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SINGLE BEAD IR MONITORING OF A NOVEL BENZIMIDAZOLE SYNTHESIS

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ABSTRACT: *A novel and efficient solid-phase synthesis of benzimidazoles and the monitoring of all conversions in this synthesis are reported.*

Combinatorial chemistry[1] has been recognized as a powerful tool to enhance drug discovery efforts in pharmaceutical industry. The majority of the small molecule combinatorial libraries made to date were prepared on solid supports through solid-phase organic synthesis (SPOS).[2] In general, intense efforts are needed to adapt known solution reactions to solid-phase or develop new solid-phase reactions. Developments of both new solid-phase organic reactions and methods for quick, on-resin monitoring of novel SPOS are required to support the efforts of combinatorial chemistry. In this paper, we report a novel and efficient solid-phase benzimidazole synthesis and the monitoring of all reactions by single bead IR.[3]

Solution synthesis of benzimidazoles from various benzaldehydes and phenylenediamines in nitrobenzene at high temperature (150 ^{o}C) have been reported in good yields.[4] However, routes leading to efficient solid-phase benzimidazole synthesis have not been fully explored. Recently, a benzimidazole synthesis by making phenylene diamine on resin and then coupling it to soluble imidate was reported.[5] In the following, we present an alternative approach to benzimidazole synthesis. 4-Carboxylbenzaldehye was first attached to resin support and then it was coupled to phenylenediamines in solution (Scheme 1). In the latter step, a 10 equiv. of phenylenediamines was used at elevated temperature (130 ^{o}C) to drive the reactions to completion.

The time course for the synthesis of compound **3**[6] was measured by single bead IR. The IR spectra taken at various times during the reaction are shown in Figure1A. Among other spectral features, two distinct IR bands are introduced: an ester carbonyl band at 1720 cm^{-1} and an aldehyde carbonyl band at 1703 cm^{-1}. At the same time, the hydroxyl band at ~3500 is diminishing. In about 20 minutes, the intensity of the hydroxyl band reaches zero and those of carbonyl bands reach a constant maximum values. The kinetics of this conversion is shown in Figure1B. Both processes fit to an identical pseudo-first-order rate constant suggesting that IR data is consistent with the existence of only one chemical conversion. The IR data also indicate a nearly quantitative conversion from Wang resin to the resin-bound compound **3**. The yield of 97% for this transformation was

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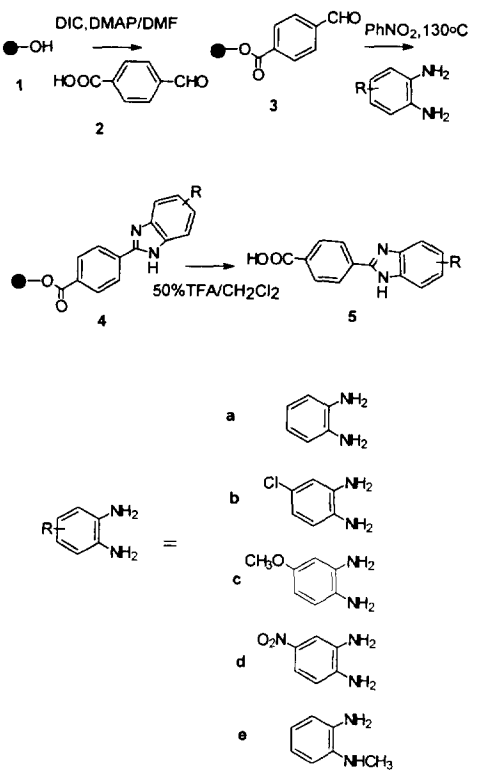
Scheme 1



