Preparation of Resin-Bound *N*-(α-Methoxyalkyl)amides: An Advantageous Use of Solid-Phase Chemistry for the Handling of Unstable Precursors of the Versatile *N*-Acyliminium Ions

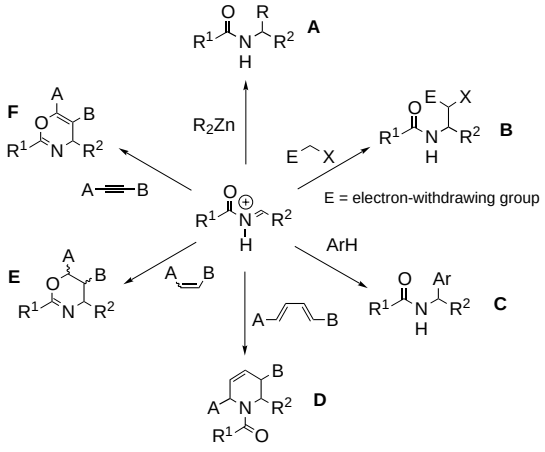
Cécile Vanier, Alain Wagner,* and Charles Mioskowski*[a]

Abstract: The development of a new and efficient synthesis of resin-bound *N*-(α-methoxyalkyl)amides is described. The condensation of aldehydes on a supported amide in the presence of trimethyl orthoformate afforded, in acidic media, the resin-bound *N*-acyliminium ion precursors. Repeating the reaction a second time led to a great improvement in yields, demonstrating one advantage of the solid-phase chemistry for the handling of sensitive intermediates difficult to isolate.

Keywords: acyliminium ions · amides · solid-phase synthesis

Introduction

N-Acyliminium ions are versatile intermediates for carbon–carbon bond-forming reactions, such as Mannich-type condensations. They also undergo reactions with many nucleophiles, for example, alkyl zinc reagents (path A, Scheme 1), activated methylene derivatives (path B, Scheme 1) or aromatic and heteroaromatic compounds (path C, Scheme 1).



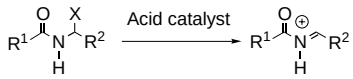
Scheme 1. *N*-Acyliminium-ion chemistry allows access to important structural diversity through reactions with nucleophiles, dienes or dienophiles.

[a] Dr. A. Wagner, Dr. C. Mioskowski, Dr. C. Vanier
Laboratoire de Synthèse Bio-Organique
Université Louis Pasteur, UMR 7514 associée au CNRS
Faculté de Pharmacie, 74 route du Rhin
67401 Illkirch cedex (France)
Fax: (+33) 390-24-43-06
E-mail: wagner@bioorga.u-strasbg.fr
mioskowski@bioorga.u-strasbg.fr

They have been reported to be valuable partners in cycloaddition reactions: as dienophiles (path D, Scheme 1) or as electron-poor 4π components in [4+2] cycloadditions with alkenes (path E, Scheme 1) or alkynes (path F, Scheme 1).[1]

Such versatility is very attractive for solid-phase chemistry, since it would enable the generation of structural diversity from a common precursor. However, the synthesis of these intermediates on a solid support is not an easy task.

N-Acyliminium ions are highly reactive and unstable species that have to be generated in situ. The most straightforward preparation is the direct condensation of an amide and an aldehyde in strongly acidic media. Although often applied for Mannich- or Friedel–Crafts-type reactions, these conditions are not compatible with many sensitive substrates nor applicable to all the above types of chemistry. Thus, alternative methods that allow access to *N*-acyliminium ions under milder conditions have been investigated. Most methods involve precursors of the *N*-(α-heteroatom-alkyl)amide type. The *N*-acyliminium ions are subsequently generated through acid-assisted ionization (Scheme 2).



X = OH, NHCOR[1], Cl, OR, Bt

Scheme 2. Acid-catalyzed generation of *N*-acyliminium ions from various precursors.

In practice, the syntheses of the various types of precursors are often problematic, and none of the reported methods can be applied to a wide variety of substrates. Hence, if the X group has no or little influence on the activation step, it appears to be crucial for the preparation of the precursor.[2]

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For instance, the preparation of *N*-(α-hydroxyalkyl)amides (X = OH) or *N*,*N*′-alkylidenebisamides (X = NHCOR[1]) requires strongly acidic reaction conditions (such as concentrated sulfuric acid or hot polyphosphoric acid), which are so severe that they limit its scope. Moreover, they seem to be restricted to the cases where R^2 is an electron withdrawing group.

