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On-line Reaction Monitoring of Lithiation of Halogen Substituted Acetanilides *via in situ* Calorimetry, ATR Spectroscopy, and Endoscopy

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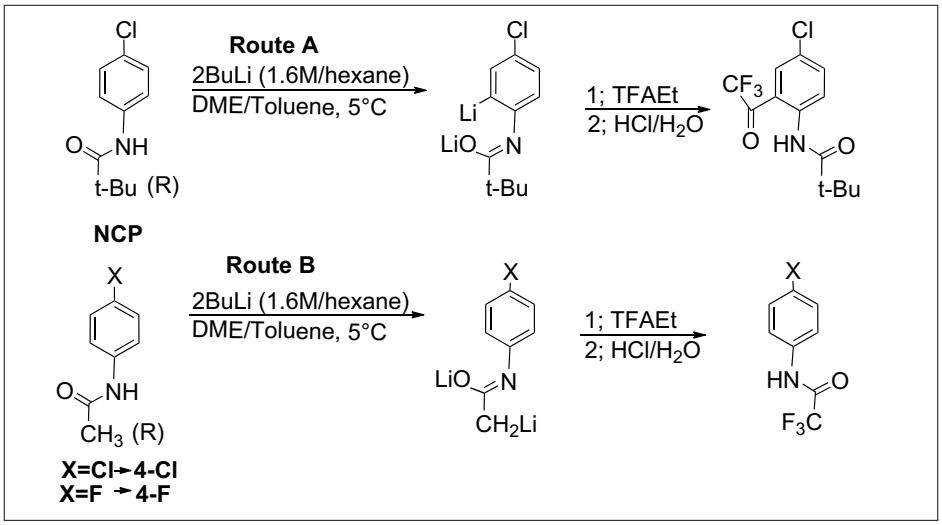
§SCS DSM Prize for best poster

Abstract: Lithiation of N-(4-chlorophenyl)-pivalamide (NCP) and two additional substituted acetanilides: 4-fluoroacetanilide (4-F) and 4-chloroacetanilide (4-Cl) has been monitored by means of calorimetry, on-line ATR-IR and UV/vis spectroscopy and endoscopy. The combined on-line monitoring revealed the differences between the reaction paths of the chosen substrates. Thus the product structure and the reaction times for the individual reaction steps can be determined *in situ*.

Keywords: Acetanilides · Calorimetry · Lithiation · On-line spectroscopy

Introduction

Substituted acetanilides are important precursors in the pharmaceutical industry. Functionalization of the aromatic ring or the amide side chain is often achieved by sequential steps of lithiation, alkylation/acylation and hydrolysis. As an example, lithiation-fluoroacetylation reaction of NCP is a key step in the synthesis of efavirenz (L-743,726),[1,2] a highly potent reverse transcriptase inhibitor of the human immunodeficiency virus (HIV) type 1. The dynamic description and understanding of the course of such multi-step reactions is of great importance in industry during early process development but also for on-line optimization at plant scale.



Scheme 1. Possible pathways for lithiation-fluoroacetylation reactions of various halogen-substituted acetanilides. Product structures were verified by GC/MS. Reaction conditions: reagent amounts BuLi/TFAET/HCl= 2.2/1.3/2.2 equiv., substrate (NCP/4-Cl/4-F) conc.: 0.22 M, solvent: 22 mL DME/toluene (V/V=/7), dosing rates: $f_{BuLi}/f_{TFAEt}/f_{HCl}$ = 1.0/0.2/0.2 mL/min, waiting times after dosing steps: 60/30/10 min, T_{react} = 5 °C, stirrer speed: 600 rpm.

In recent years, we have developed high-performance reaction calorimeters with *in situ* monitoring by means of ATR-IR and UV/vis spectroscopy, alongside with endoscopic visualization.[3–5] The latest reactor generation is particularly suited for low-temperature processes such as lithiation reactions.[6]

In this context, we investigated the lithiation of three acetanilide derivatives. We show how *in situ* analysis allows to optimize the dosing schedule, to follow heterogeneous steps (*e.g.* precipitation/dissolution of intermediates), and to detect endpoints of the reaction steps.

