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

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Abstract

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, 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 synthesis[1] 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 method[8]), 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 bonds formations, 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.

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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.

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 R^1 side-chain is used for immobilization to the linker-derivatized resin. The R^2 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 (R^2 = 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 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 indazoles[9] and imidazoles.[7] Wang resin[20] was used to immobilize amino alcohols (**1a**), diamines (**1b**), and amino acids (**1c**) and yielded alcohols, amines, and acids. Rink amide resin[21] acylated with amino acids provided amides (**1d**, R′ = H); the use of backbone amide linker (BAL) resin[22] 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 R^3 and the carbonyl group of R^2 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** (R^3 = H) were treated with triphenylphospine (PPh_3) 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 R^2 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 R^2. On-resin transformation to the triphenylphosphonium derivative **3** was followed by base mediated cyclization. There is one 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 biologicaly relevant compounds such as tetramic acid derivatives.[36,37] However, 3-pyrrol-2-one core moiety is also found in natural products, e.g. in pulchellalactam, 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 = 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 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 = H), **2b** (R^3 = 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 literature involved nucleophilic substitution of chloride by azide. Subsequent reaction with PPh_3 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 piperazinones.[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 from α-amino hydrazones.[43] Two reports described syntheses of 1,2,5-triazepin-3,6-diones[44] 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 sulfonyl[47] 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,R^2,R^3,R^4)** 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,R^2,R^3,R^4)** 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-aminometylpiperidine).[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-quinoxalinones.[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-acetylderivatives **16**. After saponification and attempted reaction with mesyl chloride (for further derivatization) and cleavage from 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 = OEt) were acylated with bromoacetic acid. To convert α-acylamino esters **2a** (R^3 = 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-phase[58] 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 camptothecin[59] 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 synthesizer[63] (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 × with DCM. A solution of α-bromocarboxylic acid (5 mmol) in 10 mL DCM was made in polypropylene reaction vessels and DIC (2.5 mmol, 387 μL) was added. After 5 min *N*,*N*′-di-*i*-propylurea (DIU) was filtered, DIEA (2.5 mmol, 436 μL) added and solution added to resin **1** and reacted 4 h. The resin was washed 5 × with DCM.

Acylation with Fmoc-α-amino acid (resins 2c)

Resin **1**, ~250 mg, was washed 3 × with DCM. A solution of Fmoc-α-amino acid (1 mmol) and DIC (0.5 mmol, 77 μL) in 2.5 mL DCM/DMF (1:1) was added to the resin and reaction slurry was shaken overnight. The resin was washed 3 × with DMF and 3 × with DCM.

Acylation with 2-carboxybenzaldehyde (resins 2d)

Resin **1**, ~1 g, was washed 3 × with DCM and solution of 2-carboxybenzaldehyde (10 mmol, 1.5 g) and DIC (5 mmol, 770 μL) in 10 mL DMF/DCM (1:1) was added. After overnight reaction the resin was washed 3 × with DMF and 3 × with DCM.

1,3,4-Derivatized 1,5-dihydro-pyrrol-2-ones 5

Preparation of triphenylphosphonium salt (resins 3)

Resin **2a**, ~250 mg, was washed 3 × with anhydrous DCM and 3 × 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 × with DCM.

Cyclization (resins 4)

Resin **3**, ~250 mg, was washed 3 × with anhydrous DCM and 3 × with anhydrous NMP. A solution of TEA (0.25 mmol, 35 μL) in 2.5 mL anhydrous NMP was added to the resin and slurry was shaken two hours. The resin was washed 3 × with DCM.

1,3,5-Substituted 1*H*-pyrazin-2-ones 7

Route 1

Cyclization (resin 6′)

Resin **2c**, ~250 mg, was washed 3 × with DMF and treated with 2.5 mL 50% piperidine in DMF for 15 minutes. The resin was washed 3 × with DMF and 3 × with DCM.

Route 2

Cyclization (resins 6″)

Resins **2a, 2b**, ~250 mg, was washed 3 × 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 × with THF and 3 × with DCM.

2,3,5,7-Substituted 4,5-dihydro-1,2,5-triazepin-6-ones 9

Cyclization (resins 8)

Resin **2a**, ~250 mg, was washed 3 × 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 × with DMF and 3 × with DCM.

2,4,6-Substituted morpholin-3-ones 15

Cyclization to 1,4-oxazine-3-ones (resins 14)

Resin **2a** (R^2 = aryl), ~250 mg, was washed 3 × with anhydrous NMP and a solution of BEMP (0.09 mmol, 25 μL) in 2.5 mL anhydrous NMP and resin slurry was shaken 5 min. The resin was neutralized with 3% AcOH in DMF, washed 3 × with DMF, 3 × with DCM, 3 × with MeOH and 3 × with DCM.

Cleavage from resin to obtain morpholin-3-ones (15)

Resin **14**, ~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 × with 50% TFA in DCM, combined extracts were evaporated by a stream of nitrogen and 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**, ~250 mg, was heated in a solution of 2.5 M ammonium acetate (25 mmol, 1.93 g) in 10 mL AcOH at 100 °C overnight. The reaction was repeated when the cyclization was not complete. The resin was washed 5 × with DCM.

Ester cleavage (resins 17)

Resin **16**, ~250 mg, was treated washed 3 × 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 × with THF, 3% AcOH in THF, 3 × with DCM.

Reaction with mesyl chloride (resins 18)

Resin **17**, ~250 mg, was washed 3 × with pyridine. A solution of mesyl chloride (2.5 mmol, 192 μL) in 5 mL pyridine was added and left for 1 h. Resin was washed 3 × with pyridine and 3 × with DCM.