When X is a halide, the compounds are so unstable that they are very difficult to generate and isolate.[2] In contrast, *N*-(α-alkoxyalkyl)amides (X = OR) are usually stable molecules that can be activated under mild acidic conditions. However, their synthesis remains problematic, since the condensation of amides with aldehydes or acetals is an equilibrium process that usually disfavors the alkoxy adduct. Thus, this preparation is limited to reactive aldehydes like formaldehyde, chloral, or glyoxylic acid and its esters. Other aldehydes generally require electrochemical preparation: anodic oxidation of *N*-alkylated amides in alcohols.[3] Alternative indirect routes, such as ionization rearrangement of *N*-trifluoromethanesulfonylamides,[4] or acylation of imidate nitrogen,[5] are reported, but are not of synthetic use,[6] especially for solid-phase synthesis.

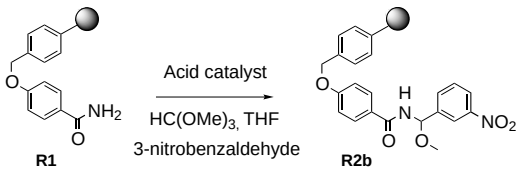
N-(1-Benzotriazolylalkyl)amides (X = benzotriazole) have been widely investigated by Katritzky et al.[7] Condensation of an aldehyde, an amide, and benzotriazole in toluene with azeotropic removal of water gives, after crystallization, the desired product in high yield and good purity. This preparative method affords versatile precursors of *N*-acyliminium ions, but has some drawbacks such as long reaction time, limited choice of aldehydes (mainly aromatics), and low solubility of the triazole adducts in usual organic solvents.

The few papers dealing with the preparation of *N*-acyliminium ions and their precursors on solid supports highlight the synthetic potential of these versatile species for the generation of structural diversity, but also the difficulty in handling such reactive species. Hiemstra et al. reported the reaction of *N*-acyliminium ions, generated from an alkoxy precursor, with allyltrimethylsilyl derivatives, leading to valuable pyrrolidine derivatives.[8] The same author described the synthesis of a library of homoallylic amines in a one pot process involving a transient resin-bound *N*-acyliminium.[9] In the same way both Ganesan[10] and Pátek,[11] described the synthesis of complex structures through intramolecular nucleophilic addition of a pyrrole moiety on a transient *N*-acyliminium ion. To enlarge the scope of *N*-acyliminium chemistry on solid supports we undertook an investigation to set up a versatile and mild preparation of stable resin-bound *N*-acyliminium ion precursors.

Results and Discussion

We first embarked upon the transposition of Katritzky's procedure to solid phase chemistry. A supported aromatic amide was allowed to react in toluene with benzaldehyde and benzotriazole. The slurry was heated under reflux in a reactor equipped with a Dean–Stark apparatus for up to 72 hours. No or very little formation of the desired compound was observed by FT-IR analysis. The usually employed azeotropic removal of water was quite inconvenient to adapt to the solid phase synthesis situation: it is hardly possible to obtain a regular boiling and the amount of removed water is too large to be efficiently trapped. Alternative attempts to synthesize these resin-bound derivatives in the presence of water scavengers such as trimethyl orthoformate or trimethylchlorosilane (TMSCl) also remained unsuccessful.

Therefore, we turned our attention to the preparation of *N*-(α-alkoxyalkyl)amides, which seemed to be the most adequate precursors. None of the reported solution phase preparations were efficient enough nor compatible with solid-phase synthesis. We thus opted to investigate the development of an original protocol involving the condensation of an amide resin **R1** with an excess of aldehyde in the presence of trimethyl orthoformate. Resin **R1**, with a theoretical loading of 1.245 mmol g^{-1}, was prepared in one step from Merrifield resin (1.5 mmol g^{-1}) by reaction with seven equivalents of 4-hydroxybenzamide, pretreated with sodium hydride, in anhydrous DMF. The synthesis of the *N*-(α-alkoxyalkyl)amide was optimized on a model system in which 3-nitrobenzaldehyde was selected as standard aldehyde, since it allows easy FT-IR monitoring of the reaction (Scheme 3).



Scheme 3. Model system used to optimize the experimental conditions for the synthesis of the supported *N*-(α-methoxyalkyl)amide.

Several parameters such as the amount and nature of acid, and the stoichiometry of all reagents were varied. According to observations under homogeneous conditions, the first step of the reaction involves the in situ quantitative transformation of the aldehyde into its corresponding dimethyl acetal. It is only in a second step that the resin-bound amide reacts with the acetal. Consistently, reaction carried out using the acetal as substrate gave comparable results. The reaction was first run with one and five equivalents of acid calculated from the theoretical resin **R1** loading, along with five equivalents of aldehyde and ten equivalents of orthoformate. In all cases the best results were obtained by using five equivalents of acid.