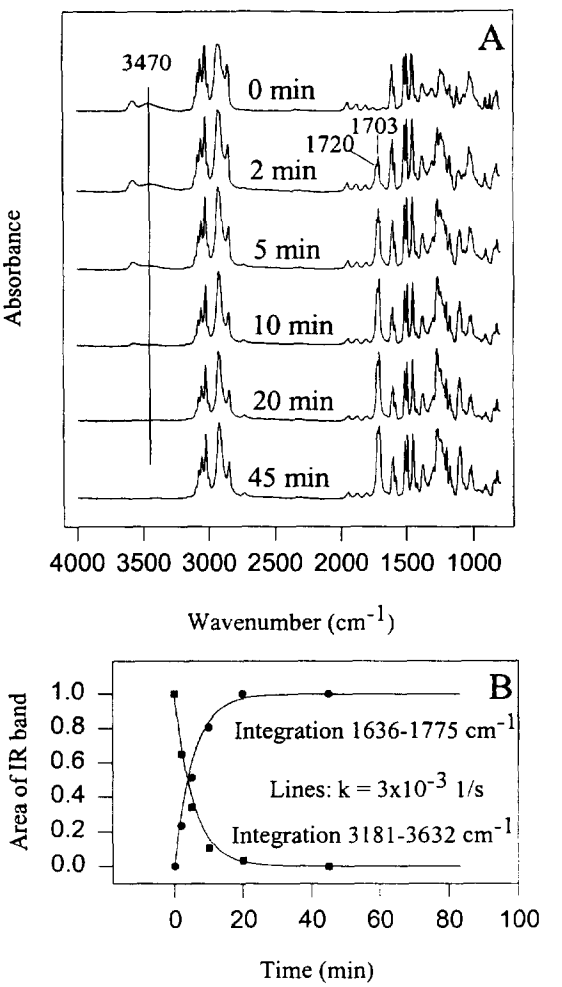


Figure 1. (A) Single bead IR spectra at various times during the synthesis of **3**. A drop of resin suspension was taken out of the reaction mixture at various times and washed with DCM. The microscope was adjusted to focus on a single bead and spectra were taken as previously described.[3a,b] (B) The kinetics of the reaction in step 1.

independently determined directly on resin using a 6-mg resin sample by a novel fluorescence dye consumption method.[7] A series of benzimidazoles **5a** - **5e** was then synthesized. The reaction was carried out at 130 °C for 8 h using nitrobenzene as solvent. The success of this reaction is confirmed by the disappearance of the aldehyde carbonyl band at 1703 cm^{-1} (Fig. 2) and the formation of the N-H stretch for **5a** - d at ~3400 cm^{-1} (not shown).

Due to the overlap between the ester and aldehyde carbonyl bands (Fig. 2), it is not evident that the band at 1703 cm^{-1} disappears completely. Therefore, it can not be concluded that the reaction in the second step is

complete without further analysis. Since the only detectable change in IR spectra after the second step is the formation of IR bands corresponding to the desired products **5a-e** such as -NH stretch (observed for **5a-d**), the

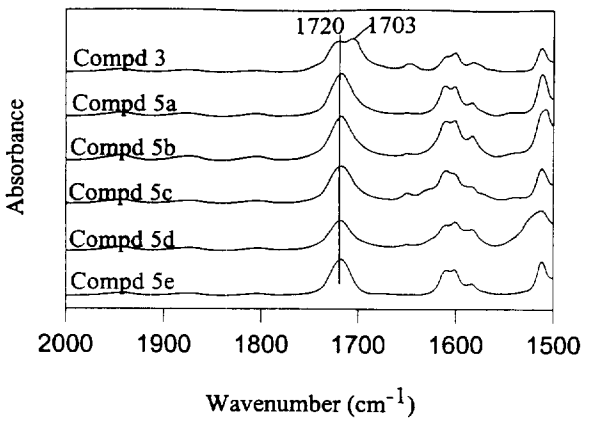


Figure 2. Single bead IR spectra for resin-bound product **5a - 5e**. Five sealed tubes with dried resin (100 mg, 1.0 mmol/g), one of five amines a - e (1 mmol) and 3 ml nitrobenzene were heated at 130 °C overnight. The resins were then transferred to the filtration tubes and washed as described in Figure1 legend after cooling to room temperature.

