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Piperazine Amide Linker for Cyclative Cleavage from Solid Support: Traceless Synthesis of Dihydroquinoxalin-2-ones

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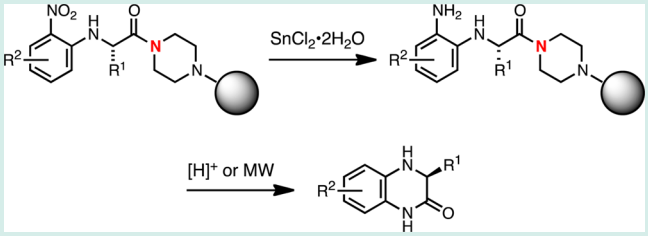
Supporting Information

ABSTRACT: A piperazine amide linker for cyclative cleavage from solid support and its use in the traceless solid-phase synthesis of dihydroquinoxalinones are described. Piperazine was attached to Wang resin via a carbamate linkage and acylated with Fmoc-amino acids. Following Fmoc group removal, resin-bound amines were reacted with 1-fluoro-2-nitrobenzenes. The nitro group of the resulting 2-nitroanilines was reduced, and acyclic precursors, in contrast to traditional ester-type linkage, remained attached to the resin. Target dihydroquinoxalinones were obtained either by acid- or microwave-mediated cyclative cleavage. The synthesis provided crude compounds of high purity and enabled the preparation of stable immobilized linear intermediates. The linker is suitable for combinatorial synthesis of compound libraries.

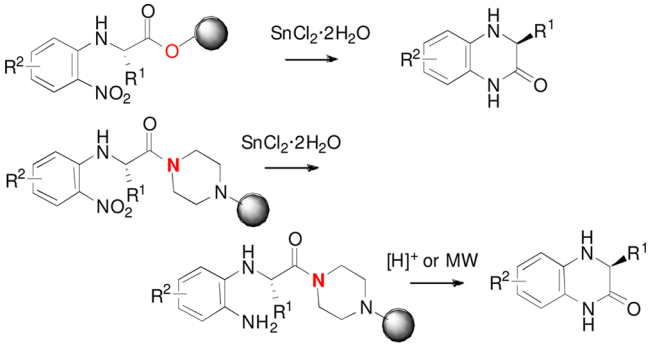


KEYWORDS: *solid-phase synthesis, cyclative cleavage, linker, piperazine, dihydroquinoxalinone*

Cyclative cleavage is a very effective methodology for the synthesis of amide-containing heterocycles in the solid phase (for a review, see ref 1). Typically, a nucleophile of an acyclic precursor attacks an electrophilic carboxylate immobilized on a solid support. Esters of the Merrifield resin are the most often used precursors for cyclative cleavage (Scheme 1). This synthetic strategy was used to prepare various five-, six-, and seven-membered amide-containing heterocycles.[1]

Solid-phase syntheses of quinoxalinones have been reported several times. The key intermediate for the synthesis was frequently 1-fluoro-2-nitrobenzene.[2−7] A synthetic route of choice is ring closure by nucleophilic displacement of an ester by aniline nitrogen of alkyl 2-((2-aminophenyl)amino) acetate. Rink amide resin was acylated with 4-fluoro-3-nitrobenzoic acid and the resin-bound fluorine was displaced using nucleophilic substitution with amino acid esters. After reduction of the nitro group, the six-membered ring was spontaneously closed. 4-Fluoro-3-nitrobenzoic acid also was the key component in the synthesis of a library of dihydroimidazolyl dihydroquinoxalinones.[5] An analogous reaction sequence was reported with an α-amino acid esterified to the Merrifield resin and 1-fluoro-2-nitrobenzene in solution. After reduction of the nitro group, the product was spontaneously released from the resin.[6] Traceless synthesis of quinoxalinones on BAL resin also was reported.[7] All the above-mentioned six-membered ring closures were between aniline nitrogen and carboxylate. The drawback of the ester route is the spontaneous cyclization of alkyl 2-((2-aminophenyl)amino)acetates to quinoxalinones, thus preventing further modification of alkyl 2-((2-aminophenyl)amino)-acetates before cyclization.