On-line Monitoring of the Lithiation of Halogen-substituted Acetanilides

Lithiation reactions of halogen-substituted acetanilides can follow two reaction paths, depending on the amide sidechain (Scheme 1). If the amide side-chain (R) does not contain an α-hydrogen, the aromatic core (Ar) is lithiated (route A). When R contains an α-hydrogen, this will be removed by n-butyllithium (BuLi) and substituted upon acylation or alkylation (route B)[7] because of its higher acidity. Corresponding acidity constants are: $pK_a^{Amide\text{-}H}$ =

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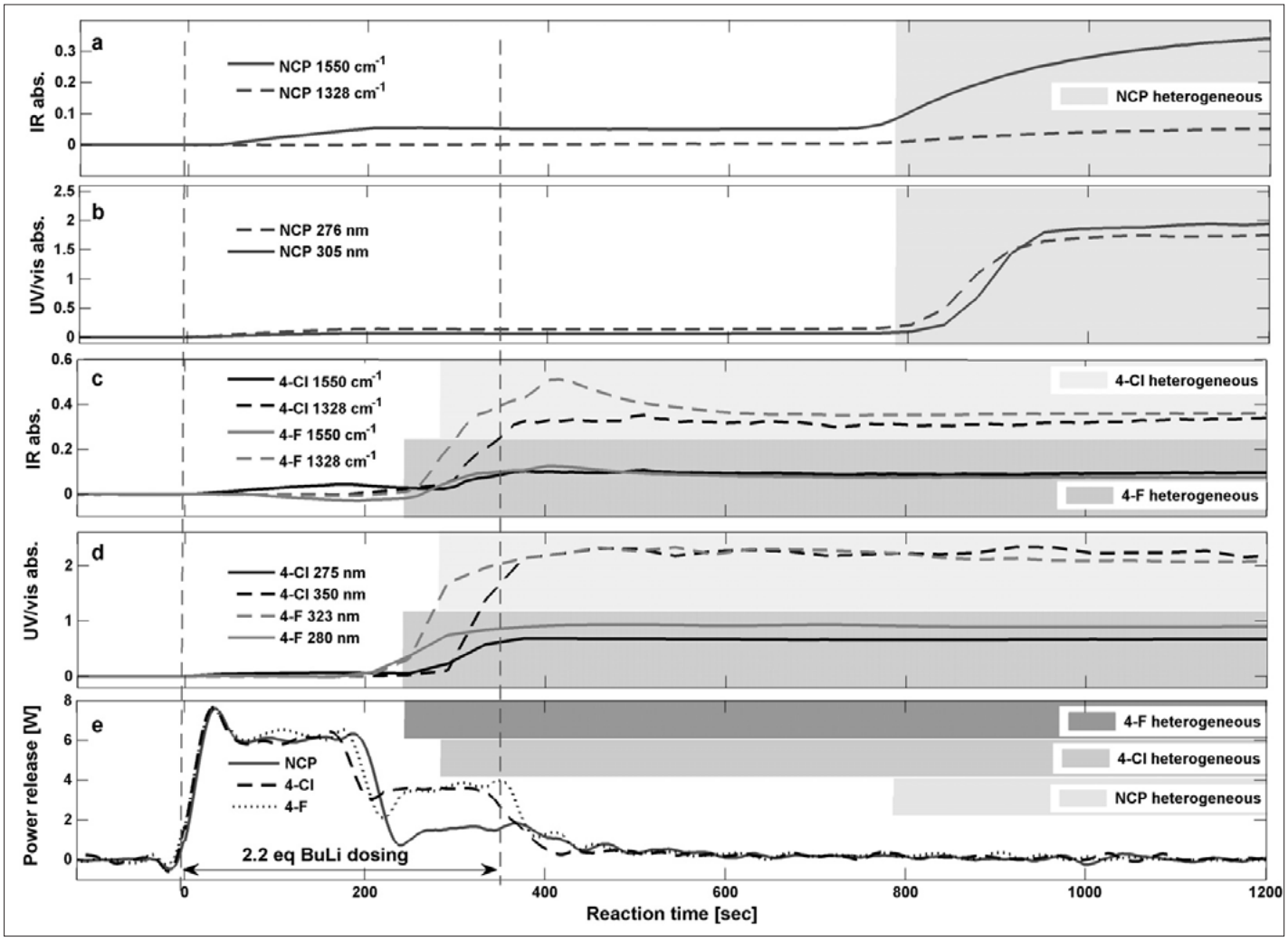

