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Report

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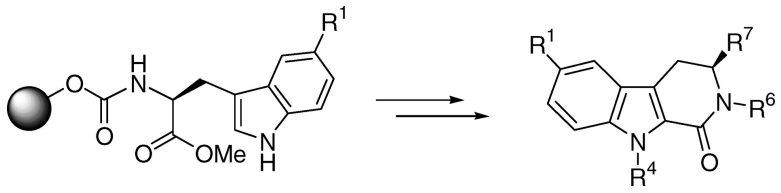

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Traceless Solid-Phase Synthesis of Carbolinones

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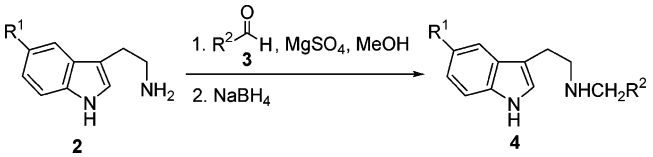
Introduction. The search for organic lead compounds as a part of drug discovery necessitates screening a large number of compounds.[1,2] Solid-phase synthesis is an effective tool to prepare libraries of drug candidates in a time- and cost-effective manner. Liquid-phase synthesis is also rapidly developing as a useful adjunct to the solid-phase technique.[3] We have developed a new methodology to synthesize carbolinones using soluble and insoluble polymer supports. Tetrahydro-β-carbolines are found abundantly in the plant kingdom, and many of them exhibit bioactivities.[4] β-Carbolinones, that is, 1-oxo derivatives of β-carboline, occurring in many natural products also possess significant bioactivities, such as affinity for the benzodiazepine receptor, antileukemic properties, and central nervous system depression.[5] Strychnocarpine, found in *Strychnos elaeocarpa* and *Strychnos floribunda*, contains the carbolinone moiety and is reported as a weak muscle relaxant and 5-hydroxytryptamine receptor stimulant.[6] Due to such a broad range of interesting activities, researchers are interested in the chemistry of β-carboline related derivatives in solution[4−8] as well as on solid supports.[9−15] Most of the reported solid-phase syntheses of carbolines leave residues on the final products. Moreover, syntheses of β-carbolinones on solid supports or in liquid-phase are not reported. We present here the first traceless solid- and liquid-phase methodology to prepare β-carbolinone derivatives (**1**) possessing four points of diversity.

Results and Discussion. Liquid-Phase Synthesis (Entries 1−6). The secondary amines **4** used in liquid-phase synthesis were obtained by a traditional solution reaction (Scheme 1) using reductive amination of compounds **2**, which were treated with aldehydes **3** in methanol in the presence of $MgSO_4$, and the resulting imine adducts were reduced with $NaBH_4$. This was to enhance the applicability of the present methodology by avoiding the potentially difficult alkylation of carbamates in liquid- or solid-phase synthetic sequence. However, some of primary amines **2** were alkylated by liquid- and solid-phase reactions, also (entries 1−4, 7−9 and 11−12 in Table 1). In liquid-phase synthesis (Scheme 2), a primary amine **2** or a secondary amine **4** was coupled to obtain carbamate **7** with a soluble resin—poly(ethylene glycol)monomethyl ether—of MW 5000 (MeO−PEG-OH) (**5**) which was activated by reacting with 4-nitrophenyl chloroformate (**6**).[16,17] The indole nitrogen in carbamate

