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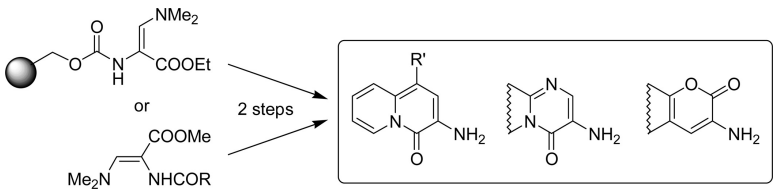

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Parallel Synthesis of 3-Amino-4*H*-Quinolizin-4-ones, Fused 3-Amino-4*H*-Pyrimidin-4-ones, and Fused 3-Amino-2*H*-Pyran-2-ones

Petra Čebašek, David Bevk, Samo Pirc, Branko Stanovnik, and Jurij Svete*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P.O. Box 537, 1000 Ljubljana, Slovenia

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On the basis of the enaminone methodology, libraries of 3-amino-4*H*-quinolizin-4-ones, fused 3-amino-4*H*-pyrimidin-4-ones, and fused 3-amino-2*H*-pyran-2-ones were synthesized by the solid-phase and by the solution-phase parallel synthesis. The solution-phase approach turned out to be advantageous over the solid-phase approach. The solution-phase synthesis afforded, in most cases, analytically pure products in high yields, whereas the solid-phase approach gave products in poor yields and in low purity.

Introduction

Functionalized heterocycles are interesting scaffolds for the preparation of diversity-oriented compound libraries for medicinal and pharmaceutical applications.[1−8] Due to their ability to mimic structures of peptides, as well as their ability to reversibly bind proteins, various 5,5-, 5,6-, 6,7-, and 6,8-fused saturated heterocycles with a dipeptide structural motif have recently been prepared as conformationally constrained mimetics of dipeptides.[3,8] In this context, also the unsaturated bicyclic systems, such as quinolizinones,[9] fused 4*H*-pyrimidin-4-ones,[10] and fused 2*H*-pyran-2-ones,[11] represent useful scaffolds for various biological and pharmaceutical applications. For example, 4*H*-quinolizin-4-one derivatives exhibit antimicrobial,[12−14] integrin inhibition,[15] and antiallergic activity,[16,17] and ethyl 1-(2,7-dihalo-6-hydroxy-3-oxo-3*H*-xanthen-9-yl)-4-oxo-4*H*-quinolizine-3-carboxylates and *tert*-butyl 6-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)-4-oxo-2*H*-chromene-3-carboxylate have been designed, synthesized, and applied as highly sensitive and selective probes in intracellular 3D Mg^{2+} imaging.[18] 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones have been used as anticancer agents,[19,20] as isoform-specific phosphoinositide 3-kinase inhibitors,[21] and as HIV-integrase inhibitors.[22] 3-Aminocoumarin derivatives, such as clorobiocin, novobiocin, coumermycin, and their analogues, exhibit potent activity against Gram-positive bacteria.[23−30] Just recently, various coumarin scaffold-containing compounds were reported as antitumor agents,[31] selective aromataze inhibitors,[32] and nitric oxide production inhibitors.[33]

Probably the most straightforward synthesis of quinolizinones,[9] fused 4*H*-pyrimidin-4-ones,[10] and fused 2*H*-pyran-2-ones[11] is cyclocondensation reaction between a (hetero)-cyclic 1,3-dinucleophile with an appropriate 1,3-dielectrophile, for example, with a 1,3-dicarbonyl compound or its analogue. 2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of easily available enamino masked alkyl α-formyl acetates, which are versatile reagents in heterocyclic synthesis. They were used in the synthesis of various heterocyclic systems, including functionalized heterocycles, such as heteroarylalanines, heterocyclic analogues of amino acids and dipeptides, and natural products, such as aplysinopsins, meridianins, and their analogues. Until now, several reviews on utilization of 3-(dimethylamino)-prop-2-enoates and analogous reagents in heterocyclic synthesis have been published.[34−42] Recently, the use of 3-(dimethylamino)prop-2-enoates in combinatorial synthesis of heterocycles [43−45] and protected 3-(arylamino)alanines[45] has also been reported.

In connection with the synthesis of fused heterocycles, reactions of alkyl 2-acylamino- and 2-(2,2-disubstituted ethenyl)amino-3-(dimethylamino)prop-2-enoates with pyridineacetic acid derivatives, with aminoazines and aminoazoles, and with cyclic 1,3-dicarbonyl compound analogues in refluxing acetic acid, followed by deprotection of the amino group, offer an easy access to 3-amino-substituted 4*H*-quinolizin-4-ones, fused 4*H*-pyrimidin-4-ones, and fused 2*H*-pyran-2-ones, respectively, which cannot be prepared efficiently by other methods. Within this context, methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**8**) was found to be the most suitable reagent.[37,41,46−48] These fused heterocyclic amines are interesting scaffolds and useful intermediates for further transformations and derivatizations. For example, transformation of 4*H*-quinolizin-4-ones into the corresponding stable heteroaryldiazonium tetrafluoroborates, followed by treatment with primary alcohols at 60 °C results in aza-Wolff-type ring contraction into indolizine-3-carboxylates.[49] Under the same conditions, fused 4-oxo-4*H*-pyrimidine-3-diazonium salts undergo "ring switching" transformations into 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylates,[50−52] which exhibited in vitro inhibition against *Mycobacterium* tuberculosis $H_{37}R_v$.[52] Thus, it seemed reasonable to us to develop an efficient parallel synthesis of 4-oxo-4*H*-quinolizin-3-amines, fused 4-oxo-4*H*-pyrimidin-3-amines, and fused 2-oxo-2*H*-pyran-3-amines as building blocks which might be useful for further applications.

