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Liquid-phase combinatorial reaction monitoring by conventional ^{1}H NMR spectroscopy

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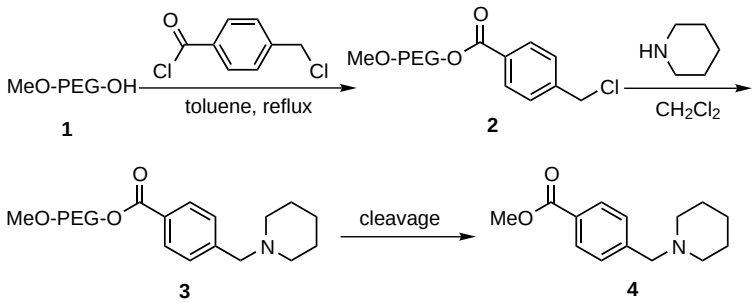
Abstract—The application of ^{1}H NMR spectroscopy for complete analysis of soluble polymer-supported reactions is described. This conventional analytical technique enables us to determine the extent of liquid-phase reactions without cleavage of the soluble matrix. The polymer matrix permitted us to obtain ^{1}H NMR spectra with a resolution comparable with that of spectra of the molecule in solution.

Recently, combinatorial chemistry has facilitated the process of lead discovery and optimization for new drugs and catalysts.[1–5] Solid-phase organic synthesis has emerged as a powerful tool for the synthesis of small molecule libraries.[6–10] One of many challenges in this program is to develop a high-throughput characterization method for identification of reactive intermediates attached to the solid support through the synthesis and for monitoring the reaction progress without cleavage.[11] During the optimization of reaction conditions, it is necessary to release the product from the solid support to analyze it for each experiment. However, harsh reaction conditions are usually required for cleavage and this often causes impurities and side products, which make it difficult to identify the desired molecules. Due to these types of disadvantages, several labs have focused their research on liquid-phase combinatorial synthesis.[12–14] In liquid-phase combinatorial synthesis, PEGs are presently used as a soluble matrix for the synthesis of small organic molecules.

In our laboratory, MeO-PEG-OH polymer based small heterocyclic libraries with a large diversity have been synthesized.[15–19]

In this paper we wish to report our experience using conventional ^{1}H NMR methodology to monitor the reaction directly on the polymer support during the course of liquid-phase combinatorial synthesis. This method has important advantages compared to *cleavage-and-analyze* characterization, particularly for optimizing reaction conditions. We have recently reported[16] the soluble polymer-supported synthesis of aryl benzyl piperazine and piperidine derivatives. During the synthesis of benzyl piperidine as shown in Scheme 1, all reactions and intermediates could be monitored by conventional proton NMR spectroscopy.



Scheme 1.

Keywords: combinatorial chemistry; liquid-phase synthesis; substitution; cleavage; NMR.

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Thus, 4-(chloromethyl)benzoyl chloride was loaded to the MeO-PEG-OH in refluxing toluene. Conventional ^{1}H NMR (300 MHz) was used to monitor the progress of the linker loading as shown in Fig. 1 (**A**→**D**). Spectrum **A** is the initial reaction mixture recorded after stirring for 30 minutes at room temperature.[20] The proton NMR spectra **B**, **C**, **D** are recorded after 3 h intervals. We observed that the benzylic protons of 4-(chloromethyl)benzoyl chloride ($ClCOC_6H_4\underline{CH_2}Cl$, δ 4.64) were slightly shifted upfield at δ 4.61 ppm after attaching to the support. Similarly, the two clusters of aromatic protons of the linker (δ 7.4 and 8.0 ppm) were shifted upfield at δ 7.3 and 7.8 ppm.

In spectrum **D**, the aromatic absorption of 4-(chloromethyl)-benzoyl chloride disappeared completely after the coupling reaction was finished. The reaction proceeded smoothly in toluene at reflux to