Scheme 1



7 was difficult to alkylate selectively in the presence of unsubstituted carbamate nitrogen. The use of NaH either in dimethyl formamide (DMF)[18] or in dimethyl sulfoxide (DMSO)[19] gave adequate selectivity in solution. However, in liquid- and solid-phase synthesis, the selectivity was poor even when the solvent was changed to tetrahydrofuran (THF). Other reagents, such as Cs_2CO_3, CsOH, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), did not yield the desired product in good yields. After extensive trials, selective alkylation was achieved using potassium *tert*-butoxide in DMF to give resin **8**.[20] In this conversion, not only the proportion of reagents (alkyl halide/base, 1:2) but also the reaction time (15 min) was critical for the desired selectivity. After obtaining resin **8**, two routes (routes A and B) were followed. Route A was for the case in which R^3 was a hydrogen atom, and route B was for the case in which R^3 was an alkyl substituent. In route A, the carbamate nitrogen was substituted with an alkyl group (R^5) using various alkyl halides in the presence of NaH in DMF to afford resins **9**.[18] Resins **9** (route A) and **8** (route B) were further cyclized by the Bischler−Napieralski reaction.[21] There are several reports of the use of Bischler−Napieralski cyclization reaction in solution chemistry;[4,22−29] however, the application of this reaction in liquid- and solid-phase chemistry is reported rarely.[30,31] After a considerable number of experiments, phosphorus pentoxide in distilled $POCl_3$ was applied successfully to cleave products **1** (entries 1−6) from the solid supports.[25]

Solid-Phase Synthesis (Entries 7−12). After successful application of the above approach in the liquid-phase synthesis, compounds **1g−i** were synthesized on solid supports to prove the versatility of this methodology for solid-phase synthesis. In the solid-phase route, hydroxymethyl resin (**10**) was used as a solid support (Scheme 3) that was activated as described previously[16,17] and was coupled with hydrochloride salts of amines **11** to obtain resin **12**. The hydrocholoride salts **11** were prepared in solution from the corresponding amino acids and thionyl chloride in methanol.[32] The resin-bound methyl ester in **12** was reduced with $LiBH_4$ to the corresponding alcohol. Mitsunobu coupling[33−35] with thiophenol was attempted to transform the resulting alcohol into thioether under traditional solution reaction conditions, which gave a chromatographically inseparable mixture in 80% yield. However, in solid-phase synthesis, Mitsunobu coupling gave very low yield (<10%). Alternatively, the hydroxyl group was converted to a good leaving group (OMs, compound **13**) by reacting with methanesulfonyl chloride (MsCl) in the presence of diisopropylethylamine (DIPEA) in methylene chloride.[36−38] Me-

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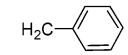
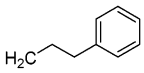
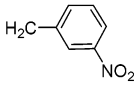
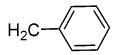
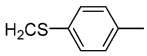
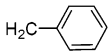
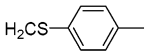
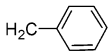
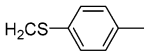
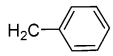
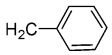
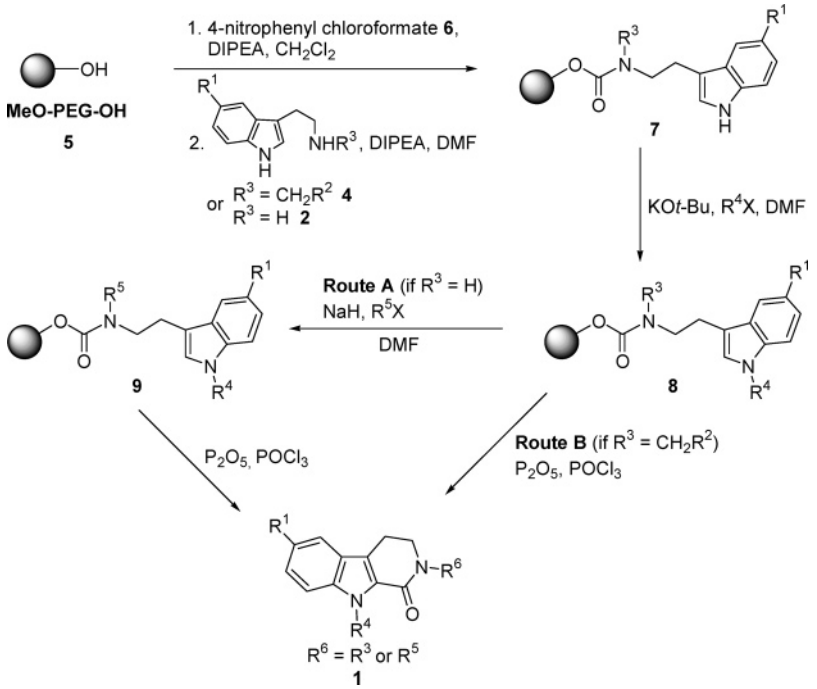
Table 1. Carbolinones Generated on Solid Support[a]

