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Article

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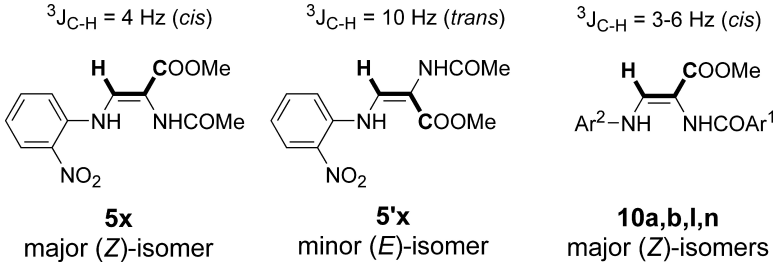

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Parallel Solution-Phase Synthesis of (*Z*)-3-(Arylamino)-2,3-dehydroalanine Derivatives and Solid-Phase Synthesis of Fused Pyrimidones

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N-Protected (*Z*)-3-(arylamino)-2,3-dehydroalanine esters **5** and **10** were prepared in one step from methyl (*Z*)-2-acylamino-3-(dimethylamino)prop-2-enoates **3** and **9** and anilines **4** employing a parallel solution-phase synthetic approach. In most cases, analytically pure products **5** and **10** were obtained. On the other hand, a three-step parallel solid-phase synthesis of 2-acetylamino-4*H*-azino[1,2-*x*]pyrimidin-4-ones **15** via the polymer-bound methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**12**) was also developped.

Introduction

In organic synthesis, especially in combinatorial chemistry, the use of versatile scaffolds, synthons, building blocks, and reagents is of great interest, since they enable the preparation of diversity-oriented compound libraries for medicinal and pharmaceutical aplications.[1−7] Especially, functionalized and highly substituted heterocycles have recently been found to be interesting scaffolds and target compounds due to their ability to mimic structures of peptides as well as their ability to bind reversibly to proteins.[3,8] On the other hand, α,*β*-unsaturated amino acids and their derivatives represent an important class of compounds having several applications, particularly as biologically active substrates or their constituents and as key intermediates in the synthesis of nonproteinogenic amino acids and heterocycles.[9−17]

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are an example of such a versatile group of reagents and building blocks. In the past decade, the studies in this area showed that 3-(dimethylamino)prop-2-enoates can be used as versatile reagents for the preparation of a variety of heterocyclic systems; 3-substituted 2,3-dehydroalanine derivative and analogues; functionalized heterocycles, such as heteroarylalanines and related types of compounds; heterocyclic analogues of amino acid and dipeptides; and natural products, such as aplysinopsins and their analogues. To date, several reviews on utilization of 3-(dimethylamino)prop-2-enoates and analogous reagents in heterocyclic synthesis have been published.[18−24] Various types of biologically active compounds are available from 3-(dimethylamino)prop-2-enoates and related enaminones: 3-arylamino-2,3-dehydroalanine esters have been used as intermediates in the synthesis of 3-(arylamino)alanine derivatives with anticancer activity,[25] and some aplysinopsins have been found to be cytotoxic[26] and affecting neurotransmission,[27] whereas 4*H*-pyridino[1,2-*a*]pyrimidin-4-one derivatives exhibit various biological activities.[28] Just recently, the use 3-(dimethylamino)prop-2-enoates in combinatoral synthesis of heterocycles has also been reported.[29,30]

Previously, we reported syntheses of various N-protected 3-(hetero)arylamino-2,3-dehydroalanine esters and fused pyrimidones with a bridgehead nitrogen atom from a series of alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and their analogues.[18−24] As an extension of our studies toward applications of 3-(dimethylamino)prop-2-enoates and related enaminones in combinatorial chemistry, we now report a one step solution-phase parallel synthesis of *N*-acyl-3-arylamino-2,3-dehydroalanine esters **5a**−**z** and **10a**−**x** and a three-step solid-phase parallel synthesis of fused 3-acetylamino-4*H*-pyrimidin-4-ones **15a**−**j** as functionalized heterocycles with incorporated α-amino acid structural element.

Results and Discussion

The first starting compound, methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**3**), was prepared from *N*-acetylglycine (**1**) via 4-[(dimethylamino)methylidene]-2-methyl-5(4*H*)-oxazolone (**2**), followed by base-catalyzed methanolysis, according to the literature procedure.[31] Treatment of **3** with anilines hydrochlorides **4a**−**v** in aqueous ethanol at room temperature afforded the corresponding dimethylamine substitution products **5a**−**w** in 62−100% yields. In the case of water-soluble aniline hydrochlorides **4a**−**o**, reactions were performed by mixing ethanolic solutions of **3** with aqueous solutions of aniline hydrochlorides **4a**−**o** (procedure A). A slightly modified procedure was employed for the preparation of compounds **4p**−**w**, in which aniline hydrochlorides **4p**−**v** were formed in situ by addition of 1 equiv of aqueous hydrochloric acid to solutions of **3** and the free anilines **4p**−**v** in ethanol (procedure B). In the reaction of **3** with diamine **4r**, selectivity was dependent on stoichiometric amounts of the diamine and hydrochloric acid.

