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Polymer-supported α -Acylamino Ketones: Preparation and Application in Syntheses of 1,2,4-Trisubstituted-1*H*-imidazoles

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Abstract

Polymer-supported α -acylamino ketones were prepared from resin-bound amines, bromoketones, and carboxylic acids. Selective monoalkylation of amines by bromoketones was carried out via 4-nitrobenzenesulfonamides. There was a striking difference in the reaction outcome between 2-Nos and 4-Nos derivatives. α -Acylamino ketones were converted to imidazoles. The cyclization was performed on resin, allowing further polymer-supported elaboration of imidazoles including synthesis of bis-heterocyclic compounds. A small combinatorial array of imidazoles was synthesized. Target compounds were prepared under mild conditions using commercially available building blocks for the introduction of three points of diversity.

Introduction

Our ongoing research interest focuses on development of efficient chemical transformations yielding high purity and yield of diverse drug-like heterocyclic compounds. At the same time, we prioritize chemical routes that use building blocks with diverse side-chains that are commercially available or can be prepared in a straightforward manner (for our recently published solid-phase syntheses cf. references 1–4). This contribution is dedicated to solid-phase synthesis of α -acylamino ketones and their use in imidazole syntheses.

α -Acylamino ketones, in addition to being attractive compounds *per se*,^{5–7} represent an intriguing class of compounds that offer a wide range of chemical transformations and 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.

Syntheses of α -acylamino ketones on solid support were reported by several research groups. The resin-bound α -acylamino ketones were prepared by Ugi four components condensation (4CC) reaction from resin-bound isocyanides, arylglyoxals, amines, and carboxylic acids (Scheme 1),⁸ and, alternatively, with polymer-supported aldehydes and amines.⁹

Traceless cleavage of benzylic acylammonium chloride prepared from *N*-alkyl-*N*-(β -keto) amides yielded α -acylamino ketones that were cyclized to imidazoles in solution.¹⁰ Parallel synthesis of 1,2,4-trisubstituted imidazoles was also described via *N*-alkyl-*N*-(β -keto) amides

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using a carbazate linker.¹¹ An alternative route to α -acylamino ketones, using traceless sulfone linker, was reported by Li and Lam.¹² α -Acylamino ketones were released from the solid support and converted to imidazoles, thiazoles, and oxazoles using amines, Lawesson's reagent, and I_2/PPh_3 , respectively.

Pulici and coworkers¹³ reported a detailed study aimed at preparation of α -acylamino ketones on solid phase for subsequent synthesis of oxazoles. Several methods were evaluated including direct alkylation of resin-bound primary amine (Rink amine resin), reductive alkylation of Rink resin with keto aldehydes, reaction of MAMP-Br resin (Merrifield alpha-methoxy phenyl) with amino alcohols, followed by oxidation; and protection of Rink amide resin with either 2,4-dinitrobenzenesulfonyl or allyl group, followed by alkylation and removal of protecting group. According to the authors,¹³ the method of choice comprised the reaction of MAMP-Br resin with an amino ketone followed by acylation (Scheme 2).

α -Acylamino ketones were prepared as target compounds from Weinreb amides in solution,^{5,6} from polymer-supported Weinreb amides,⁷ and also by oxidation of acylamino alcohols.⁵ Polymer-supported α -acylamino ketones were frequently used for the synthesis of imidazoles, formation of the five membered ring was typically carried out by ammonium acetate in acetic acid at elevated temperature (Scheme 3).^{8–12}

Alternative syntheses of imidazoles on solid phase included a traceless synthesis on backbone amide linker (BAL), reported by Bilodeau and Cunningham,¹⁴ on-resin cyclization of 3-*N,N*-(dimethylamino)isocyanoacrylate-Wang-resin with amines in a microwave cavity.¹⁵ Incorporation of 1,3-azoles (oxazole, thiazole, imidazole) into peptides and peptidomimetics was realized by cyclodehydration of corresponding dipeptides.¹⁶

In this contribution we describe solid-phase synthesis of α -acylamino ketones from resin-bound amines, bromoketones and acylating agents *via* alkylation of 4-nitrobenzenesulfonyl (Nos) activated/protected amines (a variant of the Fukuyama method¹⁷). We observed a striking difference in the reaction outcome between 2-Nos and 4-Nos derivatives. Alkylation of resin-bound 2-nitrobenzenesulfonamides by bromoketones and bromoacetates yielded the expected product. However, attempted cleavage of the 2-Nos protecting groups led to unexpected tandem carbon-carbon followed by nitrogen-nitrogen bond formation and yielded indazole oxides of excellent purity (Scheme 4).⁴ We extended our study to 4-Nos derivatives and in this contribution we describe efficient solid-phase synthesis of α -acylamino ketones.

