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Development of the One-Carbon Homologation of a 4-Methylcoumarin Assisted by In-Line FTIR

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Abstract:

In-line FTIR was applied as a suitable PAT (process analytical technology) to monitor and control the enolate formation step in the one-carbon homologation process of a 4-methylcoumarin with chloromethyl pivalate. The techniques to determine the endpoint of the reaction and to obtain kinetic and stability data both in THF and DMF as reaction solvent are presented. The valuable chemical data obtained by this PAT was used to support the scale-up of the homologation process.

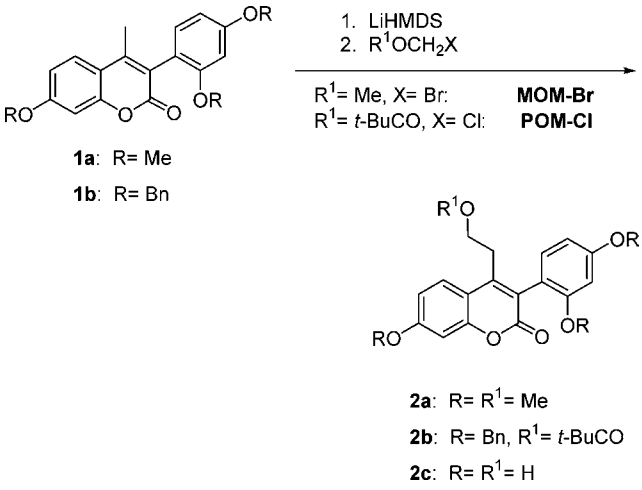
Introduction

As a key step in the synthesis of a selective estrogen receptor modulator, we needed to perform a one-carbon homologation on a 4-methylcoumarin derivative (**1**) (Scheme 1). The medicinal chemists offered us a high yielding solution by deprotonation of **1a** with lithium hexamethyldisilazide (LiHMDS) and quench with bromomethyl methyl ether (MOM-Br).[1] All methyl groups were removed at the next stage of the synthesis to obtain **2c**, conveniently done on lab scale using boron tribromide (BBr_3).

On scale-up of the reaction sequence, we found that BBr_3 formed an insoluble complex with **2a**, which was intractable on larger scale, resulting in incomplete conversions. Other demethylation methods[2] failed to give the desired product in the required yield and quality. On the other hand, it was also highly desirable to avoid handling of the known carcinogen and unstable MOM-Br on large scale.

After screening a series of possible homologation reagents,[3] without satisfactory results, we turned our attention to the stable, nontoxic, cheap, and readily available chloromethyl pivalate (pivaloyloxymethyl chloride, POM-Cl).[4] The first results were, however, disappointing, since the outcome of the reaction was very variable. We suspected

Scheme 1. **One-carbon homologation of 4-methylcoumarins 1**



that the underlying cause of the problem was the batch-to-batch variation of the substrate/base ratio, much less problematic for the MOM-Br reaction. We thus performed a screening with different ratios in order to elucidate the fluctuation in impurity profile upon varying the quantity of base. Table 1 presents the yield and composition of the isolated crude reaction product from these experiments.

Overcharging LiHMDS in the first, deprotonation step led to the presence of excess strong base; this induced elimination of the pivalate group from the desired product **2b** in the next process step when the solution of deprotonated **1b** was added slowly to a solution of POM-Cl. (Similar elimination did not occur from **2a** under these conditions, since methoxide is a poor leaving group compared to pivalate.) Compound **3** (Scheme 2) formed from **2b** by elimination reacted further by, e.g., vinylogous Michael additions of nucleophiles present in the reaction mixture. Although we were not able to isolate **3** in pure form due to its high reactivity, we identified **3** and its reaction product **4** (with the anion of **1b**) by LC-MS in the reaction mixtures and we detected **5** in the mother liquors after workup, respectively. Formation of **5** is thought to occur by the addition of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) to **3** followed by cleavage of the TMS groups during workup. As expected, when the addition order was changed and POM-Cl was added slowly to the solution of the deprotonated **1b**, compound **4** was formed as the main product in low yield via the intermediate **3**.

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(1) Kanojia, R. M.; Jain, N. F.; Ng, R.; Sui, Z.; Xu, J. *PCT Int. Appl.*,WO 2003053977.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons Inc.: New York, 1999.

