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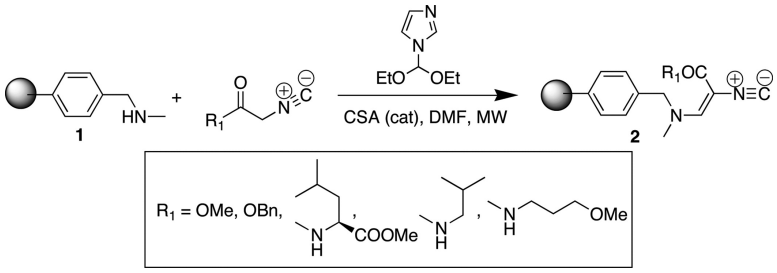

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Synthesis of 1-Alkyl-4-imidazolecarboxylates: A Catch and Release Strategy

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The novel alkyl *N*-methyl-*N*-polystyreneamino-2-isocyanoacrylate was used for the synthesis of 1-substituted imidazole-4-carboxylates utilizing a "catch and release" methodology. The reactions were performed under microwave irradiation, affording the title compounds in both high yields and chemical purity directly to solution, from the solid phase support.

Introduction

The imidazole moiety is found in many medically important compounds such as fungicides,[1] benzodiazepine antagonists,[2] antibacterials,[3] antibiotics,[4] and other drugs. Numerous syntheses of substituted imidazoles are described in the literature, and many synthetic strategies have been developed.[5] Within this field there has been much interest in the development of methods for solid-phase synthesis of small-molecule libraries.

The discovery of solid-phase synthetic routes toward heterocyclic derivatives is an area of continued creativity for organic chemists. In particular, low molecular weight heterocyclic compounds are important as pharmaceutical lead compounds because they are highly functionalizable scaffolds. In solid-phase organic synthesis (SPOS) resin-bound multifunctional compounds are key intermediates for the production of heterocyclic compound libraries; however, the possibility of efficiently obtaining specific substituents is often limited, and new synthetic methodologies need to be developed.

In the solution phase, a bifunctional compound, 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate, has been used for the regioselective synthesis of several heterocycles, such as imidazoles,[6] tetrazoles,[7] and thiazoles.[8] A solid-phase version of this method was used to generate libraries of thiazoles[9] via a Ugi-MCR[10] with the use of resin-bound 3-*N*,*N*-(dimethylamino)-isocyanoacrylate for the synthesis of regioselective 1-substituted 4-imidazolecarboxylates.[11]

Although combinatorial solid-phase methods enable the efficient generation of large numbers of new compound entities,[12] difficulties are often associated with SPOS, such as long reaction development and optimization times, the need for large reagent concentrations to drive reactions to completion, and the inability to purify intermediate resin-bound intermediates, has refocused attention on developing methods for high-throughput solution-phase synthesis.

In this context, the application of resin "catch and release" protocols can be particularly useful since the reaction product can be separated from solution by immobilization onto an activated resin[13] such that the introduction of a suitably functionalized building block provokes concurrent derivatization and release of a new product back into solution. Significantly, only derivatized material is released from the resin, thereby facilitating the preparation of compounds with inherently high purities. Resin "catch and release" has the added advantage that it facilitates solvent exchange without the added complexities associated with the introduction of evaporation steps.

As part of a series of studies toward new techniques for combinatorial heterocycle synthesis under mild conditions,[14] we wish to report herein the use of a resin-bound 3-*N*-methylen-*N*-methylamino isocyanoacrylate for the synthesis of 1-substituted 4-imidazole carboxylates (Table 1) through a "catch and release" methodology. To give a rapid synthesis of a library of compounds that might be delivered directly onto solution, we decided to anchor the reagent to an amine-functionalized support. Thus, the commercial *N*-methyl aminomethylated polystyrene **1** (1.38 mmol/g) was charged with alkyl isocyanoacetate and *N*-formyl imidazole diethylacetal under acid-catalyzed conditions (10% CSA) in DMF (Scheme 1).

Results and Discussion

Although the formation of the functionalized support **2** can be achieved heating the mixture at 80 °C for 36 h, the reactions were preferentially conducted under microwave irradiation to shorten the reaction time.[15] Thus, the reaction mixture was heated in a sealed tube (CEM-designed 10-mL pressure-rated reaction vial) and exposed to microwave irradiation for 10 min at 80 °C.[16] The free amine on the polymer was monitored using the chloranil test.[17] This rather sensitive assay enables the detection of even very small amounts of free secondary amines on the resin, a negative test indicating complete anchoring to the solid support. Then the resin was washed thoroughly with portions of DMF, hexane, THF, hexane, and *n*-butanol in sequence.

