Novel Solid-Phase Synthetic Method for Combinatorial Generation of a 4-Hydroxyquinolin-2(1*H*)-one-Based Library

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Abstract: Utilizing polymer-bound anthranilic acid derivatives, we were able to obtain 4-hydroxyquinolin-2(1*H*)-ones in 50–99% five- or six-step overall yields and 65–95% purities through the adaptation of a Dieckmann-type condensation reaction to a C–C bond-forming cyclative cleavage step. The reactions on solid phase were monitored by on-bead ATR-FTIR spectroscopic methods, colorimetric tests, and/or cleavage experiments.

Key words: combinatorial chemistry, solid-phase synthesis, quinolinone, Dieckmann condensation, cyclative cleavage

Solid-phase synthesis of combinatorial libraries has emerged as a powerful tool for an efficient drug discovery process.[1] In particular, derivation of various core structures with the same or different substituents from a versatile intermediate resin has been an interesting strategy for the construction of small molecule libraries on solid phase, in that varying the scaffold as well as the substituents might further increase the diversity of the libraries compared to relying on a single scaffold.[2] The strategy has been called skeletal diversity generation in diversity-oriented synthesis (DOS),[2d] combinatorial scaffold approach,[2c] and multiple core structure library approach,[2b] with subtle differences among them in their capacities. In this context, we have recently been exploring the potential of resin-bound anthranilic acid derivatives **1** and **2** as versatile intermediates for combinatorial generation of drug-like heterocyclic compound libraries.[3] Previously, we reported the preparation of the intermediate resins **1** and **2** and the solid-phase synthesis of 2-cyanoquinazolin-4(3*H*)-ones **3** and **3′**, and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones **4** from the resins[3a] (Figure 1). Herein we would like to present the novel solid-phase synthetic method for combinatorial generation of 4-hydroxyquinolin-2(1*H*)-one-based library from resin-bound anthranilic acid derivatives **1** together with monitoring of the solid-phase reactions by ATR (attenuated total reflection)-FTIR spectroscopy, colorimetric tests, and/or cleavage experiments.

During the past decade 4-hydroxyquinolin-2(1*H*)-ones and their derivatives have attracted much attention for their interesting biological activities including glycine/NMDA receptor antagonistic,[4a] $5HT_3$ receptor antagonistic,[4b] GnRH receptor antagonistic,[4c] antiangiogenic,[4d] and antinephritic[4e] activities. The solution-phase synthetic methods for 4-hydroxyquinolin-2(1*H*)-one derivatives may be primarily divided into three categories from the viewpoint of the skeleton construction: (i) condensation of anilines with malonates,[5] (ii) Dieckmann-type condensation of N-acylated anthranilate esters,[6] (iii) condensation of isatoic anhydrides[4d,e,7a,b] or 4*H*-3,1-benzoxazin-4-ones[7c] with acetic esters. Some other methods have also been reported involving such intermediates as furan-2,3-dione,[8a] 4-hydroxycoumarin,[8b] 2′-aminoacetophenone,[8c] and 2-nitrobenzoic acid.[8d] On the other hand, there has been only one report regarding the solid-phase methods for combinatorial synthesis of 4-hydroxyquinolin-2(1*H*)-one derivatives:[9] condensation of Wang resin-bound cyanoacetic acid with isatoic anhydrides or their N-alkylated derivatives.[9a] As a novel approach to solid-phase synthesis of 4-hydroxyquinolin-2(1*H*)-one derivatives, we envisioned that the resin-bound anthranilic acid derivatives **1** could be adapted to the second solution-phase protocol mentioned above, Dieckmann-type condensation of N-acylated anthranilate esters, encompassing more diverse substituents at 3-position of 4-oxyquinolin-2(1*H*)-one skeleton and introducing the alkyl substituents at its 1-position on solid phase (Scheme 1).

