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Solid-phase synthesis of 2-cyanoquinazolin-4(3*H*)-one and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-one derivatives utilizing resin-bound anthranilic acid derivatives

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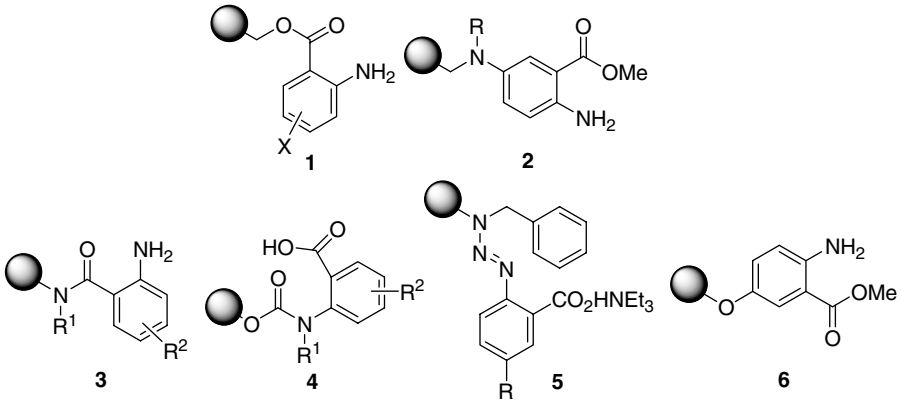
Abstract—We were able to obtain 2-cyanoquinazolin-4(3*H*)-ones **11** in 35–60% four-step overall isolated yields and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones **12** in 20–71% four-step overall isolated yields utilizing polymer-bound anthranilic acid derivatives **1**, and 6-amino-2-cyanoquinazolin-4(3*H*)-ones **19** in 30–44% six-step overall isolated yields making use of anthranilic acid derivative resin **2** via dithiazole resins **10** and **17**. The reactions on solid phase were monitored by single bead ATR-FTIR spectroscopic method.

Solid-phase synthesis of combinatorial libraries has emerged as a powerful tool for 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 construction of small molecule libraries on solid phase in which varying scaffold as well as substituents might further increase the diversity of the libraries compared to depending on single scaffold.[2] In this context, resin-bound anthranilic acid derivatives have served as important intermediates for the solid-phase synthesis of some biologically interesting heterocyclic compounds such as quinazolin-4(3*H*)-ones,[3a–c] quinazoline-2,4(1*H*,3*H*)-diones,[3d–f] pyrrolo[2,1-*c*][1,4]benzodiazepines,[3g] and 3*H*-benzo[*a*][1,2,3]triazinones.[3h] In connection with our ongoing drug discovery project,[4] we



Keywords: Solid-phase synthesis; Quinazolinone; Anthranilic acid; Dithiazole.
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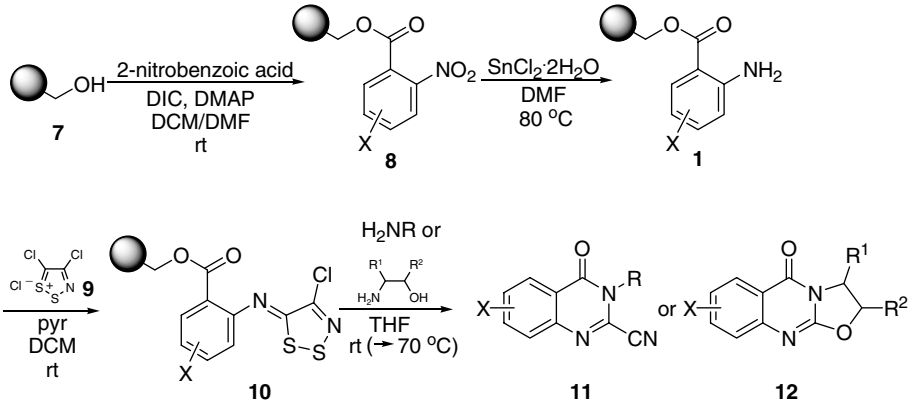


Scheme 1.