Scheme 1. Quinaxolinones by Cyclative Cleavage from an Ester and Amide



We have recently observed that secondary amides can perform in an analogous route. In this paper, we report the expeditious synthesis of quinaxolinones by cyclative cleavage from a tertiary amide rather than ester (Scheme 1). This alternative allows the preparation of stable immobilized linear intermediates and their cyclization triggered by specific reaction conditions.

To evaluate the tendency of an amide for cyclative cleavage via amide nucleophilic displacement, we prepared three model compounds (Figure 1) that differ by the type of amide. We

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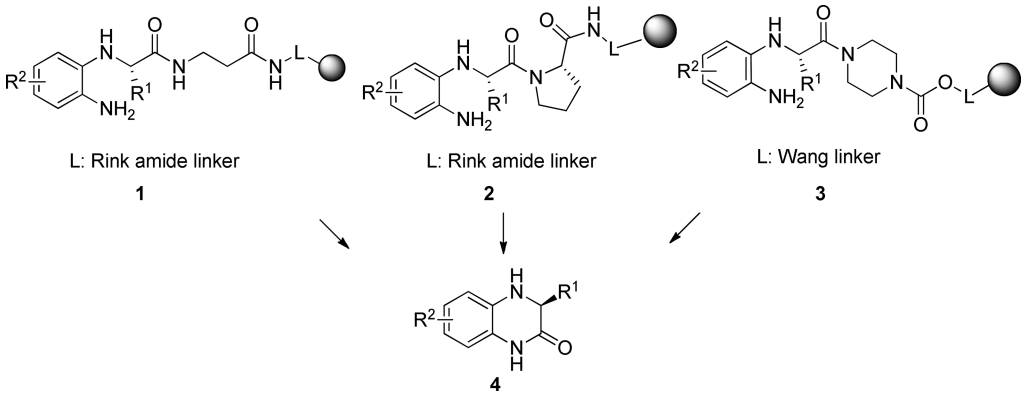
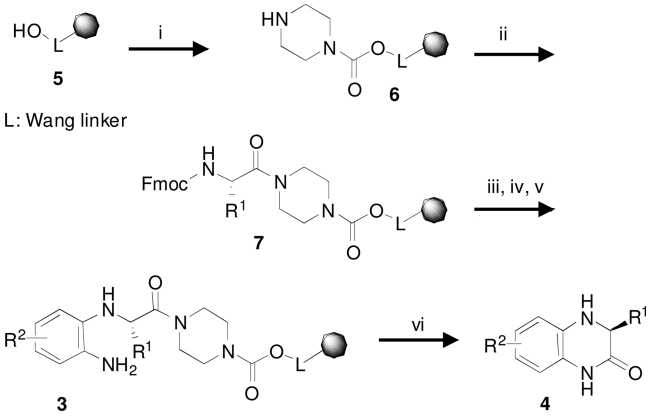


Figure 1. Model compounds designed for amide cyclative cleavage.

examined one secondary amide synthesized using Fmoc-β-Ala-OH and two tertiary amides prepared from Fmoc-Pro-OH and piperazine. Model compounds **1** and **2** containing Fmoc-β-Ala-OH and Fmoc-Pro-OH were prepared on Rink amide resin; the piperazine-containing compounds **3** were made on Wang resin **1** via carbamate linkage (Scheme 2). The starting amines **6**

Scheme 2. Solid-Phase Synthesis of Dihydroquinoxalinones 4 via Acid-Mediated Cyclative Cleavage[a]



[a]Reagents and conditions: (i) CDI, pyridine, DCM, rt, 3 h, then piperazine, DCM, rt, 16 h; (ii) Fmoc amino acid, HOBt, DIC, DMF/DCM, rt, 16 h; (iii) 50% piperidine, DMF, rt, 20 min; (iv) 1-fluoro-2-nitrobenzene, DIEA, DMSO, see experimental procdures in Supporting Information for time and temperature; (v) $SnCl_2 \cdot 2H_2O$, DIEA, DMF, rt, 16 h; (vi) 50% TFA, DCM, rt, 1 h.

