilic addition to the oxocarbenium cation A generated from 1,3-dioxolan-4-ones under the action of Lewis acids are known (Fig. 1) [9].

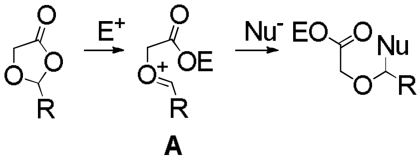


Figure 1. Nucleophilic addition to an oxocarbenium cation.

In the present work, we report examples of the Lewis acid-mediated reaction between 1,3-dioxolan-4-ones and C-nucleophilic reagents, which can result in either mono- and bis-addition depending on the nature of the nucleophile.

2. Materials and Methods.

^{1}H and ^{13}C NMR spectra were recorded on an ECA 400 (JEOL) instrument in $CDCl_3$ or $(CD_3)_2SO$ (Cambridge Isotop Laboratories Inc.) using residual solvent signals as the internal standard. IR spectra were recorded on an IR Prestige instrument (Shimadzu) in KBr pellets. The course of the reactions was monitored by gas chromatography–mass spectrometry (GC/MS) using a GC-2010 instrument (Shimadzu) with QP-2010 Plus mass selective detector (Shimadzu): the column was Supelko SLB-5ms, 30 m; programmed heating from 60 to 265°C at a rate of 30°C/min. Melting points were measured in open-end capillaries on a Stuart SMP30 instrument. The reagents used were commercially available from Aldrich, Acros, or ABCR.

General procedure for the synthesis of acids 3a-d. To a solution of dioxolanone 1a (144 mg, 0.6 mmol) and allyltrimethylsilane (144 µL, 0.9 mmol) in dry CH$_2$Cl$_2$ (5.5 mL) under an argon atmosphere, FeCl$_3$ (9.7 mg, 0.06 mmol) was added at room temperature. The reaction mixture was stirred for 30 min, poured into water, and extracted with EtOAc. The organic phase was dried with anhydrous Na$_2$SO$_4$ and evaporated. The residue was purified by column chromatography using EtOAc :Hex(1 : 9) as eluent to give 2-phenyl-2-((1-phenylbut-3-en-1-yl)oxy)acetic acid (3a) (142 mg, 84%) as a mixture of diastereomers (dr = 1 : 1.5).

Minor diastereomer: M.p. 119-120 °C. IR (KBr), ν/cm-1: 3028, 2903, 1722, 1703, 1454, 1238, 1188, 1113, 727, 698. ^{1}H NMR (600 MHz, CDCl$_3$, δ, ppm): 10.27 (bs, 1H, OH), 7.40-7.41 (m, 2H, H$_{Ar}$), 7.31-7.36 (m, 6H, H$_{Ar}$), 7.27-7.28 (m, 2H, H$_{Ar}$), 5.88-5.95 (m, 1H, CH$_2$=C-H), 5.10-5.15 (m, 2H, =CH$_2$), 4.82 (s, 1H, CH), 4.58 (t, J=6.6Hz, 1H, CH), 2.72-2.77 (m, 1H, CH$_2$), 2.52-2.56 (m, 1H, CH$_2$). ^{13}C NMR (CDCl$_3$), δ, ppm: 176.6, 140.4, 136.2, 134.5, 128.8, 128.7(4C), 128.3, 127.2 (2C), 127.1 (2C), 117.8, 81.6, 77.8, 42.6. Mass (EI, 70 eV), m/z (I_{rel} (%)): 269 (8%); 163 (21); 135 (13); 132 (11); 131 (100); 107 (13); 91 (29); 79 (12); 77 (13).