intended to utilize some resin-bound anthranilic acid derivatives such as **1** and **2** to develop solid-phase synthetic methods for generation of drug-like heterocyclic compound libraries. The resins **1** and **2** have been rarely utilized for solid-phase synthesis of heterocyclic compounds even though the former was reported[5] and they have possibilities other than the previously reported resin-bound anthranilic acid derivatives **3**,[3a–c] **4**,[3e,f] **5**,[3h] and **6**.[3d] Herein, we wish to describe the solid-phase synthesis of 2-cyanoquinazolin-4(3*H*)-ones and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones from polymer-bound anthranilic acid derivatives **1** and **2** utilizing the solution-phase chemistry of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles.[6] There has been no report regarding the solid-phase synthesis of 2-cyanoquinazolin-4(3*H*)-ones and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones derivatives even though quinazolinone derivatives have shown broad spectrum of biological activities and numerous methodologies for solid-phase synthesis of them have been reported.[3a–c,7]

Table 1. Yields and purities of the compounds **11** and **12**

Compound	X	R		Yield[a] (%)	Purity (%)
11a	H	*n*-Pr		60	95[b]
11b	H	$MeOCH_2CH_2$		50	98[b]
11c	H	Cyclohexanemethyl		53	100[b]
11d	H	4-Methoxybenzyl		42	100[c]
11e	H	Phenethyl		43	98[b]
11f	H	Furfuryl		35	100[c]
11g	7-Cl	*n*-Bu		45	85[b]
11h	7-Cl	$MeOCH_2CH_2$		60	95[b]
11i	7-Cl	Cyclohexanemethyl		57	82[c]
11j	7-Cl	4-Methylbenzyl		55	100[b]
11k	7-Cl	2-Methoxyphenethyl		43	90[b]
11l	7-Cl	Furfuryl		57	83[b]
11m	7-Cl	3-(2-Oxopyrrolidin-1-yl)propyl		46	84[b]
11n	7-Me	$MeOCH_2CH_2$		54	98[b]
11o	7-Me	Cyclohexanemethyl		60	98[c]
11p	7-Me	4-Methylbenzyl		52	95[c]
11q	7-Me	4-Chlorobenzyl		41	96[c]
11r	7-Me	Phenethyl		44	99[c]
11s	7-Me	4-Fluorophenethyl		43	98[c]
11t	7-Me	4-Methoxyphenethyl		44	99[c]
11u	7-Me	Furfuryl		50	100[b]
		R^1	R^2		
12a	8-Cl	H	H	71	91[b]
12b	8-Cl	H	Me	69	100[c]
12c	8-Cl	H	Ph	37	99[b]
12d	8-Me	Me	H	32	99[c]
12e	8-Me	H	Me	40	100[b]
12f	8-Me	(*R*)-Ph	H	25	100[b]
12g	8-Me	H	Ph	20	100[b]

[a] Four-step overall isolated yield from Wang resin (loading capacity 0.92 mmol/g).
[b] Determined on the basis of LC–MS spectrum after column chromatography.
[c] Determined on the basis of GC–MS spectrum after column chromatography.

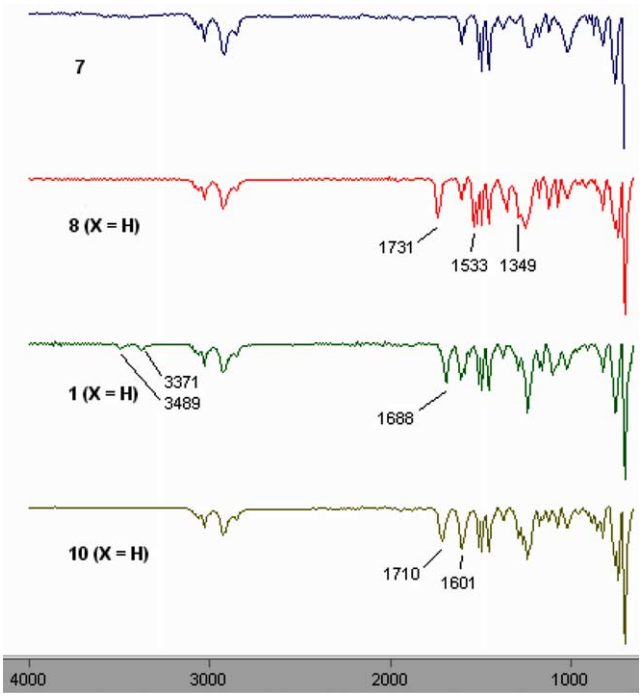
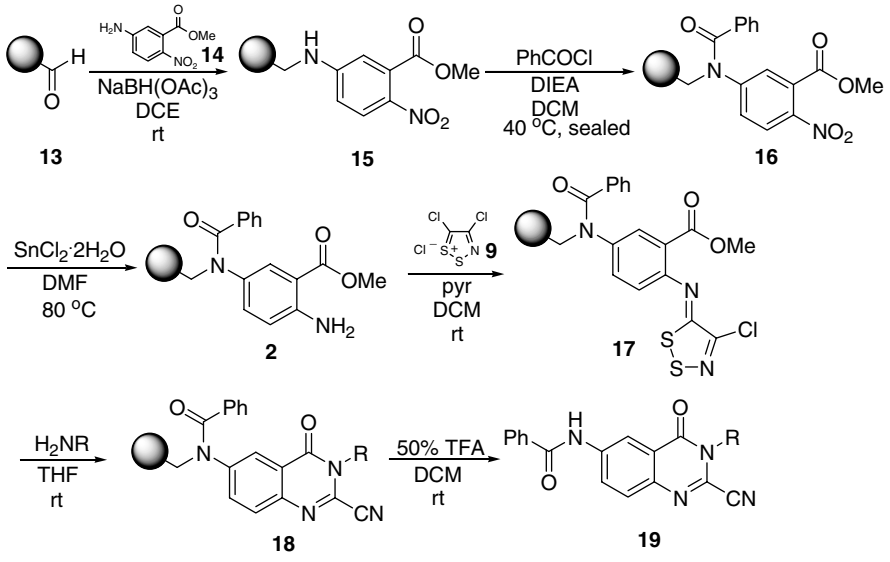