* Corresponding author. Phone: +386 1 2419 100. Fax: +386 1 2419 220. E-mail: jurij.svete@fkkt.uni-lj.si.

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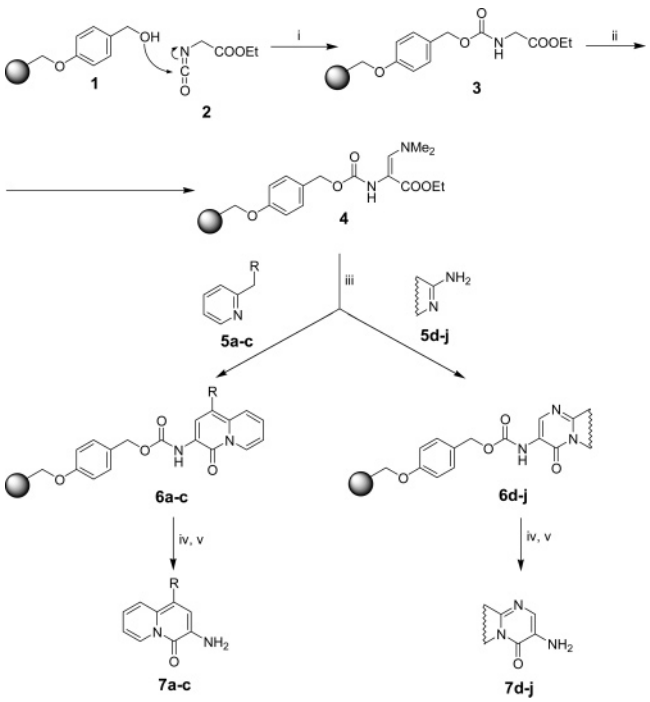
Previously, a solid-phase parallel synthesis of fused 3-acetylamino-4*H*-pyrimidin-4-ones has been reported.[45] In continuation of our work in this field, we now report two solution-phase parallel syntheses and a solid phase parallel synthesis of 3-amino-substituted 4*H*-quinolizin-4-ones, fused 4*H*-pyrimidin-4-ones, and fused 2*H*-pyran-2-ones as heterocyclic scaffolds with incorporated α-amino acid structural element.

Results and Discussion

For the parallel synthesis of the desired types of fused heterocyclic amines, three methods were studied: (a) a two-step solid-phase synthesis from polymer-bound (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**4**) (method A), (b) a two-step solution-phase synthesis from methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)-prop-2-enoate (**8**) (method B), and (c) a two-step solution-phase synthesis from methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**10**) (method C).

Parallel Solid-Phase Synthesis of 3-Amino-4*H*-quinolizin-4-ones 7a−c and Fused 3-Amino-4*H*-pyrimidin-4-ones 7d−j (Method A). In the previously reported solid-phase synthesis of 3-acetylamino-4*H*-pyrimidin-4-ones,[45] a polymer-bound 2-acetylamino-3-(dimethylamino)prop-2-enoate attached to the polymer at position 1 via the ester group was used. This approach enabled us to carry out selective substitution of the dimethylamino group with heterocyclic amine, followed by heating in acetic acid, which resulted in simultaneous cyclization and cleavage of the product from the resin. The limitation of this method was that the deprotection into the free amines should be carried out separately.[45] To overcome this limitation, another synthetic approach based on utilization of immobilized ethyl 2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**4**) attached to the resin at the α-amino group via the urethane group was studied. First, polymer-bound propenoate **4** was prepared in two steps by heating of a Wang resin (**1**) with 5 equiv of ethyl isocyanatoacetate (**2**) in toluene at 100 °C to give the immobilized benzyloxycarbonylglycine ethyl ester (**3**). Stirring of **3** with 3 equiv of Bredereck's reagent in toluene at 100 °C afforded the desired polymer-bound ethyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**4**) in 99% yield. The propenoate **4** was then cyclized in acetic acid at 90 °C with the following ambident nucleophiles, pyridineacetic acid derivatives **5a**−**c**, 2-aminopyridine derivatives **5d**−**h**, 3-aminopyridazine (**5i**), and 2-aminothiazole (**5j**), to give the corresponding polymer-bound 3-amino-4*H*-quinolizin-4-ones **6a**−**c**, 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **6d**−**h**, 3-amino-4*H*-pyridazino-[1,2-*b*]pyrimidin-4-one (**6i**), and 6-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**6j**), respectively. Finally, deprotection and cleavage from the resin was achieved with TFA/CH_2Cl_2 (1:1) at room temperature. However, the products were contaminated with substantial amounts of various impurities, and additional parallel purification had to be carried out. The crude products were redissolved in methanol, stirred with Dowex WX8-200 ion-exchange resin (H^+ form) at room temperature, followed by washing off the impurities, and elution of the products from the resin with methanolic ammonia. In this manner, the desired heteroarylamines **7a**−**j** were obtained in 18−39% yields over two steps. However, the average purity of compounds **7a**−**h** was still not satisfactory, since only the amines **7a**, **f**, **g**, and **h** were prepared in ≥80% purity (Scheme 1, Table 1).

