JOURNAL OF combinatorial CHEMISTRY

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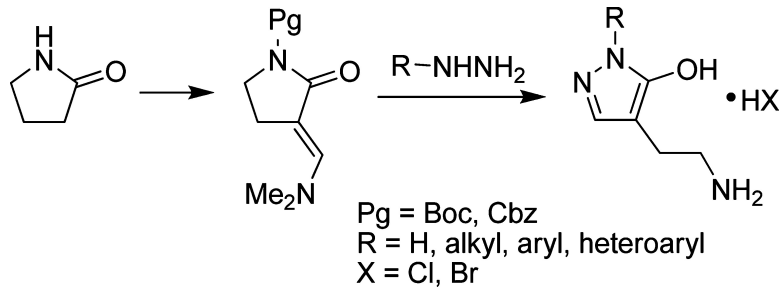
J. Comb. Chem., **2008**, 10 (5), 664-670• DOI: 10.1021/cc8000794 • Publication Date (Web): 17 July 2008



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One-Pot Parallel Solution-Phase Synthesis of 1-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols†

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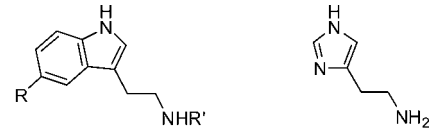
Received May 12, 2008

Two variations of enaminone-based parallel solution-phase synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8** and their NH-tautomers **8′** were developed. The synthetic strategy comprises a two step preparation of the *N*-protected α-enamino lactams **3a** and **3b** from 2-pyrrolidinone (**1**), "ring switching" transformation of **3a**,**b** with monosubstituted hydrazines **4a**−**u**, and acidolytic removal of the *N*-protecting group. In order to ensure a clean and fast conversion, reactions of Cbz-enaminone **3a** with hydrazines **4a**−**k** were carried out under microwave irradiation to afford the "ring-switched" intermediates **7a**−**k**. Deprotection of **7a**−**k** with HBr−AcOH at 50 °C gave a library of 11 analytically pure 4-(2-aminoethyl)-1*H*-pyrazol-5-ols (di)hydrobromides **8/8'a**−**k** in 16−75% yields over two steps. The other reagent, Boc-enaminone **3b**, was more reactive and ring switching transformations with hydrazines **4b**,**d**,**k** proceeded smoothly and cleanly under conventional heating. Finally, a parallel one-pot transformation of the Boc-enaminone **3b** with hydrazines **4a**−**u** followed by subsequent deprotection of the intermediates **9a**−**u** with HCl−EtOAc furnished a library of 21 analytically pure 4-(2-aminoethyl)-1*H*-pyrazol-5-ols (di)hydrochlorides **8/8'a**−**u** in 40−100% yields.

Introduction

Various functionalized monocyclic, fused, and spiro heterocycles represent important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications, due to their ability to mimic structures of peptides and reversibly bind proteins.[1–5] 2-(Heteroaryl)ethylamines, such as tryptamine, serotonine, melatonin, and histamine (Figure 1) are representative chemical messengers playing a crucial role in biological processes. Therefore, the preparation of their novel synthetic analogs represents an important target in medicinal and synthetic organic chemistry. Within this context, combinatorial synthesis of libraries of novel 2-(heteroaryl)ethylamine derivatives and analogues is of particular interest.[1–6]

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related α-enamino ketones, α-enamino esters, and α-enamino amides are easily available and versatile reagents in the preparation of heterocycles.[7] In addition to their utilization in the synthesis of heterocyclic systems, enaminones have also been widely used as the key intermediates in the synthesis of functionalized heterocycles and natural product analogues.[7–9] Recently, enaminones have also found use in combinatorial applications.[10–14]



tryptamine (R = R' = H)
serotonine (R = OH, R' = H)
melatonin (R = OMe, R' = Ac)

