J. Chem. Research (S), 1999, 574–575†

Tandem Fries Reaction–Conjugate Addition under Microwave Irradiation in Dry Media; One-pot Synthesis of Flavanones†

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An $AlCl_3$–$ZnCl_2$ mixture supported on silica gel is found to be an efficient medium for the Fries rearrangement of acyloxybenzene or naphthalene derivatives in solvent-free conditions under microwave irradiation.

Acylphenols are useful organic compounds and versatile intermediates in the synthesis of biologically active naphthoquinones, pesticides, photographic agents and UV absorbents.[1–3]

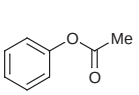
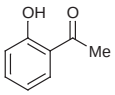
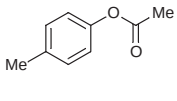
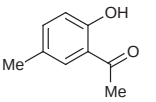
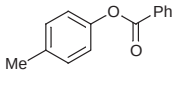
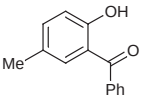
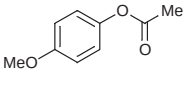
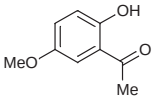
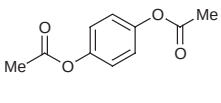
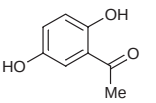
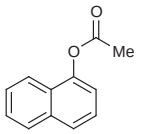
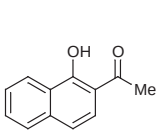
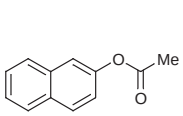
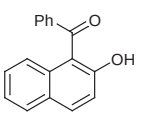
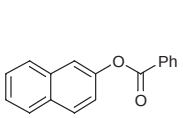
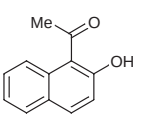
Although the Fries rearrangement of acyloxy benzenes provides useful routes to acylphenols, a long reflux time with more than a stoichiometric amount of a Lewis acid such as $AlCl_3$ is required.[4,5] Thermally conducted Fries reactions give rise to mixtures of *ortho*- and *para*-substituted products, the proportion of each being strongly influenced by the temperature (high temperature favors *ortho*-shifts) and reaction media. To overcome these problems, new catalysts such as $Hf(OTf)_4$,[6] $Sc(OTf)_3$[7] and $ZrCl_4$[8] have been developed recently for this reaction.

However, with these catalysts a long reflux time is required and the catalysts are not readily available. Therefore, the development of a new catalyst, which promotes the Fries rearrangement cleanly and regioselectively, is required. The efficiency of microwave irradiation for promoting organic reactions has been demonstrated.[9] In continuation of the study of microwave assisted organic reactions in our research group,[10–13] we were interested in developing a new catalyst for the Fries reaction, under microwave irradiation. Also the use of microwave irradiation for this reaction is known to be effective but was not ideal, requiring in our hands, more than one equivalent of $AlCl_3$ in chlorobenzene and use of a sealed tube, and was not regioselective for non-substituted phenyl acetate.[14] Also the high pressure developed in the sealed tube may cause hazards. It appeared the Lewis acids supported on a solid phase might be good alternative condition for this reaction in dry media.[15] We have found that an $AlCl_3$–$ZnCl_2$ mixture supported on silica gel is an efficient medium for promotion of the Fries rearrangement without solvent under microwave dielectric heating. It should be noted that, the reaction does not proceed on $ZnCl_2$ or $AlCl_3$ supported on silica gel alone.

When neat phenyl acetate was mixed with the support (1 : 3, w/w)[16] and subjected to microwave irradiation for 7 min, after work-up a 95% yield of the *ortho*-directed product (2′-hydroxyacetophenone) was obtained. Several further examples have been investigated. In most cases a single product derived from the *ortho*-shift of the acyl group to the sterically less encumbered neighboring carbon center was obtained (Table 1).

Interestingly, when a cinnamyl ester of phenols and naphthols (Table 2) was used as a substrate, the *ortho*-rearranged product chalcone spontaneously cyclized by intramolecular conjugate addition of the phenolic hydroxy group to the α,β-unsaturated system to afford flavanones in excellent yields. One-pot synthesis of flavanones are of interest as flavanones are biologically active compounds and recently, dioclein, a flavanone of plant origin was found to be biologically active for the treatment of kidney stones and prostate gland disorders.[17] To the best of our knowledge, this is the first example of a tandem Fries reaction–conjugate addition in dry media under microwave irradiation. To demonstrate the efficiency of this methodology, α-naphthyl acetate (Table 1 entry 6) mixed with support, was heated to *ca.* 300 °C (the reaction mixture reached this temperature in a microwave oven after 7 min.) for 7 min in an oil-bath, to give a 10% isolated yield of the reaction product along with starting material.

Table 1 Fries rearrangement of aryl ethers

Entry	Substrate	Product[a]	Yield[b](%)
1			95
2			97
3			90
4			62
5			90
6			95
7			80
8			92

[a] All products were characterized by mp, IR, ^{1}H NMR, and their spectroscopic data were similar to those reported in the literature.
[b] All yields refer to isolated products.

