

Short Communication

Effects of high pressure on Friedel–Crafts benzoylation

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ABSTRACT: A study of Friedel–Crafts benzoylation under high pressure is reported. Activated (toluene) to non-activated (benzene) and deactivated (fluorobenzene) aromatic substrates were acylated (benzoyl chloride) at 34 °C for 3 h 50 min in the presence of the usual Lewis acid AlCl₃, raising the pressure from atmospheric pressure (1 bar) to 10 kbar. Non-activated and deactivated aromatic substrates were found to be more sensitive to the effect of the high pressure. Indeed, fluorobenzene led to the expected aromatic ketone with a 56% yield under the conditions mentioned above (5 kbar), whereas the yields constantly decreased for toluene when the pressure increased. Hyperbaric activation has the advantage of being able to conduct such a transformation on deactivated substrates, avoiding very acidic catalysts such as trifluoromethanesulfonic acid or expensive activators such as gallium nonaflate. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: high pressure; friedel–crafts; benzoylation; deactivated aromatic substrates; aluminum trichloride

INTRODUCTION

Friedel–Crafts benzoylations are an important class of reactions in organic synthesis. The access to numerous aromatic ketones follows this synthetic route,^{1–3} and various efforts have been especially conducted to achieve electrophilic benzoylations from deactivated benzenes. Thus, halobenzenes,^{4–6} nitrobenzene^{5b,7} and even α , α , α -trifluorotoluene⁷ have been functionalized using specific reagents for acylation and/or catalysts. For instance, benzoylations of fluorobenzene, chlorobenzene and dichlorobenzene have been successfully carried out using a catalytic amount of gallium nonafluorobutanesulfonate (1–5 mol%)^{6c} as they afforded the corresponding aromatic ketones in good (71%) to excellent (99%) yields. The single example of acylation of α , α , α -trifluorotoluene⁷ (nitrobenzene was also studied in this work) using methyl benzoate as the acylating reagent with trifluoromethanesulfonic acid as the catalyst gave access to the corresponding ketones in yields up to 80%. Unfortunately, we have been unable to repeat these latter results. However, the great opportunities that such a transformation offers in terms of industrial valorization prompted us to examine an alternative solution resorting to high pressure.

Relatively little is known about high-pressure effects on S_EAr and the few studies conducted on this topic are mostly

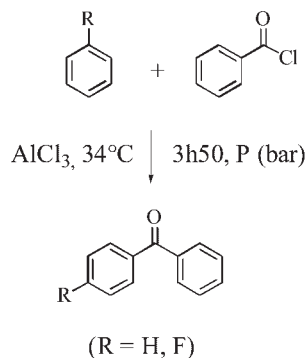
related to nitration reactions at 2–3 kbar.⁸ One example of hydroxyalkylation⁹ and only one acylation¹⁰ have been described under similar conditions. Concerning this last application, reported by Coillet *et al.*,¹⁰ toluene and benzene were reacted with benzoyl chloride in the presence of aluminum trichloride at 29.6 °C while the pressure was raised up to 1.5 kbar. It was found that the second-order rate constant for the benzoylation of benzene was doubled on going from 1 bar to 1.5 kbar, a result from which a negative activation volume ($\Delta V^\ddagger = -11.4 \text{ ml mol}^{-1}$) was calculated, suggesting that Friedel–Crafts benzoylations could be favoured under high pressure.

As a second example, we report in this paper our results and observations on Friedel–Crafts benzoylations under hyperbaric activation. Activated (toluene) to non-activated (benzene) and deactivated (fluorobenzene) aromatics were studied and compared.

RESULTS

We first decided to work using Coillet *et al.*'s conditions¹⁰ with benzoyl chloride in the presence of AlCl₃ at 34 °C for 3 h 50 min. The aromatic substrate was introduced as the solvent (molar fractions: [aromatic substrate]:[Lewis acid + ArCOCl] = 0.94:0.06) and the pressure was raised from 1 bar to 10 kbar. Benzene and fluorobenzene could be acylated under these conditions (Scheme 1, Table 1) despite the low solubility of the catalyst at atmospheric pressure in such mixtures.