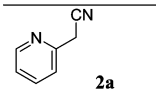
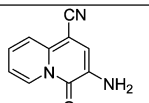
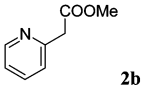
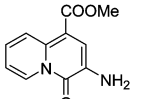
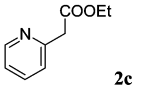
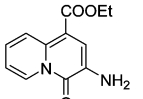
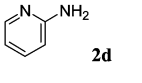
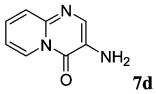
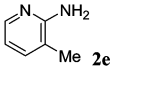
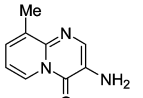
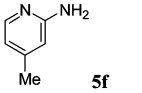
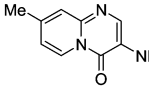
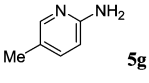
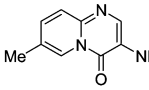
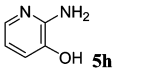
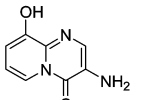
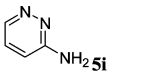
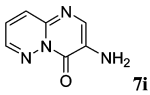
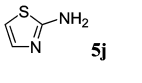
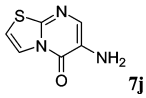
Scheme 1[a]



[a] Reaction conditions: (i) toluene, 100 °C; (ii) *t*-BuOCH(NMe_2)$_2$, toluene, 100 °C; (iii) pyridineacetic acid derivative (**5a**−**c**) or heterocyclic amine (**5d**−**j**), AcOH, 90 °C; (iv) TFA−CH_2Cl_2 (1:1), r.t.; (v) Dowex WX8-200 (H^+), then ∼2 M NH_3–MeOH.

Parallel Solution-Phase Synthesis of 3-Amino-4*H*-quinolizin-4-ones 7a−c, Fused 3-Amino-4*H*-pyrimidin-4-ones 7d−o, and Fused 3-Amino-2*H*-pyran-2-ones 7p−v from Methyl (*Z*)-2-Benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (8) (Method B). Since the solid-phase synthesis of a library of fused heterocyclic amines **7a**−**j** did not give products of sufficient purity, we turned our attention toward the solution-phase approach, which has been quite successful in the previously reported classical synthesis, especially with methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**8**) as the key reagent.[46,47] Thus, treatment of **8** with pyridineacetic acid derivatives **5a**−**c**, heterocyclic amidines **5d**−**o**, and 1,3-dicarbonyl compound analogues **5p**−**v** in acetic acid at 100 °C for 10 h afforded the corresponding cyclocondensation products **9a**−**v** as crystalline precipitates, which were filtered off, washed, and dried in vacuo (without taking them out of the reaction vessels). Intermediates **9a**−**v** were then treated with 33% HBr−AcOH at 50 °C to afford aminoquinolizinones **7a**−**c**, fused aminopyrimidinones **7d**−**o**, and fused aminopyranones **7p**−**v** hydrobromides as crystalline precipitates in 23−100% yields over two steps. Two novel intermediates, **9b** and **9f**, were also prepared separately by conventional synthesis and fully characterized. All compounds within this library were obtained in >90% purity, only upon filtration, washing, and thorough drying. In addition, compounds **7a**−**i**, **l**, **r**, **t**−**v** were obtained in analytically pure form (Scheme 2, Table 2).

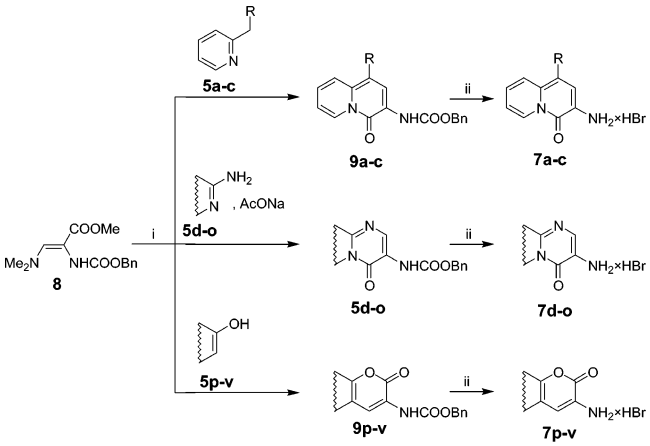
Table 1. Library of Fused Heteroarylamines **7a**−**j** Prepared by Method A

Dinucleophile →	Product	Yield[a] (%)	Purity[b] (%)
 **2a**	 **7a**	25	83
 **2b**	 **7b**	19	79
 **2c**	 **7c**	18	77
 **2d**	 **7d**	39	79
 **2e**	 **7e**	36	78
 **5f**	 **7f**	33	80
 **5g**	 **7g**	33	82
 **5h**	 **7h**	31	83
 **5i**	 **7i**	29	32
 **5j**	 **7j**	20	25

[a] Over two steps. [b] Products were characterized by IR, ^{1}H and ^{13}C NMR, MS, and HRMS. Purity was determined ^{1}H NMR.