1,3-Substituted β-lactams 21

Cyclization (resins 20)

Resin **2a** (R^2 = OEt), ~400 mg, was washed with DCM and anhydrous NMP and treated with BEMP (40 μL) in 4 mL NMP for 30 min. Resin was washed 3 × with DMF, 3 × with DCM, 3 × with MeOH, and 3 × with DCM.

2,3,6-Substituted 2*H*-isoquinolin-1-ones 23

Cyclization (resins 22)

Resin **2d**, ~250 mg, was washed 3 × with DMF and solution of 0.2 M DBU (150 μL) in 5 mL DMF was added and tumbled for 30 min. The cyclization was monitored by LCMS analysis of a sample cleaved from the resn. The resin was washed with 3 × with DMF, 5 × with DCM, 3% *n*-propylamine in DCM, DCM, 3% AcOH in DCM, and 3 × 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, resin was washed 3 × with 50% TFA in DCM and combined extracts were evaporated by a stream of nitrogen. All crude products were purified by semi-preparative HPLC.

The crude compound **9(3,R^2,R^3,R^4)** was dissolved in 2 mL acetonitrile, diluted with 10 mL 10 mM ammonium acetate buffer and filtered through C18 cartridge. The compound was eluted by acetonitrile and the solvent was evaporated, oily residue dissolved in 10 mL DCM and heated at 30 °C overnight to yield fused ring system **13**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Burke MD, Schreiber SL. Angew Chem, Int Ed 2004;43:46–58.
2. Lee SH, Clapham B, Koch G, Zimmermann J, Janda KD. Org Lett 2003;5:511–514. [PubMed: 12583756]
3. Lee SH, Clapham B, Koch G, Zimmermann J, Janda KD. J Comb Chem 2003;5:188–196. [PubMed: 12625710]
4. Matsushita H, Lee SH, Yoshida K, Clapham B, Koch G, Zimmermann J, Janda KD. Org Lett 2004;6:4627–4629. [PubMed: 15548092]
5. Krchňák V, Holladay MW. Chem Rev 2002;102:61–91. [PubMed: 11782129]
6. Sauer WHB, Schwarz MKJ. Che Inf Comput Sci 2003;43:987–1003.
7. Kočí J, Pudelová N, Krchňák V. J Comb Chem 2009;11:397–402. [PubMed: 19354277]
8. Fukuyama T, Jow CK, Cheung M. Tetrahedron Lett 1995;36:6377–6374.
9. Bouillon I, Zajíček J, Pudelová N, Krchňák V. J Org Chem 2008;73:9027–9032. [PubMed: 18937414]
10. Tice CM, Michelotti EL, Mata EG, Nicolís E, Garcia J, Albericio F. Tetrahedron Lett 2002;43:7491–7494.
11. Garcia J, Nicolàs E, Albericio F, Michelotti EL, Tice CM. Tetrahedron Lett 2002;43:7495–7498.

12. Tice CM, Hormann RE, Thompson CS, Friz JL, Cavanaugh CK, Saggers JA. Bioorg Med Chem Lett 2003;13:1883–1886. [PubMed: 12749890]
13. Morwick T, Hrapchak M, DeTuri M, Campbell S. Org Lett 2002;4:2665–2668. [PubMed: 12153204]
14. Garcia J, Mata EG, Tice CM, Hormann RE, Nicolas E, Albericio F, Michelotti EL. J Comb Chem 2005;7:843–863. [PubMed: 16283794]
15. Sarshar S, Siev D, Mjalli AMM. Tetrahedron Lett 1996;37:835–838.
16. Lee HB, Balasubramanian S. Org Lett 2000;2:323–326. [PubMed: 10814313]
17. Cobb JM, Grimster N, Khan N, Lai JYQ, Payne HJ, Payne LJ, Raynham T, Taylor J. Tetrahedron Lett 2002;43:7557–7560.
18. Li W, Lam Y. J Comb Chem 2005;7:644–647. [PubMed: 16153057]
19. Pudelová N, Krchňák V. J Comb Chem 2009;11:370–374. [PubMed: 19245249]
20. Wang SS. J Am Chem Soc 1973;95:1328–1333. [PubMed: 4687686]
21. Rink H. Tetrahedron Lett 1987;28:3787–3790.
22. Jensen KJ, Alsina J, Songster MF, Vagner J, Albericio F, Barany G. J Am Chem Soc 1998;120:5441–5452.
23. Dauben WG, Gerdes JM, Bunce RA. J Org Chem 1984;49:4293–4295.
24. Nader FW, Brecht A, Kreisz S. Chem Ber 1986;119:1208–1216.
25. Ikuta H, Shirota H, Kobayashi S, Yamagishi Y, Yamada K, Yamatsu I, Katayama K. J Med Chem 1987;30:1995–1998. [PubMed: 3118023]
26. IbrahimOuali M, Sinibaldi ME, Troin Y, Gardette D, Gramain JC. Synth Commun 1997;27:1827–1848.
27. Boisse T, Rigo B, Millet R, Henichart JP. Tetrahedron 2007;63:10511–10520.
28. Creech GS, Kwon O. Org Lett 2008;10:429–432. [PubMed: 18173275]
29. Krchňák V. J Comb Chem 2005;7:507–509. [PubMed: 16004488]
30. Flitsch W, Hampel K, Hohenhorst M. Tetrahedron Lett 1987;28:4395–4396.
31. Flitsch W, Hohenhorst M. Liebigs Ann Chem 1990:397–399.
32. Brennan J, Murphy PJ. Tetrahedron Lett 1988;29:2063–2065.
33. Inagaki H, Takeda T, Miyauchi RN, Kawakami K, Takahashi H, Takemura M. Heterocycles 2004;63:699–706.
34. Irie H, Shibata K, Matsuno K, Zhang Y. Heterocycles 1989;29:1033–1035.
35. Lorsbach BA, Kurth M. J Chem Rev 1999;99:1549–1581.
36. Huang PQ, Wu TJ, Ruan YP. Org Lett 2003;5:4341–4344. [PubMed: 14601995]
37. Paintner FF, Metz M, Bauschke G. Synlett 2003:627–630.
38. Alvi KA, Nair B, Gallo C, Baker D. J Antibiotics 1997;50:264–266.
39. Taguchi H, Yokoi T, Tsukatani M, Okada Y. Tetrahedron 1995;51:7361–7372.
40. Gilchrist TL, Healy MAM. Tetrahedron 1993;49:2543–2556.
41. Ackrell J, Galeazzi E, Muchowski JM, Tokes L. Can J Chem 1979;57:2696–2702.
42. Dinsmore CJ, Zartman CB. Tetrahedron Lett 2000;41:6309–6312.
43. Gnichtel H, Salem WI. Liebigs Ann Chem 1982:729–733.
44. Mahran MA, El-Sayed OA, Fahmy HTY, Ashour FA. Alexandria J Pharm Sci 1996;10:133–135.
45. Zaleska B, Trzewik B, Grochowski J, Serda P. Synthesis 2003:2559–2563.
46. Koenig JJ, Wermuth CG. Tetrahedron Lett 1973;14:603–606.
47. Wiethe RW, Stewart EL, Drewry DH, Gray DW, Mehbob A, Hoekstra WJ. Bioorg Med Chem Lett 2006;16:3777–3779. [PubMed: 16678409]
48. Kalyanam D, Dave KG, Likhate MA. Synth Commun 1988;18:2183–2191.
49. Feng DZ, Song YL, Jiang XH, Chen L, Long YQ. Org Biomol Chem 2007;5:2690–2697. [PubMed: 18019544]
50. Dolle RE, Macleod C, Martinez-Teipel B, Barker W, Seida PR, Herbertz T. Angew Chem, Int Ed 2005;44:5830–5833.
51. Zhang CZ, Moran EJ, Woiwode TF, Short KM, Mjalli AMM. Tetrahedron Lett 1996;37:751–754.