Entries	1	R^1	R^4	R^6	R^7	Overall Yields
1	1a	H		CH_3	H	61%
2	1b	H	CH_3	CH_3	H	62%
3	1c	OMe	CH_3	CH_3	H	55%
4	1d	H		CH_3	H	58%
5	1e	H	CH_3		H	72%
6	1f	H	CH_2CH_3		H	65%
7	1g	H	CH_3	CH_3		57%
8	1h	H		CH_3		56%
9	1i	H		CH_2CH_3		54%
10	1j	H	H		H	50%
11	1k	H	CH_3	H	H	65%
12	1l	H		H	H	63%

[a] Reported yields are isolated yields after flash chromatography on silica gel. The overall yields are based on the initial loading of the soluble resin, MeO−PEG-OH, or the hydroxymethyl resin.

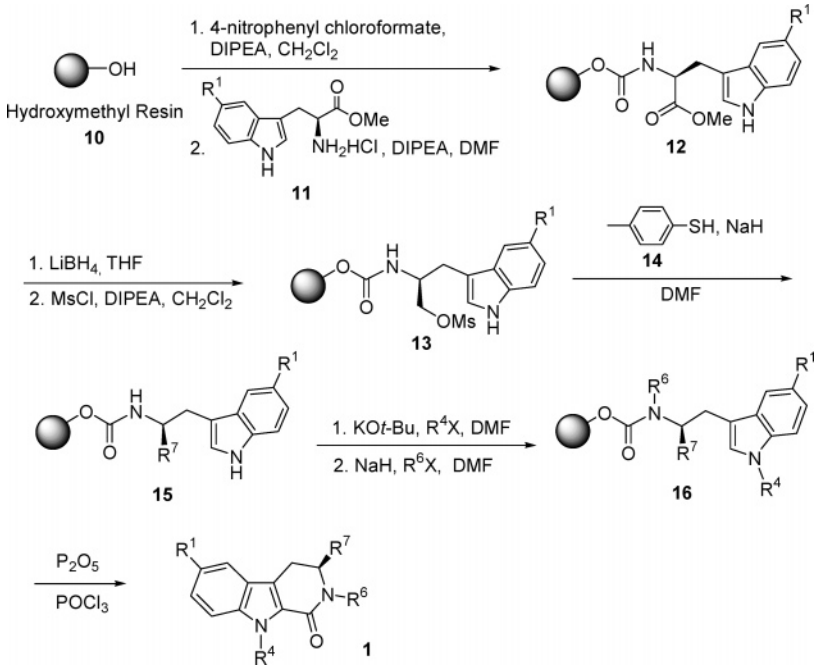
Scheme 2



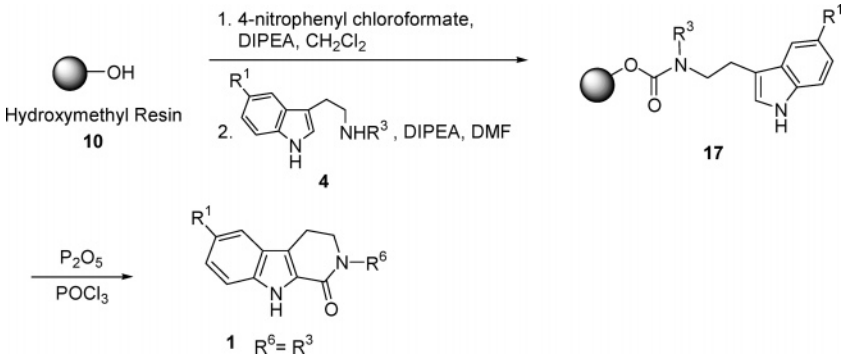
sylate **13** was further treated with thiophenol **14** using NaH in DMF to obtain the desired thioether **15**.[39,40] The selective alkylation of the indol nitrogen in thioether **15** and the subsequent alkylation of the carbamate nitrogen as described in Scheme 2 furnished resin **16**. The Bischlern−Napieralski reaction was used as described above to cyclize and cleave products **1** (entries 7−9) from solid supports, with overall yields ranging from 54 to 57%, as shown in Table 1.

