

Multiplicity of Diverse Heterocycles from Polymer-Supported α -Acylamino Ketones

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Polymer-supported α -acylamino ketones were transformed to seven types of structurally unrelated heterocyclic compounds. Syntheses involved variety of chemical routes and comprised diverse chemistries (C–C, C=C, C–N, C=N, and C–O bond formations). Different sizes of heterocycles (4-, 5-, 6-, and 7-membered rings) were prepared, including dihydro-pyrrol-2-ones, pyrazin-2-ones, dihydro-triazepin-6-ones, morpholin-3-ones, imidazoles, β -lactams, and isoquinolin-1-ones. Further elaboration to fused ring systems was also documented.

Introduction

A very efficient strategy for diversity-oriented synthesis¹ takes advantage of common intermediates that are converted to chemically and structurally unrelated diverse scaffolds. This strategy has been successfully used on several occasions. For example, the Janda group reported syntheses of structurally diverse scaffolds using polymer-bound α -diazo- β -ketoesters.^{2–4} We prepared polymers-supported *o*-phenylenediamines with two diversity positions that were subsequently elaborated to various nitrogen containing heterocyclic structures.⁵ The multiplicity of structural types accessible from a common precursor increased the diversity of compounds: it has been demonstrated that single scaffold libraries are restricted to a limited number of molecular shapes, as opposed to smaller libraries around multiple scaffolds.⁶

We have recently developed a robust and high-yielding synthesis of α -acylamino ketones on solid phase (Scheme 1) using easily accessible building blocks (polymer-supported amines, bromoketones, and carboxylic acids).⁷ The synthesis was carried out using polymer-supported primary amines via alkylation of nitrobenzenesulfonyl (Nos) activated/protected amines (a variant of the Fukuyama method⁸), followed by N-alkylation with bromoketones. We observed a striking difference in the reaction outcome between 2-Nos and 4-Nos derivatives. The attempted cleavage of the 2-Nos protecting group led to an unexpected tandem carbon–carbon, followed by nitrogen–nitrogen, bond formation and ultimately yielded indazole oxides.⁹ To change the course of this otherwise very useful transformation leading to indazole oxides, we replaced the 2-Nos group by 4-Nos derivative by reacting resin-bound amines with 4-Nos chloride. The alkylation with bromoketones proceeded smoothly under the same condition developed for alkylation of the 2-Nos derivative. Cleavage of 4-Nos group was accomplished by treatment with 2-mercaptoethanol in the presence of a base.⁸ Subsequent acylation

of the secondary amino group yielded resin-bound α -acylamino ketones.

α -Acylamino ketones, in addition to being attractive compounds per se,^{10–14} represent an intriguing class of compounds that offer an extensive range of chemical transformations and that can serve as a versatile starting point for syntheses of diverse heterocycles. However, their synthetic potential has not been fully explored; so far, α -acylamino ketones have mostly been exploited for the synthesis of imidazoles and oxazoles.^{15–18} In this contribution, we describe the use of resin-bound α -acylamino ketones for the synthesis of structurally unrelated heterocyclic compounds. In addition, we showed that these heterocycles are amenable to subsequent transformations, namely, to the formation of an additional fused ring. We have already successfully applied this approach for the synthesis of dihydropyrazino[1,2-*b*]indazoles.¹⁹

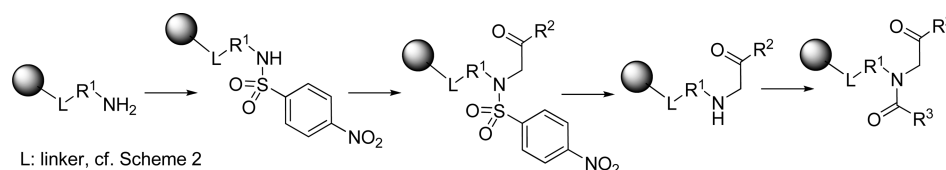
Results and Discussion

A generic structure of α -acylamino ketones is portrayed in the Figure 1. The R¹ side-chain is used for immobilization to the linker-derivatized resin. The R² substituent is derived from the bromoketones. To increase the multiplicity of target heterocyclic compounds, we carried out the alkylation also with α -bromocarboxylic acid esters. In such cases the α -acylamino esters (R² = *O*-alkyl), instead of ketones, were obtained. The R side-chain was introduced by acylation with carboxylic acids.

A deliberate selection of acylation agents that introduced the R groups and reaction conditions for the cyclization step enabled the syntheses of diverse and structurally unrelated heterocycles. In this contribution we describe the transformation of α -acylamino ketones/esters to several different heterocyclic motifs: dihydro-pyrrol-2-ones, pyrazin-2-ones, dihydro-triazepin-6-ones, morpholin-3-ones, imidazoles, β -lactams, and isoquinolin-1-ones (Figure 1).

We prepared resin-bound amines used for the synthesis of α -acylamino ketones/esters using three different types of bifunctional building blocks: amino alcohols, diamines, and

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Scheme 1. Synthesis of Resin-Bond α -Acylamino Ketones⁷

amino acids (Scheme 2), to obtain target compounds with different functional groups on the R substituent. Immobilization of all amine-containing building blocks was carried out using established protocols and we have already used this approach for the synthesis of indazoles⁹ and imidazoles.⁷ Wang resin²⁰ was used to immobilize amino alcohols (**1a**), diamines (**1b**), and amino acids (**1c**) and yielded alcohols, amines, and acids. Rink amide resin²¹ acylated with amino acids provided amides (**1d**, R' = H); the use of backbone amide linker (BAL) resin²² for reductive amination followed by acylation with amino acids (**1d**, R' = alkyl) yielded secondary amides.

