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Synthesis of imidazole-4-carboxylic acids via solid-phase bound 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate

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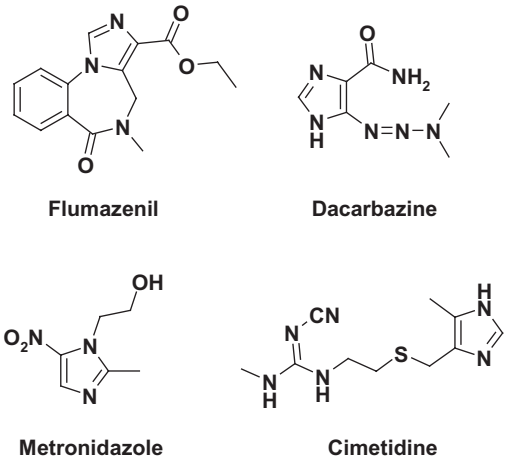
Abstract—The novel 3-*N*,*N*-(dimethylamino)isocyanoacrylate-Wang-resin is used for the synthesis of imidazole-4-carboxylic acids. The syntheses are performed in a microwave reactor with reaction times of only 15 min at 220 °C in the solvent dimethoxyethane.

The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole[1] and its relatives, the benzodiazepine antagonist Flumazenil,[2] the antineoplastic drug Dacarbazine,[3] the antibiotic Metronidazole,[4] the antiulcerative agent Cimetidine,[5] the antihyperthyroid drug Methimazole,[6] the prohormone Thyroliberin,[7] the muscarinic receptor agonist Pilocarpine[8] and the hypnotic agent Etomidate[9] (Scheme 1).

Different synthetic strategies for this nucleus are described in the literature,[10] whereby 1-substituted 4-imidazole carboxylic acids represent a special case due to the formation of regioisomeric mixtures upon alkylation of 4-imidazole carboxylate. A solution to this synthetic problem was first reported by Allgeier[11] and later by Helal and Lucas[12] who both used 3-*N*,*N*-(dimethylamino)isocyanoacrylate as starting material, which was reacted with different amines. This afforded quite long reaction times especially when using aromatic or sterically hindered amines. The applicability of 3-*N*,*N*-(dimethylamino)isocyanoacrylate for the synthesis of different heterocycles has been communicated elsewhere.[13]



Scheme 1. Examples of imidazole-containing drugs.

Here, the use of resin-bound 3-*N*,*N*-(dimethylamino)-isocyanoacrylate is described for the synthesis of 1-substituted 4-imidazolecarboxylates. HMBA-linker bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate (4-(hydroxymethyl)benzoic acid = HMBA) has already been used for the synthesis of thiazoles[13] (Scheme 2).

Wang-resin bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate was obtained simply by reacting a twofold excess of the potassium salt[14] of isocyanocarboxylic acid with (4-bromomethylphenoxy)methyl polystyrene in DMF.[15] Thereafter the intermediate so obtained was treated with dimethylformamide diethyl acetal in a mixture of ethanol and THF (Scheme 3). The loading could be determined as already cited in another article[16] and was 0.36 mmol/g.

Different protocols were tested for the reaction of resin-bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate with amines. The best results were obtained with the following process: The amine was added in an eightfold excess to the resin, which was swollen in dimethoxyethane

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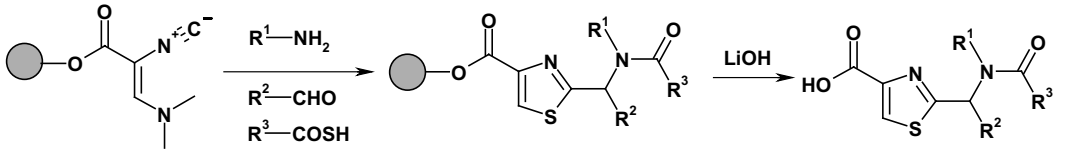
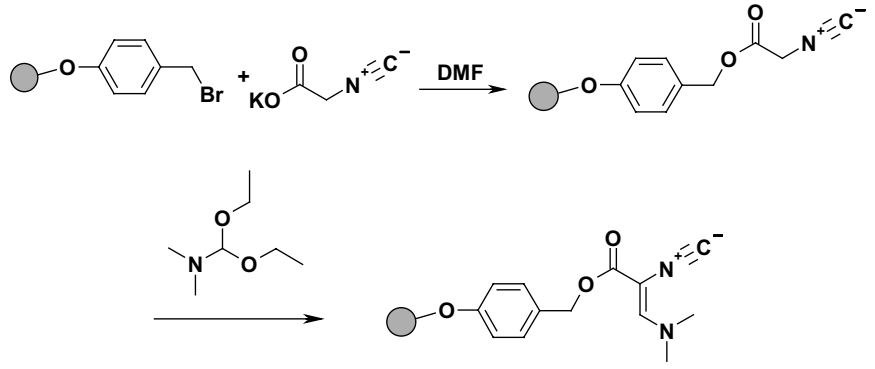