histamine

Figure 1

Cyclocondensations of enaminones with hydrazine derivatives represent a convenient way for a regioselective synthesis of pyrazoles.[7,8,15] Within this context, several regioselective syntheses of pyrazole derivatives functionalized with a carboxy,[16] terpene,[17] alanine,[18] β-amino alcohol, 2-phenylethylamine,[19] and diol[20] structural motif have been developed. Recently, we reported a simple enaminone-based method for the preparation of 4-(2-aminoethyl)-1*H*-pyrazol-5-ols as the pyrazole analogues of histamine utilizing 1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]pyrrolidin-2-one as the key-intermediate.[21] Though very efficient for the conventional synthesis of pyrazoles with common alkyl and (hetero)aryl substituents at the ring nitrogen atom, a disadvantage of this method are harsh hydrolytic conditions (refluxing in 6 N aq. HCl) required for the removal of the benzoyl group in the last (deprotection) step. These reaction conditions do not allow the presence of hydrolytically labile functional groups, such as cyano, ester, and carboxamido group. Besides, somehow tedious isolation of the final products makes this method unsuitable for application in high-throughoutput synthesis of the title compounds. In order

† Dedicated to Professor Branko Stanovnik, University of Ljubljana, on the occasion of his 70th anniversary.

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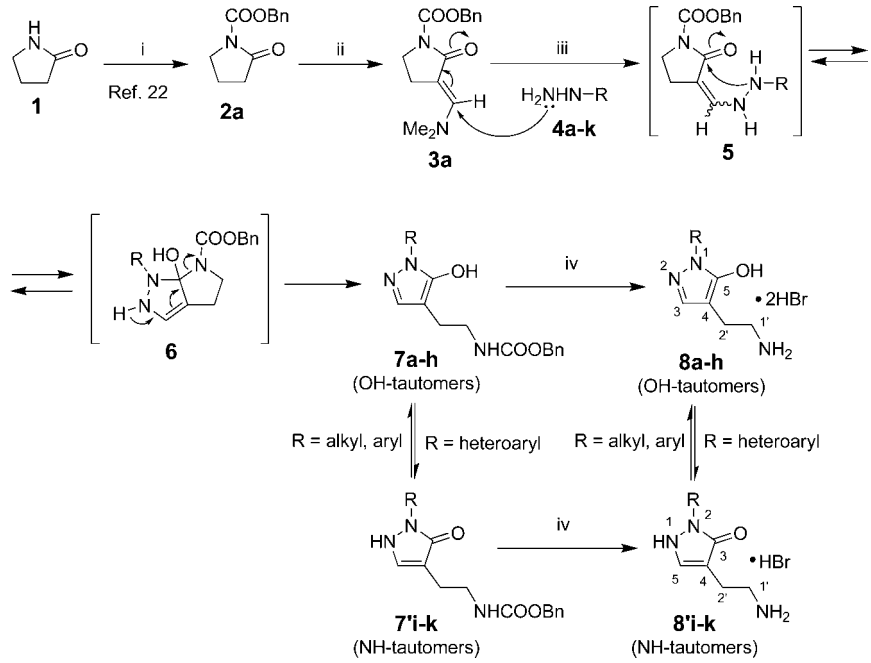
10.1021/cc8000794 CCC: $40.75
Published on Web 07/17/2008

Scheme 1[a]



[a] Reaction conditions: (i) LDA, THF, −78 °C, then ClCOOBn, −78 °C → r.t.;[22] (ii) *t*-BuOCH(NMe$_2$)$_2$, toluene, reflux; (iii) R-NHNH$_2$·HCl (**4a**−**k**), EtOH, MW (300 W, 120 °C, 30 min); (iv) 33% HBr−AcOH, 50 °C.

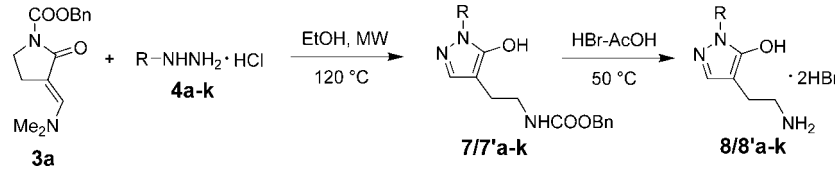
to overcome these limitations, modified synthetic procedures utilizing easily cleavable *N*-protecting groups were studied. As a result of this study, we herein report two novel variants of the enaminone-based "ring switching" synthesis of 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8/8′**, which evolved in a one-pot parallel solution-phase synthesis of pyrazole analogues of histamine **8/8′**.