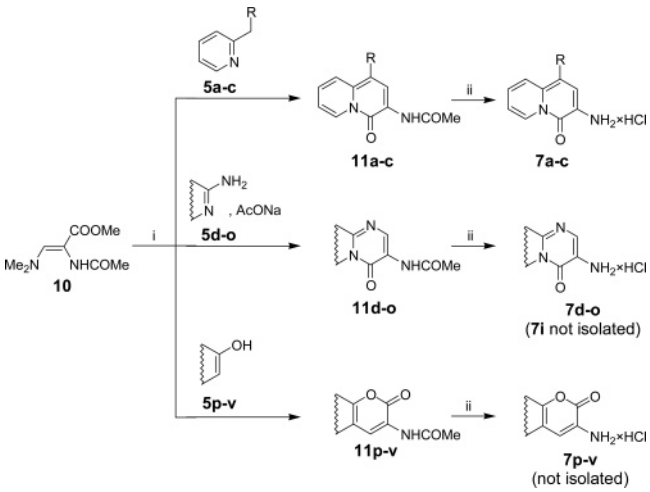
Parallel Solution-Phase Synthesis of 3-Amino-4*H*-quinolizin-4-ones 7a−c and Fused 3-Amino-4*H*-pyrimidin-4-ones 7d−h, j−o from Methyl (*Z*)-2-Acetylamino-3-(dimethylamino)prop-2-enoate (10) (Method C). Although the above-described solution-phase synthesis of amines **7a**−**v** hydrobromides from the propenoate **8** was quite efficient, its disadvantage was the formation of noxious and toxic benzyl bromide in the last, deprotection step. To avoid handling and disposal problems connected with benzyl bromide, we decided to study a variation of the above-described solution-phase approach. Thus, methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**10**)[53] was used as the starting propenoate and was treated with ambident nucleophiles **5a**−**v** in acetic acid at 100 °C for 10 h to afford the corresponding cyclocondensation products **11a**−**v**. Removal of the acetyl group was achieved by addition of 37% hydrochloric acid to the reaction mixtures and heating at 80 °C for 8 h to give the free amines **7a**−**v**. Subsequent cooling to 5 °C resulted in precipitation of the amines **7a**−**h**, **j**−**o** hydrochlorides, whereas the amines **7i**, **p**−**v** hydrochlorides did not precipitate. Upon filtration, washing, and thorough drying, the amines **7a**−**h**, **j**−**o** were obtained as hydrochlorides in 29−100% yields over two steps. Compounds **7i**, **p**−**v**, which did not precipitate from the cooled reaction mixtures, were not isolated, since we were particularly interested in a simple and practical procedure using just a filtration workup. However, formation of compounds **7i**, **p**−**v** was confirmed by TLC. The novel intermediates **11k**−**n**,**p** were also prepared separately by a classical synthesis and fully characterized. According to ^{1}H NMR, the purities of the products **7a**−**h**, **j**−**o** were found to be >90% only upon filtration, washing, and thorough drying. With the exception of 6-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**7j**) hydrochloride, 6-amino-2-methylpyrazolo[1,5-*a*]pyrimidin-7(1*H*)-one (**7l**) hydrochloride, 6-aminoimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**7n**) hydrochloride, and 6-amino[1,2,4]triazolo[1,5-*a*]pyrimidin-7(3*H*)-one (**7o**) hydrochloride, all other compounds were obtained in analytically pure form (Scheme 3, Table 3).

Scheme 2[a]



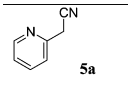
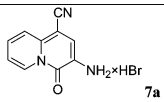
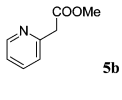
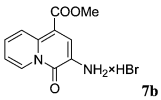
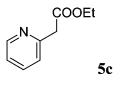
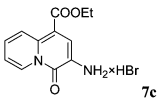
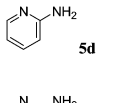
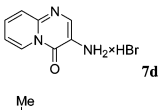
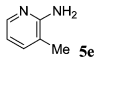
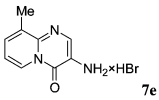
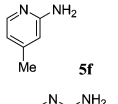
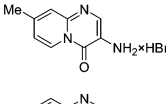
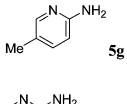
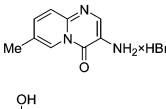
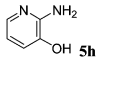
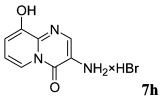
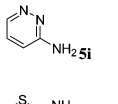
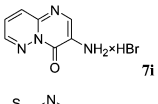
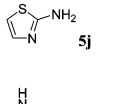
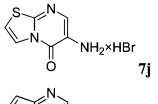
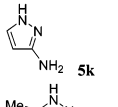
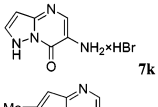
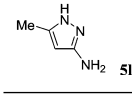
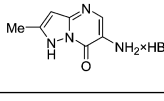
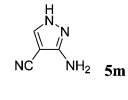
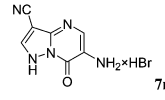
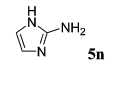
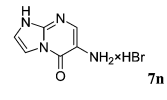
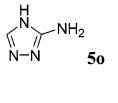
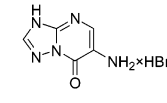
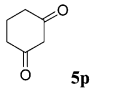
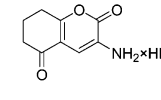
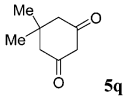
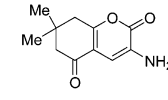
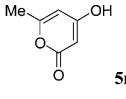
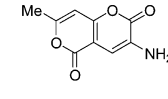
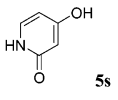
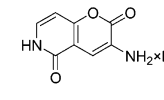
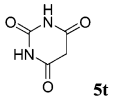
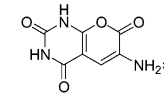
[a] Reaction conditions: (i) AcOH, 90 °C; (ii) 33% HBr−AcOH, 50 °C.