The aldehyde/orthoformate ratio appeared to have an important influence on the outcome of the reaction. When large excess of trimethyl orthoformate (10 equivalents/aldehyde) was used only poor yields were obtained (24 % at most), while better ones were reached (up to 85 %) when introducing only two equivalents of aldehyde.

Some acid catalysts were screened in the above established experimental conditions, that is, five equivalents of acid, five of aldehyde, and ten of trimethyl orthoformate. The most significant results are summarized in Table 1.

Poor results were obtained with 4-methyl benzenesulfonic acid (TsOH), camphorsulfonic acid (CSA), TMSCl, and acetic acid. No or very weak nitro bands at 1531 and 1349 cm^{-1} could be detected by single beam FT-IR analysis

Table 1. Acidic conditions tested for the synthesis of the resin-bound *N*-(α-methoxy-3-nitrophenylmethyl)amide model.

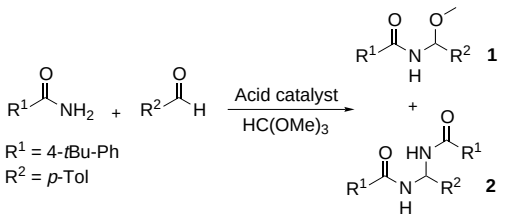
Entry	Acid catalyst	Yield [%][a]
1	*p*-toluenesulfonic acid	< 10[b]
2	camphorsulfonic acid	< 10[b]
3	TMSCl, 5% MeOH	< 10[b]
4	AcOH	< 10[b]
5	TFAA	61
6	triflic acid	76
7	TFA	85

[a] *N*-(α-Methoxyalkyl)amide resins were hydrolyzed in ethanol/HCl 10% at 100 °C for 24 hours. The cleaved aldehyde was weighed to determine the efficiency of formation of resin **R2** (based on a theoretical loading of 1.07 mmol g^{-1}). [b] No or weak nitro signals were detected by IR analysis.

of the resins. In contrast, with trifluoro acetic anhydride (TFAA), trifluoromethanesulfonic acid (TfOH), and trifluoroacetic acid (TFA), IR analysis showed intense nitro bands. Moreover an additional C-O-C band at 1097 cm^{-1} could also be detected. In addition, ^{13}C NMR analysis of the resin **R2b**[12] showed characteristic signals of NH-*C*H-O at $\delta = 80.7$ and O-*C*H$_3$ at $\delta = 55.9$. These resins were subjected to cleavage under aqueous acidic conditions in a 1:1 ethanol/10% HCl mixture. After filtration, the recovered aldehyde was mass-balanced and analyzed by NMR spectroscopy. Isolated yields were 61%, 76%, and 85%, respectively. Furthermore, elemental analysis of resin obtained upon coupling with 4-bromobenzaldehyde gave a total bromine content of 5.4 w/w% corresponding to a loading of 0.68 meq g^{-1} consistent with the amount of aldehyde recovered after cleavage (Table 2, entry 4).

In summary, the optimized experimental conditions were shown to be a resin/TFA/aldehyde/trimethyl orthoformate ratio of 1/5/5/10 in THF at a concentration of about 0.5 M in aldehyde at 30 °C for 12 hours.

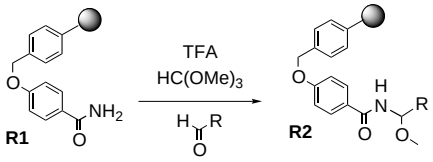
For comparison, similar experiments were carried out in solution by using 4-*tert*-butylbenzamide with three equivalents of *p*-tolualdehyde and 3 equivalents of trimethyl orthoformate in the presence of one of the above-mentioned acid catalyst in DMF, methanol, or dichloromethane (Scheme 4).

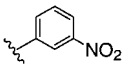
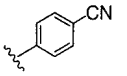
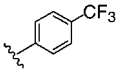
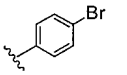
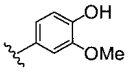
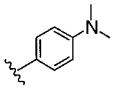
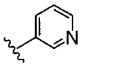
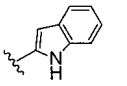
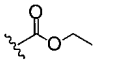
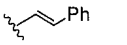
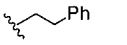


Scheme 4. Synthesis of *N*-(α-methoxyalkyl)amide in solution.