When compared to previously reported solid-phase syntheses of α -acylamino ketones, our approach does not require preparation of dedicated building blocks such as isocyanides and arylglyoxals,⁸ amino ketones,¹³ keto aldehydes,¹³ but uses commercially available building blocks, mild reaction conditions, and tolerates a variety of functional groups and any primary amine functionalized resin. It allows formation of heterocycles on-resin, advantageous feature for further elaboration of primarily formed heterocycles (examples shown).

We also describe application of α -acylamino ketones for 1,2,4-trisubstituted-1*H*-imidazole synthesis. The whole plethora of structurally unrelated diverse heterocycles prepared from resin-bound α -acylamino ketones will be reported in our following contribution (Pudelová & Krchňá, manuscript in preparation).

Results and discussion

Our objective was to design a general route to polymer-supported α -acylamino ketones with the following criteria in mind: (i) use commercially available and easily accessible building blocks with a variety of side-chains, (ii) application of mild reaction conditions compatible

with diverse functional groups, (ii) accessibility to on-resin elaboration to diverse heterocycles, and (iv) transformations providing high purity and yield of crude α -acylamino ketones.

The most straightforward method, monoalkylation of resin-bound primary amines by bromoketones followed by acylation, has been reported,¹³ however, the route was problematic due to contamination of the target product by non- and di-alkylated species. Our alkylation experiments with several resin-bound primary amines confirmed reported results and yielded mixtures of non-, mono-, and di-alkylated species. In accord with reported results,¹³ we did not arrive at reliable reaction conditions for clean monoalkylation of the resin-bound primary amino groups.

To achieve selective monoalkylation we decided to use the Fukuyama method.¹⁷ However, cleavage of the 2-Nos groups with a thiol in the presence of a base (DBU) unexpectedly yielded indazole oxides.⁴ To change the course of this otherwise very useful transformation, we replaced the 2-Nos group by the 4-Nos group and reacted resin-bound amines **1** with 4-nitrobenzenesulfonyl chloride to arrive at resin **2** (Scheme 5). The alkylation of **2** with bromoketones proceeded smoothly under the same conditions developed for alkylation of the 2-Nos derivatives.

We evaluated alkylation reaction with bromoketones bearing both electron-donating and electro-withdrawing substituents, their combinations and different position on the aromatic ring. Our set contained 2-Me, 4-Me, 2,4-diMe, 4-OMe, 4-CF₃, 4-F, 4-Cl, 2-Br, 3,5-diCl-4-NH₂, 3-NO₂, and 4-NO₂ phenacyl bromides. Most alkylation reaction resulted in complete reaction, irrespective of substitution position or nature of substituents. However, the alkylation with 4-nitrobromoketone and 4-pyridylbromoketone was incomplete. Repeating the alkylation, changing solvent for DMSO or elevated temperature (40°C) did not provide satisfactory results.

At this point, we focused on cleavage of the 4-Nos group, the critical step in our reaction sequence. Deprotection of the 4-Nos group from resin **3** was accomplished by treatment with thiolate nucleophiles including thiophenol, 2-mercaptoacetic acid and 2-mercaptoethanol in the presence of a base.¹⁷ We screened number of combinations of thiols (thiophenol and 2-mercaptoethanol) with bases (DBU, *N,N*-diisopropyl-*N*-ethylamine (DIEA), triethylamine, *n*-propylamine, proton sponge) in different solvents (DMF, NMP, dichloromethane (DCM)) and reaction time. During an extensive optimization study to cleave the 4-Nos group from resin **3** we gratifyingly found that 0.6 M 2-mercaptoethanol and 0.2 M DBU in DMF cleaved the 4-Nos group quantitatively within minutes and provided aminoketones **4** without any significant side reaction. The excess of 2-mercaptoethanol over DBU appeared to be critical for clean 4-Nos group removal. The reaction outcome was also sensitive towards substitutions on the aromatic ring of the bromoketones used in the preceding alkylation reaction. The LC/MS analysis of a sample cleaved from the resin revealed major peaks of products with high purity in the case of 2-Me, 4-Me, 2,4-diMe, 4-OMe and 3,5-diCl-4-NH₂ derivatives. The 4-Cl and 4-F derivatives were accompanied with acceptable minor impurities. The purity of crude products using 4-CF₃, 2-Br and 3-NO₂ was ~ 50% only. The formation of product from 4-NO₂ derivative was not observed.