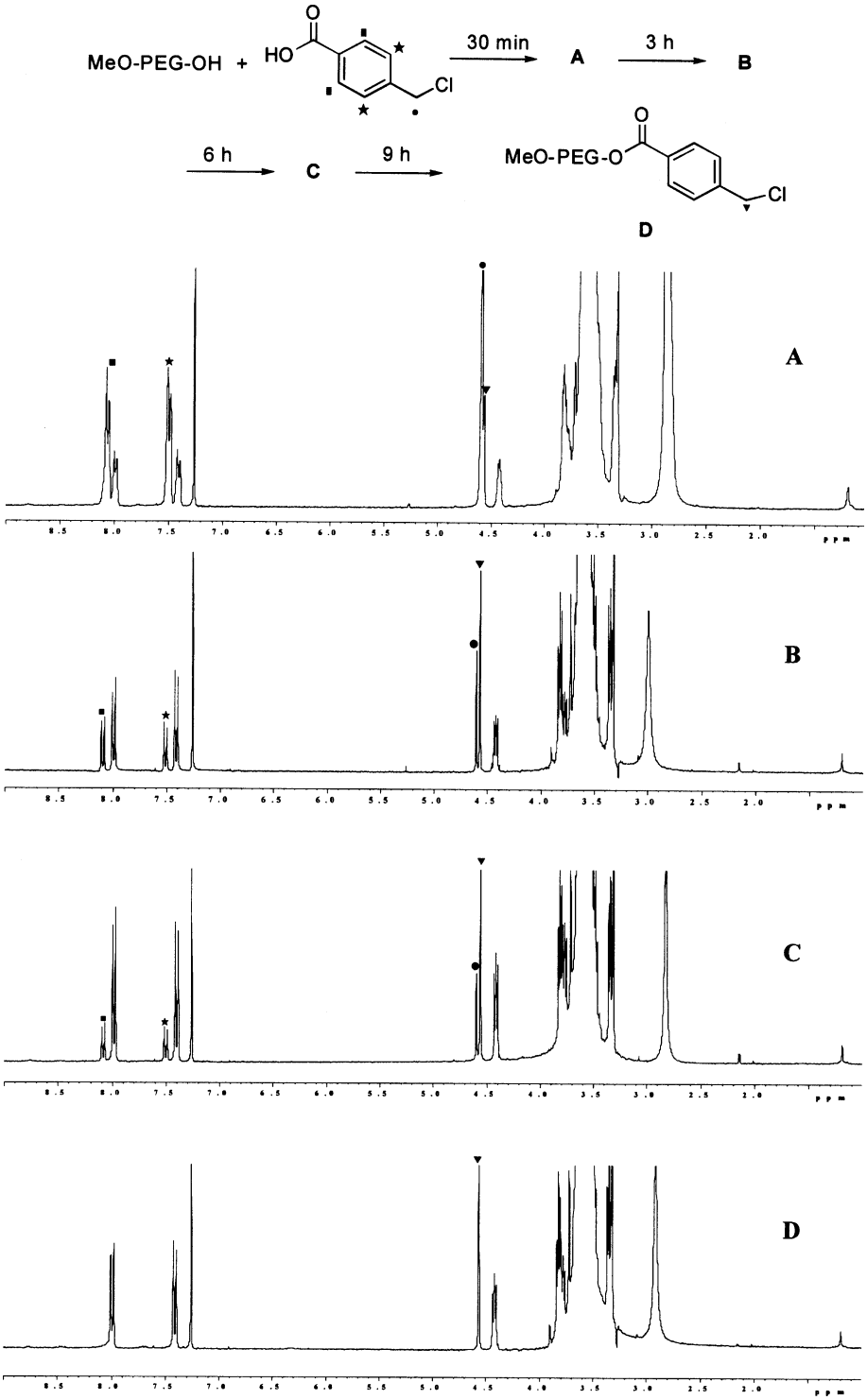

Figure 1. Loading of the linker to MeO-PEG-OH.

deliver uneventfully PEG-bound benzyl chloride **2** in excellent yield. The resulting polymer-supported benzyl chloride was then reacted with various diamines including piperidine, piperazine and homopiperazine to give the corresponding PEG-supported organic moieties **3**. All these nucleophilic substitution reactions were also easily monitored by ^{1}H NMR spectroscopy. For example, Fig. 2 shows a typical change in chemical shift during the (**D**→**F**) nucleophilic substitution reaction with piperidine. After the reaction was complete, the benzylic protons (δ 4.61 ppm) of the PEG bound benzyl chloride **2** completely disappeared and were shifted upfield into the poly(ethylene glycol) protons ($\sim$3.5 ppm). However, no change was observed in the aromatic region. This evidence showed complete transformation of **2** to PEG bound amine **3**. Similar results were also obtained by employing other nucleophiles such as piperazine and homopiperazine.