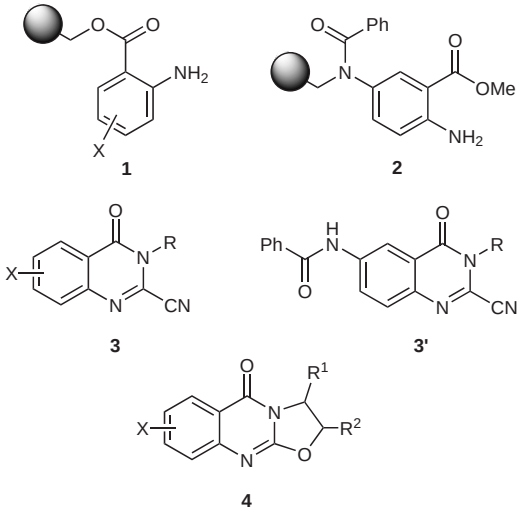

Figure 1

The resin-bound anthranilic acid derivatives **1** were prepared from coupling of Wang resin **5** with 2-nitrobenzoic acids[10] (2 equiv) in the presence of DIC (3 equiv) and

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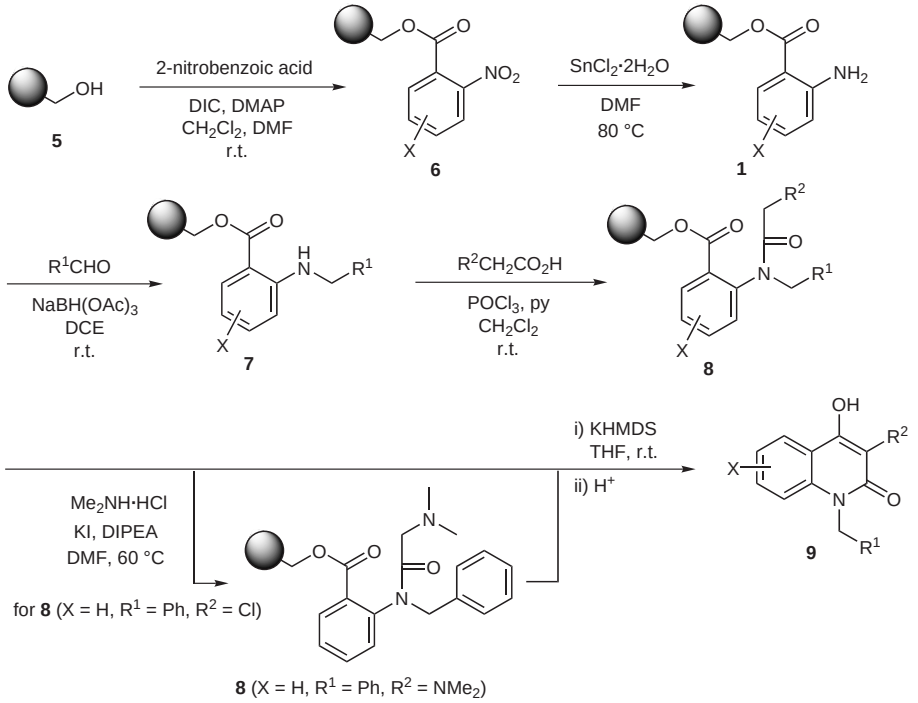

Scheme 1

DMAP (3 equiv) in CH_2Cl_2–DMF (4:1) at room temperature and subsequent reduction of the resultant resins **6** with $SnCl_2{\cdot}2H_2O$ (10 equiv) in DMF at 80 °C (Scheme 1 and Table 1) according to the previously reported procedure.[3a] Treatment of the resins **1** with aldehyde building blocks (3 equiv) under typical reductive alkylation conditions [in the presence of $NaBH(OAc)_3$ (3 equiv) in DCE] at room temperature gave the N-alkylated anthranilate resins **7**. The progress of the reductive alkylation step was monitored utilizing both on-bead ATR-FTIR spectroscopy[11] and cleavage experiment. As exemplified in Figure 2, a NH_2 band (3485–3490 cm^{-1}) observed on the IR spectra of the resins **1** disappeared as the reactions proceeded. However, the IR data were insufficient to confirm the completion of the reactions due to the weakness of the N–H bands. In order to confirm the reaction completeness, we performed a cleavage experiment involving methanolysis of resins **7** by the use of NaOMe/MeOH (3 equiv) in THF at room temperature. For example, the methanolysis of resin **7** (X = H, R^1 = Ph) gave methyl 2-benzylaminobenzoate in 80% yield, with a satisfactory purity when judged on the basis of its ^1H NMR spectrum.