Subsequent acylation of the resin-bound secondary amino group proceeded without any unexpected complication and we arrived at resin-bound α -acylamino ketones **5**. The acylation was carried out with acetic anhydride in pyridine, with isonicotinoyl chloride hydrochloride and 6-chloronicotinoyl chloride in the presence of DIEA in DCM. Fmoc-amino acids and 4-fluoro-3-nitrobenzoic acid were activated by *N,N'*-diisopropylcarbodiimide (DIC) to pre-form symmetrical anhydrides.

Polymer-supported α -acylamino ketones **5** can serve as useful synthons for preparation of various heterocycles. Here we describe transformation to 1,2,4-trisubstituted-1*H*-imidazoles.

The cyclization to imidazole derivatives **6** was carried out on resin by ammonium acetate in AcOH at elevated temperature (100 °C) following a reported procedure.^{8–12} We observed that not all compounds completely cyclized and some contained the acyclic precursor in range of 5–30% and the cyclization was repeated under the same conditions. It is important to mention, that the reaction was carried out under acidic conditions and that the product could be partially cleaved from the resin. Thus we also analyzed the solution for the presence of any cleaved imidazole and found that in average 5 % of the product was cleaved from the resin.

Alternatively, we carried out cyclization in solution, after cleavage of the acyclic products from the resin. We observed that cyclization in solution was faster (6 – 10 h), the purity and yield of crude product was comparable with the product cyclized on resin. However, cleavage in solution required isolation of the product from ammonium acetate solution in AcOH.

We prepared the resin-bound primary amines **1** from three different bifunctional building blocks: amino alcohols, diamines, and amino acids (Scheme 6). 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.⁴ Wang resin was used to immobilize amino alcohols (**1**{1}), diamines (**1**{2}), and amino acids (**1**{3}) and yielded imidazole alcohols, amines, and acids. Rink amide resin acylated with amino acids (**1**{4}) provided amides, the use of backbone amide linker (BAL) resin for reductive amination followed by acylation with amino acids (**1**{5}) yielded secondary amides.

Cleavage of imidazoles with TFA afforded crude products of good to excellent purity. All compounds were purified by semi-preparative HPLC. Selected compounds were characterized by HRMS and ¹H and ¹³C NMR. All analytical data are summarized in the experimental section.

To document the versatility of our synthetic scheme, we included two examples of further chemical transformations of resin-bound α -acylamino ketones and imidazoles. Scheme 7 portrays imidazole synthesis using 6-chloronicotinoyl chloride. The chloride in **5**{R¹,R²,5} was replaced by secondary amines and this aromatic nucleophilic substitution was evaluated at a stage of α -acylamino ketones **5**{R¹,R²,5} and also after on-resin imidazole formation (resin **6**{R¹,R²,5}).

The reaction was carried out in DMSO at ambient and elevated temperatures. The aromatic nucleophilic substitution with pyrrolidine proceeded smoothly after overnight reaction at ambient temperature with a high degree of conversion (78%). Piperazine and piperidine provided only 50 % conversion. Elevated reaction temperature to 60 °C led to disappearing of starting material, however the product was contaminated by significant amount of side-products. In the case of piperidine and piperazine, the sequence of reactions was reversed [on-resin cyclization followed by substitution: **5**{R¹,R²,5} to **6**{R¹,R²,5} to **6**{R¹,R²,7–8}]. With pyrrolidine, while complete conversion was observed with this reversed sequence, the reaction mixture contained impurities. Thus, with pyrrolidine substitution prior to on-resin cyclization was preferred [**5**{R¹,R²,5} to **5**{R¹,R²,6} to **6**{R¹,R²,6}]. In all three cases the resin-bound products **6**{R¹,R²,6–8} were cleaved to give products **7**{R¹,R²,6–8}.

The next example includes synthesis of bis-heterocyclic structures such as imidazolyl-quinoxalinones. Amino ketones **4** were acylated with 4-fluoro-3-nitrobenzoic acid (Scheme 7). Nucleophilic substitution of fluorine by an N ^{α} -amino acid ester followed by reduction of the nitro group resulted in spontaneous cyclization to 3,4-dihydro-1*H*-quinoxalin-2-ones **5**{R¹,R²,9}. Imidazole cyclization and cleavage from the resin yielded 7-(1*H*-imidazol-2-yl)-3,4-dihydro-1*H*-quinoxalin-2-ones **7**{R¹,R²,9}.