Results and Discussion

Solution-Phase Synthesis of 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols 8/8′ from the Cbz-Protected Enamino Lactam 3a (Method A). 1-(Benzyloxycarbonyl)pyrrolidin-2-one (**2a**) was prepared from 2-pyrrolidinone (**1**) and benzyl chloroformate following the literature procedure[22] and then treated with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) to give the enamino lactam **3a** in 80% yield. Much to our surprise, **3a** was less reactive than its *N*-benzoyl analogue.[21] Reactions of **3a** with hydrazine hydrochlorides **4** in refluxing 1-propanol were quite slow and minor amounts of byproduct formed upon prolonged heating complicated the isolation of the "ring-switched" products **7/7′**. This difficulty was overcome by microwave-assisted heating of mixtures of enamino lactam **3a**, hydrazine hydrochlorides **4a**−**k**, and ethanol in a pressurized vessel at 120 °C (∼5 bar) for 30 min. Under these conditions, complete and clean conversion of **3a** into the ring-switched compounds **7/7′a**−**k** took place to give 1-substituted benzyl *N*-(5-hydroxy-1*H*-pyrazol-4-yl)ethylcarbamates **7a**−**h** (OH-tautomers) and 2-substituted benzyl 2-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-ethylcarbamates **7′i**−**k** (NH-tautomers) in 18−82% yields. The reaction mechanism can be explained by initial substitution of the dimethylamino group to give the enhydrazine **5**. Addition of the second nitrogen atom to the lactone carbonyl group gives the bicyclic intermediate **6**, which then tautomerises into **7** via opening of the pyrrolidine ring.[15−21] Final deprotection of **7a**−**h** and **7′i**−**k** with 33% HBr−AcOH at 50 °C furnished the corresponding 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols (di)hydrobromides **8a**−**h** and 2-substituted 4-(2-aminoethyl)-1*H*-pyrazol-3(2*H*)-ones (di)-hydrobromides **8′i**−**k** in 76−100% yields and in analytical purity. In the reaction of **7′j** with HBr−AcOH, substitution of chlorine atom at the pyridazine ring took place to furnish the corresponding bromo compound **8′j** (Scheme 1, Table 1).

Solution-Phase Synthesis of 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols 8/8′ from the Boc-Protected Enamino Lactam 3b (Method B). Thus, 1-benzyloxycarbonyl-3-[(dimethylamino)methylidene]pyrrolidin-2-one (**3a**) proved to be a suitable reagent for parallel synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8/8′**. However, the use of highly corrosive HBr−AcOH at 50 °C and formation of noxius benzyl bromide as the side product prompted us to do further optimization toward a greener and more user-friendly method. We chose the Boc-group as the *N*-protecting group, since it can be cleaved under mild acidolytic conditions, e.g. with HCl−EtOAc at room temperature. 1-Boc-pyrrolidin-2-one (**2b**) was prepared from **1** and Boc-anhydride in acetonitrile according to the literature procedure,[23] and the crude **2b** was subsequently treated with Bredereck's reagent to furnish the desired enamino lactam **3b** in 74% yield. Surprisingly, reactivity of the Boc-enaminone **3b** was higher than reactivity of its Cbz-analogue. Preliminary reactions with the model hydrazines, methylhydrazine (**4b**), phenylhydrazine (**4d**), and 3-hydrazino-6-phenylpyridazine (**4k**), proceeded smoothly in refluxing 1-propanol to give the ring-switched compounds **9b**, **9d**, and **9′k** in 63%, 92%, and 72% yield, respectively. Removal of the Boc-group with 2 M HCl−EtOAc at 0−20 °C then