52. Sheehan JC, Bose AK. J Am Chem Soc 1951;73:1761–1765.
53. Perez-Faginas P, Garcia-Lopez IAMT, Gonzalez-Muniz R. Tetrahedron Lett 2008;49:215–218.
54. Perez-Faginas P, O'Reilly F, O'Byrne A, Garcia-Aparicio C, Martin-Martinez M, de Vega MJP, Garcia-Lopez MT, Gonzalez-Muniz R. Org Lett 2007;9:1593–1596. [PubMed: 17381101]
55. Santa Z, Nagy J, Nyitrai J. Tetrahedron-Asymmetry 2006;17:3111–3127.
56. Bonache MA, Cativiela C, Garcia-Lopez MT, Gonzalez-Muniz R. Tetrahedron Lett 2006;47:5883–5887.
57. Bonache MA, Gerona-Navarro G, Garcia-Aparicio C, Alias M, Martin-Martinez M, Garcia-Lopez MT, Lopez P, Cativiela C, Gonzalez-Muniz R. Tetrahedron-Asymmetry 2003;14:2161–2169.
58. Gerona-Navarro G, Royo M, Garcia-Lopez MT, Albericio F, Gonzalez-Muniz R. Molecular Diversity 2003;6:75–84. [PubMed: 14761158]
59. Shamma M, Novak L. Tetrahedron 1969;25:2275–2279.
60. Alonso R, Castedo L, Dominguez D. Tetrahedron Lett 1986;27:3539–3542.
61. Goff DA, Zuckermann RN. J Org Chem 1995;60:5748–5749.
62. Trotter BW, Nanda KK, Kett NR, Regan CP, Lynch JJ, Stump GL, Kiss L, Wang J, Spencer RH, Kane SA, White RB, Zhang RN, Anderson KD, Liverton NJ, McIntyre CJ, Beshore DC, Hartman GD, Dinsmore CJ. J Med Chem 2006;49:6954–6957. [PubMed: 17125248]
63. Krchňák V, Paděra V. Bioorg Med Chem Lett 1998;22:3261–3264.
64. Bouillon I, Soural M, Miller MJ, Krchňák V. J Comb Chem 2009;11:213–215.