Imidazoles prepared using Fmoc-amino acids in the last combinatorial step provided the opportunity for derivatization on the amino group. On-resin cyclization followed by Fmoc group removal exposed the amino group for subsequent acylation (e.g. by N-protected amino acid in peptide synthesis). We intend to incorporate an imidazole ring into a peptide chain as peptidomimetics.

Library compounds were submitted for evaluation of biological activities to High Throughput Screening in the Molecular Libraries Probe Production Centers Network and the results are available in PubChem (<http://pubchem.ncbi.nlm.nih.gov/>).

Conclusion

An efficient solid-phase synthesis of α -acylamino ketones with three diversity positions from commercially available building blocks was described and applied for synthesis of 1,2,4-trisubstituted-1*H*-imidazoles. All reaction steps were optimized and completed in high purity with no significant side-reactions observed.

Experimental part

Solid-phase syntheses were carried out on manually operated Domino Block synthesizer¹⁸ (www.torvqi.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 volume in DCM of resins was measured before syntheses and resins with swollen volume greater than 7 mL/g of dry resin were used.¹⁹ All reactions were carried out at ambient temperature (21 °C) unless stated otherwise.

Reaction with 4-Nos-Cl (resin 2)

Resin **1**, 1 g, was washed 3× with DCM, a solution of 4-Nos-Cl (4 mmol, 884 mg) and lutidine (5 mmol, 580 μ L) in 10 mL DCM was added to the resin and reaction slurry was shaken for 16 h. The resin was washed 3 × with DMF and 3 × DCM.

Reaction with bromoketone (resins 3)

Resin **2**, 500 mg, was washed 3 × with DCM and 3 × DMF. A 0.5 M solution bromoketone (2.5 mmol) and 1 M DIEA (5 mmol, 870 μ L) in 5 mL DMF was added. The reaction slurry was shaken for 16 h. The resin was washed 3 × with DMF and 3 × DCM.

Cleavage of Nos group (resins 4)

Resin **3**, 500 mg, was washed 3× with DMF. A solution of 0.6 M 2-mercaptoethanol (3 mmol, 210 μ L) and 0.2 M DBU (1 mmol, 150 μ L) in 5 mL DMF was added and resin slurry was shaken for 5 min. The resin was washed 3 × with DMF and 3 × DCM.

Acylation with acid chloride (resins 5)

Resin **4**, 250 mg, was washed 3 × with DCM and a solution of acid chloride or acid chloride hydrochloride (1 mmol) and DIEA (1 or 2 mmol, 174 μ L or 348 μ L) in 5 mL DCM was added and the reaction slurry was shaken for 30 min. The resin was washed 3 × with DMF and 3 × DCM.

Acylation with Fmoc-amino acid (resins 5)

Resin **4**, 250 mg, was washed with DCM and a solution of Fmoc- β -Ala-OH (1 mmol, 311 mg) and DIC (0.5 mmol, 77 μ L) in 5 mL DCM/DMF (1:1) solution was added to the resin and reaction slurry was shaken for 16 h. The resin was washed 3 $\times$ with DMF and 3 $\times$ DCM.

Cyclization by ammonium acetate in AcOH (resins 6)

Resin **5**, 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 for 16 h. The reaction was repeated when the cyclization was not complete. The resin was washed 5 $\times$ with DCM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
SP synthesis of α -acylamino ketones via Ugi 4CC reaction⁸

Scheme 2. Preparation of α -acylamino ketones from MAMP-Br resin and amino ketones13

Scheme 3.
Synthesis of imidazoles from α -acylamino ketones8–12

Scheme 4.

Attempted cleavage of 2-Nos group and unexpected formation of indazole oxides4

Scheme 5.

Solid-phase synthesis of α -acylamino ketones and their conversion to 1,2,4-trisubstituted-1H-imidazoles

^aReagents and conditions: (i) 4-nitrobenzenesulfonyl chloride, lutidine, DCM, 16 h; (ii) bromoketone, DIEA, DMF, 16 h; (iii) 2-mercaptoethanol, DBU, DMF, 5 min; (iv) carboxylic acid chloride or anhydride, DCM, 16 h; (v) AcOH, ammonium acetate, 16 h; (vi) 50% TFA, DCM, 1 h; (vii) AcOH, ammonium acetate, 100 °C, 6 – 10 h.

