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A solid-phase traceless synthesis of tetrahydroquinoxalines

Viktor Krchňák,* Jennifer Smith and Josef Vágner

SIDDCO, 9040 South Rita Rd., Tucson, AZ 85747, USA

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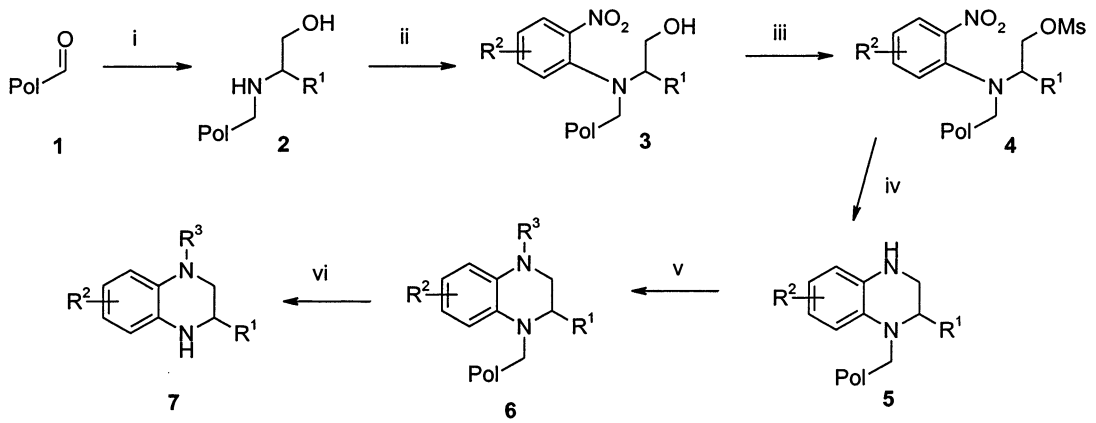
Abstract—A solid-phase traceless synthesis of tetrahydroquinoxalines with three combinatorial steps is reported. An aldehyde functionalized polystyrene resin was reductively aminated by amino alcohols, and then the resin bound secondary amines were reacted with *o*-fluoronitrobenzenes. The hydroxy group was mesylated and the nitro group was reduced by tin(II) chloride to the anilines, which spontaneously cyclized. The secondary aniline nitrogen of the resulting tetrahydroquinoxalines was further derivatized with acyl chlorides and isocyanates. After acidolytic cleavage from the resin, tetrahydroquinoxalines with three points of diversity were obtained.

We have recently described a solid-phase traceless synthesis of benzimidazoles,[1] quinoxalinones,[2] and 2-arylaminobenzimidazoles.[3] Our strategy for traceless synthesis of nitrogen-containing heteroaromatic compounds is based on the acid lability of *N*-arylbenzylamines. An aldehyde linker is derivatized to form a resin bound *N*-alkyl-*N*-arylbenzylamine, allowing acid 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 the solid support followed by off-resin cyclization, while the traceless synthesis of quinoxalinones included on-resin cyclization. In this letter we wish to report the traceless solid-phase synthesis of tetrahydroquinoxalines based on the same concept. To our knowledge, combinatorial solid-phase synthesis of tetrahydroquinoxalines has not yet been reported.

The individual steps of the traceless synthesis of tetrahydroquinoxalines are shown in Scheme 1. The key step is the formation of the heterocyclic six-membered ring via nucleophilic displacement of the mesylate by the aniline nitrogen. The nitro group of the *o*-fluoronitrobenzene serves two functions. It activates the aromatic ring for the nucleophilic substitution by



Scheme 1. Traceless synthesis of tetrahydroquinoxalines. Reagents: (i) amino alcohol, $NaB(AcO)_3H$, DMF/AcOH; (ii) *o*-fluoronitrobenzene, DMSO, 75°C, 16 h; (iii) MsCl in pyridine or MsCl, proton sponge in DCM, rt, 1 h; (iv) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (v) acyl chlorides, anhydrides or isocyanates in DCM or NMP, 16 h; (vi) TFA or gaseous HF, rt, 2 h.

* Corresponding author. Tel.: 520-663-4001; fax 520-663-0795; e-mail: krchnak@siddco.com

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resin-bound amines, and it serves as a precursor for the nucleophilic amino function while the hydroxy group is converted to a mesylate.