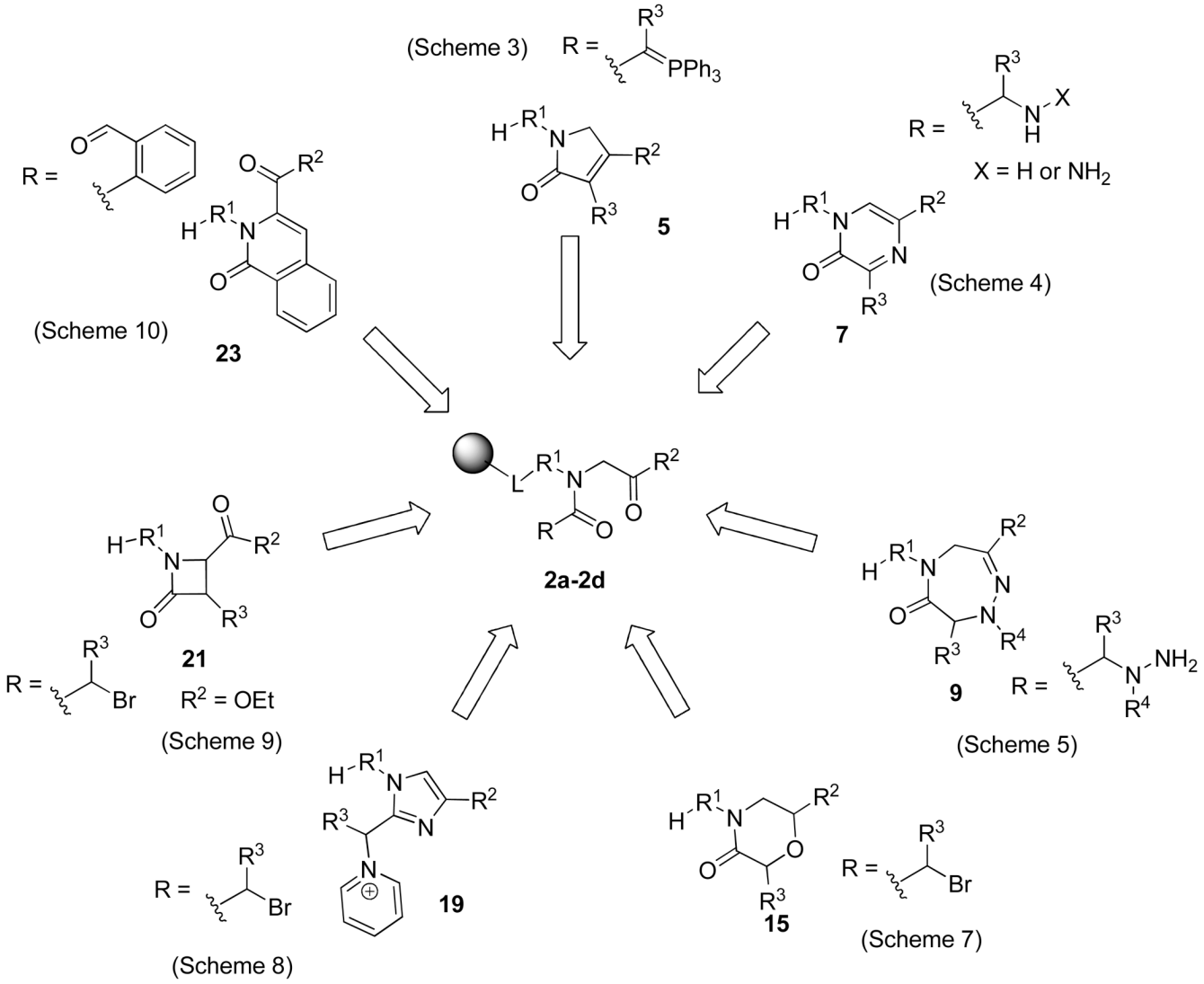


Figure 1.
α-Acylamino ketones/esters as intermediates for the syntheses of seven different heterocycles

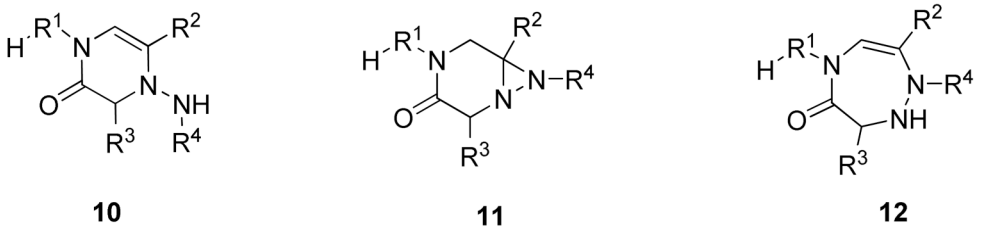
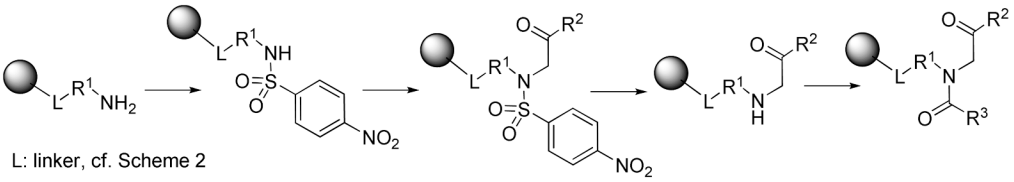
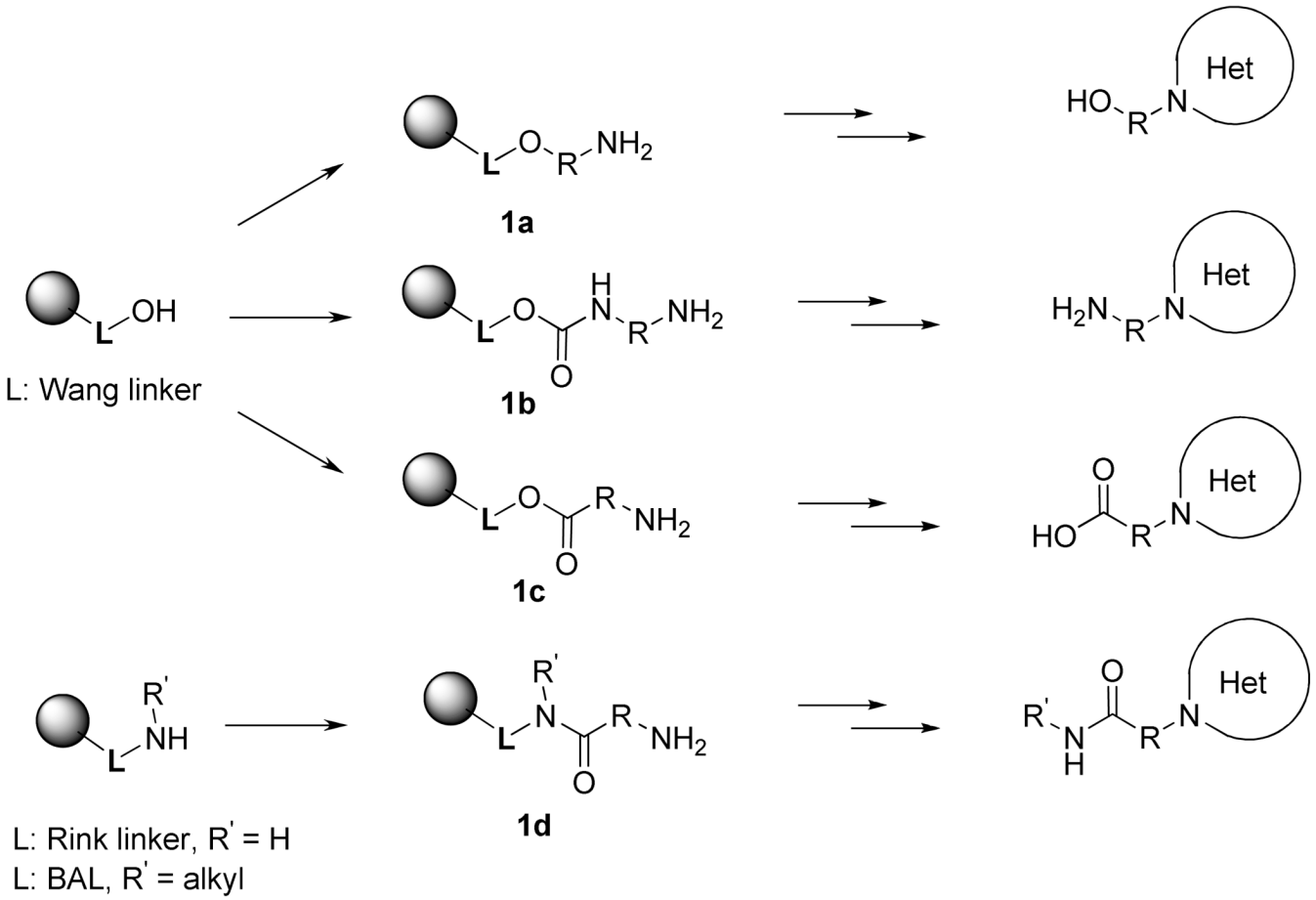