To address the scope and limitation of resin-bound α -acylamino ketones for the synthesis of diverse heterocycles, we evaluated the transformations leading to seven heterocycles and prepared a set of model compounds for each heterocycle (Table 1). Then we focused our attention on syntheses of 1,5-dihydro-pyrrol-2-ones **5** and 1 *H*-pyrazin-2-ones **7** and prepared small combinatorial arrays of these compounds.

1,3,4-Derivatized 1,5-Dihydro-pyrrol-2-ones 5. Synthesis of 1,5-dihydro-pyrrol-2-ones **5** involved cyclization between the side chain R³ and the carbonyl group of R² side-chain by intramolecular Wittig reaction. The resin-bound amino ketones **1** were acylated with bromoacetic acid (Scheme 3) via in situ prepared symmetrical anhydride. L represents any

linker described in Scheme 2. A tertiary base (*N,N*-diisopropylethylamine, DIEA) was added to the reaction mixture to prevent premature cleavage from the resin by the bromoacetic acid.

The bromoacylamino ketones **2a** (R³ = H) were treated with triphenylphosphine (PPh₃) in anhydrous 1-methyl-2-pyrrolidinone (NMP) to yield triphenylphosphonium salts **3**. Synthesis of triphenylphosphonium salts from bromo derivatives in solution was reported on several occasions^{23–28} and we observed phosphonium salt formation as a side-product during the Mitsunobu reaction on solid phase.²⁹ Exposure of resins **3** to a base (triethylamine, TEA) afforded polymer-supported 1,5-dihydro-pyrrol-2-ones **4**. Cleavage from resin with a 50% solution of TFA in dichloromethane (DCM) yielded 1,5-dihydro-pyrrol-2-ones **5**.

This Wittig transformation was used only a few times in solution, e.g., for the synthesis of 3-hydroxypyrroles^{30,31} and 4-alkoxy-1,5-dihydro-pyrrol-2-one moiety of tetronic acid.³² The Horner-Wadsworth-Emmons reaction was also used to prepare 4-alkyl-1,5-dihydro-pyrrol-2-one derivatives.^{33,34} The use of Wittig chemistry on solid phase was reviewed.³⁵

To extend the diversity of R² substituents, we also prepared α -acylamino esters for the synthesis of 1,5-dihydro-pyrrol-2-ones with an alkoxy substituent in the position of R². On-resin transformation to the triphenylphosphonium derivative **3** was followed by base mediated cyclization. There is one

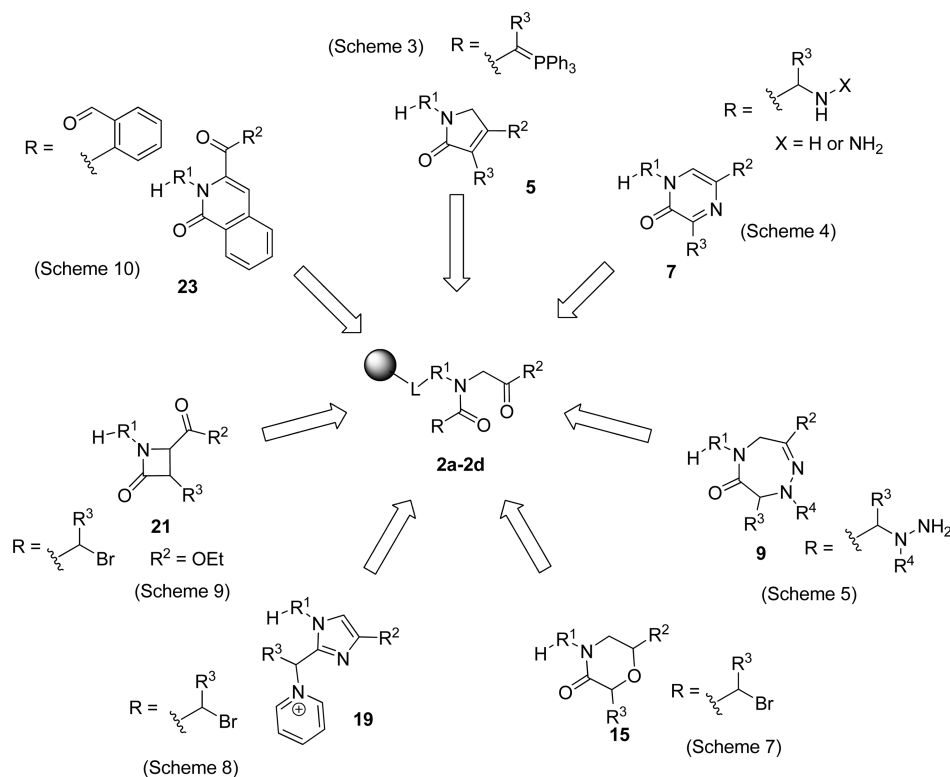
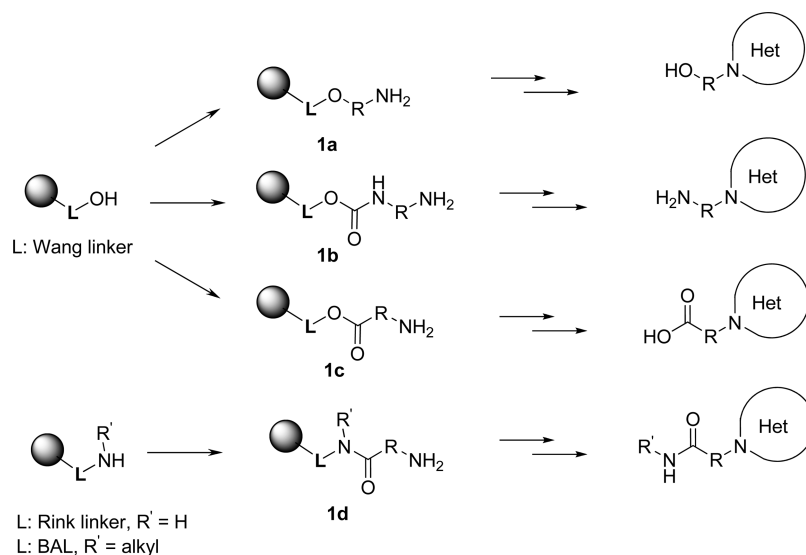


Figure 1. α -Acylamino ketones/esters as intermediates for the syntheses of seven different heterocycles.