For the next acylation step, we selected monosubstituted acetic acid building blocks as acetyl group source instead of the corresponding acetyl chlorides considering the former broader commercial availability compared with that of the latter. We examined a variety of reaction conditions such as $POCl_3$/pyridine (3 equiv/6 equiv), NCS/PPh_3/pyridine (3 equiv /3 equiv/6 equiv), NBS/PPh_3/pyridine (3 equiv/3 equiv/6 equiv), NIS/PPh_3/pyridine (3 equiv/3 equiv/6 equiv), Br_2PPh_3/pyridine (3 equiv/6 equiv), CDI (3 equiv), CMPI/pyridine (3 equiv/3 equiv), DPPA (3 equiv), and DIC (DCC or EDC)/HOBT (or DMAP; 3 equiv/cat.) combinations for the reaction of the resin **7** (X = H, R^1 = Ph) with 4-methoxyphenylacetic acid in CH_2Cl_2 at room temperature or elevated temperature.[12] The $POCl_3$/pyride (3 equiv/6 equiv) or NCS/PPh_3/pyridine (3 equiv/3 equiv/6 equiv) conditions at room temperature gave the desired intermediate resin **8** (X = H, R^1 = Ph, R^2 = 4-$MeOC_6H_4$), for which the on-bead ATR-FTIR spectrum showed two carbonyl bands at 1722 (O–C=O, shift from 1680 cm^{-1} to a higher frequency due to loss of intramolecular hydrogen bonding with N–H) and 1660 (N–C=O) cm^{-1} with the disappearance of a NH band confirming the complete transformation as shown in Figure 2. Meanwhile, the other conditions did not bring any change on the IR spectrum of the resin **7** (X = H, R^1 = Ph) at room temperature or reflux. The $POCl_3$/pyridine (3 equiv/6 equiv) system in CH_2Cl_2 at room temperature was selected as a standard taking into account of its handling simplicity and could successfully be applied to the coupling of resins **7** with variously substituted acetic acids (Table 1, R^2) except dimethylaminoacetic acid (R^2 = NMe_2), which resulted in no reaction based on the inspection of IR spectrum of the resin. So, the dimethylaminoacetyl derivative resin **8** (X = H, R^1 = Ph, R^2 = NMe_2) was prepared from the reaction of the chloroacetyl resin **8** (X = H, R^1 = Ph, R^2 = Cl) with dimethylammonium chloride (3 equiv) in the presence of DIPEA (6 equiv) and a catalytic amount of KI in DMF at 80 °C as shown in Scheme 1. The progress of the reaction was checked by a fluorescein test[13] combined with ATR-FTIR spectroscopy. The resin **8** (X = H, R^1 = Ph, R^2 = NMe_2) showed a negative response for the test and exhibited the same IR spectrum before and after the test.