Fig. 1. On-line recorded IR and UV/vis absorbance profiles corresponding to routes A (a, b) and B (c, d – see Scheme 1) and power release of the reactions (e, Savitzky-Golay smoothing was applied for clarity). The grey shaded ranges indicate when the corresponding reaction mixture is heterogeneous (observed by endoscopy).

21, $pK_a^{R\text{-}H}$ = 30, $pK_a^{Ar\text{-}H}$ = 37–40.[8,9] These values also suggest that the lithiation of the amide group precedes C-lithiation.

Further alternatives, such as the removal of the halogen X from the aromatic core, which is preferred if X = Br,[10] and combined α and aromatic hydrogen removals, using >3 equiv. BuLi are not parts of this study.

Combined calorimetric, spectroscopic and endoscopic monitoring of the lithiation reactions was performed in a low-temperature reaction calorimeter. During lithiation, precipitation occurs and simultaneously a significant absorbance enhancement can be observed at specific IR and UV/vis bands (Fig. 1). If the reaction follows route A (Scheme 1), the largest absorbance enhancement can be observed at 1550 cm^{-1} (IR) and 305 nm (UV/vis). In contrast, if route B is preferred absorbance peaks at ~1327 cm^{-1} and ~330 nm show the biggest change. This spectral difference may arise from the different intermediates involved in routes A and B.

Infrared and UV/vis spectroscopy provided consistent results. The indications for start and endpoints of the individual reaction steps (and of the precipitation) are in good agreement (Fig. 1a,b and Fig. 1b,c). Accordingly, the dosing schedule can be tuned to minimize side reactions. IR and UV/vis absorbance profiles indicate different kinetic behavior for routes A and B. Route A shows a slow, kinetically controlled evolution of peaks including a metastable state (t = ~400–800s, Fig. 1a,b) while route B is fast and dosing controlled.

The initial part of the lithiation produces nearly identical reaction enthalpies (~ –210 kJ/mol) with very similar power signals (Fig. 1e) in all cases (at reaction times, t = 0–200, Fig. 1e). Therefore we assume that the lithiation of the amide group is common in routes A and B. After ~1 equiv. BuLi is dosed (t = 200 s), the two reaction pathways can be distinguished. Aromatic lithiation (route A, Scheme 1) results in lower reaction enthalpy (–54 kJ/mol) while α-deprotonation of R (route B) produces higher enthalpies (more than –100 kJ/mol). The reaction enthalpies of the lithiation steps are shown in Table 1.

Table 1. Reaction enthalpies for the individual steps. Values are calculated as integrals of the corresponding power profile[11]

Lithiation step	Reaction enthalpy [kJ/mol]		
	NCP	4-F	4-Cl
Amide	–214	–216	–214
Aromatic-C	–54	–	–
Methyl-C	–	–108	–101

Conclusion

On-line spectroscopic and calorimetric monitoring of the lithiation-acylation of different halogen-substituted acetanilides reveals different reaction pathways. The *in situ* characterized kinetic behavior of the systems allows for a comparison of the reactivity of the different substrates

and helps to interpret the different reaction paths. Ultimately, we gain an insight into the reaction mechanism.

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