Table 1. Synthesized Heterocycles **5**, **7**, **9**, **13**, **15**, **19**, **21**, **23**, and **24**

product	R ¹ -H	R ²	R ³	purity ^a [%]	yield ^b [%]	MS ESI+
5(1,1,1)	-(CH ₂) ₂ -COOH	4-Me-Ph	H	59	44	246
5(1,2,1)	-(CH ₂) ₂ -COOH	4-OMe-Ph	H	65	75	262
5(1,3,1)	-(CH ₂) ₂ -COOH	4-NH ₂ -3,5-diCl-Ph	H	68	9	315
5(2,1,1)	-(CH ₂) ₂ -OH	4-Me-Ph	H	55	77	218
5(2,3,1)	-(CH ₂) ₂ -OH	4-NH ₂ -3,5-diCl-Ph	H	58	56	287
5(3,1,1)	-(CH ₂) ₂ -NH ₂	4-Me-Ph	H	46	37	217
5(3,2,1)	-(CH ₂) ₂ -NH ₂	4-OMe-Ph	H	53	23	233
5(3,3,1)	-(CH ₂) ₂ -NH ₂	4-NH ₂ -3,5-diCl-Ph	H	38	41	286
5(3,4,1)	-(CH ₂) ₂ -NH ₂	-OEt	H	71	44	171
5(4,1,1)	-(CH ₂) ₂ -CONH ₂	4-Me-Ph	H	55	28	245
5(4,2,1)	-(CH ₂) ₂ -CONH ₂	4-OMe-Ph	H	57	38	261
5(4,3,1)	-(CH ₂) ₂ -CONH ₂	4-NH ₂ -3,5-diCl-Ph	H	62	27	314
5(5,4,1)	-(CH ₂) ₂ -CONH(4-Me-Bn)	-OEt	H	80	53	303
7(1,1,1)	-(CH ₂) ₂ -COOH	4-Me-Ph	H	81	30	259
7(1,2,1)	-(CH ₂) ₂ -COOH	4-OMe-Ph	H	60	38	275
7(1,3,1)	-(CH ₂) ₂ -COOH	4-NH ₂ -3,5-diCl-Ph	H	55	12	328
7(1,1,3)	-(CH ₂) ₂ -COOH	4-Me-Ph	Et	35	24	287
7(2,1,1)	-(CH ₂) ₂ -OH	4-Me-Ph	H	99	61	231
7(3,1,1)	-(CH ₂) ₂ -NH ₂	4-Me-Ph	H	47	40	230
7(3,2,1)	-(CH ₂) ₂ -NH ₂	4-OMe-Ph	H	83	52	246
7(3,3,1)	-(CH ₂) ₂ -NH ₂	4-NH ₂ -3,5-diCl-Ph	H	93	62	299
7(3,1,2)	-(CH ₂) ₂ -NH ₂	4-Me-Ph	Me	81	12	244
7(4,1,1)	-(CH ₂) ₂ -CONH ₂	4-Me-Ph	H	57	21	258
7(4,2,1)	-(CH ₂) ₂ -CONH ₂	4-OMe-Ph	H	36	36	274
7(6,1,1)	-(CH ₂) ₃ -CONH ₂	4-Me-Ph	H	71	39	272
7(6,2,1)	-(CH ₂) ₃ -CONH ₂	4-OMe-Ph	H	68	42	288
7(7,1,1)	-CONH-(CH ₂) ₂ CH ₃	4-Me-Ph	H	66	11	362
9(1,1,1)^c	-(CH ₂) ₂ -COOH	4-Me-Ph	H	48	19	366
9(1,4,1)^c	-(CH ₂) ₂ -COOH	4-NH ₂ -3,5-diCl-Ph	H	50	25	435
9(3,1,1)^c	-(CH ₂) ₂ NH ₂	4-Me-Ph	H	48	18	337
13(10,1,1)^c	NA	4-Me-Ph	H	51	ND	319
15(4,1,1)	-(CH ₂) ₂ -CONH ₂	4-Me-Ph	H	31	23	263
15(8,1,1)	-CH ₂ Ph-(4-COOH)	4-Me-Ph	H	61	22	326
19(3,1,4)	-(CH ₂) ₂ -NH ₂	4-Me-Ph	H	78	16	293
19(5,1,4)	-(CH ₂) ₂ -CONH(4-Me-Bn)	4-Me-Ph	H	68	29	425
21(8,4,1)	-CH ₂ Ph-(4-COOH)	-OEt	H	78	23	278
23(1,2,5)	-(CH ₂) ₂ -COOH	4-OMe-Ph	NA	51	5	352
23(9,1,5)	-(CH ₂) ₂ -CONH(CH ₂) ₂ CH ₃	4-Me-Ph	NA	58	15	377
24(10,1,5)	NA	4-Me-Ph	NA	76	13	289

^a Purity of the crude product before purification. ^b Yield after purification by HPLC. ^c R⁴ = Bn; NA, not applicable; ND, not determined.

