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Traceless Solid-Phase Synthesis of 2,4-Diaminoquinazolines

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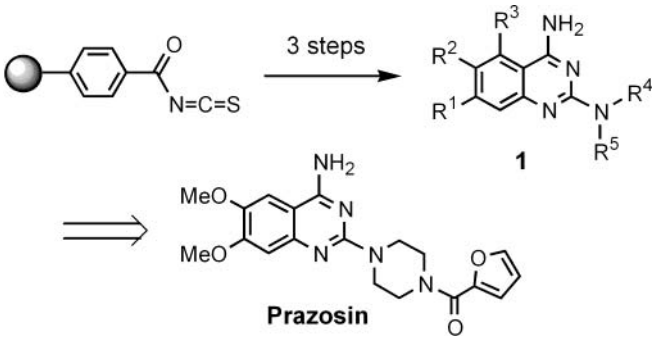
ABSTRACT



The solid-phase synthesis of 2,4-diaminoquinazolines is presented. The chemistry involves the sequential condensation of 2-aminobenzonitriles and amines starting from an acyl isothiocyanate resin via a traceless cleavage and cyclization. The α-1 antagonist prazosin was synthesized, as well as several other examples, in good yields and purity.

The use of solid-supported synthesis in combinatorial chemistry and drug discovery is having a profound effect on the way synthetic chemistry is carried out as a result of inherent advantages it has to offer. Heterocyclic molecules play an important role in pharmaceutical research and development as a result of their desirable physical and chemical properties, and the solid-phase synthetic methodology for many types of ring systems have been developed.[1] As part of our ongoing program for the development of solid-supported methods for heterocycle formation,[2,3] we focused on the 2,4-diaminoquinazoline ring system (**1**). This heterocyclic class has been shown to exhibit a wide range of pharmacology, including α-1b receptor antagonism,[4] antibacterial activity,[5] dihydrofolate reductase inhibition,[6] neuropeptide Y_5 and thrombin receptor antagonism.[7,8]

We envisioned that the 2,4-diaminoquinazoline nucleus **1** could be assembled on the basis of earlier methodology we developed for the synthesis of guanidines utilizing a traceless linker approach through acyl isothiocyanate resin **2** (Figure 1).[9] Traceless approaches offer many advantages, especially overcoming the "navel" effect.[10] We thought that a traceless synthesis of these heterocycles could be accomplished through use of two readily available building blocks,

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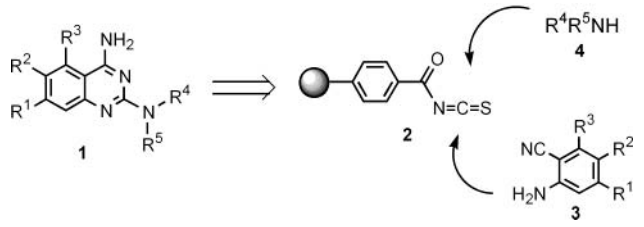
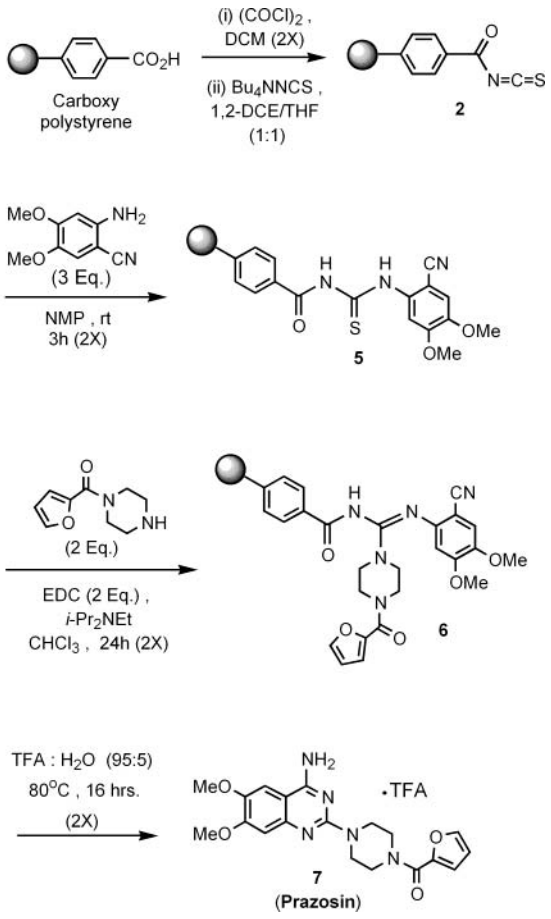


Figure 1. 2,4-Diaminoquinazoline retrosynthesis.

