Aromatic Acylation/Reduction: An Efficient Friedel–Crafts Alkylation Reaction

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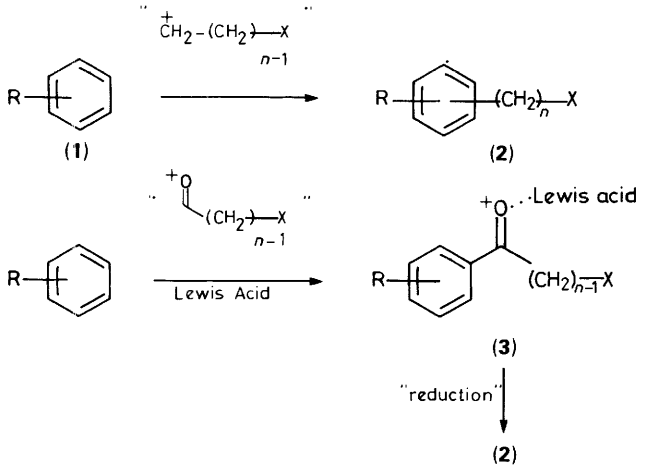
Friedel–Crafts acylation of aromatic compounds with branched or polyfunctionalised acyl halides followed by *in situ* reduction of the resulting carbonyl–Lewis acid complex with triethylsilane or polymethylhydrosiloxane (PMHS) polymer gives alkylated aromatic products in high yield.

During the course of a synthetic programme we required an efficient method for preparing alkyl aromatic compounds where the alkyl group was further substituted with distal, reactive groups such as halogen (see Scheme). In principle, Friedel–



(1) (2) (3) (2)

Scheme.

Crafts alkylation with a dihalogenoalkane could provide a simple route to (**2**). However, well-known problems intrinsic to the Friedel–Crafts alkylation, polyalkylation,[1] carbon/hydrogen migration and rearrangement,[2] and in the case of (**2**), multiple alkylation, combined to make this sequence unworkable. Here we report an equivalent to the classical Friedel–Crafts alkylation which proceeds in high yield with good chemoselectivity and which accommodates an array of functionalized alkyl groups.

The chemoselectivity of the Friedel–Crafts acylation derives from the intermediacy of Lewis complexes [Scheme, (**3**)] which are less reactive than either (**1**) or the acylium ion formed from acyl halide and Lewis acid. It occurred to us that while the intermediate (**3**) was deactivated toward further Friedel–Crafts reaction, the highly polarised carbonyl group might undergo reduction/deoxygenation if allowed to react *in situ* with a suitable hydride source. Indeed, precedent for the desired deoxygenation could be found in the reduction of electron-rich aromatic ketones by Et_3SiH/CF_3CO_2H[3] or Et_3SiH/BF_3OEt_2[4] mixtures.

We have found the Lewis salt intermediates produced *in situ* from the reaction of representative aromatic compounds with acyl chlorides undergo a smooth deoxygenation upon further reaction with 2.4 equiv. of Et_3SiH. Aqueous work-up followed by standard purification yields the alkylation product (see Table).† In some cases it is possible to substitute the inexpensive polymer polymethylhydrosiloxane (PMHS)[5] for triethylsilane. When the polymeric reducing agent is used, work-up consists simply of stirring the reaction mixture with damp silica gel, followed by filtration through a plug of silica gel. In a typical experimental procedure, a solution of isobutyryl chloride (3.86 g, 36.3 mmol) in CH_2Cl_2 (30 ml) was stirred during the addition of anhydrous $AlCl_3$ (4.4 g, 33.0 mmol). A solution of toluene (2.76 g, 30.0 mmol) in CH_2Cl_2 (10 ml) was added at 25 °C and the resulting solution was treated with Et_3SiH (9.25 g, 80.0 mmol). After aqueous work-up and purification by chromatography, 4-$MeC_6H_4CH_2Pr^i$ (3.81 g, 86%) was obtained (b.p. 100 °C/0.02 mmHg).

High yields in this sequence depend upon the solubility of the incipient Lewis salt complex in the reaction medium during reduction. With a few exceptions, CH_2Cl_2 is the solvent of choice. In cases where the Lewis salt is insoluble in CH_2Cl_2,

† The combination of $AlCl_3$ and Et_3SiH produces a reducing mixture of considerable power. Even aromatic ketones as unreactive as 4-nitroacetophenone react (CH_2Cl_2, 35 °C), although the major product in this case is 4-$NO_2C_6H_4CH(Me)Cl$.

Table. Friedel–Crafts alkylation of substituted aromatic compounds

ArH	RCOCl	Product,[a] b.p./m.p.	Yield[b] (%)	Ref.
MeC_6H_5	$Br(CH_2)_5COCl$	4-$MeC_6H_4(CH_2)_6Br$,[c] 118 °C/0.02 mmHg	77[c]	6
MeC_6H_5	Pr^iCOCl	4-$MeC_6H_4CH_2CH(CH_3)_2$, 100 °C/0.02 mmHg	86	7
MeC_6H_5	$Cl(CH_2)_3COCl$	4-$MeC_6H_4(CH_2)_4Cl$, 97—100 °C/0.01—0.02 mmHg	85	8
MeC_6H_5	$CH_3CH{=}CHCOCl$	Mixture		
MeC_6H_5	Bu^tCOCl	Mixture		
$MeOC_6H_5$	$Cl(CH_2)_3COCl$	4-$MeOC_6H_4(CH_2)_4Cl$, 103—105 °C/0.02 mmHg	87, 94[d]	9
$MeOC_6H_5$	$(CH_2CO)_2O$	4-$MeOC_6H_4(CH_2)_3CO_2H$, 57—58 °C	23, 58[e]	10
$MeOC_6H_5$	Bu^tCOCl	4-$MeOC_6H_4CH_2Bu^t$, 86 °C/0.02 mmHg	35[f]	11
PhC_6H_5	$Cl(CH_2)_3COCl$	4-$PhC_6H_4(CH_2)_4Cl$, 179—180 °C/0.02 mmHg	43,[g] 94	12
ClC_6H_5	$CH_3(CH_2)_4COCl$	4-$ClC_6H_5(CH_2)_5Me$, 118—120 °C/0.02 mmHg	35	
C_4H_4S	$Cl(CH_2)_3COCl$	Mixture		
$C_{10}H_8$	$CH_3(CH_2)_4COCl$	7:3 Mixture of 1-and 2-hexyl products	89	

[a] All products were purified by flash chromatography and/or distillation and were characterised by standard spectroscopic and analytical techniques. [b] Yields for isolated, purified products. [c] Approximately 5% of the corresponding chloroalkane was also identified. [d] PMHS used. [e] $PhNO_2$ used as solvent. [f] Light petroleum used as solvent. [g] CCl_4 used as solvent.

$PhNO_2$ may be substituted to advantage (see Table). The reaction proceeds well with a variety of acyl halides bearing straight or branched chains, halogens such as chloride or bromide or carboxylic acid functionalities. Complex reaction products are formed with either unsaturated acyl halides or acid-labile aromatic reactants, results consistent with the known reactivity of these functional groups toward Lewis acids. Not surprisingly under standard conditions, decomposition is observed with pivaloyl chloride, which is expected to expel CO upon acylium ion formation. Note, however, that with the very reactive anisole substrate, the rate of acylation is faster than the rate of loss of CO and neopentylanisole can be isolated in reasonable yield.

We have found this efficient Friedel–Crafts alkylation sequence to be widely applicable to other acyl halides and aromatic substrates and economical on a large scale.

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