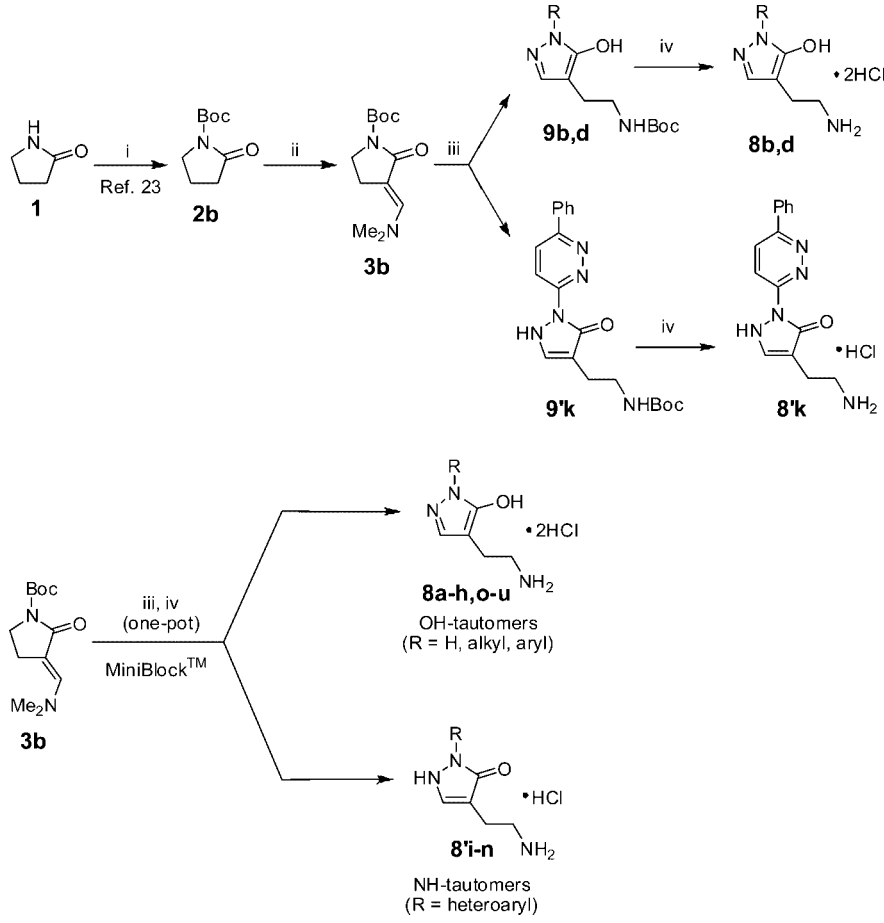
Table 1. Experimental Data on Compounds **7/7′** and **8/8′** Obtained from the Enamino Lactam **3a**[a]



compound	R	yield (%) 3a → 7/7′	7 → 8/8′	3a → 8/8′
4a, **7a**, **8a**	H	81	93	75
4b, **7b**, **8b**	Me	71	82	58
4c, **7c**, **8c**	$PhCH_2$	18	91	16
4d, **7d**, **8d**	Ph	82	88	72
4e, **7e**, **8e**	4-carboxyphenyl	52	89[b]	46
4f, **7f**, **8f**	4-fluorophenyl	79	85	67
4g, **7g**, **8g**	4-chlorophenyl	58	92	53
4h, **7h**, **8h**	4-methoxyphenyl	59	76	45
4i, **7′i**, **8′i**	pyridin-2-yl	71	87	62
4j, **7′j**	6-chloropyridazin-3-yl	35		
8′j	6-bromopyridazin-3-yl[c]		78	27
4k, **7′k**, **8′k**	6-phenylpyridazin-2-yl	57	100	57

[a] All products were obtained in >95% purity according to ^{1}H NMR and elemental analyses. Unless otherwise stated, the found values for C, H, and N were within ±0.4% range with respect to the theoretical values. [b] The found value for N was within ±0.42% range with respect to the theoretical values. [c] Upon treatment of **7′j** with HBr−AcOH, halogen substitution at the pyridazine ring also took place.

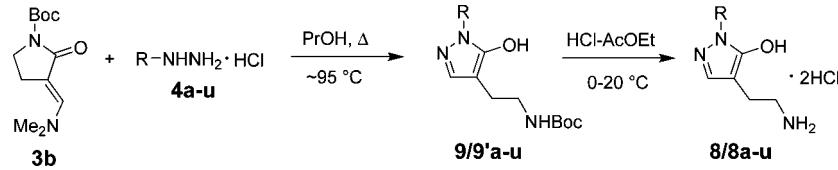
Scheme 2[a]



[a] Reaction conditions: (i) Boc_2O, DMAP (cat.), r.t.;[23] (ii) *t*-$BuOCH(NMe_2)_2$, toluene, reflux; (iii) R-$NHNH_2$·HCl (**4a**−**u**), *n*-PrOH, 95 °C; (iv) 2 M HCl−AcOEt, 0 → 20 °C.

