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New method for the preparation of solid-phase bound isocyanocarboxylic acids and Ugi reactions therewith☆

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Abstract—A novel method of synthesizing solid-phase bound isocyanocarboxylic acids is reported. The potassium salts of four different isocyanocarboxylic acids are coupled onto a brominated resin in DMF in good yields. 32 Ugi reactions were performed using these resins and 24 products were obtained in good to viable purities.

Several groups have reported about the preparation of solid-phase bound isocyanides.[1–10] These resins can be used for multicomponent reactions like the Ugi or the Passerini reaction[3,7,8,10] giving straightforward access to compounds bearing three or more points of diversity that can be generated in a single step. In most cases these isocyano resins are manufactured via a solid-phase bound amine that is converted to the formamide followed by a dehydration step that can be performed for example with PPh_3/CCl_4,[3,4,6] with $POCl_3/NEt_3$[5,10] or with *p*-toluenesulfonic acid/pyridine.[1,9] In our hands these methods did not lead to neat resin-bound isocyanocarboxylic acids, the formamide still being present after the dehydration step. This was also confirmed by ATR measurements in a recent report.[9]

Therefore we decided to develop a strategy for the direct coupling of isocyanocarboxylic acids onto different resins. This can be achieved via potassium salts of the respective isocyanocarboxylic acids that can easily be obtained by saponification with ethanolic KOH.[11] These salts are reacted with brominated resins like 4-(bromomethyl)phenoxymethyl polystyrene or 4-(bromomethyl)benzoic acid coupled onto aminomethyl polystyrene (Scheme 1) leading to the acid-labile Wang-resin-bound and to the base-labile resin-bound isocyanocarboxylic acids.[12] The loading was determined as already described in the literature.[9]

In order to test these resins in solid-phase synthesis four potassium salts of isocyanocarboxylic acids were synthesized and coupled onto brominated HMBA-resin (hydroxymethylbenzoic acid) which should be used for Ugi reactions (Scheme 2). The loadings were 0.37 mmol/g for isonitrile **IN 1**, 0.38 mmol/g for **IN 2**, 0.34 mmol/g for **IN 3** and 0.41mmol/g for **IN 4**.

The Ugi reactions were executed with a tenfold excess of the reactants in methanol/dichloromethane = 1:1 for 70 h. Every batch was divided into two proportions and different cleavage methods applied. The first portion was treated with a twentyfold excess of 3-methylbutylamine in DMF, the second portion with a fourfold of LiOH in a mixture of THF and water leading to amides on the one hand and to compounds with a free carboxylic acid on the other hand. In this manner a fifth element of diversity can be introduced. The purities of the crude products which were obtained as diastereomeric mixtures are given in Table 1. Diastereomeric ratios could not be determined by analytical HPLC due to incomplete resolution of the product peaks. From the purities of the crude products **13–16** it can be seen that the Ugi-reactions of **IN 3** and **IN 4** give only poor results when using 2-ethylbutyraldehyde, 4-bromoaniline and Boc-Ala-OH as reaction components. In some cases the resin-bound products could not be cleaved from the polymer with both cleavage mixtures.

Keywords: solid-phase synthesis; multicomponent reaction; Ugi-reaction; isocyanocarboxylic acid.