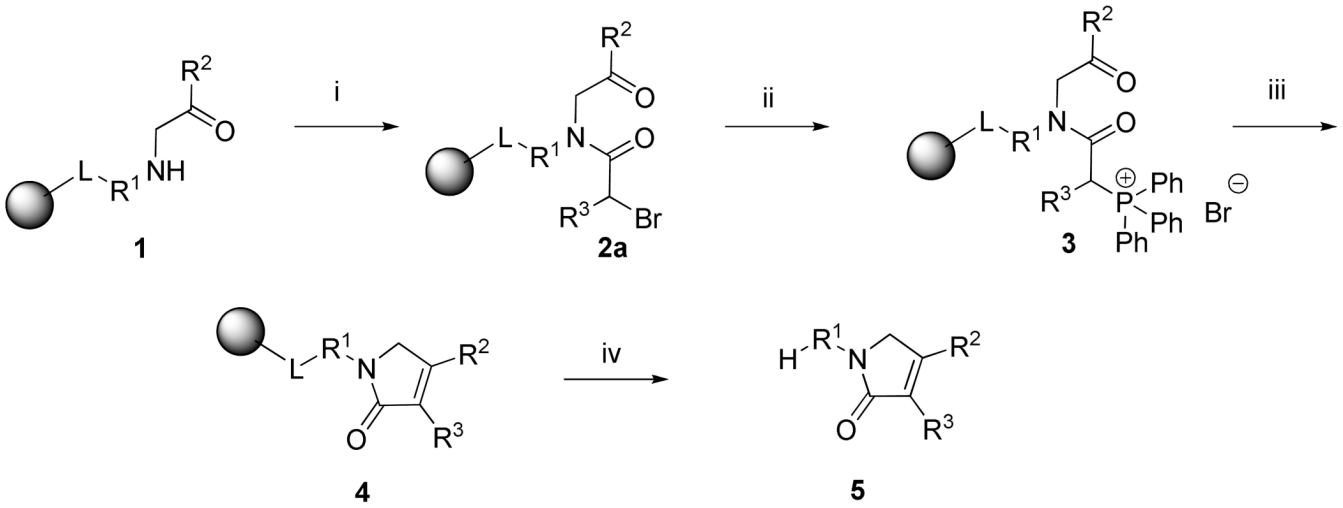
Figure 2.
Alternative structures with identical molecular mass



Scheme 1.
Synthesis of resin-bond α-acylamino ketones[7]