(3) Other homologation reagents tested included BOM-Cl, formaldehyde, Eschenmoser's salt, Vilsmeier's reagent, trimethyl orthoformate, CH_2Cl_2, CH_2Br_2, and *N*-formyl piperidine.

(4) POM-Cl has been used for C−C bond formation in the α-position of (a) esters: Boeckman, R. K., Jr.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1977**, *18*(*51*), 4485; see also Lau, H.-H.; Schoellkopf, U. *Liebigs Ann. Chem.* **1981**, *8*, 1378. (b) lactams: Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Panagiotaki, M. *Heterocycles* **2003**, *60* (11), 2485

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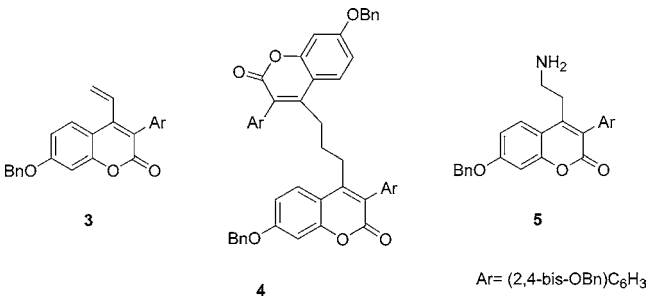
Table 1. **Yield and composition of the isolated crude product 2b vs base/1b ratio**

		LC profile			
equiv base[a]	physical yield (%)	product **2b** (w/w %)	unreacted **1b** (w/w %)	**3** (%)	sum of other impurities (%)
0.9	87	74.4	20.4	0.7	3.9
1.0	95	70.8	13.9	0.7	7.0
1.1	89	77.4	9.1	1.5	8.9
1.2	93	85.4	6.8	1.6	5.5
1.3	95	42.8	1.1	3.8	44

[a] By comparing the results of these 20 mL scale experiments (no extreme measures were taken to completely exclude moisture) with those of the larger batches monitored with FTIR, it occurs that for these reactions the deprotonation was completed when about 1.2 equiv of base was added, compared to about 1.02 equiv on large scale. This provided again a good reason to monitor the deprotonation with FTIR during scale-up.

Scheme 2. **Impurities identified in the homologation reaction mixtures**



Undercharging the base, on the other hand, gave lower conversions, and the need for repeated recrystallizations to remove residual **1b** from the product **2b** resulted in significant product loss.

The reaction was efficient though when using the "right" quantity of base. We were therefore in need of a suitable analytical method to monitor the deprotonation and to be able to eliminate batch-to-batch variations on large scale due to varying starting material quality. Off-line analysis, due to the moisture sensitive nature of the intermediate, was not feasible. We thought that process analytical technologies (PATs), specifically in-line FTIR spectrometry, could provide us with the necessary tool to control our reaction and achieve process ruggedness.

Results and Discussion

We assumed that a shift in the C═O-stretching vibration of the starting material could be used to determine the endpoint of the addition of the base. In practice we observed not a shift but the disappearance of the C═O-signal at 1726 cm^{-1}, which made the monitoring of the deprotonation much easier.

In THF as solvent, the deprotonation was confirmed by the appearance of a signal at 1625 cm^{-1} (Scheme 3), a region which is attributable to the C═C-stretching vibration of an enolate.[5] Thus, absorbance changes at two wavenumbers enable the in-line monitoring of the enolate formation: the disappearance of the C═O signal indicates the disappearance of compound **1b**, and the appearance of the C═C signal visualizes the formation of the enolate (Figure 1).

During optimization, we found that the enolate did not react with DMF at temperatures up to 25 °C and that the reaction of the deprotonated species with POM-Cl was faster and cleaner in DMF compared to THF. However, using DMF as solvent made the use of the in-line technique more difficult. The C═O signal of the solvent dominated in the spectrum, and the signal of the carbonyl of compound **1b** seemed to be lost. However, the shoulder of the C═O signal of **1b** could be made more visible by spectrum pretreatment. The second derivative of a spectrum visualizes when a function is concave upwards or concave downwards, so it shows shoulders on a graph. Further improvement was possible by multiplication of the second derivative of the spectrum by minus one, after which the C═O signal of **1b** was again seen clearly at 1726 cm^{-1} (Figure 2). Trending this signal, however, was not very useful, because noise became more pronounced (plot *iv* in Figure 3). As a consequence, we decided to plot the peak height at 1726 cm^{-1} minus the peak height of the baseline point at 1800 cm^{-1} in the untreated spectra, which allowed us a clean and simple reaction monitoring again for both the deprotonation and the reaction with POM-Cl in DMF as solvent. Figure 3 presents the in situ FTIR monitoring of the deprotonation of **1b** in DMF.

