An Improved Synthesis of Hydroxy Aryl Ketones by Fries Rearrangement with Methanesulfonic Acid/Methanesulfonic Anhydride

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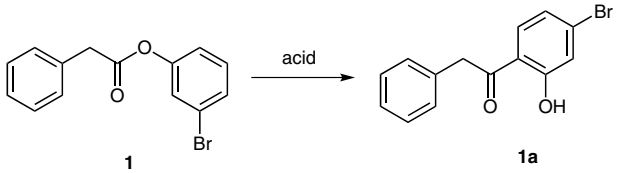
Received: 21.03.2012; Accepted after revision: 26.05.2012

Abstract: Methanesulfonic acid treated with methanesulfonic anhydride effectively mediates the Fries rearrangement of aryl esters to give hydroxy aryl ketones with high yields.

Key words: rearrangement, ketones, esters, methanesulfonic acid, methanesulfonic anhydride

Aryl esters readily rearrange to hydroxy aryl ketones via Lewis acid catalysis, a reaction known as the Fries rearrangement.[1,2] While the selective Fries rearrangement of esters of aromatic alcohols has been used to significant advantage in the production of industrial pharmaceuticals,[1,2] classical Fries rearrangements are typically catalyzed by metal halides or Brønsted acids. Often these reagents are corrosive, toxic, and react violently with water.[3–6] Classical Lewis acids are used in excess since they form complexes with both the starting materials and products. Therefore, this reaction risks corrosion and increased environmental impact due to the large amounts of acidic effluents and solid wastes,[7] as well as corrosive gases and contaminated salts.[8] These disadvantages inspired us to investigate alternative reagents to promote Fries rearrangements.

The use of methanesulfonic acid (MSA) to promote the Fries rearrangement has been described in limited examples.[4,8–11] In one example the Fries rearrangement of phenyl acetate was mediated by catalytic amounts of MSA (maximum 28.6%), at temperatures between 160 and 196 °C, leading to around 20–30% conversions. Unfortunately, the lengthy reaction time and the elevated reaction temperature partially caused degradation of the reaction mixture.[8] When the reaction was carried out at 90 °C with eight equivalents of MSA, the *para* isomer was produced with good conversion and selectively with the same substrate.[8] Recently, we found an improved procedure for Fries rearrangements mediated by MSA using methanesulfonic anhydride as an additive. We were interested in optimizing conditions using MSA because it is gaining increased importance in chemical syntheses as a nonoxidizing, readily biodegradable strong organic acid with high thermal stability.[12] Herein we describe the use of MSA treated with methanesulfonic anhydride to promote Fries rearrangements to give hydroxy aryl ketones with high yields.

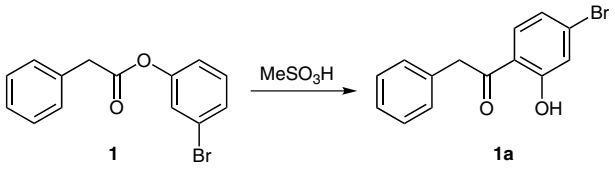


Scheme 1 Acid-catalyzed Fries rearrangement of **1**

We began by examining the use of MSA and other Lewis acids (Scheme 1) in the Fries rearrangement of 3-bromophenyl 2-phenylacetate (Scheme 2, Table 1). The Fries rearrangement of **1** using commonly used Lewis acids afforded the desired product in only 11–26% yield despite lengthy reaction time in these cases (Table 1, entries 1–4). In contrast, MSA was well suited to perform the rearrangement of **1** into **1a** regioselectively, and we were able to isolate a single isomer in higher yields (Table 1, entries 5–12). At various temperatures the Fries rearrangement of **1** provided the desired product in 53–74%, with 70 °C being preferable leading to complete conversion in three hours (Table 1, entries 5–7, 9). However, the reaction of **1** at 100 °C for half an hour in MSA afforded **1a** in only 62% yield due to degradation of the product (Table 1, entry 7). It was observed that the principal byproducts of this reaction were phenyl acetic acid and 3-bromophenol arising from hydrolysis of **1**. Technical grade MSA is typically 95% pure containing 2% water. The Fries rearrangement of **1** at higher water content showed that at the reaction onset, phenyl acetic acid and 3-bromophenol were the major products with low yield (Table 1, entry 8). Therefore, it was found to be very important to use anhydrous MSA, as elevated levels of water can hydrolyze **1** to phenol and phenyl acetic acid. In searching for suitable desiccant for MSA, methanesulfonic anhydride was found to dry MSA effectively, and the addition of 0.2 equivalents to the reaction resulted in an in-process water content of 1014 ppm and significantly improved the reaction efficiency affording the desired product **1a** in 81% yield (Table 1, entry 10). Surprisingly, attempting to improve the yield by further desiccating the MSA was not successful. We observed a detrimental effect of excess methanesulfonic anhydride on the reaction performance. Addition of greater than 0.4 equivalents (in-process water content below 500 ppm) resulted in a decrease in the yield of **1a** and the formation of new undesired byproducts caused by