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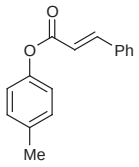
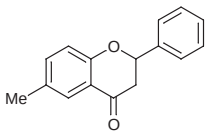
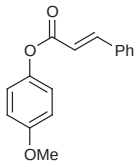
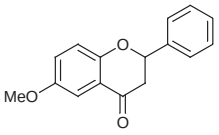
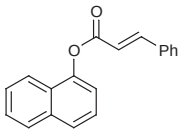
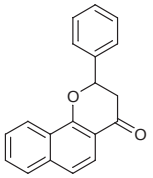
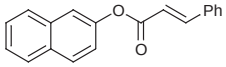
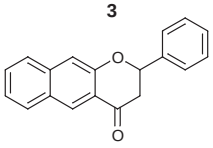
† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 Fries rearrangement of cinnamyl esters

Entry	Substrate	Product	Time/min. (% Yield)[a]
1		 **1**	7 (87)
2		 **2**	7 (73)
3		 **3**	7 (85)
4		 **4**	7 (79)

[a]Yields refer to isolated products.

Comparison with a 95% yield for the same period under microwave condition shows that the reaction is at least ten times faster. Furthermore, when the reaction mixture was heated at 300 °C for a longer period (60 min), a tarry material was obtained owing to decomposition of both product and starting material. In conclusion, we have developed a new support, which promotes the Fries rearrangement of aryl esters under microwave irradiation in dry media. The reaction proceeded smoothly with excellent yield and regioselective acylation of phenols and naphthols were achieved. The ease of work-up is another advantage of this new methodology.

Experimental

General.—The starting materials were prepared by treatment of acid chlorides with phenols or naphthols in the presence of sodium hydroxide.[18] ^{1}H NMR spectra were recorded on a Bruker FT-80 AC spectrometer. Mass spectra were obtained on a Fisson 800 Trio GC-MS with an ionizing voltage of 70 eV. IR spectra were performed on a Mattson 1000 spectrometer. Melting points were determined on a Mettler FPS and are uncorrected.

General Procedure for Microwave-induced Fries Rearrangement.—Neat substrate (0.01 mol) was mixed with the support (1 : 3, w/w) in a beaker and was exposed to microwave irradiation for 7 min. After cooling to room temperature the product was extracted with diethyl ether. Evaporation of the solvent gave almost pure product. Further purification was carried out by recrystallisation or column chromatography on silica gel.

Preparation of the Support.—To 100 g of SiO_2: $AlCl_3 \cdot 6H_2O$: $ZnCl_2$ (5:4:1 w/w/w), was added 150 ml of water and the product well mixed[19] to give a gel-like material. The water was evaporated *in vacuo* and the gel left to stand at 120 °C overnight. The resulting solid granules were ground and further activated by heating to 230 °C *in vacuo*. The catalyst was stored under dry conditions.

Compound **1**: mp 104 °C (from ethanol): IR (KBr) ν_{max}/cm^{-1} 3030, 2923, 2861, 1700 (C=O), 1615, 1492, 1299, 1230, 838, 700: δ_H (80 MHz, $CDCl_3$) 2.46 (s, 3H, CH_3), 2.9 (ABX system, 2H, $J_{AX} = 4.72$, $J_{BX} = 11.38$, $J_{AB} = 25.85$ Hz), 5.4 (dd, 1H, $J = 4.77$, 11.4 Hz), 7.04–7.90 (m, 8H, aromatic); MS (70 eV) m/z 238 (M^+, 100), 161 (19.5), 134 (6.4), 104 (22%).

Compound **2**: mp 136 °C (from ethanol): IR (KBr) ν_{max}/cm^{-1} 3007, 2961, 2930, 2830, 1676 (C=O), 1484, 1353, 1284, 1168, 1038, 869, 776, 715; δ_H (80 MHz, $CDCl_3$) 2.87 (ABX system, 2H, $J_{AX} = 4.87$, $J_{BX} = 11.38$, $J_{AB} = 25.67$ Hz), 3.74 (s, 3H, OCH_3), 5.35 (dd, 1H, $J = 4.87$, 11.37 Hz), 6.9–7.50 (m, 8H, aromatic); MS (70 eV) m/z 254 (M^+, 81.6), 177 (19.3), 150 (100), 135 (8.4), 122 (9.5), 107 (16.5), 103 (12.85).

Compound **3**: mp 126 °C (from ethanol): IR (KBr) ν_{max}/cm^{-1} 3053, 2961, 2923, 1676 (C=O), 1589, 1438, 1338, 1192, 1115, 823, 700; δ_H (80 MHz, $CDCl_3$) 3.1 (ABX system, 2H, $J_{AX} = 4.95$, $J_{BX} = 11.51$, $J_{AB} = 25.83$ Hz), 5.63 (dd, 1H, $J = 4.96$, 11.57 Hz), 7.30–8.5 (m, 11H, aromatic); MS (70 eV) m/z 274 (M^+, 66), 197 (9), 170 (100), 142 (6.7), 114 (43.3), 103 (9.5), 77 (4).

Compound **4**: mp 114 °C (from ethanol): IR (KBr) ν_{max}/cm^{-1} 3061, 3030, 2969, 1653 (C=O), 1600, 1515, 1483, 1376, 1238, 1007, 830, 753, 700; δ_H (80 MHz, $CDCl_3$) 2.95 (ABX system, 2H, $J_{AX} = 4.5$, $J_{BX} = 12.44$, $J_{AB} = 28.96$ Hz), 5.47 (dd, 1H, $J = 4.49$, 12.28 Hz), 7–7.90 (m, 10H, aromatic) 9.41 (d, 1H *peri*-hydrogen); MS (70 eV) m/z 274 (M^+, 72.6), 246 (6), 198 (14.8), 170 (100), 142 (41), 114 (72), 104 (19.5), 88 (11), 77 (12).

Received, 29th March 1999; Accepted, 10th June 1999
Paper E/9/02507C

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