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$$\frac{[\text{R-C}_6\text{H}_5]}{[\text{AlCl}_3]} + \frac{[\text{PhCOCl}]}{[\text{AlCl}_3]} = 0.94 : 0.06$$

Scheme 1. Benzoylation of benzene and fluorobenzene using the aromatic substrate as the solvent

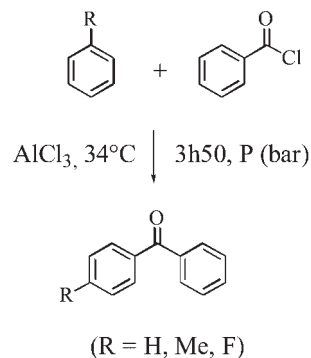
The two aromatic substrates considered behave differently under hyperbaric conditions. With benzene (entries 1–3), the yields constantly decreased with increasing pressure, whereas with fluorobenzene (entries 4–6), the yield doubled on going from 1 bar to 5 kbar. This difference in the pressure dependence might be the result of the pressure-induced crystallization of the aromatic substrate/solvent. Indeed, it is known that the melting-point of benzene increases from 5.5 °C at 1 bar to 114 °C at 5 kbar.¹¹ Hence, diffusion phenomena are likely to become critical with increasing pressure and, consequently, the yields of the reactions can be seriously altered. Fluorobenzene, which crystallizes at –40 °C at 1 bar, is probably less prone to this phenomenon. The low yields measured as a whole can be additionally assigned to the poor solubility of AlCl_3 in these reaction media, noticed when preparing the samples.

We then decided to work using the aroyl chloride as the solvent (molar fractions: [aromatic substrate]: [Lewis acid]:[ArCOCl] = 0.06:0.04:1.00) in an attempt to maintain comparable experimental conditions for all the aromatic substrates considered. Toluene, benzene and fluorobenzene were independently reacted with benzoyl chloride in the presence of AlCl_3 at 34 °C for 3 h 50 min, while the pressure was raised from 1 bar to 10 kbar (Scheme 2, Table 2, Fig. 1). This time, homogeneous

Table 1. Benzoylation of benzene and fluorobenzene in the presence of AlCl_3 at 34 °C for 3 h 50 min and using the aromatic substrate as the solvent

Entry	R	P (bar)	Yield (%) ^a
1	H	1	67
2	H	5000	48
3	H	10 000	43
4	F	1	22
5	F	5000	47
6	F	10 000	48

^a The other products identified are only starting materials.



$$\frac{[\text{R-C}_6\text{H}_5]}{[\text{AlCl}_3]} + \frac{[\text{PhCOCl}]}{[\text{AlCl}_3]} = 0.06 : 0.04 : 1.00$$

Scheme 2. Benzoylation of toluene, benzene and fluorobenzene under high pressure using benzoyl chloride as solvent

media were obtained before and after transformation, showing a better solubility of the catalyst.

The yields are generally lower for benzene and fluorobenzene than those previously measured, suggesting

Table 2. Benzoylation of benzene, toluene and fluorobenzene in the presence of AlCl_3 at 34 °C for 3 h 50 min and using benzoyl chloride as the solvent

Entry	R	P (bar)	Yield (%) ^a
1	H	1	34 (67 ^b)
2	H	1000	46
3	H	5000	34 (48 ^b)
4	H	10 000	23 (43 ^b)
5	Me	1	73
6	Me	1000	59
7	Me	5000	59
8	Me	10 000	41
9	F	1	5 (22 ^b)
10	F	1000	12
11	F	5000	56 (47 ^b)
12	F	10 000	24 (48 ^b)

^a The other products identified are only starting materials.

^b Yields obtained when the aromatic substrate is used as the solvent (cf. Table 1).

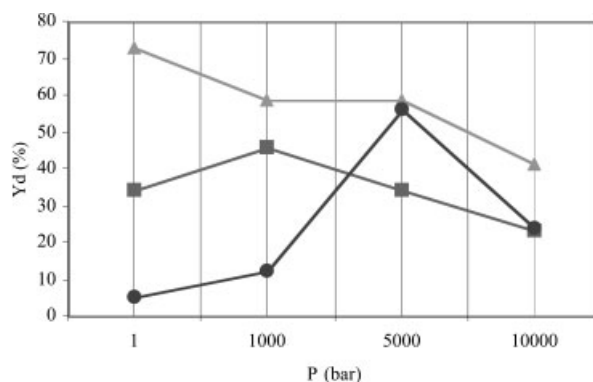


Figure 1. Benzoylation yields of (■) benzene, (▲) toluene and (●) fluorobenzene vs pressure

