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A solid phase traceless synthesis of quinoxalinones

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Abstract

A solid-phase traceless synthesis of quinoxalinones in three combinatorial steps is reported. An aldehyde functionalized polystyrene resin was reductively alkylated by amino acid methyl esters, and then the resin bound secondary amines were reacted with *o*-fluoronitrobenzenes. The resulting *o*-nitroanilines were reduced by tin chloride to the dianilines, which spontaneously cyclized. The amide nitrogen of the dihydroquinoxalinones obtained was alkylated by alkyl halides. After cleavage from the resin, the dihydroquinoxalinones were air oxidized to quinoxalinones.

We have recently described a solid-phase traceless synthesis of benzimidazoles.[1] Our concept of traceless synthesis of heteroaromatic compounds was based on the acid liability of *N*-arylbenzylamines. An aldehyde linker was derivatized to form a resin bound *N*-alkyl-*N*-arylbenzylamine, allowing acidolytic cleavage of the carbon–nitrogen bond, and leaving the nitrogen with only a hydrogen atom on the target structure. In the synthesis of benzimidazoles we constructed a linear precursor on solid support followed by off resin cyclization. In this letter we describe a traceless synthesis of quinoxalinones based on the same concept. The combinatorial solid-phase synthesis of quinoxalinones has already been described.[2] However, these syntheses used linkers that leave a carboxylate functional group on all target compounds. As reported here, complete tracelessness was achieved by off resin air oxidation of dihydroquinoxalinones **6** to quinoxalinones **7**, leaving no residual linkage functionality at all.

The traceless synthesis of quinoxalinones followed the route shown in Scheme 1. The synthesis was developed on (4-(4-formyl-3-methoxyphenoxy)butyryl) AM resin (Novabiochem, Laufelfingen, Switzerland). The aldehyde resin **1** was reductively alkylated with an amino acid ester using the standard protocol developed by others[3] and us.[1] In order to evaluate the yield and purity of this initial step, we reacted the secondary resin-bound amine **2** with Fmoc-chloroformate (Fmoc-Cl). The resin-bound Fmoc protected amino acid ester was then cleaved by acid (TFA, gaseous HCl or HF) and analyzed.

The second combinatorial step involved nucleophilic fluorine displacement using *o*-fluoronitrobenzene with the polymer-supported secondary amine **2**. The purity and yield of the product *o*-nitroaniline was evaluated using reaction with Fmoc-Cl and cleavage by TFA. In order to optimize the nucleophilic displacement, we tested a less sterically demanding linker (4-(4-formylphenoxy)butyric acid),

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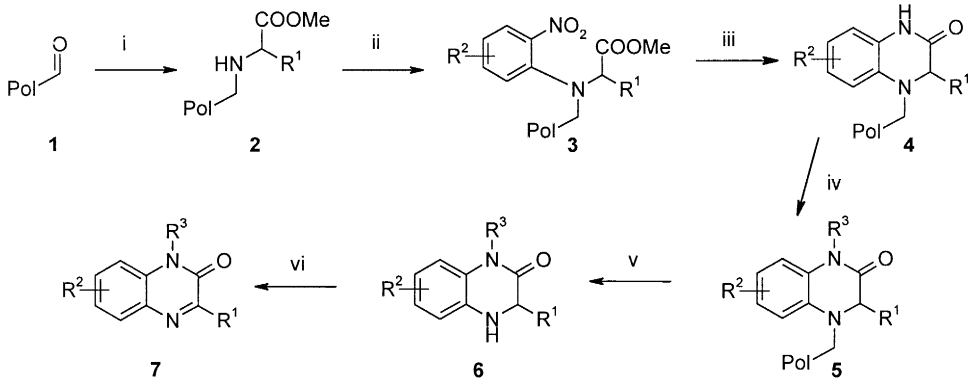


Scheme 1. Traceless synthesis of quinoxalinones. Reagents: (i) amino acid ester, $NaB(AcO)_3H$, DMF/AcOH; (ii) *o*-fluoronitrobenzene, DMSO, 75°C, 1–3 days, see Table 1; (iii) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (iv) 2-*t*-butyl-imino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), alkyl halide, DMF, rt, 2 h; (v) TFA or gaseous HCl or gaseous HF, rt, 2 h; (vi) air oxidation, MeOH, rt, overnight

several solid supports (polystyrene resin, Tentagel, Chiron's crowns), and various solvents (DMF, *N*-methylpyrrolidinone (NMP), DMSO, THF, alcohols, ionic liquid). We did not observe any substantial differences on the rate of nucleophilic substitution with solid support or linker. The best conversion was observed in DMSO at 75 to 90°C, with premature cleavage from the resin observed at higher temperatures. Typical results are given in Table 1.

