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Solid-phase synthesis of isoquinolinones using Bischler–Napieralski cyclization

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Abstract—Isoquinolinone is a structural unit found in many natural products having various important biological activities. A traceless solid-phase synthetic approach has been developed to prepare isoquinolinone derivatives. This approach enables one to synthesize isoquinolinones having various moieties on benzene nuclei and also can produce derivatives with a proton on the amide nitrogen.

Combinatorial solid-phase synthesis has been recognized as one of the powerful tools for drug discovery in pharmaceutical industries. This technique facilitates the speedy availability of closely related analogues for activity evaluation.[1,2] Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as lead structures for the discovery of potential pharmacophores. In particular, isoquinolinones[3–8] are present in a large number of natural products that possess a broad spectrum of biological activities. Thalifoline, doryphorine,[9] ruprechstyril,[10] narciclasine,[11] pancratistatin and lycoricidine[12] are some of the important examples from this family. Many interesting syntheses involving either a construction or reactions of isoquinolinones are reported.[4,7,13–18] Considering the therapeutic value of such motifs in various bioactive molecules,[19] solid-phase syntheses of compounds containing similar moieties have attracted researchers.[6,20–25]

The retrosynthetic analysis of isoquinolinone template (Fig. 1) revealed two possibilities of disconnections. Either the bond between a carbonyl carbon and a nitrogen that is amide linkage (disconnection-I) or the bond between a carbonyl carbon and a benzene ring (disconnection-II) can be disconnected. The disconnection-I leaves a little flexibility to choose a starting material

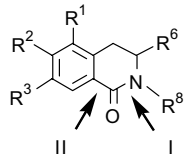

Figure 1.

and even the starting material is not readily available. However, the disconnection-II provides a wide choice for starting materials and various amino acids such as phenylethylamine, tyrosine and phenylalanine can be selected as precursors. Also, these starting materials are commercially available and inexpensive. Hence, it was preferred to follow the disconnection-II and use Bischler–Napieralski reaction for cyclization and co-comintant cleavage.

Bischler–Napieralski cyclization[26] is commonly used in solution synthesis of various biologically important compounds;[27–33] but has not been used on solid supports to synthesize isoquinolinones. In this reaction, the presence of an electron-donating group on aromatic ring in phenethylamides and carbamates is an essential precondition for cyclization using various reagents such as $POCl_3$, $SnCl_4$, BF_3 etherate, a mixture of $SnCl_4$ and $POCl_3$, PPA, Tf_2O, etc. Reported reagent viz. P_2O_5 in refluxing $POCl_3$[34] can cyclize substrates lacking electron-donating groups but can produce only N-alkylated isoquinolinones in good yields and not isoquinolinones having a proton on the amide nitrogen. Here we report the first

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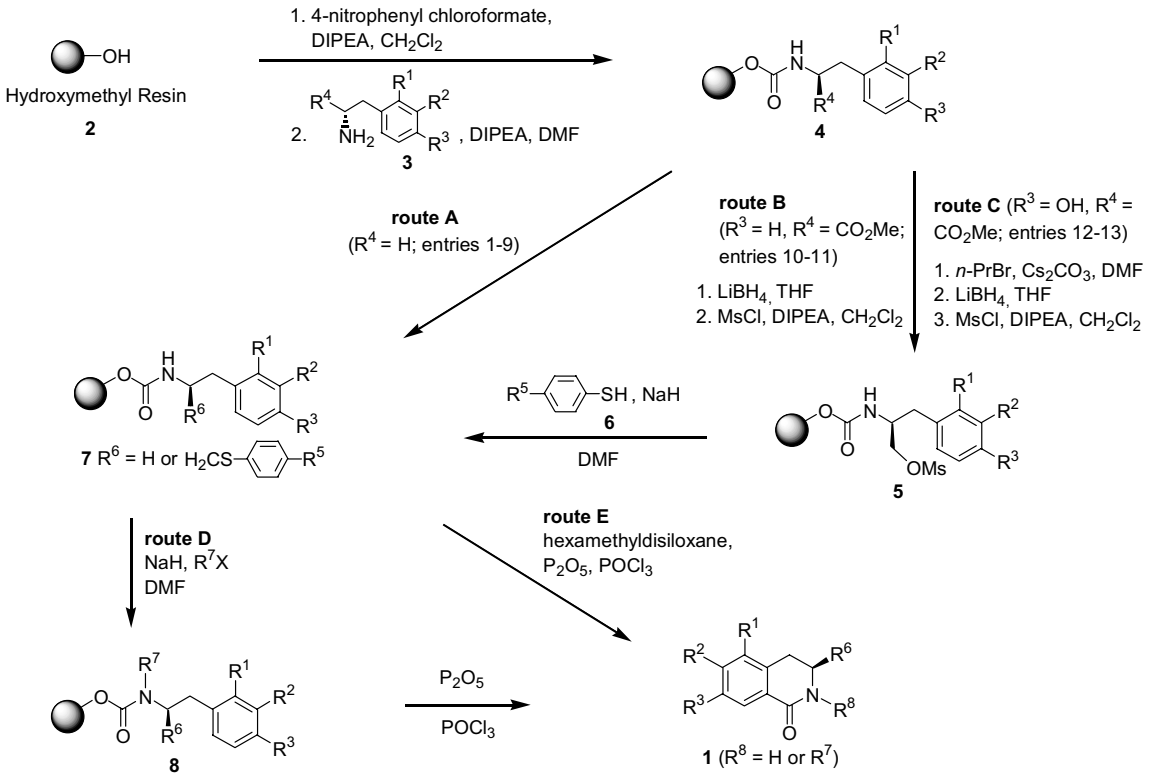
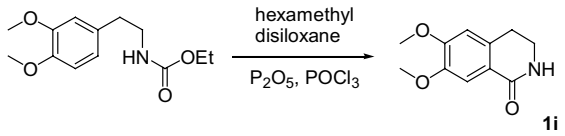