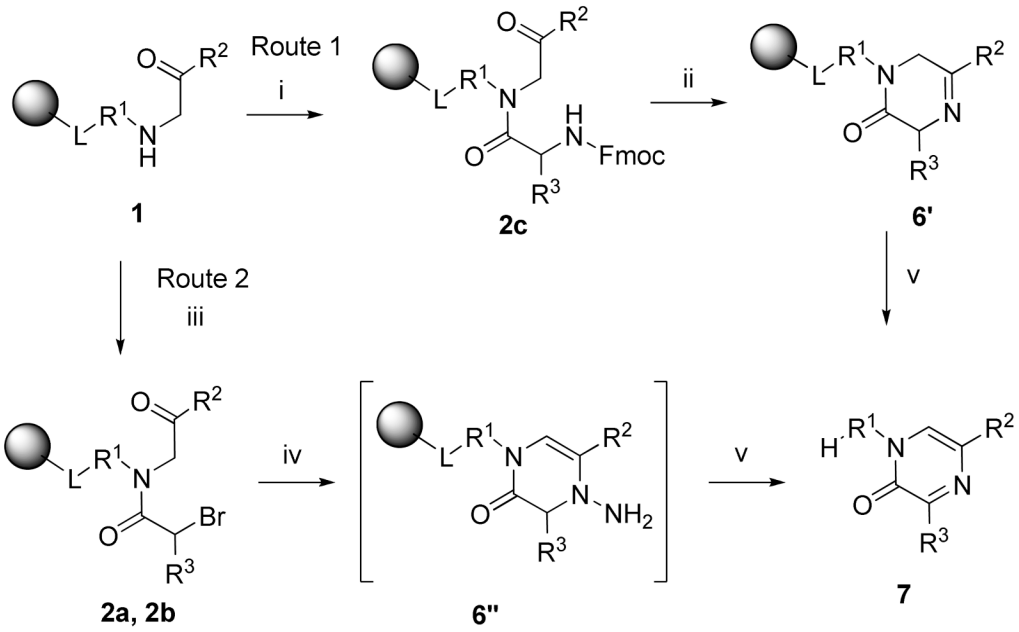
Scheme 2.
Immobilization of amine-containing building blocks



Scheme 3.

Synthesis of 1,5-dihydro-pyrrol-2-ones **5**[a]

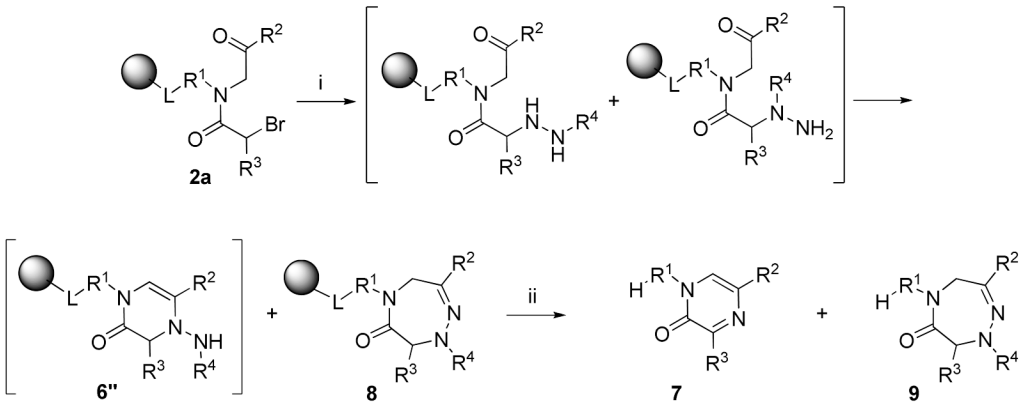
[a]Reagents and conditions: (i) bromoacetic acid (2 equiv.), DIC (1 equiv.), DCM, 15 min, then DIEA (1 equiv.), 4 h; (ii) PPh_3, anhydrous NMP, overnight; (iii) TEA, anhydrous NMP, 2 h; (iv) 50% TFA in DCM, 1 h



Scheme 4.

Synthesis of 1*H*-pyrazin-2-ones **7**[a]

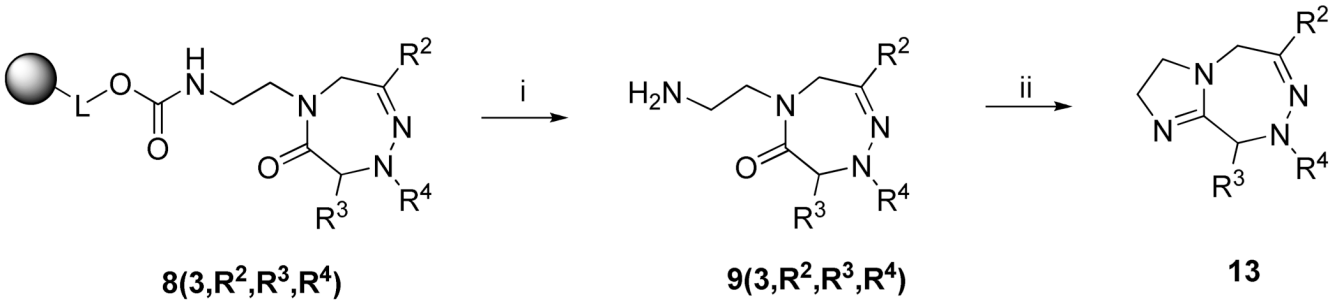
[a]Reagents and conditions: (i) Fmoc-α-amino acid (2 equiv.), DIC (1 equiv.), DCM/DMF (1:1), overnight; (ii) 50% piperidine in DMF, 15 min; (iii) α-bromocarboxylic acid (2 equiv.), DIC (1 equiv.), DCM, 15 min, then DIEA (1 equiv.), 4 h; (iv) hydrazine monohydrate, THF, 2 h; (v) 50% TFA in DCM, 1 h