In all experiments, in addition to the remaining aldehyde and amide, the reaction gave a mixture of the *N*-(α-methoxyalkyl)amide **1** and the *N*,*N*′-alkylidenebisamide **2** in various ratios depending on the catalyst used. It is to be noted that, with the presence of the unreacted amide, the methoxy derivative **1** tends to transform to the corresponding bisamide **2** upon silica-gel purification, resulting in a decrease of yield. Attempts to purify crude products on alumina or triethylamine pretreated silica gel did not give any improvement. The best results were obtained when the catalyst used was either the Amberlyst® 15-ion exchange resin: 35% of *N*-(α-methoxyalkyl)amide **1** (48% in NMR crude) and 55% of *N*,*N*′-alkylidenebisamide **2** (42% in NMR crude), or TMSCl (41% of **1** and 35% of **2**). Surprisingly TFA, the most efficient catalyst for solid phase chemistry, only led to the formation of the aldehyde's dimethyl acetal.

Table 2. Preparation of various resin-bound *N*-(α-methoxyalkyl)amides.



Entry	R	Yield [%]
1		85
2		78
3		45[a]
4		78[a]
5		80
6		88
7		75
8		85
9		60
10		65[a]
11		58[a]

[a] Yields obtained after double coupling.

Several conclusions could then be drawn. The reactivity proved to be very different between solution- and solid-phase chemistry. On the one hand, the synthesis of *N*-(α-methoxyalkyl)amides in solution only afforded moderate yields. The products were always obtained along with the *N*,*N*′-alkylidenebisamides, requiring a tedious purification. On the other hand, the preparation of supported *N*-(α-methoxyalkyl)-amides not only benefits from the usual advantages of solid-phase synthesis (easy to carry out and to purify), but also gave higher yields. This is an interesting example in which the solid support shows a clear superiority for the synthesis and handling of sensitive intermediates that are difficult to isolate.

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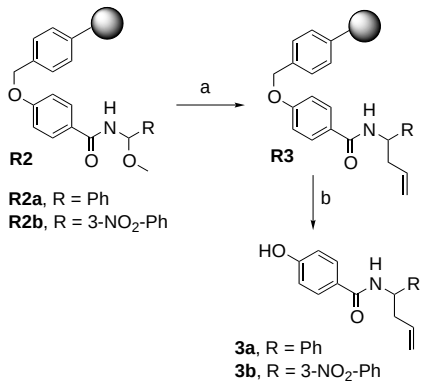
After setting up the optimized reaction conditions, we investigated the solid-phase synthesis of several supported *N*-(α-methoxyalkyl)amides. The products and their yields are given in Table 2.

The reaction ws carried out with several aromatic aldehydes and very good results were observed with most of them. Some have electron withdrawing groups -NO_2 (85% yield, entry 1), -CN (78% yield, entry 2), and others, electron donating groups -OMe (80% yield, entry 5), -NMe_2 (88% yield, entry 6). It is noteworthy that heteroaromatic derivatives gave very good yields (75%, entry 7 and 85%, entry 8). The ethylglyoxalate gave 60% yield (entry 9), which is very interesting, since it would afford, after further reaction of the corresponding *N*-acyliminium ion, a resin-bound functionality that can easily be derivatized. For aldehydes with poor coupling efficiency, repeating the sequence resulted in a dramatic increase in yields. 4-CF_3- and 4-Br-benzaldehydes which gave 25% and 44% yield, respectively, after single coupling afforded 45% (entry 3) and 78% yield (entry 4) after double coupling. Similarly, for conjugated and alkyl aldehydes (entries 10 and 11) the yield increased from 38% and 31% to 65% and 58%, respectively.

Interestingly, even for aldehydes affording the lower yields, cleavage of the methoxy adducts from the resin using the above-described reaction conditions for resin **R2**, always gave extremely clean products. This result shows that no major side reaction occurred. The resulting amide resin can be recycled and gave comparable results. Cleaved products are commercial aldehydes. The NMR spectra of the released species and the commercially-produced compounds were identical.

To ascertain that the supported methoxy adduct is an efficient precursor of *N*-acyliminium ion, we carried out some proof reactions.

Following the procedure described by Hiemstra et al.[8, 9] for analogous transformations, precursor resins were treated by boron trifluoride diethyl etherate to generate the transient *N*-acyliminium ions, which were then trapped by nucleophilic addition of allyltrimethylsilane (Scheme 5).

