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Solid-phase synthesis of quinoxalines on SynPhase™ Lanterns

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Abstract—A convenient and straightforward solid-phase synthesis of quinoxalines is described. A polymer-bound *o*-phenylenediamine was reacted with α-bromoketones in DMF at 60°C to give quinoxalines in good purity and yield after TFA cleavage. The quinoxalines were presumably formed via an initial nucleophilic substitution, followed by subsequent cyclization–oxidation. A small library of ten quinoxalines was prepared on SynPhase™ Lanterns using this simple one-pot procedure.

Quinoxaline derivatives have shown a broad spectrum of biological activities such as antibacterial and anti-inflammatory activity. In addition, quinoxaline derivatives have been evaluated as anticancer and anthelmintic agents.[1] Although there have been numerous publications on solution phase synthesis of quinoxalines,[1] and some reports on solid-phase synthesis of quinoxaline derivatives such as quinoxalinones[2] and tetrahydroquinoxalines,[3–8] it is rather surprising that solid-phase synthesis of quinoxalines has not been mentioned in the literature. Herein we wish to report the first solid-phase synthesis of quinoxalines, recently developed on SynPhase™ Lanterns.[9]

4-Fluoro-3-nitrobenzoic acid was attached to SynPhase Rink Lanterns[10] via a standard peptide coupling reaction using HOBt/DIC as coupling reagents. Substitution of the fluorobenzene **2** by an aqueous ammonia solution in 5% diisopropylethylamine (DIEA)/dimethylforamide (DMF) at 60°C for 5 h gave the corresponding *o*-nitroaniline **3** in greater than 97% purity, as judged by HPLC analysis of the cleaved compound. Reduction of the *o*-nitroaniline **3** (bright yellow Lanterns) with tin(II) chloride dihydrate at 25°C for 24 h led to *o*-phenylenediamine **4** (pale yellow Lanterns). It is worth noting that after the reduction, residual tin (or tin oxide) on Lanterns was removed by washing Lanterns with 20% H_2O/THF at 60°C.[11] Treatment of **4** with a solution of 0.25 M α-bromoacetophenone in DMF at room temperature for 16 h gave a mixture of quinoxaline isomers **8a** in moderate purity (59%). The quinoxalines **8a** are formed via a one-pot procedure, in which the amino group of **4** initially undergoes nucleophilic substitution on α-bromoacetophenone, followed by cyclization involving the remaining amino group, and final oxidation to give the quinoxaline isomers as shown in route **a**, Scheme 1. This one-pot procedure was optimized by alternating the concentration or equivalents of α-bromoacetophenone, reaction duration, reaction temperature and using DIEA as a base. The optimized reaction conditions for the one-pot quinoxaline formation involve Lantern-bound *o*-phenylenediamine **4** reacting with 2 equiv. of α-bromoacetophenone in DMF at 60°C for 4 h to give the quinoxaline **8a** in 86% purity (entry a, Table 1).[12] It is worth noting that addition of diisopropylethylamine as a base did not favor the reaction. We have also found that washing the Lanterns with hot methanol before cleavage removes small traces of DMF.[12]

In order to eliminate one of the quinoxaline isomers **8a**, it was hoped that *o*-nitroaniline **3** would undergo nucleophilic substitution, which would be followed by tin(II) reduction and subsequent cyclization–oxidation to give only quinoxaline **8a′** (Scheme 1, route **b**). Disappointingly, the nucleophilic substitution did not occur, even at high temperature (100°C). It is likely that the strong electron withdrawing *o*-nitro group results in poor nucleophilicity of the amino group.

We were also interested to see whether this one-pot procedure could be expanded to synthesize *N*-substituted 3,4-dihydroquinoxaline **14**. Thus, *N*-substituted *o*-nitroaniline **10** was prepared according to our previously published method,[13] and was converted to *N*-substituted *o*-phenylenediamine **11** using tin(II) chloride

