Solid Phase Synthesis of Quinoxalines[1]

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Abstract: A versatile method for the solid phase synthesis of quinoxalines has been developed. Polymer-linked 2-nitrophenyl carbamate is treated with α-bromoketones followed by reduction of the nitro group, which underwent spontaneous intramolecular cyclization to afford polymer bound quinoxalines. Finally acidolytic cleavage gave the desired compounds via aerial oxidation in high yields and good purities.

Key words: combinatorial chemistry, solid-phase synthesis, heterocyclic, cyclization, quinoxaline

In recent years solid phase synthesis of combinatorial libraries has emerged as a powerful tool for accelerating lead discovery in pharmaceutical research. This offers the opportunity of synthesizing compounds via novel routes, thereby providing structures with high chemical diversity. Intense synthetic efforts, and different synthetic approaches have been reported for several pharmacologically active heterocyclic systems.[2]

Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as Echinomycin, Levomycin and Actinoleutin[3,4] that are known to inhibit growth of Gram-positive bacteria and are active against various transplantable tumors.[5] In addition quinoxaline derivatives are also associated with a wide spectrum of biological activities ranging from anthelmintic and anticancer[6] to antimicrobial, antifungal, and antidepressant.[7,8] Surprisingly, despite being an interesting class of compound, its synthesis on solid phase has not yet been well established though few reports dealing with the solid phase synthesis of quinoxalinones[9] and tetrahydro quinoxalines[10–13] have been reported. The solid phase synthesis for quinoxaline, described by Wu et al.,[14] deals with its synthesis on Syn-Phase Lanterns, however, in their method quinoxalines were obtained predominantly as a mixture of two isomers. While the manuscript was under preparation, a paper by Mantellini et al. appeared dealing with the solid phase synthesis of quinoxaline from N=N-polymer bound 1,2-diaza-1,3-butadiene but the yield of the reaction were in the range of 15–31% only.[15] The work is based on their previous studies involving synthesis of quinoxaline both on solid phase as well as in solution phase.[16] Here we wish to report an efficient methodology for the solid phase synthesis of isomerically pure quinoxalines of high purity. To our knowledge this is the first report of synthesis of quinoxalines on solid phase. The solid phase synthesis of quinoxalines is outlined in Scheme 1 (Route A and B).

Monitoring the progress of reactions on solid phase by single bead FTIR and cleavage of numerous 2–5 mg of resin bound samples with subsequent LC-MS analysis of the resultant products accompanied each step during optimization of the reaction conditions. The final compounds were subjected to purification using high throughput LC-MS (Lachrom 8000; Merck) and characterized by ^{1}H NMR.

In the first step, *o*-nitrophenylisocyanate was loaded on to the Wang resin [Copolymer (styrene–1%DVB) Novabiochem, bead size 200–400 mesh; 1.13 mmol/g)] in the presence of triethylamine to get immobilized carbamates **1**. The polymer bound carbamate was characterized by SBFTIR microscopy, which showed complete disappearance of O–H stretch and the appearance of C=O at 1727 cm^{-1} and N=O stretch at 1558 cm^{-1}. The loading of *o*-nitro phenyl isocyanate was determined using HPLC and was found to be 80%. Alternatively, carbamates **1** can be also generated using either 4-nitrophenyl chloroformate and *o*-nitroaniline or by treating *o*-nitroaniline with Wang resin bound chloro carbamate.[17,18] After loading, the unreacted free hydroxyl groups of Wang resin were capped with acetic anhydride/triethyl amine in dicholoromethane. This was followed by treatment of **1** with α-bromoketones to afford N-alkylated carbamates **2** in quantitative yields. The reactions were efficiently performed in DMF by the activation of carbamate NH with NaH followed by addition of α-bromoketones and heating at 80 °C for 16 hours.[19,20] The completion of the reaction was confirmed by increased sharpness and shift in C=O stretch from 1727 cm^{-1} to 1705 cm^{-1}. The N-alkylated carbamates were cleaved from the resin and purified on highthroughput LCMS using 10 X 50 mm C_{18} reverse phase column and a gradient of MeOH–H_2O as mobile phase. The compounds were characterized by ^{1}H NMR.