SYNLETT 2012, 23, 1927–1930
Advanced online publication: 23.07.2012
DOI: 10.1055/s-0032-1316568; Art ID: ST-2012-S0264-L

excess methanesulfonic anhydride which accumulates at low KF values (Table 1, entries 11 and 12). Further optimization established that the reaction was most efficient at a water content between 800 and 1500 ppm, this typically corresponds to a 0.2 equivalent charge of methanesulfonic anhydride when employing tech grade MSA.



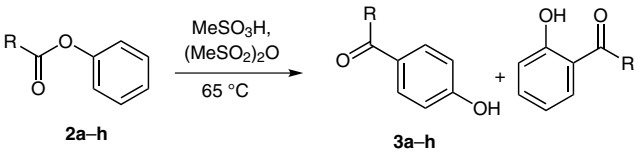
Scheme 2 Acids screen for Fries rearrangement of **1**

Table 1 Fries Rearrangement of **1**

Entry	Acid (equiv)	% KF (ppm)[c]	Temp (°C)	Yield (%)[d]
1	$AlCl_3$[a] (1)	–	65	26
2	$TiCl_4$[a] (1)	–	65	11
3	$SnCl_4$[a] (1)	–	65	0
4	$BF_3{\cdot}OEt_2$[a] (1)	–	65	0
5	MSA[b] (22)	2721	50	53
6	MSA[b] (22)	2721	70	73
7	MSA[b] (22)	2721	100	62
8	MSA[b] (22)	6582	65	42
9	MSA[b] (22)	2721	65	74
10	MSA[b] (22)	1014	65	81
11	MSA[b] (22)	447	65	75
12	MSA[b] (22)	126	65	72

[a] All reactions were conducted with 0.32 M substrate in degassed DCE under nitrogen.
[b] All reactions conducted 0.63 M substrate without solvent.
[c] MSA was titrated to determine % moisture.
[d] Isolated yield.

Since we had demonstrated that a MSA/methanesulfonic anhydride mixture was an efficient reagent system in the Fries rearrangement of **1**, we were interested in determining the scope and limitation of this procedure. The Fries rearrangement of a variety of phenyl ester derivatives in the presence of MSA/methanesulfonic anhydride occurred to give a mixture of *para*/*ortho* isomers favoring the *para* substitution in excellent yields (Scheme 3, Table 2, entries 2–8).[8,13] In one case, only a single isomer was isolated (Table 2, entry 1).[13] Branched aliphatic esters reacted more efficiently than a simple acetate (Table 2, cf. entries 1 and 7). Substrates with electron-donating substituents on the R group were found to be excellent substrates for the Fries rearrangement while substrates with electron-withdrawing substituents such as 4-$O_2NC_6H_4$ did not react.



Scheme 3

Table 2 Fries Rearrangements of Phenyl Ester Derivatives[a]

Entry	Ester	R	Product	Yield (%)[b]
1	**2a**	*i*-Bu	**3a**	91
2	**2b**	Ph	**3b**	77
3	**2c**	$PhCH_2CH_2$	**3c**	82
4	**2d**	*c*-Hex	**3d**	83
5	**2e**	4-$MeOC_6H_4$	**3e**	74
6	**2f**	*i*-Pr	**3f**	84
7	**2g**	Me	**3g**	72
8	**2h**	Pr	**3h**	61

[a] All reactions were conducted with 0.92 M substrate in $MeSO_3H$ with sufficient $(MeSO_2)_2O$ to bring the KF between 800 and 1500 ppm under nitrogen at 65 °C.
[b] Isolated yield.