Scheme 1.

solid-phase synthesis of isoquinolinone derivatives having a proton on the amide nitrogen and electron-donating or -withdrawing groups on benzene nuclei.

In the present synthetic strategy (Scheme 1), hydroxymethyl resin (**2**) was used as a solid support because it can form carbamates, which are stable under acidic conditions required in Bischler–Napieralski cleavage. To begin, the resin **2** was activated by reacting with 4-nitrophenyl chloroformate[35,36] in the presence of diisopropylethylamine (DIPEA) and the activated resin was condensed with amines **3** to obtain carbamate resins **4**. Three different routes (route A, B, and C) were adopted to introduce threefold diversity on the core structure of isoquinolinones. In route A (entries 1–9), R^4 was retained as H ($R^4 = R^6 = H$ in compound **7**). In route B, R^4 was a methyl ester moiety, which was reduced (entries 10 and 11) to the corresponding alcohol. When the reduction using $NaBH_4$ did not go to the completion, another two combinations of reducing agents that is $NaBH_4$/LiCl and $NaBH_4$/LAH were tried. Both combinations were too strong to reduce the methyl ester selectively because the carbamate was affected. Finally, $LiBH_4$ in THF was the reagent of choice to give the corresponding alcohol by reducing the methyl ester selectively. The alcohol obtained was reacted with thiophenol to afford thioether through Mitsonobu coupling. But this attempt was not successful on solid supports. Hence, it was decided to transform the hydroxyl group to a better leaving group such as OMs or OTs. The yield of tosylate was low but the alcohol was derivatized to afford mesylate **5** using DIPEA with better yield.[37,38] The mesylate **5** was not stable to long time storage and had to be used immediately for the next step. In the third route, that is route C (entries 12 and 13), the hydroxyl group present at R^3 in resin **4** was derivatized to a *n*-propyl ether and then the methyl ester, similar to route B, was reduced to the corresponding alcohol. The resulting alcohol was mesylated to yield resin **5**. To obtain a *n*-propyl ether, a weak base K_2CO_3[39] in various solvents was used but it could not complete the conversion even when the reaction was repeated. After trying several bases, Cs_2CO_3[40] in DMF was found to be an effective choice. Further, mesylates **5**, obtained from both routes (route B and C) were reacted with thiol **6** using NaH in DMF to obtain thioethers **7**.[18]

Carbamate resins **7** obtained from the above three routes were, either after alkylation (route D) or directly (route E), subjected to cyclization and subsequent cleavage. In the route D, resin **7** was alkylated with various alkyl halides using NaH in DMF. This alkylation was found to be critically temperature dependent. Reaction at room temperature for 24 h did not afford complete alkylation and even after repetition. However, when a slightly elevated temperature (40 °C) was used, the reaction was completed after 24 h to yield the alkylated carbamate resin **8**. A Brucker AVANCE-500 MHz gel-phase NMR was used to check the completion of alkylation. Bischler–Napieralski cyclization[26] reaction was utilized to obtain the isoquinolinone ring and to simultaneously cleave products from solid supports. To affect cyclization through the route D, 5 equiv of P_2O_5 was used in 0.1 M of distilled $POCl_3$ at 80 °C.[34]



Scheme 2.