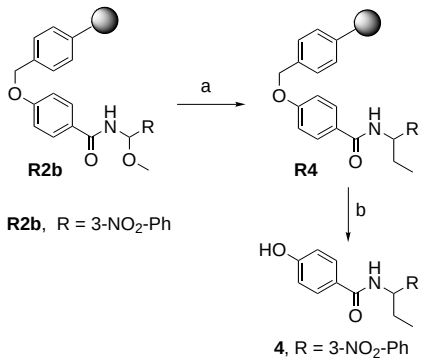


Scheme 5. Reaction sequence carried out to ascertain that supported methoxy adduct is an efficient precursor of *N*-acyliminium ion; a) $BF_3 \cdot Et_2O$ (3 equiv), allyltrimethylsilane (10 equiv), CH_2Cl_2, 0 °C to room temperature, 17 hours. b) TFA/CH_2Cl_2, 6:4; 50 °C, 14 hours.

After reaction, IR analysis of resin **R3a** showed the characteristic alkene signal at 1638 cm^{-1} and a shift of the NH and C=O signals from 3400 and 3333 cm^{-1} to 3478 and 3389 cm^{-1}, and from 1668 to 1656 cm^{-1}, respectively. Resin **R3a** was subjected to cleavage in a TFA/CH_2Cl_2 6/4 mixture at 50 °C for 14 hours. After filtration, the mother liquors were concentrated under vacuum, and the crude product was filtered through a cartridge of silica to afford the expected amide **3a** in 72% yield.

The same procedure was applied to resin **R2b**, which bears an electron-withdrawing group on the phenyl ring. Despite the presence of the nitro group, the transcient *N*-acyliminium ion was efficiently generated upon treatment with $BF_3 \cdot Et_2O$, and trapped with allyltrimethylsilane to lead to compound **3b** in 77% yield.

Furthermore, another proof-of-principal reaction was carried out. Precursor resin **R2b** was successfully engaged in a different alkylation reaction, through diethyl zinc addition, in the presence of boron trifluoride diethyl etherate, to obtain resin **R4** (Scheme 6). This resin was cleaved by using the conditions described for resins **R3a** and **R3b**. The crude product was evaporated, purified by filtration on a cartridge of silica, and the cleaved α-alkylated amide **4** was recovered in 56% yield.



Scheme 6. Reaction sequence for the alkylation of the resin-bound methoxy adduct; a) $BF_3 \cdot Et_2O$ (3 equiv), Et_2Zn (5 equiv), CH_2Cl_2, 0 °C to room temperature, 17 hours. b) TFA/CH_2Cl_2, 6:4; 50 °C, 14 hours.

It thus appears that the supported *N*,*O*-acetals prepared through this new set of conditions, are effective precursors for the generation of resin-bound *N*-acyliminium ions.

Conclusion

An original and straightforward preparation of resin-bound *N*-(α-methoxyalkyl)amides is reported. The synthesis and handling of such unstable structures proved to be much more convenient to carry out on solid support than in homogeneous phase, since solubility problems and chromatographic purifications were avoided. Moreover for poorly reactive aldehydes, yields could be increased by carrying out a double coupling sequence.

The potency of these supported precursors was demonstrated by generating the transient iminium ion and trapping it by nucleophilic addition of allyltrimethylsilane and Et_2Zn. This opens the way to further studies to exploit solid-phase chemistry of *N*-acyliminium ions.

Experimental Section

General methods: All chemicals were purchased from commercial suppliers. The Merrifield resin was purchased from Novabiochem. Filtration devices equipped with 5 μm pore size polytetrafluoroethylene membrane were purchased from Whatman. Solvents for reactions were distilled prior to use. Analytical grade solvents were used for resin washing. Single-beam IR analysis was carried out by using a Perkin–Elmer 2000 FT spectrometer coupled to an Autoimage microscope. NMR analysis were performed on Bruker 200 MHz or 300 MHz-Advance DPX spectrometer.

General procedures for the preparation of compounds 1 and 2

Method A: Under argon the *p*-tolualdehyde (2.00 mL, 16.9 mmol) and the trimethyl orthoformate (1.95 mL, 16.9 mmol) were added to a suspension of 4-*tert*-butylbenzamide (1.00 g, 5.6 mmol) in dry CH_2Cl_2 (20 mL). TMSCl (0.68 mL, 5.6 mmol) was added dropwise, and the mixture stirred at room temperature for 6 hours. The reaction mixture was evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel with EtOAc/hexane 2:8 (*v*/*v*) as eluent.