The same process was successfully extended to other derivatives (Table 3). The Fries rearrangement of *ortho*-substituted derivatives occurred to give *p*-hydroxyarylketones with high conversion and selectivity. The ratio of *para*/*ortho* isomers was greater than 15:1 (Table 3, entries 1–4). In particular, the reaction with the phenyl acetic acid ester of *o*-cresol afforded the corresponding ketone in 89% (Table 3, entry 4). The reaction seemed to be faster when the aromatic part of the acid carries an electron-donating group (Table 3, entry 4). However, the Fries arrangement of *meta*-substituted benzoates with MSA/methanesulfonic anhydride gave *o*-hydroxy aryl ketones exclusively, and only single isomers were isolated (Table 3, entries 5 and 6). These results suggest that strong electron-donating groups activate the aromatic group and provide high reactivity during the Fries rearrangement. Similarly, the Fries rearrangement of *para*-substituted benzoates with MSA/methanesulfonic anhydride gave *o*-hydroxy aryl ketones selectively (Table 3, entries 7 and 8). Following the new improved procedure, the Fries arrangement of 3-bromophenyl 2-(2,5-dibromophenyl)acetate afforded the desired product in 81% yield (Table 3, entry 9). For this reaction, the stoichiometry of MSA was further investigated to provide the best yield. Using 20 equivalents gave a robust process with consistent yields while the yield of reaction using more than 20 equivalents was slightly lower. Less than 20 equivalents of MSA addition resulted in the reaction becoming mechanically nonstirrable. Indeed, moisture content of starting material ester was also controlled and was less than the detection

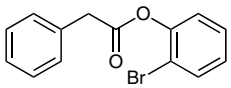
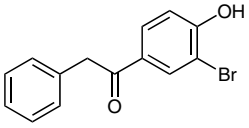
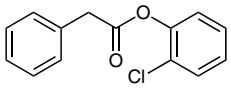
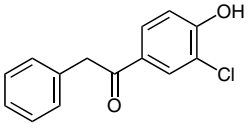
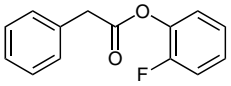
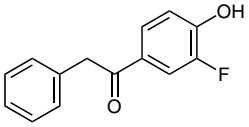
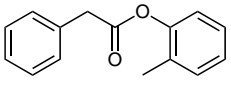
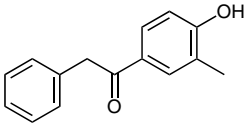
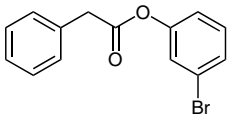
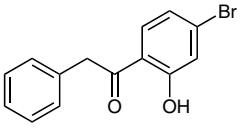
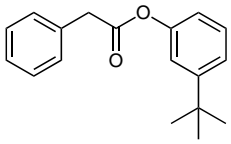
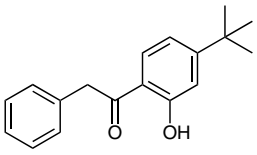
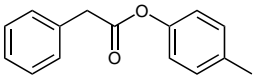
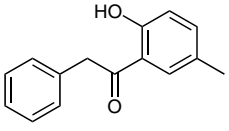
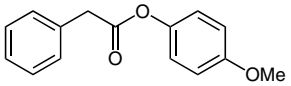
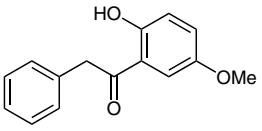
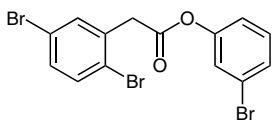
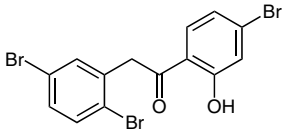
limit of the instrument (0.1%) to minimize the hydrolysis of the corresponding ester.

In conclusion, methanesulfonic acid treated with methanesulfonic anhydride as additive has been shown to be an improved procedure for the Fries rearrangement of aryl esters to hydroxy aryl ketones. Compared to classical Lewis acid, MSA is nonoxidizing, readily biodegradable, and has high thermal stability. This new efficient system might enrich the numerous applications of the Fries rearrangement.