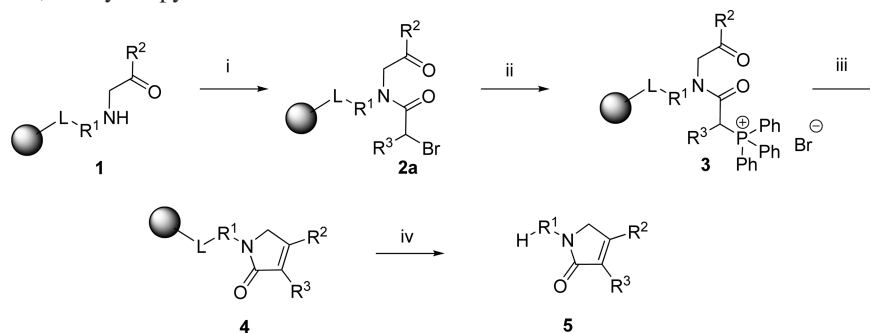
Scheme 2. Immobilization of Amine-Containing Building Blocks

literature precedent for this Wittig reaction in solution with an ester as the carbonyl component in the synthesis of this five-membered ring.³²

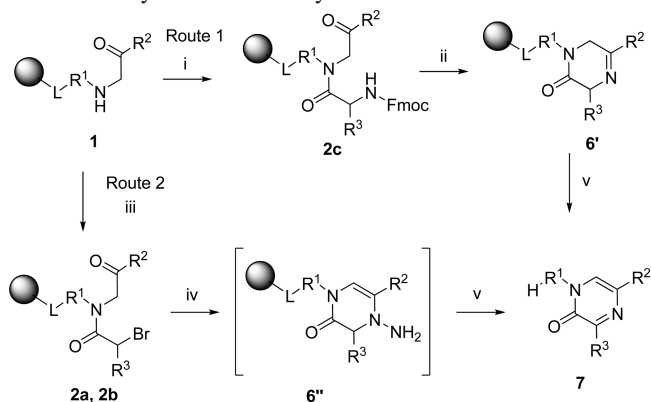
A small combinatorial array of 1,5-dihydro-pyrrol-2-ones was prepared using Fmoc- β -Ala-OH, ethylenediamine, and

ethanolamine in the first combinatorial step and three bromoketones and ethyl bromoacetate in the second step.

3-Pyrrol-2-ones can serve as a starting material for the synthesis of biologically relevant compounds such as tetramic acid derivatives.^{36,37} However, 3-pyrrol-2-one core moiety

Scheme 3. Synthesis of 1,5-Dihydro-pyrrol-2-ones **5**^a

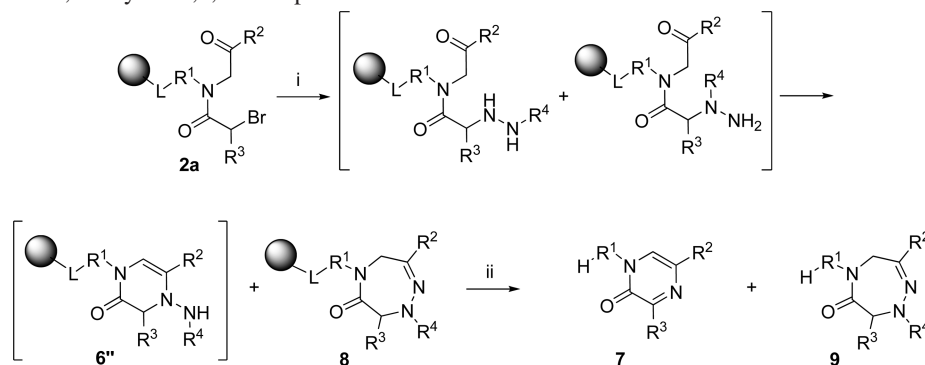
^a Reagents and conditions: (i) bromoacetic acid (2 equiv), DIC (1 equiv), DCM, 15 min, then DIEA (1 equiv), 4 h; (ii) PPh₃, anhydrous NMP, overnight; (iii) TEA, anhydrous NMP, 2 h; (iv) 50% TFA in DCM, 1 h.

Scheme 4. Synthesis of 1*H*-Pyrazin-2-ones **7**^a

^a Reagents and conditions: (i) Fmoc- α -amino acid (2 equiv), DIC (1 equiv), DCM/DMF (1:1), overnight; (ii) 50% piperidine in DMF, 15 min; (iii) α -bromocarboxylic acid (2 equiv), DIC (1 equiv), DCM, 15 min, then DIEA (1 equiv), 4 h; (iv) hydrazine monohydrate, THF, 2 h; (v) 50% TFA in DCM, 1 h.

is also found in natural products, for example, in pulchelalactam, discovered from the marine fungus *Corollospora pulchella*, a potent CD45 inhibitor.³⁸

1,3,5-Substituted 1*H*-Pyrazin-2-ones 7. 1*H*-Pyrazin-2-ones **7** were synthesized by two so far unreported routes (Scheme 4). The first route included acylation of polymer-supported amino ketones **1** with Fmoc-protected α -amino acid to yield **2c** ($R^3 = \text{Me}$). Deprotection of the amino group using 50% piperidine in DMF was followed by a spontaneous ring closure. Cyclization of α -acylamino ketones **2c** provided 5,6-dihydro-1*H*-pyrazin-2-ones **6'**, which spontaneously air

Scheme 5. Synthesis of 4,5-dihydro-1,2,5-triazepin-6-ones **9**^a

^a Reagents and conditions: (i) benzylhydrazine monohydrochloride, DMF, overnight; (ii) 50% TFA in DCM, 1 h.

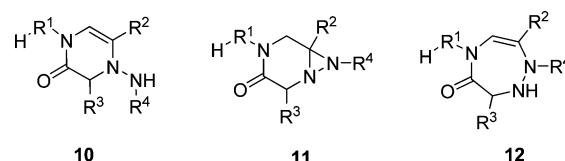


Figure 2. Alternative structures with identical molecular mass.

