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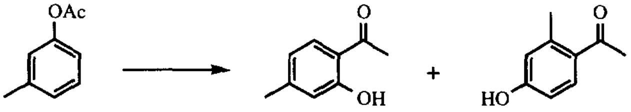
Zirconium Tetrachloride as a Mediator for Ambient Temperature *Ortho*-Fries Rearrangements

David C. Harrowven* and Richard F. Dainty

Department of Chemistry, The University, Southampton, S017 1BJ, UK

Abstract: Zirconium tetrachloride has been found to be an excellent mediator of the Fries reaction. Rearrangements occur at ambient temperature and are highly selective; giving the acetophenone derived from acetyl migration to the sterically least encumbered adjacent carbon.

Used for the preparation of aryl ketones from phenolic esters, the Fries reaction is one of the most important rearrangements in aromatic chemistry.[1] Conducted thermally in the presence of Friedel-Crafts catalysts or photochemically by irradiation with UV light, reactions typically give rise to mixtures of *ortho-* and *para*-substituted products. The proportion of each is strongly influenced by the reaction media. Generally, high temperatures favour *ortho*-shifts while low temperatures favour *para*-shifts, though many exceptions are known.[1] Indeed, this *Letter* is concerned with such an exception. For we have found that zirconium tetrachloride will mediate the Fries reaction at ambient temperature and that rearrangement to the least sterically encumbered *ortho*-carbon centre is favoured in all cases.

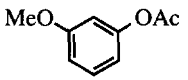
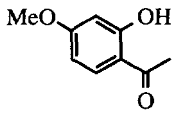
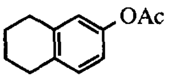
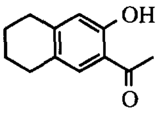
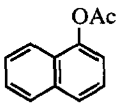
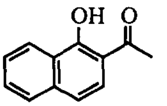
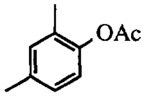
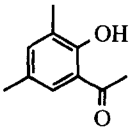
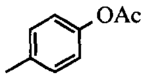
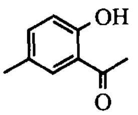
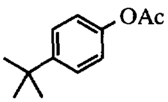
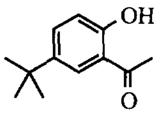


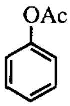
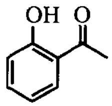
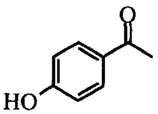
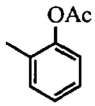
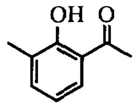
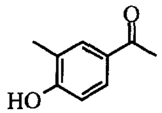
2eq. $AlCl_3$, $PhNO_2$, 25°C, 66h	28%	64%	ref. 2
2eq. $AlCl_3$, neat, 160°C, 15min	89%	7%	ref. 3
4eq. $ZrCl_4$, CH_2Cl_2, 20°C, 8h	**95%**	**<1%**	

This finding first came to light when we had cause to access 2'-hydroxy-4'-methylacetophenone.[4] The classical literature procedure of Cullinane and Edwards, which involved heating a mixture of *m*-cresyl acetate and aluminium tetrachloride neat at 160°C for 15 minutes, was effective but capricious in our hands, requiring careful control of temperature and the use of an oversized reaction vessel to minimise production of the *para*-isomer.[3] By contrast, simply stirring a dichloromethane solution of *m*-cresyl acetate with 4 equivalents of zirconium tetrachloride provided 2'-hydroxy-4'-methylacetophenone in 95% yield and in a high state of purity (>99%) after a simple extractive work up.[5]

Several further examples have been investigated. In most cases a single product was given in good yield (Table) and derived from an *ortho*-shift of the acetate to the sterically least encumbered neighbouring carbon centre (Entries A-F). Exceptions were phenyl acetate and *o*-cresyl acetate, where significant levels of the *para*-rearranged product were given (Entries G and H), and electron deficient aryl acetates which failed to give the reaction. That performing reactions in a simple ultrasound cleaning bath lead to substantial improvements in reaction rate and efficiency is noteworthy (*e.g.* Entries D-H).[6]

Table: Zirconium Tetrachloride Mediated Fries Rearrangements (in dichloromethane).

	Substrate & Conditions	Product and Yields		Substrate & Conditions	Product and Yields
A			**B**		
	r.t., 48h	85%		r.t., 48h	97%
C			**D**		
	r.t., 48h	77%		r.t.,))), 6h (r.t., 48h)	87% (56%)
E			**F**		
	r.t.,))), 24h (r.t., 5d)	83% (38%)		r.t.,))), 10h (r.t., 48h)	78% (52%)

	Substrate & Conditions	Products and Yields			Substrate & Conditions	Products and Yields	
		Major	Minor			Major	Minor
G				**H**			
	r.t., 7d	0%	0%		r.t., 2d	21%	0%
	r.t.,))), 12h	31%	10%		r.t.,))), 8h	47%	32%

In conclusion, we have found that zirconium tetrachloride is an excellent mediator of the Fries reaction. Rearrangement proceeds at ambient temperature with preferential migration towards the least sterically encumbered adjacent carbon centre. Conducting reactions in an ultrasonic cleaning bath is often beneficial.

References and Notes

1. For overviews see **a.** Gerecs, A. The Fries Reaction. In *Friedel-Crafts and Related Reactions*, Olah, G.A. Ed.; Interscience: New York, Vol. III, Pt. 1, 1964, pp 499; **b.** Walter, D.S. Ketones Bearing an α,β-Aryl or Hetaryl Substituent. In *Comprehensive Organic Functional Group Transformations*, Katritzky, A.R.; Meth-Cohn, O.; Rees, C.W. Eds.; Pergamon: Oxford, Vol. 3, 1995, pp 277.
2. Baltzly, R.; Ide, W.S.; Phillips, A.P. *J. Am. Chem. Soc.*, **1955**, *77*, 2522.
3. Cullinane, N.M.; Edwards, B.F.R. *J. Chem. Soc.*, **1958**, 2926.
4. Harrowven, D.C.; Dennison, S.T.; Howes, P. *Tetrahedron Lett.*, **1994**, *35*, 4243.
5. All compounds gave satisfactory spectroscopic and analytical characteristics. Zirconium tetrachloride was used as supplied. The quality of this reagent has a crucial baring on the efficiency of this reaction. Samples of $ZrCl_4$ with a feint pink hue should be returned to the supplier.
6. **a.** Einhorn, C.; Einhorn, J.; Luche, J.-L. *Synthesis*, **1989**, 787; **b.** Pestman, J.M.; Engberts, J.B.F.N.; de Jong, F. *Recl. Trav. Chim. Pays-Bas*, **1994**, *113*, 533; **c.** Lickiss, P.D.; McGrath, V.E. *Chem. Br.*, **1996**, *32(3)*, 47; **d.** Ley, S.V.; Low, C.M.R. *Ultrasound in Synthesis*, Springer-Verlag: Berlin, **1989**.

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