Friedel–Crafts Reactions

Electrophilic Alkylations in Neutral Aqueous or Alcoholic Solutions**

*Matthias Hofmann, Nathalie Hampel, Tanja Kanzian, and Herbert Mayr**

Dedicated to Professor Johann Mulzer
on the occasion of his 60th birthday

Friedel–Crafts alkylations and mechanistically related reactions, such as *tert*-alkylations of silyl enol ethers or alkoxyalkylations of allylsilanes and enol ethers, are usually promoted by Lewis acids in inert solvents.[1] When such reactions are carried out in aqueous or alcoholic solutions, usually Brönsted or nonhydrolyzable Lewis acids are employed to generate small equilibrium concentrations of carbocations.[2] Basic and even neutral aqueous or alcoholic

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solutions have been considered prohibitive for such reactions, since water and alcohols are intuitively considered as strong nucleophiles which instantaneously trap the intermediates of S_N1 reactions and do not give π nucleophiles a chance to intercept the transient carbocations.

In numerous papers we have demonstrated that the reactions of carbocations with nucleophiles can be described by Equation (1),[3–5] where k is a second-order ($L\,mol^{-1}\,s^{-1}$) or first-order (s^{-1}) rate constant at 20°C, s is a nucleophile-specific slope parameter, N (or N_1) is the nucleophilicity parameter, and E is the electrophilicity parameter.

$$\log k = s(N + E) \qquad (1)$$

Recently, we reported nucleophilicity parameters N_1 for some solvents[6] (Figure 1, right), and compared them with previously published nucleophilicity parameters N for π systems[3,4] (Figure 1, left). The first-order rate constants calculated from N_1 and the second-order rate constants calculated from N by Equation (1) become directly comparable if 1M solutions of the π nucleophiles are considered (pseudo-first-order rate constant $k_{1\Psi} = k[\text{nucleophile}]_0$). We had, therefore, predicted that solvolytically generated carbocations should be trapped by π nucleophiles[6] (e.g., 1M alkenes or arenes) if N of the corresponding π nucleophile is greater than N_1 of the solvent under consideration, that is, if the corresponding nucleophile is located above the solvent in a graphical representation such as Figure 1. We now report an experimental verification of this forecast and thus lay the basis for a new type of Friedel–Crafts chemistry.[7]

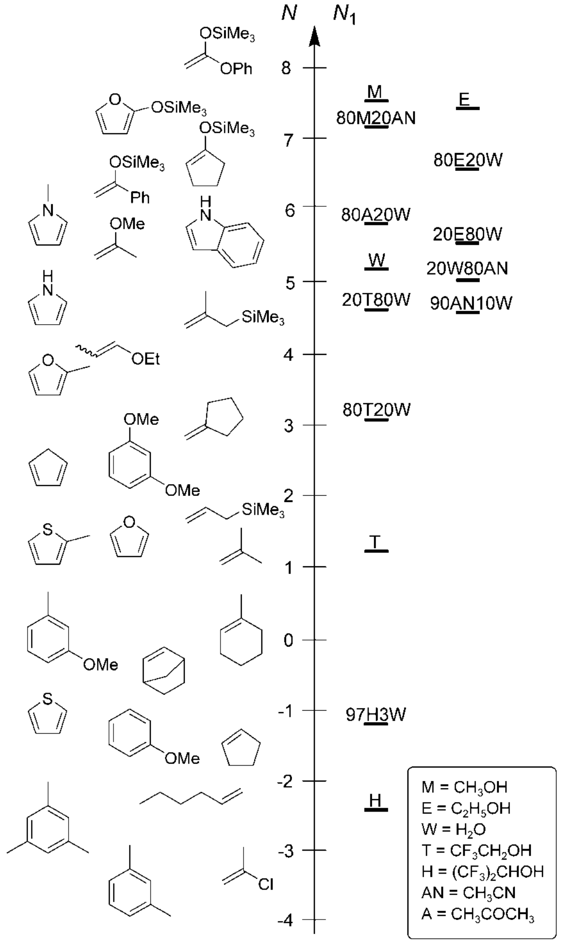
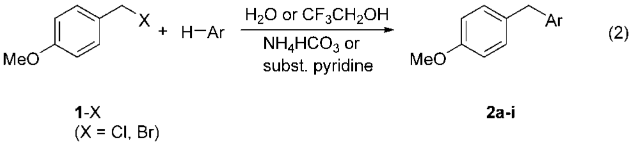
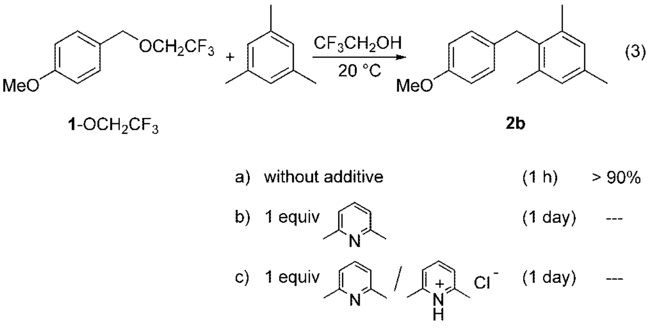


Figure 1. Comparison of the nucleophilicity parameters N_1 of solvents with the N parameters of typical π systems. Mixtures of solvents are given as vol%, for example, 80A20W = 80% acetone/20% water.

