Combinatorial Synthesis of C(2), C(3)-Disubstituted 3-Hydroxypropionamides Utilizing Baylis-Hillman Reactions on Solid Support

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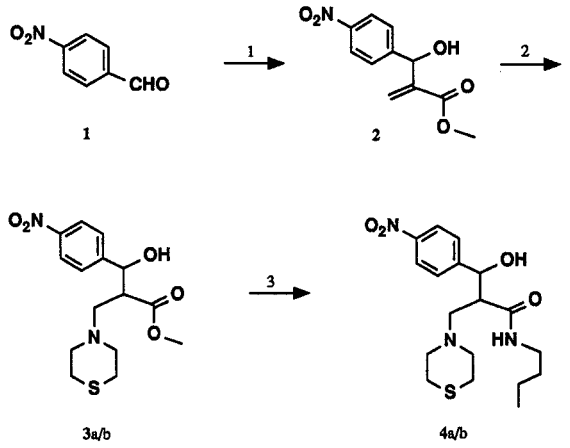
Abstract: A four-step reaction protocol for multiple polymer-supported synthesis of structurally diverse α,β-disubstituted 3-hydroxypropionamides **10** has been developed. Variable building blocks were recruited from three monomer pools: primary/secondary amines and aryl aldehydes, the latter of which underwent incorporation into target molecules via Baylis-Hillman reactions. The potential of our approach is demonstrated by machine-assisted assemblage of a small prototype library.

Numerous prominent carbon-carbon bond-forming reactions have recently been adapted for solid-phase synthesis in order to aid small molecule mass-production by combinatorial chemistry.[2] All compound library construction efforts disclosed so far, however, appear to have waived the tertiary amine-promoted addition between olefins bearing an electron-withdrawing group and aldehydes, a process commonly known as the Baylis-Hillman reaction.[3] Its attractive solution-phase features have prompted us to address library design based on this key transformation. In the present communication, Baylis-Hillman reactions on solid support are described for the first time and utilized en route to a small soluble prototype library comprised of 36 pairs of diastereoisomeric α,β-disubstituted racemic 3-hydroxypropionamides.

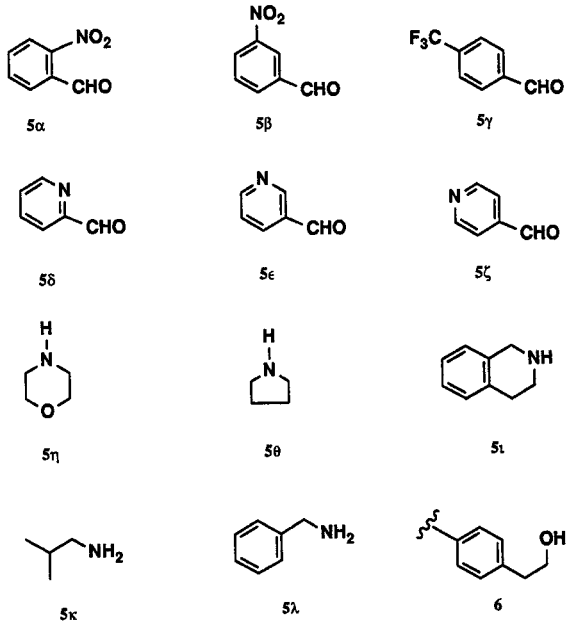
During a pilot study in solution, the sequence, along which representatives from three compound classes become attached to the propionyl scaffold, was examined for potential pitfalls such as incomplete conversion and by-product formation. A typical example is illustrated in Scheme 1.



Scheme 1. Reagents and conditions: (1) $CHCl_3$, DABCO, methyl acrylate, 22 °C, 16 h; (2) CH_2Cl_2, thiomorpholine, 22 °C, 3 h; (3) toluene, $(CH_3)_3Al$, *n*-butylamine, 0-22 °C, 8 h.