Major diastereomer: M.p. 89-90 °C. IR (KBr), ν/cm-1: 3028, 2903, 1722, 1703, 1454, 1238, 1188, 1113, 727, 698. ^{1}H NMR (600 MHz, CDCl$_3$, δ, ppm): 9.94 (bs, 1H, OH), 7.34-7.42 (m, 8H, H$_{Ar}$), 7.27-7.28 (m, 2H, H$_{Ar}$), 5.66-5.73 (m, 1H, CH$_2$=C-H), 5.01-5.04 (m, 2H, =CH$_2$), 4.74 (s, 1H, CH), 4.26 (t, J=10.2 Hz, 1H, CH), 2.69-2.74 (m, 1H, CH$_2$), 2.46-2.51 (m, 1H, CH$_2$). ^{13}C NMR (CDCl$_3$), δ, ppm: 174.4, 139.8, 135.5, 134.1, 129.2, 128.90(2C), 128.86(2C), 128.5, 127.9(2C), 127.2(2C), 117.7, 79.5, 77.3, 42.3. Mass (EI, 70 eV), m/z (I_{rel} (%)):269 (8%); 163 (21); 135 (13); 132 (11); 131 (100); 107 (13); 91 (29); 79 (12); 77 (13).

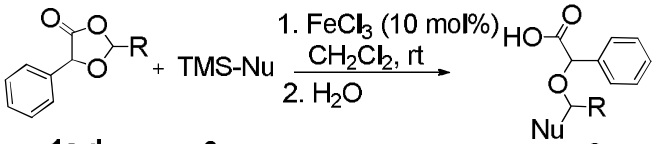
General procedure for the synthesis of acids 3e-l. To a solution of phenylacetylene (66 µL, 0.6 mmol)indrytoluene (4 mL) under an argon atmosphere, DIPEA (87 µL, 0.5 mmol) and ZnBr$_2$ (11.3 mg, 0.5 mmol) were added at room temperature. The reaction mixture was stirred for 30 min at room temperature and cooled to –10°C. A cooled to –10°C solution of dioxolanone 1a (120.1 mg, 0.5 mmol) and TMSOTf (90 µL, 0.5 mmol) in toluene (1 mL) was added. The resulting mixture was stirred for 2 h, poured into water acidified with 2N HCl (1 mL), and extracted with EtOAc. The organic phase was dried with anhydrous Na$_2$SO$_4$ and evaporated. The residue was purified by column chromatography using gradient elution with EtOAc:Hex (1:10 → 1:6) to give 2-((1,3-diphenylprop-2-yn-1-yl)oxy)-2-phenylacetic acid (3e) (128.4mg, 75%) as a mixture of diasereomers (dr = 1:1.5). Pale oil. IR (KBr), ν/cm-1: 3032, 1721, 1452, 1278, 1217, 1067, 756, 696. ^{1}H NMR (600 MHz, CDCl$_3$, δ, ppm): 9.57 (bs, 2H, OH), 7.66-7.67 (m, 3H, H$_{Ar}$), 7.56-7.60 (m, 4H, H$_{Ar}$), 7.47-7.52 (m, 9H, H$_{Ar}$), 7.31-7.43 (m, 23H, H$_{Ar}$), 5.66 (s, 1.5H, CH, major), 5.49 (s, 1H, CH, minor), 5.40 (s, 1.5H, CH, major), 5.38 (s, 1H, CH, minor). ^{13}C NMR (CDCl$_3$), δ, ppm: 176.4, 174.8, 137.7, 137.6, 135.7, 135.2, 132.0 (4C), 130.3, 129.4, 129.1, 129.04, 129.02, 129.0, 128.9(2C), 128.81 (2C), 128.77 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.0 (4C), 127.9 (2C), 127.6 (2C), 122.2, 122.1, 89.3,89.0, 85.8, 85.3, 78.1, 77.6, 71.4, 70.5. Mass (EI, 70 eV), m/z (I_{rel} (%)): 207 (31%); 192 (18); 191 (100); 189 (14); 164 (8) 105 (7).