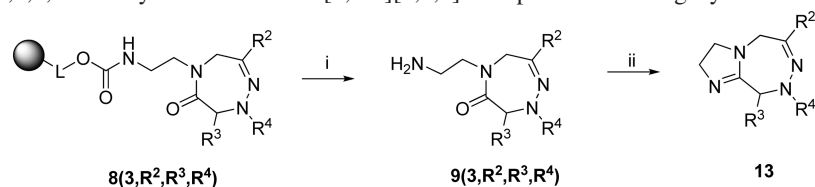
oxidized, either during TFA cleavage or reaction work up, to yield 1*H*-pyrazin-2-ones **7**.

Although there was a substantial effort dedicated to syntheses of pyrazinones, conversion of α -(2-amino)acylamino ketones has not been reported. The closest analogy to our method is the transformation of dipeptidyl chloromethyl ketones to pyrazinones under rather forcing conditions.³⁹

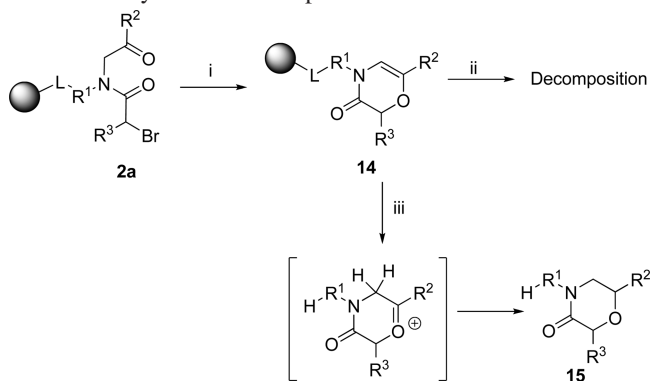
The second route that afforded 1*H*-pyrazin-2-ones **7** was rather unexpected. α -Acylamino ketones **2a** ($R^3 = \text{H}$) and **2b** ($R^3 = \text{Et}$) were prepared by acylation with α -bromocarboxylic acids. Exposure to hydrazine monohydrate afforded, after cleavage from resin with 50% TFA in DCM, 1*H*-pyrazin-2-ones **7**. This plausible mechanism involves the elimination of ammonia by cleavage of the N–N bond. This transformation has a structurally unrelated precedence.⁴⁰

A small set of 1*H*-pyrazin-2-ones was synthesized using Fmoc- β -Ala–OH, ethylenediamine, and ethanolamine in the first step, three bromoketones, three α -bromocarboxylic acids, and one Fmoc- α -amino acid in the second and third steps, respectively.

A complementary route for the synthesis of 1*H*-pyrazin-2-ones from the analogous precursors reported in the

Scheme 6. Synthesis of 3,5,8,9-Tetrahydro-2*H*-imidazo[2,1-*d*][1,2,5]triazepine Fused Ring System **13**^a

^a Reagents and conditions: (i) 50% TFA in DCM, 1 h; (ii) filtration through C18 cartridge, then DCM, 30 °C, overnight.

Scheme 7. Synthesis of Morpholin-3-ones **15**^a

^a Reagents and conditions: (i) BEMP, anhydrous NMP, 15 min; (ii) 50% TFA, DCM, 1 h; (iii) TFA/DES/DCM (5:1:4), 1 h.

literature involved nucleophilic substitution of chloride by azide. Subsequent reaction with PPh₃ formed 1*H*-pyrazin-2-ones via iminophosphoranes.⁴¹ An alternative synthesis took advantage of reductive amination of chloroacetyl derivatives with an amine in the presence of borohydride, followed by cyclization to piperazines.⁴²

2,3,5,7-Substituted 4,5-Dihydro-1,2,5-triazepin-6-ones 9. Resin-bound α -acylamino ketones **2a** ($R^3 = H$), used for the synthesis of 1*H*-pyrazin-2-ones, were also reacted with benzylhydrazine monohydrochloride in DMF in the presence of TEA. We observed the formation of two different products (Scheme 5). Besides 1*H*-pyrazin-2-ones **7**, we isolated 4,5-dihydro-1,2,5-triazepin-6-ones **9** ($R^4 = Bn$). The ratio of those two products was 1:2 (at this time, we did not carry out optimization of reaction conditions). The structure of 4,5-dihydro-1,2,5-triazepin-6-one was unequivocally confirmed by 2D NMR spectra (gHMBC) and isomeric structures **10**, **11**, and **12** (Figure 2) were eliminated.

The presence of both six- and seven-membered heterocycles can be explained by the formation of two regioisomers when resin-bound bromoacylamino ketones **2a** were reacted with alkylhydrazine. Each of the two initially formed regioisomers was transformed to a different product.

To date, 1,2,5-triazepin-6-ones have not been reported in literature. 4*H*-1,2,5-Triazepine derivatives were prepared from α -amino hydrazones.⁴³ Two reports described syntheses of 1,2,5-triazepin-3,6-diones⁴⁴ and their 4-thioxo derivatives.⁴⁵ Koenig et al.⁴⁶ attempted to synthesize 3-aryl-tetrahydro-1,2-diazepines by a reaction of aryl- δ -chlorobutyl ketones with unsubstituted and monosubstituted hydrazines. Reaction with unsubstituted hydrazine lead to an unstable product, whereas reaction of aryl- δ -chlorobutyl ketones with monosubstituted hydrazines afforded stable 1-substituted 3-aryl-tetrahydro-1,2-diazepines. Later on, the synthesis was