were acylated with Fmoc-Phe-OH (R^1 = Bn), the Fmoc group was cleaved with piperidine, and the resin-bound intermediates were reacted with 4-fluoro-3-nitrobenzotrifluoride (R^2 = CF_3). After reduction of the nitro group with tin(II) chloride dihydrate, the linear precursor **1**−**3** remained attached to the resin, and the target compounds **4** were released from the resin with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM).

The results indicated that piperazine model compound **3(1,1)** (for building block numbering, cf. Figure 2) provided complete conversion to the target dihydroquinoxalinone **4(1,1)**, whereas β-Ala and Pro-derived linear precursors **1(1,1)** and **2(1,1)** afforded the dihydroquinoxalinone **4(1,1)** in only 45% and 30% conversion, respectively. Encouraged by the conversion of linear precursor **3(1,1)** to dihydroquinoxalinone **4(1,1)**, we decided to evaluate the scope and

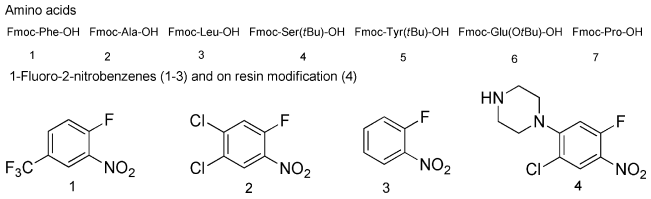


Figure 2. Building blocks used for preparation of dihydroquinoxalinones.

limitations of this synthetic route and prepared a set of compounds with various R^1 and R^2 substitutions. The building blocks used for the synthesis are portrayed in Figure 2.

From the preparative point of view, the disadvantage of the acid-mediated cleavage is the presence of piperazine in the cleaved sample. To eliminate its presence, we attempted cyclization at elevated temperature to avoid the acidic treatment that released piperazine from the resin and contaminated the cyclized products.

We evaluated the cyclative cleavage of model compound **3(1,1)** in polar solvents, such as DMF and DMSO, at an elevated temperature using conventional as well as microwave heating. The results of our experiments are summarized in Table 1. Conventional heating required 72 h to obtain 89%

Table 1. Reaction Conditions for Cyclative Cleavage

entry	temperature	time	heating	solvent	conversion[a]
1	80 °C	16 h	conventional	DMF	53%
2	100 °C	72 h	conventional	DMF	89%
3	100 °C	5 min	microwave	DMF	50%
4	100 °C	60 min	microwave	DMF	75%
5	120 °C	5 min	microwave	DMF	53%
6	150 °C	5 min	microwave	DMF	75%
7	150 °C	60 min	microwave	DMF	70%
8	150 °C	5 min	microwave	DMSO	88%

[a]Conversion is a relative amount of product released from the resin.

conversion of the acyclic precursor (entry 2). Microwave heating at the same temperature (100 °C) afforded respectable conversion (50%) after 5 min (entry 3). Increasing the temperature to 150 °C provided 75% conversion after the same time, but further prolonging the reaction time was not beneficial. However, changing the solvent from DMF to DMSO increased the yield to 88% (entry 8).