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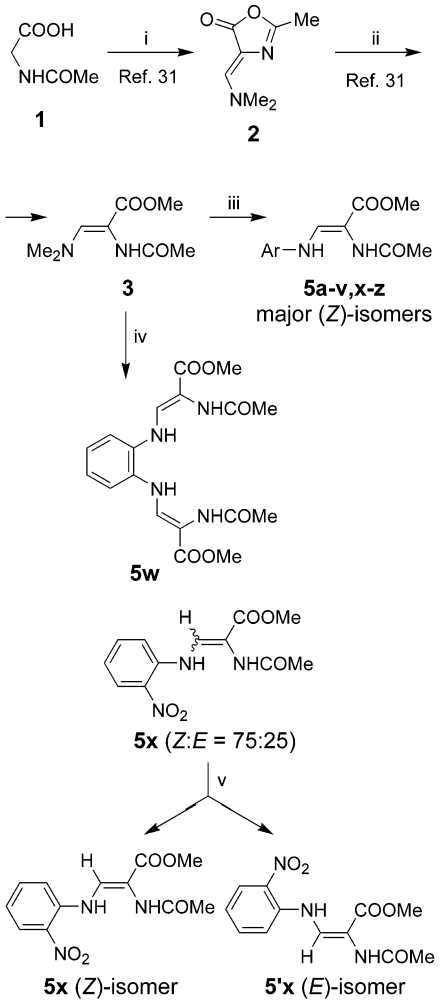
Scheme 1[a]

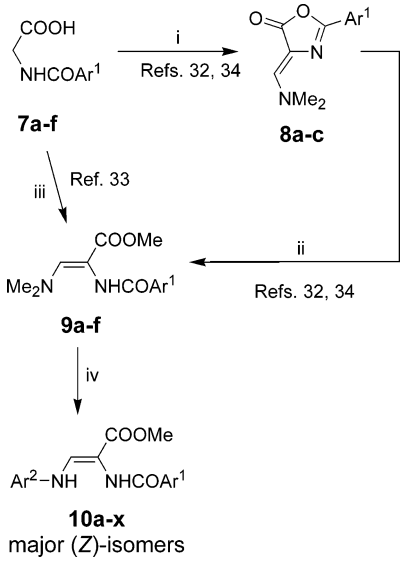


[a] Reaction conditions: (i) DMF−$POCl_3$, 0−45 °C; (ii) MeOH, K_2CO_3, reflux; (iii) Ar−NH_2 × HCl (**4a**−**y**, 1.5 equiv), EtOH−H_2O (1:1), 20 °C (procedures A and B) or 70 °C (procedure C); (iv) 1,2-benzenediamine × 2HCl (**4r**, 0.5 equiv), EtOH−H_2O (1:1), 20 °C (procedure B); (v) chromatographic separation.

Thus, the monosubstitution product **5r** was obtained selectively upon treatment of **3** with 1 equiv of benezene-1,2-diamine (**4r**) monohydrochloride, whereas reaction of **3** with 0.5 equiv of benzene-1,2-diamine (**4r**) dihydrochloride furnished the disubstitution product **5w** (procedure B). 2-Nitroaniline (**4w**), 2-amino-5-nitropyridine (**5x**), and 2,6-dimethylaniline (**4y**) did not react at room temperature. However, when the reactions were carried out at 70 °C, the corresponding substitution products **5x**−**z** were obtained in 32−69% yields (procedure C). In most cases, analytically pure compounds **5** were obtained upon filtration, washing, and thorough drying. Compounds **5b**,**k**,**n**−**p**,**r**−**t**,**v**,**w**,**y** were isolated as pure *Z* isomers, and compounds **5a**,**c**−**j**,**l**,**m**,**q**,**u**,**x**,**z** as mixtures of the major *Z* isomers **5** and the minor *E* isomers **5′**. The crude product **5x** (*Z*/*E* = 75:25), contained considerable amounts of the unreacted 2-nitroaniline (**4w**). Upon additional chromatographic purification, both isomers **5x** and **5′x** were separated and isolated in analytically pure form. In other cases, we were not able to separate the isomers (Scheme 1, Table 1).