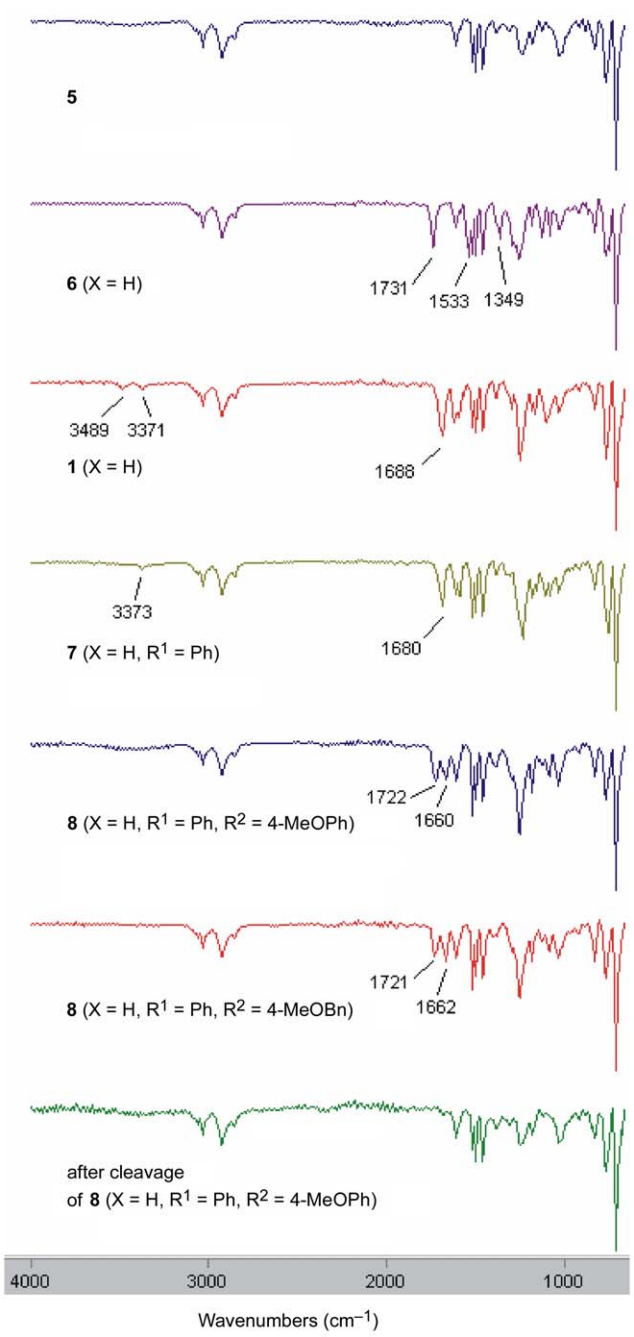

Figure 2

Table 1 Yields and Purities of Compounds **9**

Compound	X	R^1	R^2	Yield (%/%)[a]	Purity (%/%)[b]
9a	H	Ph	4-$MeOC_6H_4$	68/53	91/99
9b	H	Ph	Ph	65/44	91/99
9c	H	Ph	4-FC_6H_4	66/50	93/96
9d	H	Ph	4-$O_2NC_6H_4$	73/51	75/97
9e	H	Ph	4-MeOBn	66/44	92/98
9f	H	Ph	Bn	63/55	87/93
9g	H	Ph	4-F-Bn	68/45	80/95
9h	H	Ph	Et	59/46	84/92
9i	H	Ph	Me_2N	61/52	93/99
9j	H	Ph	MeO	95/59	83/94
9k	H	Ph	MeS	99/52	88/99
9l	H	Ph	Cl	58/36	89/94
9m	H	Ph	CN	76/43	79/97
9n	H	4-FC_6H_4	4-$MeOC_6H_4$	66/55	94/98
9o	H	4-FC_6H_4	4-MeOBn	60/43	90/95
9p	H	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	66/31	65/98
9q	H	4-$O_2NC_6H_4$	4-MeOBn	–	–
9r	H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	61/50	94/98
9s	H	4-$MeOC_6H_4$	4-MeOBn	70/35	88/92
9t	H	*i*-Pr	4-$MeOC_6H_4$	65/49	92/95
9u	H	*i*-Pr	4-MeOBn	71/47	84/94
9v	6-MeO	Ph	4-$MeOC_6H_4$	61/34	76/94
9w	6-MeO	Ph	4-MeOBn	50/22	70/96
9x	6-Cl	Ph	4-$MeOC_6H_4$	78/60	95/97
9y	6-Cl	Ph	4-MeOBn	76/55	89/96

[a] Five- or six-step overall crude/isolated yields from Wang resin (loading capacity 1.00 or 0.92 mmol/g).
[b] Determined on the basis of LC-UV(200–400 nm)-MS spectrum of crude/isolated products.