Scheme 3[a]



[a] Reaction conditions: (i) AcOH, 90 °C; (ii) 37% HCl (aq), AcOH, 80 °C.

Table 2. Library of Fused Heteroarylamines Hydrobromides **7a**−**v** Prepared by Method B

Dinucleophile	→	Product	Yield[a] (%)	Product Characterization[b]
 **5a**		 **7a**	79	A, B, D, E
 **5b**		 **7b**	54	A, B, D, E
 **5c**		 **7c**	23	A, B, D, E
 **5d**		 **7d**	100	A–E
 **5e**		 **7e**	79	A–E
 **5f**		 **7f**	100	A, B, D,E
 **5g**		 **7g**	93	A–E
 **5h**		 **7h**	86	A–E
 **5i**		 **7i**	73	A–E
 **5j**		 **7j**	72	B–E
 **5k**		 **7k**	100	B–E
 **5l**		 **7l**	100	A, B, D, E
 **5m**		 **7m**	99	B, D, E
 **5n**		 **7n**	95	B–E
 **5o**		 **7o**	81	B–E
 **5p**		 **7p**	62	A[c]–E
 **5q**		 **7q**	45	B–E
 **5r**		 **7r**	46	A, B, D, E
 **5s**		 **7s**	38	B–E
 **5t**		 **7t**	25	A, B, D, E
5u		**7u**	83	A, B, D, E
5v		**7v**	29	A, B, D, E

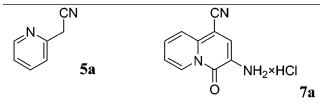
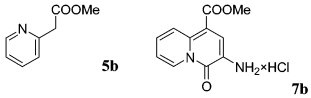
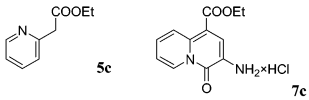
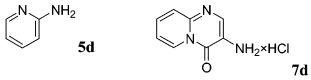
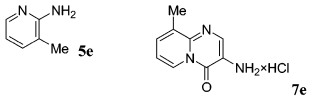
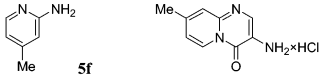
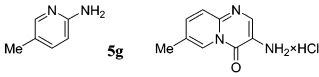
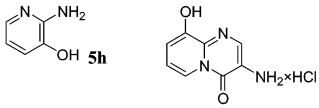
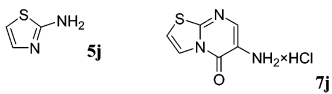
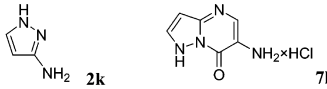
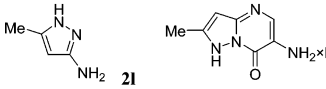
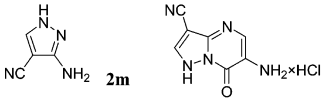
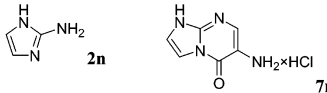
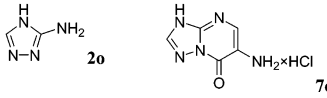
[a] Over two steps. [b] Characterization methods: (A) Elemental analysis with the found values within ±0.40% range with respect to the calculated values. Due to drying of products in vacuo at 100 °C prior to elemental analyses for C, H, and N, variable contents of HBr in the amine **7** hydrobromides were found. (B) ^{1}H NMR. (C) ^{13}C NMR. (D) MS. (E) HRMS. [c] The found value for carbon was within ±0.45% range with respect to the calculated value.

All three libraries of compounds **7a**−**v** were characterized by spectroscopic (IR, EI-MS, EI-HRMS, and ^{1}H and ^{13}C NMR) methods. Libraries of amine hydrobromides **7a**−**v** and amine hydrochlorides **7a**−**h**,**j**−**o**, prepared by methods B and C, respectively, were additionally characterized by elemental analyses for C, H, and N. Spectral data for known amines **7a**,**c**−**f**,**h**−**j**[46,47] and amine dihydrobromides **7k**,**l**,**n**,**o**[52] were in agreement with the literature data. Spectral data for novel hydrobromide and hydrochloride salts of amines **7a**−**v** were in agreement with spectral data for closely related heterocyclic compounds.[9−11,37,41] Amines **7a**−**j** (method A), amine **7j**,**k**,**m**,**n**−**q**,**s** hydrobromides (method B), and amine **7j**,**l**,**n**,**o** hydrochlorides (method C) were not prepared in analytically pure form. Their structures were confirmed by HRMS and ^{13}C NMR.