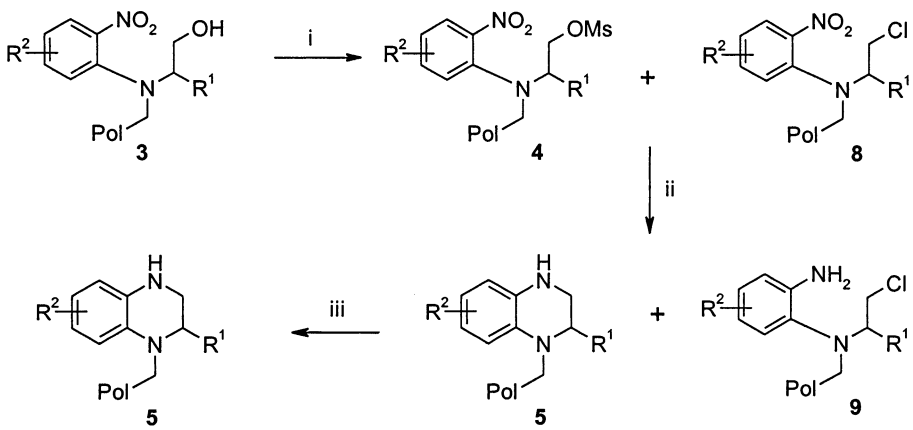
The synthesis was developed on (4-(4-formyl-3-methoxyphenoxy)butyryl) AM resin (Novabiochem, Laufelfingen, Switzerland). Resin **1** was reductively alkylated with a beta-amino alcohol (except ethanolamine, racemic amino alcohols were used) using the standard protocol developed by others[4] and ourselves.[1] Analogous to our previous work,[1,2] the yield and purity of this initial step was evaluated after the resin-bound secondary amine **2** was reacted with 9-fluorenylmethyloxycarbonyl-chloroformate (Fmoc-Cl). The resin-bound Fmoc protected amino alcohol was then cleaved by TFA and analyzed. The HPLC traces showed two peaks, the major one corresponding to the *N*-Fmoc derivative, the minor with a longer retention time belonging to the TFA ester of the product. At this time, we did not address the racemization during reductive alkylation. In an analogous case, Boojamra et al.[5] minimized the racemization of amino acid esters during on-resin reductive amination by adding the reducing agent and the amino acid ester to the aldehyde resin at the same time.

The second combinatorial step involved nucleophilic fluorine displacement using *o*-fluoronitrobenzenes with the polymer-supported secondary amine **2**. Typical reaction conditions involved 16 h reaction in DMSO at elevated temperature (75°C). Higher temperature or longer reaction time caused *O*-arylation. The nucleophilic substitution was not complete when *o*-fluoronitrobenzenes that lack an electron withdrawing substituent were reacted with substrates having a bulky R^1 substituent (e.g. phenylalaninol). The purity and yield of the product *o*-nitroaniline was evaluated after reaction with Fmoc-Cl and cleavage by TFA.

In order to close the six-membered ring, the hydroxy group was reacted with mesyl chloride (MsCl) to form a good leaving group. The reaction with MsCl and DIEA as a base is very sensitive to temperature, and the reaction has to be carried out at a temperature below 0°C. The very reactive sulfene, formed instantly after mixing the MsCl with a solution of DIEA, decomposes at room temperature before it can mesylate the hydroxy group. In order to make the reaction conditions amenable to synthesis of sizable libraries where a large number of reaction vessels has to be handled at the same time, we successfully used pyridine or proton sponge in DCM. When the reaction was carried out at room temperature for an extended period of time (2 h), the mesylate was partially converted to a chloro derivative **8** (Scheme 2). The amount of the chloro derivative **8** also largely depends on the R^2 substituent. However, the chloro derivative **8** was also cyclized at elevated temperature to the target tetrahydroquinoxaline **5** after reduction of the nitro group.

The nitro group of the resin-bound *o*-nitroaniline **4** was reduced by 2 M tin(II) chloride dihydrate solution in *N*-methylpyrrolidone (NMP) 'degassed' by argon, as recommended by Morales et al.[6] The reduction was complete in 2 h and the reduced intermediate spontaneously cyclized to tetrahydroquinoxaline **5**. It is interesting to mention that only the intermediate **4** prepared with ethanolamine (i.e. where $R^1 = H$) did not cyclize spontaneously, and after 2 h under the reducing conditions, ~20% of the mesylate was still present. Heating the resin bound intermediate to 45°C in NMP overnight completed the cyclization. These conditions were also employed when the intermediate after mesylation contained the chloro derivative **9**.

In order to increase the diversity we included the third combinatorial step that involved derivatizing the tetrahydroquinoxaline scaffold at the aniline nitrogen. Various methods were applied including acylation, alkylation and urea formation. We typically use gaseous HF or TFA for cleavage of the target compounds from acid labile linkers. However, the acylated tetrahydroquinoxalines were cleaved by TFA since the gaseous HF partially cleaved the acyl group. We have synthesized numerous target tetrahydroquinoxalines using manually operated Domino Blocks.[7] Structures of



Scheme 2. Formation of chloro derivative **8** and its cyclization to tetrahydroquinoxalines. Reagents: (i) MsCl/proton sponge, DCM, rt; (ii) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (iii) NMP, 1% DIEA, 45°C, 16 h.