Scheme 6.
Alcohols, amines, acids, and amides in R1 side-chain of imidazoles

Scheme 7. Resin-bound transformations to increase imidazole diversity^a

^aReagents and conditions: (i) 6-chloronicotinoyl chloride, DIEA, DCM, rt, 30 min; (ii) AcOH, ammonium acetate, 100 °C, 16 h; (iii) piperazine or piperidine, DMSO, 60 °C, 16 h or pyrrolidine, DMSO, rt, 16 h; (iv) 4-fluoro-3-nitrobenzoic acid, DIC, N-hydroxybenzotriazole, DCM/DMF, 16 h; (v) N^α-amino acid ester, DIEA, DMSO, 85 °C, 16 h; (vi) SnCl₂•2H₂O, DIEA, DMF, 2 h.

Table 1Structure of R groups in imidazoles **7**

BB	H-R ¹	
1

BB	H-R ¹	
2	<p>Chemical structure of 2-amino-4-methylpentanoic acid. The structure shows a five-carbon chain with an amino group (H₂N) at the second carbon and a methyl group at the fourth carbon. The carboxylic acid group is not explicitly shown, but the structure is labeled as H-R¹.</p>	
3	<p>Chemical structure of 2-amino-4-methylpentanoic acid. The structure shows a five-carbon chain with a carboxylic acid group (HO-C=O) at the first carbon, an amino group (H₂N) at the second carbon, and a methyl group at the fourth carbon. The structure is labeled as H-R¹.</p>	

BB	H-R ¹	
4	<p>Chemical structure of 4-(4-aminobenzyl)heptane, showing a benzene ring substituted with an amino group (H₂N) and a heptyl chain.</p>	
5	<p>Chemical structure of N-propyl-4-oxoheptanamide, showing a heptanamide chain with a ketone group at the 4-position.</p>	

BB	H-R ¹	
6	<chem>CCCCC(=O)NCc1ccc(C)cc1</chem>	
7	<chem>CCCCCNC(=O)Cc1ccc(cc1)CC(C)CC</chem>	
8	<chem>CCCCC(=O)NCc1ccc(C)cc1C(=O)c2ccc(cc2)CC(C)CC</chem>	

BB	H-R ¹	
9		

Table 2

Synthesized imidazoles 7

Compound	Purity ^a [%]	Yield ^b [mg]	Yield ^b [%]	MS ESI+	Compound	Purity ^a [%]	Yield ^b [mg]	Yield ^b [%]	MS ESI+
7(1,4,3)	81	19.1	52	262	7(3,4,8)	77	5.6	12	408
7(1,4,4)	91	18.9	66	296	7(3,5,3)	97	29.1	33	344
7(1,4,5)	85	15.6	49	331	7(3,5,4)	81	39.4	41	377
7(1,4,9)	66	3.0	8	379	7(3,5,5)	76	35.1	33	413
7(2,1,4)	98	13.8	37	279	7(3,5,9)	30	6.5	6	459
7(2,1,5)	84	10.5	25	314	7(4,4,3)	86	16.4	59	351
7(2,2,4)	74	5.8	39	283	7(4,4,4)	95	22.9	74	385
7(2,2,5)	75	1.7	10	318	7(4,4,5)	79	14.8	44	420
7(2,4,3)	80	23.3	35	261	7(4,4,9)	66	3.3	9	467
7(2,4,4)	98	21.6	39	295	7(5,4,3)	89	51.7	35	331
7(2,4,5)	82	26.4	60	330	7(5,4,4)	75	31.2	61	365
7(2,4,9)	49	3.0	6	378	7(6,1,2)	64	3.8	13	377
7(3,1,4)	95	5.6	17	308	7(6,1,3)	63	20.0	23	377
7(3,1,5)	81	12.8	34	342	7(6,1,4)	88	13.0	25	411
7(3,2,4)	85	7.6	23	312	7(6,1,9)	81	8.6	26	494
7(3,2,5)	83	8.7	24	347	7(6,2,2)	78	8.6	36	381
7(3,3,4)	57	15.4	36	328	7(6,2,3)	75	6.3	19	381
7(3,3,5)	77	9.7	21	363	7(6,2,4)	63	14.5	21	415
7(3,4,1)	90	33.8	46	261	7(6,2,9)	74	9.2	28	498
7(3,4,3)	89	29.2	35	290	7(6,4,3)	91	39.7	42	393
7(3,4,4)	80	9.4	42	324	7(6,4,4)	71	37.9	81	427
7(3,4,5)	90	27.3	59	358	7(7,4,2)	75	49.3	72	393
7(3,4,6)	66	7.9	14	393	7(8,1,4)	39	5.7	10	473
7(3,4,7)	66	4.4	10	407	7(8,4,2)	66	34.1	47	455

^a Purity of crude product before purification;

^b yield after purification.