Conclusion

Three methods were developed for parallel synthesis of amino-substituted 4*H*-quinolizin-4-ones **7a**−**c**, fused 4*H*-pyrimidin-4-ones **7d**−**o**, and fused 2*H*-pyran-2-ones **7p**−**v**: (a) a two-step, solid-phase synthesis from polymer-bound ethyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**4**) (method A), (b) a two-step, solution-phase synthesis from methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**8**) (method B), and (c) a two-step, solution-phase synthesis from methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**10**) (method C). Although the solid-phase synthesis led to the desired product library, it was not successful due to low yields and insufficient purity of the products. On the other hand, both solution-phase syntheses showed advantages over the solid-phase approach

Table 3. Library of Fused Heteroarylamines Hydrochlorides **7a**−**h**,**j**−**o** Prepared by Method C

Dinucleophile **5** → Final Product **7**	Yield[a] (%)	Product Characterization[b]
 **5a** → **7a**	83	A–D
 **5b** → **7b**	31	A–E
 **5c** → **7c**	31	A–E
 **5d** → **7d**	93	A–E
 **5e** → **7e**	86	A–E
 **5f** → **7f**	74	A–E
 **5g** → **7g**	29	A, B,D,E
 **5h** → **7h**	100	A, B,D,E
 **5j** → **7j**	91	B–E
 **2k** → **7k**	78	A–E
 **2l** → **7l**	93	A–E
 **2m** → **7m**	80	B–E
 **2n** → **7n**	30	B–E
 **2o** → **7o**	80	A[c], B–E

[a] Over two steps. [b] Characterization methods: (A) Elemental analysis with the found values within ±0.40% range with respect to the calculated values. Due to drying of products in vacuo at 100 °C prior to elemental analyses for C, H, and N, variable contents of HCl in the amine **7** hydrochlorides were found. (B) ^{1}H NMR. (C) ^{13}C NMR. (D) MS. (E) HRMS. [c] The found value for carbon was within ±0.41% range with respect to the calculated value.

because (a) they afforded the desired heterocyclic amines in high purity and in moderate to high yields and (b) the products precipitated from the cooled reaction mixtures and were simply isolated by filtration. Thus, a library of 22 heterocyclic amines **7a**−**v** was prepared and isolated by method B; 14 amines (64%) were analytically pure. Similarly, the same library of amines **7a**−**v** was synthesized by method C; 14 of them (64%) were isolated as crystalline precipitates, 10 amines (45%) in analytically pure form. Comparison between both solution-phase methods shows that method B is certainly the most general and efficient; its only disadvantage is formation of noxious benzyl bromide in the last step. From this point of view, method C is more convenient, yet limited to the synthesis of aminoquinolizinones **7a**−**c** and aminopyrimidones **7d**−**h**,**j**−**o**. The results of this study confirm applicability of the propenoate methodology for parallel synthesis of aminoquinolizinones, fused aminopyrimidinones, and fused aminopyranones as heterocyclic scaffolds with incorporated α-amino acid structural element.

Experimental Section

Materials and General Methods. Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nuclei using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II.

Wang resin (loading capacity ∼1.1 mmol/g resin, 100−200 mesh, cross-linked with 1% DVB), Dowex WX8-200 ion-exchange resin (H^+ form), ethyl isocyanatoacetate (**2**), pyridineacetic acid derivatives **5a**−**c**, heterocyclic amines **5d**−**h**,**j**−**o**, and (hetero)cyclic 1,3-dicarbonyl compound analogues **5p**−**v** are commercially available (Sigma-Aldrich). 3-Aminopyridazine (**13g**),[54] methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**8**),[46] and methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**10**)[53] were prepared according to the literature procedures.

Parallel Synthesis. Parallel synthesis of compounds **7a**−**v** was carried out on a Mettler-Toledo Bohdan MiniBlock compact shaking and washing station and vacuum collection base (12 positions, vortex stirring, 300 rpm in all cases). All reactions were carried out in glass reaction vessels with fritted bottom (20 mL each). Before addition of reagents, the frits were wetted with acetic acid (∼0.5 mL each).

Preparation of Polymer-Bound Ethyl *N*-(Benzyloxycarbonyl)glycinate (3). Ethyl isocyanatoacetate **2** (5.7 mL, 49.5 mmol) was added to a stirred mixture of anhydrous toluene (90 mL) and Wang resin (4.500 g, 4.95 mmol), and the mixture was stirred at 80 °C for 9 h. The reaction mixture was cooled, and the product was collected by filtration; washed with (a) toluene (3 × 30 mL), (b) dichloromethane−toluene (1:1, 3 × 30 mL), (c) dichloromethane (3 × 30 mL), (d) dichloromethane−ethanol (1:1, 3 × 30 mL), and (e) dichloromethane (3 × 30 mL); and dried in vacuo at room temperature for 12 h to give **3** in 99% yield (5.083 g). IR (KBr) ν 1734 (C═O), 1725 (C═O) cm^{-1}.

Preparation of Polymer-Bound Ethyl 2-Benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (4). Bis-

(dimethylamino)-*tert*-butoxymethane (2.5 mL, 12.4 mmol) was added to a stirred mixture of anhydrous toluene (50 mL) and the resin **3** (4.675 g, 4.51 mmol), and the mixture was stirred at 90 °C for 11 h. The reaction mixture was cooled, and the product was collected by filtration; washed with (a) toluene (50 mL), (b) DMF (3 × 30 mL), (c) dichloromethane-DMF (1:1, 3 × 30 mL), and (d) dichloromethane (3 × 30 mL); and dried in vacuo for 12 h to give **4** in quantitative yield (4.986 g). IR (KBr) ν 1720 (C═O) cm^{-1}.