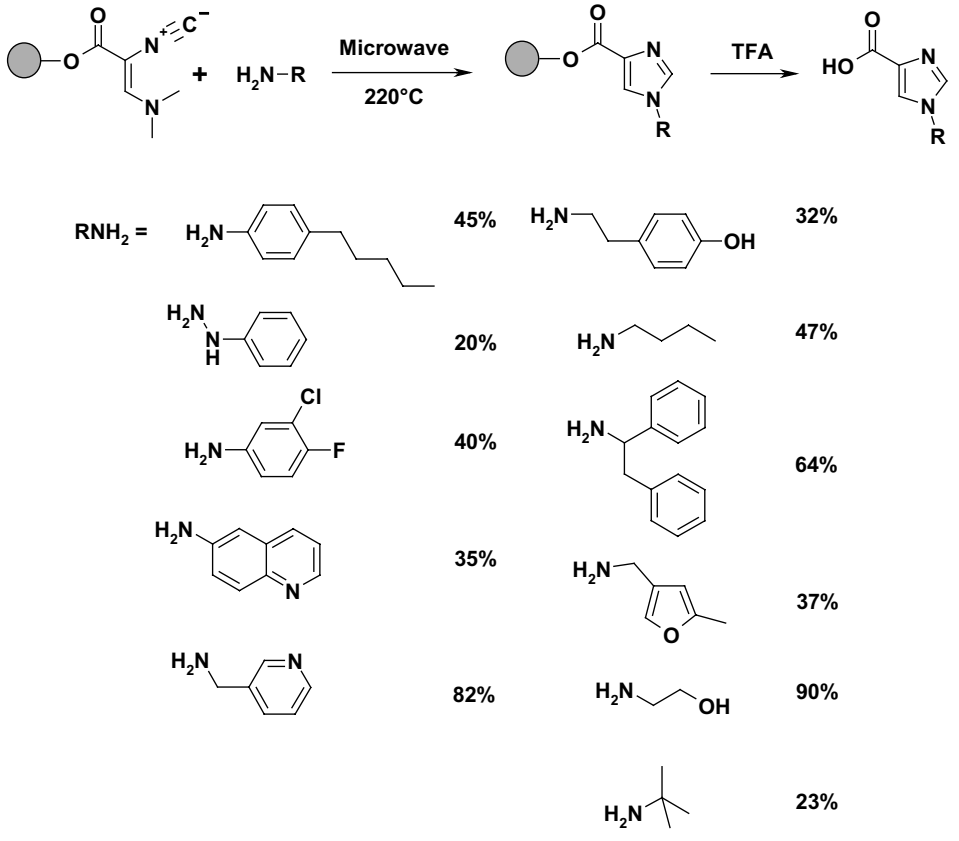
Scheme 2. Synthesis of thiazoles via HMBA-linker bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate.



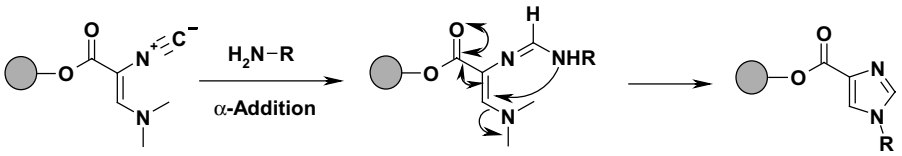
Scheme 3. Preparation of Wang-resin-bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate.

in a Smith Process glass vial. The reaction mixture was heated in the sealed vial upon microwave irradiation to 220 °C for 15 min. The resin was washed thoroughly and afterwards treated with 50% TFA in dichloromethane for 60 min. Crude products were purified via preparative HPLC using a methanol/water gradient giving yields from 20% to 90% (Scheme 4).[17]

The reaction proceeded well with different aromatic and aliphatic amines. Hydroxy groups have no negative



Scheme 4. Examples of the 1-substituted 4-imidazole carboxylates prepared with their isolated yields.



Scheme 5. Proposed mechanism for the synthesis of 1-substituted 4-imidazole carboxylates.

impact on the reaction. In the case of phenylhydrazine and *tert*-butylamine only poor yields were obtained, in the latter example due to steric hindrance.

For the reaction of resin-bound 3-*N*,*N*-(dimethylamino)-isocyanoacrylate with amines a mechanism involving α-addition of the amine to the isocyanide can be proposed similar to that already described in the literature[18] where heavy metal salts were used as catalysts (Scheme 5).

In conclusion, the resin-based synthesis of 1-substituted 4-imidazole carboxylates is reported. The majority of these compounds could be obtained in viable yields in extremely short reaction times due to execution of the reactions under microwave conditions.

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15. (a) Henkel, B. PCT Int. Appl. WO 2003051795, 2003; *Chem. Abstr.* **2003**, *139*, 68959; (b) Resin-bound 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate is available from Priaton, Bahnhofstrasse 9-15, D-82327 Tutzing, Germany (www.priaton.de).
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17. Representative example: Synthesis of 1-pyridine-3-ylmethyl-*1H*-imidazole-4-carboxylic acid: 500 mg of Wang-resin bound 3-*N*,*N*-(dimethylamino)isocyanoacrylate (0.18 mmol) was placed in a Smith Process glass vial together with 4 mL of dimethoxyethane and 0.146 mL of 3-(aminomethyl)pyridine (1.44 mmol). The vial was sealed and heated to 220 °C for 15 min with a Smith Creator Microwave System from Personal Chemistry. The vial was allowed to cool and the lid was removed. Then the resin was washed three times with dimethoxyethane and three times with methanol. The resin was dried under high vacuum and thereafter treated with 50% trifluoroacetic acid in dichloromethane for 60 min. After the resin had been filtered off, the resulting solution was evaporated to dryness. The crude product was purified via preparative HPLC (column Grom-Sil 120 ODS-5, 50×20 mm, 5 μm, flow 30 mL/min, gradient 10–100% A in 15 min, solvent A = methanol + 0.5% acetic acid, solvent B = water + 0.5% acetic acid). Yield: 30 mg (82%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 5.44 (s, 2H, CH_2); 7.63 (m, 1H, CH); 8.04 (d, 1H, CH, $J = 7.8$ Hz); 8.17 (s, 1H, CH); 8.51 (s, 1H, CH); 8.69 (s, 1H, CH); 8.78 (s, 1H, CH). ^{13}C NMR (100 MHz, d_6-DMSO): δ 47.9; 125.0; 126.1; 130.8; 133.1; 138.9; 146.9; 147.1; 158.7; 161.7.
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