To examine the scope of nucleophiles we have examined reactions of 4-methoxybenzyl halides (**1**-X) with arenes and enol ethers in different solvents. Table 1 shows that electrophilic aromatic substitutions in 1M solutions of arenes with 4-methoxybenzyl halides [Eq. (2)] have been successful in all cases where N of the arenes is greater than N_1 of the solvent. The formation of **2a–d** in 2,2,2-trifluoroethanol (T) shows that trapping with the π nucleophiles may also be possible in cases where the N parameter of the π system is slightly smaller than N_1 of the solvent.

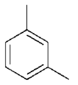
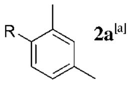
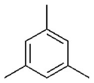
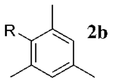
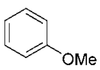
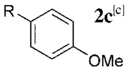
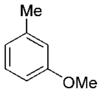
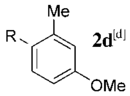
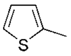
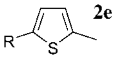
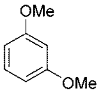
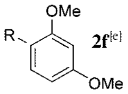
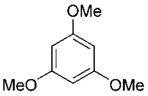
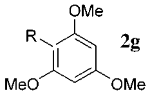
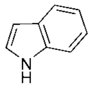
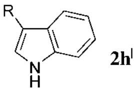
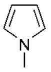
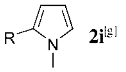


Can the formation of products **2a–d** in 2,2,2-trifluoroethanol be explained by consecutive reactions of the initially produced trifluoroethyl ether **1**-OCH_2CF_3 with the arenes? When **1**-OCH_2CF_3 and mesitylene were dissolved in 2,2,2-trifluoroethanol at ambient temperature, quantitative conversion into **2b** was observed [Eq. (3a)]. No reaction took place in the presence of 2,6-lutidine, however, [Eq. (3b,c)] indicating that the products isolated in the presence of base (Table 1) are the results of kinetic control. We conclude, therefore, that in 2,2,2-trifluoroethanol the 4-methoxybenzyl cation reacts faster with mesitylene than with the solvent.



These results indicate a noticeable increase of the nucleophilicity of π systems in hydroxylic solvents, in contrast to previous reports which showed that the rates of the reactions of carbocations with olefins are only slightly affected by solvent polarity [$k(CH_3NO_2)/k(CH_2Cl_2) = 4$].[8] Since the diphenylmethyl cation, which shows a similar electrophilicity as the 4-methoxybenzyl cation,[9] did not react with m-xylene or mesitylene, when generated from diphenylmethyl chloride in 2,2,2-trifluoroethanol in the

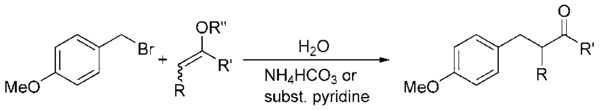
Table 1: Reactions of 4-methoxybenzyl halides (**1**-X) with arenes [according to Equation (2)].

H–Ar	*N*	Product (R = 4-$CH_3OC_6H_4CH_2$)	X	Solvent	Base	Yield [%]
	−3.54	 **2a**[a]	Cl	H	NH_4HCO_3	47
			Cl	T	NH_4HCO_3	66
			Cl	T	2,6-lutidine	+[b]
	ca. −2.6	 **2b**	Cl	H	NH_4HCO_3	85
			Cl	T	NH_4HCO_3	88
			Cl	T	2,6-lutidine	79
	−1.18	 **2c**[c]	Cl	H	NH_4HCO_3	77
			Cl	T	NH_4HCO_3	86
			Cl	T	2,6-lutidine	+[b]
	0.13	 **2d**[d]	Br	T	NH_4HCO_3	97
	1.26	 **2e**	Cl	T	2-chloropyridine	84
	2.48	 **2f**[e]	Cl	T	2,6-lutidine	91
			Cl	T	–	84
			Br	90AN10W	NH_4HCO_3	+[b]
	ca. 4	 **2g**	Cl	T	2,6-lutidine	88
			Br	90AN10W	NH_4HCO_3	65
	5.80	 **2h**[f]	Br	80A20W	NH_4HCO_3	75
	5.85	 **2i**[g]	Br	80A20W	NH_4HCO_3	70

[a] Contains traces of 1,2,3-substituted product. [b] Quantitative conversion determined by GC-MS. [c] Contains traces of 1,2-substituted product. [d] Isolated as a mixture of regioisomers. [e] Contains 7% of 1,2,3-substituted product. [f] Contains 17% of the corresponding 2-isomer. [g] Contains 21% of the corresponding 3-substituted product.

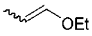
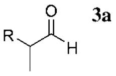
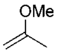
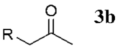
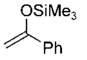
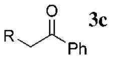
presence of these π nucleophiles, the solvent effects on these reactions are still obscure.