2-aminobenzonitriles (**3**) and amines (**4**). Guanidine formation followed by cleavage would result in cycloaromatization involving the cyanide group. Although there is a solid-phase 2-aminoquinazoline synthesis that has been reported,[11] herein we provide the first solid-phase synthesis of the 2,4-diamino variant of this ring system. This new method provides a nice complement to the widely employed procedure involving sequential chlorine displacement from 2,4-dichloroquinazolines.[7]

We began our studies by targeting the known α-1 antagonist prazosin, which is used to treat hypertension in man (**7**, Scheme 1).[12] Resin **2** was generated from carboxy polystyrene as before, with only slight modification.[9,13] Next, 2-amino-4,5-dimethoxybenzonitrile dissolved in NMP (0.4 M solution, 3 equiv) was added to the resin and allowed to react for 3 h, and the process was repeated. Analysis by infrared spectroscopy showed the disappearance of the characteristic band of the NCS functionality of **2** at 1970 cm^{-1}, and a weak band at 2210 cm^{-1} confirmed the presence of a resin bound CN group. Treatment of **5** with 1-(2-furoyl)-piperazine (2 equiv, 0.4 M) and EDC (1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride) under basic conditions gave resin-bound guanidine **6**. Infrared spectroscopic analysis at this stage indicated a weak band at 2210 cm^{-1}, confirming that the cyanide group had not participated in any further reaction. Optimal cleavage conditions were treatment with trifluoroacetic acid (TFA) and water at 80 °C, which gave prazosin (**7**) as the trifluoroacetic acid salt in 70% yield.[14] Ring closure was confirmed by infrared analysis of the product, which showed no peaks corresponding to a cyanide group. The structure was confirmed by spectroscopic analysis and comparison with an authentic sample.[15,16]

Scheme 1 Solid-Phase Synthesis of Prazosin



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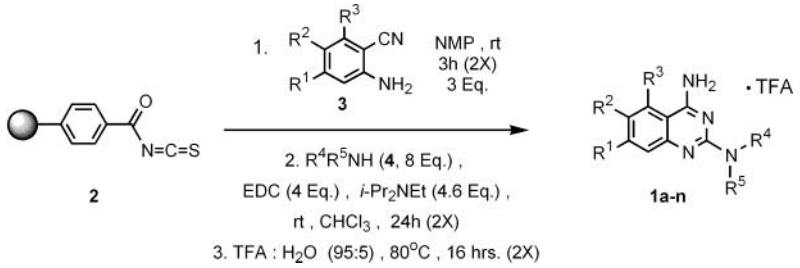
(13) **Preparation of Resin 2.** A total of 15 g of carboxy polystyrene (PS-CO_2H; loading = 2 mmol/g; Advanced Chemtech, Louisville, KY) was washed twice with 120 mL of dry dichloromethane (DCM). Then, 120 mL of DCM and 30 mL of $(COCl)_2$/DCM solution (2 M, Aldrich) was added to the resin in a 500 mL erlynmeyer flask. The solution was shaken for 8 h and filtered, and the process was repeated overnight (16 h). The resin was filtered and washed with 4 × 120 mL of DCM. Next, the resin was mixed with 22.5 g of Bu_4NNCS (Aldrich, 74.9 mmol), 80 mL of THF, and 80 mL of DCM. The reaction was shaken for 6 h and filtered, and the process was repeated overnight. The resin was filtered and washed four times each with DCM, THF, and MeOH. The resin was dried under vaccum to give 16.14 g (99.5% yield) of a yellow solid. This resin decomposes slowly over time (2−3 months) and should be stored in the freezer. Best results are obtained with freshly generated resin. IR: 3040, 2930, 1970 (N═C═S), 1700 (C═O), 1600, 1500, 1450, 1250, 1170, 1070, 1030, 910 cm^{-1}.