General procedure for the synthesis of arylmethanes 4a-e. To a solution of dioxolanone 1a (96 mg, 0.4 mmol) and 1,3,5-trimethoxybenzene (148 mg, 0.88 mmol) in dry CH$_2$Cl$_2$ (4 mL) under an argon atmosphere, FeCl$_3$ (6.5 mg, 0.04 mmol) was added at room temperature. The reaction mixture was stirred for 2 h, poured into water, and extracted with EtOAc. The organic phase was dried with anhydrous Na$_2$SO$_4$ and evaporated. The residue was purified by column chromatography using CH$_2$Cl$_2$:Hex (1:1) as eluent to give 2,2'-(phenylmethylene)bis(1,3,5-trimethoxybenzene) 4a (91 mg, 54%) as colorless crystals. M.p. 185-185.5 °C. IR (KBr), ν/cm-1: 2937, 2837, 1601, 1591, 1462, 1416, 1231, 1204, 1138, 1125. 1H NMR (400 MHz, CDCl3, δ, ppm): 7.13-7.18 (m, 2H, H$_{Ar}$), 7.04-7.07 (m, 3H, H$_{Ar}$), 6.23 (s, 1H, CH), 6.12 (s, 4H, H_{Ar}), 3.79 (s, 6H, OCH_3), 3.51 (s, 12H, OCH_3). ^{13}C NMR (CDCl3), δ, ppm: δ160.0 (4C), 159.3(2C), 145.8, 127.9(2C), 127.2(2C), 124.3, 114.5(2C), 92.0(4C), 56.3(4C), 55.2(2C), 37.2. Mass (EI, 70 eV), m/z (I_{rel} (%)):424 (M+, 71%); 257 (23); 256 (89); 255 (27); 181 (28); 179 (100); 91 (33).

3. Results and Discussion.

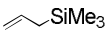
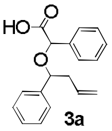
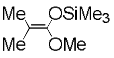
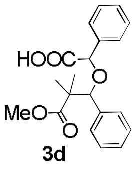
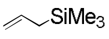
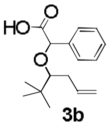
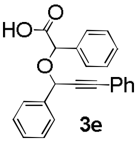
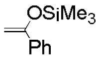
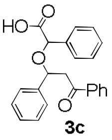
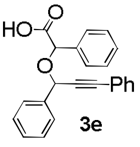
There are a large variety of catalysts for the reactions of C-nucleophiles with acetals, where $TiCl_4$ and $AlCl_3$ [10], as well as $BF_3{\cdot}OEt_2$ and TMSOTf [2,11] were among the first Lewis acids used in stoichiometric or superstoichiometric amounts. However, one of the most eco-friendly, lowest-cost, and most stable catalysts is $FeCl_3$, which exhibits a high activity in the reactions of acetals with allylsilanes and silyl ketene acetals [12]. Therefore, we focused our attention on $FeCl_3$ when studying the reaction of 1,3-dioxolan-4-ones 1 with different silicon-containing nucleophiles and 1-alkynes 2 (Table 1).

Table 1. Reaction of 1,3-dioxolan-4-ones 1a,d with different C-nucleophiles



1a,d **2** **3a-e**

1a: R=Ph; **1d**: R=*t*-Bu

Entry	Nucleophile	Product	Time (h)	Yield^b (%)	Entry	Nucleophile	Product	Time (h)	Yield^b (%)
1		 3a	0.5	84 (62:38)	4		 3d	2	63 (64:36)^c
2		 3b	24	76 (76:24)^c	5	PhC≡CSiMe3	 3e	72	ND^e
3		 3c	1	55^d (61:39)	6	Ph—≡	 3e	12	ND^e

^{a}Reaction was carried out using 0.60 mmol of the dioxolan-4-one in CH_2Cl_2 (5.5 mL), 0.90 mmol of the nucleophile in the case of 3a and 3b, 0.60 mmol of the nucleophile in the case of 3c-e, and 0.06 mmol of $FeCl_3$ under an argon atmosphere at r.t. ^{b} Isolated yields(the ratio of diastereomers is given in parentheses).^{c} Ratio of diastereomers according to NMR analysis. ^{d} Reaction was carried out at–10°C.^{e} Product was not detected.

