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An Indazole Synthesis on Solid Support Monitored by Single Bead FTIR Microspectroscopy

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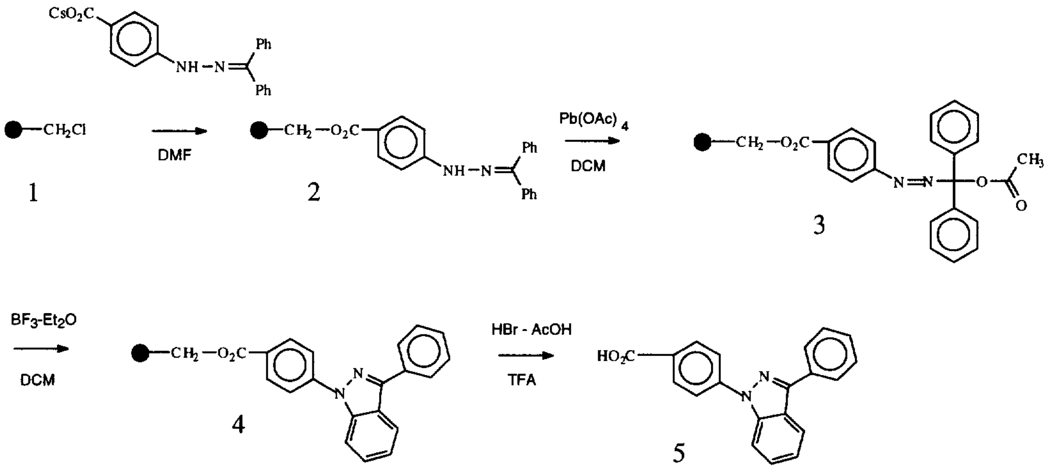
Abstract: A series of solid-phase reactions for the synthesis of 1H-indazoles was monitored using Single Bead FTIR Microspectroscopy (single bead IR). The success of the desired reactions has been assessed based on the appearance and disappearance of IR bands characteristic of the starting materials and products for each synthetic step. The results demonstrate again that single bead IR is a valuable technique for monitoring of multi-step solid-phase organic synthesis.

The majority of the compound libraries that have been assembled to date via combinatorial chemistry approaches have been synthesized on a solid support[1-7]. The optimization of solid-phase reaction conditions is the most time-consuming phase of combinatorial chemistry. The lack of simple and rapid analytical methods for monitoring solid-phase reactions directly on bead is one of the key stumbling blocks for these processes. We have developed single bead FTIR microspectroscopy (single bead IR) to monitor solid-phase reactions [8,9]. The scope of application of this technique has been extended to the monitoring of heterocyclic chemistry in this work.

In order to assemble unique libraries of heterocycles on solid supports, we carried out the synthesis of heterocycle building blocks using benzophenone-4-carboxyphenylhydrazone as the starting material. Benzophenone-4-carboxyphenylhydrazone was coupled to the unmodified Merrifield resin **1** (200-400 mesh, 1.35 mmol/g) to form the product **2** in 24 hours at room temperature (See Scheme). The resin-bound hydrazone **2** was then oxidized to the α-arylazobenzhydryl ester **3** by reaction with lead-tetraacetate in dichloromethane for 30 minutes at room temperature[10]. Subsequent treatment of **3** with Lewis acid for 30 minutes at room temperature (e.g. BF_3-Et_2O)[11] furnished indazole **4** in quantitative yield (as seen by single bead IR). The 1-(4-carboxyphenyl)-3-phenyl-1H-indazole **5** could be cleaved from the solid support by HBr-AcOH/TFA (24 hours, room temperature) in good purity and yield (identical TLC and $^1H/^{13}C$-NMR in comparison with recrystallized, authentic indazole **5** from solution synthesis; final yield: 79% assuming a quantitative conversion of **1** to **2**, purity > 95% by HPLC, $^1H/^{13}C$-NMR). Compound **3** represents a N,O-acetal with special features, where the primary cleavage reaction can be triggered from breaking the N-C-bond (aqueous proton acids) to breaking the C-O-bond (Lewis acids). The latter reaction pathway proceeds under extrusion of the carboxylate via an intermediate aza-azonia-allene, which stabilizes to the indazole heterocycle **4** by intramolecular ring-closure. The compounds **3** also represent a novel linker system with built-in safety catch principle regarding the conversion from the heterocycle to the released acid derivative.