Table 1
Reaction of resin-bound amino acid esters with 2-fluoronitrobenzenes

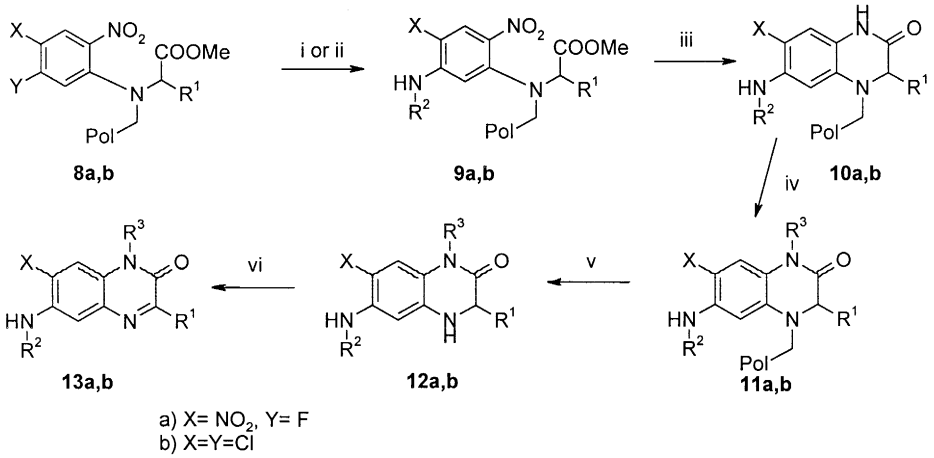
Entry	Amino acid	2-Fluoronitrobenzene	Time	Temperature	Conversion
1	Gly	4-CF_3	1 day	25 °C	50 %
2	Gly	4-CF_3	1 day	75 °C	>99 %
3	Gly	3,4-diCl	1 day	75 °C	90 %
4	Leu	4-CF_3	1 day	75 °C	8 %
5	Ala	4-CF_3	3 days	75 °C	65 %
6	Leu	4-NO_2	3 days	75 °C	77 %
7	Lys	4-NO_2	3 days	75 °C	84 %
8	Val	4-NO_2-5-F	3 days	75 °C	90 %

The percent conversion varies with the α-amino acid side-chain and the additional substituents on the *o*-fluoronitrobenzenes. Reactivity is affected by the reduced nucleophilicity of an amino group alpha to the electron-withdrawing carboxylic ester as well as by steric factors. The yields with amino acids having bulkier side-chains (Phe, Ile) or *o*-fluoronitrobenzenes with no additional strong electron withdrawing substituents often was less than 10%. Because neither TFA nor HF cleaves the unarylated amino acid ester **2** from the solid support, incomplete reaction reduces the overall yield but does not affect the purity of the final product.

The nitro group of the resin-bound *o*-nitroaniline **3** was reduced by 2 M 99.99% grade tin(II) chloride dihydrate solution in NMP degassed by bubbling argon, as recommended by Morales et al.[2b] The reduction was complete in 2 h and the reduced intermediate spontaneously cyclized to dihydroquinoxalinone **4**. During the 2 h reduction of several dinitro substituted fluorobenzenes (2,4-dinitrofluorobenzene and 1,5-difluoro-2,4-dinitrobenzene) only the nitro group *ortho* to the amino substituent was reduced.

Because the number of commercially available *o*-nitrofluorobenzenes is limited, the diversity of quinoxalinones was extended as shown in Scheme 2. We substituted the remaining fluorine or chlorine of the resin-bound fluorodinitroaniline **8a (**from 1,5-difluoro-2,4-dinitrobenzene) or dichloronitroaniline **8b**

(from 1,2-dichloro-4-fluoro-5-nitrobenzene) by amines to give **9a or 9b**, respectively. As expected, the replacement of the chlorine of **8b** was substantially slower than the fluorine of **8a** and required elevated temperature and longer reaction time.



Scheme 2. Extending the diversity of quinoxalinones. Reagents: (i) amine, DMF, rt, overnight; (ii) amine, DMSO, 75°C, overnight; (iii) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (iv) alkyl halide, BEMP, DMF, rt, 2 h; (v) TFA or gaseous HF or HCl, rt, 2 h; (vi) air oxidation, MeOH, rt, overnight

Dihydroquinoxalinones **6** were cleaved from the resin by TFA or gaseous reagents HCl or HF.[4] If TFA was used, it was evaporated in a stream of nitrogen, and the product extracted into MeOH. LC/MS analysis showed a molecular ion corresponding to the oxidized product quinoxalinone **7**. The ^{1}H NMR spectrum was also consistent with a quinoxalinone structure.[6] The oxidation of a dihydroquinoxalinone to quinoxalinone has already been described by Lee et al.,[2a] however, the dihydroquinoxalinone was the major product. In order to isolate the dihydroquinoxalinone, the product was cleaved by gaseous HCl and extracted directly into DMSO-d_6 under a nitrogen atmosphere. The ^{1}H NMR spectrum was consistent with the dihydroquinoxalinone.[5]

The last combinatorial step involved alkylation of the amide nitrogen of **4** by an electrophile. Several bases were tested and 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) in DMF provided the cleanest product, while KHMDS left some starting material (<10%). We have synthesized numerous target quinoxalinones in manually operated Domino Blocks.[5] Structures of representative examples are shown in Fig. 1. The purity of the products, evaluated by analytical HPLC,[7] was consistently high and ranged from 84 to 99% (Table 2).[8] Products were characterized by LC/MS data (Table 2) and NMR.[5]

In summary, we have developed a traceless solid-phase synthesis of quinoxalinones with three combinatorial steps. The synthetic concept, based on the use of an acid labile *N*-arylbenzylamine linker, allows for cleavage of a carbon–heteroatom bond followed by air oxidation of initially formed dihydroquinoxalinones, yielding target compounds with no trace of the linker.