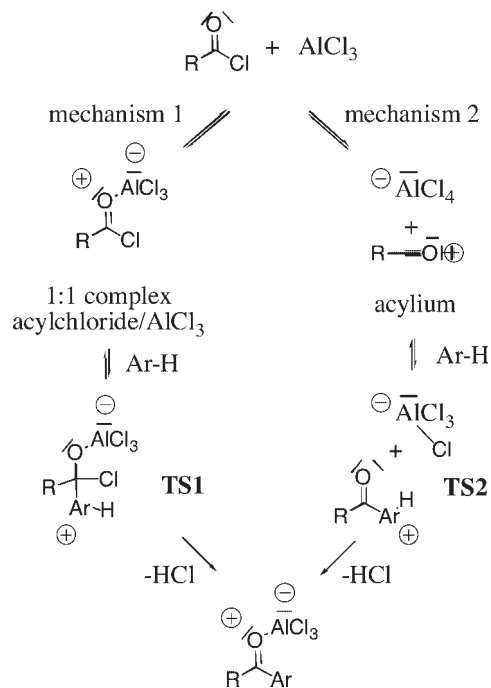
that benzoyl chloride probably crystallizes even more quickly than benzene under high pressure. However, this solvent being identical and the proportions being the same for all of the experiments conducted, the consequences of this crystallization are expected to be similar for the three aromatic substrates. It remains clear from Fig. 1 that the effect of high pressure is still fully dependent on the substrate. Maximum efficiency is observed with fluorobenzene, the benzylation yield of which doubles on going from 1 bar to 1 kbar (entries 9 and 10) and increases 10-fold between 1 bar and 5 kbar (entries 9 and 11). At higher pressure (10 kbar, entry 12), the activation becomes less effective, leading to lower conversions. Hence an 'optimum pressure' (OP) is associated with an optimal effect. A similar evolution is observed with benzene (entries 1–4), the best yield being obtained at a lower OP (1 kbar, entry 2). By contrast, for toluene the yield constantly decreases when the pressure increases (entries 5–8). This result suggests that the crystallization of the aromatic substrate cannot be held directly responsible for the yield variations since toluene, the melting-point of which increases from -95.1°C at 1 bar to 30°C at 9.6 kbar, remains probably more fluid than benzene with increasing pressure.

Such result is in complete accordance with Coillet *et al.*'s work on the nitration of toluene, benzene and chlorobenzene between 1 bar and 2.3 kbar in acetic acid or nitromethane.^{8a} The authors reported negative activation volumes for all the substrates considered, the $|\Delta V^{\ddagger}|$ values being larger for deactivated aromatics, suggesting that the latter would indeed be more sensitive to the effect of the pressure (in AcOH: $\Delta V^{\ddagger}_{\text{toluene}} = -10\text{ cm}^3\text{ mol}^{-1}$; $\Delta V^{\ddagger}_{\text{benzene}} = -22\text{ cm}^3\text{ mol}^{-1}$; $\Delta V^{\ddagger}_{\text{chlorobenzene}} = -23.5\text{ cm}^3\text{ mol}^{-1}$).

DISCUSSION

The details of Friedel–Crafts acylation are not completely understood, although two mechanisms are retained to date (Scheme 3).¹² For this reason, it is difficult to propose a rationale for the results described above. The following may nevertheless be considered.

Whatever the mechanism, the reaction between ArH and the putative 1:1 acyl chloride– AlCl_3 complex (mechanism 1) or the acylium (mechanism 2) should be disfavored on deactivation of the aromatic. This step could then become the limiting step for deactivated derivatives and the effect of pressure would consist in helping these poorly reactive entities to reach TS1 or TS2. By contrast, the next step, which is irreversible and which corresponds to HCl elimination, should be disfavored under high pressure (increased number of molecules), whatever the aromatic substrate. The 'optimum pressures' observed could therefore correspond to the balance between these two opposite effects, which would obviously depend on the substrate. As toluene would not



Scheme 3. Suggested mechanisms of Friedel–Crafts reactions

need any activation to reach TS1 or TS2, the limiting step of the reaction would become HCl elimination, which is increasingly disfavored on raising the pressure.

In conclusion, we have reported new examples of Friedel–Crafts acylations conducted under high pressure. This activation affords better results with deactivated benzenes. Further studies should involve other deactivated aromatics such as chlorobenzene, nitrobenzene and α,α,α -trifluorotoluene. Concerning the last substrate, aluminum trichloride will have to be replaced as this catalyst reacts with trifluorotoluene to give trichlorotoluene.¹³

Acknowledgments

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