The addition of LiHMDS in period A and C was clearly visualized by the increased intensity of the Si−C vibration at 844 cm^{-1}. When the addition of LiHMDS was stopped (period B, the absorbance of the Si−C signal remained constant), the absorbances of the C═C and the C═O signals remained constant too, indicating that the enolate was formed instantaneously. Undercharging of LiHMDS could be avoided by trending the C═O signal. At the endpoint of the base addition, the signal at 1726 cm^{-1} disappeared completely. Overcharging of LiHMDS could be detected by trending the absorbance of the enolate (1625 cm^{-1}). As long as enolate was formed, the signal at 1625 cm^{-1} increased, to a maximum at equivalence. When base was added after the equivalence point, the absorbance of the enolate signal decreased due to dilution (plot *ii* on Figure 3). This manner of endpoint detection proved to be practical for our case, since we found that 2−4% of base overcharge gave highest active yields and quality after one recrystallization of the product **2b**.[6]

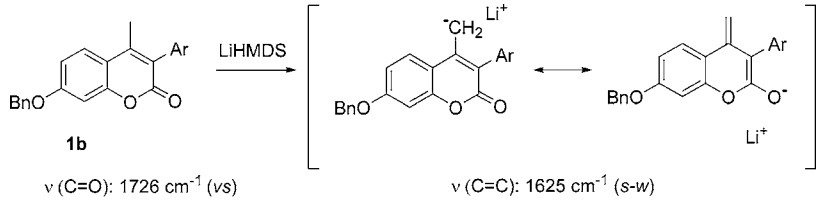
We also monitored the reaction of the enolate with POM-Cl by plotting the intensity of the C═O stretching vibration of the POM-Cl (peak height at 1756 cm^{-1} minus peak height at 1800 cm^{-1}) and the C═O-stretching vibration of the end product **2b** (peak height at 1726 cm^{-1} minus peak height at 1800 cm^{-1}) vs time (see Supporting Information).

Furthermore, we used in-line monitoring to obtain information on the stability of the enolate. We found that the IR

(5) Rein, A. R.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discovery Dev.* **2000**, *3* (6), 734.

(6) In a related deprotonation reaction, best results were obtained using a slight excess of starting material over the base, see: Watson, D. J.; Dowdy, E. D.; DePue, J. S.; Kotnis, A. S.; Leung, S.; O'Reilly, B. C. *Org. Process Res. Dev.* **2004**, *8*, 616.