Figure 1.

The resin-bound anthranilic acid derivatives **1** were prepared from coupling of Wang resin **7** with 2-nitrobenzoic acids in the presence of DIC and DMAP in CH_2Cl_2/DMF (4/1) at rt and subsequent reduction of the resultant resins **8** with $SnCl_2{\cdot}2H_2O$ in DMF at 80 °C (Scheme 1). Treatment of the resins **1** with 2,3-dichloro-5*H*-1,2,3-dithiazolium chloride (Appel's salt)[8] **9** in the presence of pyridine in CH_2Cl_2 at rt gave the dithiazole resins **10**. Cyclative release from the resins **10** by the reactions with various primary alkylamines in THF at rt gave the desired 2-cyanoquinazolin-4(3*H*)-ones **11** in 35–60% yields and 82–100% purities. In addition, treatment of the resins **10** with some ethanolamines in THF at rt to 70 °C afforded 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones **12** in 20–71% yields and 91–100% purities. The results are summarized in Table 1.[9] The progress of the reactions on solid phase was monitored by single bead ATR-FTIR spectroscopy[10] as shown in Figure 1, where the resins **8**, **1**, and **10** showed characteristic bands, that is, 1731 (C=O), 1533 (NO_2), 1349 (NO_2) cm^{-1} for **8** (X = H); 3489 (NH_2), 3371 (NH_2), 1688 (C=O) cm^{-1} for **1** (X = H); 1710 (C=O), 1601 (C=N) cm^{-1} for **10** (X = H). The final products **11a**–**u** and **12a**–**g** were all unknown and characterized on the basis of ^1H NMR, ^{13}C NMR, and LC–MS (or GC–MS) spectral data.

On the other hand, resin-bound methyl 5-amino-2-nitrobenzoate **15**, prepared from reductive amination of AMEBA resin **13** with the corresponding aniline **14**, gave benzoylated resin **16** by treatment with benzoyl chloride in the presence of DIEA in CH_2Cl_2 (Scheme 2). Reduction of the resin **16** with $SnCl_2{\cdot}2H_2O$ in DMF at 80 °C afforded the resin-bound anthranilic acid derivative **2**, which was converted to the dithiazole resin **17** under the same condition as that for the Wang resin-bound **1**. Cyclization of the resin **17** by the reactions with various primary alkylamines in THF at rt followed by cleavage from the resins **18** using 50% TFA/DCM at rt gave the 2-cyanoquinazolin-4(3*H*)-ones **19** in 30–44% yields and 85–100% purities. The results are summarized in Table 2.[11] The progress of the reactions on solid phase was also monitored by single bead ATR-FTIR spectroscopy as shown in Figure 2. The intermediate resins exhibited distinguishing bands on the IR spectra, that is, 3400 (NH), 1736 (C=O), 1504 (NO_2), 1319 (NO_2) cm^{-1} for **15**; 1737 (C=O), 1655 (C=O), 1528 (NO_2), 1342 (NO_2) cm^{-1} for **16**; 3489 (NH_2), 3369 (NH_2), 1691 (C=O), 1642 (C=O) cm^{-1} for **2**; 1723 (C=O), 1646 (C=O), 1601 (C=N) cm^{-1} for **17**; 1691 (C=O), 1646 (C=O) cm^{-1} for **18**. The final products **19a**–**h** were all unknown and characterized on the basis of ^1H NMR, ^{13}C NMR, and LC–MS spectral data.