(14) **Preparation of Synthetic Prazosin-TFA (7).** A total of 600 mg of resin **2** (theoretical loading of 1.85 mmol/g) and 360 mg of 2-amino-4,5-dimethoxybenzonitrile (Aldrich, 2 mmol) were diluted with 8 mL of *N*-methyl pyrrolidinone for 3 h. The reaction was filtered, and the process repeated. The resin was washed with DMF, DCM, and MeOH (3×). Then, 360 mg of 1-(2-furoyl)-piperazine (Acros, 2 mmol), 380 mg of EDC (Aldrich, 1.95 mmol), and 0.6 mL of diisopropylethylamine (Aldrich, 3.4 mmol) were premixed in 6 mL of $CHCl_3$. The solution was added to resin **5**, and the reaction was mixed for 24 h. The resin was filtered, and the process was repeated. The resin was then washed with $CHCl_3$, MeOH, $CHCl_3$/TFA (3/1), and MeOH (3× each in succession). Next, 260 mg of resin **6** (theoretical loading = 1.13 mmol/g) gave 102 mg (70% from carboxy polystyrene for the five steps; calculated as the mono TFA salt; MW = 497 for $C_{21}H_{22}F_3N_5O_6$) of a tan solid after heating in 95:5 TFA/H_2O (5 mL:0.25 mL; 2 × 16 h). The product was analyzed by LC-MS at 254 nm. Retention time of MW = 383 amu was 2.4 min, with a peak area of 92%. Retention time of prazosin-HCl (purchased from the Sigma Chemical Co., P7791) was 2.4 min under the same conditions. The material was recrystallized once from EtOH to give 35 mg (24% yield from PS-CO_2H) of a white solid.

(15) **Physical Data for 7.** ^1H NMR (d_6-DMSO): 3.85 (s, 4H), 3.91 (bs, 10 H), 6.68 (quart, 1H, J = 1.7 Hz), 7.09 (d, 1H, J = 3.4 Hz), 7.2 (s, 1H), 7.68 (s, 1H), 7.9 (d, 1H, J = 1 Hz), 8.7 (bs, 1H), 8.8 (bs, 1H), 11.8 (s, 1H). MS (ESI): 384 (M + H), 290 (M + H − 2-furoyl). IR (pellet): 3350, 3150, 2850, 1650, 1500, 1210, 1160, 1030, 850, 620 cm^{-1}. Anal. Calcd for $C_{19}H_{21}N_5O_4 \cdot 1.25CF_3CO_2H$: C, 49.10; H, 4.26; N, 13.32. Found: C, 49.35; H, 4.39; N, 13.03.

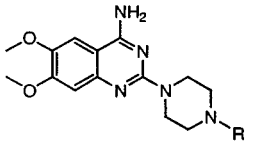
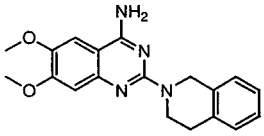
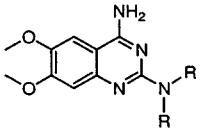
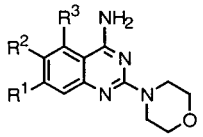
(16) **NMR Comparison.** A total of 3 mg of **7** was combined with 3 mg prazosin-HCl (Sigma, P7791) and 50 mg of ArgoPORE MP carbonate resin in 1 mL of d_6-DMSO. After standing for 30 min, the mixture was filtered into an NMR tube and the ^1H NMR was recorded. ^1H NMR (d_6-DMSO): 3.76 (s, 7H), 3.81 (s, 7 H), 6.6 (quart, 1H, J = 1.7 Hz), 7.0 (d, 1H, J = 3.4 Hz), 7.08 (bs, 1H), 7.55 (bs, 1H), 7.8 (d, 1H, J = 1 Hz).

Scheme 2. Reaction Sequence for the 2,4-Diaminoquinazoline Library **1a**−**n**



We next turned our attention to exploring the scope and generality of this method for the synthesis of other 2,4-diaminoquinazolines. We assembled a library on the Quest 210 synthesizer to test other building blocks in both categories (Scheme 2).[17] We screened nine amines (**4**) with 2-amino-4,5-dimethoxybenzonitrile and eight 2-aminobenzonitriles (**3**) with morpholine.[18] We used the chemistry developed for the synthesis of prazosin (**7**, Scheme 1), modified it only in the ratio of amine (**4**) to EDC, for which we changed from 1:1 to 2:1, and doubled the quantities. The

Table 1. Product Results from the 2,4-Diaminoquinazoline Library (Scheme 2)[18,19]

Entry	Product (1a-n)	Yield (%)[a]	Purity (%)[b]	M+H (amu)[c]	HPLC rt (min.)
					