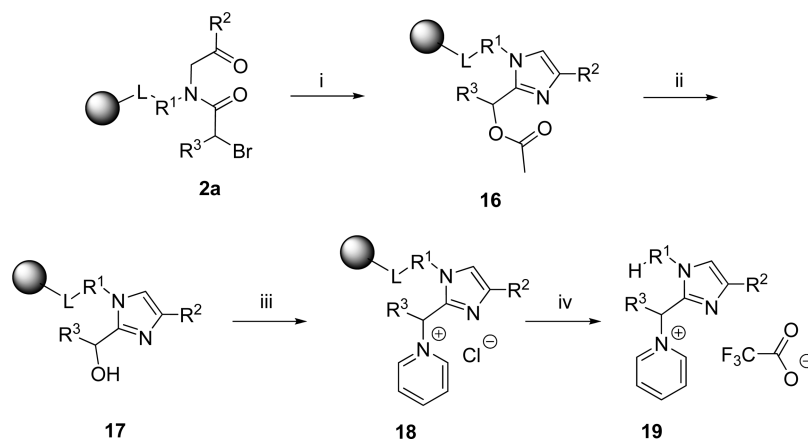
improved and the unstable 3-aryl-tetrahydro-1,2-diazepines were converted in situ to a stable sulfonyl⁴⁷ and acyl derivatives.⁴⁸

Fused Ring Systems. Synthesis of 4,5-dihydro-1,2,5-triazepin-6-ones was carried out with resin **1b** prepared using 1,2-diaminoethane. After finishing the synthesis and release from the resin, a fused ring was formed between the side chain R^1 and the carbonyl group of amide moiety. Reaction conditions for cyclization of 5-(2-aminoethyl)-4,5-dihydro-1,2,5-triazepin-6-one **9(3,R²,R³,R⁴)** to 3,5,8,9-tetrahydro-2*H*-imidazo[2,1-*d*][1,2,5]triazepine **13** (Scheme 6) were optimized. We found it important to neutralize the crude triazepinone **9(3,R²,R³,R⁴)** before subjecting to cyclization. Whereas heating in DMSO and DMF gave low conversion (<10%), THF resulted in acceptable conversion (albeit with significant contamination) to crude products **13**. Gratifyingly, under very mild conditions (DCM, 30 °C, overnight reaction), the fused ring was formed with only 16% of starting material present in the reaction mixture.

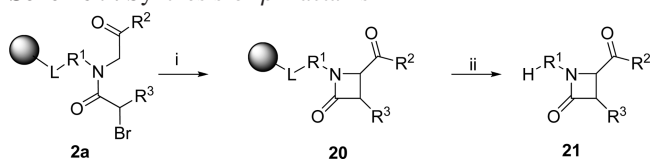
2,4,6-Substituted Morpholin-3-ones 15. The next heterocyclic compounds assembled from α -acylamino ketones were morpholin-3-ones **15**. The polymer-supported amino ketones **1** were acylated with bromoacetic acid to yield α -acylamino ketones **2a** ($R^3 = H$). 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)-mediated cyclization afforded polymer-supported 1,4-oxazine-3-ones **14**. Because the 2*H*-1,4-oxazin-3(4*H*)-ones were found not to be stable in the TFA used for cleavage from the resin, the resin-bound oxazines were cleaved from resin in solution of TFA, triethylsilane (TES), and DCM in a ratio of 5:1:4 and yielded morpholin-3-ones **15**. TES was added to the cleavage cocktail to prevent decomposition of 1,4-oxazine-3-ones **14** via oxonium ions, which could be formed during the cleavage.

Formation of 4*H*-[1,4]oxazin-3-one has been described as a side-reaction during exposure of (2-chloroacetyl)amino acetic acid methyl ester to a base (4-aminomethylpiperidine).⁴⁹ Synthesis of morpholin-3-ones on solid phase was reported.⁵⁰

1,2,4-Substituted 1*H*-Imidazoles 19. Synthesis of imidazoles by forming the five-membered ring from resin-bound α -acylamino ketones in the presence of ammonium acetate at elevated temperature has been reported.^{15–18,51} We have also used this route for synthesis of imidazoles and imidazolyl-quinoxalones.⁷ Here we extend the previously reported imidazole set to include 2-hydroxymethyl imidazoles. Cyclization of resin-bound acylamino ketone **2a** in acetic acid solution of ammonium acetate yielded O-acetyl derivatives **16**. After saponification and attempted reaction with mesyl chloride (for further derivatization) and cleavage from

Scheme 8. Synthesis of 1*H*-Imidazoles **19**^a

^a Reagents and conditions: (i) ammonium acetate, acetic acid, 100 °C, overnight; (ii) KOTMS, THF, 1 h; (iii) mesyl chloride, pyridine, 1 h; (iv) 50% TFA in DCM, 1 h.

Scheme 9. Synthesis of β -Lactams **21**^a

^a Reagents and conditions: (i) BEMP, NMP, 30 min; (ii) 50% TFA, DCM, 1 h.

the resin, we isolated the pyridinium imidazoles **19** as the only product.

1,3-Substituted 4-Oxo-azetidine-2-carboxylic Acid Esters (β -Lactams) **21.** The role of β -lactams in drugs and drug-like compounds has been well established. α -Amino acetates **1** ($R^2 = \text{OEt}$) were acylated with bromoacetic acid. To convert α -acylamino esters **2a** ($R^3 = \text{H}$) to β -lactams **21**, we tested several different bases for the cyclization; Schwesinger BEMP-mediated cyclization afforded (upon resin cleavage) β -lactams **21** in high crude purity (78%). There are several reports describing this type of cyclization^{52–57} including examination of the enantioselectivity of the cyclization.^{53,54} The synthetic route has also been applied to solid-phase⁵⁸ via immobilization of Fmoc-amino acids to Wang and BAL resins, followed by *N*-alkylation and acylation with chloroacetic acid.