The set of our amino acids also contained those that have functional groups in the side chain protected by the *t*-Bu group

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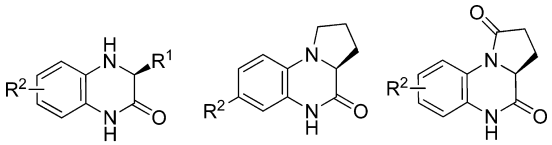
Table 2. Summary of Synthesized Compounds 4, 11, and 12

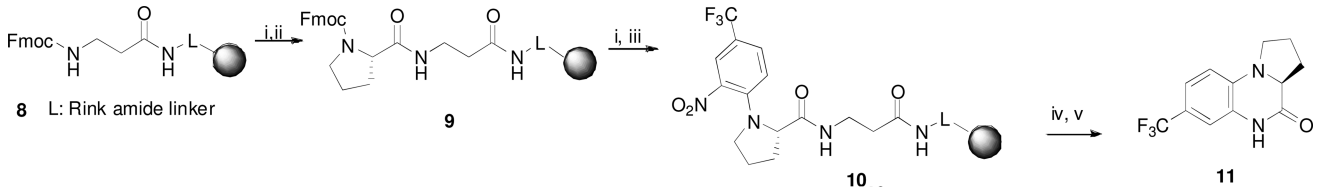


4 11 12

entry	R^1	R^2	cyclative cleavage	purity[a] [%]	MS ESI$^-$	yield[b] [%]
4(1,1)	Bn	6-CF_3	DMSO microwave	>99	305	47
4(2,1)	CH_3	6-CF_3	DMSO microwave	>99	229	45
4(2,3)	CH_3	H	DMSO microwave	>99	161	58
4(3,1)	*i*Bu	6-CF_3	DMSO microwave	>99	269	18
4(4,1)	CH_2OH	6-CF_3	TFA	90	245	40
4(5,1)	*p*-OH-Bn	6-CF_3	TFA	75	321	30
11(7,1)	*c*	7-CF_3	TFA	90	255	27
12(6,1)	*c*	7-CF_3	TFA	90	269	35
12(6,2)	*c*	7,8-diCl	TFA	80	269	28
12(6,3)	*c*	H	TFA	90	201	59
12(6,4)	*c*	8-Cl-7-pip	TFA	86	319	30

[a]Purity of crude compounds calculated from LC traces integrated at 210−500 nm. [b]Yield after HPLC purification. [c]Not applicable.

Scheme 3. Synthesis of Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one Derivative 11[a]



[a]Reagents and conditions: (i) 50% piperidine, DMF, rt, 20 min; (ii) Fmoc-Pro-OH, HOBt, DIC, DMF/DCM, rt, 16 h; (iii) 4-fluoro-3-nitrobenzotrifluoride, DIEA, DMSO, rt, 16 h; (iv) $SnCl_2 \cdot 2H_2O$, DIEA, DMF, rt, 16 h; (v) 50% TFA, DCM, rt, 1 h.

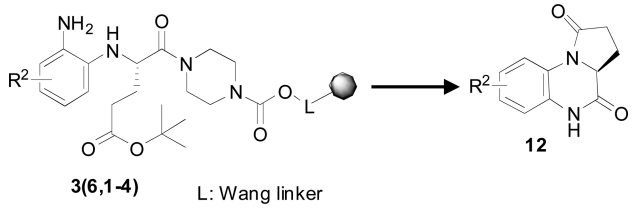
(Fmoc-Tyr(*t*Bu)-OH, Fmoc-Ser(*t*Bu)-OH, and Fmoc-Glu(O*t*Bu)-OH). In these instances, we used TFA-mediated cleavage to demask the protected side chain. Table 2 shows a summary of the results obtained in the TFA-mediated procedure used for amino acids with side chain protection and in the microwave-mediated cyclative cleavage that provided crude products of excellent purity.

Synthesis on hydroxymethyl polystyrene resin using identical sequence of reaction steps provided comparable results without contamination of crude product by piperazine. However, monitoring of individual steps by TFA cleavage of resin sample was problematic because of enhanced acid stability of the linker.