1	R = Ph (**1a**)	74	89	366	5.6
2	R = Me (**1b**)	74	93	304	1.8
					
3	(**1c**)	45	92	337	4.3
					
4	R = CH_2Ph (**1d**)	65	91	401	6.4
5	R = Me (**1e**)	38	89	249	4.3
6	R = H (**1f**; from **4** = NH_3)	24	74	221	3.6
7	R = H (**1f**; from **4** = *t*-$BuNH_2$)	76	98	221	3.6
					
8	R^1=R^2=OMe, R^3=H (**1g**)	55	94	291	4.3
9	R^1=Cl, R^2=R^3=H (**1h**)	47	94	265	4.5
10	R^1=R^2=R^3=H (**1i**)	67	88	231	3.7
11	R^1=Me, R^2=R^3=H (**1j**)	56	90	245	4.3
12	R^1=R^2=H, R^3=Me (**1k**)	54	88	245	4.2
13	R^1=R^2=H, R^3=Cl (**1l**)	54	94	265	4.3
14	R^1=R^2=H, R^3=F (**1m**)	57	87	249	3.7
15[d]	R^1=H, R^2=NO_2, R^3=H (**1n**)	0	0	0	0

[a] Yield of crude product based on the loading of carboxy polystyrene and for the five steps. Calculated as the monotrifluoroacetic acid salts. [b] Measured using UV−vis detection at 254 nm. [c] Observed parent ion via LC-MS analysis. [d] No product was observed by LC or MS for 2-amino-5-nitro-benzonitrile.

chemistry was performed, and after cleavage the compounds were dried down, weighed for crude yield, and analyzed.[19]

The results indicated the following trends (Table 1). Secondary amines (entries 1−5, 8−14) worked very well giving average to good yields (38−74%) and very good purity (>85%). Primary amines failed to give the desired products in the reaction sequence. For example, when *t*-$BuNH_2$ (entry 7) was utilized, the resulting des *t*-Bu quinazoline was formed (**1f**, entries 6 and 7). The loss of the *t*-Bu group probably occurred during the resin cleavage, and the product obtained was identical with the result from utilizing NH_3 (entry 6). Remarkably, the product from *t*-$BuNH_2$ was of higher yield and purity. The lower yield in the case of both NH_3 (entry 6) and Me_2NH (entry 5) could be due to interference of the reaction by the cosolvent in which these amines were dissolved.[18] Other primary amines gave product mixtures or evidence of quinazolinone formation.[20] In the case of 2-aminobenzonitriles (**3**), all seemed to work well, giving rise to the desired products in all but one case (entries 8−14). The reaction seemed to work with alkyl substituents, alkoxy, and halogen groups. The only substituent that failed was the nitro-substituted case (entry 15), in which no product (**1n**) was observed. In this case, it is likely that the resin thio urea was formed but that either the second step involving the guanidine formation or resin cleavage was unsuccessful.[21]

In summary, we have presented initial results that provide a method for 2,4-diaminoquinazoline synthesis via resin chemistry and a traceless linker approach. The chemistry culminated in the synthesis of the α-1 antagonist prazosin and a small library of other compounds in this series. Further work in this area will be the subject of future reports.

Acknowledgment. The author thanks those who reviewed the manuscript prior to submission. Also, the author wishes to thank Dave Portlock for assisting in and promoting this work for publication.

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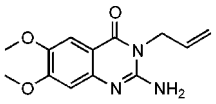
(17) The Quest 210 is manufactured by Argonaut Technologies, San Carlos, CA. In this scheme, the 10 mL 30 μm fritted reaction vessels were employed.

(18) Approximately 275 mg of resin **2** per vessel was utilized. All amines were used neat, except NH_3 (2 M in MeOH) and Me_2NH (2 M in THF).

(19) All compounds (**1a**−**m**) in Table 1 were characterized by ^1H NMR, HPLC, and LC-MS.

(20) For allylamine and 2-amino-4,5-dimethoxybenzonitrile the product observed had a MW of 261 (LC-MS 100% at 254 nm; 110 mg of product from 270 mg of resin **2**, 69% yield), tentatively assigned as quinazolinone **i**.



i

(21) In the condensation of *N*-carbamoyl thioureas, a 4-nitrophenyl substituent on the thiourea has been reported to provide lower yields in subsequent guanidine formation reactions; see: Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566−1568.