Scheme 3. **Deprotonation of 1b**



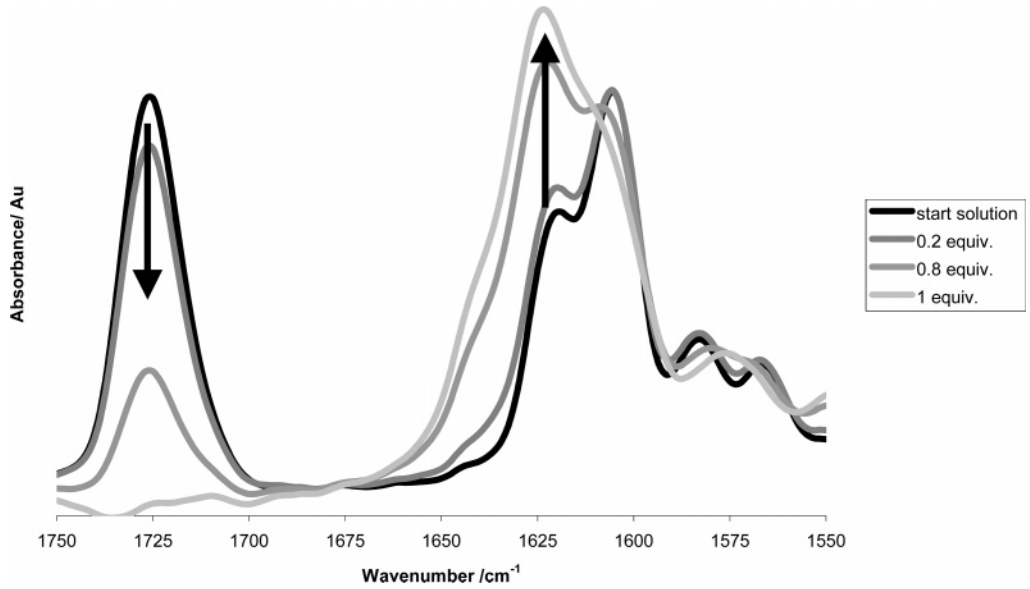


Figure 1. **Evolution of peak absorbances during addition of LiHMDS to 1b in THF.**

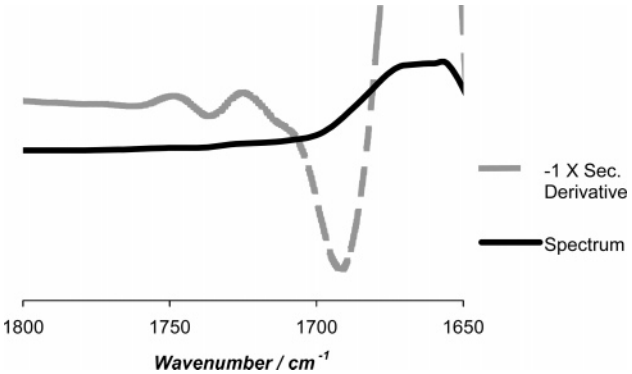


Figure 2. **Spectral manipulation tested for the monitoring of the C═O signal of 1b in DMF as a solvent.**

spectrum of the reaction mixture containing the enolate remained unchanged over a time period of 4 h at room temperature in DMF (as long as the reaction mixture was kept under rigorously inert conditions), indicating that the enolate was sufficiently stable and could be handled without problems on large scale.

Conclusions

In-line FTIR monitoring allowed us to determine the endpoint of the base addition in situ. We also rapidly obtained information on the kinetics of the deprotonation and quench, and on the stability of the enolate intermediate as well, all of which is very valuable process information. The trends of the IR signals in the 1600−1800 cm^{-1} region indicated that the enolate was formed immediately and that it was stable for a number of hours at room temperature, two important parameters from production viewpoint. The fast deprotonation suggests that the solubility of **1b** can be rate determining when the system is not mixed well (e.g., on scale-up) and the stability of the intermediate enolate in time can be defined as a noncritical or low-critical parameter. The use of in-line monitoring made possible an uneventful scale-up of this reaction.

Experimental Section

In situ experiments were performed using a ReactIR 4000 spectrometer with a DiComp immersion probe (flushed with nitrogen). Air was used as background, and every 1 min a spectrum (resolution = 4 cm^{-1}, scans 64) was collected.

2-{7-(Benzyloxy)-3-[2,4-bis(benzyloxy)phenyl]-2-oxo-2*H*-chromen-4-yl}ethyl Pivalate (2b). General Homologation Procedure with POM-Cl. A solution of LiHMDS (20 w/w % in THF) was added dropwise to a stirred suspension of **1b** (443.7 g, 0.80 mol) in DMF (1600 mL) at −5 °C under an atmosphere of nitrogen until a slight decrease in the C═C signal (peak height at 1625 minus peak height at 1800 cm^{-1}) was detected in the FTIR spectra (767 mL, 0.83 mol, 1.04 equiv). The resulting homogeneous solution was added via a cannula to a stirred solution of POM-Cl (156.6 g, 1.04 mol, 1.3 equiv) in DMF (320 mL) under an atmosphere of nitrogen and cooled to −5 °C. The mixture was allowed to warm to room temperature, and then it was added dropwise over 2 h to a solution of ammonium chloride (171 g, 3.2 mol, 4 equiv) and propylene glycol monomethyl ether (1000 mL) in water (3200 mL) warmed to 70 °C. The