afforded the free amines dihydrochlorides **8b**,**d** and free amine hydrochloride **8′k** in 66−89% yields (Scheme 2, Table 2). Furthermore, when acid-catalyzed reaction of **3b** with methylhydrazine (**4b**) and subsequent deprotection of the so formed intermediate **9b** were performed as a one-pot transformation, the final product **8b** was obtained in quantitative yield upon simple filtration workup. This successful experiment then encouraged us to carry out a one-pot parallel

Table 2. Experimental Data on Compounds **8/8′** and **9/9′** Obtained from the Enamino Lactam **3b**[a]



compound	R	yield (%) 3b → 9/9′	yield (%) 9 → 8/8′	yield (%) 3b → 8/8′[b]
4a, **8a**	H			76
4b, **8b**, **9b**	Me	63	66	100
4c, **8c**	$PhCH_2$			59
4d, **8d**, **9d**	Ph	92	89	64
4e, **8e**	4-carboxyphenyl			83
4f, **8f**	4-fluorophenyl			71
4g, **8g**	4-chlorophenyl			60
4h, **8h**	4-methoxyphenyl			100
4i, **8′i**	pyridin-2-yl			100
4j, **8′j**	6-chloropyridazin-3-yl			91
4k, **8′k**, **9′k**	6-phenylpyridazin-2-yl	72	82	85
4l, **8′l**	imidazo[1,2-*b*]pyridazin-6yl			84
4m, **8′m**	[1,2,4]triazolo[4,3-*b*]piridazin-6-yl			91
4n, **8′n**	tetrazolo[1,5-*b*]piridazin-6-yl			92
4o, **8o**	cyclohexyl			81
4p, **8p**	CH_2COOEt			71
4q, **8q**	2,2,2-trifluoroethyl			40
4r, **8r**	2-hydroxyethyl			86
4s, **8s**	4-methylphenyl			64
4t, **8t**	3-methoxyphenyl			100
4u, **8u**	3-chlorophenyl			81

[a] All products were obtained in >95% purity according to ^{1}H NMR and elemental analyses. Unless otherwise stated, the found values for C, H, and N were within the ±0.4% range with respect to the theoretical values. [b] Yield of **8/8′** upon one-pot transformation.

synthesis of a library of 21 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8a**−**h**,**o**−**u** and their NH-tautomers **8′i**−**n**. The Boc-reagent **3b** was treated first with 21 hydrazines **4a**−**u** in 1-propanol at 95 °C for 4 h, followed by cooling of the reaction mixtures to −10 °C, addition of 2 M HCl−EtOAc, and stirring at room temperature for 12 h. The products **8a**−**h**,**o**−**u** and **8′i**−**n** were isolated by filtration, washed with ethyl acetate, and dried in vacuo to give a library of 21 analytically pure final products, **8a**−**h**,**o**−**u** and **8′i**−**n**, as (di)hydrochlorides in 40−100% yields (Scheme 2, Table 2).

The structures and purity of all compounds **3a**,**b**, **7a**−**h**, **7′i**−**k**, **8a**−**h**,**o**−**u**, **8′i**−**n**, **9b**,**d**, and **9′k** were determined by spectroscopic methods (IR, NMR, MS, HRMS) and by elemental analyses for C, H, and N. Physical and spectral data for known compounds **8a**−**e**,**g**,**h**,**o**,**q**,**s**,**t** (di)hydrochlorides and **8′i**−**l** (di) hydrochlorides were in agreement with the literature data.[21] The structure of enaminone **3a** was determined by X-Ray diffraction. Tautomerism of 4-(aminoethyl)pyrazole derivatives **7/7′**−**9/9′**, which was studied by IR and ^{1}H NMR spectroscopy, was in agreement with the tautomerism, observed previously for the free amines **8/8′** (di)hydrochlorides and their *N*-benzoyl deriatives.[21] A detailed description of structure determination is given in the Supporting Information.