The selection of building blocks required for smooth Baylis-Hillman-type additions to acrylic esters capitalized on prior art according to which electron-deficient aryl aldehydes guarantee excellent conversion at reasonable rates.[4] In our hands, 4-nitrobenzaldehyde (**1**) and methyl acrylate underwent base-promoted coupling under an inert atmosphere at ambient temperature overnight to furnish an 88% yield of **2** following filtration through silica gel. Next, the incorporation of structurally diverse α-aminomethyl substituents by Michael addition was probed with a few secondary amines.[5] Thiomorpholine, for example, delivered an adduct mixture **3a/b** (6:4) in near quantitative yield at room temperature within three hours. Gratifyingly, separation into the corresponding stereoisomers **3a** and **3b** could be effected by silica gel chromatography (dichloromethane/*t*-butyl methyl ether, 3:2, gradient elution). The large benzyl proton coupling constant (J = 8.7 Hz) determined for the faster eluting entity **3a** bespeaks (2*R*,3*R*)/ (2*S*,3*S*) arrangement of stereocenters in this amino hydroxy ester. (2*R*,3*S*)/(2*S*,3*R*) Configuration in the polar isomer **3b**, on the other hand, is characterized by J = 4.5 Hz.[5,6] For a final combinatorial modification, trimethylaluminum-mediated ester aminolysis was called upon.[7] Depending on the substrate exposed to *n*-butylamine/trimethylaluminum, amides **4** were arrived at either as individual diastereoisomers **4a** (81%) and **4b** (75%) or as a mixture thereof, **4a/b** (82%). From crude aminolysis products, minor impurities, arising by elimination of water, were removed chromatographically on neutral alumina.

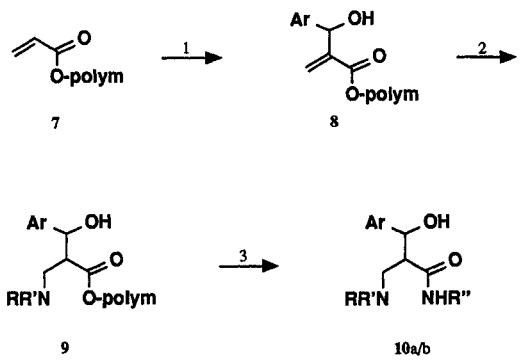
Having secured satisfactory overall efficacy for the solution-phase protocol, its implementation on solid support was turned to with some confidence. Scheme 2 displays the modular array of building blocks (**5α-5λ**) employed for initial exploratory work on resin and ultimate library generation.



Scheme 2

By immobilizing acrylic acid on 2-hydroxyethyl polystyrene (HEPS, **6**),[8] **6**→**7**, stability and reactivity of the ester linkage as well as accessibility of the conjugated double bond were considered to be appropriately balanced. The actual condensation between **6** (1.1 mequiv/g) and acryloyl chloride (THF, 22 °C, overnight, argon atmosphere) proceeded uneventfully in analogy to literature precedent.[9] When applied on resin **7** (> 0.8 mequiv/g), however, the solution-phase reaction conditions detailed in Scheme 1 afforded disappointingly poor results. Spectroscopic analysis of all major isolated by-products emerging from a typical run (Scheme 3) with components **5α**, **5η**, and **5κ** revealed incomplete addition in the Baylis-Hillman step. After some experimentation, this complication was largely overcome by changing solvent (chloroform → dimethylformamide) and base (1,4-diazabicyclo[2.2.2]octane (DABCO) → 3-hydroxyquinuclidine).[4] Even with these more favorable parameters, a second Baylis-Hillman reaction cycle was indicated to cut down the des-aryl compound level below 10% in final crude product mixtures. No difficulties were encountered for Michael additions of secondary amines to **8α** as judged by the absence of characteristic contaminants in the cleavage filtrate. Aminolytic detachment from the matrix was accompanied by some olefin formation also observed in the solution-phase scenario. In this manner, the four-step polymer-supported sequence led to diastereoisomers **10**aαηκ/bαηκ in 51% overall yield including final purification

on neutral alumina, which implies an average yield per step close to 85% based on the initial functionalization of resin **6**.



Scheme 3. Reagents and conditions: (1) DMF, 3-hydroxyquinuclidine, ArCHO (10 equiv), 22 °C, 18 h; (2) DMF, RR'NH (30 equiv), 22 °C, 18 h; (3) CH_2Cl_2, toluene, $(CH_3)_3Al$, $R''NH_2$ (20-30 equiv), 0-22 °C, 16 h.