In continuation, this methodology was applied on combinatorial solution-phase synthesis of methyl (*Z*)-2-aroylamino-3-(arylamino)prop-2-enoates **10a**−**x** by reacting methyl (*Z*)-2-aroylamino-3-(dimethylamino)prop-2-enoates **9a**−**f** with anilines hydrochlorides **4c**,**f**,**h**,**m**. Previously known propenoates **9a**−**c**,**e** were prepared from *N*-aroylglycines **7a**−**c**,**e** according to the literature procedures.[32−34] Novel propenoates **9d** and **9f** were prepared according to the one-step synthetic procedure[33] from **7d**,**f** and DMFDMA in 53 and 55% yield, respectively. Treatment of **9a**−**f** with aniline hydrochlorides **4c**,**f**,**h**,**m** in aqueous ethanol at room temperature afforded methyl (*Z*)-2-aroylamino-3-(arylamino)-prop-2-enoates **10a**−**x** in 70−91% yields. *N*-aroyl-3-arylamino-2,3-dehydroalanine esters **10d**−**i**,**l**,**p**,**t**,**x** were obtained as single *Z* isomers, whereas propenoates **10a**−**c**,**j**,**k**,**m**−**o**,**q**−**s**,**u**−**w** were obtained as inseparable mixtures of the major *Z* isomers and the minor *E* isomers. With exception of compound **10k**, all other products **10** were isolated in analytically pure form (Scheme 2, Table 2).

Scheme 2[a]



[a] Reaction conditions: (i) DMF−$POCl_3$, 0−45 °C; (ii) MeOH, KOH, rt; (iii) DMF−DMA (excess), toluene, reflux; (iv) Ar^2−NH_2 × HCl (**4c**,**f**,**h**,**m**, 1.5 equiv), EtOH−H_2O (1:1), 20 °C.

Finally, a library of 10 azino and thiazolo fused 3-acetylamino-4*H*-pyrimidin-4-ones **15a**−**j** was synthesized by the solid-phase approach. First, base-catalyzed treatment of the Wang resin (**11**) with the oxazolone **2** in toluene at 65 °C afforded the polymer-bound methyl 2-acetylamino-3-(dimethylamino)prop-2-enoate (**12**). Immobilized propenoate **12** was then treated with excess aminoazines **13a**−**i** and 2-aminothiazole (**13j**) in a mixture of toluene, DMF, and acetic acid at 60 °C to give the corresponding intermediates **14a**−**j**. Heating of **14a**−**j** in a mixture of toluene and acetic acid at 100 °C furnished 3-acetylamino-4*H*-azino[1,2-*x*]-pyrimidin-4-ones **15a**−**i** and 6-acetylamino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**15j**) in 10−85% yields over 3 steps. The yields were calculated on the basis of loading capacity of the commercially available Wang resin (**11**). Reactions of **12** with the 2-aminopyridine (**13a**), 2-aminopicolines **13b**−**d**, and 2-amino-3-hydroxypyridine (**13e**) afforded analytically pure 4*H*-pyridino[1,2-*x*]pyrimidin-4-ones **15a**−**e** in 63−88% yields. On the other hand, the yields (10−50%) and the purity of products **15f**−**j**, obtained upon treatment of **12** with the

Table 1. Library of Methyl 2-Acetylamino-3-arylaminopropenoates **5a**−**z**

reaction	Ar	method	yield (%)	*Z*/*E*	purity[a]
3 + **4a** → **5a**	phenyl	A	73	91:9	
3 + **4b** → **5b**	2-methylphenyl	A	88	100:0	
3 + **4c** → **5c**	3-methylphenyl	A	90	90:10	
3 + **4d** → **5d**	4-methylphenyl	A	78	90:10	
3 + **4e** → **5e**	2-methoxyphenyl	A	79	86:14	
3 + **4f** → **5f**	3-methoxyphenyl	A	94	91:9	
3 + **4g** → **5g**	4-methoxyphenyl	A	87	91:9	
3 + **4h** → **5h**	2-bromophenyl	A	81	91:9	
3 + **4i** → **5i**	3-bromophenyl	A	92	92:8	
3 + **4j** → **5j**	4-bromophenyl	A	100	91:9	
3 + **4k** → **5k**	2-hydroxyphenyl	A	82	100:0	
3 + **4l** → **5l**	3-hydroxyphenyl	A	62	90:10	
3 + **4m** → **5m**	4-hydroxyphenyl	A	91	90:10	
3 + **4n** → **5n**	4-fluorophenyl	A	72	100:0	±1.30% HRMS, NMR
3 + **4o** → **5o**	3-chloro-4-fluorophenyl	A	93	100:0	
3 + **4p** → **5p**	3-nitrophenyl	B	96	100:0	
3 + **4q** → **5q**	4-nitrophenyl	B	72	81:19	
3 + **4r** → **5r**	2-aminophenyl	B	81	100:0	
3 + **4s** → **5s**	4-(phenylazo)phenyl	B	95	100:0	
3 + **4t** → **5t**	4-carboxy-2-hydroxyphenyl	B	79	100:0	±1.20% HRMS, NMR
3 + **4u** → **5u**	3-benzoylphenyl	B	77	94:6	
3 + **4v** → **5v**	1-naphthyl	B	78	100:0	
3 + **4r** → **5w**	1,2-phenylene	B	73	100:0	
3 + **4w** → **5x** + **5′x**	2-nitrophenyl	C	69 (*Z*/*E*)[b]	75:25[b]	
			28 (*Z*)	100:0	
			11 (*E*)	0:100	
3 + **4x** → **5y**	5-nitropyridin-2-yl	C	32	100:0	±1.60% HRMS, NMR
3 + **4y** → **5z**	2,6-dimethylphenyl	C	63	87:13	±0.60% HRMS, NMR