Conclusion

Two closely related synthetic methods for a simple and efficient parallel solution-phase preparation of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8/8′** as the pyrazole analogues of histamine were developed. In the first variation (method A), the 1-Cbz protected enamino lactam **3a** was prepared in two steps from 2-pyrrolidinone (**1**). Microwave-assisted heating of the key intermediate **3b** with hydrazines **4a**−**k** afforded the ring-switched intermediates **7/7′**. Finally, deprotection with HBr−AcOH gave the desired products **8a**−**h** and **8′i**−**k** in good yields and analytical purity upon simple filtration workup. The second version of the synthesis (method B) is even simpler and more effective as well. It comprises two one-pot transformations: (a) transformation of pyrrolidin-2-one (**1**) into the Boc-protected enamino lactam **3b** and (b) ring switching transformation of **3b** with hydrazines **4a**−**u** followed by acidolytic deprotection with HCl−AcOEt to furnish analytically pure final products **8a**−**h**,**o**−**u** and **8′i**−**n** in good overall yields. Following method B, the synthesis is practically carried out in only two steps from inexpensive starting material **1** and the final products **8/8′** are isolated simply by filtration. In addition to the first reports by Young and co-workers[24] and in addition to our later applications,[7,8,17,18,20,21] this work represents, to the best of our knowledge, the first example of utilization of ring switching methodology in the parallel synthesis of histamine analogues.

Experimental Section

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, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ and Q-Tof Premier spectrometers, IR spectra on a Perkin-Elmer

Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Microwave irradiations were carried out on a CEM Discover Laboratory Microwave Oven. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04−0.06 mm).

Pyrrolidin-2-one (**1**), bis(dimethylamino)-*tert*-butoxymethane, and hydrazines **4a**−**i,o**−**u** are commercially available (Sigma-Aldrich). 1-Benzyloxycarbonyl-pyrrolidin-2-one (**2a**),[22] 6-chloro-3-hydrazinopyridazine (**4j**),[25] 3-hydrazino-6-phenylpyridazine (**4k**),[26] 6-hydrazinoimidazo[1,2-*b*]pyridazine (**4l**),[27] 6-hydrazino-[1,2,4]triazolo[4,3-*b*]piridazine (**6m**),[28] and 6-hydrazinotetrazolo[1,5-*b*]piridazine (**6n**),[29] were prepared according to the literature procedures.

Conventional and parallel stirring and heating were carried out on (a) Radleys Heat-On Heating System, (b) Radleys Carousel 6 Reaction Station, and (c) StarFish Multiexperiment Heating and Stirring Workstation. One-pot parallel synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **8/8′** from the Boc-reagent **3b** was carried out on a Mettler-Toledo Bohdan MiniBlock Compact Shaking and Washing Station and Vacuum Collection Base (12 positions, Vortex stirring, 400 rpm in all cases). Parallel evaporation was carried out on a Büchi Syncore Polyvap parallel evaporator.

(*E*)-1-Benzyloxycarbonyl-3-[(dimethylamino)methylidene]pyrrolidin-2-one (3a). A mixture of 1-benzyloxycarbonylpyrrolidin-2-one (**2a**)[22] (3.29 g, 15 mmol), anhydrous toluene (30 mL), and Bredereck's reagent (4.6 mL, 23 mmol) was heated under gentle reflux for 3 h. Volatile components were evaporated in vacuo and the solid residue was crystallized from ethyl acetate to give **3a**. Yield: 0.89 g (80%) of a white solid; mp 117−122 °C. IR (KBr): ν_{max} 3434 (NH), 2964, 1691 (C═O), 1638 (C═O), 1493, 1449, 1380, 1359, 1315, 1273, 1210, 1123, 962, 694 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.88 (2H, t, J = 7.7 Hz, 4-CH_2); 3.01 (6H, s, NMe_2); 3.61 (2H, t, J = 7.7 Hz, 5-CH_2); 5.18 (2H, s, CH_2Ph); 7.00 (1H, s, 3′-H); 7.29−7.43 (5H, m, Ph). Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.92; H, 6.78; N, 10.38.