The reduction of nitro group by treating **2** with 2 M $SnCl_2 \cdot 2H_2O$ in DMF at 60 °C followed by acidolytic cleavage gave quinoxaline **5** in high yield and purity (Route A). Absence of peak in ^{1}H NMR corresponding to the methylene protons and a strong singlet around 9.3–9.6 ppm ruled out the possibility for any existence of 3-subtituted-1,2-dihydro-quinaxoline. Further formation of 3-subsituted 1,2-dihydro quinoxaline, *N*-oxide or its tautomeric form could not be seen in the LCMS profile of the crude products. Thus formation of **5** may have occurred

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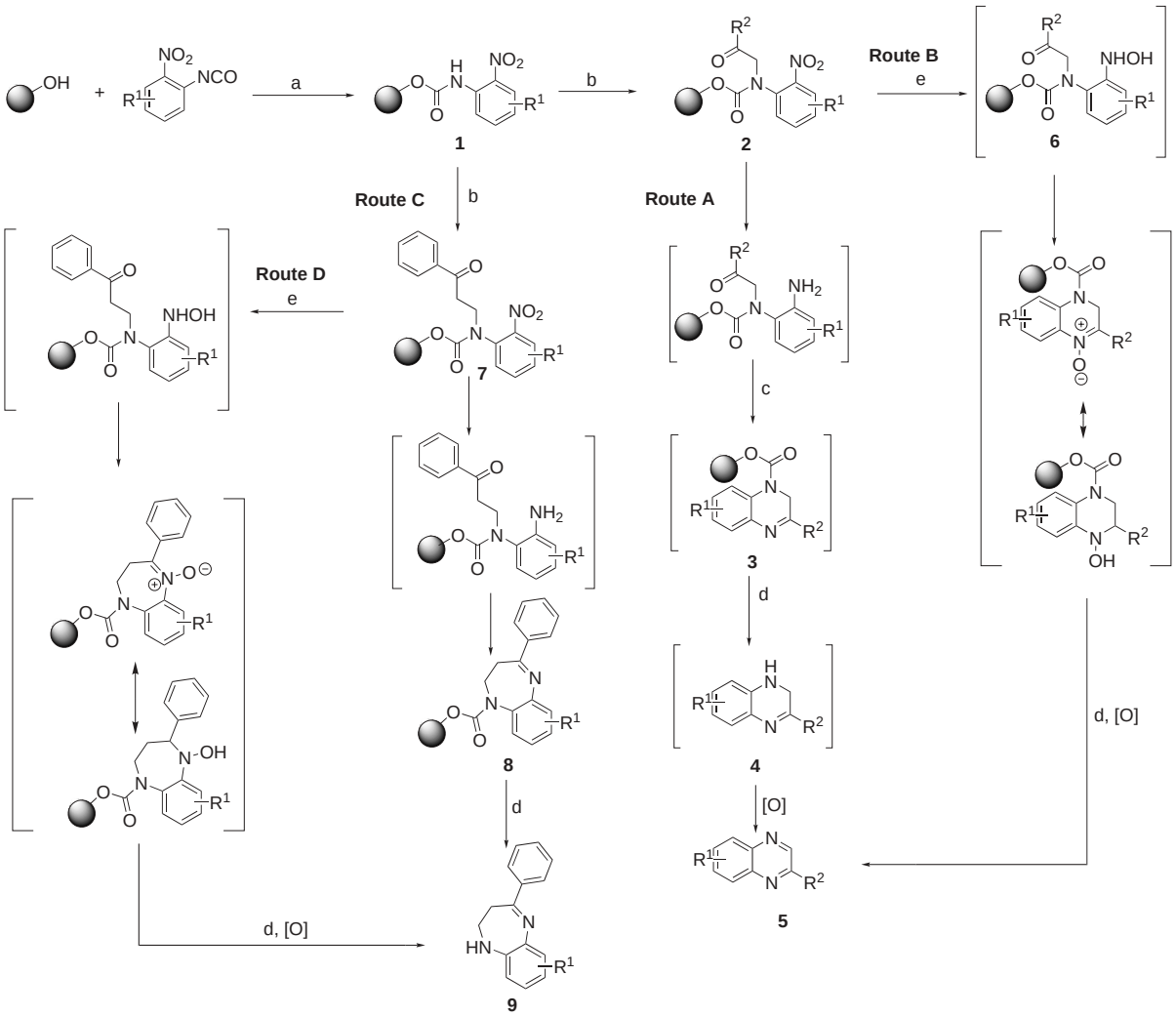

Scheme 1 *Reagents and conditions:* a) *o*-Nitrophenyl isocyanate, toluene, 100 °C, 16 h; acetic anhydride, Et_3N, CH_2Cl_2, 2 h; b) α-bromo ketone/chloropropiophenone, NaH, dry DMF, 80 °C, 16 h; c) 2 M $SnCl_2 \cdot 2H_2O$ in DMF, 60 °C, 6 h; d) 50% TFA/ CH_2Cl_2, 2 h; (e) Et_3N, PhSH, $SnCl_2$, r.t., 2 h.