Considering the presence of this kind of template in many natural products, the present methodology was extended to

Scheme 3



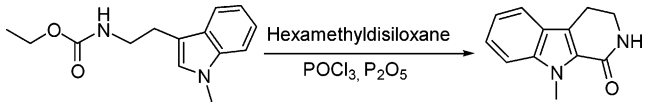
Scheme 4



synthesize compound **1j** (entry 10) having a proton on the indol nitrogen (Scheme 4). It was not possible to synthesize this type of compound using the sequence of reactions shown in Scheme 2 because temporary *tert*-butoxycarbonyl (Boc) protection of the indol nitrogen was cleaved in the next step of alkylation of the carbamate nitrogen. Hence, a prealkylated amine **4** was coupled with the activated solid support, as described in Scheme 3, to yield resin **17**, which was subjected to the Bischler−Napieralski cyclization to afford compound **1j** in 50% overall yield. This conversion is unique because none of reported methodologies is able to synthesize this kind of template on solid supports.

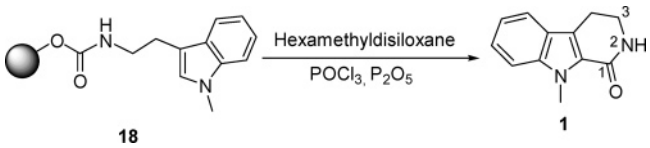
To further demonstrate the synthetic utility of this methodology, we became interested in optimizing the present methodology to produce compounds **1k** and **1l** (entries 11 and 12), in which a hydrogen atom is present on the nitrogen N-2 in carbolinones. The presence of a hydrogen atom on the nitrogen N-2 may enhance interactions with receptors through hydrogen bonding. All reported methodologies fail to produce such carbolinone analogues in good yield. To obtain such compounds, the resin having a hydrogen atom on the carbamate nitrogen was used for cyclization, but the above Bischler−Napieralski conditions provided the desired product in very low yield. Hence, model studies were

Scheme 5



performed in traditional solution reaction conditions according to reported methods using oxalyl chloride/$FeCl_3$ [22] and trifluoromethanesulfonic anhydride/DMAP,[23] but both methods gave low yields (<30%). When the Boc group was used to protect carbamate nitrogen, it was observed that NaH used in the next step for alkylation caused deprotection. Further, a different approach of temporarily protecting the carbamate nitrogen in situ was adopted. Initially, various reaction conditions using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) with P_2O_5 in $POCl_3$ were studied, but <20% yields were obtained. Finally, hexamethyldisiloxane was used instead (Scheme 5), giving the desired product in good yield (80%). This new reaction was optimized for solid-phase synthesis using various proportions of reagents to obtain maximum yield. After a considerable number of experiments, hexamethyldisiloxane and P_2O_5 in distilled $POCl_3$ afforded compound **1k** in 65% overall yield from hydroxymethyl resin (**10**) (Scheme 6).

Scheme 6



In conclusion, we have successfully developed a combinatorial methodology for the synthesis of β-carbolinones having four points of diversity and possessing a proton on the indol nitrogen. This new methodology is able to produce carbolinones possessing a proton on nitrogen N-2 for solid-phase synthesis. The four points of diversity in these derivatives provide enough freedom for the incorporation of various hydrophobic and hydrophilic groups that may be useful to enhance interactions with receptors. Moreover, this methodology is traceless because the resulted derivatives do not carry any fragment of linker moieties and is versatile to be used for solid- or liquid-phase synthesis. Thus, if explored further, this methodology may be of a significant utility in combinatorial chemistry to synthesize a library of carbolinone derivatives.

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Supporting Information Available. Representative experimental procedures and spectral data of compounds **1a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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