Method B: Under argon the *p*-tolualdehyde (2.00 mL, 16.92 mmol) and the trimethyl orthoformate (1.95 mL, 16.9 mmol) were added to a suspension of 4-*tert*-butylbenzamide (1.00 g, 5.6 mmol) in dry DMF (10 mL). Amberlyst® 15-ion exchange resin was added, and the mixture stirred at room temperature for 8 hours. The reaction mixture was filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane 2:8 (v/v) as eluent.

4-*tert*-Butyl-*N*-(α-methoxy-*p*-tolylmethyl)benzamide (1): ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.34$ (s, 9H), 2.37 (s, 3H), 3.57 (s, 3H), 6.34 (d, $^3J(H,H) = 9.4$ Hz, 1H), 6.55 (d, $^3J(H,H) = 9.4$ Hz, 1H; N-H), 7.2 (d, $^3J(H,H) = 8.1$ Hz, 2H), 7.39 (d, $^3J(H,H) = 8.1$ Hz, 2H), 7.46 (d, $^3J(H,H) = 8.67$ Hz, 2H), 7.75 (d, $^3J(H,H) = 8.67$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 21.2$, 31.1, 35.0, 56.1, 81.7, 125.6, 125.8, 127.0, 129.3, 130.9, 136.6, 138.3, 155.6, 167.2; IR: $\tilde{\nu} = 3313$, 2963, 1645, 1612, 1530, 1497, 1363, 1344, 1270, 1088, 851, 816 cm^{-1}.

4-Methylbenzylidenebis(4-*tert*-butylbenzamide) (2): ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.33$ (s, 18H), 2.33 (s, 3H), 6.81 (t, $^3J(H,H) = 7.5$ Hz, 1H; H–C(N–)$_2$), 7.15 (d, $^3J(H,H) = 7.9$ Hz, 2H), 7.39 (d, $^3J(H,H) = 7.9$ Hz, 2H), 7.45 (d, $^3J(H,H) = 8.67$ Hz, 2H), 7.8 (d, $^3J(H,H) = 8.67$ Hz, 2H), 7.88 (d, $^3J(H,H) = 7.5$ Hz, 2H; N–H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 21.1$, 31.2, 35.0, 60.1, 81.7, 125.6, 125.8, 127.1, 129.4, 130.8, 134.9, 135.8, 135.9, 137.7, 155.6, 167.5; IR $\tilde{\nu} = 3301$, 2963, 1649, 1611, 1544, 1487, 1330, 1269, 1141, 1061, 850, 775 cm^{-1}.

4-Hydroxy-*N*-(1-phenylbut-3-enyl)benzamide (3a): Resin **R3a** (200 mg, 0.31 mmol) was allowed to swell in a mixture of CH_2Cl_2/TFA 6:4 (3 mL). The suspension was heated at 50 °C for 14 hours. The resin was then rinsed alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). After concentration under vacuum, the crude product was filtered through a cartridge of silica to afford the expected amide **3a** in 72% yield (59 mg). ^{1}H NMR (200 MHz, $CDCl_3$/CD_3OD, TMS): $\delta = 2.68$ (t, $^3J(H,H) = 6.8$ Hz, 2H), 5.20 (m, 3H), 5.76 (m, 1H), 6.45 (d, $^3J(H,H) = 7.8$ Hz, 1H; NH), 6.81 (d, $^3J(H,H) = 8.8$ Hz, 2H), 7.33 (m, 5H), 7.61 (d, $^3J(H,H) = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 40.3$, 52.8, 115.0, 117.9, 125.1, 126.2, 127.1, 128.3, 128.7, 134.0, 141.6, 160.1, 167.3.

4-Hydroxy-*N*-[1-(3-nitrophenyl)-but-3-enyl]benzamide (3b): Resin **R3b** (200 mg, 0.30 mmol) was allowed to swell in a mixture CH_2Cl_2/TFA 6:4 (3 mL). The suspension was heated at 50 °C for 14 hours. The resin was then rinsed alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). After concentration under vacuum, the crude product was filtered through a cartridge of silica to afford the expected amide **3b** in 77% yield (67 mg). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 2.69$ (m, 2H), 5.26 (m, 3H), 5.75 (m, 1H), 6.45 (d, $^3J(H,H) = 7.8$ Hz, 1H; NH), 6.86 (d, $^3J(H,H) = 8.4$ Hz, 2H), 7.52 (t, $^3J(H,H) = 8.1$ Hz, 1H). 7.68 (d, $^3J(H,H) = 8.7$ Hz, 3H), 8.13 (d, $^3J(H,H) = 8.1$ Hz, 1H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD, TMS): $\delta = 44.8$, 57.1, 119.5, 122.4, 129.6, 130.6, 131.5, 132.8, 133.0, 133.3, 138.5, 146.2, 164.6, 171.7.