Solid-Phase Synthesis of 3-Aminoquinolizinones 7a−c and Fused Pyrimidones 7d−j (Method A). Mixtures of ambident nucleophiles **5a−j** (3 mmol), DMF (3 mL), anhydrous sodium acetate (25 mg, 0.3 mmol), and acetic acid (6 mL) were stirred at room temperature for 15 min. Then polymer-bound propenoate **4** (330 mg, 0.3 mmol) was added to each reaction mixture, and the suspensions were stirred at 90 °C for 16 h and cooled to room temperature. The reaction mixtures were filtered and washed with (a) AcOH−DMF (1:1, 2 × 15 mL), (b) DMF (2 × 15 mL), (c) dichloromethane−DMF (1:2, 2 × 15 mL, then 1:1, 2 × 15 mL), and (d) dichloromethane (2 × 15 mL) to give the polymer-bound heteroarylamines **6a−j**. Then dichlomethane (2 mL) and trifluoroacetic acid (2 mL) were added to each reaction vessel, and the mixtures were stirred at room temperature for 1 h. The reaction mixtures were filtered and washed with dichloromethane (2 × 3 mL) and DMF (2 mL). The combined filtrates were evaporated in vacuo to give crude heteroarylamines **7a−j**. The crude products were dissolved in methanol (5 mL) and poured back into the reaction vessels, and Dowex (H^+ form, 2.8 g) was added. The mixtures were stirred at room temperature for 8 h, filtered, and washed with (a) methanol (3 × 6 mL), (b) dichloromethane−methanol (2 × 5 mL), and (c) methanol (3 × 10 mL). The products were eluted from the resin with methanolic ammonia (2 M, 8 × 5 mL), and the combined filtrates were evaporated in vacuo to give compounds **7a−j**.

Experimental data for compounds **7a−j** are given in Table 1. Analytical and spectral data for compounds **7a−j** are given in the Supporting Information (Tables A and B).

Solution-Phase Synthesis of Compounds 7a−v (Method B). Mixtures of ambident nucleophiles **5a−v** (1.5 mmol), anhydrous sodium acetate (123 mg, 1.5 mmol), acetic acid (3 mL), and propenoate **8** (417 mg, 1.5 mmol) were stirred at 90 °C for 10 h and cooled to room temperature. Then water (1 mL) was added, the suspensions were stirred at 10 °C for 1 h, and the precipitates (intermediates **9a−v**) were collected by filtration and washed with water (5 mL). Then the reaction vessels with the intermediates **9a−v** were put in a desiccator and dried in vacuo over P_4O_{10} at room temperature for 24 h. The reaction vessels were mounted back into the MiniBlock, HBr−AcOH (33%, 3 mL) was added, and the mixtures were stirred at 50 °C for 3 h and cooled to 20 °C. The precipitates were collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo over sodium hydroxide pellets at room temperature for 24 h to give fused heteroarylamine hydrobromides **7a−v**.

Experimental data for compounds **7a−v** are given in Table 1. Analytical and spectral data for compounds **7a−j** are given in the Supporting Information (Tables C and D).

Solution-Phase Synthesis of Compounds 7a−v (Method C). Mixtures of ambident nucleophiles **5a−v** (1.5 mmol), acetic acid (3 mL), and propenoate **10** (280 mg, 1.5 mmol) were stirred at 100 °C for 10 h and cooled to room temperature. Then hydrochloric acid (37%, 3 mL) was added, and the mixtures were stirred at 80 °C for 8 h and cooled to 5 °C. The precipitates were collected by filtration, washed with ethyl acetate (5 mL), and dried in vacuo over sodium hydroxide pellets at room temperature for 24 h to give fused heteroarylamine hydrochlorides **7a−h**,**j−o**. 3-Amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrochloride (**7i**) and 3-amino-2*H*-pyran-2-ones hydrochlorides **7p−v** did not precipitate and were not isolated.

Experimental data for compounds **7a−h**,**j−o** are given in Table 1. Analytical and spectral data for compounds **7a−j** are given in the Supporting Information (Tables E and F).

General Procedure for the Preparation of Compounds 9b, e and 11k−n. A mixture of propenoate **8** or **10** (1 mmol), ambident nucleophile **5b**,**e**,**k−n** (1 mmol), and acetic acid (3 mL) was stirred at 100 °C for 1−6 h and cooled to room temperature, and the precipitate was collected by filtration and washed with water (5 mL) to give **9b**,**e** and **11k−n**.

The following compounds were prepared in this manner:

Methyl 3-benzyloxycarbonyl-4-oxo-4*H*-quinolizine-1-carboxylate (9b). Prepared from **8** (278 mg, 1 mmol) and methyl 2-pyridineacetate **5b** (151 mg, 1 mmol), 6 h. Yield: 237 mg (67%), mp 195−196 °C (toluene). IR (KBr) ν 3455, 3246, 1715 (C═O), 1699 (C═O), 1652 (C═O), 1634, 1556, 1531, 1484, 1436, 1221, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.93 (3H, s, Me), 5.26 (2H, s, CH_2), 7.13 (1H, ddd, J = 1.5, 6.6, 7.7 Hz, 7H), 7.31−7.46 (5H, m, Ph), 7.48 (1H, ddd, J = 1.5, 6.8, 9.4 Hz, 8H), 7.79 (1H, br s, NH), 9.13 (1H, deg dt, J = 1.1, 7.5 Hz, 9H), 9.23 (1H, deg. dt, J = 1.1, 9.4 Hz, 6H), 9.24 (1H, s, 2H). ^{13}C NMR ($CDCl_3$) δ 52.5, 67.6, 102.9, 116.6, 120.5, 124.5, 124.9, 127.7, 128.5, 128.8, 129.0, 130.6, 136.3, 139.6, 153.71, 154.0, 166.1. MS (EI): m/z = 352 (M^+). MS (FAB): m/z = 353 (MH^+). Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 65.09; H, 4.71; N, 7.93.