Scheme:



All reaction steps were monitored by single bead IR. Procedures for single bead IR were

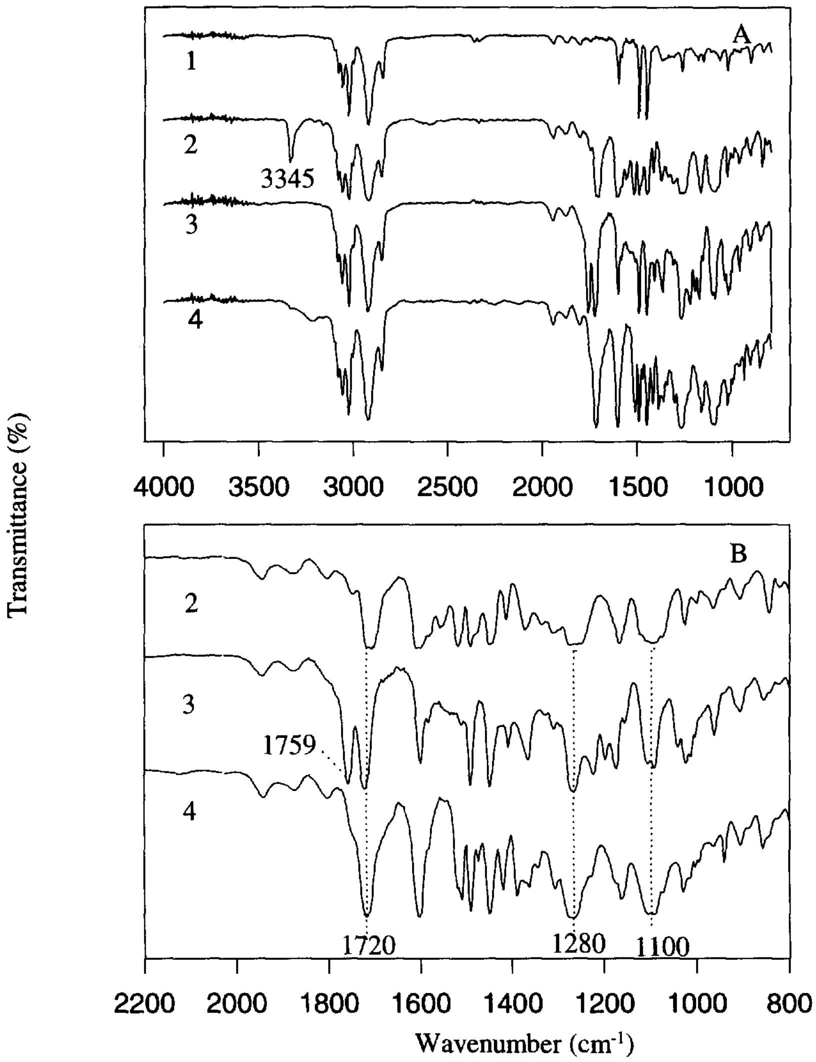


Figure 1. The single bead IR spectra were taken as previously described[8]. The spectra labeled 1-4 are for compounds **1-4**, respectively. Panel B shows spectra of **2-4** on an expanded scale from 800 to 2200 cm^{-1}.

as described previously[8,9].

From Fig.1, the coupling of benzophenone-4-carboxyphenyl-hydrazone to the Merrifield resin **1** was unambiguously identified by the appearance of many emerged spectral features in **2**: the sharp peak at 3345 cm^{-1} is assignable to ν(NH) of the hydrazone, and the striking identifiers of the aromatic ester functionality introduced in this step, namely a very strong ν(C=O) also appears at 1710 cm^{-1}. In addition, prominent C-O-C skeleton vibrations emerged at 1280 cm^{-1} and 1100 cm^{-1}.

The quantitative oxidization of the hydrazone **2** to the α-arylazo-benzhydryle acetate **3** by $Pb(OAc)_4$ is indicated by the complete disappearance of the ν(NH), due to oxidation of the hydrazone to the azo-functionality, and the appearance of a second well resolved carbonyl stretch at 1759 cm^{-1}. The latter is assignable to the ν(C=O) of the newly formed aliphatic ester. The cleavage of the N,O-acetal **3** by BF_3 and the successful formation of resin-bound indazole **4** is supported by the disappearance of this carbonyl band. The remaining ester ν(C=O) has undergone a small shift from 1710 cm^{-1} in **2** to ~1720 cm^{-1} in **3** and **4** due to changes of the p-substituent of the aromatic ring. The final product **5** was obtained at a 79% yield.

In summary, we have successfully performed a multi-step synthesis of a heterocyclic compound and direct on-bead analysis of each synthetic step using single bead IR. This work demonstrates again that single bead IR is a powerful tool for a quick and convenient analysis of a wide range of solid-phase organic chemistry. The broad applications of this method in our laboratories have already effectively assisted the time-consuming solid-phase reaction optimization stage of combinatorial chemistry.

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