4-Hydroxy-*N*-[1-(3-nitrophenyl)propyl]benzamide 4: Resin **R2b** (250 mg, 0.26 mmol, 1 equiv) was allowed to swell in dry CH_2Cl_2 (2 mL). The suspension was chilled to 0 °C, before adding diethylzinc (1.33 mL, 1.24 mmol, 5 equiv) and $BF_3 \cdot Et_2O$ (102 μL, 0,78 mmol, 3 equiv). The resulting slurry was swirled for 1 hour at 0 °C followed by 12 hours at room temperature. The resin was filtered and washed with CH_2Cl_2 (5 mL), CH_2Cl_2/Et_3N (5 mL), and five times alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). Resin **R4** (200 mg, 0,31 mmol) was allowed to swell in a mixture CH_2Cl_2/TFA 6:4 (3 mL). The suspension was heated at 50 °C for 14 hours. The resin was then rinsed alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). After concentration under vacuum, the crude product was filtered through a cartridge of silica to afford the expected amide in 56% yield (52 mg). ^{1}H NMR (200 MHz, $CDCl_3$/CD_3OD, TMS): $\delta = 1.25$ (t, $^3J(H,H) = 7.1$ Hz, 3H), 2.04 (m, 2H), 5.46 (m, 1H), 6.87 (m, 3H), 7.48 (t, $^3J(H,H) = 8.1$ Hz, 1H), 7,72 (m, 3H), 8.11 (d, $^3J(H,H) = 8.1$ Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 10.5$, 28.9, 55.2, 114.9, 115.4, 125.2, 126.3, 126.9, 128.2, 128.7, 130.3, 142.2, 160.0, 167.5.

Synthesis of carboxamide resin R1: In a 250 mL dried flask, 4-hydroxybenzamide (10.3 g, 75 mmol) was dissolved into dry DMF (200 mL) under argon atmosphere. NaH (60% in mineral oil, 3.0 g, 75 mmol) was added portionwise over a 30 min period. The reaction mixture was allowed to react at room temperature for 2 hours and Merrifield resin (10.0 g, 15 mmol) was added. The resulting slurry was swirled for 14 hours at room temperature. The resin was filtered and washed with DMF (100 mL), CH_2Cl_2 (50 mL), 10% HCl (50 mL), and five times alternately with CH_2Cl_2 (25 mL) and MeOH (25 mL). The resin was dried under vacuum. IR: $\tilde{\nu} =$ 3463, 3354, 3199, 3060, 3026, 2926, 2850, 1669, 1605, 1513, 1452, 1380, 1252, 1178, 1029, 845, 761, 700 cm^{-1}.

Preparation of resin R2—typical procedure: Resin **R1** (5.0 g, 6.2 mmol) was allowed to swell in dry THF (50 mL). Trimethyl orthoformate (6.8 mL, 62 mmol) and aldehyde (31 mmol) were added to the resin followed by TFA (2.4 mL, 31 mmol). The resulting slurry was swirled for 12 hours at 30 °C. The resin was filtered and washed with THF (20 mL), CH_2Cl_2 (20 mL), NEt_3 (20 mL), and five times alternately with CH_2Cl_2 (15 mL) and MeOH (15 mL). The resin was dried under vacuum.

***N*-(α-Methoxyphenylmethyl)benzamide resin (R2a)**: IR $\tilde{\nu} = 3400$, 3333, 3060, 3027, 2923, 2851, 1668, 1605, 1493, 1453, 1250, 1177, 1088, 1029, 845, 763, 699 cm^{-1}.

***N*-[α-Methoxy-(3-nitrophenyl)methyl]benzamide resin (R2b)**: ^{13}C NMR (75 MHz, C_6D_6/dioxane 1:3): $\delta = 55.9$, 69.7, 80.7, 114.5, 121.2, 132.2, 142.0, 145.2, 48.1, 161.8, 167.4; IR: $\tilde{\nu} = 3410$, 3315, 3060, 3027, 2926, 2851, 1663, 1606, 1531, 1494, 1349, 1251, 1177, 1097 (C-O-C), 1029, 845, 764, 704 cm^{-1}.

***N*-[α-Methoxy-(3-cyanophenyl)methyl]benzamide resin**: Table 2, entry 2; IR: $\tilde{\nu} = 3410$, 3349, 3060, 3027, 2923, 2851, 2230, 1670, 1606, 1494, 1453, 1249, 1177, 1090, 1029, 845, 763, 700 cm^{-1}.