For utilization of Dieckmann-type condensation reaction[14] as C–C bond-forming cyclative cleavage[15] step, several bases (3 equiv) were screened at room temperature for the two resins **8** (X = H, R^1 = Ph, R^2 = 4-$MeOC_6H_4$ and 4-MeOBn) under the conditions such as NaOMe/MeOH in THF, KO*t*-Bu/*t*-BuOH in THF, aq NaOH in THF, LHMDS in THF, KHMDS in THF, LDA in THF, and NaH in DMF or DMSO. Among the examined conditions, KHMDS (3 equiv) in THF at room temperature was concluded to give the best results for both resins in terms of yield and purity of product and reaction time.[16] The system was selected as a standard cleavage condition and gave satisfactory results for the various acetyl derivative resins **8** having alkyl, dialkylamino, alkoxy, alkylthio, chloro, and cyano substituents as well as aryl and benzyl groups to afford 4-hydroxyquinolin-2(1*H*)-one derivatives **9** in 50–99% five- or six-step overall yields and 65–95% purities. Exceptionally, the resin **8q** gave a complex mixture, from which any identifiable product could not be isolated. The progress of the cleavage step was checked by ATR-FTIR spectroscopy as exemplified in Figure 2, where the resins showed nearly the same fingerprints as the Wang resin **5** after the cleavage reactions. The yields

and purities of the crude and purified products **9** are summarized in Table 1.[17] The compounds **9** are unknown except **9b**,[18a] **9f**,[18b] **9i**,[18c] **9l**,[18d] and **9m**,[9a] and all final products **9a**–**y** were characterized on the basis of ^{1}H NMR, (^{13}C NMR) and LC-UV-MS spectral data.

In brief, we were able to establish a novel solid-phase synthetic method for 4-hydroxyquinolin-2(1*H*)-one derivatives **9** utilizing polymer-bound anthranilic acid derivatives **1**, securing sufficient functional group compatibility at 3-position of the skeleton, and introducing alkyl substituents at its 1-position on solid phase, suitable for library generation without amendment or with some modifications. The reactions on solid phase were checked by single-bead ATR-FTIR spectroscopic methods, colorimetric tests, and/or cleavage experiments. Now we are pursuing modified forms of the protocol, useful for construction of target-directed 4-hydroxyquinolin-2(1*H*)-one-based libraries. In addition, the investigation into efficient methods for other heterocyclic compounds utilizing the resin-bound anthranilic acid derivatives **1** and **2** is in progress.

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(10) In addition to commercially available 2-nitrobenzoic acids, they can be prepared from the regioselective nitration of benzoic acids, the oxidation of *o*-nitrotoluenes, 2-nitrobenzyl alcohols, 2-nitrobenzaldehydes, and 2′-nitroacetophenones, and the substitutions of halogenated 2-nitrobenzoic acids. On the other hand, variation of the X group would be possible for the resin-bound 2-nitrobenzoic acid derivatives **6** and will be reported elsewhere. For examples of the nitration, see ref. 8d and: (a) Coppola, G. M.; Schuster, H. F. *J. Heterocycl. Chem.* **1989**, *26*, 957. (b) Cotelle, P.; Catteau, J. P. *Synth. Commun.* **1996**, *26*, 4105. (c) Thurston, D. E.; Bose, D. S.; Thompson, A. S.; Howard, P. W.; Leoni, A.; Croker, S. J.; Jenkins, T. C.; Neidle, S.; Hartley, J. A.; Hurley, L. H. *J. Org. Chem.* **1996**, *61*, 8141. (d) Gregson, S. J.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2277. For examples of the oxidation, see: (e) Yamazaki, S. *Synth. Commun.* **1999**, *29*, 2211. (f) Sawatari, N.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 2053. (g) Venturello, C.; Cambaro, M. *J. Org. Chem.* **1991**, *56*, 5924. (h) Singh, M.; Singh, K. N.; Dwivedi, S.; Misra, R. A. *Synthesis* **1991**, 291. (i) Das, S.; Punniyamurthy, T. *Tetrahedron Lett.* **2003**, *44*, 6033. (j) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999. (k) Madler, M. M.; Klucik, J.; Soell, P. S.; Brown, C. W.; Liu, S.; Berlin, K. D.; Benbrook, D. M.; Birckbichler, P. J.; Nelson, E. C. *Org. Prep. Proced. Int.* **1998**, *30*, 230. (l) Roy, A.; Reddy, K. R.; Mohanta, P. K.; Ila, H.; Junjappa, H. *Synth. Commun.*