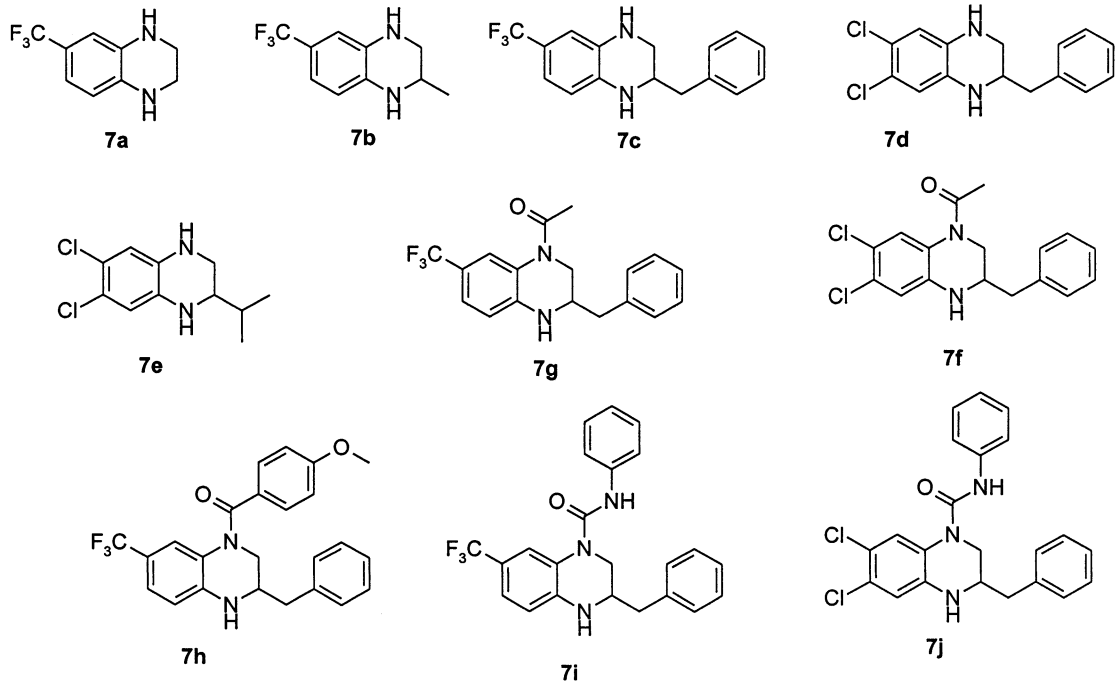


Figure 1. Structure of representative tetrahydroquinoxalines.

Table 1. Purity and yield of tetrahydroquinoxalines

Compound	Rt (min)	Purity (%)	Yield (%)	Mw	$[M+H]^+$
7a	3.6	85	79	202	203.1
7b	4.4	84	86	216	216.1
7c	7.2	87	91	292	292.2
7d	7.2	87	76	292	293.2
7e	6.7	84	88	244	245.1
7f	7.5	95	83	334	335.0
7g	7.1	94	79	334	335.1
7h	8.6	91	81	426	427.1
7i	8.0	89	96	411	412.1
7j	8.4	85	93	411	412.1

representative examples are shown in Fig. 1. The purity of the products, evaluated by analytical HPLC,[8] was consistently high and ranged from 84 to 95% (Table 1). Products were characterized by LC/MS data (Table 1) and NMR.[9]

In summary, we have developed a traceless solid-phase synthesis of tetrahydroquinoxalines involving three combinatorial steps. The synthetic strategy, based on the use of an acid labile *N*-arylbenzylamine linker, allows for cleavage of a carbon–nitrogen bond, yielding target tetrahydroquinoxalines with only a hydrogen atom at the original position of the linker.

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7. Domino Block (Torviq, Tucson, AZ, www.torviq.com) is a simple manual solid-phase synthesizer that allows parallel synthesis of up to 48 compounds using plastic syringes equipped with a frit as reaction vessels. Krchňák, V.;

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8. Analytical gradient HPLC profile was run on a ProC18 4.6×50 mm analytical column (YMC, Wilmington, NC), 7 min gradient 0–70% of ACN in water containing 0.05% TFA. The purity was estimated based on analytical traces at $\lambda = 254$ nm.
9. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of compound **7a** δ 3.28 (q, 2H, $J_1 = 3.2$ Hz, $J_2 = 11$ Hz), 3.39 (m, 2H), 6.52 (d, 1H, $J = 8$ Hz), 6.75 (s, 1H), 6.77 (d, 1H, $J = 8$ Hz); compound **7b** δ 1.12 (d, 3H, $J = 6$ Hz), 2.84 (q, 1H, $J_1 = 8$ Hz, $J_2 = 11$ Hz), 3.30 (q, 1H, $J_1 = 3$ Hz, $J_2 = 11$ Hz), 3.41 (m, 1H), 6.55 (d, 1H, $J = 8$ Hz), 6.78 (s, 1H), 6.80 (d, 1H, $J = 8$ Hz); compound **7c** δ 2.83 (q, 1H, $J_1 = 8.5$ Hz, $J_2 = 14$ Hz), 2.89 (q, 1H, $J_1 = 8.5$ Hz, $J_2 = 19$ Hz), 3.01 (q, 1H, $J_1 = 4.8$ Hz, $J_2 = 13$ Hz), 3.27 (q, 1H, $J_1 = 2$ Hz, $J_2 = 12$ Hz), 3.88 (m, 1H), 6.94 (d, 1H, $J = 9$ Hz), 7.24 (m, 3H), 7.31 (d, 2H, $J = 6$ Hz), 7.34 (d, 1H, $J = 9$ Hz), 7.38 (s, 1H). All compounds were measured as TFA or HF salts.