2,3,6-Substituted 2*H*-Isoquinolin-1-ones **23.** Resin-bound α -acylamino ketones **2d** for the synthesis of 2*H*-isoquinolin-1-ones **23** were prepared by acylation with 2-carboxybenzaldehyde. Ring closure was accomplished by intramolecular aldol condensation between the methylene carbon alpha to the ketone and the carbonyl of the carboxybenzaldehyde. DBU-mediated ring closure afforded the isoquinolinone ring **23**. An intramolecular aldol condensation that yielded the isoquinolinone moiety has already been reported and used to prepare the framework of camptothecin⁵⁹ and tetrahydroisoquinolinone derivatives.⁶⁰ Solid-phase synthesis of highly substituted 2*H*-isoquinolin-1-ones was reported by Goff and Zuckermann.^{61,62}

Fused Ring Systems. The second example of fused ring closure involved condensation between the amino group residing on the side chain R^1 and the carbonyl of R^2 side-

chain of the 2*H*-isoquinolin-1-one. 1,2-Diaminoethane was attached to Wang resin via carbamate linkage using carbonyldiimidazole (CDI) activation (Scheme 2). The synthesis was carried out according to the same protocol as described for the synthesis of 2*H*-isoquinolin-1-ones **23**. After cleavage from the resin, the intermediate spontaneously closed the six-membered fused ring and provided access to 3,4-dihydro-pyrazino[1,2-*b*]isoquinolin-6-ones **24**.

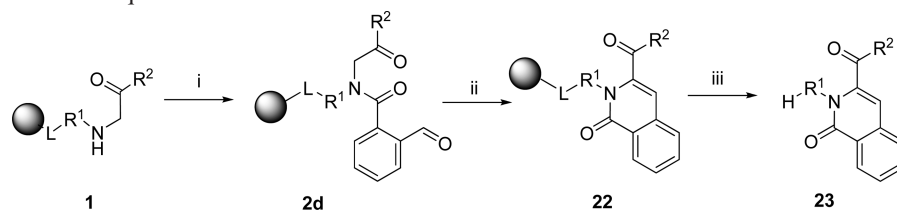
Conclusion

We have shown that resin-bound α -acylamino ketones represent versatile intermediates for transformation to diverse and structurally unrelated heterocyclic compounds. Synthetic routes included a variety of chemistries (C–C, C=C, C–N, C=N, C–O bond formations) and size of heterocycles (4-, 5-, 6-, and 7-membered rings). On two examples, we documented that the primary ring closure can be accompanied by the formation of a fused ring. Synthesized compounds were submitted for evaluation of biological activities to High Throughput Screening in the Molecular Libraries Probe Production Centers Network. The results are available in PubChem (<http://pubchem.ncbi.nlm.nih.gov/>).

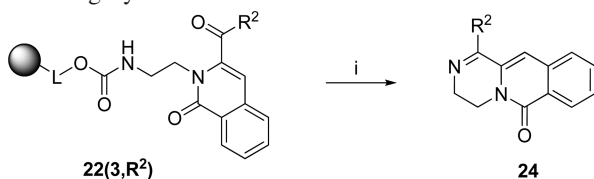
Experimental Section

Solid-phase syntheses were carried out on manually operated Domino Block synthesizer⁶³ (www.torviq.com) in disposable polypropylene reaction vessels. Commercially available solvents, resins, and reagents were used. The Rink resin (100–200 mesh, 1% DVB, 0.75 mmol/g), aminomethyl resin (100–200 mesh, 1% DVB, 0.9 mmol/g), and Wang resin (100–200 mesh, 1% DVB, 1.0 mmol/g) were obtained from Advanced ChemTech (Louisville, KY, www.peptide.com). Swelling of resins in DCM was measured before syntheses and resins with swollen volume greater than 7 mL/g of dry resin were used.⁶⁴ All reactions were carried out at ambient temperature (21 °C) unless stated otherwise. The yield was calculated based on resin loading of the first building block.

Acylation with α -Bromocarboxylic Acid (Resins **2a, **2b**).** Resin **1**, ~1 g, was washed 3 \times with DCM. A solution of α -bromocarboxylic acid (5 mmol) in 10 mL DCM was

Scheme 10. Synthesis of 2*H*-Isoquinolin-1-ones **23**^a

^a Reagents and conditions: (i) 2-carboxybenzaldehydes (2 equiv), DIC (1 equiv), DMF, overnight; (ii) DBU, DMF, 30 min; (iii) 50% TFA, DCM, 1 h.

Scheme 11. Synthesis of Pyrazino[1,2-*b*]isoquinolinone Fused Ring System **24**^a

^a Reagents and conditions: (i) 50% TFA in DCM, 1 h.

made in polypropylene reaction vessels and DIC (2.5 mmol, 387 μ L) was added. After 5 min *N,N'*-di-*i*-propylurea (DIU) was filtered, DIEA (2.5 mmol, 436 μ L) added and solution added to resin **1** and reacted 4 h. The resin was washed 5 \times with DCM.

Acylation with Fmoc- α -amino Acid (Resins 2c). Resin **1**, \sim 250 mg, was washed 3 \times with DCM. A solution of Fmoc- α -amino acid (1 mmol), and DIC (0.5 mmol, 77 μ L) in 2.5 mL DCM/DMF (1:1) was added to the resin and reaction slurry was shaken overnight. The resin was washed 3 \times with DMF and 3 \times with DCM.

Acylation with 2-Carboxybenzaldehyde (Resins 2d). Resin **1**, \sim 1 g, was washed 3 \times with DCM and solution of 2-carboxybenzaldehyde (10 mmol, 1.5 g), and DIC (5 mmol, 770 μ L) in 10 mL DMF/DCM (1:1) was added. After overnight reaction, the resin was washed 3 \times with DMF and 3 \times with DCM.