Scheme 2.

Table 2. Yields and purities of the compounds **19**

Compound	R	Yield[a] (%)	Purity[b] (%)
19a	$MeOCH_2CH_2$	30	85
19b	Cyclohexanemethyl	44	100
19c	Benzyl	35	92
19d	4-Methylbenzyl	31	90
19e	4-Chlorobenzyl	30	88
19f	Phenethyl	34	100
19g	4-Methoxyphenethyl	37	88
19h	4-Fluorophenethyl	31	93

[a] Six-step overall isolated yield from AMEBA resin (loading capacity 0.85 mmol/g).
[b] Determined on the basis of LC–MS spectrum after column chromatography.

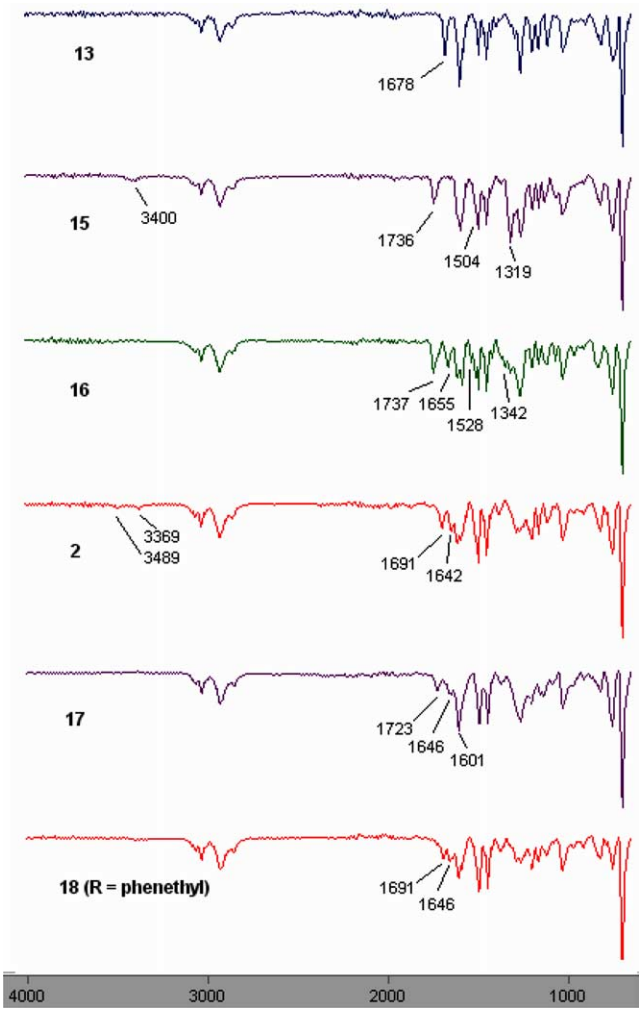


Figure 2.

Unfortunately, we could not obtain the corresponding 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones from treatment of the resin **17** with some ethanolamines in THF at rt to 70 °C and subsequent cleavage in 50% TFA/DCM at rt, whose results are in contrast with those from the similar reactions of the resin **10**.

In brief, we were able to obtain 2-cyanoquinazolin-4(3*H*)-ones **11** and 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-ones **12** from polymer-bound anthranilic acid derivatives **1**, and 6-amino-2-cyanoquinazolin-4(3*H*)-ones **19** from **2** via dithiazole resins **10** and **17**. The reactions on solid phase were monitored by single bead ATR-FTIR spectroscopic method. Now under way is the construction of the corresponding compound libraries using structurally and functionally more diverse building blocks. On the other hand, investigation is in progress into efficient methods for another heterocyclic compound utilizing the resin-bound anthranilic acid derivatives **1** and **2**.

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Supplementary data

Representative procedure for preparation of compounds **11**, **12**, and **19**, ^{1}H NMR, ^{13}C NMR, and MS spectral data of compounds **11**, **12**, and **19**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.015.

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