When 4-methoxybenzyl bromide (**1**-Br) was mixed with 1-methylpyrrole without a solvent or in acetonitrile, compound **2i**, accompanied by numerous side products, was produced considerably slower than in analogous reactions in the presence of water and base (Table 1). Less nucleophilic arenes, for example, 2-methylfuran, which formed the substitution product **4e** in 68% yield in 90% aqueous acetonitrile (90AN10W) (see below), did not react with **1**-Br in pure acetonitrile.



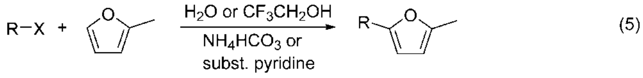
1-Br **3a-c**

Table 2: Reactions of 4-methoxybenzyl bromide with enol ethers [according to Equation (4)].

Enol ether	*N*	Product (R = 4-$CH_3OC_6H_4CH_2$)	Solvent	Base	Yield [%]
	ca. 4	 **3a**	90AN10W	NH_4HCO_3	60
	5.41	 **3b**	90AN10W	2,6-lutidine	67
	6.22	 **3c**	90AN10W	NH_4HCO_3	33

The isolation of the carbonyl compounds **3a** and **3b** from the reactions of 4-methoxybenzyl bromide with alkyl enol ethers indicates that the enol ethers react faster with the 4-methoxybenzyl cation than water in 90% aqueous acetonitrile [Eq. (4), Table 2], but that water reacts faster with the resulting α-alkoxycarbenium ions under the same conditions. This change of selectivity may be explained by the geminal interaction of two oxygen groups at the same carbon center in the semiacetals formed from α-alkoxycarbenium ions and water (anomeric stabilization).[10]

In a third series of experiments, we have examined the range of electrophiles using 2-methylfuran as nucleophile [Eq. (5), Table 3]. It is found that a wide variety of S_N1-active substrates, particularly benzyl and allyl halides, can be employed for Friedel–Crafts reactions under these conditions, and we are presently investigating the scope and limitations of this new method.



4a-f

Experimental Section

Typical procedure—preparation of **4e**: At ambient temperature, 4-methoxybenzyl bromide (1.00 g, 4.97 mmol) was added dropwise to 25 mL of a stirred solution of 2-methylfuran (2.05 g, 25.0 mmol) in 90% aqueous acetonitrile (v/v) (90AN10W) and ammonium hydrogencarbonate (786 mg, 9.94 mmol). After 2 h, water (20 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined ethereal phases were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/ether 7:1) to yield **4e** (737 mg, 73%) as a colorless liquid.

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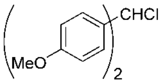
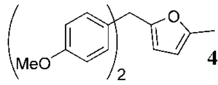
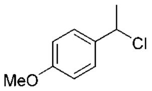
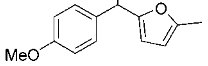
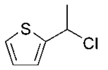
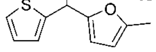
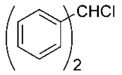
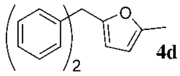
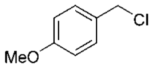
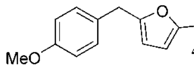
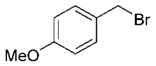
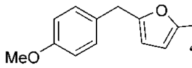
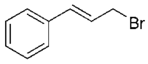
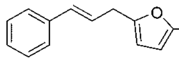
Table 3: Reactions of S_N1-active substrates with 2-methylfuran [according to Equation (5)].

R–X	Product (R = 4-$CH_3OC_6H_4CH_2$)	Solvent	Base	Yield [%]
	 **4a**	T	2-chloropyridine	85
	 **4b**	T	2,6-lutidine	70
	 **4c**	90AN10W	NH_4HCO_3	48
	 **4d**	T	2,6-lutidine	87
	 **4e**	T	2,6-lutidine	74
	 **4e**	90AN10W 90AN10W	NH_4HCO_3 –	73 68
	 **4f**[a]	90AN10W	NH_4HCO_3	61

[a] Isolated as a mixture (84:16; NMR) of **4f** and the allylic isomer 2-methyl-5-(1-phenylallyl)furan.

[1] a) C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, *32*, 725; b) G. A. Olah, *Friedel-Crafts and related reactions, Vol. 1 and 2*, Wiley, New York, **1963–1964**; c) R. M. Roberts, A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry: A Century of Discovery*, Marcel Dekker, New York, **1984**; d) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, **1990**, pp. 187–203; e) A. Hosomi, *Acc. Chem. Res.* **1988**, *21*, 200–206; f) I. Fleming, J. Dunoguès, R. Smithers in *Organic Reactions* (Ed.: A. S. Kende), Wiley, New York, **1989**, pp. 57–575; g) T. Mukaiyama, M. Murakami, *Synthesis* **1987**, 1043–1054; h) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095–1120; i) M. T. Reetz, *Top. Curr. Chem.* **1982**, *106*, 1–54; j) *Lewis Acids in Organic Synthesis, Vol. 1 and 2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**.

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