[a] Purities of products were determined by elemental analyses for C, H, and N. Unless otherwise stated, the found values were within a ±0.40% range with respect to the calculated values. [b] Crude product before chromatographic separation.

Table 2. Library of Methyl 2-Aroylamino-3-arylaminopropenoates **10a**−**x**

reaction	Ar[1]	Ar[2]	yield (%)	*Z*/*E*	purity[a]
7a + **4c** → **10a**	phenyl	3-methylphenyl	89	91:9	
7a + **4f** → **10b**	phenyl	3-methoxyphenyl	84	92:8	
7a + **4h** → **10c**	phenyl	2-bromophenyl	81	80:20	
7a + **4m** → **10d**	phenyl	4-hydroxyphenyl	70	100:0	
7b + **4c** → **10e**	4-methylphenyl	3-methylphenyl	91	100:0	
7b + **4f** → **10f**	4-methylphenyl	3-methoxyphenyl	88	100:0	
7b + **4h** → **10g**	4-methylphenyl	2-bromophenyl	77	100:0	
7b + **4m** → **10h**	4-methylphenyl	4-hydroxyphenyl	84	100:0	
7c + **4c** → **10i**	2-chlorophenyl	3-methylphenyl	80	100:0	
7c + **4f** → **10j**	2-chlorophenyl	3-methoxyphenyl	77	89:11	
7c + **4h** → **10k**	2-chlorophenyl	2-bromophenyl	82	89:11	±0.60%
7c + **4m** → **10l**	2-chlorophenyl	4-hydroxyphenyl	79	100:0	
7d + **4c** → **10m**	3-chlorophenyl	3-methylphenyl	82	95:5	
7d + **4f** → **10n**	3-chlorophenyl	3-methoxyphenyl	91	88:12	
7d + **4h** → **10o**	3-chlorophenyl	2-bromophenyl	75	83:17	
7d + **4m** → **10p**	3-chlorophenyl	4-hydroxyphenyl	78	100:0	
7e + **4c** → **10q**	4-chlorophenyl	3-methylphenyl	85	94:6	
7e + **4f** → **10r**	4-chlorophenyl	3-methoxyphenyl	91	91:9	
7e + **4h** → **10s**	4-chlorophenyl	2-bromophenyl	81	89:11	
7e + **4m** → **10t**	4-chlorophenyl	4-hydroxyphenyl	83	100:0	
7f + **4c** → **10u**	3-methoxyphenyl	3-methylphenyl	89	90:10	
7f + **4f** → **10v**	3-methoxyphenyl	3-methoxyphenyl	91	93:7	
7f + **4h** → **10w**	3-methoxyphenyl	2-bromophenyl	81	67:33	
7f + **4m** → **10x**	3-methoxyphenyl	4-hydroxyphenyl	87	100:0	

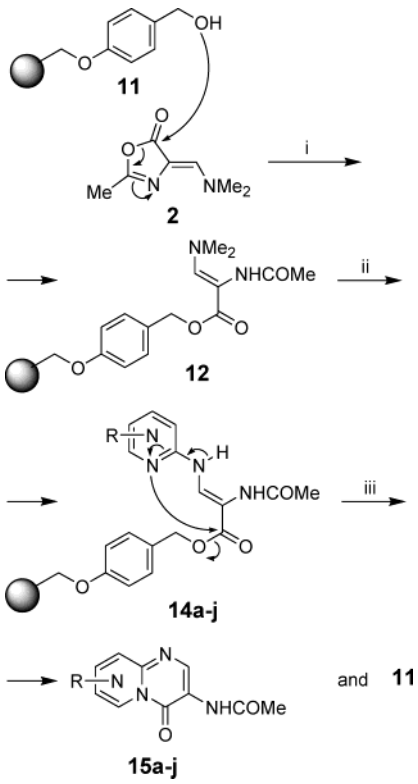
[a] Purities of products were determined by elemental analyses for C, H, and N. Unless otherwise stated, the found values were within ± 0.4% range with respect to the calculated values.

less reactive amines **13f**−**j**, were substantially lower, and their identity was characterized by NMR and EI-HRMS (Scheme 3, Table 3).