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

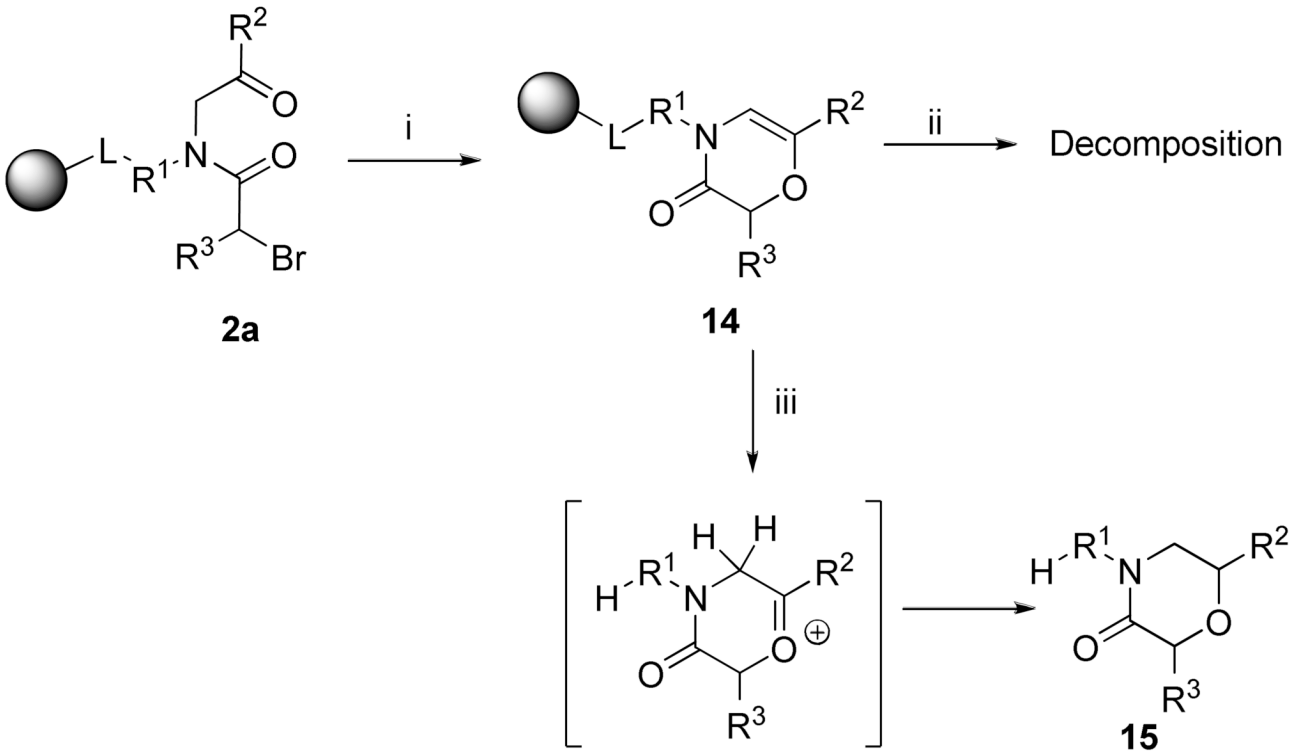


8(3,R^2,R^3,R^4) **9(3,R^2,R^3,R^4)**

Scheme 6.

Synthesis of 3,5,8,9-tetrahydro-2*H*-imidazo[2,1-*d*][1,2,5]triazepine fused ring system **13**[a]

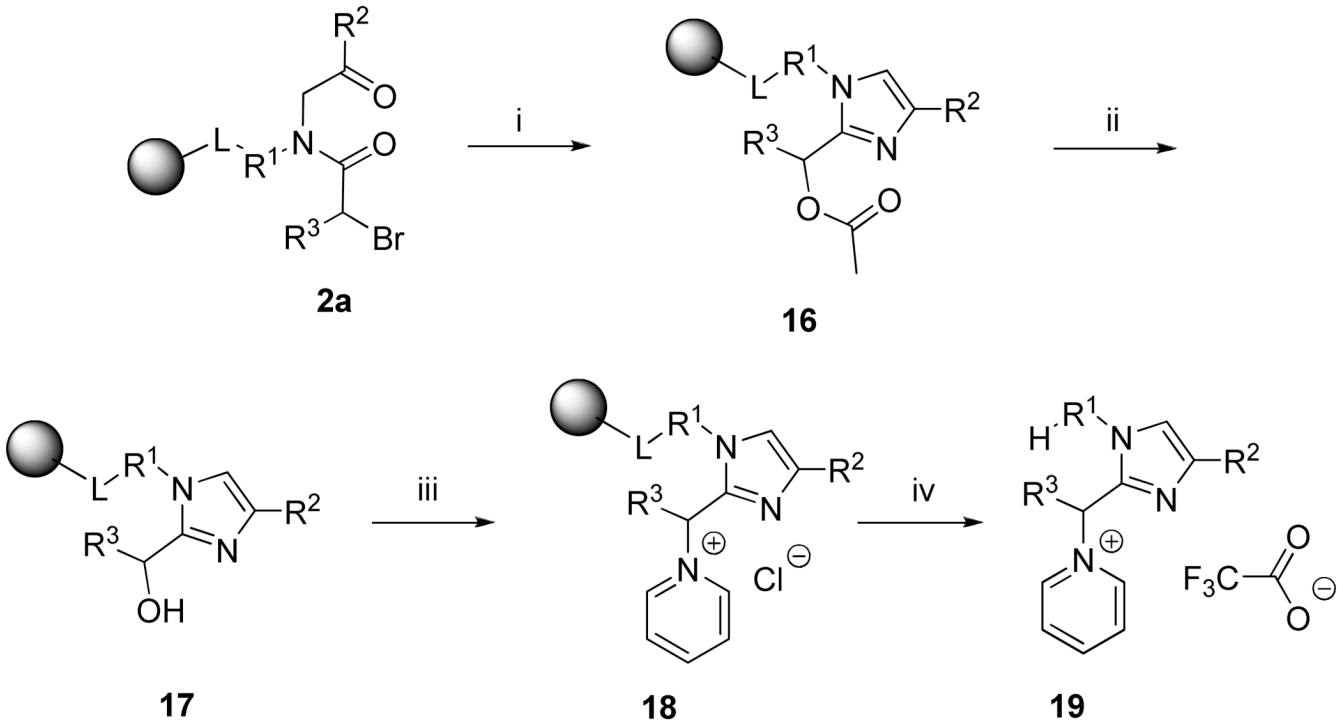
[a]Reagents and conditions: (i) 50% TFA in DCM, 1 h; (ii) filtration through C18 cartridge, then DCM, 30 °C, overnight



Scheme 7.