Treatment of the resin **2** with an amine afforded the isomerically pure alkyl 1-substituted-4-imidazolecarboxylate **3**, restoring the starting amino polyester resin **1** (Scheme 2).

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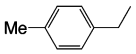
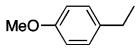
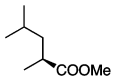
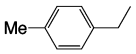
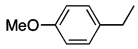
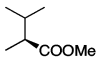
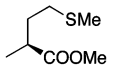
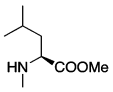
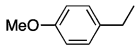
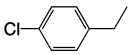
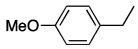
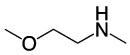
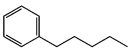
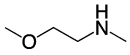
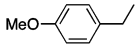
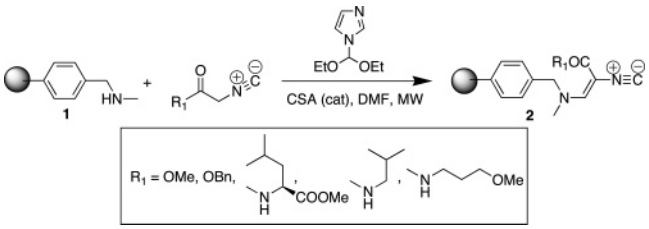
Table 1. Synthesis of Selected 1-Alkyl-4-imidazole Carboxylic Derivatives

Compd **3**	R_1	R_2	yield[a] (%)	purity[b] (%)
a	OMe		97	99
b	OMe		95	98
c	OMe		98	99
d	OMe		94	98
e	OMe	t-Bu	80	99
f	OMe		80	96
g	OMe		90	99
h	OBn		85	99
i	OBn		92	99
j	OBn		97	99
k	OBn		92	99
l	OBn		85	85
m			90	99
n			89	97
o			86	99
p			92	99
q			83	98
r			89	99

[a] Based on mass recovery of crude product. [b] Estimated by HPLC analysis at 254 nm on the crude material on area of peak corresponding to the correct molecular weight.

The cyclization step was carried quantitatively by refluxing **2** in *n*-butanol in the presence of 10 equiv of several amines or amino acid esters (Table 1). The reactions were carried out under microwave irradiation in an open flask with a reflux condenser, operating at 114 °C for two cycles of 30 min. The imidazoles **3** were recovered in pure form and in high yields simply by filtering the mixture and washing the resin with dichloromethane (Table 1).

Scheme 1



Scheme 2

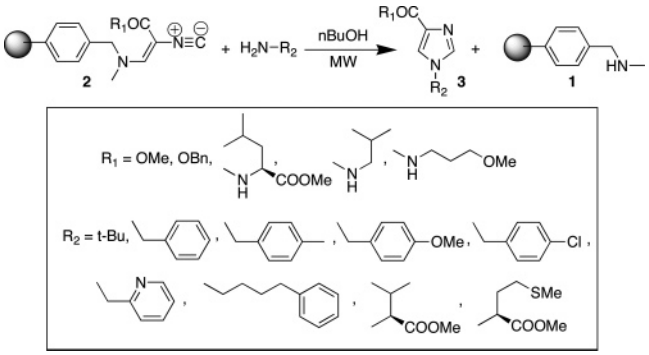


Table 2. Comparison of Conventional and Microwave Procedures for Imidazole Synthesis

imidazoles	thermal reaction: 24 h, 116 °C % yield[a]/purity[b]	microwave-assisted reaction: 2 × 30 min, 114 °C % yield[a]/purity[b]
3a	80/99	97/99
3c	96/98	98/99
3r	75/98	83/98

[a] Average yield determined on the basis of mass recovery of crude product. [b] Average purity determined by HPLC peak area at 254 nm.

As noted from the examination of the Table, the reaction tolerates a significant range of steric substitution patterns, and good yields are observed even with more hindered amines, such as *sec*-alkyl- (compounds **3g**, **3k**, and **3l**) and *tert*-alkylamines (compound **3e**). Imidazoles **3a**−**r** were obtained in very high purity (>95%, excluding the synthesis of compound **3l**), as judged by HPLC/UV254/MS measurements. The chemical identity and HPLC/UV homogeneity of a selection of these samples were further corroborated by comparison of their ^{1}H NMR data with those obtained from conventional solution-phase experiments.[6] Yields (gravimetric) were generally in the range 80−98% (over two steps, based on the initial loading of resin **1**). These microwave-assisted reaction conditions significantly reduced the reaction time for the solid-phase cleavage reactions. In Table 2 are given some results for the cleavage reactions of resin **2** under MW irradiation, as compared with those of the thermal reaction.