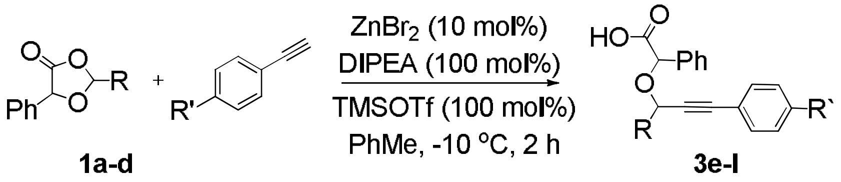
The reaction proceeded smoothly with allyltrimethylsilane, silylenol ether, and silyl ketene acetal (Entries 1-4) at room temperature in the presence of $FeCl_3$ (10 mol%) to form a mixture of diastereomers whose ratio was determined from the ^{1}H NMR spectra (in the case of 3b, 3d, 3e).

However, product formation was not occur in the case of trimethyl(phenylethynyl)silane and phenylacetylene.

It is known, that in some cases, activation not only an electrophile, but also an nucleophiles is required. For example, activation through formation of the corresponding alkynylideis applied in the case of 1-alkynes. A convenient approach proposed by Carreira and co-workers [13] to activate 1-alkynes in the reactions with carbonyl compounds and used by Watson and co-workers [14] for the reactions with acetals utilizes the generation of zinc or copper alkynylides in the presence of $ZnBr_2$ or CuI and an amine.

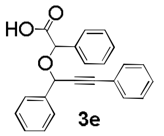
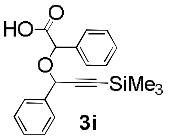
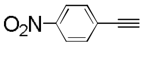
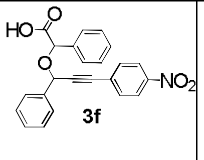
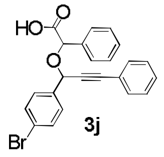
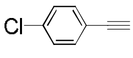
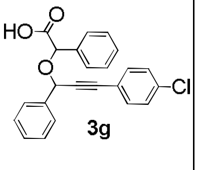
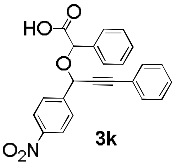
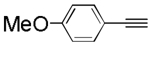
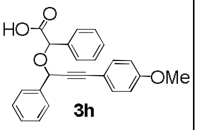
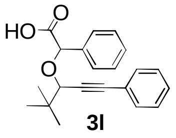
The use of this methodology in combination with TMSOTf (100 mol%) to generate the oxocarbenium cation from the acetal allowed us to obtain the alkylation products 3e-l (Table 2).

Table 2. Reaction between 1,3-dioxolan-4-one 1a-d and 1-alkynes.



1a-d **3e-l**

1b: R= 4-$O_2NC_6H_4$;
1c: R= 4-BrC_6H_4

Entry	Nucleophile	Product	Yield^{b} (%)	Entry	Nucleophile	Product	Yield^{b} (%)
1	Ph—≡	 **3e**	75 (60:40)c	5	Me_3Si—≡	 **3i**	50 (75:25)^{c}
2		 **3f**	73^{d} (80:20)c	6	Ph—≡	 **3j**	53 (75:25)^{c}
3		 **3g**	67 (75:25)c	7	Ph—≡	 **3k**	45^{f} (82:18)c
4		 **3h**	45^{e} (80:20)c	8	Ph—≡	 **3l**	33^{f} (83:17)c

^{a}Reaction was carried out using 0.50 mmol of the dioxolan-4-one in toluene (5 mL),0.60 mmol of thev1-alkyne, 0.50 mmol of DIPEA, 0.50 mmol of TMSOTf, and 0.05 mmol of $ZnBr_2$ under an argon atmosphere at –10°C. ^{b}Isolated yields. ^{c}Ratio of diastereomers according to NMR analysis. ^{d}Reaction was carried out for 3h. ^{e}Reaction was carried out for 4.5h at 0°C. ^{f}Reaction was carried out for 4 h at 0°C and, then, for 24h at 5°C.