Compounds **5a**−**z**, **9d**,**f**, **10a**−**x**, and **15a**−**j** were characterized by spectroscopic (IR, EI-MS, EI-HRMS, ^{1}H and ^{13}C NMR) and elemental analyses. Spectral data for known compounds **5y** and **15a**,**e**,[31] **10a**,**b**,[35] and **15j**[36] were in agreement with the literature data. Spectral data for all other products **5**, **10**, and **15** were in agreement with spectral data for closely related propenoates and fused pyrimidones.[21,24]

Configuration around the C═C double bond in propenoates **5x**, **5′x**, and **10a**,**b**,**l**,**n** was determined by NMR (HMBC

Scheme 3[a]



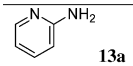
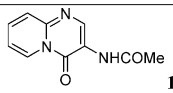
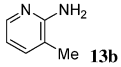
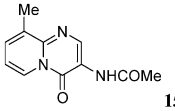
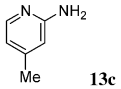
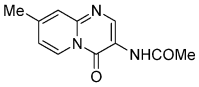
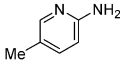
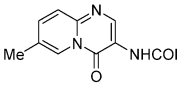
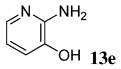
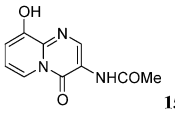
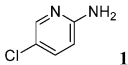
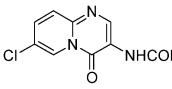
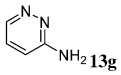
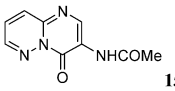
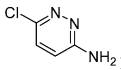
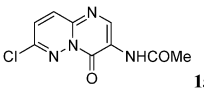
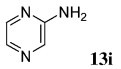
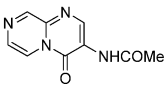
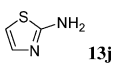
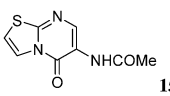
[a]Reaction conditions: (i) toluene, *t*-BuOK, 18-crown-6, 65 °C; (ii) heterocyclic amine **13a**−**j**, toluene−DMF−AcOH, 60 °C; (iii) toluene−AcOH, 100 °C.

technique) on the basis of the magnitude of the long-range $^{13}C-^{1}H$ heteronuclear coupling constant, $^{3}J_{C-H}$, which is generally smaller for cis-oriented nuclei (2−6 Hz) than for trans-oriented nuclei (8−12 Hz).[24,37−41] The *Z* configuration was established for the major isomer **5x** ($^{3}J_{C-H} = 4$ Hz) and the *E* configuration for the minor isomer **5′x** ($^{3}J_{C-H} = 10$ Hz). Similarly, the magnitudes of the coupling constant ($^{3}J_{C-H} = 3-6$ Hz) showed the *Z* configuration for the major isomers of compounds **10a**,**b**,**l**,**n** (Figure 1).

Conclusion

A library of 50 methyl (*Z*)-*N*-acyl-3-(arylamino)-2,3-dehydroalaninates **5a**−**z**, **10a**−**x** was prepared in one step from aniline hydrochlorides **4a**−**y** and methyl (*Z*)-2-acylamino-3-(dimethylamino)prop-2-enoates **3**, **9a**−**f** using a parallel solution-phase synthetic approach. Within this library, 21 compounds (**5b**,**k**,**n**−**p**,**r**−**t**,**v**,**w**,**y** and **10d**−**i**,**l**,**p**,**t**,**x**) were obtained as pure *Z* isomers, while other compounds were obtained as inseparable mixtures of the major *Z* isomers and the minor *E* isomers. An exception was methyl (*E*/*Z*)-*N*-acetyl-3-(2-nitrophenylamino)-2,3-dehydroalaninate **5′x**/**5x**, from which both isomers were obtained in pure form upon chromatographic separation. Additionally, a library of 10 α-acetylamino-substituted azino and thiazolo fused pyrimidin-4-ones **15a**−**j** as functionalized heterocycles, containing an α-amino acid structural element, was prepared in a 3-step parallel solid-phase synthesis via the polymer-bound methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**12**). The results of the solution-phase synthesis are encouraging, especially due to simplicity of the synthesis and high purity of the products. Ninety percent of *N*-acyl-3-arylamino-2,3-dehydroalanine esters **5** and **10** were obtained in analytically pure form. However, the solid-phase synthesis of fused pyrimidones **15a**−**j** via the polymer-bound propenoate **12** turned out to be limited to the synthesis of pyridino and pyridazino fused pyrimidones **15b**−**d**,**g** with either no substituents (**15a**,**g**) or with electron-releasing substituents attached to the azine ring (**15b**−**d**). The yields and purity of the other products **15f**,**h**−**j** were low. For the preparation of libraries of fused pyrimidones, the solid-phase approach could be advantageous to the classical solution-phase approach, since isolation is easier and no purification of the products is necessary. In conclusion, the results of this and other recent studies[29,30] indicate that alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and their analogues can also be employed in combinatorial synthetic applications.