One-Pot Synthesis of (*E*)-1-*tert*-Butoxycarbonyl-3-[(dimethylamino)methylidene]pyrrolidin-2-one (3b). First, compound **2b** was prepared by a slightly modified literature procedure.[23] Di-*tert*-butyl dicarbonate (44 g, 0.2 mol) was added to a cold solution (0 °C, ice bath) of 4-dimethylaminopyridine (1.42 g, 10 mmol) in a mixture of 2-pyrrolidinone (**1**) (16 mL, 0.2 mol) and anhydrous acetonitrile (200 mL). The so formed solution was stirred at 0 °C for 4 h and volatile components were thoroughly evaporated in vacuo (40 °C, 2 mbar). The residue was dissolved in toluene (100 mL) and thoroughly evaporated in vacuo (40 °C, 2 mbar) to give the crude oily 1-(*tert*-butoxycarbonyl)pyrrolidin-2-one (**2b**). The crude **2b** (∼0.2 mol) was dissolved in anhydrous toluene (100 mL), the flask was flushed with argon, and Bredereck's reagent (42.5 mL, 0.2 mol) was added. The reaction mixture was then gently refluxed under argon for 4 h, cooled and left to stand at room temperature for 12 h. The precipitate was collected by filtration and washed with hexanes (50 mL) to give the first portion of **3b**. The filtrate was evaporated in vacuo (50 °C, 2 mbar), the residue was triturated with hexanes (100 mL), cooled to 0 °C, and the precipitate was collected by filtration to give the second portion of **3b**. Both portions of **3b** were combined. Yield: 35.48 g (74%) of colorless leaflets; mp 125−128 °C. IR (KBr): ν_{max} 3409 (NH), 2969, 2918, 2874, 2812, 1740 (C═O), 1642 (C═O), 1477, 1450, 1412, 1329, 1320, 1265, 1215, 1155, 1125, 950, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.53 (9H, s, *t*-Bu); 2.89 (2H, br t, J = 7.0 Hz, 4-CH_2); 3.02 (6H, s, NMe_2); 3.65 (2H, t, J = 7.7 Hz, 5-CH_2); 7.10 (1H, t, J = 1.7 Hz, 3′-H). Anal. Calcd. for $C_{12}H_{20}N_2O_3$ (240.30): C, 59.98; H, 8.39; N, 11.66. Found: C 60.17; H 8.57; N 11.80.

Microwave-Assisted Cyclocondensation of Cbz-Enaminone 3a with Hydrazines 4a−k. General Procedure for the Preparation of Benzyl *N*-[(5-Hydroxy-1*H*-pyrazol-4-yl)ethyl]carbamates 7a−h and Benzyl *N*-[2-(3-Oxo-2,3-dihydro-1*H*-pyrazol-4-yl)ethyl]carbamates 7′i−k. A mixture of **3a** (0.274 g, 1 mmol), anhydrous ethanol (3 mL), and hydrazine derivative hydrochloride **4**[30] (1 mmol) was heated in a sealed vessel under microwave irradiation (300 W, 120 °C, P ∼5 bar) for 30 min. The reaction mixture was cooled to room temperature, volatile components were evaporated in vacuo (50 °C, 10 mbar), the residue was triturated with methanol (2 mL), and the precipitate was collected by filtration to give **7** and **7′**. Compounds **7a**−**h** and **7′i**−**k** were prepared in this manner.

Experimental data for compounds **7a**−**h** and **7′i**−**k** are given in Table 1. Analytical and spectral data for compounds **7a**−**h** and **7′i**−**k** are given in the Supporting Information (Tables 1 and 2).

General Procedure for the Preparation of 1-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols (Di)hydrobromides 8a−h and 2-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-3(2*H*)-ones (Di)hydrobromides 8′i−k. A mixture of compound **7** or **7′** (0.5 mmol) and HBr−AcOH (33%, 2 mL) was stirred at 50 °C under argon for 1 h. Then anhydrous diethyl ether (5 mL) was added, the precipitate was collected by filtration, and washed with diethyl ether (5 mL) to give **8** and **8′**. Compounds **8a**−**h** (di)hydrobromides and **8′i**−**k** (di)hydrobromides were prepared in this manner.

Experimental data for compounds **8/8′** (di)hydrobromides are given in Table 1. Analytical and spectral data for compounds **8/8′** (di)hydrobromides are given in the Supporting Information (Tables 1 and 2).