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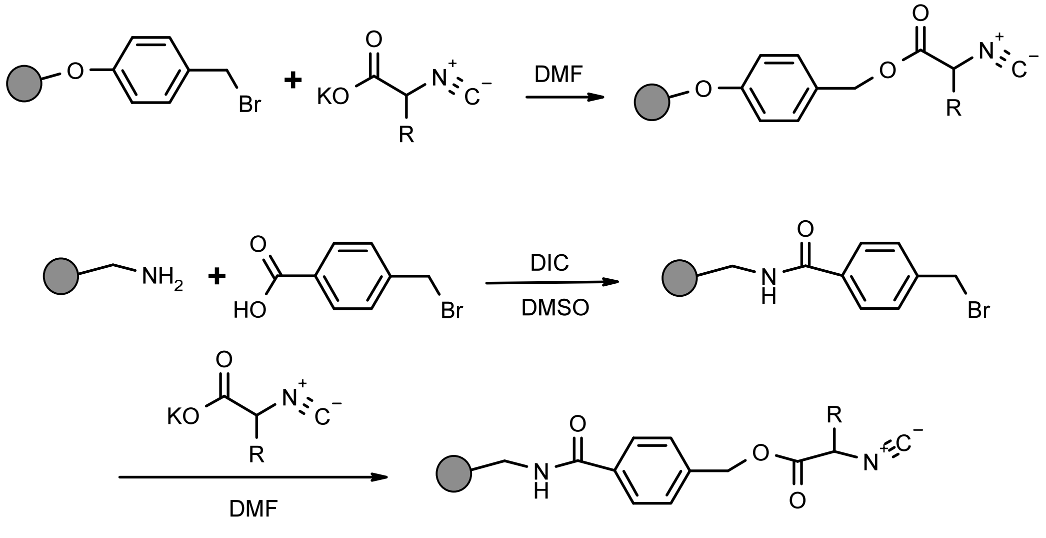
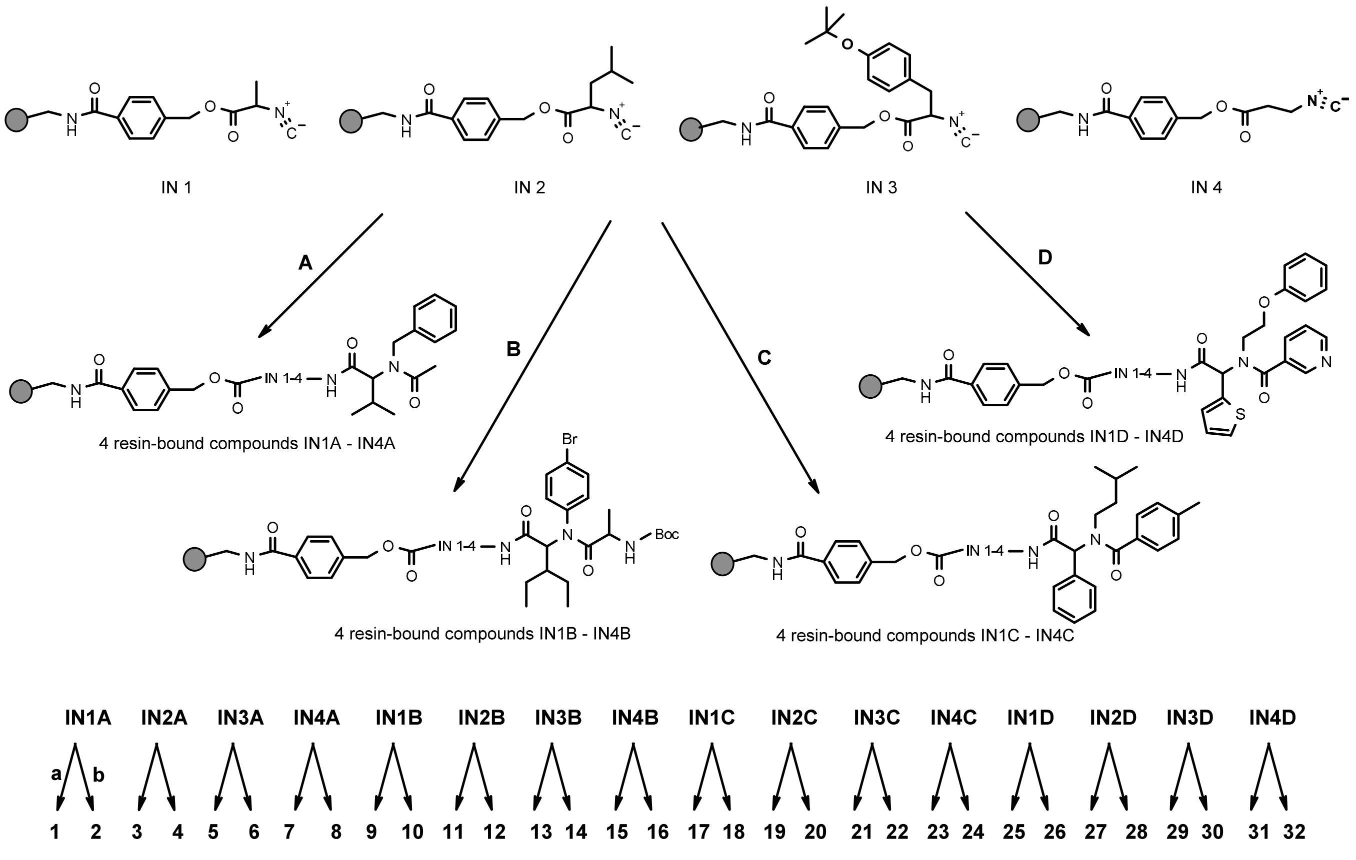