Table 3. Library of Acetylamino-Substituted Fused Pyrimidones **15a**−**j**

Aminoazine **13**	Product **15**	Yield (%)[a]	Product Characterization[b]
 **13a**	 **15a**	85	A, B
 **13b**	 **15b**	84	A, B
 **13c**	 **15c**	79	A[c], B–D
 **13d**	 **15d**	88	A, B
 **13e**	 **15e**	63	A, B
 **13f**	 **15f**	24	B–D
 **13g**	 **15g**	50	B, D
 **13h**	 **15h**	24	B, D
 **13i**	 **15i**	10	B, D
 **13j**	 **15j**	11	B–D

[a] Calculated on the basis of loading capacity of the commercially available Wang resin (**11**). [b] Characterization methods: (A) elemental analysis with the found values within a ±0.40% range with respect to the calculated values; (B) ^{1}H NMR; (C) ^{13}C NMR; (D) EI-HRMS. [c] The found value for carbon was within a ±0.45% range with respect to the calculated value.

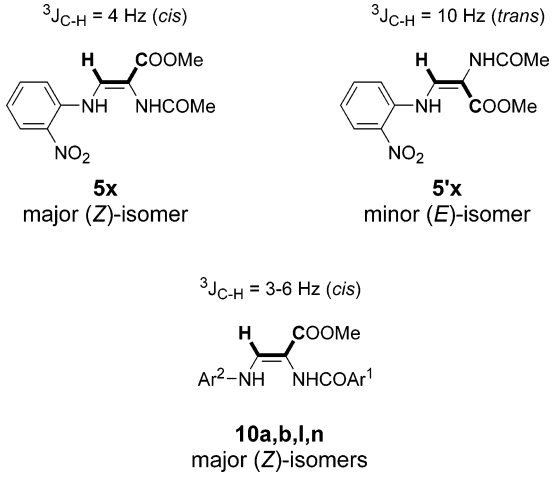


Figure 1. Determination of configuration around the C═C double bond by NMR (HMBC technique).

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 nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard as solvents. The magnitudes of the long-range $^{13}C-^1H$ heteronuclear coupling constants, $^3J_{C-H}$, were measured by Keeler's method[42,43] from the HMBC correlation spectra. 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. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04−0.06 mm). The *Z*/*E* ratio of the isolated compounds **5** and **10** were determined by ^{1}H NMR. With the exception of compound **5′x**, the minor *E* isomers **5′** and **10′** were not isolated and were characterized only by ^{1}H NMR.

N,*N*-Dimethylformamide dimethyl acetal (DMFDMA), 18-crown-6, potassium *tert*-butoxide, *N*-acetylglycine (**1**), anilines **4a**−**y**, *N*-benzoylglycine (**7a**), Wang resin (loading capacity ∼ 1.1 mmol/g resin, 100−200 mesh, cross-linked with 1% DVB), and heterocyclic amines **13a**−**f**,**i**,**j** are commercially available (Fluka AG). 4-[(Dimethylamino)methylidene-2-methyl-4*H*-oxazol-5-one (**2**), methyl (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate (**3**),[31] *N*-(3-chlorobenzoyl)-glycine (**7d**),[44] *N*-(3-methoxybenzoyl)glycine (**7f**),[45] methyl (*Z*)-2-benzoylamino-3-(dimethylamino)prop-2-enoate (**9a**),[32] methyl (*Z*)-2-aroylamino-3-(dimethylamino)prop-2-enoates **9b**,**c**,**e**,[34] 3-aminopyridazine (**13g**), and 3-amino-6-chloropyridazine (**13h**)[46] were prepared according to the literature procedures.