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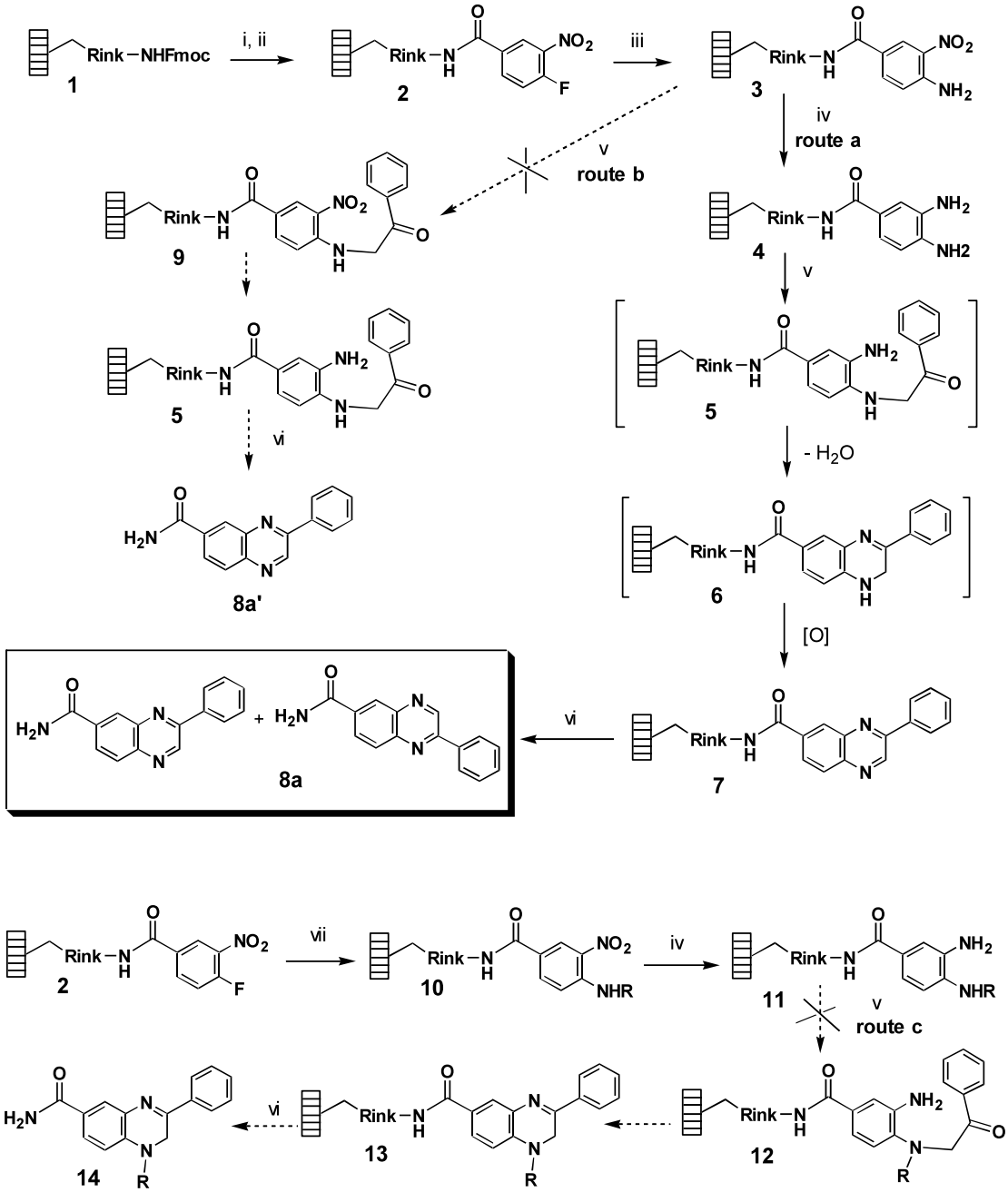


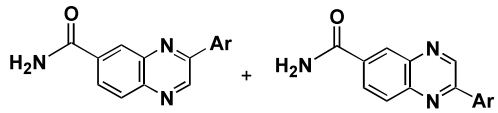
Scheme 1. *Reagents and conditions*: (i) 20% piperidine in DMF, rt, 40 min; (ii) 4-fluoro-3-nitrobenzoic acid, DIC, HOBt, DMF, rt, 16 h; (iii) 1.0 M NH_3 aqueous solution, 5% DIEA/DMF, 60°C, 5 h; (iv) $SnCl_2{\cdot}2H_2O$, NMP, rt, 24 h; (v) 2 equiv. α-bromoketones, DMF, 60°C, 4 h; (vi) 20% TFA/DCM, rt, 1 h; (vii) 0.5 M propylamine, 5% DIEA/DMF, 60°C, 5 h.

dihydrate. It was hoped that the secondary amine of **11** would preferably react with *o*-bromoacetophenone followed by cyclization involving the primary aniline to give the desired *N*-substituted 3,4-dihydroquinoxaline **14** (Scheme 1, route **c**). However, treatment of the *o*-phenylenediamine **11** with a solution of α-bromoacetophenone in DMF only led to an unidentified mixture.

Following the strategy described in Scheme 1 (route **a**), a small library of quinoxalines was prepared using the optimized one-pot procedure. Thus, ten commercially available α-bromoketones were used for preparation of the quinoxalines (**8a–j**). As expected, in all cases quinoxalines were obtained in good yield as a mixture of two isomers but free of side-products. The ratio of the quinoxaline isomers varies from 4:1 (entry d, Table 1) to 1:1 (entry j, Table 1), as determined by HPLC. All products were confirmed by ES LC-MS and selected samples gave satisfactory ^{1}H NMR spectra.[14]

In summary, we have developed a convenient and straightforward method for solid-phase synthesis of quinoxalines. To our knowledge, this method represents the first example of a solid-phase synthesis of quinoxalines.