We next studied the cleavage conditions and checked the reaction progress by regular proton NMR spectroscopy (Fig. 3). The NMR spectra of immobilized piperidine showed a triplet at δ 4.46 ppm due to the α-methylene protons at the PEG attached site (-OCH$_2$CH$_2$OCO-). This triplet slowly disappeared during the transesterification by sodium methoxide and shifted upfield to δ 3.9 ppm as shown in Fig. 3. After work up of the reaction, the CH_2 absorption of the PEG fragment vanished totally and a new singlet of three protons CH_3OCO- appeared at δ 3.9 ppm.

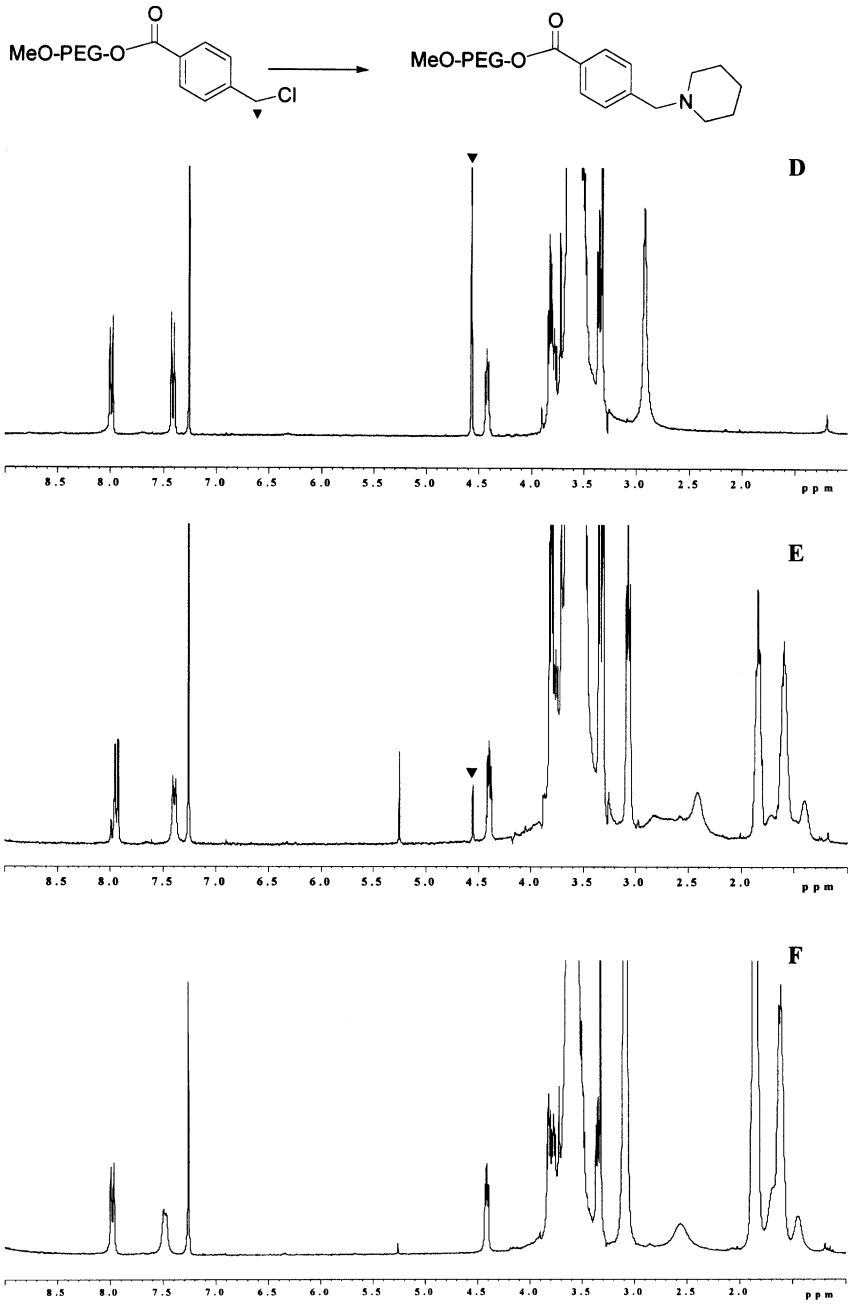

Figure 2. Nucleophilic substitution reaction monitored by ^{1}H NMR.