Parallel Synthesis. Parallel synthesis of compounds **5**, **10**, and **15** 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 bottoms (20 mL each). Before addition of reagents, the frits were wetted with ethanol (∼0.5 mL each).

General Procedures for the Synthesis of Methyl (*Z*)-2-Acetylamino-3-(arylamino)propenoates 5a−z. Procedure A: Synthesis of Compounds 5a−o. Mixtures of aqueous solutions of aniline hydrochlorides **4a**−**o** (0.5 M in water, 1.5 mL = 0.75 mmol) and ethanolic solution of **3** (0.5 M in ethanol, 1 mL = 0.5 mmol) were stirred at room temperature (rt) for 2 h. During this time, precipitation of the products occurred. The precipitates were collected by filtration, washed with 50% aqueous ethanol (1.5 mL) and water (10 mL) and dried first in a desiccator in vacuo at rt for 2 h, then in a drying oven at 70 °C for 5 h, and finally, in a desiccator in vacuo over sodium hydroxide pellets for 24 h to give compounds **5a**−**o**.

Procedure B: Synthesis of Compounds 5p−v. Mixtures of anilines **4p**−**v** (0.55 mmol) and ethanolic solution of **3** (0.5 M in ethanol, 1 mL = 0.5 mmol) were stirred at rt for ∼1 min until complete dissolution of the anilines **4p**−**v**. Then hydrochloric acid (1 M in water, 0.5 mL = 0.5 mmol) was added, and stirring was continued at rt for 2.5 h. During this time, precipitation of the products occurred. The precipitates were collected by filtration, washed with 50% aqueous ethanol (1.5 mL) and water (10 mL), and dried as described above for compounds **5a**−**o** to give compounds **5p**−**v**.

Synthesis of Compound 5w. Compound **5w** was prepared from **3** (0.5 M in ethanol, 1 mL = 0.5 mmol) and **4r** (0.027 g, 0.25 mmol) according to procedure B.

Procedure C: Synthesis of Compounds 5x−z. Mixtures of anilines **4w**−**y** (0.55 mmol) and ethanolic solution of **3** (0.5 M in ethanol, 1 mL = 0.5 mmol) were stirred at rt for a ∼1 min until complete dissolution of the anilines **4w**−**y**. Then hydrochloric acid (1 M in water, 0.5 mL = 0.5 mmol) was added, and stirring was continued at 70 °C for 10 h. The reaction mixtures were cooled to 20 °C, water (5 mL) was added, and the reaction mixtures were filtered. Upon filtration and standing at rt for 12 h, precipitation of the products occurred. Water (5 mL) was added, the suspensions were transferred back into the filtration vessels, and the precipitates were collected by filtration and dried as described above for compounds **5a**−**o** to give compounds **5x**−**z**.

Both isomers of the crude product **5x** (*Z*/*E* = 75:25) were separated by column chromatography (ethyl acetate). Fractions containing the products were combined and evaporated in vacuo to afford the major *Z* isomer **5x** and the minor *E* isomer **5′x**.

Experimental data for compounds **5a**−**z** are given in Table 1. Analytical and spectral data for compounds **5a**−**z** are given in the Supporting Information (Tables A and B).

Synthesis of Methyl-(*Z*)-2-[(3-chlorobenzoyl)amino]-3-(dimethylamino)propenoate (9d). Compound **9d** was prepared from *N*-(3-chlorobenzoyl)glycine (**7d**, 2.136 g, 10 mmol) and DMFDMA (6 mL, 40 mmol) according to the procedure reported previously for the synthesis of the propenoate **9a**.[33] Yield: 1.519 g (53%), mp 140−145 °C (toluene). IR (KBr) ν 3287, 2941, 1697 (C═O ester), 1643 (C═O amide), 1615, 1524, 1427, 1284, 1219, 1081, 949, 762, 689 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.96 (6H, s, NMe_2), 3.54 (3H, s, OMe), 7.37 (1H, s, CH), 7.49−7.56 (1H, m, 1H of Ar), 7.59−7.65 (1H, m, 1H of Ar), 7.82−7.88 (1H, m, 1H of Ar), 7.90−7.94 (1H, m, 1H of Ar), 9.14 (1H, s,

NH). MS (EI): $m/z = 282$ (M^+); HRMS (EI): $C_{13}H_{15}ClN_2O_3$ calcd 282.077120; found 282.077680. Anal. Calcd for $C_{13}H_{15}ClN_2O_3$: C, 55.23; H, 5.35; N, 9.91. Found: C, 55.01; H, 5.44; N, 10.15.