The presence of a donor substituent in the 1-alkyne (Entry 4) increases the reaction time and decreases the product yield to 45%, most likely, due to the lower acidity of

4-methoxyphenylacetylene. An increase in the reaction time along with a decrease in the product yield was observed upon introduction of an electron-withdrawing substituent to the starting dioxolanone 1b (Entry 7) or replacement of the phenyl ring with the tert-butyl group as in 1d (Entry 8). This can be explained by less effective stabilization of the intermediate oxocarbenium cation.

In all cases, the reaction products were formed as a mixture of diastereomers with dr from 1:1.5 to 1:4. We attribute this to reason, that the oxocarbenium ion produced during the reaction has, presumably, a planar structure and can undergo nucleophilic attack from both sides, but from one of its preferably.

Also we found that the starting dioxolanones 1 isomerize under the reaction conditions into a mixture of cis- and trans-isomers. For example, dioxolanone 1b isomerizes into a 1.5 : 1 mixture of trans- and cis-isomers, respectively (GC analysis, Fig.3).

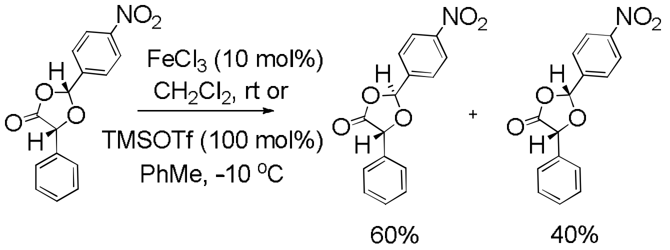
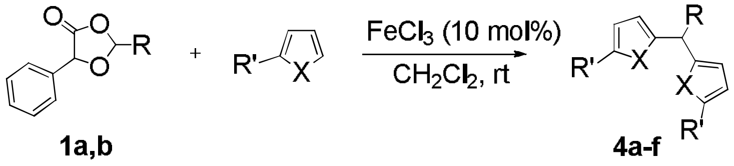


Figure 3. Isomerization of compound 1b.

During further studies, bis-addition products 4 were found to form when the nucleophiles were electron-rich aromatic compounds. The reaction time and the product yields in this case strongly depend on the nucleophilicity of the aromatic compounds used. For example, in the case of less nucleophilic *tert*-butylbenzene (Entry 3) or ethyl furoate (Entry 6), the corresponding methanes 4 were either not produced (4f) or were produced in trace amounts (4c) (Table 3).

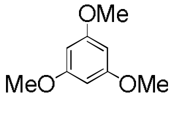
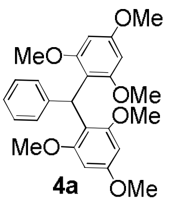
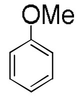
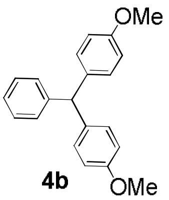
Table3. Reaction of 1,3-dioxolan-4-ones 1a,b with aromatic compounds.

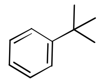
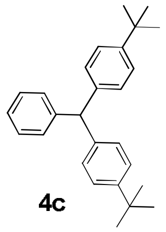
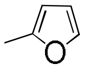
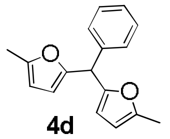
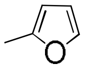
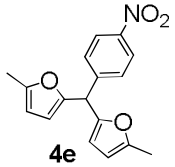
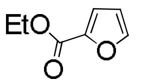
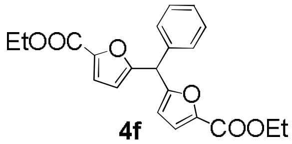


1a,b

4a-f

X: CH=CH or O

Entry	R	Nucleophile	Product	Time(h)	Yieldb(%)
1	Ph		 **4a**	2	54
2	Ph		 **4b**	6	28

3	Ph		 **4c**	72	tracec
4	Ph		 **4d**	0.5	76
5	p-NO2Ph		 **4e**	24	15
6	Ph		 **4f**	72	ND

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[a] Reaction was carried out using 0.40 mmol of the dioxolan-4-one in CH_2Cl_2 (4 mL), 0.88 mmol of the nucleophile, and 0.04 mmol of $FeCl_3$ under an argon atmosphere at r.t. [b]Isolated yields. [c]GC analysis. [d]Product was not detected.