Synthesis of morpholin-3-ones **15**[a]

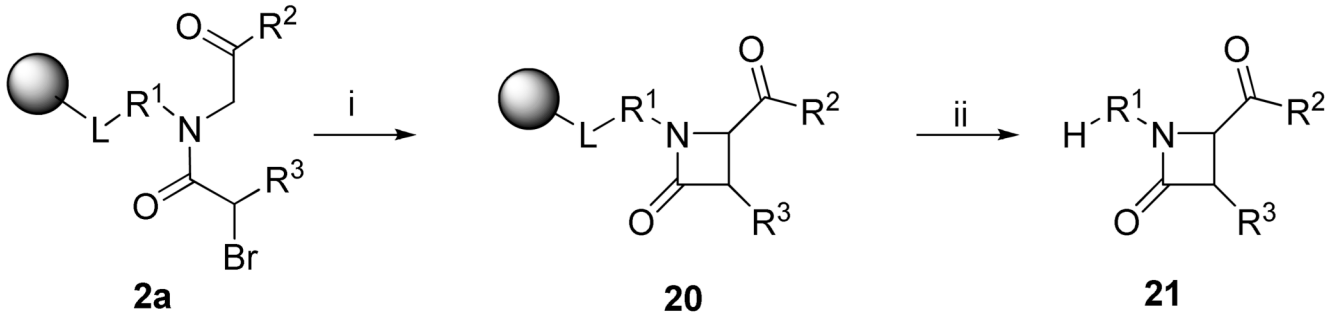
[a]Reagents and conditions: (i) BEMP, anhydrous NMP, 15 min; (ii) 50% TFA, DCM, 1 h; (iii) TFA/TES/DCM (5:1:4), 1 h



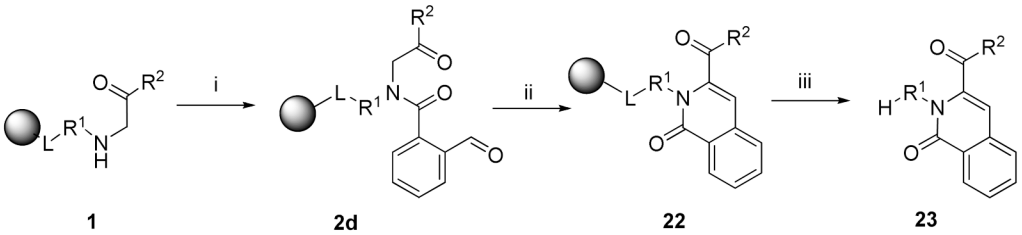
Scheme 8.

Synthesis of 1*H*-imidazoles **19**[a]

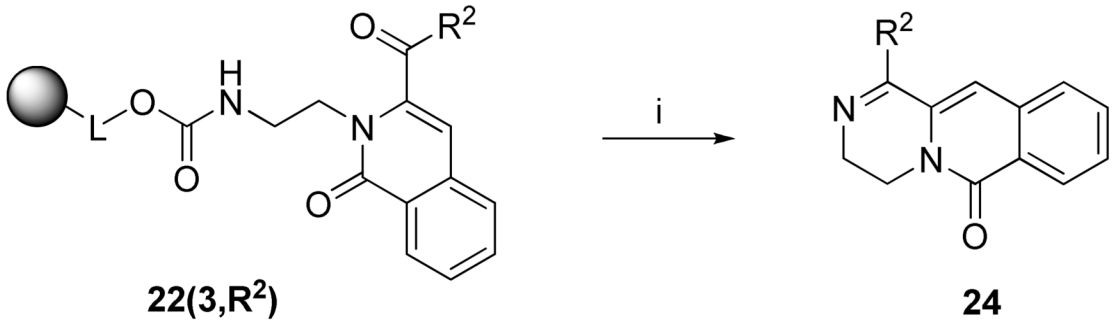
[a]Reagents and conditions: (i) ammonium acetate, acetic acid, 100 °C, overnight; (ii) KOTMS, THF, 1 h; (iii) mesyl chloride, pyridine, 1 h; (iv) 50% TFA in DCM, 1 h



Scheme 9.
Synthesis of β-lactams **21**[a]
[a]Reagents and conditions: (i) BEMP, NMP, 30 min; (ii) 50% TFA, DCM, 1 h



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

Table 1

Synthesized heterocycles **5, 7, 9, 13, 15, 19, 21, 23, 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–$(CH_2)_2CH_3$	4-Me-Ph	H	66	11	362

Product	R^1-H	R^2	R^3	Purity[a] [%]	Yield[b] [%]	MS ESI+
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)	$-CH_2Ph-$ (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)	$-CH_2Ph-$ (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)	$-(CH_2)_2-CONH(CH_2)_2CH_3$	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] R^4 = Bn;

NA, not applicable; ND, not determined