Moreover, the solid support used can be regenerated. The procedure described was, in fact, repeated using recycled solid support, and good yields of the desired products withhigh levels of purity were always obtained for at least 3−4 cycles. Thermal drawbacks of solid-supported chem-

istry, such as degradation of the polymer support caused by heating for long times, were so avoided. Unfortunately, aniline or other aromatic amines could not be used for preparing 1-aryl-4-imidazolecarboxylates due to very low yields (<20%), agreeing with reports by other authors.[6] As noted in this kind of reaction, chemoselectivity is another feature of this chemistry.

In summary, we have developed an operationally simple method for the synthesis of imidazole-4-carboxylates via solid-phase bound isocyanoacrylates under very mild conditions and through a microwave strategy. This procedure is highly comparable with other ones reported in the literature,[6,11] having the advantages of both solid and solution phase.

Experimental Section

General Procedure for Conventional and Microwave-Assisted Imidazole Synthesis. Resin-Bound Isocyanoacrylate 2. To a suspension of *N*-methyl aminomethylated polystyrene resin **1** (0.10 g, 0.138 mmol) swollen in DMF (2 mL), was added a solution of *N*-formylimidazole dimethylacetal (0.138 g, 0.83 mmol), methyl isocyanoacetate (0.816 g, 0.83 mmol), and camphorsulfonic acid (13.8 mg, 10% w/w) in DMF (8 mL). The resulting mixture was irradiated to 80 °C for 20 min in a sealed tube (CEM-designed 10-mL pressure-rated reaction vial) in a self-tuning single mode CEM Discover Focused Synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 3 min. The reaction progress was monitored by the colorimetric chloranil test (negative). After cooling to room temperature, the resin sample was collected by filtration using a sintered glass funnel. The resin was thoroughly washed with alternating portions of DMF (3 × 10 mL), hexane (3 × 10 mL), THF (3 × 10 mL), hexane (3 × 10 mL), and *n*-BuOH (3 × 10 mL). The resin sample was dried under reduced pressure. The IR spectrum of this resin sample was compared with the amine starting resin (KBr pellet) and showed a characteristic absorption band at 2106 cm^{-1} cm^{-1}, indicating successful solid support capture of isocyanide building block.

Cyclization. 1. Conventional Procedure. The resin sample **2** from the above experiment was suspended in dry *n*-BuOH (5 mL) in a round-bottomed flask with a reflux condenser. Benzylamine (0.1 mL, 1.38 mmol) was added, and the resulting mixture was heated under shaking to reflux (116 °C) for 24 h. The reaction progress was monitored by the colorimetric chloranil test (positive). After cooling to room temperature, the resin sample was collected by filtration using a sintered glass funnel and successively washed with EtOH (3 × 10 mL). All the alcoholic layers were combined and concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL), washed with a 1 M solution of $KHSO_4$, and dried (Na_2SO_4). The solvent was evaporated to dryness under reduced pressure to give the pure methyl 1-benzyl-1*H*-imidazole-4-carboxylate **3a** (23.8 mg, 80% yield, 99% purity) as colorless oil.[18] ^1H NMR δ 7.60 (s, 1H), 7.56 (s, 1H), 7.37 (m, 3H), 7.18 (m, 2H), 5.14 (s, 2H), 3.86 (s, 3H). ^{13}C NMR δ 14.1, 23.7, 60.5, 111,7, 159.4, 160.5, 163.9, 166.4, 163.0, 138.0, 134.8, 133.9, 129.0, 128.6, 127.4, 125.3, 51.5, 51.2. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.65; H, 5.55; N, 13.00.

2. Microwave Irradiation Procedure. The resin **2** was suspended in dry *n*-BuOH (5 mL) in a round-bottomed flask with a reflux condenser. Benzylamine (0.1 mL, 1.38 mmol) was added, and the resulting mixture was exposed to microwave irradiation at 114 °C for two cycles of 30 min in a self-tuning, single mode, CEM Discover Focused Synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 3 min. The reaction progress was monitored by the colorimetric chloranil test (positive). After cooling to room temperature, the resin sample was collected by filtration using a sintered glass funnel and successively worked up as above. After evaporating the solvent to dryness under reduced pressure, pure methyl 1-benzyl-1*H*-imidazole-4-carboxylate **3a** (28.9 mg, 97% yield, 99% purity) was obtained as a colorless oil.[18]

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Supporting Information Available. Synthetic procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org/.

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