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(17) **Representative Procedure for Preparation of Compounds 9**

Preparation of 2-Benzylaminobenzoate Resin (7a; X = H, R^1 = Ph)

To a mixture of the resin **1a** (X = H; 4.00 g, theoretically 3.59 mmol), prepared from Wang resin (1.00 mmol/g), and benzaldehyde (1.14 g, 10.8 mmol) in DCE (60 mL) at r.t. was added $NaBH(OAc)_3$ (2.28 g, 10.8 mmol). The mixture was stirred at r.t. for 12 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, MeOH, H_2O, and MeOH, and dried in a vacuum oven to give **7a** (4.30 g, 99%): on-bead ATR-FTIR: 3365 (NH), 3025, 2922, 1680 (C=O), 1602, 1581, 1512, 1492, 1451, 1221, 1172, 1097, 822, 750, 697 cm^{-1}.

Preparation of 2-{Benzyl[3-(4-methoxyphenyl)acetyl]amino}benzoate Resin (8a; X = H, R^1 = Ph, R^2 = 4-$MeOC_6H_4$)

To a mixture of the resin **7a** (X = H, R^1 = Ph; 1.00 g, theoretically 0.830 mmol) and 4-methoxyphenylacetic acid (413 mg, 2.49 mmol) in CH_2Cl_2 (30 mL) at r.t. was added pyridine (391 mg, 4.98 mmol) and phosphorus oxychloride (385 mg, 2.49 mmol). The mixture was stirred at r.t. for 2 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, MeOH, H_2O, and MeOH, and dried in a vacuum oven to give **8a** (1.09 g, 97%): on-bead ATR-FTIR: 3026, 2921, 1719 (O–C=O), 1662 (N–C=O), 1605, 1510, 1492, 1448, 1380, 1243, 1176, 1078, 1025, 822, 755, 697 cm^{-1}.

Preparation of 1-Benzyl-4-hydroxy-3-(4-methoxyphenyl)-1*H*-quinolin-2-one (9a; X = H, R^1 = Ph, R^2 = 4-$MeOC_6H_4$)

To a suspension of the resin **8a** (X = H, R^1 = Ph, R^2 = 4-$MeOC_6H_4$; 100 mg, theoretically 0.0739 mmol) in THF (3 mL) at r.t. was added 0.5 M KHMDS in toluene (0.440 mL, 0.227 mmol) and the mixture was stirred at r.t. for 6 h. The mixture was filtered and washed with MeOH (about 10 mL). The filtrate was evaporated in vacuo, acidified to pH 4–5 with 3 N HCl, and extracted with EtOAc (2 × 3 mL). The organic layer was dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue (18 mg, 68%; 91% purity on the basis of LC-UV-MS spectrum) was purified by a silica gel column chromatography (*n*-hexane–EtOAc, 2:1) to afford **9a** (14 mg, 53%; 99% purity on the basis of LC-UV-MS spectrum): ^1H NMR (500 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 5.56 (br s, 2 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 7.20–7.23 (m, 2 H), 7.25–7.31 (m, 5 H), 7.43–7.47 (m, 3 H), 8.04 (dd, *J* = 8.0, 1.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.2, 55.4 111.2, 114.8, 115.0, 115.7, 121.9, 123.4, 124.1, 126.8, 127.2, 128.7, 131.1, 132.0, 137.0, 138.8, 156.0, 159.8, 162.8. ESI-MS: *m/z* = 358 $[M + H]^+$.

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