Cyclocondensation of Enamino Lactam 3b with Hydrazines 4b, 4d, and 4k. General Procedure for the Preparation of *tert*-Butyl *N*-[(5-Hydroxy-1*H*-pyrazol-4-yl)ethyl]carbamates 9b,d and *tert*-Butyl *N*-{2-[3-Oxo-2-(6-phenylpyridazin-3-yl)-2,3-dihydro-1*H*-pyrazol-4-yl]ethyl}carbamate (9′k). A mixture of **3b** (0.240 g, 1 mmol), 1-propanol (4 mL), and hydrazine derivative hydrochloride **4b**,**d**,**k**[30] (1 mmol) was heated under reflux for 4 h. Volatile components were evaporated in vacuo (50 °C, 10 mbar), the residue was triturated with diethyl ether (5 mL, **9b** and **9′k**) or ethyl acetate (5 mL, **9d**), and the precipitate was collected by filtration to give **9b**, **9d**, and **9′k**.

Experimental data for compounds **9b**, **9d**, and **9′k** are given in Table 2. Analytical and spectral data for compounds **9b**, **9d**, and **9′k** are given in the Supporting Information (Tables 1 and 2).

General Procedure for the Preparation of 1-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols Dihydrochlorides 8b,d and 4-(2-Aminoethyl)-2-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-3(2*H*)-one Hydrochloride 8′k. Compound **9b**, **9d**, or **9′k** (1 mmol) was dissolved in anhydrous ethanol (4 mL) and cooled to 0 °C (ice-bath). Then, cold (0 °C) HCl−AcOEt (2 M, 7 mL) was added, the mixture was stirred at 0 °C for 5 min, and then at room temperature for 1 h. The precipitate was collected by filtration, and washed with ethyl acetate (5 mL) to give **8b**, **8d**, and **8′k**.

Experimental data for compounds **8b**, **8d**, and **8′k** are given in Table 2. Analytical and spectral data for compounds **8b**, **8d**, and **8′k** are given in the Supporting Information (Tables 1 and 2).

One-Pot Parallel Solution-Phase Synthesis of 1-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-5-ols (Di)hydrochlorides 8a−h,o−u and 2-Substituted 4-(2-Aminoethyl)-1*H*-pyrazol-3(2*H*)-ones (Di)hydrochlorides 8′i−n. General Procedure. A MiniBlock was equipped with 12 fritted vessels, charged with 1-propanol (12 × 4 mL), and hydrazine derivatives hydrochlorides **4a−u**[30] (12 × 1 mmol), and the mixtures were vortexed at 20 °C for 15 min. Then, enamino lactam **3b** was added (12 × 0.240 g, 12 × 1 mmol), the reaction mixtures were vortexed at 95 °C for 4 h, and then cooled to −10 °C. Cold (−10 °C) HCl−AcOEt (2 M, 12 × 7 mL) was added and the mixtures were vortexed at −10 °C for 5 min and then at 20 °C for 12 h. The precipitates were collected by filtration, and washed with ethyl acetate (12 × 3 mL) to give the first portions of **8** and **8′**. The filtrates were evaporated in vacuo (40 °C, 2 mbar), ethyl acetate (12 × 3 mL) and anyhdrous ethanol (12 × 1 mL) were added to the residues, and the mixtures were vortexed at room temperature for 24 h. The precipitates were collected by filtration, and washed with ethyl acetate (12 × 3 mL) to give the second portions of **8** and **8′**, which were combined with the first portions of **8** and **8′**. Compounds **8a−h,o−u** and **8′i−n** were prepared in this manner.

Experimental data for compounds **8a−h,o−u** and **8′i−n** are given in Table 2. Analytical and spectral data for compounds **8a−h,o−u** and **8′i−n** are given in the Supporting Information (Tables 1 and 2).

Acknowledgment. The financial support from Boehringer-Ingelheim Pharma (Biberach, Germany) is gratefully acknowledged. We are grateful for the financial support from the Slovenian Research Agency through grants P1-0179 and J1-6689-0103-04. We acknowledge with thanks the financial contributions of pharmaceutical companies Krka d.d. (Novo mesto, Slovenia) and Lek d.d. a new Sandoz Company (Ljubljana, Slovenia), which made the purchase of a Mettler-Toledo Bohdan MiniBlock Compact Shaking and Washing Station and Vacuum Collection Base possible.

Supporting Information Available. Analytical and spectral data for compounds **3a**, **3b**, **7a−h**, **7′i−k**, **8a−h,o−u**, **8′i−n**, **9b**,**d**, and **9′k** and X-ray data for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC8000794