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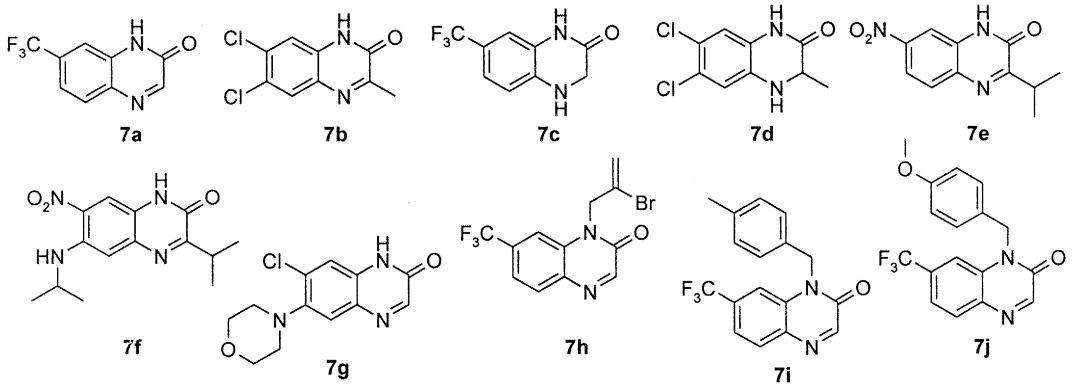

Fig. 1. Structure of representative quinoxalinones

Table 2
Purity and yield of traceless quinoxalinones

Compound	Rt (min)	Purity (%)	Yield (%)	mw	$[M+H]^+$
7a	4.8	87 %	80 %	214	215.1
7b	5.4	99 %	77 %	228	229.0
7c	4.9	nt	nt	216	217.2
7d	5.5	nt	nt	230	231.1
7e	5.4	84 %	76 %	233	234.2
7f	5.5	92 %	69 %	292	293.2
7g	4.0	89 %	53 %	279	280.3
7h	6.7	85 %	82 %	332	332.9
7i	6.9	89 %	91 %	318	319.0
7j	7.3	90 %	78 %	334	335.0

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5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of compound **7a**: δ 7.59 (s, 1H), 7.62 (d, 1H), 7.92 (d, 1H), 8.32 (s, 1H); compound **7b**: δ 2.65 (s, 3H), 8.16 (s, 1H), 8.39 (s, 1H); compound **7c**: δ 4.01 (s, 2H), 6.76 (d, 1H), 7.12 (d, 1H), 7.20 (s, 1H); compound **7d**: δ 1.25 (d, 3H), 4.04 (q, 1H), 6.87 (s, 1H), 7.09 (s, 1H); compound **7f**: δ 0.78 (d, 3H), 0.95 (d, 3H), 1.22 (d, 3H), 1.24 (d, 3H), 3.65 (m, 1H), 3.88 (m, 1H), 7.38 (s, 1H), 7.60 (s, 1H); compound **7g**: δ 2.97 (m, 4H), 3.74 (m, 4H), 7.33 (s, 1H), 7.49 (s, 1H), 8.15 (s, 1H); compound **7h**: δ 5.22 (s, 2H), 5.71 (s, 1H), 5.95 (s, 1H), 7.72 (d, 1H), 7.79 (s, 1H), 8.06 (d, 1H), 8.45 (s, 1H); compound **7i**: δ 2.21 (s, 3H), 5.47 (s, 2H), 7.11 (d, 2H), 7.15 (d, 2H), 7.65 (d, 1H), 7.70 (s, 1H), 8.04 (d, 1H), 8.46 (s, 1H); compound **7j**: δ 3.85 (s, 3H), 5.48 (s, 2H), 6.87 (d, 2H), 7.24 (d, 2H), 7.65 (d, 1H), 7.79 (s, 1H), 8.05 (d, 1H), 8.48 (s, 1H) ppm.
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7. Analytical gradient HPLC profile was run on a ProC18 4.6×50 mm analytical column (YMC, Wilmington, NC), gradient 0–70% of ACN in 7 min. The purity was estimated based on analytical traces at λ=280 nm.
8. Lower yield of compound **7g** was caused by partial cleavage during the tin(II) chloride reduction. The extent of cleavage increased with increased electron donating effect of substituent R^2 and was also observed e.g., when 2-fluoronitrobenzene, 3-fluoro-4-nitrotoluene, 2,5-difluoronitrobenzene, or 1-bromo-4-fluoro-3-nitrobenzene were used in the second combinatorial step. More acid-stable 4-(4-formylphenoxy)butyryl resin prevented premature loss of the product.