The stage was thus set to exploit this optimized protocol for parallel synthesis. Since multi-component collections created by standard combinatorial split/mix methodology are not readily analyzed in depth, our library features single pairs of diastereoisomers amenable to straightforward quality assessment. Tedious repetitive operations invariably associated with such a matrix-type format were executed with robotic assistance.[10] In a single run, 18 discrete resin-bound combinations **9** were automatically assembled in triplicate (1 mmol scale) on a 60-well reactor block (5 mL cartridges) from 6 aldehydes and 3 secondary amines (Scheme 2). Sequential groupwise manual release, utilizing primary amines **5**κ and **5**λ, provided a soluble library of crude diastereoisomers **10**a/b, which were subsequently purified to spectroscopic homogeneity by chromatography. Generally, coelution of diastereoisomers was achieved by proper adjustment of solvent polarity. For the whole ensemble, overall yields based on nominal HEPS-functionalization cover the 40-66% range (average 52%). With two arbitrarily chosen samples, separations into individual stereoisomers **10**a and **10**b were reduced to practice.[11]

It is obvious that substantially larger compound collections will be accessible merely by expanding the monomer pools (Scheme 2). Moreover, the benzylic hydroxyl group common to all intermediates and products encourages additional transformations[3] which may give rise to libraries of higher structural diversity. Research in both directions is actively pursued in these laboratories.

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References and Notes

(1) Postdoctoral Associate: (a) 1996-1998, (b) 1995-1996.

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(10) The Syro workstation offered by MultiSynTech GmbH, Am Neggenborn 113, D-44892 Bochum, Germany, was used for this purpose.

(11) Physical data for selected compounds are as follows. **3**a: mp 99-101 °C (hexanes/ ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H), 7.22 (s, 1 H), 5.11 (d, J = 8.7 Hz, 1 H), 3.44 (s, 3 H), 3.09-2.69 (ser m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 149.0, 147.6, 127.5, 123.5, 76.9, 61.0, 55.4, 51.9, 49.2, 27.9. **3**b: mp 105-106 °C (pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 5.82 (d, J = 8.3 Hz, 1 H), 5.28 (dd, J = 8.2 Hz, J = 4.5 Hz, 1 H), 3.63 (s, 3 H), 3.29-2.47 (ser m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 149.3, 147.4, 126.8, 123.5, 73.7, 56.8, 55.3, 52.0, 47.9, 27.9. **4**a: mp 101-102 °C (ether/ dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2 H), 7.55 (d, J = 8.6 Hz, 2 H), 6.53 (br s, 1 H), 6.18 (s, 1 H), 5.31 (d, J = 6.0 Hz, 1H), 3.17-2.52 (ser m, 13 H), 1.35-1.09 (ser m, 4 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 149.4, 147.3, 127.1, 123.5, 74.7, 58.9, 55.2, 49.1, 38.9, 31.4, 28.0, 20.0, 13.6. **10**aαικ: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.2 Hz, J = 1.3 Hz, 1 H), 7.92 (dd, J = 8.0 Hz, J = 1.2 Hz, 1 H), 7.78 (br s, 1 H), 7.67 (td, J = 7.6 Hz, J = 1.2 Hz, 1 H), 7.44 (td, J = 8.4 Hz, J = 1.4 Hz, 1 H), 7.18-7.01 (ser m, 4 H), 6.11 (d, J = 6.9 Hz, 1 H), 5.47 (m, 1 H), 3.80 (1/2 ABq, J = 15.0 Hz, 1 H), 3.61 (1/2 ABq, J = 15.0 Hz, 1 H), 3.22-2.66 (ser m, 9 H), 1.60 (m_c, 1 H), 0.73 (d, J = 6.7 Hz, 6 H). **10**bαικ: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H), 7.76 (dd, J = 7.9 Hz, J = 1.2 Hz, 1 H), 7.59 (td, J = 7.5 Hz, J = 1.2 Hz, 1 H), 7.43 (td, J = 8.1 Hz, J = 1.3 Hz, 1 H), 7.17-6.95 (ser m, 5 H), 5.83 (s, 1 H), 5.80 (d, J = 4.8 Hz, 1 H), 3.64 (1/2 ABq, J = 15.0 Hz, 1 H), 3.57 (1/2 ABq, J = 15.0 Hz, 1 H), 3.09-2.65 (ser m, 9 H), 1.61 (m_c, 1 H), 0.77 (d, J = 7.0 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H).