Two amino acids used for the synthesis of dihydroquinoxalinones deserved further attention. We observed that the Pro-derived intermediate **3(7,1)** built on the piperazine linker was cleaved from the resin during reduction of the nitro group. The premature cleavage was proven by treatment of a sample of a resin with Fmoc-OSu and subsequent LC/MS analysis. The only product was the corresponding Fmoc-piperazine, indicating that, in this case, the cyclization and cleavage occurred spontaneously after the reduction of the nitro group. To avoid the premature loss of the compound, we replaced the piperazine with Fmoc-*β*-Ala-OH attached to the Rink resin (Scheme 3). In this case, the Pro-derived intermediate **1(7,1)** did not undergo the unwanted cyclization after tin(II)-mediated reduction of the nitro group.

We also attempted to prepare dihydroquinoxalinones using Fmoc-Glu(O*t*Bu)-OH. After the acid-mediated cleavage of intermediates **3(6,1−4)**, we observed spontaneous cyclization to 3,3a-dihydropyrrolo[1,2-*a*]quinoxaline-1,4(2*H*,5*H*)-diones **12** (Scheme 4).

Scheme 4. Synthesis of 3,3a-Dihydropyrrolo[1,2-*a*]quinoxaline-1,4(2*H*,5*H*)-diones 12



Synthesis of compounds **4(1,1)**,[8] **4(2,1)**,[9] **5(7,1)**,[10] and **12(6,3)**[11] using different synthetic strategies already has been reported.

Reduction of the nitro group in 2-((2-nitrophenyl)amino)-acetates triggers spontaneous cyclization to dihydroquinoxalinones.[2,3] Thus, when the 2-((2-nitrophenyl)amino)acetate is attached to the resin via an ester bond and the nitro group is reduced, the target compound is released from the resin into a solution containing the reducing agent, typically tin(II) chloride in DMF. The product has to be isolated from this complex mixture as reported, for example, in ref 6. On the other hand, the amide linker allows reduction of the nitro group without spontaneous release of product. Thus, the resin can be thoroughly washed after reduction, and the product is released in a subsequent step. The purity of released target products is high, and it is comparable for both types of linkers.

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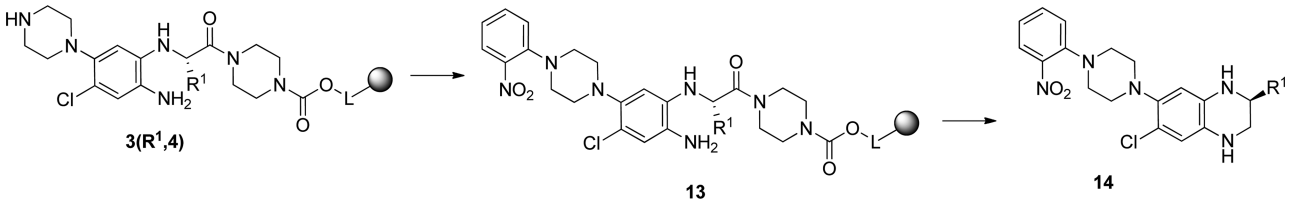
Scheme 5. On-Resin Transformation of Reduced Acyclic Precursor[a]



[a]Reagents and conditions: (i) 1-fluoro-2-nitrobenzene, DIEA, DMSO, rt, 2 days; (ii) 50% TFA, DCM, rt, 1 h.

An additional benefit of the amide linker is potential for on-resin modification of the linear precursor **3**, exemplified by synthesis of nitro derivative **13**. The resin-bound amine **3(R^1,4)** was reacted with 1-fluoro-2-nitrobenzene, and the target compound **14** was released from the resin by acid-mediated cyclative cleavage (Scheme 5).

In conclusion, a piperazine amide linker for cyclative cleavage from solid support was developed, and its use was portrayed in an efficient, traceless solid-phase synthesis of dihydroquinoxalinones. The key step of this synthetic route is cyclative cleavage from an amide rather than the typically used ester. Target dihydroquinoxalinones were not cleaved from the resin after reduction of the nitro group; they were released by acid- or microwave-mediated cyclative cleavage. The synthesis provided crude compounds of high purity and enabled the preparation of stable immobilized linear intermediates, and their cyclization was triggered by specific reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The details of the experimental procedures, the analytical data for the synthesized compounds, and copies of the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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