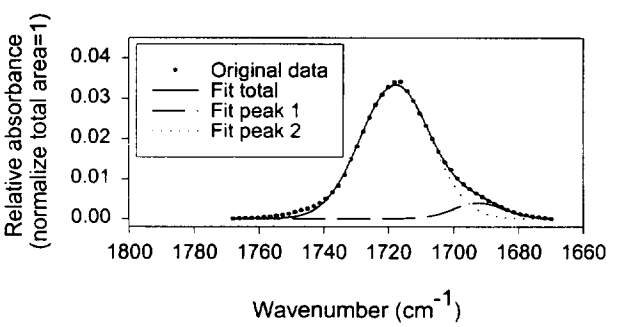


Figure 3. Curve - fit analysis of IR spectrum for resin-bound compound **5a**.

Table 1. On-resin and off-resin purity of benzimidazoles 5a-e

product	IR_{1703} area%	RP-HPLC* area%
5a	94	94
5b	95	90
5c	96	92
5d	95	96
5e	100	79

* Waters HPLC, UV 254 nm, C-18 Symmetry column, A = 0.1% TFA in CH_3CN, B = 0.1% TFA in H_2O, Gradient 95% B ->5% B in 20 min and hold for 5 min.

decreased intensity at 1703 cm^{-1} may correlate with the product formation (confirmed later by analysis of the cleaved product). The unreacted compound **3** was estimated by curve - fitting analysis of carbonyl bands as shown in Figure 3. The estimated on-resin purity of the product is listed in Table 1. Note the fit is not good near 1750 cm-1. We did not further improve this fit since it is not the spectral region of our concern.

All crude cleaved products were subject to characterizations by MS and HPLC. The crude 5a was also characterized by ^{1}H and ^{13}C NMR.[8] NMR of **5a** indicated that the desired product **5a** is more than 90%. MS identified all desired products as the major compound in the solution and HPLC showed a major band plus

minor impurity peaks. Based on HPLC peak areas, the estimated purity is >90% for cleaved crude compounds **5**a-d and 79% for **5e** (Table 1). TFA cleavage reaction is an unavoidable source for introducing impurities and causing lower yield. Compound **5e** is a typical case. The reaction is very clean on resin (~100% conversion by IR band area analysis). However, the HPLC of the cleaved products showed the existence of the desired product plus 9 impurities (4 major and 5 minor impurities) and the purity based on HPLC peak areas (UV 254 nm) is only 79%.

In summary, this synthetic scheme was efficient, and easy to operate and monitor. Molecular diversity can be introduced at various position of the molecule: on R group, by alkylation of the NH group on benzimidazole, and by modification of the carboxyl group. Due to the lack of sufficient data on the thermostability of resins, it is often assumed that resin may not be accessible to high temperature reaction. We proved in this work that reactions at an elevated temperature can be easily adapted to resin.

Acknowledgments

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6. Wang resin (100 mg, 1.0 mmol/g) was washed with 4 m*l* of DMF for 15 min and then trained. Diisopropylcarbodiimide (63 mg, 0.5 mmol) was added to a solution of 4-carboxylbenzaldehyde (75 mg, 0.5 mmol) in 1 m*l* dry DMF. The mixture was added to the resin after stirred for 5 min. Then 4-(N,N-dimethylamino)pyridine (DMAP) (1.2 mg, 0.01 mmol) was added to the resin suspension. The reaction then was stirred in a orbit shaker.

7. Bing Yan; Wenbao Li, *J. Org. Chem.* **1997**.*62,* 9354-9357.

8. ^{1}H NMR for 5a (300 Mhz, DMSO-d_6) 7.22 (2H, dd, J = 4.0, 2.1), 7.62 (2H, dd, J = 3.6, 2.2), 8.10 (2H, d, J = 5.5), 8.28 (2H, d, J = 5.5), 13.20 (2H, broad); ^{13}C NMR (DMSO-d_6) 114.73, 124.18, 127.19, 129.97, 130.53, 132.89, 135.85, 149.06, 166.46.