Alkoxybenzenes and 2-methylfuran were the most reactive (Entries 1,2,4,5). The presence of an electron-withdrawing substituent in the starting dioxolanone 1b increases the reaction time and decreases the product yield (Entry 5).

The GC/MS and TLC studies of a competitive addition reaction showed that, when using a mixture of aryl and silicon-containing nucleophiles, both mono- and bis-addition products can form depending on the nucleophilicity of the substrates used. In both cases, the alternative product is produced only in trace amounts (Fig. 4).

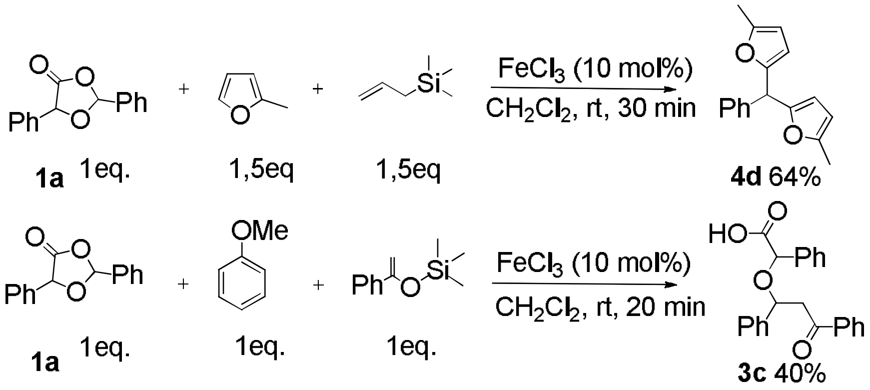

Figure 4. Competitive addition of nucleophiles to dioxolanone 1a.

Based on the data obtained, we assume that, depending on the ability of a nucleophile to stabilize the intermediate cation, two possible pathways for additionare realized. For example, in the case of nucleophiles after addition of which a CH_2 unit or carbon-carbon triple bond forms near the cationic site, the reaction terminates at the step of mono-addition. In the case where an aromatic ring is adjacent to the cationic site, the addition of the second nucleophile molecule then occurs (Fig.5).

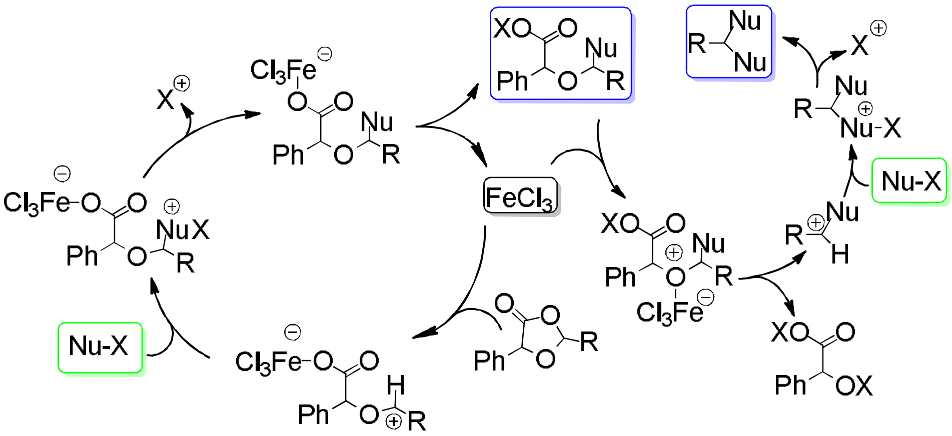

Figure 5. Proposed mechanistic scheme for the transformations

Conclusion

The reaction between 1,3-dioxolan-4-ones and C-nucleophiles was studied. The reaction proceeds either as mono-addition to form O-substituted mandelic acids or bis-addition to form tri-(hetero)arylmethanes.

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