via aerial oxidation of **4** to attain aromaticity. Such an aerial oxidation on solid phase leading to aromatization has been reported earlier by Wu et al.[14]

Another plausible mechanism may be cyclization at the hydroxylamine stage formed as an intermediate during the reduction of the nitro group. In order to establish the feasibility, the reduction was performed under basic condition using Et_3N/PhSH/$SnCl_2$ (Route B), which is known to produce hydroxylamine instead of primary amines.[21] Even under this condition the product obtained after acidolytic cleavage was found to be the desired compound **5** instead of any *N*-oxide or its tautomeric form. This led to the conclusion that even if some percentage of cyclization might have occurred during the reduction of nitro group by 2 M $SnCl_2$ via hydroxylamine intermediacy, it will ultimately undergo deprotection/dehydration to yield quinoxaline **5**. Formation of **5** gets further support from the fact that N-alkylation of carbamate **1** using chloropropiophenone instead of phenacyl bromide resulted in a 7-membered structure benzodiazepine (Scheme 1) without undergoing any dehydrogenation (based on Hueckel rule). The reduction of nitro group of **7** either by 2 M $SnCl_2 \cdot 2H_2O/CH_2Cl_2$ (Route C) or by Et_3N/PhSH/$SnCl_2$ (Route D) followed by acidolytic cleavage resulted in 4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (**9**) under both the conditions.[22] The intermediate compound 3-(2-nitro-phenylamino)-1-phenyl-propan-1-one obtained after the acidolytic cleavage of resin **7** and the final compound **9** was purified and characterized using highthroughput LC-MS and ^1H NMR respectively. Interestingly, a careful survey of the literature revealed that this is the first report for the synthesis of benzodiazepines on solid phase, though synthesis pertaining to the related class of compounds such as 1,4-benzodiazepine-2-one, 1,5-benzodiazepine-2-one, and 1,4-benzodiazepine-2,5-dione have been extensively studied.[23–25] Different chloropropiophenones and isocyanates derivatives can be used to build large library of this biologically important pharmacophore.

Table 1 Purity and ESMS of Mini Library of Quinoxalines

Compound No.	R^1	R^2	ESMS $(M + H)^+$	T_R (min)[b]	Yield[a]/ Purity (%)
5a	H	Phenyl	207.2	20.4	78/92
5b	H	4-Fluoro phenyl	225.2	20.3	72/75
5c	H	4-Bromo phenyl	287.3	20.8	70/80
5d	H	4-Methoxy phenyl	237.4	20.6	73/93
5e	H	4-Chloro phenyl	241.7	21.1	70/79
5f	Cl	Phenyl	241.4	23.7	72/87
5g	Cl	4-Methoxy phenyl	271.5	23.5	76/82
5h	Cl	4-fluoro phenyl	259.7	22.5	70/72
5i	Cl	4-bromo phenyl	321.4	22.2	71/76
5j	Cl	4-chloro phenyl	275.4	23.4	69/71

[a] Crude yields based on weight of cleaved compounds.
[b] Analysis of crude products was carried out on Agilent liquid chromatograph using a 5 μm, 4.8 × 150 mm C_{18} reverse phase column with a linear gradient 0–100% MeCN in H_2O (v/v) over 25 min. The flow rate was 1.0 mL/min, and UV detection at 220/254 nm.

To investigate further the scope and limitation of our strategy depicted in Scheme 1 (Route A) for quinoxaline **5**, we synthesized a mini library of 14 compounds using 7 different α-bromoketones and two isocyanates (Table 1).

The compounds were obtained in good yields with purities ranging from 70% to 93% except for 2,4-dichloro and 3,4-dichlorophenacyl bromides, which failed to give desired compounds. The final compounds were characterized using LC-MS and ^{1}H NMR.[26]

In summary we have for the first time developed a straightforward, isomerically pure approach for the solid phase synthesis of isomerically pure quinoxalines and benzodiazepine from polymer bound *o*-nitro phenyl carbamate. It can be successfully used for the generation of large libraries of quinoxalines using an automated synthesizer.