R = side chains of amino acids

Scheme 1.



IN1-4 = HMBA-resin-bound isonitriles 1-4; A = Ugi-reactions with isobutyraldehyde, benzylamine and acetic acid; B = Ugi-reactions with 2-ethylbutyraldehyde, 4-bromoaniline and Boc-Ala-OH; C = Ugi-reactions with benzaldehyde, 3-methylbutylamine and p-toluic acid; D = Ugi-reactions with thiophene-2-carbaldehyde, 2-phenoxyethylamine and nicotinic acid; IN1A – IN4D = 16 different resin-bound Ugi compounds; a = cleavage with 3-methylbutylamine in DMF; b = cleavage with LiOH in THF/water; 1-32 = compounds obtained.

Scheme 2.

Table 1. Purities of the diastereomeric Ugi products calculated from HPLC at 220 nm[13]

Compound number	HPLC purity at 220 nm[a] (%)	Compound number	HPLC purity at 220 nm[b] (%)
1	60	**2**	N.o.
3	36	**4**	51
5	38	**6**	58
7	43	**8**	41
9	75	**10**	77
11	66	**12**	22
13	N.o.	**14**	17
15	18	**16**	14
17	N.o.	**18**	88
19	46	**20**	N.o.
21	85	**22**	84
23	58	**24**	N.o.
25	86	**26**	75
27	82	**28**	N.o.
29	N.o.	**30**	72
31	44	**32**	N.o.

N.o. = not obtained.

[a] Purities determined after an acidic extraction step to remove excess 3-methylbutylamine.

[b] Crude products contain LiCl from neutralisation of LiOH with HCl; LiCl cannot be seen by UV.

Furthermore some distinct reactions were performed using 2-isocyano-3-methylbutyric acid methyl ester and 3-(4-*tert*-butoxyphenyl)-2-isocyanopropionic acid methyl ester to compare the solid-phase strategy with the reactions in solution. The respective methyl esters of the compounds **4**, **12** and **14** were obtained in a purity of less than 10%, whereas the methylesters of **6**, **22** and **30** were obtained in a purity of less than 40%. The reactions were carried out with equimolar amounts of the reactants in methanol for 70 h. The higher purities in the solid-phase strategy are caused by the use of excesses of reactants.

In conclusion, we have shown a new and uncomplicated method for the generation of solid-phase bound isocyanocarboxylic acids that can be used for multicomponent reactions like the Ugi reaction with the benefit of not having unreacted formamide in the crude product after cleavage from the resin. A further advantage when using these resins is obvious: A fifth point of diversity can be incorporated into the Ugi product upon cleavage from the HMBA resin. Additionally it can be said that the solid-phase strategy is clearly superior to the execution of the reaction in solution.

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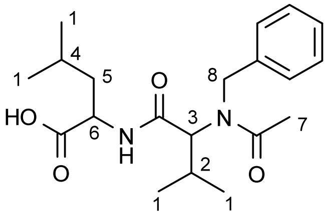
12. Patent pending; resin-bound isocyanocarboxylic acids are available from Priaton, Bahnhofstrasse 9-15, D-82327 Tutzing, Germany (www.priaton.de).
13. Representative examples for the solid-phase Ugi reaction: Synthesis of **4**:



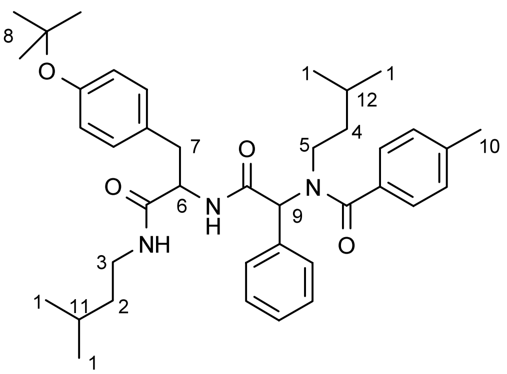
Isobutyraldehyde (0.062 ml, 0.68 mmol) was dissolved in 2 ml of absolute methanol together with 0.074 ml benzylamine (0.68 mmol). This mixture was stirred for 16 h. Then both 2 ml absolute dichloromethane was added and 180 mg of **IN 2** (0.068 mmol) and 0.039 ml of acetic acid (0.68 mmol). This mixture is agitated for 72 h at room temperature. The resin is filtered off and washed three times with dichloromethane and methanol. Finally the polymer is dried under high vacuum. Cleavage is performed with 6.5 mg of LiOH (0.27 mmol) in 3 ml THF/water = 1:1 for 16 h. The resin is filtered off and washed twice with THF/water. The filtrate is neutralised with 2N HCl and evaporated to dryness. Purification via preparative HPLC afforded 11 mg of diastereomeric **4** (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8–1.0 (m, 12H, 4 $CH_3{}^1$); 1.5–1.65 (m, 1H, CH^2); 1.65–1.75 (m, 2H, $CH_2{}^5$);

2.1 (s, 3H, $CH_3{}^7$); 2.35–2.5 (m, 1H, CH^4); 4.3–4.5 (m, 1H, CH^3); 4.5–4.85 (m, 3H, $CH_2{}^8$, CH^6); 7.1–7.35 (m, 5H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1; 19.2; 19.7; 19.8; 22.1; 22.2; 22.8; 22.9; 23.2; 25.1; 27.3; 27.8; 40.8; 41.4; 126.3; 126.5; 127.5; 127.6; 128.9; 137.0; 170.0; 174.0; 174.5.

Synthesis of **21**:



Benzaldehyde (0.063 ml, 0.62 mmol) was dissolved in 2 ml of absolute methanol together with 0.072 ml 3-methylbutylamine (0.62 mmol). This mixture was stirred for 16 h. Then both 2 ml absolute dichloromethane was added and 152 mg of **IN 3** (0.062 mmol) and 84 mg of *p*-toluic acid (0.62 mmol). This mixture was agitated for 72 h at room temperature. The resin was filtered off and washed three times with dichloromethane and methanol. Finally the polymer was dried under high vacuum. Cleavage was performed with 0.144 ml of 3-methylbutylamine (1.24 mmol) in 3 ml of absolute DMF for 16 h. The resin was filtered off and washed twice with DMF. The filtrate was evaporated to dryness. Purification via preparative HPLC afforded 24 mg of diastereomeric **21** (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.48–0.84 (m, 12H, 4 $CH_3{}^1$); 1.22–1.3 (m, 4H, $CH_2{}^2$, $CH_2{}^4$); 1.32 (s, 9H, $C(CH_3)_3{}^8$); 1.38–1.5 (m, 2H, CH^{11}, CH^{12}); 2.39 (s, 3H, $CH_3{}^{10}$); 3.05–3.15 and 3.37–3.5 (m, 2H, $CH_2{}^7$); 3.14–3.28 (m, 4H, $CH_2{}^3$, $CH_2{}^5$); 4.58–4.65 (m, 1H, CH^6); 5.34 (s, 1H, CH^9); 6.74–7.44 (m, 13H, aromatic protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7; 22.6; 25.8; 25.9; 29.1; 36.5; 37.8; 37.9; 38.3; 38.4; 54.8; 67.3; 124.6; 124.7; 126.9; 128.9; 129.0; 129.1; 129.2; 129.6; 129.7; 129.8; 130.0; 131.5; 135.2; 140.1; 140.4; 154.3; 169.3; 170.3; 170.4.