***N*-[α-Methoxy-(4-trifluoromethylphenyl)methyl]benzamide resin**: Table 2, entry 3; IR: $\tilde{\nu} = 3410$, 3332, 3060, 3027, 2923, 2851, 1668, 1605, 1493, 1453, 1373, 1310, 1250, 1177, 1088, 1029, 845, 762, 699 cm^{-1}.

***N*-[α-Methoxy-(4-bromophenyl)methyl]benzamide resin**: Table 2, entry 4; IR: $\tilde{\nu} = 3410$, 3332, 3060, 3027, 2923, 2851, 1668, 1605, 1493, 1452, 1374, 1250, 1175, 1089, 1030, 762, 701 cm^{-1}.

***N*-[α-Methoxy-(4-hydroxy-3-methoxyphenyl)methyl]benzamide resin**: Table 2, entry 5; IR: $\tilde{\nu} = 3510$, 3350, 3060, 3027, 2926, 2851, 1668, 1605, 1493, 1453, 1375, 1266, 1246, 1177, 1088, 1030, 845, 762, 700 cm^{-1}.

***N*-[α-Methoxy-(4-dimethylaminophenyl)methyl]benzamide resin**: Table 2, entry 6; IR: $\tilde{\nu} = 3410$, 3060, 3027, 2924, 2851, 1671, 1605, 1493, 1453, 1372, 1250, 1176, 1029, 844, 761, 700 cm^{-1}.

***N*-[α-Methoxy-(pyridin-3-yl)methyl]benzamide resin**: Table 2, entry 7; IR: $\tilde{\nu} = 3332$, 3060, 3027, 2926, 2851, 1668, 1605, 1579, 1494, 1453, 1375, 1251, 1177, 1090, 1029, 845, 762, 700 cm^{-1}.

***N*-[α-Methoxy (1*H*-indol-2-yl)methyl]benzamide resin**: Table 2, entry 8; IR: $\tilde{\nu} = 3410$, 3332, 3060, 3027, 2923, 2851, 1668, 1605, 1493, 1453, 1373, 1250, 1177, 1088, 1029, 845, 762, 699 cm^{-1}.

Methoxy(benzoylamino)acetic acid ethyl ester resin: Table 2, entry 9; IR: $\tilde{\nu} = 3410$, 3357, 3060, 3027, 2925, 2851, 1746, 1668, 1605, 1493, 1453, 1375, 1251, 1177, 1097, 1029, 845, 762, 699 cm^{-1}.

***N*-[α-Methoxy-(3-phenylallyl)]benzamide resin**: Table 2, entry 10; IR: $\tilde{\nu} =$ 3410, 3332, 3060, 3027, 2924, 2851, 1670, 1605, 1493, 1453, 1372, 1250, 1176, 1029, 844, 762, 700 cm^{-1}.

***N*-[α-Methoxy-(3-phenylpropyl)]benzamide resin**: Table 2, entry 11; IR: $\tilde{\nu} = 3332$, 3060, 3027, 2923, 2851, 1668, 1605, 1493, 1453, 1375, 1251, 1177, 1088, 1029, 844, 761, 699 cm^{-1}.

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Hydrolysis of resin R2—typical procedure: Resin **R2** (200 mg) was allowed to swell in ethanol (2 mL). Hydrochloric acid (10%, 2 mL) was added, and the slurry heated at 100 °C for 24 hours. The resin was filtered and washed five times alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). The crude products were evaporated and analyzed by NMR spectroscopy. Collected data are identical to spectra of commercial compounds.

Synthesis of *N*-(1-phenylbut-3-enyl)benzamide resin (R3a): Resin **R1** (200 mg, 0.18 mmol, 1 equiv) was allowed to swell in dry CH_2Cl_2 (2 mL). The suspension was chilled to 0 °C, before adding allytrimethylsilane (290 µL, 1.80 mmol, 10 equiv) and $BF_3 \cdot Et_2O$ (70 µL, 0.54 mmol, 3 equiv). The resulting slurry was swirled for 1 hour at 0 °C followed by 12 hours at room temperature. The resin was filtered and washed with CH_2Cl_2 (5 mL), CH_2Cl_2/Et_3N (5 mL) and five times alternately with CH_2Cl_2 (5 mL) and MeOH (5 mL). The resin was dried under vacuum. IR: $\tilde{\nu} = 3389$, 3478, 3059, 3026, 2929, 2850, 1656, 1638, 1605, 1453, 1251, 1174, 1129, 1030, 847, 701 cm^{-1}.

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