Acknowledgment

The authors would like to thank Dr. Cheng Chen (Merck) for helpful discussions

Table 3 Comparison of Results Obtained from the Fries Rearrangement of Phenyl Ester Derivatives in the Presence of MSA[a]

Entry	Ester	Product	Yield (%)[c]
1			77
2			79
3			80
4			89
5			81
6			71
7			81
8			70
9[b]			81

[a] All reactions were conducted with 0.9 M substrate in $MeSO_3H$ with sufficient $(MeSO_2)_2O$ to bring the KF between 800 and 1500 ppm under nitrogen at 65 °C unless otherwise noted.
[b] Reaction was conducted with 0.64 M substrate in $MeSO_3H$ with sufficient $(MeSO_2)_2O$ to bring the KF between 800 and 1500 ppm under nitrogen at 65 °C.
[c] Isolated yield.

References and Notes

(1) Martin, R. *Org. Prep. Proced. Int.* **1992**, *24*, 369.
(2) Gerecs, A. *The Fries Reaction in Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, **1964**, Part 1, Vol. 3.
(3) For HF-mediated reactions, see: (a) Davenport, K. G. EP 251552, **1988**. (b) Yanagawa, T. JP 63132 855, **1988**. (c) Patton, J. R. EP 228172, **1987**. (d) Fukuoka, S. JP 62114927, **1987**.
(4) For HF-, $AlCl_3$-, and BF_3-mediated reactions, see: Hocking, M. B. *J. Chem. Technol. Biotechnol.* **1980**, *30*, 626.
(5) For $TiCl_4$- and $SnCl_4$-mediated reactions, see: Ramesh, B. B. IN 171970, **1993**.
(6) For BF_3-mediated reaction, see: Boyer, J. L. *J. Org. Chem.* **2000**, *65*, 4712.
(7) Mouhtady, O.; Iloughmane, H. G.; Roques, N.; Roux, C. L. *Tetrahedron Lett.* **2003**, *44*, 6379.
(8) Commarieu, A.; Hoelderich, W.; Laffitte, J. A.; Dupont, M. P. *J. Mol. Catal. A.: Chem.* **2002**, *182*, 137.
(9) (a) Staniland, P. A. EP 57503, **1982**. (b) Kusuda, M. JP 62234041, **1987**. (c) Behr, A. DE 19736905, **1998**.
(10) Sharghi, H. *J. Chem. Res., Synop.* **1998**, *10*, 628.
(11) Kaboudin, B. *Tetrahedron* **1999**, *55*, 12865.
(12) Springbor Laboratories, Inc., An acute oral toxicity study in rats with methanesulfonic acid, SLI Study No. 3255.11, November 7, 1997.
(13) **Typical Procedure for the Fries Rearrangement with MSA/Methanesulfonic Anhydride**
The methanesulfonic anhydride (59.1 mmol) was added to a MSA (384 mL) at 90 °C. The reaction mixture was stirred for 1 h, at this time KF (%) was measured. To MSA/methanesulfonic anhydride solution, 139.43 g of 3-bromophenyl 2-(2,5-dibromophenyl)acetate (295 mmol, Table 3, entry 9) was added under nitrogen atmosphere at 65 °C. The resulting solution was stirred for 22–24 h, at this time TLC indicated completion. After reaction was completed, batch was cooled to r.t. followed by addition of 2-PrOH–H_2O (3:1, 1115 mL) while maintaining batch temperature at below 65 °C. Batch was then stirred for 20 min, filtered, and dried to afford 108 g (81% yield) of the desired product as a crystalline solid (Table 3, entry 9). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.60 (s, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 7.67 (d, J = 2.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.45 (dd, J = 8.7, 2.4 Hz, 1 H), 7.26 (d, J = 1.9 Hz, 1 H), 7.20 (dd, J = 8.4, 1.8 Hz, 1 H), 4.59 (s, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 199.5, 160.7, 138.4, 135.5, 134.5, 132.6, 132.1, 129.2, 124.5, 123.0, 121.5, 120.9, 120.8, 47.9.