1,3,4-Derivatized 1,5-Dihydro-pyrrol-2-ones 5. Preparation of Triphenylphosphonium Salt (Resins 3). Resin **2a**, \sim 250 mg, was washed 3 \times with anhydrous DCM and 3 \times with anhydrous NMP. A solution of triphenylphosphine (1 mmol, 262 mg) in 2.5 mL anhydrous NMP was added to the resin and slurry was shaken overnight. The resin was washed 3 \times with DCM.

Cyclization (Resins 4). Resin **3**, \sim 250 mg, was washed 3 \times with anhydrous DCM and 3 \times with anhydrous NMP. A solution of TEA (0.25 mmol, 35 μ L) in 2.5 mL anhydrous NMP was added to the resin and slurry was shaken two hours. The resin was washed 3 \times with DCM.

1,3,5-Substituted 1*H*-pyrazin-2-ones 7. Route 1. Cyclization (Resin 6'). Resin **2c**, \sim 250 mg, was washed 3 \times with DMF and treated with 2.5 mL 50% piperidine in DMF for 15 min. The resin was washed 3 \times with DMF and 3 \times with DCM.

Route 2. Cyclization (Resins 6''). Resins **2a** and **2b**, \sim 250 mg, were washed 3 \times with THF, and a solution of hydrazine monohydrate (6 mmol, 0.3 mL) in 2.5 mL THF was added and reacted two hours. The resin was washed 3 \times with THF and 3 \times with DCM.

2,3,5,7-Substituted 4,5-Dihydro-1,2,5-triazepin-6-ones 9. Cyclization (Resins 8). Resin **2a**, \sim 250 mg, was washed 3 \times with DMF, and a solution of benzylhydrazine monohydrochloride (1 mmol, 170 mg) and TEA (1 mmol, 0.15 mL) in 3 mL DMF was added and reacted overnight. The resin was washed 3 \times with DMF and 3 \times with DCM.

2,4,6-Substituted Morpholin-3-ones 15. Cyclization to 1,4-Oxazine-3-ones (Resins 14). Resin **2a** ($R^2 = \text{aryl}$), \sim 250 mg, was washed 3 \times with anhydrous NMP, and a solution of BEMP (0.09 mmol, 25 μ L) in 2.5 mL anhydrous NMP and resin slurry was shaken 5 min. The resin was neutralized with 3% AcOH in DMF, washed 3 \times with DMF, 3 \times with DCM, 3 \times with MeOH, and 3 \times with DCM.

Cleavage from Resin to Obtain Morpholin-3-ones (15). Resin **14**, \sim 250 mg, was treated with a solution of TFA, TES, and DCM (5:1:4) for one hour. TFA solution was collected; resin was washed 3 \times with 50% TFA in DCM. The combined extracts were evaporated by a stream of nitrogen, and the crude products were purified by reversed-phase HPLC.

1,2,4-Substituted 1*H*-Imidazoles 19. Cyclization by Ammonium Acetate in AcOH (Resins 16). Resin **2a**, \sim 250 mg, was heated in a solution of 2.5 M ammonium acetate (25 mmol, 1.93 g) in 10 mL AcOH at 100 $^{\circ}$ C overnight. The reaction was repeated when the cyclization was not complete. The resin was washed 5 \times with DCM.

Ester Cleavage (Resins 17). Resin **16**, \sim 250 mg, was treated washed 3 \times with THF and reacted with solution of 0.5 mL 10 M NaOH in 10 mL THF/MeOH (1:1) for 1 h. Resin was washed 3 \times with THF, 3% AcOH in THF, and 3 \times with DCM.

Reaction with Mesityl Chloride (Resins 18). Resin **17**, \sim 250 mg, was washed 3 \times with pyridine. A solution of mesityl chloride (2.5 mmol, 192 μ L) in 5 mL pyridine was added and left for 1 h. Resin was washed 3 \times with pyridine and 3 \times with DCM.

1,3-Substituted β -Lactams 21. Cyclization (Resins 20). Resin **2a** ($R^2 = \text{OEt}$), \sim 400 mg, was washed with DCM and anhydrous NMP and treated with BEMP (40 μ L) in 4 mL NMP for 30 min. Resin was washed 3 \times with DMF, 3 \times with DCM, 3 \times with MeOH, and 3 \times with DCM.

2,3,6-Substituted 2*H*-Isoquinolin-1-ones 23. Cyclization (Resins 22). Resin **2d**, \sim 250 mg, was washed 3 \times with DMF and solution of 0.2 M DBU (150 μ L) in 5 mL DMF was added and tumbled for 30 min. The cyclization was monitored by LCMS analysis of a sample cleaved from the resin. The resin was washed with 3 \times with DMF, 5 \times with DCM, 3% *n*-propylamine in DCM, DCM, 3% AcOH in DCM, and 3 \times with DCM.

Cleavage from Resin (Compounds 5, 7, 9, 13, 19, 21, 23, 24). Target compounds were obtained after cleavage from resin with 50% TFA in DCM for 1 h. TFA solution was collected, and the resin was washed 3× with 50% TFA in DCM. The combined extracts were evaporated by a stream of nitrogen. All crude products were purified by semi-preparative HPLC.

The crude compound **9(3,R²,R³,R⁴)** was dissolved in 2 mL of acetonitrile, diluted with 10 mL of 10 mM ammonium acetate buffer, and filtered through C18 cartridge. The compound was eluted by acetonitrile, and the solvent was evaporated; the oily residue was dissolved in 10 mL of DCM and heated at 30 °C overnight to yield fused ring system **13**.

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Supporting Information Available. Details of experimental procedures, spectroscopic data, and NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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