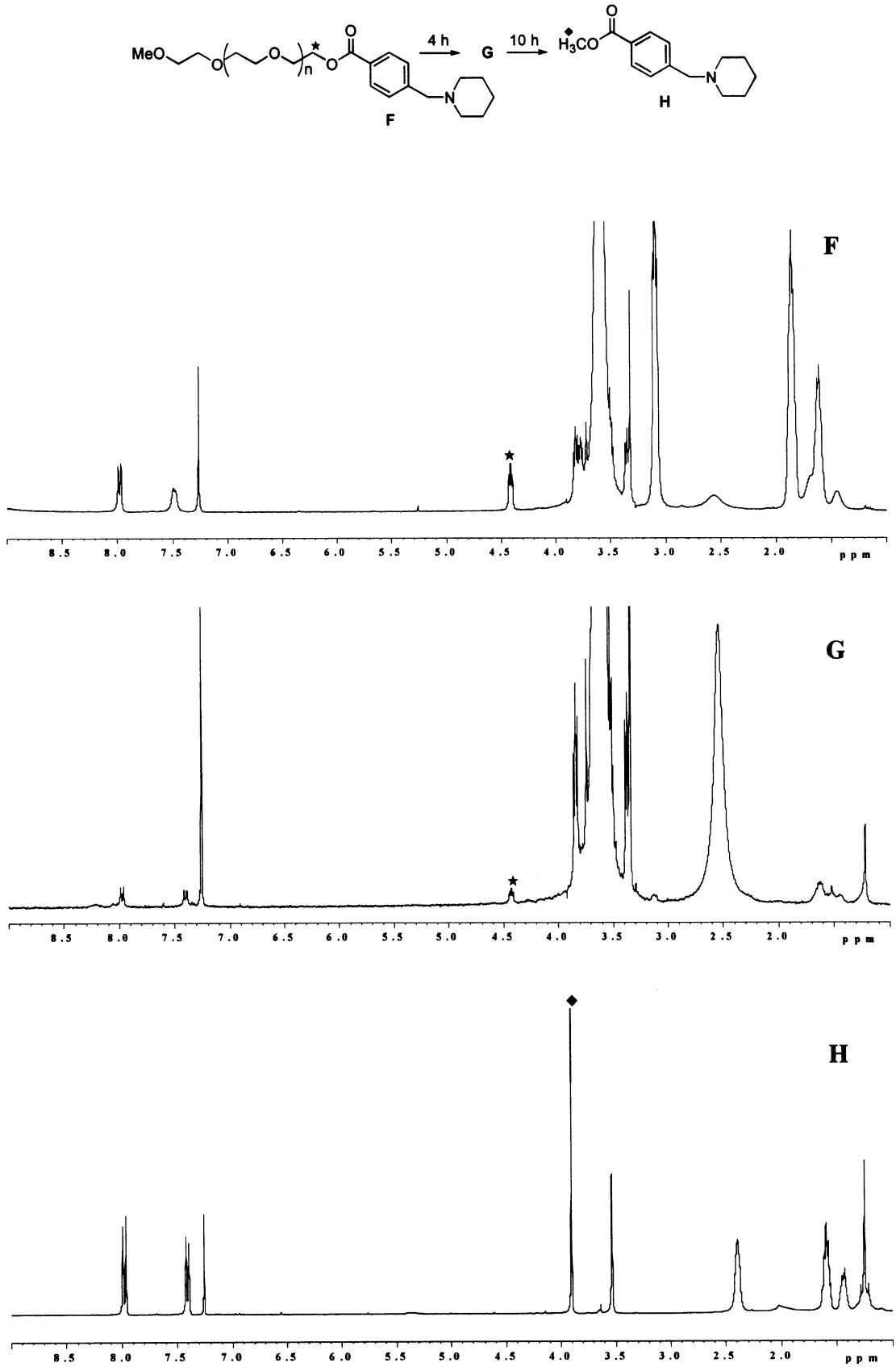

Figure 3. Cleavage reaction monitored by ^{1}H NMR.

In summary, we have demonstrated that liquid-phase methodology provides a rapid means of monitoring chemistry carried out on a polymer support that has been applied for the synthesis of piperidine and piperazine derivatives. The use of the analytical technique descried here allows high quality ^{1}H NMR spectra to be obtained in a minute without any cleavage of the reactive intermediates from their support. This non-destructive approach to follow reaction progress makes the LPCS method even more valuable.

Acknowledgements

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20. All the NMR spectra were recorded on a Bruker NMR spectrometer (300 MHz/52 mm) in $CDCl_3$ solvent. NMR spectra (**A→H**) were obtained within 3 min using 50 mg dried polymer supported compounds.