Unsubstituted carbamate resins **7** were cyclized and cleaved from solid supports through route E. As the above method did not give the desired product in good yield, route E was optimized in solution (Scheme 2). The cyclization in the solution using P_2O_5 and $POCl_3$ gave only 20% yield and also the use of either triflic anhydride/4-(N,N-dimethylamino)pyridine[41] or oxalyl chloride/$FeCl_3$[42] furnished very low yields. A new approach to temporarily protect the carbamate nitrogen with hexamethyldisiloxane in situ was adopted. Phosphorus oxychloride and hexamethyldisiloxane were used as a co-solvent system (1:1) with 5 equiv of P_2O_5. As shown in Scheme 2, this approach yielded the desired product **1i** in 81% yield. Further, this methodology was applied to cyclize and cleave isoquinolinones on solid supports in excellent yields (route E).[43] Representative products were prepared on solid supports in excellent yields and purities by the protocol described above and these results are summarized in Table 1. Each compound was fully characterized by ^1H, ^{13}C NMR and mass spectrometric techniques. There was a notable observation for entry 8. Along with the expected product, isomer **9** was also produced in 13% yield.

In conclusion, the present solid-phase synthesis is a traceless approach to 1,2,3,4-tetrahydroisoquinolinones. As per our knowledge, this is the first methodology, which introduces electron-donating and electron-withdrawing substituents at R^1 and R^3 positions on solid supports and also allows modifications at R^3 position as demonstrated by entries 12 and 13. Moreover, most of the presently reported methods produce isoquinolinones having an alkyl substituted nitrogen. This methodology facilitates solid-phase preparation of isoquinolinones having a hydrogen at R^8 position (on the nitrogen). Such proton may enhance interaction of a substrate with a receptor and thus this approach should find broad application in producing pharmaceutically important derivatives.

Acknowledgements

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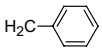
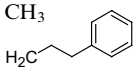
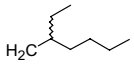
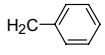
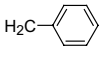
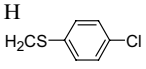
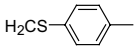
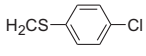
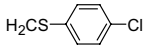
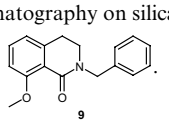
Table 1. Isoquinolinones generated on solid supports

Entry	1	R^1	R^2	R^3	R^6	R^8	Overall yields[a] (%)
1	**1a**	H	H	H	H	CH_3	74
2	**1b**	H	H	H	H		72
3	**1c**	H	OCH_3	OCH_3	H	CH_3	64
4	**1d**	H	OCH_3	OCH_3	H		61
5	**1e**	H	H	Br	H		74
6	**1f**	F	H	H	H	CH_2CH_3	67
7	**1g**	H	H	OCH_3	H		68
8	**1h**	H	OCH_3	H	H		52[b]
9	**1i**	H	OCH_3	OCH_3	H	H	82
10	**1j**	H	H	H		CH_2CH_3	74
11	**1k**	H	H	H		CH_2CH_3	63
12	**1l**	H	H	$O(CH_2)_2CH_3$		H	63
13	**1m**	H	H	$O(CH_2)_2CH_3$		CH_3	53

[a] Reported yields are isolated yields after flash chromatography on silica gel. The overall yields are based on the initial loading of the hydroxymethyl resin.

[b] Total yield: 65% (**1h**: 52% and it's isomer **9**: 13%). 
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43. General procedure for the traceless cleavage of resin-bound carbamate **7**: resin **7** (100 mg, 0.101 mmol) was treated with P_2O_5 (71.0 mg, 0.5 mmol) and hexamethyldisiloxane (0.5 mL, 2.3 mmol) in $POCl_3$ (0.5 mL) under an argon atmosphere. The mixture was agitated at 80 °C for 12 h, the reaction mixture was then quenched with ice-water and left to shake for 2 h. The suspension was neutralized to pH = 7 with KOH and the resin was collected by filtration. The resin was washed with EtOAc (3 mL × 3) and the filtrate was concentrated in vacuo. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by column chromatography, eluting with EtOAc/hexane (1:9) to afford compound **1i** (17.2 mg) in 82% yield: ^{1}H NMR in $CDCl_3$ (δ, ppm): 2.90 (t, 2H, J = 6.7 Hz), 3.53–3.61 (m, 2H), 3.90 (s, 6H), 6.40 (br s, 1H), 6.65 (s, 1H), 7.54 (s, 1H); ^{13}C NMR in $CDCl_3$ (δ, ppm): 28.01, 40.48, 56.06, 56.12, 109.58, 110.15, 121.39, 132.65, 148.04, 152.17, 166.55; HRMS calcd for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0894.