3-Benzyloxycarbonyl-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9e). Prepared from **8** (278 mg, 1 mmol) and 2-amino-5-methylpyridine **5b** (108 mg, 1 mmol), 1 h. Yield: 278 mg (90%), mp 152−153 °C (toluene). IR (KBr) ν 3294, 1724 (C═O), 1665 (C═O), 1643, 1535, 1481, 1441, 1227, 1192, 1128 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, d, J = 0.8 Hz, Me), 5.25 (2H, s, CH_2), 7.31−7.46 (6H, m, Ph, 8H), 7.52 (1H, br s, NH), 7.59 (1H, d, J = 9.0 Hz, 9H), 8.72 (1H, s, 6H), 9.21 (1H, br s, 2H). ^{13}C NMR ($CDCl_3$) δ 18.8, 67.8, 119.5, 124.1, 126.3, 126.5, 128.6, 128.8, 129.03, 136.2, 136.4, 140.2, 145.1, 153.3, 153.8. MS (EI): m/z = 309 (M^+). MS (FAB): m/z = 310 (MH^+); Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.24; H, 5.06; N, 13.42.

6-Acetylamino-1*H*,7*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (11k). Prepared from **10** (186 mg, 1 mmol) and 3-amino-1*H*-pyrazole **5k** (83 mg, 1 mmol), 3 h. Yield: 61 mg (32%), mp 299−303 °C. IR (KBr) ν 3315, 3129, 1673 (C═O), 1652 (C═O), 1579, 1545, 1471, 1456, 1372, 1362, 1272, 1264, 1204 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.07 (3H, s, COMe), 6.17 (1H, d, J = 2.0 Hz, 3H), 7.90 (1H, d, J = 2.0 Hz, 2H), 8.47 (1H, s, 5H), 9.30 (1H, br s, NHCOMe), 12.31 (1H, br s, NH). MS (EI): m/z = 192 (M^+). HRMS Calcd. for $C_8H_8N_4O_2$: m/z = 192.064 726 (M^+). Found: 192.065 250. Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.93; H, 4.36; N, 28.84.

6-Acetylamino-2-methyl-1*H*,7*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (11l). Prepared from **10** (186 mg, 1 mmol) and 3-amino-5-methyl-1*H*-pyrazole **5l** (97 mg, 1 mmol), 2 h. Yield: 169 mg (82%), mp >350 °C. IR (KBr) ν 3313, 3125, 1651 (C═O), 1586, 1545, 1485, 2337, 1273 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.06 (3H, s, COMe), 2.29 (3H, s, Me), 5.98 (1H, s, 3H), 8.41 (1H, s, 5H), 9.26 (1H, br s, NHCOMe), 12.11 (1H, br s, NH). MS (EI): m/z = 206 (M^+). HRMS Calcd. for $C_9H_{10}N_4O_2$: m/z = 206.080 376 (M^+). Found: 206.081 030. Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.50; H, 5.03; N, 27.09.

6-Acetylamino-3-cyano-1*H*,7*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (11m). Prepared from **10** (186 mg, 1 mmol) and 3-amino-4-cyano-1*H*-pyrazole **5m** (108 mg, 1 mmol), 2 h. Yield: 141 mg (65%), mp >350 °C. IR (KBr) ν 3546, 3345, 3122, 3003, 2884, 2798, 2232, 1660 (C═O), 1589, 1541, 1498, 1375, 1284, 1209 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.10 (3H, s, COMe), 8.42 (1H, s, 2H), 8.62 (1H, s, 5H), 9.54 (1H, br s, NHCOMe), 13.50 (1H, br s, NH). MS (EI): m/z = 217 (M^+). HRMS Calcd. for $C_9H_7N_5O_2$: m/z = 217.059 975 (M^+). Found: 217.060 450. Anal. Calcd. for $C_9H_7N_5O_2$: C, 49.77; H, 3.25; N, 32.25. Found: C, 49.48; H, 3.44; N, 31.99.

6-Acetylamino-1*H*,5*H*-imidazo[1,2-*a*]pyrimidin-5-one (11n). Prepared from **10** (186 mg, 1 mmol) and 2-aminoimidazole sulfate **5m** (278 mg, 1 mmol), 4 h. Yield: 63 mg (33%), mp 318−320 °C. IR (KBr) ν 3291, 2741, 2685, 1687 (C═O), 1668 (C═O), 1612, 1545, 1459, 1296, 1227 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.04 (3H, s, COMe), 7.52 (1H, d, J = 2.4 Hz, 2H), 7.63 (1H, d, J = 2.4 Hz, 3H), 8.35 (1H, s, 7H), 9.12 (1H, br s, NHCOMe), 12.52 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ 23.4, 107.4, 111.7, 120.0, 145.2, 146.0, 153.6, 169.3. MS (EI): m/z = 192 (M^+). HRMS Calcd. for $C_8H_8N_4O_2$: m/z = 192.064 726 (M^+). Found: 192.065 120. Anal. Calcd. for $C_8H_8N_4O_2 \cdot 0.2H_2O$: C, 49.08; H, 4.32; N, 28.62. Found: C, 49.13; H, 4.31; N, 28.64.

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Supporting Information Available. Analytical and spectral data for compounds **7a**−**v** obtained by methods A−F. This material is available free of charge via the Internet at http://pubs.acs.org.

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