Table 1. Analytical results[a] of the quinoxalines (**8a–j**)



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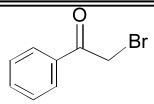
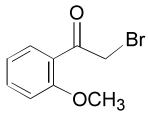
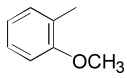
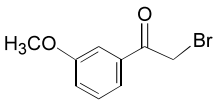
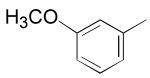
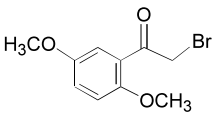
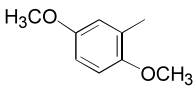
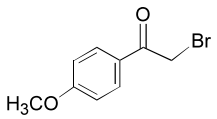
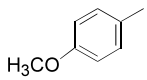
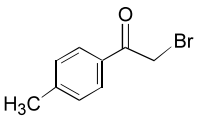
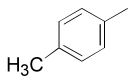
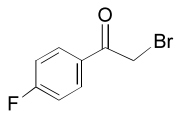
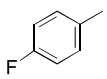
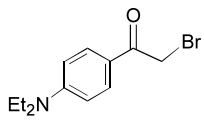
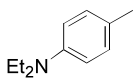
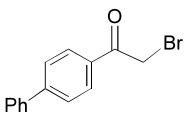
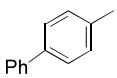
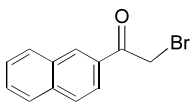
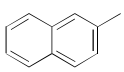
entry	α-bromoketone	Ar in quinoxalines (8a-j)	HPLC purity %	(M+H) (calculated)	(M+H) (found)
a			86 (39+47)	250	250
b			76 (22+54)	280	280
c			71 (41+30)	280	280
d			77 (16+61)	310	310
e			67 (49+18)	280	280
f			77 (49+28)	264	264
g			66 (46+20)	268	268
h			86 (25+61)	321	321
I			65 (45+20)	326	326
j			71 (33+38)	300	300

[a] Notes: (1) HPLC purity is the sum of quinoxaline isomers. (2) Crude yields are approximately 80%, based on weights of cleaved compounds.

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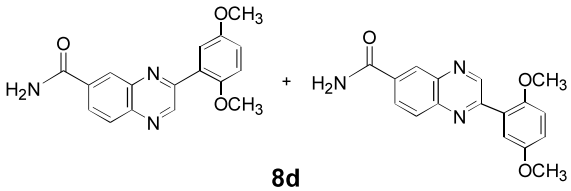
10. Product code: SPPSDRAM. SynPhase Lanterns are commercially available from Mimotopes Pty Ltd. See www.mimotopes.com.
11. A typical procedure for tin(II) reduction of aromatic nitro group on Lanterns: Each *o*-nitroaniline D-Series Lantern **3** was treated with 0.5 mL of a solution of tin(II) chloride dihydrate (2.0 M, 28 mol equiv.) in DMF at 25°C for 24 h. The reagent solution was decanted. The Lanterns were washed with DMF (3×3 min), 20% H_2O/THF (60°C, 3×30 min), MeOH (2×3 min) and DCM (2×3 min).
12. A typical procedure is as follows: Each *o*-phenylenediamine D-Series Lantern **4** was treated with 0.5 mL of a solution of α-bromoketone (0.15 M, 2 mol equiv.) in DMF at 60°C for 4 h. The reagent solution was decanted. The Lanterns were washed with DMF (3×3 min), MeOH (60°C, 4×3 min) and DCM (3×3 min), and air dried. Each Lantern was cleaved in a polypropylene tube with 0.7 mL of 20% TFA/DCM for 1 h. The Lantern was removed and the cleavage solution was evaporated. The residue was dissolved in 90% CH_3CN/H_2O for HPLC and MS analysis.
13. Wu, Z.; Rea, P.; Wickham, G. *Tetrahedron Lett*. **2000**, *41*, 9871.
14. For example, Compound **8d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.311 and 9.296, (1H, 2xs), 8.60 and 8.57 (1H, 2xs), 8.31 (1H, s, broad), 8.24–8.20 (1H, m), 8.12 (1H, d, $J=8.8$ Hz), 7.56 (1H, s, broad), 7.352 and 7.345 (1H, 2xs), 7.15 (1H, d, $J=8.8$ Hz), 7.09–7.07 (1H, m), 3.79 (3H, s), 3.74 (3H, s).



8d