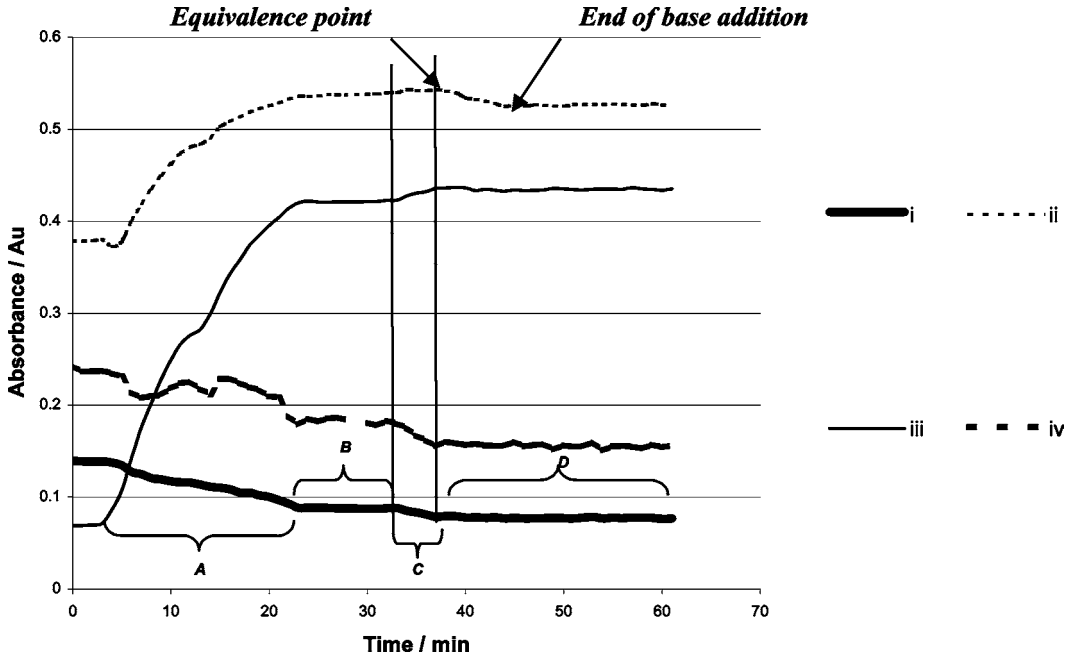


Figure 3. **Plots of the C═O, C═C, and Si−C signals over time during deprotonation of 1b in DMF. (i) C═O (peak height at 1726 minus peak height at 1800 cm^{-1}), (ii) C═C (peak height at 1625 minus peak height at 1800 cm^{-1}), (iii) Si−C (peak height at 844 cm^{-1}), and (iv) the second derivative of the C═O vibration at 1726 multiplied by −5000.**

mixture was then allowed to cool slowly to room temperature while stirring. The precipitate was filtered and washed with water. This crude reaction product was recrystallized from propylene glycol monomethyl ether (2650 mL) to yield **2b** (432 g, 80.7%). HPLC: (**2b**) 93.9% w/w; (**1b**) 4.8% w/w. MS (CI) *m*/*z* 669 (MH^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 9 H) 2.86 (m, 1 H), 2.93 (m, 2 H), 4.02 (m, *2* H), 5.08 (AB, J = 12.5 Hz, 2 H), 5.13 (s, 2 H), 5.26 (s, 2 H), 6.72 (dd, J = 8.3, 2.3 Hz, 1 H), 6.84 (d, J = 2.3 Hz, 1 H), 7.08 (dd, J = 8.8, 2.5 Hz, 1 H), 7.11 (d, J = 2.5 Hz, 1 H), 7.15 (d, J = 8.3 Hz, 1 H), 7.23−7.28 (m, 5 H), 7.32−7.50 (m, 10 H), 7.87 (d, J = 9.1 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.50, 28.24, 37.90, 62.27, 69.32, 69.40, 69.73, 100.78, 101.60, 106.06, 112.73, 112.89, 115.91, 121.67, 126.87, 127.05, 127.51, 127.73, 127.77, 127.83, 127.95, 128.19, 128.36, 128.41, 131.44, 136.22, 136.80, 136.88, 148.51, 153.92, 156.85, 159.65, 159.68, 160.84, 177.26.

Supporting Information Available

IR monitoring data for addition of LiHMDS to **1b** and addition of enolate to POM-Cl. This material is available free of charge via the Internet at http://pubs.acs.org.

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