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(22) **General Experimental Procedure for 5 and 9**: To the 100 mg of Wang resin (1.13 mmol/g) in 1mL dry toluene was added *o*-nitrophenyl isocyanate (5 equiv, 1.13 mmol) and 78.7 μL of Et_3N (10 equiv, 0.565 mmol). The reaction mixture was stirred at 100 °C for 16 h. Finally the resin was filtered and washed with with DMF (3 × 2 mL), MeOH (3 × 2 mL), CH_2Cl_2 (3 × 2 mL), and Et_2O (3 × 2mL) and dried in vacuo to get resin bound *o*-nitrophenyl carbamate **1**. To the resin **1** in 1 mL of dry DMF was added 12.4 mg of NaH (5 equiv, 0.565 mmol) and reaction was allowed to stir at 35 °C for 90 min. Substituted phenacyl bromide/ chloropropiophenone was added (10 equiv, 1.13 mmol) to the above reaction mixture and the reaction was allowed to stir at 80 °C for 16 h. Finally the solvent was drained and the resin was washed sequentially with DMF (3 × 2 mL), MeOH (3 × 2 mL), CH_2Cl_2 (3 × 2 mL), and Et_2O (3 × 2mL) and dried in vacuo to get **2** or **7**. To this was added either 1.5 mL of 2 M of $SnCl_2{\cdot}2H_2O$ in DMF or a mixture of 393.0 μL of Et_3N (25 equiv, 2.84 mmol,), PhSH (20 equiv, 2.26 mmol, 232.0 μl) and $SnCl_2$ (5 equiv, 0.564 mmol, 106.8 mg) in dry THF. For reduction under acidic condition the reaction mixture was stirred at 60 °C for 6 h whereas under basic condition it was shaken at r.t. for 2 h. Finally the resin was washed sequentially with DMF (3 × 2 mL), MeOH (3 × 2 mL), CH_2Cl_2 (3 × 2 mL), and Et_2O (3 × 2mL) and dried in vacuo to get the resin bound desired products **3** or **8**. The intermediate and final compounds were cleaved from the resin by 50% TFA in CH_2Cl_2 by shaking for 2 h. The filtrate was collected and evaporated to dryness. The residue was freeze dried after dissolving in *t*-BuOH/H_2O (4:1) to get the desired compounds.
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(26) **2-(2-Nitro-phenylamino)-1-phenyl-ethanone Trifluoroacetate** (cleaved product from resin **2**, R^1 = H, $R^2 = C_6H_5$): ESI-MS: 257.3 [M + H$^+$]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.7 (s, 2 H, CH_2), 6.71–6.84 (m, 2 H, Ar-H), 7.36–7.66 (m, 4 H, Ar-H) 8.05 (d, *J* = 6.9 Hz, 2 H, Ar-H), 8.24 (d, *J* = 8.4 Hz, 1 H, Ar-H), 8.91 (br s, 1 H, NH). Anal.

Calcd for $C_{14}H_{12}N_2O_3 \cdot CF_3COOH$: C, 51.90; H, 3.54; N, 7.57. Found: C, 51.78; H, 3.76; N, 7.38%.

3-(2-Nitro-phenylamino)-1-phenyl-propan-1-one Trifluoroacetate (cleaved product from resin **7**, R^1 = H): ESI-MS: 271.52 $[M + H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.41 (t, *J* = 13.5 Hz, 2 H, CH_2), 3.80 (br s, NH), 3.83 (t, *J* = 12.8 Hz, 2 H, CH_2), 6.65–6.79 (m, 1 H, Ar-H), 6.96 (d, *J* = 8.7 Hz, 1 H, Ar-H), 7.45–7.63 (m, 4 H, Ar-H), 7.99 (d, *J* = 8.1 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8.7 Hz, 1 H, Ar-H). Anal. Calcd for $C_{15}H_{14}N_2O_3 \cdot CF_3COOH$: C, 53.13; H, 3.93; N, 7.29%. Found: C, 53.42; H, 3.61; N, 7.33%.

2-Phenyl-quinaxoline 5a: ^1H NMR (300 MHz, DMSO-d_6): δ = 7.51–7.61 (m, 3 H, Ar-H), 7.83–7.91 (m, 2 H, Ar-H), 8.11–8.16 (m, 2 H, Ar-H), 8.34 (dd, *J* = 8.1, 1.3 Hz, 2 H, Ar-H), 9.50 (s, 1 H) Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58%. Found: C, 81.35; H, 5.01; N, 13.63%.

4-Phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine 9: ESI-MS: 223.32 $[M + H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.12 (t, *J* = 13.5 Hz, 2 H, CH_2), 3.25 (t, *J* = 12.8 Hz, 2 H, CH_2), 5.72 (br s, NH), 6.84–6.92 (m, 2 H, Ar-H), 7.04–7.24 (m, 5 H, Ar-H), 7.90 (d, *J* = 8.1 Hz, 2 H, Ar-H). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60%. Found: C, 81.25; H, 6.02; N, 12.52%.