Synthesis of Methyl-(*Z*)-2-[(3-methoxybenzoyl)amino]-3-(dimethylamino)propenoate (9f). Compound **9f** was prepared according to the modified procedure reported previously for the synthesis of the propenoate **9a**.[33] A mixture of *N*-(3-methoxybenzoyl)glycine (**7f**, 2.092 g, 10 mmol), anhydrous toluene (10 mL), and DMFDMA (6 mL, 40 mmol) was heated under reflux for 4h and cooled, and the volatile components were evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate). Fractions containing the product were combined and evaporated in vacuo to give **9f**. Yield: 1.530 g (55%), mp 124−126 °C (ethyl acetate). IR (KBr) ν 3251, 2943, 1692 (C═O ester), 1641 (C═O amide), 1609, 1524, 1435, 1298, 1238, 1219, 1086, 803, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.03 (6H, s, NMe_2), 3.68 and 3.86 (6H, 2s, 1:1, 2 × OMe), 7.00 (1H, s, NH), 7.03 (1H, m, 1H of Ar), 7.31−7.40 (2H, m, 2H of Ar), 7.40−7.44 (1H, m, 1H of Ar), 7.46 (1H, s, CH). MS (EI): $m/z = 278$ (M^+); HRMS (EI): $C_{14}H_{18}N_2O_4$ calcd 278.126657; found 278.127350. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.03; H, 6.49; N, 10.19.

General Procedure for the Synthesis of Methyl (*Z*)-2-Aroylamino-3-(arylamino)propenoates 10a−x. Mixtures of ethanolic solutions of propenoates **7a**−**f** (0.1 M in ethanol, 5 mL = 0.5 mmol) and aqueous solutions of anilines hydrochlorides **4c**,**f**,**h**,**m** (0.5 M in water, 1.5 mL = 0.75 mmol) were stirred at rt for 12 h. During this time, precipitation of the products occurred. The precipitates were collected by filtration, washed with water (10 mL), and dried (a) in a desiccator in vacuo at rt for 2 h, (b) in a drying oven at 100 °C for 5h, and (c) in a desiccator in vacuo over sodium hydroxide pellets for 24 h to give compounds **10a**−**x**.

Experimental data for compounds **10a**−**x** are given in Table 2. Analytical and spectral data for compounds **10a**−**x** are given in the Supporting Information (Tables C and D).

Preparation of Polymer-Bound 2-Acetylamino-3-(dimethylamino)propenoate (12). Oxazolone **2** (4.00 g, 26 mmol) was added to a stirred mixture of anhydrous toluene (100 mL), potassium *tert*-butoxide (0.078 g, 0.78 mmol), 18-crown-6 (0.130 g, 0.52 mmol), and Wang resin (5.200 g, 5.72 mmol), and the mixture was stirred at 65 °C for 5 h. The reaction mixture was cooled, and the product was collected by filtration and washed with toluene (100 mL), dichloromethane-toluene (1:1, 100 mL), and dichloromethane (100 mL) to give **12** in quantitative yield (6.081 g).

Preparation of Fused Pyrimidones 15a−j. Mixtures of heterocyclic amines **13a**−**j** (0.55 mmol), toluene (6 mL), and DMF (3 mL) were stirred at 80 °C for ∼30 min until complete dissolution of amines **13a**−**j** and cooled to 60 °C. Then acetic acid (100%, 0.21 mL, 3.5 mmol) and polymer-bound propenoate **12** (0.526 g, 0.495 mmol) were added, and stirring was continued at 59 °C for 62 h. During this time, another six portions of acetic acid (100%, 6 × 0.21 mL, 6 × 3.5 mmol) were added in 9-h intervals. The reaction mixtures were filtered hot and washed with warm (∼50 °C) (a) toluene−DMF (1:1, 2 × 15 mL), (b) DMF (2 × 10 mL), (c) dichloromethane−DMF (1:1, 10 mL), and dichloromethane (2 × 5 mL) to give the polymer-bound propenoates **14a**−**j**. Then toluene (6 mL) and acetic acid (3 mL) were added, and the reaction mixtures were stirred at 100 °C for 13 h. The reaction mixtures were filtered hot and washed with warm (∼50 °C) (a) toluene−DMF−AcOH (4:2:1, 5 mL), (b) DMF (5 mL), (c) DMF−dichloromethane (1:1, 3 mL), and (d) dichloromethane (3 × 5 mL). The combined filtrates were evaporated in vacuo to give fused pyrimidones **15a**−**j**.

Experimental data for compounds **15a**−**j** are given in Table 3. Analytical and spectral data for compounds **15a**−**j** are given in the Supporting Information (Tables E and F).

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Supporting Information Available. Analytical and spectral data for compounds **5a**−**z**, **5′x**, **10a**−**x**, and **15a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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